

# FEDERAL RESPONSE TO THE ALZHEIMER'S EPIDEMIC

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## 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 THE FEDERAL RESPONSE AND ADVANCES BEING MADE  
TOWARD DEFEATING THE EPIDEMIC OF ALZHEIMER'S DISEASE

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JULY 17, 2007

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## FEDERAL RESPONSE TO THE ALZHEIMER'S EPIDEMIC

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TUESDAY, JULY 17, 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 3:17 p.m., in Room 628, Dirksen Senate Office Building, Hon. Barbara Mikulski, chairman of the subcommittee, presiding.

Present: Senators Mikulski, Burr, and Isakson.

### OPENING STATEMENT OF SENATOR MIKULSKI

Senator MIKULSKI. Good afternoon, everyone. This afternoon, the Subcommittee on Retirement and Aging is hosting a roundtable on the subject of the Federal agency response to the epidemic of Alzheimer's. This is set up a lot more starchy than what I had originally intended it to be because to me, it looks like a hearing. If it looks like a hearing, it is a hearing but we're not going to act like it's a hearing. We wanted a far more casual, more interactive approach and I hope that we can do this.

Today, the reason we're here and I really want to welcome four very distinguished Americans who have devoted their life to public health, to saving lives and to caring about the people in the United States of America. Dr. Zerhouni, the Head of the National Institutes of Health, Dr. Gerberding, our Director for the Center for Disease Control and Prevention, Dr. von Eschenbach, our Commissioner for Food and Drug Administration and Dr. Hodes, who is the Director of the National Institute of Aging and Dr. Hodes, we had a very robust hearing on research a couple of weeks ago.

But today, where are we heading? Well, everyone knows the data about Alzheimer's. Five million Americans are currently living with it. As the baby boomers age, we expect to have more of Alzheimer's in our community, a disease right now for which there is no cure, yet the possibility of very realistic cognitive stretch-out. One hundred years ago, it was the first year that Alzheimer's was diagnosed but we don't want to wait another 100 years to see what we can do.

In talking about this, what we realized is that was 10 years after the first diagnosis of HIV/AIDS that a cocktail was produced that enabled people to live longer and to live better. It was a stunning time of cooperation. The wonderful work at NIH. Certainly our good friend, Dr. Fouche played a lead role working with obscure vi-

ruises that led the way and paved the way. It was the best of research. The Center for Disease Control mounted this incredible medical detective work when young men in San Francisco and throughout the country were developing the disease that we began to recognize—and FDA worked in this intense and concentrated way to see how we could take the best of what we knew in research, what we were noting in epidemiology to come with up where we were.

Well, we wonder if we're not at this point now, where we need to think along the lines of where are we going with the issue of Alzheimer's. What we wanted to discuss with you today is the Federal response. To talk about what is happening in the area of research but knowing where we are with research, how this is being transmitted into essentially work that the CDC can troubadour out for either prevention or what clinicians can use. We've heard stories of one, misunderstanding and misdiagnosis by well-meaning, primary care doctors. Patients worry about what's happening to them and their family wonders, what should they do and where could they turn?

At the same time, we know that there are drugs that are being developed, drugs that are being explored but we wonder, is there a kind of a focal point where, in the issue of speed, we still maintain the very rigorous standards of safety and efficacy and don't let our fear and our hope move things too quickly but then, a sense of urgency.

So what we're looking for today is to hear where we are in kind of much-needed research but at the same time, what we're looking at as we mark up the Alzheimer's Breakthrough Research Program, what we could be doing to help you be you? We need you. We already count on you but what can we do to help you deal with the fact that this is an epidemic and we look forward to your thoughts and then we hope that we can progress in a conversational way.

We expect to be able to really have a conversation. We expect more of our people to come but we scheduled this meeting in coordination with your very complicated schedules as well and we appreciate your cooperation but there is an intense debate going on, on the Iraq War and about the deployment of our troops.

But we have here Senator Burr, our very wonderful colleague from North Carolina whose passion for public health is well known and his dedication to research and advancing medical science is well known. So why don't you—and I see you're wearing the purple colors of the Alzheimer's Association.

#### OPENING STATEMENT OF SENATOR BURR

Senator BURR. Well, Madam Chairman, thank you. More importantly, I'd like to also welcome this prestigious group of panelists today. As I look down, doctor, doctor, doctor, doctor, I'm not sure whether Dr. Gerberding's sign is indicative of anything other than the fact that she brought her own. But it is larger.

[Laughter.]

Senator MIKULSKI. It's kind of the new world order, isn't it?

[Laughter.]

Maybe I ought to get a bigger one.

Senator BURR. A rose among thorns—Madam Chairman, I commend you for your leadership and your support for Alzheimer's patients, your passion on the issue and more importantly, what I've had the opportunity to learn from you in a short period of time. Again, I want to thank each of you for taking time out from what I know is an incredibly busy schedule and I've had the opportunity already once today to meet with Dr. Zerhouni on some other issues.

I believe promising research exists for Alzheimer's. Each of your agencies play an important part of how we treat, how we educate, how we care for the 5 million individuals in the United States living with Alzheimer's disease and the many more who will be added as they age or become diagnosed.

As we know all too well, Alzheimer's is truly costly to treat and quickly becoming a financial burden on the Nation's health care system. Loved ones and family members are feeling the financial and emotional burdens of Alzheimer's disease as well. Ten million caregivers are providing 8.5 billion hours of care each year, valued at \$83 billion.

Simply put, we must find a disease modifying treatment. There are many reasons for optimism. Both the public and the private sectors have identified Alzheimer's as a priority for research and development dollars and we've learned during our last couple hearings that we're on the cusp of a number of potential scientific breakthroughs, which is exciting. It's critical that we translate the information learned through research and through clinical practice and personal experiences into effective public health practices and more importantly, medical treatment.

I look forward to hearing how each of your agencies are advancing in this very, very important research and stand with the Chairman to say we are committed to try to explore any and all avenues that provide a better level and quality of care for patients and also provide us a way to fill that gap of a disease that is extremely costly, not just to us but to individuals and to their families and I thank the Chair.

Senator MIKULSKI. Thank you. Dr. Zerhouni, we're going to ask you to kick it off. Dr. Zerhouni is the Director of NIH. He's a respected leader in the field of radiology medicine. He is a well known scholar, worked at Johns Hopkins as the Vice Dean in the School of Medicine and has a distinguished history. Then we'll go right down the line.

Dr. Zerhouni, we look forward to what you have to say but it's not only where we are in research but one of our questions is, can the Congress either through authorizing more appropriations, do something that would really accelerate where we are on breakthroughs, never underestimating the solid, basic research that needs to go on. But how do you see this? What are we doing and could we do more and what would be the best way to do it? And of course, we want to hear from our very wonderful head of the National Institute of Aging.

**STATEMENT OF ELIAS ZERHOUNI, M.D., DIRECTOR, NATIONAL  
INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND  
HUMAN SERVICES, BETHESDA, MD**

Dr. ZERHOUNI. Well, Senator Mikulski and Senator Burr, it's a pleasure to be here and to address your question, I think it would be important for us to A, review a little bit of the recent past and then tell you where we are and where we intend to be, if we have the ability to follow the pathways that I think are becoming very clear today.

Over the past 30 years, Americans have—the average life expectancy of Americans has gone up by 6 years or about 1 year every 5 years. What that means is that you have a 65-year-old American today, their average survival beyond 65 is 18 years. If you're 85, your average length of life is going to be 6 years longer or more.

And that has changed the demographics of our country, as you well know and this is what makes Alzheimer's a disease that has been with us a long time, a current priority and a future urgency, if you will, that we need to address. We need to address forthrightly with programs that I think will, at the end, change the paradigm with which we treat chronic diseases and the thing that is very obvious to us is that the landscape of disease has changed and is continuously changing in the country. As you mentioned, there is no doubt that our population continues to age but a striking change is the fact that chronic diseases now make up 75 percent of health care expenditures and are continuing to grow at a rapid pace.

Alzheimer's disease is a major component of that, as you said, where up to 4.5, 5 million individuals affected with this disease but if you really think forward, you're going to have up to 16 million Americans affected by this disease and as Senator Burr mentioned, it is a costly disease.

So how do you change the paradigm? How do you really affect the outcome of this disease? What does NIH need to do? What I think is obvious is that with the completion of the human genome and the discovery of fundamental causes of diseases, especially diseases like Alzheimer's disease that are long-term diseases where it's obvious that the disease started many, many years before it struck the patient. What we need to do is strike the disease before it strikes the patient.

This is what we call the ERO, the Four P's of the future of medicine. Where we have to go from a paradigm where we wait for the patient to get very sick, to intervene to an era where we are much more predictive about who, how, when is a patient going to suffer from Alzheimer's disease and that implies, Senator, a different kind of research. We need to do research not just on the late effects of a disease but on the early effects and the early signs of the disease by developing biomarkers.

The second is that these conditions require us to understand not only the fundamental causes of the disease but also to manage the symptoms of the disease and lessen the burden of the disease on our patients. For example, we know that patients with Alzheimer's disease suffer from depression. They suffer from cognitive deficits and we need to intervene at that level.



At the end of the process, what will be the ultimate solution for us to usher in an era where we will be much more predictive of the disease process being there 20 years before it strikes; B, very targeted approaches to treating the disease at the stage we find it, and; C, if we can pre-empt the disease all together, that would be the ideal and we've shown that in certain cases, we can. For example, last year we introduced the vaccine to prevent cervical cancer and there are areas of research that the National Institute of Aging is funding where a vaccine is being entertained for Alzheimer's disease as well.

So we have to really cover the entire spectrum of the disease and this is what I think needs to be understood. We will not make progress unless there is total coordination between all aspects of the disease process, remembering that we are seeing correlation and associations between—in these patients—between the presence of diabetes and the likelihood of developing Alzheimer's disease, heart disease and Alzheimer's disease.

We also know that the disease has great impacts on caregivers and therefore the delivery of the care has to be thought through and it has to be improved. So for researchers today, earlier and more accurate diagnosis is going to be critical. That will require a better molecular understanding of the disease process in its earliest stages.

It will require us to develop biomarkers, the ability to either through imaging or blood tests, to detect who is at risk for Alzheimer's disease. The completion of the human genome has given us hope that we will be able to find genetic signatures of susceptibility for the disease. We are launching a genome environment initiative that will allow us to find out if there are environmental factors that accelerate or provoke the development of Alzheimer's disease.

All in all, I think that the key here is the transformation of our research from a curative paradigm of the past to the pre-emptive paradigm of the future is truly within our grasp and it is the priority that we should sustain and support aggressively.

I think 10, 15 years ago, we didn't know what the causes of Alzheimer's disease at the fundamental level were, we have multiple theories of the disease. You will hear from my colleague, Dr. Hodes, about the progress we're making but there are still remaining challenges and the challenges, I think, in this case, are that the opportunities for science to make a difference are many but we will not succeed unless we have an all-front attack on Alzheimer's disease, from the very moment it starts, before anybody knows that the disease is there and the patient feels no symptoms, to the moment it strikes. We have to be able to do research across that entire spectrum. Thank you very much.

[The prepared statement of Dr. Zerhouni follows:]

PREPARED STATEMENT OF ELIAS A. ZERHOUNI, M.D.

Senator Mikulski and members of the committee, good afternoon. I am Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services, and I am pleased to be here today to talk about the advances we are making toward defeating Alzheimer's disease (AD), a devastating condition with a profound impact on individuals, families, the health care system, and society as a whole.

Peer-reviewed reports estimate that up to 4.5 million Americans ages 65 and older are currently battling AD. Moreover, the rapid aging of the American population threatens to increase this burden significantly in the coming decades: Demographic studies suggest that if current trends hold, the incidence of AD will begin to sharply increase around the year 2030, when all the baby boomers (born between 1946 and 1964) will be over age 65. By the year 2050, the number of Americans with AD could rise to as many as 16 million.<sup>1</sup> In addition to the tremendous emotional and physical toll AD exacts upon patients and their caregivers, financial costs of AD are high: Some experts estimate direct and indirect costs of Alzheimer's and other dementias to be more than \$148 billion annually.<sup>2</sup>

AD's complex pathology and relentless clinical course have presented daunting challenges for the medical and research communities. However, the National Institutes of Health is poised to meet these challenges through a comprehensive program of research into the underlying causes, diagnosis, prevention, and treatment of AD.

At the most basic level, our understanding of the brain and cognition in both normal aging and disease states is increasing rapidly and exponentially. Advanced imaging technologies have opened a window into the inner workings of the brain and made it possible to visualize the brain's activity, including changes in the brain that could herald the onset of disease, with a specificity that was impossible even a few years ago. For example, the development of new tracer compounds such as Pittsburgh Compound B, the first molecule that can be used to map amyloid plaques (one of the pathological hallmarks of AD) in the brains of Alzheimer's patients, could allow earlier diagnosis of AD and facilitate the evaluation of new treatments.

Because research suggests that the earliest AD pathology begins to develop in the brain long before clinical symptoms are apparent, scientists are now searching for reliable, valid, and easily attainable biological markers that can identify cases very early in the course of disease. Early diagnosis of AD benefits affected individuals and their families, clinicians, and researchers. For patients and their families, a definitive early diagnosis provides the opportunity to plan for the future while the patient can still take an active role in decisionmaking. For clinicians, accurate early diagnosis facilitates the selection of appropriate treatments, particularly as new interventions are developed to stop or slow progression of symptoms. And for researchers, earlier and more accurate diagnosis will facilitate clinical studies of new therapies and preventive measures by allowing clinical trials on early intervention, before cognitive loss becomes significant. We expect programs such as the ongoing Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private partnership which Dr. Hodes discusses in his statement, to provide a wealth of information about both brain pathology and biomarkers that can aid us in early diagnosis.

Successful early diagnosis also depends upon the identification of people who are at particular risk for developing the disease. Although we do not yet fully understand what causes AD, it is apparent that genes play an important role, and NIH is supporting the development of new techniques to speed the identification of genes that are associated with AD. For example, genome-wide association studies (GWAS) rely on newly available research tools and technologies to rapidly and cost-effectively analyze genetic differences between people with specific illnesses such as Alzheimer's disease or diabetes and to healthy individuals. Identifying the differences may facilitate our understanding of genetic risk factors that influence the development or progression of disease.

Several NIH Institutes recently launched, or are planning, GWAS initiatives with the expectation that the results will eventually accelerate the development of better diagnostic tools and the design of new, safe, and highly effective treatments. NIH is also developing a data-sharing policy for GWAS to harmonize the practices NIH-wide through which data will be made available for research use.

As with other chronic diseases and conditions, however, genes are only part of the story. In addition to the genetic component, cognitive health can be influenced by concurrent medical conditions, environmental factors, and even an individual's social environment. An ongoing NIH initiative aimed at elucidating the underpinnings of cognitive health and preventing disease is the Cognitive and Emotional Health Project. The goal of this trans-NIH initiative is to assess the state of epidemiologic research on demographic, social, and biologic determinants of cognitive and emotional health in aging populations and the pathways by which cognitive and emo-

<sup>1</sup>Hebert, L.E., et al. Alzheimer Disease in the US Population: Prevalence Estimates Using the 2000 Census. *Archives of Neurology* 60: 1119–1122, 2003.

<sup>2</sup>Alzheimer's Association, Alzheimer's Disease Facts and Figures: 2007. [http://alz.org/national/documents/Report\\_2007\\_FactAndFigures.pdf](http://alz.org/national/documents/Report_2007_FactAndFigures.pdf). Figure includes Medicare and Medicaid costs and the indirect cost to businesses when employees are burdened with the care of persons with Alzheimer's.

tional health may reciprocally influence each other so that the most likely interventions for maintenance of cognitive and emotional health may be targeted. As a first step, a comprehensive review of measures that are associated with maintenance of cognitive health has been published and was a starting point for the development of the recently published Centers for Disease Control and Prevention/Alzheimer's Association's *Healthy Brain Initiative: A National Public Health Roadmap to Maintaining Cognitive Health*.

By learning more about the diverse factors that may increase risk of cognitive decline or AD, we hope to identify interventions that could delay or prevent its onset. For example, we have learned from epidemiologic studies that diabetes, a condition affecting nearly 21 million Americans,<sup>3</sup> is associated with cognitive decline in older people. ACCORD-MIND, an ongoing substudy of the NIH-supported Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, is currently testing whether the rate of cognitive decline and structural brain change in people with diabetes treated with standard care guidelines is different than in people with diabetes who adhere to more rigorous treatment.

The translation of findings from basic research into new interventions to prevent or treat disease is another major focus of the NIH. In recent years, new insights into amyloid, tau, and inflammatory and oxidative stressors have enabled us, for the first time, to create highly specific treatments for AD that are targeted at particular molecules and processes in the brain; Dr. Hodes describes in his statement some of the newer targets that have been identified through this research. Some of those compounds have significant proprietary potential and are currently undergoing pre-clinical and clinical study by pharmaceutical and biotech companies. Others are being tested in NIH-supported clinical trials.

Finally, NIH supports the national infrastructure that makes basic and clinical research possible. For example, researchers at NIH-funded Alzheimer's Disease Centers (ADCs) are working to translate research advances into improved diagnosis and care for Alzheimer's disease patients while at the same time focusing on the program's long-term goal—finding a way to cure and possibly prevent AD. Areas of investigation range from the basic mechanisms of AD to managing the symptoms and helping families cope with the effects of the disease. ADC staff conduct basic, clinical, and behavioral research and train scientists and health care providers who are new to AD research.

The Alzheimer's Disease Cooperative Study (ADCS) is a major Alzheimer's disease clinical trials effort. Now in its 16th year, the goal of the ADCS is to plan and conduct clinical trials on promising compounds designed to improve cognitive functioning, ameliorate behavioral disturbances, slow the rate of decline, or delay the onset of Alzheimer's disease. In general, the ADCS tests drugs that are not typically studied by large pharmaceutical companies, such as drugs that are off patent or were patented and marketed for another use but might be useful for treatment of AD, or novel compounds from individual investigators or from small companies without adequate resources for clinical trials. ADCS studies thus fill an important resource gap between the identification of a potentially useful compound and its eventual adoption in clinical practice. October 2006, NIH announced a \$52 million award to the ADCS over the next 6 years to conduct several new clinical trials. Dr. Hodes describes some of these upcoming clinical trials in his statement.

An exciting trans-NIH initiative that will facilitate research into AD and other neurological disorders is the NIH Blueprint for Neuroscience Research. The Neuroscience Blueprint brings the 16 NIH Institutes, Centers, and Offices that support neuroscience research into a collaborative framework to coordinate their ongoing efforts and to plan new cross-cutting initiatives. By pooling resources and expertise, the Blueprint aims to accelerate neuroscience research and to reduce the burden of nervous system disorders. Working together, representatives from the partner Institutes, Centers, and Offices identify pervasive challenges in neuroscience and any technological barriers to solving them. This enables the Blueprint to support the development of new tools, training opportunities, and other resources to assist neuroscientists in both basic and clinical research. Each year from fiscal year 2007 to fiscal year 2009, the Blueprint will focus on one of three themes: Neurodegeneration, neurodevelopment, and neuroplasticity. Four funding announcements related to the neurodegeneration theme were released in fiscal year 2007. These initiatives support the identification of biomarkers for neurodegeneration, the development of new ways to deliver therapeutics to the nervous system, and two interdisciplinary training programs in neurodegeneration research.

<sup>3</sup>National Diabetes Statistics." National Institute of Diabetes and Digestive and Kidney Diseases, 2005. <http://diabetes.niddk.nih.gov/dm/pubs/statistics/index.htm>.

Finally, NIH conducts a number of research studies that support caregivers of AD patients. AD caregiving is highly stressful, emotionally and physically, and Dr. Hodes will tell you about some of the ways NIH works to develop and disseminate interventions to help the millions of Americans who care for a loved one with AD. To further explore the economic, social, and psychological costs of AD, the NIH supports studies such as the Health and Retirement Survey, the leading source of combined data on health and financial circumstances of Americans over age 50. Now in its 14th year, the HRS follows more than 20,000 people at 2-year intervals, and gathers important data that informs health care policy regarding AD and a number of other health conditions.

It is important to note that the NIH cannot and does not conduct its important work in a vacuum. We work closely with partners in academia, in the private sector, and elsewhere in the government to develop new diagnostic tools and methodologies, to conduct clinical trials, to disseminate the results of our research, and to implement new interventions and policies resulting from our research at the community level. For example, the AD Neuroimaging Initiative is a joint venture between NIH and a number of academic and industry partners. Another is the AD Cooperative Study, which I described earlier, is conducted in close collaboration with our partners at the University of California–San Diego and scores of clinical sites across the Nation. Compared to even a decade ago, the field of neuroscience is moving at an extraordinary pace. We know, however, breakthroughs cannot come quickly enough for the millions of Americans touched by Alzheimer's disease. I can report to you today that real progress is being made, and that we at NIH are committed to seeing that progress continues toward treatment, and ultimately prevention, of Alzheimer's disease.

This concludes my statement, and I will be happy to discuss these matters further with the subcommittee.

Senator MIKULSKI. Thank you, Dr. Zerhouni. We would now like to hear from Dr. Hodes, who heads up the National Institute of Aging and has been a long time advocate of what we need to do on the concept of both basic research and breakthrough and I think what we're looking for is, of course, stay the course but what are your ideas and recommendations here?

**STATEMENT OF RICHARD HODES, M.D., DIRECTOR, NATIONAL INSTITUTE OF AGING, NATIONAL INSTITUTES OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, BETHESDA, MD**

Dr. HODES. Well, thank you, Senator Mikulski.

Senator MIKULSKI. We kind of have this sense of urgency and to move the kind of breakthrough thinking along.

Dr. HODES. Yes, you in your opening comments and Dr. Zerhouni as well, have stressed the burden at present of Alzheimer's disease—emotional, and financial to the public health system as well as the urgency imposed by the demography and the increased number of individuals who will age, hopefully successfully, and be at risk.

As Dr. Zerhouni has stressed, the new paradigm of trying to understand diseases from their earliest beginnings so one can intervene at an early stage rather than treat at a later stage, perhaps have their most impressive prototype where it's been showed that years and indeed, decades before the disease can be identified clinically, there are changes in the brain that can be detected.

For this reason, the research supported by NIH and I should in collaboration with the other agencies here, have focused broadly to find risk factors for disease, which can be translated into opportunities for intervention. These clues have come from a number of directions. They come from basic science, where genetics has been most informative, identifying the genes which can pre-dispose or

cause Alzheimer's and providing, therefore, targets that have been translated, in fact, in clinical trials, to a point to which we could intervene in that process.

As recently as a few months ago, yet a new Alzheimer's risk factor gene, SORL1, was described and this impetus has continued in now a formalized genetics initiative, which is typical of the directions researchers are taking now in that. This initiative, for example, is collecting 1,000 families with multiple members with Alzheimer's disease.

This goes far beyond the work that any single investigator or academic institution can do. It's a coalition of investigators that are generating these data, who can be made available to the whole international and national community of investigators and this, I think, in terms of breakthroughs and trends, is one of the advances we're making to move from privatized research to research that becomes maximally leveraged in populations of scientists. In addition, we're learning about risk factors that accompany epidemiologic studies. As Dr. Zerhouni alluded to, the risk factors for cardiovascular disease such as hypertension earlier in life, diabetes, increased homocysteine levels are all associated as risk factors and these, too have led to translation to clinical trials, intervening in each of these variables in an attempt to determine whether the causal link can be made and indeed, intervention to these variables will have an impact on preventing or slowing progression of Alzheimer's disease.

It's stressed, appropriately, the importance in all of these studies for identifying the disease early so that one can make early diagnosis and can track progression. Most importantly perhaps, is that one can identify more accurately and more rapidly the effect, positive or negative of any of the interventions and trial and among the markers being used to do this, as Dr. Zerhouni alluded to, are markers that come from nerve imaging techniques. Quite striking in the last years, we've seen the development, previously unimaginable, of dyes that can actually identify both plaques and tangles, the lesions in the brain of Alzheimer's patients in the living patient and the hope is that by tracking the progress of this and the ability of drugs, vaccines, other interventions to arrest this progression, we can have far more cost efficient and more rapid answers to clinical trials that are underway.

An initiative called the Alzheimer's Disease Neuro Imaging Initiative is really a landmark of its kind. I think it stresses the kind of innovation in terms of collaboration that is required. This is an initiative that is looking at a number of older American men and women who either have no disease, have mild cognitive impairment or have Alzheimer's disease and it's over time, following them for their clinical state, their psychological testing results, their new imaging results as well as the results of tests of cerebral spinal fluid and serum and other evidence of biological markers, including genetics.

What's noteworthy about this initiative is that it will create a panel of materials that will be used, once again, by all qualified scientists and equally remarkable, is the nature of the partnership involved. This initiative was carried out by NIA in collaboration with other institutes at NIH with very close association with the FDA,

recognizing that the progress in this initiative has to feed into the ability of the FDA to access the efficacy of drugs. It involves as well, partnership with more than 20 pharmaceutical companies and the bio-technology companies who are contributing not only their expertise but funding, recognizing that the outcomes of studies such as this will serve all of the public and private sectors with a common goal of identifying ways to intervene successfully in Alzheimer's disease.

So long as we are progressing in this direction, so long as we are faced with Alzheimer's disease to be cared for, we also need to be cognizant of the burden on caregivers. As Dr. Zerhouni noted and was noted in the introductory comments as well, the burden on those taking care of loved ones, family members, people with Alzheimer's disease is itself, huge. It has an impact not only financially but on the health and mental State of those taking care of individuals with Alzheimer's disease. We're happy to identify the results of the clinical trial, which was targeted, in this case, at Caregivers, an intervention that can improve the State of caregivers. The study was successful, in fact, identifying the kind of intervention that can reduce stress and improve quality of life, both for those afflicted with the disease and those who care for them.

So long as we are progressing in the direction of preventing disease and treating those already afflicted, as well as easing the burden of those providing important care for them. We will continue in our collaboration across agencies, across sectors to this end.

Finally, in all of this, we maintain the sense of responsibility that was enacted in the congressional establishment of a facility through NIA in leadership to provide information to the public, not only a clearing house for publications but a multimedia effort to keep the public informed of progress of the state of medical knowledge, of needs to recruit people and their interests into clinical studies in support of our overall enterprise.

I thank you again for this opportunity to speak with you and to continue our long and I hope, soon to be, successful partnership in attacking Alzheimer's disease.

[The prepared statement of Dr. Hodes follows:]

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

Senator Mikulski and members of the committee, thank you for inviting me to appear before you today to discuss Alzheimer's disease (AD), an issue of interest and concern to us all. I am Dr. Richard Hodes, Director of the National Institute on Aging (NIA), the lead Federal agency for Alzheimer's disease research. NIA is one of the 27 Institutes and Centers that comprise the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services (HHS). I am delighted to be here today to tell you about the progress we are making toward understanding, treating, and preventing AD.

Dr. Zerhouni's statement cites the number of Americans whose lives are deeply affected by AD. The numbers are indeed stark and are growing with the aging population. But there is another part of the Alzheimer's story that we can tell; although AD remains a major public health issue for the United States, we have made, and are continuing to make, dramatic gains in our ability to understand, diagnose, and treat the disease. This progress offers us hope of reversing the current trends so that the risk of AD can be reduced for millions of older adults and their families.

As the lead Federal agency supporting AD-related research, the National Institute on Aging conducts and supports a portfolio of research that encompasses topics across the spectrum of AD-related inquiry. Active areas of research include basic brain biology, pre-clinical and clinical research on potential interventions, and population-based assessment of the epidemiology, economic, social and psychological

costs of dementia to the family and society. Our research agenda is broad, and we pursue that agenda in partnership with scientists across the Nation. In October 2006, NIA convened a major scientific planning meeting to discuss future directions for Alzheimer's disease research at NIH, with particular attention to research issues that need to be addressed in order to improve diagnosis and treatment of AD. This meeting brought together internationally-recognized experts in the field, and the results will influence the direction of the research we support over the next few years.

#### RISK FACTORS AND EARLY DIAGNOSIS

Identification of risk factors for AD may enable us to develop interventions to delay or even prevent its onset, and NIA-supported researchers are making important advances in several key areas.

*Genetics.* Discovery of risk factor genes will help illuminate the underlying disease processes of AD, open up novel areas of research, and identify new targets for drug therapy. Researchers recently determined that variations in a gene known as SORL1 may be a risk factor for the development of late-onset AD. While this discovery provides a new genetic clue about the late-onset forms of AD, further research is needed to determine the role of SORL1 in AD pathogenesis.

Research is continuing in this important area through the AD Genetics Initiative, which to date has recruited nearly 1,000 families to establish a resource for studies of the genetics of late-onset AD. In addition, NIA has established a national genetics data repository to facilitate access by qualified investigators to genotypic data for the study of the genetics of late-onset AD. Investigators have already begun submitting data to this repository and requesting additional data for genetic studies. We also expect genome-wide association studies, mentioned by Dr. Zerhouni, to provide important information about AD's genetic underpinnings.

*Health Conditions Affecting Risk.* Population studies suggest that conditions affecting cardiovascular and cerebrovascular systems may be associated with higher risk for dementia or that the presence of vascular disease may influence the progression of AD. One recent report indicated that AD dementia may be exacerbated by other cerebrovascular problems such as small strokes, while another linked untreated high blood pressure in mid-life with increased risk of dementia in later life. The possible association of diabetes, insulin resistance, and AD is garnering increased attention as well. Recent findings from at least four long-term studies link diabetes with decline in cognitive function. The NIA is currently supporting three clinical trials to examine directly whether diabetes-related interventions might be effective in preventing or delaying cognitive decline or development of AD or AD progression.

*Early Diagnosis: Advances in Neuroimaging.* Research suggests that the earliest AD pathology begins to develop in the brain long before clinical symptoms yield a diagnosis. Therefore, it is critical that we find a way to detect signs of the disease at the earliest point possible so that we can test interventions and, ultimately, treat the disease as early as we can. Toward that end, the NIA has embarked on ambitious efforts to find new ways to measure AD changes in the brain or in other systems including blood and cerebrospinal fluid. These programs are already yielding results. Improvements in brain imaging, coupled with the development of more sensitive cognitive tests, are enabling us to diagnose AD in the research setting with greater precision than ever before. The discovery of compounds such as Pittsburgh Compound B and, more recently, FDDNP that enable the visualization of AD's characteristic amyloid plaques and neurofibrillary tangles in the living brain—an impossibility only a few years ago—will not only enable scientists to diagnose AD earlier, but may also help researchers and clinicians develop new treatments and monitor their effectiveness, as well as reduce the time and cost of clinical trials.

Research in this area has been intense and productive. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is currently the major venue for facilitating neuroimaging research relevant to AD. Early results from ADNI show that, in addition to aiding early diagnosis, researchers may be able to reduce the time and expense associated with clinical trials by improving methods and developing uniform standards for imaging and biomarker analysis. For example, one ADNI study found that a standard physical model can be used successfully to monitor performance of MRI scanners at many different clinical sites; this will help ensure accuracy of the MRI images produced from ADNI volunteers. Investigators on another ADNI study compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and AD, and they found that scans correlated with symptoms of each condition and that images from different clinical sites were consistent across sites, suggesting the validity of PET scans for

monitoring the effectiveness of therapies in future clinical trials. This study will continue to provide a foundation for future efforts to identify biomarkers.

An important achievement of ADNI is the creation of a publicly accessible database available to qualified researchers worldwide. The database contains thousands of MRI and PET scan brain images and clinical data and will include biomarker data obtained through blood and cerebrospinal fluid analyses. ADNI includes samples and brain scans from 200 people with Alzheimer's, 400 people with mild cognitive impairment and 200 cognitively healthy people. All volunteers are between ages 55 and 90. Confidentiality of the participants is rigorously protected. To date, over 200 researchers have signed up for database access.

#### TRANSLATIONAL RESEARCH: MOVING BASIC FINDINGS INTO CLINICAL PRACTICE

New findings about AD's characteristic pathology are leading to insights that may eventually inform treatment strategies. Amyloid and amyloid-producing enzymes, tau, oxidative damage to the brain, and mediators of inflammation are all under consideration as treatment targets, and investigators are also looking at new ways to protect brain cells as they age and to validate ways to enhance memory and improve cognition with age. For example, recent discoveries have provided support for the validity of beta-secretase (BACE1) as a therapeutic target. BACE1 comes from a family of enzymes known as secretases that cut, or cleave, the amyloid precursor protein (APP) in the brain; working in concert with a partner enzyme, gamma secretase, BACE1 is responsible for the formation of amyloid in AD. In a recent study, NIA-supported investigators were able to silence the production of BACE1 in mice that were genetically engineered to develop AD-like pathology. They found that reducing BACE1 levels slowed the production of amyloid plaques and diminished the damage to neurons and synapses in the brains of the mice receiving the treatment. Notably, the mice in which BACE1 production was halted had less difficulty learning a new task than control mice. NIA's Translational Research Initiative aims to speed research across the continuum of intervention development, from drug discovery to full-scale clinical trials. Components of the effort include grant solicitations to stimulate the discovery, development, and preclinical testing in cellular, tissue, and animal models of novel compounds for the prevention and treatment of the cognitive impairment and behavioral symptoms associated with AD. The ultimate goal of this initiative is to facilitate submission of investigational new drug applications to the Food and Drug Administration so that more clinical trials testing promising therapies can be started. NIA also supports toxicology services for investigators or small companies that have a potentially viable candidate drug for AD treatment but lack the resources to begin the formal drug testing process.

In addition, NIA is currently supporting approximately 25 AD-related clinical trials. These include studies of:

- Physical exercise, which epidemiological studies suggest may have a specific influence on aspects of cognitive decline. Small clinical trials are currently testing the effects of exercise on cognitive decline and brain function, both in older adults with normal cognition and in persons with mild cognitive impairment with memory decline.
- Statins, which lower cholesterol levels, to determine whether these drugs can modify disease progression in people with mild AD.
- Valproate, which is used to treat epilepsy and some psychiatric disorders, to determine whether this drug can slow decline or help delay the agitation and psychosis that often accompany AD.

Dr. Zerhouni mentioned in his statement that the Alzheimer's Disease Cooperative Study will implement several new clinical trials over the next 6 years. One, a study to determine whether docosahexaenoic acid (DHA), an omega-3 fatty acid, will slow cognitive decline in AD, has begun recruitment. Other trials planned by the ADCS include:

- *Intravenous Immunoglobulin (IVIg)*. IVIg, a form of passive immunization, contains naturally-occurring antibodies against beta-amyloid, and preliminary studies have shown that IVIg promoted clearance of beta-amyloid from cerebrospinal fluid, as well as improved cognition in AD. The new ADCS trial will demonstrate whether IVIg is useful clinically for treating AD.
- *Lithium*. Lithium, commonly used to treat bipolar disorder, has been shown in animal studies to block abnormal changes in tau and to regulate beta-amyloid. ADCS investigators will undertake a pilot biomarker study to see whether the drug can lower tau and beta-amyloid levels in cerebrospinal fluid and be safely tolerated in older AD patients.



We have also been encouraged by several recent studies related to AD prevention and the maintenance of cognitive health in old age. In 2006, results from the Active Cognitive Training for Independent and Vital Elderly (ACTIVE) study demonstrated for the first time in a randomized, controlled trial that certain mental exercises can offset some of the expected decline in older adults' thinking skills and show promise for maintaining cognitive abilities needed to do everyday tasks such as shopping, making meals, and handling finances. Some of the benefits of the short-term training tested in this study lasted for as long as 5 years. Investigators also recently announced the discovery of the first agent shown to delay the clinical diagnosis of Alzheimer's in people with amnesic mild cognitive impairment (MCI), an MCI subtype strongly correlated with the later development of AD. The investigators found that individuals who took the drug donepezil (Aricept®) were at reduced risk of progressing to a diagnosis of Alzheimer's disease during the first year of the trial. In addition, there was benefit over a longer 2-year period that was limited to those individuals positive for the APOE-4 gene allele, which confers a strong predisposition to the development of late-onset AD. Although donepezil's effects were limited, the results are nonetheless encouraging. And although too little is known about donepezil's long-term effects to support a recommendation for its routine use to forestall the diagnosis of AD in people with mild cognitive impairment, these findings do suggest that chemoprevention of AD is possible and support our hope that future clinical studies will lead to more significant progress.

#### CAREGIVER SUPPORT

Most Americans with AD today are cared for outside institutional settings by an adult child or in-law, a spouse, another relative, or a friend. Research has shown that the stress of caring for a loved one with AD can have a profoundly negative impact on health and well-being. NIA-supported investigators have found that a personalized intervention consisting of home visits, structured telephone support sessions, and telephone "check-ins" can significantly improve the quality of life for AD caregivers. The study, Resources for Enhancing Alzheimer's Caregiver Health II (REACH II), was funded by NIA and NIH's National Institute of Nursing Research and is the first randomized, controlled trial to look at the effectiveness of an AD caregiver support intervention for ethnically diverse populations. Follow up studies are needed to examine how the intervention might be used through existing community networks of health and aging services.

#### OUTREACH TO THE PUBLIC

Since its inception, NIA has provided the public and health professionals with information about Alzheimer's disease and age-related cognitive change. Twenty-one years ago, Congress established NIA's Alzheimer's Disease Education and Referral (ADEAR) Center to "compile, archive, and disseminate information concerning research, demonstration, evaluation, and training programs and projects concerning AD and related dementias." Today, that mission is being accomplished through a wide variety of materials, resources, and activities for the general public, health professionals, and people with Alzheimer's disease and their families.

ADEAR's programs are active and comprehensive. For example, the number of print materials distributed went from about 377,000 in 2005 to more than 645,000 in 2006. As more and more Americans turn to the Internet for health information, the Center has experienced a striking increase in the number of web visits, up from 1.9 million in 2005 to 2.9 million in 2006. Further, the NIA and ADEAR Center staff, based in Silver Spring, MD, proactively invite the public to use its resources. In 2006, the ADEAR Center distributed 43 e-mail alerts to various subscriber lists, letting subscribers know about research news, new publications, and other updates.

The effectiveness in developing information products and strategies is based in part on the NIA's collaborations with agencies, academic institutions, and other organizations. The success of new easy-to-read publications involved collaboration between the ADEAR Center and the NIA's network of Alzheimer's Disease Centers. A new project aims to respond to a lack of materials for the newly emerging audience of people with early-stage AD and their families. In this effort, ADEAR is working with the Northwestern University School of Medicine's Alzheimer's Research Center to produce a publication *What Happens Next: A Booklet About Being Diagnosed with AD and Related Disorders*. The booklet is actually written by early-stage patients to provide those newly diagnosed with resources and with comfort and support from others who have walked the same path.

## CONCLUSION

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

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

Senator MIKULSKI. Well, we'll come back to you but now we want to hear from Dr. Joy Gerberding, our Director of the Centers for Disease Control and Prevention. I want to acknowledge the fact that our colleague from Georgia, Senator Isakson, has joined us. He has a long time, both personal and professional interest in this issue and his advocacy is really most welcome, his prudent advocacy on this committee.

Dr. Gerberding, we're anxious to hear from you. You've been at CDC now for 10 years and you were there as the Deputy Director for Infectious Disease, dealing with things like Anthrax, but now tell us how you're going to deal with another A word. But we really count on CDC for this kind of news that you can use.

**STATEMENT OF JULIE GERBERDING, M.D., DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ATLANTA, GA**

Dr. GERBERDING. Thank you very much and CDC is very privileged to be here and to have a chance to speak to our Senators and we thank Senator Isakson for coming. We really appreciate the support the Georgia delegation brings us as well.

You know, when you think about Americans, all of us are aging and when you think about what people really want when they age, they want to be able to work productively and then retire and enjoy some leisure time, do the things that they missed doing when they were working. They want to enjoy their loved ones and their friends. They want to be able to contribute to their communities and I think most of all, they want to be independent.

But what do Americans fear? Well, about 30 percent of them fear loss of physical functioning but about two-thirds of them are afraid that they are going to lose their mental capacity and sadly, for about 4.5 million people today, the worst has happened. They have developed Alzheimer's disease and they really truly are suffering the most severe form of cognitive impairment.

What we need to focus on is not just the 4.5 million people who are robbed of their independence. I like to think of this as the great brain robbery because it truly does take away people's ability to do the things that they value most in life. But we also need to think about their caregivers who are profoundly impacted, about 7 out of every 10 people with Alzheimer's disease live at home and we need to remember that there are things that we can do today to help ameliorate this burden on individuals, their caregivers and our society.

I want to thank Congress for supporting CDC to bring together the collaboration that helped create this roadmap, the Healthy Brain Initiative. This represents the input of many people at this table but I would also like to acknowledge a quartet of people who are not here today and that would be Josefina Carbonell from the

Aging Group at HHS, Betty Duke from HRSA, Carolyn Clancy from AARC and Leslie Norwalk from CMS, in four other agencies and those women would have big signs, too, if they were here at the table because they've made some tremendous contributions to this issue and I think across HHS, we recognize that Federal leadership really is important but we also need to work with the Alzheimer's Association and others to create and enact this kind of roadmap.

There are two tragedies. One is the tragedy of not knowing what to do and you've heard, I think, some of the exciting research that our collaborators at NIH are working on. You'll hear from Dr. von Eschenbach about what the FDA can do. So there is the tragedy of not knowing and I think we are investing in learning more and being able to do more.

But there is also the current and ongoing tragedy of not doing what we know and I think that's what this roadmap is all about, that there are things that we can and should be doing now. We need to make a commitment. We need to inspire people to share that commitment. We need to build the partnerships and I think most importantly, we need to get the word out that prevention is possible.

We already know that vascular disease is a major risk factor for the development of cognitive dysfunction. There are some hints that physical activity may be important, some early hints that maybe diabetes, exposure to passive tobacco and in fact, if you look at the health promotion agenda for health aging, many of the things that we should already be recommending to our seniors are the same constellation of things that may end up having a very important role in protecting cognitive health as well.

So we need to reach out and help seniors achieve the best possible health span and I think importantly, that includes a much greater emphasis on cognitive health.

I'd just like to end with one little vignette of hope. There is a wonderful program that was supported in Seattle, in part through one of CDC's Prevention Research Centers, whom were using some volunteer physical trainers in the community facility for seniors. They initiated an exercise program and what they were able to show with a very small investment that the participating seniors had better balance. They were overall better fit. They were happier. They reported better mental health and most importantly, their program was associated with a 23 percent reduction in group health expenses. So a very small investment, a very significant improvement in health, even for some very senior people and I think it means that we have to never give up. There is always room for health promotion and always room for prevention at every age. Thank you.

[The prepared statement of Dr. Gerberding follows:]

PREPARE STATEMENT OF JULIE L. GERBERDING, M.D., M.P.H.

Good afternoon, Madam Chair, Senator Burr, and distinguished members of the subcommittee. I am Dr. Julie Louise Gerberding, Director of the Centers for Disease Control and Prevention (CDC) within the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to talk with you about the importance of safeguarding the cognitive health of our Nation's aging population. We, at CDC, share your commitment to doing all we can to address the im-

pact of cognitive impairment, which includes Alzheimer's disease and other forms of dementia. We recognize the impact it has on individuals, families and society. As you know, the numbers of people with Alzheimer's disease and other dementias are expected to increase substantially over the coming decades unless these conditions can be prevented.

Thanks to funding provided by Congress, CDC has established an Alzheimer's disease segment within the Healthy Aging Program, which we refer to as the Healthy Brain Initiative. We have reached out to collaborate with the National Institutes of Health and the Administration on Aging, and we have formed a strong partnership with the Alzheimer's Association. A critical outcome from this partnership is the release last month of The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health. I will tell you more about this Road Map shortly.

With the increase in life expectancy over the past century, most older adults look forward to having a long life. However, one of the greatest worries about living to age 75 and beyond revolves around memory loss.<sup>1</sup> The public's concerns about losing their mental capacities as they age are also reflected in a recent national poll conducted by Research!America.<sup>2</sup> When asked to think about aging and losing either physical or mental capacity, 62 percent of respondents indicated they feared losing their mental capacity as compared to 29 percent who feared losing their physical ability. These fears of declining mental capacity and Alzheimer's disease have led to increased attention by the public, the media and public health professionals. Despite all the attention, the public and even many health care providers still know very little about the specific factors that increase a person's risk of experiencing cognitive decline.

CDC recognizes the importance of considering the entire person and not focusing on physical health alone. One of our four key Health Protection Goals is to ensure that all people, and especially those at greater risk of health disparities, will achieve their optimal lifespan with the best possible quality of health in every stage of life. This holistic approach takes into account mental and cognitive health as well as physical health.

I would like to briefly define cognitive decline and talk about how the aging of our population is expected to affect the national burden posed by cognitive impairment. I will then talk about the role of public health, including a brief highlight of our achievements to date and where we expect to take these activities in the future.

#### DEFINITION OF COGNITIVE DECLINE

Much like physical health, cognition can be viewed along a continuum—from optimal functioning to mild cognitive impairment to severe dementia. While there are certain cognitive changes that occur with age—what we call normal age-related changes—such as a slower pace of learning and the need for new information to be repeated, cognitive decline is not a normal part of aging. It is more serious. Cognitive decline can range from mild cognitive impairment to severe dementia, but these two conditions are not necessarily manifestations of the same condition. Many people never develop any serious decline in their cognitive performance and those who develop mild cognitive problems do not necessarily develop dementia or Alzheimer's disease.

#### IMPLICATIONS OF A RAPIDLY AGING POPULATION

The aging of the U.S. population is expected to place demands on our public health system, medical services and social services. The growth in the number and proportion of older adults is unprecedented in the history of the United States. A hundred years ago, only 3 million people in this country were aged 65 or older. Today, more than 36 million Americans are in this group, and that number is expected to grow during the next 25 years to more than 70 million as the baby boomers age. Public health's prevention efforts and improved medical care have contributed to a significant increase in life expectancy in the United States during the past century. However, this success has been accompanied by a major shift in the leading causes of death for all age groups, including older adults, from infectious diseases to chronic and degenerative illnesses. Alzheimer's disease is one of the top 10 leading causes of death. We know Alzheimer's disease and cognitive impairment

<sup>1</sup>American perceptions of aging in the 21st century. Washington, DC.: The National Council on Aging, Inc., 2002.

<sup>2</sup>Research!America. America speaks. Poll data summary, volume 7. Alexandria, VA: Research!America; 2006. <http://www.researchamerica.org/polldata/2006/mentalhealth9-06.pdf> (slide 6).

have economic costs and impacts on individuals and their families. Recent scientific advances have highlighted potential risks associated with cognitive decline and may ultimately pave the way for preventing cognitive decline.

Alzheimer's disease and cognitive impairment can cause years of disability, and loss of function and independence. We must focus on preventing or delaying disability and the loss of function. Although the risk for disease and disability clearly increases with advancing age, poor health is not an inevitable consequence of aging. It is a priority for all of us that we work to find ways to prevent or postpone functional loss including losses to physical, mental and cognitive health.

#### BURDEN OF COGNITIVE DECLINE

In the United States, the burden of cognitive impairment has been expressed mainly in terms of prevalence, incidence, and mortality for dementia generally or for Alzheimer's disease in particular. An estimated 4.5 million people currently have Alzheimer's disease, and census population projections indicate that by 2050, as many as 16 million individuals will have the disease. More recently, prevalence statistics for mild cognitive impairment have become available. Mild cognitive impairment refers to a level of impairment that is more serious than normal age-related changes, but it is not as severe as Alzheimer's disease or other forms of dementia. Studies from the United States and Canada have suggested that mild cognitive impairment may be a problem for 16–25 percent of older adults aged 65 years and older.

#### SOCIETAL AND ECONOMIC IMPACT

Alzheimer's disease and other dementias place a costly burden on the Nation's health care system. Individuals with Alzheimer's disease make up less than 13 percent of the Medicare population, yet they account for 34 percent of Medicare spending (approximately \$91 billion in 2005). In 2000, Medicare spending for persons with Alzheimer's disease and other dementias was nearly three times as much, on average, as spending for individuals without these conditions (Urban Institute, unpublished tabulations from the 2000 Medicare Current Beneficiary Survey and Medicare Claims, 2005; published by the Alzheimer's Association, Alzheimer's Disease Facts and Figures, 2007).

Cognitive decline can have profound implications for a person's health and quality of life. It affects a person's ability to use words, identify objects, make decisions, and communicate with loved ones. Gradually, people experiencing severe cognitive decline may be unable to care for themselves or to engage in necessary activities of daily living or instrumental activities of daily living, such as preparing meals or managing their finances. Cognitive decline may also limit one's ability to effectively manage medications and existing medical conditions. Adverse changes in cognitive abilities can make an individual more vulnerable to malnutrition, improper use of medications, injuries, and even abuse and other crimes.

The adverse effects of cognitive decline go well beyond those suffering from it. Seven out of every ten people with Alzheimer's disease live at home. Caregivers often find the task of caring for a person with Alzheimer's disease to be physically exhausting and emotionally challenging. The demands on caregivers adversely affect their lives and eventually impact our economy when caregivers must take time off from work, work part-time instead of full-time, take less demanding jobs, opt for early retirement, or stop working altogether. Because of these adjustments, Alzheimer's disease costs American businesses billions of dollars each year—more than \$36 billion in lost productivity (absenteeism, productivity losses, and worker replacement costs) plus nearly \$25 billion for the businesses' share of coverage for health and long-term care expenses (Koppel R. Alzheimer's disease: the costs to U.S. businesses in 2002. Chicago, IL: Alzheimer's Association; 2002.).

#### THE ROLE OF PUBLIC HEALTH

Public health's role in physical health is well defined. Thanks to decades of multidisciplinary research, prevention efforts are now applied to a variety of chronic conditions and their associated risk factors. In the area of cognitive health, however, we have only recently begun to delineate public health's roles and responsibilities.

Alzheimer's disease and other dementias are costly and debilitating, and we anticipate the incidence of Alzheimer's disease and other dementias will increase markedly as our population ages. Recent scientific findings by the National Institutes of Health focus on factors such as high blood pressure, diabetes and physical inactivity associated with cognitive decline. According to the Cognitive and Emotional Health Project report, a large number of lifestyle and health behaviors may

alter the risk for maintenance of cognitive and emotional health.<sup>3</sup> However, the report cautions that it is not yet possible to develop individual prescriptions.

Public health has an opportunity to build upon existing knowledge, anticipated future breakthroughs, and the public's desire for information. By embracing cognitive health as a priority issue, the public health community with CDC's leadership can be mobilized to study, identify, implement, and monitor effective interventions that preserve this key component of health and well-being, and help to maintain independence and quality of life.

#### COGNITIVE HEALTH: AN EMERGING PRIORITY AT CDC

CDC recognizes the vital role that physical, mental and cognitive health play in shaping our overall well-being. We are committed to ensuring that all people, especially those at risk for health disparities, enjoy good health and the best possible quality of life at every stage of life. For older adults, a primary goal is to ensure that the years gained through increased life expectancy are healthy years and to prevent or delay illness and functional decline. It might be said that our goal is to help ensure Americans live a vibrant and productive life throughout their aging years.

CDC takes a multi-faceted approach to improving cognitive health. Some of the outcomes CDC has either achieved or is working to advance include the following:

- Last month we released *The Healthy Brain Initiative: A National Public Health Road Map to Maintaining Cognitive Health* ([www.cdc.gov/aging/roadmap](http://www.cdc.gov/aging/roadmap)). This call to action proposes priority actions to move cognitive health into the national public health arena. The Road Map is a major accomplishment. Under shared leadership of the CDC and the Alzheimer's Association, and in close collaboration with the National Institutes of Health, the Administration on Aging and others, we embarked on an intensive process to develop the *Road Map*. Several cross-cutting areas of focus are recommended drawing on the proven expertise and capacities of the public health community. These include communicating the current state of science about cognitive health to Americans; developing tracking measures to better understand the public health burden of cognitive impairment; and delineating the potential value of public health strategies known to be effective for other health issues, such as physical activity, in maintaining cognitive health and preventing cognitive decline.

- CDC is bringing public health practice and research communities together to move them forward on getting out current scientific information about cognitive health. CDC is funding the Healthy Aging Research Network, within its larger Prevention Research Centers Program (PRC-HAN), to increase our understanding of the public's, including caregivers and health care providers, needs and perceptions about cognitive health. Assessing the public's needs and how they think and talk about this issue is an important part in addressing cognitive health.

CDC is excited to be at the forefront of national efforts, working in collaboration with Federal and private sector partners, to advance cognitive health. Cognitive health is a cross-cutting issue that touches upon areas such as vascular risk factors, physical activity, social engagement, and caregiving. It fits within CDC's healthy aging agenda and older adult health goal to promote health at every stage of life. It is aligned with CDC's commitment to increase the number of older adults who live longer, high-quality, productive, and independent lives. Our involvement with the Healthy Brain Initiative also is aligned with CDC's strategy to create and disseminate the knowledge and innovations people need to protect their health now and in the future.

CDC is known for monitoring changes in health status, translating research into practice and providing high-quality health information. Maintaining cognitive health and preventing cognitive decline is a cross-cutting issue. CDC's activities to prevent cognitive decline already touch on several promising areas, such as physical activity, and managing diabetes and cardiovascular risk factors. However, our work also extends to new areas, such as the benefits of social engagement and caregiving concerns. Working within the framework set out by the Road Map, CDC has identified several national public health efforts we can best advance and support to safeguard Americans' cognitive health. We hope to build upon our existing activities with the Alzheimer's Association and other partners to put critical public health elements in place to promote cognitive health and prevent cognitive decline. As the science evolves, we hope to develop community-based public health interventions designed

<sup>3</sup>Hendrie HC, Albert MS, Butters MS, Gao S, Knopman DS, Launer LJ, et al. The NIH cognitive and emotional health project: report of the critical evaluation study committee. *Alzheimer's & Dementia* 2006;2:12–32.

to help Americans maintain their cognitive health. And, as we proceed on this journey together, we look forward to collaborating with our colleagues across the Department of Health and Human Services to inform the Nation's public health infrastructure about the science undergirding our knowledge about cognitive health and promising interventions.

#### CLOSING SUMMARY

Thank you for the opportunity to speak on the issue of cognitive health and the benefits of addressing cognitive health within the public health arena. No less than cardiovascular disease, cancer or diabetes, addressing cognitive impairment should be a critical public health priority and deserves committed national public health action. Promising research findings coupled with public health action in the areas of epidemiology, surveillance and evidence-based interventions can translate to a difference in our understanding of cognitive decline, and our ability to address this issue in a positive way for the benefit of all Americans. We at CDC appreciate your continued commitment to efforts related to Alzheimer's disease and other dementias, and we look forward to working with you and our national partners in ensuring that cognitive health is addressed in an aggressive manner commensurate with the fundamental role that it plays in our overall health and quality of life. I would be happy to answer any questions you might have.

Senator MIKULSKI. Dr. von Eschenbach, you've come to us from FDA that has the job of standing sentry over our food supply and our drugs to go into clinical practice and our medical and biomedical products and devices. You come with an incredible background and you were at NIH yourself, heading the National Cancer Institute. And now, of course, you come with a background in oncology. We'd like to hear, then, from you, how you see FDA's role in dealing with the epidemic, at the same time having the mandate. We ask you to do two things. We ask you to move things as quickly as possible into clinical practice but at the same time, including this committee, has been very demanding in terms of the safety issues as well as efficacy.

So tell us how you see we can deal with the epidemic, the new thinking, how you work with the private sector.

#### **STATEMENT OF ANDREW C. VON ESCHENBACH, M.D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ROCKVILLE, MD**

Dr. VON ESCHENBACH. Thank you very much, Senator and thank you for framing it so well, but let me first thank you and Senator Burr and Senator Isakson and other members of the committee for convening this really extremely important discussion. I'm joined today from the FDA by Dr. Bob Temple and Susan Winkler, Rph, Esq., but it's a particular honor for me to appear on the same panel with my colleagues from CDC and from NIH.

Dr. Zerhouni, Dr. Gerberding and I have been working hard to make our relationships productive and integrated so this is not simply a ceremonial gathering. This is evidence of a commitment on our part for close collaboration to be able to accomplish progress in the diseases like Alzheimer's.

Every promising new drug, every diagnostic test, every imaging technology that's designed to help Alzheimer's patients must come through the FDA before it reaches those people. So our responsibility is to help make sure that those products are available and to determine that they are safe and effective. We are doing this im-

mersed in the 21st century revolution in science and technology that I personally describe as the molecular metamorphoses.

It's particularly important because it now provides us, as you heard from Dr. Hodes, unique opportunities to understand diseases like Alzheimer's at the genetic, molecular and cellular level and therefore be able to make possible extraordinary new opportunities, new interventions, new solutions to prevent, treat and slow the progression of this disease.

In that context, FDA—the FDA of the 21st century must be a bridge and not a barrier to that new future. From the very discovery of promising new therapies through their development and ultimately to its delivery to Alzheimer's patients, FDA is committed to be immersed in promoting and fulfilling our promise to the American people.

We must be actively engaged at every step along that continuum and we want to do that in a way to be an efficient and effective pathway so that we're free of speed bumps and potholes in our regulatory process. But as you pointed out, also be sure that we have strong guard rails on that pathway with guidances, regulations and standards that will also protect the American people.

Central to our efforts in this regard to modernize the FDA is the Critical Path Initiative, which is bringing the tools of modern science and technology to the regulatory journey that these medical products, these solutions must make from the earliest stages of development to their use in patients. We, among the Critical Path Initiatives, have many activities that are being carried out in partnership with NIH and others, particularly, for example, around the area of developing biomarkers that can be used to determine the impact of a drug on the amyloid plaque that is associated with Alzheimer's disease or to use new clinical trial designs that will not require 20 years for us to determine whether a new product can help prevent this dreaded disease.

We are, in a sense, attempting to try to open the floodgates of the development of products for Alzheimer's disease and we will continue to move this process forward in concert with and in collaboration not only with our partners but with the community. Over the past year, I've personally met with two prominent Alzheimer's disease patient advocacy organizations, the Alzheimer's Association and the organization, Accelerate New Treatments for Alzheimer's disease. I share their concerns around the urgency of FDA's ability to bring these new products to patients.

We are continuously, throughout FDA, remaining in contact with these organizations and particularly to be able to understand the opportunities that we must be addressing. We also are engaged with the academic industry and particularly seeing this as a problem in which we are all in this together: industry, government, caregivers and the scientific community.

I just want to highlight a few of the important initiatives that I think are tangible contributions to this overarching strategic perspective. During fiscal year 2006, our Division of Neurological Products and our Center for Drug Evaluation and Research held 18 formal meetings with industry and this doesn't include internal FDA meetings to discuss sponsors' investigational new drug applications. To this date, the Division has met with industry six times



in an effort to help facilitate their ability to develop and bring to the regulatory process, successful drugs for Alzheimer's disease.

We need to also be able to leverage progress that's being made in other neurologic diseases. For example, we are conducting a planning meeting to help determine the best designs for clinical trials for Parkinson's disease but we are doing that in a way in which we expect to extrapolate those results for our formal guidance that would be directed and applicable to trials, clinical trials, in Alzheimer's.

We're working to improve our internal processes, our standards, our processes for expediting review and we've established within the FDA, an inter-agency neurological working group so that we're focused across the agency on the critically emerging problems that we're discussing today. This group meets monthly, includes members from our Center for Biologics Evaluation and Research, our Center for Drug Evaluation and Research, our Center for Devices and Radiologic Health, along with the Office of the Commissioner, Office of Critical Path Programs, Office of Special Health Issues and Office of Science and Health Coordination. This is an effort to bring the full force of the FDA to bear on this critically important problem.

We're also attempting to contribute to the underlying understanding of this disease and the tools that we must apply so that within the FDA's National Center for Toxicological Research in Arkansas, we have two very specific Alzheimer's-related projects underway. One is to develop a non-invasive automated technology for assessing patients with Alzheimer's disease so that we may be able to provide reliable and objective measures to monitor the progression of the severity of the disease and the impact of these innovations on that progression. We see this as an invaluable tool that will spur academic research in the pharmaceutical and biotechnology industry in the development of these medical products.

We're also looking at a new histochemical test battery that will enable us, as regulators, to assess the efficacy and toxicity of potential drugs for Alzheimer's and this could help us be able to streamline and improve the development of these drugs to be able to bring them more reliably, more safely and sooner to patients that are threatened by this degenerative disease.

These are just a few examples of how we at the FDA want to be a bridge and not a barrier to providing hope and expectation for those with and those threatened by Alzheimer's disease for a new future, a future in which they will not fear the consequences of this terrible degenerative process.

[The prepared statement of Dr. von Eschenbach follows:]

PREPARED STATEMENT OF ANDREW C. VON ESCHENBACH, M.D.

#### INTRODUCTION

Madam Chairman and members of the subcommittee, I am Dr. Andrew C. von Eschenbach, Commissioner of Food and Drugs at the Food and Drug Administration (FDA or the Agency). I would like to applaud the subcommittee for holding this roundtable discussion to discuss Federal initiatives to address the cruelly debilitating condition known as Alzheimer's disease. FDA shares your commitment to vigorously addressing Alzheimer's disease, and shares your hope that safe and effective treatments for this condition will be approved in coming years. It is a pleasure to

be here today with my colleagues from the Department of Health and Human Services, Dr. Julie Gerberding, Dr. Elias Zerhouni, and Dr. Richard Hodes.

I very much appreciate the opportunity to join this discussion to explain FDA's role as it applies to new products being developed for treatment of Alzheimer's disease. Further, I will describe several initiatives FDA is undertaking to transform the Agency in an effort to meet the regulatory challenges arising from rapid advancements occurring in all areas of medical research including Alzheimer's disease, and several special initiatives underway at FDA that are directed toward Alzheimer's disease.

In the two recent hearings on Alzheimer's disease before this subcommittee you heard current statistics recently released by the Alzheimer's Association including that this disease now afflicts one in eight Americans over the age of 65 and some 47 percent of Americans over the age of 85. At the present rate, the estimated 4.5 million cases of Alzheimer's disease today can be expected to rise to around 16 million by 2050. With the aging of the baby boom generation over the next several decades, without safe and effective treatments and preventatives, a huge population of seniors stands to be robbed by this disease of the enjoyment of their later years. In addition to the burdens placed on patients and their families, insurance programs surely will face overwhelming demands on their services and resources.

There is cause for some cautious optimism. You also heard of exciting advancements in research on Alzheimer's disease such as identification of amyloid peptide as a possible molecular cause of Alzheimer's disease. Some researchers believe it is realistic to expect that the progress of Alzheimer's disease can be slowed or halted by products developed to affect the amyloid peptide. However, researchers also have emphasized that this is a very complex disease that will need to be approached from several different directions. A number of promising new treatments in many areas are in the works; a few were mentioned in your previous hearings as approaching the stage of clinical trials.

As you may know, FDA is legally restricted from discussing any individual products that already may be under review by the Agency. This precludes me from being able to discuss specific unapproved products in today's public forum. I can tell you, however, that Alzheimer's and other neurological diseases are very active areas of research and of work within the Agency. FDA reviewers interact constantly with manufacturers and sponsors of prospective new products (drugs, biologics, medical devices or combination products) to help develop, and then to review, suitable clinical trials to test whether their products are safe and effective. This is a very intricate and time-consuming process. Our reviewers work with industry in all phases of the development of a new product, both before and during clinical trials, as requested by the sponsors. As always, FDA stands ready to expeditiously review applications for any breakthrough products that are presented to us.

FDA recognizes its dual role as evaluator of the safety and effectiveness of new therapies and as the encourager and facilitator of efforts to apply new scientific discoveries to patients who are in need. FDA serves as a bridge to the future of successful new medical product development. The Agency has a proud record over the past hundred years of being the world's gold standard in medical product regulation, but FDA cannot rest on its past and must come to grips with the new realities of our regulatory responsibilities. Therefore, we have embarked on a process of looking internally at transformations that must occur within the Agency, and to identify opportunities to collaborate with drug developers and other scientists on the discovery, development, assessment and delivery of new treatments. I would like to share some of these efforts with you.

#### THE CRITICAL PATH INITIATIVE

In today's world of health care and medicine, we are on the brink of unprecedented advances in our ability to predict, diagnose, and treat disease. Approximately 100 years ago, our ability to understand disease moved from the macro level, where we were limited to what was visible to the naked eye, to the micro level—when we gained a microscopic view of disease at the cellular level. In the last decade or two, we have been able to approach disease at the molecular level, where we now can observe and understand disease as a process. As our knowledge of genetic molecular mechanisms evolves and our understanding improves, we will be uniquely positioned to develop interventions against disease processes at the molecular level.

Yet a problem emerges. Despite an unprecedented increase in funding for biomedical research, both in the private sector and through Federal funding, this increased research has not translated into many new medical products being available in the medical marketplace. There are exceptions, of course, notably in the development of new treatments for cancer and AIDS, and some inflammatory diseases.

Close to 9 in 10 pharmaceutical products in phase 1 clinical testing are never approved for marketing, and half of all drugs that enter phase 3 clinical trials are never approved. In an effort to help expedite and simplify the medical product development process, in 2004, FDA advanced the notion of focusing on the critical path which medical products must travel from the earliest stages of development to their use in patients. The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured.

FDA is working with the academic community, the public, the pharmaceutical industry, and other Federal health agencies (e.g., the National Institutes of Health (NIH), the Centers for Medicare & Medicaid Services, and the Department of Veterans Affairs) to modernize and transform the development and use of medicines. After intensive consultation with many stakeholders, last year the Agency published our *Critical Path Opportunities Report*, which details 76 specific scientific projects with great promise for smoothing the path from lab to bedside. Last December, we followed up by announcing more than 40 very promising scientific projects that we have helped launch. These projects support the development and approval of new treatments for conditions such as Alzheimer's, diabetes, cancer, and chronic pain. For example, improved predictive and evaluative tools that help identify candidate products that are likely to fail early in the development process will enable the investment of resources in those products most likely to succeed. Streamlining clinical trials—making them more efficient and safer—will help move new therapies to patients sooner while protecting clinical trial participants. Among many other activities, the Initiative also supports the implementation of information technologies that will enable us to tap into existing data repositories to expand research into disease areas and improve efficiencies. The Critical Path Initiative is a long-term, national effort that is helping to ensure that promising new therapies in the development pipeline today will reach the patients who need them sooner and at less cost. The projects under way today as part of the Critical Path Initiative will improve treatment, improve safety, and improve patient access.

Another example of the Critical Path Initiative is The Biomarkers Consortium launched in October 2006. This is a public-private biomedical partnership established by FDA and many colleagues in the scientific community that is supported by the Foundation for the National Institutes of Health. The Biomarkers Consortium strives to accelerate the delivery of successful new diagnostic approaches and therapies to prevent, detect early, diagnose, and treat a wide variety of diseases. Among other efforts, the Consortium seeks to identify biomarkers and develop tests to determine whether a drug is appropriate for an individual patient. It also is working to find "markers" that will show whether a drug is having the right effect in the patient. For example, researchers have found that patients whose tumors have specific genetic mutations or surface properties respond to particular treatments. This mutation then serves as a "marker" to identify the patients who are best treated with these medications.

Over time, similar discoveries related to other tumors, other diseases and conditions, and other drugs will yield a major public health impact—and that is the point of the Critical Path Initiative. Working with all stakeholders, the Critical Path goal is to get the right medicine to the right patient, in the right dose, and at the right time. It will make innovative medical products available sooner, increase our ability to monitor their safe use once they have reached the medical market, provide for personalized diagnosis and treatment, and introduce great efficiencies while reducing risk.

#### TWO EXAMPLES OF ALZHEIMER'S RESEARCH WITHIN THE AGENCY

Now, I would like to talk about two Alzheimer's-specific projects that FDA has undertaken. First, FDA scientists from our National Center for Toxicological Research (NCTR) collaborated recently with scientists at the University of Arkansas for Medical Sciences, the University of Arkansas at Little Rock, and the Central Arkansas Veteran's Health Care System to conduct an automated cognitive assessment of persons with and without Alzheimer's disease. The study investigated performance on metrics for a variety of behavioral test tasks that measure timing perception ability, short-term memory, and learning ability using an automated system called the NCTR Operant Test Battery (OTB). The study outcome indicated that the persons with Alzheimer's disease were significantly less accurate in the time perception and short-term memory tasks and were rarely responsive in the learning task. The OTB is a non-invasive, automated, non-threatening assessment technology that can differentiate between normal controls and persons with Alzheimer's disease. This automated assessment instrument has the potential to provide reliable, objective meas-

ures that can be used to monitor the progression and severity of the disease process and assess effectiveness of interventions over time. A report on this study is in preparation.

Currently, FDA/NCTR scientists are initiating a study to develop a histochemical test battery for assessing the efficacy and toxicity of putative anti-Alzheimer's disease drugs, the safety of which will need to be evaluated in the FDA regulatory review process. There are two broad categories of anti-Alzheimer's drugs: those that provide symptomatic relief and those designed to prevent or slow the degenerative process. So far, those in the first category have been developed and shown effective, and are approved for use by FDA. Those designed to cure or reverse the disease process are in early development or, in some cases, in clinical trials. The development of a therapeutic histochemical test battery has the potential to help identify earlier and more reliably drugs that might slow the degenerative process. This study is scheduled to begin later this fiscal year.

#### THE PATIENT REPRESENTATIVE AND CONSULTANT PROGRAMS

FDA also has engaged with the Alzheimer's disease patient advocacy community regarding that community's involvement in FDA decisionmaking during development of new medical products. Through FDA's Patient Representative Program, they will be able to participate in FDA advisory committee meetings, advising the Agency on marketing approval decisions and in response to issues arising with marketed products, as well as help advise the Agency about the development of investigational drugs. Their involvement is important to FDA's capacity to make informed regulatory decisions that are sensitive to the needs and preferences of those affected by this disease.

This expansion of FDA's programs has involved considerable challenge, as FDA has negotiated with Alzheimer's disease advocacy organizations regarding the role of Alzheimer's disease patients themselves. FDA considers patient involvement important, since patients with a given disease are generally best able to speak for others with that disease. Involvement of patients with Alzheimer's disease is also an important priority to the Alzheimer's disease advocacy community. However, participation of patients with Alzheimer's disease is problematic because of diminished intellectual function that is a primary manifestation of this disease. This challenge is exacerbated by Alzheimer's disease patients' deterioration in intellectual function over time.

After extensive negotiation, we have agreed to recruit advocates from the Alzheimer's community, including couples consisting of a patient with early-stage disease and his or her caregiver, both of whom have a background appropriate for involvement as FDA patient advocates. The caregiver will serve as the primary spokesperson for the couple, but both parties will have access to materials for review, will be able to review and discuss those materials prior to their engagement with FDA, and will have the opportunity to participate. When the patient is no longer able to participate, the caregiver will continue to serve with FDA. FDA and the Alzheimer's community agree that this approach involves challenges, but both parties are willing to work to maximize involvement of patients.

#### THE FDA INTRA-AGENCY NEUROLOGY WORKING GROUP

Next, I would like to mention FDA's Intra-Agency Neurology Working Group. Neurology products regulated by FDA, comprised of drugs, devices, biologics, and combination products, are a diverse group of products aimed at advancing patient care in a number of disease areas for which the unmet therapeutic need is great. Some diseases affect a large number of patients, such as Alzheimer's disease and Parkinson's disease, while others affect smaller numbers of patients. In either case, the consequences can be devastating for patients and their families.

FDA's goal is to improve communication about neurological disease across the Agency among the various groups charged with regulating these products. To accomplish this end, FDA has established a Working Group to serve as a forum for information exchange on leading-edge developments, enable sharing of technical and regulatory expertise, and provide for greater consistency of review standards and processes across the Agency. Further, we are expanding patient advocate involvement in FDA neurological disease-related review and decisionmaking to include Parkinson's disease, Alzheimer's disease, and other neurological diseases as Agency resources allow.

Meetings occur monthly and are chaired by Dr. Celia Witten, Director, Office of Cellular, Tissue, and Gene Therapy in our Center for Biologics Research and Evaluation (CBER), and Dr. Robert Temple, Director, Office of Drug Evaluation I and Director of the Office of Medical Policy in our Center for Drug Evaluation and Re-

search (CDER). Other members include Dr. Russell Katz, Director of the Division of Neurology Products (CDER), and supervisors, reviewers, and project managers from CDER, CBER, and our Center for Devices and Radiological Health. Also included are staff from the Office of the Commissioner, including the Office of Critical Path Programs, the Office of Special Health Issues (OSHI) and the Office of Science Health Coordination. Standing agenda items include policy development (guidance, workshops, and advisory committee meetings), opportunities for Critical Path projects, significant review projects (major investigational/marketing applications under review, marketing approvals, studies of interest, etc.) upcoming neurology-related meetings and patient advocate involvement, and OSHI updates.

#### ADDITIONAL FDA ALZHEIMER'S-RELATED ACTIVITIES

The Agency is engaged in a number of additional Alzheimer's-related activities. For instance, FDA is helping with a study called the Alzheimer's Disease Neuroimaging Initiative. This is a 5-year public-private initiative involving industry, academia and the NIH. The goal of this study is to obtain standardized MRI, biochemical, and clinical data over several years in prospectively followed groups of normal elderly patients with mild cognitive impairment, considered the very early stages of Alzheimer's disease, and patients with diagnosed Alzheimer's disease. We anticipate that this study will help in the use of some of these measures in future clinical studies to expedite the development and approval of drugs to treat patients with Alzheimer's disease, especially in its very earliest stages. A particularly exciting and important aspect of this study is that the data are available to scientists all over the world in real time as the data are acquired and entered into the database.

Additionally, FDA has a productive and close working relationship with the Alzheimer's disease advocacy community. For example, FDA has worked closely for many years with the Alzheimer's Association on scientific, technical, and advocacy issues. Their counsel and direct assistance to FDA have been invaluable as we have worked to improve our regulation of Alzheimer's disease treatments and to expand patient involvement in FDA decisionmaking.

FDA recently met with, and remains in contact with, the Accelerate Cure/Treatments for Alzheimer's Disease (ACT-AD) Coalition. They are concerned that the Agency retains a strong focus on drug development for Alzheimer's disease. The Agency works and keeps in contact with these organizations through OSHI. I certainly encourage this important exchange of ideas with advocacy groups.

Development of drugs with an effect on disease progression is the most critical need in Alzheimer's disease, as it is with other progressive neurological diseases. FDA is planning a future public meeting to discuss design of clinical trials and how to design studies to determine whether or not a drug for Parkinson's disease has an impact on the underlying cause of the disease and not just the symptoms of the disease. It is expected that the designs useful in Parkinson's disease should be equally applicable to drugs for Alzheimer's disease.

In addition, FDA is organizing an upcoming meeting with neurological disease organizations involved in advocacy and medical research. This meeting will involve discussion of scientific, technical, and advocacy issues related to their and FDA's roles in development of important new treatments for serious neurological diseases, including Alzheimer's disease.

#### CURRENTLY APPROVED DRUGS FOR ALZHEIMER'S TREATMENT

Finally, I want to make sure that I mention to the committee that there currently are five drugs approved for the treatment of Alzheimer's disease: Cognex (tacrine); Exelon (rivastigmine); Razadyne (galantamine); Aricept (donepezil); and Namenda (memantine). All except Namenda are approved for the treatment of mild to moderate Alzheimer's disease. In addition, Aricept also was approved recently for severe Alzheimer's disease. Exelon was approved on July 6, 2007, in the form of a transdermal patch, which reduces gastrointestinal side effects compared to the oral form of the medication. All of these drugs except Namenda act by increasing brain levels of acetylcholine, a neurotransmitter that is abnormally low in patients with Alzheimer's disease. Nerve pathways in the brain that are thought to be involved in memory and cognition, that "use" acetylcholine as a neurotransmitter, degenerate in patients with Alzheimer's disease.

Namenda is approved for the treatment of moderate to severe Alzheimer's disease only. It works differently than the other approved drugs. It interacts with a receptor that is thought to be involved in preventing the death of certain cells in the brains of patients with Alzheimer's disease. However, the drug has never been shown to prevent or slow the underlying nerve degeneration in these patients, nor have any

of the other approved drugs been shown to do anything other than treat the symptoms of Alzheimer's disease.

#### CONCLUSION

We await, together with the rest of the world, for new drugs that may some day be able to treat the underlying cause of this insidious disease as well as other neurological diseases, not just the symptoms. We are very encouraged by the progress being made in the scientific community and pharmaceutical industry on products you heard about in testimony in the previous two hearings. As indicated earlier, FDA stands ready to facilitate any breakthrough product applications that are submitted to the Agency for review.

This concludes my formal statement. I will be pleased to respond to any questions from the subcommittee.

Senator MIKULSKI. Well, thank you very much, Dr. von Eschenbach. I think already—did you want to ask a couple of questions and I'd be happy—but I just wanted to say first of all, it's a very impressive group but it's impressive already at the level of coordination and communication that's going on. So I said, this is not to be a roundtable. Our friend, Senator Isakson, has to leave and I didn't know if you had a couple of questions you'd like to pose and the way we see it, is we're just going to kind of jump in and even though you might pose it to someone, if somebody else has got something to add, we don't have to be starchy and choreographed here.

#### OPENING STATEMENT OF SENATOR ISAKSON

Senator ISAKSON. Well, thank you, Madam Chairman. I am going to have to leave because I have another Georgia company waiting in the office but anytime Dr. Gerberding shows up, I show up because I am her biggest cheerleader. She's done a marvelous job for CDC and I'm very grateful for the many contributions that she makes.

I won't ask a question. I'll just make a comment. The reason I have a passionate interest in this, I lost my mother to Alzheimer's. But over the years, I've had some experiences that illustrate to me how important it is for us to get into the surveillance business that you talk about in your pathway and look for some answers because I've had one of my doctor's wife, at the age of 46, who was diagnosed with Alzheimer's, Governor Carol Campbell, a great governor of South Carolina in his fifties was diagnosed and died in 3 years and in my church. I have two members whose wives—both of their wives have had Alzheimer's for a significant period of time and it's apparent in the last decade that some pharmaceutical therapies and other treatments are beginning to work to prolong and improve the quality of life of those individuals with it but it's a must—and I agree with what Dr. Gerberding said that everybody fears physical impairments but everybody is more fearful of cognitive impairment.

So I appreciate the Chairperson's diligence on this effort and her real passion in seeing to it that we raise the eligibility and as I told her a few months ago, I'm here to be a soldier in that army and I'm grateful to you all for what you do.

Senator MIKULSKI. Thank you very much, Senator. At the end of this conversation, we will begin to meet on getting ready for our markup on our Alzheimer's Breakthrough bill, particularly the research component. It would be the goal of Senator Burr and myself

to have this marked up either by the end of July or certainly in September and move it on through to get it done. So we've heard from the Alzheimer's Association, research community and we're going to have more conversation with you.

Let me jump in with my question. Of course, we agree with Dr. Zerhouni that intervention, even before physical or mental manifestations of anything from heart disease—you don't want to wait for that out-of-breath shooting pain or for women, fatigue and other symptoms. And we'll be talking about that. But one of the things that I'm interested in is how we can now take basic research findings that we already know that might not need a pharmaceutical intervention and move it into clinical practice, better diagnosis because we've heard that in many instances, it's misdiagnosed as depression early on or when people start that 36-hour day, the agitated behavior where other medications are prescribed.

That's one—use information we already have, say at NIH or the private nonprofit community and then how does that get translated into clinical practice or what we fund. Let me go to something else, which is what seems to be emerging from the research is the low-tech solution that what is needed of good diet, exercise of both the body and the mind, is very good. If you have heart disease, diabetes—any propensity that you might have that is starting back here, though you might not be able to beat change, you can delay the consequences of genes and so on and my question then is, if that's so and that's thoroughly been validated and I think it has, then how does it get out to both clinical practice and then even to entities like the Office on Aging? What does all that mean while we're working on even more sophisticated and more precise breakthroughs? Do any of you want to comment on translating research into clinical practice? I just throw out diagnosis and I just put that out for discussion, the techniques we now know for the management of any chronic illness seems to have a major role also or significant role in preventing cognitive decline, whether it's Alzheimer's or something else. Do any of you want to comment on that?

Dr. HODES. I think you posed a very critical question about our translation from scientific findings from what we know into practice and let me try to give two examples because I think it's important that we recognize our obligation to do the most we can with what we know.

Now let me first take one of the more precise examples of an attempt to translate genetic and biological information at the interventions and this comes from the original observations 100 years ago, when the initial patient with Alzheimer's disease, by the professor of the same name, identified plaques and tangles in the brain and we've seen over the past years, his remarkable identification of the biochemical nature of these plaques and tangles, the genes that encode the products. This has led, in turn, to the ability to generate animal models that reproduce much of the lesion, the memory defect of Alzheimer's disease caused by introducing a particular gene product. So there is very strong evidence that it is quite possible that a particular molecular lesion is responsible for Alzheimer's disease.

This is now leading to clinical trials. The only way to completely verify the ability to intervene in this pathway and have an effect—the trials are not simple as with any drug trials but they are attempts to modify the effect of the enzymes that cause the amyloid plaque or as we've heard, immunization treatments to try to prevent or reverse the accumulation of amyloid plaque.

So this is an example of translating the most basic molecular level through very rigorous levels of evidence to establish whether or not an intervention, pharmacological, immunological, have the desired impact and this is one important pathway to pursue. It's important that our basic science from institutions like NIH are translated to both private sector enterprise and academic enterprise and ultimately to the FDA to deal with final demonstration of efficacy.

There is another pathway and one that you've eluded to that deals with evidence or associations of certain lifestyle factors and risk factors with Alzheimer's disease. So as you've noted, there is strong epidemiologic data that indicate that individuals who have many of the risk factors for cardiovascular disease, diabetes, high levels of homocysteine are more likely to have Alzheimer's disease. Therefore, it is important that we carry out rigorous clinical trials to see whether the interventions for those treatments will or will not have effect on Alzheimer's disease.

Now, do we need to wait until we have that information before recommending that people follow lifestyle interventions such as diet, control of blood sugar in individuals with diabetes, diets that are demonstrated to protect against cardiovascular disease—of course not. So this is a case in which we don't have the highest level of evidence to show these interventions will, without doubt, from randomized clinical trials, prevent Alzheimer's disease. We know enough to recommend to the public that in terms of general, successful aging in health, these are strong measures that should be translated while at the same time, I would suggest we pursue the rigorous science to see just how they affect variables such as cognitive function.

I think the same is true for——

Senator MIKULSKI. It wouldn't hurt, would it?

Dr. HODES. We certainly think it wouldn't help. It's been demonstrated that these interventions are helpful for many other aspects.

Senator MIKULSKI. Well, let me tell you when I first heard about this and Dr. Zerhouni, you'll enjoy this. Senator Burr, you might want to come with me. The National Institutes of Aging is the one campus called Bayview at Johns Hopkins but it's not in the main Broadway campus, which is like the mother ship, contiguous to a neighborhood called Greek Town. Now, Greek Town is where a large number of Greek immigrants settled and oh gosh, they have food that is both the Mediterranean diet, which we're supposed to follow but then they've got the fried calamari and they have the baklava—you get it?

Dr. ZERHOUNI. You tell me where to eat and I'll go.

Senator MIKULSKI. And I'll get it for you. So I went to visit then, that old creaking building that I know we're replacing, but one of the first things that we heard was the research in animals that



really, the reduction in calories, the improvement of exercise enables, at least it seemed to have a positive impact. But what we also know is diabetes is a factor, maybe. That this is a preventive act that does no harm, which as all of you have taken that oath that the first thing is, we could do things that do no harm. So Dr. Gerberding, what you do think about that? Should we now, as a major public policy, take what you're saying in the Healthy Brain Initiative but really, what we already know for heart-smart, we could really be troubadouring and promulgating. Do you have a reaction to this and what you already know, knowing that we could always validate more? And also then, what is CDC doing about this, say in conjunction with the Office on Aging that funds every senior center in America.

Dr. GERBERDING. My reaction is enthusiasm in a short word. I think we've got to set a stage to get this ball rolling and one of the remarkable things that I observed on the times that I was participating in some of the Medicare sign-up events or some of the Welcome to Medicare, get your prevention screening activities going on at the grass roots level, is how extensive the network of support for seniors really is in our communities because of the Agency on Aging and HERS and others and many, many not private and other organizations. We have an extensive network of community support in many communities and even reaching into those populations that are hard to reach and have the worst health disparities. But that network is not aware that this is a critical strategy for protecting brain health and I think the concept of social marketing, getting out to the grass roots level and really informing people that it's not only good to do these health promotion activities because they are heart healthy. Some aspects of them are highly likely to preserve mental functioning and as the database for that grows, it will be able to give us stronger scientific basis for that.

So the first thing is to get the word out into the community to the affected people but also that incredible hidden network of support that already exists and mobilize it to start really adding this to the perspective.

Senator MIKULSKI. Is that what CDC does and are you meeting with the Office on Aging to do that?

Dr. GERBERDING. Absolutely. And I think we did not have these strong ties, admittedly in our Department but we have come together in many different ways to support some of the modernization of Medicare activities and we've discovered how much leverage we actually have within HHS. I mean, Medicare pays \$91 billion a year for Alzheimer's disease. That's a tremendous investment and we ought to be able to work with that kind of resource and do more to help people prevent this in the first place. But the other piece of this that we can't forget is that clinicians also play a very important role and I do think we need to be more aggressive about clinician education.

You've described in your written testimony, some centralization of testing for Alzheimer's and cognitive dysfunction so that we make a more accurate and early diagnosis in those patients that can benefit from drug treatments, get access to them but also it helps us understand the relationship between cognition and capac-

ity to engage in physical exercise and the other Heart Healthy activities.

The tragedy here is as your cognitive function declines, your ability to take your medications and to maintain your mobility and control your blood sugar declines concomitantly so you get into a vicious cycle of deterioration.

Senator MIKULSKI. Exactly.

Dr. GERBERDING. I think we can do a lot more at the clinical interface to prevent that deterioration.

Senator MIKULSKI. Well, I know Dr. von Eschenbach wants to talk. I'll turn to Senator Burr but as we now get ready for our markup, would you have your team meet with us to see how, as part of our Alzheimer's Breakthrough, where we move to increase funding for research, we look at how we can also more effectively involve the role of CDC exactly in this coordination in kind of moving out what we do know.

That if nothing else, how it's managed, the chronic illness that Dr. Zerhouni said, you said, 75 percent of those people over 55 consulting a clinician is for the consequence of a chronic condition, not an acute episode or a fall or an orthopedic injury or anything like that. So we want to come back to you. Dr. von Eschenbach, did you want to say something?

Dr. VON ESCHENBACH. With your permission, I'd just like to amplify on two points I made in my statement, which go along with the comments that have already been made. I indicated this fact that today, we're in the midst of this molecular metamorphosis. I also indicated that we're all in this together and I think that bodes very well for tomorrow.

First of all, one of the implications of this tremendous progress in biomedical research is the fact that as Dr. Zerhouni alluded to, health care will be personalized, much more predictive, pre-emptive and more participatory. And the implications of those four P's for tomorrow is that first of all, one of the things that's going to go a long way for us having these public health interventions is to be able to define populations at risk and to do that in a way that we can really hone in on where these targeted interventions have to occur that are going to be much more preventative and we'll know that they'll be predictive because we know the evidence of their outcomes.

At the same time, when we look at what's happening today with information technologies and communications, we're seeing health care become much more participatory. Faces no longer are just passive recipients but actively participating in their care and we now have the tools of communication and interaction that enable us to help continuously guide patients in terms of interventions that they should be carrying out day by day and that's where agencies and organizations like the Alzheimer's Associations have alluded to and others, like AARP, have a real role in continuing the impact of these interventions at the public health or community level and to do that in a way that mobilizes and moves us to a better level of health.

I think it's comprehensive, it's integrated but I don't—and I think the tools are going to enable us to do it far more effectively tomorrow than we could do it yesterday.

Senator BURR. Thank you, Madam Chairman. I was struck, as I listened to Dr. von Eschenbach, that we have a tendency to focus on specific diseases and it just struck me with some of the things you were saying, Andy, that we have a health care delivery system designed in America not to fully engage us in prevention and wellness and not really in disease management unless someone is triggered from a quality of life standard to do it.

And I would say to my good Chairman, maybe it's an area that we can explore. I'm sure the answer to this is in the challenge of how do you continue to see a population of a country increase at the rate we are, while we devote 16½ percent of the GDP to health care and not be influenced by other models around the country where they say, "well, we do it so much cheaper" and the reality is that we can look here today and as Dr. Zerhouni said, in X number of years that 5 million individuals with Alzheimer's are going to be 16 million with Alzheimer's and there's full agreement at the research table that the answer here is, we have to get ahead of the curve. We have to be preventive. We have to be predictive.

We have to be willing to personalize and that's a tremendous goal that NIH is under and it puts tremendous strains on you from a standpoint of the agency at the end that's going to be trying to approve therapeutics and vaccines that are trying to keep somebody from getting the disease. What a tremendous step we've made.

Dr. Hodes, today, how is the typical patient with Alzheimer's diagnosed? What is it that triggers that person to go in and say, "boy, I think I got it." Or that family member—who is it that initiates that and what process do they go through?

Dr. HODES. I think the simple answer is that it's very heterogeneous and very variable. With a spectrum from individuals who are very sophisticated, families are very perspective and connected to a medical care system so that at the early appearance of changes in behavior, including changes in memory, they turn to physicians who are informed and capable.

All too sadly, though, a large percentage of our population is unfamiliar with the concept of these changes or anything more than a part of aging and they are accepted as such and diagnosis is, therefore, delayed. It isn't so many years ago that everyone accepted dementia as an accompaniment of aging and so we're at a point of transition where I think the best informed and we need to make all of Americans better informed, are tuned to seeking medical attention.

Once having come to medical attention, to a physician or care provider, in the best of settings, estimates are that approximately 90 percent accuracy in diagnosing Alzheimer's disease is the theme. This is what we see in the best of hands and far less accurate in others. So here, our commitment is to try to identify the psychological test and our imaging tests that can continue to refine a standard strategy for diagnosis that will allow all of the care providers around this country to be more astute in making diagnoses.

The impetus for making diagnosis is, of course, an important issue. What is the motivation? Right now, a great deal of the motivation is to rule out other causes of dementia that are clearly treatable and reversible and one of the greatest tragedies would be to

be missing one of those. If Alzheimer's disease is diagnosed and diagnosed early, of course, there are real advantages to the individual and the family in terms of planning and understanding prognosis and finding those treatments, which are able to modify the course of the disease.

But we have to concede that those treatments, those interventions are currently of limited effectiveness and effective for a limited period of time so that the motivation to identify disease early, to come to diagnosis and to treat, is going to become more critically important as we identify and communicate interventions that make a difference.

Senator BURR. Well, we probably all agree that the first interventions are probably going to be therapies that potentially either slow or stop the progression of disease, therefore the earlier we can detect, the better off the quality of life and the outcome is.

Dr. HODES. I should maybe just comment that while we have great hopes and need for much more improved interventions, it was just in the past months that there was a statistical significance from a clinical study showing that one agent, Donepezil, was in fact able to reduce the risk of moving from mild cognitive impairment to a diagnosis of Alzheimer's disease. It was a limited effect. It occurred only over the first year of the study in most individuals but I think it provides the first prototype, if you will, of an intervention that can actually prevent the onset of disease.

I should also reinforce what's been said by my colleagues about the importance in the area of public education, of organizations that are in the grass roots. The organizations prominently including the Alzheimer's Association, with whom we have great interactions, not only in the planning of research agendas but in the grass roots contact with individuals who are affected in their families, important to providing and communicating information, to recruiting individuals interested in participating in clinical studies, which I need to stress, is very important to progress so that all of the Federal agencies, private sector organizations need to work together to inform the public so they can both understand early signs, seek diagnosis and then participate with us in the research that is necessary to come to better means of intervention.

Senator MIKULSKI. I just want to come back to Senator Burr's point about diagnosis. My father died of the consequences of this, but these early signs—no one was quite sure what it meant and this is when we had access at Johns Hopkins, to a geriatric evaluation program, where a geriatrician, someone skilled in the diseases or effects of aging, could evaluate, what is the medications Dad was taking for some other things, where the synergistic effect affected his cognitive ability? Was it that he needed that shot of Vitamin B-12, which we all hoped he needed, et cetera.

Well, unfortunately, it wasn't that but it could have been that. And isn't this where, really, there needs to be some type of really overall assessment? But do you feel that also, there needs to be more of the specialized centers where a primary care physician to validate what they suspect would occur? Or do you feel that you can develop these—I don't want to say check, but prototypes for at least the primary care people to make some type of diagnosis?

That's not a catch-22 but it all goes to what should be supporting here, one of which is accurate diagnosis even though we might not have some magic bullet now. There are tools available.

Dr. ZERHOUNI. I'd like to, if I may, really stress the point you just made and that is, if you look on the forecast basis, on how many geriatricians are going to be available to really take care of an age population, what you find, in fact, is that the number of geriatricians is not growing. It's actually flat or decreasing in terms of the number of people who graduate to study the diseases of old age.

So I think if you were from the 50,000-foot view before we go to Alzheimer's, we have a fundamental issue in orientation of resources toward creating the human capital needed to take care of this population as we go forward. There will be a deficit in healthcare providers at all levels. It will be care providers at home, care providers at the intermediate levels of care.

So it's clear that when you really look at the total system, we have an issue and we need to really work together on finding ways of preventing the loss of the talent.

The other is that Alzheimer's disease today is a diagnosis of elimination. You try to eliminate every possible potential causes of cognitive deficit before you can make this diagnosis because it is only diagnosable at this point through a biopsy and we're not going to perform biopsies on live individuals, biopsies of the brain.

So one of the things that need to be done is more standardization of the diagnostic tests, an educational program for centers to diffuse around them because we're not going to be able to do it just with geriatricians. So we're going to have to educate, at a very fast pace, not only in terms of the prevention activities that Dr. Gerberding was talking about but just pure clinical medicine for family doctors, internal medicine doctors, a little bit of what we did for heart attacks.

I mean, it was clear they didn't have enough cardiologists to take care of heart attacks so you had to really diffuse the knowledge way beyond the specialists. I think if you really think about it, Senator, what you have to have—you have to have a systems approach to the disease, from the first point of contact, the loss of cognitive function, mood disorders, wandering, losing your keys, losing the address of your house, knowing how to go back, all these signs are overlapping with many other conditions. So you have to eliminate it but at the end, we as scientists, have to agree on a standard set of parameters and tests to develop sets that are more objective. There is no blood test today like there is for diabetes, for Alzheimer's and we need to really come up with something, some answers.

We've funded very innovative research at the NIH. We funded nano-medicine, to pioneer, to in fact tell us whether he could detect the very first signs of Alzheimer's disease in the fluid that is within the brain, what we call the CSF, the cerebral spinal fluid. And for the first time, we had a positive result so there is hope to be able to do that on an objective basis.

My message here is this: if you look at any one point and try to improve that, you're not going to get to your goal. In other words, fighting Alzheimer's disease is only as strong as the weakest link

in the chain of research, intervention, prevention, payment systems—how do you cover that? The workforce planning, how many healthcare providers do you need? This is truly, I think, the challenge that we have.

We have tried to educate, from our standpoint, we're just releasing today the progress report on the research, on the Discovery Pathways for Alzheimer's Disease and I want to commend the National Institute of Aging and all our sister agencies participating in this but this, in fact, is the message that you will not solve this problem with a one magic bullet approach.

Senator BURR. I'm sure Senator Mikulski agrees with me that we really need each of you to pledge to work with us on this legislation. There's only one way to get a perfect bill and that's to make sure that all the stakeholders are on board at the beginning of the process rather than to shoot at a bill that we think is a pretty good product and I hope you'll do that.

I remember years ago, Dr. Zerhouni, among the—almost the completion of the mapping of the human genome. I was at SAS Corporation in North Carolina, the largest privately owned software company in the world and they envisioned at the time that when they got the final genome mapping that they would be able to go in and write a computer program that could then take all of the known drugs and things that we had and could potentially test them on what they had learned. How far are we from that?

Dr. ZERHOUNI. We've made tremendous progress. I have to tell you that over the past 3 years—when I became NIH Director, I can recount the story about the fact that the human genome had been completed. We, in diabetes, we knew one gene, suspected gene. This was the effect of 30 years of work and it was p-parg gamma as an enzyme and that's what we knew. Since then, just this year, we found 10 very, very strong candidates to understand at the genetic level, what makes a person diabetic and why is it that they become diabetic, very, very early in their natural history.

If you look at all of the progress that has been made because of the biotech advances and the technologies today, we have a project and it's called pharmacogenetics. It started about 4 years ago and we have over 400 discoveries that show why you or I would respond differently to a drug. The next step is what we call the Gene Environment Initiative, which we launched this year, where we're going to find the common genetic traits of the 10 most common diseases, including Alzheimer's, actually, which is also being researched.

We're very close to this. We have to accelerate our research there. The opportunities are enormous. This is the basis, actually, of this personalized medicine idea that you and I, even though our DNA is only different by .1 percent, we can react to the same treatment in completely different ways. To know that ahead of time is very important.

Let me give you a very specific example. Today, we use cholesterol lowering drugs, statins—Lipitor and Zocor on millions of people but we know from the epidemiology that only 10 maybe, 10 percent of these people would ever develop a heart attack or cardiovascular disease. Yet we give it to a hundred percent of the people.

Wouldn't it be great if I had a signature that told me I am part of the 10 percent that's going to get it and I need that drug and you're part of the 90 percent that do not need to have that drug. So you can see the impact on the cost of health care, the precision with which we will treat people—all of this is related to the advances of the past 2 years.

Senator BURR. Let me ask, I'm sure somebody has put together information that's more global in scope for Alzheimer's. The percentage of the American people that are affected by Alzheimer's, is the percentage consistent with the percentage of other countries in the world?

Senator MIKULSKI. Good point. Interesting.

Dr. ZERHOUNI. That's a good question. I actually will defer to my colleague here.

Dr. HODES. Well, there's incomplete information but enough to be responsive. That is, I don't think that we have comparable information on the prevalence of Alzheimer's by similar standards in so many countries that we can answer that with precision. But we do have information from very specific studies that have, for example, compared the risk of Alzheimer's disease in particular populations, one versus the other. For example, in the population of individuals still residing in Nigeria versus population in Indianapolis, in fact, a very direct Nigerian descent and one can find in that sort of comparison, a very significant increase in the proportion of Alzheimer's disease in those individuals who now reside in the United States.

Similarly, there have been comparisons of Japanese, Japanese Americans in Hawaii, Asian Americans, which have indicated the change and prevalence of Alzheimer's, it appears, over a generation with a change of environment. These are important because it is unlikely although not yet definitely established that these changes result from selective genetic differences but more likely, do reflect the impact of environmental risk factors.

So we know that populations, when studied in some of these discreet areas, do differ. We don't have a global national/international comparison.

Senator MIKULSKI. You could also go to diet. Dr. von Eschenbach, you seem eager to say something here.

Dr. VON ESCHENBACH. Dr. Gerberding is right. I just wanted to emphasize one other element of this equation. I think it has been pointed out, we really do need to continue our investment into the discovery end of the continuum, to learn more about this disease so we're not just recognizing it when we're looking at the end stages of the degenerative process and people have already lost function. And at the same time, we have to have attention to the deliver end of the continuum so we get the kind of prevention and intervention that Senator Mikulski was talking about.

But there's that middle piece between discovery and delivery of development and I think we need a strategic approach to that from the perspective that we are going to need platforms, be they genetic or genomic platforms or whatever that helps to find risk. Who is likely to succumb to this disease? We need platforms for earlier diagnosis. They may be imaging strategies. They may be nano-technology strategies. We need development of interventions that are going to prevent the disease at its very earliest stages before some-

one has obviously lost the ability to remember where their keys are.

So that development piece has to be thought of strategically, as where in this disease process, given what we know about its molecular basis, can we target and define and develop interventions that are going to help us predict, detect, prevent and when necessary, intervene and hopefully even reverse. I don't think we should lose sight of that in this overall approach that you are fostering, to say we, as a nation, have to do something about this disease from the very beginning through its entire course.

Senator MIKULSKI. Thank you. I think that's an excellent point. I just want to ask one other question and then maybe we can go to wrap-up. I know Dr. Gerberding has got to leave and we already delayed the hearing and I'm sure you all have, we know you have ongoing responsibilities.

Dr. Zerhouni, you talked in your testimony about the Alzheimer's disease cooperative study and in it, you talk about something called the ADCS drugs. You say they are not typically studied by the large pharmaceutical companies that are off patent or were patented and are marketed for another use. Here goes my question—is this an area when we look at our overall framework for our legislation, we should be sure that we specifically mention and also in Appropriations that this is an area where you do things that the private sector—that's not where the private sector is going to go. They might add value to what you're doing but you're spending \$52 million on this over 6 years, which is what? Seven million dollars a year or five, six and a half million?

Dr. ZERHOUNI. Eight, eight and a half.

Senator MIKULSKI. Yes. Is this an area that we should—

Dr. ZERHOUNI. Right. There is definitely a need for that because obviously as you know, what we do at NIH—think of it as a pyramid for our budget and our efforts. Sixty percent of what we do is really the basic discovery, understanding the disease. Twenty-five percent is what we call translational. When we have an idea and we want to have a proof of concept at a very early stage so that eventually, this will become an incentive, if you will, for the private sector to take it and develop it further and 15 percent, we spent on really doing, for example, things in orphan diseases where at one point there was no incentive, really, to develop these treatments for rare conditions.

So in the ADCS, what the institutes—the National Institute of Aging, National Institute of Neurological Diseases have come together in a collaboration to say, when we have gaps like this, how do you tackle them and it's not so easy. Because you're talking about doing, for example, trials on things that may be very useful but they are not patentable and therefore, no one is going to do them. So you have cracks in the system from either the need for us to do a trial on drugs that exist that are not patented, that the FDA has already approved, but that may be useful—in fact, one of the treatments for Alzheimer's disease actually was out of patent and became quite useful in the treatment of Alzheimer's disease early, and delayed the onset of the disease.

So we do need to have a framework to understand the gaps in the system. Like the Institute for example, will fund young sci-



entists with good ideas who have no access to what a drug company would have access to. They can't figure out if the idea they have is going to be positive and then be followed. So that's something that NIH has to do but it's very, very expensive and very difficult.

One of the things that we did through the Roadmap for Molecular Research is we built what we call a molecular library system for all academic sector investigators who can have access to it for all diseases so that we can at least allow our scientists to fill those gaps.

Senator MIKULSKI. Well, first of all, I find that very instructive. I want to thank all of you for coming. I think it's been a very enlightening and instructive conversation. I'm going to reiterate what Senator Burr said, which is an invitation now to take a look at our legislation. Our legislation really has two parts. What we call the Alzheimer's Breakthrough doubles the funding for NIH research and some of the others and then there is a second component that will really go to the Finance Committee on some tax breaks for caregiving and we'll be looking at caregiving later on. But we're not going to slow that down for what we want for our Alzheimer's Breakthrough. So we ask you now to think about what we could be emphasizing in the bill or authorize that would really enhance prevention and be willing, as an approach, for prevention of all chronic challenges that our population is facing because there seems to be so many similarities that there will be consensus within the public health community.

Second, how you think in our legislation, we can make sure that we help with the Healthy Brain Initiative, which everyone worked on and is so promising because I think the way we both see it, is one, we don't want to be disease d'jour. This is a very important issue. A national epidemic is on its way but we want to do this in a way that's really a groundwork to help you be you that would have a multiplier effect with so many other things you're working on.

But to just conclude about Alzheimer's, I do see an analogy with diabetes again and that's a situation where my own mother died because of the consequences of it. She started on oral insulin at age 40 and died at about 82. But look at where we are now. When Mother was first diagnosed, it was diabetes, yes or no. And you had either the injected insulin or this enormous breakthrough called Diabinese, which was of great help. Then she had to go for her test but then came something called Home Testing, which looked like a 13-inch TV set. Now you can test at home with reasonably 75 percent accuracy, Senator Burr, with something that looks like a stopwatch. And when you look at the array now, one would say this is a genetic propensity.

We start back here. You have to say goodbye to the baklava, you have to say goodbye to the pirogue. You have to say hello to broccoli and so what. It sure beats some of the other things and then moving along to dealing with insulin resistance to all these other kinds of tools. There are now 300 or more things that her primary care physician or endocrinologist could have had of avail. And this is, I think, the way we see here. Back here, the prevention we're talking about would be for all chronic illness and really get that

going because we will do no harm in helping diet and exercise, physically and mentally and really getting this out in any way we can and particularly in the centers where seniors gather and then to look at what are the other continuum of things like we now see because it's no longer diabetes, yes or no. It starts before you see it. It's been insulin resistance and then it progresses.

But at the end of the day, you don't want to have that disintegration in mitro-vascular disintegration of your neurons, your kidneys and your eyes and with what we now know, look what's already happening. So diabetes now, rather than a cure, is viewed as a chronic illness and if controlled and managed with so many tools, you're preventing the consequences of it and so on.

So this is where we see heading to diet with Alzheimer's and this is the continuum here. But we want to work with you to get this going and I mention this because I think this is the way you see it, too. From genetic propensity—not genetic determinism—but genetic propensity, all the way through to what we can do for prevention, intervention and in each passing year, to get even more precise about it.

So Senator Burr, do you want to say something?

Senator BURR. I'd only end this way, Madam Chairman. I think the big question is, what is our role? We need you to share that with us, not just limited to Alzheimer's. What is the role Congress can play today in the agencies that you head that best helps you to do what we've asked you and your many talented employees to do? Because at the end of the day, this is about the impact that we can make on the quality of life of individuals and what the cost of healthcare looks like in the future.

I thought as the Chairman talked about the advances in diabetes, a month ago, actually being at a Community Health Center, seeing a remote monitor where an individual could take it home or could run the software on their computer where it could check their blood sugar multiple times a day, not just for the purposes of them but for the purposes of their doctor electronically receiving it and knowing exactly the tolerance that they've been able to maintain on their blood sugar or for the congestive heart patient who hooks up to five times a day, remotely transmits that to a cardiologist.

The cardiologist can detect whether there is fluid that's beginning to form, can verbally call and change that individual's medication, which eliminates that emergency room visit. The 3-day stay, as they begin to mobilize again and then a routine back on medication.

We have the capabilities today to make sure that a physician and a patient do exactly the right thing on disease management and it's back to something you said, Dr. Zerhouni. At some point, we have to figure out how to pay for it, if in fact we want people to implement it and to use it. I go back to, I think what we started on, this hearing, when the Chair talked about HIV/AIDS and the reality is that when did people get serious about a cure for HIV/AIDS? It was really when we realized that it was cheaper to make sure that everybody with HIV got drugs because we knew exactly how many hospital visits they were going to have that year. We knew the cost of those hospital visits at the time, the original time, was about \$25,000 a year. A case of pneumonia. A case of retinal eye infec-

tion. They'd visit twice but for \$14,000, we could give them the medication and save ourselves a \$25,000 inpatient experience twice a year.

That's a budgetary answer to something that also has a quality of life component and that's that we stop disease in its tracks, but the reality is that sometimes it takes understanding what we're saving to understand what we're willing to invest. Unfortunately, we don't have a scoring mechanism within the Congress that we can dynamically score things to show us what we save. It will only show us what we spend. That's where we're going to have work in partnership together to make sure that we implement the right types of policies that not only address the quality of life but address the budget savings that is absolutely vital for us to be able to pay for it. I thank the Chairman. I thank our witnesses.

Senator MIKULSKI. Well said and yes, this committee stands in adjournment, subject to the call of the Chair and at that time, we will begin to proceed to mark up our bill. We want to thank all of our witnesses for their outstanding contribution.

[Additional material follows.]

## ADDITIONAL MATERIAL

## PREPARED STATEMENT OF SENATOR CLINTON

I would like to thank Chairman Mikulski and Ranking Member Burr for convening today's hearing on what we are presently doing at the Federal level to combat the growing threat that Alzheimer's poses to the health of our citizens, our healthcare system, and our Nation's financial resources.

I applaud Senator Mikulski for her tireless work on issues related to Alzheimer's disease, and I'm proud to work with her and Senator Bond on the *Alzheimer's Breakthrough Act*. This important legislation is critical in our fight against the disease, and I look forward to its markup in the HELP Committee next week.

Last week I joined Senators Mikulski and Burr, as well as my fellow co-chair of the Senate Alzheimer's Task Force, Senator Collins, in welcoming the creation of a new Alzheimer's Disease Study Group. As envisioned by the Alzheimer's Association, this Study Group would be an independent, non-partisan collection of health policy experts who will assess America's current approach to Alzheimer's and will develop new strategies for how the private and public sectors can better meet the challenges posed by this devastating disease.

Former Speaker Newt Gingrich and former Senator Bob Kerrey have agreed to take the lead as co-chairs of the Alzheimer's Disease Study Group. The combination of balanced, independent viewpoints and expert opinion should make a strong contribution to America's current efforts to combat Alzheimer's disease, and I look forward to the release of the Alzheimer's Disease Study Group's findings and recommendations.

While outside advice is important in the fight against this terrible disease, it is our responsibility as elected officials to do all we can to advance the cause of prevention, diagnosis, and treatment of Alzheimer's, including rigorous examination of whether we are doing all we should at the Federal level.

Are we setting aside enough resources so that current researchers have the tools they need to investigate the etiology of this disease? Are we prioritizing the recruitment and training of the next generation of scientists and physicians who will make finding a cure for this disease their life's work? Are we doing all we can to support the millions of caregivers who make tremendous personal sacrifices—and suffer emotionally, mentally, physically and financially—in order to take care of and advocate for someone who is suffering from Alzheimer's? Are we making every effort to safeguard the mental health and physical well-being of adults with Alzheimer's and other dementias—who constitute one of our most vulnerable populations?

Even as we pause to take assessment of our actions and ask ourselves these questions—the toll of the disease continues to grow. An estimated 5.1 million Americans now have Alzheimer's—and their loved ones and caretakers wake up every day and not only provide support and comfort for a loved one, but confront the difficult toll of the disease. We are approaching a crisis as the Baby Boom generation grows older. By the year 2050, up to 16 million older Americans are expected to be living with Alzheimer's.

This stark increase is more than a statistic. It represents millions of families facing an emotional struggle and tremendous financial pressure; a new strain on our healthcare system; new costs for Medicaid and Medicare.

For the past 3 years, Senator Collins and I have co-chaired the Senate Task Force on Alzheimer's Disease. We have highlighted the importance of early detection of Alzheimer's; helping people with Alzheimer's and providing support services for their families and caregivers; highlighting promising research findings that suggest that healthy diet, regular exercise, as well as social and mental activity may help to decrease the risk of Alzheimer's; and the latest innovations for facilitating early detection and intervention.

Senator Collins and I are also working to improve older Americans' access to mental health services. Diseases such as Alzheimer's can contribute to depression and anxiety for both those who suffer from the disease as well as their caretakers. In last year's reauthorization of the Older Americans Act, we successfully enacted Title I of the *Positive Aging Act of 2005* which authorized grants for the delivery of mental health screening and treatment services for older adults and grants to promote awareness and reduce stigma regarding mental disorders in later life.

While this took an important step toward improving mental health services for older adults, significant efforts are necessary to ensure comprehensive geriatric mental health care. That is why Senator Collins and I introduced the *Positive Aging Act of 2007*, which will integrate mental health services into primary care and community settings.

But improving access to mental health services is just one element of responsibly providing the care that Alzheimer's patients require. The majority of caregivers have outside employment in addition to their caregiving responsibilities at home. Research tells us that, because of the lack of support services, most caregivers either miss work or quit their jobs in order to meet the health needs of their family members.

Respite care services provide temporary relief for caregivers and decrease the likelihood of formal long-term care, thereby resulting in significant savings for the healthcare system and taxpayers. Further, respite care also provides family caregivers with the relief necessary to maintain their physical and mental health, as well as bolster family relationships.

Last December, my *Lifespan Respite Care Act* was enacted after 4 years of bipartisan effort. The law will help millions of Americans who struggle to provide care for a family member with a chronic illness or disability so they may remain at home and out of more expensive institutional care. Now we are working to fund the bill with \$300 million over 5 years. Compare that to nearly \$300 billion—the cost of the services family members provide as caretakers of a sick or disabled loved one.

A great deal has been achieved in the last 15 years in the awareness, diagnosis, and treatment of Alzheimer's disease. But much more still needs to be done. We must continue to make Alzheimer's a national priority. The more we learn, the further we travel on the path toward a world without Alzheimer's—and we know that we cannot travel on that road quickly enough.

[Whereupon, at 5:04 p.m., the hearing was adjourned.]

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