NIH: RE-ENGINEERING CLINICAL RESEARCH

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SUBCOMMITTEE ON HEALTH

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NIH: RE-ENGINEERING CLINICAL RESEARCH

THURSDAY, MARCH 25, 2004

HOUSE OF REPRESENTATIVES,
COMMITTEE ON ENERGY AND COMMERCE,
SUBCOMMITTEE ON HEALTH,
Washington, DC.

The subcommittee met, pursuant to notice, at 10 a.m., in room 2322, Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Upton, Greenwood, Norwood, Wilson, Buyer, Pitts, Brown, Green, DeGette, and Capps.

Staff present: Jeremy Allen, health policy coordinator; Cheryl Jaeger, majority professional staff; Eugenia Edwards, legislative clerk; John Ford, minority counsel; Jeff Donofrio, minority staff assistant; and Kamilah Pickett, minority congressional fellow.

Mr. BILIRAKIS. The hearing will come to order.

Good morning.

First, I would announce that we apply the sort of unwritten new rules of the Committee to the point where someone waives their opening statement, they would have as much as 8 minutes to question, to inquiry of our witnesses. So, hopefully we would all maybe go or bend that way rather than have our witness like yesterday's hearing. We had a hearing yesterday downstairs and we had one witness, Secretary Evans, Secretary of Commerce. He sat around for almost 1½ hours while members gave their opening statements. And that's sort of an unfair thing to the person testifying.

But in any case, today's Health Subcommittee hearing is the fifth that I've held or we've held over the past two Congresses. It is part of an effort to examine a number of issues related to the National Institutes of Health.

The NIH is an enormous agency with an appropriation in fiscal year 2004 of approximately $27.68 billion. While NIH has not been reauthorized in over 10 years, I firmly believe that our investment in biomedical research—they have received their funding by the way even though they have not been authorized. I firmly believe that our investment in biomedical research through NIH is probably one of the wisest uses of our limited resources. However, it does remain incumbent upon us here in Congress to ensure the taxpayer dollars are used in the most effective manner possible. To that end, I've been very impressed with the leadership of our current NIH Director Dr. Alias Zerhouni. The leadership that he has shown in developing the NIH Roadmap. I believe that this initiative will help NIH refocus its priorities and improve its track record. I am glad that Dr. Zerhouni was able to take time out of

his very busy schedule to join us this morning and to speak to 1 of the 3 primary components of the NIH Roadmap, which is the reengineering of the clinical research enterprise.

Clinical research is a critical part of our efforts to ensure the taxpayers research gets translated into new therapies. We explored another major part of this effort last year when we examined the technology transfer activities of the NIH and how laws like the Bayh-Dole Act have helped research from the bench to the bedside. I'm hopeful that the subcommittee will learn more today about both clinical research activities of the NIH and Dr. Zerhouni's vision for reengineering the clinical enterprise.

I also want to take a moment to thank our second panel of witnesses for appearing for the subcommittee. I think it's important that this hearing also focuses on clinical research activities that occur outside the realm of NIH and how we can leverage these efforts and speed new medicines to patients. As our panelists all know, new therapies for patients are more often than not the result of very productive collaborations between the Federal Government, the university-based research community and the private sector. Our system allows each of these entities to play a role that their best suited for, and I hope members keep in this mind as a delve further into these complicated topics today.

Again, I would thank Dr. Zerhouni and all our witnesses that are joining us. Your perspectives will prove valuable as the Health Subcommittee continues its review of NIH and considers strategies to help this agency better meet it's stated goals.

Thank you. And I now yield to the gentleman from Ohio for an opening statement.

Mr. BROWN. Thank you, Mr. Chairman, for holding today's very important hearing. Dr. Zerhouni, thank you. We welcome you. Thank you for being here. We greatly appreciate your willingness to appear before us.

2002 NIH under Dr. Zerhouni's leadership and with significant contributions from academia, industry, government and public laid out its Roadmap as a tool to guide the agency's medical research into the next decades. By addressing new scientific challenges, identifying potential roadblocks, the Roadmap outlines how NIH can continue to lead future scientific discoveries rather than merely keep pace as science advances.

Today we are taking a closer look at the need for advance clinical research, the scientific tool used to discover mechanisms of disease prevention, diagnoses and treatment.

At the heart of Dr. Zerhouni's vision is the need to improve the research partnership among patient communities, community-based health care providers and academic researchers. It also involves improving how clinical research information is recorded developing new models of cooperation between NIH and patient advocates in creating new strategies to re-energize our clinical research workforce.

One question I have about this effort is how the NECTAR system at NIH, which as I understand will use medical informatics to coordinate clinical research initiative intersects with private sector initiated clinical research. I'm interested in how NIH will coordi-

nate with the private sector and what efforts are underway in the private sector to modernize the collection of clinical trial data.

In the interest of time, I will submit this as a question for your written response, Dr. Zerhouni.

I find myself asking the same question I have raised before: Does NIH have the resources to maintain support for existing research to advance new research and to implement the critical components of the Roadmap? Congress allocated significant budget increases, bipartisanally agreed to over the last 5 years to support basic research in the biomedical sciences at NIH. The research accomplishments achieved throughout the country, in large part because of public sector NIH investments, have been nothing short of remarkable. But as a contemplate improving the smallest budget increase NIH has received in decade, in large part because of budget mismanagement by the White House and because of tax cuts that the President continues to ask for, I wonder which NIH priorities will be neglected due to inadequate funding. This Congress today makes a decision on the budget. Do we keep doing more tax cuts or do we fund health care and education and other priorities.

What are we going to neglect? Will it be research on Parkinson's or breast cancer or cystic fibrosis? Will the research on a yet unknown treatment for HIV/AIDS or for tuberculosis? Will the advances outlined in the NIH Roadmap including advancing clinical research be put aside because of budget mismanagement and lack of resources? Will we in the long run, and this speaks directly to outsourcing in terms of lost job internationally kind of outsourcing and our economy overall, will we in the long run lose our competitive edge in their field because we are not appropriating money we should for NIH and CDC?

Dr. Zerhouni, your effort to maintain leadership in NIH is outstanding. We very much appreciate that. The Roadmap is not only comprehensive, but obtainable.

I hope the members of this Committee and the Congress will make good in their promises to the many constituencies who seek research dollars for the diseases that affect their families and support a budget that will see the implementation of your Roadmap.

I want to switch gears for a moment and raise an issue that involves previous NIH investments. The patent AIDS drug Norvir was discovered in the early 1990's by Abbott Labs under a multi-year/multi-million dollar grant from NIH. Despite the fact that NIH resources, tax dollars, contributed to the development of Norvir, its price has always been higher, significantly higher in the U.S. than any western European country. And that was before in December Abbott Labs increased the U.S. price by 400 percent.

Hundreds of organizations and physicians have asked the FTC and HHS to step in and do something about this outrageous price increase, which cost people's lives and they've requested a public hearing on this issue, which I understand has been denied. Again, in the interest of time I would like to discuss this further during the question period.

I thank the Chairman.

Mr. BILIRAKIS. I thank the gentleman.

The remainder of opening statements will be limited to 3 minutes. Hopefully, many of you will defer to that 8 minute period of questioning.

And without objection, all the opening statements of all members of the panel will be made a part of the record, including this one by Mr. Dingell.

The Chair now recognize Ms. Buyer for an opening statement.

All right. Let's see, Ms. Capps for an opening statement.

Ms. CAPPS. Thank you, Mr. Chairman. And thank you also, Director Zerhouni for making yourself available to us today. We appreciate your time and your willingness to share your expertise.

And like, I would venture to say every member, I am a very proud supporter of the NIH and the work you do there. And National Institutes of Health are truly the crown jewels of the Federal Government.

The United States has some of the best medical research in the world, and much of the most advanced health care is available to some here. These achievements are directly the result of the amazing job that the National Institutes of Health has done and the researches that Congress has provided them. And I think of this often when we see a lot of bashing of government. I always think to myself and say to as many people as I can, if you ever question the use of public funds, look at the National Institutes of Health.

The Congress has just completed the doubling of the NIH budget. It shows you the bipartisan support for it. But I hope that this does mean that we will think our job is done and shortchange the NIH on funding now.

The budget being considered this week here in the House asks for just minimal increases for the NIH, increased so small that many in the scientific community are concerned that the scientific gains from the doubling could be lost. This is an incredibly poor way for us to handle previous investments. And I believe the Congress needs to provide an adequate increase for NIH funding so that the trajectory that has been established with the doubling in the past can lead to the fruition of many of the projects that are just underway. We need to do this in order to take advantage of the investments already made.

I also want to address an issue that has come up before this Committee in the past and may come up again today. Some members have raised questions about NIH grants on human sexuality. While I do think it is important for Congress to conduct oversight, it is also important for us to keep politics from interfering with science.

Many of my colleagues advocate for the use of so called sound science which seems more about advancing political goals, not science. It's become quite a buzz word. But when the world's best scientific institution makes a decision based on truly sound science, some of our colleagues object to the results.

NIH was set up to dramatically improve Americans' lives, in fact lives around the world by increasing the quality and amount of biomedical research conducted here. And I believe NIH does this job admirably. And our job in Congress should not be to micromanage scientists about how to conduct their research. Our job should be to make sure that they have the support and resources they need

to advance medical science. We can and should make sure that NIH is run effectively and that its procedures meet quality standards. We should make sure that advisory councils are established with broad, diverse bases, but we should not engage in witch hunts to discourage research into particular areas.

There is no question that some Americans engage in self-destructive behavior. If we want to help them make lives better, we cannot pretend that the behavior does not exist. We must come to understand it and its effects on public health so that it can be addressed more effectively. And that is what scientific research is for, I believe.

Dr. Zerhouni, I was very impressed by a letter which I have here that you wrote to Chairman Gregg on this very issue. It was comprehensive and a very thoughtful response to criticism. And I, for one, am glad to have you with your background in professional science in a position to explain and to defend the NIH. And I look forward to hearing from you today.

Mr. BILIRAKIS. The Chair thanks the gentlelady.

Mr. Upton, for an opening statement? Waive.

Ms. DeGette?

Ms. DEGETTE. Thank you, Mr. Chairman. And thank you also, Dr. Zerhouni, for coming today.

I want to talk about two issues that I have been working very hard on; stem cell research and human subject protection. As many people here know I have been working with a bipartisan group for 2 years now talking about a change in the President's policy on stem cell research. After working with colleagues on both sides of the aisle, we now believe that there is broad bipartisan support for stem cell research expansion.

After more than 2 years, we know that the current policy on stem cells does not work. Instead of the promised 78 embryonic stem cell lines, today we have only 15 and there is general agreement that these lines which have aged and may be contaminated with mouse feeder cells may be unsuitable for therapeutic use in humans.

Instead of the promised $100 million in funding for NIH stem cell research, only $17 million was allocated in 2003. Last year, Dr. Zerhouni, when you came before this Committee you said that this policy is based on this President's moral and ethical considerations. I am concerned that the policy is not based on science, and I know members of this Committee are also concerned.

This kind of research can cure diseases that affect millions of Americans, and we should not be making policies based on moral and ethical considerations. We should be making them on scientific considerations. And I hope that the Administration working with NIH will reexamine its stem cell policy, because it is thwarting disease prevention into so many important areas.

I also want to talk very briefly about human subject protection. Today I was pleased to see Dr. Zerhouni in your testimony you say the coordination of clinical research policies is described. This is an essential effort that Congress and all effected agencies must undertake.

I began working on this issue in 1999 when the FDA shut down medical research programs at the University of Colorado Health

Sciences Center, which is in my District. The Health Sciences Center had not adequately addressed its institutional review board's inability to keep up with the overwhelming volume of research projects. And Mr. Greenwood and I have been working assiduously on this issue ever since.

I've introduced legislation right now which shores up protection for research subjects and researchers. I think that if we can haver this kind of harmonization, it will be very effective. It is a part of human research protection. And I look forward, Dr. Zerhouni, when you talk later in your testimony to talk to you about that, because that's going to be essential for protecting subjects of human research.

And with that, I yield back the balance of my time.

Mr. BILIRAKIS. Mr. Green for an opening statement.

Mr. GREEN. Thank you, Mr. Chairman. And I always appreciate you holding these hearings on oversight, because I don't think there's anything more important than what we do than looking at the clinical research efforts of the National Institutes of Health. There are few issues on which more Americans agree that we need to boost scientific funding at National Institutes of Health. The groundbreaking research done at NIH is the lifeline of hope for countless individuals living with AIDS, cancer, diabetes or many other illness. And I find it amazing every time I have an opportunity to visit either MD Anderson in Houston or Texas Children's Hospital or Baylor Medical School to see some of the research projects being done and the hope for the future. And a lot of that is with both local funds, but also with NIH grants because of the strong support Congress has committed resources to double the NIH's budget from 1999 to 1903 and most recently providing $27.7 billion for 1904, a dramatic increase to accelerate our progress in many areas and contributed a breakthrough such as mapping of human genome. Yet the NIH has not been reorganized in any substantive way in over 120 years. And despite major advancements and changes in our Nation's health needs, and a result it has grown to more than 27 institutes and centers. With this rapid growth and with the many changes in the scientific research community there are legitimate questions about NIH's structure and design help or hinder our progress. That's why Congress mandated a report from the Institute of Medicine at IOM to determine whether the structure changes to the NIH was necessary.

IOM's report was released summer and indicate there are indeed problems with NIH's current and organizational structure that inhibit research and make several recommendations to improve research activities at NIH. One of these, I think, is today's hearing, the reengineering of clinical research enterprises is of particular interest because clinical research translate to scientific knowledge of the laboratory and to the treatments and procedures to use with patients, just like I see in Houston. If there are obstacles in our current structure that slow the path of life saving research from reaching the patient, then we must overcome them. And I know that the road map includes a number of initiatives including harmonizing clinical research requirements, integrating clinical research networks, enhancing workforce training, improving data sharing and many other provisions. And I noticed in your testi-

mony you talk about regional centers to make sure that that happens.

They are all interesting approaches and one I think will help bridge that gap between the bench and the bedside. And I look forward to hearing your testimony, Dr. Zerhouni. And, again, welcome to our Committee.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. The Chair thanks the gentleman.

Mr. Pitts for an opening statement? Waived. Good.

[Additional statement submitted for the record follows:]

PREPARED STATEMENT OF HON. JOE BARTON, CHAIRMAN, COMMITTEE ON ENERGY AND COMMERCE

Thank you, Chairman Bilirakis, for holding this hearing today.

Two weeks ago, the Committee heard testimony from Department of Health and Human Services Secretary Tommy Thompson about HHS' fiscal year 2005 budget request. At that hearing, I raised the point that many health care programs are currently being funded in the appropriations process without the requisite authorizations from this Committee. I don't think this is a responsible practice. The National Institutes of Health is America's and the world's premier medical research institution. It is also one of the agencies at HHS with the greatest number of expired authorizations.

For a variety of reasons, this Committee has not moved legislation to modernize the National Institutes of Health. It's a shame. The NIH is one of the best examples of a public-private partnership. Eighty-five percent of the NIH research budget is dedicated to investigator driven research. These research grants support more than 50,000 scientists affiliated with approximately 1,700 organizations including universities, medical schools, hospitals, and small businesses in every state of the nation. Study after study has shown that partnerships between universities and the private sector are a powerful local economic driver. The NIH research infrastructure helps to keep this engine moving. More importantly, it breeds a research environment that stresses and promotes innovation so that we can better understand disease, and develop products that will treat and ultimately cure disease.

There is no question that advancing medical research should be a top priority of this Committee. NIH does many things well—that's why Congress doubled the budget of the agency. But that doesn't mean that NIH is perfect. For example, the more I learn about NIH, the more concerned I am about the existing authority of the Director and his ability to set priorities and manage the research portfolio of the entire agency. I am also concerned that without greater transparency of NIH program activities, it will be close to impossible for this agency to be held accountable for the sizeable taxpayer investments we have made.

NIH Director Dr. Zerhouni recently announced his strategic plan to optimize NIH's increased budget and research portfolio. It is a privilege to have Dr. Zerhouni with us today. Dr. Zerhouni has set an ambitious agenda, placing considerable emphasis on the clinical research component of NIH portfolio. Today's hearing will provide Members an opportunity to focus specifically on the clinical research activities of NIH.

I look forward to the testimony today.

Mr. BILIRAKIS. We will now go right to Dr. Zerhouni.

Sir, as you know, your written statement is already a part of the record. And we would hope that you would sort of supplement, compliment it, whatever the case might be.

We'll set the clock at 10 minutes and give you whatever time you might need.

Please proceed.

STATEMENT OF ELIAS A. ZERHOUNI, DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Mr. ZERHOUNI. Thank you, Mr. Chairman, minority ranking members and members of the committee. I'm really pleased to be here and I thank you for your interest in our efforts in clinical re-

search, as well as your historical support for the mission of the NIH over the years.

What I'd like to do is really give you the salient points of why is it that we think at NIH that we need to reengineer the clinical research enterprise.

I would like you to direct you to the screens on the side. I will use slides, if you don't mind.

First and foremost, it is clear that clinical research is the key to translating discovery into practice. It is the capstone of all of our efforts. What we discover in the laboratory, what clinical research tells us to look for in the laboratory, can only have a reality if we apply it to our patients.

It is clear that NIH is spending a significant portion of its budget on clinical research, about a third of our budget is directly spent on clinical research issues. Three thousand clinical trials are currently active at NIH recruiting patients throughout the country. There is not one State in the Union in which we do not conduct clinical research at this point in time.

What I would like to tell you is that over the years clinical research has been very successful. Because we have been successful we have reduced mortality for coronary heart disease by 50 percent, mortality to stroke by 50 percent, mortality from AIDS by a factor of six, transforming many disease from acute to chronic. We have lengthened life expectancy by about 1 year every 5 years, which also raises new issues that we have to tackle.

So the evolving public health challenges that require new strategies of research are as follows:

First and foremost is the transformation of the diseases we have researched from acute, lethal short term diseases 30, 35 years ago to more chronic, more long term, more permanent diseases today.

Second is the aging of our population. We need to tackle that issue. It would be a huge burden to our society if we are not able to find better ways of maintaining health throughout life expectancy.

Third, a remaining priority is health disparities. We cannot afford to have a research enterprise that does not address the diversity of our population and the inequities that come from not having a research strategy that attacks that specifically.

Last, is emerging disease. Not just from the infectious diseases that we see from time to time in our country, but also diseases that are emerging at a rapid rate, like obesity, which we have to tackle because their consequences are dramatic if we do not.

And last but not least, over the past 3 years biodefense has become a new priority for NIH.

I would like to show you here a curve of U.S. health expenditures as a percentage of GDP as they have evolved until 2002. As you can see, there was a flattening of the cost curve in the 1990's due primarily to managed care but also to the fact that the aging of the population flattened in the 1990's because in the 1990's we were seeing the effects of the depression and the Second World War, whereas birth rates were lower than after the war. So we are going now to a period where again we are going to see an acceleration of health care costs. We have already seen that in 2001/2002 and 2003 with increases in the 8 to 10 percent range. If this continues

unabated, we will have a greater percentage of our GDP used for health care. Therefore, we think at NIH that we have to accelerate the progress that we make in translating our discoveries in finding completely new ways, revolutionary ways, of preventing disease from reaching a cost that would not be sustainable.

So how do we need to transform the medical research enterprise in the 21st century? On your left hand side is the paradigm of the 20th century. On your right hand side is the paradigm of the 21st century.

In the 20th century and for 5,000 years before that the paradigm of medicine was that we treated disease when symptoms appeared and normal function was lost. That's how you went to the doctor. You didn't go to the doctor unless you felt sick. Why? We didn't understand what happened before you became ill. We didn't understand at the time that before you developed cancer, many, many years before that, certain changes occurred in cells that then led years later to the development of a cancer.

When you developed diabetes, we didn't realize that years before that there were dysfunctions in your metabolism that led to diabetes. Because we didn't understand the molecular and cellular events that led to disease, we didn't know how to intervene sooner to prevent the disease. That was very expensive in financial and disability costs.

What is the paradigm of the 21st century? We will intervene before symptoms appear and preserve normal function for as long as possible. This is the strategy that we want NIH to go into—study the preclinical stages of disease and delay, reduce or eliminate the onset of disease.

Why do we think that this is possible today? Because we have better methods. We have decoded the human genome. We understand basic biology a lot better than we ever did. And we think we have the tools. If we deploy them well to understand disease processes, then we think we have the ability to detect those patients at most risk where interventions will preempt the development of disease. This has the prospect of creating a new world of medicine that is orders of magnitude more effective than the world we know today.

So that's in a nutshell what the NIH Roadmap goal is: How do we accelerate basic research discovery, what we know today, with the events that have been remarkable over the past 10 years and speed the translation of those discoveries into clinical practice?

And the Roadmap was essentially an explicit exercise to address the roadblocks with the entire community, analyze them explicitly, transparently and identify those roadblocks that slow the pace of medical research in improving the health of our people.

Clinical research became and emerged as a key component of the Roadmap. There are three components to the Roadmap. One is called New Pathways to Discovery. It is our effort to accelerate our understanding of the very complex biological mechanisms that lead to disease.

We also understand that medical research now is a lot more complicated than it used to be. It requires disciplines such as physics, mathematics, computer sciences and we need scientific teams that are more interdisciplinary than they were in the past. And last but

not least, the topic of our hearing today is we need to tackle the issue of the effectiveness of our clinical research enterprise.

How do we do this? I am just going to give you some examples of where we are and where we want to be.

If you look today at a typical disease network, typically what you see is an academic health center with sites around the academic health center or multiple academic health centers focused on that disease with perhaps data coordinating centers. There are some best practices out there that you will hear from my colleagues who are following me, in particular the cystic fibrosis model which I think is a good model to emulate. However, when you look at research in cancer for example, we do not have a common language between cancer centers so that the data can be commingled and analyzed prospectivly.

I'll give you an example. This year we showed that hormone therapy on a long term basis is not a good public health measure. We have reduced the utilization of these approaches by almost 60 percent because of the research we did. If we had a system whereby we were able to have networks of centers that are interoperable, as I show on the graph, where we could have had if we had good informatics, we could have tracked down online what the effect of introducing a new therapy was on the population and found out years sooner than we did that, in fact, the dogma that this was a good thing was not correct.

So we want to build what I call the integration framework, the grid for clinical research networks. How do we do this?

We create an interoperable network of networks. There is a specific initiative called the National Electronic Clinical Trials and Research Network, called NECTAR. NECTAR extracts, if you will, the knowledge that we need to make conclusions about the health of our people. This will develop common data standards, informatics specifically for research, and software tools. More importantly, it will be web-enabled so that we can then deploy that system at the practice sites. Because there is a fundamental change we have to tackle, and that is that before we had acute diseases that were seen in academic centers in in-patients. Today we have chronic diseases that are seen in communities on an out-patient basis. And we need to really research the disease before it hits. So those are issues that can only be tackled at the community level.

So we need to have a system that the country will benefit from if we could have an implementation where there will be an information system whereby your doctor will have access to the most up to date information to do the right thing for the patient who is suffering from that disease at the time.

So we will use existing networks. We have done a lot of work that is very effective. But we want to get to the next step of integration.

The second is how are we going to do this? How are patients going to interact with the clinical research system of the future? We need trusted intermediaries. Academic scientists are in their academic centers. They do very advanced research. Many of the scientists we have trained, in fact, have left academic practice. Many

of them had had training in clinical research, and then they went into practice. And then the connection is severed.

We need to reestablish that connection. The idea that I think will change the landscape of how research is done is the idea of creating a national clinical research associates corps.

Essentially this would be a diverse national group of trained and certified community health care providers linked to regional academic centers. They will enroll and follow their own patients. They will be trained in the latest best practices in the diseases they are interested in such as Alzheimer's or Parkinson's. Patients will then have access to the information about clinical trials, but also to the best practices at the time and access to the NIH NECTAR information system at the practice site. We are determining feasibility as we speak and we are developing the core competencies. And we want this system to dovetail with the department-wide initiative of the health information infrastructure that the department is working on.

The other point that Ms. DeGette brought up, is the clinical research regulatory environment. We want to maximize human subject protection.

It is not a good idea when you try to perform clinical research to have duplicative and overlapping Federal requirements and variability among and within agencies. FDA has different requirements than NIH in terms of information. But this creates uncertainty about how to comply. And if you have uncertainty about how to comply, your safety and your protection is not as good as they could be. So we want to lead an effort across the Federal Government and with Congress to try to find better ways of implementing modern ways of tracking safety. A good example is a collaboration currently between FDA and NIH to establish an electronic adverse event reporting system.

When something happens in a clinical trial, right now you report it many different ways. We want it reported in one data base so FDA and NIH can immediately find out what is harmful in any one trial.

And then we need to engage the public in clinical research. And this sounds like something that is nice to say anyway, but this is not just a nice thing to do. It has become a core requirement for research.

If you do not have public participation, if you don't build trust and enhance the needed partnerships between patients and researchers, participation rates fall. We only have the 1 percent participation right now in Parkinson's disease research; 3, 4 percent in cancer. We need to have a much more efficient way of testing the thousands of good ideas that are coming out of our laboratories. And we need to do it quickly. We need to provide ongoing communication and educate patients and their doctors about research access. It would add to the translation and speed it up.

A good example already in place is this website of the National Library of Medicine called clinicaltrials.gov, whereby any patient anywhere in the country can go to the web now, and find any of the 3,000 trials that NIH is supporting. For example, if they are interested in heart attack research in Los Angeles. This is something that is a real advance. We want to build on those advances.

So in the end, the reengineering of the clinical research enterprise is really a comprehensive, systemic look at how research needs to be conducted in the 21st century. We need to integrate clinical research networks and also enhance our community-based research. It will serve our purpose. It will link existing networks so clinical studies and trials can be conducted more effectively. But clearly the solution is partnerships of research. That means that we need to create communities of research around specific problems, whether it be Parkinson's disease or Alzheimer's or any other disease that links patients, their physicians and the scientists to truly understand very quickly what the best practices are, what works, what doesn't work in the translational research that we need to do.

So we are committed to that. We have developed an approach. Some of the approaches we have developed may work, some may not. But the key thing here is what you regret in life is not what you fail at, but what you don't try to do. So NIH wants to lead and this is why we are here. And I would be be happy to answer your questions.

[The prepared statement of Elias A. Zerhouni follows:]

PREPARED STATEMENT OF ELIAS A. ZERHOUNI, DIRECTOR, NATIONAL INSTITUTE OF HEALTH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman, Members of the Subcommittee, I am Dr. Elias Zerhouni, the Director of the National Institutes of Health (NIH). I am delighted to appear before you today to testify about NIH's role in clinical research.

With the support of Congress and the White House, NIH has been the driving force behind perhaps the greatest era of discovery in the history of biomedical research. We are gaining unprecedented knowledge about human biology and medical conditions. The human genome has been sequenced. The scientific community is learning how proteins and molecules function and about the mechanisms of disease. In general, the knowledge gap about human biology is shrinking quickly.

Of course, these discoveries have far less meaning if we cannot translate them into prevention methods and treatments for diseases and disabilities. This translation, commonly known as the "bench to bedside" process, cannot happen without clinical research. Broadly defined, clinical research involves the participation of human subjects in various aspects of research. It is the linchpin of the Nation's biomedical research enterprise. Clinical research ultimately establishes the safety, effectiveness and availability of new diagnostic, preventive and therapeutic approaches.

Approximately one-third—$8.4 billion—of the grants awarded by NIH support clinical research. We have established integrated clinical research networks for HIV/AIDS, heart disease, and cancer, among others, that have significantly enhanced the translation of basic discoveries. At all times, our primary concern must be the safety of the people participating in clinical studies and trials. The Federal Government has a rigorous process for ensuring the well-being of human subjects participating in Federally conducted, supported, or regulated research, ranging from the initial reviews by Institutional Review Boards (IRBs), to ongoing reviews by Data Safety and Monitoring Boards, to the authority to investigate and discipline researchers and institutions that do not abide by Federal requirements.

NIH continues to expand its clinical research program and provide resources for infrastructure and training. We have established new programs to support the professional development of medical students and medical school graduates in the conduct and ethics of clinical research. We are funding young clinical investigators and their mentors; reorganizing study sections to enhance the evaluation of grant applications about clinical research; and providing educational loan repayments for new, including minority, clinical investigators. Longstanding programs for the support of clinical research, including the General Clinical Research Centers located in academic health centers around the country and the NIH Clinical Center, also have developed new training initiatives designed to advance translational research. These programs and an array of other infrastructural activities and training mechanisms are aimed at ensuring that the "critical mass" of highly skilled personnel and state-

of-the-art resources necessary for a vigorous clinical research enterprise are available.

As the Director of the largest biomedical research agency in the world, I believe it is my responsibility to continually review our programs to ensure that they are working well, and further, to be certain we are heading in the right direction. So for all our success in the clinical research area, the question is: have we done all we can do to speed the process of translation of results from bench to bedside? The answer is, we can do more and we can do it better.

When I arrived at NIH two years ago, I implemented an initiative across all of our Institutes and Centers to explore the key scientific challenges facing investigators today and to delineate the central roadblocks to scientific progress. With a focus on those activities that would require the efforts of the agency as a whole, and through broad consultations with scientists inside and outside NIH, this extensive planning effort has led to formulation of a "Roadmap" for medical research in the 21st century. One of the key goals of the Roadmap is to re-engineer the clinical research enterprise. The purpose of the re-engineering effort is to overcome obstacles to the conduct and translation of clinical research by transforming its very structure. The NIH Roadmap plan on "Re-engineering the Clinical Research Enterprise" has four main parts: Facilitating Translational Research; Enhancing the Clinical Research Workforce; Integrating Clinical Research Networks; and Coordinating Clinical Research Policies.

Facilitating Translational Research

To improve human health, scientific discoveries must be translated into practical applications. Such discoveries typically begin with observations of patients with diseases then move to the "bench" with basic research—where scientists study the mechanisms and progression of a disease at the molecular or cellular level—then progress again toward the study of these phenomena in patients at their "bedsides.".

Scientists have become increasingly aware that this bedside-to-bench-to-bedside approach to translational research requires a variety of non-traditional expertise and intense two-way collaborations with clinicians. Not only do basic scientists complement the expertise of clinicians in making novel observations, clinical researchers also make unique observations about the nature and progression of disease that can, in turn, stimulate basic investigations. Thus, translational research is a key junction in the process, where new knowledge is both tested and gained, producing new observations and hypotheses that keep the system productive and rich with discovery. However, I believe that by strengthening the infrastructure, this critical process and component of the clinical research enterprise can be accelerated.

Key to building a strong infrastructure will be the ability to increase the interactions between basic and clinical scientists, and cross-training of basic and clinical scientists in each other's disciplines, thus easing the movement of powerful new tools from the laboratory into the clinic. In one approach aimed at accomplishing this interaction, NIH intends to develop regional translational research centers. These centers would provide sophisticated advice and resources to better enable scientists to master the many steps involved in bringing a new product from the bench to clinical use. Such steps involve laboratory studies to understand the mechanisms of action of a therapeutic agent, preclinical studies in animals to evaluate how the agent is absorbed by the body and distributed to target tissues, and assessing its effectiveness as well as tendency to cause unanticipated side effects.

Once a potential new drug is developed, sufficient amounts of the drug have to be produced according to rigorous standards for testing first in animals and then in people. The clinical research re-engineering plan also envisions translational research core facilities to provide clinical researchers access to sophisticated manufacturing capacity, along with expert advice to ensure that drug-development regulations are observed. Some of these core facilities will be modeled on, or may evolve through expansion of, existing programs such as the National Cancer Institute's Rapid Access to Innovation Development program, which currently provides support for these types of resources to members of the cancer research community. Their availability to the broader research community should expedite discoveries for other disease research as well.

This re-engineering initiative will also support translational research by developing new technologies to improve the assessment of clinical outcomes. Many of the most debilitating, chronic illnesses gradually erode the quality of life because of the associated fatigue, pain and emotional challenges. Currently, these critical symptoms cannot be measured objectively in the same way as, for example, blood sugar levels or blood cell counts. More sensitive, well-validated tools need to be developed to improve measurements of these types of symptoms. Technologies, such as a computerized adaptive health assessment, could revolutionize how symptoms and treat-

ment outcomes are assessed. Scientists will be better equipped to understand how patients perceive changes in their health status resulting from new interventions, thereby directing research to therapies that would be most highly valued by patients.

Enhancing the Nation's Clinical Research Workforce

The second component of the re-engineering plan is aimed at enhancing the Nation's clinical research workforce. To fulfill the promise of 21st century medicine and to make further progress in controlling major human diseases, the Nation must cultivate and properly train a cadre of clinical researchers skilled in translating the findings from clinical trials and other clinical research studies to applications on the front lines of care. Clinicians must be trained to work in multidisciplinary, team-oriented environments. Specific training in disciplines important to the conduct of clinical studies (e.g., epidemiology, behavioral medicine, and patient-oriented research) is needed, and the expert skills of engineers, mathematicians, physicists, and computer science experts also must be incorporated. This component of the re-engineering plan will enhance and empower the clinical research workforce through two programs—the Multidisciplinary Clinical Research Career Development Program and the National Clinical Research Associates Program.

The Multidisciplinary Clinical Research Career Development Program will be an NIH-wide effort to train doctoral-level candidates in clinical research settings that are multidisciplinary and collaborative. The emphasis will be on new strategies and curricula with training opportunities that span a variety of disease areas; a broad range of clinical disciplines, including medicine, nursing, dentistry, pharmacy and other allied health professions; and a variety of research areas, including biostatistics, behavioral medicine, clinical pharmacology and epidemiology. The new program will be coordinated with and complement other NIH training programs that support scholars who wish to become clinical researchers. NIH plans additional programs to help smooth out the early career development pathway spanning from college to professional school, thus promoting the early identification and training of students who will become the future leaders in clinical research. By exposing students to clinical research early in their careers, it is hoped that this program will also enhance the integration of clinical research into both basic science and clinical medicine.

The clinical research workforce also must be broad enough to support the testing of ideas in large scale studies at the community level, as well as the translation of proven concepts into medical practice at the community level. The National Clinical Research Associates program will help increase the number of clinical investigators and diversify the settings in which clinical research is conducted. Through partnerships with academic investigators, the Associates will form a corps of community-based physicians trained to carry out clinical studies in their own health care settings. Together they will form a robust and versatile infrastructure of researchers well-trained in the responsible conduct of clinical research and positioned to bring research opportunities to patients while rapidly disseminating the best science-based practices.

Several projects will be required to realize the vision of the Associates. These include a study that will examine the challenges involving community practitioners in clinical research. Building on the results of this study, recommendations on ways to reduce barriers to building a model workforce for conducting clinical research are expected to evolve. Other efforts will focus on the establishment of national core competencies and best practices needed to conduct high-quality clinical research and to translate research into clinical practice. These efforts will apply to researchers working in both community and academic settings. Competencies would include relevant board certification; knowledge of clinical research design and implementation, and conflict-of-interest policies; and documentation of training in protecting participants in clinical trials. To train the Associates, the NIH plans to create several nationally recognized regional Centers of Excellence in Clinical Research Training that will be based on the results of the feasibility and pilot studies. These centers will use an integrated approach to conduct training in "real-world" settings.

Integrating Clinical Research Networks

Another component of the re-engineering plan, Integrating Clinical Research Networks, is designed to promote synergy among diverse clinical research activities through the development of linkages among research institutions, medical centers, and existing research networks. Because of the vast number of therapies, diagnostics, and preventive approaches that must be evaluated through clinical trials, many clinical research networks operate simultaneously, but independently of each other.

Over time, this initiative aims to link research centers and existing networks in order to develop a National Electronic Clinical Trials and Research Network (NECTAR). This network will create a revolutionary new clinical research infrastructure model, which will result in greatly enhanced communication, computational capacities, access to resources, and research and analytical tools. Such a system will ultimately offer economies of scale by allowing complex research programs to benefit from a common infrastructure, rather than recreating infrastructure resources time and time again at multiple sites. Networking will provide for broad access to data and allow investigators to learn from, utilize and build upon existing data. Integration of data will encourage the formulation and study of new research questions and the cross-fertilization of major fields of inquiry in the process.

This effort will promote and expand clinical research networks that can rapidly conduct high-quality clinical studies that address multiple research questions. An inventory of existing clinical research networks will be undertaken to explore existing infrastructures for informatics and training, in order to pinpoint characteristics that promote or inhibit successful network interactivity and productivity and expand or broaden research scope. Once identified, "Best Practices" can then be widely disseminated, further enhancing the efficiency of clinical research networks.

To function effectively, these clinical research networks will need to harness and help integrate information technology and develop a national informatics network using standardized data, software tools and network infrastructure. NECTAR, which will dovetail with current medical informatics initiatives in the Department of Health and Human Services, will maximize connectivity among existing and newly created clinical research networks and help researchers to generate, use and share data, thereby reducing duplication and unnecessary overlap among trials.

To accomplish this, NECTAR will create common vocabularies, research and business tools, and common platforms and architectures. NECTAR will enable more efficient business practices and processes; enhanced data sharing and analysis; coordinated oversight and improved patient protections; and rapid translation of research into clinical findings and practice. NECTAR ultimately will assist in accelerating the pace of discovery and development, thereby helping clinical researchers better serve their patients.

Coordinating Clinical Research Policies

The last critical component of re-engineering the clinical research enterprise recognizes that other potential impediments to efficient clinical research are the diverse regulations and policies of the multiple federal agencies that fund, conduct and oversee clinical research. For example, researchers face varying requirements that pertain to reporting adverse events to NIH, the Food and Drug Administration, the Office for Human Research Protections and IRBs, among others. Clinical researchers must understand and fulfill these varying requirements.

NIH is working in concert with regulatory agencies, research communities, and patient advocacy groups to catalyze Federal-wide coordination of policies pertaining to clinical research, to develop better processes, and to standardize requirements for reporting adverse events, human subjects protections, privacy and conflict-of-interest policies, and standards for electronic data submission. Coordinating policies and reporting requirements will help minimize unnecessary burdens that slow research while enhancing patient protections. Thus, the goal of NIH's Clinical Research Policy Coordination Initiative (CRPCI) is to work within the federal system of clinical research oversight to promote the coordination of policies, requirements, and procedures concerning clinical research, and, where appropriate, to help create streamlined approaches. The CRPCI will examine an array of issues and activities on behalf of the NIH and all its Institutes and Centers and work with other Departmental components and Federal agencies to help stimulate the development of coordinated policies, practices and new tools for compliance that take account of the goals and points of view of NIH's varied organizational components and stakeholders. As the most important part of our system of human subjects protections, IRBs will be a primary audience for our efforts. Some representative activities will include:

1. Studying existing requirements for the conduct and oversight of clinical research to assess the extent to which unnecessary or duplicative rules can be addressed without diminishing protections;
2. Exploring the expanded use of central Institutional Review Boards to facilitate and achieve greater efficiency in the review of multicenter clinical trials, such as the National Cancer Institute's Central Institutional Review Board program for adult oncology trials;
3. Developing tools and materials to help ensure and facilitate compliance with existing rules;

4. Promoting the development of coordinated clinical research policies by working with other Federal entities (such as FDA, OHRP, and the Departments of Defense and Veterans Affairs) that fund, conduct, oversee, and establish policy for clinical research;
5. Soliciting input on various policy goals from key communities, such as patients, scientists, institutional leadership, IRB members, and other constituencies with a stake in the conduct of clinical research; andDeveloping educational and training tools to assist investigators and IRBs in the interpretation of and compliance with human subjects and related research requirements.

While NIH has assumed a leadership role in conceptualizing and implementing this plan to reconfigure the clinical research enterprise, many other stakeholders have broader roles and vital responsibilities in assuring the future of clinical research, including other federal agencies, academic health centers and biomedical research institutions, private foundations, the pharmaceutical and biotechnology industries, the health insurance industry, patient advocacy groups, and the general public. In implementing the re-engineering plan, NIH recognizes that success will depend on continuing close collaborations and consultations with these many partners.

Conclusion

In taking bold steps to re-engineer the clinical research enterprise, NIH hopes to create a new infrastructure to support clinical research that will facilitate the rapid translation of discoveries from the laboratory to the clinic and provide a robust force of clinical investigators to test new diagnostic, therapeutic and preventive strategies in patients far sooner than is possible at present. By enhancing the interoperability of clinical research networks, and by improving the coordination of the important rules and regulations that ensure the safety and ethics of these studies, the system will be more efficient and there will be far fewer impediments to the conduct of clinical research. Clinical research will advance more swiftly, more and better therapies and preventive measures will be developed more quickly, and, ultimately, significant improvements will be made in human health and the quality of life. We look forward to keeping Congress apprized of our continuing progress in Re-engineering the Clinical Research Enterprise.

Mr. BILIRAKIS. Doctor, thank you. It is about as concise and informative a statement as I have heard in a long, long time.

Doctor, do you reflect the views of your colleagues at NIH and, I might say, other colleagues in other research facilities in the research area, if you will? Yes, do you feel that you for the most part would be speaking for them, too, in terms of what is needed, what the future looks like?

Mr. ZERHOUNI. Right.

Mr. BILIRAKIS. The Roadmap, the concept, etcetera?

Mr. ZERHOUNI. Right. I have to say that this concept is not my concept. The only thing I did was to create an explicit process of consultation. And over a 1-year period we had over 300 experts and scientists come together and work very diligently on analyzing the roadblocks, the opportunities, what it is that no single institute can do but that NIH as a whole needs to do. That was the framework. And what came out of it is this Roadmap.

In fact, a good test is that people put their money where their mouth is. And for the first time all NIH institutes have agreed to put shared resources into this common pool of initiatives called the Roadmap. So every institute is contributing in fact to implementing this, because everyone realizes that this framework enhances research across the board. So I think the answer is yes.

Mr. BILIRAKIS. The answer is a good solid yes? That is good to hear.

Are you getting all of the cooperation that you need?

Mr. ZERHOUNI. So far so good.

Mr. BILIRAKIS. So far so good. Do you feel you have the resources?

Mr. ZERHOUNI. Never enough resources.

Mr. BILIRAKIS. Never enough. Well, I guess any human being still alive would make that comment regarding resources.

Mr. ZERHOUNI. Right. I think that the communication that needs to occur is a new phenomenon for NIH. We have not historically engaged in processes that do trans-NIH forward-looking planning processes. That was never really part of the mechanisms by which we operated at NIH, but it was something that really was felt to be necessary by the community.

The IOM report, which was the one that you conducted a hearing on a few months ago, recommends a more explicit way of undertaking these processes regularly, every 2 or 3 years, to inform the public, inform Congress of what analysis is, why do we think this is important and why do we need to do it across the agency.

Institutionalizing such a process will be very helpful, Mr. Chairman.

Mr. BILIRAKIS. Well, do you feel that the current NIH organization structure encourages clinical research across multi institutes, encourages basically the vision of the Roadmap?

Mr. ZERHOUNI. Yes, I think so. I think that the realization—the trends that I have described to you going from acute to chronic. For example, a realization that people in the field are coming to understand is that as patients age, they do not suffer from one disease at a time. There are multiple diseases that affect you at the same time. You can have heart disease, diabetes, renal disease, musculoskeletal disease at the same time. So the approach that every single disease needs a network and one approach is obviously not the approach of the future. And the institutes are realizing that we have many trans-NIH collaborations to combine the strength of various institutes and various diseases in the context of what we call co-morbidities.

Mr. BILIRAKIS. So the institutes are realizing that?

Mr. ZERHOUNI. They are realizing it.

Mr. BILIRAKIS. You feel that that's happened?

Mr. ZERHOUNI. But again——

Mr. BILIRAKIS. You know, this turf thing that we have here in Washington, protecting one's turf and whatnot——

Mr. ZERHOUNI. It is alive.

Mr. BILIRAKIS. It exists. Live and well up there.

Mr. ZERHOUNI. It's alive and well, and it's not bad. Because you have decentralization so that you do not make a top down decision that could be wrong. But the balance is what is in question. I think we need to have a good balance between the two and find explicit ways to do this.

One of the things that the directors have agreed to do is to find a way to better code and analyze the portfolio across NIH. Do we have a good way of looking at the entire portfolio and making decisions? That is a valid question. I do not have the answer to that. We are working on it.

Mr. BILIRAKIS. Well, Doctor, we requested at the last hearing that you give us an idea of what help you might need from the Congress in terms of additional authorities that might be legisla-

tively required. Hopefully, not, but it might be. And I am not sure, really, that we—you have basically said to us that hey we need this or we need that in terms of legislative fixes.

So I guess what I am saying, I am not asking for a response at this point in time, but I am just reminding you that we have not reauthorized NIH for various reasons for years. Obviously, it has not interfered with their work. We made sure they got their resources and we have spent a lot of time with NIH, too. But, you know, in the process of considering whether we go through a reauthorization this year or whatnot, what you might need in terms of this Roadmap would be significant in making our decision. So, please let us know.

Mr. ZERHOUNI. I should let you know, we are working on every single recommendation of the IOM report. We are analyzing those. We are preparing a response to your request.

Mr. BILIRAKIS. Good. Thank you very much.

Mr. Brown for 5 minutes.

Mr. BROWN. Mr. Chairman, thank you.

Dr. Zerhouni, thank you again.

As I mentioned in my testimony, I want to talk about Norvir, the patented AIDS drug discovered roughly ten plus years ago by Abbott Labs under a multi-year/multi-million dollar grant from all of you, from taxpayers.

By year end 2001, Norvir had generated more than a billion dollars in sales for Abbott. There is evidence to suggest that development costs borne by Abbott for the drug were relatively minimal. Norvir sold $7,800 a year in the United States while the price is less than $720 in Canada and less elsewhere. Despite the fact that NIH resources, taxpayers, contributed to the development of Norvir its price has always been higher in the U.S., as you know, than any other western European country. And that was before last December, Abbott increased the price of Norvir by 400 percent. Now we are talking about AIDS patients.

Norvir is typically used as a booster for other AIDS drugs. So the price of those drugs skyrocketed. Abbott insulated its own Norvir boosting product Coletra from the price increase, giving Abbott a tremendous price advantage.

Two hundred organizations and physicians have asked both the FTC and the Department of Health and Human Services to step in and do something about this price increase. My understanding is that the HHS petition is currently pending in the Office of Technology Transfer at NIH, right? Okay.

These groups have requested a public hearing. Again, 200 organizations and physicians have requested a public hearing. They recently received a letter from NIH saying that representatives from your agency would be willing to meet with them after a decision is made on the petition.

I am concerned about the after decision. These groups want to make the case regarding the viability of using Bayh-Dole the compulsory licensing patent allowing a generic in, given that specific patents on this product and other issues that make this case complex. These groups, I believe, deserve the opportunity to make their case before the decision is made. Will you give them that opportunity to make their case in a public hearing prior to?

Mr. ZERHOUNI. Right. You know my feeling is always transparency is better than any other process. However, in this context our regulatory and legal requirements, that the agency has to review the petition, the facts and this is what we're doing right now. And that review under the Bayh-Dole Act has to be done by the agency on the basis of all the historical data, and I'm told that this is in process right now.

Mr. BROWN. But what is the harm before a decision is made of doing a public hearing? Why cannot you commit——

Mr. ZERHOUNI. Our technology transfer office is in charge of implementing Bayh-Dole and all the march-in rights, and we need to let them do their analysis. At this point I don't have their——

Mr. BROWN. Well, I do not disagree with letting them gather the information, letting them do the analyses, but before a decision is made——

Mr. ZERHOUNI. Right.

Mr. BROWN. Before a decision is made, not just an announcement that it is public——

Mr. ZERHOUNI. Right.

Mr. BROWN. Can you commit to doing a public hearing before the actual decision is made? You always have believed in transparency.

Mr. ZERHOUNI. Yes, I understand.

Mr. BROWN. And you have been open with this Committee, with me personally.

Mr. ZERHOUNI. Right.

Mr. BROWN. I think with all of us here.

Mr. ZERHOUNI. Right. I can only tell you that if this is something that doesn't jeopardize the function and obligations of the agency, I have no objection to it.

Mr. BROWN. How could it jeopardize that? I do not understand.

Mr. ZERHOUNI. Because of the legal requirements. You have certain rules and regulations. For example, the majority of drugs in this market are not developed with NIH's dollars directly. And the rules say that if you have a component of government contributions to basic science which is not really patented within the subsequent patents, the subsequent patents rule. So that we have to look at that very carefully before an agency can say there is merit or there is no merit to a particular approach. We need to do that work. And that work needs to be done in the context of the regulations that are there.

The second issue that you are raising is the issue of pricing. This is an issue that goes way beyond NIH, as you well know.

We need to know what authority we have in that context. And the analyses are being made as we speak. But you have my commitment that if this is something that we can do, that the legislation allows us to do and if we have any leeway, I would tend toward open——

Mr. BROWN. Okay. Thank you.

Real quickly, Mr. Chairman, I will ask this quickly. To switch to another drug, Taxol, a breast cancer drug developed with NIH funding almost entirely with NIH funding including much of the clinical trials, is my understanding. 2003 GAO criticized NIH for not collecting adequate royalties for its contribution in developing Taxol. Share with us, if you would, NIH has done to ensure that—

again, the taxpayers receive royalties for the efforts that we all as taxpayers put forth.

Mr. ZERHOUNI. Yes. Let me tell you, I think the facts as we hear them are not the facts as I know them. So maybe one of the things we can do is tell you my version of the facts as I have learned them. I was not there then.

First of all, Taxol was a drug that was developed initially in the 1950's as a contraceptive and it failed. It wasn't a patented drug, No. 1.

No. 2, the specific NIH contribution to that was not the drug itself, it was a method of delivery of the drug. That's all that NIH did. At the time, NIH wanted to stimulate a relook at that drug, which we thought could have cancer potential. It was out of patent. And the only thing that we contributed was perhaps it could be delivered this way.

It turns out that the subsequent work, the relative contribution to say that NIH funded 100 percent of it and gave away its intellectual property rights, is inaccurate. That is not what we are told.

Now, could NIH have a different strategy in terms of licensing when it has a real right? We do that when we have the majority of the intellectual property. NIH received $50 million a year in royalties from inventions that we have had a significant contribution to.

So in the Taxol case, I think you are dealing with a drug that was not invented at NIH. We are dealing with a drug that was off-patent. The NIH contribution itself from what I am told, was not the significant contribution. However, NIH funded the chemistry research that was needed to avoid using the bark of the yew tree and funded the University of Florida to invent a synthetic method to do it. That method was licensed to Bristol-Myers. That patent from the University of Florida received $400 million in royalties which has allowed the University of Florida to do research. It didn't come to NIH, but it came to an NIH grantee.

So I agree with your concern that we are sort of undervaluing government property. But Taxol, I don't think is a——

Mr. BROWN. Was GAO wrong? Was GAO wrong?

Mr. ZERHOUNI. No, no, no. What the GAO was reporting was the GAO said do we have a system, do we have a system by which the analysis that we are talking about can be done before licensing? Do we have a way? For example, some of the conditions we impose on some of our licensees when we have solid rights.

Remember, in the Bristol-Myers thing there is nothing in what they did that is directly related to what we did.

Mr. BILIRAKIS. I share the concern that Mr. Brown has raised, and I think he would like the answer that he really wants. But it is basically—but basically I think he is interested in how the NIH functions in that regard and what criteria they use in determining proper royalties forthcoming, and that sort of thing.

Mr. BROWN. Right.

Mr. BILIRAKIS. And not just that particular drug?

Mr. BROWN. Right.

Mr. ZERHOUNI. And we are following that.

Mr. BILIRAKIS. Good. Thank you, sir. And we would maybe request that in writing from you after the hearing, along with all the other questions.

In that case, Mr. Greenwood?

Mr. GREENWOOD. Mr. Upton and Mr. Buyer said that if I buy them lunch I can go next, since I have leave. And I appreciate that. Lunch is in the mail.

Ms. DeGette I think raised the issue of human subjects, and she and I, as she mentioned in her opening statement are working on legislation to try to create the harmonization that is not there now. Could you be a little bit explicit as to whether you believe, in fact, that legislation is needed and what specifically you think needs to be in that legislation? And to the extent that you are aware of some of the controversies that have impeded our progress getting unanimity on this, you might comment on that?

Mr. ZERHOUNI. We are looking into that. We are actually analyzing right now what common ground you can find between NIH, FDA, other Federal agencies. We are actively putting a work group together. We have already done so in the area of safety. We have worked extensively within NIH on electronic submission. Someone was asking me about what are we doing with the other elements of the health care system. What I think we are doing, is we are trying to bring in the fully-installed interface for computers to be able to do it. In terms of the ranking function, it may be necessary at some point after we do the analyses to come back to you and——

Ms. DEGETTE. Will the gentleman yield for just 1 second?

Mr. GREENWOOD. Yes.

Ms. DEGETTE. Doctor, what kind of timeframe are you looking at for the NIH to complete its work?

Mr. BILIRAKIS. The mike—is the mike working?

Mr. ZERHOUNI. You are right. It is not on.

I'm going to co-chair the Committee on Science with Dr. Marburger, so we have already reached across to the OVA and other agencies. And we are doing this in the effort to improve human subject protection while at the same time making the rules clear, coordinated and effective.

Mr. GREENWOOD. Thank you.

On the issue of the clinical researchers themselves, in the past we have noted a need to have more better trained, trained not only in the clinical matters but in the ethical matters and so forth. And legislation that I helped, I was involved in, to provide funding to do just that; to educate young researcher in medical school. Are you able to comment on how we're progressing in that arena?

Mr. ZERHOUNI. This is a very important area. And NIH has in fact funded what we call human subject protection enhancement grants at all the institutions that applied for it to do two things. One was training of the scientists and actually we mandated that every scientist that does clinical research, performs clinical research, has to be certified. That's one.

The second is the significant investment we have made in terms of clinical research infrastructure. We have developed, for example, what we call K30 awards which are institutional awards to provide formal training on a permanent basis to all of their scientists, all their clinical researchers.

These two programs alone, you are talking about $30, $35 million a year of investment since 2001, I believe.

We are continuing to look at because we believe that it is actually important to also look at the structure of how human subject protection is done relative to data and safety monitoring boards. That is the goal of this policy coordination group that I have put together. So we are doing it, but I think you are right, I think that we need to make sure that it is effectively done on the ground.

Mr. GREENWOOD. Thank you, Dr. Zerhouni.

My time is about expended, but I just wanted to say that I think that the intelligence, the integrity and the ability that you bring to this job are the best thing that has happened to NIH in a long time. I commend you. Nice to work with you.

Mr. ZERHOUNI. Thank you.

Mr. BILIRAKIS. Thanks to the gentleman.

Ms. Capps for 5 minutes.

Ms. CAPPS. Thank you.

Mr. BILIRAKIS. And then we will break. We have a series of votes. Three or four. We will just get back as quickly as we can. I am not sure what else I can say.

Ms. CAPPS. And I will try to be brief and maybe not even use the whole 5 minutes. But I do have three different topics, each of which could take a long conversation, and I hope you appreciate the way we kind of do business here.

But the first topic is genetic nondiscrimination. Mapping of the human genome has been a remarkable accomplishment and seems to be opening up so many new doors. A lot of what you were talking about, I kept think that is all because of the mapping that has occurred. Obviously, this is a very positive step. But some are concerned about the downside and genetic discrimination being one of those concerns. Do you think we need legal or law to protect people from genetic discrimination?

Mr. ZERHOUNI. The answer is yes.

Ms. CAPPS. Okay.

Mr. ZERHOUNI. We are very supportive. There is a bill that has passed the Senate.

Ms. CAPPS. Do you support it?

Mr. ZERHOUNI. Which we support.

Ms. CAPPS. Okay.

Mr. ZERHOUNI. We would like the House to do the same.

Ms. CAPPS. All right.

Mr. ZERHOUNI. If possible. And we have talked actually to Chairman Barton an we are talking to the members of this Committee to try to see if we could have an equivalent bill in the House.

Ms. CAPPS. Thank you.

Mr. ZERHOUNI. It is very important to that issue.

Ms. CAPPS. I agree with you, and that is exactly what I wanted to hear.

Another area, which I hope you can answer briefly, because then I want to talk about a third topic and give you more time. And this is a huge topic, too, which is the seeds of distrust sewn in racial ethnic minority communities with regard to clinical research and how will you go about persuading more minorities of their importance in such trials given you're operating in 50 States, which is

remarkable in itself because that speaks to a lot of diversity. But within those areas there is probably—I know there are challenges. If you could address that, please.

Mr. ZERHOUNI. This is actually the reason why I put public interaction and public involvement as a very key component of the Roadmap for NIH. We know from research that you cannot conduct research in the community unless you have good, trusted intermediaries that are in the community. That is why the clinical research corps will be important to have members of the community connected to the scientific research system. And this is the only way we are going to be able to do it is by having community partnerships, otherwise it is hard for me to see how you go over that distrust there.

Ms. CAPPS. I agree with you, and I think that is an important subset of issues, that the regionalization and also attracting a variety of peoples into science fields so that there is that connection to cultural. I know you agree with that, too.

Mr. ZERHOUNI. Right.

Ms. CAPPS. I just want for whatever time remaining to have you talk a little bit more about one of the slides you put up which talks about the translation of results from bench to bedside and back and forth. Anyone who has ever been a part of cancer treatment knows the treatment of clinical trials in the treatment, not just the study. And I would like to give you a chance to explain this more fully and how we could support some of those efforts here.

Mr. ZERHOUNI. It's very important. We have two translational issues: One is when there is a discovery and then you need to really go in for a very early proof of concept. This is a difficult step to undertake.

Actually in cancer, cancer is probably more advanced than any other field.

Ms. CAPPS. Yes.

Mr. ZERHOUNI. And we have programs now that accelerate the development. And we have a program with FDA to try to accelerate, work together very early so that there will be no obstacles downstream.

Ms. CAPPS. And some of us believe the ensuring clinical, allowing people to use their health insurance for participation would be a good step, too.

Mr. ZERHOUNI. Right. That is a difficult issue, obviously.

Ms. CAPPS. It is very difficult.

Mr. ZERHOUNI. But clearly what would help us the most is truly connected and organized communities that partner so that they can participate in clinical trials—that the doctors know about trials and participate actively in the research effort.

Ms. CAPPS. So that, again, is part of your rationale for decentralizing, if you will, and becoming a part of the people.

Mr. ZERHOUNI. That is correct. That is what our community researchers are telling us.

Ms. CAPPS. What ways could Congress assist you this effort? I know money, but money where, how?

Mr. BILIRAKIS. Would the gentlelady defer? Are you coming back?

Ms. CAPPS. Yes, I plan to.

Mr. BILIRAKIS. You are planning to? Why do we not go ahead and break? I am afraid we are really going to have to really run to make that vote.

Ms. CAPPS. Okay.

Mr. BILIRAKIS. And then you can continue. You will have another minute when we get back.

Would you mind waiting, Doctor? I know it is going to be a while.

Mr. ZERHOUNI. No, I do not mind.

Ms. CAPPS. It will be. Thank you very much. I am happy to come back. Leave my things here.

[Recess.]

Mr. GREEN [presiding]. The Committee will come to order.

Ms. Capps, I think we ended with you in the middle of your questioning, and so you are now recognized to complete that for 1 minute.

Ms. CAPPS. I got a few extra seconds out of that deal. I think that was pretty good.

As I went to the floor to vote, Dr. Zerhouni, I reflected on a pattern that I think you gave both in your testimony and in your response to me so far, which is the importance of the, and I forget the title that you have designated these scientists to be, no less than full participants in NIH but dispatched, if you will, into the community within perhaps academic or treatment centers. And well I guess my final question to you then is, because I want to be pragmatic about this, would there be legislation that we could craft in a bipartisan way that could further help you to articulate that? Funding always help, but also the articulation of that idea that we could perhaps help within the Congress?

Mr. ZERHOUNI. I am not sure we need legislative language. The NIH National Clinical Research Associates Program is a way for us to formalize connections between academic centers and the communities. In particular, in many areas, you see those doctors who are in the community in fact trained at the academic centers. The tie has been severed because there was no connections that we supported. We need to support it financially, obviously, and we need to support it through training and an infrastructure.

I am not sure we need legislation, but I am not sure either that we don't.

Ms. CAPPS. Right. Well in other words you are making the connections within the structure of NIH to tie these entities together?

Mr. ZERHOUNI. Well, we're going to stimulate—as you know, NIH 85 percent of our budget goes to about 2800 institutions, 212,000 scientists out there. We want to stimulate them and challenge them to establish models of collaboration and cooperation within their own communities. And that's how we will do this.

We will, however, have common training, common understanding of human subject protection, common guidelines and a presence at the practice level.

Ms. CAPPS. I guess if I could make a final comment. The place then where we would be interested in this, I would be as if one these sites is my congressional district. And that is how members could then connect at the local level, which we appreciate being able to do anyway.

Thank you for your time.

Mr. ZERHOUNI. Thank you.

Mr. GREEN. Thank you, Ms. Capps.

Mr. Buyer, you are now recognized for questions.

Mr. BUYER. Thank you.

I apologize I was not here for all of Mr. Greenwood's questioning, so I did not get to hear your responses on human subject research protections.

Mr. ZERHOUNI. Yes.

Mr. BUYER. I took that issue on with the VA, and we have institutes, from oversight with that. I remember some testimony at our hearings relative to perhaps even a need that whatever we do at NIH we really should do for everyone so we are all on the same sheet of music. and I would only invite—I suggest that you invite as you go into this process everyone who is in government that does these types of clinical researches, that we all really get on the same sheet of music. Does that sound like a good idea?

Mr. ZERHOUNI. It is a terrific idea. We support your idea. We have actually implemented this harmonalization effort Mr. BUYER. I just wanted that harmonization to be beyond you.

Mr. ZERHOUNI. Yes, it is. It is.

Mr. BUYER. Okay.

Mr. ZERHOUNI. We can give you the details of how we go about it.

Mr. BUYER. All right.

Mr. ZERHOUNI. But it involved the VA, it involved the Department of Defense. And, as I said, I am co-chair of the Committee in Science under Dr. Marburger, and we have brought that up.

Mr. BUYER. That is great.

Mr. ZERHOUNI. We have a trans-agency look at it.

Mr. BUYER. All right. That is wonderful.

The other is you captured my attention because of my work also with the VA and DoD with regard to information technology architecture and how costly this is to integrate these systems not only by hardware and software. So my question goes to what is your cost assessments to implement your architecture?

Mr. ZERHOUNI. Right now our cost assessment is about $233 million over 5 years. Our goal, obviously, is not to pay for all the systems. For example, this year we invested about $8 million to create a single language that all clinical data will be recorded under, it is called SNOMED. We had seven before. So we have basically made this software off the shelf available for free to all clinical investigators who want to use that.

The second is the idea of web-based standards. So what NIH wants to invest in are the common technologies that are needed, but we have also worked with the VA because the VA actually has a very good system called VISTA, and we want to enhance that system and work with them to make it a platform that everybody can use. But the number is $233, million if I am correct.

Mr. BUYER. But right now what you have are multiple stovepipes that really cannot communicate well with each other, correct?

Mr. ZERHOUNI. Right. Correct.

Mr. BUYER. Our goal is to be able to have everyone deal with——

Mr. ZERHOUNI. Talk.

Mr. BUYER. Communicate, share informations, correct?

Mr. ZERHOUNI. Right. And doing it while protecting privacy. You see, one of the reasons why you need a system that is dedicated to clinical research is this issue of patient privacy. And right now what you have are multiple systems, different languages, no firewalls and privacy is very hard to protect. By doing what we are doing, we think it will enhance the protection and the privacy protection by having sort of a security strategy for the data that is common across all clinical research.

Mr. BUYER. Well, I am surprised you can do this at $200 million. I mean, when I compare what this cost us in the VA to do this integration for seamless with the DoD, this is well over a billion.

Mr. ZERHOUNI. Right. We are not paying for the computers. We are using what is available today. We have already invested quite a bit of money on what we call Abilene 2, which is the high-speed Internet. And we are investing in the infrastructure for Abilene 3, which will mean that all academic institutions will have access to a high-band width, high-speed Internet. So we are not making the investments in terms of the institutions themselves. The VA has to pay for all of that, we do not. The institutions already have systems in place. What we need to populate them with is common software, common standards and interoperable systems.

Mr. BUYER. Well, I compliment on your goals and for willing to take something as complicated as this on. I think it will pay great dividends down the future. I really believe that. So I compliment you for taking that on.

I switch gears to a subject about sexually transmitted diseases, because I do not always get a chance to talk with you. In some reading that I had done, and this really surprised me so I did a little more research on genital herpes. And what really surprised me was, and this is of the CDC website, results of a nationally represented survey shows that genital herpes infection is very common in the United States. Nationwide at least 45 million people ages 12 and older, 1 out of every 5 adolescents and adults have genital HSV infections. Between the late 1970's and early 1990's the number of Americans with genital herpes infection increased 30 percent. To me that was pretty shocking.

And I suppose if I can continue to read on VD and gonorrhea and other sexually transmitted diseases, I would probably still be as shocked.

So my question is this, and I notice you do your decisionmaking processes and a lot of your funding goes to diseases for that which are life threatening. But I do not know how you define an epidemic. If we have a population where you have one out of every women are infected with this type of disease and men and it is growing at this rate, is it prudent for us to take a look at investments to go after this virus?

Mr. ZERHOUNI. I think you have put your finger on something that we have also said in our response. There are 65 million Americans suffering from sexually transmitted diseases of one kind or another, increasing by 4 million a year in teenage age. We have an issue. We have a public health issue.

Most of our investment, as you guess, is in the HIV/AIDS prevention area. That is where some of the knowledge comes. HPV is an-

other sexually transmitted disease that is also related to cancer of the cervix, so we have connections there.

There is no doubt that we have to have a comprehensive national strategy. CDC is obviously concerned. We have seen an increased rate of syphilis across the country. And we are also seeing increasing sexually transmitted disease in the senior population. So we do have an issue.

Mr. BUYER. So do we have such a plan? Do we have such compliments of approach? Are you going to turn to Congress and ask us to fund such a thing, or where are we in this?

Mr. ZERHOUNI. There is tremendous amount of research already done on that.

Mr. BUYER. Is there?

Mr. ZERHOUNI. Yes.

Mr. BUYER. All right.

Mr. ZERHOUNI. Both by medical and by behavioral research, and we need both. Because in many ways these are issues that relate to the environment of the individual as much as the physiology or biology of the disease.

Mr. BUYER. When you think of 200 million people in our country and if 65 million are infected, if that is not an epidemic, I do not know what is, right?

Mr. ZERHOUNI. It is.

Mr. BUYER. Would you concur?

Mr. ZERHOUNI. I concur.

Mr. BUYER. All right. Well, I look forward to going a little further on this issue with your expertise. Not only yours, but those for whom you can share with me.

Mr. ZERHOUNI. Sure.

Mr. BUYER. All right. Thank you, sir.

Mr. GREEN. Thank you, Mr. Buyer.

I recognize myself just for one question.

Now, it is pretty clear Congress has great interest in NIH. It is indicative of the fact that almost every year Congress continues to raise the amount of money appropriated to NIH. My concern over the years is that we got too interested and tried to meddle too much inside of how sometimes you use that money. But we do have some oversight responsibility here. So I hope that is not construed as meddling, but we do have a responsibility, too. And with that thought in mind, the clinical research initiatives that you have going on, how would you recommend that Congress measure the success that you are having in these incentives. I mean, how do we—we have to, we should, we want to know are you doing good, doing bad, where are we? How should we measure that?

Mr. ZERHOUNI. That is an excellent question. Basically our approach is to look at the disability rate in a particular disease condition. For example, one thing that we track is the disability rate of seniors over the years. We have done this for 20 years. You can see from the statistic that because of drugs that we have developed against osteoporosis, the drugs that we have now developed against arthritis; that if you look at the disability rate of our seniors, we should have now in the country, if nothing had been done since 1982, almost 10 million seniors with a disabled acquired condition.

We are at 7 million. So you can tell from tracking the data that that is what is happening.

Other areas the opposite is true. For example, if you look at coronary heart disease, we can show you over the years that if we had not done anything, we would have 1.3 million people dying this year from coronary artery disease and heart attacks. We have 500,000. But what has happened also is that you now see increased prevalence patients who have what we call cardiac failure from aging or hypertension.

So you have to keep track in a systematic fashion of the disease burden, and this is something that the CDC is working on to develop measures of burden rather than how many—because in the context of chronic disease and like acute diseases, like in cancer, you can measure mortality. Now in cancer it is not mortality that is important, it is survival.

So I think we need to have an explicit discussion between the agency, Congress, the public, everyone to say what measures can we develop that will track now chronic diseases over the years?

We have done terrifically well, as you know, in stroke for example. We have reduced the amount of stroke. Hypertension we are doing well, but not well enough. Only 58 percent of the patients who should receive the medications that they should receive them.

So we have a multi-factorial measure that you need to have and we need to develop for you so you can tell what the progress is.

Mr. GREEN. Well, you imply that you agree and think that we should do that. How do we convert that into action? I think it would help Congress greatly to have a measurement like that sooner rather than later.

Mr. ZERHOUNI. We have many measures in the main diseases. We do not have them all across-the-board. But certainly perhaps one thing we could start doing is to have a more explicit way of representing them to you.

Mr. GREEN. Doctor, thank you very much for your testimony. We appreciate your time and effort into this. And you are dismissed. Thank you.

And if the other panel will seat itself.

Gentlemen, I know that you do not have time to waste, and I apologize for the 45 minutes that has gone back by as we cast some really important votes. But all of us are very impressed that you are here and appreciative that you are here. And I think that I am absolutely amazed at who we were able to get here for this particular hearing. We have got a table full of good folks out there, and I am anxious personally to hear you and get your statements into the record.

So, Dr. Barron, let us start with you. And you are now recognized for your statement.

Does everybody want to work at Genentech?

STATEMENTS OF HAL BARRON, CHIEF MEDICAL OFFICER, GENENTECH; ROBERT J. BEALL, PRESIDENT AND CEO OF THE CYSTIC FIBROSIS FOUNDATION; AND EUGENE BRAUNWALD, HARVARD MEDICAL SCHOOL, ON BEHALF OF THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES

Mr. BARRON. That is what I hear.

Good morning, Mr. Chairman, and thank you for the opportunity to testify here before this subcommittee.

The task that I think I have been asked to perform today is to talk to you a little bit about the clinical trials in the drug development process within a different model, that is within the biotech industry. What I would like to do is go over three specific ideas, concepts that drive what we do at Genentech, as I think that it is a model for a lot of different biotech and some pharmaceutical companies.

Just as introduction, my name is Hal Barron. I am a cardiologist and the Chief Medical Officer at Genentech responsible for both the preclinical component of drug development as well as the clinical piece.

I thought what I could do is describe to you the drug development process from its beginnings in the research arena and follow it through the various stages that ultimately translate into a therapeutic for patients. Tell you a little bit about the exciting, what we call, pipeline. The molecules that are in the development phase and have recently been approved, and show you as an example how that has resulted from great science from bench to bedside. And finally, just comment a little bit on the discussions this morning from Dr. Zerhouni about how we see the great accomplishments of the NIH complimenting the work that we are doing.

So just to begin, the efforts that we put forth in drug development really start in the discovery phase. Our scientists come up with an idea of what we call a hypothesis about how a drug might work and begin to test it in various animal models to try, in many respects, to disprove their idea so that we can actually weed out those bad ideas and find the ones that are most exciting to move forward.

The Genentech scientists are one of the most prolific in the biotechnology industry, publishing at a rate of almost a paper a day in peer review journals. They are considered some of the best researchers in the world as reflected by the number of citations that they get in the published literature. They have secured over 4300 patents to date and have another 5,000 pending.

And our research complex, which is over 500,000 square feet, is the single largest biotech facility in the world.

The projects, although most do not make it out of the research setting, once they do, once the data is compelling enough, move into the clinical development arena where we perform numerous clinical trials on the molecules to determine whether they are both safe and effective in the indications that are being studied. We do this in collaboration with other industry, with collaboration with academics and many trials are designed and developed within house.

Currently the process that I just described has resulted in 13 molecules that have been approved and around 30 or 35 projects that are in our development portfolio right now. I just thought I would highlight three recent approvals, which is really to your question earlier. Our metric for success is how many of these ideas ultimately 10 or 15 years down the road get approved and translate into therapeutics for patients. And in the last 10 months, we have

actually had three which is for us, and for any biotech, is a remarkable accomplishment.

About 10 months ago we had the approval of a drug called Xolair, which is a monoclonal antibody, which is one of our focus areas that it basically blocks the interaction of molecule with its receptor by binding to it. And these monoclonal antibodies can be developed to virtually any antigen that we identify as being in a process that involves a disease.

In asthma, research has defined that the elevations of a molecule called IGE are central in the disease process. And by blocking that with an antibody to IGE, we were able to intervene in patients with asthma and reduce their incidence of asthma severity. That was approved, as I mentioned in June.

Raptiva is another drug that intervenes on a central pathway in psoriasis where it has been known for a while from research that we have done as well as at the NIH and academia, that the T-cells, immune cells in the body which are in the blood vessels marginate and move into the skin and cause placque psoriasis. By blocking that through this antibody that centrally targets that mechanism, we have been able to make major advances in psoriasis.

And most recently, just several weeks ago we had approval of an antibody against one of the most important proteins that a cancer makes that blocks cancer's ability to form blood vessels and therefore it starves, if you will, a tumor. And this molecule called Avastin is approved for the treatment of Metastatic colon rectal cancer where it was shown in clinical trials to improve survival.

So these recent studies as well as numerous other studies treating macular degeneration, the leading cause of blindness, looking at various other cancer therapeutics to target, prostrate, ovarian, lung, breast and other typical cancers that affect patients and a whole slew of immunology products that are developed to specifically target patients with lupus erythematosus, rheumatoid arthritis, MS and other diseases.

Just because I am running out of time, I just wanted to conclude with some final remarks about how we think we can best with the NIH. There has been quite a bit of clinical research—I'm sorry.

Mr. GREEN. Mr. Barron, I am not going to cut you off at 5 minutes. If you need a few more minutes, please not.

Mr. BARRON. Okay. Well, then I will make one more comment before I conclude.

I think there are two things that really drive some of the same themes that Dr. Zerhouni's sort of described in his talk. And that is that we really strive to do three things at Genentech. One is to really develop new chemical entities that are novel. We are not in the business, nor do I think most biotech companies are in the business of developing "me too" drugs as they are called. These are intended to be novel therapeutics for major unmet medical needs as he describes and virtually all of what we do.

The second is to really follow the science. Many people thought the whole story with Avastin and inhibiting blood vessel growth was not going to translate into a reality. And, in fact, we ourselves had a negative clinical trial, a very large phase three clinical trial. But we really followed the science and I think like the NIH, that translated into the success in a different cancer, in the colon can-

cer. And we knew that it would not be active in every cancer, but one needs to really follow the science and strive to improve patient care.

And third, and probably most important from where I sit, is to always ensure that the drugs that we are developing are for unmet diseases and that patient safety is No. 1, as we design these trials.

So I think with that we have had successful drug development. We, as I say, measure ourselves by the number of drugs approved. And having three in the last 10 months and 13 over the history of the company is been a rewarding experience in many different ways.

I think just finally, the success stories that I have just described I think could not have happened without the excellent basic science that has emerged from NIH funded programs. The partnership with the NIH has enabled us to conduct many successful clinical programs that we could not have conducted without that collaboration. As Dr. Braunwald reminded me earlier, even one of our first drugs, Tissue Plasminogen Activator, TPA, was developed in collaboration with the NIH and Dr. Braunwald Graham back in the early 1980's.

We have other examples, including Evastin for kidney cancer, a disease that is a relatively small population but certainly an unmet need that is being done in collaboration with the NCI and a very small disease, but very, very problematic called vasculitis or associated vasculitis that we are doing with the Immune Tolerance Network. and these are just three of many examples where collaborations with the NIH have resulted in fruitful therapeutics for patients.

So in summary, the drug development process at Genentech, although I only highlighted the research and the development component, really is much more complicated. There is the manufacturing, the process sciences, the scale up of small fermentations from research grade material to patient grade material. The quality controls, the regulatory controls. There is a lot of different, in fact thousands of people that work at Genentech just on these areas to enable the discoveries from the clinic to actually translate into a vial that doctors can use to treat patients. And that component is, again, another expertise of us that enables this, as well as the component that comes from the commercial arena where it is the education of the physicians about the data so that it can ultimately be translated into use. But, as I say, none of this could happen without the excellent people that work at the company, the collaborations that we have and importantly and maybe the most important is all the patients who volunteer for these trials and really provide us with the opportunity to learn about this.

So, I will end there.

[The prepared statement of Hal Barron follows:]

PREPARED STATEMENT OF HAL BARRON, CHIEF MEDICAL OFFICER, GENENTECH, INC.

Good morning, Mr. Chairman, and thank you for the opportunity to testify before the Subcommittee on the most important issue of clinical trials. My name is Dr. Hal Barron. I am Chief Medical Officer for Genentech, one of the nation's leading biotechnology companies headquartered in South San Francisco, California. As you are no doubt aware, Genentech was founded in 1976 by Herb Boyer and Bob Swanson, and has the unique distinction of being the very first biotech company. Since 1976,

a robust and productive industry has grown from the foresight, innovation and risk-taking of Dr. Boyer and Mr. Swanson. Genentech alone has discovered, developed and currently manufacture 13 therapies targeted at such unmet medical needs as cardiovascular disease, Cystic Fibrosis and cancer. Last month, the Food and Drug Administration (FDA) approved Avastin, a groundbreaking therapy that reduces blood supply to tumors. This product was approved for the treatment of colorectal cancer and we are in the process of studying whether the drug is active in a number of different cancers.

Ours is a terrific—and unusual—success story. We are a soup-to-nuts company, doing everything from basic research to clinical development to manufacturing to marketing. My written testimony describes for you in detail the myriad steps and challenges present in the discovery, development and manufacturing of breakthrough biologics. My presentation today will focus on one critical piece of the development process absolutely essential to our success—the clinical trials we conduct with our patients. I am delighted to have the chance to discuss with you Genentech's rich experience in drug discovery and development, our experience with clinical trials, and our valuable interactions with the National Institutes of Health (NIH). Also for your edification, I have attached a presentation that provides comprehensive review of our development organization.

Genentech has one of the biotechnology industry's most extensive track record in all phases of bringing new disease treatments to patients—from discovery research through development, commercialization and product operations. With 13 protein-based products on the market for serious or life-threatening medical conditions, Genentech has experience taking a drug from A to Z, transforming the seed of an idea in a lab into a novel therapy for a patient in need. Such a fully integrated approach differentiates Genentech from many other biotechnology companies. Although I won't be focusing on how we partner with other biotech/pharmaceutical companies, Genentech has worked closely with such companies as Xoma, Novartis, OSI pharmaceutical, Amgen, and Roche

DISCOVERY RESEARCH

Research is the wellspring of potential products, and Genentech's research organization is among the worlds finest. Genentech scientists are the most prolific in the biotechnology industry, publishing at a rate of 250 to 300 scientific papers a year, and are among the top one percent of researchers in the world in terms of total citations. In addition, Genentech's scientists have secured more than 4,300 patents worldwide and have another 5,000 pending.

Discovery research at Genentech focuses primarily on three areas of medicine where there is a strong need for safer, more efficacious therapies: oncology, immunology and vascular biology. In addition, Genentech remains open to other projects where the company has significant opportunities to fill a therapeutic void in important areas of medicine. To ensure continued scientific excellence, Genentech opened the Founders Research center, a 275,000 square-foot, $85 million research facility devoted solely to biotechnology, in October 1992. It was dedicated to Bob Swanson and Dr. Herbert Boyer in honor of their pursuit of the promise of biotechnology when they established Genentech 28 years ago in 1976.

In April 2001, the company celebrated its 25th anniversary by breaking ground on the 280,000 square foot expansion of the Founders Research Center. The complex—comprising the existing facility and the new expansion—is the single largest biotechnology research facility in the world, with more than 500,000 square feet of research space containing specialized laboratories and state-of-the-science equipment in several interconnected buildings.

CLINICAL DEVELOPMENT

Genentech uses a rigorous set of criteria, including scientific factors, medical need and market potential, to determine which projects to move from discovery research into development. The physicians, scientists and medical professionals in Development play the essential role of translating basic science into patient benefit. They help Genentech determine which potential new drugs are tested against specific diseases in the clinic and determine how the chosen drug candidates should move through the many phases of clinical testing. Since these therapeutic proteins must be delivered into the body safely, and their effectiveness must be measured and documented in order to secure marketing approval. These scientists leverage their expertise in clinical medicine, clinical study design, epidemiology, bio-statistics and health care economics to design these trials. They incorporate some of the newest technologies such as molecular diagnostics, imaging studies (such as CT and MRI scans) as well as novel biomarkers into these trials as well.

Genentech's development pipeline has both breadth and depth, with projects targeting a range of disease areas across all phases of clinical development. This very broad pipeline requires leadership from the best experts. Our MDs and PhDs come from many prestigious academic institutions such as Harvard, Yale, Stanford, University of California, San Francisco (UCSF) and many other top institutions.

COMMERCIALIZATION

Commercial translates research and development innovations into changes in medical practice that enhance and extend patients' lives. The Commercial team introduces multiple products into new and different markets, directs pre-launch commercial development activities, and utilizes cutting-edge sales approaches. The Commercial organization is also involved with development activities that bring forward products in the pipeline in the most efficient way to meet the demands of the market and the healthcare community—directing market research, sponsoring medical education efforts, and developing a leading patient reimbursement program. The Commercial team's unique consultative education, sales, marketing, and distribution models have resulted in 13 successfully marketed products to date and have made Genentech a valuable and sought-after partner.

PRODUCT OPERATIONS

Biotech's rich promise is only truly fulfilled when its scientific breakthroughs are transformed into safe, effective therapies and made available in quantities sufficient to treat all those in need. This extremely complex and demanding task is the responsibility of various product operations groups in the company, including Process Sciences, Engineering, Quality and Manufacturing.

PROCESS SCIENCES

At Genentech, the transition from laboratory production to full-scale manufacturing is the work of the Process Sciences group. This group is made up of five divisions: Cell Culture & Fermentation R&D, Recovery Sciences, Analytical Chemistry, Pharmaceutical R&D, and Manufacturing Sciences. The Cell Culture group grows increasingly larger and more efficient cultures of cells that produce the desired protein. Recovery Science extracts and purifies the protein molecules from the cell cultures, with the goal of both high yield and high purity. Analytical Chemistry is the function that checks to ensure the purified protein is the right one, and that it is active and able to be made into a medicine. And Pharmaceutical R&D determines the formulation—or recipe—for the final medicine, how it should be administered and its packaging. Finally, Genentech's Process Sciences group works closely with the FDA to ensure an approved manufacturing process is in place and pure product is available to patients upon approval of new pharmaceuticals.

QUALITY

The Quality group is comprised of two main areas: Quality Control, which executes the many different procedures for testing Genentech's products; and Quality Assurance, which evaluates all documentation to determine whether each procedure was completed correctly. Genentech strictly adheres to federal requirements for quality and collaborates with the FDA to ensure its processes are of the highest standards. Every medicine that leaves Genentech has been subjected to stringent standards and procedures to ensure its quality and purity.

MANUFACTURING

Genentech was the first biotechnology company to scale up protein manufacturing successfully from the small quantities used for research to the much larger quantities needed for clinical trials and marketing. With state-of-the-art facilities in the United States and Europe, the company continues to be a world leader in the manufacture of human bio-therapeutics, processing approximately three million liters of product annually for clinical research and the marketplace through a variety of fermentation and proprietary purification processes.

In 1998, Genentech completed its second manufacturing facility in Vacaville, California. The largest multi-product biotechnology manufacturing facility in the world, the Vacaville plant occupies 420,000 square feet on 100 acres. It became operational in 1999 and received FDA licensure in April 2000. Also in April 2000, Genentech further expanded its manufacturing capacity with the purchase of a cell culture manufacturing facility in Porriño, Spain. When renovated and licensed, the facility will supplement Genentech's existing bulk cell culture production capacity.

THE NIH AND DRUG DISCOVERY AND DEVELOPMENT

It is these many complex and interrelated steps that explain why the vast majority of drugs approved for patients have been discovered and developed by companies like Genentech. As a research-intensive company, we learn a great deal from the basic research conducted by the NIH. The NIH performs this function extremely well and we support and appreciate the continued increases in funding you have given the NIH over the past several years. In addition, we partner with the NIH on clinical trials particularly in areas outside our area of expertise or where trials could not be conducted without NIH support. This collaboration is extremely important as Genentech or any company for that matter, cannot do everything alone and we greatly benefit from the expertise of the NIH and academia in general.

The opportunities for industry/government collaboration have been fruitful and could be even more substantial. One area in which the NIH is particularly well suited to make important advances is that of molecular diagnostics and discovery of novel "bio-markers"-markers that identify which patients with a given disease have the worst prognosis. Advances in identifying biomarkers presents a real opportunity to benefit patients at a much faster pace than today's R&D efforts, and is an area that could enable industry to be more successful in their endeavors to bring targeted therapeutics to market.

In addition, there is an opportunity for industry to work with the NIH in developing drugs for indications that the company decides not to pursue. It is clear that a company such as Genentech cannot design and implement all the necessary clinical trials to maximize the benefit of their new therapeutics. Thus, certain patient populations may not always be examined. Whether it is because the trials will take too long, represent too small a population or fall outside a company's focus area, providing the NIH access to our novel therapeutics can and has been invaluable. We hope such activities continue to be funded as they have the opportunity to make a significant difference in patient care.

I hope that this presentation has given you a better understanding of the processes and challenges we face in bringing new, breakthrough biologic to market for patients. I hope you also have a better understanding of the relationship between the NIH and private industry. We look forward to exploring these and other partnership opportunities with Dr. Zerhouni and this Subcommittee. Thank you again, Mr. Chairman, for this opportunity to testify before you and the Subcommittee. I am happy to answer any questions you may have.

Mr. GREEN. Thank you very much, Doctor. And you are the CMO at Genentech and have all the way from California. And you need to understand we are grateful for your efforts to be here.

Mr. BARRON. Thank you.

Mr. GREEN. Mr. Beall, Robert Beall, President and CEO of the Cystic Fibrosis Foundation. I was talking too fast there. That is hard for a southern, too.

We are delighted you are here and we look forward to your testimony. And you are now recognized.

STATEMENT OF ROBERT J. BEALL

Mr. BEALL. Thank you.

As you said, I am the President and CEO of the Cystic Fibrosis Foundation. This is a private, nonprofit voluntary health organization dedicated to find a cure and control for cystic fibrosis.

It is particularly an honor for me today to be able to have the opportunity to follow Dr. Zerhouni, because we believe that he has inspired some great vision for the NIH. And it is a very critical juncture that at the NIH that we are all looking at through your efforts and through the NIH, and through the voluntary health organizations in academia.

I actually spent the very part of my own professional career at the NIH, and I can tell you that under Dr. Zerhouni's leadership and vision, I have never been more optimistic about the future role

of the NIH and how it can play a great part improving the quality of life and length of life for all Americans.

We believe the changes that are set forth in the Roadmap are necessary to ensure that the NIH continues to be the biomedical research leader that we expect of it in the 21st century.

In the last decade, the Cystic Fibrosis Foundation has reengineered its own research approach to ensure the success of our mission to cure this genetic disease, cystic fibrosis. And as Dr. Zerhouni mentioned in his comments, we have created a model infrastructure of basic and clinical research to promote and accelerate the development of new therapies to treat cystic fibrosis. With the discovery of our CF gene in 1989 and the increased understanding of the pathogeneses of this disease, we made a big leap in the 1990's of translating this knowledge from the lab to the bedside.

As a result of our comprehensive approach, we now have nearly two dozen drugs that are in clinical trial. This is our metric for success at this point. Any one of these drugs could have a major impact on the quality of life and the length of life of CF patients and more importantly, to provide for the ultimate cure for cystic fibrosis.

I would like to share with you a few points about the lessons we have learned in this process that may be appropriate something that we can think about as the NIH Roadmap moves forward.

The first thing is that it is mandatory that new cutting-edge technologies like high-throughput screening, proteomics, structural genomics be utilized to expedite discovery of new and novel compounds. During the past 5 years, our organization has committed more than $100 million to apply these technologies to cystic fibrosis. It used to take 2 or 3 days for a single chemist to be able to evaluate one or two compounds. We can now screen more than 20,000 compounds per day to see if they might be the drugs of the future for CF. In fact, we have identified several lead compounds for CF that we hope will enter clinical trials within the next 18 months. None of these compounds would have been discovered were it not for the application of these incredible new technologies for cystic fibrosis. The Roadmap's focus on new technologies could be just as fruitful.

Second, creative mechanisms must be put into place to entice the biopharmaceutical industry to develop drugs for orphan diseases like cystic fibrosis. With the cost of development drugs approaching the billion dollar level, many companies are not willing to make the investment needed for orphan diseases like cystic fibrosis. As a result, our foundation has made commitments to companies for up to $25 million to reduce their financial risk and to help them develop CF drugs. Most of the drugs that I mention in our pipeline are the efforts of these financial alliances between the foundation and without biopharmaceutical partners. NIH should join forces with the private sector nonprofits to facilitate orphan drug development for diseases like cystic fibrosis and other orphan diseases.

Third, clinical trial networks are essential for coordinating the clinical research efforts of industry, academia and the Federal Government. In 1998, we established our own clinical trials network that now includes 18 centers, linked by the web to a coordinating

center at Children's Hospital and Regional Medical Center in Seattle. The CF Foundation's Therapeutics Development Network has played a major role in bring biopharmaceutical companies into the area of cystic fibrosis.

Equally important, the network facilitates access to the CF patients who are absolutely eager to participate in safe, well-designed clinical trials.

Since this network was established, nearly 30 clinical trials have been completed or underway. We are grateful to Genentech for showing us the need for these networks as we worked with them very closely in the early 1990's in the development of Pulmozine, which is now being used by over 18,000 patients with cystic fibrosis.

Our work to bring new drugs to people with CF and the successful improvements in the health of the CF population really reaffirms Dr. Zerhouni's vision for the NIH. There comes a time in any research organization when the accumulation of knowledge is not an end in itself. Efforts must be made to translate this knowledge into treatments for people with disease.

The CF Foundation is very fortunate to have a productive relationship with several institutes and centers at the NIH. The future at NIH is critical to all of us.

Certain changes at the NIH would clearly strengthen its ability to advance clinical research. Clearly the Roadmap addresses most of these issues, and we endorse its aggressive implementation. We strongly encourage the Congress to provide Dr. Zerhouni with the resources and the authorization and the support to capitalize on the potential of the Roadmap.

Toward that end, the CF Foundation's recommendations for the NIH include:

An increase in the NIH's role in the discovery and development of new drugs for orphan disease.

We encourage the improved training of clinical researchers and the recognition that clinical research is a viable career in academic medicine.

We encourage the establishment of special emphasis research panels to improve the peer review process of clinical research proposals.

We want to see the increased collaboration among the NIH, amongst academic institutions and private foundations and industry for the support of NIH supported clinical trials network.

And finally, we want to see, and it could be one of the most important, a reduction in the redundancy of bureaucratic hurdles that impede the efficient conduct of clinical trials but in no way facilitate patient safety.

We believe that the NIH must embrace the opportunity to translate knowledge fathered from basic research to assure the development of new therapies.

We certainly thank you for holding these hearings. Congress has reason to be proud of its role in supporting the NIH over the years, and we now feel that you can have a great role in terms of supporting the shape of the future of the NIH and in terms of improving the quality of health care for all Americans during the 21st century.

CF Foundation can serve as a model for clinical research on other orphan diseases. We stand ready to work with the NIH and congressional leaders as they consider these important changes for the future.

Thank you very much.

[The prepared statement of Robert J. Beall follows:]

PREPARED STATEMENT OF ROBERT J. BEALL, PRESIDENT AND CEO, CYSTIC FIBROSIS FOUNDATION

Good morning, Mr. Chairman and Members of the Committee. I am Robert J. Beall, Ph.D., President and CEO of the Cystic Fibrosis Foundation, a private non-profit foundation with a mission of finding a cure for cystic fibrosis (CF). It is a great pleasure to appear before the Committee today to discuss the research approaches that the CF Foundation has adopted, and it is certainly an honor to appear at this hearing with Elias Zerhouni, M.D., who is providing strong and creative leadership at a critical juncture in the history of the National Institutes of Health (NIH).

In the last decade, Congress has generously increased funding for NIH. Between fiscal years 1999 and 2003, Congress accomplished the impressive goal of doubling the NIH budget. The substantial funding of NIH contributed to significant advances in basic research, including the mapping of the human genome, and deepened our understanding of a number of diseases.

It is now vital to assess our ability to translate the basic research advances of the last decade into treatment advances. The CF Foundation has, in the last decade, reformulated its own research approach to encompass many types of research, from basic research through Phase III clinical trials, and has created the infrastructure required to accelerate the development of new CF therapies. As a result, we now have a pipeline of nearly two dozen potential therapies that are being examined to treat people with CF. We applaud Dr. Zerhouni for undertaking a meticulous review of NIH, its structure, and its methods of funding research, as we believe progressive changes are necessary to ensure that NIH continues to be the biomedical research leader of the 21st century.

LIVING WITH CYSTIC FIBROSIS

Before I present the CF Foundation's comprehensive approach to research, I would like to describe CF and its effects on the individuals living with the disease. Each year, 1,000 children in the United States are born with CF, and there are about 30,000 Americans living with CF. In 1989, CF Foundation-supported researchers discovered the gene that is altered in CF, and since that time our fundamental understanding of the disease has improved significantly.

The defective CF gene causes the body to produce abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. The thick mucus in those with CF also can obstruct the pancreas, preventing digestive enzymes from reaching the intestines to break down and aid in the absorption of food.

The common symptoms of CF include chronic cough, wheezing or shortness of breath, excessive appetite but poor weight gain, and greasy, bulky stools. CF symptoms vary from patient to patient, due to the fact that there are more than 1,000 mutations of the CF gene.

CF has been transformed to a chronic disease, but living with CF as a chronic disease requires a rigorous daily regimen of therapy. Treatments for individuals with CF include enzymes that aid digestion, antibiotics administered during bacterial infections and as a preventive measure, and daily therapy to loosen the mucus in the lungs. Several new drugs have been approved in the last decade that have improved the health of people with CF, including Pulmozyme, which thins the mucus so that it can be coughed up, enabling the individual to breathe easier and reducing the chance for infections. Strict adherence to CF treatments improves the health status and quality of life for individuals with CF, but the stringent regimen can be a physical, emotional and financial challenge for patients and their families.

When the CF Foundation was founded in 1955, people with CF often did not live to attend elementary school. Over the past five decades, the median age of survival has improved significantly and is now in the early 30s. This improvement in the life expectancy for those with CF can be attributed to research advances, which I will discuss in some detail later, and to the teams of CF caregivers who offer specialized care of the highest quality. The CF Foundation supports a nationwide network that includes 117 CF care centers at large academic and medical institutions,

and a number of smaller affiliate care centers, as well as nearly 85 programs that are focused on the care of adult patients who are 18 years and older. The CF care center network ensures that information about advances in care can be immediately disseminated to all CF caregivers who provide cutting edge care to the more than 90 percent of the individuals with CF who receive care at these centers. The care center network also functions as a training ground for those who seek careers in CF care or research. Together, Dr. Zerhouni has referred to this as the CF "community of research," as the CF community works to bring research to the bedside to improve care.

THE RESEARCH MISSION OF THE CF FOUNDATION

The cornerstone of the CF Foundation's effort has been to quickly put into place the critical elements necessary to translate basic research knowledge to new therapies. I'd like to share a few points with you today about lessons learned by the CF Foundation which may be appropriate for the NIH as it moves forward in the Roadmap effort.

We believe that the key to finding the cure for CF, and improving the quality of life of those with the disease, lies in the CF Foundation's research program. There are several key elements to the CF research program that are making it successful:

1) *An aggressive program to discover potential CF drug candidates.* Although the discovery of the CF gene in 1989 was an important step forward, there is still much to be learned about the disease. As a result, the CF Foundation continues to invest in basic research on CF to deepen our knowledge of the disease and to understand how we may intervene in the disease course. During the past five years, we have committed more than $100 million for cutting-edge technologies to aid in the discovery of new compounds for CF. We have now identified several lead compounds that we hope will begin clinical trials in CF in the next 18 months. None of these compounds would have been discovered without the application of these cutting-edge technologies.

2) *Establishing a clinical trials network.* The CF Foundation established a network for clinical trials, called the Therapeutics Development Network (TDN), in 1998 specifically to work with industry to pursue new treatments for CF. The network is a critical enticement for industry to focus on CF, as its leaders provide expert advice on trial design and its very structure facilitates patient recruitment. The usefulness and efficiency of such a network were demonstrated through collaborations in the early 1990s with Genentech, Inc. on the development of Pulmozyme and with Pathogenesis (now Chiron) on the development of TOBI. The network links key CF clinical research centers with a centralized coordinating center at the Children's Hospital and Regional Medical Center at the University of Washington at Seattle. Expanded twice, the network now includes 18 centers across the country to further enhance recruitment, while building on the core features of centralized data management and analysis, and a coordinated system of data safety monitoring with disease-specific expertise for protection of patients. Since the TDN was put into place, nearly thirty clinical trials—including Phase I, II, and III trials—have been completed or are underway. Anyone of these drugs in clinical trials could have a major impact on the disease or provide an ultimate cure.

3) *A matching awards program for companies to develop CF therapies.* Because CF is an orphan disease—with fewer than 200,000 persons affected—it presents companies developing new drugs a smaller possible financial return than other diseases. To encourage companies to become engaged in CF drug development, the CF Foundation established the Therapeutics Development Program, which includes awards to companies to undertake research and development of promising drug candidates. We established financial collaborations with biotechnology and pharmaceutical companies to bring them into the field of CF. These commitments, ranging up to $25 million, help companies reduce their financial risks in order to focus on CF. Most of the drugs in our current pipeline would not be tested in CF patients were it not for these initiatives.

4) *Evaluation of existing drugs to determine their utility in treatment of CF.* While the CF Foundation pursues strategies for the development of new CF treatments, it simultaneously employs a "low-hanging fruit" approach, investigating new uses of drugs that have been approved by the Food and Drug Administration (FDA). This strategy has already proven successful, with the completion in 2002 of a Phase III trial that tested the use of the oral antibiotic azithromycin in individuals with CF who had chronic Pseudomonas aeruginosa infections in their lungs. The results of the trial, coordinated by the TDN, showed that those who received azithromycin three times a week for 24 weeks experienced improved lung function, gained weight, and spent only half as many days in the hospital as those who received a placebo.

OVERHAULING CLINICAL RESEARCH AT CF FOUNDATION AND NIH

Our efforts to bring new drugs to people with CF reaffirm Dr. Zerhouni's vision for the NIH. There comes a time in the history of any research organization when the accumulation of critical knowledge must be translated into treatments for people with disease. The NIH Roadmap provides the opportunity for the NIH to do this. However, unless the NIH takes an active role in translation, many of the diseases for which we now have identified the gene and possess a strong understanding of their pathophysiology will never be researched, as few organizations have the financial resources to exploit the basic research opportunities to find new therapies.

When the CF Foundation undertook the establishment of the CF clinical trials system in 1998, we asked several fundamental questions about the status of the CF research effort and our ability to translate basic research findings into new CF treatments. When we read the NIH Roadmap at the time of its release in September 2003, we found that NIH, under the leadership of Dr. Zerhouni, had asked the same basic questions about the NIH. Those questions were: 1) What are today's scientific challenges? 2) What are the roadblocks to progress? 3) What do we need to do to overcome those roadblocks? and 4) What can't be accomplished by any single Institute—but is the responsibility of NIH (or the CF Foundation)—as a whole?

The answers to those questions—as they applied to CF research—led us to the determination that we had to form the TDN to streamline CF clinical trials and accelerate the translation of basic research into new treatments. We are pleased that the team that worked on development of the NIH Roadmap reached a parallel conclusion—that the clinical research enterprise supported by NIH must be re-engineered. The Roadmap recommends the integration of clinical research networks, improvements in the training of the clinical research workforce, and the development of core services for translational research initiatives. The CF Foundation applauds Dr. Zerhouni for undertaking a thorough evaluation of NIH and assembling a team to assist in the redesign of key NIH clinical trial programs.

We believe lessons learned in the CF Foundation's TDN will be instructive as NIH proceeds with establishing clinical trials networks and will provide special insights regarding the most efficient means of conducting clinical trials on orphan diseases. Supporting orphan disease research must be a central tenet of NIH, as few in the private sector can undertake this difficult and costly work.

THE PARTNERSHIP BETWEEN CF FOUNDATION AND NIH

The CF Foundation has enjoyed a productive relationship with several institutes and centers at NIH. The National Center for Research Resources (NCRR), under the leadership of Judith Vaitukaitis, M.D., appreciated the CF Foundation vision for improving its clinical trials capacity and provided important early financial support for the TDN coordinating center. The support the coordinating center has received is in keeping with the NCRR mission of providing CF clinical researchers the tools they need for the efficient completion of their studies, and we look forward to a continued strong relationship with NCRR.

A number of basic and clinical CF research projects have received support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI), and research on the human genome—of tremendous importance to CF—has been supported by the National Human Genome Research Institute (NHGRI). We are very pleased that NIDDK recently released a Request for Applications for Cystic Fibrosis Research and Translation Core Centers to support both basic and clinical research on CF. As envisioned by NIDDK, the Core Centers will provide shared resources to support research to develop and test new CF therapies and will foster collaboration among strong CF research centers.

While the CF Foundation is fortunate to have incredibly dedicated volunteers who are willing to raise significant dollars to support the mission of finding a cure, this undertaking cannot be successful without a strong partnership with the NIH. All of these relationships with NIH institutes and centers are critical to our efforts to advance CF research.

RECOMMENDATIONS FOR RE-ENGINEERING CLINICAL RESEARCH

We offer several recommendations for reform at NIH. While the CF Foundation has worked productively with NIH, we believe that certain changes would strengthen the ability of NIH to advance clinical research. Most of the issues we identify below are addressed in large part by the NIH Roadmap, and we endorse its aggressive implementation. We encourage Congress to provide Dr. Zerhouni and the NIH with the tools and resources to capitalize on the potential of the Roadmap. In order

to realize the benefits of the substantial investment this country has made in basic research, we must take this enterprise to the next level to benefit Americans living with life-threatening diseases today. Toward that end, the CF Foundation recommends:

- **Improved training of clinical researchers and acceptance of clinical research as a viable career in academic medicine.** A number of blue ribbon panels have reported in recent years the various influences on young physicians that discourage them from choosing a clinical research career. If steps are not taken soon to improve training of clinical researchers and ensure these researchers a means of succeeding in academic institutions, the nation's clinical research enterprise will be crippled.
- **Collaboration among NIH, academic institutions, private foundations, and industry in NIH-supported clinical trials networks.** The CF Foundation has learned, through direct experience, that cooperation among all players must be ensured early in the clinical trials process. The involvement of industry is critical. Moreover, the traditional roles that the players in clinical trials have assumed may not be the most appropriate ones in all circumstances. For example, the CF Foundation chose to fund biotechnology companies, as that strategy appeared to be the best way to stimulate development of a new treatment. Another potential reform is action by academic institutions to streamline their research review processes to ensure that multi-institution clinical trials can function smoothly. We must all work together to facilitate clinical trials so that we can improve the health of our country.
- **The improvement of peer review of clinical research proposals through routine establishment of special emphasis panels.** As noted in the article in JAMA (2004 Feb18;291 (7):836-43), clinical research proposals submitted to NIH fare poorly when they are reviewed by basic scientists who may not have appropriate experience or knowledge to review such proposals. In certain disciplines, special emphasis panels have been established for review of clinical research proposals. We recommend that such panels be established on a more routine basis to encourage appropriate consideration of clinical research proposals.
- **Bureaucratic obstacles to the speedy completion of clinical trials must be eliminated.** Efforts must be made to reduce duplication in the review of trials by institutional review boards (IRBs). Although patient safety must be a primary concern in any clinical trial, the current system of review allows duplication and delay without improving patient protection.

THE FUTURE OF CLINICAL RESEARCH

The CF Foundation is committed to pursuing whatever steps necessary to bring new treatment options to people with this disease. To date, those steps have included funding basic and clinical research; in the future they may encompass other aspects of drug development if public or private collaborations are not forthcoming. Our vision is unswerving, as we have shown that we can fill a pipeline with promising options for patients. We believe the NIH must embrace the opportunity to translate the knowledge gathered from basic research to securing the development of new therapies. Just as the CF Foundation does not have all the answers from CF basic research, we believe it is essential to move forward and to take risks to find new treatments. No lives can be saved without taking risks while at the same time assessing patient safety. And, the risks of not taking such steps are unacceptable to the CF Foundation.

On behalf of the Cystic Fibrosis Foundation, I would like to express my appreciation to the Committee for holding this hearing to discuss the future of NIH. Congress has reason to be proud of its role in supporting NIH, which is the world's leader in biomedical research. The NIH has strong leadership to move into the new century, when we will see the translation of basic research into new treatments for many diseases. We believe the experience of the CF Foundation in clinical research can serve as a model for research on other orphan diseases, and we stand ready to work with NIH and Congressional leaders as they consider changes for the future.

Mr. GREEN. Thank you, Dr. Beall.

And our last distinguished witness today is Dr. Eugene Braunwald, Hersey Distinguished Professor of Medicine and Faculty Dean for Academic Programs, Partners Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Association of Medical Colleges.

And, Doctor, you are here on behalf of the Association of Medical Colleges today.

And you are recognized for whatever time you might consume.

STATEMENT OF EUGENE BRAUNWALD

Mr. BRAUNWALD. Thank you, sir. Thank you for inviting me to testify on this important subject.

Clinical research is the bottleneck through which all scientific developments in biomedicine must flow before they can be of real-world benefit. And the academic community has an essential role to play in loosening this bottleneck, and I am pleased to be here to represent the Association of American Medical Colleges, which I'll refer to as the AAMC.

The AAMC represents the Nation's 126 medical schools, 400 major teaching hospitals and more than 105,000 faculty in 96 academic and scientific societies.

Now, I have conducted clinical research for more than 50 years, and 12 of these years was at the NIH. And since 1972 I have been at Harvard and my own work is in cardiovascular disease.

And the opportunities and the challenges that we face now are greater than they have been at anytime through my professional life. Now the opportunities referred to about all morning, namely that useful life now has the potential of being prolonged and major chronic illnesses such as stroke, cancer, Alzheimer's Disease, mental illness which has not been mentioned can all be ameliorated. And this comes from the landmark developments of genetics, bioengineering, neuroscience; the work that the NIH has done and that has been so wonderfully supported by the Congress.

So that is the tremendous opportunity; to take advantage of this information.

The challenge is to translate it. And if we are unable to translate it, then we will have missed the opportunity. Without a robust national program of clinical research that enjoys the participation of patient groups, that enjoys the involvement of academics, of industry, then the effect on the public health could be quite deleterious, and I am sorry to say that the national program of clinical research is anything but robust right now. And there is a lot of work that needs to be done.

So what is the problem? The problem that we see and one that I encounter in my work everyday, is a lack of coordination among the different pieces. The pieces are very strong, but they are not well coordinated. So there is a fragment of cottage industry which investigators each going in their own directions. There are tremendous inefficiencies. As teams are assembled for specific projects and then they are quickly disbanded when the project is completed and the funding ceases. And you have lost a tremendous amount in that process of putting it together and in breaking it apart.

The regulatory burdens are enormous. And they do not really help and protect patients in the field. I mean, they are well intentioned, but they slow the process down.

The information systems that are used in clinical research, they are based on billing records. And there is no good way of having information systems that ties clinical research together in the way Dr. Zerhouni showed. And basically what we're using now in clin-

ical research are pretty much a gerryrigged system off the clinical record keeping and clinical billing.

Another problem is protecting the integrity of research and fostering the public trust. So we invite subjects to participate in clinical research and it's essential that they have our trust. The AAMC and the member organizations recognize that there's a very special relationship between investigators and their subjects. And that safety of the human participants in trials is of paramount importance. And we need to go beyond the simple compliance and create a culture of conscience that we train our young people in.

Clinical researchers need very clear standards of conflict of interest. And these standards have to be clear and absolute. and it is my understanding from discussions with colleagues at the NIH, that some of the rules have been a little ambiguous. And I think it is important to clarify them, but at the same time it is equally important that industry should not be deprived of valuable information and valuable advice and consultation that can be offered by government scientists and by academic scientists.

Another problem that's faced by clinical research is a shrinking pool of clinical investigators. Now it has been my privilege to train a number of successful clinical researchers over the years. And the route is not an easy one. You have to get an advanced doctoral degree, M.D., then serve an internship, serve a residency, then do a rigorous research fellowship in a specialty. And the first faculty position where you can actually conduct research on your own, is usually obtained until the person is the thirties or the mid, sometimes in the late thirties. And success depends in large part on being able to obtain funding, which in turn depends on the fortunes and sometimes the whims of the sponsoring agency or the sponsoring company.

So Instability of funding coupled with the need to support a family is a tremendous deterrent to talented young physicians who are considering a career in clinical research. And, of course, they are the future and they are the ones we have to find a way of bringing them into the system.

So I think that the answer lies with both research sponsors and academic partners. We have to increase training opportunities. The NIH has done well in the last 3 or 4 years, but it is just a drop in the bucket. We have to provide more mentored programs. We have to expand the Federal loan repayment programs, and I've served on the NIH committee that has done that for the National Health Institute. It is just in its infancy. It is going to have a great impact, but that needs to be supported.

And most important, it is important to provide longer commitments of support so that there is a feeling of stability in a career in clinical research.

So I think that to conclude, I think we need a balance tripartite system for clinical research.

One partner in this tripartite system, of course, is the Federal Government, which supports clinical research through a number of agencies, the VA, DoD, the Agency for Healthcare Research and Quality and of course the NIH, which is the lead agency.

And the plan that the NIH has developed and that Dr. Zerhouni has articulated is a plan that the AAMC, and I can say that all

of us at the academic institutions around the country support with tremendous enthusiasm. So that is one partner.

The second partner in this trio is academic medicine; the medical schools, the teaching hospitals where the actual research is conducted. And the majority of researches are at these institutions and they are the institutions that train the future clinical investigators. And so I am here representing the AAMC which speaks for these institutions.

Now the third partner who is equally important is industry. And we have the biotechnology industry, the pharmaceutical, the informatics industry. And they provide ideas, resources and expertise and without that you cannot really bring a product and make it available to the public.

And the private foundations, as we have just heard, such as the Cystic Fibrosis play a vital role.

So each of these partners has a stake in the success of the other. And they tend to be working in separate directions most of the time. And if it is good for the Federal Government, it has got to have a tremendous impact on the academic institutions which is where the scientists come from that populate the laboratories at Genentech and vice versa.

So I think that getting to the specific case of clinical research, I think that the multiple medical schools and hospitals and clinics have to be tied together in networks and using modern information systems. And these need to be stable networks and they should carry out clinical research that has both industrial, private as well as Federal sponsorships whenever possible.

Then we have stable networks, then they will attract the most creative young minds for long term careers in research. And if we develop a robust clinical research enterprise, then the ultimate win, of course, is going to be the public who have the greatest stake of all in this proceed.

Thank you very much for inviting me.

[The prepared statement of Eugene Braunwald follows:]

PREPARED STATEMENT OF EUGENE BRAUNWALD, HERSEY DISTINGUISHED PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, CHAIRMAN, TIMI STUDY GROUP, BRIGHAM AND WOMEN'S HOSPITAL

Good morning. Thank you Mr. Chairman and members of the subcommittee for inviting me to testify today on this important subject.

I am a Professor of Medicine at Harvard Medical School. I have conducted clinical research on heart disease for almost 50 years, from 1955 to 1968 at NIH, then at the University of California, and since 1972 at Harvard. I have also served as Chief Academic Officer and Faculty Dean at Partners HealthCare, an integrated academic health care system that includes two Harvard affiliated hospitals—Massachusetts General and Brigham and Women's.

Clinical research is the neck of the scientific bottle through which all scientific developments in biomedicine must flow before they can be of real-world benefit to the public. I believe that the academic community has an essential role to play in loosening this bottleneck and I am pleased to be representing the Association of American Medical Colleges (AAMC). The AAMC represents the nation's 126 accredited allopathic medical schools, some 400 major teaching hospitals and health systems, and more than 105,000 faculty through 96 academic and scientific societies. The Association is the most appropriate representative of the academic community in this policy arena because the performance of clinical research is a defining characteristic of medical schools and teaching hospitals. The AAMC membership conducts a very large share of the biomedical and behavioral research performed in this country, and has been the source of many of the dramatic breakthroughs that have revolutionized biology and are transforming medicine. My testimony today will focus

on the role of academia in clinical research and where there is room for improvement.

The AAMC has been concerned about the clinical research enterprise for several years and convened a consensus development conference in 1998, out of which came a broadly inclusive definition of clinical research that led to the conception of a national "clinical research enterprise," and recommendation of actions to strengthen that enterprise. That conference led to the establishment of the Clinical Research Roundtable in the Institute of Medicine (IOM) and an AAMC Task Force on Clinical Research. The Task Force was charged with assessing the opportunities and challenges facing clinical research in medical schools and teaching hospitals, and developing a set of findings and recommendations to strengthen clinical research in those institutions. The Task Force report, "*For the Health of the Public: Ensuring the Future of Clinical Research*" was issued in January 2000. It concluded that the future of clinical research in medical schools and teaching hospitals is synonymous with the viability of their defining academic missions and their commitment to advancing the health of the public. The conclusions of the Task Force still hold true today and my testimony will focus on the ideas generated by the Task Force and the current thinking in this important policy arena.

Too often, clinical research has been considered synonymous with clinical trials. Clinical research is a component of medical and health research intended to produce knowledge essential for understanding human disease, preventing and treating illness, and promoting health. Clinical research embraces a continuum of studies involving interaction with patients, diagnostic clinical materials or data, or populations, in any of these categories: disease mechanisms; translational research; clinical knowledge, detection, diagnosis, and natural history of disease; therapeutic interventions including clinical trials; prevention and health promotion; behavioral research; health services research; epidemiology; and community-based and managed care-based research. This broad and inclusive definition is responsive to the dynamic changes that are taking place within the biomedical and health sciences and in the organization and financing of health care. The support and conduct of this research enable advancements across diverse fields of science to be applied to human health and may well transform the practice of medicine and the delivery of health care in this century.

Both the opportunities and challenges that we face in clinical research today are greater than at any time during my professional lifetime. The basic research resulting from the doubling of the NIH budget and the sequencing of the human genome have provided vast possibilities for improving human health, by improving diagnosis, treatment and prevention. Opportunities now exist to prolong useful life by combating the major chronic illnesses such as cancer, hypertension, stroke, heart attack, arthritis, emphysema, Alzheimer's disease, and mental illness.

Actually, at no time in human history has the potential been greater for translating biological knowledge and technological capability into powerful tools for preventing and treating disease and caring for our communities' health.

However, the landmark developments in genetics, bioengineering, neuroscience, and molecular and structural biology that have occurred during the past twenty years will mean little in practical terms if clinical researchers are unable to translate this science into new and effective medical and health practices. Without a robust and coherent national program of clinical research that enjoys the participation and harnesses the full strength of all components of the health sector, the impact of revolutionary advances in the biomedical and health sciences on the health of the public will be greatly slowed. And the national program of clinical research that now exists is anything but robust or coherent.

The major blocks in biomedical science are now at the interface of basic research and clinical care. The lack of coordination of the clinical research enterprise has led to a fragmented cottage industry of investigators each going in their own separate directions. There are great inefficiencies as teams are assembled for specific projects, then quickly disbanded when the project is completed and funding ceases. Regulatory burdens are enormous and growing; they impose delays, costs, and daunting disincentives on clinical researchers and dissuade many bright young medical graduates from choosing careers in clinical research. Information systems available to clinical investigators and designed to support clinical research are relatively primitive. Most of these systems are based on the financial and administrative needs of provider organizations, and virtually all are inadequate for clinical research.

Advances in information technology will be critical to the future of clinical research and to improvements in health care in the 21st century. The creation of federated, inter-operable databases is essential to help exploit the power provided by the Human Genome Project to enrich our understanding of human diseases, guide

the development of therapeutics and preventives, identify potential subjects for clinical trials, and track long-term outcomes through post-trial and post-marketing surveillance. There is presently a profound lack of public or private investment in technology development in the clinical research arena, perhaps due to the lack of financial incentive; I believe that this is an area of urgent need that should be an attractive target for novel public-private partnerships. Since progress in this area is almost certain to increase efficiency in all aspects of clinical research, it is imperative that academia and the federal government work together to develop principles for the standardization, collection and sharing of research data, as well as a nationally inter-operable clinical research information system that is designed to meet the needs, and exploit the opportunities, now presented in clinical research.

Protecting the integrity of research and sustaining the public's trust is as important a building block for clinical research as other more tangible items such as informatics, molecular libraries, and physical facilities. The AAMC and its members recognize that academic medicine and the American public have forged a special relationship rooted in trust that is nowhere more evident, or more fragile, than in clinical research involving human participants. The safety of human participants in research is of the utmost importance and must continue to be our highest priority. In this regard, the AAMC is pleased to have played a leadership role in recently creating the Association for the Accreditation of Human Research Protection Programs (AAHRPP). AAHRPP is a non-profit entity that the AAMC believes can help to lead the nation's clinical research community beyond compliance to a culture of conscience and responsibility in every investigator, every individual who participates in clinical research, and every supervisor of the research.

To accomplish this will require that clinical researchers operate under a standard policy on conflicts of interest that is clear and absolute. For example, it is my understanding from discussing this issue with colleagues at the NIH that some of the rules have been ambiguous. This ambiguity must be removed, but at the same time industry should not be deprived of valuable advice and consultation, nor academic research of the enrichment provided to both governmental and academic scientists, through appropriate consultative interactions. The recent reports by an AAMC task force on individual and institutional financial interests in clinical research provide a helpful framework for structuring and monitoring such interactions.

In a paper published in the February 18, 2004, issue of the *Journal of the American Medical Association* (JAMA), Kotchen, et al., state "[I]t appears that the greatest threat to clinical research, however, is the relatively small and shrinking pool of clinical investigators." AAMC President Jordan Cohen, M.D., made similar arguments in a November 2003 commentary, stating "the NIH's grand vision will become reality only if we can produce a steady supply of well-trained physician-scientists who are both clinically and scientifically competent, and offer them attractive, stable career pathways."

It has been my privilege to train a number of successful clinical researchers. The route is not an easy one. After obtaining the MD degree, an internship and residency, and rigorous research training in a specialty are required, and a first faculty position is not usually obtained until the persons are in their mid or late thirties. Success depends in large part on being able to obtain funding, which in turn depends on the fortunes and sometimes the whims of the sponsoring agency. Instability of funding coupled with the need to support a family is the greatest deterrent to talented young physicians considering a career in clinical research.

The answer to this problem lies with both the research sponsors and the academic partners. The NIH has been responsive to the recommendations of the 1997 Nathan Report, and has established a number of clinical research training mechanisms such as the K awards and the loan repayment programs authorized by the Congress. We need to continue to increase training opportunities in all areas of clinical research by providing additional mentoring programs, expanding the existing federal loan repayment programs, and most importantly by providing longer commitments of support to the most creative, energetic and humane clinical researchers. Just as important, once they finish their training, clinical investigators must be supported not only with adequate opportunities for funding for their research but also with "nurturing environments" that offer reasonable, long-term career paths.

There are many important tasks ahead in developing a workable clinical research enterprise. One of the first challenges is in the organization of the system. I believe that we need a balanced tripartite system. One partner must be the federal government, which supports clinical research through several agencies, including the NIH, the Department of Veterans Affairs (VA), the Centers for Disease Control and Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ). The NIH, as the lead agency, has developed a visionary plan for clinical research in its Roadmap initiative, a plan that we support with enthusiasm. The second partner

is academic medicine—the medical schools and teaching hospitals where most innovative, hypothesis-driven clinical research is conducted. A large majority of clinical researchers in this country are faculty members and the trainees at these institutions are the future clinical investigators. These institutions are represented by the AAMC.

The third partner is industry—largely the pharmaceutical, biotechnology and information technology industries. Industry provides ideas, resources, and expertise that are essential to bringing a product to market and actually making it available to the public. Each of the three partners has a stake in the success of the other. Stable clinical research networks involving multiple medical schools and hospitals and their patients should be created and tied together with modern information systems, and these networks should conduct research sponsored by both the government and industry. Many projects should have dual sponsorship. The stability and resources of these networks, in turn, will attract the most creative young physicians who are eager to engage in a career of research. After training at our medical schools they can then conduct clinical research in a variety of sites, including academic, industrial and federal laboratories, as well as teaching hospitals and health systems.

The ultimate winner, of course, will be the public, which has the greatest stake in the outcome of this noble effort.

Once again, thank you for the opportunity to testify before you today. I would be pleased to respond to any questions you might have.

Mr. BILIRAKIS. And thank you very much, Doctor.

I am fascinated by your testimony, and I apologize to Doctors Barron and Beall for not being here. It is just amazing the life that we lead here running from hearing to hearing and meeting to meeting, and that sort of thing. You are very important to us and I apologize for the fact that we do not have more members here.

I appreciate Mr. Green returning.

All right. So you have already indicated that you certainly agree with the views, I guess more than anything else, the vision of Dr. Zerhouni in terms of the Roadmap.

Now, Dr. Braunwald, you mentioned the lack of coordination, you have gone into it in many different ways. I would imagine possibly maybe we might have heard the same thing from Drs. Barron and Beall. I do not know. But do you feel that Dr. Zerhouni's Roadmap if implemented, once implemented, will basically satisfy that, will take care of that problem adequately?

Mr. BRAUNWALD. Yes. I think will go a very, very long way, sir. I think that what it is implicit in the Roadmap, though it was not explicitly articulated, is that these networks are going to have some stability. And that does not mean that they should be frozen and never change. But people who work in them have to feel that this is a career; whether the worker is a physician or a nurse. And I think that it is very important to provide them with the authority and then ultimately with the funding so that these are not turned on and off like a water spigot.

Mr. BILIRAKIS. Yes. Dr. Beall, you wanted to add to that?

Mr. BEALL. Yes, I would like to add. As I mentioned in my testimony, we have a network and it is in the coordinating centers in Seattle. We have 39 employees there. We also have 18 sites around the country where we provide core resources so that when a clinical trial stops from one clinical trial, these people do not have to get fired. They do not have to leave. There is a continuity in terms of people. And so we have a carry over of ideas of how to design the clinical trials. And that only provides a value added to when the industry comes to us and it certainly facilitates it.

So I think that these networks, and I think ours has proven to be an excellent network that is all coordinated by the Internet. If a patient comes to us today and undergoes a clinical study today, we add data back. It literally goes back to our network in Seattle, goes to a data safety monitoring board tomorrow and we can have the decision whether or not to move forward for another dose the next day.

So it is a continuity of people and it is taking advantage of the web and it has taken advantage of the great opportunities that we have with bioinformatics now to make it move very efficiently.

Mr. BILIRAKIS. So you are basically satisfied that you are on top of or at least knowledgeable of all the cystic fibrosis clinical research that has taken place at various locations?

Mr. BEALL. Absolutely. We have been very fortunate in that the community has accepted us as the leader. And I think in any kind of a disease, you obviously have to have somebody take a leadership role. And fortunately for us, the basic researchers, the clinical researchers, the caregivers, the parents and so forth have really looked upon the foundation as that organization that will develop a new therapy. So I think we are very blessed.

And fortunately Bill Gates gave us $20 million for our effort——

Mr. BILIRAKIS. That helped.

Mr. BEALL. [continuing] to move forward in some of these things. And he liked our innovative approaches. And we have a great group of volunteers around the country that raise a lot of money so we can make these investments like $25 million or $100 million.

Mr. BILIRAKIS. Well now, and forgive my ignorance, might there be clinical research taking place regarding, let us say, another illness in parts of the country whereby possibly some of the byproducts of that research would be helpful as far as cystic fibrosis is concerned? And if that is possible or probable that that could be taking place, are you sort of cranked into that at all to be knowledgeable of it?

Mr. BEALL. Absolutely. Dr. Zerhouni talked about his clinical trial net that lists all the clinical trials that are going on in the United States and supported by the NIH. And I think those things help us. I think there is a lot more information exchanged than we have ever had before. But as he said, there are a different systems that are out there. But I clearly believe that with the integration of this I think we are all going to be more informed about what is going on. But I do think that with communication, with the availability of papers on the web, access to information quicker than we ever had before, I think we are pretty well informed. But I think we have to consolidate it and get it under the leadership of the NIH.

Mr. BILIRAKIS. Great.

Dr. Barron, the bell just rang again. It is only one vote, but still we are going to have to break. So hopefully we can get through and let you all go.

Did you have anything you wanted to sort of add?

Mr. BARRON. Maybe just one comment to add. I think Dr. Braunwald's point about this being a bit of a tripartite is one to keep in mind.

And while I think the networking theoretically can facilitate exactly what is being described here, I think that in designing the network has to be, I think, ensure that the process does not impede either academia or industry from doing the kind of trials that are needed for the success of all three groups.

So I think if it is viewed as an infrastructure to enable the bottleneck of clinical research to be de-bottlenecked, if you will, then it will provide a tremendous opportunity. I think that to some extent maybe the devil could be in the details when one looks at the issues around how the networks are set up.

Mr. BILIRAKIS. Well, all three of you heard Dr. Zerhouni's testimony and you heard us, basically, pretty well beg for recommendations. Because if we are going to be helpful in this regard, I mean the more information we have the better.

And I am going to turn it over to Mr. Green now. But I would ask you to please, I know you have made some recommendations and whatnot in your written remarks. But anything at all that you can furnish us in writing. There will be questions that we will furnish you and ask for your responses there, too. But anything above and beyond that, any recommendations, whatnot, keep in mind.

You know, are we going to reauthorize or reauthorize NIH this year? I do not know. It is a tough political year. If we do not do it this year, more likely we will do it next year. If we don't this year, probably. So we need your input. And you are the grass—I hate to refer to you as grassroots. But you know you are at that level where you basically see it happening on a day-to-day basis; what regulations that you mentioned, Dr. Braunwald and whatnot. So please feel free to submit any of that information to us because it can be very helpful.

And I would yield to Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman.

I have a question for both Dr. Barron and Dr. Beall, but if I do not get to them before we have to go vote, can we submit them and ask for a response.

Mr. BILIRAKIS. By all means.

Mr. GREEN. Because both, obviously, on the private sector and from the Cystic Fibrosis as a representative of the foundations and the efforts is so important to the partnerships with NIH.

But, Dr. Braunwald, you mentioned in your testimony the factor that influencing shortages of qualified clinical research and the instability of funding. Now, I can imagine the 5 year increases in the NIH budget, did that do something to help with those concerns? And also if it did, then what is the impact of the last—the recent reductions in the increases in funding on having clinical researchers into the system?

Mr. BRAUNWALD. Yes. I can tell you that, you know, working in the trenches, as it were, the growth or lack of growth of the NIH budget has an enormous impact on decisionmaking on career decisions that young people make. And I think before the Congress generously increased the doubling, I think there was a feeling research is not valued and the opportunities were few and although the opportunities for research were great, the career path was not there. So during this period of the doubling, there has been a tremendous feeling of optimism. I think people now are scared again

because they can do the arithmetic, and the arithmetic suggests that if we are flattened at 2 or 2.5 percent, that really represents about a 5 percent decline.

So I think that I can tell you, sir, that this is watched very, very closely by in particularly the young people who have other career choices. And what we are so afraid of is that an entire generation may become lost to this.

Mr. GREEN. The next question I was concerned about it so much of our medical research is done at our academic medical institutions, just like yours. So there are lots of other Federal programs other than NIH, for example Medicare and Medicaid programs that are also part of teaching hospitals, for example. I would imagine that much of the clinical research we are discussing takes place at these hospitals. And when you see cuts in direct or indirect medical education programs with caps on residencies, you also see that as a problem in attracting your researchers.

Beyond the NIH and the Roadmap, what more can the Federal Government do to support the academic medical institutions?

Mr. BRAUNWALD. Well, I think that you put your finger on something very important. If an academic medical institution, if the indirect and the direct calls for education disappear or shrivel, then again it breaks a very important link in the chain, and that is the training opportunity for students and the training opportunity for residents who then go into research. And I think that that is an equally important problem.

Mr. GREEN. Mr. Chairman, I have one more general question, though, that I would like to ask and I know we are within the 10 minutes I guess.

Mr. BILIRAKIS. Why do you not ask it and possibly we can get some very brief responses.

Mr. GREEN. Okay. This is for all the panelists. And, gain, I have specific questions for Dr. Beall and Dr. Barron that I will submit.

and I understand in the NIH Roadmap with respect reengineering clinical research it seeks to foster collaboration among research and emphasize the importance of training clinicians to work in multiple disciplinary and also team oriented environments. While this may indeed help future generations of clinicians, what is being done to foster desired levels with established clinical researchers? And, again, this is a cross whether it be at the academic institutes, whether it be at the non-profits, for example, Cystic Fibrosis, and how they interface with the profit making in, for example, the Genentech. And just in a general does that Roadmap foster that effort to have all of us involved?

Mr. BEALL. I will comment first. I think it does, because I think it does foster the increased relationship between special industry and academics because these networks that we talk about there, the development of the clinical researchers, can only facilitate the entire clinical structure.

It is clearly that the biopharmacuetical industry cannot do what it needs to do without the academic environment. The networks that we talked about being created can only facilitate the ability of Genentech and others to do clinical trials. And I think that that whole process is really being integrated much more in the concept

of the Roadmap because you are going to bring technology people, institutions and companies altogether under a single umbrella.

Mr. GREEN. Dr. Barron?

Mr. BARRON. Yes. I think from the industry standpoint the training that is needed within the company is actually a little different than the training that maybe the academic people need, although the specific training is similar in terms of what is needed for clinical research. and I think part of the problem that exists is having the time for the academic folks to actually take the courses.

I know at the institution I trained, USCF and many other institutions. There is actually training programs to become better clinical researchers. The problem is taking the time for 1 or 2 years to actually immerse yourself in this clinical training requires to be funded for those 2 years. So at Genentech we actually take the time and put the resources toward training of the clinicians that join. So we have about docs and we have specific programs for them. The NIH Roadmap will facilitate the number and quality of these training programs that we can send people to. So I think, as Dr. Braunwald said, it is really just trying to increase the resources really earmarked for training and then putting programs in place to facilitate that will be very advantageous.

Mr. GREEN. Thank you, Mr. Chairman.

Mr. BILIRAKIS. Thank you, Mr. Green. Again, thanks for returning.

Gentlemen, we are so very grateful to all three of you, not only for being here today but for your dedication over the years. Your work, of course, is the magic that we look forward to to keep us well or to get us well, or whatever the case may be. In keeping well, I guess, as Dr. Zerhouni accented is our biggest problem. Take a look at me and how overweight I am. It is just ridiculous.

But anyhow, thanks so very much. And, again, please we would be disappointed if we did not receive—now we are going to furnish you with questions. But in addition to that, if you could just furnish us with suggestions. Put yourself in the shoes of a Member of Congress and see what we can do maybe to help you.

Thank you so much.

Hearing is adjourned.

[Whereupon, at 12:50 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

RESPONSES TO QUESTIONS FOR DR. HAL BARRON FROM HON. JOHN D. DINGELL

Question 1. The mapping of the human genome has been a remarkable accomplishment and already seems to be opening doors for biomedical research. Obviously this is a positive step. But some are concerned about the possibility of generic discrimination. Do you think we need a law to protect people from genetic discrimination?

Response. Genentech has consistently supported legislation and regulations that create federal standards to protect the confidentiality of patient health information, including genetic information. With the implementation of the Health Insurance Portability and Accountability Act (HIPAA) medical privacy regulations in 2003, we believe patients are provided with far greater assurances that any health information created and used in the health care context will not be inappropriately disclosed to insurers, employers or other third parties. As with all law and regulation in this area, it is critical that Congress balance the important goals of protecting the privacy of an individual's health information, including genetic information, while also allowing for appropriate use of certain data for critical research purposes.

Question. The Senate recently unanimously passed S. 1053, a bill to prohibit discrimination on the basis of genetic information with respect to health insurance and employment. Do you support this legislation?

Response. Genentech certainly supports strong protections against discrimination of individuals based on genetic information in both the workplace. It is important for research participants to feel confident in the protection of this information so as to encourage robust participation in clinical research. Genentech worked closely with our trade association, the Biotechnology Industry Organization (BIO), to make significant improvements to S. 1063 to ensure appropriate access to health information for research purposes.

April 21, 2004

The Honorable JOE BARTON, *Chairman*
The Honorable JOHN D. DINGELL, *Ranking Member*
U.S. House of Representatives
Committee on Energy and Commerce
Washington, D.C. 20515-6115

DEAR REPRESENTATIVE BARTON AND REPRESENTATIVE DINGELL: Thank you for your letter with additional questions after the hearing about "NIH: Reengineering Clinical Research."

Question 1. The mapping of the human genome has been a remarkable accomplishment and already seems to be opening doors for biomedical research. Obviously, this is a positive step. Bust some are concerned about the possibility of genetic discrimination. Do you think we need a law to protect people from genetic discrimination?

Question 2. The Seante recently unanimously passed S. 1053, a bill to prohibit discrimination on the basis of genetic information with respect to health insurance and employment. Do you support this legislation?]

Response. In response to your questions about genetic discrimination, we wanted to let you know that we are supportive of legislation to protect people from genetic discrimination in general, and we support of the Senate's bill on this issue, S. 1053.

Cystic Fibrosis (CF) is genetic disease; people with this disease must inherit two copies of the gene to have the disease and individuals with one copy are non-symptomatic carriers. Individuals with CF participated in research, which led to the discovery of the CF gene in 1989. Now, more than 1000 mutations of this gene have been identified. Nearly 80 percent of people with CF have been genotyped; researchers are using the information about the genetic make-up of the disease to identify new treatments or a cure. (add genotyped done . . . in research situation? Or with consent?)

Research to develop gene therapy to treat CF is critical, and the CF community has been on the forefront of this research for much of the last decade. In addition to supporting gene therapy, the CF Foundation has invested in numerous potential therapies based on the genetic defect and the types of mutations involved.

For example, this week we will announce an investment into a product that could impact individuals with the main mutation called DeltaF508. This mutation allows the CF gene to make its protein, but the protein is not delivered to the spot on the cell membrane where it can do its job of shuttling ions in and out of the cells. This product has potential to correct this defect. But it is less clear if it will impact individuals with other mutations. We will send you a copy of the press release/a copy is attached. This is just one example of the types of genetic research we are pursuing to find new treatments based on genetic information.

The CF Foundation believes this legislation is necessary for many reasons. Clearly, the public is afraid of the misuse of genetic information and therefore hesitant to participate in genetic research. This legislation addresses that public fear by prohibiting the misuse of genetic information in the most serious situations—denial of health insurance, and impact on employment. People who are carriers of one copy of the CF gene, but who do not have CF, are most likely to benefit from this legislation. This legislation is a step forward to address inappropriate uses of genetic information about which individuals have no control and which may not impact their health or employability. We believe no one should be subjected to discrimination on this basis.

Legislation to prohibit genetic discrimination by health insurance carriers and by employers can make individuals more secure that their genetic make-up will not be used to harm them. While this legislation does not solve all problems related to genetic discrimination, it makes positive progress to better enable individuals with genetic diseases or risk factors to obtain and retain health insurance and to be treated fairly in employment settings.

We encourage you and the House leadership to take up the legislation banning genetic discrimination. Research holds the key to a positive future and better health. Genetic research holds great hope for the future. If people fail to participate in research because of fear of genetic discrimination or misuse of genetic information to affect health insurance or employment opportunities, critical, life saving research will be undermined and future cures will be delayed if not deterred altogether. This research holds great possibilities to change the future of many individuals now suffering—and dying—from genetic diseases.

The CF Foundation appreciates the invitation to testify before this Committee. We continue to take assertive measures to examine promising new treatments for people with CF through our clinical trials network, and to reengineer the clinical trials process. While the lives of people with CF have improved in the last few decades with the increase in expected life span from early kindergarten to the early thirties today, there is still much more to be done. Your efforts to facilitate oversight of the clinical trials regulatory system and to protect the public from unintended consequences of genetic research advances are key.

Please let us know if you have additional questions.

Sincerely,

ROBERT J. BEALL, *Ph.D.*
President & CEO, Cystic Fibrosis Foundation

cc: The Honorable Michael Bilirakis, Chairman, Subcommittee on Health
The Honorable Sherrod Brown, Ranking Member, Subcommittee on Health

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RESPONSE TO QUESTIONS FOR DR. EUGENE BRAUNWALD FROM HON. JOHN D. DINGELL

Question 1) The mapping of the human genome has been a remarkable accomplishment and already seems to be opening doors for biomedical research. Obviously, this is a positive step. But some are concerned about the possibility of genetic discrimination. Do you think we need a law to protect people from genetic discrimination?

Response. The mapping of the human genome is an extraordinary scientific advance. This achievement is the foundation for research that is expected to one day reveal every person's genetic predisposition to a variety of diseases. While this genetic information will be an important tool to prevent and treat disease, it can also be misused to discriminate against individuals. The Association of American Medical Colleges (AAMC) is concerned that many Americans will be discouraged from participating in vital medical research for fear of discrimination by employers or health insurance providers who improperly use genetic information. Accordingly, protections are needed to prevent this information from being used inappropriately. The AAMC has encouraged Congress to pass legislation that provides sufficient protection against job loss, health insurance cancellation or denial of coverage as a result of genetic discrimination. It is essential that the American people are reassured that participating in medical research will not compromise their health insurance or their livelihoods.

Question 2) The Senate recently unanimously passed S. 1053, a bill to prohibit discrimination on the basis of genetic information with respect to health insurance and employment. Do you support this legislation?

Response. The AAMC supports enactment of S. 1053, and joined over 90 other organizations as part of the Coalition for Genetic Fairness in a Nov. 4, 2003, letter to House Speaker Dennis Hastert urging him to schedule a vote on the legislation. The coalition represents patients, people with disabilities, consumers, women, health and health professional and civil rights organizations, and many others.

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

April 16, 2004

The Honorable JOHN DINGELL, *Ranking Minority Member*
Committee on Energy and Commerce
United States House of Representatives
Washington, DC 20515

DEAR REPRESENTATIVE DINGELL: I am responding to your April 7, 2004, letter to Dr. Elias Zerhouni, Director of the National Institutes of Health (NIH), following up on the March 25, 2004, hearing entitled: "NIH: Re-engineering Clinical Research." Enclosed are responses to the questions you forwarded from members of the

Subcommittee on Health. We continue to look forward to working with the House Energy and Commerce Committee as it continues to review NIH.

I have also provided a copy of this response to Chairmen Joe Barton and Michael Bilirakis.

Sincerely,

MARC SMOLONSKY
Associate Director for Legislative Policy and Analysis

Enclosures

cc: The Honorable Joe Barton, Chairman, Committee on Energy and Commerce
The Honorable Michael Bilirakis, Chairman, Subcommittee on Health

QUESTIONS FOR DR. ZERHOUNI FROM THE HONORABLE SHERROD BROWN

Question. The NECTAR system at NIH, which uses medical informatics to coordinate clinical research initiatives, intersects with private sector-initiated clinical research. How will NIH coordinate with the private sector, and what efforts are underway in the private sector to modernize the collection of clinical trial data?

Response. An early step in the development of NECTAR will be an extensive inventory of ongoing public and private sector initiatives that have advanced the development of data standards and vocabularies, applications and tools, and informatics infrastructures and architectures, which are the critical elements of a nation-wide network of clinical research information systems. NIH is consulting widely with the clinical research community, health care providers, and informatics vendors to gather data on best practices in systems design and standards development. For example, innovative information systems in academic institutions such as the Mayo Clinic, Partners HealthCare, Columbia University College of Physicians and Scientists, and the Regenstrief Institute, whose systems are designed to fulfill the specific information needs of clinical research, are being studied. IBM's Information Based Medicine system, Cerner Corporation's Integrating the Health Enterprise program, and Kaiser Permanente's Electronic Health Record are a few of the commercial and non-profit sector initiatives that are also being reviewed. Through site visits, workshops, and conferences, NECTAR's development will be informed by and build upon best practices and state-of-the-art tools that will enable us to create a clinical research informatics system that will be fully responsive to evolving technology and the changing needs of the dynamic clinical research environment.

QUESTIONS FOR DR. ZERHOUNI FROM THE HONORABLE GENE GREEN

Question 1. In 2001, National Cancer Institute (NCI) researchers published two articles on breast implant patients, which found that women with implants were more likely to have cancer compared to other plastic surgery patients of the same age. In fact, breast implant patients were twice as likely to die from brain cancer, three times as likely to die from lung cancer, and four times as likely to commit suicide, compared to other plastic surgery patients.

Five years have passed since those data were analyzed. Dr. Louise Brinton and other NCI researchers had hoped to follow-up on the women who were still alive five years ago, to find out how many are still alive and how many are healthy. That will provide more conclusive evidence about a possible link between breast implants and cancer or suicide. Is that research being done?

Response. Although the NCI study did not find that breast implant patients were more likely than other plastic surgery patients to develop any cancer, it is true that there were some excess risks for certain sites, including brain and lung cancers. These excesses were difficult to interpret given that they were based on small numbers. The NCI therefore has plans to continue following the patients from the study to evaluate future deaths from different causes. Data from the National Death Index, now available through 2002, will provide an additional five years of important information. These additional years will yield considerably more statistical power for evaluating rare outcomes of interest, including brain cancers.

The timeline for the completion of this work will be similar to other epidemiology studies of this size and complexity. We anticipate that data collection and analysis, writing, and initial review will be completed in Spring of 2005. Draft materials will then be submitted to a scientific journal for peer review and publishing. We hope, therefore, that results from this follow-up may be published in early 2006.

Question 2. Another issue of concern for me is the role of NIH's newest institute, the National Institute of Biomedical Imaging and Bioengineering (NIBIB). As a proud co-sponsor of legislation to create this Institute, with my friends Congressman Burr and Congresswoman Eshoo, I feel that the National Institute of Biomedical Imaging and Bioengineering should have a prominent role in your effort to re-engi-

neer the clinical research enterprise at the NIH as well as in the entire NIH Roadmap.

What is your view of the role of the NIBIB in the NIH Roadmap and over the long term as the focus for the development of new technologies at the NIH? Would you work with this Committee and the Appropriations Committee to develop a long-range plan for the Institute?

Response. The NIH Roadmap for Medical Research focuses on the most compelling opportunities in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise. These cross-cutting areas span the missions of the 27 Institutes and Centers (ICs) of the NIH. As such, all ICs support and actively participate in the development and implementation of Roadmap initiatives.

The mission of the NIBIB is to improve human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance basic research and medical care. To that end, the NIBIB strongly supports the NIH Roadmap, since a major Roadmap goal is to facilitate the development of innovative, novel and multi-disciplinary science and technology that has the potential to further advances in health care. For example, the NIBIB is participating in an initiative that will facilitate the formation of collaborative research teams capable of generating novel probes for molecular and cellular imaging. The overall goal is to establish programs to create complete tool sets for the detection of single molecule events in living cells and to generate new strategies for dramatically increasing the imaging resolution of dynamic cellular processes.

Other Roadmap areas of immediate interest to and supported by the NIBIB include the development of nanomedicine technologies, new tools for the study of proteomics and metabolic pathways, data and techniques for computational biology, and advances in bioinformatics. For example, in the theme area of new pathways to discovery, NIBIB program staff are participating in the formulation and execution of initiatives relating to metabolomics and proteomics as well as an initiative for the National Centers for Biomedical Computing. The NIBIB is also participating in the planning for the Nanomedicine Development Centers.

In the theme area of re-engineering the clinical research enterprise, NIBIB Program Staff are active participants in the Trans-NIH Informatics Committee (TNIC) which is coordinating the informatics components in all three Roadmap areas. The TNIC is currently focusing on the National Electronic Clinical Trials and Research System (NECTAR) which will allow community-based clinicians from the NIH Clinical Research Associates to participate in national studies, facilitate the sharing of data and resources, and augment clinical research performance and analysis.

In the theme area of research teams of the future, several initiatives have been developed to encourage and enable an interdisciplinary workforce through the implementation of novel training programs. Training a new cadre of interdisciplinary researchers is an important component of the NIBIB mission and the Institute is actively participating in the development and implementation of Roadmap initiatives in this area.

Regarding long-range planning, in February 2004, the NIBIB embarked on a strategic planning process which will culminate in a draft of the Institute's first strategic plan later this year. The NIBIB has created a Strategic Planning Working Group, composed of the Senior Staff of the Institute and has also formed a Strategic Planning Subcommittee within its' National Advisory Council. The Institute is soliciting broad public input on their web site (http://www.nibib1.nih.gov/about/SP/strategicplan.htm) which also serves to update interested individuals on the ongoing, iterative planning process.

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