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TACKLING DISEASES OF AGING: WHY RESEARCH COLLABORATION MATTERS

ROUNDTABLE

BEFORE THE

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TACKLING DISEASES OF AGING: WHY RESEARCH COLLABORATION MATTERS

TUESDAY, OCTOBER 29, 2013

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The Committee met, pursuant to notice, at 4:09 p.m., in Room SD–562, Dirksen Senate Office Building, Hon. Bill Nelson, Chairman of the Committee, presiding.

Present: Senators Nelson, Donnelly, and Warren.

OPENING STATEMENT OF SENATOR BILL NELSON, CHAIRMAN

Chairman NELSON. Well, good afternoon. Thank you for being here. Thanks to all of you for participating.

We are going to discuss advancing research on aging and the impact on health and chronic disease, and in the next few days, NIH, along with the Alliance for Aging Research and the Gerontological Society will hold a summit in Washington to examine the latest biological research on aging. Five hundred attendees will be on hand to produce research recommendations to advance aging research. I am pleased that some of the brightest attendees came early and they are a part of this roundtable. I want to thank Dr. David Morgan from USF for being with us and his contributions to Alzheimer's research.

Medical research on ways to improve health of our nation's aging population should be a top priority. The need to increase collaboration among researchers has never been more important, especially in light of some of the ridiculous political environment that we are having to navigate, including sequestration, which bring about drastically reduced research budgets. This recent showdown, or, shall I say, debacle, demonstrated just how critical NIH is to our nation's fiscal and physical health, and I want to thank Senator Collins for her work in helping getting us out of that catastrophe.

There is a lot to discuss this afternoon and I want to thank all of you again for being here, and I want to turn it over to Dr. Hodin to begin our roundtable and take the opening statements from the panelists. Dr. Hodin.

Mr. Hodin.

STATEMENT OF MICHAEL W. HODIN, PH.D., EXECUTIVE DIRECTOR, GLOBAL COALITION ON AGING, AND MANAGING PARTNER, HIGH LANTERN GROUP

Mr. HODIN. Thank you, Senator, and welcome to all. We are delighted and I am honored, as Executive Director of the Global Coa-

lition on Aging, to open this roundtable session. Let me provide perhaps a minute or so of context setting from a policy, a political, and economic point of view.

Population aging is arguably—oh, Senator Collins?

The CHAIRMAN. No, this is Senator Warren——

Mr. HODIN. Senator Warren.

The CHAIRMAN [continuing]. From Massachusetts.

Mr. HODIN. Yes.

The CHAIRMAN. Susan Collins is in a markup right now, and that is what is preventing her——

Senator WARREN. Right, and I apologize for being late. I was doing student loans.

[Laughter.]

The CHAIRMAN. You are doing great. You just keep it up.

Mr. HODIN. I thought you were getting prepared for the game tonight.

Senator WARREN. Well, we are ready.

Mr. HODIN. If you would like to say a word or two before we continue——

Senator WARREN. No, thanks.

Mr. HODIN. Thank you, Senator Warren.

So, population aging is arguably the most seminal topic of our day. It is about a shift in society from young to old. There are more of us that are over 60 than under 15, and in that context, it is about a transformation that we have not seen since perhaps the dawn of the industrial age.

S&P, in their 2010 report, put it this way. Global population aging—no other force is likely to shape the future of national economic health, social and public finances, as the irreversible rate at which the world's population is growing older. This is a social phenomenon. It is built on a demographic structure that we have before us an historical opportunity.

And I am delighted to be here to help moderate this and take remarks from some truly eminent scientists from around our great country.

But, perhaps, Senators, as you lead us in this and we think about it, I would suggest that this topic is as much a fiscal challenge as any social or health issue. We simply cannot afford to continue with public policy the way we invented it in the 20th century, in a different demographic time.

And as I thought about what this means, and particularly from a public policy context, it is the notion of thinking about spending as an investment rather than a cost, and what better investment for the individual and for society as the 21st century has us living in an era where there are more old than young.

So, I thought a little bit about it historically in this great body, and I would suggest to you there are three examples that America has before it that could lead us in thinking about this in a different way. One is what we did in the 1950s in creating the Interstate Highway System. We made a decision. It was politically tough, but it was an investment in our future.

A second is our spending on the children. We do it for education and we do it in childhood immunization. In the 21st century, it is in our self interest to think of adult immunization, for example.

And thirdly, as you well know, Senator, the space program. It is one of the great courageous moments in our time, and at the core of it was the notion that we decided to invest and think of spending in that way and not as a cost.

We cannot afford this any different, as one-quarter of our total population will be over 60 within the next two decades. It is not fiscally sustainable to continue thinking and acting as we did in the 20th century.

I submit to you, this is a big deal. More old than young demographically is baked in for the next two next generations, and it comes about as a result of two factors. One is longevity, we are living longer, but the other are these steadily low birthrates. And what America does here will affect everyone around the world because this is a global phenomenon.

The oldest country on the planet is Japan. It is a place we will get to. And in 2020, the Japanese will sell more adult diapers than baby diapers. This is a place we want to avoid here, and if a way to do that is by addressing our NCDs from the standpoint of the biology of aging, then we should rethink this paradigm, rethink this structure.

And I commend all of you for being here. We are delighted. And I think, at this point, I would like to turn it over to our esteemed colleagues, the great scientists who are with us, and if you would introduce yourselves as you begin your three- to five-minute openings, after which we will then have a discussion and some questions among us.

The CHAIRMAN. Why do I not just introduce everybody so that we know.

Richard Hodes, Director of the National Institute on Aging at NIH.

John Alam, M.D., Head, Therapeutic Strategic Area for Diseases of Aging.

James Kirkland, M.D., Ph.D., Professor, Noaber Foundation Professor of Aging Research, and Director at the Kogod Center on Aging at the Mayo Clinic in Rochester?

Dr. KIRKLAND. [Off microphone.]

The CHAIRMAN. Too bad you are not in Jacksonville.

[Laughter.]

Richard Morimoto, Ph.D., Professor, Department of Molecular Biosciences, and Director, Rice Institute for Biomedical Research at Northwestern.

And David Morgan, Ph.D., Chief Executive Officer and Director, the Byrd Alzheimer's Institute, and Director of Neuroscience Research at the University of South Florida College of Medicine.

Okay. Please, Dr. Hodin.

Mr. HODIN. Thank you, Senator.

Dr. Hodes.

STATEMENT OF RICHARD J. HODES, MD, DIRECTOR, NATIONAL INSTITUTE ON AGING, NATIONAL INSTITUTES OF HEALTH

Dr. HODES. Mr. Chairman, members of the committee, thank you very much for the opportunity for all of us to join with you in this

discussion of the basic biology of aging and its relevance to age-related diseases and conditions.

This is really a spectacular and unique time in which there is a convergence of imperatives for this kind of effort. One of those imperatives has to do with the remarkable advance that science has made, and you will be hearing from some of the leaders about the areas in which our insight about basic biology that underlies aging has advanced.

The other, Dr. Hodin was alluding to, relates to the demography, and there are lots of numbers that express this well. Some time during this decade, for the first time, there will be more people on the planet—first time in human history—age 65 and older than under five. Between now and 2030, even 2050, it is actually estimated that, worldwide, there will be very little growth in the population of individuals through age 64. However, there will be a doubling or more of those over 65. Those over 100 will increase by four- to fivefold. So, we are going to be seeing unprecedented societal as well as medical implications of all this. And this is itself a remarkable tribute to the advances that have been made in medical and public health areas.

But what comes with it is the challenge of the fact that aging is, in fact, a primary risk factor for many conditions, and so our attention turns, in addition to the extension of longevity, to improving health spans, so we live longer lives free of disease with a maximum of health and independence.

Recognizing this, the NIH has come together, as has the scientific community, to advance what has become known as geroscience, a new integrative science that explores the possibility of the growing insight into the fact that the basic processes of aging are related to the risks for many diseases and conditions, and so understanding the process of aging will help us to identify targets, ways to intervene and prevent disease and disability.

As was noted, together with the Gerontological Society of America and the Alliance for Aging Research, NIH will be sponsoring a summit that will begin tomorrow and go through the end of the week in which scientists from around the world will come together to try to explore the most exciting of these opportunities and dictate for us what the priorities ought to be in pursuing them.

There will be a number of topics that will be undertaken at that summit. Just to give you an idea of some of the integrating principles, exploration of the importance of inflammation, which we think of in terms of immune response and infectious disease but, in fact, is much more than that—inflammation, which is a growing parameter of aging and also appears to be associated with many—most, if not all, chronic diseases of aging.

Adult stem cells, the stem cells in all of us which perpetuate the health and integrity of our organs and tissues, change with age, and understanding how and why that happens to maximize the effectiveness of those cells is important. In addition to the cells themselves, the milieu environment in which they exist is important, and one striking example recently reported here is the identification of a circulating factor in the blood of young mice which, when injected into old mice, actually reverses cardiac disease that is very similar to the cardiac pathology that affects many older Americans.

Proteostasis, the way in which the proteins of the body that are the composition of many of our organs and tissues, the way in which it is monitored to make sure that integrity sustains itself, changes with age and it also is the heart of many diseases of the brain and other organs and tissues. So, again, a commonality that is to be seen there.

It is our hope that what will be achieved at the summit and which we can communicate and discuss with you here will lead to a growing coordination among the scientific disciplines that have focused on specific diseases or organs and tissues to recognize that paying attention, as well, to the commonalities of aging is a means to maximizing the efficiency with which we carry out this research. The Geroscience Interest Group at NIH, with leadership provided by some of our guests here, Felipe Sierra, Ron Kohanski, Kevin Howcroft, and John Birch, reflect now a coalition of some 20 of the Institutes across NIH who have come together to sponsor this, recognizing the commonality of their own purposes with understanding, a better understanding of the aging and aging process.

So, I look forward to what we will be experiencing in the next days in this summit and I look forward to the opportunity to share with you and address questions that you will have during this hearing. Thank you again for the opportunity to be here.

Mr. HODIN. Thank you, Dr. Hodes.

Before we proceed, Dr. Morimoto, I would like to recognize Senator Donnelly from Indiana. Thank you for joining us. If you would care to say anything or——

Senator DONNELLY. I will say that I am a Sox fan, but a White Sox fan.

[Laughter.]

Mr. HODIN. So, coming from New York——

Senator DONNELLY. So, you and I are on the same team, then.

Mr. HODIN. Coming from New York, our season ended a long time ago, so——

[Laughter.]

Mr. HODIN. Dr. Morimoto, please.

STATEMENT OF RICHARD I. MORIMOTO, PH.D., BILL AND GAYLE COOK PROFESSOR OF BIOLOGY, AND DIRECTOR, RICE INSTITUTE FOR BIOMEDICAL RESEARCH, NORTHWESTERN UNIVERSITY

Mr. MORIMOTO. Well, Mr. Chairman, other members of the committee, thank you very much for this opportunity.

So, I am a basic biomedical scientist at Northwestern. I am very interested in what is called cell stress and quality control. It is an ancient process. Every organism on the planet actually can detect changes in the environment and then it mounts a response that is protective. When it works well, it keeps our cells robust and healthy. The problem is that aging and disease challenge the cell stress response. The consequence is quality control goes awry.

Every time our cells divide, it would be just fine if the parts replaced were as good or better than the ones that were taken away. Unfortunately, what we have learned, at least for proteins, which is the major molecule, proteostasis that Dr. Hodes talked about, is

that the proteins that get replaced are imperfect and the system starts to slowly decline.

The question is, can we detect it early? Can we detect it well before it leads to clinical cognitive decline that leads to adult onset diabetes, to cancer, to neuro-degeneration? But even if we could detect it early, do we have any small molecules that we could use to treat people with Alzheimer's and Parkinson's and ALS? But I think this emphasis on healthy aging, what is it that keeps cells robust, is very important, because if we could understand that, that is the underpinning, really, for a healthy society and actually pushing back what would otherwise be premature aging and disease.

Senator Warren will appreciate that in 2008, a couple of colleagues and I formed Proteostasis Therapeutics on Main and Albany in the wonderful town of Cambridge, really to address for the first time some of these diseases of aging, to identify the molecular biomarkers that occur early, and to actually study the course of retinal degeneration, of cystic fibrosis, of Alzheimer's and Parkinson's. But I think the key point is trying to emphasize what are the molecules that change, when do they change, and what can we do about them? Could we even restore it so that someone lives a healthier, more productive life?

Thank you.

Mr. HODIN. Thank you, sir. I might tell you that the kind of science that we are dealing with here is very, very exciting, and looking at it from a public policy point of view and economics, it is the type of future that we will want, so thank you very much.

Dr. Kirkland.

STATEMENT OF JAMES L. KIRKLAND, MD, PH.D., PROFESSOR, NOABER FOUNDATION PROFESSOR OF AGING RESEARCH AND DIRECTOR, ROBERT AND ARLENE KOGOD CENTER ON AGING, MAYO CLINIC

Dr. KIRKLAND. Chairman Nelson, Senators Warren and Donnelly, and other attendees, thank you very much for having me here, and I commend your efforts in looking at ways to improve the health span of our aging population.

I am a clinical geriatrician. I am also a basic scientist. And in my career, I have noticed a number of really, really exciting changes that have been accelerating over the past couple of years. When I went to medical school, I was taught that the biggest risk factor for most of the age-related chronic diseases, which account for the bulk of health care costs, was aging itself. It was chronological aging was the biggest risk factor for dementias, for cardiac disease, for various cancers, for diabetes, for arthritis and a long list of other things. And then we quickly moved own the list to other risk factors because we were told, there is nothing you can do about aging, so let us mess around with people's blood pressure a little bit, their cholesterol, and play around the edges and maybe reduce the risk a little bit.

What has been particularly exciting is in the last few years, we have moved from thinking that aging is an inevitable risk factor to one that might actually be modifiable in some ways. A little bit science fiction at the moment, but it does seem, especially since the end of the—around 2009—that we have interventions that are

pharmacologic that can actually manipulate these processes in the same way, to some degree, as lifestyle interventions that we have discovered before, things like caloric restriction and exercise. And this has accelerated to a great degree, and the NIH, and particularly the NIA, are really responsible for providing the resources to get to this point.

There is something called the Interventions Testing Program, which is a consortium of three centers, and it tests drugs that are suggested by the aging community in experimental animals, mice, and so far, 16 drugs have been tested and five of them so far have increased lifespan in mice, five. And there are many others that—approaches that seem to be effective in this.

But, we do not want to increase lifespan at all costs. We do not want to live to be 130 and feel like we are 130. What we want to do——

Senator WARREN. [Off microphone.]

[Laughter.]

Dr. KIRKLAND. Yes, exactly. What we want to do——

Senator WARREN. [Off microphone.]

[Laughter.]

Dr. KIRKLAND. That is even worse. But the ideal would be to—can we figure out a way where we could live to maybe be 100 and feel like we are 50, as occurs in some centenarians, some of the people in our population who have a genetic predisposition to live to advanced old age.

And there might be a chance that we can do this, and there does appear a chance that with some of these drugs and genetic manipulations that we have been finding recently will affect health and lifespan, we are beginning to delay, at least in most models and other experimental animals, the onset of age-related chronic diseases.

And as Dr. Hodes mentioned, there is a big intersection between fundamental aging mechanisms and the genesis of these diseases. The prospect that we might be able to target fundamental aging mechanisms and delay them as a group instead of dealing with them one at a time, only to have another one take over a few months later, is extremely exciting.

So, the basic biologic field has moved from a period of description through a period of discerning mechanisms that are responsible for age-related processes and now we are at the point of developing interventions at least that work in vertebrates and lower mammals. We are coming fast to the point of translating these things into clinical application. And, in fact, some early stage clinical trials with some of these agents are, indeed, underway, or are at least contemplated.

So——

The CHAIRMAN. This is in animals?

Dr. KIRKLAND. In humans, very, very early with some of the drugs that were found on the intervention testing program and other approaches. There are other ways of doing this, as well. For example, eliminating senescent cells is one of the things which appears to improve health span, and there are potentially ways to target these cells and maybe some of these drugs act partly

through processes affecting these particular kinds of cells and other things that are going on.

So, the field has become extremely exciting. Our students are energized. You know, one of the things that I use as a bellwether to figure out if an area of science is moving forward is whether young students are choosing to put their careers on the line and go into this area and it is happening, and it is happening big time. We have got a very small medical school at Mayo. We have only got six M.D.-Ph.D. students. The last time around, four out of the six decided to combine geriatrics and basic aging research. So the young people are moving into this.

Now, we have got a lot of challenges. At the moment, as I mentioned, this is science fiction with regard to humans. We need to test whether these things that we can do in mice are, indeed, translatable. We need to expand our discovery pipeline so that we can develop more of these agents. We need to know if they really do target age-related diseases across species.

And we need to begin to explore this in a rational way in humans. We cannot study lifespan in humans. We cannot even study healthspan in humans. So we have to have the right clinical trials, paradigms, for doing this, and that means having the right kinds of study populations and looking at the right kinds of outcomes. We will have to have agents that act in people when they are already beginning to feel a bit under the weather or at risk. We do not want to develop necessarily interventions that you have to give to people in their 20s to have an effect when they are 80 because that will not be realistic. But I am cautiously optimistic that we are moving in this direction.

A challenge—there are several challenges. One is that we do not have many people who are trained in the intersection between basic biology and clinical geriatrics. There are 7,000 geriatricians in the United States. There are around a dozen who have basic science grants from the National Institute on Aging. That is very small. We need to do a lot of work on curricula and training.

Since we are moving into a period of translation into clinical application, that becomes, and I am sure you do not want to hear this, but it becomes expensive, and the question is, how can we do this and how can we do this without cannibalizing the basic research which is so important to keep the pipeline going. So I commend what has been happening at the NIH with the GSIC initiative, which Dr. Hodes and Dr. Sierra and others have formulated where a variety of Institutes—I think 20 out of the Institutes or 21—across the NIH have come together to look at the intersection between the particular disease that that Institute is focused on and aging, and I think that is a very good way to go.

And we have started to emulate that within Mayo, and through the generosity of the NIH, we have been able to establish now—as of a few weeks ago, we got funding to establish a transnational geroscience initiative of aging centers across the country so that we can try to coordinate our efforts and save costs by approaching things in a rational way.

I just hope all this can be done. I think it is potentially exciting. I think you mentioned potentially transformative endeavors in

moving our health forward and this is potentially one of them. Thank you.

Mr. HODIN. Thank you.

The CHAIRMAN. Doctor, one of the requirements to be a member of the Aging Committee is that you volunteer to offer yourself as a guinea pig——

[Laughter.]

So I want to offer the Aging Committee, both Republicans and Democrats——

[Laughter.]

For any of your experiments.

[Laughter.]

Dr. KIRKLAND. I am first on the list, though.

STATEMENT OF JOHN ALAM, MD, HEAD, THERAPEUTIC STRATEGIC AREA FOR DISEASES OF AGING, SANOFI-AVENTIS

Dr. ALAM. Good afternoon. Thank you very much, Senators Nelson, Warren, and Donnelly, for your interest in this very important matter, and thank you to everyone in the audience for coming today.

I am a physician scientist who has been, for the last almost 23 years now, working in biotech and pharma in R&D of novel, innovative medicines, mainly, actually, in my hometown of Cambridge, and I am, yes, a Red Sox fan.

Senator WARREN. Go Sox.

Dr. ALAM. I am today head of an R&D group at SANOFI dedicated to research in aging and age-related diseases. It is actually one of the few units, I believe, across the pharmaceutical industry that is focused specifically on aging and age-related diseases. SANOFI, otherwise, it is a top five global pharmaceutical company that is active in a wide range of medical disease conditions—cardiovascular, diabetes, cancer, rare diseases, and multiple sclerosis.

The R&D unit that I lead, which is called TSU Aging, was created a little bit more than three years ago with an objective of discovering and developing medicines that are specifically directed at older individuals and patients with chronic disease. We believe that we have been pioneering in this approach to aging with a—and moving towards, rather than studying diseases in isolation, to the study of a collection of certain major age-related diseases in parallel as well as the integrated health needs of the elderly with the aim of maximizing overall the capacity for independent living with aging.

Today, our R&D activities are attempting to address both age-related chronic disease, such as Alzheimer's disease, Parkinson's disease, stroke and osteoarthritis, as well as what are called age-related geriatric syndromes, such as chronic pain, age-related muscle loss, or sarcopenia, and frailty.

When we set this unit up, our thinking was that along with, I think, many of the people around this table, that to approach aging and the chronic diseases of aging, that what was required was a fundamental shift in the scientific approach to discovering and developing innovative medicines for age-related diseases.

In my written statement, I actually give a lot more color and detail on the rationale and what makes the chronic diseases of aging

very different from the more obvious diseases, such as infectious disease and cancer, in younger and middle-age people, where the basic biologic mechanisms are that much more distinct from what is otherwise healthy and normal.

But for the moment, what I will say is that, based on that perspective, we set up the scientific strategy with three pillars at the core of the aging group. Number one is in order to cross-fertilize ideas and concepts as well as developing therapies that address common age-related biologic mechanisms, we integrated the scientists working in the major age-related diseases and syndromes under one R&D organization and leadership.

Second, we are placing greater emphasis on intervening earlier in the disease process rather than intervening late in the stage of disease where, particularly in older individuals, there may be irreversible damage and loss of function.

And, third, wherever possible, consider multi-pronged strategies and integrated health care solutions that not only provide pharmaceutical products, but also address health care needs more broadly and integrated solutions that may encompass novel technologies and services.

Otherwise, across global R&D at SANOFI, from an operating model standpoint, we have recognized that our internal efforts can—for complex diseases, such as a variety of diseases of aging, cannot be enough, and so we have adopted over the last several years an open innovation model whereby we work in a network manner with academia, with governments and other players in the biotech and pharmaceutical industry, both directly and in one-on-one private collaborations and partnerships, as well as in larger public-private consortia.

Before concluding, I just want to make one comment on the article that has been circulated regarding the potential impact that the—the potential greater cost impact of extending life. In our view, that increased cost might arise from increasing life could be an outcome if, in fact, we continued with business as usual, that is, developing treatments that intervene late in life and extend life only in the context of already existing disease and morbidity. However, we believe that the opportunity in aging research is that through this research, we are able to develop interventions that are early enough in the process that they can primarily extend healthy life years where, in fact, in the end, we might be able to decrease health care costs rather than add to the burden of health care costs. In addition, we believe that integrated aging solutions that incorporate technology services such as nutrition, exercise counseling, and other complements of pharmaceuticals have the opportunity to further impact health care costs positively.

In conclusion, by developing novel, innovative medicines and integrated health care solutions for the aging population, notably through partnerships involving public and private stakeholders, we, or SANOFI, is dedicated to finding solutions to the problem of this century, the worldwide challenge of increasing demand for health care with aging populations. Thank you.

Mr. HODIN. Thank you, Dr. Alam.

Dr. Morgan, before I turn to you, perhaps I could just highlight some points you were just making that are so critical, which is that

this is about and for the children as much as anything else, and the children's children, because this is about a demographic historical change in our 21st century, and oftentimes, people think of it as a particular moment in time related to the baby boomers. That has catalyzed this for us, but what it is really about is our demographic condition that we will be living with at least over the next two to three generations. That is how these things work. And so when we think about it as, well, are we going to spend for K through eight education or old people, that is not how to think about investment in this kind of research.

Dr. Morgan.

STATEMENT OF DAVID MORGAN, PH.D., CHIEF EXECUTIVE OFFICER AND DIRECTOR, BYRD ALZHEIMER'S INSTITUTE, AND DIRECTOR OF NEUROSCIENCE RESEARCH, UNIVERSITY OF SOUTH FLORIDA COLLEGE OF MEDICINE

Mr. MORGAN. Thank you. So, I, first of all, want to thank the members of the committee for coming here and listening to us today and giving us an opportunity to share with you some of our opinions on these issues.

My name is David Morgan. I have been working on Alzheimer's disease for about the last 25 years. But 32 years ago, I actually moved from Northwestern University, where—I feel very out of place here; I am actually a Cubs fan——

[Laughter.]

To the University of Southern California to the Andrus Gerontology Center, where I began studying aging and brain function, aging and neuroscience, to try and understand not necessarily diseases, because at that time, Alzheimer's was still really applying to people under the age of 65, not normal people in their 70s and 80s who have the same type of pathology, but we were trying to understand what were the normal changes with brain aging, and it became a very interesting topic for me. I developed personally a certain perspective on this that may be useful as this geroscience community moves forward.

We have often thought about diseases as having an interaction between genes and the environment. It is your inheritance and it is your lifestyle and it is what you are exposed to and all these things interact to cause—increase your risk for heart disease versus diabetes, versus cancer, et cetera. But I think the third factor is aging, and it is something that often is not considered in any of the models that we have about specific diseases.

And one of the things I noted in going through the literature when I started working on Alzheimer's is if you looked at people who died from Alzheimer's in their 60s and you looked inside their brains and you looked at the amount of atrophy and the amount of degeneration and the amount of damage that was there, it was always much, much greater than when you looked at somebody who died with the same symptoms at the age of 90. And part of the reason is that the major change with age physiologically is a loss of our reserve capacity, our capability of overcoming challenges and insults to our physiological well-being.

You know, even back then, this notion that it would be much more beneficial at a population level to slow the aging process and,

therefore, extend the health span, that this was viewed in a very positive way, and if you got rid of heart disease, you got a year or two, and you got rid of cancer, you got a year or two because something else would come along and be a major problem. But that never really seemed to develop and take hold, and it is interesting now that after I have shifted into a very disease-specific modality in my science that this very simple concept is coming forward.

So, I think it is useful. I think it is valuable. I think, as we go through this today, I am going to actually bring up a few things that concern me about it. I think there are some potential limitations. We have some experience with this through the animal system with a thing called caloric restriction. It may not be applicable in humans, and certainly, I do not know if I would want to live a long time if I had to be completely restricted in calories, but I think it gives us an example of something that we are pretty convinced can slow aging.

But another feature that I am struck by as I work in Alzheimer's disease is how the major risk factors for Alzheimer's disease, we think age, you know, too many birthdays is the biggest risk factor for Alzheimer's. But beyond that, we also noticed that the cardiovascular risk factors are also important. The diabetic risk factors are important. And it all boils down, ultimately, to lifestyle choices that people have made about exercise, about what they eat, about what they expose themselves to, about cigarette smoking, et cetera.

And I think what these are really doing, because they affect all these neurodegenerative diseases, is genuinely modifying the age process and that some people may get them earlier, some people may get them later, but we also have these additional influences on our aging. And while genes and the environment influence aging, as well, I think they affect disease-specific phenomena as well as this general biological phenomenon of aging. And finding ways to try and slow that will obviously be permitting us to get greater gains in longevity than we would have otherwise.

But, just one caution that I have, and you brought this point up. If there is someone who already has dementia and they are at the point where they are really not knowing exactly who they are or who their relatives are, the quality of life is impaired, I do not know if I would want to extend their lifespan from that point forward. That would certainly be a concern of mine.

So, I think—I personally believe there is going to be a very strong role for disease-specific approaches, as well. I think that you have got factors that increase your risk for a disease. I think you have factors that increase, or speed up or slow down your rate of aging.

I am a lead representative for an organization called Researchers Against Alzheimer's and we are advocating to get more and more funding for Alzheimer's because we think it is a relatively neglected disease, that the research dollars we are investing in it relative to the medical costs are not even beginning to be comparable to these other major diseases we have discussed.

But, I do agree. I think that the aging process is a very fundamental phenomenon and I think that part of the reason it becomes so critical is that the amount of damage you need gets less and less as your years get higher and higher.

Mr. HODIN. Thank you all.

Senators, did you——

Senator WARREN. Well, I actually am going to have to go preside. I just want to say, I wish I could stay for another two or three hours. One of the things that happens, I am learning, in this job, is we get pulled in a lot of different directions.

But I do want to say on this, I want to commend the Chairman. The Aging Committee, my sense is, we want to be your partners. Putting this in context, that the challenge we face in the 21st century is we are getting old as a—not in this room, of course, but, I mean, collectively.

[Laughter.]

Mr. HODIN. Well, including this room.

Senator WARREN. Not really.

[Laughter.]

In the country, and so it really is the question of how we think about the policies that make life possible at the end of the 21st century when the fastest-growing age group is those over 100 and the next-fastest is those over 90 and those over 80. And so how we think about dealing with that, and it seems to me it is a two-pronged strategy.

One is we need to treat every child like a gold nugget. Polish them up and get maximum value out of them, that each of them needs to be able to perform at the height of their potential and kind of move that curve forward if we can.

But the other half is to invest every nickel we can in the research that will help us manage our health, our beings as we age.

And so this is just exactly right. I am just sorry I cannot stay and take advantage of all you are talking about. You have sparked at least 100 new ideas in here. And I just want to thank the Chairman for doing this and say that the Leader will scold me if I am one minute late, so I just want to thank you.

Mr. HODIN. Thank you, Senator.

Senator WARREN. Thank you.

The CHAIRMAN. Well, Doctor, it was quite telling, what you said, that by a certain year, that we are going to have more people in adult diapers than in Pampers. That is kind of stunning, but it is the trend. So, to increase that quality of life as we continue to age, to be productive and healthy, do you have any magic potions, any supplements you want to recommend, any brain exercises that I should engage in? I have a lot of torment that we have to go through here in this political cauldron, but what are some of the things that you would suggest?

Mr. HODIN. Well, thank you, Senator, and adding to Senator Warren's point about thanking and congratulating you on calling this session today. So, perhaps we can engage in a little discussion and maybe even a little controversy.

Let us start on this basic question of the relationship between the biology of aging and the other NCDs that we are dealing with. Maybe Dr. Kirkland, Dr. Hodes, others, but we have talked a little bit beforehand. You could—by the way, this Doctor is the only—I am a political scientist, so I can be a layman here. Maybe you can explain this to us and also get us through this concern that Dr. Morgan raised about sort of a suggestion of one versus the other

in the reality of funding. How does the biology of aging lead to addressing the NCDs themselves?

Dr. HODES. I think all of us would be happy to address that. As you have heard, there is the strongest kind of research evidence to indicate that the aging process itself is an underlying factor in common to many diseases and pathologies, and maybe I will give you one example. It is a little science fictionist, but it is Jim Kirkland's work, so he will not dare talk about it too much out of self-consciousness. And it is illustrative of the way in which disease-specific research has informed the principles we are talking about now.

And I am thinking about a gene like P16, a gene which was described, perhaps first appreciated in terms of its regulation of cell division from a cancer point of view. And then the observation that in an animal, and probably with some assurance all of us, as we age, there is a population of cells, relatively small, in every organ and tissue that have become what is called senescent. They do not function so well. They do not divide so well. And these cells happen to express a high level of this gene product P16.

So through a very ingenious strategy, Dr. Kirkland and collaborators generated an experimental mouse by genetic manipulation such that at any point in time, they could give a drug that would selectively eliminate, kill off, just this very small fraction of cells that were senescent. And the outcome, I think quite dramatic and surprising to all of us, maybe to those who carried out the experiments themselves, were that eliminating the small number of cells in an animal that was already old, showing the effects of old age, would actually reverse in tissues such as muscle the effects of old age. So these animals, taking out just these few cells, could now run further, run longer, and perform the way younger animals could. In this case, although we all understand that prevention is likely the more effective treatment than reversal, in this case, even reversing the damage in a particular organ, in this case muscle and musculoskeletal systems.

So I cite this as one example on the verge of science fiction but coming to reality in which understanding, taking advantage of investing in cancer research, understanding the basic biology, what regulates cell cycle, and then translating that into an intervention that now may be the basis for taking it beyond mice and into animal species that could give some guidance in humans is one of these examples that I cite.

The CHAIRMAN. Thanks for that. When did you start working on those mice?

Dr. KIRKLAND. We started working on it a long time ago, the original ideas, but it was published in 2011, that particular mouse, but there is a lot of other stuff that is equally or even more exciting that is occurring around the country and across the world, showing related interventions or even other kinds of interventions that show this kind of promise.

It is very early. As Dr. Hodes said, it is still science fiction. But there are a lot of groups now working around the world on various aspects of the fundamental biology of aging that the NIH has largely supported that appear to be beginning to bear fruit. At least we

can get really, really healthy, highly functional mice that are older, you know, and can attack your kitchen and things like that.

[Laughter.]

Dr. KIRKLAND. What we—the next really, really big step is to—well, there are two things. We need to maintain that pipeline. This is extremely important. We cannot cannibalize our basic research efforts to pay for the very expensive translational efforts that we have to embark on, and we have to start the translational efforts and we have to do it the right way and a smart way.

And there are a lot of steps. There are a lot of potential red lights going through the tunnel before we reach the end of it that have to be addressed. But I am much more cautiously optimistic than I was ten years ago that this might—this kind of approach, in general, or a related approach, might actually work with respect to multiple age-related chronic diseases and targeting them together instead of one at a time.

I think, as Dr. Morgan was saying, it is very, very important, also, not to cannibalize disease-specific research because it is going to be very important to deal with situations once they have gotten out of hand.

But we need to think of strategies to do this translational research and continue the other things or even expand the other things that we are currently doing. It is going to take a lot of rethinking in medical paradigms and clinical trials paradigms and how we go through, interact with regulatory agencies and what sort of trial design do we use, what study populations do we use. There are a lot of details that have to be worked out, and I think this conference that is being organized by the NIH is a major stepping stone towards getting people to think about some of these strategies around these potential obstacles.

And, similarly, I think the NIH's support of bringing—the concept of bringing together the various aging centers around the country through a grant that they provided is going to help us think collectively and in a competitive way, but not a destructive competitive way, how can we achieve these milestones in the most economic way possible.

There is going to need to be an investment, though, and I do not know how much of that investment should be public or private. I think as the public becomes more and more aware of what could potentially be done and they see these old mice running around that look pretty healthy, there might be increasing support for moving in this direction, and certainly industry has recognized this increasingly and is beginning to make investments in this area. You are to be commended in thinking way ahead of other people in doing some of this, as are you.

Mr. HODIN. Dr. Morimoto, please.

Mr. MORIMOTO. One of the remarkable aspects of biology and really has contributed greatly to the biology of aging is that how all biological systems respond to age turns out to be quite similar. And the ability to do these wonderful studies in mice and to translate it may come as a surprise to some that the discoveries were made in yeast, bakers' yeast, or in a fruit fly, or in a nematode, C. elegans. The genes that actually regulate aging were not discovered in humans or mice. It was actually a little worm.

But this actually helps us, because unlike many things where it is highly specific to a particular organism or a particular tissue, it is a fundamental of life on earth at some level. And, therefore, as we make these discoveries, there are great partnerships, I think something that is very important, collaborations across the basic sciences through the clinical, and I think here is a very important opportunity. When the genes are discovered, the pathways are worked out about how aging works, it is really not related to a disease. It is just aging. But it becomes a fundamental if we understand that, and when it goes away, that is when it then leads us to Alzheimer's, Parkinson's, diabetes, and cancer. And I think it is when the mismanagement occurs.

So, I think we have done a good job of investing in very good basic science. I would agree and concur with my colleagues, we do not ever want to get into a position of competing because that is nonproductive. What we have to find a way is better partnerships to optimize the resources and, yes, certainly see if there are other opportunities, but to now take some of these fundamental discoveries.

There is, however, a real phase shift here. Even though it is called the National Institutes of Health, it is really the National Institutes of Disease. There is not that much emphasis on what is the underlying biology to keep your molecules, your genes, your cells healthy. And I think a lot of the emphasis here is tied into healthy aging. So, what can we learn to keep ourselves more robust and functioning better and longer and perhaps by that putting off the early onsets.

Dr. HODES. Just reinforcing what has been said, I do want to take the chance, as well, to thank you, the Senate, the Congress, the administrations that have been enlightened. You have heard about the diversity of basic research that has ultimately led to important insights, whether it is studying yeast or worms, whether it is studying the behaviors of organisms that are a single cell. And we have all seen, heard, and understood, sadly, even though the present, strong criticisms of this kind of research, which, on the face of it, unless one understands what their relevance is, do appear to be questionable.

But these examples you have heard today and many more converge on this continuing conviction, I think, that we have to maintain basic research and the biological and in the behavioral side because it ultimately has proven to be the grist out of which these great translational opportunities have developed.

So, we thank you and all of the Congressional support we have had, bipartisan, over the years for this very important perspective.

The CHAIRMAN. Well, you are talking about the amount of money that goes to NIH so that you all can give it out in grants. That is what you are talking about. There is an example. I assume yours was a grant from them, doing what you are doing. But you are talking to the wrong person, talking to me.

[Laughter.]

You need to go and visit with some of these folks that continually want to cut, and NIH is a good example. Dr. Collins came down here, told us he had to stop 700 grants going out because of the sequester in this last fiscal year. And, of course, we are facing the

potential, if we cannot work it out, of another major round of cuts in the sequester come January 15. So that is part of the problem.

Mr. HODIN. Well, picking up on, perhaps, this collaboration theme, I would like to—Dr. Kirkland, when we were talking beforehand, you mentioned—I found it very interesting that our friends in Europe, you would suggest, are a little bit ahead of us in this. So, I guess I have two sort of related questions. One is if you could explain that a little and whether we can—you know, what this means for American competitiveness and America's future, but secondly, in one sense, I mean, this is a global challenge. We are all aging, and as we know, it is happening across the planet. The emerging markets of Turkey and Mexico and, of course, China, due to as much their longevity and their low birthrates, are aging even more rapidly than we are.

So, I guess one question is, why is Europe, or how you would describe Europe as it were ahead of us, but the second related one, Senator, is how do we perhaps collaborate. I mean, one thinks of the HIV/AIDS model, which was a collaboration globally, and maybe the E.U.-U.S. Trade Agreement might be an interesting place.

Dr. Kirkland.

Dr. KIRKLAND. Well, I would hesitate to say or assert that Europe is ahead of us in basic aging research. I think the United States has really led the world in that, and it is because the National Institute on Aging has done such a great job amongst—and other organizations who are represented here.

What Europe has recognized, I think, is that they have, because of the single-payer systems, they have older populations, they recognize the demographic imperative in a very strong way. And one of the things that they have done is to focus on creating networks across Europe and funding them quite substantially to coordinate and collaborate in aging research across centers, which is something we are beginning to do here. Regulatory agencies in Europe are also fairly far ahead with respect to understanding some of the parameters within clinical trials and so forth.

I would say the United States is heavily represented and ahead in a lot of ways when it comes to basic aging research.

Now, I—so, Europe has different strengths and weaknesses than we do and they have chosen to make quite a bit of investment into bringing groups together and they are accelerating, unlike our situation here, their investment into aging research. So they are putting huge amounts into some of the universities in Europe that—so, their increments are very high. Their fold increase in spending on aging research has been high relative to what we have been able to do in the United States.

So, one of the things that various groups around the United States have been looking at, we are beginning to come together as networks and we are beginning to speak to the European networks that are established. And we have had a number of discussions, including with leadership at the NIH, about potentially finding ways that we can collaborate with European networks so that if there are big, expensive projects, we can cost share. If there is infrastructure needed for aging research, for example, databases or specimen storage kinds of paradigms, that we can cost share.

So, I think we are looking for every possible way we can do this kind of research on a collaborative way, not only nationally, but internationally.

Mr. HODIN. Dr. Alam. Oh, yes.

The CHAIRMAN. [Off microphone.] I have to excuse myself for a vote. Would you flesh that out for our staff, going through the European-U.S. trade route, what it is that you want with respect to this shared relationship. I want to thank you all very, very much.

Mr. HODIN. Thank you, Senator.

So, Dr. Alam was going to say something, and then Dr. Morimoto. Please. And then Dr. Morgan.

Dr. ALAM. Well, the comment I was going to make was just that I think beyond the science, to translate this into clinically actionable outcomes, and particularly as we move beyond disease-specific into the geriatric syndromes and thinking about aging and how we can impact patients or individuals who may not have something we would traditionally consider a disease, such as frailty, and that we need to also be thinking about in discussing how we can support the regulatory pathway and perhaps even the clinical paradigm of managing older individuals who have declining function and increasing incapacity but do not have a diagnosable disease.

And I think in that respect, it is actually in that arena where Europe is probably further advanced than the American system, is because they recognized the function—the impact from a financial standpoint of that loss of function and they are really starting a whole range of initiatives in public-private consortia of trying to intervene and in management strategies that may not have actually a pharmaceutical around it but can have impact in improved function. And they are supporting that, I think, both from a regulatory perspective and from a reimbursement perspective more actively than we are here in the U.S.

Mr. HODIN. Very interesting. I guess Dr. Morgan, please—or Dr. Morimoto. Yes. Sorry.

Mr. MORIMOTO. I just wanted to add to what Dr. Kirkland said about Europe. It is really different rates of acceleration. I think what we are seeing in Germany is a tremendous investment of funds. After all, Germany and Japan are the two fastest-aging countries on the planet.

Just to add a little bit more detail, in the past five years, the German government invested into a huge countrywide Center for Neurodegenerative Disease with 12 centers with the headquarters in Bonn. It is a huge investment, nearly 1,000 scientists. Just, actually, a week ago, I was at the opening of the Max Planck Institute on Aging in Cologne, which is an extraordinary event focused all around, now, in this case, the biology of aging. There is very little translation. This is something they are hoping to do. But they have recognized that that is where they are going to put their investment.

I think, by comparison, Japan is aging so fast that they are not putting their money into the biology of aging but they are putting into robotics to take care of the individuals who are aging and other directions like that.

Dr. KIRKLAND. Korea.

Mr. MORIMOTO. Yes, and Korea. But I think that there is a very important opportunity here for the United States to take the lead in partnerships. That is something we do well. We are good at reaching across to other countries and saying, look, how a Japanese, a German ages is the same as an American and let us work together because we now have larger populations we can study. We can compare the various treatments, the modalities. I think that is going to be critical, for us to take the lead in the world.

Mr. MORGAN. So, I just have a couple of quick comments. I think one of the things about the sequester that we are seeing, combined with the increased investment overseas in various research, is scientists are talking with their feet. They are leaving. They are going back to the countries from which they originated. You know, the history of the United States' scientific superiority has been the ability to attract these people from overseas to come here and I think we are starting to see the reverse of that, in part because of reductions in funding.

I think another way to approach some of these things is the public-private philanthropy partnership, and I think the best example of that I have seen is ADNI, sponsored by the NIA. This is an incredibly successful organization where the pharmaceutical industry recognizes there is a pre-competitive space where they can make investments without necessarily worrying about it costing them in competition with the other pharmaceutical industry members. And I think your company's engagement in this is actually just probably the beginning of this, and I think there are opportunities to start considering engaging in that type of activity, as well.

In terms of the international collaborations, there is a G–8 summit that is coming up and Alzheimer's disease is going to be one of the major issues to be discussed there. And I think there are some limitations in trying to set up international collaborations. Besides the distance, there are restrictions on NIH funding to be used overseas. You have to have a special justification for it. I think there are ways in which this can be made—the regulations regarding these things can be made less onerous and more capable of permitting those types of interactions in order to support that type of multiple-country collaboration.

Mr. HODIN. Thank you.

Another point which several of you have touched on and was alluded at the very beginning, Dr. Kirkland, you talked about your young scientists who are choosing to go into the field. How are we doing on skills and competencies? Do we have what we need? Do we need to invest in that, as well? Where is that, and do we have—I mean, that is going to take a different kind of, or a separate kind of funding stream, as well.

Dr. KIRKLAND. Yes. From—the field is moving into a new realm, and that is a realm of clinical translation. And I am a geriatrician and most of us in geriatrics, we have—for a long time, we have had nothing fundamental that we could do. We have been able to—it is very important work, and I do it as a clinical geriatrician. We figure out ways of providing better devices, better walkers, better incontinence devices, better ways of providing exercise and other kinds of interventions, ways of trimming drugs, ways of managing the long list of chronic diseases that people have, but we have had

nothing fundamental, really, really fundamental and transformative, that we can do, unlike what has happened in other specialties where there are agents and approaches that are novel and fundamental and require investigational new drug development.

So there are very few geriatricians who have had experience with translation from the bench to the bedside, with investigational new drug work, and this is a real gap. We do not have a lot of people who understand the kinds of outcomes we need to look at in clinical trials, things like frailties, or things like, say, recovery after chemotherapy or surgery or treating multiple age-related chronic diseases in a population that is elderly with comorbidities and living at home and following more than one outcome at a time and doing the right statistics. We just do not have people who are trained how to do that and understand the basic biology enough to be able to do the translation.

As I mentioned, there are 7,000 board-certified geriatricians in the United States, around 12,000 geriatricians, some of whom have been board-certified in the past, but very, very few of them have formal basic science training to the kind of level where they are competitive for research grants in the basic biology of aging arena.

It is totally unlike—I am also an endocrinologist. In endocrinology, a lot of my colleagues who are in academic institutions are quite comfortable walking into a laboratory and writing an R01 grant. It is not true in geriatrics. We do not have those people trained. So we have got to create training programs for these people.

In the meantime, what we have to do is get groups of people working together, basic biologists working with people who are experienced with clinical trials. The way we have done it at Mayo is by using a lot of people who have been experienced in cancer clinical trials and then people with IND experience and forming teams. But, eventually, we will need some captains of those teams and we do not have them.

Mr. MORIMOTO. One of my former hats was as the Dean of the Graduate School at Northwestern. So I thought deeply about education and training, about the M.D.-Ph.D. programs, about the—anything that fell under my umbrella. And I think what you bring forth is the necessity for our institutions to be creative and create new programs to meet these needs. Often, what we do is we take our existing programs and tuck students in and just hope it works. But science is more complicated, and if you want to train someone who understands aging, it would not be a good idea for them to just understand a molecule or another one just to be a geriatrician.

I think what Dr. Kirkland brings forth is that we need to train a new breed of, whether you are a Ph.D. or an M.D.-Ph.D., actually, it should not make much difference. As a Ph.D., you need to understand epidemiology, understand the social situation of aged individuals. As an epidemiologist, you really should start to understand what is happening to cells. This does not happen, even in the best American institutions, because they tend to be somewhat Balkanized.

But I think this is something where NIH has had an opportunity. It can stimulate new behavior by calling, you know, creating or encouraging people to come up with new programs. And it may be

that in this area and in this era, that we could put forth an idea of developing some new programs to cross-train people to meet these needs.

Mr. HODIN. So as we are, perhaps, coming to a conclusion of our discussion, and as you go into the two days of conference, maybe, and certainly for the Senate, Dr. Morgan, starting with you, what is the one message you want to leave here for the Senators that you would like them to address or answer, and maybe each of you could conclude on that.

Mr. MORGAN. I do not know that I have a single message. I think aging and disease interact in very important ways. I personally do not believe that aging is a unitary process. I think we are going to find it is just as complicated as all the factors that cause disease and we are going to whittle away at this phenomenon. It is not going to be one day we will wake up and there will be a dramatically reduced rate of aging.

I think, however, that this is an investment that will be something that would benefit us in a long time in the future. I do not think it is going to have an immediate impact, but I think it is a very worthwhile activity. I think—the one thing I have noticed in science is you never really know exactly where the most important discovery is going to be made. It is a process of serendipity. I think, in some sense, it is actually Darwinian. It is random variation and selective retention.

Nonetheless, I think aging is something that has always intrigued me. I think that it is a fundamental research question of great interest. There are organisms that do not age, interestingly. There is negligible senescence is a number of them. But that is kind of beside the point.

I think——

Mr. HODIN. Tell me one, just as——

Mr. MORGAN. Organisms that do not ready mature body sizes do not seem to show aging, so alligators, for example, is one.

So, these——

I never got close enough.

Ah. Well——

[Laughter.]

We count the rings on their teeth when we get really close.

[Laughter.]

But I think that the issue of being able to slow aging, extending healthspan, and really diminishing the impact of these diseases on our society is a very, very worthwhile endeavor.

Mr. HODIN. Thank you.

Dr. ALAM. You wake up 20 years from now. What have we achieved as a result from this? Where are we 20 years from now?

So, I think we are actually—where we are going to be is through this, actually, to be able to address the diseases of aging by having started in the science of thinking about the basic aging processes. And, I guess, in my mind, I do not see disease-specific signs versus biology of aging being mutually contradictory or exclusive, rather that I think we need to—perhaps one can start acknowledging that we have been, from a science and R&D standpoint, we have struggled in the chronic diseases of aging and that maybe scientifically, that we need to think about other ways of bringing in actually new

thinking and new scientific perspectives. And one of the ways, I believe, is through focusing on the more fundamental biologic processes of aging.

It is also from a, I believe from a—perhaps this is 1(b)—that if we are going to address—bring innovative medicines that actually do also reduce health care costs, the disease-specific paradigm inherently seems to keep compounding the problem rather than actually being a solution to the problem.

Mr. HODIN. Very interesting.

Dr. Kirkland.

Dr. KIRKLAND. I think, put simply, we need to put more resources into this particular area, the intersection between the basic biology of aging and the genesis of age-related chronic diseases at the basic level and at the clinical and translational level. And I think that particular investment could potentially have a major payoff with respect to the morbidity and mortality that I see as a geriatrician with my patients and could have a huge impact on health care costs, especially if it turns out—and we need to test this—if it turns out we are able to compress the period of morbidity at the end of life or at least increase healthspan while keeping lifespan more or less constant and thereby decreasing the period of morbidity at the end of life.

So I think it is an extremely important area. We could be, and it is science fiction, but we could be approaching a transformative level. It could turn out to be something like—and I hope it will be—like the space program or these other kinds of major endeavors. It has the trappings of that. Who knows if it will come to that.

But I think we need to be moving faster than we are at the moment and that involves not only coordination, but it does require increased resources, and not only increased resources from the private sector and donors but also government, because it is going to turn out to be government that is going to be spending a lot of the money on dealing with issues with respect to our aging population if we do not do something sooner rather than later.

Mr. HODIN. Thank you.

Dr. Morimoto.

Mr. MORIMOTO. Can we control our own inevitable fate? Can we separate chronological age from the molecular health of the cell? And if we could identify molecules that tell you that you are healthy or that there is disruptions of various sorts that might lead to risk for a disease, to then be able to apply therapeutics or other genetic forms of therapies to change that course. So, 20 years from now, if I woke up, I would be happy if that happened.

Mr. HODIN. Dr. Hodes.

Dr. HODES. So, I think the way you first raised the questions there, what thoughts we might want to leave to this committee, to send to the policy makers who view what we do, and I guess for me, the starting point I think we would all agree upon is that the goal is to maximize the quality as well as length of life. This is the obligation we have in pursuit of research to that end.

I think you have heard from the representatives of a brilliant group of researchers who have growing perspectives—we will be hearing more in the next days—as to the specific strategies and approaches and priorities for getting there. But I would just applaud,

again, this committee for bringing us here. I think we have an obligation to report back in a way that is understandable, compelling, and convincing, and I would invite future opportunities to do more of the same with individual members, with a committee, because we need to be held to the task. I think there is brilliance and commitment up to it, but we welcome the scrutiny, the reminder of what the goal of all this is, and I think we all have a very common sense of that.

So, my final words would be thanks and a request to please bring us before you again for periodic updates and questions and a chance to converse with you.

Mr. HODIN. Thank you, Dr. Hodes.

I will conclude on the notion of also thanking the Senator and the committee for having the foresight and courage to bring us together. It has been an honor for me to sit around the table with some great researchers, great minds. Thank you for that.

I would offer the thought that really builds on, Dr. Hodes, what you just said about being convincing and compelling, and it is interesting that during the course of this discussion, probably the one word other than "aging" that has come up more than any other around the table has been Alzheimer's. I have seen some maps of the world—I am sure we have all seen them—with dots of prevalence, and when you look at this movement through the 20th century and then up to 2150, you see not just a health challenge or a social crisis, but you see a fiscal nightmare. And it is the fiscal nightmare that will get the attention around this building and in this political milieu.

And that is why, when I opened up, I attempted to focus on the point that sometimes it is important to understand that spending might not be as much a cost as it is an investment. And I do not have the scientific background to know whether we are going to find a cure for Alzheimer's or diabetes through the aging process or through a direct approach, but I do know that if we do not, we are not going to make it fiscally. And it is a global challenge. And so, therefore, I also suggest that while this is a part of America's future, it is a part of the world's future and there may be some very interesting collaborations that we can enable there, as well.

So, thank you all, and we would like to thank again the sponsors and all of those who will be meeting in the next two days. Thank you.

[Whereupon, at 5:29 p.m., the committee was adjourned.]

APPENDIX

Prepared Witness Statements

Global Coalition on Aging

Opening Statement of
Michael W. Hodin, PhD
Executive Director, Global Coalition on Aging

Presented Before the Members' Roundtable of the
Special Committee on Aging
United States Senate

October 29, 2013

Chairman Nelson and Ranking Member Collins, thank you for inviting us to discuss the importance of U.S. investment in basic scientific and medical research to better understand and prevent age-related chronic diseases, the prevalence of which are exploding as our population ages.

I am joined by some of the country's finest scientists, representing our foremost research organizations, including of course Dr. Hodes from the National Institute on Aging itself. So I am honored to be able to moderate our panel. But before I turn it over to the experts, perhaps I might set the context of today's Roundtable on how and why population aging drives us to this urgent need for better, more effective research strategies toward understanding and curing non-communicable diseases. NCDs,

To begin, there is the simple but profound fact that this phenomenon we call population aging is emerging in our 21st century as the most seminal structural change the world has experienced since the dawn of the industrial age. It is, to be clear and direct, the demographic fact of a society where there are more of us we call "old" than "young". Standard & Poor's, the sovereign rating company put it this way in their 2010 report, *Global Population Aging: An Irreversible Truth*: "No other force is likely to shape the future of national economic, health and social public finances as the irreversible rate at which the world's population is growing older." Whatever we understood to be true about public policy in the 20th century must change. This transformation, moreover, requires a new social contract fit for our 21st-century demographic realities. Economic and social policies created in the 20th century will no longer apply; and worse, could well have deleterious effects. This is huge, and we have barely begun to assimilate its consequences, which is why, Senators, your leadership demonstrated today is so welcome.

As the Executive Director of the Global Coalition on Aging (GCOA), I represent the global cross-sector business voice on aging policy and strategy. Through research, public policy analysis, advocacy and communication, GCOA is working to ensure global aging is a path for fiscally sustainable economic growth, social value creation and wealth enhancement. From this perspective, I can tell you this is truly the global challenge of our time. To use the vernacular the media and global leaders seem to like, population aging is

indeed now on the list of mega-trends. And so, what we do here today and in the next two days will have impact not only in and for America, but globally, too.

The aging of the American population is not simply a matter of the baby boomers growing old and living longer. This is part of the equation, certainly, but of equal importance is the steady, parallel decline in birth rates. Taken together, these two demographic forces – longevity and low birth rates -- are creating a new structure of society with an unprecedented and historically new ratio of old to young that will be with us far beyond the current "baby boomer effect", and well into our children's' children's century.

Hence, population aging prompts questions that are far more fundamental than how to increase funding for this disease or that entitlement program. Indeed, population aging demands a fresh, innovative approach to policymaking where the incompatibility between 20th-century approaches and 21st-century demographic realities is fundamentally challenged.

But I am optimistic that we Americans actually know how to do this; to take huge challenges and find real solutions. Let me suggest three models that have been the basis for wealth creation and prosperity and driven by our unique sense of American optimism . They are models for how we can view today's challenge of population aging.

The first is the creation of the national interstate highway network in the mid-20th century. American leaders recognized that investing in highways would connect regional economies to spur national economic synergy, and a federal-state partnership was formed to undertake the project. Despite plenty of political wrangling, the transcontinental network was built, and it laid the foundation for national economic development unparalleled before or since. It did not have to be. Yet it was done – and done in a way that connected excellent execution, vision, good ideas and ideals. We are better off as a nation for it. And, at its core, it happened through a deep understanding that spending on new transformative ideas should be viewed not as a cost but as an investment in our future – and that the price of not investing is far greater than the reverse. In its implementation it also showed what can be achieved through a comprehensive and integrated approach to public policy that broke down silos and generated cooperation, collaboration and excellence. My esteemed colleagues today will talk a great deal about this need of silo-busting and more comprehensive approaches for our research into the diseases of aging.

The second big American project is the steady, generous investments that we make in children. We do this in childhood education and in a stunningly progressive approach to immunization that have become rites of passage where it is now a part of the culture to be expected and welcome. It is the driving force behind enduring American success. And so too, we understand, intuitively, that investment in childhood immunization is not only good for the children, it is essential for a strong, successful and good America. Our children's health as they age is an essential component of a healthy society. And so we invest. And we understand this spending not as a cost but as an investment. The returns by any standard – human and economic – are unfathomably huge.

A third American project was the Space Program into which we put trillions over the decades that have yielded us and the world countless benefits in technology, medicine and science. But at its core was the underlying notion that this was to be understood less as a cost and more as an investment. An investment as much in a a set of ideas and a vision of the future, which has come to pass.

So, Mr. Chairman, I suggest this is exactly the situation we face today with the aging of our population. This huge shift, in ratio of old to young, brings us as a society to a moment where spending on research to find the solutions to the NCDs of aging can no longer be viewed as a cost, but must be seen as an investment. An investment in human capital. An investment in the national strength. An investment in our future. An investment for children, too. It will be worth it.

The profound shift in how we as a nation view the process of getting old will also come to be understood differently. It need not be a process of increasing dependence and disability as that part of life has historically been assumed to be, but ones that can be active, engaged, productive, and happy. Nor can we afford a view any different, as one-quarter of our total population will be 60 and over within the next two decades. It is not fiscally sustainable to continue thinking and acting as we did in the 20th century. The arithmetic just does not work. But at the center of this new vision for the growing number of those of us over 60 must be a healthier aging. It is a healthier aging to turn our 20th century miracle of longevity to a welcome and wonderful circumstance.

It is a big deal, and nothing short of a new social contract for all Americans. More old than young is demographically baked in for the next two generations. It may well be the condition for even longer, but it is certainly with us for our children and their children's lives. This is how these things work. And, therefore, a new way of thinking about how we do research to address the diseases of aging is for all America, young, old and unborn. We must find the cures for Alzheimer's, diabetes, cardiovascular disease and cancer – those NCDs that are the barriers to a healthy and active aging. And if those cures can better come through an innovative approach to the biology of aging then that is the path we ought to take.

We Americans have always had the capacity and imagination to make progressive public policies that anticipate emerging societal transformations. We did it with our highway system in the 1950s, we continue with how we approach education and health for children, and so too with our space program. It is a matter of self-interest and public interest perfectly colliding, which is precisely the crossroads the challenge – opportunity – of population aging presents us as a nation.

Aging as a Risk Factor for Disease and Disability: The National Institutes of Health GeroScience Interest Group

Richard J. Hodes, M.D.
Director, National Institute on Aging

Senate Special Committee on Aging
October 29, 2013

Senator Nelson, Senator Collins and Members of the Committee:

Good afternoon. I am Dr. Richard Hodes, Director of the National Institute on Aging (NIA) at the National Institutes of Health (NIH). It is a pleasure to be here today to talk about some of the remarkable scientific advances we've made recently regarding the basic biology of aging, as well as the initiatives we support to generate and maintain momentum in this increasingly important area.

The extraordinary increase in life expectancy for both men and women represents one of the great public health triumphs of the twentieth and early twenty-first centuries. In 1900, life expectancy at birth was just over 47 years; today, it is almost 79. The number of Americans over age 65 is also continuing to increase at a rapid rate. In 2010, there were approximately 40 million Americans over age 65; by 2030, demographers estimate that this number will jump to 70 million. The number of "oldest old" – people age 85 or older – is expected to more than triple between 2010 and 2050. Globally, most nations are experiencing a similarly significant increase in the over-65 population.

However, after about age 65, people become increasingly susceptible to progressive declines in physical and mental abilities. Age is well established as a primary risk factor for many disabling diseases and conditions, and even today, recent demographic studies are beginning to show increases in activity limitations among members of the enormous baby boom cohort. For this reason, the development of new interventions to improve and maintain health into old age – to improve *healthspan* – is an increasingly urgent frontier for modern medicine.

Since its inception in 1974, the NIA has supported groundbreaking research on the basic biology of aging in research laboratories around the country and within our own Intramural Research Program. Exciting findings from NIH's ongoing support of studies in the basic biology are suggesting new avenues for the development of interventions for age-related diseases and conditions, some of which are described in this summary. Some of the latest findings are described here. Until recently, the study of

the fundamental processes that underlie aging has often been dissociated from clinical work on aging-related disease and disability. In an attempt to bridge this gap, researchers have established the emerging field of geroscience, which is focused on the mechanisms by which the basic biology of aging drives chronic disease.

As you have heard, NIH's GeroScience Interest Group (GSIG) promotes innovative approaches to increase our understanding of the relationships between the biological processes of aging and age-related chronic diseases and disabilities. Established in 2011, the GSIG currently includes members from over 20 NIH Institutes and Centers and is one of the fastest growing Interest Groups at NIH – a testament to both the high level of cross-disciplinary interest in the topic and its critical importance with respect to public health.

Tomorrow, the GSIG and its partners, the Gerontological Society of America and the Alliance for Aging Research, will present a historic summit on "Advances in Geroscience: Impact on Healthspan and Chronic Disease." Over 50 leading geroscientists will participate, and more than 500 attendees have registered to join. Discussion and deliberation at the Summit are expected to generate research recommendations that will advance this critical area of science.

The Summit will focus on seven broad areas of research in which the basic biology of aging is believed to inform multiple disease processes. These include:

Inflammation. A pervasive feature of aging – and most, if not all, age-related diseases – is chronic inflammation Several epidemiological studies indicate that high blood levels of inflammatory biomarkers are the most significant risk factor for both morbidity and mortality in the elderly. However, many unanswered questions remain about the etiology of age-associated inflammation, whether inflammation is a cause or consequence (or both) of disease and the extent to which inflammation might also be beneficial.

Adaptation to stress. The ability to properly respond to chronic stress appears to be necessary for healthy aging, and an enhanced ability to adapt and adequately respond to stress has often been observed in long-lived organisms. In fact, mild stress appears to be protective (via a mechanism called hormesis, by which the organism's internal defenses against stress are activated). The point at which hormetic stress becomes damaging is not well understood. However, this remains an active area of study.

Metabolism. Scientists believe that many aspects of metabolism are implicated in basic aging processes, and a number of interventions to slow aging by altering metabolism have been tested in animal models. The most startling results have been seen with caloric restriction – sharply reducing caloric intake while ensuring optimal nutrition. Dietary manipulation has been found to extend the lifespans of several species under certain conditions. Although evidence of lifespan benefit in higher-order primates has been equivocal, most studies have shown beneficial effects of dietary restriction on health, and this remains a vibrant area of study.

One recent development has been the identification of the immunosuppressant drug rapamycin as a means to extend lifespan in mice. Working through the mTOR cellular pathway, rapamycin acts by interfering with nutrient sensing machineries, thus affecting the way cells respond to metabolic changes. Researchers are working to discover agents that may provide the positive effects of rapamycin without accompanying side effects. More recently, investigators in the NIA Intramural Research Program found that the drug metformin, commonly prescribed as a treatment for diabetes, also extends health and longevity in male mice by mimicking caloric restriction's beneficial effects.

Epigenetics. Aging and susceptibility to disease are driven by both genetic and environmental factors. While considerable success in basic aging research over the past few decades has revolved around genetic variants associated with extended lifespan, the focus has more recently shifted to

epigenetics, or heritable chemical "switches" that attach to the DNA and can activate or inactivate genes. Epigenetic activity is influenced by the environment and for this reason offers unprecedented opportunities for intervention. Recent advances in this field include the work of NIA-supported scientists who found that in worms, certain epigenetic changes that positively affect longevity can actually be passed on to future generations, so that the "grandchildren" of affected worms still had increased longevity. In another study, investigators found a strong correlation between a particular epigenetic mark and chronological age in humans, suggesting that this "molecular clock" could be used as a potential biomarker for physiological aging.

Macromolecular damage. Aging is accompanied by dramatic increases in damage to proteins, lipids and DNA. The extent to which this damage – or which specific types of damage – is related to aging and susceptibility to disease remains the subject of intense scientific scrutiny. While recent work has shifted attention away from the classical free radical theory of aging – that atoms or molecules with a single unpaired electron rattling around can cause cellular injury, which accumulates over time – a provocative alternative explanation for the role of free radicals in aging is that they may in fact serve as an intracellular signal that alerts the cell and the organism of potential danger.

Proteostasis. Scientists have recently identified proteostasis, the intra-and extracellular networks that serve to maintain the quality of cellular proteins, as a set of processes that may profoundly affect both aging and susceptibility to disease. Optimal function of the proteins within the cell is essential to the cell's ability to respond and adapt to the changing environment, but the efficiency of the proteostasis network decreases with age. Current advances in the understanding of proteostasis and its changes during aging have opened opportunities to investigate potential therapeutic approaches. Researchers are currently pursuing interventions that will preserve the proteostasis network into older ages, thus paving the way to preventing a number of degenerative diseases.

Stem cells and regeneration. Much recent work has focused on characterizing the states of stem cells and their activities during aging. Investigators have found that stem cells are often still present in the tissues of older individuals, but the "niches" in which they reside have been altered. If we can understand the underlying causes for the reduction in function, rejuvenation of adult stem cells in older tissues may be possible. For example, NIA-supported investigators have found that the protein GDF-11, present in young mice, reversed aging-related heart disease in older mice – the first time a circulating factor has demonstrated the potential to reverse aging-related organ dysfunction. Stem cell/niche interactions, as well as mechanisms involved in preserving genomic and macromolecular quality of stem cells during aging, are topics of intense study.

These seven topics represent only a slice of the broad and rich field of geroscience. We anticipate that the discussions at the Summit will foster a better appreciation of the multiple levels at which all of these variables interact with each other, and will energize the field to develop the studies that will lead to a "systems level" understanding of the relationship between aging biology and susceptibility to disease. In turn, this may facilitate the identification of new interventions that prevent or treat multiple diseases and disorders by addressing aging as a single underlying risk factor, thereby increasing both lifespan and healthspan in humans.

Thank you, and I look forward to answering your questions.

Presentation to the Senate Special Subcommittee on Aging – Tackling Diseases of Aging: Why Research Collaboration Matters

29 October, 2013

Dr. Richard I. Morimoto
Bill and Gayle Cook Professor of Biology
Director, Rice Institute for Biomedical Research
Northwestern University
Evanston, IL. 60201

I would like to thank the Senate Special Subcommittee on Aging for the opportunity to speak to you today.

I am the Bill and Gayle Cook Professor of Biology at Northwestern University. I trained at the University of Illinois, The University of Chicago, and Harvard before joining the Northwestern faculty in 1982. My research is in basic biomedical sciences, and I have spent my entire academic career to understand how cell stress and cellular quality control systems function in cells and animals. As biological systems age, we have learned that our molecules accumulate errors and interfere with function, causing tissue dysfunction, and increasing risk for disease. Consequently, we believe that aging is the biological platform and basis by which some succumb prematurely to disease and others age well, retain our health and cognitive abilities. It is now widely appreciated that our ability to enhance our quality control systems may have profound benefits to our cellular health, lifespan, and the prevention of some of the most devastating diseases.

While my perspectives have come mostly from an academic career, I like everyone else here today have worn multiple hats. In my time at Northwestern, I have served in academic administration as the Chair of Biochemistry, Dean of The Graduate School, and Associate Provost of Graduate Education. To alumni, I recently gave a series of lectures in their continuing studies program on the Biology of Aging. For many years, I have served on various committees for the National Institutes of Health, on the advisory boards for the National Institutes for General Medical Sciences and now for the National Institute on Aging, and previously for numerous review panels assessing grants. I have also served on boards and review panels for many disease foundations including Huntington's Disease Society for America, the Hereditary Disease Foundation, and the ALS Association, which has brought me in close contact with patients, their families, and with advocacy groups. With an interest towards human health, I was a founder of a Biotech company, Proteostasis Therapeutics in Cambridge, MA together with Prof. Jeff Kelly of Scripps Institute and Andy Dillon at UC Berkeley in 2008. The purpose of Proteostasis Therapeutics is to develop new therapeutics for age-associated degenerative diseases.

Aging is the common platform for all of biology and the basis for all degenerative diseases. By mid-century in the percentage of Americans over 65 will have grown substantially as we join

Japan, Germany, France, Italy, Britain, and most of Europe. With this demographic shift will be the inevitable explosion in neurodegenerative diseases, dementia, cancer, and metabolic diseases such as adult onset diabetes. The problem facing us is clear, without new drugs or treatments for age-associated degenerative diseases, why would anyone want to know that they are at risk. While at the same time, it will be essential to have biomarkers that detect changes in quality control that predict enhanced risk for age-associated disease. Either alone will be insufficient, so we must find ways to advance both approaches simultaneously.

The adult organism is mostly about replacing its parts as each component wears out. However, unlike the pyramids, the Golden Gate Bridge, or even a fine Swiss watch, biology does not use inert parts. Rather, in biology the replacement parts are transient in nature and often imperfect, and most often they are just good enough. Consequently, all biological systems decline with age, and eventually the system (the body) breaks down. Despite this, there is hope as humans are living longer. But will this be useful and productive if living longer is not living healthy lives? Of what value to society will be a lifespan of over 100 years if the body begins to fail three decades earlier?

Therefore, rather than to wait until disease is evident, which is the current state of medical affairs, we must identify the earliest markers of quality control collapse, when the cell stress response has been pushed beyond its capacity and can no longer protect the cell against damage. Only then, perhaps years if not decades before the inevitable decline can we promote an alternative path, towards healthy aging.

Research on the biology of aging is therefore the base of knowledge onto which we can understand the course of life and transitions from apparent health through aging to disease. An understanding of how cells and animals maintain their robustness, to identify the genes and networks that maintain balance, and how these stress response systems get overwhelmed and become dysfunctional will be invaluable to both health and disease. To accomplish this task will require new investments and new teams. Moreover, these teams should represent new partnerships of academic and industrial researchers working towards a new goal that is not necessarily to cure any particular disease.

The efforts beginning tomorrow at the NIH on the Geroscience Interest Group will bring together over 500 scientists from around the world to discuss how aging affects all organisms and all tissues. Hopefully, these efforts will stimulate new cross-institutional programs, trans-NIH, and between academic institutions and the Biotech and Pharma industry to stimulate progress.

Statement of

James L. Kirkland, M.D., Ph.D.

Director, Robert and Arlene Kogod Center on Aging

Mayo Clinic

Submitted for the Record

Senate Special Committee on Aging

United States Senate

Roundtable on Tackling Diseases of Aging: Why Research Collaboration Matters

October 29, 2013

Chairman Nelson, Senator Collins, senators, staff of the Senate Special Committee on Aging, fellow participants and members of the public, thank you for the opportunity to appear before you today to participate in this roundtable, "Tackling Diseases of Aging: Why Research Collaboration Matters." As the director of the Mayo Clinic Robert and Arlene Kogod Center on Aging, I commend you for your efforts to facilitate and enhance basic and clinical research on mechanisms of aging and the age-related chronic diseases. Age-related chronic diseases account for most of the morbidity, mortality and health expenditures borne by the people of the United States. Exciting, recent advances in our field are beginning to suggest that, by intervening in fundamental aging processes, we may one day be able to prevent, delay and cure multiple age-related conditions, including cancers, dementias, heart attacks, strokes, vascular disease, diabetes, kidney disease, arthritis, blindness, frailty and loss of independence, as a group, instead of one at a time.

In addition to being the director of the Kogod Center on Aging at Mayo Clinic, I am a clinical geriatrician who sees patients, as well as a basic laboratory scientist. I am investigating ways to delay chronic diseases and disabilities by designing interventions that target the fundamental aging mechanisms that predispose us to these diseases.

Mayo Clinic is the first and largest integrated, not-for-profit, medical group practice in the world. Mayo Clinic provides care for more than one million people annually from around the nation and the world at locations in 6 states. Mayo Clinic operates according to the guiding principle *the needs of the patient come first*. Mayo focuses its work within three shields, practice, research and education. Mayo conducts both laboratory-based and clinical research. A distinguishing feature of research at Mayo is an emphasis on translational research — bringing scientific findings into clinical practice. This is enabled by the organizational and physical structure of Mayo, which brings researchers into close proximity with clinicians, and an institutional philosophy of collaboration for the best interests of our patients. All patients at Mayo Clinic are treated as a whole patient, not simply a cardiology patient, a neurology patient or an endocrinology patient. This approach has allowed Mayo Clinic to successfully and cost-effectively treat patients for almost 150 years. Mayo has research complexes in Rochester, Minn., Jacksonville, Fla., and Scottsdale-Phoenix, Ariz. Mayo has a graduate school that grants Master's and Ph.D. degrees, a medical school, extensive postgraduate training programs for scientists and clinicians, and it provides continuing medical and public education.

The Robert and Arlene Kogod Center on Aging involves all departments, both basic science and clinical, and sites of Mayo Clinic. In this respect, its structure parallels that of the Geroscience Interest Group (GSIG) that spans the National Institutes of Health. The mission of the Kogod Center is to understand, promote and extend healthspan, the portion of our lifespan during which we are healthy, independent and free of chronic pain or disability. The Center has five programs: Cellular Senescence, Healthy Aging and Independent Living; Regenerative Medicine of Aging; Aging Bone, Muscle and Joints; and Diabetes, Metabolic Syndrome and Aging. Mayo has an Alzheimer's and Related Disorders Center headed by Dr. Ronald Petersen that is closely aligned with the Aging Center.

Investigators and clinicians in the Aging Center at Mayo Clinic publish over 15 scientific and clinical articles per month and hold over 90 major grants for aging research. In addition to basic scientists, the center includes 48 board-certified geriatricians, 9 geriatric psychiatrists, as well as over 35 physicians and surgeons whose practices are mainly focused on older patients. There are over 150 active human studies underway on aging or conditions affecting the elderly. The Center includes over 45 laboratories. It supports core laboratories that assess healthspan and functional and cognitive outcomes in aging laboratory animals and parallel outcomes in human subjects. Diagnostics to evaluate healthspan and frailty and interventions to enhance healthspan and treat frailty and age-related chronic diseases are being actively developed across the Center.

In the spirit of fostering collaboration and preventing disruptive competition, the Mayo Clinic Center on Aging has initiated and will lead the implementation of a Geroscience Network that involves 10 other leading aging centers across the nation. This network recently received financial support from the National Institute on Aging (NIA). The goal of the Geroscience Network is to enhance healthspan by coordinating areas of focus among aging centers, minimize duplication of effort, develop joint research protocols, curricula, clinical trials subject populations and clinical trials networks, and support faculty and student exchanges among centers. Links to a network of seven additional aging centers in Europe are being developed.

As previously highlighted, aging is the leading risk factor for most of the chronic diseases that account for the bulk of morbidity, mortality and health costs in modern society. Therefore, by targeting fundamental aging mechanisms it may one day be possible to prevent or treat multiple age-related diseases together, instead of one at a time. The aging field has progressed from describing changes that occur in different tissues with aging, to determining mechanisms responsible for these changes, to now designing interventions that delay them. The next step will be to translate these interventions into clinical application.

Exciting new advances in the basic biology of aging include discoveries of drugs and drug targets that extend healthspan or lifespan in mammals. Some are approaching the point of becoming the subject of clinical trials. Some are showing indications of effectiveness in not only increasing healthspan or lifespan, but also delaying or treating chronic age-related diseases in laboratory studies in experimental animals or human tissues. The pace of this work has accelerated dramatically since the demonstration that a drug, rapamycin, was effective at increasing lifespan in mice, published in 2009 by the NIA Interventions Testing Program. Importantly, 5 of the 16 drugs tested so far in this multi-institutional program have increased lifespan in mice.

At Mayo Clinic, we are conducting basic, and in some cases, early stage clinical studies, with each of these drugs. In an important separate direction, we recently found that removing senescent cells enhances healthspan in mice. We are working on the next generation of this research which includes developing new ways, including drugs and lifestyle interventions, to remove these damaging cells or reduce their negative effects on surrounding tissues. Much of this work is supported by the NIA and most involves interdisciplinary collaborations among investigators and clinicians within and outside Mayo Clinic.

Mayo Clinic is doing significant work in the field of cellular senescence. Cells undergo a limited number of divisions before they stop dividing. Once they stop dividing, these cells reach a state of limbo — called cellular senescence — where they neither die nor continue to multiply. They produce factors that damage adjacent cells and cause tissue inflammation. The immune system sweeps out these dysfunctional cells on a regular basis, but as we age, our immune system becomes less effective at "keeping house," thus allowing the accumulation of these deleterious cells. Senescent cells are associated with many age-related chronic diseases. They accumulate in the damaged blood vessels that lead to strokes, heart attacks and vascular disease, in the brain in Alzheimer's and other neurodegenerative diseases such as Parkinson's, in fat, the kidneys, the pancreas, and elsewhere in diabetes, in arthritic joints, and around cancers.

In a significant study at Mayo Clinic, mice were engineered to express a suicide gene only in senescent cells. This suicide gene makes a protein that can be activated by a drug that has no effect on normal cells. In this genetically modified mouse, healthspan can be increased by activating the engineered suicide gene product with the drug. In mice with features of accelerated aging, we found that removing senescent cells substantially delays age-related muscle weakness, improves exercise tolerance, delays age-related fat tissue dysfunction, delays cataracts, and ameliorates other age-related disabilities. This work attracted considerable public attention and was featured in over 250 newspapers worldwide, television broadcasts, and even *Saturday Night Live*. We are currently developing drugs that we hope will have similar effects in non-genetically modified experimental animals and human subjects. We are excited that considerable progress has been made. We also are testing if multiple age-related diseases and disabilities can be delayed by removing senescent cells with drugs, genetically, or through lifestyle interventions, such as exercise.

The national aging research community aspires to soon initiate human clinical studies on some of the interventions discovered to enhance healthspan and ameliorate age-related chronic diseases in experimental animals. Considerable proof of principle and pre-clinical studies need to be done, but many in the aging field are becoming increasingly, though cautiously, optimistic about translating these interventions into clinical practice. If successful, the impact of increasing healthspan and delaying age-related chronic diseases would be transformative for health care and our society. Curing individual diseases of aging, such as cancer, would add approximately four years to median life expectancy, but not impact the likely onset and consequences of other age-related conditions such as atherosclerosis or dementia. In experimental animals, we can enhance healthspan and delay death by relatively much more than this through targeting the fundamental aging processes that also appear to make a major contribution to causing most or all of these age-related diseases.

Among the work that needs to be done soon is:

- Discovery and development of even more potential interventions, so we can maintain a pipeline of emerging treatments.

- Testing effects of each potential intervention in multiple age-appropriate animal models of age-related chronic diseases as well as in normal animals just with advanced chronological aging.
- Testing across a range of species before we move to human studies.
- Understanding and minimizing potential complications.
- Testing of combinations of treatments in experimental animals to optimize outcomes and minimize side-effects.
- Conducting initial, small proof of principle trials in human subjects, and eventually full clinical trials.

Obviously, we cannot study the impact of such interventions on lifespan in humans. Also, successful interventions will need to be effective in older or at risk subjects. Drugs that have to be given in early life to have a late life effect will be difficult to study in humans.

The types of study populations we will need are also very different from those in usual clinical trials to date. We will need to test interventions in older populations with multiple co-morbidities and look for benefits using markers of more than one age-related chronic condition, rather than single outcomes. For example, these agents could be tested in trials measuring memory, physical function, vascular function and metabolic parameters in elderly subjects with a combination of atherosclerosis, insulin resistance, and early dementia, a common clinical scenario. Other scenarios might include effects of agents in improving recovery after chemotherapy or surgery in pre-frail older subjects, or local or topical use of these agents in conditions with focal dysfunction due to processes associated with chronological aging, such as senescent cell accumulation in arthritic joints.

Research in aging and clinical care for older patients is best pursued using interdisciplinary approaches. Therefore, we feel that creation of initiatives across departments within our own institution and among aging centers nationally and internationally could help to accelerate discovery and implementation of interventions to enhance healthspan and quality of life. The GSIG initiative at NIH is based on the same principles and has helped to guide the types of collaborative efforts within and among institutions that are necessary for development and implementation of interventions to enhance healthspan and delay, prevent, or treat age-related chronic diseases. Tomorrow's interdisciplinary summit in Bethesda entitled *Advances in Geroscience: Impact on Healthspan and Chronic Disease* exemplifies these efforts.

In summary, the aging field is at an exciting juncture, with recent discoveries of interventions that hold potential for increasing healthspan and lifespan and combatting major age-related chronic diseases as a group, instead of one at a time. While by no means fully certain, it appears increasingly likely that some of these interventions may soon be ready to be tested in clinical trials. There is enough promise now that a major initiative to accelerate this work is warranted.

Clinical translational research is expensive and is a new area within the aging field. It needs to be supported without cannibalizing discovery and hypothesis-driven research in the aging field. Support for these areas is already meager and must be sustained or increased to

maintain or expand the discovery pipeline, so new and better interventions can continue to be devised. We in the aging research and clinical care community are doing our best with what we currently have. We are coordinating efforts among and within our academic institutions, setting priorities to advance basic and clinical research, creating stronger links between scientists and clinicians, including not only those studying aging mechanisms, but also individual age-related diseases, and developing training programs and curricula to create the new breed of clinician-scientists in aging research who will be needed as translation progresses and clinical trials begin. More could be done, and hopefully will be, as these steps are taken and increased funding allows us to move faster in this area. We are optimistic that support might increase as the potential benefits of targeting age-related diseases as a group and enhancing healthspan are recognized by the public, governments, donors, industry, and our colleagues across scientific and clinical disciplines. Since the first wave of baby boomers started turning 65 in 2011 and 11,000 people per day will continue to reach this milestone until 2030, the potential gains for society with this approach are substantial, possibly even transformative.

Prepared Statement of John Alam, M.D., Head, Therapeutic Strategic Area for Diseases of Aging, Sanofi-Aventi

As a major global public health actor focused on patients' needs and recognizing that older people want to continue living full and active lives in spite of medical challenges, SANOFI has created a research& development group, called TSU Aging, dedicated to better management of chronic diseases affecting older individuals and patients. The innovation in our approach to aging is a paradigm shift from the study of one disease in isolation, to the study of certain major diseases and disease processes of aging in parallel, as well the integrated health needs of the elderly, with the aim of maximizing their overall capacity for independent living.

SANOFI's research teams are looking for innovative, inter-connected ways to increase the timeframe of healthy ageing through strategies centered both on prevention and improved management of multi morbidities. We are attempting this through a multidisciplinary, multi-team approach based on an in-depth analysis of the older populations' unmet needs.

Our R&D strategy in aging targets both age-related chronic neurodegenerative diseases such as Alzheimer's, Parkinson's, recovery after stroke, and osteoarthritis; as well as, age-related syndromes such as chronic disabling pain, age-related muscle loss (sarcopenia), and physical frailty.

The vision in establishing TSU Aging was to organize the team in a manner that would allow it to address the principle scientific challenges facing biomedical research generally, and the pharmaceutical industry in particular, in developing innovative medicines to tackle the major age-related disease of aging.

Historically, the industry has been most successful in discovering and developing medicines for either acute illness, such as bacterial and viral infections, and cancer; or major chronic illness that strikes otherwise healthy younger middle-aged individuals, such as heart disease, autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis) and diabetes. In such contexts, because there are high levels of physiologic distinction between health and disease, science has been able to develop models defining that distinction and uncover biologic pathways whose modulation specifically addresses the disease state. In contrast, with perhaps the exception of chronic cardiovascular disease, the industry and biomedical research generally has been less successful in developing appropriate models and new medicines for most of the chronic diseases of aging. In many of the conditions, while symptomatic therapies have been developed, medicines that address the underlying cause of such diseases and conditions remain elusive. As a result, patients continue to develop increasing disability and morbidity, while incurring ever more health care costs.

The major scientific challenge posed by chronic diseases of aging and the geriatric syndromes is that the distinction between what would be considered "normal" aging and disease are less clear because more complex, than with acute illnesses of younger populations; often subtle dysfunctions accumulate in each of multiple organ systems leading to decreased autonomy and lack of well-being on the part of an individual patient. This is particularly true of geriatric syndromes such as Frailty, where various combinations of

disease and aging processes come together to lead to an overall decline in function. Indeed the treatment and management of geriatric syndromes is a challenge for medicine overall as no one abnormality drives the physical complaint, and as a result no one treatment is able to address the medical problem; instead, often frail individuals are treated with multiple medications that treat each of the individually identified laboratory abnormalities, but the underlying conditions of aging and physical frailty remains unaddressed. For pharmaceutical R&D the challenge that is posed by these subtle changes and the overlap between normal aging and disease is that it is scientifically difficult to define and model the specific biologic mechanism that is aberrant and therefore to find a medicine that specifically addresses the mechanisms causing the medical condition.

Additional challenges in addressing age-related chronic disease is that as we grow older our inherent capacities for repair and recovery after injury diminished, and we become more sensitive to environment stress. As a result, disease interventions should ideally be considered early in the disease process, at a point when the body still has the capacity to repair and recover. In addition, therapeutic interventions must take into account environmental factors, such as nutrition, degree of physical activity, etc., as well as the internal biology to optimally address these conditions; and doing so may require combining pharmaceutical interventions with non-pharmaceutical interventions, technologies or services designed to address environmental stressors.

To address these challenges, Sanofi and many others active in the aging field believe that what is required are fundamental shifts in the scientific approach to discovering and developing innovative medicines for age-related diseases. In accordance, the three pillars of the TSU Aging's scientific strategy are as follows:

- In order to cross fertilize ideas and concepts, as well as developing therapies that address common age-related biologic mechanisms, integrating the scientists working on the major age-related disease and syndromes under one Aging R&D organization.
- Place greater emphasis on intervening earlier in disease process, rather than treatments at late stages of disease, when there may already be irreversible loss of function.
- Whenever possible, consider multi-pronged strategies in integrated healthcare solutions that not only provide pharmaceutical products, but also address healthcare needs in integrated solutions that may encompass novel technologies and services.

From an operating model standpoint, SANOFI R&D globally has recognized that our internal efforts for such complex disease situations will not be sufficient and has adopted over the last several years an Open Innovation model, whereby we work in a networked manner with academia and other players in the biotech and pharmaceutical industry; both in direct one-on-one private partnerships as well in larger public-private consortia.

More broadly, for this concept of R&D that is specifically focused on Aging and Age-related diseases/syndromes to succeed, policy change within and outside government will also likely be required to move away from the traditional structures and perspectives. For example, the regulatory process and framework for novel drug development, as well as the treatment paradigm in clinical medicine, is very much based on assumptions of frank disease with a clearly definable disease process and cause that can then be addressed with a specific medicine. And again, geriatric syndromes such as Frailty do not follow such direct rules and principles, and as a result is generally not recognized as a distinct entity in either clinical practice or by regulatory guidance. Establishment of Frailty as distinct clinical entity would allow for research to be conducted to understand underlying disease mechanisms, potentially paving the path for developing specific medicines directed towards the syndrome.

Moving earlier in the disease process also poses challenges that may need to be addressed by policy change. While moving earlier in disease, particularly to preventing disease, improves the probability of success from the scientific standpoint, proving the effect of an intervention with traditional clinical endpoints of irreversible morbidity or mortality may take 5, 10 or more years of clinical studies. As a result, for the industry to succeed in developing medicines for many of the chronic diseases/syndromes of aging will require the identification of surrogate endpoints that then will need to be adopted by regulatory agencies. In addition, for reimbursement and business success, systems will likely need to be put in place to capture the long-term health benefits and cost reductions from intervening earlier in the disease process.

Finally, of the three pillars, the one that may be the most difficult for the industry to realize is the development of effective integrated health care solutions because it may require significant business model innovation as it moves far beyond our traditional product commercialization strategy and will involve stakeholders with whom we traditionally do not work (e.g. telecommunications companies for remote monitoring). Sanofi and others in the industry today are working on establishing pilots generally through public-private partnerships to explore how one could best propose such solutions, but the field remains in its infancy.

By developing novel innovative medicines and integrated healthcare solutions for the aging population, notably through partnerships involving public and private stakeholders, SANOFI is dedicated to finding solutions to the 21st century worldwide challenge of increased demand in healthcare for an aging population. Our goal is to become a leader in this field, making a real difference for older adults and their caregivers.

Statement to the Senate Special Committee on Aging from David Morgan, PhD.

Dear Committee Members

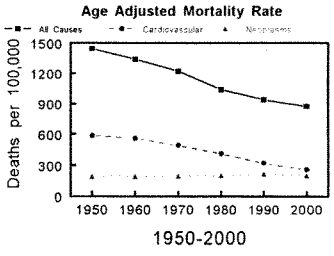
I am David Morgan, PhD, Director of the Byrd Alzheimer's Institute at the University of South Florida and Distinguished Professor of Molecular Pharmacology and Physiology. The Byrd Alzheimer's Institute is an Interdisciplinary Translational Research Center based in Tampa Florida. The Institute activities include Basic Science research, clinical research, clinical patient services, and educational services to caregivers and health professionals. I have a long history or research in aging and neuroscience starting at the Andrus Gerontology Center at the University of Southern California in the 1980s and continuing to this day at the University of South Florida. I am also the Lead Representative of an organization called ResearchersAgainstAlzheimers, an advocacy organization of active scientists with over 400 current US members. Below I respond to the Suggested Panel Questions

1. How have sequestration and financial uncertainty impacted aging research? It has clearly diminished the capabilities of many centers engaged in such research. Both across the board cuts to existing grants and reduced funding rates for new grants have a discouraging impact, particularly on the next generation of researchers. A number of laboratories have increased their activity in contracts with industry and grants from private foundations, but these cannot fill the void left by reduced support from the NIH. Some investigators have either closed their laboratories or, in some cases, returned to their home countries due to a better funding environment than in the US.

2. Expectations for the summit. First I believe it will highlight the benefits of engaging in basic and clinical research into the aging process. The arguments were made in the 1980s that for the purposes of the greatest extensions of life span and health span (aging without morbidity), slowing aging would have greater benefits than eliminating major diseases. Second, I believe we will see there have been considerable enhancements in both lifespan and healthspan over the last half century. This may now be slowing, as less healthy generations enter the retirement period.

3. Views on balancing research in the underlying process of aging with the need for funding disease specific research. If we can gain insight into the basic mechanisms of aging, it would have more impact on lifespan that disease-specific approaches. However, this occurs largely in the realm of preventing the onset of diseases associated with aging. Slowing aging will likely have minimal impact on those who already have contracted such diseases. For people with dementia, who have lost any sense of self-identity, it would probably be ethically inappropriate to extend their lives by slowing their rate of aging.

It is important to recognize the considerable benefits that have come from disease-specific research. The figure to the right shows the age-adjusted mortality rate (that is, takes into consideration the overall increase in longevity) for All Causes (solid black line) cardiovascular disease (dashed line with circles) and cancer (dashed line with triangles). Data are from the National Center for Health Statistics. This shows that our investment in cardiovascular disease research has cut by 50% the risk of dying from heart disease at a specific age. People are still dying from heart disease, but from congestive heart failure in their 70s and 80s instead of heart attacks in their 50s



and 60s. I fact most of the overall reduction in mortality can be accounted for by changes in heart disease deaths. Only after 2000 has cancer research started to show reduced mortality, 30 years after launching the War on Cancer.

I believe that aging has a major impact on the development of chronic degenerative diseases that have antecedent pathologies over decades before the damage reaches the stage of producing symptoms. These include disorders such as diabetes, cardiovascular disease, chronic obstructive pulmonary disease, Alzheimer's disease and cancer (among many). Fascinatingly, the major lifestyle risk factors for most of these diseases (beyond your number of birthdays) are all the same lifestyle choices. Obesity, blood lipid profiles, blood sugar levels, smoking, exercise are known to increase the risk of all of these diseases. I suspect this is because these activities are modulating the rate of aging, rather than directly impacting specific disease risk factors. Unfortunately, it is very challenging to randomly assign folks to these lifestyle choice groups randomly and at known dosages. Thus we will never be able to prove their aggregate benefits directly, or determine if the impact might be on aging *per se*.

4. Is NIH funding initiatives for the delayed aging model? Yes. I presently serve on a review committee for the Interventional Testing Program to identify agents that can be administered which might extend the lifespan of mice. This is a very rigorous program that has identified one agent, rapamycin that can extend longevity. On this basis it is argued that this slows the aging process. Over 20 other agents have completed testing or are in process. This is a highly objective means to try and identify chemoprevention for aging. However, expanding to other species that may have causes of death different than those of mice would seem a good use of funds. Research on caloric restriction and caloric restriction mimetics continues to receive such funding. Unfortunately, the studies in nonhuman primates had inconsistent outcomes, and these were long and expensive research studies. This leaves open the question regarding caloric restriction and longevity in humans.

5. How would NIH consider partnership with industry? Most certainly it would. A fine example of the government, industry and private philanthropic partnership is the Alzheimer's Disease Neuroimaging Initiative (ADNI). Almost 1000 publications have come from the data collected in this very large multicenter study. This is an example of the "precompetitive " research space, where the pharmaceutical industry sees that all can gain benefit before competing with specific proprietary drugs. These are ideal relationships.

6. How has the delayed aging model been received by the medical and academic research communities? I have been aware of the argument since the 1980s. Extending overall longevity has considerable advantages in improving individual productivity and quality of life. A key unanswered question is the purported compression of morbidity. Will this happen or simply be extended to the same degree as the overall extension of the lifespan? There is little current evidence.

7. What are some of the major concerns in researching the delayed aging model? Perhaps one of the most vexing is how to measure "aging". One means often used is longevity, but this is often biased due to species specific causes of death in different test models. There are a large variety of potential biomarkers of aging that shift throughout the lifespan. A collection of these might be used to more rapidly assess success or failure (without requiring death of subjects). But, these may be difficult to agree upon. With the possible exception of caloric restriction, we do not have any agreed upon means of slowing the aging process. These models would have to be developed and validated. Another concern is that whatever might be used as a chemopreventive of aging, it would have to be extremely safe. We would propose giving this to perfectly healthy young individuals. In the early days of caloric restriction studies, it was not uncommon for 5-10% of the cohort to succumb when the restriction paradigm was imposed. This has improved, but what fraction of the population having side effects would be tolerated for an anti-aging chemopreventive approach (we have some data

regarding aspirin and the risk of heart attack, with a recent study arguing the benefits in women do not outweigh the liabilities).

8. What are the ways technology could be used to advance the delayed aging model? Not an area of specialization for me. I think the use of very large datasets, and aggregation of well characterized clinical data (in easily queried databases) would be very useful.

9. Could delayed aging health cost savings be enhanced using technology? I would have to see specific technologies proposed to have an opinion here.

10. Do you envision public private partnerships to develop technology to develop drugs to slow aging? Absolutely. Industry is decreasing its funding of internal basic research in part because of costs and in part because of the success of the public sector in this area. Universities are investing in drug development centers to move prospective agents into early stage development, leading to biotechnology spin-offs and, if fortunate, licensing for clinical trials by major pharmaceutical companies.

11. How important is prioritizing efforts to find interventions to extend healthspan right now? This is very challenging question. I believe we have made important advances in benefiting the lives of people who have contracted age-associated degenerative diseases. This has come from specific and targeted investments. There are millions of American suffering from chronic degenerative disorders today. Ignoring them would be very challenging and a little heartless. The benefits of delayed aging are, at least for the present, theoretical. We do not know that morbidity will be compressed, which might just extend suffering. The beneficiaries will be those future generations, not the ones presently paying into the research pool. Even the tools to measure aging *per se* are not fully agreed upon. In the 1980s when I worked in Tuck Finch's laboratory, we never did a survival study, because he did not believe that death was aging. I will admit as one who studies an age-associated disease, I have a personal investment in this regard that may influence my opinion. However, I did study fundamental processed of aging while at the Andrus Gerontology Center. While the field has advanced considerably, there is no clear Roadmap to seek these purported means of slowing the aging process. I believe the present balance is probably about right.