Informal Discussion Transcript:
General Session IV – Could Moses Live to be 100

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General Session IV – Could Moses Live to be 100

TIMOTHY F. HARRIS: This afternoon's general session is "Could Moses Live to be 120," and our featured speaker is Dr. [Nir] Barzilai, M.D., professor of medicine and genetics and director of the Institute for Aging Research at Albert Einstein College of Medicine. This is the home of two Nathan Shock Centers of Excellence for the basic biology of aging. His studies on families with centenarians have provided genetic, biological insights on the protection against aging. Several drugs are developed based in part on these paradigm-changing studies. Dr. Barzilai was awarded over $25 million of National Institute of Health funding for these efforts, and he has published over 200 peer-reviewed papers, and is the recipient of numerous prestigious awards. So join me in welcoming Dr. Barzilai. (APPLAUSE)

DR. BARZILAI: Thank you for this kind introduction. When I hear what I've done, all I can think of is how old I am, just if you live long enough. It's a real great pleasure to be here with you guys today. I've met actuaries throughout my career, and it always was challenge and provocations, and I'm really looking forward to today. I'll tell you what my plan is. I have like 30 slides and I have two videos that are like two minutes each. I really want to do provocations and stop and let's have a real nice discussion going on. I hope it can work.

Just to shift you to my world, I'll tell you this story. When people—Hey, you're a good example. You say to people who are asking what you are doing, you say, I'm an actuary and people are waiting, right? And so this is how I present my study. I just say it's really this story about an elderly person that goes into a life insurance office and he wants life insurance, and the clerk looks at him and says, "Just a minute, how old are you?" And he says, "I'm 100 years old," and the clerk says, "We're not giving life insurance to 100-year-olds," and the old guy says, "That's not true, my mother is insured here." "How old is your mother?" "She's 120." "She's alive?" "Yeah, she's alive." "Is she well?" "Yeah, she's well." So the clerk thinks for a second, goes to the boss, they both come to him and said, "You know what, we'll be happy to do life insurance. In fact, why don't you come on Tuesday? We'll have all the papers done and you'll just sign and you'll have life insurance." The elderly gentleman says, "You know, I'm sorry I'm busy on Tuesday." They said, "Yeah, what do you have on Tuesday?" He said, "It happens on Tuesday my grandfather is getting married." (LAUGHTER) They said, "How old is your grandfather?" He says, "150." "He's 150 and he wants to get married?" "He said he doesn't want to; his parents put lots of pressure on him." (LAUGHTER) OK, so welcome to my world.

By the way, the title of my talk—Why Moses Lived to be 120—I don't remember giving exactly this title of the talk. That's actually not the title of my talk really, and I want to remind you that there are many people in the Judeo-Christian religion that believe in everything that's written in the Bible, so it's not why or could it be, OK? If it's anything, it's how. The talks that I give now are more of this: how to die young at a very old age. Because the point is not how to die an older age, but how to stay healthy longer, and this is really what we are trying to say.

So let me put in a slide that you might have seen here before. It's a slide from the government that shows the relationship between death from age-related diseases according to age, and because it's a government slide, you always need to improve it a little bit, so I just put in here lines representing cancer, cardiovascular disease, diabetes and Alzheimer's. This is the kind of data that many of us have seen when we entered the field of biology of aging, and we looked at that and we said just a minute, there is a log, right, a log increase from many age-related diseases according to age. So age is really the major risk for all those diseases. In other words, cholesterol is a threefold risk for heart disease, but when you go from ages 30 to 80, you get a thousandfold increase in heart disease.

And so in many other diseases, so if aging is the common and major risk factor for all age-related diseases, our conclusion was if you don't delay aging, you're not going to do much. All you could hope for is to change one disease [for] the other, and it's proven to be right now.

I don't know if you've seen the paper, in the *New York Times* this weekend, about cancer and aging and other things, but what really happened, heart disease was a success. We know how to prevent it and we know how to—When you have a heart attack, you come, you get the stent or a bypass, OK, you have a local treatment here, but we never change the rate of aging. So what happened to those people who recovered from heart disease? Within two years, if they're not dead from heart disease, they get cancer or as the *New York Times* showed, cancer, diabetes or Alzheimer's. In fact, my big fear is that I'm doing everything to prevent heart disease, and I think I'm going straight to Alzheimer's, and I'm not totally happy with that.

This is point one that I wanted to make, that if you survive one disease, you get [the] next disease, unless you can delay aging. Delaying aging—I'm going to ask you this question, and I'm going to take a vote here. Do we humans age at a different rate? Do you know somebody your age who looks 10 years older? I'll also ask, is there someone your age that looks 10 years younger? I know that's not going to

be so popular. If you think we humans age at different rates, please raise your hands. And everybody looks around. I just cannot believe how consistent. You don't ask questions where everybody agrees usually. By the way, as professors, we have to divide the audience, not to unite them like that, so don't tell in my university. We all intuitively know that people age at different rates, and yet we never use this information effectively to understand what is in the biology that some people age quicker than others, and maybe that's why you understand why we went to study 100 years old, because we're assuming that for most of them their aging has been slowed down. So let's see what's so special about them.

I've seen this afternoon a presentation where part of the adjustment in a population was for the age of death of parents. So apparently this is very clear to you, and the effect is very remarkable. In other words, the age of parents with correlation to the age of death to their children. I want to show you something that is even more important for you to realize and I'll give you two examples. This is a study that's called the diabetes prevention trial. Let me take this slide, because this doesn't show the trial. I'll tell you the trial and then show you the data.

The Diabetes Prevention Program was designed to take

people with high risk of diabetes and either watch them or give them the drug metformin or change their lifestyle so that they exercise and diet and see if diabetes can be prevented, and diabetes was prevented by 30 percent. This study was stopped early because it wasn't fair not to give people with pre-diabetes metformin or lifestyle changes. OK. So I've asked the DPP investigator to go back and see what happens if for the people whose parents had longevity, and actually what I'm going to show you—I'm showing you only one. It's paternal or maternal. Here it's only paternal. It's the same for maternal. What happens to the children, to the diabetes of the children if their father lived to be over the age of 80. Diabetes was prevented by 30 percent. Having a parent, a mother or a father that lived to over the age of 80 prevented diabetes by 30 percent. So longevity in this sense—that's not exceptional longevity, it's just over the age of 80—has a really remarkable effect on the occurrence of age-related diseases, and if you think it's specific to diabetes, no. It's specific to Alzheimer's also, and this is a study that we conducted in a retrospective—We looked retrospectively at the cohort that was studied longitudinally to see if a parent who lived, one parent over the age of 85, prevented Alzheimer's or cognitive decline, and the answer is the same. It was a 30 percent effect. If you had one parent

that lived to over the age of 85, your Alzheimer's was delayed by 30 percent. OK. So longevity in the family, the heritability of that, and its effect that you can monitor in age-related disease is quite remarkable. We know that the environment is also a lot, but look how the effects of genetics is almost similar, like in the DPP. Lifestyle changes and parents have the same effect on preventing diabetes.

So let me tell you some of the challenge for us as biologists when we're trying to study aging. What you see here is just a scheme of youthfulness and how it declines by age, and you all know that sex hormones, testosterone for men, estrogen for women, is declining, growth hormone is declining, but maybe you don't see it clearly, but there are lots of lines, hundreds of other lines, and each one of us in the biology of aging has its favorite thing and we think that's what's going to cause aging. OK.

This is really the big challenge that we have. Some of those things are maybe the causes of aging, primary, secondary, major, minor, but can be causing aging. Some of the things that we can be monitoring, maybe are biological markers of aging, but maybe in our maximum life span they're not going to shorten our life span. It's still very important, but they're not going to be the ones that are causing us to die or our organs to age. So that's OK, but

this is the thing that takes sleep out of us. This is, some of the things that we're measuring are going to be protective mechanisms, things that are causing us to adapt in response to stress, to modify our response. In other words, when you have infection, you have inflammatory response to fight infection. When you have the breakdown of aging, there are a lot of mechanisms that are going to fight it. OK. So we can measure things that are going up and going down, and by the way, this is going—youthfulness is going down, but of course, I'm talking about things that you can measure that can go up or can go down, it doesn't matter, but let's say you have something that goes up, or goes down, doesn't matter, and you say maybe that's aging, but if it's actually a mechanism that protects from aging, you're going to kill the person, right? Because you don't want to take the protective mechanism away, and this is a really huge challenge for us.

Now, let's take this person who is, let's say, 70 years old and see what happens in his body, and I'm going to give you a biological slide, but don't be afraid. It's just a picture, and the picture, the things that you need to see in the picture, it's a biological essay, and you see many squares that are yellow here and blue here, and the differences between the yellow and blue is that the yellow are expressing proteins in much higher levels than the

blue. It's taken from a variety of cells that were made to senescence. So, our cells are dividing how many times Hayflick told us? Is he here? Then they get senescent. What does it mean, they get senescent? One of the things, they're secreting other things that they have not been secreting before. A lot of them are actually cytokines, an inflammatory response, and the reason I'm showing you, the only reason I'm showing you that is that when we get older, we have more of those cells. They secrete more of those peptides to our environment so that the old body biologically is not like the young body. So what does it mean that our old body is not like the young body? Let's see what happened to this idea of maybe because estrogen goes down in women, maybe if we replace estrogen, then we're going to delay the whole process of aging.

By the way, when this study started, I said, "Just a minute, what about men?" OK. Because aging is something that happens very similarly in men and in women. Lots of common features. So how would estrogen be really changing the rate of aging and if it's only female stuff. Anyhow, the idea was maybe estrogen is important and is going to change the rate. So there are a few problems here.

The first problem is it's a very—Growth hormone is also going down. It's not a dimensional study. It's just the biology is so complex, you take just one thing and you

change it. What about the other things? That's one problem. The second is I just showed you that there are really different interactions now, because the body has different peptides that are circulating in the old body and the new body and the young body, so how do you know that estrogen— How does estrogen interact with those inflammatory markers? Is it a good interaction? Is it a bad interaction? Third, you also assume that the fact that there's the lower estrogen, that it's not protective of aging, but maybe it is protective of aging. Maybe it is important to have low estrogen in order to increase the viability of the body, and as you know, the study was done. It's called the Women's Health Initiative. Estrogen was given. It had some good effects like on the skin, but the study was stopped because there were cardiovascular events, cognitive decline, breast cancer. So from where I'm standing, from an age-related disease perspective, estrogen is a pro-aging, it's not an anti-aging, hormone.

By the way, I should say that I'm a little provocative here. I'm telling you how you could look at this study. It's a little bit more complex. The scientists are thinking maybe they gave the estrogen too late, maybe there's a window of opportunity. But I gave you this example as a real example to say that not everything that we measure that goes up with age, we can just normalize or replace or

something like that. It's not as easy as that because this biology is hard to figure out.

I also want to say that there's an evidence for success and the biology of aging has been concentrated on three major legs. One is the aging of the genome, one is the aging of the cells, and one is what happened to metabolism when it ages. Each one of them have shown to be a cause, but also each one of them is affected by another. So it's very hard to say how it starts. We see that all three components are failing, and there are some common mechanisms for that. But the thing that scientists have done beautifully, because aging is so complex—it's complex more than any one of the other diseases that combine for the aging—what we've done really terrific is we said you know what, we'll figure out what's aging, but let's go from the perspective of longevity. Let's try and get, by genetic manipulation, by drugs, animals that live longer, and by doing that, we're just jumping ahead. Instead of understanding what goes down, let's find how we can maintain something and we'll discover what's aging, but in the meantime, maybe we'll have something that we can do. And I will tell you that healthy life span has been extended in numerous models, and I'll tell you that relevant drugs have been used also in humans, and I'll come back to that.

I want to go now back to my study of centenarians, and show you some of the interesting things that happened. When I started this study more than a decade ago, I was impressed by the fact that out of the population, at that time, only one out of 10,000 was 100 years old. As you see, I'm very defensive here, and I would argue that we really don't know the true rates. In Japan they found centenarians in the closets of people. There's lots of motivations. I did my own little trial. I went to the Bronx to look at registered voters, voters that were supposedly active in the last election, and the rate of centenarians in the Bronx is amazing. It's like most of the Bronx is centenarians. Also they are 160, 140, 130 years old. Definitely something is not right, and I think it's a problem all over the world. I don't know how many are really centenarians, but the important thing is that it's very rare.

We collected over 600 people, but when I say collected, we collected—because we're trying to find really the healthy aging—we collected people who considered themselves healthy and were independently living at age 95. So I'm not telling you anything out of the population. I'm selecting here. In this study, we're selecting the best of the best, and so we have 600 of those that are ages between 95 and 116 and their average age is 100. As we collected

and others collected—some of you heard Tom Perls, who preceded us in collection of centenarians—we all discovered an interesting thing, that there's a really strong family history of longevity. I think Gavrilov and Gavrilova have really showed very nicely how maybe the genetic component of longevity is not so striking like at the ages of 70, 80, but when you go to 100, all of a sudden there's a huge genetic component here. In our study, it's a tenfold effect. In other words, when we look at the relationship between longevity of the parents of centenarians compared to an appropriate control, it's a tenfold effect. In Tom Perls, it's up to 18 effect, but there's really, the striking thing is, a lot of the centenarians come and say hey, our parents. Actually that's the first thing they say as far as their beliefs.

So, with this study, we had two hypothesis that we could look at. One is that those centenarians have the perfect genome. Very simple. If we have a lot of mutations or changes, we call them SNPs. We identify SNPs on the general typing that we're doing, that's our general typing that are associated with diabetes, with cardiovascular, with Alzheimer's. You know what? Our centenarians, those one of 5,000, 10,000, they're just going to have the perfect genome, and that's why they stay alive. The answer to that, I'll tell you in all our studies, is that's not

true. In fact, in most studies, they have just as many bad snips as others, which means you have to reform the theory, and the reformation of the hypothesis is that it's not that they have perfect genome, they have actively—they have certain genes that are ensuring their longevity, in fact, genes that are protecting also from the effect of those bad genes that are associated in many other people with the diabetes, cancer, Alzheimer and so on. OK. This is the theory that we're working on.

Let me introduce you for a second, to—not for a second, actually. I'm taking three minutes to introduce you to some of our centenarians, and I'm going to show you a video of centenarians, and the reason I'm showing you that is because many people are thinking that those centenarians are maybe vegetables, and what is it to be 100 years old? I want to show you a guy who was almost 105 when this video was taken, who celebrated last week his 108th birthday, and in the video you'll see him in a certain condition, but I want to prepare you that—by the way, this is the gentleman here. I want to prepare you that his sister who died when she was 110, a year or two ago, dropped in to a visit while we were filming him. So you'll see the effect. Those are, by the way, siblings that lived over 102. She died first. She was the younger sister. She died at 102. They were shocked. (LAUGHTER) She died at 110 and the brothers are

still alive, 108 and 106. OK. So let me just—I'll just show you a piece of the video in order for you to get impressed of what it is to be healthy.

(VIDEO SHOWN)

OK. There's a website, superagers.com. There are several other people there if you want to be impressed, but I hope I made the point that when you're 100 years old, healthy and working, life is beautiful. OK.

Another thing to remember on those people, which I think it's always something—When we write the grant, we have to say what is the public perspective here. And the perspective here—That's from the CDC, and this is from 1993. It's the same date, just the numbers are different. The end of life, the two last years of life. Medical costs in somebody who dies at 100 is a third of those who die between the ages of 60 and 70. If everybody will be 100, it's a huge thing that you'll have to take care of, but from a medical cost perspective, those people are living and then dying, and so they don't cost much. In fact, they have a contraction of morbidity—I don't know if Tom Perls has shown you that. We have similar data, so if we can imitate those 100-year-olds and you can live healthy and just die one day, it's really a huge dividend. I don't know if, Professor Olshansky, have, did you talk about longevity dividends? Anyhow, open for discussion.

You can still come and say OK, you told us something about the genetics, but maybe those people are very special, because they are doing exactly what the doctors told them to do. OK. So what are their interactions with the environment? Let's see. Overweight or obese: 48 percent of the men and 44 percent of the women. They are not thin. There are no caloric restriction as a group. OK, quite the opposite. What about smoking? 60 percent of the men, 30 percent of the women. Alcohol daily; we want everybody to have a cup of alcohol a day, two if you're a man, not much. Physical activity, and I have it broken down in many ways, but let's look at moderate, regular walking, bicycling, housework: Less than half of the people. If we have here vegetarians—I'm sorry to show you that on 2/3% are vegetarians. (LAUGHTER) Probably we have less vegetarians. Shula Steakhouse is paying me for that. (LAUGHTER)

By the way, this study, when we published this study, it was controlled by another study of their cohort that showed that they are either the same or worse than population at their time. The point is that they were not very special. This is one of those really terrible moments for a researcher. What I'm saying here is if you have longevity, you could have done all those things. If you have longevity genes, you could have done all these things.

Jay Leno has another take of that when he heard about

this study. So I'm showing you what Jay Leno, my biggest nightmare, what he says.

(VIDEO PLAYING)

OK. It wasn't intended to sound like that. (LAUGHTER) By the way, my dean—I don't know if you noticed, at first he said, "At the Albert Einstein College of Medicine, I have no idea where it is," and my dean saw that and said you cannot show this video. And I have a friend who knows Jay Leno, and I said, "What's this thing with Albert Einstein College of Medicine? Why does he have to say he doesn't know?" He said, "Listen, Jay Leno knows two words in science: Cedar Sinai. That's all he knows." He said don't be upset.

This was a picture of those guys 90 years before, and when he received this gun, she got permission to start smoking. So when she died, she celebrated almost 95 years of two packs of cigarette smoking. So Jay Leno said if you smoke 95 years, you live a long life, and that's true, right? (LAUGHTER) But the point here, and I hope you understand, the point here is for those people, they're very unique. As a group, they didn't do what the doctor says to do, and they're still there doing really quite well.

Now, I'm showing you that, but there's a major barrier in doing a centenarian study, and a genetic study of

centenarians, and that is what is the appropriate control group? After all, life expectancy for somebody who was born in 1910, it was 40 years when he was born, and if he got to the age of 40, it was up to 60. Basically their friends, their cohort died 50 years before. So how do you do a study without the control group, and what we've done—initially kind of naïve, but then it worked out beautifully for us—we said we're going to take only centenarians who can bring their offspring with them. Really, one of the major thoughts here is, look, the 100-year-olds are great, but at 100 your chances to die in the next year is 30 percent. So on one hand, they had, like, the best biology. On the other hand, at age 100, they might have a biology of somebody who is going to die, and that again goes into—Let's say, I'm measuring something in those 100-year-olds. What does it mean? OK. If it's high, maybe it's high because now they're going to die, and actually all their life it was low and that's why they got there, right? Things like that.

One of the ideas is if the offspring of centenarians are in reach with all the genes that we're going to find in the family tie, then we should take them, because the advantage is we can fit them with age and gender match control. The age and gender match control are unrelated people to the centenarians. So you can compare the genome of unrelated people, and then do some work with their

offspring. So that is the idea.

Another important thing and also increasingly important in genetic studies these days is the diversity of the population. If you can stick to a population that's relatively homogenous, you're getting many more results. It's things that if somebody will ask, I can talk about it later, but that's the reason. It's a technical reason why we took the Ashkenazi Jewish population, the Jews from eastern Europe, because they are more similar. When I say they're more similar, it's when we do genetic study, we take one change in the time and we compare it across population, but we are not made of one change at a time. Each one of us is made from many differences from somebody else, and if you worked with a diverse population, you can kind of get rid of that and enrich your population with people of the same genotype, so you can see what's so special about them.

To show you that we're kind of where we want to be, what happens when we recruit those offspring of centenarians and control? We see that although they are the same age, they have less hypertension, the offspring. Less hypertension, less diabetes, less myocardial infarction and stroke. I want to bring in the centenarians, at least our centenarians, and show you that although they are 20, 30 years older than this group, the prevalence of hypertension

is almost the same, much less diabetes, and about the same prevalence of myocardial infarction and stroke. So the population in our study, their aging was delayed by 20, 30 years and that's why they're so important for us to understand.

I want to just make a point and maybe Tom Perls has shown it this morning, but when you look at the relationship between longevity and the onset of a specific disease, basically what it shows, that the longer you lived, the later you got the disease. In other words, those are the controlled population people, less than 100, less than 105, less than 110 and over 110. So those are people with exceptional longevity, but whether you look at cardiovascular disease or cognitive function, the longer they lived, the later they got the disease. So there's a real match between how long you live and when you get the disease, which is kind of what I showed also with the DPP and other studies.

So how do we do the genetics here? And why do we have advantage that nobody else has really in the field of human genetics? Because we have the age axis. We have the age axis, and remember that at age 80, half of the population in the United States is dead pretty much. By the way, I'm sure that I didn't say it in your terms, but you kind of understand the gist.

We can populate here lots of people. We have 600 people between 95 and 116, and we have a similar amount of unrelated people everywhere here, but, remember, they're highly selected. They're highly selected, so there's only one out of 10,000 that gets here. So what does it mean? It means that if we see a change in genotype, a change in the DNA that goes like that, goes down, and it's hardly presented in centenarian, we would say it's killing the people, because the older the age, we cannot see it any more. How does it disappear like that? We'll say that's an aging gene and we're very interested in that, but we're much more interested in something else. We're interested in a genotype that may be a little bit rare, and it's monotonically increased and it's presented here in 100 years old, and we'll call it longevity genotype or it will be a candidate for longevity genotype, and that's how we are looking for our genotypes. It has a statistical side to it. There's lots of issues why it's good, and I'm just showing you very briefly, without going into many details.

The longevity genotypes that we found were validated by other groups or at least by one other group, and I'll get to that in a second, but those are CETP and APOC3 are_lipid_ that their genotype homozygosity is between 18 and 20 percent, but it's double at age 100. This is a fat derived hormone that's called an adiponectin, and this is

the TSH receptor. OK. So there's variety of mainly metabolic genes that are associated with longevity. Now, you can imagine that not everybody who has this genotype is going to be 100, and also not everybody who is 100 has this genotype, but those are at least risk for having longevity.

I want to talk briefly about—From now on I'm going to tell you interesting things, not developing stories, but tell you some interesting things. In nature, the small dogs live longer than the large dogs, the ponies live longer than the horses. There are nematodes, these little worms, you disrupt their growth, hormone access, they live much longer. You take mice in the lab, whether they are spontaneously born dwarfs or you mutate their growth hormone in IGF, then they live longer, and if you have an access growth hormone, they live shorter. You take mice and you take their IGF receptor, it's a growth hormone thing, they live longer. We found in 2 percent of our population, we found functional mutation in one of the growth hormones that suggests that this thing that was observed in many kind of models is also relevant to humans. There are also humans who are called Laron dwarfs. There's a colony of them in Ecuador, and they don't get cancer and diabetes as they age. So this story of how you modulate growth hormone and get longevity is very interesting, but also it stands in contrast to what happens out there. The doctors and

other people are prescribing growth hormone as an anti-aging, when actually we think by several mechanisms that the more growth hormone, the less longevity you will have. I'm throwing that in.

Another important thing, like everything aging—There's no doubt that aging is interaction between genes and the environment. So how does the environment itself affect genes? So there are epigenetic mechanisms, and that's a big biological story, but the essence of epigenetic mechanisms is it's not changes in the sequence of DNA, it's something that happens on top of the DNA that switches the genes on and off. One such thing is methylation. The DNA can undergo methylation, and what I'm showing you in this picture, everyone here is one methylation site, but I'm showing you people over the age of 95, and people 65, and you see that the patterns are very different. This is hyper methylated, and hypo methylated. You see that there's a big change between 65 and 95 in methylation, and this is definitely associated with some of the changes that we see with aging.

I'll show you another example that is epigenetics, and it's called microRNA. Those are small RNA that have been discovered really late in the genetic game, that they come from one place and they can regulate the expression of genes. We found here in red in some of our centenarians, those are 20 centenarians and 20 control, we seen in some

of our centenarians, patterns of microRNA that we call longevity microRNA. Actually one of them is the regulator of the growth hormone axis. So we have another reason to believe that the growth hormone axis is involved here.

Epigenetics is kind of another game that's coming into play when we look at aging, because it's not only how we were born and destined, it's also what happens with the interaction to the environment.

Back to Moses. Moses looked at the promised land and never got there. Let me say a few words about the promised land. There is a drug such as metformin which is a treatment for diabetes that recently showed to extend life span in animal models. In the diabetic patients that are treated with metformin, they have less cardiovascular disease and less cancer, probably less cognitive impairment. This is an example for a drug out there that probably works somewhere on the biology of aging. GSK pharmaceutical invested in a drug that imitated resveratrol, which is this wine extract that showed to be associated with longevity. They bought it because they thought it's promising against diabetes, which it hasn't been, but resveratrolhas increased life span in a variety of animals, and it's out there, having been tried enough for many end points of longevity. Rapamycin is an interesting story. It's an immunomodulator that is given to

patients after transplant, but in animal models it elongated life quite significantly. So it's another drug out there that has been tried in humans, has many other problems. Rapamycin is not going to be the end game drug. It has to be modulated, because during, for example, cataracts and some other thing, but it's a drug that probably works on the biology of aging.

Based on our studies—When I say based on our study, I'm not saying it right. In fact, I claim that based on our study, America has developed CETP inhibitor and Isis developed APOC3 inhibitor. Those are the two genes that I showed you are overrepresented in centenarians, but they didn't take it because of longevity. They are doing it because of cardiovascular, because they're trying to find cardiovascular effects. The reason they use our study is not because of the longevity, but because there is longevity, they assumed that those are safe mechanisms, unlike developing estrogen that would kill more people. If more centenarians have actual naturally occurring an inhibition of CETP and APOC C3, for them it's a signal that it's probably safe. So they're on phase three trial and will be out soon, and there are other biotechs that are providing other mechanisms.

I'm showing you here several interesting drugs. All of them have been tried in human, whether they are in trial in

humans or developed in humans. I didn't mention the IGF-1 receptor antibody that blocks the growth hormone action. It's been used in patients with advanced cancer. It wasn't good in cancer, because something happened with the biology of cancer, but it was tried in humans, so it can be tried for other things. So there's really lots of discoveries and promising discovery that should be tried in humans, so [that's] why it's only a promised land.

The first thing you need to realize that aging is not an indication for development of drug, and that is very, very frustrating. By the way, hypertension wasn't an indication to prevent cardiovascular disease. It's only after drug companies show that they prevent cardiovascular disease that hypertension became a disease that you could treat. Aging is not an indication. So if you come to a pharmacy and say hey, let's look at aging, they throw you out. The way to come to companies is to find an indication for those drugs. Find an indication to those drugs and develop it from there, but if you cannot have an indication like preventing cardiovascular disease, it's going to be very difficult unless aging will become an indication.

Another obstacle is that the National Institute of Aging budget is 3 percent of the NIH budget, while the elderly are, you say, 20 percent, depending on what age you call elderly, and the sickness is mainly in the elderly,

but the budget of the NIA is really not enough to have enough scientists to go on and follow up on those discoveries. The funding is less than the 10 percentile, and this is a major obstacle, and it's a political obstacle. The NIA cannot go to other institutes and say hey, give [us] some of your money for aging so we delay aging and we help you, because every institute wants to preserve their money. So you have to be more creative and actually the effort at the NIA level is to take a grass-roots approach and convince every other institute that they should have aging as something that they develop there. Diabetes and aging and cardiovascular and aging so that it's their money, but please make it relevant to aging. So that's a big challenge. The other challenge is that some of our supporters like Ellison Medical Foundation, that supported about 30 percent of the studies on biology of aging, decided to go—They didn't go out of business, they just decided to go somewhere else. So not only the NIA's in trouble, but many of our other funding are. There, I just wanted to talk with you about the challenges.

Let me summarize by saying a few things. So Moses was 120. Anybody knows any other ages here? Methuselah 969. Definitely after the flood there was a decrease in longevity genes. It shows you that the environment is very important. I also noticed Joseph was 110, which means to be

a minister with a pharaoh in Egypt hasn't been such a great job ever. You don't get the same longevity.

As I told you, there are people who believe in every word that it says in the Bible, but they don't buy the ages for some reason, or they have excuses. This is really fascinating for me. Three things I want to tell you about Moses. First of all, he had a stressful life. Now, the stress, the chronic stress is bad, but periods of stress, or acute stress like exercise, like going to the gym, is actually not bad. We say decreased stress, everybody shouldn't be stressful, but it's a bit more complicated than that. Moses was going with those bunch of complainers in the deserts for 40 years. It sounds quite chronic to me, but just let you know that stress is involved.

The second thing in the biology of aging is caloric restriction. There are lots of models. When you caloric restrict them, compared to their brothers, they live much longer, like 40 percent longer is the animals, the rodents, would live. Why does it happen and what's the mechanism of that is a major part of our studies, and it's possible that the limitation of good nutrients in Sinai desert had to do with longevity if he did, indeed, live 120 years.

There's some other provocation that I want to make here. In nature, there is an exchange between reproduction and longevity. You can prove it in animal models in many

ways. We looked at how many children our centenarians have, whether male, female or both, compared to a control without. In other words, remember, we had the offspring generation, so we ask how many brothers and sisters you have for the offspring of parents with exceptional longevity and those without, and they had significantly less kids. Both the men and the female. So there's some exchange in reproduction. By the way, I think we are underestimating because it's estimated that a third of the centenarian women in the world don't have children. We are recruiting only people who have children. So in fact I'm thinking maybe we should do something with the other women, because maybe we'll find more correlation with the biology of reproduction, and why they live long.

The point I want to make here, if this is true, if in every generation we have half a kid less, this is huge from an evolution perspective. This is huge. So we are losing longevity genes, right? Our centenarians have less kids than people who are not going to be centenarians. Every generation we're losing longevity genes. If we're losing longevity genes, maybe Moses and Methuselah and all that did live longer. We know that humans didn't live longer than on average, but maybe the capacity to be 100 was preserved then.

It's interesting that I got some system biologies to

work on that. You don't need to go so many generation to see how it's effective, how it should effect longevity. You don't need to go so much back, because this is a big effect. So maybe we're losing reproduction and we're losing longevity genes. That's a possibility.

Another thing I want to tell you is that we found skin youthful genes. We sent the pictures of all our centenarians control offspring to dermatologists. They covered the hair, just had the skin, and we looked at the genotype for those who looked much younger than their age and much longer than their age, and we found three genes, but the important thing with these three genes, they are not longevity genes. So you can be pretty or you can live long, it's not the same genes. (LAUGHTER)

The last point I want to make, this was—*National Geographic* in May wrote about our study. They came and there are many aspects of the study obviously I didn't say, and I got this paper, and by the way the headline here is "This Baby Will [Live to] be 120." OK. I saw that. I went to the newsstand to buy the journals and give to all the people that are involved in longevity. I go there and I see this and I'm looking at that and I'm saying, I'm losing my mind. That's the Alzheimer's part. I'm losing my mind, I thought it was black. It was a black baby. Then I realized that *National Geographic* is doing what *Sports Illustrated*

is doing. Everywhere in the world they have different babies, but still it's the same title, "This Baby Will [Live to] be 120," and I want to say something about that.

I know Jim Vaupel talked about it. I think the point that is missing in this discussion is that we might have a maximum life span as a species, OK, that is dependent on not only the biology, but on physics. There is probably limitation. We know that the oldest person in the world died at age 122 that we can be sure of. Somewhere between 100 and 122 there is a limitation to what we can do, at least with the biology. I'm not talking about cell replacement or what Aubrey de Grey reviewed. He starts about that, but there is a maximum life span, and I think we're reaching it. So we are going to have this seaming effect.

I think it's wrong just to say based on what happened, what is going to continue, and that's ignoring the fact that until now it was medical progress and the NIA's not paying us to find how to get people to age 100 and 120. They're not paying enough. So ignore the fact that you have to have, actually budget to improve life span, but I think there's the roof effect that people are ignoring. They're just assuming that it goes forever. Remember that this starts, this trend of increase starts, I don't know, let's say 200 years ago, but human evolution, pretty much life

span was at about 35, probably for thousands of years. So this is a new phenomenon and you cannot just assume that you are going until the end. I'm not saying you won't be able to reach that, but the way we are now, let's get somewhere to 100 and 120, but I think it's not so easy. So I hope that I told you a few things. I hope that I convinced you that if you prevent aging, you might prevent its diseases and maybe that's the way to go. I showed you the research to the biology and genetics of aging is bearing fruit, and there are medications that are used in humans that have been shown to affect both biology of aging and healthy longevity, and I kind of made the point that being healthy as we age, lots of issues. Social security, retirement age, all the things that you've been discussing, but from a health cost perspective, it's probably going to be a large dividend. Let me just put up people who have done these studies, and thank you very much for listening, and I think we have time for discussion. Thank you very much. (APPLAUSE)

TIMOTHY F. HARRIS: We'll go ahead and field some questions.

LES LOHMANN: This is great. What a terrific seminar. Thank you, doctor. I'd love to see a study—We know that testosterone is poisonous. I'd love to see a study that related the onset of puberty with longevity.

DR. BARZILAI: Absolutely. Two things you said. First of

all, testosterone is toxic. There is actually an effort of the NIA, there is a multi-central study to give testosterone to old people for safety only. OK. So we would know more about really when and why maybe testosterone can be done, but the second point is very interesting, and it's very interesting because there's data now that's not published that shows that when you do those longevity genes in several animals, when they're young, their performance is much higher than even to the control. So it's not only the aging, they're better also when they are young. So I'm trying to set up the calibration. In fact, I'm having dinner on Saturday with the head of our children's institute to start taking some of the genotypes for exceptional longevity and identifying those genotypes in children, and start to assess those children to see, can we measure there something, and it could all be something that happens intertwined and during puberty, and then you're set for aging. That's what you're saying, absolutely.

AUBREY de GREY: That was a lovely, lovely talk. I think it was a very good complement to the talk I gave at lunch actually. The only thing I want to take you up on really is something that you said in your concluding slide. Maybe you can go back just one slide. (LAUGHTER)

DR. BARZILAI: Next time bring your own slides. (LAUGHTER)

AUBREY de GREY: I often complain about gerontologists not

being quite courageous enough with their language, and I think I would like to take issue with your top statement: If you prevent aging, you may prevent its diseases. I would say that any scenario in which if you prevent aging, you don't prevent its diseases is simply a scenario at which you have the wrong definition of aging, because can it be? a disease of old age, other than by being an aspect of the later stages of this lifelong process.

DR. BARZILAI: Let's not disagree on what you said. One of the things that you have to understand always in our discussions—First of all, I'm an M.D. Also, I get my grants from the NIH, and I need to find a way to say things that are not going to upset anyone. OK. (LAUGHTER) I really believe, and I thought that I made it clear, I really believe that aging is the way to prevent diseases. OK. But unless you did a study, a double blind, crossover study, where you took one group and a second group and did it, improved it. Until that it's a promise, I need to say MAY.

AUBREY de GREY: Well, kind of. I mean you could do a double blind study to say whether two plus two equals four, but it wouldn't really change whether it was true or not.

DR. BARZILAI: But you know, that's what the people who gave estrogen said. When the estrogen study started, people were angry that they're doing it. They said why are you wasting time, let's just put everybody on estrogen, we have all

this data and how it failed because of beliefs. By the way, on the animal level, what they did is they took young animals, took their ovaries out, replaced estrogen in half of them and induced stroke, heart disease, whatever. So on those young bodies it worked. Estrogen is a useful hormone in a young body. The only investigator that said I'm not taking young animals, I'm taking old animals and do the studies, she got the opposite result, but everybody said they are old, they are sick. They used this against her. My point is, OK, we all believe, it's a religion for us, but we really haven't proven it on humans.

AUBREY de GREY: Well, I think what we haven't done is decided on a definition for aging, for which your top statement is true by definition. I think that's what we need. I think we need to understand that the reason why there is so much resistance to biomedical gerontology to actually doing something about aging is precisely because we are too cowardly, I think, in stating what aging is as being synonymous with the precursors of age-related ill health. That's the really important thing.

DR. BARZILAI: The common stance. That's it guys, that's all the provocation I'm getting? (LAUGHTER) I mean there was a 105-year-old man talking about sex and you cannot ask any questions? (LAUGHTER)

EVAN INGLIS: I guess I just wanted to clarify your thinking

on the ceiling, this life-expectancy ceiling. You seem to be thinking that right now there's a ceiling of about 120 years, and are you also—Do you also believe that at the time of Moses that the same ceiling existed of 120 years, or was the ceiling lower at that time?

DR. BARZILAI: Yeah. First of all, you said it right. I believe, of everything that I said, I'm less certain about the ceiling. I don't know how to measure the ceiling. I'm saying just show me that somebody lived to be 300, and I say yeah, let's go there. If people lived only to 112, and by the way there's a lot of—I mean Hayflick has the best arguments. He goes to physics straight and tells you from physics point of view, it's just not going to happen, we don't have the chemical engineering to last longer for that. Now, you're using that against me to defend the fact that there was longevity and I don't know what to say. I would say maybe 120 was the ceiling for Moses and Methuselah is somebody didn't count right, don't know. (LAUGHTER)

EVAN INGLIS: No. I guess my question is really do you think that that ceiling has changed over the years because, for whatever reason, technology or biological evolution?

DR. BARZILAI: No, I don't think so. I think there is probably in the last—when human evolution became closer to what we are now, we have our ceiling, but I'm not sure at

all.

JAY OLSHANSKY: Great talk as always, of course. Two questions. In terms of a therapeutic intervention that you or somebody else is eventually going to develop, how might it happen? That's my first question. The second one is here in Florida it is really common for some of these clinics to give growth hormone to people with the promise that it's going to make them live longer, and of course the evidence that you presented indicated the exact opposite. I'm wondering if you might want to comment on that as well.

DR. BARZILAI: You distracted me with the second one. Repeat just the first one again fast. Oh, how do we go with therapeutics, right? OK. I'll do that first. So this is really a great challenge, and I should tell you Jay knows a little bit about this answer, because we are several people who are dealing with it, but I told you that aging—Not only aging is not an indication, but suppose it was an indication. So what kind of study would you tell pharmaceutical to do? Would you tell them take a bunch of 50-year-olds? I don't know when to start to treat, right? Let's take 50-year-olds and give them a drug and watch them for 30 years and see what happens, and then we can improve the drug. Is that what we can do? Makes no sense, right? So we're trying to get more sophisticated and say—And I'll tell you what I'm doing. Resveratrol, the wine extract that

has extended life span of many species. So in our institute we decided to take elderly people who just became glucose intolerant, they're not diabetics, but their glucose tolerance is not normal. So they just failed. So they are elderly, they've just failed, can we bring them back now? Can we get them resveratrol and show that we improve the glucose intolerance and some other biological factors? And to do that, we do it with 24 patients in an arm, in a crossover design. We don't need to do that much in order to show this concept.

Can we do things like that with other drugs? In elderly people who just got a heart attack and are recovering from heart attacks, can the drug enhance the recovery from heart attacks or from stroke, or after getting chemotherapy for cancer, for example? We need to start being creative and do what's known more as the phase II trial, the principal studies. Do it in a variety of ways and show that we have drugs that actually can have effect when the elderly are just starting to fail.

The Florida question—I kind of said that the evidence is against growth hormone being a longevity thing, but I actually want to give another example, and by that I'll maybe end, right, it's almost time?

I'll say that and if there are more questions also. People are coming to me and saying you have to see these

centenarians, they're incredible, and I showed you. I know that they're incredible and I cannot see all of them. They said no, she's 104, she's in Florida, when you're in Florida you have to see her. So I came. It wasn't here in Orlando, it was in, I think, West Palm Beach. I was there for another reason and the next morning I went to see this person. I have needles with me so I can take blood and stuff, and I go to this house and beautiful house, nice garden and she's out dressed very lovely, just beautiful, elegant woman. She just came from shopping. We went into the house, she baked a cake. The smell was wonderful. We were sitting on a couch and she was really incredible. We were starting to talk and all of a sudden she turns to me and says, "You haven't asked everything you should ask," and I said, "Yeah, what?" She said, "About sex, you didn't." So I'm sitting down with a 104-year-old woman in Florida and I'm like I don't know what to do, she wants to talk about sex. (LAUGHTER) I say, "You're a widow and you know, we don't ask, but tell me, what do you want to say?" She said, "Look, I became sexually active in 1917." She was 16 then. "And until I was 93, and when I was 93, I took yoga, but it's not the same." (LAUGHTER)

SANDRA TIMMERMANN: I think this is a good segue into my question. Many of the centenarians that you showed in your video and the research findings of Tom Perls and Gene Cohen

seem to indicate that mental activity and purpose in life correlate with living longer. I'm wondering if you in any of your studies have looked into that factor?

DR. BARZILAI: I'm so delighted about this question. The cause and effect here is really always a challenge. Let's say I have the answer. Is it the fact that they're healthy that they have good performances? Or is the good performances making them healthy? And that's always the thing. Doing the crossword puzzle that was published in *New England Journal of Medicine* and stuff, so what does it mean? It means they're healthy to do the crossword puzzle. Does it mean that the crossword puzzle is what's making them healthy? Right, it's a problem. So we have those bunch of centenarians and what we have done—I mean we're doing cognitive thinking, but I'm going to the other part of your question, which is their personality, what's their personality. We found that they have an incredible personality. We published several papers showing that there are extrovert, there are optimists, there are forward looking, they don't have grudges. You never see a centenarian saying something bad about his son- or daughter-in-law, things like that. So there is a really great personality and you think wow, we know that personality doesn't change with age, so wow, that's important. So maybe the longevity genes are also genes for

personality or something until one day I run into the son of this lovely guy that I just met, and his son is 80. So I say to him, "I spent time"—by the way, 80 that looks like 60—I said, "I just spent time with your father and he's such a great guy, such a nice guy," and the son looks at me and says, "You should have seen the son of a bitch when he was 80." (LAUGHTER) Then I realized—I started actually reading a little bit about it, and then I realized you know, maybe personality doesn't change, or part of the personality doesn't change until you're 70, but between 80 and 100 when you are actually getting older, the cognition is—You're losing a little bit of the cognition, you don't live at home maybe any more, you moved. It's not the same personality, and there's actually a great paper from the University of Pennsylvania where they took young and old people and showed them slides. Some of the slides were like islands in Hawaii, and some of the slides were cockroaches crawling in pizza. Nice slides, and disgusting slides. The young people remembered everything. The old people tended to remember only the good things.

By the way, I'm looking forward to this part of my aging. (LAUGHTER) That everything looks good. I think it's right there. I think there are changes in these healthy centenarians. There are changes that all of a sudden you measure personality that is the end of their life, and

doesn't mean really anything before. I went to other children and I sense—Look, most of children don't say my father is a son of a bitch, but there's definitely feeling in most of the offspring that there is a behavioral changes in the centenarians. That's as much as I can give you insights now.

I'd like, if we have a few minutes, if I could ask Jay to talk about the longevity dividend. I mentioned something that he really worked on. Jay, if you want to. I don't want to put you on the spot, but in two minutes to talk about, you're leading a great effort.

JAY OLSHANSKY: Ironically enough, I actually was going to say something a minute ago, and then whatever it was that preceded that discussion forced me to go back and sit down, because I didn't want to follow up on that discussion of sex and 104-year-old woman. Let me preface it by saying that for those of us who study the history of public health, there have been very few dramatic shocks that have influenced health and longevity in human history, very few. What Nir presented here and the first part of Aubrey's talk at lunch is, in my view, going to be one of the most important, ground-breaking events in public health in the 21st century. When this intervention is developed, however it is developed, whoever develops it, I think it is going to have a profound effect on human health and longevity

going forward, and so it's an extraordinarily exciting time to be following the science. You got a small dose of it just now, and it's very exciting.

The longevity dividend initiative is an effort to accelerate research funding designed to address the kinds of issues that a number of research scientists are focusing on now, basically suggesting exactly what was suggested earlier, and that is, the time has arrived to begin focusing our attention not just on the diseases of aging, but on the underlying risk factor for almost everything that goes wrong with us, which is in essence itself. This work that's being done on the genetics of long-lived people, I think, is perhaps some of the most interesting work that's going on, but there's a lot of other research that Nir had presented as well. To make a long story short, we're beginning to gain an enormous amount of traction in this area, and hopefully the effort to pursue additional funding at a dramatically higher level is going to begin in this year, and Nir and others are going to be a part of this essentially traveling road show that's going to go around trying to draw in money from places other than the government to accelerate research designed to slow aging, as a way to prevent. As I said earlier at a previous meeting, delayed aging is basic primary prevention with a capital P. If you want to go after heart disease, cancer,

stroke and diabetes, go after aging, and that's exactly what Nir was saying and a number of other researchers as well.

DR. BARZILAI: Jay, can you say just a word about the dividend, the economy, I mean?

JAY OLSHANSKY: Well, last October we published an article in *Health Affairs*, which took about two years to finish and publish, which basically documented the economic and health benefits associated with delayed aging. So if we make significant progress against cancer, or significant progress against heart disease, indeed there would be more healthy, older people going forward between now and the middle of the century. But if you delay aging by just a small amount, and we documented this in the paper, just a small deceleration in the rate of aging yields huge health impacts for the population, because it just doesn't influence heart disease or cancer or stroke, it influences all fatal and disabling diseases simultaneously. So a minor deceleration in the rate of aging has a cascading effect on everything else, and that's the promise of this kind of research. In terms of the economic value, we documented that a very small deceleration in the rate of aging would yield about a $7.1 trillion benefit between now and 2050, and we think that that's a gross underestimate, frankly.

DR. BARZILAI: Thanks.

GARY MOONEY: Google announced a project recently called Calico. Can you comment on that project or if you're involved or anybody within this group is involved in that project, because that's something completely separate?

DR. BARZILAI: Yeah. All leaders in the field are waiting for Calico to interact with us. I have actually, just in the last week, a lot of insights on what happened, but this is the bottom line: The Google's founders have decided that they want immortality. That's how they were quoted sometimes, and they decided we're going for that, and the next thing they did is they took somebody who is a really great scientist, [Arthur] Levinson, who was the CEO of Genentech, and really the state of the art is that they don't have a plan now. They are talking with some people. They are putting a plan that we're all curious to see. We're trying to bring them to the discussion. The one thing we don't want is for them to come—We've made lots of progress in the field. We did experiments that went bad. We did experiments that went good. We are eager for them to talk with us so that we can complement what they are thinking about, but I think what really happens is they don't know what they are doing yet, but it seems that they are going somewhere and we hope that they'll do something that's mainstream and inclusive. For example, for me, I'm very much hoping that Google will take up the policy issue

of defining aging as a target, which means it has to be FDA approved for drug development, things like that. So we're very happy that somebody's joining in, in a big way, but we don't know what it means yet.

TIMOTHY F. HARRIS: Thank you. Let's all thank Dr. Barzilai for his presentation. (APPLAUSE)

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