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ALZHEIMER'S DISEASE: CURRENT AND FUTURE BREAKTHROUGH RESEARCH

HEARING

BEFORE THE

SUBCOMMITTEE ON RETIREMENT AND AGING

OF THE

COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

ON

EXAMINING ALZHEIMER'S DISEASE, FOCUSING ON CURRENT AND FUTURE BREAKTHROUGH RESEARCH

MAY 15, 2007

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C O N T E N T S

STATEMENTS

TUESDAY, MAY 15, 2007

ALZHEIMER'S DISEASE: CURRENT AND FUTURE BREAKTHROUGH RESEARCH

TUESDAY, MAY 15, 2007

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

The subcommittee met, pursuant to notice, at 10:05 a.m. in Room SD–628, Dirksen Senate Office Building, Hon. Barbara Mikulski, chairman of the subcommittee, presiding.

Present: Senators Mikulski and Burr.

OPENING STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Good morning, everybody. The subcommittee on Retirement and Aging will come to order to conduct a hearing on Alzheimer's disease, and specifically research that is going on that focuses on current and future breakthroughs.

My very able and collegial colleague Senator Burr is on his way from Russell, but I'm going to open it with my remarks while we're waiting for him, because there is a vote at quarter of 12, and I think we want to leave time for both your testimony, and discussion on how we can accelerate the breakthrough process without jeopardizing safety.

This morning we want to thank all of our witnesses for coming. We have two from the private sector and two from academic centers of excellence that are doing research. And I'll be introducing them shortly—these are researchers who are doing breakthrough Alzheimer's research—two supported by the NIH, and those that are also, as I said, from the private sector. We're going to be very excited to hear about the cutting-edge work that they are doing.

The reason we, the committee, feel an urgency to do this is that we know that Alzheimer's is an epidemic. With the aging population living longer, with even new sophisticated tools of diagnosing Alzheimer's we're doing early detection at an even younger age than when people reach their 80s, which seems to be a catastrophic point.

We know that both the direct and indirect cost of Alzheimer's and other forms of dementia amount to over $100 billion annually, a tremendous cost to families, of high risk for long-term care insurance, and also, then, for the Federal Government, over $91 billion is spent on beneficiaries with Alzheimer's or other forms of dementia.

They talk about Medicare, but I'm also deeply concerned about the cost of Medicaid. Medicaid—80 percent of the beneficiaries of Medicaid are children, but 80 percent of the Medicaid money goes to paying for long-term care and the catastrophic spend-down that, often, families face. If we could find even 2 or 3 years of cognitive stretch-out, the impact on the family budget and on the Medicaid budget, and on, really, private insurance willing to underwrite this, would really be significant.

So, this is why we want to listen to you, to get your ideas. Millions of individuals have not yet been diagnosed, but there will be millions more to come.

Like so many Americans, I'm familiar with this disease. My father was 1 of 5 million currently suffering. My father passed away more than a decade ago. My family and I know—even today, I get fairly emotional about it—the very long goodbye. My mother lived the 36-hour day, and it was our job, as a family, to try to help her. It was devastating to him, it was heartbreaking to my mother, and heart-wrenching for my sisters and I.

What was so difficult about it is that we felt we were powerless, because there were no cures. Fortunately, we lived in Baltimore—we could get an appropriate geriatric evaluation, so we knew it wasn't just a vitamin B12 shot and sending mom and dad on a long-delayed cruise. We also had the benefit of, again, the work that was done under the pioneering thinker, Dr. Mason Lord. Dad could go to an adult daycare program that engaged in the new thinking on cognitive stretch-out. But, at the end, it was the end. And we all face this.

So, our vow, as so many here in the Senate and in the Alzheimer's Association, is to try to find a breakthrough. Working on a bipartisan basis, we have legislation now that would double the funding for Alzheimer's research, that would bring us to a cure, possibly a vaccine, and certainly cognitive stretch-out. We want to create a summit on Alzheimer's to discuss the most promising breakthroughs and to chart a new course. We want to work on family support, which is also news that you could use, and working with our colleagues in the Finance Committee, a long-term-care tax deduction so people could give help to those practicing self-help, as well as a tax credit for helping with family caregiving.

Today, what we want to hear about is the research. Ninety-five percent of what we know about Alzheimer's disease, we've learned in the last 15 years. This is why, again, this acceleration of the breakthrough is so important. We also know that expanding the cognitive stretch-out for people, with 3 to 5 years, could probably save $12 billion annually in public investments in Medicare and Medicaid alone. That's a lot of money.

So, what we want to do today is listen to you, so we can hear what you're doing, and how your Federal Government could be helpful. And I, too, will be interested in knowing what your thoughts would be as we look to NIH, FDA, and CDC on how we can move what we do know out to either patient information, news you can use, or to clinical practice. Many physicians, themselves, if they were—families will tell you, it's misdiagnosed—as well as what we can do to get FDA and CDC to realize this is really an epidemic that's facing America.

I now want to turn to Senator Burr, who's a very able and most collegial colleague, for his thoughts, and then we want to hear from you.

OPENING STATEMENT OF SENATOR BURR

Senator BURR. Thank you, Madam Chairman, and my apologies for my tardiness, to you and to the witnesses.

It is incredibly difficult when a disease affects us personally, or individuals that we know, and the reality is that it happens every day. But our firsthand experience, and our ability to share it, makes passion contagious. And, I think, in many cases, it's that contagious passion that we need, in order to solve some of the challenges that either get mired down in inevitable policy differences or the eventual effect of politics in this town, and in this institution. And I have deep respect for the chairman of this subcommittee, because she doesn't let politics trump policy. And it's refreshing, every time I come to a hearing, to know that we're focused on how to find policy solutions to real problems that affect real Americans.

I join her in welcoming our guests, this morning, who are here to discuss the potential breakthroughs in Alzheimer's disease research. Thanks, to each one of you, for taking the time to be here, to share with us the promising research that you're doing to help develop new treatments for the 5 million people in the United States living with Alzheimer's disease, and many more who will get Alzheimer's as they age.

Currently, it's very costly to treat Alzheimer's disease. According to the Alzheimer's Association, the direct and indirect cost of Alzheimer's and other dementias amount to $148 billion annually. With the aging of our population, the total will continue to grow, at what I believe is an alarming rate.

Academic, scientific, and biopharmaceutical institutions are trying to identify and to develop new treatments for Alzheimer's. I'm proud to have a North Carolina company here testifying today regarding their promising research. Targacept is a Winston-Salem-based company, working with AstraZeneca in the development of a pharmaceutical product for Alzheimer's disease.

Targacept has an interesting history, Madam Chairman, as I'm sure Dr. deBethizy will describe. It started with research being done by R.J. Reynolds Tobacco Company on the therapeutic effects of nicotine, and now they're on the cusp of a breakthrough product for Alzheimer's and schizophrenia.

Madam Chairman, one out of eight Americans over the age of 65 is living with Alzheimer's. Your leadership, your passion for this issue could not have found a better time in history to be displayed. Thank you for shining a light on the need for a coordinated national strategy to accelerate the development of Alzheimer's treatments.

I also welcome our friends from Wyeth, who have a presence in North Carolina, and to our friend from Georgetown and the University of Illinois, we've got some good academic institutions, but if you're ever looking at moving, we'd love to have you in North Carolina.

[Laughter.]

Senator MIKULSKI. Now, now.

[Laughter.]

Senator MIKULSKI. Now, now.

Senator BURR. Madam Chairman, I——

Senator MIKULSKI. Don't stretch it too—the bipartisanship.

Senator BURR [continuing]. Never miss a recruitment opportunity for great minds, and it's these great minds across the country and around the world that I believe will help us to find a successful cure for this disease.

I yield back. Thank you.

Senator MIKULSKI. Well, thank you very much, Senator Burr. And, you know, it is true that in this country you would have both those engaged in publicly funded research, and privately funded research, at the same table.

What I'm going to do is introduce Aisen, Kramer, and Essner. And I know you've already introduced your guest, unless you want to introduce him again—then I'll just ask you to go across the room giving your testimony, and then, because—it seems there are only two of us, because of what's going on, on the floor, we're going to then open it up almost like a roundtable. I'll kick it off, with some questions and Senator Burr, and I'd look for a freeflowing give-and-take, with so much talent, and also experience, both in doing—so much experience in both the field of Alzheimer's research, and in the field of dealing with the bureaucracies involved in Alzheimer's research.

Let me just say that we welcome Dr. Aisen, who comes to us from Georgetown, a professor of neurobiology and medicine. He founded the Georgetown Memory Disorder Program in 1999, and is currently the acting director of the Alzheimer's Co-op Disease Study, which I know he'll tell us more about.

Dr. Kramer is a professor at the University of Illinois, in the Department of Psychology in the Campus Neuroscience Program, a full-time faculty member at the famous Beckman Institute of Human Perception and Performance. And his field is cognitive neuroscience and aging attention and perception. Essentially, all these cognitive issues we're talking about. His research has been funded, interesting enough, from not only NIH, the National Science Foundation, but FAA, DARPA, and General Motors.

And, of course, we welcome Mr. Robert Essner, the CEO and chairman of Wyeth, who has been with the company since 1989. Wyeth has, for the past 15 years, been focused on new and better treatment for Alzheimer's and investing, already, a half a billion dollars in this. And he's—we want to hear, really, where Wyeth—without going into propriety issues, of course, where you see it going. We also note that Mr. Essner is the chairman of the Children's Health Fund Corporate Council, and we salute you for that work.

Senator BURR. Madam Chairman, in addition to what I said about Targacept and their great——

Senator MIKULSKI. Is that how you say it, "Targacept"?

Senator BURR [continuing]. Targacept—and their great CEO—Don was recognized by Ernst & Young as an Emerging Company Entrepreneur of the Year for his leadership in founding Targacept. He has served on the board of directors of the Winston-Salem

Chamber of Commerce, Forsythe Technical Community College Foundation, a number of Winston-Salem-based organizations. I share that with you to tell you this is a person, and a company, that understands their role in the community that they're involved in, even though they're on the cutting edge, in the country, with some of the research they're doing. He was also recently elected to the emerging company's section governing board of the Biotechnology Industry Organization, BIO.

So, Don, I welcome you here, as I do the other witnesses, and I, like the chairman, look forward to your testimony.

Thank you.

Senator MIKULSKI. Why don't we start there and just go right down the table.

STATEMENT OF PAUL AISEN, M.D., PROFESSOR OF NEUROLOGY AND MEDICINE, DIRECTOR OF THE GEORGETOWN MEMORY DISORDERS PROGRAM, GEORGETOWN UNIVERSITY, WASHINGTON, DC.

Dr. AISEN. Thank you.

Madam Chairman, Senator Burr, thank you for the opportunity to address you this morning.

Alzheimer's disease is among the world's most important healthcare problems. It's a disease of aging, and the population of this country is getting older. Senator Mikulski, as you said, we have about 5 million cases today, and, on the basis of the aging of the U.S. population, we may have 15 or 16 million cases by mid-century, so effective treatment and prevention are essential.

As you pointed out, most of the advances in AD research are recent. Our first treatment became available in 1993. Before that, there was a general assumption that this disease would never be treatable. A group of academic investigators demonstrated that we could improve memory in AD, and, through collaboration with the pharmaceutical industry, worked on the development of our current therapeutic options. They provide meaningful cognitive benefits, but, of course, we have a long way to go.

Academic investigators with NIH funding continue to make major advances that will help us to the next step of breakthrough therapy for AD. What's the most important advance in the past decade in AD research? It's the discovery of the specific molecular cause of the disease, which is the amyloid peptide. It's a long story that I don't have a chance to go through, but I can tell you that, on the basis of the knowledge that every known genetic cause of this disease directly affects the generation of this peptide. The only conclusion is that this peptide is driving the disease process. What does that mean? It means that we have a specific target for therapeutic research. It means that it's appropriate for us to be optimistic that we will have breakthrough therapy soon. We have the target, we have the model systems in the laboratory that allow us to screen molecules and test them, and we're now bringing them to human trials.

I believe that we can realistically expect to slow or halt the disease process in the relatively near future, and how long it will take us to get there depends upon the resources brought to bear.

NIH funding has played an instrumental role in bringing us to where we are today and to where we will be in a few years. As you mentioned the Alzheimer's Disease Cooperative Study is a large consortium of academic centers in the United States funded by the National Institute on Aging to develop the tools and conduct trials to improve the treatment of Alzheimer's disease. ADCS investigators conducted the first major trial of Tacrine that led to the first treatment, in 1993. And this group is responsible for a number of milestones, including the establishment and refinement of the most widely used assessment tools in clinical trials today, establishment of the diagnostic criteria and study methodology for mild cognitive impairment, which is the prodromal stage of Alzheimer's, demonstration of the effectiveness of antioxidant therapy for AD, demonstration of the lack of efficacy of some widely used treatments, including anti-inflammatory drugs and estrogen, demonstration of the only known treatment effective at the stage of mild cognitive impairment. And the ADCS, with NIA funding, provides the infrastructure for the Alzheimer's Disease Neuroimaging Initiative, which is a landmark collaboration between NIH investigators and the pharmaceutical industry to establish the best biomarkers of this disease to better enable the development of disease-modifying therapies.

The work of the ADCS has been pivotal in nearly every Alzheimer's disease trial conducted by the academic world and industry. We are currently investigating therapies used for other diseases for their potential in AD, including statin therapy. DHA, which is an Omega-3 fatty acid, turns out to be deficient in the brain. We've found that we can restore DHA levels with supplements, and are just now launching the first major trial of DHA supplementation for AD.

The demonstration that pooled human immunoglobulin, that is used to treat inflammatory and immune diseases, contains naturally occurring antibodies targeting the molecular cause, the amyloid peptide, and we're about to launch a large multicenter trial of IVIg therapy to remove amyloid from the brain and slow the progression of Alzheimer's disease.

There are many other examples, and I see that I'm just about out of time.

I would just remind you that funding priority should be determined not only by the magnitude of the problem being addressed, but by the likelihood that investment will yield important results. And, at this point in time, there is no investment carrying more promise than funding for AD therapeutic research.

Thank you.

[The prepared statement of Dr. Aisen follows:]

PREPARED STATEMENT OF PAUL S. AISEN, M.D.

Alzheimer's disease is among the world's most important health care problem. It is a disease of aging, and as the U.S. population gets older, this problem grows: we have over 5 million cases today, and may reach 15 million by 2050. Effective prevention and treatment are essential.

Useful treatments for the cognitive symptoms of AD have only been available since 1993. Today's treatments represent a significant advance, built on basic and clinical studies conducted by NIH-funded investigators, then followed through by the pharmaceutical industry. This pattern continues: academic investigators have

made tremendous advances in recent years, and have worked with industry to move us closer to breakthrough disease-modifying treatment.

Most important among these advances is identification of the specific molecular cause of AD: the amyloid peptide. This peptide is the principal component of the amyloid plaque, one of the hallmark lesions in the Alzheimer's disease brain. How do we know that this peptide is the pivotal molecule? Because every known genetic cause of the disease directly influences the generation of the amyloid peptide. The only reasonable conclusion is that this peptide drives the disease process.

Therapeutically, this means that we can now realistically expect to slow or halt the disease process. We have a specific, feasible target for therapeutic interventions. We have confidence that treatments that successfully reduce the accumulation of the amyloid peptide in human brain will slow or stop progression of this disease. And coupled with earlier identification of disease (even before the symptoms indicative of the diagnosis are present), we can hope to dramatically reduce the impact of Alzheimer's disease.

We have the tools to develop effective anti-amyloid treatments. We have model systems in our laboratories that allow us to screen and test potential treatments for impact on amyloid accumulation. The result is that numerous promising therapies are reaching the stage of clinical testing.

NIH funding has played an indispensable role in bringing us to this point, and will continue to be pivotal in the final clinical development programs.

The Alzheimer's Disease Cooperative Study (ADCS) is a large research consortium funded by the National Institute on Aging to develop tools and conduct trials to improve the treatment of Alzheimer's disease. The ADCS has been continuously funded since 1991. Accomplishments of this program include:

- establishment and refinement of the most widely used assessment tools for clinical trials in AD;
- establishment of diagnostic criteria and study methodology for "Mild Cognitive Impairment," the Alzheimer's prodromal syndrome;
- demonstration of the effectiveness of antioxidant therapy for AD treatment;
- demonstration of lack of effectiveness of widely used treatments including anti-inflammatory drugs and estrogen;
- demonstration of the only treatment effective in the management of Mild Cognitive Impairment; and
- the ADCS provides the infrastructure for the Alzheimer's Disease Neuroimaging Initiative, a landmark collaboration between the pharmaceutical industry and NIH to establish the best biomarkers of the disease, to better enable the development of disease-modifying treatments.

The work of the ADCS has been pivotal in nearly every major Alzheimer's trial conducted by the academic community and the pharmaceutical industry.

The ADCS is currently conducting clinical studies of promising new treatments for Alzheimer's disease. The ADCS is particularly focused on the evaluation of treatments currently used for other indications, or not otherwise being pursued by the pharmaceutical industry as therapy for AD.

For example:

Statins are among the most widely prescribed drugs in the world. Laboratory studies have shown that cholesterol and statin drugs have an important influence on the accumulation of the amyloid peptide. The ADCS is now completing a definitive trial of a readily available statin (simvastatin) to determine whether it can slow the progression of AD.

DHA (docosahexaenoic acid) is an omega-3 fatty acid present in algae and fish. DHA plays a critical role in the function of brain cells, and levels are depleted in the brains of individuals with Alzheimer's disease. Oral supplements with DHA are effective in restoring brain levels, and, for reasons incompletely understood, DHA markedly reduces amyloid accumulation in brain. The ADCS has just launched a large multicenter study to determine the impact of DHA supplementation on the rate of progression of AD.

One very exciting approach to reducing amyloid accumulation involves the use of antibodies directed against the amyloid peptide. A number of pharmaceutical companies are conducting active and passive amyloid immunotherapy programs, using either vaccinations derived from amyloid or manufactured antibodies to reduce amyloid levels in brain. IVIg is pooled human immunoglobulin, essentially human antibodies derived from donated blood; it is a standard treatment for certain immune and inflammatory diseases. IVIg has been found to contain substantial amounts of naturally occurring anti-amyloid antibodies, and preliminary studies suggest that infusions of IVIg result in stabilization or improvement of AD. The

ADCS is preparing to launch the first definitive study of the safety and effectiveness of IVIg infusions to treat AD.

Huperzine A is a natural extract of a Chinese herb. The purified compound is a highly effective and well tolerated cognitive enhancer, and may be superior to currently available symptomatic treatments for AD. In addition, laboratory studies show that huperzine A protects brain cells against amyloid. The ADCS is currently completing the first controlled study of huperzine A conducted outside China.

As we move closer to effective disease-modifying treatments for Alzheimer's, we are looking toward the testing of preventive measures. But to assess the impact of a preventive treatment, a large number of healthy older individuals must be studied for a number of years. We do not yet have workable tools to allow the efficient conduct of such studies. The ADCS is now conducting a study of Home-Based Assessments, cognitive assessment procedures utilizing computers, interactive phone systems and mail-in tools, to develop the most efficient methods for the conduct of prevention studies without requiring participants to leave their homes.

This is an incredibly exciting time in the field of Alzheimer's disease therapeutic research. We are close enough to be confident of success in the development of breakthrough therapies. How fast we get there, whether it will take a few years or 15, depends on the resources brought to bear. With academic-industry cooperation, and adequate funding from both, progress will be rapid.

There are potential breakthrough studies waiting for funding now. For example, a collaboration between NIH and Israeli scientists has led to the discovery of a compound called NAP. NAP is a fragment of a natural brain protein. In the lab, NAP is the most potent neuroprotective compound ever discovered; it can rescue brain cells from many toxins, including the amyloid peptide. Recently completed lab studies show a remarkable effect of NAP on the pathological cascade of Alzheimer's disease. Human studies of NAP have been initiated, but a definitive trial in AD requires NIH funding; an application is currently in review.

Funding priorities should be determined not only by the magnitude of the problem being addressed, but by the likelihood that investment will yield important results. At this point in time, no investment carries more promise than funding for Alzheimer's disease therapeutic research.

Senator MIKULSKI. Thanks very much, Doctor. Actually, that's a pretty stunning summary.

Dr. Kramer.

STATEMENT OF ARTHUR KRAMER, PH.D., PROFESSOR, UNIVERSITY OF ILLINOIS DEPARTMENTS OF PSYCHOLOGY AND NEUROSCIENCE, AND BECKMAN INSTITUTE, UNIVERSITY OF ILLINOIS, URBANA, ILLINOIS

Dr. KRAMER. I'd like to thank Senators Mikulski and Burr for the invitation to speak with you today about our research, and that of other scientists, on maintaining healthy minds and brains throughout the adult life span.

Over 200 years ago, John Adams, our second President, argued that, "Old minds are like old horses, you must exercise them if you wish to keep them in working order."

My goal in the next 5 minutes or less is to tell you about the highlights and gaps in our scientific knowledge regarding nonpharmacological, or behavioral, approaches to maintaining, and even enhancing, our minds and brains as we age, and as we're older.

The context of the research I'll tell you about is quite varied. It includes a number of different kinds of human studies, including prospective epidemiological studies in which some lifestyle factor is measured at one point in time, and then cognition, or diagnosis, of Alzheimer's or other forms of dementia are measured somewhat later, to look at the relationship between the choice of what we do and its implications. Human randomized clinical trials are the gold standard in medical research of various lifestyle factors. And, fi-

nally, invaluable research from our animal colleagues on molecular and cellular mechanisms of preventative effects of various lifestyle factors on Alzheimer's models, some gene-knockout models and some others, of Alzheimer's, and—as well as cognitive decline.

So, what do we know, with respect to the current state of scientific knowledge, about maintaining healthy brains and minds? And this will be oversimplified, but there's more information provided to the congressional record.

Research has shown that exercise and physical activity is associated with better memory, attention, decisionmaking, executive control abilities, reduced risks—risk for Alzheimer's and other forms of dementia, and increased brain structure and function in clinical trials, that NIH has been so good to support, in older humans.

How do all these effects happen? Well, we certainly don't know all of the mechanisms, but one set of mechanisms has to do with reduced risk for a variety of diseases that accompanies exercise, such as cardiovascular disease, type-2 diabetes, colon and breast cancer, and osteoporosis. But we also know a lot about molecular and cellular mechanisms—again, not enough, but quite a bit more than we did a decade ago. We know that exercise increases the expression of various neurotrophin factors, such as brain-derived neurotrophic factor and others; neurogenesis; or the creation of new neurons from adult stem cells, selectively in the brain; synaptogenesis, the creation of new neuronal connections; as well as angiogenesis, or the construction of new vascular structure, to support increased neuronal firing, and learning and memory.

It's interesting that these exercise effects, the human effects—I've talked about the animal molecular and cellular mechanisms briefly—but the human effects are found with very moderate exercise. In our randomized clinical trials, we take older sedentary adults between the ages of 60 and 80, and put them on a walking protocol for 6 months, 3 days a week. By the end of the 6 months, everybody's walking further and a little bit faster, but nobody's winning any gold, silver, or bronze medals. So, these are very moderate effects that promote improvements in a variety of cognitive functions, as well as a healthier brain, which is quite interesting. And the really neat aspect of this, as my colleague Pat Heyn at the University of Colorado found, very similar effects in early AD patients. Exercise alone clearly isn't sufficient. There has been a good deal of research, and it continues, with support from NIH and other sources, on intellectual engagement, such as playing cards, chess, visiting museums, and so forth; social activities—participating in social, church, and volunteer activities; and diets—food that's high in antioxidants, Omega-3 fatty acids, low in saturated and trans fats—have similar effects to exercise on cognition and reduction in risk of dementia. And this is mostly from observational prospective epidemiological studies.

So, what don't we yet know? Well, we don't yet know quite a bit, and we need your help, Senators—and we need the help of NIH and other government science agencies—to help the scientific community to move along and develop more knowledge that'll be beneficial to our citizens.

No. 1, we need to know much more about the mechanisms which underlie the beneficial effects of lifestyle factors, such as diet, social

interaction, intellectual engagement, and exercise, on the maintenance of healthy minds and brains, so perhaps we don't get to the point of being diagnosed with mild cognitive impairment of Alzheimer's dementia for 2 or 3 years, or even longer, as Senator Mikulski has discussed earlier on.

We need to know how and when, and how much, to best combine different behavioral and pharmacological treatments to maximize the payoffs, in terms of healthy minds and brains throughout the life span. I personally care little to live longer if I can't live well. And I think most of us feel the same way.

We need to know more about how to capitalize on the rapidly expanding field of molecular genetics to customize individual treatments, both pharmacological and behavioral, to encourage healthy minds throughout the life span.

And perhaps the hardest part is how best to encourage our citizens to continue what they start, in terms of exercise, intellectual engagement, social engagement, and eating right to ward off the effects of different forms of dementia, and maintain healthy brains and minds.

Thank you.

[The prepared statement of Dr. Kramer follows:]

PREPARED STATEMENT OF ARTHUR F. KRAMER

INTRODUCTION

The mantra of "successful aging" appears to be ever present in our fast paced high tech society. A visit to your local electronics store will quickly reveal an increasing number of computer games, such as Nintendo's Brain Age and Mattel's Brain Games, that are touted to train your brain and keep you mentally young. Of course, these products, and many others, are also easily downloadable, for a fee, from a multitude of Web sites. The number of books offering solutions to age-related declines in cognitive function, including many aspects of memory, are also proliferating at a rapid pace. Claims in the media, and on the shelf's of health food stores, also abound with regard to the beneficial effects of nutraceuticals and supplements on health and functioning throughout the lifespan.

The increasing interest in products and lifestyle factors that engender successful aging is driven, in large part, by the aging of populations in many industrialized nations as well as the change in our conception of aging. For example, as of 2004 there were 36.3 million Americans over the age of 65, 12.4 percent of the population. This number is projected to grow to 71.5 million individuals, approximately 20 percent of the population, by 2030. Increasing numbers of 65+-year olds have been entering the workforce, both out of financial necessity and in search of continuing intellectual and social stimulation, and are expected to continue to do so in the future (Administration on Aging, 2005). Hence the desire to maintain cognitive as well as physical health.

In the present document we primarily focus on one factor that has been suggested to have a positive influence on cognition and brain function, that is, physical activity and exercise. However, other factors such as intellectual engagement, social interactions, and nutrition are also discussed, albeit to a lesser extent, with regard to their potential beneficial effects on cognition and brain function. We evaluate the claim that staying physically active can maintain and even enhance cognition and brain function as well as reduce the risk of age-associated neurological disorders such as Alzheimer's disease. We begin our review by examining the epidemiological or prospective observational literature which has explored this issue, often with middle age and older adults. Next, we examine randomized clinical trials which have examined the influence of fitness training programs on cognition and less frequently, measures of brain function and structure. We then provide a brief review of the ever expanding animal literature which has begun to elucidate the cellular and molecular mechanisms of physical activity effects on brain and cognition. Next, we briefly examine the role of other lifestyle factors such as the pursuit of intellectually engaging activities and social engagement in the maintenance of cognition and reduction in risk for age-related neurological disorders such as Alzheimer's disease.

We then discuss a small but growing literature which examines the combination of different lifestyle factors, including intellectual engagement, social engagement, physical activity and nutrition as a means for enhancing cognitive and brain health of older adults. Finally, we conclude with a brief prescription of future directions for research on maintaining cognitive vitality across the adult lifespan.

HUMAN OBSERVATIONAL STUDIES OF PHYSICAL ACTIVITY & EXERCISE

In recent years there has been an increasing interest in the relationship between physical activity and exercise at one point in the lifespan and cognition or the diagnosis of age-associated neurological diseases at a later point in time. Clearly, one reason for this interest is the burgeoning literature on the reduction in risk for a multitude of diseases, including cardiovascular disease, breast and colon cancer, obesity, and type II diabetes, associated with physical activity (Dishman et al., 2006). However, another important factor influencing the interest in physical activity and cognition is the animal research on the positive effects of enriched environments, which often include a physical activity component, on learning, memory and brain function (Rosenzweig & Bennett, 1996).

Observational studies generally assess physical activity and exercise with self-report questionnaires and then followup, often 2 to 9 years later, with an examination of cognitive function or diagnosis of Alzheimer's and other forms of dementia. Given that the decision to partake in physical activity is often related to other lifestyle choices and medical conditions these studies also assess such factors which are then used as covariates in the examination of physical activity effects on cognition.

A number of prospective observational studies have found a reduction of risk for Alzheimer's disease and other forms of dementia for more physically active individuals. For example Larson et al. (2006) assessed 1,740 adults over the age of 65 on the frequency of participation in a variety of physical activities (e.g. walking, hiking, bicycling, swimming). After a mean followup of 6.2 years 158 of the original participants had developed dementia. After adjusting for age, sex and medical conditions, individuals who exercised more than 3 times per week during initial assessment were found to be 34 percent less likely to be diagnosed with dementia than those who exercised fewer than 3 times per week. Similar relationships between exercise and dementia have been reported in other studies (Laurin et al., 2001; Podewils et al., 2005; Scarmeas et al., 2001). Some studies have focused specifically on walking and its relationship to dementia. Abbott et al., (2004) examined the distance that 2257 physically capable men, aged 71 to 93, walked on a daily basis and then followed up an average of 4.7 years later with an assessment of dementia. After adjusting for cognitive ability, education and medical conditions at baseline, both walking speed and distance were associated with a reduced risk for dementia.

A reduction of risk for cognitive decline, often measured with a general test of cognitive function such as the mini-mental State examination (MMSE), has also been found for physically active individuals who have not been diagnosed with dementia (Almeida et al., 2006; Lytle et al., 2004; Weuve et al., 2004; Yaffe et al., 2001). A particularly noteworthy study was reported by Barnes et al. (2003) who obtained both subjective and objective measures of cardiorespiratory fitness in a sample of 349 individuals over 55. Six years later these individuals were tested on both the MMSE and more focused tests of executive control, attention, verbal memory and verbal fluency. Higher fit individuals at time 1 showed benefits on tests of all of these abilities at the final assessment and the relationship between fitness and cognition was stronger for the objective than for the subjective measure of fitness.

Although in general the majority of the observational studies have found that physical activity has beneficial effects on cognition, it is important to note that some observational studies have failed to find a relationship between fitness and cognition or dementia (Sturman et al., 2006; Verghese et al., 2003; Wilson et al., 2002; Yamada et al., 2003). It is difficult to know, given the current scientific literature, which factors are most important in moderating the influence of physical activity on later life cognition and dementia. However some possibilities that merit further research include: the distinction between aerobic and non-aerobic physical activities (Barnes et al., 2003), the utility of self-report versus more objectively measured physical activities and fitness, the relative contribution of social, intellectual and physical factors to different everyday activities (Karp et al., 2006), the role of physical activity duration, intensity, and frequency (van Gelder et al., 2005), the nature of the components of cognition that serve as the criterion variables (Colcombe & Kramer, 2003; Hall et al., 2001), the age of participants at initial and final assessment, and genetic factors (Etinier et al., 2007; Podewilis et al., 2005, Rovio et al., 2005; Schuit et al., 2001).

BEYOND OBSERVATION: RANDOMIZED CLINICAL TRIALS IN HUMANS

Observational studies have provided intriguing support for the relationship between physical activity and cognition. However, such studies cannot establish causal links between these constructs. Over the past several decades there have been a relatively small but increasing number of clinical trials in which relatively sedentary individuals, often over the age of 60, are randomized to an aerobic training group (i.e. walking, swimming, bicycling) and a control group that often entails non-aerobic activity such as toning and stretching. Training is usually conducted for an hour a day for several days a week and can last from several months to 2 years. Cognition, and less frequently brain function and structure, is examined prior to and subsequent to the interventions.

Results of such studies have been mixed with some reporting that aerobic exercise differentially benefits aspects of cognition while other studies have failed to observe such a relationship. Several potential reasons for this mixed pattern of results include: (1) the manner in which cardiorespiratory fitness was characterized from resting heart rate to the gold standard, VO2 max, (2) the length, duration and intensity of exercise training, (3) the cognitive processes examined in the studies, and (4) the age, health, sex, and fitness levels of participants. Given the substantial variability in individual and experimental characteristics several meta-analyses have been conducted in recent years to determine, first, whether a robust relationship between exercise training and cognition can be discerned and second, which factors moderate such a relationship (Etnier et al., 2006; Heyn et al., 2004; Kramer & Colcombe, 2003).

The results are clear with respect to the first question, exercise training positively influences cognition. Several additional results are noteworthy. First, the effect size of exercise training, approximately .5 over analyses, is quite similar for both normal and cognitively impaired adults. Thus, older adults with early dementia appear able to benefit from exercise training, albeit from a different cognitive baseline. Second, studies with more women generally show a larger effect of exercise training on cognition than studies with fewer women. Third, while fitness training has relatively broad effects across a variety of perceptual and cognitive processes, the benefits of exercise training appear to be larger for executive control processes (e.g. planning, scheduling, working memory, dealing with distraction, multi-tasking). This observation is quite interesting given that executive control processes show substantial declines over the adult lifespan. Fourth, overall there was little evidence of a significant relationship between fitness change and cognitive change. At first glance this observation appears perplexing. However, upon further consideration this may not be surprising given that the measures of fitness obtained in these studies are global in nature (i.e. sensitive to both peripheral and central nervous system changes) and not specific to brain function.

As compared to the study of the relationship between exercise training and cognition, relatively few studies have been conducted to examine exercise training influences on human brain structure and function. Colcombe et al. (2004) investigated changes in the neural network which supports attentional control, as indexed by fMRI activation obtained in a high field magnet, over the course of a 6 month aerobic exercise program. Older adults performed the flanker task, which entails focusing on a subset of information presented on a visual display and ignoring task-irrelevant distractors, before and after the exercise training interventions. Individuals in the aerobic training group (i.e. walking) showed a reduced behavioral distraction effect and change in pattern of fMRI activation similar to that displayed by younger controls (i.e. increased right middle frontal gyrus and superior parietal activation). Participants in the toning and stretching control group did not show such behavioral and fMRI changes. More recently, Colcombe et al. (2006) reported increases in brain volume, as indexed by a semi-automated image segmentation technique applied to high resolution MRI data, for an aerobic but not for a non-aerobic exercise training group. The individuals who walked 3 days a week for approximately 1 hour per day displayed increases in gray matter volume in the frontal and temporal cortex as well as increases in the volume of anterior white matter. Finally, Pereira et al. (2007) reported increases in MRI measures of cerebral blood volume (CBV) in the dentate gyrus of the hippocampus for a group of 11 middle aged individuals who participated in a 3-month aerobic exercise program. These CBV changes were related to both improvements in cardiorespiratory fitness and performance on a test of verbal learning and memory. Increases in CBV in a parallel study of exercising mice was found to be related to enhanced neurogenesis. Therefore, the results of this study are particularly exciting in suggesting that CBV may serve as a biomarker for neurogenesis in humans.

ANIMAL RESEARCH: CELLULAR AND MOLECULAR MECHANISMS

Research using non-human animals complements human research in several ways. First, many of the uncontrolled variables in human research can be more easily controlled or systematically manipulated in non-human animal research, thereby allowing for a more precise examination of some of the factors influencing brain and cognition. Second, the capabilities to assess the molecular and cellular mechanisms of exercise are substantially greater in non-human animals than in humans. Therefore, animal research provides an important translational approach to understanding neurocognitive plasticity in humans.

In rodents, voluntary exercise enhances the rate of learning on hippocampal dependent tasks such as the Morris Water maze, a task that requires the use of extramaze cues to determine the location of a submerged platform (Adlard et al., 2004; Vaynman et al., 2004). For example, in older animals, van Praag et al. (2005) reported that 45 days of access to a running wheel resulted in faster acquisition and greater retention on the water maze than age-matched sedentary controls. Other tasks, such as the passive avoidance task, in which animals are trained via footshock to refrain from entering into a dark chamber, also show performance improvements with exercise (Alaei et al., 2006). Similar behavioral benefits of exercise have been reported in rodent models of Alzheimer's disease (Adlard et al., 2005) and Huntington's disease (Pang et al., 2006). Therefore, there is ample evidence that exercise promotes faster rates of learning and improved retention on hippocampal-dependent tasks.

Enhanced learning on water maze tasks has been associated with an increased production of neurotrophic molecules such as brain-derived neurotrophic factor (BDNF). BDNF is involved in neuroprotection and promotes cell survival, neurite outgrowth, and synaptic plasticity (Cotman & Berchtold, 2002). For example, direct administration of BDNF increases cell proliferation in the hippocampus, whereas blocking BDNF activity reduces cell proliferation. Voluntary exercise increases both mRNA and protein levels of BDNF in the hippocampus, cerebellum, and frontal cortex and blocking the binding of BDNF to its tyrosine kinase receptor abolishes the exercise-induced performance benefits on the Morris water maze (Vaynman et al., 2004). Therefore, exercise increases BDNF levels, which seem to be inextricably related to the behavioral improvements observed with an exercise treatment.

BDNF is not the only molecule in the brain affected by exercise. For example, insulin-like growth factor-1 (IGF-1) is critical for both exercise-induced angiogenesis (Lopez-Lopez et al., 2004) and neurogenesis (Trejo et al., 2001). By blocking IGF-1 influx into the brain, exercise-induced cellular proliferation and BDNF production are effectively rescinded. In addition, IGF-1 also moderates the secretion of other molecules such as vascular endothelial growth factor (VEGF), a prominent growth factor involved in blood vessel growth. For example, Lopez-Lopez et al. (2004) reported that blocking IGF-1 blocked the secretion of VEGF, which resulted in a significant suppression of new capillaries. Furthermore, by blocking the influx of VEGF into the brain, exercise-induced neurogenesis is abolished, but baseline levels of neurogenesis are unaffected (Fabel et al., 2003). Therefore, a plethora of molecules and molecular cascades are up-regulated with exercise that influence learning and memory operations, cortical morphology, angiogenesis, and cell proliferation.

Exercise induces the development of new capillaries in the hippocampus, cerebellum, and motor cortex of young rats (Black et al., 1990; Kleim et al., 2002; Swain et al., 2003) and reduces the volume of cortical damage caused by the induction of stroke (Ding et al., 2004). One function of new capillaries is to deliver necessary nutrients to existing or newly dividing neurons. In relation to this, exercise increases both cell proliferation and cell survival, which has been related to enhanced learning rates on the Morris water maze (van Praag et al., 1999). Neurogenesis is diminished with age, but exercise reliably reverses the normal decline in neurogenesis accompanied by improved Morris water maze performance (van Praag et al., 2005; Kronenberg et al., 2006).

It is clear from this review that rodent research provides strong support for the positive effects of exercise on the brain and cognition. Voluntary wheel running in rodents results in enhanced learning and retention on hippocampal-dependent tasks, the induction of a variety of molecular cascades including BDNF, IGF-1, VEGF, and an increase in neurotransmitter release in dopaminergic, cholinergic, and serotinergic systems. In addition, both angiogenesis and neurogenesis are upregulated with exercise in young and old animals. This evidence provides an important mechanistic and molecular basis for understanding the effects of exercise on the human brain and cognition.

BEYOND PHYSICAL ACTIVITY & EXERCISE: THE INFLUENCE OF INTELLECTUAL AND SOCIAL ENGAGEMENT IN PROMOTING HEALTHY MINDS THROUGHOUT ADULTHOOD

Similar to the studies of physical activity there have been an increasing number of longitudinal human studies to examine the influence of participation in intellectually stimulating activities such as reading, playing cards or chess, attending a play, doing crossword puzzles, taking classes, going to museums and other similar activities on the maintenance of cognitive health and reduction in risk for Alzheimer's disease in older adults. These studies generally assess number and frequency of participation in intellectually engaging activities at one point in time, in populations of adults between 60 and 80 years of age, and then follow up six or more years later with an assessment of cognition and age-associated neurological disorders. The great majority of such studies conducted over the past decade have found that participation in a greater number (and with greater frequency) of intellectually engaging activities is associated with higher levels of cognitive function and reduced risk of dementia in older adults (Bosma et al., 2002; Verghese et al., 2003, 2006; Wang et al., 2006; Wilson et al., 2002, 2003).

A similar approach has been taken to examine the influence of participation in social activities and maintaining social interactions on cognition and brain health of older adults. Studies that have examined social activities such as meeting friends, participating in cultural or social groups, engaging in family and charitable activities, and attending church activities have generally produced positive results both in terms of maintenance of cognition in normal elderly and in reducing the risk for Alzheimer's dementia (Barnes et al., 2004; Lovden et al., 2005; Wang et al., 2002). The size of social networks has produced a mixed pattern of results with some studies finding benefits for individuals with larger social networks and other studies failing to observe relationships between social network size and cognition or dementia risk (Fratiglioni et al., 2000; Helmer et al., 1999). Indeed, social relationship quality rather than social network size may be more important with regard to maintaining healthy minds and brains.

One potential concern with these longitudinal studies, however, is whether reduced intellectual or social engagement at initial assessment may be an early sign of decline or dementia rather than a predictor of latter function. While reverse causation is always a concern in studies that do not involve randomized trials, the fact that some of the studies have found relationships between cognitive or social engagement over 15 or 20 years considerably reduces this concern (Crowe et al., 2003)

EFFECTS OF MULTIMODAL LIFESTYLE FACTORS ON COGNITION AND BRAIN HEALTH

As described in the sections above, the great majority of laboratory studies of factors that influence the level and trajectories of cognitive function focus on single factors. This is a reasonable scientific approach given the potential complexity and cost of simultaneously studying multiple interacting factors. However, clearly a disadvantage of such an approach is that it may miss the potential power of interactions for maintaining and enhancing cognition.

There are at least two different approaches that have been pursued in the literature to the study of multi-factor influences on cognition. One approach is represented by the early study of complex or enriched environments on brain function and performance of non-human animals (Black, Isaacs, Anderson, Alcantara & Greenough, 1990; Ehninger & Kempermann, 2003; Jones, Hawrylak, & Greenough, 1996; Kempermann, Kuhn & Gage, 1997; Rosenzweig & Bennett, 1996). Such an approach can establish the influence of some combination of either separately acting or interacting factors such as social interaction, cognitive challenge, physical activity and nutrition on performance and brain. However, this approach can not assess the relative contribution of individual factors (or their interaction). Nonetheless such an approach has been instrumental in establishing the importance of potential lifestyle factors in cognitive maintenance and enhancement. A second approach which has been represented in observational studies for some time and is beginning to evolve in human and non-human interventions is the orthogonal examination of multiple factors and their interactions in separate groups of subjects. Such an approach is costly in terms of time and the number of subjects required. However, this approach also has the potential to decompose the relative benefits of different factors and their potential mechanisms. Studies that have pursued each of these approaches will be discussed below.

Prospective Observational Studies. A number of prospective observational studies, some of which have been reviewed above in the context of single lifestyle factors, have investigated the relative contribution of intellectual, physical and social engagement as predictors of cognitive change and transition to dementia. For example, Wilson et al (2002a&b) reported that while participation in cognitive activities (such

as reading, listening to the radio, playing games) reduced the risk of succumbing to Alzheimer's Disease; participation in physical activities (such as jogging, gardening, bicycle riding, dancing) was unrelated to the development of AD 4 years in the future (see also Verghese et al., 2005; Wang et al., 2006). Both the cognitive and physical activities were assessed via self report and while the cognitive activities were assessed relative to a 1-year timeframe, physical activities were referenced to a 2-week period prior to the assessment.

A study by Sturman et al. (2006) is particularly interesting in that these investigators addressed the question of whether, over a 6.4 year period, participation in physical activities by older adults reduces the rate of cognitive decline after accounting for participation in cognitively stimulating activities. Prior to adjustment for cognitive activities, each additional hour per week of physical activity was associated with a slower rate of cognitive decline. However, this relationship was no longer significant after adjusting for cognitive activities. On the other hand, Richards et al (2003) reported that physical activity at 36 years of age was associated with a slower rate of decline in memory from 43 to 53 years of age and this relationship was unchanged after adjusting for cognitive activities. Cognitive activities were not associated with change in memory over this interval.

The studies described above generally employ different activities to represent cognitive or physical demands. However, a recent study by Karp and colleagues (2006) has taken a different approach to examining the relative contribution to cognitive, physical and social engagement to cognitive change and dementia. They argue that most leisure activities engage some combination of these three types of demands. On this basis, they had the researchers and a panel of older adults rate the relative intensity, on a scale of 0 to 3, of social, cognitive and physical demands of a set of 30 leisure activities. Agreement was quite high among raters. As an example of the ratings attending courses was rated 3,1 and 2 for mental, physical and social demands, respectively (with 3 being the most intense). These ratings were then applied to the activities pursued by 776 individuals over the age of 75 years of age to predict diagnosis of dementia 6 years in the future. After adjusting for a variety of covariates social, cognitive and physical activities were each found to be associated with a reduced risk for dementia. In any event, characterizing leisure activities in terms of their multidimensional nature is an interesting and potentially important alternative to the dichotomous approach adopted by other observational studies.

In summary, in observational studies that examine more than one lifestyle factor, cognitive activities appear to be the strongest predictor of cognitive change. However, this could be the result of the several factors including: (1) rarely are physical activities characterized in terms of intensity, frequency and duration, (b) the period across which activities are assessed has been different for cognitive and physical activities, (c) with one exception, activities have been treated as unidimensional in nature. Clearly, these issues require additional consideration in future studies.

Human Intervention Studies. To our knowledge there have been only two randomized trials that have examined the separate and combined influence of multiple lifestyle factors on the cognitive function of older adults. Both of these studies were conducted by the same research group and involved 2 months of training with eight 60- to 75-year-old participants in each of four experimental groups. In both studies subjects either participated in an aerobic training group (walking & jogging), a memory training group (including general encoding & retrieval instructions, association & attentional training), a combined group, and a control group. Fabre et al. (1999) found that all three training groups but not the control group showed improved performance on logical and paired associate memory tasks across the 2-month intervention. However, combined training did not show additional benefits as compared to the aerobic or memory training. Fabre et al. (2002) used an elaborated memory training protocol and a similar physical training protocol as compared to their previous study. A more thorough assessment of changes in memory was also used in this study. Results indicated improvements in a general memory metric in all three of the training groups. However, in this experiment, benefits were largest for the combined training group.

The two studies described above attempted to decompose the relative contribution of cognitive and physical training to improvement in cognitive function. A number of other human intervention trials have taken a multimodal approach, much like enriched environment experiments with animals, in examining the influence of multiple lifestyle factors on cognition. The Experience Corps project, conducted at Johns Hopkins, is an example of one such project (Fried et al, 2004). This project places teams of older adults in inner city elementary schools to address unmet needs. The older adult participants are trained to provide literacy, numeracy, library and other support in kindergarten through 3rd grade. Once entering the program and com-

pleting training the older adults devote at least fifteen hours per week for an academic year to the schools. The Experience Corps program stresses a combination of social, cognitive and physical activity engagement in support activities in the schools. An intervention with 128 participants who were randomized to the Experience Corps program and a wait list control group found that individuals with poor baseline executive function showed a 44 to 51 percent improvement in executive function and memory in the post intervention followup. These improvements were not observed for the control participants (Carlson et al., submitted). In another small randomized intervention (Carlson et al., 2006) Experience Corps subjects, but not control subjects, displayed improved efficiency in brain activation, as indexed by event-related fMRI, and performance in an inhibitory control task.

Another recently completed multimodal intervention was conducted by Small and colleagues (2006). In this study a small group of middle-aged participants were randomized either to a 2-week healthy lifestyle program or a wait-list control group. Subjects in the healthy lifestyle group, which included a healthy diet, physical exercise, relaxation training and memory training, showed improvements in verbal fluency and decreases in activation in left dorso-lateral prefrontal cortex as assessed via Positron Emission tomography. Other multimodal interventions that have combined social and cognitive components have also shown training specific benefits as compared to wait-list control groups in cognition and psychosocial function (Fernandez-
Ballesteros, 2005; Stine-Morrow et al., in press).

In summary, thus far there are few studies that have systematically examined either the separate or combined contribution of multimodal interventions to enhanced cognitive and brain function in older adults. Clearly, the nature and mechanisms of multimodal intervention programs, particularly those that can be implemented in community setting such as the Experience Corps project, are important topics for future longer-term studies.

Multimodal Animal Research. As described above the great majority of animal studies that have examined the influence of multimodal interventions on brain function, learning and memory have done so in the context of enriched or complex environments in which animals are often housed together with the opportunity for physical activity and exploration of a multitude of novel objects (Black, Isaacs, Anderson, Alcantara & Greenough, 1990; Ehninger & Kempermann, 2003; Jones, Hawrylak, & Greenough, 1996; Kempermann, Kuhn & Gage, 1997; Rosenzweig & Bennett, 1996). These studies have generally found beneficial effects of this multimodal environment on brain structure, function and performance. However, a smaller set of studies have examined the separate and joint contributions of different interventions to brain health and cognition.

Two studies have focused on the separate and combined effects of diet and cognitive training or exercise. Molteni et al. (2004) examined the effects of a high fat diet and voluntary exercise on learning and a variety of molecules which support neural function. Female rats were randomized into four different groups created by combining a regular or high fat diet with voluntary exercise or a sedentary environment. After 2 months of the interventions the regular diet/exercise group was found to show the fastest spatial learning on the Morris Water maze task followed by the regular diet/sedentary and high fat/exercise groups, with the high fat/sedentary group showing the poorest learning. Additionally, a combination of a regular diet and exercise was observed to produce the largest increase in brain-derived neurotrophic factor (BDNF), a neuroprotective molecule that facilitates synaptic transmission, as compared to the regular diet/sedentary group. Furthermore, decreases in BDNF engendered by a high fat diet were abolished by exercise. Thus, these data suggest that the costs of a high fat diet can, under some conditions, be offset by regular exercise. Milgram et al. (2005) conducted a 2-year intervention with separate and combined diet (regular & enhanced anti-oxidant) and enriched (including discrimination training and exercise & non-enriched control) conditions with older beagles. Both the antioxidant diet and enriched environment groups displayed a number of benefits in learning in memory across a variety of discrimination tasks. Furthermore, the group that received both the antioxidant diet and enriched environment showed the most dramatic benefits in learning and memory. Indeed, these data suggest reduced cognitive decline, over the 2-year period of the study, for older dogs with behavioral enrichment and/or dietary fortification with antioxidants.

In a recent study, Stranahan et al. (2006) examined the interaction between social isolation and exercise on neurogenesis in the hippocampus of adult male rats. Animals were either housed individually or in groups and either did or did not have access to a running wheel. Several interesting results were observed. First, individual housing precluded the positive effects of short term running on adult

neurogenesis in hippocampus. Furthermore, in the presence of additional stressors the influence of short-term running was negative for the socially isolated animals, resulting in a net decrease in the number of neurons relative to sedentary animals. Second, group-housed runners produced the largest number of new neurons in the hippocampus. Finally, longer duration running was able to enhance cell proliferation of the socially isolated animals but not to the level of group-housed animals.

In summary, the studies reviewed above and others (Berchtold et al., 2001; Russo-Neustadt et al., 1999) suggest potentially mutually interdependent relationships of a number of different lifestyle factors on brain and cognitive health of both young and older organisms. Clearly, however, although the extant literature provides some clues concerning the molecular and cellular pathways that support the interactive effects of different factors much remains to be discovered in additional research on multimodal interventions (Gobbo & O'Mara, 2006; Wolf et al., 2006).

FUTURE DIRECTIONS

Our brief review of the literature suggests that a number of lifestyle factors provide multiple routes to enhancing cognitive vitality across the lifespan—through the reduction of disease risk and in the improvement in the molecular and cellular structure and function of the brain. Thus, as has been suggested for other factors such as education (Elkins et al., 2006; Stern, 2006), physical activity, intellectual engagement, social interaction and nutrition appear to provide a cognitive reserve which buffers us against the many challenges experienced during the course of aging. However, despite all that we have learned about the benefits of exercise much remains to be discovered in future research.

We present here several directions for future research to isolate and delineate the cognitive and neural effects of exercise. First, as reviewed in this manuscript, both animal and human research point to similar conclusions regarding the beneficial properties of exercise on the brain and cognition, but whether the underlying mechanisms are the same in both humans and rodents remains unresolved. An important avenue for future research will be to assess the concentration of molecular markers in human blood and brain tissue as a function of an aerobic exercise treatment (Pereira et al., 2007; Reuben et al., 2003). Such a link would provide compelling evidence that the same molecular mechanisms are functioning in both humans and rodents. Of course, the same issues are of interest for other lifestyle factors.

A few studies have reported that the effects of aerobic exercise are not independent of factors such as estrogen, diet, and intellectual and social engagement (Vanyman & Gomez-Pinilla, 2006). However, the study of interactions among lifestyle factors is in its infancy and the degree and direction of these interactions needs to be more fully elucidated. An important future direction is to examine the effects of lifestyle factors within a multi-factorial framework which also incorporates pharmacological treatments for age-associated disorders and diseases.

A third avenue involves determining the relationship between lifestyle factors and certain genetic profiles. For example, people with certain alleles have higher risks for dementia, disease, or cognitive dysfunction. Whether exercise, intellectual engagement, social engagement or good nutrition offsets or diminishes the risks associated with such genetic predispositions remains an understudied question. Characterizing the genetic profiles of those people who benefit the most and those that benefit the least from particular lifestyle regimens is clearly needed.

In addition, the benefits and limitations of lifestyle factors in preventing or reversing the cognitive and neural deterioration associated with neurological diseases have not been fully investigated (Heyn et al., 2004). It will be important for future research to examine the efficacy of lifestyle factors such as exercise, intellectual, and social engagement in relation to symptom severity, duration of illness, comorbidity of diseases, the brain areas and molecular factors most affected in the disease, and possible interactions with pharmaceutical treatments. Given the medical and social significance of this research, these questions should be pursued with vigor.

Another direction for future research is to specify which cognitive operations are most affected by different lifestyle factors. For example, it appears that in humans aerobic exercise affects executive functions more than other cognitive processes (Colcombe & Kramer, 2003). However, what remains unaddressed is what aspect(s) of executive function is being most affected with exercise: response preparation, response selection, conflict detection, task-switching, task and goal maintenance in working memory, etc. The nature of exercise effects on tasks that rely on the temporal lobes, consistent with the demonstration of hippocampal neurogenesis in non-human animals (Pereira et al., 2007; Van Praag et al., 2005), is also an important research topic. Therefore, more refined task manipulations in the context of exercise

and other interventions will allow for a detailed characterization of the relevant cognitive processes.

Finally, very few experimental studies investigate whether the benefits of lifestyle factors extend outside the laboratory to everyday cognitive functioning. Although the effects are often assumed to transfer outside the laboratory, evidence to support such a claim does not currently exist. It will be important for any future research to also investigate the transfer of such cognitive and neural benefits to everyday activities involved in independent living and workplace activities.

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Senator MIKULSKI. Well, that was very, very, very instructive, and we have tons of questions to ask.

Mr. Essner.

STATEMENT OF ROBERT ESSNER, CHAIRMAN AND CEO, WYETH, MADISON, NEW JERSEY

Mr. ESSNER. Thank you. Thank you, Senator Mikulski and Senator Burr, for allowing me to testify on a subject that is very important to me, my company, Wyeth, and certainly Alzheimer's patients and their families.

I'd like to share, very quickly, three key messages with you today. First, that, as you've all said, Alzheimer's disease is an epidemic that requires an epidemic-level response. Second, to tell you that Wyeth is very active in the war on Alzheimer's disease. And third, that our efforts would be aided by a focused national strategy targeting this disease. And let me give a little more detail on each of these.

First, that Alzheimer's disease is an epidemic. That's what we're headed for as we go out into the future. I know many of you appreciate the scope of what we're facing, but, despite the wealth of data that's available, I'm concerned that, in general, the public does not see Alzheimer's disease as an epidemic, at least not yet. Avian flu and AIDS come to mind as epidemics. Alzheimer's just does not. And, frankly, I think we may have become almost desensitized to it. It was first identified over 100 years ago, and maybe, in some way, we've just gotten used to it.

We're all familiar with the statistics on the economic and social burdens of this disease. I'm turning 60 this year, and I'm starting to take this personally, because today, as Senator Burr said, one out of eight Americans over 65 has Alzheimer's. I think even more startling is the statistic that says if you live to be 85—and I think many people in my generation have that expectation today—your chances of developing Alzheimer's disease are almost 50 percent.

A second point is that Wyeth, the organization I lead, has committed itself to doing everything it can to control this epidemic. Wyeth, today, has the most extensive pipeline of Alzheimer's discovery and development programs in industry. We've been working on this disease, as was mentioned, for 15 years, and are focused on identifying and developing novel approaches to it. We have spent, as you heard, almost half a billion dollars on Alzheimer's research in the past 5 years alone. Nearly 3,000 of our scientists participated in this work, and over 350 of them are dedicated exclusively to Alzheimer's disease.

Currently, we have about 30 projects in various stages of development across each of our technology platforms. We work in pharmaceuticals, extensively in biotechnology, and also in vaccines. Of these projects, eight are currently being studied in Alzheimer's patients, and four more will move into clinical research in the near future, we hope.

I think the most exciting part of the research is the work we're doing to delay, halt, or even reverse the progression of the disease, or maybe even to prevent it altogether with an Alzheimer's vaccine.

Our two most advanced projects are work we do in partnership with Elan Corporation to develop immunotherapeutics. One approach uses an engineered monoclonal antibody to target the beta amyloid that Dr. Aisen mentioned, a substance that many, obviously, believe are a key cause of Alzheimer's disease. The other approach focuses on stimulating the body's own immune system to

clear this amyloid. These approaches represent the two, we believe are the most promising and advanced programs in development today.

We're working on a number of other approaches to ridding the brain of beta amyloid, including a gamma secretase inhibitor and a plasminogen activator inhibitor. And we're also working on treatments targeting the symptoms of Alzheimer's disease. Our symptomatic efforts include serotonin agonists and a novel oral medication that seeks to modulate neurotransmitter pathways to improve cognitive function. While we hope that each of these therapies will prove useful on its own, it may well be that it will take a combination of approach to manage this disease as well as possible.

We intend to leave no stone unturned in this fight. We are targeting multiple approaches, because we believe that it is crucial that we explore all possible avenues. While we believe that beta amyloid is likely to be a key causative factor, we understand there well may be other factors that play a role in this disease. There are still many unanswered questions about the human brain and about Alzheimer's, and we hope to pursue as many valid targets as possible until these questions are answered.

While Wyeth is proud of its position as a leader in Alzheimer's and of our pipeline, obviously we're not the only company engaged in the fight against this disease, and important work is occurring across the industry. And many large and small pharmaceutical companies are working on this disease today.

We hope that in the next few years regulatory filings for important new therapies will begin to reach FDA, giving patients and their families new reasons for hope.

My third, final, message is that we could use your help in taking the fight against Alzheimer's to the next level by calling for a national strategy targeting the disease. While we are seeing a growing awareness of the problem of Alzheimer's, a real understanding of its epidemic proportions still has not penetrated the national consciousness. We need to increase the focus on this disease and accelerate our ability to respond to it.

As a nation, we have been successful in this type of effort before. The story of AIDS, I think, is both instructive and a little bit inspirational. In the war against AIDS, government regulatory agencies, other governmental groups, scientists in industry and academia, and patient groups worked hand-in-hand to develop new therapies and evaluate them as rapidly as possible. As a result of that focused effort, the first useful therapy for AIDS was available within 6 years of the time the phrase "AIDS" was actually coined, and the disease went from being a lethal diagnosis to a treatable chronic condition for many people.

We approach Alzheimer's disease with the same urgency and coordination. We'll be able to accelerate scientific advances, and, we hope, alter the course of this epidemic.

To that end, I would like to commend Senator Mikulski for her legislative efforts in this area. I'd like to particularly note the provision of S. 898, that calls for Secretary Leavitt to convene the Alzheimer's summit. Alzheimer's disease needs to move forward into the forefront of our national research agenda, and that proposal, I think, is an excellent start.

Alzheimer's disease is an epidemic. We know it's coming. All the warning signs are in place. Unless we act now, the impact on our healthcare system, healthcare budgets, and, most importantly, our families, will be overwhelming. With active cooperation and commitment from all parties involved in this fight, we believe we can create tools that will be decisive in bringing this disease under control. We've done this before, with AIDS, and we can do it again, with Alzheimer's. With focused cooperation and support, we believe we can, and will, make a difference. As someone's who's turning 60 this year, the sooner the better.

Thank you.

[The prepared statement of Mr. Essner follows:]

PREPARED STATEMENT OF ROBERT ESSNER

Thank you to Senators Mikulski and Burr and the other members of the Subcommittee for holding this second hearing and allowing me to testify on a topic that is very important to me, my company Wyeth, and Alzheimer's patients and their families. It is my pleasure to share my thoughts on how the private sector is trying to harness science to overcome Alzheimer's disease.

I'd like to address three key points with you today:

- Alzheimer's disease is a public health epidemic facing the Nation and as a result it requires an epidemic-level response.
- There is a tremendous amount of activity in the private sector aimed at identifying and developing therapeutic candidates to alter—or even prevent—the progression of this disease. My company Wyeth is a leader in these efforts.
- Our efforts would be greatly aided by a focused national strategy targeting Alzheimer's disease.

ALZHEIMER'S AS A PUBLIC HEALTH EPIDEMIC

This is an important time to be thinking about Alzheimer's and evaluating whether we are prepared for the coming epidemic. I say "epidemic" because that's what we're headed for—an epidemic of enormous proportion. I know many of the members of this subcommittee understand the scale and scope of what we are facing. But despite the wealth of data documenting the threat of Alzheimer's disease, I am fairly certain that the population at large does not really see Alzheimer's disease as an epidemic—at least not yet.

I have spoken about the pending threat of an Alzheimer's epidemic for several years now. During each of those opportunities—from the White House Conference on Aging to the Visions Roundtable Wyeth co-hosted with Newt Gingrich and the Center for Health Transformation—I expressed my concern that the term "epidemic" does not raise the specter of Alzheimer's disease for most Americans. Instead, most people think of diseases like Avian flu or AIDS. There has been massive media attention on these two diseases. This attention served to focus people's fear about the unknown on these diseases and highlighted their potential for decimating the population.

These fears are not entirely groundless. AIDS, particularly in the developing world, and Avian flu are serious concerns and should be matters of national interest. But it is important to remember that Avian flu—scary as it is—is only a potential threat that we may or may not actually have to deal with. And while AIDS does continue to ravage many developing countries, in many parts of the world a diagnosis is no longer an automatic death sentence.

Unfortunately, the same cannot be said about Alzheimer's disease. This is a very real threat that we do have to deal with, and at this time a diagnosis is a death sentence.

I have spent a great deal of time asking myself why avian flu and AIDS resonate as epidemics, but Alzheimer's does not. Is it their impact on the public health or the public's imagination? Is it the scientific etiology of the diseases or their widespread threat? Is it that AIDS and avian flu are "new"—that they were identified and discovered within our lifetimes?

Frankly, I think that the latter question is the pertinent one. Alzheimer's disease was first identified 100 years ago. It seems to have always been with us. We cannot remember a world without Alzheimer's. As a result, I think it's possible that we've simply gotten used to the presence of this disease. But that is a mistake. The disease is no less dangerous and carries no lesser burden simply because it predates

all of us. If anything, the fact that the disease has continued virtually unabated for 100 years should draw our attention all the more.

Alzheimer's disease dramatically affects the public health and stirs the public imagination, and we know what its impact will be—we can, in fact, predict with chilling accuracy its incidence and prevalence. A half-million new cases will be diagnosed in America every year, as 78 million baby boomers turn 65, the typical threshold age of the disease. That could mean 14 million people suffering and dying from Alzheimer's in our lifetime.

The fact that startles me the most is that 1 out of every 100 60-year-olds will develop the disease, because this year I turn 60. And if you are lucky enough to miss the disease at 60, there is the even more startling fact that one out of every two people over 85 will develop it. If my wife and I live to be 85, that means that one of us is likely to be stricken by Alzheimer's.

We know the horrifying and ultimately fatal course of this illness. We know the collateral damage it does to the families of those who suffer from it—damage that often ironically carries a worse toll than the direct impact of the disease on its victims. And we can project with reasonable precision the enormous financial toll that caring for patients who suffer from it will take on our country's health care budget and our economy.

Many people do not know that Alzheimer's disease is the third most costly disease to treat in the United States. And most do not know that annual Medicare costs for beneficiaries with Alzheimer's are expected to increase 75 percent over the next 5 years and that Federal and State Medicaid spending for nursing home care for Alzheimer's patients is expected to nearly double by 2025.

And these estimates are limited to cost of care alone. Consider the staggering cost of Alzheimer's from a more holistic perspective: A new economics study announced yesterday by the ACT–AD Coalition calculated for the first time the combined monetary equivalent of supposedly subjective social issues like quality-of-patient life, productivity and longevity. If we could mobilize treatments to delay the onset of Alzheimer's by 1 to 3 years, this social value would reach $3.97 trillion in the United States alone by the middle of this century.

But the costs of Alzheimer's disease don't strike governments alone—they also strike individual families and our Nation's businesses. Over the course of the disease, Alzheimer's patients and their families spend more than $200,000 on health care per patient. And employers lose approximately $60 billion a year on lost productivity as adult caregivers are forced to leave their jobs—either permanently or on a temporary basis—to care for a family member with the disease.

And while the economic picture is certainly grim, the social picture is even worse. What is so horrifying about Alzheimer's is not just that it kills but how it kills—it is the debilitating and dehumanizing nature of this disease that strikes me so forcefully. Alzheimer's essentially eats away at the very essence of its victims—not just their physical and mental capabilities but also their personalities and the qualities that make us all human. As the disease progresses, everything falls away—connections, understanding, relationships, and even family. The threat of Alzheimer's is here, it is very real, and it needs to be stopped.

THE PRIVATE SECTOR IS RESPONDING TO THIS EPIDEMIC

The general public still may not consider Alzheimer's disease to be an epidemic. But the world's scientists are starting to do so. They are not just sitting by and watching the devastation approach. Efforts to respond to the epidemic of Alzheimer's are under way across academia, industry and government.

I would like to share the story of my company, Wyeth, and our journey into the field of Alzheimer's disease research. Wyeth is not the only company engaged in the fight against Alzheimer's. Important work is occurring everyday across the industry, with nearly all of the world's major pharmaceutical companies devoting time and resources to this disease. We are proud of our position as a leader in Alzheimer's research and of our pipeline—which is second-to-none in the industry.

The Genesis of Wyeth's Involvement in Alzheimer's Disease

Wyeth has been involved in Alzheimer's disease research for 15 years. Our research efforts were focused in the year 2000, when a group of our scientists came to me with a proposal. They wanted to enter into collaboration with another, much smaller company to advance a new technology against Alzheimer's. The team members told me that this was, in their opinion, the single best approach to creating a really effective treatment for this disease and that they thought it had the highest chance of success of anything in development. I, of course, had to ask a few questions.

First, why were they so enthusiastic, and why did they think we had any chance of success in a disease that had proven so elusive? They explained that this technology was aimed at quickly ridding the brain of the beta-amyloid plaque that was—and still is—thought to be an important causal factor in Alzheimer's and that the work done so far on this principle in animal studies had produced the most dramatic results ever seen in these types of tests. So, second, I asked them how long it would take before we would have any real idea about whether or not this would be useful in people because we all know that animal work, particularly in diseases involving the brain, is not very predictive. They told me that they expected it would take about 3 or so years of research effort before they would know whether the project could move into full-scale development. Then I asked them a critical question: How much would we have to spend over those years to get even a preliminary appraisal of efficacy? After a little hemming and hawing, they told me they thought it could cost up to $100 million to do those studies.

Then I asked the really hard question: If we invested that much money over the next 3 years, what was the probability that when we were done with that work the answer would be "yes"—that we would have sufficient preliminary evidence about the drug's safety and efficacy to move into the larger-scale research studies necessary for approval. This brought a lot more hemming and hawing and a little shuffling about until someone said, "There's maybe a 30 percent probability of success,"—to which I responded, "Really!" Then someone said, "Well, maybe it's more like 10 percent." When I challenged that, the real answer came out—which was that the odds of success were so low that no one could say what they were. In the end, we made the decision to go ahead—our scientists were so passionate that if I had turned them down, I would have had a mutiny.

Wyeth created a partnership with the Irish company, Elan Corporation. It was an unprecedented effort in that, for the first time, we brought together scientists from Wyeth's three research divisions. We asked leaders from our central nervous system drug discovery and development units to work in day-to-day collaboration with some of our leading biotechnology specialists and experts from our vaccine research effort.

The problem-solving abilities of these scientists, together with those of our partner, have brought to this project the unusually broad array of scientific tools and creativity that have kept us going. More than 5 years have gone by since we made our decision, and about all I can say after years of effort is that the program still has the tantalizing possibility of success. The development of our initial research program was stopped when we saw some early signs of a safety issue in a few patients. But we've come back with revised approaches, and our program is progressing very nicely.

Where We Are Today

Wyeth has the most extensive pipeline of Alzheimer's discovery and development programs in the industry. We have been working on this disease for the past 15 years, and are focused on identifying and developing novel approaches to it. Wyeth has spent over $450 million on Alzheimer's research in the past 5 years—$125 million in 2006 alone. Nearly 3,000 of our scientists are or have been involved in this work, and over 350 are focused exclusively on it. Currently, we have 23 projects in various stages of development, across each of our technology platforms—pharmaceuticals, biotechnology, and vaccines. Of these, 12 are drugs in clinical research.

Wyeth is uniquely positioned to pursue novel approaches precisely because of our ability to work across these three platforms. As the only biopharma company with a presence in all three areas, we are able to draw on a wide pool of technological capabilities. Our Alzheimer's disease work is a great example of this.

I think the most exciting part of this research is the work we are doing on compounds that show the potential to delay, halt or reverse the progression of the disease—or even to prevent it altogether. These projects bring together our biotech and small molecule neuroscience capabilities. Our most advanced projects are in passive and active immunotherapy, undertaken with our partner Elan Corporation. The passive approach uses an engineered monoclonal antibody to target toxic beta-amyloid, a substance many believe is a key cause of Alzheimer's. The active approach focuses on the use of the body's own immune system to clear the brain of the toxic amyloid plaques by stimulating an immune response so the body produces antibodies that attach to existing plaques and destroy them. These approaches represent some of the most promising efforts in Alzheimer's research today.

We are also working on a number of alternative anti-amyloid approaches, including gamma secretase and plasminogen activator inhibitor small molecule pharmaceuticals. And we are also working on treatments targeting the symptoms of Alzheimer's disease. Our symptomatic therapy efforts include serotonin antagonists and a novel oral medication that seeks to modulate neurotransmitter pathways to im-

prove cognitive dysfunction. Our scientists believe the key to Alzheimer's treatment likely lies in combination therapies, bringing together agents to affect the course of the disease and those to manage its symptoms.

As you can tell, we intend to leave no stone unturned in this fight. We are targeting multiple approaches because we believe that it is crucial that we explore all possible avenues. While we believe the beta-amyloid theory is very likely to be a key causative factor, and therefore a promising target, we understand there may be other factors. There are still too many unanswered questions about the human brain and this disease, and we intend to pursue as many targets as possible until those questions are answered.

And, by the way, that $100 million estimate has long ago been spent—in fact, our partnership has invested well over twice that. Our programs have the potential to be the kind of new tool we need to treat or even prevent Alzheimer's disease—if we get really lucky. But risks are high, and, in the current environment, even if things go perfectly—which they rarely do—we still are looking at potential approval toward the end of this decade. I can tell you with complete candor that if this were a program in virtually any other disease, it would have been terminated years ago.

But the power of this disease and the challenge of conquering it drive us on. Wyeth is not alone on this path in trying to find a solution for Alzheimer's; there are other companies at work, as well as scientists in academia and research institutes who are making their own contributions.

Industry-wide Efforts

But Wyeth is not alone on this path. Important work is occurring everyday across the industry, with nearly all of the world's major pharmaceutical companies devoting time and resources to this disease. There are hundreds of therapies in development, and the first compounds with the potential to actually change the course of the disease are starting to reach FDA. The possibilities for improving the lives of patients and families are staggering.

Among the leading drugs in development for disease modification, many of the most advanced agents are, like Wyeth's leading efforts, targeted at beta-amyloid. These compounds include immunotherapy as well as agents targeting amyloid aggregation and synthesis. In addition to these late-stage therapies, there are over 100 other potential disease-modifying candidates in early-stage development with similar targets. Wyeth and other companies are targeting other mechanisms in the disease, including mechanisms that target tau, the protein that accumulates in neurofibrillary tangles, and neuroprotection.

There are also over 80 symptomatic therapies in various development stages, many of which are believed to have the potential to significantly improve the quality of life of people with Alzheimer's, particularly when used in combination with the coming disease modifying agents. And generic versions of the leading symptomatic therapies are expected in the next several years, as the existing products reach patent expiry.

In addition to the identification and development of promising drug candidates, there are significant research efforts into better diagnostic and screening tools. Currently, establishing a clear diagnosis of Alzheimer's disease is difficult, particularly in early stages. Nearly 50 percent of patients are only diagnosed after the disease has already progressed to its middle stage.

One reason for this is a reluctance to assign a diagnosis of Alzheimer's disease, given the current state of treatment. But perhaps the most significant challenge is the difficulty in distinguishing signs of cognitive decline from normal aging, as we currently lack a sensitive and specific biomarker to aid diagnosis. Surrogate endpoints and biomarkers have the potential to dramatically alter how we identify patients—and potential patients—and measure their clinical outcomes over time, and their development is a major focus of the scientific efforts around Alzheimer's disease.

An example of these efforts is the Alzheimer's Disease Neuroimaging Initiative, or ADNI, a 5-year public-private partnership. It brings together industry, academia and the National Institutes of Health to validate biomarkers and develop neuroimaging tools. This broad-based effort has the potential to dramatically alter how we predict the onset—and monitor the progression—of Alzheimer's. Diagnosis and monitoring are essential to any effort to study and eventually control this disease.

With Your Help, We Can Move Even Faster

So why, given all the attention across various stakeholders, does the war against Alzheimer's disease continue to progress so slowly? There are a number of significant challenges facing Alzheimer's drug development. Among them:

• Challenges related to the design and implementation of clinical trial protocols;
• The lack of urgency about the disease at a national level; and
• The lack of scientific consensus about what it means to "modify" the course of the disease rather than merely treat its symptoms.

The problem is that while companies like Wyeth are moving forward as rapidly as possible, the war against Alzheimer's is multi-faceted, requiring advances on many fronts. Unlike my examples of AIDS and Avian flu, there is no national focus on Alzheimer's. Scientific work and drug development go on but at too slow a pace. Public health agencies are perhaps understandably engaged in dealing with the current devastation of the disease as much as working toward its cure. And regulatory agencies sometimes deal with Alzheimer's in the cautious way they do diseases where major therapeutic options already exist. On the regulatory front alone, worldwide cooperation between reviewers and researchers could significantly improve the probability that we will succeed and reduce development times by years.

While we are seeing a growing awareness about the Alzheimer's epidemic, this growth is gradual and not keeping pace with the growth of the problem. It is critical that we increase the national focus on this disease and accelerate efforts to respond to it.

What we need is a sense of commitment analogous to that which arose around AIDS or Avian flu. In the war against AIDS, government, regulatory agencies, scientists in industry and academia, and patient groups worked hand in hand to develop new therapies and to evaluate them as rapidly as possible. The results were remarkable. AIDS was first identified around 1980, and, just 6 years later, there was a breakthrough medication that helped people manage the symptoms. And, today, there are a number of therapies that, when used in combination, allow people with HIV/AIDS to live much longer than anyone would have dreamed possible in the early 1980s. The war has not been won, but we have made significant progress—progress that is lacking on the Alzheimer's front.

To that end I would like to commend Senator Mikulski for her legislative efforts in this area. I would like to particularly note the provision in S. 898 that calls for Secretary Leavitt to convene an Alzheimer's summit. Alzheimer's disease needs to move to the forefront of our national research agenda, and this proposal is a very good start.

Knowing all of this, how do we convince the Nation that Alzheimer's is the next epidemic and truly drive a change in the way the disease is approached? Public awareness of the disease is high—so are assumptions, misconceptions and complacency. To many, the disease is still seen as a slow, progressive and inevitable step in the aging process; in fact, the disease can progress through its entire course in as few as 3 years. This misperception, compounded by the lack of treatments with long-term effectiveness and the social stigma attached to the disease, results in a health care system that often appears to be focused more on dealing with the seemingly inevitable devastation of the disease than in working toward its cure.

Existing therapies for Alzheimer's disease address symptoms of the disease, but not its underlying causes. With the aging of the population, there is a critical need for therapies that will modify—or even halt—disease progression. We believe that this urgent need for innovative therapeutic agents warrants a formal governmental strategy to accelerate development of safe and efficacious disease modifying treatments.

The government has been successful in this area before. We need the kind of bold, innovative effort that has been generated in the past. The AIDS story is instructive and inspirational. The recognition of the urgent need for innovative therapies led to the development of new procedural strategies for drug review and approval and to the focusing of research efforts—and dollars. If we approach Alzheimer's with the same fervor and the same commitment, we will be able to harness the potential of scientific advances and truly alter the course of this epidemic.

Within the pharmaceutical industry as a whole, there are dozens of Alzheimer's compounds in development. And, given the complexity of Alzheimer's, no single organization has the resources required to research all facets of this disease as quickly as we must. At Wyeth alone, we've committed hundreds of millions of dollars toward this research and we know our colleagues at other companies are doing the same. Right now, no one can say that any one approach will work. But, by taking multiple "shots on goal" in our research labs, we believe that a treatment can be found.

But it is imperative for industry, scientists and government to work together to help us reach our goal even faster. It typically takes 10 to 17 years to bring a new drug to market, but this is far too slow, given the imminent threat. We need a sense of urgency, a commitment to collaboration that will lead to a concerted, focused effort to prevent this impending epidemic. To eradicate Alzheimer's, we need to make it America's No. 1 research priority. We need the public and private sectors—the

pharmaceutical industry, health care practitioners, the public, and legislators—to call for putting epidemic-strength resources toward eradicating Alzheimer's.

For every month we hesitate, millions more Americans will tangle helplessly in the disease's lethal net and we will continue to find ourselves spending down the Nation's health care budget to care for the demise of millions of people. More wisely, we should be preparing now to cure them. We could make my generation the last to dread Alzheimer's. It is time to accelerate the pace of our efforts and take the battle to a level on a par with our hope.

As I mentioned earlier, I turn 60 this year. I have been a witness to the impact of this disease and have watched family and friends fall prey to it. Without tools like those that Wyeth is currently developing, the impact on our budget—and our psyche—will devastate our Nation. The suffering that individuals and families endure must not be extended to our entire country. If we cannot develop therapies to halt this epidemic, we will either face untenable systemic costs that break our national bank or we will be put into the equally untenable position of having to deny treatment to those who need it.

I commend you for your efforts and look forward to working with you in the war against Alzheimer's. If we can generate a passionate commitment analogous to that around AIDS or avian flu, I believe that within our lifetime we can turn this disease from a death sentence to a treatable chronic diagnosis. The sooner we begin, the better.

Thank you.

Senator MIKULSKI. Thank you.

Doctor.

STATEMENT OF J. DONALD deBETHIZY, PH.D., PRESIDENT AND CEO OF TARGACEPT, INC., WINSTON-SALEM, NORTH CAROLINA

Dr. DEBETHIZY. Good morning, Madam Chairman and Senator Burr and members of the subcommittee and their staff. Thank you for holding today's hearing and inviting me to provide testimony on this very important subject of breakthrough research on Alzheimer's disease.

I'd like to speak, today, about the promising research our company is doing in the area of cognitive disorders, and specifically in Alzheimer's disease, a devastating disease that affects more than 37 million people worldwide.

At Targacept, we're a small pharmaceutical company, but we're engaged in important innovation in the design, discovery, and development of a new class of drugs for the treatment of multiple diseases and disorders of the central nervous system.

Alzheimer's disease is our primary focus, and we also have conducted clinical research in other conditions on the spectrum of cognitive decline that too often culminates in Alzheimer's. We call our pharmaceutical product candidates "NNR therapeutics" because they modulate the activity of a class of specialized proteins in the body known as neuronal nicotinic receptors, or NNRs.

As you may recall from your basic biology class, nerve cells, or neurons, are the primary elements in conducting the activity in the nervous system. They almost act like electrical wires, sending signals from the brain—across the brain and through the body. However, unlike the kinds of electrical circuits we have in our homes, the communication between nerve circuits is not controlled mechanically, but actually chemically. In this process, the electrical impulses of a neuron are converted into essential chemicals, such as serotonin, dopamine, acetylcholine, and norepinephrine. It's these chemicals that are released by the neuron and then land—essentially land on another neuron that sends the trigger to the

next neuron, sends the impulse across the brain, and on and on and on, across many billions of neurons in the brain. This process repeats itself. And I'd like to use this metaphor, that NNRs are like the volume knob on the central nervous system. They boost the degree of neuron communication if the nervous system is understimulated, and they reduce the degree of neuron communication if the system is overstimulated, almost like a volume knob. If NNRs don't do their job correctly, it can lead to a chemical imbalance that is associated with a number of debilitating central nervous system diseases and disorders, such as Alzheimer's disease. That's why we have targeted NNRs as a very important therapeutic target.

Now, Targacept is the leader in the development of NNR therapeutics. We have extensive experience in the biology and chemistry of the NNR receptor family, and hold the largest patent estate in the NNR space. Our history began with a program initiated at R.J. Reynolds Tobacco Company in 1982 to study the activity and therapeutic effects of nicotine, which is our prototypical NNR modulator. We don't work on nicotine, we don't work on tobacco, but we work on brand new small molecules that are discovered to enhance the ability that was discovered with nicotine on attention, learning, and memory, which are well documented. And there's also lower prevalence of Alzheimer's disease and Parkinson's disease in smokers compared to nonsmokers, which was really a clue that this was an important system.

As another example, more than 70 percent of people suffering with schizophrenia smoke. It is believed that, in smoking, these people could be actually medicating themselves by providing nicotine that helps them focus and enhance their cognitive performance. So, nicotine, of course, is not viable as a drug, because it causes a number of deleterious side effects. The reason for this is that, in addition to NNRs in the brain, there are NNRs in the muscle and the ganglia that control heart rate and blood pressure, and you want to eliminate these side effects.

So, the researchers at Reynolds recognize that drugs capable of modulating NNRs could remedy the chemical imbalance characteristic of these CNS diseases like Alzheimer's. However, to be useful, these drugs had to target specific NNRs while, at the same time, avoiding the interaction with these other receptors in the rest of the body. And really that's what led to the name of our company—"Targacept" is for "targeted receptors"—because over the last 20-plus years our scientists became very good at it, and it's led to these breakthrough technologies and therapeutics that are moving into the clinic and working so well.

Now, we are conducting some of our most promising work in Alzheimer's, as well as other cognitive disorders. Our lead product candidate is a novel small molecule that we refer to as TC–1734. There'll be a test on that later. TC–1734 selectively modulates specific NNRs, which creates the potential for therapeutic benefit and reduces the risk of side effects. We've done 12 clinical trials in up to 540 subjects so far. Now, as a small company, this is a very large initial start with this drug, and, in fact, we licensed this drug to AstraZeneca, who has seen it to be very promising in the Alzheimer's-disease area.

As reported in a very recent issue of Nature Reviews, the economic burden of Alzheimer's is massive. We've already talked about it. It's $100 billion alone. We're also working in areas called age-associated memory impairment and mild cognitive impairment, which are earlier forms of cognitive impairment. Not all people with age-associated memory impairment go on to Alzheimer's, but 80 percent of people with mild cognitive impairment will go on to Alzheimer's disease within 6 years. So, the earlier we can get drugs in—and this is really a regulatory challenge, because, as you can imagine, as you move upstream to healthier people, drugs have to be safer. So, this is an area we can talk about later.

So, in conclusion, we recognize that Alzheimer's disease has impacted the lives of millions of people and represents an area of enormous unmet medical need. It is extremely gratifying to us to contribute to the body of knowledge in this area and to help people understand the potential treatments for this disease.

Thank you.

[The prepared statement of Dr. deBethizy follows:]

PREPARED STATEMENT OF J. DONALD DEBETHIZY, PH.D.

Good morning, Madam Chairman, Senator Burr and members of the subcommittee. Thank you for holding today's hearing and for inviting me to provide testimony on the very important subject of breakthrough research on Alzheimer's disease.

My name is Dr. J. Donald deBethizy, and I am President and Chief Executive Officer of Targacept, Inc, a publicly traded biopharmaceutical company located in Winston-Salem, North Carolina. I would like to speak today about the promising research our company is doing in the area of cognitive disorders and specifically in Alzheimer's disease, a devastating disease that affects more than 37 million people worldwide.

At Targacept, we are engaged in the design, discovery and development of a new class of drugs for the treatment of multiple diseases and disorders of the central nervous system. Alzheimer's disease is a primary area of focus for us, and we have also conducted clinical research in other conditions on the spectrum of cognitive decline that too often culminates in Alzheimer's.

We call our pharmaceutical product candidates "NNR Therapeutics" because they modulate the activity of a class of specialized proteins in the body known as neuronal nicotinic receptors, or NNRs. As you may recall from your basic biology class, nerve cells, or neurons, are the primary element in the human nervous system and act like electrical wires to send various signals to the brain and throughout the body. However, unlike the kinds of electrical circuits we have in our homes, the communication between nerve circuits is not controlled mechanically, but chemically. In this process, the electrical impulses of a neuron are converted into essential chemicals such as serotonin, dopamine, acetylcholine and norepinephrine. These chemicals are released by the neuron and then land, so to speak, on another neuron—where they trigger the release of essential chemicals by the second neuron. This process then repeats itself, usually resulting in the successful transmission of signals and the normal functioning of our nervous system. NNRs are the landing sites on the neurons and, as such, are responsible for modulating the transmission of these essential chemicals. I like to use the metaphor that NNRs are like the volume knobs of the central nervous system. They boost the degree of neuron communication if the nervous system is understimulated and reduce the degree of neuron communication if the system is overstimulated. If NNRs don't do their job correctly, it can lead to a chemical imbalance that is associated with a number of debilitating CNS diseases and disorders, such as Alzheimer's disease. This is why NNRs are important therapeutic targets.

Targacept is the leader in the development of NNR Therapeutics. We have extensive experience in the biology and chemistry of the NNR receptor family and hold the largest patent estate in the NNR space. Our history began with a program initiated by R.J. Reynolds Tobacco Company in 1982 to study the activity and therapeutic effects of nicotine, which is the prototypical NNR modulator. Nicotine's ability to enhance attention, learning and memory is well documented, and there are a number of studies showing the lower prevalence of diseases such as Alzheimer's dis-

ease and Parkinson's disease in smokers as compared to non-smokers. As another example, more than 70 percent of people suffering with schizophrenia smoke. It is believed that in smoking, these people could be actually medicating themselves, by providing nicotine that helps them focus and enhances their cognitive performance. Nicotine, of course, is not viable as a drug because it causes a number of deleterious side effects. The reason for this is that, in addition to NNRs, nicotine affects other receptors in the body's muscles and ganglia that are associated with the side effects.

The researchers at Reynolds recognized that drugs capable of modulating NNRs could remedy the chemical imbalance characteristic of nervous system diseases like Alzheimer's disease. However, to be useful, these drugs had to target specific NNRs while at the same time avoiding interaction with nicotinic receptors associated with harmful side effects. This recognition of the need to exploit only Targeted Receptors led to the creation of Targa Cept. Our scientists' 20-plus years of focused NNR research has led to a particular expertise in designing and developing pharmaceutical product candidates that have the required NNR selectivity.

We are conducting some very promising work in the area of Alzheimer's disease as well as other cognitive disorders. Our lead product candidate is a novel small molecule that we refer to as TC–1734. TC–1734 *selectively* modulates specific NNRs, which creates the potential for therapeutic benefit and reduces the risk of side effects. This product candidate has been evaluated in 12 clinical trials to date, involving a total of about 540 subjects.

As reported in a very recent issue of Nature Reviews (Drug Discovery), the economic burden of Alzheimer's is massive, with an estimated direct and indirect annual cost of patient care estimated at $100 billion in the United States alone. The number of therapeutic options for Alzheimer's is severely limited and only a fraction of patients respond well to those that are on the market. Moreover, none of the approved treatments have demonstrated the ability to substantially delay the progressive deterioration and death of neurons in the brain that can lead to more severe stages of cognitive impairment and debilitation. The need for more effective drugs is clear.

What we find very exciting about NNR-based therapeutics is their potential at every stage of cognitive dysfunction. As I mentioned earlier, Targacept has conducted clinical research in other conditions on the spectrum of cognitive decline. I'm speaking specifically of conditions known as age associated memory impairment, or AAMI, a condition associated with normal aging, and mild cognitive impairment, or MCI, which is a condition that is more severe than AAMI but less severe than Alzheimer's disease. In fact, we would argue that perhaps the most effective and efficient manner for addressing Alzheimer's disease would be to treat these earlier stages of cognitive decline, which could potentially mean that a patient may never suffer from Alzheimer's disease. TC–1734 has shown evidence of neuroprotective properties in our preclinical testing. This means that it had the effect of protecting neurons under conditions that would otherwise have caused them to deteriorate and die. If it has the same effect in humans, our position regarding prevention as the optimum way to address Alzheimer's disease and other neurodegenerative diseases would only be strengthened.

In 2006, Targacept completed a Phase II clinical trial TC–1734 in age associated memory impairment (AAMI). In the trial, TC–1734 achieved *statistically significant results* on all three co-primary endpoints, demonstrating its cognitive-enhancing potential. The development of AAMI has been set aside in favor of Alzheimer's disease, for now, largely due to the difficult and uncertain path to regulatory approval for AAMI. However, if that path were clarified so as to support the substantial investment of large-scale Phase III clinical trials, we would be well on our way to developing a drug that could act in early intervention against cognitive dysfunction. Moreover, the data from these trials could be extremely useful as TC–1734 is developed to address Alzheimer's disease directly. A Phase II clinical trial of TC–1734 in approximately 500 patients with mild to moderate Alzheimer's disease is scheduled to get underway in mid-2007, as is a similar size Phase II clinical trial in cognitively impaired patients with schizophrenia.

We recognize that Alzheimer's disease has impacted the lives of millions of people and represents an area of enormous unmet medical needs. It is extremely gratifying to us to contribute to the body of knowledge in this area and to help people understand potential treatments for this disease.

Thank you.

Senator MIKULSKI. Let me just open with a question or two, turn to Senator Burr, and perhaps then a more freely give-and-take with, really, a very able and engaging panel.

Mr. Essner, I'm going to go to you first. First of all, one, I do agree that we're kind of numb to it. Alzheimer's, 100 years ago, first diagnosed in Germany, then, for years, the kind of melancholy attitude—for example, with my own father, the diagnosis was in the mid-1980s, and all we could do was keep him comfortable and try some of those new things at the adult center at the Mason Lord Hopkins program.

Tell me, from the private sector's viewpoint, what are the greatest impediments to you—meaning not only as a company, but the private sector—to moving forward in this? And, No. 2, what would you think would be the elements of a national strategy? In other words, there you are, you've put in a lot of money. Obviously, you've made a big bet of the company in this area. It is an epidemic——

In other words, is it that we need to do more basic research? What is it that we need to work with the—because government is important, but government doesn't invent pharmaceuticals.

Mr. ESSNER First, I think, the scientific challenges, you know, are great. I mean, our understanding of the brain is probably less than any other organ in the body. And certainly, Alzheimer's disease, although it's been known for a long time, is certainly not well understood, and more basic research would certainly be helpful. But, you know, as I said, we are now in clinical development, studying many of our drugs in Alzheimer's patients. And some of the obstacles there, I think, are maybe not that difficult to remedy. One issue today is, when you go to study a drug that you hope will have an impact on the progression of the disease, what, really, do you need to study? There are a multiplicity of different cognitive scales that can be used. There are various brain imaging techniques. What standards do you need to meet? And I think one of the most important things that could be done is to create a consensus between the scientific establishment, the regulatory agencies, and also industry, to say—if you're trying to develop a drug, to show a stabilization or a slowing down of the progression of the disease—what, in fact, do you need to study, for how long, and what do you need to demonstrate for those results to be acceptable? Right now, we're doing the work, but doing the work without a clear understanding of what standards those studies are going to have to meet to result in a drug that will actually be useful to people.

Another smaller issue, but potentially a big stumbling block, is just the issue of informed consent. If you think about an Alzheimer's patient, getting their informed consent to participate in a trial is a genuine issue. And, although there are mechanisms to accomplish this through the family, those standards are different from place to place. So, if you're going to do a trial across the United States or a trial that involves patients in the United States and other countries, very frequently you can't do that, because the standards they're using are not acceptable in that particular location or in that particular country. So, it's a small obstacle, but a real one.

And then, maybe, finally, trying to decide, in terms of the scientific evaluation and the regulatory process, what is the role of imaging techniques. Can they be primary endpoints in a clinical

trial? In that, if you can show an improvement in brain size or brain functioning through imaging techniques, what role should that play in the ultimate decision of whether or not a drug is useful?

So, creating a kind of consensus that would allow the Food and Drug Administration to say, "Here are the standards that you should try to meet when you're developing a drug," I think would make it easier to evaluate drugs, have them move along more quickly and speed the development of this work.

Senator MIKULSKI. Well, one of the things that my bill calls for is a summit, after the bill is passed, to identify what are the breakthrough areas and how they could be accelerated—again, always keeping safety in mind.

Mr. ESSNER. Right.

Senator MIKULSKI. What your recommendation is, you need a summit even before that to have a set of standards and measurements—or a set of standards that declare what is the measurements, in terms of the ability to evaluate, essentially, efficacy. Is that——

Mr. ESSNER. I think that would——

Senator MIKULSKI [continuing]. Correct?

Dr. DEBETHIZY [continuing]. That would be helpful. And that actually would encourage, I think, more development in this area, because once those standards are established, companies are able to more easily evaluate, Is it worth going ahead and trying to develop a specific compound?

Senator MIKULSKI. Well, later on this summer we are going to get FDA, NIH, and CDC here, along with Dr. Hodis, who I think's been an outstanding leader. He couldn't be here today, because of a trip abroad. But we'll want to come back to that.

Mr. ESSNER. Yeah, I——

Senator MIKULSKI. My 5 minutes are up. Why don't—did you want to——

Mr. ESSNER. No, I just said, if, at some point, industry could have a seat at that table, I think it turns into the most productive possible dialogue.

Senator MIKULSKI. Well, essentially, this is why we're holding these hearings. And my colleague here is really, I think—he chaired a subcommittee of this committee, on public health. His big passion, as is mine, is public health, the prevention aspects of everything. And I know Dr. Coburn, who's on the floor now—when we were talking about drug safety, our big thing was also on what are those kind of tools that go into the preventive side——

Mr. ESSNER. Right.

Senator MIKULSKI [continuing]. For large populations, et cetera. But we believe that we need to begin to de-escalate the adversarial environment in our country. And so, we're so worried about antitrust, and, "Can we be in the room?" that we don't trust each other. And, I'll tell you, if we knew that 5 million people were going to get avian flu 32 years from now, we sure in hell would all be in the same room doing shooters of Mylanta trying to figure this out.

[Laughter.]

Mr. ESSNER. I see.

Senator MIKULSKI. You see? So—and it was Senator Burr who actually got all of us in the room, in a war-game exercise on a breakout of a pandemic, that I think really led to very important legislation moving through. So, I think we understand—we, two, understand the elements of when we use the term "epidemic," but, because Alzheimer's is not viewed as an infectious disease, and the history has been such a—this melancholy powerlessness that many of us felt. If we take our time, we'll get to it." But I don't believe that. And so——

Senator Burr.

Senator BURR. She has proven my passion for prevention. I'm trying to put Mylanta out of business. So——

[Laughter.]

Senator MIKULSKI. I shouldn't have used——

[Laughter.]

Senator BURR. Let me assure you, I've got questions for all of you, and I thank the Chairman for this format—using it for more of a roundtable.

Let me ask, Bob, you expressed the lack of structure in, maybe, FDA's knowledge or direction on the clinical trial design. Do they have advisory panels that they can call upon regarding trial design?

Mr. ESSNER. Yeah, absolutely, they do. And believe me, I'm not faulting FDA here, because this is an area where the knowledge is—really, has never been brought together in any kind of cohesive way to define——

Senator BURR. Nor——

Mr. ESSNER [continuing]. These trials. So——

Senator BURR [continuing]. Nor is my question a shot at them, because I think this is one of the—from a layman's standpoint, looking at this, this is one of the most difficult things that I could imagine, How do you—what is it you choose to gauge?

Mr. ESSNER. Right.

Senator BURR. And what's the definition of a successful trial, given that you've got a disease which is a continued deterioration? When do you know it's stopped?

Mr. ESSNER. Yeah. You know, I think the advisory committee system, which FDA has, and which, in general, works very well for them, may not be the best tool here, because I think this is going to be a complicated discussion that will require a lot of iterations. And I think the advisory committees tend to work best when there is a discrete question on which they can provide a discrete answer. So, my guess is something that was a longer-term organized collaboration between the various scientific organizations in the government, especially the NIH, and the regulator, would probably produce the best result.

Senator BURR. Has there ever been an Alzheimer's application that was fast-tracked at the FDA?

Mr. ESSNER. I don't know the answer to that. Bob, do you? Several have.

Senator BURR. Okay.

Dr. Kramer, you talked about exercise and diet. And I've got to admit, I know you're right, I know there's some piece there. But sitting here looking at the direction our country is going, and the

generation that are the most obese we have ever raised, thinking of selling to my 86-year-old father the need for him to exercise, when the surroundings suggest, you know, diet and exercise are not that important, how do we change that? And can we have enough of an effect that it's worthwhile?

Dr. KRAMER. Yeah. I think, to start off with, we don't need—we don't know much about dose response effects, how much exercise——

Senator MIKULSKI. Dr. Kramer, pull your microphone closer.

Dr. KRAMER. Oh, sorry. We don't know much about dose response effects with respect to exercise and the brain, or cognition, but we do know, from a number of randomized clinical trials funded by the NIH and other government agencies all over the world, that fairly moderate exercise, even if you've been a couch potato for 60 years, can set back the clock 2 or 3 years with respect to cognitive decline in normal aging. So, we can think of this as a preventative measure.

But I do agree with you, when we look at the United States, we look at how we advertise, what products we advertise, and the obesity rate, unless you're living in Boulder, Colorado, in which everybody looks good—kind of like Prairie Home Companion, I think—that, in the United States and in the Midwest, where I'm coming from, lack of exercise is a major problem. I think there are many ways to encourage exercise. Schools in my local town have taken the soda, or pop, machines out of the schools. The kids—my daughter is in the back here, and she'll testify to that, I think, if you'd like her to—hate it. But when you provide healthy snacks for young kids, you start to build a sense of what is important and the kinds of foods that they can enjoy in school. I think we could provide incentives with respect to insurance policies and healthcare policies, for exercise.

And, again, I'm not talking about people getting out and running marathons or doing triathlons, I'm talking about walking 30 minutes to an hour a day.

Senator BURR. Fine, I——

Dr. KRAMER. This is a tough nut to crack, I agree.

Senator BURR [continuing]. I would agree with that last statement. And I know that Senator Mikulski and I will talk as the year goes on. It's impossible to believe that if 4,000 employers in the United States negotiate all the healthcare for 200 million people, that one's personal decisions which lead to healthier choices or the use of prevention are not going to be reflected in a reduction in their premiums; therefore, there is no financial incentive for them. It's only a marginalizational of the increase, and that's a model that we've got to change if, in fact, we want to have people make decisions based upon not only their longevity, but the cost for them to get there.

Paul, let me turn to you just for a second, because you talked about the molecular causes and our ability to identify the molecular cause. Does that mean that we either have the ability to recognize a genetic marker or we are close to identifying a genetic marker that might give us an indication of a person's susceptibility to Alzheimer's, or is Alzheimer's and dementia something the entire

population is susceptible to, and some preventative medication or exercise or diet will determine when we get it, or if we get it?

Dr. AISEN. Alzheimer's comes in a number of types. Some are genetically determined, where a single gene mutation is driving the disease. These are rare, but there are families that carry this gene, and, in those families, everybody that inherits the gene, which means half of the children of an affected individual, will develop Alzheimer's disease at a young age. That subset of the disease is genetically determined. We refer to it as familial autosomal dominant AD. And it represents less than 1 percent of all cases, but is exceedingly important in understanding the disease, because the disease looks the same. It's the same as the sporadic disease that affects 5 million people, same plaques and tangles in the brain, and it was by determining what the genes do that cause the disease in those families that we understood that one molecule is pivotal in everybody.

Now, why do people who don't carry those genetic mutations that lead to excess amyloid peptide—why did they develop an amyloid peptide-mediated disease? Well, here it gets complicated. And there are many factors—apart from a single-gene cause, many factors that influence the generation and trafficking of the amyloid peptide. Some of those factors are linked to aging; and, hence, this is an age-related disease. Some are linked to trauma, so head trauma up-regulates the precursor to this peptide. And lifestyle probably influences the accumulation of the amyloid peptide. So, we know, for example, that in animals that develop this peptide accumulates in the brain, if you exercise and stimulate those animals, you reduce the peptide.

So, the peptide is the central player, it's the molecular cause. And many things can influence that peptide. And I believe that we are coming to an understanding of the mechanisms by which lifestyle changes, various types of medications, as well as specific treatments, can influence the accumulation of this peptide.

The pivotal role of the peptide means that one thing we can do is develop a magic bullet for Alzheimer's. So, we can develop—we can educate the population as to the lifestyle changes that will tend to reduce this peptide. But we can also develop a specific antibody that will find the peptide and remove it from the brain. That's the idea behind the Wyeth/Elan collaboration on vaccines, passive and active vaccines. And I believe it is amazingly exciting that, in addition to learning how to influence the peptide with lifestyle changes, we can work, now, on a magic bullet to remove that peptide from brain.

Senator MIKULSKI. Mr. Essner, did you want to elaborate on what he said, or did——

Mr. ESSNER. No, I'd—I mean, he said it. You may notice I'm the only one without a "Dr." before their name here, so I'm going to stay out of too much depth in the science. But I think that was a very good explanation of what we're trying to do.

You know, people think of a—say, a flu vaccine—what a flu vaccine does is stimulate the body's immune system to basically rid the body of a virus. What we're trying to do is to create a vaccine that stimulates the body's immune system to rid the brain of this amyloid plaque.

Senator MIKULSKI. Well, I've found many things compelling about your testimony, Dr. Aisen, but the fact that you said, "We now have confidence that treatments that successfully reduce the accumulation of amyloid peptides will slow or stop the disease," that's a blockbuster thing to declare. I mean, I think it ought to have us on the rooftops, that we've been able to, even since we last had our hearing, 2 years ago, to be that precise. And it might not be the only reason, but, for all indications, now, you would say it is the primary reason, which then can lead to the science.

Let me kind of put this in layman and contemporary term. You talked about the genetics, lifestyle. Would you say that one day—or you would anticipate that we would look at Alzheimer's the way we now look at diabetes? No. 1, that it's a chronic condition, in some ways genetically driven, but also lifestyle—certainly lifestyle, either, driven or exacerbated. And, in my own family, this was a challenge that my mother faced. She was on oral insulin at 40. If she were alive today, there would be 300 different medications that her doctor could have, on back to identifying early insulin resistance, an A1C that could evaluate every 3 months, and a home detection tool with the fairly reasonable accuracy that looked like a stopwatch, for which she could monitor her food, her medications, and her exercise. Do you—is this, kind of, a framework where you think one day we would have? Because, for example, in some families, you might not be able to beat the genes, but you can delay the onset of the consequences of genes, dealing with insulin resistance, diet and exercise, aggressive monitoring, and the biofeedback that's associated with something like that.

Dr. AISEN. Yes——

Senator MIKULSKI. Is this a good way to think about it, or not?

Dr. AISEN. I think this may prove to be correct. So, we now have one molecule, this amyloid peptide, and it may be that we can treat that molecule the way we treat cholesterol in the prevention and management of arterial disease, and the way we treat blood sugar and hemoglobin A1c in the management of diabetes. It may be true, and we are moving in that direction. So, we now study the level of this peptide—the peptide does its damage in the brain—we now study the level of the peptide in blood, and we look for ways to reduce levels in blood. We study the peptide in the cerebral spinal fluid that we——

Senator MIKULSKI. Excuse me, can you now do a blood test to see the peptide level?

Dr. AISEN. Yes, you can, but it's not at the point where we know that reducing the level in blood will be helpful. This is still under investigation. It's the brain level of the peptide that's critical. There's a relationship between the blood level and the brain level, but it's complex, not predictable at this point.

One of the things that we're working on comes back to something else Mr. Essner said, which is ways of using neuroimaging. One of the very exciting neuroimaging modalities actually shows the accumulation of the peptide using a PET scanner. So, we have an amyloid PET-scanning method that we are currently testing, in collaboration with the pharmaceutical industry and with NIH, that will allow us to monitor the level of amyloid in the brain, and monitor the impact of medications or antibodies or vaccines or exercise

on the level of amyloid in the brain. And we are thinking that, yes, down the road, this will be a controllable process that, by looking at the peptide in the periphery and in the brain, and intervening against that peptide before the symptoms start could be a way of preventing Alzheimer's disease.

Senator MIKULSKI. Well, it's been the pattern of this committee to not treat legislation like prescriptions, so when we write our legislation, we want to create a framework that encourages breakthroughs, but not being so prescriptive as to micromanage our research field. So, let me come to this. Did a lot of what you're talking about come out of the Alzheimer's Disease Co-op Study? And would it be your recommendation as where we look for authorizing essentially a—we'll call it a breakthrough acceleration framework rather than new frameworks—that we stick to what's—that this is the place where a lot has been done, funded, and so on—could you——

Dr. AISEN. Yeah——

Senator MIKULSKI [continuing]. Along with the basic research. We're not talking about a zero-sum game here.

Dr. AISEN. Right. So, I certainly think that the ADCS has played a critical role from the beginning in Alzheimer's therapeutics, and will continue to do so, and deserves a great deal of support——

Senator MIKULSKI. But would you say that is "the place" that the breakthroughs are being stimulated?

Dr. AISEN. I think that the breakthroughs come from a collaboration among industry, the FDA——

Senator MIKULSKI. Which is what——

Dr. AISEN [continuing]. Just as you're saying the——

Senator MIKULSKI [continuing]. Essner was saying.

Dr. AISEN [continuing]. The government agencies, industry, and academia. And we are moving very much in that direction, and I would continue to move in that direction. So, the Alzheimer's Disease Cooperative Study Group collaborates actively with industry. We share the methods that we develop. And with the——

Senator MIKULSKI. But is it a consortium of academic institutions?

Dr. AISEN. It is. It is. Under NIH guidelines, we can work with industry. We can share all of what we learn, all of the tools, all that we learn about neuroimaging, about cognitive testing, about biomarkers in blood, in cerebral spinal fluid, with industry, and work with industry to develop the best clinical trials to test the best molecules. I have to emphasize again what you said, though, that the ADCS is a critical piece, but you have to keep working on the basic science, as well. And——

Senator MIKULSKI. It's "yes/and," not "either/or."

Dr. AISEN. Absolutely. And I would just point out that today, as I try to build my own department with young basic scientists, the funding rate for basic research now is about 10 percent, meaning that about 10 percent of qualified applications to NIH are being funded, and it's very hard to get the best scientists to stay in the field when the likelihood of creating a career with NIH funding is such a longshot.

Senator MIKULSKI. And it's been cut $310 million this year. That's one of the things the appropriators will be working on.

Did you want to comment on this, Doctor?

Dr. DEBETHIZY. You know, there are three areas that are already in place, where just focused funding in the Alzheimer's disease would be important. Obviously, we had the Decade of the Brain in the '90s, which generated a tremendous amount of learning and really generated the therapies that exist today. So, basic NIH funding needs to be focused on Alzheimer's disease to fund these young scientists, because their ability to get grants has been reduced dramatically, and get through the peer-review process. The other part is by—Elias Zerhouni, the director of the NIH, has instituted this translational medicine initiative. This is exactly the kind of initiative that we were talking about, in terms of developing diagnostics and surrogate markers that you could use to get more rapidly to the answers that you want to address. Normally, this process takes forever, because you need a lot of validation, you need a lot of work, and it's really, essentially, the thing that holds up being able to get answers quickly.

And then, the third component—and we haven't talked about this yet—is the interface with the regulatory body, the FDA. They have their critical path initiative, this path of getting things moving quickly. But it's very underfunded, and it's not focused on Alzheimer's disease at all. So, I think some focused effort in that area would be very helpful in terms of getting attention and really making it somewhat more receptive to us as we go in. Rather than going in and us having to make the arguments and persuade people, having people call us and say, "Look, can you come and help us do this?" That would be a very—that would be a big change.

Senator MIKULSKI. Well, that's why we want to get them in the same room later on—I think, within the next month. It's just really being able to get a Zerhouni, Gerberding, and Eschenbach in the same room, but we feel that's one of the ways to then think in terms of epidemic research, news you can use, CDC's role, as well as FDA. Well, thank you.

Dr. Kramer, I'd like to come back to you and your research. And those of others that are in the—focusing on this prevention—and also, now, immediate intervention.

Dr. KRAMER. Right.

Senator MIKULSKI. First of all, would you say that your work is now—kind of, that there is a consensus that diet, exercise, both physically and intellectually, now would be like a mainstream thought that we should be looking into doing?

Dr. KRAMER. Yeah, I——

Senator MIKULSKI. Because I want to come back to the Office on Aging.

Dr. KRAMER. Sure. It goes beyond diet and exercise. It's also intellectual engagement. Many older folks—the old notion of retirement doesn't exist anymore, thank God, and shouldn't—that older folks get involved in volunteer activities, in many kinds of activities, and we've found that continued intellectual engagement is also a way to slow down the transition to Alzheimer's, mild cognitive impairment; as is social interaction, being involved with others, which becomes a problem as we age, and we don't—we are some what socially isolated. But the CDC and the Alzheimer's Association has recently teamed up with NIH to work on getting out these

public messages about lifestyle factors and how useful they can be, both to reduce a variety of different diseases, not just Alzheimer's, but type-2 diabetes and so forth.

Senator MIKULSKI. Yes. This takes me to, then, my question.

Dr. KRAMER. Yes.

Senator MIKULSKI. We're the subcommittee that has oversight over the Office of Aging. The Office of Aging runs the senior centers across the country.

Dr. KRAMER. Right.

Senator MIKULSKI [continuing]. Throughout the United States of America. It also oversees the Meals on Wheels Program. It also oversees the so-called Eating Together programs, where seniors come for congregate meals. I'm not so sure—and I feel that right now, this would be the place to introduce this type of approach——

Dr. KRAMER. Right.

Senator MIKULSKI. And, in many instances, I have a feeling that it's already being done. And then—but it also goes to the meals that we serve under government funding.

Dr. KRAMER. Exactly.

Senator MIKULSKI. Would you share with us how you see this being implemented? Do you know if there's any interaction between the body of knowledge that you and your colleagues are developing that are going out to the Office on Aging? What is CDC doing? Is this what we should ask? Is this what we should push?

Dr. KRAMER. I think we should always ask more. I think a lot of the approaches are relatively piecemeal. I went to a conference last year in Atlanta with CDC, the Alzheimer's Association, and NIH, and one of the things that they are considering is how to get out a public health message that these lifestyle factors are important, for a multitude of reasons, for a healthy brain and cognitive aging. But, I think, more of a concerted effort and focus through the Congress to make sure these things happen, and to make sure they happen in a coordinated way, would be very welcome.

These are very tough issues, as Senator Burr referred to, to get people to exercise. We all know it's good for us. Why don't we do it? And the science is there. And more of the science is coming out every day; not just in our country, but throughout the world, you can see these studies. So, I think to have a focus through Congress, perhaps with some legislation or with some meetings, much in the same way that you're focusing on the development of new pharmaceuticals, taking the science on lifestyle factors, and getting it out to the public, making sure there are some incentives for maintaining a healthy lifestyle. And we are—you know, in terms of new research, we are pretty deficient in terms of looking at the interaction of lifestyle factors and pharmaceuticals. That's clearly an area for the future that gets very little treatment.

Senator MIKULSKI. What do you mean?

Dr. KRAMER. Oh, the drug companies getting together, and the small and the large pharma, both getting together with academics and government agencies that work on lifestyle factors, and those who work on pharmaceuticals, and looking at the joint interaction of these multimodal interventions, which, in the end, have to be the way to go, to deal with Alzheimer's, to deal with prevention,

and to deal with many other maladies that affect the mind and brain of our older citizens.

Senator MIKULSKI. Senator Burr, you know, this Office on Aging—and when we listen to CDC, could be something to really encourage, when you think—I forget how many senior centers are available in the country. They exist in every State. Senator DeWine and I helped the reauthorization—where we could keep local flexibility, because rural America is different than urban America.

Dr. KRAMER. Sure.

Senator MIKULSKI [continuing]. But I believe that this is the area where at least we know people come every day, or several times a week——

Dr. KRAMER. Right.

Senator MIKULSKI [continuing]. To interact and to eat. And that's what you're saying is the key——

Dr. KRAMER. Yeah.

Senator MIKULSKI [continuing]. One of the keys to prevention: interaction and the foods you consume. And I believe that one of the things we should ask is, Well, what is the food that goes out to most senior centers?

Dr. KRAMER. Yeah.

Senator MIKULSKI. What is the food that goes out to most Meals on Wheels? That's one thing. So——

Dr. KRAMER. I think those are great questions.

Senator MIKULSKI. So, do you all ask those?

Dr. KRAMER. We do assess diet. I do put people in MRI machines. I do a lot of——

Senator MIKULSKI. No, no. No, you assess diet. But has anyone looked at what the government pays for, and——

Dr. KRAMER. I——

Senator MIKULSKI [continuing]. Whether it's smart?

Dr. KRAMER. I don't, personally, know that. I'm sorry.

Senator MIKULSKI. No, that's—no, we're not trying to—but, you see—that is a good question. And when we talk about exercise—I know Senator Burr was talking about his 85-year-old dad, but his father might like dancing, his father might like horseshoes.

Dr. KRAMER. Exactly.

Senator MIKULSKI. I think there is a variety of ways. Because when we hear "exercise," we sometimes think of body-beautifuls and spandex outfits and the latest cool clothes.

Dr. KRAMER. Right.

Senator MIKULSKI. But what you're talking about is movement.

Dr. KRAMER. Exactly. And the——

Senator MIKULSKI. Sustained——

Dr. KRAMER [continuing]. Intervention we use is walking.

Senator MIKULSKI. Sustained, pleasurable movement.

Dr. KRAMER. Right.

Senator MIKULSKI. Well, in some instances other people have problems with walking, so then what are other things that——

Dr. KRAMER. Aerobic——

Senator MIKULSKI [continuing]. They can do?

Dr. KRAMER [continuing]. Exercise in the pool, riding a bicycle. There are many alternatives. Gardening, playing golf without the golf cart. Throwing horseshoes would be good. There are many

ways to get physically active. And it doesn't have to be intense to reap some of the benefits that we've seen, and others have seen, in our research.

Senator MIKULSKI. Senator Burr, did you want to pick up?

Senator BURR. Yes, ma'am.

Just for the record, my dad still works out at the "Y" at 86 years old, 2 hours——

Dr. KRAMER. That's fantastic.

Senator BURR [continuing]. A day. So——

Dr. KRAMER. That's fantastic.

Senator BURR. I've tried to absorb everything that's been said while Senator Mikulski was asking questions. And I go back to—you started with an Adams quote. Let me, in my conclusion, end with a Jefferson quote,

> "I'm not an advocate of frequent changes in laws and constitutions, but laws and institutions must advance to keep pace with the progress of the human mind."

I think that's what I've heard from all of you, is, you know, we're going down this pathway, and we're making tremendous progress toward learning, and the FDA has to change to reflect the framework of where we are as a field on this disease. NIH needs to change relative to where they're focused. And part of that, as you said, Don, Dr. Zerhouni has already done. And I'm not telling you anything new when I say that Washington fights change, in a huge way. It's not comfortable. I personally believe that 10 years from now the drug approval process in this country will look totally different than it does today. It will be every bit as safe, but there'll be no reason that we have to wait for the first clinical trial to be done to analyze the entire data from the trial before we design the second one, that we'll actually have reviewers that look at clinical data on a daily basis, that are assigned to an applicant, that are fairly certain, halfway through the first clinical trial, of what they want to look at for the second clinical trial, and that the results are that we're still able to meet that bar of safety and efficacy, but we're able to do it in a reduced amount of time, not just for Alzheimer's drugs, but for every drug.

Don, you talked some in your testimony about prevention. I think you suggest the most effective, efficient way to address Alzheimer's disease would be to treat early stages of cognitive decline, which would mean a patient may never suffer Alzheimer's if, in fact, there was intervention—successful intervention at that time. But you've set aside research into the early stages, if I understand it right. Can you sort of expand on that?

Dr. DEBETHIZY. Sure. We originally started in age-associated memory impairment, but recognized right away there's no approved therapies there. And just so I define that for you, these are people that are 50 to 80 years of age that have one standard deviation—statistical standard deviation unit below younger matched controls, so they don't have dementia, they don't have—only 3 percent of those people go on to Alzheimer's disease eventually. But these people are concerned. They think they have Alzheimer's. They're going into memory clinics. But there's no approved therapy, because these are normal, healthy people that have age-related cognitive decline. They would benefit from having a therapeutic, but

that therapeutic would have to be safe. And that's the position the FDA has taken.

But, since there's no clarity around that, and no agreement around that, and no agreement on the diagnosis, no agreement on the objective measures, no agreement on the subjective measures, we chose, with our partner, AstraZeneca, to go after Alzheimer's disease in a very clear path to approval, which is symptomatic improvement. So, right now all the drugs on the market have all been approved through a label around symptomatic improvement. We believe we have a superior drug, so we feel like we're—it's much better than the current therapies. But that's, sort of, the conservative approach to this.

I would recommend that there be some focus put on age-associated memory impairment and mild cognitive impairment, because I fundamentally believe that a nicotinic drug, entering early in this progression, would be beneficial to delay disease modification.

Senator BURR. Now, Bob, I think you alluded, in your testimony, as well, that we could save $4 billion in this country alone by delaying the onset of Alzheimer's by 1 to 3 years, not dissimilar to delaying diabetes onset, I might say. But I think you referred to the fact that the regulatory agencies are cautious as it relates to Alzheimer's in a way similar to diseases where major therapeutic options already exist. Is that sort of in sync with what Don's saying?

Mr. ESSNER. Well, I think, you know, in diseases like hypertension or cholesterol, where there are many good therapies today, certainly the regulatory agencies, I think appropriately, are very cautious with any new, less-well-studied medication. But I think I was trying to draw a contrast to Alzheimer's disease, where today the therapies that are available are, you know, at best, marginally helpful for most patients, and where that kind of caution, may not be the right balance, given the fact that Alzheimer's patients have such a——

Senator BURR. So——

Dr. KRAMER [continuing]. Sad future.

Senator BURR [continuing]. The leak-over from the more prevalent model of caution leaks over even into some areas where we don't have that overlap of options.

Dr. KRAMER. Yeah. And, you know, if you put yourself in the chair of an FDA reviewer, and you look at the world in which they live, certainly—a certain amount of conservatism probably is appropriately built into their jobs. And what we're hoping is that a real spotlight—national spotlight shined on Alzheimer's disease will encourage FDA, as they have done in the past with some other diseases—AIDS, avian flu—to take a much more activist approach and do exactly what I think you described, work actively with companies to see that medicines are evaluated thoroughly, carefully for efficacy and safety, but do that in realtime rather than in the current very staccato way the drugs are developed and reviewed.

Senator BURR. Don, there are a number of companies around the world that are investing a tremendous amount of money—companies like yours. What do you see as the biggest hurdle before you that we need to overcome to achieve a success in Alzheimer's disease treatment?

Dr. DEBETHIZY. Well, you know—and this is appropriate. I agree that the FDA has to take a conservative approach and—with focus on safety; because that's their job, to protect human health. But the time that it takes for us to get—so, we discovered 1734 in 1997, and so now it's 2007. That's 10 years later. Now, it hasn't been a straight path for us. You know, when you're a small company, you have to move with priorities. But I would say, you know, it's 12 to 15 years from discovery to the market for compounds. And your relative success rate is extremely low. It's about 10 percent for compounds that get out of the early discovery process.

The challenge is the time. And part of that is the abundance of caution that we have built into the system. And I'm a toxicologist, originally, and I do know there's been tremendous efforts to try to streamline that process. We're starting to get there, but it's been very, very slow coming. These surrogate markers—everybody wants to go to the gold standard, and the gold standard is a whole animal study that's 90 days or a year or 2 years, and then they want to do clinical trials, where there are thousands of patients, to make sure that it's safe, before you get into the market. There are some modifications of that you could do, where you could move quicker through the process, through the clinical trials, as you've said, by analyzing along the way, but it does bring some risk with it, and we're not very good at relative risk in this process.

Senator BURR. Last question, with the Chairman's indulgence. And it really goes to the heart of our ability to diagnose at an earlier point. And I'll open it to anybody that would like to comment. We've talked about MRIs, we've talked about PET. Clearly, imaging is a concern of mine, and that's one of the reasons we now have an institute at NIH, because imaging shouldn't just be the accumulation of imaging dollars that we used on cancer studies, it should be an effort to try to produce diagnostic tools that far exceed anything we've got today. And I think that effort is underway.

We still annually fight—usually in Congress—an attempt to cut down on our ability to bring radioactive materials from outside the country, materials that are used, in many cases, in PET and other imaging tools. Can you share with Senator Mikulski and myself any advances in imaging that are happening that might give us better capabilities to diagnose, at an earlier period, a potential Alzheimer's patient?

Dr. AISEN. Before I come to imaging, let me just broaden my answer and say that there's an effort to use many different tools to identify people at an early stage. There are genetic markers, so there are—even for sporadic AD, there are genetic markers that indicate something about risk. There are cognitive tests that actually work quite well, so I'm—cognitive tests that are sensitive to change years before a diagnosis of Alzheimer's disease. I think it's actually going to use information from multiple modalities that will allow us to identify people at the earliest stage. But, yes, imaging is definitely part of this.

And we've learned a lot about this. We've known now, for example, that just using structural imaging, with MRI scans, and with our current magnet strength, we can see very, very small structures in the brain, and we know the structure where Alzheimer's disease starts; it's the hippocampus entorhinal cortex. And we can

now see that clearly, and, using a couple of scans, 6 months or 12 months apart, we can determine the rate of shrinkage of that area of the brain where we know that Alzheimer's disease starts, many years before the symptoms appear. And that appears to be a very promising tool, using neuroimaging, for identifying people before there are any symptoms. That's structural imaging.

We are also using functional imaging of a couple of types, using something called functional magnetic resonance imaging, as well as the standard PET scanning. So, I'm not talking now about amyloid PET scanning, but the standard metabolic PET scanning, which can show changes not of brain structure, but of brain function that occur prior to the symptoms of Alzheimer's disease.

When we couple cognitive testing, genetic testing, biochemical marker measurement in blood—for example, the amyloid peptide—coupled with amyloid quantitation in brain, using PEP-PIB imaging and rate of structural atrophy in the brain, we're getting pretty accurate at identifying people before there are symptoms of disease. And since we're all, I think, optimistic that we're learning how to control the amyloid peptide. And that's key. I believe it's a reasonable possibility that before too many years arrive—too many years pass, we will be able to identify these people before symptoms, and treat the peptide, and stop the disease before the symptoms occur.

Senator BURR. Anybody else?

[No response.]

Thank you, Madam Chairman.

Senator MIKULSKI. Well, as part of my, kind of, concluding both comments and questions, we want to personally thank you for your participation, and I want to thank Senator Burr for such active engagement. I think we have heard a couple of things—one is that we need to lower the whole issue of adversarial conversation, both in the country and in the way we all work, so that there can be greater collaboration between academia, government, and the private sector. The other is, I would add, we've got to keep an open mind about what are the promises. Dr. deBethizy, as you spoke, I noted, in the audience, as soon as you were identified as being from R.J. Reynolds, or once were, and that you were looking at the nicotine, there were a lot of smiles and shrugs, and even smirks. But yet, I'm reminded of a time when we had thalidomide that caused terrible, terrible birth defects, but yet, I'm also now reminded that, for those who are facing certain forms of blood cancer, this is the first tool that we turn to. The very things that caused the birth defects are the very things that slow down this terrible blood cancer. So, I think we need to keep an open mind. I don't know if you're onto something. I don't know if you're not. But you very well might be. And you identified there were other very negative side effects to smoking, which we all now recognize, but, Who knows?

So, I think, No. 1, let's keep an open mind. Research is about being smart. It's not always about being correct.

The other is, this then goes to how the Federal agencies essentially help you do what you need to do, to do these breakthroughs. As I said, we hope to be bringing in NIH, FDA, and CDC. I also would like to have a meeting with the Office on Aging with Senator Burr to talk exactly about the type of work you, Dr. Kramer, and

your other colleagues, are doing. So, if there's a consortium or something working on prevention, we'd like to be able to get that and ask the Office on Aging what they're doing. Who knows?

But let's go to our future meeting, and then we'll go to a markup in the legislation later this summer.

If you had those three gurus here, what would you recommend, questions that we would ask and/or ideas that we would encourage?

Dr. Aisen? And we can just go right down the room.

Dr. AISEN. Yeah, I think this is a great idea, and I think that, actually, I've seen a lot more cooperation in the last few years than in the past. So, already, I think, the idea that we need to have cooperation across industry and academia and the government has started to take hold, and absolutely needs to be encouraged so that there is open communication and sharing of methodology and industry pre-competitive collaboration, which is a very interesting notion that seems to be taking hold——

Senator MIKULSKI. What would you ask either FDA, NIH, or CDC?

Dr. AISEN. The FDA needs to be involved at the earliest stages, including the development of the surrogate markers of disease. In other words, the FDA has to be talking to the companies and to the academic investigators about what they will need, and what they should need, to identify nontraditional populations for treatment, and how we will measure the effects of the treatment.

Senator MIKULSKI. Which goes to what you were saying.

Dr. AISEN. To NIH, you know, I think NIH needs a lot more money. I think they need a lot more money. I think there needs to be more money in clinical investigation of the sort that our group does, and more money in basic investigation, as well. I think we are so close that the amount of money we spend now will have a huge payoff.

And finally, I think all these groups can work together to get the message out, which I think you started with, Senator Mikulski, that we need everyone to be aware of what's going on with this disease, not only in terms of what they can be doing now—preventive measures, diet, exercise—but also to support those of us who are trying to develop treatments. If we had a larger portion of the population at risk, and affected by this disease, volunteering to participate in clinical trials, then everything would move more quickly.

Senator MIKULSKI. Very good.

Dr. Kramer.

Dr. KRAMER. Yeah. I think I'd like to echo Dr. Aisen's suggestion that communication is critical here. And I think all too infrequently, the heads of CDC, FDA, and NIH communicate about these important issues.

I also agree that funding for basic research, as well as applied research, has become problematic over the last several years at NIH. And I really do worry—and I'd like to echo that—that we're losing a generation of young scientists, who are getting extremely frustrated. I rotated off, about a year ago, an NIH study section, and, on the study section I was on, we were down to the 8th percentile of funding. This hasn't happened for a long time, and I hope funding comes back up again soon.

I think there is the possibility of coordinated programs between NIH and the CDC. As I've mentioned before, I do go to a meeting with the NIH, CDC, and Alzheimer's Association. I think this is starting to happen. I think more cooperation on public health messages based on solid science makes a lot of sense and really needs to be incorporated to a much greater extent in the future.

Senator MIKULSKI. Thank you.

Mr. ESSNER. Good. I agree with the comments the previous panelists have made, but I—maybe I'd add just two things. One is that the Food and Drug Administration also, in terms of the reviewing divisions, especially in this area, definitely needs more resources. And, without that, it would be very difficult for them to implement a number of the things that have been talked about.

And, secondly, I would not underestimate the importance of just shining a massive spotlight on this disease, of having the heads of these two groups say, "We want a war on Alzheimer's disease. We're setting goals here of, you know, creating really useful therapies to help control or reverse this disease, you know, in some period of time, and we're going to do everything in our power to make it happen." It has an impact on their staffs and on the public, that can, in itself, make a big difference.

Senator MIKULSKI. Very good.

Dr. deBethizy.

Dr. DEBETHIZY. I would agree with all that, and I would emphasize the role of leadership. I think just your leadership now, the focus that you're placing on it is incredibly important. And I think that will get people's attention. So, this pathway of the translational-medicine effort at NIH, you know, ask them specifically what are they doing for Alzheimer's disease in that process of bringing in these surrogate markers, because—then, going to the FDA with their critical-path initiative. They have very little funding for that critical-path initiative. And I'm almost certain they have very little going on in the Alzheimer's disease area. But some of these imaging techniques would be outstanding for us to be able to use early in our clinical trials if we had agreement that they would be meaningful and acceptable to the agency as a surrogate marker for efficacy.

Senator MIKULSKI. Well, first of all, I think those are excellent ideas. We're going to incorporate them, certainly, in our hearing. We would also add a sense of urgency, because I feel that time is not on our side, both in our own country and around the world. In our own country, the Boomers are aging. So, when we talk about how they're coming of age now, at 60-ish, when you talk about these trials or things 10 years, 15 years, they'll be 75 when—there are interventions we could be looking at now, preparing now, and viewing it, and essentially avoiding a catastrophic personal and governmentally fiscal situation.

Second, our planet is aging. So, when you look at Europe, you look at industrialized countries, like Japan, there is an aging population. And they, too, will be looking at these issues. And what a great form of public diplomacy for us to be able to engage in how we can improve the lives of our citizens, how we can improve the lives of treasured allies. And maybe some people aren't so friendly with us now, but, nevertheless, we know—demography now could

be destiny, and yet Alzheimer's doesn't have to be part of that destiny.

So, we want to thank you, first of all—I believe each and every person at this table is making a difference, and we want to thank you for the difference you already are making. But, you know, when we work together, we can make change.

So, thank you very much, and the committee stands adjourned.

[Whereupon, at 11:40 a.m., the hearing was adjourned.]

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