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DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2008

MONDAY, MAY 7, 2007

U.S. SENATE,
SUBCOMMITTEE OF THE COMMITTEE ON APPROPRIATIONS,
Washington, DC.

The subcommittee met at 1:31 p.m., in room SD–116, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senator Harkin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF DR. JEREMY BERG, DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Committee will come to order.

This is the subcommittee's fourth hearing on the National Institutes of Health this year. We've heard from nine institutes, today we'll hear from four more: The National Institute of General Medical Sciences, the National Human Genome Research Institute, the National Library of Medicine, and the National Institute of Biomedical Imaging and Bioengineering.

We asked these four Institutes to appear together because they're all involved in expanding the frontiers of science. Unlike many of the institutes at NIH, none of these are charged with attacking a particular disease. Instead, they develop cutting-edge tools and resources that benefit research on all diseases—things like sequencing the human genome, combining huge, easily searchable databases, developing new imaging technology or basic research training.

What I'd like to ask is if each of you could speak for 5 to 7 minutes. Summarize the research that you've overseen over the past year or so, and give us a look ahead at the initiatives that you are planning for fiscal year 2008 and beyond.

Senator Specter cannot be here today, but I will keep the record open for his opening statement, and any questions that he might want to submit.

At the outset, I just want to thank each one of you for the work that you do in the Institutes that you direct, all that you're doing

to improve people's health. We are grateful for your dedication and skill, each and every one of you, for so many years.

I started these forums—these hearings, like this—I don't know if you've talked to any of your fellow Institute Directors, but I feel it's good to be able to get into these in a little bit more depth. Actually, the first person that started these in this room, and having them in this manner was Senator Lowell Weicker, and I was a freshman Senator at the time. I just thought they were great sessions for us to learn more in depth about what the Institutes are doing, and that's why we're doing it in this manner again.

So, I've had, basically, four at a time, like this, and try to group them in some kind of a semblance of rationality of what the Institutes were doing.

So, I'd like to, again, just kind of get into it. I'll have some questions when you finish, but I'd like to just go through, perhaps all the Directors once, I may even ask you a question in between, so we have kind of a free-flow, more than any structured kind of a presentation.

So, I will start first with Dr. Jeremy Berg, Director of the National Institute of General Medical Sciences since 2003. He received his M.S. in Chemistry from Stanford, his Ph.D. in Chemistry from Harvard. His own research focuses on the way that proteins regulate gene activity.

Dr. Berg, welcome and please proceed. By the way, all of your statements will be made a part of the record in their entirety.

SUMMARY STATEMENT OF DR. JEREMY BERG

Dr. BERG. Well, thank you very much, Senator Harkin, both for your leadership and for this opportunity.

NIGMS, the National Institute of General Medical Sciences, is often referred to as the "basic science institute," because we support research on fundamental biological processes. As one measure of how successful this approach has been, NIGMS has supported a total of 62 Nobel Prize winners over the 45-year history of the Institute, including three this past year.

The research that NIGMS has supported has also done things like enabling the Human Genome Project and contributed substantial, to the technology that led to the biotechnology industry, which current estimates indicate has created about 200,000 jobs in the United States and has an annual revenue base in the United States of about $40 billion.

The research that we support really depends on scientists working on the advances that others have made in the past, as all of our research does. One illustration of this, there's a handout which I think you have a copy of——

Senator HARKIN. Or, do I have it?

The "Central Dogma" of Molecular Biology

FIGURE 1

Dr. BERG. Figure 1 reveals the so-called "Central Dogma" of molecular biology. This goes back to the 1960's, and shows the information flow from DNA, where the genetic information is stored, through RNA, and converted into proteins, which are the molecules that do most of the work in the body.

RNA VERSUS DNA

Senator HARKIN. What's the difference between RNA and DNA?

Dr. BERG. Chemically, there's a very minor difference, there's one extra hydroxyl group in RNA. The major difference: is that DNA is very stable, and is present in the cell very robustly. RNA is used much more as a signal or a messenger, so the DNA information is translated to RNA, that's then used, and the RNA is degraded, in general, very rapidly. It is a way of sending a message out, and then the message is destroyed, so the new messages can——

Senator HARKIN. So, RNA exists for short periods of time?

Dr. BERG. Most RNAs exist for just seconds or a few minutes, some much longer than that.

But, as you'll see in one of the examples I've described, RNA is also very actively involved in many processes, some of which we're just beginning to understanding.

Even though this idea has been around for 50 years or so, there are still lots of new discoveries, both bolstering it and adding new loops to this simple information diagram.

The Nobel Prize last year in chemistry went to Roger Kornberg for determining the structure of RNA polymerase. This is something that's been known since the late 1960s, and is exactly how the information in DNA is converted into RNA. It was known that there was this very important and very complicated protein enzyme, RNA polymerase, that converts the information in DNA into RNA. See figure 2.

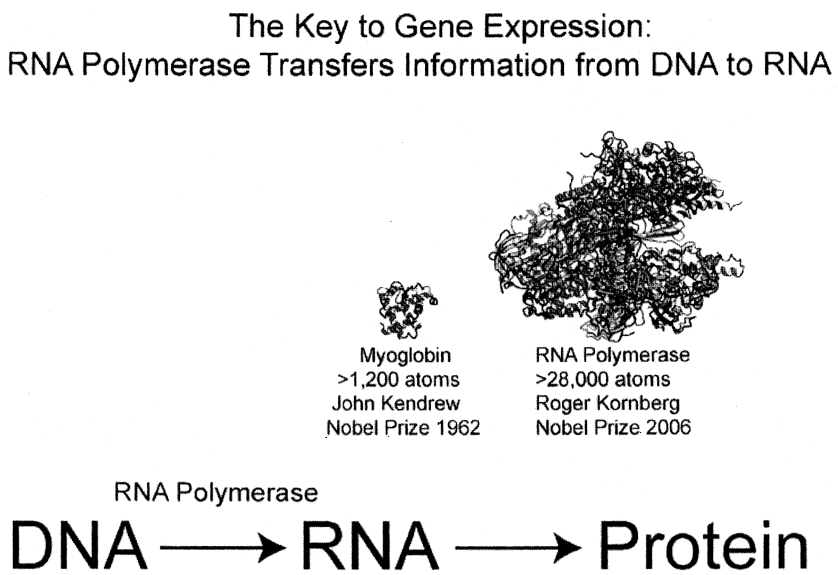


FIGURE 2

It was known to be very complicated, and starting about 20 years ago, Dr. Kornberg made it one of his missions in life to figure out what this enzyme looked like, in order to understand how it works. It is the key protein which collects information and figures out which genes should be turned on and which ones should be turned off.

He was funded for a long period of time when he started on this quest, and I must say, personally, that I think a lot of people regarded it a sort of a Don Quixote-esque quest to go do something very important, but that had a very small chance of ever succeeding.

Starting in 1999, he got the first real glimmers that he was going to succeed. Subsequently, he has been reporting more and more interesting structures, revealing the overall structure, which is incredibly complicated, and how it works—both the chemical mechanism, and now more and more information about how it collects information from the outside, and from the other things within the cell.

This really sets the stage for a much deeper understanding of gene regulation, a process that is fundamental to many aspects of health, and also a mechanism that is regulated in diseases like cancer and many others as well.

The other Nobel Prize that we supported was in physiology and medicine to Andrew Fire and Craig Mello for something that was really much more of a discovery, something that was completely unanticipated, which is that RNA actually regulates itself. The discovery was the result of an experiment that turned out very differently than they thought, and they were clever enough to realize that there was something very interesting going on. It was an experiment that was predicted not to work, that worked. They fol-

lowed that up, and discovered this process which we call RNA interference, or RNAi, which allows small pieces of RNA, that are either present in the cell, or introduced into the cell, to shut down genes in a very specific way. Again, this was something that was completely unanticipated.

One measure of how important it is, is Fire and Mello's discovery was reported in 1998, and they won the Nobel Prize only 8 years later, which is incredibly fast on the Nobel Prize timescale. One, RNAi is a fundamentally important discovery, second, it's a very powerful research tool. See figure 3.

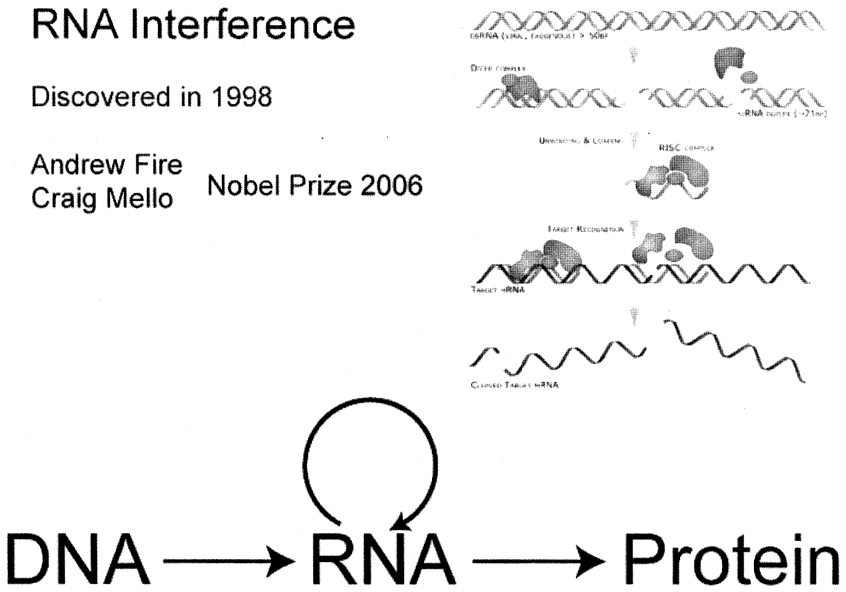


FIGURE 3

As investigators are building on the work from the Human Genome Research Institute, one of the questions they are pursuing is, what does each gene do? RNAi gives a way for scientists to specifically go through and turn off one gene at a time in a given cell type, then see what happens. The tool just didn't exist before, and it has dramatically cut down the cost of doing this type of gene-by-gene analysis.

The second really exciting thing about RNAi, is that it's immediately adaptable to new therapeutics, and there are a large number of different therapeutics being developed using RNAi. The most advanced is a treatment for macular degeneration, which is now in Phase II clinical trials. Basically, there's a specific RNA molecule that can be injected directly into the eye to shut down the expression of a particular protein, which blocks the process that underlies macular degeneration.

There are many other areas that are being advanced with RNAi. One particularly exciting area is pandemic influenza. With RNAi, one of the challenges of planning for pandemic influenza is the virus has not yet—thank goodness—been transferred from birds

into humans to a very large degree. If we have to wait for that to occur to develop medicine, or develop a vaccine, that puts in a lag-time which could be very devastating to the human population. With RNAi, we already know a lot about influenza viruses, and can find things which are common to all of the different influenza viruses, and potentially develop a therapy or a sort of a vaccine-like treatment that will be completely independent of the strain, some sort of a universal flu vaccine.

Again, this is still very much in development, and there are lots of problems to be solved. The RNAi approach opens up a new avenue, which has the potential to save hundreds of thousands of lives, and billions of dollars to the world economy.

In terms of the future, there are two important aspects. First off, although we can't anticipate and predict what new discoveries will be made, we can anticipate that they will occur. If you look at what's happened since the Central Dogma was first coined, on average about, every 5 years there's some new, revolutionary discovery that no one anticipated and that really changes the landscape of biomedical research. We still don't think we know all there is to know by any stretch of the imagination, so there will be new discoveries. I can't tell you what they will be, but I can tell you that they will exist.

To foster those sorts of discoveries, NIGMS has been involved in two new programs: one is the NIH Director's Pioneer Award, which was started a few years ago as part of the NIH Roadmap; and more recently, the NIH Director's New Innovator Award, which was started this year, thanks to the funds that were provided in the joint resolution.

The idea of these awards is really to encourage the scientific community to send forth their most creative ideas, really out of the box sorts of things, and have a home for funding some of those ideas. We want to push the sort of creative things that might be difficult to fund in the relatively conservative environment that we find ourselves in.

The second thing that we're sure we're going to have to deal with is complexity. If you look at the last handout, even though the Central Dogma is relatively simple, it's occurring with, about 20,000 genes. There are many other modifications to the Central Dogma that we know occur, and all of these things take place in concert in each of thousands of different cell types in our body and respond to interactions from other cells and environmental signals. We need to find the sort of conceptual frameworks for dealing with systems that are this complicated. We know what the parts are now, but trying to understand systems or machines, this is complicated, really a daunting challenge.

PREPARED STATEMENT

We have a program, Centers for Systems Biology, which is bringing together biologists, computer scientists, and other people who are accustomed to dealing with this sort of complexity to try to take the first baby steps to address this. Not only do we have to deal with complexity, but also variations from individual to individual, which are key to health and disease. With the information that's coming from NHGRI and other Institutes, we now are start-

ing to know more and more about what sort of variability there is, and we're trying to stay ahead of the curve in developing conceptual frameworks and tools that will help us interpret this information when it becomes available.

So, with that, thank you very much.

[The statement follows:]

PREPARED STATEMENT OF DR. JEREMY BERG

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for the National Institute of General Medical Sciences (NIGMS). The fiscal year 2008 budget includes $1,941,462,000.

Throughout its 45-year existence, NIGMS has been a wellspring of discovery. The fundamental knowledge generated by NIGMS research impacts every other NIH component and has broad applications in the pharmaceutical and biotechnology industries. NIGMS contributes to the health of the biomedical research enterprise in other important ways, as well. A prime example is our cutting-edge research training program, which produces a substantial number of well-prepared new scientists. Their ideas and talents contribute to our growing knowledge base, allowing continued progress toward treatments and cures for countless diseases that rob us of friends, family, and years of productive life.

NURTURING INTELLECTUAL CAPITAL

When discussing science and medicine, we often focus on compelling research advances and medical breakthroughs. But behind every "what" is a "who," a creative individual asking and answering a crucial question—the brainpower driving scientific progress. NIGMS is steadfast in its commitment to nurturing and maintaining this intellectual capital through its significant support of investigator-initiated research and research training.

In the context of this opening statement, it has become habit to reference the past year's NIGMS-supported Nobel Prizes. Of course, this is a ritual I am extremely proud to continue by reporting that the 2006 prizes in the two areas most relevant to biomedicine, physiology or medicine and chemistry, went to three NIGMS grantees. But I would like to go further, using the prize-winning research to show you how NIGMS support creates opportunities for major discoveries to happen.

Two geneticists, Andrew Fire and Craig Mello, received the 2006 Nobel Prize in physiology or medicine for their discovery of a gene-controlling mechanism called RNA interference. Their breakthrough came about by surprise, when they had the keen insight to figure out why an experiment failed. Fire and Mello's seminal finding, made relatively recently in 1998, has dramatically transformed biomedical research and has already led to new treatments that are being tested in the clinic for a range of diseases.

The 2006 Nobel Prize in chemistry is a very different story. In this case, the achievement resulted from painstaking persistence on a fundamentally important question. The prize went to a biochemist who refused to give up on a problem that even today would be perceived as ferociously difficult. Combining biochemical research with novel biophysical methods, Roger Kornberg captured a detailed, three-dimensional snapshot of the enzyme that reads our genes. This work has deeply enriched our understanding of one of the most fundamental life processes: how DNA gets copied into RNA. While the mindset, creativity, and acumen were Kornberg's, decades of unwavering NIGMS support enabled him and a talented set of coworkers to pursue this groundbreaking accomplishment, which has had a significant impact on biomedical research.

TOOLS BREED INNOVATION

To capitalize on creative ideas, scientists need tools as well as funding. These tools can take many forms, from new technologies to model organisms. Research with bacteria, yeast, insects, worms, and rodents continues to confirm that the basic operating principles are nearly the same in all living things, and that studies in other organisms yield important knowledge applicable to human health.

Thus, we are no longer surprised to learn that a gene or a process in a mouse, a worm, or a fruit fly is the same, or very similar, as that in a person. Examples of high-impact research done using model organisms abound, including the 2006 Nobel Prize-winning discoveries, which were made in roundworms and yeast. A more recent study in roundworms showed how early cell damage contributes to the development of Huntington's disease. The researchers who did this work discovered

that an error in how proteins fold leads to the massive protein clumping inside cells that typifies Huntington's disease. Because protein clumping is also linked to other neurological conditions such as Alzheimer's and Parkinson's diseases, it is likely that this work will have far-reaching implications.

Along with essential new knowledge about life processes, health, and disease, basic research can yield technologies with direct medical relevance. A case in point is an unexpected discovery by bacteriologist Yves Brun. While studying bacteria to better understand cell division, he found that the organisms produce a remarkable, natural form of "superglue." Additional studies revealed that the bacterial glue is the strongest biological adhesive ever measured, capable of holding nearly 5 tons per square inch. What's more, it doesn't dissolve in water. Brun is now working to learn more about the properties of the natural glue, which could be an ideal candidate for a surgical adhesive.

For a further demonstration of uncharted exploration as a powerful engine of discovery, consider the study of the three-dimensional structures of biological molecules. This research, which relies heavily on tools and expertise from the physical sciences, has been a prime source for the development of life-saving medications like those used to treat AIDS, many types of cancer, asthma, and several other health conditions. NIGMS has provided significant support for structural studies and other research at the interface of the biological and physical sciences. In addition, we continue to communicate and collaborate with Federal agencies focused on the physical sciences to maximize the benefit of our funding activities to the scientific community.

Of course, technology is only useful if it is available and affordable to many bright minds across the country. Every investment NIGMS makes has this end goal in mind, and currently the Institute is supporting several databases, materials repositories, genetic and genomic tools, and other shared resources that provide vital information and equipment to thousands of biomedical researchers. The Institute's team science efforts in such areas as high-throughput protein structure determination (the Protein Structure Initiative), how genes affect individual responses to medicines (the Pharmacogenetics Research Network), and new approaches to significant and complex biomedical problems via collaborations among scientists from diverse fields ("glue grants"), have all matured to a level where the fruits of progress are being shared widely with scientists everywhere.

INVESTING IN THE FUTURE

Perhaps the most important element in determining the future of biomedical research is providing young people with opportunities to develop an understanding of the scientific process and to become fascinated with the challenges and opportunities that scientific careers present. Who will make the discoveries that will drive research in the future? If we went back in time, could we have known that Fire, Mello, Kornberg, and many other unnamed scientists would have gone so far in advancing our understanding of key life processes?

Some individuals can hardly avoid catching the science bug. Roger Kornberg grew up in a household dominated by science: His father, Arthur (also a long-time NIGMS grantee), shared the Nobel Prize in physiology or medicine when Roger was 12 years old. Roger took advantage of the many opportunities available to him and began learning about science at a very early age.

Most people, however, do not grow up in such a rich scientific environment. Take Ryan Harrison, who caught the science bug a few years ago, while attending a Baltimore City public high school that has a large population of underrepresented minority students. Ryan, the son of a teacher and a former corrections officer, met Jeffrey Gray, a biophysicist at Johns Hopkins University, through an outreach program. Ryan spent 2 years working in Gray's laboratory and then came in 5th place in the Intel Science Talent Search, the most prestigious high school science competition in the country. He continues to pursue research as an undergraduate at Johns Hopkins, and we look forward to following his progress and achievements.

In order to address the health needs of our Nation, we must tap the full diversity of the talent pool of our country to attract the best minds into research. NIGMS has been a pioneer in this arena through its programs that provide opportunities for underrepresented minorities to pursue scientific careers. We recognize that underrepresentation is a challenging and complex problem. Single interventions are unlikely to effect lasting, multidimensional changes in diversity. As these programs mature, we are committed to conducting and rigorously evaluating the effectiveness of a broad range of biomedical workforce diversity programs.

Once scientists have embarked on their careers, we must continue to provide opportunities for them to contribute fully to biomedical research. An effort to do just

that is the new NIH Pathway to Independence award, which facilitates the transition of highly promising postdoctoral scientists from mentored to independent research positions. NIGMS was delighted this year to receive, and fund, a healthy number of applications for this unique program. In addition, we continue to give special consideration to regular research grant applications from new investigators as another way to help them get a solid start.

We also realize the need for scientists to be able to test unconventional, potentially paradigm-shifting hypotheses and use novel, innovative approaches to solve difficult technical and conceptual problems that impede scientific progress. Toward this end, we are developing a new grant program based primarily on the innovativeness and potential impact of a scientist's ideas. We will launch the program later this year and anticipate that it will serve as a model for other NIH institutes and centers. The design of this program has benefited from our experience with the NIH Director's Pioneer Award program, an intriguing experiment on how to fund scientific research that is part of the NIH Roadmap for Medical Research.

Through the efforts I have described today, we hope to continue our strong record of identifying and supporting the talented and creative scientists whose work paves the way for future medical advances.

Thank you, Mr. Chairman. I would be pleased to answer any questions that the Committee may have.

Senator HARKIN. Thank you very much, Dr. Berg. I've got some follow on things, but we'll move on through here.

Dr. Francis Collins, has served as Director of the National Human Genome Research Institute since 1993, received his Ph.D. from Yale University, and his M.D. from the University of North Carolina School of Medicine. Dr. Collins has discovered numerous important disease genes, and is well known for his leadership from the beginning to the end of the Human Genome Project.

Again, my thanks for your leadership in that area, but I continue to hear just glowing comments, last week, about your presentation to our group about a week and a half ago. It was just a great presentation.

Welcome, again, Dr. Collins, to the committee, and please proceed.

STATEMENT OF DR. FRANCIS S. COLLINS, DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Dr. COLLINS. Thank you, Senator Harkin, thank you for those kind comments about the event 10 days ago.

I'm very happy to be here with my colleagues, as part of this hearing on Frontiers of Science, and ever since this Congress—led by your vision, Senator Harkin—got the Human Genome Project off the ground, we've had the privilege of working at that frontier. I'm pleased to report, we've made a lot of progress in the 4 years since the Human Genome Project completed all of its goals, in April 2003, famously ahead of schedule, and famously under budget—we've used that foundation to build a real future for personalized medicine.

You're going to hear a lot more about exciting developments in that regard in the coming weeks and months, describing dramatic genetic discoveries for common diseases, with important public health consequences.

Let me tell you about one that's particularly exciting for me. Just last week in Science magazine there were two reports about identifying genetic risks for heart disease, for heart attacks, specifically. These funded—one of them by the Heart, Lung and Blood Institute—are very important, because they scan the entire genome and identified a region that confers a substantial increased risk of heart

attack in an area of the genome we had no idea was involved in this disease before.

But stunningly, just a week before, my team and two other teams, who had been studying Type II Diabetes, the adult-onset form of diabetes, reported also in Science magazine, the identification of a total of 10 genes involved in that important disease, where as previously, only three had been known.

Stunningly, one of the regions of the genome identified in the diabetes study appears to be the same one that is involved in heart attack. Nobody expected this. This is like winning the lottery 2 weeks in a row by picking the same number. It just shouldn't happen. After all, the genome is a big place. But instead, we've zeroed in on this place on chromosome 9, which must be a very important part of the genome in terms of its role in human health, and identified ways in which it can influence risk of diabetes on the one hand, and heart attack on the other. Everybody involved in these studies is scratching their heads, not having expected this outcome, but clearly we're onto something pretty important.

Now this kind of discovery can open new doors to prevention and treatments. Take diabetes, for instances, where we sorely need that. Estimates are we spend $132 billion a year in the treatment of diabetes and its complications, as well as the consequences to the 21 million Americans who have this disease, as far as loss of work, and premature mortality and morbidity. Yet, we don't really understand that disease nearly as well as we need to, in terms of the precise molecular basis of what's going on.

With this outpouring, now, of these 10 new gene variants, I would say, only three of which you might have guessed at, and the others are complete surprises—we can finally shine a light on this mysterious disease in a way that should, both offer us the chance to do better prevention, and we know prevention can work for diabetes. We know that if you identify the people at high risk, and get them into an exercise program, you can reduce their chance of becoming diabetic by as much as 58 percent.

We can also use these new discoveries to pinpoint pathways for which new drug therapies could be designed, instead of continuing the same process we have up until now, based upon what we knew about the disease, now we know so much more.

How did this come about? Well, in the little handout, figure 4 and I hope it's somewhere there in your little pile. Okay, so this is a simple diagram that shows what it is that geneticists are doing now with common diseases, which we couldn't do before.

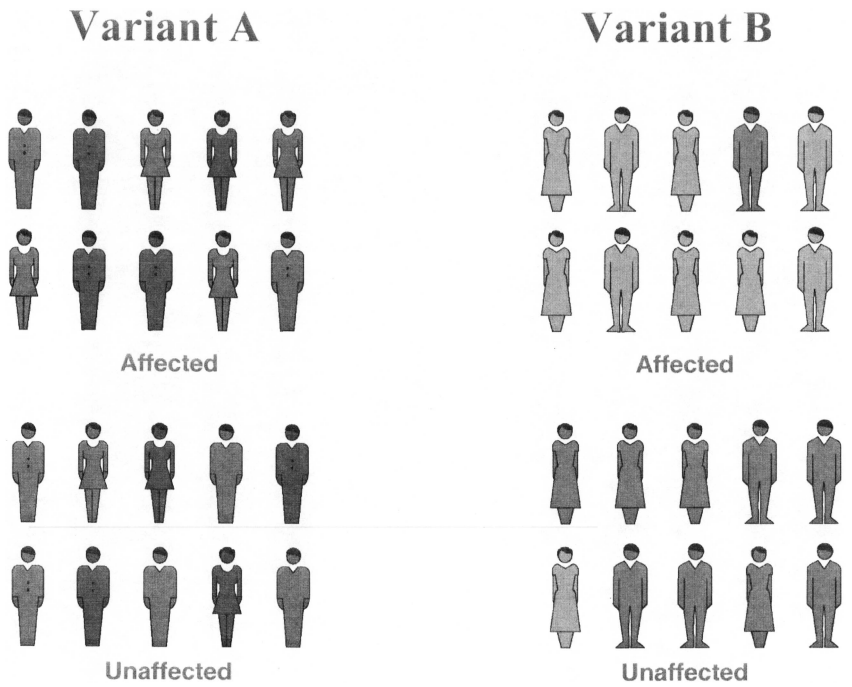


FIGURE 4

It looks very simple in this cartoon—basically, you identify people with the disease, the affecteds, as it were, and you identify controls, that is, people who clearly don't have the disease—and then you want to check, across the entire genome, places where there are difference in the spelling, "variants" as we call them, and see, are there any out there that look like Variant B—where, in my color-coding here, the orange spelling of Variant B is more common in the "affecteds" than the "unaffecteds" and that will tell you that Variant B may be a risk factor for that disease.

Most of the variants in the genome aren't going to look like B, they're going to look like A, where there really isn't any difference, because most variation doesn't affect diabetes.

But, the problem with this strategy was, until very recently, we didn't have the power to do this. Because, while this cartoon looks very simple, to do this right, you need 1,000 or more affected individuals, and 1,000 or more unaffected individuals, and we thought you might have to check as many as 10 million different places in the genome in order not to miss the answer.

Well, the HapMap came along, a project which I had the privilege of leading, as a natural follow-on the Human Genome Project, which basically built a catalogue about all of these variants, and figured out how they traveled in neighborhoods, so that you didn't have to check all 10 million if you chose wisely, you could choose a much smaller set, and they served as proxies for the ones that you didn't actually look at. That made it possible to do something which, 5 years ago, would have cost $10 billion, the study of diabe-

tes that I just mentioned. Now we can do that for less than $1 million. I don't know too many areas of science where costs have come down by that kind of curve, in just 5 years.

If you look at the next image figure 5, the next thing in your little packet, you can see what the consequences of this are starting to be, in terms of this are starting to be, in terms of discovery, so above the line are, in fact, major common diseases for which we have been learning about genetic factors involved, and you can see, as we sort of blow up the scale here, in the last 2.5 years, a lot of findings coming along, prostrate cancer, lupus, macular degeneration, inflammatory bowel diseases, Type 2 Diabetes, psoriasis, heart attack.

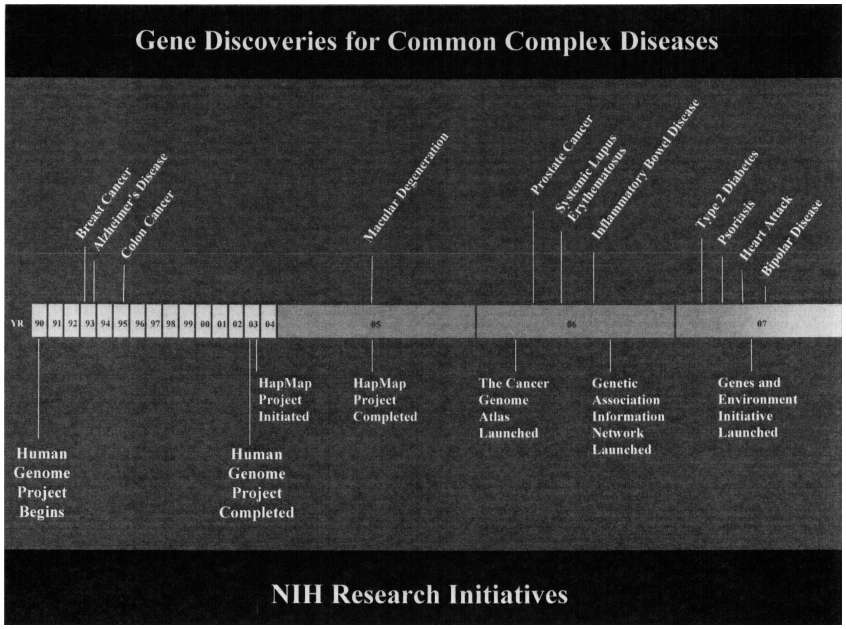


FIGURE 5

I put bipolar disease on here, because in a publication tomorrow in a major journal, there will be a description of what happened to a group at the NIH, led by Dr. McMahon that applied this same strategy to looking at manic-depressive illness, and came up with a very surprising finding of a gene that appears to be involved in that disease, that maybe is even involved in the lithium pathway, which makes a certain amount of sense, but it's not a gene that anybody would have guessed that. I hear through the rumor mill, there are other studies of bipolar disease, also using this same new, very powerful strategy, discovering similar findings.

So, this is really the year, where all of a sudden, we're going to learn a great deal about the genetics of common disease, with many consequences, and if you go to the last picture here, it's an attempt to show how that's going to play out in terms of the practice of medicine.

The top part of the diagram, figure 6, which says, "Accelerated By Human Genome Project," is what's now happening—the ability to identify these genetic risk factors using the tools that have come out of this effort.

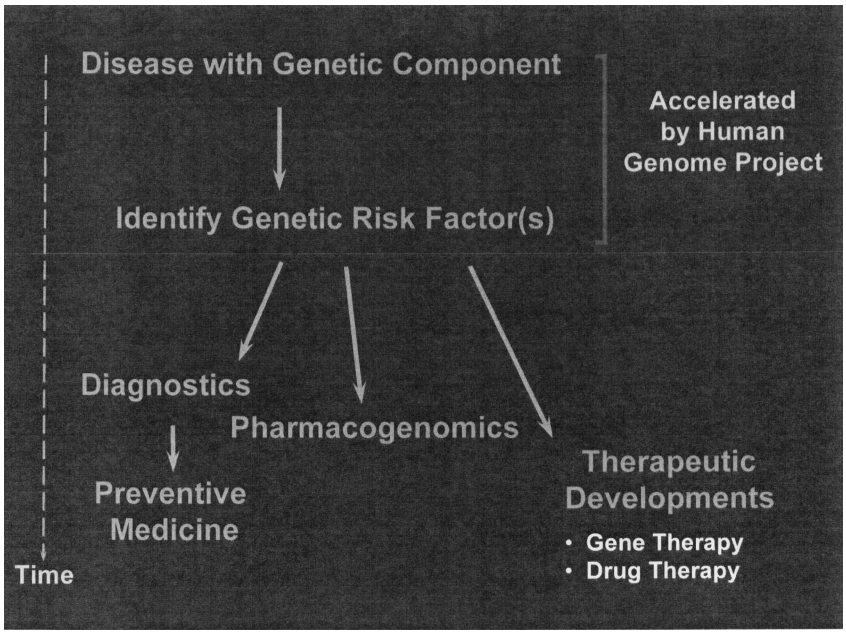


FIGURE 6

What happens next, in the clinic, is going to be the ability, diagnostically, to predict who's at risk, and if you have an intervention that will reduce that risk, people will probably be interested, especially now that we're seeing the Genetic Information Nondiscrimination Act getting close to passage, finally——

Senator HARKIN. Finally.

Dr. COLLINS [continuing]. Which will mean that people won't be afraid to take advantage of that information, as they have been in the past.

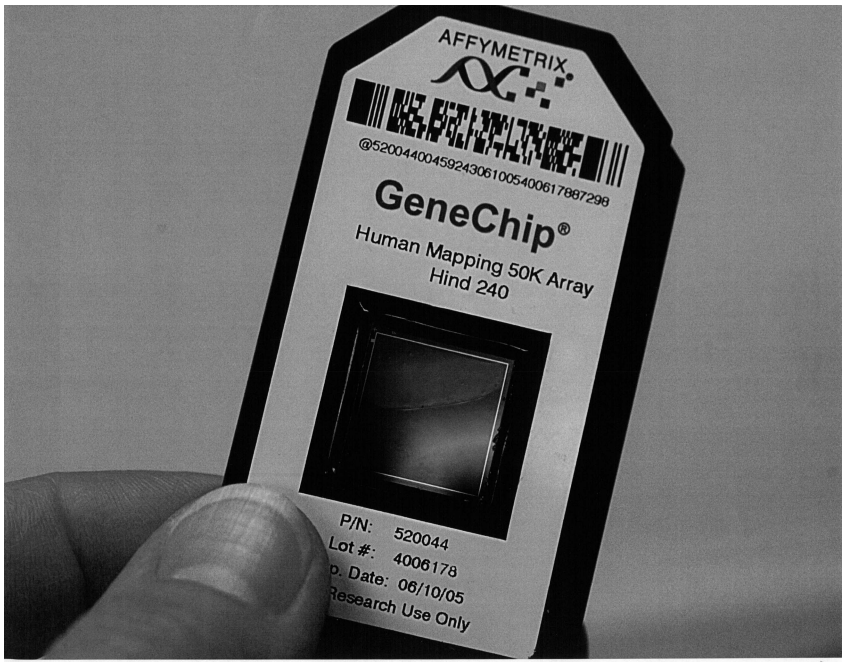
We'll also be able to use these same tools for pharmacogenomics, this effort to identify the right drug at the right dose for the right person, knowing that we're all a little different there, too, the same tools can be used to figure out why that is.

Perhaps most importantly in the long term, these gene discoveries shine a bright light on pathogenesis that gives you the chance to develop treatments that will be more efficacious, because they're really targeted towards the primary problem, and perhaps, if we do this right, also less likely to cause side effects, because you are going right to the primary problem.

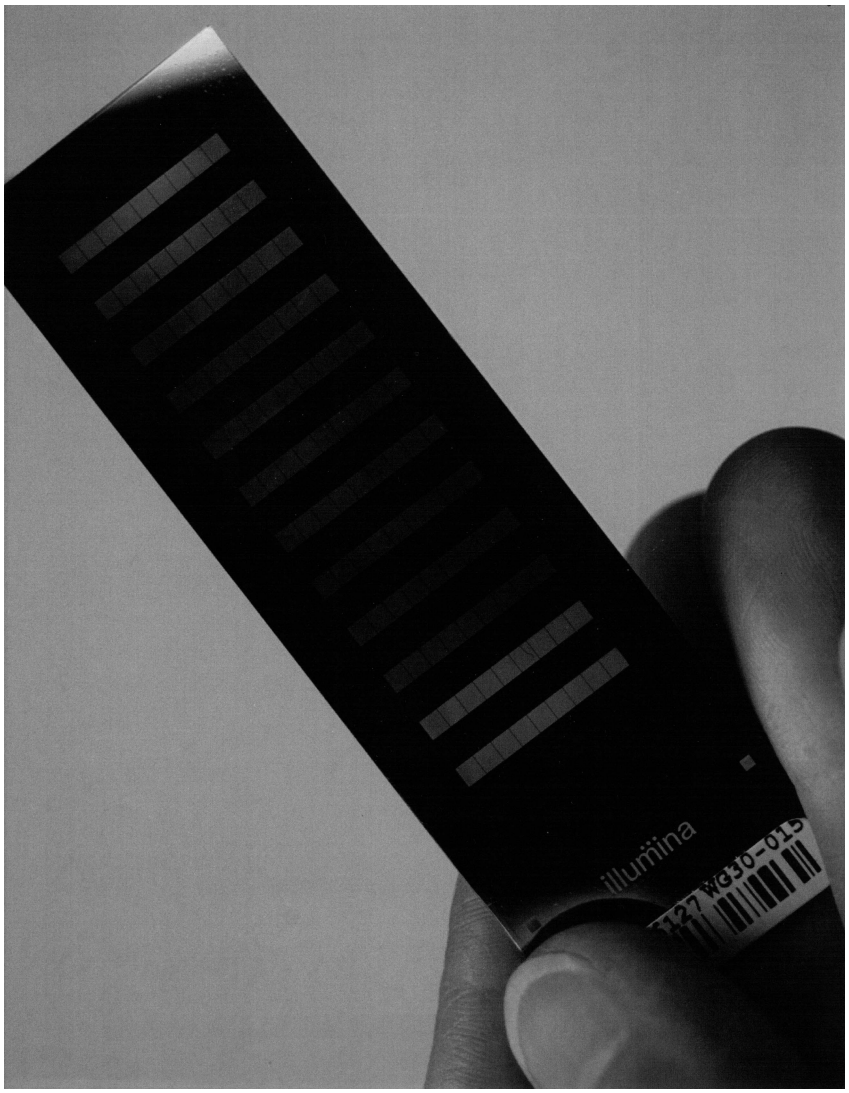
So, it's a very exciting time for this kind of strategy. How are we able to do that? I should bring along my show-and-tell here, I brought you a couple of chips to indicate the kind of technologies that have come out of this sort.

Senator HARKIN. What am I looking at?

Dr. COLLINS. The one in the little plastic case, here, is an Affymetrix Gene Chip, this one chip can be used to detect 50,000 different variable places in the genome in one experiment. This particular company, Affymetrix, was actually founded on an NIH SBIR grant from the Genome Institute, about 14 years ago, and has now become a major contributor to the revolution in genomic medicine that we see.



The other one, called Illumina, is a separate company, what you're looking at there is a microscope slide, and you see stripes on it, each one of those stripes has about 60,000 different DNA spelling detectors, so it is basically a detector, and so with the whole slide, you can then look at a very large number of variations in a single DNA sample, and test those extremely reliably, and for a cost of about an 8th of a penny per particular genotype, per particular DNA spelling. Again, that's come down dramatically in cost, over the last 5 years.



So, these are exciting times, not only are we focused on this approach to look at those variants in the genome, I might mention, we're also pushing hard, Senator, to get to the point of being able to sequence anybody's complete genome, all of the letters of their 3 billion letter code, for $1,000.

Senator HARKIN. I read that in your testimony.

Dr. COLLINS. Yeah, that's ambitious, isn't it?

Senator HARKIN. Yeah.

Dr. COLLINS. A couple of years ago, it would have cost $10 million, we are now probably on the brink of a totally new technology, really turning out to work in high throughput that will bring that cost down to, perhaps, $100,000 for human genome. So that's three

orders of magnitude—I'm sorry, two orders of magnitude in a fairly short period of time.

To get down to $1,000, we've got two more orders of magnitude to go, but that's an explicit goal of our Institute, working with other collaborators, and we are putting a lot of our own technology development money into that. So, imagine what that's like, that you get your entire genome set?

Senator HARKIN. What makes you think you can do that?

Dr. COLLINS. We don't have to——

Senator HARKIN. That's a big order.

Dr. COLLINS. It is. We don't have to violate any laws of physics, though, it is quite possible to do this, so investing in various technologies, and Dr. Pettigrew has some of these same approaches in his portfolio, particularly using nanotechnology, one of the more promising ideas, is you take a nanopore, a tiny little pore in a membrane, and you thread DNA through it in a way that there's a change in the electrical current as each base goes by, whether it's an A, or a C, or a G, or a T, it gives you a slightly different signal. People are seriously looking at that, as a way to read out—very fast—because DNA would just fly through this pore, from a single molecule of DNA—a very large amount of DNA sequence.

Whether that's actually going to work in practice? I guess I'd give it about a 50/50 chance right now, but there are other kinds of technologies right behind it, that are also lining up to do this. I'm counting on the ingenuity of the investigators that have already pushed this envelope so far, that I would think it would be a mistake for anybody to bet against it, and we do expect that the $1,000 genome will be a reality, sometime in the next 10 years.

One of the areas, just to conclude, that we're specifically focused on, in terms of applying all of these technologies, is cancer.

So, working with the Cancer Institute, we have gotten together in a partnership called the Cancer Genome Atlas, where we are applying, not only DNA sequencing technology, but also a host of other ways of looking at what's going on in cancer, in terms of which genes are turned on or turned off, which parts of the genome are duplicated or deleted.

We have a large number of investigators all working together, initially on brain tumors, on ovarian cancer, and on lung cancer. But, if this pilot looks as promising as we expect it to, we hope to expand that to perhaps as many as 50 different cancer types, after the pilot concludes in a period of 3 years. That's a very exciting project, and all of the data is being placed into a database, where any qualified investigator can see it right away, following up again on our premise that data access is really important, for speeding up this kind of research.

PREPARED STATEMENT

So, in this brief time, I'm just scratching the surface of some of the things that are happening now in the field of genomics. Having been at NIH for 14 years, people are occasionally asking me, "Well, aren't you getting tired of it? Isn't it time to move on?" My only answer is, "This is the best part." This is the part that we really worked to get to, where we have the foundation, and now we can apply it in ways that are really going to transform medicine.

Thank you, Senator, I'd be glad to answer your questions.
[The statement follows:]

PREPARED STATEMENT OF DR. FRANCIS S. COLLINS

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for the National Human Genome Research Institute (NHGRI). The fiscal year 2008 budget included $484,436,000.

The theme of this hearing is "The Frontiers of Science." In leading the Human Genome Project, we at NHGRI have had the privilege of working at the frontiers for many years. And the projects I will describe today demonstrate how research at NHGRI is advancing ever more rapidly to catalyze a true revolution in medicine.

In February 2006, the Department of Health and Human Services announced the creation of two related groundbreaking initiatives in which NHGRI is playing a leading role. The Genetic Association Information Network (GAIN) and the Genes, Environment and Health Initiative (GEI) will accelerate research on the causes of common diseases such as asthma, schizophrenia, the common cancers, bipolar disease, diabetes, and Alzheimer's disease and help develop strategies for individualized prevention and treatment, thereby moving towards the possibility of personalized medicine.

GAIN is a public-private partnership among the NIH, the Foundation for the NIH, Pfizer, Affymetrix, Perlegen, the Broad Institute, and Abbott. GEI is a trans-NIH effort combining comprehensive genetic analysis and environmental technology development to understand the causes of common diseases. Both GEI and GAIN are powered by completion of the "HapMap," a detailed map of the 0.1 percent variation in the spelling of our DNA that is responsible for individual predispositions to health and disease. Beginning in fiscal year 2007, GAIN will produce data to narrow the hunt for genes involved in six common diseases and GEI will provide data for approximately another 15 disorders. Additionally, GEI will develop enhanced technologies and tools to measure environmental toxins, dietary intake and physical activity, and an individual's biological response to those influences.

ONGOING NHGRI INITIATIVES

Use of Comparative Genomics to Understand the Human Genome

NHGRI continues to support sequencing of the genomes of non-human species because of what they say about the human genome. The honey bee genome was published in the journal Nature in October. This bee's social behavior makes it an important model for understanding how genes regulate behavior, which may lead to important insights into depression, schizophrenia, or Alzheimer's disease. The genome of the sea urchin was sequenced and analyzed in November, revealing unexpected sophistication among its sensory and immune system genes.

Medical Sequencing

When it becomes affordable to sequence fully any individual's genome, the information obtained will allow estimates of future disease risk and improve the prevention, diagnosis, and treatment of disease. NHGRI is particularly interested in having a sequencing program that both drives technology and produces data useful to biomedical research. To this end, NHGRI has developed a medical sequencing program that utilizes DNA sequencing to: identify the genes responsible for dozens of relatively rare, single-gene diseases; sequence all of the genes on the X chromosome from affected individuals to identify the genes involved in "sex-linked" diseases; and survey the range of variants in genes known to contribute to certain common diseases.

Sequencing technology advances, on the way to the $1,000 genome

DNA sequencing enables a detailed ordering of the chemical building blocks, or bases, in a given stretch of DNA, and is a powerful engine for biomedical research. Though DNA sequencing costs have dropped by three orders of magnitude since the start of the Human Genome Project (HGP), sequencing an individual's complete genome for medical purposes is still prohibitively expensive. However, bold new advances in sequencing technology developed by NHGRI-funded researchers promise to reduce this cost greatly. NHGRI's ultimate vision is to cut the cost of whole-genome sequencing to $1,000 or less. This could potentially enable sequencing of individual genomes as part of routine medical care, providing health care professionals with a more accurate means to predict disease, personalize treatment, and preempt the occurrence of illness.

New findings in genetics of common disease

Technology development and new research approaches enabled by the HGP, the HapMap, and related NIH initiatives have led to important new understanding of the role of genetic factors in a number of common diseases. For instance, the Hap Map made possible research that recently identified two major genes that influence risk for developing adult macular degeneration, a leading cause of vision loss, with those at lowest risk having <1 percent chance of developing the disease, and those at highest risk a 50 percent chance (Klein et al., Science 2005; Yang et al., Science 2006). Other similarly derived recent discoveries include that variations in the genes *TCF7L2* (Helgasson et al., Nature Genetics 2007) and *SLC30A8* (Sladek et al. Nature 2007) elevate risk for developing type 2 diabetes, variations in the genes *IL23R* (Duerr at al., Science 2006) and *ATG16L1* (Hampe et al., Nature Genetics 2007) affect risk for Crohn's disease, a gene on chromosome 8 plays a role in prostate cancer, and the gene *SORL1* (Rogaeva et al., Nature Genetics 2007) plays a role in Alzheimer's disease. Each of these discoveries opens a new door toward prevention and treatment.

Knockout Mouse Project

The technology to "knockout" or inactivate genes in mouse embryonic stem cells has led to many insights into human biology and disease. However, gene knockout cells in mice have been made available to the research community for only about 10 percent of the estimated 20,000 mouse genes. Recognizing the wealth of information that mouse gene knockouts cells provide, NHGRI coordinated an international meeting in 2003 to discuss the feasibility of a comprehensive project. These discussions have now resulted in a trans-NIH, coordinated, 5-year cooperative research plan that will produce gene knockout cells in mice for every mouse gene and make these mice available as a community resource.

Chemical Genomics and the Molecular Libraries Roadmap Initiative

The NHGRI has taken a lead role in developing a trans-NIH chemical genomics. Part of the NIH Roadmap, this project offers public-sector researchers access to high throughput screening of libraries of small organic compounds that can be used as chemical probes to study the functions of genes, cells, and biological pathways. This powerful technology provides novel approaches to explore the functions of major cellular components in health and disease. In its first year, the ten centers in the Molecular Libraries Screening Centers Network entered screening data from 45 assays in the PubChem database at the National Library of Medicine. The team also published a new high-throughput screening approach that is speeding the production of data to be used to probe biological activities and identify leads for drug discovery.

NEW AND EXPANDED INITIATIVES

Population Genomics

To promote application of genomic knowledge to health, NHGRI recently established an Office of Population Genomics. The mission of the office is to stimulate multi-disciplinary epidemiology and genomics research and develop new resources for the study of common disease. It will take on challenges such as developing standards for genetic and phenotypic data and improved analytic strategies for relating them, stimulating novel research approaches, and supporting cross-disciplinary training to prepare researchers for new opportunities to improve health made possible through programs such as GEI and GAIN. This February, NHGRI's Advisory Council approved two new initiatives in this area. One funds development of a "basic tool set" for phenotypic and environmental exposure measurements in large-scale genomic research; the other supports existing biorepositories to conduct genome-scale studies with phenotype and environmental measures in electronic medical records. In the tradition of the HGP, the Office will promote widespread sharing of data, to stimulate the broadest possible application of knowledge and maximize public benefit.

The Cancer Genome Atlas (TCGA)

The Cancer Genome Atlas (TCGA) is a joint NCI–NHGRI effort to accelerate understanding of the molecular basis of cancer through application of genome analysis technologies. Technologies developed by the HGP and recent advances in cancer genetics have made it possible to envision mapping the changes in the human genome associated with all forms of cancer. TCGA began in 2006 with a 3-year, $100 million pilot project to determine the feasibility of a full-scale effort to explore the universe of genomic changes involved in all human cancers. Over the 3 years, NCI and NHGRI each plan to contribute a total of $50 million. The first diseases being explored are glioblastoma multiforme, ovarian cancer, and squamous cell lung cancer.

TCGA will provide (1) new insights into the biological basis of cancer; (2) new ways to predict which cancers will respond to which treatments; (3) new therapies to target cancer at its most vulnerable points; and, (4) new strategies to prevent cancer.

The Human Microbiome

There are more bacteria in the human gut than human cells in the entire human body. Furthermore, gut microbes have a profound effect on many human physiological processes, such as digestion and drug metabolism, and play a vital role in disease susceptibility and even obesity. The human microbiome project represents an exciting new research area for NHGRI, which, except for the bacterium *E. coli*, has focused its large-scale sequencing program on higher organisms rather than bacteria. Sequencing the genomes of 100 microorganisms that represent a significant, but unknown, fraction of all microbes in the human gut should provide a more complete picture of this aspect of human biology than has been available previously.

OTHER AREAS OF INTEREST

The U.S. Surgeon General's Family History Initiative

The family medical history is an effective and inexpensive means to determine more accurately an individual's risk for specific diseases; however, it is underutilized in health care. The U.S. Surgeon General's Family History Initiative was established to focus attention on the importance of family history, and NHGRI has taken a lead role in this initiative. To further the effort in 2006, NHGRI selected the 12,000 employees at Brigham and Women's Hospital for a 1-year demonstration project to educate and engage the health care community about the family history. To spread the importance of family history to the public, the software tool, "My Family Health Portrait," was enhanced for easier use, and resource materials were distributed to chronic disease and genetics experts in the State health departments of every U.S State and territory.

Genetic Discrimination

NHGRI remains concerned about the impact of potential genetic discrimination on research and clinical practice. A wealth of research has demonstrated that many Americans are concerned about the possible misuse of their genetic information by insurers or employers. The Genetic Information Nondiscrimination Act of 2007, S. 358, and its companion House bill, H.R. 493, are presently under consideration by the Congress. In 2005, the administration supported S. 306, the Genetic Nondiscrimination Act of 2005. In January of this year, President Bush visited the NIH and reiterated the administration's desire to see Congress pass a bill to protect Americans from genetic discrimination.

Thank you, Mr. Chairman. I hope I have offered you an informative view of the newest frontiers of science from the front lines of genomic science. I would be pleased to answer any questions that the Committee might have.

Senator HARKIN. Thank you, Dr. Collins. I want to come back to this knock-out project. I don't understand it, but I want to understand it a little bit more, but we'll get to that later.

Dr. Donald Lindberg has served as the Director of the National Library of Medicine since 1984. He has an M.D. from Columbia University. Dr. Lindberg is a noted pathologist and a pioneer in applying computer technology to health care.

Dr. Lindberg, welcome again to the committee. You've been here many, many times over the years. Good to see you again.

STATEMENT OF DR. DONALD A.B. LINDBERG, DIRECTOR, NATIONAL LIBRARY OF MEDICINE

Dr. LINDBERG. Thank you, Senator Harkin.

Senator HARKIN. Please proceed.

Dr. LINDBERG. Since 1836, the National Library of Medicine (NLM) has been extremely fortunate to have received good help and consistent funding from the Congress. Thanks for this, and for today's opportunity to be present, again, before the committee.

What does NLM do? Libraries, we too, are really part of science infrastructure. For much of our history, it was sufficient for NLM

to acquire, organize and disseminate biomedical knowledge from the world for the benefit of the public health. But, biomedical knowledge has radically changed, both in volume and in form, and now, in addition to doctors and scientists, we also serve the public directly.

To do this work, we now spend a lot of time, money, effort and space in creating and maintaining the electronic networks, databases, and information technology standards. These are essential now to support both new discoveries, and the use of these in good patient care. The number of papers we're indexing has gone up roughly 100-fold, database entries 1,000-fold. In addition, we now link genetic data directly online to the formulary and even the three-dimensional structures of the small molecule and protein products, pretty different from the old days.

These, and over 40 highly specialized NCBI databases are important to researchers exploring the questions, how genes work, and how genomic medicine can help us. In some ways, the task of helping patients and families to understand their medical situations, is as difficult—maybe more difficult—as helping the scientists.

Taking both groups together, we responded by computer to a billion online inquiries last year. They tell me that—petabytes and all of that doesn't mean too much to most people—but basically every 3 days, we download an amount of data totally equivalent to the contents of the Library of Congress. So, this information is really used.

NLM is the largest medical library in the world and, by far—more than even an ordinary modern library. Since our beginning, Congress added a number of explicit responsibilities, and I'll mention some. The two large ones, of course, are the Lister Hill Center for communications research, and more recently, NCBI for biotechnology information.

In addition, we have responsibility for collection of information on toxicology, environmental health, healthcare technology, and most recently, for the establishment of a national—speedily becoming international—clinical trials registry.

So, we're infrastructure. As such, we note that scientific infrastructure responsibilities, and hence, expenses, must increase faster than the growth of the experimental science we serve. This is because all of the Institutes share Dr. Collins' infectious belief that molecular biology and whole genome studies are science's best bet. I do, too.

Thus, more experimental data needs to be acquired, organized and made available online to investigators. Successful databases grow in size, and in the number of users, and the costs go up, even with increases in our efficiency.

We are most grateful to the committee for increases in funding, specifically for that which it provided for this purpose this year.

Some might think that infrastructure role a bit dull, but for us, with the current growth of insights and discoveries stemming from use of our information service, it's more like a great roller coaster ride on a sunny day.

ELECTRONIC HEALTH RECORDS

I want to mention very briefly, we have an interest in the full deployment of electronic health records. Across the United States, this is one of our top priorities. It's one of the Department's top priorities. It's important for two major reasons.

First, long experience has shown that quality control warnings, clinical guidelines, best practices are simply so numerous and complex that they are not helpful when left to either doctors or patients alone to remember and use. We need computer-based medical informatics support. NLM does, in fact, support informatics research and training in the universities. We ourselves produce and disseminate information technology standards nationally, and as an official HHS function.

Electronic health records are key for a second important reason, namely to get family and genomic studies into the patient record.

ACCESS TO SCIENTIFIC LITERATURE

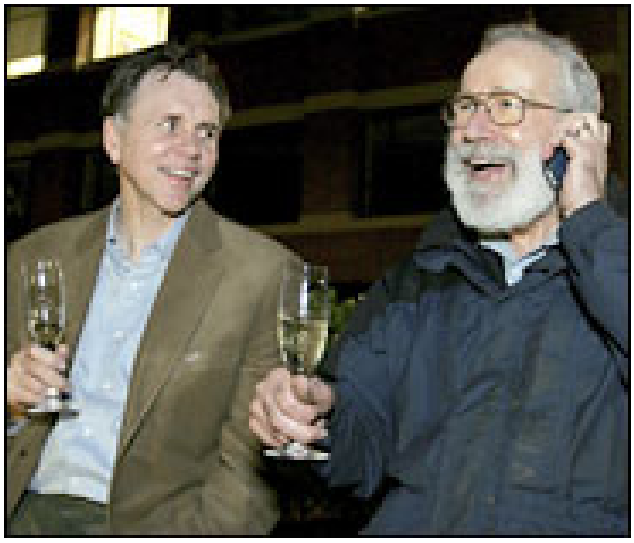
Briefly, the future now holds new discoveries that will come from new directions and new measurements, such as the genomic work that Dr. Collins describes. These will be based on ready access to full text sources of scientific literature and scientific databases, but new discoveries will also come from reexamination of some old ideas.

The following shows Barry Marshall and Robin Warren on October 4, 2005, receiving their telephone call from the Nobel Prize Committee in Stockholm; lifting a glass, of course, on the occasion.

[From The New York Times, October 4, 2005]

TWO WIN NOBEL PRIZE FOR DISCOVERING BACTERIUM TIED TO STOMACH AILMENTS

(By Lawrence K. Altman)



Barry Marshall and Robin Warren, celebrating their Nobel Prize

. . . "made an irrefutable case that the bacterium Helicobacter pylori" causes ulcers and other diseases. . . .

. . . A famous experiment Dr. Marshall conducted on himself. . . .

. . . Dr. Marshall said that information he obtained from the National Library of Medicine, a part of the National Institutes of Health in Bethesda, Md., aided his discovery. . . . Dr. Marshall worked in a hospital in Port Hedland, in the Australian outback about 1,000 miles from Perth. . . .

. . . bundles of references . . . "a whole lot of literature showing that many patients with ulcers had gastritis that the ulcer experts in the 1980's had forgotten about."

The prize honored their discovery that—and proof—that peptic ulcer is actually caused by infection by a bacterium, *Helicobacter pylori*—not by neurosis, stress, spicy food or all the other nonsense we used to be taught about.

Now, when he received the call, Marshall immediately said to the press, "Information from the National Library of Medicine aided my discovery." Dr. Marshall himself worked in a hospital in Port Hedland, Australia in the outback, 1,000 miles even from Perth, but he got what he described as "bundles of references" showing that many patients with ulcers had gastritis that the ulcer experts had forgotten about.

So, of course, we're grateful for this discovery, and for the acknowledgement. But frankly it makes one hope that whatever else in medicine is not true will also get re-examined by some doubters with library cards.

NLM FUTURE PRIORITIES

Now, for the next year, just three areas we have great interest in. Dealing with the space problem, which we're seriously at NLM and the committee has helped us with that in the past by providing money for planning. We are also very keen on the outreach to consumers, patients' families and the public, and the NIH MedlinePlus magazine, which again, you helped us with a Capitol Hill launch. That was great.

Senator HARKIN. Yeah, I remember that. Yep, yep.

Dr. LINDBERG. Mary Tyler Moore. Then we think we ought to be doing something more in our Long-range Planning Committee from the Board of Regents thinks that we ought to be doing more to try to be involved in helping the country with disaster—at least health information management. So those are our hopes and desires.

Senator HARKIN. Yeah, it was, a nice event. How often do you come out with that?

Dr. LINDBERG. Quarterly.

Senator HARKIN. Quarterly. Online also?

Dr. LINDBERG. Online also. Anyone can actually request it online and get it free.

Senator HARKIN. Yeah, oh, I understand. Yeah.

PREPARED STATEMENT

Dr. LINDBERG. Lance Armstrong was on the cover of the first edition, as you remember. He was helpful, too.

Senator HARKIN. Oh yeah?

Dr. LINDBERG. Mary Tyler Moore was on the cover of the second edition.

[The statement follows:]

PREPARED STATEMENT OF DR. DONALD A.B. LINDBERG

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Library of Medicine (NLM) for fiscal year 2008, a sum of $312,562,000.

The National Library of Medicine has a remarkable track record of preserving the past while serving the present and preparing for the future. A just completed Long Range Plan done by the Library's Board of Regents lays out in broad terms the challenges the Library will face over the next decade and charts a course for action to successfully meet these challenges.

Prominent among the challenges is the need to create the information resources essential to achieving the goal of "personalized medicine," in which prevention and treatment strategies are tailored to an individual's specific genetic make-up. The first step is to provide huge linked databases and software tools that allow scientists to correlate clinical, genomic, and chemical compound data with published research findings to determine how genetics and a person's environment interact to cause disease and to identify potential new therapies. Such resources, now being developed by NLM, will speed scientific discovery and can ultimately transform medical care by allowing clinicians to customize treatments to a patient's genetic characteristics.

In an era of increasing chronic disease, a related challenge is the need to empower people with the knowledge and motivation to improve their health and play a more active role in their health care. The information that pours out of the Nation's laboratories—and often finds its way into the public media—has the potential of improving the health status of our citizens. The National Library of Medicine has created heavily used Web-based information services aimed at the public. These services transmit the latest useful findings in lay language and provide guidance that can be easily understood by the public. NLM works with libraries and community-based organizations to increase public awareness and use of these valuable resources.

Electronic health records with advanced decision support capabilities will be essential to achieving personalized medicine and will also help people manage their own health. Much of the seminal research work in this arena was supported by the National Library of Medicine or undertaken by people who received NLM-funded informatics education. This work builds on two decades of research and development of the Unified Medical Language System (UMLS) resources which help computer systems behave as if they "understand" the language of biomedicine. The NLM also serves as an HHS coordinating center for standard clinical vocabularies and supports, develops, or licenses for U.S.-wide use key clinical vocabularies.

No information source is useful if it is unavailable. A third major challenge facing the National Library of Medicine is ensuring uninterrupted access to critical information resources in the event of disaster or other emergency, natural or man-made. As recent hard experience demonstrated, this requires careful advanced planning, strong inter-organizational arrangements, and skillful management of information during the emergency, in addition to robust technical backup arrangements for computer and communication systems. NLM's new Long Range Plan specifically recommends that the Library establish a new Disaster Information Management Research Center and ensure effective recognition and use of libraries as a major and largely untapped resource in the Nation's disaster management efforts.

This opening statement is built around these three themes—scientific information resources that can lead to personalized medicine, information services that enable greater personal involvement in health and health care, and marshalling the Library's resources to assist the country's in emergency situations.

SCIENTIFIC INFORMATION RESOURCES—NEAR AND LONG TERM

Fueled in part by funding from the National Institutes of Health, the pace of discovery in today's world of biomedical research is amazing. The NLM is now at the center of much biomedical research—not only receiving, storing, and disseminating published research results, but actually serving as a crossroads for the genomic and other data coming from laboratories around the world. NLM databases and systems are essential tools in all aspects of biomedical research. Users conducted more than 1 billion searches of them in the last year.

The core of the National Library of Medicine is its expanding collection of more than 8 million books, journals, and other materials. The Library subscribes to more than 20,000 periodicals of which some 5,000 are indexed for Medline/PubMed, the immense online database of the journal literature. From the more than 16 million records in Medline/PubMed one may link to a tremendous variety of relevant Web-accessible online resources at NLM and elsewhere. NLM's National Center for Biotechnology Information (NCBI) has already begun building the Medline/PubMed of the future by redesigning its displays and interfaces to make it easy for users to see important links and retrieve information they might not otherwise have noticed.

The NCBI is the source of GenBank, the genetic sequence databank that contains all publicly available DNA sequences. GenBank is produced from thousands of sequence records submitted directly from researchers and institutions prior to publication. NCBI has also created PubChem, a repository for what are called "small molecules" that are crucial in drug development. Small molecules are responsible for the most basic chemical processes that are essential for life and they often play an essential role in disease.

The NCBI's effective performance on these and other trans-NIH priorities has earned NLM a prominent role in the important new Genome-Wide Association Studies (GWAS) project. GWAS is an NIH-wide initiative directed at understanding the genetic factors underlying human disease. It involves linking genotype data with phenotype information in order to identify the genetic factors that influence health, disease, and response to treatment. NCBI is building the databases to incorporate the clinical and genetic data, link them to the NLM's molecular and bibliographic resources and, for the first time, make these data available to the scientific and clinical research community. dbGaP (database of Genotype and Phenotype) debuted in December 2006 to archive and distribute data from Genome-Wide Association Studies.

PubMed Central, a Web-based archive of biomedical journal literature also developed by the NCBI for the NIH, provides free access to the full-text of peer-reviewed articles. PubMed Central is also home to full-text journal articles submitted by scientists with NIH funding under the NIH Public Access policy.

NLM's Lister Hill National Center for Biomedical Communications also produces important tools for biomedical and informatics research, including digital image libraries—sets of image data that can be used in research, clinical care, and training. In one example, NLM is currently collaborating with NIH and other researchers to

develop advanced imaging analysis tools for research in human papillomavirus infection and cervical neoplasia. The tools will allow effective analysis of some 100,000 images of the uterine cervix and they will become the primary resource for professional training and testing in this field. Another set of imaging tools being widely applied in the scientific community, for education and other purposes, is related to the "Visible Humans." These two enormous data files (one male and one female) were created under the guidance of the Lister Hill Center and provide detailed image data sets that serve as a common reference for the study of human anatomy, for testing medical algorithms, and as a model for image libraries that can be accessed through networks.

INFORMATION SERVICES FOR THE PUBLIC

The audiences served by the Library have multiplied in recent years. In addition to providing researchers and health care providers with access to scientific information, the NLM also now has services for the public—from elementary school children to senior citizens. The Library's main portal for consumer health information is MedlinePlus, available in both English and Spanish. Much of this information is based on research done or sponsored by the NIH Institutes. In addition to more than 700 "health topics" (main entries on diseases and disabilities), MedlinePlus has interactive tutorials that are useful for persons with low literacy, medical dictionaries, a medical encyclopedia, directories of hospitals and providers, surgical videos that show actual operations, and links to the scientific literature. Just last September we launched here in the Congress a major initiative to put into doctors' offices and share with the public good health information in the form of a new publication, the NIH MedlinePlus Magazine. We were joined in unveiling the publication by Senator Tom Harkin and Congressman Ralph Regula.

Several databases for consumers are byproducts of research in NLM's Lister Hill Center. One of these is the ClinicalTrials.gov database, which describes clinical research studies funded by NIH and others around the world. The site contains information on more than 37,000 federally and privately supported trials and is searched daily by some 30,000 people. Another Lister Hill Center database is the Genetics Home Reference, a Web site for consumer-friendly information about genetic conditions and the genes or chromosomes related to those conditions.

NLM's toxicology and environmental health program also produces heavily used consumer information resources. The Household Products Database provides easy-to-understand data on the potential health effects of more than 2,000 ingredients contained in more than 6,000 common household products. The colorful Tox Town looks at an ordinary town and points out many harmful substances and environmental hazards that might exist there. ToxMystery, an unusual interactive Web site for children between the ages of 7–10, provides an animated, game-like interface that prompts children to find potential chemical hazards in a home.

Of inestimable help to the NLM in meeting its varied responsibilities—both to the scientific community and to the public at large—are the 5,800 member institutions of the National Network of Libraries of Medicine. The Network comprises eight Regional Medical Libraries, 120 "resource libraries" primarily at schools of the health sciences, and thousands of hospital libraries and community-based organizations. Together they form an efficient way to ensure that the published output of biomedicine is easily accessible by scientists, health professionals, and the public. They cover the critical "last mile" to familiarize researchers, health professionals and the public and to develop sustainable partnerships with community organizations to improve access to health information for underserved populations.

MANAGING VITAL INFORMATION IN TIMES OF DISASTER

A number of NLM's advanced information services and tools are designed for use by emergency responders when disaster strikes. The Library has a history of providing assistance in such cases, for example the gas leak disaster in Bhopal, India, in the eighties, and Hurricane Mitch and the earthquakes in Central America in the nineties. NLM's TOXNET, a cluster of databases covering toxicology, hazardous chemicals, toxic releases, environmental health and related areas, provides a foundation for services to first responders, such as WISER (Wireless Information System for Emergency Responders). Used in Louisiana after Hurricane Katrina, WISER provides information via handheld mobile devices to help identify unknown substances.

Among other such projects, the Library: (1) supported pioneering work on automated biosurveillance, self-healing wireless networks, and smart tags to track patients during emergencies; (2) built the Influenza Virus Resource with the National Institute of Allergy and Infectious Diseases to provide vaccine researchers access to

genomic data of many influenza strains; (3) developed OSIRIS (Open Source Independent Review and Interpretation System), a software package to assist in identifying 9/11 victims' remains via DNA; (4) worked via the National Network of Libraries of Medicine to re-establish and maintain a level of health information services in the Katrina-affected region; and (5) developed the Radiation Event Medical Management (REMM) system, in collaboration with the HHS Office of Public Health Emergency Preparedness, the National Cancer Institute, and the CDC.

In summary, the National Library of Medicine is well positioned to make a maximum contribution to the Nation's health—by making increasing amounts of scientific data available to researchers and health practitioners, by contributing to the national effort to improve the information infrastructure of the health care system, by providing to the public access to authoritative information for use in maintaining their personal health, and by enabling health sciences libraries to make substantial contributions of disaster information management. All of these activities will depend on a strong and diverse workforce for biomedical informatics research, systems development, and innovative service delivery. To that end, the National Library of Medicine will continue its longstanding support for post-graduate education and training of informatics researchers and health sciences librarians and redouble its efforts to improve the diversity of these fields.

Senator HARKIN. Right, right.

Thank you very much, Dr. Lindberg.

Now we turn to Dr. Roderic Pettigrew, first appointed as the first Director of the National Institute of Biomedical Imaging and Bioengineering in 2002. He received his M.S. in Nuclear Medicine and Engineering from Rensselaer Polytechnic Institute and a Ph.D. in Applied Radiation Physics from Massachusetts Institute of Technology and an M.D. from University of Miami School of Medicine. His own research has focused on imaging of the heart using MRI. Interesting.

Welcome, Dr. Pettigrew. Please proceed.

STATEMENT OF DR. RODERIC I. PETTIGREW, DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Dr. PETTIGREW. Thank you, Senator Harkin. It is my pleasure to report to this committee, the remarkable advances that have been made in another frontier of science, that of medical technology. This field claims the top ring advance in clinical medicine of the last quarter century, three-dimensional human imaging via magnetic resonance imaging, or MRI, and computed tomography, or CT.

In addition, the U.S. medical technology industry has grown to be a $90 billion enterprise with positive trade surplus, and perhaps more importantly, these technologies have significantly improved the Nation's health care.

My Institute, the National Institute of Biomedical Imaging and Bioengineering is the youngest at the NIH and leads the development of a broad range of emerging biomedical technologies. It was created to focus on the science of technological innovation, create new tools that will improve our understanding of disease, and translate these types of new knowledge into practical solutions.

Our research domain is the interface of the physical and the life sciences, and our vision is one of disease detection on a personalized basis, sufficiently early to pre-empt serious consequences of many illnesses, such as heart disease and cancer.

When therapies are needed, these too, will be personalized, and targeted to the offending biologic process. I offer from our young, but broad, portfolio illustrative examples, and you have a handout.

Senator HARKIN. Got it here.

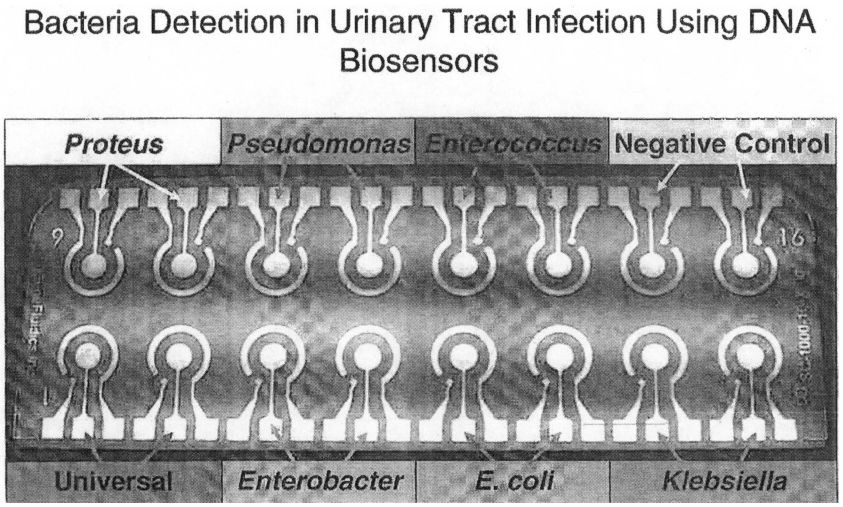


FIGURE 1

Dr. PETTIGREW. See figure 1.

These are three examples, or from three areas that are already transforming modern healthcare. We have just heard about the tremendous advances being made in understanding the genetic basis of disease, such as diabetes and heart disease from Dr. Collins. The use of DNA sequences and genetic variations, as determined in HapMap studies, combined with advanced bioengineering technologies is beginning to be used for routine diagnostics at the first point of physician contact, and this, we term the point of care. A practical example of a very recent development of a DNA-based electrochemical sensor that can quickly identify the specific bacteria responsible for an infection is shown here.

This is actually similar to the type of chip that Dr. Francis Collins gave you. Normally, identifying bacteria responsible for urinary tract infections or infections in general, takes about 2 days. But, with the euro-sensor that you see there, this can be accomplished in about 30 minutes. This——

Senator HARKIN. What you mean, is the specific type of the bacteria can be identified.

Dr. PETTIGREW. Yes.

Senator HARKIN. Within 30 minutes.

Dr. PETTIGREW. That's right.

Senator HARKIN. Okay.

Dr. PETTIGREW. Thank you for clarifying that, the bacteria specifically responsible for the urinary tract infections can be identified in 30 minutes, from the normal panoply of bacteria that are commonly responsible for this type of infection.

This also allows for a more personalized prescription of the most specific and effective antibiotic treatment, and helps reduce the growing problem of antibiotic resistance caused by non-specific use of antibiotics.

Perhaps more importantly, Senator, this type of device as indicated, is indicative of the type of exciting technological innovation

that is leading to tools for personalized diagnostics on a routine basis. These systems, like the one you have on the board there, obviously are portable, they employ nanotechnologies that are ultimately responsible for this type of portability, and as a result of the portability, these can be available in all communities, including the rural and underserved areas.

Another example of an engineered point of care diagnostic device is figure 2, a contact lens that senses the glucose in tear fluid, and shows a level of glucose simply by changing colors.

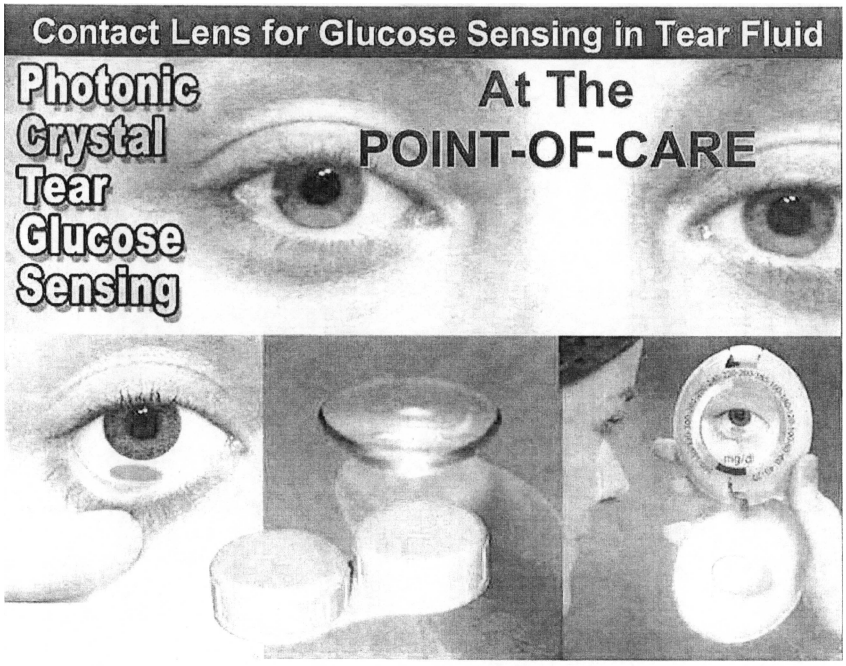


FIGURE 2

A second area of transformative technology supported by my Institute is tissue engineering and regenerative medicine. This, as you heard from the National Institute of Arthritis and Musculoskeletal Disease, in the earlier testimony session, is an emerging technology in which tissues are grown to repair or replace diseased or damaged tissues or organs.

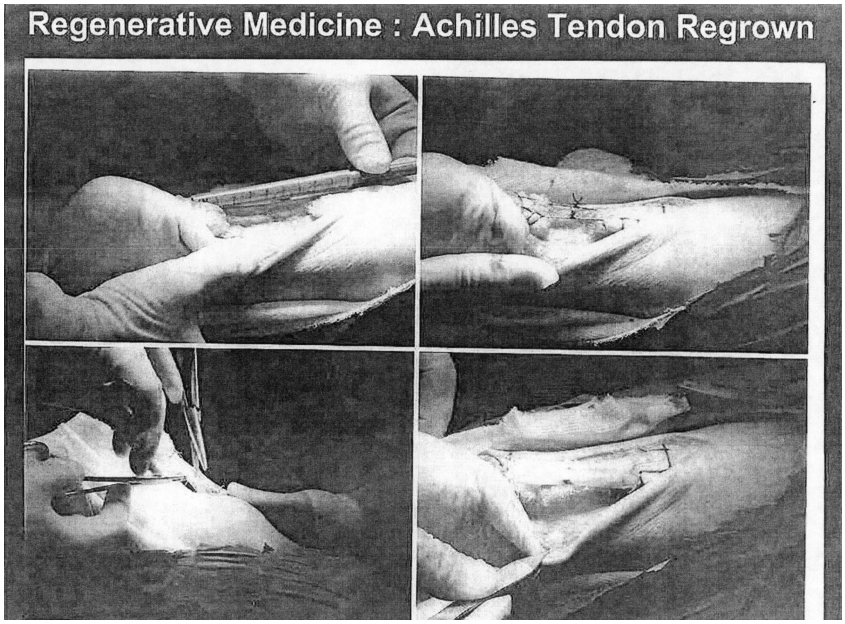


FIGURE 3

Figure 3 shows a subject who has a ruptured Achilles tendon in the upper left quarter panel. You can see the defect which was completely re-grown after placing a matrix material seeded with biologically active molecules. In the bottom right quarter panel, you can see the placement of this matrix material, on which normal Achilles tendon tissue was re-grown. Six months after this particular procedure, this individual patient had a normal tendon repair.

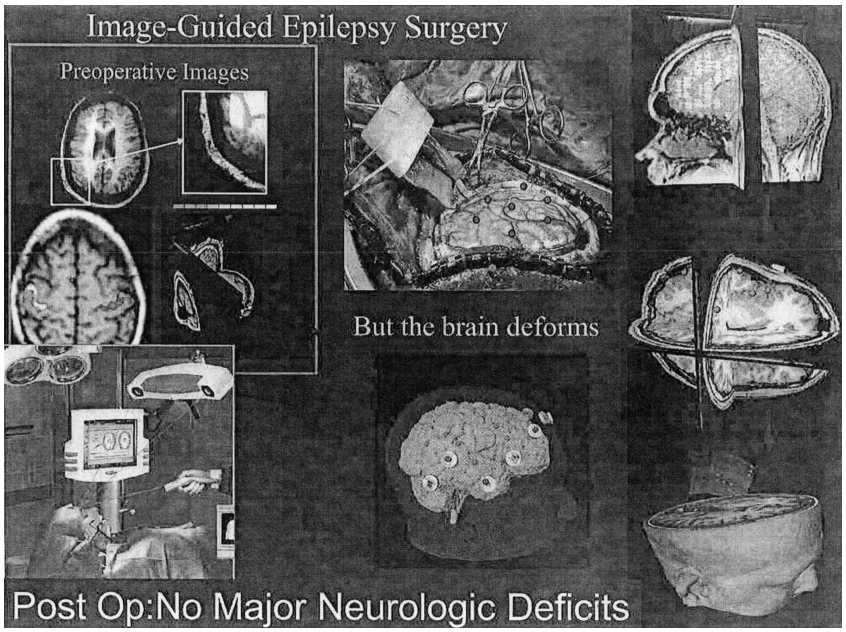


FIGURE 4

Figure 4, the innovation is on a larger anatomic scale. This example illustrates the additional modern advances of image-guided interventions, or also team or inter-disciplinary science, as it has been referred to in the recent past.

These are areas that we also specifically promote at our Institute. The problem being addressed in that particular handout that you have is identifying in the brain the very tiny site responsible for epileptic seizures, while also identifying surrounding normal critical structures. The goal is to show all of this structural, metabolic and electrical information in three dimensions to the surgeon with live updates while he or she is operating, so as to affect a successful removal of the offending tissue with minimal damage to the normal brain tissues.

The team involved in this study is truly inter-disciplinary. It involves a neurosurgeon, mechanical engineer, radiologist, computer scientist, bioengineer and so forth, all who have worked together to dramatically transform the way in which brain surgery will be performed.

Specifically, this team already reports being able to treat up to 60 percent more patients with epilepsy, and in doing so, they've also been able to reduce the operating time by 1.5 hours, and perhaps even as importantly, if not more so, they accomplish this with no neurologic deficits after the operative procedure.

PREPARED STATEMENT

In the future, the vision of an even earlier, preemptive identification of disease will be achieved, as will less invasive approaches to treatment, which will target disease at the cell, and molecular,

level. The NIBIB is working to create more of these types of transforming technologies, that will help realize this vision and improve the Nation's health.

I thank you for this opportunity to present this overview, and also will be delighted to respond to any questions that you might have.

[The statement follows:]

PREPARED STATEMENT OF DR. RODERIC I. PETTIGREW

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2008 President's budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The fiscal year 2008 budget included $300,463,000.

BRIDGING THE PHYSICAL AND LIFE SCIENCES

The mission of the NIBIB is to improve human health by extending the frontiers of biomedical science, through the development and application of innovative biomedical technologies. A major focus of NIBIB is bridging the physical and life sciences in order to develop new biomedical technologies and methodologies that have a profound, positive impact on human health. Translating these technological breakthroughs from the bench to bedside is also a very important aspect of the NIBIB mission, and is demonstrated in some of the examples given below.

TRANSLATING EMERGING TECHNOLOGIES INTO PRACTICE

A Quantum Project to Treat Stroke

Ultimately, NIBIB seeks to translate technological advances into solutions that improve human health by reducing disease burden and enhancing quality of life. To accomplish this goal, NIBIB must be well-positioned to utilize ideas and techniques that are at the cutting edge of science. Also, NIBIB must be bold and far-reaching in generating some of its initiatives in order to more rapidly facilitate discoveries and translate them to clinical practice. NIBIB recently launched the Quantum Grants Program, which supports very high impact, high risk, interdisciplinary and transformative research focused on major biomedical problems. The goal of this program is to solve or dramatically improve a major, previously intractable medical problem through the development and application of new and/or emerging technologies. Interdisciplinary teams of scientists will conduct collaborative research resulting in a prototype product, technology or procedure that promises to solve a significant healthcare problem, and that can be translated into clinical practice in an accelerated time frame. The first grant, awarded in September 2006, aims to develop a novel treatment for stroke, based on implantable units that will lead to neurovascular regeneration of cerebral tissue. This is the first application that has as its target, a treatment for stroke that seeks to restore functional tissue.

Seeing and Treating Heart Arrhythmias

Heart arrhythmias are a major health problem. In particular, atrial fibrillation, a disorder found in about 2.2 million Americans, is a significant cause of stroke. This occurs when a blood clot forms in the fibrillating heart chamber and then breaks loose and travels to the brain. Minimally invasive surgery can be used to treat atrial fibrillation. However, the procedure is complicated and lengthy, often lasting many hours. NIBIB investigators are developing new imaging techniques that permit the abnormal electrical activity to be identified and mapped onto a patient-specific image of the heart. This potentially permits the procedure to be done in one hour instead of six. Beyond the time saving, this approach has the potential for lower cost, decreased exposure to x-rays, greater success rates, and fewer complications. The effort involves collaboration between radiologists, computer scientists, bioengineers, and cardiologists.

Addressing heart diseases of a medically underserved population is the central focus of the Jackson Heart Study. The National Heart, Lung and Blood Institute, the National Center for Minority and Health Disparities, and NIBIB co-fund this study to assess risks factors for cardiovascular diseases, including diet, exercise, and co-morbidity factors such as diabetes and obesity.

Help for the Paralyzed

Paralyzed or "locked in" individuals who retain normal cognitive function but are unable to move parts of their bodies to communicate now have a means of using the computer, based on an interface technology developed by NIBIB grantees. Brain

waves, detected by a skullcap with attached electrodes, are decoded and used to communicate with a computer. By simply thinking of the letters, the user can spell words on the computer. No interaction with a keyboard or mouse is required. Over the past year, a team of neuroscientists has worked intensively to move this system from the laboratory to home use. For one NIH-funded neuroscientist with late-stage amyotrophic lateral sclerosis (ALS, or Lou Gehrig's Disease), this device has enabled him to continue his research. "I couldn't work independently without it," he wrote recently for an article posted on the NIBIB web site entitled "Brain-Computer Interfaces Come Home."

NANOTECHNOLOGIES FOR PERSONALIZED AND PREEMPTIVE MEDICINE

Point-of-Care Systems

Empowering clinicians to make decisions at the bedside, or the point-of-care, has the potential to profoundly impact health care delivery and to help address the challenges of health disparities. The success of a potential shift from curative to predictive, personalized, and preemptive medicine will rely in part on the development of portable diagnostic and monitoring devices for near-patient testing. The NIBIB has contributed to advances in this area by funding the development of sensor and platform-based microsystem technologies. These instruments combine multiple analytical functions into self-contained, portable tabletop devices that can be used by non-specialists to rapidly detect and diagnose disease, and can enable the selection of a definitive therapy at the time of the visit to the physician. A prototypic example under development and funded by NIBIB can identify, from a single drop of urine, the DNA of the specific bacteria responsible for a given urinary tract infection. Moreover, this test can be completed in just a few minutes, compared to the 2 days often required by standard culture techniques.

A second example is in the area of improved diabetes control through non-invasive continuous glucose monitoring. Several NIBIB-funded researchers are working to engineer such a device. One has developed a contact lens that changes colors in response to the concentration of glucose in tears. The lens wearer can compare the color of the contact lens to a chart in order to determine his glucose concentration. If indicated, medications to control blood glucose, such as insulin, can then be administered.

NEXT GENERATION MINIMALLY-INVASIVE TECHNOLOGIES

Restoring Touch in Robot-assisted Surgery

Robot-assisted surgery is expanding the applications and reducing the complications of minimally invasive surgery. Nonetheless, this expansion has been inhibited due in part to the lack of a sense of touch. When surgeons operate on their own, their hands provide important tactile feedback. Although all fields of surgery could benefit from tactile feedback, cardiac surgery is among the fields that have the most to gain. Because of the large number of sutures used, the delicate tissues involved, and the need for precise work, tactile feedback is essential in cardiac surgery. An NIBIB-funded research team is working closely with a cardiac surgeon to create a robotic system that delivers required touch sensitivity. Use of this system could result in fewer broken sutures, more consistent application of force to tissues during surgery, and suture knots with superior ability to stay together. This system is now in development, and it could also serve as an important teaching tool for surgical residents. Rather than the current practice of teaching students exclusively on live patients, new surgeons could obtain more extensive practice in the lab before performing live surgery. Using computer algorithms that recognize motion, a trainee's movements can also be compared to an expert's performance and assessed.

NON-SURGICAL BIOPSY THROUGH NEW APPROACHES TO OPTICAL IMAGING

The diagnosis of many conditions such as cancer depends on microscopic evaluation of tissue samples. Typically these samples go through a process of fixation and staining before they are looked at under a microscope in the pathology laboratory. NIBIB researchers have made significant progress in developing techniques to image tissue in place without the need for surgical biopsy, fixing, and staining. This new imaging approach makes use of the different fluorescent characteristics of normal and diseased tissue, and offers the potential for examining the tissue at the point of care, in the operating room or medical office. Many potential human applications exist, including imaging tissues that form as a sheet such as the bladder or bowel lining. Physicists, biophysicists, imagers, engineers, biologists and clinicians are working together to advance this technology.

FEEDING AND SUSTAINING THE SCIENTIFIC TALENT PIPELINE

Interdisciplinary Training Programs

An important goal of the NIBIB is to train a new generation of researchers equipped to meet the modern needs of interdisciplinary and transdisciplinary research. The Institute's proactive approach is to develop creative and flexible opportunities that will fill critical gaps in the career continuum while also enhancing the participation of underrepresented populations. As examples, the NIBIB has a program to co-train basic and clinical investigators, a Residency Supplement Program to provide research experiences to clinical residents and fellows, and postdoctoral support programs for interdisciplinary training to individual postdoctoral fellows.

The NIBIB also supports and participates in a number of programs to address gender and diversity issues in biomedical imaging and bioengineering. The NIBIB partners with the NSF in the University of Maryland, Baltimore County, Meyerhoff Scholarship Program alliance. This has been an exceptionally effective diversity honors program. Eighty-five percent of the 511 students who have graduated since 1993 have earned a science, technology, engineering, or math doctoral degree.

The NIBIB has also partnered with the Howard Hughes Medical Institute to support the HHMI–NIBIB Interfaces Initiative, a program to develop new curricula to train Ph.D.-MD level scientists at the interface of the physical and life sciences and give them the knowledge and skills needed to conduct research. Collectively, these programs will help to train a new generation of researchers equipped to better meet the challenges of the 21st Century.

Once trained, it is critical that we encourage those who aspire to be great scientists to pursue research careers. New investigators are the innovators of the future and their entry into the ranks of independent researchers is essential to the health of the research enterprise. In addition, the recent closure of the Whitaker Foundation—a catalyst in the evolution of bioengineering as a forefront discipline—has left many in the scientific community concerned about new and early career investigators. For these reasons, the NIBIB is specifically targeting new investigators for special funding consideration. This policy has proved to be successful; in fiscal year 2006 nearly one-third of the NIBIB-funded traditional research grant investigators were new NIH investigators. The NIBIB also participates in the trans-NIH "Pathways to Independence" program which will support recently trained scientists conducting independent, innovative research.

Senator HARKIN. Thank you very much, Dr. Pettigrew.

NIH COLLABORATION

You know, it just seems like, every one of you, in your written testimony that I read, and sort of what you were saying here, you're all involved in this sort of personalized medicine. I guess I'm curious about that, and how that is proceeding, and whether or not there's enough correspondence, or I think, overlap—what's the word I'm searching for, when you talk together?

Multiple SPEAKERS. Collaboration.

Senator HARKIN. Collaboration, thank you, that's the word—is there enough collaboration going on among you and other people at NIH on this? Is this a direction that's sort of, something new at NIH that I'm picking up on? Is there enough collaboration? I just throw it out there for anybody.

Dr. LINDBERG. I think it's endorsed by all.

Senator HARKIN. Yeah?

PERSONALIZED MEDICINE

Dr. COLLINS. If you've seen Dr. Zerhouni's presentations—and I know you have because he's been in front of this committee, he has very articulately, I think, put forward this notion of the four P's—of personalized, preemptive, predictive and participatory—as the emblems that need to be applied to medicine of the future, if we're going to move away from treating advanced disease in a direction

that, in fact, prevents that disease in the first place, because clearly we can't sustain the curve we're on right now, as far as healthcare costs.

I think we are all very much attached to that vision as the promise of the future. You know, you wouldn't go to a shoe store and just pick up a pair of shoes without noticing what size it was, and carry it off to the cashier. But, for medicine, we've been doing the one-size-fits-all approach, most of the time, because it was the best we could do, we didn't have enough information about how to personalize the prevention strategy, so everybody kind of got told to do the same thing, and most of the time they ignored us. Or the treatment strategies, because, you know, you had a diagnosis, well, here's what you're supposed to do, but that might not be the right drug for that person.

We now have, I think, a golden opportunity to really change that perspective into one that is much more individualized, recognizing that while we're a lot alike, we're also different in really important ways that affect our chances of getting sick, and our abilities to prevent that. I do think—to answer your question about collaboration, this is one of the major topics the Institute Directors have gotten together on, the road map the common fund, has provided opportunities to bring projects of this sort more to the forefront, even when no single institute could do.

So, certainly for me, after being at NIH for 14 years, I've not seen an atmosphere more in favor of collaboration and sharing of initiatives and willingness to not worry too much about which Institute gets the credit than what I see right now. Of course, in times of budget constraints, it's even more critical to do that, it's critical at any time. But now, with things being so tight, I don't think any of us want to let an opportunity go by that we might be able to get together and do.

That also extends to collaborations outside of NIH. One of our big projects to look at the genetics of common disease is a public/private partnership where a good deal of the costs of the project are being covered by a pharmaceutical company, even though they get no benefit from it, other than the assurance that it's going to get done right, and the data will be accessible to them and everybody else and everybody else at the same time.

NIH COLLABORATIONS

Senator HARKIN. Anybody else on that?

Dr. COLLINS. Just on pharmacogenetics, pharmacogenomics, are the differences in responses to drugs, that's actually a trans-NIH program that's been in place before the Roadmap, the pharmacogenetics research network and then now involves, I think, 10 or 11 different Institutes and Centers, working on different diseases and different drugs, but sharing a common knowledge base, and sharing expertise in how to design trials appropriately, and, I mean, use the available technology. I think it's very much a collaborative effort that's much more than the sum of the parts, because it's been so well coordinated from the get-go.

Senator HARKIN. In the back of my mind in all of this is that the cost of healthcare keeps going up and up and up and up. It seems

like every time we come up with new discoveries, it just costs more money. So, should we quit discovering things?

Dr. LINDBERG. I'd like to comment on the collaboration, because——

Senator HARKIN. Oh, okay. Because I want to follow-up on this idea that I was, just a—but, go ahead, go ahead, on the collaboration, go ahead.

Dr. LINDBERG. Well, often we've been asked, "Do you ever collaborate with anyone?" I always come prepared with, starting to make a list, and it's—it always is a very, very long list for NLM——

Senator HARKIN. Yeah.

Dr. LINDBERG [continuing]. Because it's natural to collaborate.

But, I think in this list that I made for this particular moment, in case you asked, I was surprised to find that we're actually, there's more collaboration within HHS than I've ever seen in 23 years.

For example, we work with FDA now, you know, when you get a medication, there's a little tiny thing in there that tells you all the things that could happen, and if you can, got eyesight good enough——

Senator HARKIN. You need a 50 power magnifying glass, that's for sure.

Dr. LINDBERG. Yeah, I mean, it's a totally ridiculous thing.

But anyway, we have a team that has worked to produce a new thing through a RX Norm that's a new way to identify those drugs, and it was done with VA and with FDA, surprisingly enough, and FDA now sends us, every day, 300 or 400 new sort of packaging of that stuff, so it can go up online, and an ordinary person can read and halfway understand it.

That's—that's sort of amazing. We're working with the Office of the Secretary on a Radiation Event Medical Management little, a chippy, like this one, and—for toxicology with the National Institute of Environmental Health, and also the CDC, so actually, there's more collaboration in the health agencies than I've seen in past years. Of course, lots at NIH, as well.

I think you'd—I think you actually can be sure that that's happening.

Senator HARKIN. That's good, that's reassuring.

Dr. BERG. Senator, can I comment, briefly on your point about costs going up?

HEALTH CARE COSTS

Senator HARKIN. Yes.

Dr. BERG. With improved diagnostics—and actually knowing what disease it is that you're treating, and treating the right people—I think there's a real hope that the costs will go down. One example is breast cancer treatment. One of the first personalized medicine products that's out there is a gene chip that looks at expression patterns and is reasonably good at predicting whether or not someone is likely to benefit from chemotherapy.

Senator HARKIN. Yeah.

Dr. BERG. The potential consequences of this is that you do this test early on and only treat the people who are likely to benefit

from the very expensive treatment. Don't treat in the same way, people who aren't going to benefit from the expensive treatment anyway.

Senator HARKIN. Well, it was said to me once, you know, if you took the money that goes into health care now, how many trillion is it now? Whatever it is. I don't think people would mind so much the expenditure, in terms of percentage GDP if, in fact, that money went for preventative medicine, early detection, so that people didn't have to go through these excruciating illnesses, and have to go through chemos and radiation and all of the other things you go through—we've done pretty well there, in terms of patching and fixing and mending later on, but that costs a lot of money.

In fact, it ought to be shifted, now, to an earlier point in time for identification, risk factors, and then getting people on the right course of action as they go through their life to prevent the onset of illness—I don't think there would be that much consternation on the spending of money. Most of the people just see it as just going for the same old, you know, patch and fix me up once I get in trouble.

So, I'm encouraged that, what you're all talking about here is moving that point of interaction with the patient earlier on some point in time. That's going to cost money. It's going to cost money, but hopefully as we reach—as we develop these new research regimes, and new techniques, new interventions, that some of the other stuff will start coming down. That's our hope, anyway. I hope it's not a false hope.

Dr. COLLINS. No, I think that's a very wise vision, and one that could be achieved, it really does require a change in mindset, and of course, it requires a change in reimbursement also——

Senator HARKIN. That's true.

Dr. COLLINS [continuing]. In terms of how health care is paid for in this country.

Senator HARKIN. That's the ticket.

Dr. COLLINS. Which is a big issue.

Senator HARKIN. Is how we reimburse.

Dr. PETTIGREW. If I could just interject here, and follow-up on an earlier question—what you just described, Senator, is the paradigm that we currently operate under in health care, and that is a curative paradigm.

Senator HARKIN. Sure.

Dr. PETTIGREW. Where the response is after there's a symptom, and an obvious problem. And, what you also described is, where we're headed and going as a preemptive paradigm, in which technologies—like the one we've talked about, that we've all talked about—will be able to provide an indication that there is a developing disease, early enough so that we can intervene at a time where the technologies that we have to prevent serious consequences, are effective.

You notice that all of us sounded the same tone of personalized health care. I think the reason for that, is that the more that we learn about disease, the more we appreciate that a disease that has a given name can be quite different in different people, and typically is quite different in different people. So, Dr. Berg mentioned breast cancer as an example, and we know that there are signifi-

cant differences in the gene expression patterns associated with breast cancer, and consequently, the treatment should be different—it's not a one-size-fits-all-type of paradigm or approach. That is certainly where we're headed.

I think all of the technologies that we certainly support, really are aimed at being able to see things when they are earlier in the disease process, and in addition to that, developing therapies which are very targeted, specifically to the offending biologic process.

NIH GENES, ENVIRONMENT AND HEALTH INITIATIVE

Dr. COLLINS. Senator, can I add one other thing to this discussion, because I think it's a really important one, and that is the importance of paying attention to the environmental contributions, as well as the genetic ones. I think sometimes people get the sense that we're so excited about genetics—and, believe me, some of us are—that we're ignoring the fact that common diseases like heart disease and diabetes and cancer, are some interplay between hereditary predisposition, and some environmental trigger, and we need to understand both.

We particularly need to understand the environment, because that's the part we might be able to change in somebody who's at high risk, in order to reduce that risk.

In that regard, and this also plays into your question about collaboration, there is this initiative called the Genes, Environment, and Health Initiative, which has now participation by virtually all of the NIH Institutes, and for which $40 million a year have been allocated for the current year, and three more years after this, assuming the budget allows for that.

This is explicitly an intent to both identify what hereditary factors are involved in common disease, but also to develop new and more accurate technologies for assessing environmental exposures—in the air, in the water—and also what the effect of those exposures are on the individual. So, you not only want to know what's out there, and you not only want to know what the body burden is, you want to know what the response was, biologically, of that person. Because it might have been that a particular substance was handled just fine by one person, was actually quite dangerous for another.

David Schwartz, the Director of NIEHS, and myself, are co-leading this effort, this Genes, Environment and Health Initiative, and already a large number of scientists have gotten engaged in helping to lead this, and we will fund, in the next few months, a substantial number of new proposals to try to accomplish this hand in hand, not studying genes in isolation, or environment in isolation, but really getting those two fields together, in a cohesive way. And, I think that's a very exciting and timely effort, at the present time, where we could finally really begin to get our minds around what are the causes of these common disorders, and what we could do about it.

KNOCKOUT MOUSE PROJECT

Senator HARKIN. One other thing you mentioned in your written testimony, you didn't mention it here, was this—tell me about this Knockout Mouse Project, I just don't understand it.

Dr. COLLINS. All right, I'm happy to, Senator. That's another example of a wonderful collaborative effort, because this involves 19 Institutes that have gotten together to support this.

So, what's a Knockout Mouse? Probably conjures up images of people in a boxing ring punching a little rodent, that's not quite what we had in mind.

Senator HARKIN. Or just rubberstamping the same mouse or something, I don't know.

Dr. COLLINS. No, the idea here is, the mouse remains our best laboratory research model for trying to understand human disease, and mice have about 20,000 genes, just like humans do. If you can find a human gene and look at it, you can almost certainly find the mouse homologue of that gene, and it will have a similar sequence. Many times, what we've learned about human diseases, in terms of exactly what's wrong when a gene is misspelled, we've learned first by looking at what happens when that gene is misspelled in the mouse, because there we can do breeding, we can do careful examination in ways that we can't with people.

So, about 2000 or so, mouse genes have been systematically knocked out, that is, inactivated, to see what the consequences would be. That has been a major part of NIH-funded research now, for more than 20 years. But, it's been done in an individual laboratory way. Many of the papers in the medical literature describe the consequences of these knockouts, and it's taught us a prodigious amount about biology and disease.

But, we think we've reached a point where this kind of cottage industry knockout is maybe not the way to go forward. We want to see what happens, now, systematically, if you were to knock out, one at a time, all 20,000 genes, and do it in a sort of Genome Project mindset where you would do it with high-efficiency, low-cost, and easy access to the outcome. That's been another problem, some of the mouse knockouts have been made multiple times, because people haven't been willing to share, and we want to make sure that this time these are all made in a way that anybody with a good idea can get access.

So, all of the institutes got together—even in a tough budget time—and agreed to donate parts of the budget here to make this happen, and we also joined up, quite vigorously, with the Europeans, who have a similar interest in this, and the Canadians, who have a similar interest. Just this past March, we had an international meeting in Brussels, where we pulled together an International Knockout Mouse Consortium, with all agreeing to work together to get this done, as quickly as possible, at low cost as possible, with high quality, and to make all of these mice accessible to any investigator who wants it.

So, basically, what we're going to end up doing here, is saving the NIH a ton of money.

Senator HARKIN. Help me understand this, you're going to knock out one gene——

Dr. COLLINS. At a time.

Senator HARKIN [continuing]. At a time.

Dr. COLLINS. Yes. These days that can be done in a sort high through-put way.

Senator HARKIN. So then you've got a mouse with a gene knocked out.

Dr. COLLINS. Yes.

Senator HARKIN. What are going to do with that mouse?

Dr. COLLINS. So, basically, those will be available as frozen embryonic stem cells to anyone who then wants to investigate that one, and see, "Okay, what happens when that gene is knocked out?" We, at the present time, we don't have the funds to take all 20,000 and put them through a very elaborate set of measurements to see, "Well, is there a problem with the nervous system, is there a problem with the blood system, do they have some birth defect of some sort?" We're going to count on the community to, one by one, as they get interested in a particular knockout, to do that, and then put that information in the public domain. But, what we won't expect them to do, is to actually go and do this tricky thing of knocking out that specific gene, which people have been doing, but at a very inefficient sort of basis.

Senator HARKIN. How long will it take you to do this?

Dr. COLLINS. Five years is the estimate, to get all 20,000 of these knocked out and available, I hope we can do it sooner.

Senator HARKIN. They're done in different places around the globe?

Dr. COLLINS. So we at NIH, we're funding two major centers to do this, but in Europe, there's a major center, in Canada, there's a major center. We are all now working together to make it clear that we don't duplicate the effort—each center has their own list of which genes they're responsible for, we watch closely to see what progress is being made, we'll reassign some if people fall behind in one place, and get the centers that are going faster to pick up the slack, just like the Genome Project, it's international, it requires a lot of careful management and tracking, but it's very achievable.

Senator HARKIN. That's interesting. The one thing that comes to mind is that if I'm not mistaken, genes interplay. So, if you knock out one gene, maybe that doesn't do much. But, maybe if you knocked out one 10 notches down, it might have another effect.

Dr. COLLINS. It's a very good point, Senator, and in fact, if you have them all generated as knockouts one at a time, by mouse breeding, you can make any combination you would then, like, to look at the interactions.

Senator HARKIN. Yeah, I guess that——

Dr. COLLINS. That's the beauty of being able to figure out who mates with whom—which you can do in the mouse cages.

Senator HARKIN. I guess that just comes about through various studies and things, and looking at different genes that have an effect on one thing or another, and matching those up. Yeah, I can see how that would work.

Dr. COLLINS. So, take for cancer, for instance, what we're learning about these "tumor suppressor" genes, that is, genes that normally keep cells from growing out of control when they're not supposed to. A lot of what we've learned is to knock those genes out in the mouse, those mice generally do develop a cancer of some sort, you can then understand by breeding in other kinds of mouse genetic changes, is there some way to suppress that cancer, by activating some other part of the pathway—exactly like you say. It's

a very powerful system. You can do some of these things by cells growing in laboratory dishes, but there's no substitute, really, for having an intact animal, where you have complete control over the whole system.

EXPLANATION OF HAPMAP

Senator HARKIN. Explain that HapMap to me again.

Dr. COLLINS. Yeah, what is this thing?

Senator HARKIN. My question is, cost reduction on studies?

Dr. COLLINS. Yes.

Senator HARKIN. Detailed map of the one-tenth percent variation—tell me about that?

Dr. COLLINS. All right, sure, I'm happy to, this is one of my favorite topics, Senators.

So, your DNA and mine are 99.9 percent the same, that would be true if I picked anybody else to compare myself to, we're all that similar. But, that point .1 percent is still a lot of differences, because the genome is such a big place, with 3 billion letters in the genome, .1 percent of that, well, that's still 3 million changes between you and me, and if we looked at the whole room, and asked, "How many places are there in the genome where, as a roomful of people, we have common differences?" I'm not going to talk about the rare ones that you might find only once, but the common ones, because those are the ones that often drive the risk of common diseases—there would be about 10 million of those in the whole genome.

So, in that collection of 10 million variants, there are some we really want to discover, that play a role in diabetes risk, or heart disease or cancer or asthma or schizophrenia. Yet, finding which one is a real needle in a haystack.

What HapMap set out to do, was two things. One was, first of all, to build that catalog of those 10 million variations, because when HapMap started in 2002, we only knew of about 2 million, and we clearly needed a more thorough look.

But, the other thing that HapMap did, which turned out to be an incredibly useful shortcut, was it figured out that these variations in the genome are not traveling independently of each other. They're basically traveling in neighborhoods. So, if there's a neighborhood on a chromosome where you have 30 or 40 SNPs, there's a good chance if you check two or three of those, and see what their variation is—a SNP, by the way, is a Single Nucleotide Polymorphism which is just a fancy word for saying a "difference in DNA spelling." If you check two or three out of those 30 or 40, you can probably predict what the others are going to be without even looking at them, and that's a reflection of the fact that we're a young species, and these segments of the chromosomes, neighborhoods, if you will, have been traveling in unbroken form since our common ancestors.

Well, you see how that's valuable. That means, if you're looking for a variant that plays a role in asthma, for instance, you don't have to check all 10 million. If you check a carefully chosen 300,000, it turns out, is about the number—and I say carefully chosen because you've got to know what the boundaries of these neighborhoods are, some of them are little, some of them are bigger,

what HapMap did was to tell you how those neighborhoods are organized—then for a fraction of the effort, you can actually look at the entire genome, and you won't miss the answer, you'll find the neighborhood where the culprit is hiding. That saves about a factor of 30 or 40 in the amount of work you have to do.

That, plus these technologies, like these chips that I brought to show you—which have greatly cut down the laboratory costs, mean that we got from this $10 billion price tag for doing a diabetes study, to less than 1 million, and that is a profound change in the space of just 5 years.

So, HapMap plus technology forward is a magnitude drop in cost. Phenomenal.

INTRAMURAL PROGRAM

Senator HARKIN. All right, nice explanation.

Dr. Berg, I want to ask you some—I was reading over your testimony, you mentioned Jeffrey Gray and Ryan Harrison, caught the bug, he was in high school, he met a person at Johns Hopkins through an outreach program, he spent 2 years working in his laboratory, came in fifth place in the Intel Science Talent Search, et cetera, et cetera—what outreach program got him interested?

Dr. BERG. There's a program he attends at the Baltimore Polytechnic Institute that has a program of scientists from around the area who can come and just give talks about what careers in science. I think it was when he was in 10th grade he went to one of these, and thought this sounded, he didn't——

Senator HARKIN. It wasn't an outreach program from you?

Dr. BERG. It wasn't supported by NIH, no. Although we do have programs—not at the high school level—but at other levels that try to do the same sort of thing.

Senator HARKIN. I guess that was my question. Is there a specific program for high school kids to intern with scientists in labs that's backed by NIH? Is there such a thing?

Dr. BERG. We have a diversity supplement program for high school kids. If someone has a lab and wants to have a high school kid come in and work in their lab, there's a way of, to get some support through that program for a particular person. But it's an NIH-wide program.

Senator HARKIN. What do you mean, it's NIH-wide, I mean, don't you handle it?

Dr. BERG. Every Institute has their own version of it. For us, it's a supplement to a grant. So if they have a grant from NIGMS, they can apply, but if they have a grant from any other institute, they can apply as well, and that particular grant is supplement.

Dr. COLLINS. The other big program we have is summertime internships in the intramural program at NIH, we have hundreds of high school students who compete avidly for the opportunity to come and spend 10 or 12 weeks in a laboratory. Generally, in my lab, I take one or two each summer. They are full of talent, it's a very competitive program——

Senator HARKIN. High school? High school?

Dr. COLLINS. High school kids. We also take college kids, but the high school program is very hotly sought after.

Senator HARKIN. How about—that would be a limited number, I mean, these come here for your intramural program.

Dr. COLLINS. Right.

Senator HARKIN. But, I mean, this kid was at a lab at Johns Hopkins?

Dr. BERG. Yes, he is now an undergraduate at Johns Hopkins, and working.

Senator HARKIN. How about when he was a high school student, he worked in a lab?

Dr. BERG. Right.

Senator HARKIN [continuing]. At Johns Hopkins?

Dr. BERG. Right.

ADOPT A SCHOOL PROGRAM

Senator HARKIN. How much of this is done around the country? We've got labs all over the country that are funded by NIH. Do we have any program, that you know of, do you know of any program at NIH where high school students, who have exhibited an interest in science, and would like to spend an internship, a summer, testing out whether or not they really want to get into this kind of research, and do that? Is there a——

Dr. LINDBERG. This is a little bit harder to do than it sounds like, but we're trying to get at that.

I should say, first of all, that many of the Institutes at NIH have an Adopt-A-School Program. We, for instance, have adopted, in Series Two inner-city high schools in The District of Columbia and that's pretty successful, so there's a lot of movement back and forth there. But, I mean, high school kids are young, so they can't just drop out and tool around, they might get a summer. But, anyway, we're trying hard to do that, we've had several outreach programs with high school—large numbers of high schools, five or six together, for instance, New York we just did, with NYU being the host.

You can get them for a day, and that's about it. We tried one in Chicago, and they, the schools let us down on the transportation with busses, and we had—so we had those kind of basic problems.

I would say the best program that I know of is in Houston, and it's the, now-called the Michael DeBacky High School for Science, and it's associated with Baylor. It's taken them over 25 years to get the thing really working, it took 20 years before they even called it the Michael DeBacky School, but he and the other Baylor faculty have pitched in, and it is, again, an inner-city school, but it's got something like 98 percent of the kids going into college, and most of those going into science. So, it's a very intense activity, but a very successful one.

We're trying to follow that model, of course.

Dr. BERG. Let me add one other program, so, another way that we try to influence early science education is we have a series of curriculum supplements that are developed that we make available to teachers from around the country, and NIGMS developed one less than 2 years ago on doing science, so it's not on any particular disease, but it's about the scientific process, curiosity, and designing experiments and controlled experiments, intended for 7th and 8th graders, and that is—was developed in partnership with the

NIH Office of Science Education. We went through all 25,000 copies of it in, I think, a little less than a year, I think it's the first—most widely-distributed supplement that they've done. So, this gives tools for the, for teachers to develop strong programs.

Senator HARKIN. How many students come out to NIH every summer for this?

Dr. COLLINS. I don't know the exact numbers, it's in the hundreds.

Senator HARKIN. Oh, yeah?

Dr. COLLINS. Yes, and every university I know——

Senator HARKIN. These are high school kids, they've got a place for them? I'm getting into the weeds now, on this, but I'm really curious as to——

Dr. COLLINS. I can get you those numbers, Senator. I don't actually know how many high school, how many college are there in the summer, but the place is crawling with summer trainees, which makes it a great place to be in the summertime, all kinds of irreverent questions being asked about science.

Every university that I've ever been involved in has a similar program in the summer in their own location to try to bring students in.

One thing we do, on April 25, which is DNA Day every year, because of the publication of Watson and Crick's paper in 1953 on April 25—we send all of our post-docs and graduate students out to high schools, and they spend the day, all over the country, talking about the excitement about the science that's happening as a consequence of our understanding of DNA. That's been, this has been the fifth year we've done that, this year. It is both great for the students, and it also activates the post-docs to take this on as part of their own professional future, that they're going to spend some part of their time reaching out to high schools in their own vicinity, and trying to teach about what they do.

Senator HARKIN. I'm looking for, I just, ideas, ways of which we get high school students interested, provide access to post-docs and people like that who can kind of bring them along a little bit.

Dr. LINDBERG. I can give you another number, because every summer we bring a dozen to 15 students from this inner-city school, and we used to bring six faculty. So that we were, we thought, helping them. I would say that the net results of that is that the students are fantastic, they're really good, and I think they make progress even in the course of one short summer, and the faculty flunk.

We've stopped—we think that's throwing good money after bad, and we stopped supporting it. We still bring the students. But, they have different things to learn, I mean, for instance, the first bunch we brought through, we gave them—like you're giving us—5 minutes to say something about what do they accomplish in the course of the summer, and two actually passed out, I mean, this was a tremendously threatening thing. You know, a board room, and all of these adults, and you know, it was awful. So, we decided that, you know, one of the top things they've got to learn over the course of the summer, is stand up and make a presentation, look in the eye and tell you, and that is top of the list, and they do very, very well.

Now, they're actually doing multi—they're doing Power Point and Keynote and all of these kinds of things.

PUBLIC ACCESS

Senator HARKIN. Yeah, sure.

There's a lot of talk about publication of research articles, and how soon it should be done. We're getting input from private publications and others, I don't know the answer, but I just want to know—if Congress were to require that all NIH-funded research articles be deposited in the PubMed Central Database, which is the public access plan that NIH has proposed—how would that improve scientists' ability to conduct research?

Dr. LINDBERG. Well, I think it probably would improve it quite a bit. I mean, one of our tests, probably, is from PubMed Central right now, and that is the place that these things would go and the proposals that we've described. The number that are coming in voluntarily is way less than 5 percent of the amount that should come in, but lots of other sources are putting in articles, that are free forever, the publishers and so forth—there's a million articles now in that three set, and it's very, very heavily hit, something like 12 million per month get looked at.

If you looked at it another way, like, "Are all of those of any interest?" Well, 75 percent are of interest. This includes many that we're scanning in from, well, the old issues, let us say, when one publisher says, or society, "You may have this thing," then we say, "Okay, if at our expense you would allow us to go and scan in all of these old ones, back to Volume 1, Number 1, you know, which you have copyright to," so they have a right to say yes or no, would you do that, and then we'll do that if it can be made freely available forever.

Well, lots have said yes, and the Wellcome Trust in England has partnered with us on that, I mean, they, it's dollar for dollar, although actually the pound is going up faster than the dollar has, so we've made a little money on the deal, and so that's going forward very, very well, and that's part of this experiment, in which I said, David Lipman is here, he can confirm all of this for me, but he tells me that 75 percent of those articles do get used right away, so they are of real interest. I think it would make a big difference.

MEDLINE PLUS MAGAZINE

Senator HARKIN. Well, I appreciate that for the record. We don't really know exactly what we're going to do yet.

But, I wanted to ask you about MedLine Plus magazine.

Dr. LINDBERG. Great, I love it.

Senator HARKIN. Again, I've felt for a long time that——

Dr. LINDBERG. There's a new one.

Senator HARKIN [continuing]. That NIH—yeah, you just showed it to me.

Dr. LINDBERG. Yeah, okay, good.

Senator HARKIN. I've got it right here, I have it right here. I have felt for a long time that NIH had to be more aggressive in getting their stuff out to the general public, both at basic science base, but also in translation, so people can understand it. That's why I was happy to join you when you started putting this magazine out, be-

cause this is readable. I mean, you know, even I can understand some of this stuff.

So, I think it's a great resource. And, again, I'd like to see copies of this in every doctor's office around the country. People ought to come in, and they ought to have access to it, and online, you say they can get access online now.

Dr. LINDBERG. Yeah, but most people don't yet have computers and access.

Senator HARKIN. I understand that.

Dr. LINDBERG. I'd like to see it, just as you say, sitting in that waiting room, when they're so boring.

Senator HARKIN. Well, how many copies are you putting out?

Dr. LINDBERG. Well, we're putting out around 50,000 right now, between 40,000 to 50,000, and that's being financed partly by the Friends of NLM found the money to do this, some contributions from the NIH Institutes on a passing-the-hat basis. In order to do what you said, we think that we probably could do it by—there are around 500,000 doctor's offices, so if you schedule, say, three per office, that would be 1.5 million each quarter, 6 million per year, would cost around $3.6 million.

Senator HARKIN. $3.6 million per year?

Dr. LINDBERG. Yeah, and we have about $.4 million, so we're lacking $3.2 million. How to get it, obviously would be childishly simple, to get it through advertising, but that would defeat the purpose, we think, of the whole operation, so——

Senator HARKIN. Yeah, true.

Dr. LINDBERG [continuing]. We've just sworn we're not going to do that. So, we've got to get it either by private contributions, or appropriations.

Senator HARKIN. Well, would doctor's offices subscribe to it? I mean just, you know, would they pay for it out of their——

Dr. LINDBERG. I don't know, we could try it. We haven't tried it, I must say. But we could try it.

Senator HARKIN. There's some good stuff in here.

Dr. LINDBERG. Actually, it would be—it is the only case in which NIH is delivering information, publications, directly to patients. I mean, of course, there's lots of information on all of the Institutes' websites, just as ours, but that's a little different, that's not a publication, often it's as much for scientists as for patients, but this is aimed right at, between the eyes of the patient.

I must say, I was interested in the conversations we've just had, because some of the things Dr. Collins spoke about are really, the doctors and the researchers. You're communicating with them magnificently, even if you've got to go to poor old Belgium to do it.

But, a lot of the other things you spoke about first just won't happen, at all, unless the patients understand it, and agree to it. Including this environmental thing. Because, I mean, who knows where the exposure is, the patient is the expert on the exposure. Unless they believe in this, and participate and understand it, you know, maybe through this kind of a magazine, maybe through everyone else's efforts, none of this stuff will happen. First of all, if they don't trust us, I mean, you have now your Federal legislation pending, that would be a big help. But, I think they have to understand, as well.

I mean, if this whole genetic experiment runs up against stem cells, that's, that we don't want to put up with, we don't want to have it stopped, we want it understood and welcomed.

Senator HARKIN. I missed that, if it's up against what?

Dr. LINDBERG. Well, if people were to conclude that the genetics, the experiments you're talking about have any sort of a political or religious bias, or——

Senator HARKIN. Oh.

Dr. LINDBERG [continuing]. Obstacle, that would be very, very bad. It would be incorrect, we don't want that to happen, but it would be an obstacle to getting this work done, this personalized health experiments. So, I think these magazines, this effort is an important one.

Senator HARKIN. Well, I'm just saying——

Dr. LINDBERG. I appreciate your help.

Senator HARKIN [continuing]. Is there, what more can we do? I mean, $3.2 million, that gets it to every doctor's office, now you want to get it also out to community health centers. I suppose maybe your doctor's offices include community health centers——

Dr. LINDBERG. Yeah.

Senator HARKIN [continuing]. Maybe.

Dr. LINDBERG. Well, I think the higher the volume, the less, you know the prices decrease. These things are about a dollar apiece, I think they can get it now for something like 50 cents, that would give us our 6 million, if you get that, maybe we can drive it below that, find some other way to get it done. Because they can download them right now, free, and copy it themselves.

Senator HARKIN. I thought you said I could download this.

Dr. LINDBERG. You can, yes, yeah, sure. But, I don't know how many people would do it, maybe we can more people doing it, maybe that's what the doctors could do, instead of paying a fee.

Senator HARKIN. Yeah, still, people like to pick up stuff, and read it.

Dr. LINDBERG. I agree, I agree, I agree. But, I think the volunteer agencies, for instance, the alliances have been wonderful to work with, you have lots of work with them and——

Senator HARKIN. Which one can I get the money from?

What are your budgets here?

Dr. BERG. Senator, let me give you one other thing we've been doing, in terms of trying to communicate the basic science messages. It's an electronic newsletter called Biomedical Beat, where we go through the press releases for the investigators that we support, and write one- or two-paragraph, plain language, understandable, hopefully, descriptions of some of the advances. It's been growing for a little bit more than a year now, and the number of people who actually subscribe has increased.

Senator HARKIN. Let's take a look at that $3.2 million, huh?

Dr. LINDBERG. Yes, sir.

Senator HARKIN. All right.

Dr. LINDBERG. The price is good until midnight.

HUMAN MICRO BIOME PROJECT

Senator HARKIN. We'll see what we can do about that.

Let's see, what else did I want to go over here?

Dr. Collins, you mentioned the new effort called Human Micro Biome Project, trillion of microbes in the human gut, you went to talk about obesity and intestinal—could we also find out what causes irritable bowel syndrome and things like that, too? It seems to be an exponential rise up.

Dr. COLLINS. So, this Micro Biome opportunity is another example of something we couldn't have dreamed of doing as recently as 3 or 4 years ago.

You know, our bodies are both populated by microorganisms in various body cavities and orifices, some not proper to mention in a Senate hearing, and there are also, of course, many microorganisms in our skin. It's clear that we coexist with those organisms, happily most of the time, in fact it's clear they contribute to our health. But if something goes awry and the balance is off or you get the wrong microorganism in the wrong place, then one can result in an unfortunate disease situation.

Yet, we don't know nearly enough about this. We've been limited in our understanding of microbiology by what kinds of bacteria we can actually culture in the laboratory. It's clear, that's only a tip of an iceberg. There's lots of other microbes, particularly in our GI tract, that you can't grow. Yet, they're there, and many of them are probably helping us and some of them have the capacity to hurt us. So, how would we get at those?

Well again, the promise of being able to do very high throughput, very cheap DNA sequencing comes to mind, because these microbes have DNA also. DNA is their instruction book, just like ours. So, even if you can't culture them, you can determine what their DNA is by simply doing a—what we call a metagenomic experiment, where you make DNA from a whole collection of microbes and you read out the sequences and you piece together what must have been there.

Again, because this would have been prohibitively expensive until 3 or 4 years ago, it hadn't been approached in a very big way.

A very recent experiment that I think got everybody's attention about this, done by Jeff Gordon at the Washington University in St. Louis, relates to obesity. Where he was able to show—initially in mice, and then in people—that the particular collection of microbes in the gut have a lot to do with whether that mouse is going to be obese or not obese.

In fact, you can take an obese mouse and put the microbes into that animal that had previously been in a skinny mouse, and the fat mouse starts to get skinny too, without any other change. So, there's something going on there, in terms of an interaction between the host and the bacteria that live in their intestinal tract. That's been possible also now to show with people, that a change in body weight can be accomplished by a change in microbes.

Now, imagine what a wonderful circumstance that would be, if we could figure out how to help people lose weight or not gain weight, simply by altering their intestinal flora. It's not unimaginable that might not be the case.

So, we have, in fact, again as a collaborative effort involving lots of institutes, come up with a plan, which we hope will be funded as part of the Common Fund—because this is one of those that touches upon all of the institutes you see here and many that you

don't—to enable a really organized effort to try to characterize what bacteria are present in these various parts of the body. How variable are they from person to person? What happens when you take antibiotics for an ear infection? Does it just throw everything off? How long does it take it to recover?

If you looked at identical twins, do they have the same microbes, or are they different? If they're different, why are they different? Particularly, what happens with inflammatory bowel disease or with vaginitis or with a particular kind of dental problem like periodontitis, that changes those microbial flora in a way that we currently really don't understand, that might lead you into a pretty good idea about how to correct the situation.

So, it's very exciting. Again, another international opportunity here, because the Europeans are very interested in this and I think you're going to hear a lot about this in the course of the next 3 or 4 years as the amount of data we can generate really goes up very quickly. This instrument, this sensor that Dr. Pettigrew told you about, could, of course, be a way in which whatever we learn about microbes could be quickly translated into a diagnostic, yes, once you know what to put on that diagnostic in order to access what particular thing is there that you want to know about right away.

Senator HARKIN. Well, that's all well and good. I hope you don't mind if I remain skeptical.

Dr. COLLINS. Don't mind at all.

Senator HARKIN. I mean come on, look, I mean, calories in, calories out. More calories in, less calories out, it's stored, it's stored as fat.

Dr. COLLINS. We used to think it was just that simple. To first approximation it is, but clearly the microbes in your gut are a big part of your digestive process.

Senator HARKIN. It has to do with the rate of how fast you burn up your energy, too.

Dr. COLLINS. Also, whether you're really efficient at absorbing what you take in, or whether some of it doesn't actually get absorbed. That has a lot to do with what goes on in the distal small intestine, and particularly the colon, and the microbes apparently have a bigger part of that. I think we were all surprised. I was skeptical too, until I saw this paper in Nature from Dr. Gordon. It looks quite compelling.

It only takes a tiny change in your efficiency of absorbing what you eat over the course of many weeks to have a significant effect on what happens with body weight. It doesn't mean that it has to be this drastic difference based on what microbes are there. A little bit makes a big difference over the course of a long period of time.

Senator HARKIN. I, again, I remain skeptical. I just find that, it seems to me that we just need to change some diets and habits and what we consume as kids in this country, in terms of carbohydrates and fats and starches and sugars and everything else that we consume too much of. We get in these habits and habits are hard to break.

Dr. COLLINS. Senator, I think you're absolutely right. This may be a modification of that fundamental principle that might make it a slightly easier case for somebody who's really struggling, but you're basically correct.

Senator HARKIN. That is true. Some people have different rates of metabolism. People have to exercise and eat less than other people in order not to become obese. I understand that, I understand.

MACULAR DEGENERATION

I want to ask about macular degeneration. Dr. Berg, you talked about macular degeneration in a way—and I wrote this down—reverse damage. Is what you're doing, is it at the point of stopping it from progressing, or can you actually reverse the damage?

Dr. BERG. This is not something that we're directly funding. The idea is that it does not reverse the damage, but stops the progression.

Senator HARKIN. Yeah.

Dr. BERG. The way that the pathways contribute to the progression of a disease are understood, to some degree, you can block them with this RNA interference-based therapy.

Senator HARKIN. Where are we in that? I mean, are we in human trials right now?

Dr. BERG. Yes, the phase one trials were successfully completed, the phase two trials are underway now.

Senator HARKIN. It actually stopped the degeneration?

Dr. BERG. That's my understanding. The initial trials are just safety related, but they're into the phase two trials now and the expectation is that this therapy, if all goes well, will be on the market, I believe, in 2009.

Dr. LINDBERG. I think even before that, though, the eye guys have reported that, you know, once they've—well, first of all, the important thing is that a single gene could be seen as responsible for this disease, which was thought in the past to be one of these complex things that must be complicated, but wasn't.

So, once having found that that has to do with capillary growth, the ophthalmologists just reached out and took a syringe full of Avastin and injected it in the globe. If you do this every 10 days for four or five times, you know, metaphorically, they give you back your driver's keys, you know, that you can go from those big things to those small things and you can drive a car again. So I mean, it's a pretty enthusiastic kind of response.

Senator HARKIN. Fascinating.

Dr. COLLINS. This is really a wonderful success story and comes from several directions, Senator. So, basically, macular degeneration, particularly the wet type, does seem to be something that's gone awry, in terms of capillaries. But the treatment that Dr. Lindberg's referring to actually came out of the study of cancer, where we realized, particularly from the work of Judah Folkman, that cancer seems to have the ability to grow, particularly because it recruits blood vessels. Of course, if you can block the blood vessels, you can starve the tumor and it might be a very effective approach.

That's what this drug Avastin is all about, it's an antibody against a particular factor, VEGF, which is what blood vessels need in order to proliferate. So, you're blocking that proliferation. It's a very powerful scheme.

But, it turns out that this same strategy works quite nicely for this wet form of macular degeneration because, there again, your

goal is to try to block the proliferation of these blood vessels that are causing the blindness issue. In fact, there is a fragment of Avastin that's called Lucentis, I think it is, which was approved by the FDA for treatment, which is just as effective but I gather, has some economic disadvantages.

So, here we are in a circumstance where a disease that we considered to be both untreatable and probably not possible to understand, in the space of a short period of time, we've come a long way.

The mention of genetics has also been a big surprise. Most people thought this disease, which comes on in your 70s, 80s, or sometimes even 90s, was not going to have anything to do with genetics. But it turns out there are a couple of genes which play the major role, along with smoking. If you basically can put those together, you can make a very strong prediction about who's at risk. Here's a chance to do prevention. Coming back to our idea about focusing on preventing the disease, instead of waiting until it happens.

If we now know what the pathway is that causes risk here, which has something to do with inflammation, then perhaps by blocking inflammation in the eye, which we have drugs that are pretty good as anti-inflammatory agents, we might be able to—with those people at very high genetic risk, to prevent them getting the disease in the first place. The Eye Institute is investigating that vigorously right now.

Dr. LINDBERG. But Avastin's pretty cheap.

Dr. COLLINS. It is pretty cheap.

Dr. LINDBERG. It's an off-label use, of course, but, and I think the ophthalmologists are amazingly gutsy to do it. They impress me.

Dr. BERG. The potential advantage of the RNA-based therapy, is the same pathway. What this RNA molecule does, it blocks the expression, not of VEGF, but the receptor, what VEGF docks into. As I understand it, what the trials have indicated is it might be longer lasting, so you wouldn't need to get these injections as frequently.

RNA AND FLU VACCINE

Senator HARKIN. You mentioned RNA also, in terms of pandemic flu virus. I've had different people in my office talking about, you know, producing the vaccines. You're right, we really have to wait until we find out exactly what strain it is that is going from human to human. Once you do that, then you can develop the vaccine, but it takes a while to develop the vaccine, obviously, ape-based, long time. Then there was another process. Cell-based.

Then, someone came out and said, "Oh, there's an RNA-based method and it's even quicker than anything." But you were talking about it in terms of, excuse me, getting all these different strains and finding some RNA-based system of covering them all, but that was different than what I had heard. What I had heard, you'd wait until you found out exactly what the strain was, then you would develop an RNA-based vaccine to that exact strain and you could do it in just a couple months or something like that. What am I not understanding here?

Dr. BERG. Because we now have sequences of many flu strains, we can see which parts of the viral RNA genome are conserved. Those are things which presumably the virus can't change to avoid,

without damaging itself. Because RNA interference is so general, you can target the RNA molecules anywhere you want. We can go after regions in the viral genome which don't vary from strain to strain. This concept has the potential to be something which I was very skeptical about, sort of a universal flu vaccine.

Senator HARKIN. Universal flu vaccine. Is that being pursued right now? Is that——

Dr. BERG. It is. There's a company that's been developing it in partnership with Novartis (it originally started with an SBIR grant from NIH). Again, it's early stage, but——

Senator HARKIN. So how come they were talking to me about—again, I'm just, I don't know much about this, everyone on my staff does, but I was led to believe that RNA could only be used to develop a vaccine for a specific strain, not for a universal vaccine. That's why I don't, I'm having a hard time understanding this.

Dr. BERG. Right. This is a whole new world of therapeutics and, again, the macular degeneration example is the one that's most advanced. This requires a whole new pharmacology. We still don't know very much about how to deliver these RNA molecules as drugs.

Senator HARKIN. So it's possible——

Dr. BERG. It's possible.

Senator HARKIN [continuing]. To get a universal flu vaccine, no matter what strain comes out.

Dr. BERG. That's the promise. Again, this is very early——

Senator HARKIN. But again, should we be putting more energy and effort and money into that, or into building facilities that, when the strain comes out we can put people to work right away developing the vaccine on an RNA basis?

Dr. BERG. For the time being, I would say, you absolutely need to continue to invest in the technology to make the vaccine available. The whole concept of this technology is only a few years old. There are lots of potential problems, such as how do you deliver RNA molecules? How do you keep them stable enough so that they work? There are lots of hurdles to be overcome, but advances in any one area have the potential to impact the whole field.

Senator HARKIN. My gosh, if you could develop a universal vaccine, that would be the answer to everything.

Dr. BERG. Absolutely. We're investing, and NIAID is investing very heavily in moving this forward.

Senator HARKIN. When is Dr. Fauci here?

Mr. FATEMI. May 21.

Senator HARKIN. Anyone here talk to the Doctor, tell him I'm going to ask him that.

Dr. BERG. I will warn him.

Dr. COLLINS. I have a feeling he'll hear about this.

Senator HARKIN. Warn him I'm going to tell him, "Dr. Berg's got a different approach."

Dr. BERG. Well, they're the ones who are supporting it, so it really just stems from this discovery of RNA interference, which opened up this whole new approach and that's obviously an area where, if we could do it, it would have a huge impact.

NANOTECHNOLOGY

Senator HARKIN. Dr. Pettigrew, I didn't much get into it with you, but this whole area of nanotechnology that I know a little bit about, we hear it being applied in all different areas of physics and material sciences and things like that, nanotechnology, but I don't hear too much about it in health. Most of what I read about nanotechnology as to material sciences, physics, that type of thing, but—computers, but not too much in health. So what is there in nanotechnology that I don't know about? What implications does it have for health and health research?

Dr. PETTIGREW. Well, it's actually quite involved in health, and much of the technology that I refer to in my testimony regarding the ability to detect diseases at the cellular and molecular level would, in fact, involve devices that are constructed at the nanometer scale. As you know, a nanometer is a billionth of a——

Senator HARKIN. The delivery mechanism?

Dr. PETTIGREW. As a delivery mechanism, and also, as a mechanism for observing the response to a therapeutic intervention.

For example, we've talked several times now about breast cancer and heart disease and so forth. One might envision—in fact, there is considerable work already under way in this area, to develop a probe that consists of a nanometer-sized particle, which carries three components on this particle. The first component is a homing agent that delivers the particle to the specific target, such as the HER2 receptor in breast cancer. The second component on this particle would be an imaging agent that allows you to see that, in fact, it went there. It also allows you to see how much went there, and the size of the tumor, in the case of cancer. The third thing would be to deliver a therapeutic agent, such as a gene that codes for vascular cell death, apoptosis, which actually has been demonstrated in some early studies.

So, you'd have this one particle that is target-specific, goes directly to the target of interest, say a cancer cell, or the vascular supply to the cancer cell, as Francis mentioned about angiogenesis and the role that that plays, in which the goal is to destroy the antigenic activity.

The gene is delivered specifically, by way of this targeted nanoparticle, to the cells that make up the lining of these tiny blood vessels, kills them, and destroys the vascular supply.

So, I think that nanotechnology is very much involved. I don't know if you've had the NCI participate in the hearings yet, but when you talk with them, you'll hear about their large nanotechnology research effort aimed at developing just these kinds of probes. My Institute, as well, is very involved. We have a substantial part of our funding, is active in this, in this area. These devices are termed biosensors, in the sense that they send out a signal when they interact with the particular biologic process you're trying to discover.

Another example would be to identify tumors on the basis of the enzymes that they produce, such are protease, which lyses proteins. You have a structure that's constructed in such a way, and this is nanometers in size, that it has two components linked chemically

by a bridge. The two components are such that one emits light and the other one absorbs light.

When they're closely constructed, the emitted light is absorbed by the counter-component, but the bridge is constructed in such a way that is it lysed specifically by the enzyme that the cancer produces. So, when this nanostructure reaches the cancer, and is tailored to be lysed by a specific protease, that lyses, breaks these two components apart and, as a result of that, you can see it and you see the light.

So, the detection of light means that you've found the cancer. This allows you to identify cancer at an early stage, this is where the preemption comes in, is because you can identify it at the cellular stage. Also, monitor the response to various therapies. So——

Senator HARKIN. This is part of translating what you're doing into actual?

Dr. PETTIGREW. Yes. Yes. Absolutely. So again, just to emphasize, I mean, much of the work that's going on now in developing innovative new technologies that will allow you to identify disease early on, this happens at the nanometer scale, one. Then two, deliver therapy specifically targeted to that expression of the disease in that individual, also done by nanotechnology.

GENE THERAPY RESEARCH IN EYE DISEASE

Senator HARKIN. Anything else, Dr. Collins, about gene therapy—what was that dog's name?

Lancelot, the dog. I met Lancelot the dog a few years ago and Lancelot was blind and they did gene therapy and the dog sees. I understand that's now been done, replicated on a number of other dogs. I think the last I heard they were now going to primates.

Dr. COLLINS. Going to primates called people.

Senator HARKIN. Oh, I thought we were just going into——

Dr. COLLINS. So, there is a clinical trial about to get underway, which is supported by NIH. Yeah, this is a really fascinating story. So, the condition here is Lever's congenital amaurosis.

Senator HARKIN. That's it.

Dr. COLLINS [continuing]. Which causes blindness.

Senator HARKIN. Exactly.

Dr. COLLINS. In this case, different than macular degeneration, it's a degeneration of the retina.

Senator HARKIN. Right.

Dr. COLLINS. This particular version of it is caused by mutations in a gene called RPE65, which doesn't mean very much, but it turns out the briard dogs have this same genetic problem, which is why Lance was such a good model to try it out. I've also seen the films of these dogs before and after treatment, which are really dramatic——

Senator HARKIN. It's dramatic.

Dr. COLLINS [continuing]. Going from bumping into everything to clearly having a good grasp of what's around them through their corrected vision.

So, this is a circumstance where gene therapy injected into the eye, carrying in the gene therapy vector, the right version of this gene to make up for the fact that the one that the patient has is not working, shows a lot of promise. In fact, I don't know whether,

in fact, they've enrolled the first patients. This must be about the time where they were getting ready to do so, and I think I just saw last week, there's also a study getting underway in Europe for the same condition also using the same gene therapy vector. So, I think we all wait with bated breath to see if what worked so nicely for the dogs is going to work for people as well, with, I think, a good reason for optimism.

Senator HARKIN. That's great. That's great. That would be under probably the National Eye Institute I assume, right?

Dr. COLLINS. Yeah.

Senator HARKIN. But you, obviously know about it since it has to do with genes and everything.

Dr. COLLINS. Yeah, exactly, but Dr. Sieving could tell you even more.

Senator HARKIN. Exactly.

Well, thank you all very much, thank you again for your leadership, all that you're doing at NIH.

Does anybody have any last thing for the record, before we——

Dr. PETTIGREW. Yeah, I just wanted to comment on the earlier question regarding training for students.

Senator HARKIN. Yeah.

Dr. PETTIGREW. While I think it is more of a challenge to get high school students at the NIH, we do have two programs directed at undergraduate students, both on the NIH campus where we bring in a group of undergraduate students, and train them specifically in bioengineering, and we also have a program, in conjunction with the National Science Foundation where we establish 10 sites around the country at 10 universities, where students at the undergraduate level, and early graduate level, come and work specifically in these areas of new technologies.

Senator HARKIN. Mm hm.

Dr. PETTIGREW. We have a third program that we've recently created in partnership with the Howard Hughes Medical Institute, to develop a new training curricula, focusing specifically on team science and interdisciplinary sciences, as I mentioned before, which is very much one of the waves of the future, where you bring together scientists of multiple disciplines.

We think that these will be the scientists of the future, and that in order to really make that a reality, that the curricula that exists today need to be modified, so that the languages of these different disciplines—mathematicians, and biologists and physicists talk in different languages and know different things—are brought together and understand human biology and disease, as well as a physical science world, so that once they finish school, the can serve and function more effectively in a team science situation.

Dr. COLLINS. Senator, if I could——

Senator HARKIN. Yeah.

Dr. COLLINS [continuing]. Just as one final comment, express thanks from all of us, to you and Senator Specter for the leadership that you've shown through these years in supporting NIH. In my 14 years at the Institution, I've never seen more scientific opportunity, more excitement, more young scientists champing at the bit to jump in and solve problems that are going to have profound implications on human health. It is really a remarkable time.

Yet, we are caught in this dilemma where, we're not limited by ideas, we're not limited by talent, we're not limited by potential for transforming medicine, we're really limited by the ability to take the resources that we've got and try to stretch them as far as we can. We really appreciate the way in which you and Senator Specter have led this process to try to make it possible for us to do as much as we can.

This diabetes discovery that I'm so excited about, just in the last 2 weeks, opens up a whole new set of opportunities in terms of prevention and treatment——

Senator HARKIN. Sure.

Dr. COLLINS [continuing]. Yet when I look and see that we spend the equivalent of one latte per year, per American, on diabetes research—not a venti, mind you——

More like a grande—it does seem sort of discordant, we could do so much more.

Senator HARKIN. Well, thank you all very much, thanks, Dr. Collins. Well, it's been a great partnership with Senator Specter and with me, and over all of these years, and we've seen some great things happen, and right now we're really concerned about the budget crunch, and the fact that we've doubled the funding at NIH, but now it's been leveling off and it's going back, and we never, ever intended for that to happen. We wanted to get it on a higher plateau, and then keep going up. We're both very dismayed by this, and we're going to try to everything we can to get a better allocation this year for NIH.

But, that's just another battle we'll have to fight, I guess, on the budget.

But, I agree with you, there's just a lot of exciting things out there. I mean, this is why I really talked about these young people, getting young people enthused and excited about a career in science, and getting them when they're young. I think during that period when we were doubling it, I kept asking questions about it, because young people now see that they could have a career in research, and I don't want to destroy that, I don't want to have them say, well, maybe yes, maybe no.

Dr. LINDBERG. Now they're stranded.

Senator HARKIN. Yeah.

We've floated them out there, now they're stranded out there. So, hopefully we can fix that, with better budgets and that kind of thing.

Dr. LINDBERG. Many thanks for all you've done.

ADDITIONAL COMMITTEE QUESTIONS

Senator HARKIN. There will be some additional questions which will be submitted for your response in the record.

[The following questions were not asked at the hearing, but were submitted to the Department for response subsequent to the hearing:]

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

NLM FACILITIES

Question. Dr. Lindberg, I understand that NLM faces increasingly stringent space constraints stemming from the continued expansion of its collections, the growing

need for computing infrastructure for storage, search and retrieval of electronic media and the successful implementation of its many important programs. Can you provide some examples of how space limitations affect the Library's ability to fulfill its many functions for information services, research and training?

Answer. Space limitations affect a range of NLM operations and services.

NLM's onsite space for new manuscript collections, such as the papers of eminent biomedical scientists and the records of important professional societies and foundations is at capacity. It is anticipated that the Library may be completely out of space for all collections, including printed books and journal volumes, films, pictures, and electronic collections, by 2010, even projecting a yet-to-be seen decline in hard copy publications. NLM serves as an archive-of-last-resort for the health community, provides access to materials that are not available elsewhere in the world and preserves materials that other health sciences libraries discard. Due to space limitations NIH no longer maintains on-campus training facilities used to teach NIH researchers and other staff to use NLM's search and retrieval systems. The rate of expansion NLM's National Center for Biotechnology Information (NCBI) has been partially governed by the speed with which NIH can locate and reconfigure office and work space for NCBI staff in other on-campus facilities.

NLM's Go-Local service provides consumers and physicians with links from Medline search results to facilities that provide related health care services within their geographic regions. Existing facilities support 17 Go-Local sites, which cover one-quarter of the U.S. population. Additional space would be needed for servers that would allow expansion of Go-Local to cover the entire U.S. population. Space is also one factor that could delay the addition of servers and storage devices needed to house the molecular sequences data key trans-NIH research initiatives, such as whole genome association studies and metagenomics projects.

Question. Can you tell us what steps NLM and NIH are taking to address these concerns and what more is needed?

Answer. NLM is implementing a number of steps to provide additional space for its collections and operations. NLM currently leases space in other buildings, both on- and off-campus. As of spring 2007, NLM leased approximately 33,000 square feet of space in other on-campus facilities and approximately 23,000 square feet of office space off-campus. These figures compare to 312,000 square feet of space in the two NLM buildings (Bldgs 38 and 38A). In coming months, NIH has arranged for NLM to take occupancy of additional on-campus space to house staff of the NCBI. In addition, NLM plans to lease off-campus space for the expansion of NLM's computer facilities. To make additional space for its physical collections, NLM also plans install additional compact shelving in building 38. This will require structural reinforcement of the building to support the additional load of more densely packed books and manuscripts.

Question. How cost-effective is it to lease additional space/facilities?

Answer. On campus, administrative space can be leased at a rate of approximately $19 per square foot, compared to approximately $37 off campus. Rental of on-campus space involves additional costs associated with moving NLM staff to the new site and relocating displaced NIH staff to other—typically off-site—facilities. Other costs must also be taken into account. In evaluating options for expanding its computer facilities, NLM found local expansion considerably less expensive than off-site locations due in no small part to the lower cost of electricity on campus.

Question. What is the status of plans to construct the new building at the National Library of Medicine for which planning funds were appropriated several years ago?

Answer. Architectural plans were completed in 2003 for a building that would provide additional space for Library collections and collaborative workspace for NLM's expanding research and development capabilities, in particular those of the NCBI. NIH did not request funding for construction in the fiscal year 2008 Budget.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUYE

BASIC BEHAVIORAL RESEARCH

Question. Dr. Berg, over the past 8 years, this subcommittee and our colleagues in the other body have pressed the NIH to find or assign a home for basic behavioral research at your institute. The NIH has not responded to positively to this matter even though this same request was a recommendation of the National Academy of Sciences and of Director Zerhouni's advisory committee. It is also a part of the NIGMS statute. Basic behavioral research needs dedicated leadership at the NIH

in this important field of science. When will it be possible for NIH to respond favorably to this request?

Answer. Basic behavioral research, like basic biomedical research, is supported throughout the NIH, both in disease- and stage-of-life-specific institutes and in the institutes and centers with more general missions. An analysis performed by the working group of the Advisory Committee to the Director, NIH, indicated that nearly $1 billion in basic behavioral research is supported across NIH, including support within NIGMS. There is, and should be, basic behavioral research supported by each of the Institutes that relates to its mission.

The authorization language for NIGMS states: "The general purpose of the National Institute of General Medical Sciences is the conduct and support of research, training, and as appropriate, health information dissemination, and other programs with respect to general or basic medical sciences and related natural or behavioral sciences which have significance for two or more national research institutes or are outside the general area of responsibility of any other national research institute." In response to congressional inquiries and in keeping with this mission, NIGMS has initiated two programs recently. The first, "Collaborative Research for Molecular and Genetic Studies of Basic Behavior in Animal Models," is intended to facilitate research involving basic behavioral scientists and investigators with expertise in modern molecular biology and/or genomics. The second, "Predoctoral Training at the Interface of the Behavioral and Biomedical Sciences," will support institutional training grants that provide new scientists with rigorous and broad training in behavioral, biological, and biomedical sciences. These new programs reflect the potential high impact of integrating behavioral and biological approaches to advance fundamental understanding and yield new approaches to promoting human health and treating disease.

The NIH Office of Behavioral and Social Sciences Research (OBSSR) was established by Congress to stimulate research in behavioral and social sciences research throughout NIH and to integrate these areas of research across the NIH institutes and centers. Coordination across NIH is also enhanced by the establishment of the Division of Coordination, Portfolio Analysis, and Strategic Initiatives by the NIH Reform Act of 2006. NIGMS and the other institutes and centers are working with OBSSR and the new division to ensure that NIH supports a broad portfolio of basic behavioral research to further the broad NIH mission. This broad base of support provides a wide range of opportunities for behavioral scientists to find support for their research that is relevant to the NIH mission. In addition, basic behavioral research, just like basic biological and chemical research, that underpins the NIH mission at a deeper level, can find support at the National Science Foundation.

INFORMATION RESOURCES FOR HAWAIIANS

Question. Dr. Lindberg, last year you visited one of our native Hawaiian programs at Papa Ola Lokahi. I am most appreciative of the National Library of Medicine's continued interest in increasing access to health information and health resources for Native Hawaiians. What were your impressions of the Native Hawaiian programs at Papa Ola Lokahi?

Answer. An NLM team visited Hawaii in July 2006 and came away impressed with the effectiveness of Papa Ola Lokahi in working with Native Hawaiian communities and health providers.

Question. How can the National Library of Medicine and Papa Ola Lokahi work together to increase access to healthcare information in Hawaii?

Answer. The National Library of Medicine and Papa Ola Lokahi are working together in a variety of ways to improve access to healthcare information in Hawaii. Working with Papa, NLM has supported two pilot projects—one to strengthen the community library at Miloli'i so that residents have online access to health information; a second to install a computer in the waiting room of the Waimanalo Health Clinic so that patients can access health information. Both projects have made very good progress and are nearing completion. Also, with NLM support, Papa organized a one-day meeting in July 2006 to discuss needs and options for preserving and strengthening the collections of Native Hawaiian Health materials. The meeting was attended by various Hawaiian museum, archival, academic, and community organizations with an interest in this topic. NLM was pleased with Papa's work to arrange and conduct this meeting, and is exploring possible follow up. NLM has also provided support to Papa for improvement of Papa's web site, and, earlier, for participation of two Papa staff persons in NLM's Native American Internship Program. Additionally, Papa is represented on the NLM-supported Health Information Task Force of the National Congress of American Indians. And a Papa staff person was invited to participate in the NLM-sponsored Tribal Outreach Conference held in

July 2006 in Albuquerque, NM. NLM will continue its multi-dimensional relationship with Papa Ola Lokahi in order to enhance access to healthcare information throughout Hawaii.

QUESTIONS SUBMITTED BY SENATOR ARLEN SPECTER

PUBLIC ACCESS

Question. Dr. Lindberg, please provide the following information on eligible articles deposited with NIH under the NIH Public Access Policy. Please include all articles that are eligible for deposit under the policy, including manuscripts and final published articles submitted by authors and publishers:

(1) The total number of articles that have been deposited with NIH since the May 2, 2005 implementation date and the overall percentage of deposits to date. Please describe how you arrived at the total number of eligible articles.

(2) The month-by-month deposits of articles, shown as a percentage of eligible articles available for deposit, and as a monthly total of the number of deposited articles from May 2005 to April 2007.

Answer. (1) Total articles deposited with NIH under the NIH Public Access Policy, May 2, 2005 to April 30, 2007

Articles deposited under the Public Access Policy: 6,196

Total articles eligible for deposit under the Public Access Policy: 142,000

Percent Deposited: 4.4 percent.

Using 2005 publication data as a baseline, we estimate that 71,000 articles per year (or 5,916 per month) should have been deposited as a direct result of the Policy. This is a conservative baseline because of a general upward trend in publication rates from year to year.

(2) The month-by-month deposits of articles, shown as a percentage of eligible articles available for deposit, and as a monthly total of the number of deposited articles from May 2005 to April 2007.

TABLE 1.—AVAILABLE ARTICLES BY MONTH, AS OF MAY 31, 2007

Month	Articles deposited [1]	Eligible articles	Percent of target
May 2005	110	5,916	1.9
June 2005	107	5,916	1.8
July 2005	186	5,916	3.1
August 2005	146	5,916	2.5
September 2005	146	5,916	2.5
October 2005	156	5,916	2.6
November 2005	143	5,916	2.4
December 2005	161	5,916	2.7
January 2006	208	5,916	3.5
February 2006	172	5,916	2.9
March 2006	175	5,916	3.0
April 2006	166	5,916	2.8
May 2006	231	5,916	3.9
June 2006	220	5,916	3.7
July 2006	160	5,196	2.7
August 2006	168	5,916	2.8
September 2006	252	5,916	4.3
October 2006	302	5,916	5.1
November 2006	317	5,916	5.4
December 2006	482	5,916	8.1
January 2007	746	5,916	12.6
February 2007	651	5,916	11.0
March 2007	639	5,916	10.8
April 2007	[2] 152	5,916	2.6
Total	6,196	142,000	4.4

[1] Articles that are approved for release in PubMed Central, including articles that may not actually be released until 12 months after publication, as specified by the author.

[2] Authors of articles submitted in April 2007 have only had a few weeks to review and approve them after conversion to the PubMed Central archival format. We expect the number of approved articles for April to rise in the coming weeks to the same level as for previous months, as authors have time to respond.

At the request of publishers, NLM deployed a mechanism in December 2005 (http://www.nihms.nih.gov/publishers.html#q2) to allow publishers to deposit author manuscripts on behalf of their authors. The welcome growth in deposits from September 2006 forward has been due mostly to a large publisher, Elsevier, beginning to use this system. As of April 2007, Elsevier is submitting all of its author manuscripts based on NIH funded research.

Author manuscripts need to be converted to an archival format for posting on PubMed Central. This conversion must be verified by the author. When author manuscripts are submitted by the authors themselves, the authors almost always complete this verification step. However, NIH is only able to post a portion of bulk deposits being made by Elsevier to PubMed Central, because many authors do not follow up with the necessary verification and approval. Author participation is voluntary under the policy.

In previous reports on the Policy, we counted the initial submissions of files as the number of manuscript deposited. (The actual number of articles that could be publicly released was slightly lower, but the difference was not significant as long as the majority of deposits were made by individual authors.) However, because of the large dropout rate associated with Elsevier's bulk deposits in recent months, it is more accurate to count as deposits only those articles that have the author's final approval for release in PubMed Central. These numbers include author manuscripts that may not actually be released until 12 months after publication, as specified by an author.

This more accurate measure of compliance applies to all of the articles reported in Table 1. As a result of this change in metrics, the deposits for 2005 and the first half of 2006 will be slightly lower than the corresponding numbers in earlier reports to Congress.

For reference, Table 2 shows the total number and percent of author manuscripts sent to NIH via bulk deposit, made by Elsevier between September 2006 and April 2007. The right column shows the number that received the author's final approval for release to PubMed Central and is included in Table 1.

TABLE 2.—ELSEVIER BULK DEPOSIT SUBMISSIONS, AS OF MAY 31, 2007

Month	Manuscripts sent to NIH via bulk deposit	Manuscripts approved for public release by authors	Percent
September 2006	77	52	67.5
October 2006	76	42	55.3
November 2006	204	120	58.8
December 2006	521	251	48.2
January 2007	711	398	56.0
February 2007	796	419	52.6
March 2007	810	389	48.0
April 2007	1,012	106	[1] 10.5
Total	4,207	1,777	(42.2)

[1] Authors of articles submitted in April 2007 have only had a few weeks to review and approve them after conversion to the PubMed Central archival format. We expect the number of approved articles for April to rise in the coming weeks to the same level as for previous months, as authors have time to respond.

We should note that Bulk Deposit is only one method by which publishers can submit content to PubMed Central. Under the Public Access Policy, two scientific societies have signed agreements to deposit all of their final published articles based on NIH funded research to PubMed Central. These PubMed Central (NIH Portfolio) agreements will result in 100 percent of their deposited articles posted on PubMed Central without author involvement.

Independent of the Policy, a number of journals routinely deposit their complete contents in the PubMed Central archive. Many, including the Proceedings of the National Academy of Sciences and the eleven journals of the American Society for Microbiology, have been doing so since 2000 or 2001, years before the Public Access Policy took effect. Authors who publish in these journals do not have to deposit their manuscripts based on NIH funded research under the Policy, because a copy of the journal's published article is already available to the public through PubMed Central. These articles were not included in the baseline total of articles eligible to be deposited under the Policy (71,000 per year or 5,916 per month) and, therefore, are not included in Table 1. Approximately 700 articles based on NIH-funded research come into PubMed Central each month from regularly participating journals.

SUBCOMMITTEE RECESS

Senator HARKIN. Well, thank you all very much, and thanks for taking the time to come down here today, and your expertise, and wish you the best, and keep on doing what you're doing.

May 21 will be our next NIH hearing.

Thank you very much. The subcommittee will stand in recess to reconvene at 2 p.m., May 21, 2007, in room SD–116.

[Whereupon, at 3:29 p.m., Monday, May 7, the subcommittee was recessed, to reconvene at 2 p.m., Monday, May 21.]