CENTER FOR HEALTH TRANSFORMATION

"PREPARING THE COUNTRY FOR THE ALZHEIMER'S EPIDEMIC: A VIEW FROM SCIENCE, BUSINESS, GOVERNMENT, AND CAREGIVERS"

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NEWT GINGRICH: (In progress) – and let me say very directly, as somebody who is now 63, to remind the baby boomers that this is a topic that they should pay attention to now because now there's still time to make substantial breakthroughs. And from a baby boomer perspective, there is almost no topic more pertinent to the quality of their life than Alzheimer's.

We have in our own family – I have a sister-in-law whose mother currently has Alzheimer's. I used to teach the oldest men's bible study in Carrollton, Georgia, and first came into touch personally with Alzheimer's when I was still in my early 30s because we had members of our Sunday school class who ended up with Alzheimer's. And so from my perspective, this is a very difficult, very complicated disease state, which has an extraordinary emotional impact on families. I was just out a few weeks ago with Nancy Reagan at the Reagan Library and talking about it. And it is a problem, which deserves our direct involvement.

I'm fascinated with it because of two different patterns. One is, Alzheimer's is clearly – it's a disease of success. Alzheimer's tends to occur when you've lived far longer than historically humans lived. As late as 1900, the average person lived to be 46. Since 1900 we've added – in Japan the average – a young girl born last year in Japan will live on average to be 88.

So we've added over 40 years of lifespan. And it turns out as you add lifespan and manage to avoid dying, other things happen to you. Alzheimer's is the most common single other thing. And so we need to see this at one level as a consequence of an enormous success. But as you look at the size of the baby boom generation, and the fact that virtually all of them are going to refuse to die – I mean, they're going to demand living as long as possible, and therefore they've got to confront the reality that if you want to live a long time you increase dramatically the potential for you to get Alzheimer's. In fact, I think it doubles every five years after 65 so that each successive five years, you increase substantially the risk of getting Alzheimer's.

So the first thing that fascinates me about this is just the sheer scale of what's coming down the road. There's one estimate, for example, that if we kept the current payment patterns and we kept the current probabilities of epidemiology, that by 2050, which is within the retirement cycle of current college students, that about the time they are retiring, CMS, the Center for Medicare/Medicaid Services, would be spending a projected trillion dollars a year on Alzheimer's. So the first point I want to make is this is a large enough topic that it's worth focusing on at a national level.

The second point I want to make, and the reason I'm so excited – if it's just a problem then we could hold a meeting, we could wring our hands, we could think, well this is sad. The second reason I'm so fascinated is that over the last 20 years the

acceleration in brain sciences has been so phenomenal, starting with our ability to do the kind of imaging that allowed us for the first time ever to actually watch a living brain while it was functioning. I mean, historically, prior to that point, we reversed engineered brains based on autopsy, and that's a fairly limited level of understanding.

We are now in the early stages of an accelerating understanding of the brain in a way that is quite extraordinary. This is part of a larger pattern, which I think we don't understand how to deal with. And I want to just divert for one minute because I think whether it's FDA or NIH or CMS or whether it's the private sector, we have a pervasive challenge coming down the road. There will be four to seven times as much new science in the next 25 years as there was in the last 25. And I think these are literal numbers. I used to say four times as much, and I gave a speech at the National Academy of Science's Working Group on Computation and Information, and afterwards the chairman came over and said that's too small a number; he said it's got to be at least seven.

I went to New York to one of my favorite institutions, the American Museum of Natural History, and I asked the chief scientist there, Michael Novacek, what he thought. He said he thought 10 times, but I thought about it for a while, and Novacek is a vertebrate paleontologist, and it is an under-invested field, and, therefore, they are playing catch up with technologies that things like cancer research have been using for 20 years.

So I think four to seven is a reasonable number. Now, the reason – now I want to just slow down for a second because it takes you a little while to think about this, and when you do, it changes how you think about the world. Four times as much new knowledge – but let me just say this as an aside, the reason is pretty straightforward. There are more scientists alive than all of previous human history. They're connected by cell phone and e-mail, so they send information about breakthroughs faster. They are then connected to better computers and better instruments every year. And brain science is one of the areas we're having the fastest evolution of new technology compared to the baseline 15 years ago. Then they're connected by licensing venture capital and royalties to the marketplace, and that's connected to China and India's reserve centers of production. If you take that equation and you lay it on the board and you think about for a while, four to seven is a reasonable number.

Now, why does that matter? Well, it matters because if we're trying to deal with Alzheimer's by 2031, a four-fold increase in scientific knowledge means we are the equivalent of an 1880 planning committee trying to understand this meeting. That's what four times the level of change would be. Now, in 1880 planning committee is pre-automobile, pre-airplane, pre-motion-picture, pre-electric-light, pre-long-distance-telephone, pre-computer, pre-air-conditioning. I mean, how would you even start the conversation if you were explaining this meeting to somebody from 1880? How would you explain the television? How would you explain the Blackberry? How would explain the car that got you here? But if it's seven times as much new knowledge, it is as though we're having a conversation with Sir Isaac Newton in 1660, trying to understand calculus.

Now, the reason I'm laying this out is there's no reason to believe that the current NIH model of gathering and disseminating research, or the current FDA model of understanding breakthroughs in science, or the current models of thinking about public policies as it relates to CMS have any capacity to absorb this level of change, and to do so at an optimum rate. And yet, every day that we are behind the curve, people die, money is wasted. And so the opportunities here are much greater than you might think.

So from our perspective we really are very excited at the Center for Health Transformation because we do believe it is possible to bring together science, business, government, and caregivers to truly create a roadmap for a dramatic series of breakthroughs. And we believe that for the baby boomers and their children this one of the two or three highest-value health opportunities rivaling, I would argue, diabetes and cancer, as the three largest single challenges we're going to have in the next generation.

And so it's a great thrill for me to be here personally. I do one to take just one second and say that I want to introduce Rob Egge because Rob has actually coordinated all this and helped put it together, and he does a tremendous job for us at the Center. And now what I'd like to do is ask Harry Johns, who is president and CEO of the Alzheimer's Association, to introduce our first formal speaker.

HARRY JOHNS: Thank you. Good morning. Thanks, first of all, to Newt Gingrich for putting together this forum and your overall leadership in health in America. I think it's great that we have this opportunity to have this discussion today for what is, I agree, one of the very most important health issues facing America, but has yet to be fully embraced by the populace and in a way that moves policy.

At the Alzheimer's Association, we are inspired by what is our vision of a world without Alzheimer's disease, to play an essential role as a leader and a catalyst in driving, not only an urgent research agenda, but also treatment, detection, and support agenda. The rapid progress we've seen over the last 15 years is in no small part due to the kinds of partnerships we have at the association with the FDA, and with the National Institute on Aging, the scientific community, and the pharmaceutical industry. Through the strength of these collaborations, Alzheimer's disease has moved from relative obscurity to the forefront of science, but not, as of yet, to the forefront of investment and the kind of strategic investment that I think is necessary to make the changes we're going to discuss today.

We have many longstanding partners, I should say, in this room. Dr. Andy Von Eschenbach, I am happy to say, I have known as a friend and a colleague since his days at the M.D. Anderson Cancer Center and certainly in his role at the National Cancer Institute as its director. I know him to be an innovative, thoughtful, and very capable leader. And I know that I look forward to working with him further in his organization as we advance this cause.

In addition, I just gotten to know better, Bob Essner, have been talking with him. You know, I think, that he has been a leader in Alzheimer's disease in general for the cause, but also in his industry. And we look forward to the further working relationship we have with Wyeth.

I'm also pleased to say that today marks the beginning of newer association with Newt Gingrich and his organization, the Center for Healthcare Transformation, that I believe is working in the right direction to advance this cause. While phenomenal progress has been made, much more, much, much, more is needed, of course. We must increase our total investment in Alzheimer's disease to save multiple generations from the human impact and devastation as well as the country from the financial impact and devastation of this disease.

We are of course, at the Alzheimer's Association, advocating for increased federal funding and research, but again, on a strategic basis so that we can accomplish this task for the whole of the country. We are also working, along with our partners, to accelerate the development process for new treatments. And that's why the Alzheimer's Association earlier this year launched the Effective Treatment Initiatives.

The Effective Treatments Initiative, which Dr. Sam Gandy will talk about more in a moment in detail, has several key elements: Working with Dr. Von Eschenbach and the FDA to focus on Alzheimer's disease more specifically increasing the resources that the FDA has available for reviewing Alzheimer's and other neurological interventions; finding ways to bring the voices of caregivers and early-stage individuals who have the disease to the table for the drug review process; and finally, increasing the speed of clinical trials by directly supporting a recruitment process.

Underpinning everything the Alzheimer's Association does is a strong evidence base that stems from solid, scientific research. And we are fortunate to have the very best researchers and scientists from around the world on our medical and scientific advisory council.

The chair of that council is Dr. Sam Gandy. Dr. Gandy is director of the Farber Institute for Neurosciences at Thomas Jefferson University. He is an international expert on the metabolism of the sticky substance called amyloid that clogs the brain in individuals who have Alzheimer's. In 1989, Dr. Gandy and his team discovered the very first drugs that could lower the formation of amyloid in the brain. Dr. Gandy has written volumes on this topic and his writings have become some of the very most quoted in Alzheimer's disease. It is my great pleasure to welcome a great scientist and a great friend, Dr. Sam Gandy.

(Applause.)

DR. SAMUEL GANDY: Thanks, Harry. Let me also just mention to you about the association's tripartite mission, and that is not only caregiving, but also advocacy, and with increasing intensity, research. And the reason for that is that for the first time in

medical history we can actually contemplate rational therapy for Alzheimer's disease. One of the numbers that you might or might not have heard before, but just to reinforce – half of the over-85 population has a dementing illness. That is, if both parents live to 85, statistically the likelihood is that they will – one of them will have Alzheimer's disease; will have a dementia, usually Alzheimer's disease.

Harry mentioned the Effective Treatments Initiative, and that's really because the association is poised in an especially opportune place to coordinate the activities of the private sector, the federal sector, and the academic institutions in terms of trying to bring together the most important science and bring together fields that might otherwise be disparate. So what I'm going to do for the next bit is to be the designated hitter for science teaching for this morning. And you will have heard over and over that most of what we know about Alzheimer's disease we've learned in the past 20 years. And I'm going to tell you exactly what that knowledge is and show you and try and communicate to you why it is we are so excited.

So here's my title, "A Pivotal Moment is Within Reach" and that's absolutely certain; there's no doubt about that. We are now entering human clinical trials that will tell us if what we are fairly certain is true about Alzheimer's disease is in fact provable in humans.

So Alzheimer's is really characterized by three key criteria. The first you will have been acquainted with: the characteristic change in memory, typically the inability to form and retrieve new short-term memories. Equally frequent, patients with Alzheimer's may present with changes in personality. Eventually, all of the outside surface of the brain, all of the cerebral cortex, the part that's responsible for thinking, all of that part of the brain degenerates and patients die bedbound in what we call a vegetative state.

There is very early on a profound loss of a chemical called acetylcholine. Now, this is a chemical that nerve cells use to talk to each other called a neurotransmitter. And the currently approved medicines, at least three of the four, all target this deficiency; that is, they help the brain to compensate at the very earliest stages of the disease. However, for these medicines to be effective, intact nerve cells are required. So once nerve cells become impaired to the point of degenerating, those medicines that we currently have wear off. So these medicines don't appreciably slow the progression of the disease and don't really attack the underlying pathology. And that's what I'm going to talk about for the rest of the moment, and that is the accumulation of the abnormal, gummy structures. And this is really what's been the heart of the advances in Alzheimer's science.

Now, before I start throwing around all this jargon, let me try and define a few terms for you because these are – there's really only a handful of words that you need but unfortunately, there's absolutely no getting around them. So in order for you to understand what has the scientific community so excited about Alzheimer's disease, you need to know what an amyloid plaque is, and this is a clump, a build-up of a gooey material – you'll see some images in a moment – in between nerve cells.

Now, these plaques are composed of a protein called the beta amyloid peptide, and that can be written Greek beta amyloid; it can be abbreviated a beta. If you see anything with the Greek beta or the word beta, or the word amyloid, it's all talking about the same thing. And this is a protein. And the body, as you are aware, the body is made up of three main substances: fats, sugars, and proteins, and this is a protein.

You are going to hear in a moment about enzymes called secretases and you can think of them, essentially, as being equivalent to scissors. And some of these scissors do good things and some do things that ultimately don't go so well. Finally, aggregation, and that's essentially equivalent to clumping. And it's really important to understand this concept because this is now a key theme in all late-life degenerative diseases of the nervous system: Parkinson's, Huntingdon's, ataxias, Amyotrophic Lateral Sclerosis, they're all due to clumping of protein inside nerve cells, outside nerve cells, or both.

So the term amyloid, unfortunately – you would think, if you knew the definition, it might help you. Unfortunately, the definition is actually very misleading. The word itself means sugar-like, and that's because pathologists in the 1800s first visualized these materials, like grains of salt in the brain, with a particular reaction that visualized sugar. And they then applied this name, amyloid, for sugar-like. It turns out that only a very tiny amount of the actual deposit is sugar. So, again, the protein, the amyloid deposits are 99-percent protein.

Okay. Now, I'm going to walk you through basically how we get from the initial protein that's made from a gene to the amyloid deposit. So the protein that you're going to see depositing in the brain in just a moment is represented by the red bar here on this image. So the part that will ultimately give rise to the plaques is a small piece of a much larger protein called, very originally, the amyloid parent protein and this undergoes these scissors-like cleavages, which we call processing.

This is just for orientation. This shows the amyloid parent protein seated inside at the surface of the cell. So one alternative is for one of these scissors to come through and snip exactly in the middle of this red piece. In this case, which we call alpha cleavage, for historical reasons, the amyloid region that forms plaques is destroyed. By breaking this red bar, this pathway now prevents amyloid from ever forming. So this is what we call a good pathway or a non- amyloidogenic pathway. But let's just stick with good.

(Laughter.)

So now, alternatively, assume that this cleavage hadn't happened. An alternative way is for a scissors to come in and snip here, precisely at the top of this red bar. This piece, which is labeled here as C99, subsequently is cut by another pair of scissors and that releases this substance, the amyloid beta peptide. So the real problem in Alzheimer's disease, in particular, and in other aggregation diseases, is that normal proteins, proteins that are always with you all throughout life, somehow, for reasons that are often mysterious – not always – change their shape, and in this altered shape, they then plump. And that's really the bottom line.

Let me just walk you through and say the amyloid peptide is normally in between nerve cells in your blood, in your spinal fluid all throughout life. The challenge is why it crashes out after six decades of being happy. So lets say this is the same amyloid region before, and think of it as normally being like a sort of floppy noodle. Well, misfolding is literally what it says. So you see the protein, this red piece, gradually bending back on itself. And once it forms what is basically a bobby-pin-like structure, it becomes locked in that structure. These bobby pins can then accumulate, can then build up to form amyloid plaques because these bobby pins now expose the very sticky gooey parts of amyloid. And so, as you just saw these red bars accumulate, here now you see the characteristic lesion of Alzheimer's disease.

This is the amyloid material, the deep pink here in the center of this sterical structure. The brown flame shapes that you see on the outside are nerve cells that are incredibly unhappy or being poisoned by this amyloid material. If you look under a microscope, you can see that these things actually have very characteristic shapes. Now, they often form – spontaneously form these fibers or these clumps. In fact, these clumps are now believed to be the most poisonous shape.

Now, you heard before about the advent of PET scans that allow you to see brain functioning. Within the past few years, we've now been able to develop – we the field; we, not me – have been able to develop PET scans that allow the visualization of amyloid buildup in the brain during life. So for the first time in a living human, you can watch amyloid buildup. So what you see here is a dye that has a positron emitter attached to it, and these are brain scans of a subject with Alzheimer's disease, above, or a normal subject below. So this is a pseudo color image and the red then yellow represents accumulation of amyloid in the brain of living people.

So this is an incredibly important breakthrough and is being evaluated worldwide now, especially for the testing of new medications because now, for the first time, we can see the target; we can see what we are aiming our drugs at because we're developing these anti-amyloid drugs, and most peripheral markers have not been satisfactory. This particular imaging tool is being added to a large international initiative called the Alzheimer's Disease Neurolimaging Initiative and these particular scans are supported by a project from the Alzheimer's Association.

So you will hear that there's a controversy over amyloid. Is this a cause or an effect? And the likely answer is both, because we know there is some instances in which the disease begins with amyloid and we know that there are other forms in which we can't trace the exact beginning. But all the evidence indicates we are better off without this misfolded form.

What's the most compelling reason for focusing on amyloid for drug discovery? And that's the following: In very rare cases about 5 percent of all Alzheimer's disease is caused by mutations either in the amyloid gene, the gene for that red bar, or the gene for one of those pairs of scissors. That explains the autosomal dominate, the most common

forms of genetic Alzheimer's. So that shows that in those cases, and they are indistinguishable from common Alzheimer's, in those cases the disease begins with the mistake in the DNA and the mistakes there are focused on amyloid metabolism.

So even if amyloid is not the whole story in common Alzheimer's, we know very well that these clumps in nerves, and if we look at nerve cells in a dish, are poisonous. So this is not good. The only way now we can really resolve how much of the dysfunction in Alzheimer's disease is due to amyloid is in human clinical trials in which we develop successfully anti-amyloid agents, purge the brains of humans so there's no amyloid left, and see what happens cognitively. Ideally, we'd like to actually be in the prevention mode so that we identify ways to screen people, begin anti-amyloid interventions, and prevent the scenario from ever happening. But we won't know how bad amyloid really is until we purge it completely and follow the clinical outcome.

Now let me just show you how dramatic the results are in the laboratory in a couple of examples. Among the major benefits of discovering Alzheimer's genes has been the ability to put those genes into laboratory mice. Normally mice would never, ever get Alzheimer's disease no matter how long they lived because their amyloid protein has changes in its building blocks that make it less sticky. So the mouse amyloid will never – the mouse A-beta peptide will never clump.

So all the strategies that are currently being tested really fall into one of three categories. I'll walk you through just some examples. The first is the immunotherapeutic approach, the vaccine. The second is a new group of compounds called plaque busters. They are anti-clumping medicines. And others are modifiers of these scissors. So anti-amyloid immunotherapy has been effective, and you'll see in just a moment, in mouse models. The initial clinical trials were complicated by serious side effect of allergic encephalitis but new current trials appear to be able to get around that so this approach continues to be viable and is actively being pursued.

Speaking of active, there are two types of immunotherapy. In one case, in the vaccine, the actual amyloid itself is used to immunize subjects. Then they develop their own antibodies and that destroys the amyloid in their brains. The other strategy is to actually make the antibodies in the laboratory and infuse them periodically like chemotherapy and this also is effective. So let me just give you an example of what this effectiveness looks like. So let me walk you through this slide, although it looks very – I've seen this slide a million times, let me walk you through it.

So these are brains from a mouse that's been engineered with a human Alzheimer gene to develop amyloid plaques. And all this brown material, this brown, spotty material you see here, here, and here in column A, that's all amyloid, that's all human amyloid, this building up in the brain.

It turns out that these mice, all the images in column A, come from a single mouse and all the images in column B come from a brother or sister mouse from the same litter that is genetically identical. That is, both mouse A and mouse B contain the Alzheimer

gene. What the difference is, that mouse A on the left has not been vaccinated but mouse B on the right has been vaccinated with the amyloid beta peptide. So you can see that this mouse has been able to essentially purge its brain completely of this material that we think is so poisonous and causative in Alzheimer's disease. So these are very dramatic images. It's day and night. It's not really – the changes themselves are not subtle.

Anti-aggregation drugs – also effective in mice. Two that you might hear about: Alzemed and PBT2 are in clinical trials. There was another one called clioquinol that has been abandoned because of toxicity. And the ways these act is to interfere with the clumping reaction that's normally accelerated by sugars and metals. And so now things will get a little monotonous because there is plaques and no plaques. The untreated mouse has plaques and the treated mouse does not.

So here again you have sibling mice. This mouse has been treated with clioquinol. You can barely even see the brain here on the left, and the mouse on the right has not been treated. And the brain of this mouse is riddled with these amyloid plaques that can be indistinguishingable from those that develop in the brains of humans with Alzheimer's.

So these plaque busters keep the bobby pins from clumping. And by keeping them disbursed, the brain can then break them down. And that's really how these medicines act. These and the other medicines are all new drugs. These are not derived from drugs that we have lying around in large part; these are novel strategies that have never been attempted before. So this is – it's amazing that within 20 years we've been able to discover Alzheimer genes, give Alzheimer's to a mouse, and cure mice with medicines that have never been seen before.

Just an example of information coming down the pike, this is just from last week from a paper published online about the compound Alzemed. And what's been observed so far is that there's a dose dependent change in spinal fluid levels of amyloid beta peptide. So it looks like the medicine is hitting its target. That's where we are in this particular clinical trial. We're waiting now to see what the cognitive outcome will be.

Now, to tell you about the last group of medicines, let me just remind you of this processing diagram, where there is the good cut that breaks the amyloid or there are the two bad cuts that generate the amyloid peptide. So those scissors are called secretases and they're known by Greek letters, alpha, beta, and gamma. Alpha is good so if you could activate alpha that would be good because you'd increase those scissors that destroy the amyloid. Alternatively, if you blocked one or the other or both, you might be able to block amyloid formation.

So this is, Harry mentioned, some of our work from the late 1980s. This was from that work and where we were able to develop for the first time medicines or drug-like structures that could totally block amyloid formation. So just to show you, these are supernatants; that is, these are the fluid above cells or in a dish. And this bar here represents the amyloid generated under controlled conditions. Here are examples of a

couple of model drugs and when added together, the amyloid generation is totally abolished. So we can do this in cells in culture and we can show that they work in animals.

In another group of compounds that are in clinical trials, or another compound called flurizan – that acts at this very last step; that is the final set of scissors. And it's the sort of complicated mechanism here but I am – unlike Mr. Rumsfeld, I will explain this to you. (Laughter.) What happens is that the length of this peptide is key in determining how sticky it is. So what's normally 42-building-blocks long is now interfered with by flurizan, and two of those or four of those building blocks are knocked off and only 38 remain.

That 38 building block form is much less sticky. This medicine is already in late-stage clinical trials and in fact, there are data from Myriad Genetics that suggest that these compounds can slow progression of Alzheimer's disease over an extended period. And this is to show, as an example of some of the date that they have presented, this shows a decline in mental function over a period of days, over up to 400 days, with a sugar pill, will a low dose of flurizan or with a high dose. So you can see that the slope of the decline, the change, the worsening over time is slowing down, is diminishing with this medicine. So again, this is a medicine that makes sense biologically, works in mice, and there are promising data from humans.

And this is really the state of Alzheimer's research. Mouse models of Alzheimer's amyloid can be caused with these amyloid-parent protein genes and cured with either vaccines, anti-aggregates, or these scissors modifiers. The real question that we're now answering in clinical trials, because these medicines are already being given to humans, is will these mouse cures arrest or prevent the dementia with humans with Alzheimer's?

One place to which I often refer my audiences is clinicaltrials.gov. There, there are a hundred different Alzheimer trials currently available and one can click through those screens and actually immediately find the qualifications for each trial to determine whether your loved one might be suitable for a trial and even go directly to the telephone number in the contact of the person at that site to enroll and inquire about clinical trials. The site, in my experience, is very well maintained. These phone numbers work – (laughter) – and these people actually answer them. So this is actually an incredible resource for keeping up with Alzheimer science.

So I think that gives you a bit of an overview of how dramatic we've been able to – the dramatic progress we've been able to make in the last 20 years in Alzheimer's. And the pivotal moment now is having these anti-amyloid medicines in human trials, washing the humans with these plaque-low PET scans to see if the anti-amyloid medicines work and following them with cognitive exams to see if they will stabilize or ideally, improve. And this is exactly where we are at this moment. So thank you very much.

(Applause.)

So I'm going to turn the podium over now to George Vradenburg from the D.C. area, a terrific advocate for Alzheimer's and for the Alzheimer's Association, and president of the Vradenburg Foundation. George?

GEORGE VRADENBURG: You're going to hear a different perspective from me. I am here, really, to speak with the voice of caregivers. I would like to add my thanks to Newt Gingrich and the center for putting on this event this morning, Bob Essner for your leadership and for your company's commitment to trying to address this disease. To Mr. von Eschenbach for what I know you are doing to try and bring more attention to neurological diseases and capacity within the FDA. And to the Alzheimer's Association who provides leadership for all of us caregivers in this terrible disease.

This is the 100th anniversary of the discovery of Alzheimer's, and it is sending a chill of despair through the millions of Americans living with this disease. Why? One hundred years after discovery, there is no cure. Now, I know that there is a fair amount of optimism, the growth and the expansion of knowledge, the dramatic progress made in the last 20 years, and if I were a mouse, I'd have a lot of hope. But we humans have been hearing about the imminent arrival of disease inhibiting drugs now for 10 years, 15 years, 20 years, and they haven't come. Make no mistake – Alzheimer's is not a soft passing into the night. This disease is a cruel, vicious, ripping of life and soul and identity out of the human psyche. Comforting messages about the disease and its treatment – memories should last a lifetime; the long goodbye; maintain your brain – ignores the daily horrors faced by its victims and their caregivers.

The story you are about to see in this PBS video is of my friend, Meryl – Meryl Comer who was taking care of her husband, Harvey, who has Alzheimer's. Keep in mind that the Alzheimer's victim you are about to see in this segment was a senior researcher at the NIH in hematology. He did two crossword puzzles a day in ink in 10 minutes; had over 200 published research papers to his name; was fluent in three languages; a long-distance runner. He maintained his brain; he maintained his body. It didn't matter. This disease consumed him.

And the caregiver, my friend, Meryl Comer, an Emmy-award winning broadcast journalist, the first to report on the intersection of business and politics and policy, a beautiful, innovative, talented professional engaged in the world; it didn't matter. The disease that consumed her husband now consumes her. Here is a look at their story, the story of Harvey and Meryl.

(Video.)

MR. VRADENBURG: You saw a few minutes of one day in the life of an Alzheimer's victim and his caregiver. Imagine 24 hours a day, 365 days a year – in Harvey and Meryl's case, for 12 years. You are each now a witness to our shared future. You should be terrified. I know I am. My wife's mother died of Alzheimer's; my wife is at risk. One in ten of us at 65 will have this disease, one in two at 85. If my wife doesn't

get the disease, I will, and one of us will be the initial victim and the other will be the caregiver.

I'm glad Meryl wasn't here. She hasn't been able to watch this video. She cannot bear to see what her own life has become, but of course she lives it. There is a stigma to this disease. There is a disease hidden by closed doors. It's only through Meryl's courage that you are seeing it in its full terror. Meryl is my friend, forced to abandon a career for part-time employment, forced into early retirement, risking her own chance of an economically secure retirement herself just doing what has to be done for a loved one. But what happens to Harvey if something happens to Meryl. What happens to Meryl if Harvey lives another 10 years? Care costs, medicines, diapers, catheters, wheelchairs, home renovations, nursing care, well over $100,000 a year. Private insurance doesn't pay for it; Medicare doesn't pay for it. What happens to Harvey and Meryl when the money runs out? If Harvey lives for two more years, Meryl is going to have to sell her house to generate cash for Harvey's care. What happens to America when hundreds of thousands of Americans are bankrupt each year by this disease?

And consider this – it turns out the better the care that Meryl provides, the longer Harvey lives. He's already lived longer than doctors thought possible. The more compassionate our families, the deeper the hell they're thrown into. There is something deeply disturbing about that. In the United States, there are over 4.5 million Alzheimer's victims and millions of caregivers, and tens of millions of family and friends who report feeling personally impacted by this disease. Each has their personal story; we've only seen one for a few minutes of one day.

There are 24.5 million victims worldwide with tens of millions of caregivers and hundreds of millions of family and friends personally impacted. We have no diagnostic test for Alzheimer's; we have no cure. We have no treatment; we have no defenses. And this disease begins its corrosive march through our brains 10 to 20 years before symptoms appear. Many of us in this room now have Alzheimer's and now don't know it. And if we did, we couldn't do anything about it. It's a public health emergency. We're living in the midst of an undeclared pandemic. Researchers no doubt in their laboratories – and you've heard their reports – and their clinics searching for answers; but Harvey and Meryl and millions upon millions of other Americans are on the front line at the bedside just trying to survive the cruel indignities caused by the slow pace of our medical research and drug approval system.

Where is the outrage of this disease? Where is the urgency for helping those in need? Where is the national plan to attack this disease? Where is the global Alzheimer's fund? Where is the call to action and how is leading the charge? We have models – HIV/AIDS, breast cancer, pandemic flu – now we need the will. It's not my role today to propose a particular strategy or policy, but speak on behalf of my friend Meryl, my wife, myself – I sure hope that today is the start of something of a comprehensive national effort, public and private, to fight this disease. Meryl is our Paul Revere. She is warning us, the disease is coming, the disease is coming. It's up to us baby boomers to ring the

alarm bells across this nation and I thank you so much for listening to the story. Thank you.

(Applause.)

MR. GINGRICH: Thank you very much, George, and I hope you will take our thanks also to Meryl as a part of today, and let her know that in many ways, we are shaped by her experience and Harvey's experience. I think you can take from what you've heard so far two very different components – intensity and scale. The experience of Alzheimer's is a stunningly intense reality that is happening today while we're meeting. The scale of it is already large and will escalate dramatically over the next generation. And so the question is whether we can in fact find a different path than the one we are currently on, because we're currently on a very slow incremental path, dramatically smaller and dramatically less intense than either the scale or the reality of what you just saw Meryl and Harvey are living through.

This particular conference was inspired in part by an article in the Washington Post called "Open the Door to Curing Alzheimer's: Why this Research Must Become an Urgent Priority," by Bob Essner at Wyeth. And I'm going to introduce Bob when I'm done. But I want to start by acknowledging what he and Wyeth have done, because they really led me to ask the question, are we at a turning point where the scientific knowledge base makes it plausible that you could design a roadmap of extraordinary power that could in fact provide dramatically better futures for people.

I think you heard a little bit from Sam Gandy that there are very exciting breaks; and not to steal George's line, but as he said earlier, if I was a mouse, I'd feel more secure. Although based on what you told me, if I was a mouse and you weren't messing around with me, I wouldn't get it anyway. So you first give it to me and then cure me, which I think from a mouse perspective is probably a limited return for the cheese invested in the relationship.

But the breakthroughs are real and they're extraordinarily exciting, and they are driven by fundamental breakthroughs in science. I want to suggest to you that we are at the edge of an opportunity that is truly extraordinary, but that requires a willingness to think beyond the normal. And I am particularly delighted that one of our participants this morning is Andy von Eschenbach, because Andy first drug me kicking and screaming into looking at cancer as a national strategic challenge – cancer, which is something that has been deeply part of my life, both with my family and with close friends – he convinced me that looking at cancer that there were ways to rise above the detailed daily research and care regimen and begin to think strategically about the opportunity to eliminate cancer as a cause of death, the project that we at the center have taken very seriously.

In his new role at FDA, he has a similar opportunity to think strategically. And knowing how his mind works, I think he represents an enormous opportunity for looking

at brain science and looking at the potential in Alzheimer's and other conditions that are involving brain science. But Alzheimer's is clearly quantitatively the largest.

In that context, I want to talk just a little bit about where we are both in investment strategies and in intellectual strategies. But I want to start with two quotes that have shaped our thinking a lot. The first is from Einstein who said that insanity is when you think that by doing more of what you're already doing, you'll get a different result. And I just want to put that on the table because if, over the next six or nine months, we can't develop a roadmap, which meets the intensity, the scale and the scientific opportunity, then we have met the Einstein test and we're insane. And so I really want to remind yourself over and over again, just because you're already doing something, if you want a different outcome than you're currently getting, you'd better think about how you're going to change what you're doing.

The second example, said from a slightly different angle, was General Eisenhower in the Second World War who said, looking backwards after the war was over, that when he faced a problem he couldn't solve, he had never managed to solve it by trying to make it smaller. But if he could make it large enough, he could find a solution. And so he'd always try to expand the problem until he got to the solution. This is actually paralleled by an Einstein quote. Einstein said that most problems cannot be solved within the framework of their own definition, but have to have a larger definition in order to find the solution – very parallel.

So I want to try for the next couple minutes to lay out a framework that starts with the premise that we need to think differently to meet the Einstein test and we need to think larger to meet the Eisenhower test. In the model we used, we believe the most important single statement for the next quarter century, because of the scale of change we're going to see is that real change requires real change. So as you look at your own effort to implement after today, you might ask yourself to what extent are you involved in real change and to what extent are you involved in very marginal kind of changes.

And let me also say, I want to thank Rob Egge for this analogy because I think it's so powerful. If you were to look at what the cost would have been to have fixed the levies prior to Katrina and what the cost has been since then, you would see a perfect case study of prevention and failure. And one of the great challenges for the Congress and the president to confront is that if we allow annual budgeting to define our investment strategies, we guarantee in the baby-boomer retirement years catastrophic disasters, because you never generate the resources to make the breakthroughs to avoid the catastrophes, and this has been very evident in the last five or six years. I mean, it is a process; it literally fits the model of penny wise and pound foolish from the 18th century phrase that you should never try to save a penny if it cost you a pound in British terms. In our case, it is million-dollar wise and trillion-dollar foolish. And it's just utterly irrational. And yet it requires you to say, okay, what would an investment strategy approach look like?

Let me also say that one of the things that is most stunning – if you take the five-year cost of a breakthrough – if you could get a research advance that would delay the onset of Alzheimer's by five years, which is not complete victory, but a non-trivial breakthrough, the difference would be a 40 percent reduction and prevalence – 5.3 million lives saved, a $444 billion annual Medicare saving, a $70 billion annual Medicaid savings, and a total $515 billion savings for the Center for Medicaid and Medicare services. And as you just saw with Meryl Comer's story, you can multiply that number by about seven to get the private savings for human beings who are using their own money today to deal with the challenge of Alzheimer's in their family. That's what just a five-year delay means as a difference.

I believe that the scale of change we need – and I'm just going to go over this very briefly but I want to set a stage here – the scale of change we need starts with how do you maximize the evolution of imaging capabilities so that you can have a very inexpensive real-time capability on a routine basis. Ultimately, in the long-run, you want brain scans to be comparable to getting your teeth X-rays, and that's largely a research – it's a combination of the National Science Foundation, NIH, Siemens, General Electric, and other systems that focus on it. But that's a box that has to be dealt with.

The second box is to design both basic and applied research tracks to essentially try to figure out what are the six or eight or nine biggest breakthroughs we need? And what level of resourcing does that require, and what level of access to data does that require? We're entering a world where if you look at Kaiser Permanente, the Veterans Administration, a number of other fairly large systems, we have over 30 million electronic health records today. We have a potential capacity to build Framingham-style studies to give you the epidemiology of a wide range of things, and we don't use them very well because we don't think like that. And so you want to look at could you identify every person who is in an early onset Alzheimer's situation out of the 30 million we already have electronic health records for and how could you knit them together into a learning system?

But this whole notion, we have to fundamentally reassess what do we mean by basic and applied research in the information age. And how do we maximize the rate of change and maximize the rate of discovery? And how do we bring together – it's very parallel to what Andy began doing at the National Cancer Institute in trying to accelerate the evolution with cancer. We need the same kind of pattern and we need to recognize, because of the emergent nature of brain science, which is at a much earlier stage than oncology, that you really want a lot more National Science Foundation involvement, because a fair amount of this is physics and mathematics; and you want NIH involvement and you want the corporations. And you want some kind of public/private research partnership to build a very high-tempo process.

The third thing you want to do, frankly, if I can take a few seconds to preach in public here, is we need an FDA brain science model of operation. Brain sciences are different. They're going to cut across all sorts of existing FDA systems. They require a level of sensitivity and intuitiveness, because today, it is my understanding as a non-

scientist, we actually determine for sure you have Alzheimer's during the autopsy. Well, that defies all the FDA requirements for figuring out who the subjects are. And so we really need to fundamentally from the ground up erase the blackboard and say, okay, in this newly emergent science involving one of the two or three largest items facing the American people, what is it we need to understand to maximize the rate of testing and maximize the rate – and again, I want total federal testing from a human safety standpoint, but I want it done in a brand new kind of framework.

This is particularly important because – my sense, again, as a non-scientist but as a historian who looks at the evolution of technology – my sense is you're going to see three parallel patterns going on simultaneously. You're going to see symptom management where you get a breakthrough that is partially palliative. But if you look at Meryl Comer's life, it sure as heck isn't palliative. It makes a huge difference if you can manage the symptom. You're going to get actual disease management. How can you in fact suppress the effect of it, make it better? And third, you are eventually going to start getting disease prevention or literally disease suppression, which his what you were seeing in the mouse brains. Now, those three tracks need to simultaneously be coordinated because you want to make progress on all three, and you don't want to give up any one of those waiting for some kind of magic breakthrough.

Fourth, I think the Center for Medicare and Medicaid Services and public policy in general, including the Veterans Administration and the federal employee health benefit plan and Tricare should all be looking from the Meryl Comer side back. What is the optimum way to help people be good caregivers? What is the optimum public policy to maximize the opportunity for families to have decent lives while struggling with this terrible disease? What is it we can do, for example, we should have a center which is developing the maximum number of tools that would help people who are caregivers.

This, by the way, has an exact parallel with people with disabilities, because many of the patterns you need for independent living in terms of both whether its expert system technology or its actual physical technology are very parallel. You can both liberate people by shifting from disabilities to capabilities and you can increase dramatically the capacity of individual caregivers to give much more sophisticated care, but you'll never develop that one caregiver at a time. They don't have the time; they don't have the energy; they're not a large enough market. And yet, the total market for all the caregivers would be a very dramatic improvement. And it's something we should be thinking about. How do we maximize the capacity of an individual to help somebody they love live independently for as long as possible, and what are all the technologies we can bring to bear to make that dramatically better? And how do we then incentivize, whether through tax credits or other devices, abilities for people to be able to do this?

I mean, this is a newly emergent problem that is no different than the epidemics of the 19th century or the famines of the 18th century or the industrial-era diseases of the 20th century. It's something we're going to have to learn to solve. We have to be practical about it. And the more aggressive we are and the more innovative we are, the faster we'll be successful. And so I'm thrilled to have a chance on behalf of the center to thank all of

you for being involved and to say that we very much want to work with you. And I would urge you to contact Robert Egge if you're interested in pursuing this in terms of working with us.

But I also want to go back to where I started this particular presentation and that is to thank Bob Essner. His determination that making a real breakthrough in Alzheimer's would in fact be the right focus for what he's doing; his personal commitment of all the different topics that Wyeth gets involved with; the degree to which he is now systematically and methodically engaged in helping provide real leadership in this field is to me a very inspirational thing, and I'm sure after seeing that film again, it reminds you with renewed passion how very important, how very real this is. And I recommend if you have not read the article he wrote in the Washington Post several months ago, I really strongly recommend it to you as a very clear-cut call that action is possible, that action is necessary, and that we could do it. And so it's a great privilege to me to ask Bob to come up and share with us.

(Applause.)

ROBERT ESSNER: Thank you very much, Newt, for that very kind introduction, and even more for organizing this great morning. And I hope this will turn out to be a very important morning in the future. It's really a pleasure for me to be here today and share some thoughts on the intersection between science and patient care – in other words, how Wyeth and the private sector research-based pharmaceutical industry are trying to harness science to overcome Alzheimer's disease. This is, as you've heard already from many of the speakers I think, a very important time to be thinking about Alzheimer's disease and evaluating whether we are prepared for the coming epidemic. I say epidemic because obviously that is what we're headed for, an epidemic of enormous proportions. And I know many of you that are in the room this morning have spent your lives dealing with this and the devastation that the disease causes.

I'm pretty certain that still the population at large does not really see Alzheimer's disease as an epidemic, at least not yet. Last year, I spoke at the White House Conference on Aging, and pointed out that if you were to say the word epidemic then – and maybe still today – I bet most people would immediately think about avian flu, the so-called bird flu that's on the front pages of newspapers still all the time. And it's received massive attention in the media and people are genuinely and understandably frightened about the possibility of this new disease sweeping the world. But with all the intense interest around avian influenza, I sometimes think we've lost sight of the fact that this disease or potential disease, scary as it is, is only a potential threat, and that we may or may not actually have to deal with it.

The next disease probably most people would think about as an epidemic is HIV/AIDS. Reports in the 1980s of the devastation of AIDS quickly garnered widespread attention. The fear factor of this new disease with dramatic mortality rates was extraordinary. Scientific advances and a significant amount of effort across a multiplicity of stakeholders have rendered the threat of AIDS today to be very different

than the way it was 10 or 20 years ago. While AIDS does continue to ravage many developing countries, in many parts of the world today, a diagnosis is no longer an automatic death sentence. Although much remains to be done in that field, in many ways, this is kind of a miraculous fact. And I think it feeds the imagination of a world in which AIDS is no longer an epidemic, but a manageable chronic illness. Unfortunately, obviously the same cannot be said about Alzheimer's disease.

So what is it about avian flu and AIDS that resonates epidemic? Is it their impact on the public health or public imagination? Is it the scientific ideology of the diseases or their widespread threat? And why is it that Alzheimer's still doesn't resonate, I think, in quite the same way? Is it that AIDS and avian flu are new, that they were identified and discovered within our lifetimes? Alzheimer's was first, I guess, identified a hundred years ago. And no one today remembers a world without Alzheimer's. I think it's possible that we've simply gotten used to the presence of this disease and that it's threat has been somewhat mitigated in the public eye by virtue of its longevity. But that's a mistake. This disease is no less dangerous and carries no lesser burden simply because it predates all of us. If anything, the fact that the disease continues virtually unabated should draw our attention to it all the more.

Alzheimer's disease dramatically affects the public health and stirs the public imagination and we know what its impact will be. You've already heard a number of statistics this morning. We can in fact predict with chilling accuracy its incidence and its prevalence. We know the horrifying and ultimately fatal course of the illness, and I couldn't think of a more dramatic demonstration than the one that George showed just a few minutes ago. And we know, as you saw, the collateral damage it does to the families of those who suffer from it, the damage that I think, as we have seen ironically carries the worst toll on the family than the direct impact of the disease on its victims. And we can project with reasonable precision the enormous financial toll that caring for patients who suffer from it will take on our countries healthcare's budget and on our economy.

Many people do not know that Alzheimer's disease is the third-most costly disease to treat in the United States right now, and most do not know that annual medical care costs for beneficiaries with Alzheimer's are expected to increase 75 percent over the next five years, and that federal and state Medicaid spending for nursing home care alone for Alzheimer's patients is expected to nearly double by the year 2025.

The costs of Alzheimer's disease don't strike governments alone; they also strike individual families and businesses like ours. Over the course of the disease, Alzheimer's patients and their families spend more than $200,000 on healthcare for a patient, and employers use approximately $60 billion a year on lost productivity as adult caregivers are forced to leave their jobs, either permanently or on a temporary basis to care for a family member with the disease. I think ya'll get the picture.

What is so horrifying about Alzheimer's is not just that it kills, but that it is debilitating and dehumanizing. Alzheimer's essentially eats away at the very essence of its victims, not just their physical and mental capabilities, but also, as you saw, their

personalities and the qualities that I think we all believe make us human. Yet the general public still does not, by and large, consider Alzheimer's disease to be an epidemic, but he world's scientists are starting to do; they are not just sitting by and watching the devastation approach. Efforts to respond to the epidemic of Alzheimer's are underway across academia, industry, and government as Dr. Gandy pointed out just a moment ago.

And now let me tell you a little bit about our story. Wyeth's research efforts in Alzheimer's began in earnest in the year 2000 when a group of our scientists came to me with a proposal. They wanted to enter into a collaboration with another much smaller company to advance a new technology against Alzheimer's. The team members told me this was, in their opinion, the single best approach to creating a really effective treatment for this disease and that they thought it had the highest chance of success of anything in development in industry or academia.

I of course had to ask a few questions. First, why were they so enthusiastic and why did they think we had any chance of success in a disease that had proven so elusive? They explained that this technology was aimed at quickly ridding the brain of the beta amyloid plaque, that Dr. Gandy talked about this morning, that was and still is obviously, thought to be an important causal factor in Alzheimer's, and that the work done so far on this principle in animal studies – that is, those Alzheimer's mice that we talked about already today – that those results had been the most dramatic ever seen in these types of tests.

So second, I asked them how long it would take before we'd have any real idea about whether or not this would be useful in people because we all know that animal work, particularly in diseases involving the brain, particularly in mice, is not very predictive. They told me that the expected it would take about three or so years of research effort before they would know whether the project could even move into a full scale development.

Then I asked them a couple more critical questions. How much would have to spend over those years to get even a preliminary appraisal of efficacy? Would this in fact work? After a little hemming and hawing, and there was a lot of hemming and hawing, they told me they thought it would cost up around $100 million to do that preliminary work. Then I think I asked them the really hard question: If we invested that much money over the next three years, what was the probability that when we were done the answer would be yes, that we would have at least sufficient preliminary evidence about the drug safety and efficacy to move into the larger scale research studies necessary for a drug's approval?

This brought a lot more hemming and hawing, a quite a bit of shuffling around, until someone literally said, well there's maybe a 30-percent chance of success. I said, really? Then someone else said, well maybe 10 percent. (Laughter.) And when I challenged that I think the real answer finally came out, which was that the odds of success were so low, so unpredictable that no one could really say what they were.

In the end, we made the decision to go ahead. I think our scientists at that point were so passionate that if I had turned them down I would have had something like a mutiny. Wyeth created a partnership with the Irish company Elan, and it was an unprecedented effort in that for the first time we brought together scientists from Wyeth's three research divisions. We asked leaders from our central nervous system drug discovery group to work day to day with some of our leading biotechnology specialists, those people who specialize in the development of proteins, and also, experts from our vaccine research effort. And Wyeth is lucky that we have all three of those technologies very strongly within the company.

And the problem-solving abilities of these scientists, together with those of our partner, have brought this project an unusually wide array of scientific tools and a kind of creativity that has kept us going. More than five years, obviously, have gone by since we made our decision. And about all I can say, after years of effort, is that the program still has this sort of tantalizing possibility of success.

The development of our initial research program, as you heard from Dr. Gandy, was stopped when we saw some early signs of a safety issue in a few patients. But we've come back now with revised approaches and the two leading candidates today are an antibody and a vaccine, which Dr. Gandy described, both of which are now proceeding through clinical development. And by the way, that $100-million estimate has long ago been spent and in fact our partnership has invested multiples of that figure.

Either of these programs has the potential to be the kind of new tool we need to treat or prevent Alzheimer's disease if we get really lucky. But risks are high and in the current environment, even if things go perfectly, which they rarely do, we still are looking at potential approval at the end of this decade at best. I can tell you with complete candor that if this were a program in virtually any other disease, it would have been terminated years ago. But the power of this disease and the challenge of conquering it really does drive us on.

Wyeth is not alone obviously on this path to trying and find a solution to Alzheimer's. There are other companies that work, as well as scientists and academia and research institutes, who are making their strong contributions. The scientific, pharmaceutical, and research communities have been seeking to identify and develop new therapeutic targets that could dramatically alter the treatment for Alzheimer's. There are a lot of people on this path, and a few dozen programs each have the potential to fundamentally transform the treatment of this disease.

In addition to the identification and development of promising drug candidates, there are scientific research efforts into better diagnostic and screening tools. Surrogate end points and biomarkers have the potential to dramatically alter how we identify patients, and also potential patients, and measure their clinical outcomes over time. An example of this is the Alzheimer's Disease Neuroimaging Initiative, which Dr. Gandy mentioned, which is called ADNI, a five-year public/private partnership and it has brought together industry, academia, and the National Institutes of Health to validate

biomarkers and develop neuroimaging tools. This broad-based effort has the potential to dramatically alter how we predict the onset and monitor the progression of Alzheimer's.

Diagnosis and monitoring are essential to any effort to study and eventually control this disease. So why, given all the attention across various stakeholders, does the war against Alzheimer's disease continue to progress so slowly? There are a number of significant challenges facing Alzheimer's drug development, among them: challenges related to the design and implementation of clinical trial protocols, the lack of urgency about the disease at a national level, the lack of scientific consensus about what it means to modify the course of the disease rather than just treat its symptoms, the problems that multiple parties have an interest in resolving those challenges, but none can be addressed by any one of them alone. That brings me to what I consider a great challenge facing Alzheimer's: the lack of a coherent strategy to respond to this disease.

Unlike my examples of AIDS and avian flu, there is no global or even national focus on Alzheimer's. Scientific work and drug development go on, but at too slow a pace. Public health agencies are perhaps understandably engaged in dealing with the current devastation of the disease as much as working towards its cure, and regulatory agencies sometimes deal with Alzheimer's in the cautious way they do with diseases where major therapeutic options already exist. On the regulatory front alone, worldwide cooperation between reviewers and researchers could significantly improve the probability that we will succeed and reduce development times by years.

Although there are reasons for hope, our better understanding of the disease and its progression, better diagnostic tools, and some modestly useful therapies that are available today, the reality is that our efforts against Alzheimer's are moving at a pace that is no way commensurate with the problem that we're all trying to solve. What we need is a sense of urgency analogous to what arose around AIDS.

In the war against AIDS, government regulatory agencies, scientists in industry and academia, and patient groups who have played a major role worked hand in hand to develop new therapies, to evaluate them as rapidly as possible. The results were truly remarkable. AIDS was first identified around 1980 and just six years later, there was a breakthrough medication that helped people manage the systems. And today there are a number of therapies that, when used in combination, allow people with HIV/AIDS to live much longer than anyone would have dreamed possible in the 1980s. The war has not been won, but we have made significant progress, progress that is yet lacking in the Alzheimer's front.

Knowing all of this, how do we convince the world that Alzheimer's is the next epidemic? Public awareness of the disease is high, but so are assumptions and misconceptions. Unlike avian flu, which has popped into the public eye over a relatively short period of time, a disease like Alzheimer's disease has, as I said, been known for generations.

Too many people still believe that it's part of some natural process or just a part of growing old, or there is nothing much that can be done. We have all known somebody, as you have heard already today – a parent, an aunt, a friend who has fallen to prey to this disease. A recent Gallup poll found that nearly 50 percent of respondents worry about developing Alzheimer's; however, instead of spurring people into action, this knowledge seems to engender in some, at least, a sense of resignation or inevitability.

What we lack is a worldwide clamor for immediate action and a solution. We need to generate a sense of urgency because even with the best of luck, the answers won't come overnight, but we need those answers now. Those of you in this room are invaluable in this effort, and we need your leadership, your voice, and your passion. The efforts of scientists across the globe are essential to developing a response to the Alzheimer's epidemic, but they are clearly not enough.

What we also need is a sense of urgency driving a coordinated response to this disease. Scientists and academia, government and industry must work and in hand with regulators, healthcare providers, and patients and caregivers. We need the kind of bold innovative effort that has been generated in the past, and the AIDS story I think is instructive and inspirational. If we approach Alzheimer's with the same fervor, we'll be able to harness the potential of scientific advances and truly alter the course of this epidemic.

We at Wyeth are trying to do our part. Wyeth has been researching innovative treatments for Alzheimer's for more than 15 years now. We have more than two-dozen projects in our pipeline, and have over 350 people in our research group who work exclusively on Alzheimer's disease today. And we have projects ranging from very early development through later-stage clinical trials. And our projects today use all of our available technology platforms, drugs, biotech skills, and vaccines because we want to explore every option available to us. And I have already mentioned our financial commitment.

Wyeth is fully committed to Alzheimer's and will continue to do our part to try to harness scientific advances to overcome Alzheimer's disease and improve the lives of patients and families. So once again, it's been a real pleasure to be a part of this program today and thank you very much.

(Applause.)

Now I would like to introduce our next speaker. It's a great pleasure for me to introduce the FDA's acting commissioner, Andy von Eschenbach. Prior to joining FDA, Dr. von Eschenbach was director of the National Cancer Institute. And he is a nationally recognized urologic surgeon and oncologist, and he has been a committed advocate for innovative patient care throughout his long and distinguished career.

DR. ANDREW C. VON ESCHENBACH: Thanks, Bob.

MR. ESSNER: Pleasure to have you.

DR. VON ESCHENBACH: Thank you, Bob, very much. You know, before getting up here, the urologist in me leaned over to Newt and said, do they need a break? (Laughter.) He is said – he is a slave driver. I mean, he said, no; we are going right ahead; we're plowing right ahead, but if you do, the urologist in me will understand. So, please, don't hesitate if you need to move to that door.

If some of you hear a thump in the room, will you please go over and pick up Michelle Weiland (ph) who is my staff assistant who is sitting in the back because when I leave the FDA to come out to a meeting like this, they give me a speech box, and I invariably never give it. And this morning is not going to be any exception because having sat and listened to this morning's presentation, and particularly from having to – having the opportunity to review the video, and to experience what you are all experiencing, that realization of the suffering and the pain, and the devastation that is all around us, I am going to speak to you more today from the heart than I am from a prepared text to talk to you about the importance of this conference and the importance of you all be here, and what in fact you are involved in, and what you will be responsible for.

The video brought me back in the context of listening to Dr. Gandy, scientific presentation, to my roots. My roots at M.D. Anderson, where I spent 26 years living with this dual reality, which on one hand allowed me to be a part of what have been some of the most profound breakthroughs in biomedical research, and in science and in technology, and yet at the same time every single day being confronted with the suffering and death and the ravages due to a disease like cancer.

And I knew that those two realities needed to be and could be reconciled, that all of that progress, the kind of progress that Dr. Gandy talked about this morning, could now lead us to a point where we no longer had to witness and tolerate that suffering and death, whether it was a disease like cancer or the ravages of Alzheimer's. That is within our grasp. That is our opportunity. That is why this meeting and your involvement and participation is so important.

And five – almost five years ago, I had the privilege to come to Washington to lead the National Cancer Institute with that vision, with that passion and with that commitment, and set a goal that we would focus and commit our effort to eliminate the suffering and death due to cancer, and bring that about by the year 2015. And I was immediately criticized, perhaps appropriately in terms of not yet having had the opportunity to explain the rationale and the reason behind that goal.

But the one person who didn't criticize me as being overly ambitious, or perhaps even irrational was Newt Gingrich, who reminded me that not only as I explained to him the rationale as to why it was feasible for us as a nation to make that kind of a commitment – reminded me that our challenge, and perhaps my challenge was not only

to lead us to a better way of dealing with cancer, but in fact to help catalyze a transformation in healthcare.

And I would present that same perspective to you this morning, that as you are engaged passionately and appropriately in seeking and driving for a solution to the problem of Alzheimer's, you also are involved and a part of a larger transformation, a transformation in health, in healthcare, and in fact in our healthcare delivery system.

What you, what we, what we are all involved in, what the challenge for this nation is with regard to ensuring this future is that we are in the midst of the most profound transformation to occur in the entire history of medicine, the entire history of medicine. That history has been based on the fact that for thousands of years – and we have practiced medicine based on what we could know about diseases using our five senses; what we could see, what we could feel or touch, what we could hear, and even what we could smell.

For thousands of years, we based our decisions about treatment on what we could tell using our five senses. And a hundred years or so ago, we went from that very macroscopic perspective to a microscopic perspective. Technology provided us tools, like a microscope and an X-ray machine. And we could see better; we could see the cells that were responsible for a tumor under the microscope; we could see a lump not just on the surface but deep inside the body. We could look at an autopsy and see a plaque in a brain that was responsible for what we had observed as a disease like Alzheimer's.

We may think of that macroscopic and that microscopic perspective of disease as ancient history, but when I began my career in oncology at M.D. Anderson, the world's largest cancer center, the only way I had of detecting prostate cancer was what I could feel with the tip of my finger on digital rectal examination, and I was wrong 50 percent of the time. That has been, and up until very recently is the history of medicine, a macroscopic and microscopic perspective. And it was discontinuous with being able to determine what we should do about a disease once we observed it. Our diagnosis did not inform us with regard to therapy, and so therapy was discontinuous and based on a very empiric trial and error, trial and error model.

But about midway through the 20th century, perhaps with the discovery of DNA, a transition occurred. And throughout the latter half of this 20th century, science and technology, the science that you listened to this morning so eloquently presented by Dr. Gandy, has led us to a transformation.

And about 10 years ago or so, we crossed a threshold, a threshold in which medicine and our understanding of diseases no longer based on a macroscopic and microscopic perspective, but based on a molecular perspective. For the first time, we cannot just see, but understand diseases at their molecular and genetic level in which we are beginning for the first time to understand the mechanisms that are responsible for those disease processes that we formally were just observing.

And that understanding of those fundamental mechanisms is opening up the door to immediately understand the interventions that will enable us to modulate those diseased processes by either preempting them from every occurring in the first place, by being able to detect them earlier in a way that we can eliminate them, by being able to modulate or control them. And some of the things that you heard from Bob Essner with regard to the vision of Wyeth around a concept of disease modulation is for the first time bringing to us those tools, that new armamentarium that even only 10, 15 years ago, we could not begin to even imagine or understand.

It leads us to Newt's challenge to recognize that we are in the midst of a change process that is so profound that it is not a linear extrapolation of the past; it is so profound the transformation that it is a metamorphosis, a metamorphosis in the sense that we will be looking at a future in health and healthcare that is no more like the past than a butterfly is like a caterpillar. It is that profound and it is that significant.

And it is a change process that will affect not just one part or piece of this equation, but every single component. It is a change process that we are all immersed in because it transcends the full continuum from our very notions and concepts of understanding of health to what those interventions are that we will be able to deliver and use in our healthcare system as part of healthcare, and the actual system itself that will be required itself to deliver to every single one in need the new concepts and the new context that emerge out of this molecular metamorphosis.

We are focused of course on immediate and present concerns: Alzheimer's, cancer, AIDs, diabetes, obesity, aging in general, acute diseases, pandemic, avian influenza. But one of the most important considerations that we must be challenged with is that as we focus on them, as Newt has challenged us, we must see this in a larger context. And so it is not that things will be cancer-centric but that opportunities can be led – cancer-led; not that things necessarily will be Alzheimer's-centric, but they can be Alzheimer's-led.

We are together collectively cooperatively in the midst of being able to change the entire future of health and healthcare. By embracing and fully developing across the continuum of discovery, development, and delivery the new molecular reality and the molecular opportunity. And it holds the promise for being able to radically conquer diseases like Alzheimer's. And not only is the magnitude of change that significant, but the pace of change is equally significant, such that we no longer need to think of time horizons that are something in decades and centuries away as we did in the past, but to see this as not evolution but revolution in medicine.

As we look at this new future of discovery and development and delivery, I now have the privilege to have moved from the National Cancer Institute, where we had the opportunity to drive the agenda of our understanding of molecular mechanisms of a disease process like cancer, and begin to think about that disease not as an event but as a process in which those genetic and molecular and cellular events occurred over a period

of time, and offered us ample targets for intervention that could preempt its outcome, the suffering and death.

And one's listens to this morning's presentations and recognizes that that is exactly the same paradigm for Alzheimer's. It is a disease process that occurs over time, and as we understand the fundamental mechanisms, as outlined by Dr. Gandy, we can begin to develop interventions, as presented by Bob Essner, that could be prevent or preempt, or modulate that disease process in a way that we eliminate the outcome, that tragic, horrible outcome that we witnessed on that video.

And the FDA is positioned as the bridge that needs to be responsible for making certain that all of the fruits of that discovery and that development come to be applied to patients who are in need. And it is the FDA's commitment to be that bridge, to be that bridge not of the past, but to be that bridge of the future. And for that, like you, and like every other part of this equation, FDA must change. It has a proud record over the past hundred years of being the world's gold standard, but the FDA of the past is not adequate or equipped for this new reality, and therefore it must change, and it must change not in isolation, but in context and in collaboration and integration with all of the other parts and pieces of the equation.

And so we have embarked upon an opportunity to look internally about what those transformations are that must occur within the agency itself, and what those opportunities are to collaborate and integrate both on the discovery and development end of the continuum, as well as on the delivery end of the continuum to bring that process about.

I don't have the opportunity this morning with the amount of time to present to you all of those initiatives, and all of those opportunities that we will be embracing and embarking upon, but you are familiar with some of the preliminary outlines – for example, critical path – and the need to fully implement many of the strategic initiatives in critical path so that we bring the new science that is making possible discovery and development into the regulatory process: the use of biomarkers instead of simply waiting for the kinds of outcomes that were alluded to earlier this morning having to do with autopsy findings; the ability to completely revamp our clinical trials process and to begin to look at different adaptive trial designs and models that are adapted to the new realities; to begin to bring tools of modern information technology and bio-informatics into the regulatory process; and to collaborate and cooperate with the industry in being able to assure that we are effectively, proactively facilitating the development of these new interventions in ways that assure not just their efficacy but their safety, and to be able to stay invested no only on the front end of their development, but also to continue to monitor and modulate the behavior once they are being applied to much larger populations.

The FDA is looking forward to continuing to work with you in providing us insight and opportunity for the kinds of changes that we will need to embrace. I know the efforts of your organization are extremely important. And having met with Harry Johns,

and others, we are looking forward to that continued dialogue. And one of the things that we have done is to begin to look at ways in which we can bring the advocacy groups more actively into the process. The patient consultant program will of course include the ability to bring advocate participation into FDA's regulation and development of new treatments for serious neurological diseases, and the patient representative program will welcome your participation in advisory committees.

We have created an FDA interagency, neurology working group that will enable us to integrate across the entire portfolio of the FDA – our opportunities to begin to look at use of neurologic diseases, like Alzheimer's, as a model, just like we can look at cancer as a model through the activities that we have around the interagency oncology taskforce to drive this integrative and collaborative process.

For example, and Bob commented about globalization of this problem, this week, the very first time I have the privilege to host 24 of my peers, regulators from entire world to come together – and invited them to Washington – 24 of them from China, India, all of Europe, South America are coming to spend one day to talk about how we as regulators can collaborate and cooperate to embrace this new era and these new challenges of molecular medicine, and to avoid fragmentation since we are in fact dealing with global problems in a global industry.

There is much for us to change and much for us to do, but it is also a truism that the only human organism that likes change is a six-month old with a dirty diaper. (Laughter.) And so change for FDA will be difficult. Change for you will be difficult. And clearly change for our nation is difficult. But change we must. We, like, the caterpillar are in the midst of a metamorphosis, and we have no choice about that change. That metamorphosis is already occurring.

Unlike the caterpillar, who always has no choice about what it will be – it is destined to be a butterfly – we do have a choice about what we will be. We are creating a new reality for which there is no description, and we must come together collaboratively and cooperatively in a design-build mode to find that way forward to create that new reality in which no one need suffer and die from a disease like cancer or Alzheimer's, or AIDS, diabetes, or even infectious diseases like avian flu. The tools, the opportunities, the knowledge is emerging. That butterfly is coming out of that cocoon, and we must seize and capture this opportunity.

And this meeting typifies what we need. We need knowledge coming from scientists. We need commitment coming from the developers of these interventions. We need visions coming from public leaders, like the Center for Health Transformation, and we need leadership, and advocacy, and passion coming from you. And collectively, cooperatively, together, we will create a new world, not just for Alzheimer's or cancer, but for everyone. And you have the opportunity to help make that happen. And it's a privilege for me to have listened to you this morning and remind me why I am here. Thank you.

(Applause.)

MR. GINGRICH: We were supposed to go to Q&A, but based on advice from my favorite urologist, I am going to declare a 10-minute break, and then we'll do the Q&A section of this. Thank you. (Laughter.)

(Break.)

MR. : (In progress) – very much for your time this morning. It's greatly appreciated. And now we want to take some time for question and answers. And thanks to our speakers this morning, if you're up for a little bit more time after that break, we appreciate it. And so, we're going to come around with microphones and we ask you to wait for a microphone to reach you and for you to introduce yourself with your question, we'd appreciate that. So with that point then, if there are any questions, we'd love to hear them. Yes, thank you. The microphone is right behind you.

Q: Oh, I'm sorry. Hi. Excellent program. Thank you all very much. I'm Mike Parkinson. I'm with Lumenos but also a physician interested long term about what's being said across the board here. And for any of – Dr. von Eschenbach or Dr. Essner, anybody – or Dr. Gandy, it seems like all diseases of chronic nature, not using a medical term, but what they really are doing is sludging or clumping of something or some substance or things like that.

And to get to Newt's comment about the collaboration with NSF research as opposed to biomedical research, it would seem to me that we're getting back to some basic physical properties here, that perhaps underlie coronary artery disease, cancer, Alzheimer's, brain diseases. Where are we with collaboration with NSF and basic research as oppose to biomedical research on that continuum? What could we do to foster that around some basic physical properties perhaps and is that even viable to be talking about?

MR. : I'll go ahead and kick off. No, it's absolutely viable and I think it is the next horizon in this journey. One of the things that we've tried to promote at the National Cancer Institute was a very significant collaboration with the federal laboratories. So integrating our cancer center network and some of the academic institutions along with the private sector, but then integrating Los Alamos, Sandia, Lawrence Livermore, on and on; every single one of them – Oakridge, where they're doing a great deal of work in nanotechnology and a lot of the physical sciences and beginning to bring that into the arena.

The other part of it is that we're talking about functionality but that is an extrapolation of structure. And so as we – moving back and forth between a chemical model of disease, we also have to have a physical model of disease as well, and the integration of structure, and an understanding of structure is going to be critical. So you're going to see an emergence of engineers, physicists, and many of the physical sciences integrated into this biomedical research spectrum.

MR. : One initiative that both the Alzheimer's Association and the National Institute on Ageing has embarked upon is a series of working groups to try to identify experts in these particular areas of chemistry and physics, who are squirreled away working on their own problem of their interest, and inform them and try to bring them into the areas of Alzheimer's, Parkinson's, ALS. Since this is a pervasive problem, that you're very right, is at very basic levels of physics and physical chemistry.

MR. : Yes, next question. Yes, thank you. And here's a microphone coming.

Q: Hi, Suzanne Stone with the Society for Women's Health Research. I noticed in Mr. Essner's talk, one of the slides had a list of a number of companies that were developing products and most of them had gone through the typical phase zero, phase one, phase two, and possible into phase three. But some seemed to have skipped some phases so I was curious if there was any thought being given within the critical path or other things at FDA about the regulatory review of drugs of this nature?

MR. : Yes. One of the important areas that we will be working on over the next year is the issue of the clinical trials and what we have to do to try and revamp the way in which we apply the clinical trial paradigm to the regulatory process. I talk in terms of adaptive trial design, the different biostatistical model, in terms of Bazian models. This is clearly an area that we have to begin to address because I think that prospective randomized trials have serviced us well and there are places where we will continue to depend upon them but it is not necessarily the paradigm that fits all of the emerging new reality. We have to change; we have to adapt.

Q: And, Dr. Gandy, do you see differences in the Alzheimer's that are distinct from your colleagues that are approached in other areas in terms of client trial design?

DR. GANDY: Well, certainly designing trials of this scope are unparalleled. Clinical trials, trying new drugs along the lines of antibiotics, even anti-epileptics, you get results that you can see in days, weeks, seconds. With Alzheimer's, it takes at least six months, usually a year before you can really contemplate potentially seeing an effect of a compound. So in both scope and expense, they're really unparalleled.

MR. : Let me add maybe to Dr. von Eschenbach's comments about adaptive trials in that, you know, we have tried to move away from the classic phase one, phase two, phase three development, which are basically a series of trial and error; usually trial resulting in error, frankly, and sometime allowing us to get all the way to the end of the development process and not having optimized a product. It's just something we're going to learn and confirm really, a two-stage process using, especially in the early stages, adaptive clinical trials to really optimize our understanding of what we have in development and optimize how it could be used. And then used the second stage of development to prove that what we learned in the learned phase was in fact correct.

MR. : Yes, a question up here.

Q: John Dwyer -- and since he's not here to defend himself, one of George Bradenburg's colleagues. It's two part – first, a broad, narrower question or observation really. All the conversation we've had and I would like to join everyone else in thanking Wyeth for their leadership. But my world is largely in the venture capital and small, emerging growth company area. It is the single most difficult area in venture capital right now in biotech fund, is in neurological disease therapy, diagnostic, or biomark; period. There's no money. And the reason is, in part because there's no approved – the FDA's leadership needs to be accelerated in that area because folks won't put money behind what they can't see has an end point.

So I would only observe that some things need to be accelerated, which leads to the larger true question, which is – and I direct at Mr. Gingrich – is, you know, what's the next steps? This has been a tremendous gathering but it would be a waste of human resource and opportunity if you don't use this momentum to establish next steps to a solution and I'd ask you what those are?

MR. GINGRICH: Well, I think – I mean, first of all, I think Dr. von Eschenbach has already indicated steps he's taking out at FDA that are significant. I think Bob Essner has indicated steps he's taken that are significant. I think other companies would also want to say that there are number of things they're doing. At the center, what we would like to do is over the next three to four months outline a roadmap that is comprehensive, that would allow people to see how the different pieces integrate together, and that would set a public policy and might be a benchmark.

Frankly, if we're looking at congressional hearings late next spring, to look at what a comprehensive approach to Alzheimer's would be like if the U.S. government were take it as a serious comprehensive issue rather than seeing only as an annual cost number. And so, I think that's something we obviously would want to consult with the FDA and HHS and VA and the White House, as well as consulting with companies and scientists and with groups who represent direct concern for the caregivers and for the families. But I think, you know, Bob Egge is going to have the problem up here but I think pulling that together, ideally so, in its most simple form would literally be a wall map that you could put up on the wall somewhere and say this is the roadmap.

And then, secondarily, a publication and an ability to start looking both for the executive branch and the Congress at the patterns, we ought to be looking at, I think, would be a very, very helpful project. It might lead to a sort of assessing the draft roadmap meeting sometime in early March or late February. They have a real working group spend a day rolling up their sleeves and saying, yes this right; that's wrong.

It's basically going to work, as Bob Essner said. You know, we know we've done this several times now. We're beginning to learn how to do this and if you look at what Andy did at NCI or you look at the AIDS project; you look at the Avian flu vaccine project – I mean, we're beginning to develop some ability to think about an overarching

approach to disease rather than a series of silos that are disjointed. But you all may want to comment.

MR. : Yes. I'd just like to follow up on the way you prefaced your question in that I think we have a number of challenges with regard to this change process, one of which is most people are staying in the box and envisioning a future that is an extrapolation of the past. And that is really an impediment or barrier to us being able to really fully embrace the implications of what's occurring. I mean, they're extraordinary when you begin to think about just the implications of what is happening in imaging and how that changes cycle time in terms of our ability to deliver an intervention and assess whether that intervention is working or not. The old macroscopic model – you had to wait three months, six months to see if something changed on the CT scan. And the molecular model you can do a scan with a nuclear tracer and know within 24 to 48 hours. That radically transforms a lot of things.

But what's missing in the other end of the spectrum is a lot of people are putting together visions around this from a medical and a scientific point of view. What we don't have is the business model and we haven't thought through what are the implications if this is true. There is going to be this metamorphosis. Fifteen, twenty years from now healthcare and health will look nothing like what we've been talking about in the past. What are the implications of that and how do we develop a business model around that. A business model to invest on the front end and what the activation costs are going to be and what is the return on investment on the back end? And until we get that business model in place, you can't sell this. It's a big, bold visionary idea and it goes nowhere. And so, if you can help or others can help develop the business model that goes along with the medical/health model then I think that could bring pieces together that will catalyze a lot of the change.

MR. : No, I agree very much, actually. I just spent part of last week going around a number of large European countries talking, in some cases, to health ministers. And, you know, remarkably from where they sit today when you talk about, you know, the potential for some really useful tool in Alzheimer's disease, their first instinct is to think, not so much how much will that help, but how much will it cost. And I think the notion of a business model – what do we want to incent in the way that we allocate the resources that have and the government has. Unless we get that clear, I think it's going to be very hard to make progress.

MR. : Other questions?

Q: Harry Johns, the Alzheimer's Association, you know from a –

MR. : Wait, wait.

MR. : Get the microphone.

Q: From my seat, it appears to me that even if as we get these newer disease modifying compounds, these newer disease modifying drugs – even the first ones, we're going to see a much increased need for earlier detection and the infrastructure that goes with that. I think it has implications for FDA and for, certainly, the industry. It certainly does for our organization at the Alzheimer's Association and for patients and families. Could you speak to that and how you think we can coordinate improving that, especially in the near term as we get the newest – the first disease modifying drugs.

MR. : Want me to try that? Okay.

MR. : I'll add to it.

MR. : Okay. I'm a little out of my depth but, you know, we have seen in a number of other disease areas that the availability of a good therapy prompts a revolution in need and the desire for diagnostic treatment. I think cholesterol is a good example. Doctors knew how the measure cholesterol in the blood for a very long period of time but it wasn't until the availability of the first statins, which have been improved on subsequently, that there was any great drive to do this. And now it's become, I mean, just background noise. I mean, you just totally expect it.

And so I will take your question as a comment in that if we do get a tool in the next several years that really allows people to deal somewhat effectively with Alzheimer's, just somewhat effectively, the need for I think a new kind of medical service that doesn't exist today, that allows people to identify Alzheimer's disease early, which is probably the last thing many people would like to do today, is going to have to be developed. And the infrastructure to do that and the tools to do that, my guess is don't really exist today. But, you know, he'd like to add.

MR. : Well, there are a couple of points that you are addressing, Harry. One of the important implications of this molecular metamorphosis is that healthcare will be personalized, it will be predictive, it will be preemptive, and it will be much more participatory. And some of the implications of what's underneath those four words gets us to a point that I've alluded to in my talk in which in the old model, diagnostics and therapeutics would discontinue.

In the new model, they are integrated. They're seamless. And the tools that you're using for "diagnosis" are the tools that are inter, really, associated with the modulation and of the therapy of the intervention. And so to the point that was made earlier about where are the diagnostics in this, the diagnostics are going to have to be integrally associated with the therapeutic intervention. They're going to be seamless and you're going to be creating a different model and a different regulatory model as well.

So those biomarkers are going to be a part of the intervention just as much as the vaccine is a part of the intervention and that leads us in a more upstream model. So instead of waiting for this macroscopic manifestation of disease, you're picking it up at a much earlier level, at the molecular level, the earliest changes, both diagnostically and

from a therapeutic intervention point of view, it's more preemptive. And you're monitor and modulating that with that biomarker so it's all an intergraded product at that point. They're not something that are discontinuous. That's a different regulatory challenge as well as a different developmental challenge as well.

MR. GINGRICH: Can I offer a, I guess, maybe a slightly different perspective, historically. It seems to me that if you think about the emergence of breast cancer – of mammograms and the emergence of convincing women to examine their breast at much earlier age than you would have 40 years ago. I mean, there's a whole process that – and my memory began with, I think, Betty Ford being very public about having breast cancer, where breast cancer became an acceptable thing to discuss. And then prevention became – or early detection, not prevention, but early detection became an acceptable thing to discuss. And I think in the morning paper there's some article about red meat may be accelerating the likelihood of breast cancer so you'll presently have prevention strategies.

Then there was the discovery of the breast cancer gene so people who think they might have that pattern can actually get a genetic test to find out whether they ought to have anticipatory action taken prior to breast cancer developing, I mean, all these different pieces. I suspect – and this is why I said the instrumentation is a part of this – that there are three things that strike me, and again the scientists up here can correct me. There are genetic markers, particularly for all the early onset Alzheimer. There are chemical markers, which I don't think we yet have but one would look for and then there is analysis by radiation effect. I mean, having – whether it's a PET scan or what the next generation of very sophisticated brain scan so that you would actually pick it up as early as possible.

My hunch would be that what you'd want to do is first of all figure what are the appropriate markers that indicate you ought to get a genetic test to find out whether or not you have a propensity for early onset because somebody who is facing it at 55 years of age has a totally different challenge. And even though you may not have a cure for them this morning, everything you can do to accelerate their understanding and to know that they're on sort of the email list for each breakthrough so that they have the optimum speed of getting involved, strikes me as something you want to do.

The second thing would be to ask epidemiologically – and this is why I think the very large databases are much more important assets than we're currently using. If you looked at the 30 million-plus people who are currently on electronic health records, are there any distinctions for the most likely, who are not genetically early onset, but who nonetheless acquire Alzheimer's? And could you find a way to say, okay if you fit the following six factors, you ought to start with an early brain scan?

And then the third is how do you get the companies who produce brains scans to figure out breakthroughs in production costs because, you know, you want to bring brain scans down so they cost about as much as having your teeth x-rayed at the dentist, not so they are a major radiological, you know, activity at a hospital that cost so much that you

can't afford to do it. I mean, it's got to be like the mobile mammogram services that can go to neighborhoods that really do bring down dramatically the cost of intervention.

Those three patterns, it seems to me, is how we will move towards an early detection process. And then strongly encouraging people with early detection to be deeply involved in an information system to maximize their being part of both learning as rapidly as possible, connecting to the right breakthroughs, and being a source of data for future development. I know that makes sense or –

Q: If I could follow up, you know, I think that the track you're on is exactly right in the sense about – (inaudible). We're going to be in a multi-phasing situation here where we first get these modifying drugs that have some effect about them and we'll then be the earlier detection in the immediate terms –

MR. : Your mike's is not on so you're being captured for posterity.

(Laughter.)

Q: Posterity that won't suffer from Alzheimer's disease will help. And so I think what we'll get is we'll get an immediate need for what is that earlier detection for people who have these first drugs. And as you suggest then, what will be phasic situation where we have new iteration of drugs, more tracking along what Andy's describing, I think seeing that forward with the business model you're talking about is what we need so that – whether it's the brain scans or whatever the technology may be that helps us identify the disease, we can see it going forward. So I think if we can get to the point we can do this earlier detection, along with the other science advancement, it would be huge for us. And I don't know, Sam if you wanted to comment on any of that iterative process.

MR. : Well, certainly there's a bit of a catch-22 in that the medicines that we are developing that look the most promising are aimed at the earliest molecular changes that initiate the disease. And so that goes hand in hand, really, with trying to develop new models or new mechanisms, and new technologies for determining who is at risk because those are the people where you can identify people pre-symptomatically.

And, you know, I guess the vision would be that, you know, potentially – I'll give you one example – would be the plaque level PET scan that would join the colonoscopy and the mammography with the things that are done with the annual physical triggered by a particular age.

MR. : We have time for two more questions. Are there other questions? Yes.

Q: Hi. I'm Phyllis Greenberg. I'm from the Society for Women's Health Research. I think one of the big issues that we haven't addressed, and I don't know that we can at great length here, but we all know that the FDA is strapped for financial resources. And my concern is that with the new restructuring and all the things that you

want to do, Dr. Von Eschenbach there, whether there are going to be resources to be able to be able to do that and –

DR. VON ESCHENBACH: That's one of those –

Q: For you to answer, right?

DR.VON ESCHENBACH: That's one of those questions I have to start out with, if I am confirmed – (laughter). I think if I am confirmed, it's incumbent upon me to do what I just asked and that is to create the business case. To present to the administration, to policymakers, lawmakers, and to the American people, a business case that an investment in the FDA of the 21st century, with all that implies, is appropriate and justified and that there will be a return on that investment.

A better bridge that will enable us to move more products of different nature and different type in characteristics, then we've seen before, rapidly and efficiently to the American people and to the world and still, at the same time, ensure that they are safe and effective. And I believe we can and must and will do that. But you're absolutely right that it will require an investment and a commitment but I think it's my job to have to present that.

Q: This is just a quick follow up, doctor; I'm a rabid Democrat, which is more popular than an – (inaudible). And I can tell you that if you will make – I can tell you that there are a lot of us that believe if you'll make that case in your confirmation hearings, there'll be a ground swell of support out of the Congress to help you move the FDA in the direction you want to.

DR. VON ESCHENBACH: Confirmation hearings are – I've already had those but I'm looking for other opportunities to try and present my case.

Q: Write a letter.

MR. : Yes.

(Laughter.)

MR. : And a final question. Well then, if I could ask you then to –

MR. GINGRICH: Well, let me first of all thank everybody who participated. We really appreciate your work with the Alzheimer's Foundation. We also – I want to thank George Vradenburg and the work he is doing. I am very, very much delighted that Dr. Gandy could be here, and, as I said earlier, we really owe it to Bob Essner. It was his initial article and his initial thoughts about the breakthrough that actually led to this entire event. Obviously it is a tremendous honor to us to have Dr. von Eschenbach here and I really look forward to working with here in this. And any of you who are interested in pursuing this, if you'll get in touch with Rob Egge, we really would like to develop a

roadmap approach that we think could, over the next year, dramatically move the entire dialogue in the right direction, so we really appreciate your involvement. Thank you very much.

(Applause.)

(END)