

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

FRIDAY, JUNE 22, 2007

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

The subcommittee met at 10 a.m., in room SD-116, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.
Present: Senators Harkin, Reed, Specter, and Cochran.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF RUTH L. KIRSCHSTEIN, M.D., ACTING DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Subcommittee on Labor, Health and Human Services will come to order. This is the last of our six hearings we have had on the National Institute of Health. We have heard from 18 Institutes so far, today we will hear from five more. The National Center for Complementary and Alternative Medicine, the National Institute of Dental and Craniofacial Research, the National Institute of Environmental Health Sciences, the National Eye Institute, and the National Institute of Child Health and Human Development.

I want you all to know, I've really enjoyed the informality of these hearings. This is just like we've had all of the other ones, actually. When I first came on this committee in 1985, Senator Weicker, had sort of established this process of having these kinds of hearings. I thought they were very informative, and this is the way we have done it. I kept thinking, up until the mid-1990's I wanted to re-institute, reinstate that again.

I found that these hour and a half or 2 hour hearings that we have had, for me, it's like being in class again. I get to learn a lot of things I didn't know about, and it's extremely informative, not just for me, but for our staffs on both sides, and people right here. I think we get a little bit more in-depth knowledge of what each of the Institutes are doing, what we're looking ahead for, and I think it gives us a better idea of, perhaps, where our allocations

of money ought to be going. So, it has been great to get into little bit more in depth than we have had.

I just want to say a few words about the fiscal year 2008 budget that we marked up yesterday, by the way. We proposed a \$1 billion increase for NIH. This will allow NIH, for the first time since fiscal year 2005, to plan on increasing the average cost of new grants by 3 percent. I know that's not big, but it's better than what we have had, and it will provide the full-blown committed level for non-competing grants for the first time.

We also increased the common fund by 10 percent. We've set aside the full amount to continue the National Children's Study, and provided additional support for young investigators. I know Senator Specter and I both wish we could have done more for NIH, and who knows, when it goes to conference, maybe we will even do more. We don't know, but we'll do as much as possible.

I want to thank both Senator Specter and Senator Cochran for their support of NIH, and for this proposal that we have, that we passed yesterday in full committee.

With that, I will yield to my colleague, and good friend, Senator Specter.

OPENING STATEMENT OF SENATOR ARLEN SPECTER

Senator SPECTER. Thank you very much, Mr. Chairman. Thank you, ladies and gentlemen for coming in today. The work of this subcommittee is well known, and our vigorous advocacy for NIH, and is even better known for our success in raising the funding level through the efforts of Senator Harkin, Senator Cochran and others on this committee.

When I take a look at the complementary alternative medicine line, my recollection is it was \$7 billion before my wife told me how important it was. I shared that information with Senator Harkin. We have talked about the change of the gavel being seamless—it doesn't matter who is there. Senator Cochran has been a member of this subcommittee longer than either of us has—and as chairman and ranking member of the full committee, and has given tremendous support to these efforts.

I wanted to come by to send my personal greetings to you. I regret that I have commitments in Pennsylvania today. Friday is the day when we try to take care of the home front, except Senator Harkin who works 7 days a week, so he schedules hearings on Friday morning. You can shoot a canon through the Senate and the House today and have no risk of hitting anybody. Except for Senator Harkin and Senator Cochran. So, I'm going to excuse myself, but my staff will stay and report to me of the preceding, and I will be following it very closely.

Senator HARKIN. Thank you very much, Senator Specter, have a good weekend.

Senator Cochran, did you have a statement?

STATEMENT OF SENATOR THAD COCHRAN

Senator COCHRAN. Mr. Chairman, I'm pleased to join you and Senator Specter to welcome our panel of witnesses to the committee today. We appreciate the opportunity to continue our review

of the fiscal year 2008 budget request for the National Institutes of Health.

Today, we have five representatives of different Institutes conducting research to talk about their requests for the coming year, and we appreciate the participation of this panel in hearing and discussing with us your plans for the coming year.

The National Center for Complementary and Alternative Medicine has provided, for the last 7 years, a foundation of scientific research in the emerging area of alternative medicine and therapy. Dr. Stephen Straus served as the Institute's first Director. We convey our condolences to the NIH family for the recent loss of Dr. Straus. A great deal was accomplished under his leadership to further our understanding of alternative therapies, and their role in integrating medicine.

Also, the role that dental health plays in one's overall well being has received more attention recently. The death of a 12-year-old child in Maryland due to a dental infection raised awareness of the importance of good dental care. I am co-sponsoring legislation—the Children's Dental Health Improvement Act of 2007—with Senators Bingaman and Cardin, which seeks to provide disadvantaged children with better access to dental services. The work being done by the National Institute of Dental and Craniofacial Research is important to improving dental health for all Americans.

We're learning that a number of conditions afflicting our population are connected to environmental factors. It's important that we extend our resources from simply treating existing diseases, to identifying ways to prevent them. As we learn more about the impact the environment has on different disease processes, we're better positioned to identify prevention measures. The work in this area through the National Institute of Environmental Health Sciences is very important, and I look forward to hearing about recent advances in this research.

In my State of Mississippi, diabetes is a very challenging situation, presents a very challenging situation. There's been a big increase in the prevalence, and this causes many complications to the health of our citizens. What was once thought to be an adult disease is occurring now more often in children, as we see numbers of overweight and obese young people increase. Progress in this area is very important to me. We have more diabetes as a percentage of our State's population than any other State in the union. So, progress in this area could help a significant number of people.

I'm not going to go through the list and talk about every Institute that is represented here today, but issues like infant mortality, the National Children's Study being done at NIH through the National Institute of Child Health are uncovering disparities which need our attention, and your suggestions as to what we can do about this in terms of national policy and funding priorities.

Dr. Zerhouni has testified before this committee on a number of occasions, in March, he talked about the medical advances resulting from NIH-supported research, and we are aware of the importance of our continuing to be generous in the appropriation of funds for these activities—translating basic science, knowledge into improved and lifesaving therapies is very challenging, but it is very important as we work to improve the work being done by our Fed-

eral Government agencies. I appreciate the hard work all of you are turning in, and your dedication to ensuring that NIH is successful in these important areas of inquiry.

Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Cochran.

Let's just go from left to right. I would like to ask each of you, all of your statements will be made a part of the record in their entirety. I would just like to ask if each of you would just please speak for five to seven minutes, and we'll just go from left to right, then we'll just open it up for kind of general discussion at that point in time.

First I will introduce Dr. Ruth Kirschstein who I don't really need to introduce very much, I'll do it anyway. She has served as Acting Director of NCCAM since August 2006. I want to join with Senator Cochran in expressing my condolences on Dr. Straus' passing. He fought that brain cancer for a long time, it kept coming back, and right up until the end, just did an outstanding job of leading that Institute.

But, Dr. Kirschstein's career at NIH spans 33 years. In 1974, became the first woman to serve as the Institute Director, head of the NIGMS, and her positions also included a 2-year period as Acting Director of all of NIH, and I remember we worked together at that time. In 2002, I had the great pleasure of surprising her by renaming the National Research Service Awards, as the Ruth L. Kirschstein National Research Service Awards.

Dr. Kirschstein, welcome back, as we have for so many years, back to the committee, and please proceed as you so desire.

SUMMARY STATEMENT OF DR. RUTH L. KIRSCHSTEIN

Dr. KIRSCHSTEIN. Thank you, Mr. Chairman, Senator Cochran, and Senator Reed. I want to thank you also for providing us with the opportunity today to discuss NCCAM's vision for the future, and to tell you how much we at NIH are grateful for your ongoing support, and thank you for your efforts on behalf of the health of the American public. Today as Senator Harkin has said, I'm here as the Acting Director of the National Center for Complementary and Alternative Medicine. I'm delighted to be back, and to see you once again.

I have some material from NCCAM, which I want to provide to you, I think some of you have a strategic plan, but just in case, since NCCAM was established by Congress, thanks to your vision, Mr. Chairman, the Center has built a global scientific research enterprise, for the study of complementary and alternative medicine.

The progress that has been made in understanding the scientific basis of CAM is greatly attributable, as you said, to the leadership of Dr. Stephen Straus, NCCAM's founding Director. And I want to thank you and your staff for your kindness in postponing the hearing on the day of his funeral, and to thank the staff for attending the funeral.

INTEGRATIVE MEDICINE

Today, we know that many Americans are using CAM modalities in an effort to promote health and well-being, and to preempt disease, and that it is driven largely by consumer demand for com-

plementary and alternative medicine. Integrative medicine is rapidly becoming the major force-shaping healthcare in the United States.

Integrative medicine makes use of both conventional and complementary therapies to address all aspects of health and wellness. In addition, we know well, that better communication between patients and their medical practitioners is absolutely vital to ensure well-coordinated, comprehensive and safe care.

In NCCAM's pursuit of rigorous science to understand complementary and alternative medicine, is the foundation that will build the evidence to facilitate the adoption of integrative medicine in our society. Our efforts to study and understand CAM continue to grow, and in the past year we have launched three new activities, a new program to assess the potential of community-based, primary care research networks, which will increase our knowledge about the efficacy and the cost-effectiveness of CAM modalities, as well as the safety of the approaches.

We're also studying the mechanism of action underlying manipulative and body-based practices, such as chiropractic. We're developing innovative tools and technologies to study the biologically based aspects of mind body intervention.

Our overall strategy is to support a diverse portfolio of basic translational and clinical studies. The study of acupuncture is an example of this approach. Clinical studies have demonstrated the potential of acupuncture for a number of conditions, such as osteoarthritis, and the basic and translational research using state-of-the-art neuroimaging technology has now elucidated mechanisms of brain function that have direct relevance to pain relief.

Advances of similar importance are beginning to emerge in other areas. In the last year alone, NCCAM supported-research has demonstrated the potential of CAM for addressing a number of conditions, and I would like to give you a few examples.

The spice turmeric, which has long been important as a component of Ayurvedic medicine, is being used in the treatment of many inflammatory disorders. Preliminary evidence shows that turmeric contains specific compounds that may have anti-arthritis activity. This suggests potential ways in which turmeric may be used, and could yield insights into the mechanisms of arthritic disease.

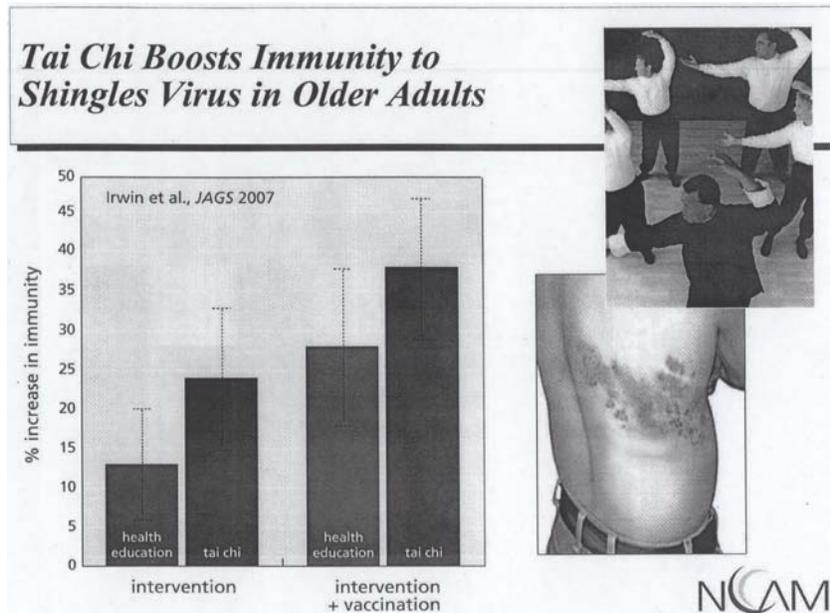
In another example, we have supported studies of the herb Ginkgo Biloba. This is a popular dietary supplement that is purported to promote brain health. Our studies in animal models of Alzheimer's disease have found that ginkgo reduces both the formation of the specific brain abnormalities that are also seen in humans, as well as preventing the paralysis seen in these animals.

These studies of animal models are very important, and will serve as leadership into the hypothesis that is now being tested in a large clinical trial of Ginkgo—the prevention of dementia. This trial is supported, not only by NCCAM, but by a number of the other institutes.

A very recently recognized clinical trial which you have referenced in your folders relates to Tai Chi, which is a traditional Chinese form of exercise. This modality may help older adults avoid getting shingles by increasing their immunity to the

varicellus zoster virus, and enhancing the body's immune response to the vaccine.

Shingles, you know, affects the nerves, and causes pain and blistering in adults. There is a picture (Figure 1) of that in your folders. Shingles is caused by the same virus that causes Chicken Pox in children. Tai Chi combines aerobic activity, relaxation and meditation, and the combination of the shingles vaccine and Tai Chi out does the vaccine alone. This study was supported by the National Institute on Aging and NCCAM.



RESEARCH TRAINING

But in addition, Senator Harkin alluded to the importance of research training. NCCAM mandate to train the next generation of CAM researchers. This must involve collaborations between CAM practitioners, and experienced scientists, and it's absolutely fundamental to our approach to research training and career development.

Since its inception, NCCAM has increased the percentage of funds committed to research, training and career development from 1.3 percent in 1999, to 8.3 percent in fiscal year 2006.

OUTREACH

Now, the other, and third, component of our mission, is to provide authoritative, evidence-based information on CAM. We have a growing communications program that distributes information in English and Spanish, and in both print and electronic form, and includes CAM on PubMed, which is a database developed in partnership with the National Library of Medicine. It indexes more than 470,000 articles related to CAM.

We have an online continuing education program that offers information on a variety of topics, to help professionals and to the public. In addition, this year, we have a new patient provider educational initiative to encourage communication between patients and physicians about CAM use. The program, which is outlined in two pieces of paper in your folder (exhibits A&B), is called, "Time to Talk," to ensure physicians talk to their patients, and that patients talk to their physicians about the use of CAM. It will ensure safety and integrated health care. We look forward to building on NCCAM's foundation of scientific accomplishments in 2008. We will include new activities, such as the partnership with the Centers for Disease Control and Prevention to support the first national, population-based survey, assessing CAM use among the United States' pediatric population. This survey will help to fill an important information gap, and help NCCAM to set additional priorities.

TIME TO TALK. ASK your patients about their use of complementary and alternative medicine.

Ask

Did you know that almost two-thirds of people aged 50 and older are using some form of complementary and alternative medicine (CAM)? According to a recent survey¹ less than one-third of those people talk with their providers about CAM use.

What is complementary and alternative medicine (CAM)?

CAM is a group of diverse medical and health care systems, practices, and products that are not currently considered to be part of conventional medicine. CAM includes such products and practices as herbal supplements, meditation, chiropractic manipulation, and acupuncture.

Why should I ask my patients about their CAM use?

- Most patients do not proactively disclose use of CAM to their physicians.
- Patients with chronic and acute medical conditions—including cancer, diabetes, back pain, and depression—turn to CAM in large numbers.²
- As more patients use CAM therapies, you need a full picture of all conventional and CAM practices they are using so that you can effectively manage their care.

How can I find the time to discuss CAM with my patients?

- Include a question about CAM use on medical history forms.
- Ask your patients to bring a list of all therapies they use, including prescription, over-the-counter, herbal therapies, and other CAM practices.
- Have your nurse, nurse practitioner, or physician assistant initiate the conversation.

With so little information available about most CAM therapies, what can I tell my patients?

- You can refer your patients to credible, Federal resources to get evidence-based information and patient education materials. You do not need to know everything about all CAM treatments.
- Rigorous scientific research on CAM is taking place at major academic and medical institutions throughout the United States.

Federal Resources for Providers

National Center for Complementary and Alternative Medicine
at the National Institutes of Health
nccam.nih.gov

CAM on PubMed

Journal citations specific to CAM:
nccam.nih.gov/camonpubmed/

Online Continuing Education Series
Video lectures available for CME/CEU credits:
nccam.nih.gov/videolectures

Resources for Patients

National Center for Complementary and Alternative Medicine
nccam.nih.gov
Toll-free clearinghouse: 1-888-644-6226

MedlinePlus
medlineplus.gov

¹ Survey by AARP and NCCAM

² Barnes P, Powell-Griner E, McFain K, Nahin K. CDC Advance Data Report #343. Complementary and Alternative Medicine Use Among Adults—United States, 2002. May 27, 2004.



NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
National Institutes of Health U.S. Department of Health and Human Services

TIME TO TALK. TELL your doctor about your use of complementary and alternative medicine.

Tell

Did you know that almost two-thirds of people aged 50 and older are using some form of complementary and alternative medicine (CAM)? According to a recent survey¹ less than one-third of those people talk with their providers about CAM use.

What is complementary and alternative medicine (CAM)?
CAM is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. CAM includes such products and practices as herbal supplements, meditation, chiropractic manipulation, and acupuncture.

Why tell your health care providers about CAM use?

- Giving your health care providers a full picture of what you do to manage your health helps you stay in control.
- Some CAM approaches can have an effect on conventional medicine. Talking to your health care providers about CAM use will help ensure coordinated and safe care.
- Talking to your providers about CAM use helps them to be fully informed and your partners in health care.

Tips for talking to your health care providers about CAM

- When completing patient history forms, be sure to include all therapies and treatments you use. Make a list in advance.
- Tell your health care providers about all therapies or treatments—including over-the-counter and prescription medicines, as well as herbal and dietary supplements.
- Don't wait for your providers to ask about your CAM use. Be proactive.
- If you are considering a new CAM therapy, ask your health care providers about its safety, effectiveness, and possible interactions with medications (both prescription and nonprescription).

¹ Survey by AARP and NCCAM

CAM Resources from the National Institutes of Health

National Center for Complementary and Alternative Medicine nccam.nih.gov or 1-888-644-6226 MedlinePlus medlineplus.gov	NIH Office of Dietary Supplements www.ods.od.nih.gov National Cancer Institute Office of Cancer Complementary and Alternative Medicine www.cancer.gov/cam
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NCCAM NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
National Institutes of Health U.S. Department of Health and Human Services

Finally, we are also launching a new initiative to examine the potential influence of genetic variation on the likelihood of response to selected CAM interventions.

With these, and other studies, NCCAM will continue to provide leadership in the research area.

PREPARED STATEMENT

Thank you, Mr. Chairman. I thank Senator Specter, Senator Cochran, and Senator Reed for your continued support. I would be pleased to answer any questions.

[The statement follows:]

PREPARED STATEMENT OF DR. RUTH L. KIRSCHSTEIN

Mr. Chairman and members of the committee: I am pleased to be here to present the President's fiscal year 2008 budget request of \$121,268,000 for the National Center for Complementary and Alternative Medicine (NCCAM).

In the 7 years since it was established, NCCAM has built a global enterprise of scientific excellence and leadership in research on complementary and alternative medicine (CAM). NCCAM-supported studies, carried out at more than 260 institutions, encompass the wide range of CAM practices and have resulted in more than 1,500 scientific papers published in peer-reviewed journals. The progress that has been made by the research community in understanding the scientific basis of CAM is, in large part, attributable to the leadership of Stephen E. Straus, M.D., NCCAM's director from 1999 to 2006. Under his leadership, CAM research has been established as a legitimate field of scientific inquiry that is laying the scientific foundation for the emerging discipline of integrative medicine.

This effort continues. In the past year, NCCAM has launched studies to: (1) develop innovative tools and technology for studying biologically based and mind-body interventions; (2) assess the potential of community-based primary care research networks to increase scientific knowledge about the safety, efficacy, and cost effectiveness of CAM; and (3) increase scientific understanding of the mechanisms underlying manipulative and body-based practices.

NCCAM'S ROLE AND THE CHANGING NATURE OF MEDICINE

Large numbers of American health care consumers are using CAM modalities in an effort to preempt disease and disability or promote health and a sense of well-being. Despite the relative paucity of information about the effectiveness and safety of these uses, Americans are de facto personalizing medicine through approaches that often require their active ongoing participation in a diverse variety of health practices and behavior change approaches.

Driven largely by consumer demand for CAM, integrative medicine—which can be defined as a health care approach that makes use of all appropriate evidence-based disciplines, therapies, and health care professionals to achieve optimal health and healing—is rapidly becoming a major force shaping health care systems in the United States and around the world. At the same time, studies continue to show that open communication between conventional medical practitioners and their patients about CAM use is uncommon. Such communication is vital to ensure well-coordinated, comprehensive, and safe care.

The ultimate goal of NCCAM is to inform, through science, the discipline of integrative medicine. Thus, NCCAM's mission is to support rigorous research intended to fill the CAM knowledge gap; train CAM researchers; and disseminate authoritative information regarding CAM to the public (only one in three of whom consult their physicians about their CAM use), and to physicians and other health care professionals who rarely ask patients about CAM use.

BUILDING THE EVIDENCE BASE OF INTEGRATIVE MEDICINE

Because CAM interventions are widely used by the public, NCCAM supports a diverse portfolio of basic, translational, and clinical studies. The benefits of this strategy are well illustrated by the example of acupuncture. Clinical trials supported by NCCAM have documented the efficacy and safety of this widely used CAM practice in many but not all conditions studied. More recently, basic and translational research employing state-of-the-art neuroimaging technology has led to important insights into the mechanisms of action for acupuncture's effects, and has elucidated mechanisms of brain function that will have direct relevance to other approaches to pain relief.

Advances of similar importance are emerging in other areas of CAM research. As is the case with acupuncture, clinical and preclinical information fills gaps in knowledge about a number of CAM practices and builds a fuller understanding of what CAM can offer. Whether a study's result is positive or negative, we expand our knowledge not only about the tested therapy, but also learn more about the condition it is supposed to treat. Several examples from the past year illustrate this point further:

—*Arthritis*.—As the U.S. population ages, the need for better, safer, and more effective treatments for arthritis increases. Through basic studies, NCCAM-supported investigators determined that extracts of the spice turmeric, an important component of Ayurvedic medicine that is used in the treatment of a number of inflammatory disorders, contains specific compounds with anti-arthritis activity, as well as others that can inhibit this activity. This research suggests

the need for further investigation of the potential of turmeric, points toward ways in which its use might be optimized, and yields insight into the mechanisms of arthritic disease.

- Neurodegenerative Diseases*.—Ginkgo biloba is a dietary supplement widely used for its purported beneficial effects on brain function. NCCAM-funded investigators studying it in an animal model of Alzheimer's disease found that it reduces both the formation of the specific brain abnormalities seen in humans, and the resulting paralysis seen in the animals. These experiments lend support to the hypothesis that Ginkgo biloba may be useful in slowing the progression of Alzheimer's disease. That hypothesis is being tested in a large clinical trial of Ginkgo biloba for the prevention of dementia, supported by NCCAM and several other NIH Institutes.
- Yoga for Chronic Low Back Pain*.—Chronic low back pain is prevalent and has few treatment options. NCCAM supported researchers have concluded a randomized clinical trial studying the effectiveness of yoga, exercise, or a self help book in improving back function and decreasing chronic low back pain. The results of the trial demonstrated that yoga was more effective and produced longer-lasting pain relief than exercise or the self-help book.
- Menopause and Black Cohosh*.—Given concerns about the use of hormone replacement therapy to treat symptoms of menopause, many women have turned to the dietary supplement black cohosh for relief, although evidence supporting this approach has been scant. In 2006, a clinical trial supported by the National Institute on Aging and NCCAM failed to show relief of menopause-associated symptoms by treatments containing black cohosh. Two other large clinical trials of black cohosh continue.

TRAINING THE NEXT GENERATION OF CAM RESEARCHERS

The rigorous basic, translational, and clinical research required to understand integrative medicine must involve collaborations between CAM practitioners and experienced scientists. This multidisciplinary approach is the fundamental tenet of NCCAM's strategy in support of research training and career development. Since its inception, the Center has increased the percentage of funds committed to research training and career development—from 1.3 percent in fiscal year 1999 to 8.3 percent in fiscal year 2006—to support research training, career development, and educational opportunities. Recipients of CAM doctoral degrees are now among those eligible for the National Research Service Awards, as well as for the NIH-wide loan repayment program.

DELIVERING AUTHORITATIVE INFORMATION

NCCAM is recognized as a source of authoritative, evidence-based information on CAM. Information on CAM treatments, herbs and dietary supplements, advice for consumers, research results, and clinical trials are available in English and Spanish in print and electronic form. In 2006, NCCAM's website, cited by Prevention magazine for "Best Alternative Medical Information," had more than 2.6 million visitors. CAM on PubMed, a database developed in partnership with the National Library of Medicine, now indexes more than 467,000 articles related to CAM. NCCAM's online continuing education program offers information on a variety of topics to the public and health professionals. Of particular note is a new patient/provider education initiative—"Time to Talk"—that encourages informed and open communication between patients and physicians about CAM use, to ensure safe, integrated, personalized and participatory care.

GOING FORWARD

NCCAM will build on the foundation of scientific accomplishment and leadership that it has established during its first 7 years. Specific new activities planned for fiscal year 2008 include the following:

- Working in partnership with the Centers for Disease Control and Prevention, NCCAM will support the first national, population-based survey assessing CAM use among the U.S. pediatric population. This study will fill an important information gap in knowledge of CAM use in children and help NCCAM and the broader scientific community in establishing pediatric CAM research priorities.
- A new initiative will examine the potential influence of genetic variation on the likelihood of response to selected CAM interventions. This phenomenon, an important factor in the variation observed in responsiveness to conventional medicine, will be examined through linking new basic research to ongoing clinical trials, maximizing the value of the investment in both.

—A multidisciplinary workshop will bring together scientists from a broad range of the physical, social, and biological sciences to explore novel methodologies for clinical research of complex CAM approaches that make up whole medical systems.

Through these and other activities, NCCAM will continue to provide leadership in establishing the emerging discipline of integrative medicine. Thank you, Mr. Chairman. I would be pleased to answer any questions that the committee may have.

Senator HARKIN. Thank you very much. That last point, I want to follow up on in open questions on this.

Now we'll move to Dr. Lawrence Tabak, who became Director of the National Institute of Dental and Craniofacial Research in 2000, received his D.D.S. in dentistry from Cornell, his Ph.D. in Biology from Sunni at Buffalo. He's also one of the co-chairs of an effort to promote inter-disciplinary team science at NIH.

Dr. Tabak, welcome.

STATEMENT OF DR. LAWRENCE A TABAK, D.D.S, Ph.D., DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

Dr. TABAK. Thank you, Mr. Chairman. I would like to thank you, Senator Cochran, and Senator Reed, for providing us with the opportunity to discuss our vision for the future, and of course, I want to thank each of you for your steadfast support of the National Institutes of Health.

This morning I would like to discuss the NIDCR strategies to address the many complex diseases and conditions that fall within the mission of our Institute. I hope you have these materials. If not, I would just give them to you.

As you can see, in the first figure, Figure 1, that I provided, complex diseases are those resulting—if I could refer you to Figure 1 of the handout that I've provided to you, complex diseases and conditions are those that result from an interplay between and among one's genes and environment, infectious agents and behavior, societal issues and the unknown.

Figure 1. Solving the “Puzzle” of Complex Diseases and Conditions

**Genes
Behavior
Diet/Nutrition
Infectious agents
Environment
Society
???**



National Institute of Dental and Craniofacial Research

EARLY CHILDHOOD CARIES

One good example of a complex disease is early childhood caries, and if I could refer you to the next figure, Figure 2, you can see that in this condition, primary teeth can be decayed down to the gum line. This is a condition that is found disproportionately amongst underrepresented minority children.

Figure 2. Early Childhood Caries



Fluoride varnish is an effective approach to preventing ECC in very young, high risk children

Increasing the number of fluoride applications decreased the percentage of children with ECC

The results provide additional rationale for early preventive oral health assessment

Raul Garcia, Boston University

Weintraub, et al. J Dental Res 85:172, 2006

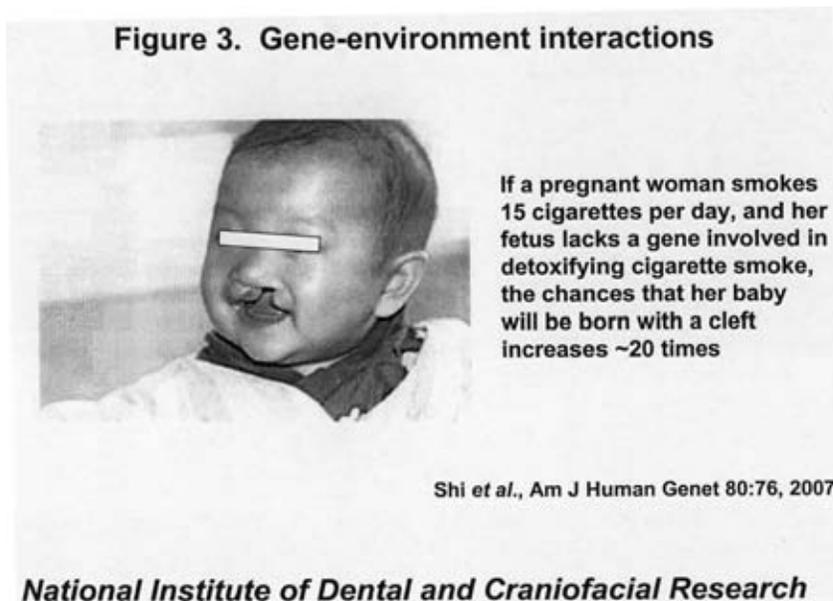
National Institute of Dental and Craniofacial Research

NIDCR supports a research centers program to reduce oral health disparities, and we presently have 5 centers based around the country. What is unique about these centers is that they are embedded within their communities. What is needed to overcome conditions such as early childhood caries, are inexpensive, simple and culturally acceptable interventions.

One such example is the use of a fluoride varnish, which has been worked on in a study conducted by the center at the University of California, San Francisco. What they have shown is that this approach can be highly effective in preventing early childhood caries in the very young, and in children at greatest risk.

SMOKING, GENETICS, AND CLEFT PALATE

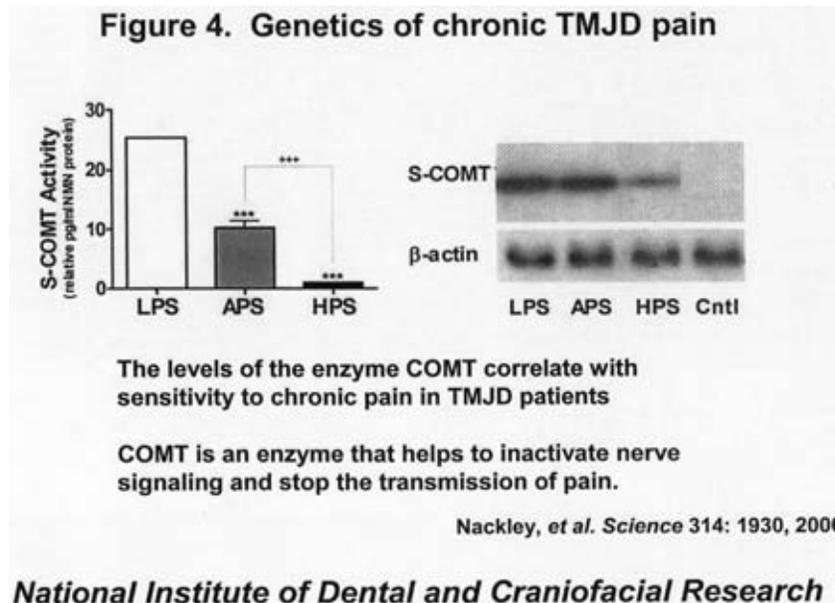
If I can refer you to the next figure, Figure 3—gene-environment interactions, are typified by recent studies, which are summarized in this figure, conducted by NIDCR-supported investigators at the University of Iowa, together with colleagues at NIEHS. This work showed that babies of European ancestry—up to 25 percent of them, and up to 60 percent of babies of Asian history lack a gene. That is important in detoxification of cigarette smoke. If a pregnant woman smokes 15 cigarettes a day, and lacks this important factor, the chances of her baby clefting increases 20-fold.



CHRONIC PAIN

NIDCR scientists at the University of North Carolina are slowly unraveling the genetic basis of chronic pain by studying patients with temporomandibular muscle and joint disorder. If I can refer you to Figure 4, differences in susceptibility to pain correlate with the levels of a particular enzyme, the so-called COMT enzyme. On the left-hand portion of this figure, you see individuals who have

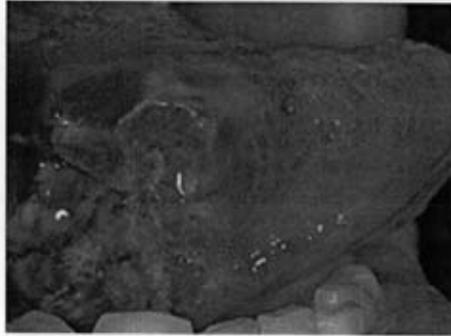
low pain sensitivity and very high levels of this enzyme. Then at the far end, those which have the highest pain sensitivity have very low levels of this enzyme. This makes sense because this enzyme is involved in the transmission of pain and this enzyme is involved in breaking down the transmitters of pain. So, if you have large levels of this enzyme, you are less susceptible to painful activity.



What's very, very important about this is, for the first time we're beginning to understand the true biological basis for diseases and conditions, such as TMJ, which heretofore had proved very enigmatic. We now understand the real biological basis for these diseases and conditions. By unraveling the molecular basis, we have an opportunity for early detection and diagnosis, as well as potential interventions in the future.

ORAL CANCER

If I can refer you to the next figure please, Figure 5. You see an example of an oral cancer. Oral cancer kills. The best hope is to detect cancer at its earliest stage. NIDCR has invested in a comprehensive tool kit of complimentary diagnostic approaches that will lead to bio-markers with both diagnostic and predictive value. An exciting advance in bio-markers research has been the use of saliva as a diagnostic fluid.

Figure 5. Oral and Pharyngeal Cancer

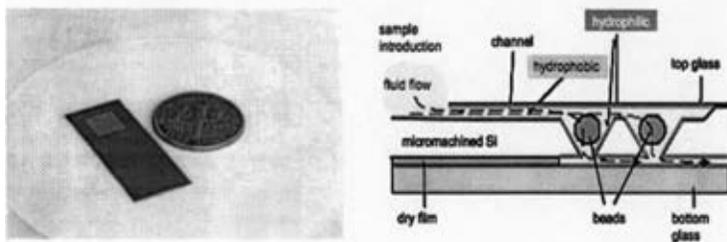
Early detection is key to oral cancer survival

New tools and approaches for early detection are integrating molecular biology, cytology, and visualization

National Institute of Dental and Craniofacial Research

SALIVARY DIAGNOSTICS

If I can refer you to the final figure, figure 6. On the left you see a lab on a chip, which currently is the size of a U.S. dime. This lab on a chip can already analyze multiple markers simultaneously, including the genetic signatures that are associated with oral cancers. What we have done is married the expertise of bio-engineers with the knowledge of oral biologists and what is in saliva to create this program. Ultimately we will be able to use saliva to measure a wide range of bio-markers. It doesn't take too much imagination to see that if we can shrink the size of that lab on a chip from the size of a U.S. dime down to the size of a pinpoint, we would have the opportunity to place that device in the mouth, so that we could have the opportunity for real-time surveillance, constantly. Of course, this is the ultimate goal with this program.

Figure 6. Salivary diagnostics

John McDevitt & Eric Anslyn, University of Texas at Austin

National Institute of Dental and Craniofacial Research

PREPARED STATEMENT

I appreciate the opportunity to tell you about these few exciting new approaches to address the many complex diseases and conditions that affect oral, dental, and craniofacial tissues. This is a time of tremendous scientific opportunity for oral health research, and of course, I would be pleased to answer any questions that you have.

Thank you.

[The statement follows:]

PREPARED STATEMENT OF DR. LAWRENCE A. TABAK

Mr. Chairman and members of the committee: I am pleased to present the President's budget request for the National Institute of Dental and Craniofacial Research (NIDCR) of the National Institutes of Health (NIH). The fiscal year 2008 budget request for NIDCR is \$389,722,000.

FACING THE FUTURE: INTEGRATIVE APPROACHES TO ADVANCE PUBLIC HEALTH

Innovation has long been the great engine of progress in American life, including the tremendous progress made in improving the Nation's oral health over the last half century. From the tube of fluoridated toothpaste in the medicine cabinet to the high-resolution digital X-ray unit in the dentist's office, scientific innovations have helped more people than ever keep their teeth for a lifetime.

The Nation's oral and craniofacial researchers stand on the threshold of even greater innovations to improve the lives of millions of Americans. No longer must they attempt to understand health and disease one gene and protein at a time. Today, they can click the computer mouse on their desks and call up vast databases of biological information. In essence, thousands of pieces to the biological puzzle are now on the table. If we meet the challenge to integrate the pieces—intentionally blurring in the process the lines that have defined the traditional research disciplines—great progress can be made in understanding the molecular underpinnings of oral and craniofacial health and disease. This year, I would like to offer a few of the many examples of how integrative science will lead to greater innovation. I'd also like to highlight how this innovation ultimately will lead to more personalized dentistry and medicine in which treatment can be tailored to a patient's specific disease and healthcare needs.

CRANIOFACIAL CONSTRUCTION AND RECONSTRUCTION

The human face has been celebrated in art and literature since time immemorial and rightfully so. It is among the body's most distinctive structures and, is also one of the most developmentally complex structures of nature. Tremendous progress has been made in recent years in unraveling the genetic programs that are activated in the embryo to produce the face and the skull. Similar progress has been made in pinpointing which genes can go awry to produce a cleft lip and/or palate.

But much work remains. We must decipher the developmental programs that give rise to the various craniofacial tissues, hard and soft. By knowing how the craniofacial complex is assembled, it will be possible to better reassemble tissues that are damaged, either at birth or due to injury later in life. Exciting research is under way to explore the viability of regenerating damaged bone, teeth, and soft tissues with stem cells, novel biomaterials, and growth-promoting proteins. NIDCR-supported researchers recently reported success using stem cells to engineer a replacement root/periodontal complex that could support a porcelain crown and provide normal tooth function in studies with mini pigs. Other investigators are well on the way to creating a replacement gum tissue that can be produced in sufficient quantity to repair large oral defects.

The developmental programs will be helpful not only in treating craniofacial abnormalities but in preventing them. This year, for example, a team of NIDCR grantees determined that women who smoke during pregnancy and carry a fetus whose DNA lacks both copies of a gene involved in detoxifying cigarette smoke substantially increase their baby's chances of being born with a cleft lip and/or palate. About a quarter of babies of European ancestry and possibly up to 60 percent of those of Asian ancestry lack both copies of this gene. This finding reinforces in a concrete, personal way the public health message that women, especially those who are pregnant, should not smoke.

HEAD AND NECK CANCER

The NIDCR also has made a major investment in promoting integrative approaches to head and neck cancer. Our intent is to move beyond the current imprecise clinical definitions of these tumors, which are generally based on their appearance and patterns under a microscope. We need to examine the genetic hard drives of these tumors' cells to understand their abnormal and often deadly behaviors. This work already is taking place. NIDCR scientists have compiled comprehensive profiles of proteins expressed in some head and neck cancers. This information should help in developing true biomarkers with diagnostic and prognostic value.

NIDCR-supported scientists are also developing new and exciting visualization tools and approaches to improve diagnosis of oral cancer. One such tool being tested is called the VELscope®. It is a simple hand-held device that emits a cone of blue light into the mouth, which excites various molecules within the tissue, causing the tissue to absorb the light's energy and re-emit it as visible fluorescence. Because changes in the natural fluorescence of healthy tissue generally are different from those indicative of developing tumor cells, the VELscope® allows dentists to observe telltale differences.

In a recent follow-up study, the scientists reported that the VELscope® performed extremely well in accurately and rapidly delineating the real borders between tumor and healthy oral tissue during biopsies in the clinic. Intriguingly, 19 of the 20 examined tumors in the study had fluorescence changes that extended in at least one direction beyond the clinically visible tumor. These extensions, which are undetectable to the unaided eye and thus would likely not be excised, extended up to an inch beyond the visible lesion. Leaving these abnormal cells in the mouth increases the chance of other tumors arising over time. The instrument was developed as one component of an integrative approach to oral cancer detection and treatment that combines cytology, molecular biology, and staining to improve early detection. This finding and others will allow practitioners to gain a better molecular characterization of developing tumors, providing the intellectual basis for more personalized treatment and a future in which fewer people will undergo disfiguring surgery to fight the disease and/or die from these cancers.

SALIVARY DIAGNOSTICS

Other diagnostic tools are under development as well. The NIDCR is a national leader in development of the use of saliva as a diagnostic fluid. Several Institute grantees are working to develop tiny automated machines, which can rapidly and precisely perform many diagnostic functions that previously required painful needle sticks. One group recently fabricated the first disposable, low-cost, miniaturized di-

agnostic platform that can process small amounts of saliva, amplify its DNA and detect the levels of genetic sequences of interest. Work is proceeding to ultimately create a fully functional hand-held instrument for everyday use to detect conditions ranging from oral cancer to cardiovascular disease to AIDS.

TEMPOROMANDIBULAR MUSCLE AND JOINT DISORDERS

Integrative approaches are proving productive in our ongoing efforts to understand temporomandibular muscle and joint disorders, or TMJDs. Previously, NIDCR-supported scientists found that different sets of common sequence variations in the COMT gene correlate with low, moderate, and high susceptibility to chronic pain. This finding makes good biological sense. The COMT gene encodes an enzyme that helps to inactivate nerve signaling compounds and stop the transmission of an unpleasant sensation. The scientists recently showed that each of these sets of sequence variations changes the resulting structure of the corresponding messenger RNA. When a gene is expressed, it is copied into messenger RNA which, like an order form, contains the information to produce a specific protein. The scientists determined that the genetic variations that correlate with high sensitivity to pain produce messenger RNA with long, rigid loops in their structure, which reduces the rate of COMT protein synthesis and thus slows the nerve's ability to turn off an unpleasant sensory signal. The likely result: those with the "sensitive" variations will personally experience the sensation of pain longer and possibly more intensely.

Such findings are particularly exciting because these studies could not have been conducted just a generation ago. Not enough was known about the basic mechanisms of pain. But as more of the biochemical pieces to the puzzle are found in the years ahead, great progress in controlling pain will be possible, and the NIDCR will help in leading the way for all those battling chronic pain conditions, including TMJDs, to find relief through a more accurate diagnosis and more personalized care.

DENTAL DISPARITIES: RIGOROUS SCIENCE, PRACTICAL RESULTS

It now has been 7 years since the U.S. Surgeon General issued the report *Oral Health in America*. As many will recall, that report pulled together for the first time the stark statistics of the Nation's "silent epidemic" of tooth decay and other oral diseases among its minority and underserved populations. The reasons for these disparities are complex, but two facts were indisputable in the report: Many oral diseases are either preventable or easily controlled, and new strategies are needed to ensure that all Americans are aware of and ultimately benefit from the latest research advances.

To meet this need, the Institute established five Centers for Research to Reduce Oral Health Disparities in 2001. This approach allows scientists to assemble multidisciplinary research teams that lend a greater wealth of expertise to understand and address the complex elements underlying oral health disparities at the community level. Building on the knowledge and evidence amassed by the initial health disparities centers, the Institute has begun preparations to re-compete its center grants with a specific public health aim. That aim is to assemble a more seamless investigative team structure that can take a well-defined clinical issue and with the participation of a community-based population, test the effectiveness of promising interventions on a wider scale. This approach holds considerable promise to yield rigorous science, participatory research with those in underserved communities, and a significant reduction in oral health disparities.

PRACTICE-BASED RESEARCH NETWORKS

The Institute awarded grants in early 2005 that established three regional practice-based research networks, or PBRNs. Their mission is to create networks of practicing dentists and dental hygienists with their patient populations to participate in clinical studies on a variety of pressing everyday issues in oral healthcare. In 2006, the PBRNs were enlisted to investigate an important emerging health issue. Millions of Americans currently take a type of drug called bisphosphonates, typically to ease cancer-related pain or to prevent osteoporosis. But recent reports indicate that newly formulated bisphosphonates can cause in some people a debilitating thinning of the jawbone called osteonecrosis. What remains unclear is the prevalence of this unwanted side effect and, more importantly, who precisely is at risk. A few years ago, NIDCR would have lacked the clinical infrastructure in place to investigate these and other related questions. The PBRNs have changed the equation. The NIDCR has rapidly organized the needed studies to investigate the problem and will provide in the near future more meaningful data for the millions of Americans at risk.

Traditional research approaches have produced extraordinary benefits to the Nation's public health. But we now face a new scientific frontier, and new possibilities confront our researchers. These opportunities require novel approaches that fall under the rubric of integrative science. From this coordinated approach to science, the biological complexity before us will give way to simplicity and once unimaginable public health advances in which personalized health and medicine become a reality.

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

Next, we will turn to Dr. David Schwartz, Director of the National Institute of Environmental Health Sciences. He has been Director since 2005, earned his M.D. from the University of California, San Diego, and his Ph.D. degree from Harvard School of Public Health. But most importantly of all, he spent the better part of 12 years at the University of Iowa. Is that about right?

Dr. SCHWARTZ. Very formative years.

Senator HARKIN. His own research focuses on environmental lung diseases. Dr. Schwartz, welcome to the committee.

STATEMENT OF DR. DAVID SCHWARTZ, M.D., DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH AND SCIENCES

Dr. SCHWARTZ. Thank you very much, Mr. Chairman, Senator Cochran, and Senator Reed. It's a pleasure to be here, thank you for providing us the opportunity to discuss our collective vision for the future of medical research.

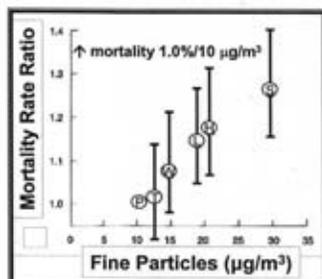
I do have a handout that may be of help to the members of the committee.

Just by way of introduction, NIEHS protects the Nation's health by understanding the role of the environment, in terms of the development and also the distribution of disease in society. Our view is, understanding the causes of disease will provide the types of insights that are absolutely necessary to preventing disease in society. That's the focus of the Institute. The work of NIEHS in the past has improved the average length and quality of life by looking at disease etiology, and also prevention of exposures that are relevant to disease etiology.

If you look at the second page of the handout, Figure 1, I will give you two examples of work that has been done in the past at NIEHS that exemplifies this approach. The two examples focus on air pollution and lead exposure. NIEHS funded a very important study called "The Six City" study, that focused on air pollution and identified air pollution as a major cause of morbidity and mortality, especially as related to heart and lung disease.

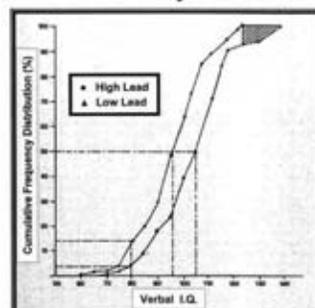
Impact of NIEHS on Human Health

Air Pollution Reduces Survival



- New air standards in the U.S.
- 10 yr f/u - improved survival with \downarrow concentration of PM

Lead Impairs IQ



- New lead standards in gasoline
- Reduced concentration of lead in children in the U.S.

In the graph on the left-hand panel, the letters on the graph refer to the six different cities that the study was done in. You can see very clearly, as you move from left to right, that the level of air pollution increases, and the mortality, and also the morbidity, from lung and heart disease increases.

As a result of this very compelling research, new standards were adopted by the EPA under the Clean Air Act, which changed the standards in the United States for air pollution. As a result, there have been marked decreases in the level of air pollution, but marked improvements in morbidity and mortality related to air pollution exposure.

The second example is an example of collaborative work between NIEHS and the National Institute of Children's Health and Human Development. On the right-hand side, the second figure on the second page shows a very striking relationship between the concentration of lead in the blood of children, and IQ. The higher the lead levels, the lower the IQ. This research resulted in the elimination of lead in gasoline, and subsequently resulted in improvements—substantial decreases—in the concentration of lead in the blood of children around the United States.

STRATEGIC PLAN

If you look at the next page of the handout, figure 2, between 2005 and 2006, shortly after my arrival at NIEHS, we developed a strategic plan, and our strategic plan lays out a very clear vision—to prevent disease and improve human health by using environmental sciences to understand human biology and human disease. Embedded in this plan, we have several challenges that face us, that keep us focused on our mission—our mission focusing on specific exposures and diseases that are relevant to those specific exposures.

NIEHS Strategic Plan 2006-2011

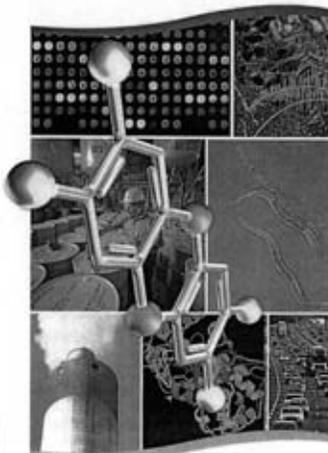
www.niehs.nih.gov/external/plan2006/home.htm

Vision: *Prevent disease and improve human health by using environmental sciences to understand human biology and human disease*

Challenges:

1. Prioritize relevant diseases and exposures
2. Integrate scientific disciplines
3. Empower people and society with knowledge to improve environmental choices and live healthier lives

Transparency and Accountability



If you look at page four of the handout, Figure 3, we have developed 7 specific goals that help keep us on track in terms of the development of research priorities at NIEHS that are consistent with our strategic plan. So, although we've made a lot of progress in each one of these goals, and we've implemented programs in each one of these goals, I just want to tell you about three distinct programs.

Implementation of Strategic Plan



Goals and Progress:

1. Clinical research
Clinical Research Unit, and Head off Environmental Asthma in Louisiana
2. Basic mechanisms in human biology
Support investigator-initiated research (> 20% success rate)
3. Integrated environmental health research
New programs in translational research
4. Global and community-linked research
Global Environmental Health Workshop
5. Next generation of environmental health scientists
Training and career development (high school, college, and early careers)
6. Partnerships across disciplines and agencies
NIH Institutes, Roadmap, CounterAct, EPA, CDC, and FDA
7. Personalized measures of exposure, response, and genetic susceptibilities
Exposure Biology Program of the Genes, Environment and Health Initiative

HEAD-OFF ENVIRONMENTAL ASTHMA IN LOUISIANA

The first program is called the HEAL Program. It stands for Head-off Environmental Asthma in Louisiana, and it's based on in fact that children moving back to New Orleans are at very high risk for the development of asthma, as a result of exposure to a contaminated environment—the molds and the bacteria that have overgrown many of the environments in New Orleans as a result of Hurricane Katrina.

This is a collaborative project, and it's a community-based project. The community is very, very involved in this project, and the Department of Public Health is very involved in this project, as is Tulane University. It's a collaboration between NIEHS and the National Center on Minority Health and Health Disparities, and also the Merck Childhood Asthma Network. It represents a public/private partnership, in addition to a collaboration within NIH. Again, the project is focused on an intervention program, and studying that intervention program to see if we could reduce the burden of airway disease in these children that are at very, very high risk of developing and exacerbating their underlying airway disease.

TRAINING AND CAREER DEVELOPMENT

The second area of development that I want to highlight is in training and career development. We've revitalized our training—in fact, our training programs now go all the way from high school through college, including training for foreign scientists. The training reaches out to minority students, as well as physicians-scientists—two very important groups that are underrepresented in the NIEHS portfolio—and also focuses on new investigators to help them develop a focus in environmental sciences and have an opportunity for research in environmental sciences.

EXPOSURE BIOLOGY PROGRAM

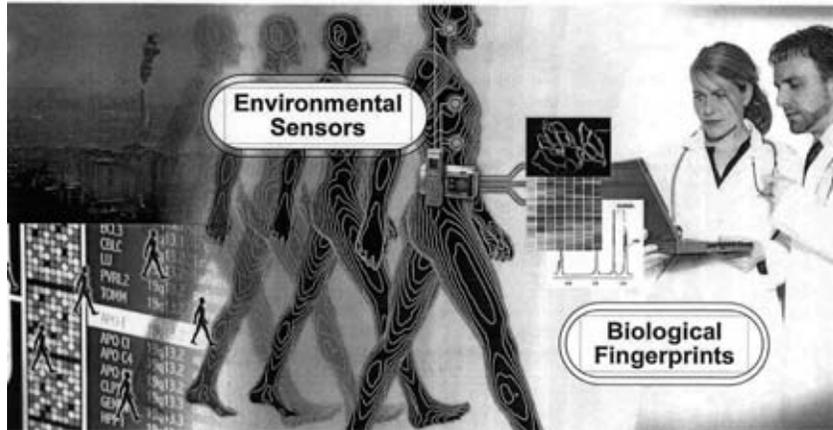
The third area I want to highlight is the development of personalized measures of exposure, very similar to what Dr. Tabak was talking about, in terms of these miniaturized exposure measurements and biological response indicators, that are very important in terms of identifying how much someone has been exposed to, and how biologically responsive someone is to that exposure.

If you look at the next page of the handout, Figure 4, you can see that we've developed a program called the Exposure Biology Program that is part of the Genes, Environment, and Health Initiative. This new initiative is supported by all institutes across the NIH, and is led by me and Francis Collins and at NHGRI. The overall goal of the Exposure Biology Program is to develop personalized sensors of exposure, and also, biological response indicators. Step back for a second, and consider how we're able to precisely measure genetic variation across the human genome and how crude our tools are to measure individual differences in terms of environmental exposures—and you realize very quickly that this program is essential to be able to look at the interaction between genes and environment, in terms of the risk of developing disease. After all, for the foreseeable future, our main way of preventing

disease will be to intervene in the environment, not to intervene genetically.

GEI: Exposure Biology Program

Bridging the Gaps in Personalized Medicine

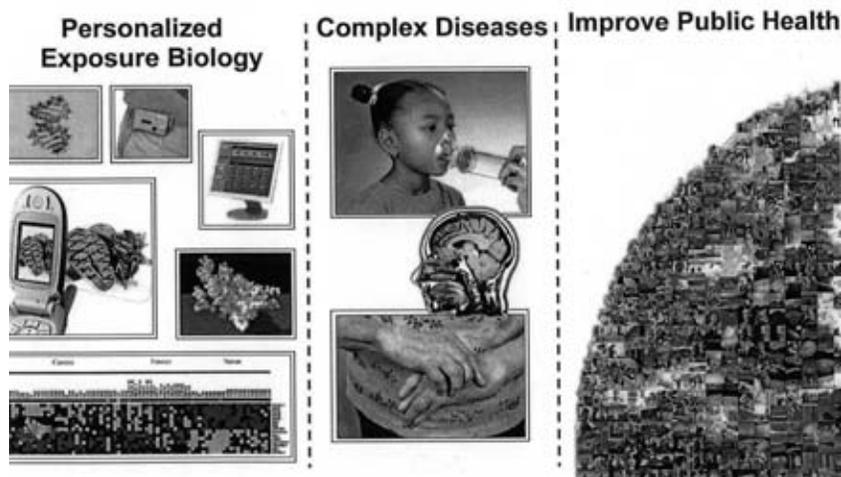


So, it's essential that we understand this relationship between genes and environment, as a way of understanding risks related to human health. Outgrowths of the Exposure Biology Program might include specialized wrist bands or smart shirts that could alert a person, or a physician, to an exposure that could be detrimental to an individual's health.

OPPORTUNITIES

If you turn to the last page of the handout, Figure 5, as we look forward, we're focused on three main opportunities. First, as I mentioned, through the Exposure Biology Program, we're developing these personalized measures of exposure and response indicators.

Future Goals: Five Year Plan



Second, we're focusing on a number of new research programs on complex diseases, such as asthma and neurodegenerative diseases and arthritis, that are caused by both genetic and environmental factors. We believe very strongly that the environment will be very helpful in identifying the genes that are important in terms of the risk of developing disease.

The third aspect that we're focused on is populations that are exposed to high concentrations of toxins, such as arsenic, or high concentrations of air pollution, so that we can reduce the burden of disease in these populations and improve health.

PREPARED STATEMENT

So, I want to thank you for your attention. I look forward to your questions, and I would yield to my colleagues, and look forward to the informal discussion that we will have following everyone's formal presentation.

[The statement follows:]

PREPARED STATEMENT OF DR. DAVID SCHWARTZ

INTRODUCTION

Lives saved by environmental health research can be counted in millions. By the Environmental Protection Agency's (EPA) estimates on air pollution alone, the Nation's commitment to cleaner air will prevent 23,000 premature American deaths; 1,700,000 new asthma attacks or aggravation of chronic asthma; 67,000 new cases of acute and chronic bronchitis; 22,000 respiratory-related hospital admissions; and 42,000 cardiovascular hospital admissions (EPA 410-R-99-001) by the year 2010. The commitment to new air standards arose from NIEHS-supported research on air pollution such as the Six-Cities Study which revealed important associations between air pollution and mortality from respiratory and cardiovascular disease.

Air pollution is only one example of the public health impact of environmental health research. Studies on adverse effects of lead, much of it funded by NIEHS, revealed lead-associated decrements in the IQ scores of young children, as well as increased tendencies by affected children to aggressive behaviors. It was these types of neurobehavioral problems that led the Nation to ban sources of lead contamination, a move that has led to a 78 percent decrease in average blood lead levels in

this country (JAMA, 272:284–91 (1994)) and a corresponding improvement in the health of our children. Further NIEHS-supported research involving adults found that long-term exposure to lead is associated with an increased risk of high blood pressure (hypertension), kidney problems and cataracts. Reduced lead levels in the environment are expected to translate in the future into a decreased incidence of hypertension, kidney failure, and cataracts among the elderly.

NIEHS-supported researchers have made other recent discoveries with high potential for public health impact. Some examples include identification of a novel biological mechanism that controls airway tone and could be targeted for the treatment of asthma; discovery of important mechanistic linkages between exposure to inhaled particulate matter and cardiovascular disease; new insight into regulatory mechanisms within the brain that affect learning and memory; and identification of the structural basis of errors in DNA synthesis that may result from environmental stress and have profound effects on a variety of human diseases, including cancer.

As these examples illustrate, environmental health science can exponentially return its investments on improvements in a wide spectrum of diseases and disabilities. Operating on multiple molecular and cellular pathways, environmental agents can track these complex molecular pathways that lead to chronic diseases such as cancer, birth defects, hypertension, and neurological disorders. Because environmental agents often operate early in the disease process, they can be useful for identifying very early events in disease, suggesting ways to diagnose and remedy diseases before they progress. The challenge now is to develop techniques needed to assess environmental exposures as they operate at the level of individual health. This will require the development of sensitive devices that can assess the environmental exposures to which individuals are exposed in their daily lives. Ideally, these small, specialized, wearable sensors would measure environmental exposures, as well as the actual biological changes that arise as early markers of response in environmental agents. Such devices would allow scientists and physicians to access the more dynamic, real-world exposures of the American population and would provide information that could be useful to identify very early events in disease, suggesting ways to diagnose and remedy diseases before they progress.

Many of NIEHS' recent achievements have been possible because of powerful tools used to study events at the genetic and molecular level that would have been impossible ten years ago. With so many promising avenues to explore, NIEHS developed a new strategic plan, New Frontiers in Environmental Health Sciences and Human Health (www.niehs.nih.gov/external/plan2006/home.htm) that focuses on three major challenges and seven specific goals to prevent disease and improve human health by using environmental sciences to understand human biology and human disease. Steps to implement the Strategic Plan have led to research in exposure biology (personalized measures of exposure), epigenetics (inheritance not based on the sequence of DNA), comparative genomics (use of model systems to understand the biological effects of environmental exposures), translational research (integrating basic and applied sciences to understand the effect of the environment on human health), and focused training and career development programs to expand the workforce in environmental sciences. Our success will be measured in the disease and suffering that we are able to prevent.

EXPOSURE BIOLOGY PROGRAM

The Exposure Biology Program, a component of the larger Genes, Health and Environment Initiative at the National Institutes of Health (NIH), was created to develop tools to precisely measure the exposure to chemical/biologics, dietary changes, physical activity, psychosocial stress, and addictive substances and subsequently assess the effect of these exposures on human health. This program will produce non-invasive tools that can be used to track exposures critical to human health. While new technology will be developed, this program will also borrow and re-engineer tools from other fields that have focused on measuring various component of the environment. Possibilities include the use of molecularly imprinted polymers that show promise in identifying antibodies, enzymes, and animal tissues or cells; small labs-on-a-chip that can be made through recent advances in silicon and glass micro-machining; and the use of nanoparticles in biomolecular sensors. These technologies would be combined with new techniques to assess co-modifiers of response such as diet and physical activity. As these technologies are incorporated into large-scale epidemiological studies, much of the background "noise" obscuring our ability to identify environmental components of disease will be reduced. Furthermore, the program is soliciting researchers to develop these new tools in ways that can also provide insight into the molecular underpinnings of disease response, thus identifying therapeutic targets for intervention.

One exciting outgrowth of this project will be in the area of personalized and participatory medicine. The sensor technologies developed through the Exposure Biology Program are envisioned to be small, portable devices that can measure actual exposures to environmental agents, as well as monitor diet, physical activity, heart rate and respiration. An example would be a device that could alert an individual with asthma to dangerous air pollution levels. Another example would be a device that could determine harmful pesticide levels and cross-reference this information with an individual's own genetic risk profile for neurodegenerative diseases like Parkinson's disease. Alternatively, data derived from such sensor devices could be used by physicians to tailor treatment and prevention strategies based on actual exposure risks. The strategies could range from altering the environment or modifying behavior through disease risk education to selecting pharmaceutical treatments that would more accurately target the underlying molecular changes resulting from environmental exposures.

EPIGENETICS—BEYOND THE SEQUENCE OF DNA

The field of epigenetics is uniquely related to environmental health sciences. Epigenetics refers to a modification of gene expression that does not involve a change in gene sequence; rather, a sometimes slight modification of DNA or its associated proteins or sugars that can dramatically change gene function, sometimes into subsequent generations. Almost all known factors causing epigenetic change are from the environment, diet, or supplements. Epigenetic mechanisms are being linked to multiple illnesses, including cancer, cognitive dysfunction, and respiratory, cardiovascular, reproductive, autoimmune, and neurobehavioral diseases.

Recently, NIEHS developed a program in epigenetics that supports research to understand how the epigenome is affected by environmental exposures and how this ultimately affects human health. This field is particularly promising in identifying how early life exposures can generate disease outcomes later in life. One purpose of this program is to identify critical windows of susceptibility to epigenetic changes, particularly during pregnancy, early life, and puberty. The fruits of this research will help us develop biomarkers of early exposure, as well as identifying possible therapeutic strategies to prevent disease later in life.

CLINICAL AND TRANSLATIONAL RESEARCH

In the summer of 2007, NIEHS will complete construction of its first clinical research unit that will be used to study how human subjects respond to a variety of environmental stressors. This facility will foster integrated, interdisciplinary research opportunities between our basic and clinical scientists to speed the translation of knowledge from bench to bedside. NIEHS' Office of Translational Research is also focusing on taking discoveries from our basic and population-based studies and translating them into research findings that have direct relevance to human health and disease. New integrative research programs are designed to promote an interdisciplinary approach to focus environmental sciences on important human health conditions. Two examples are the extramural DISCOVER (Disease Investigation through Specialized Clinically Oriented Ventures in Environmental Research) Program and the intramural Director's Challenge. The approach being taken in these programs is to closely integrate basic, mechanistically driven laboratory research directly with patient-oriented research to speed the translation of the environmental health sciences into clinical and public health applications. Awards made under both the intramural program and the DISCOVER Centers will be for multi-project, interdisciplinary programs to understand the etiology, pathogenesis, prognosis, and epidemiology of disease processes such as respiratory diseases, cancer, or neurodegenerative diseases.

WORKFORCE TO MEET NEW CHALLENGES

The much greater complexity of research techniques and the new focus on human health and disease requires a new, specialized workforce. The new environmental health workforce must be increasingly collaborative and must have skills to work across multiple research disciplines. NIEHS is refashioning its training program in order to produce researchers with the skill sets needed in the future. For promising high school and college students, the Short Term Educational Experiences for Research (STEER) program provides needed support for attracting and developing this next generation of environmental health scientists. NIEHS and NHGRI developed a collaborative training program for pre- and post-doctoral students in environmental genetics. The Outstanding New Environmental Scientists Award (ONES) program is a new way to recruit talented young independent researchers into environmental health science research. These programs complement existing training

programs and, in concert, will help develop a workforce that can meet the many demands of environmental health research.

SUMMARY

The opportunities within environmental health sciences are greater than ever. New programs initiated this past year will produce a more sophisticated understanding of the environmental components of disease, as well as a better knowledge of how individuals vary in their response to exposures. This information will enhance our ability to develop personalized approaches that can decipher an individual's actual exposures, their individual risks for adverse effects from these exposures, and ultimately lead to a customized strategy for reducing these risks and circumventing undesirable health outcomes. This more extensive understanding of environment-disease associations will, in the aggregate, lead to improved intervention and therapeutic strategies that can lessen the disease burden of our citizens. I would be happy to answer your questions.

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

Now, we'll turn to Dr. Paul Sieving. He became Director of the National Eye Institute in 2001, received his M.D. and a Ph.D. in biomedical engineering from the University of Illinois and conducted research focused on retinal conditions, such as retinitis pigmentosa.

Dr. Sieving, welcome to the committee.

STATEMENT OF DR. PAUL A. SIEVING, M.D., Ph.D., DIRECTOR, NATIONAL EYE INSTITUTE

Dr. SIEVING. Thank you, Senator Harkin and congratulations on saying retinitis pigmentosa. That's a big word as are many of the words we use in medicine, but these words have very important implications for disease and health of the American people. As Director of the National Eye Institute, it's my privilege to tell you, to report to you today on some of the remarkable advances that are happening in vision research.

We are at a precipice in medicine as I've heard my colleagues also report, where we're really able now to move from basic research into the phase of improving health. In my case, the eye health of the American people. It's a very exciting time. With the support of the United States Congress our vision scientists are developing treatments to prevent vision loss and, even more remarkably, in some cases to partially restore sight for some common eye diseases, including age related macular degeneration that affects the older age population. Conditions that affect children, such as amblyopia, start in childhood, but the vision loss can persist for a lifetime.

I think all of us can understand and appreciate that the loss of sight really affects people in a fundamental way. It threatens independence. It is socially isolating, we can't look at one another. It affects the quality of life. The number of the eye diseases that we suffer actually increase with age. They strike later in life. As the American people live longer and the baby boom generation ages, unfortunately, we can expect an increasing prevalence and incidence of some of these conditions that are related to aging.

AGE-RELATED MACULAR DEGENERATION

I would like to focus my comments on one storyline of remarkable success involving age-related macular degeneration or AMD. This is a condition in which central vision is affected. You look at the person sitting across from you and his or her face dissolves into

a blur. It's difficult to see the face of a friend. It's difficult to read a book. Obviously driving a car, that privilege is lost. Even simple things, such as cooking, those simple tasks become very difficult.

But, the last 2 years have been a watershed time for AMD, both in terms of new treatments, remarkable new treatments and genetic factors that are now coming online. Over the past 2 years, attention to a particular molecule called vascular endothelial growth factor, just about as big a word as retinitis pigmentosa. Vascular endothelial growth factor or VEGF is a molecule that was pursued quite vigorously by the cancer research community for many years. It turns out that abnormal blood vessel growth is also involved in one of the severe forms of age-related macular degeneration, causing abrupt loss of central vision. Now, over the past 2 years, an anti-molecule, anti-VEGF, administered to the eye, injected into the eye, literally, can stabilize the vision. In some cases, even improve reading ability somewhat.

Senator Cochran, you mentioned the incidence of diabetes in your State. Diabetes is a problem of blood vessels that also involves the blood vessels in the eye, as you alluded to, and causes a condition called diabetic retinopathy, a blood vessel problem in the eye. So, this same molecule, the VEGF molecule is involved and anti-VEGF therapy is now being tried for diabetic retinopathy. We can hope that that will be successful. But, we need to intervene at an earlier course of disease.

I would like to go over some old ground that I have presented here to this committee previously, called the Age-Related Eye Disease Study, in which prevention was the focus. This was an NEI sponsored study. It ran for 7 years. It focused on the daily use of antioxidant vitamins and minerals.

After work, hard experimental work with some 4,000 individual subjects, participants, it was found that this approach delayed the onset to serious vision loss and advanced macular degeneration, delayed that by about 25 percent. That is a remarkable success. So, that if this dietary intervention could be fully utilized by the American people who need treatment, we could anticipate over the next 5 years, it would rescue the vision of some 300,000 people. In that study, the AREDS study, is now in a second phase of AREDS2, testing other dietary components, such as DHA or omega-3 fish oils.

But, let's move back even one step further. So far we've talked about treatments and prevention, but we can actually go right to the root causes of AMD by looking at the genetic factors that predispose us, literally sitting around this table, to have AMD in later ages. Now, we have suspected for many years that genetic factors play a role in developing AMD and just 2 years ago, in April 2005, 26 months ago, the NEI-supported researchers identified the first gene that predisposes to developing AMD in a large population. One gene, first time in history, a remarkable event. In the intervening 26 months, four additional genes have been found. So now, there are five genetic risk factors that are contributing, we believe, about 75 percent of the risk for those of us around the table to ultimately develop AMD.

These genes are also surprising in their molecular theme, their biological theme. They're in the immune system of the body, the

compliment cascade. The first factor was compliment factor H. Another gene was compliment factor B. These are components that operate normally in the body's immune defense against microbial infections. The way we think about it is, it's suboptimal control of this very vigorous defense system in the body. A normally protected pathway in which suboptimal control leads to chronic inflammation of the tissues of the retina and ultimately causes AMD to develop.

This gives us then the first handle on something that, in fact, we can take to the American people from this very basic genetic study. That is the recognition that the environmental factors, as my colleague next to me has just mentioned, and lifestyle factors play on this genetic background to further increase the risk of us developing AMD.

EYEGENE

This, my mentioning of these four or five genes for AMD are just part of the genetic story that is now rapidly evolving. There are some 450 genes that have been found to cause eye disease. These diseases include cataracts, glaucoma, strabismus, retinal disorders, corneal opacities, eye motility problems. With this wealth of genetic information, the Eye Institute, over the past 2 years, has developed a collaborative national network of research laboratories to support genetic testing.

We are calling this eyeGENE. You can go to Google and type in "NIH eyeGENE" and come up with a few pages on it. It is a consortium of 20 universities across the country that participates actively, with oversight, and setting directions to make available genetic information, both to research, to move the research along to appropriate conclusions. At the same time, as a corollary to provide genetic direct information to families. The research group is really quite excited about that. We will have a centralized registry for research data mining. We will have a secure blood collection for research, a research repository. EyeGENE is now receiving samples from physicians across the country.

So, what I have given you is what I think is a very exciting story of treatment for macular degeneration, genes for macular generation, the ability to provide information to all of us before we are, literally, patients. So that, perhaps, we can avoid becoming a patient for these conditions. I think this is in the tradition, as I'm hearing, already down the table of real opportunities for personalized and certainly, ultimately, participatory medicine. The first time in history, I think, we are really making tremendous progress. So, it is a rich and rewarding opportunity for us to move forward.

PREPARED STATEMENT

With that, thank you for the opportunity to testify. And, I will certainly be pleased to answer questions.

[The statement follows:]

PREPARED STATEMENT OF DR. PAUL A. SIEVING

Mr. Chairman and members of the committee: I am pleased to present the fiscal year 2008 President's budget request for the National Eye Institute (NEI). The fiscal year 2008 budget includes \$667,820,000 in the President's request.

As the Director of the NEI, it is my privilege to report on the many research opportunities that exist to reduce the burden of eye disease.

AGE-RELATED MACULAR DEGENERATION

The loss of sight affects us in fundamental ways, threatening independence, mobility and quality of life. Most eye diseases strike later in life. Thus, as life expectancy has increased and the baby boom generation ages, more Americans are becoming susceptible to vision loss and blindness. One such disease, age-related macular degeneration (AMD), is the leading cause of legal blindness. Based on published study data, 8 million older-age Americans are at high risk to develop advanced AMD. AMD causes a progressive loss of central vision, making it difficult to read, recognize faces, drive a car, or perform even simple tasks that require hand-eye coordination.

ANGIOGENESIS AND AMD

Angiogenesis is the term used to describe the growth of new blood vessels. Angiogenesis plays a crucial role in the normal development and maturation of tissues. It also plays a role in many diseases, including eye diseases such as diabetic retinopathy, retinopathy of prematurity and advanced AMD. In advanced AMD, new blood vessels grow abnormally beneath the retina. These abnormal blood vessels leak blood and fluid, producing scarring and severe vision loss.

NEI-supported researchers have established that a protein called vascular endothelial growth factor (VEGF) plays an important role in triggering angiogenesis in AMD and diabetic retinopathy. Thus, VEGF is an important target for drug development. Two anti-VEGF therapies have recently been approved by the FDA for the treatment of AMD. More recently, NEI-supported researchers have found that in animal models, combination therapies that control diverse elements of angiogenesis can completely inhibit some forms of abnormal blood vessel growth. Anti-VEGF therapies are also being evaluated in clinical trials for diabetic retinopathy. NEI and NIH have invested considerable resources in understanding and controlling angiogenesis. That investment is already paying handsome dividends.

DISEASE MECHANISMS IN AMD

Another critical area in developing treatments of AMD is to identify the causes and mechanisms of the disease early in its pathology. Researchers have long held that AMD can result from the confluence of genetic predisposition and chronic exposure to environmental risk factors, such as diet and smoking. In this scenario, a gene or genes contain subtle variations that hamper cellular function but may not necessarily cause disease directly. However, years of cumulative environmental insult can further strain the underlying genetic predisposition and trigger disease.

On the genetic side of the equation, NEI-supported investigators have identified common variations in four genes that are associated with AMD and may account for 75 percent of the risk of developing AMD. Two of these genes—complement factor H (CFH) and complement factor B (BF)—contain instructions to encode proteins that help regulate the body's immune defense against microbial infections. This defense, called the complement system, provokes inflammation, a common response to foreign pathogens. It is thought that certain variations in these genes result in sub-optimal control of the complement system and cause chronic inflammation. Chronic inflammation may damage tissues of the retina and could lead to AMD.

Chronic inflammation is thought to play a role in many other common diseases beyond the eye, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, kidney disease, stroke, and atherosclerosis. Although the cells, tissues, and molecular events in these diseases are diverse, they may share some common disease mechanisms that present an opportunity to cross pollinate findings from diverse research areas.

The genetic discovery of the possible role of inflammation and the immune system in AMD is a watershed moment. We have now uncovered a possible central disease mechanism that may lead to a better understanding of this major disease and the development of therapies that prevent vision loss. We now hold the possibility to learn an individual's risk vulnerability well before the disease is detectable clinically, and to intervene effectively, thereby preempting the disease process at its early stages.

PUBLIC HEALTH AND PREVENTION

Another critical and fruitful area of research is the development of public health strategies to prevent or delay AMD. Several epidemiologic studies, published in the 1990s, found evidence to suggest that diets rich in leafy green vegetables, which contain antioxidants, might be associated with a reduced risk of AMD. To leverage these findings, the NEI initiated a large, multi-center prospective study and clinical

trial called the Age-Related Eye Disease Study (AREDS). Data from the AREDS study, published in 2001, found that over a 5-year period, a daily formulation of antioxidant vitamins and minerals (vitamins C, E, beta-carotene and zinc with copper) delayed the onset of advanced AMD by 25 percent.

An estimated 8 million older-age Americans are at high risk to develop advanced AMD and vision loss. Of these 8 million, 1.3 million will develop advanced AMD within 5 years. However, now with the successful AREDS treatment, 300,000 of these individuals could be rescued from severe vision loss associated with advanced AMD over a 5-year period. This simple and relatively inexpensive dietary intervention offers to the American public a valuable intervention to prevent severe vision loss and to reduce the need for more aggressive and expensive therapies.

On the heels of this success, the NEI launched AREDS2. One of the primary objectives of AREDS2 is to determine whether oral supplementation with lutein and zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids will further decrease the progression to advanced AMD or formation of cataract. Previous NIH-funded studies have found high concentrations of these nutrients in the macula of the eye. Moreover, several studies have found an inverse relationship between dietary intake of these compounds and AMD. AREDS2 could result in a more effective but still inexpensive treatment regimen to prevent severe vision loss.

GENOMIC MEDICINE

AMD research is but one example of genomic medicine, the effort to diagnose and treat patients at the molecular level. Over the past 15 years, NEI-supported researchers have identified more than 450 genes that are involved in various eye and vision diseases. Considerable progress has been made in understanding the resultant disease mechanisms, and treatments are now beginning to emerge. As genomic medicine progresses, we must grapple with the obvious opportunity and challenge of genotyping individuals with eye disease and delivering therapies that are specifically tailored to the individual patient. This personalized approach to medicine is vital to improving the health of all Americans.

The NEI initiated eyeGENE to address this issue. EyeGENE is an organized national network of research laboratories to support genetic testing for individuals with eye diseases. As testing services are not routinely available, the diagnostic information from eyeGENE will directly benefit such patients and families. The initiative will significantly aid vision research through a centralized registry that can be used to locate individuals who may wish to participate in clinical trials for new therapies. eyeGENE fills a critical research need that will advance the field. It includes a secure research blood collection and a centralized research repository of disease phenotype features which coupled to genes that cause disease will allow for the creation of the large datasets necessary to identify novel genetic risk factors and other epidemiologic questions. Programs like eyeGENE will drive genomic research and become the necessary fabric for individuals to benefit from advances in genomic medicine.

ADDITIONAL ADVANCES

Recently, a number of developments have added further excitement to the field of vision research. The NEI is supporting projects that address the possible restoration of vision in blinding retinal degenerative diseases by building on recent advances in cell transplantation and precursor cell biology, including the use of bone marrow stem cell transplantation, and on "re-engineering" the production of light-sensitive proteins in retinal neurons.

Research will continue in efforts to control angiogenesis in a number of eye diseases, and will include the conduct of clinical trials in this area. In support of this research is the Diabetic Retinopathy Clinical Research Network (DRCR.net). This collaborative network, supported by the NEI, is dedicated to facilitating multicenter clinical research on diabetic retinopathy, diabetic macular edema and associated conditions. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well. The DRCR.net was formed in September 2002 and currently includes more than 150 participating sites (offices) with more than 500 eye care providers throughout the United States. The success of this new model for bringing improved treatments for diabetic retinopathy more rapidly to patients is dependent upon the active participation of clinical research centers across the United States, as well as the participation of the patients they treat.

Program plans for fiscal year 2008 include pursuing the research finding of several genes involved in Leber's Hereditary Optic Neuropathy, a genetic disease that

frequently results in a substantial loss of central vision. The development of animal models carrying these mutations could lead to successful gene-based therapy for this disease. Research will also pursue remarkable new findings about how the activity of certain brain cells allows us to perceive a stable view of our surroundings despite constant head and eye movements, as highlighted in NEI's strategic plan. This research will help us to understand better the neural control of eye movements and associated disorders, and may have applicability in other sensory systems.

Senator HARKIN. Thank you Dr. Sieving.

Now, we'll end with Dr. Duane Alexander, served as the Director of the National Institute of Child Health and Human Development since 1986. As I understand, you were there since 1968, is that right?

Dr. ALEXANDER. That's right.

Senator HARKIN. Received his M.D. from Johns Hopkins University, some research specializes in developmental disabilities. Welcome, again, back to the committee. Dr. Alexander, please proceed.

STATEMENT OF DR. DUANE F. ALEXANDER, M.D., DIRECTOR, NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Dr. ALEXANDER. Thank you, Mr. Chairman. I'd like to join with my colleagues in thanking you and the committee members for holding this hearing, and for your many years of strong support for the NIH that's allowed us to do what we've accomplished.

Since the National Institute of Child Health and Human Development was established nearly 45 years ago, our scientists have made discoveries that have improved the health and well being of children and adults.

For example, our research has contributed largely to the Nation's 70 percent reduction in infant mortality rate over that span of time, and 93 percent reduction in transmission rate from mother to child of the AIDS virus, the near elimination of five major causes of mental retardation, successful treatments for infertility, an effective intervention for reducing a major cause of premature birth, and many other benefits.

Our current research agenda builds on its past discoveries, addresses some of our country's and the world's most crucial health needs, and moves us closer to predicting or pre-empting diseases and conditions such as infertility, birth defects, disability from limb loss and infant mortality from premature birth.

FERTILITY PRESERVATION

One area of our current focus is fertility preservation for women facing cancer treatment. The chemotherapy and radiation used to treat cancer can irreparably damage the body's reproductive tissues, and render both men and women infertile.

Males may have the pre-treatment option of storing their frozen sperm for later use, but no comparable option currently exists for women. Eggs seldom survive the freezing and subsequent thawing process required for storage. However, our scientists are developing new techniques to protect the egg during the freezing, thawing and maturation process. When a woman who has had chemotherapy or radiation is ready to start a family, these follicles can be thawed and then cultured. The resulting eggs could be fertilized, and implanted in the uterus to establish a pregnancy.

PREVENTING DISABILITY

Preventing disability by newborn screening is another current emphasis for the Institute. It allows us to predict whether an infant has one of hundreds, literally, of genetic or metabolic disorders by testing a single drop of a newborn's blood, and treating the condition as soon as it's identified, preempting the infant's early death, or a lifetime of mental retardation or physical disability.

The screening and treatment, developed in large part through NICHD research, now is provided universally in the United States, but only for a few disorders.

One such disorder is congenital hypothyroidism. It occurs once about 3,000 births, affecting 1,300 children every year in the United States. Without treatment, the child with congenital hypothyroidism will suffer irreparable brain damage within months, and require a lifetime of special care.

However, as a result of our research, children with congenital hypothyroidism are now routinely identified at birth and given treatment immediately. One thyroxin pill daily spares them from the brain damage that would otherwise result, thus eliminating congenital hypothyroidism as a significant cause of mental impairment. The cost of treatment is just a few pennies a day. The lifetime amount of dollar savings is about \$140 million a year, and the human suffering prevented is priceless.

NEWBORN SCREENING

An NICHD initiative to develop the technology to markedly expand newborn screening to hundreds of conditions is being funded in fiscal year 2007, and will expand in 2008 by establishing a national network to pilot test these new successful treatments. This is a card (Exhibit A) that they use in New York State newborn screening program. Each State runs its own program, and determines which conditions it screens for. You can tell from what's listed here that we have moved in just the last year from a system which screened for 3 to 5 conditions only, to where a majority of States are now using tandem mass spectrometry to screen for 30 disorders, and we're working with other technology developments using micro array chips, luminex beads, or others to markedly expand this to literally hundreds of genetic disorders, immunodeficiency diseases, muscular dystrophies, and other conditions.

Newborn Screening

BFC-4588

Lab ID: 152129147

Parent's Last Name: _____
 Parents: _____

A blood specimen has been taken from your new baby for testing by the State Newborn Screening Program. This program is described in the brochure "For Your Baby's Health" given to you by hospital staff. To learn the outcome of this important health service, take this notice to your baby's doctor, who can obtain the test results either from this hospital, or by calling (800) 525-3079. Under NY State law, these results can only be reported to your doctor and cannot be sent directly to parents.

Do your children have health insurance? If not, they may qualify for NY's health insurance program, Child Health Plus. Call: 1 (800) 522-5006 for information.

Instructions to hospital:
 After entering infant's name, remove this pink copy and give it to the parents of this newborn, along with the educational brochure "For Your Baby's Health."

Newborn Screening Program
 Serving New York
 Since 1965



Wadsworth Center
 NYS Department of Health
<http://www.wadsworth.org/newborn>

SEE REVERSE OF FORM FOR INSTRUCTIONS
 SATURATE ALL CIRCLES COMPLETELY

<p>Yesterday</p> <p>Screen for 3 to 5 disorders, including: Phenylketonuria (PKU), Congenital Hypothyroidism (CH), and Galactosemia</p>	<p>Future</p> <p>Screen for these plus cancers, cardiovascular disease, diabetes, eye diseases, and many other disorders, including some developmental disorders</p>
↓	↑
<p>Today</p> <p>Screen for these plus 27 other disorders (Using mass spectrometry)</p>	<p>Tomorrow</p> <p>Screen for these plus:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Neurodegenerative genetic diseases (200+) <input type="checkbox"/> Immunodeficiencies (100+) <input type="checkbox"/> Hemoglobinopathies (10+) <input type="checkbox"/> Clotting disorders (10+) <input type="checkbox"/> Genetic deafness (20+) <input type="checkbox"/> Spinal muscular atrophy, muscular dystrophies, and other neuromuscular disorders (10+) <input type="checkbox"/> Malignant hyperthermia (1+) <input type="checkbox"/> Adverse drug reactions (many) <p>(Using other new technologies)</p>

→

NECROTIZING ENTEROCOLITIS

Another cause of infant mortality, that NICHD is attacking is necrotizing enterocolitis (NEC). We have made major advances against other causes like respirator, distress syndrome, severe jaundice, meningitis or sudden infant death syndrome, but NEC is a continuing problem. In 40 years, we've really made little progress against this condition. It causes death or disability by destroying the intestines of premature infants, and it attacks about one-tenth of all infants under 1,500 grams.

Our efforts have identified some potential treatments. One is epidermal growth factor, which in mice and rats is highly protective against NEC. Another human study, has demonstrated that interleukin-10 in breast milk is highly protective.

These and other potential treatments for NEC are going to be tested in a special initiative, launched by NICHD, about to be published, and funded in 2008.

MEDICAL REHABILITATION

As our country's armed forces return from stations abroad, and as the Nation's population continues to age, increased attention is needed on medical rehabilitation, to prevent immobility and dependence. Among the initiatives in the NICHD portfolio is developing mechanical limbs that allow for better comfort at the socket and improved mobility. Advances in this area can be particularly helpful to veterans who have lost limbs in combat.

One exciting new finding from this research is a new type of prosthetic arm, that connects in a way that allows the amputee to use it simply by thought—thinking about using the arm stimulates the chest muscles that are tied into it to contract with relative ease, and move the arm with greater speed and precision.

Researchers hope to use similar technology to restore natural movement and sensation to the limbs of individuals paralyzed by injury or stroke.

PREPARED STATEMENT

Mr. Chairman, committee members, I would like to thank you again for your continued support of our research, as we try to understand disease, and improve the health and well-being of men, women, children and future generations. I'll be pleased to answer any questions.

[The statement follows:]

PREPARED STATEMENT OF DR. DUANE F. ALEXANDER

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 Child Health and Human Development (NICHD). The fiscal year 2008 budget includes \$1,264,946,000.

With continuous support from this committee, the NICHD has made significant discoveries that have improved the health and well-being of children and adults. For instance, in the 45 years since the NICHD was founded, our research has been largely responsible for a decline in infant mortality of more than 70 percent, a 93 percent reduction in the rate of mother-to-child transmission of the AIDS virus, the elimination of five major causes of mental retardation, successful treatments for infertility, an effective intervention for reducing a major cause of premature birth, and many other benefits. Our scientists around the country are grateful to this committee for providing the opportunity to pursue research in these areas.

The Institute's research agenda builds on the discoveries from the last decade, addresses some of our country's and the world's most critical health needs, and moves us closer to major breakthroughs against diseases and conditions such as infertility, birth defects, infections, limb loss, premature birth, and maternal death.

PRESERVING FERTILITY FOR WOMEN FACING CANCER TREATMENT

The chemotherapy and radiation used to treat cancer can irreparably damage the body's reproductive tissues and render men and women infertile. Males may have the pre-treatment option of storing their frozen sperm for later use, but no comparable option currently exists for women. Eggs seldom survive the freezing and subsequent thawing processes required for storage. Currently, the only option for women facing the prospect of such infertility is in vitro fertilization and long-term

storage of the embryos, which tolerate freezing. However, this option is not always suitable. Young women with cancer may be forced to forego having their own children in order to receive life-saving treatment. The NICHD's new Fertility Preservation Research Program seeks to develop treatments to preserve fertility among patients with cancer or environmental risks for infertility. Building on current research, such as using a gelatin mixture to surround the follicle containing the egg, our scientists will be developing new techniques to protect the egg during the freezing, thawing, and maturation process. The goal is to allow a small section of the ovary to be removed and frozen for later use. When the woman is ready to start a family, the frozen follicles could be thawed and then cultured. The resulting eggs could be fertilized and implanted in the uterus to establish a pregnancy.

PROTECTING OUR CHILDREN AS WE TREAT THEIR ILLNESSES

The Best Pharmaceuticals for Children Act (BPCA)—enacted by Congress to increase information about the safety, usefulness, and dosage of medications for infants and children—is an important part of the nation's ongoing effort to assure that our treatments for children do not harm them. As we have learned, children's immature body systems and metabolic rates make pediatric clinical trials essential for studying the impact of widely prescribed drugs on children and infants. Within its work on the BPCA, the NICHD, in consultation with the Food and Drug Administration, identifies and prioritizes drugs for pediatric clinical study. The NICHD collaborates with manufacturers and academia in designing and implementing pre-clinical and clinical studies of drugs that are widely used or integral to the care of children with specific medical conditions. Currently 29 studies are under way evaluating drugs to provide information for labeling to guide pediatric use.

PREVENTING DISABILITIES THROUGH NEWBORN SCREENING

Imagine being able to know if an infant has one of hundreds of genetic or metabolic disorders by testing a single drop of a newborn's blood. Imagine being able to treat the condition as soon as it is identified, sparing that infant an early death or a lifetime of mental retardation or physical disability. This screening and treatment, developed in large part through NICHD research, now is provided universally in the United States for a few such disorders. For example, the National Newborn Screening and Genetic Research Center reports that congenital hypothyroidism (CH) occurs once in every 3,000 births, affecting 1,300 children each year in the United States. Without treatment, an infant with CH will suffer irreparable brain damage within months and require a lifetime of special care. Because an NICHD grantee developed a screening test for the disorder in the 1970s, children with CH are now routinely identified at birth and treatment begins immediately. One thyroxine pill daily spares them from the brain damage that would otherwise result, thus eliminating CH as a significant cause of mental impairment. The cost of treatment: a few pennies a day; the lifetime net dollar savings: \$140 million each year; the human suffering prevented: priceless.

Currently, the number of conditions for which newborns are screened varies widely from state to state. The March of Dimes notes that nearly all of the 4.1 million American infants born each year undergo screening for some disorders, and about 5,000 are diagnosed with an abnormality. Treatments exist for the conditions for which we now screen, as well as for others for which screening is not yet possible. To remedy this situation, the NICHD is funding a series of contracts to develop gene-based technologies that can identify hundreds of rare genetic disorders in a single test. In addition, the Institute will fund new projects to spur research on new treatments for potentially screenable disorders. Examples of conditions in these categories are Spinal Muscular Atrophy, the leading genetic cause of infant death, and Fragile X Syndrome, the leading inherited cause of mental retardation. Expanded efforts in fiscal year 2008 will include creating a multi-site newborn screening translational research network to test the most promising new screening technologies and experimental treatments in collaboration with state newborn screening programs.

REDUCING ANOTHER CAUSE OF INFANT MORTALITY: NEC

Through research led by the NICHD, one cause of infant mortality after another has yielded to treatments based on new discoveries. Respiratory distress syndrome, severe jaundice, meningitis, and Sudden Infant Death Syndrome cause far fewer deaths today. One remaining problem is necrotizing enterocolitis (NEC). This condition affects 10 to 12 percent of infants weighing less than three pounds, and about 30 percent of those affected will not survive. NEC attacks and destroys their intestines. Unfortunately, its incidence and mortality rate have not changed in 40 years.

Now, new NICHD studies give hope that prevention or effective treatment can become a reality. One study in mice demonstrated that epidermal growth factor, administered orally, was highly protective against NEC. Another study, in humans, demonstrated protection against NEC from interleukin—in breast milk. These and other potential therapies will be tested in a new NICHD initiative on NEC to be launched in fiscal year 2008.

DEVELOPING IMPROVED PROSTHETICS

As the country's Armed Forces return from stations abroad, and as the nation's population continues to age, increased attention is needed on medical rehabilitation. The Institute's National Center for Medical Rehabilitation Research is a leader in such efforts and provides a Federal focal point for research in this important field. Among the initiatives in the Center's portfolio is developing mechanical limbs that allow for better comfort and mobility. Advances in this area can be particularly helpful to veterans who have lost limbs in combat. One exciting new finding from this research: an amputee can move and have functional use of a prototype prosthetic arm simply by thought. Thinking about moving the arm stimulates the chest muscles to contract. Microprocessors in the arm read the nerve signals sent by the chest muscles, and movement flows with relative ease and greater speed and precision. Researchers hope to use similar technology to restore natural movement and sensation to the limbs of individuals paralyzed by injury or stroke.

HELPING DEVELOPING NATIONS OVERCOME DISEASE

Every 30 seconds, malaria takes the life of a child somewhere in the world. The mosquito-borne disease kills more than one million people each year and severely sickens millions more in developing countries, crippling economic growth. It is one of the world's leading health concerns. Researchers at the NICHD's Laboratory of Developmental and Molecular Immunity—in partnership with researchers in the Malaria Vaccine Development Branch of the National Institute of Allergy and Infectious Diseases, and the Biotechnology Unit of the National Institute of Diabetes and Digestive and Kidney Diseases—may have a solution.

These researchers have developed an experimental vaccine that stops the spread of malaria, mosquito by mosquito. The vaccine eliminates the parasite responsible for malaria from the digestive tract of a malaria-carrying mosquito after it has fed on the blood of a vaccinated individual. Future bites from this mosquito then no longer transmit the disease. If it is proven safe and effective, the vaccine could free entire geographic regions from this destructive disease.

The NICHD's research investments to improve health in developing nations go beyond laboratory benches. The Institute supports the Global Network for Women's and Children's Health Research, an initiative devoted to addressing the leading causes of illness and death in pregnant women and their infants in developing countries. This year one network study, a randomized double blind clinical trial conducted by birth attendants in rural India, demonstrated that giving women a single dose of misoprostol, a uterine muscle constrictor, just after delivery nearly eliminated the incidence of severe post-partum hemorrhage, a leading cause of maternal mortality in developing countries worldwide. India immediately took action to make misoprostol treatment available as standard care throughout the country, and other nations are doing the same. This one simple and cost effective intervention will save the lives of millions of women throughout the developing world.

Mr. Chairman and members of the committee, I would like to thank you for your continued support of the Institute's research as we strive to understand disease and improve the health and well-being of men, women, children, and future generations in the United States and around the world. I will be pleased to answer any questions.

Senator HARKIN. Dr. Alexander, thank you very much.

It's hard to know where to begin, but thank you all very much for excellent testimony. Very pointed, very to the point. We might as well start where we started with Dr. Kirschstein.

RESPONSE TO COMPLEMENTARY AND ALTERNATIVE MEDICINE

I'm very interested in what you mentioned about looking at genetic variations, and I want you to just tell me a little bit more about that, because it seems to me, every time we talk about people who have had an experience with a complementary or alter-

native medicine approach, were over the counter or something like that. Sometimes it seems to work for some people, and it doesn't for others. So, why does it work for some, and not for others? So, maybe there is some genetic variation there that allows for something to be done, and is therapeutic, but on the other hand, for someone else it isn't. Is that what you're looking at?

Dr. KIRSCHSTEIN. That's what we plan to look at. We know that that's true, also, for the use of more conventional drugs. We know that the people respond differently to drugs, and that there are times when the dose has to be cut, or they actually have to substitute one drug for another. We don't have that knowledge about these complementary materials, particularly the biologically based ones that people have been using on their own that they can purchase in various stores. This is what we want to take a look at, now that we know so much about the sequencing of the genome and the variation as to what could be happening. We're going to launch studies to that effect. We have not started as yet.

NATIONAL ADVISORY COUNCIL ON COMPLEMENTARY AND ALTERNATIVE
MEDICINE

Senator HARKIN. I see. I just want to cover one other thing with you, Dr. Kirschstein, and that is the structure of the advisory council.

Dr. KIRSCHSTEIN. Yes, sir?

Senator HARKIN. Here's the law that set it up.

First of all, you know we had it first as the Office of Alternative Medicine, and then we changed it to NCCAM, and when we changed it to NCCAM in 1998, many people were disappointed in how the structure of the advisory panels had been set up previous to that. So, we wrote into law certain guidelines, put it right into the law. Of the 18 appointed members, 12 shall be selected from among the leading representatives of the Health and Scientific Disciplines, relative to the activities of the NCCAM. Particularly, representatives of the health and scientific disciplines in the area of complementary and alternative medicine members shall be practitioners licensed in one or more of the major systems with which the Center is involved.

Then it says, "Six shall be appointed by the Secretary from the general public and shall include leaders in the fields of public policy, law, health policy, economics, and management. Three of the six shall represent the interests of individual consumers of complementary and alterative medicine."

I understand that earlier this week you named six new members to the advisory Council. I've had concerns about this going clear back to 1991. As you know, as I said, I just read to you that 50 percent of the Council's non-staff members should be licensed CAM practitioners. Three, as I mentioned, from the consumer population. I don't believe that statute has always been met, and I want to ask you, where do we stand now with these additions to the panel? If you don't know that, you can respond to me later on.

Dr. KIRSCHSTEIN. I will expand on the question for the record.
[The information follows:]

NATIONAL ADVISORY COUNCIL ON COMPLEMENTARY AND ALTERNATIVE MEDICINE

Question. The statute for the National Center for Complementary and Alternative Medicine (NCCAM) stipulates that at least half of the members of NCCAM's Advisory Council, who are not ex officio members, shall include practitioners licensed in one or more of the major systems with which the Center is concerned, and at least three individuals representing the interests of individual consumers of complementary and alternative medicine. How close is NCCAM coming to meeting the law?

Answer. There are several factors that influence the composition of NCCAM's National Advisory Council:

- NCCAM's mission encompasses a diverse body of research. The scope of NCCAM's research includes all organ systems and medical/scientific disciplines, as well as a range of CAM modalities and practices within the four major CAM domains or systems (manipulative and body-based practices, biologically based practices, energy medicine and mind-body medicine) as well as the whole medical systems of which they are a part. The collective expertise of NCCAM's Advisory Council, which is responsible for second-level peer review of the grant applications that NCCAM receives, must reflect this diversity.
- Regulation of and licensure to practice any medical or CAM discipline is within the purview of the states, and requirements vary widely. For example:
 - All states license chiropractors.
 - All states license medical doctors and most include within the medical licensure standards degrees obtained from schools of osteopathy.
 - Most states have some form of licensure for practitioners of acupuncture and/or oriental medicine and practitioners of massage therapy.
 - A large majority of states do not have any specific form of licensure for practitioners of naturopathy or homeopathy.
 - Specific licensure does not exist in any state for many of the CAM disciplines involved in research grant applications reviewed by NCCAM's Advisory Council. Of these disciplines, many can be legally practiced for health care purposes by or under the auspices of licensed medical providers, such as allopathic physicians, doctors of osteopathy, or licensed mental health care professionals, and always within the legal framework and limitations of their licensed discipline.

Table 1, attached, lists the current NCCAM Advisory Council members, their areas of CAM and/or medical/scientific expertise, and their research and professional interests relevant to their service on the council. The table illustrates how the composition of the Advisory Council reflects the need to simultaneously address relevant statutory requirements, and to ensure appropriate scientific and CAM expertise needed to carry out its charge.

The terms of four Council members listed in Table 1 (Calabrese, Ezzo, Manyam, and Pickar) expire in 2007. Those members are slated to be replaced by six individuals whose appointments are in the final stages of completion. Table 2 lists the areas of CAM, medical/scientific expertise, and the research and professional interests relevant to the Advisory Council for the pending new members.

NCCAM will continue to assure that it has an appropriately qualified and balanced Advisory Council, as required by statute, that permits the Center to support the highest quality of scientific investigation of CAM, such as the examples highlighted in my testimony before the Subcommittee.

TABLE 1.—NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE—MEMBERSHIP, EXPERTISE, AND RESEARCH/PROFESSIONAL INTERESTS

Member degree(s)	Institution location	CAM expertise	Medical/scientific expertise	Professional/research interests and activities
Lori Alvord, MD ^{1, 2}	Dartmouth Medical School, Hanover, NH	Native American Medicine.	Surgery	Integrative medicine. Health services research on patterns of care for Native Americans.
Stephen Barnes, Ph.D. ¹	U Alabama at Birmingham, AL	Botanicals/natural products. Pharmacognosy Naturopathy	Biochemistry Pharmacology Toxicology Clinical research	Botanical research. Research on diseases of aging and chronic disease prevention. Clinical research on CAM natural products.
Carl Calabrese, ND, MPH ^{2, 3}	National College of Natural Medicine, Portland, OR. Carnegie Mellon, U Pittsburgh, PA		Psychology Mind-body medicine Psychosomatics Inflammatory bowel diseases Mucosal immunology Endocrinology	Role of stress, coping, and social support in health and well-being. Psychoneuroimmunology.
Fabio Cominelli, MD, Ph.D. ¹	U Virginia, Charlottesville, VA	Gastroenterology Cell biology		Type II diabetes and metabolic syndrome.
Silvia Corvera, MD	U Massachusetts Medical School, Worcester, MA.	Massage therapy	Epidemiology Biostatistics Cell biology	Systematic reviews evaluating CAM evidence base. Health policy—breast cancer advocacy. Cardiovascular disease; mechanisms of action of mind-body practices affecting cardiovascular disease.
Jeanette Ezzo, Ph.D., M.S.T., MPH ^{2, 3}	James P. Swyers Enterprises, Takoma Park, MD.	Reiki		Women's health. Osteoporosis, menopause. Acupuncture.
Joan Fox, Ph.D.	Case Western Reserve, University, Cleveland, OH.		Obstetrics and Gynecology	Clinical and basic research on the placebo effect and its implications for practice and research methodology.
Marjorie Gass, MD ^{1, 2}	U. Cincinnati, Cincinnati, OH	Asian medicine Acupuncture	Neurology	Research on movement disorders. Ayurvedic herbal medicine approaches to Alzheimer's disease.
Ted Kaptchuk, OMD, LAc	Harvard Medical School, Osher Institute, Boston, MA.		Physiology	Neurophysiology of chiropractic manipulation.
Bala Manyam, MD ³	Hindu University of America Odessa, FL	Ayurveda	Clinical trials Pharmacokinetics Toxicology	Immunotherapeutic approaches to treatment of cancer. Herb-drug interactions.
Joel Pickar, DC, Ph.D. ^{2, 3}	Palmer College of Chiropractic, Davenport, IA.	Chiropractic		
Bruce Redman, DO	U of Michigan, Ann Arbor, MI	Osteopathy		
Danny Shen, Ph.D.	University of Washington Seattle, WA			

TABLE 1.—NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE—MEMBERSHIP, EXPERTISE, AND RESEARCH/PROFESSIONAL INTERESTS—Continued

Member degree(s)	Institution location	CAM expertise	Medical/scientific expertise	Professional/research interests and activities
Frank Torti, MD, MPH ¹	Wake Forest U School of Medicine Salem, NC		Oncology	Cancer biology. Antioxidants and cytokines.
Stephanie Vogel, Ph.D.	U of Maryland Baltimore, MD		Immunology Microbiology	Mechanisms of immune defense.

¹ The appointment of these six individuals was announced on June 21, 2007.

² Public member.

³ Terms expire in 2007.

TABLE 2.—NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE—
EXPERTISE AND RESEARCH/PROFESSIONAL INTERESTS OF MEMBERS PENDING APPOINTMENT

Pending	CAM expertise	Medical/scientific expertise	Professional/research interests and activities
1 ¹	Naturopathy	Integrative oncology. Cancer Prevention. Public policy.
2 ¹	Osteopathy	Osteopathic practitioner.
3 ¹	Chiropractic ...	Clinical trials	Research on CAM treatments for low back pain, neck pain, asthma, infantile colic, and headache.
4	Acupuncture ..	Psychiatry	Practice of acupuncture.
5 ¹	Qi Gong	Biochemistry	Cell biology.
	Tai Chi	Biophysics	Research on mechanisms of action of qigong and acupuncture.
	Cell biology	Teaching of Oriental Medicine.
6	Internal medicine	Cardiovascular Disease.
	Cardiology	Epidemiology of cardiovascular disease in African Americans.
	Epidemiology	Epidemiology and preventive medicine.

¹ Public member.

Dr. KIRSCHSTEIN. I do know we have tried very hard to fulfill the law. We submit two names for each spot on the advisory council. We have been in discussion with the people who have worked on this, and we are always working to improve the submissions for the advisory council.

On the other hand, we need a very balanced advisory council, because we need individuals who can take a look at things like the genetic variation studies that we will be setting up. So, this is a challenge to us, and we're going to work hard to meet it.

Senator HARKIN. I appreciate that, Dr. Kirschstein, could you please get to my staff within the next week or so, the rundown of the members, the six that have been appointed, I want to know how close we've come to meeting the law?

Dr. KIRSCHSTEIN. Yes, sir, I will do that.

Senator HARKIN. I'm still concerned about that.

Dr. KIRSCHSTEIN. I will work with you on it.

Senator HARKIN. I appreciate that. It's something, as you know, I've been hot on this for a long time.

Dr. KIRSCHSTEIN. Yes.

CAM AND INFLAMMATION RESEARCH

Senator HARKIN. I don't mean to let up on it.

It's interesting that you mentioned in your written statement—I read it last night—but you mentioned something about the use of turmeric as an anti-inflammatory thing. Is that investigation ongoing right now?

Dr. KIRSCHSTEIN. Yes, sir. It is an investigation ongoing right now, and some preliminary data have indicated that it has anti-inflammatory effects, and possibly anti-arthritis effects, therefore we are planning to expand those studies.

Senator HARKIN. I've always asked a lot of doctors—if you look at my hands and look at my two little fingers, there's little bumps on the last thing of that digit—do you know what that's called?

Dr. KIRSCHSTEIN. I have one called—

Senator HARKIN. What's that called?

Dr. KIRSCHSTEIN. Osteoarthritis.

Senator HARKIN. What is that called? Aheberden's nodes, but it's only because it comes to the little fingers and the thumbs, basically

where it affects—there was a Scottish doctor that found this, and it's prevalent among people from that area of the world—Scotland, Ireland, it happens to be where my ancestors come from. But, a very painful, arthritic conditions.

It's interesting, because you know, I've been interested in complementary and alternative medicine for a long time. I was in Iowa last fall in the campaign and what do you do during the campaign? You shake a lot of hands. Well, these can be very painful, can you imagine shaking hands with this? It was so painful, I couldn't even stand to shake hands.

I just happened at that time to have dinner with a couple of doctor friends of mine, brothers, Dr. Neil Sahai and his brother Sabash, they're from India. They have a medical practice in Webster City, Iowa, and they invited me over for dinner, great family. Their mother was there, and the best Indian food I've ever had in my life. So, I went there for dinner, just as a social thing, I know them. I was complaining about my hands hurting. I had arthritis in my fingers, and Neil Sahai, Dr. Sahai said, "Well, I think I may have something to help you from India, we've got this, something called turmeric."

Well, I'd kind of heard of that as a spice before, and so he asked me to take two of these every day for a month, and just see if it had any effect, and I didn't change any other thing I did in my life. I changed nothing in terms of my eating habits or sleep, basically went on as I've been going, except I started taking this turmeric every day, and after about 30 some days or something, I just had no problem, and I have no more pain left in my hands at all. I take turmeric every day now. Now, is that the reason for it? I don't know. All I can tell you, I didn't change anything else. It's interesting, when I read your testimony last night I thought, "Oh my gosh," I thought maybe it was just mental stuff with me, I didn't know what was going on. It was amazing, I had to have that happen.

Dr. KIRSCHSTEIN. Maybe next year or the year after, the permanent Director of NCCAM will be able to tell you the answer.

Senator HARKIN. Well, it's just interesting that you're interested in that, and looking at it. Anyway, I didn't mean to get into my own health thing or anything like that.

Well, I have a lot more questions, but Senator Cochran, I would yield to you for another 5 or 10 minutes, and then I'll come back.

Senator COCHRAN. Mr. Chairman, one thing that could have helped your hand is you quit running for President, you don't have to shake as many hands.

NATURAL RESEARCH PRODUCTS

Senator HARKIN. That's a good point.

Senator COCHRAN. I think it's very interesting, to hear the testimony this morning. I've enjoyed the opportunity to hear your remarks about the different areas of inquiry the National Institutes of Health is engaged in, and your areas of expertise.

I remember, too, in connection with dietary supplements, there's a growing popularity among American people in these kinds of things, and at our University of Mississippi, there's a natural prod-

ucts center that has been established, and it's been working now for some time, exploring health beneficial uses of natural products.

It all started, frankly, with an idea someone had for undertaking marijuana research, and it's the only place in the country that I know about where the Government actually encourages the growing of marijuana, and testing and analysis, and trying to figure out what the medicinal properties might be that can be useful, and that has expanded now to include a lot of other areas of inquiry. It's become an international center for research and exchange of information, and we're very proud to host that in our State in Mississippi.

I just wonder if the National Institute has had any connection or correspondence, communication with people down there who are working in these areas.

Dr. KIRSCHSTEIN, do you know of any connection or exchange of information?

Dr. KIRSCHSTEIN. We have a great deal of contact with the people down there, indeed we support research at the University of Mississippi on natural products botanical center, and we just—there was recently a meeting there which we helped support, so we're very active in that area, sir.

CAM AND PEDIATRIC POPULATIONS

Senator COCHRAN. I know that one area of interest is in alternative medicine for children. I know I grew up in a family that didn't believe in taking medicine. My mother always said, "If you eat right, you don't have to take medicine, you'll be healthy." If you exercise and do all of these right things. Of course I've learned later that it's probably the genetic properties we were born with have an awful lot to do with good health, too, and disposition towards disease and illness.

How important is it for us to concentrate on education in these areas of factual information that could be helpful, at least, to reducing anxieties, contributing to unnecessary use of medicines, if we can change the mindset by just improving the level of knowledge and understanding and appreciation of what the facts are? What really does matter in good health, for children, particularly?

Dr. KIRSCHSTEIN. It's extremely important. Dr. Alexander, of course, can expand on this. But one of the reasons we are doing this survey with the CDC is to determine how extensive the use of complementary and alternative practices is in children. We know that their parents are using a great deal of this, and therefore some of them, of course, are giving similar treatments or modalities to their children. We really don't have good follow up on that, and we need to begin to do some research, being very mindful that the child is not just a little adult—there are differences between children and adults. We must be sure that we are protecting our children at the same time, and that we know what we're giving them.

The other part about education is that what we know, Senator Cochran, is that people, consumers, of complementary medicines and alternative medicines, when going to the regular practitioner, their doctors do not tell them that they are using the alternative or complementary products, and vice versa. The doctors do not ask them. As a result, the communication about all of the materials

that an individual is using does not get transmitted. That is why we have started these new campaigns—education in this field, just like in all medical fields—is very important.

PRETERM BIRTHS

Senator COCHRAN. Thank you. I know, Dr. Alexander mentioned in his testimony the problem of premature births. I think the statistics that we have show that this has increased by 30 percent, just in the last 20 years. That is a substantial number, it's now the leading cause of newborn death. What factors, do you think, are the cause, or can be attributed to the pre-term births? What do we do in terms of national policy or education to improve on these numbers?

Dr. ALEXANDER. This is a real puzzle to us, Senator Cochran, because there's no question about these statistics. The change, the increase in premature birth is real. It's also accompanied by an increase in low birth weight, not unexpectedly.

After many years in which this declined, it has now started to go up again, and the trend has persisted in spite of our efforts to reverse it. So, people talk about a variety of things that may be contributing to it. One of the first things people talk about is the increased prevalence of assisted reproductive technology—invitro fertilization, and other efforts to assist people who are infertile to have children. For a variety of reasons—sometimes because multiple fetus pregnancy is established—two, three, four, fetuses—all of which tend to increase the likelihood of prematurity. We have now, 1 to 2 percent of our population born as a consequence of assisted reproductive technology. So, as that has increased, the likelihood of prematurity has increased. What we're trying to do here with the obstetric community is encourage, when people do IVF, only to put one embryo back, and to establish a pregnancy with a single embryo, rather than two, three, four, five, as has been done in the past to increase the likelihood of establishing the pregnancy. That is one tactic.

In addition to that, there probably is a factor of increased efforts to save very, very low birth weight babies, so that babies that might have been classified previously as still births, now are classified as live births, and are entered as babies who are live births, and thus contribute to infant mortality, whereas previously they would have been considered stillbirths because they were so small, that no efforts were made to help them start breathing or start a heart rate. That is another factor.

But, there are others that we just don't understand. We're in the process of working with the Office of the Surgeon General to put together a report on prematurity that was called for by the Premie Act that the last Congress passed. So, we're involved in that, and we hope through our very intense examination of that, which follows on the work of an Institute of Medicine committee focusing on prematurity, we will learn some more useful routes to pursue to try to get at this question of what is causing the increase, and what can we do to reverse it?

Senator COCHRAN. Thank you. Thank you, Mr. Chairman.

Senator HARKIN. Thank you, Senator Cochran.

TEMPOROMANDIBULAR JOINT/MUSCLE DISORDERS

Dr. Tabak, I think you and I talked about this a long time ago. That included report language, for many years, on TMJ, and you mentioned it briefly. We discussed it several years ago again. Very briefly, could you tell what advances have been made recently in the area of TMJ? On the muscle and joint disorders? Are you doing some research on regenerating damaged bone and tissue, but just again, give me a couple of minutes on that.

Dr. TABAK. Surely, and thank you for the question.

We've actually done quite a bit in this area. The most important thing is that we are now attracting researchers with different talent sets to study this enigmatic set of diseases and conditions. We have finally been able to attract geneticists, neurologists, neuroscientists, individuals who are able to look at the entire system, as opposed to the very specific joint.

By bringing in these additional people with their expertise, we're beginning to get a much more balanced view of this complex, and probably heterogeneous, set of diseases and conditions. The work that you alluded to, work related to replacement of diseased joints, is ongoing. We have a very extensive bioengineering program, which makes use of advanced material development. The materials are not stagnant, they are typically impregnated with so-called growth factors, similar to those that Dr. Sieving spoke to you. These growth factors can help inform the surrounding cells as to what they should be doing to facilitate regeneration and regrowth. So, we're really looking at this at all levels.

A final point that I will make is that we recently funded a longitudinal study at the University of North Carolina termed OPERA, which is looking at individuals before they even develop symptoms of temporomandibular joint/muscle disorders. What we're doing in this prospective longitudinal study is collecting a large amount of data—including biological samples—so that as the individuals within the cohort begin to develop symptoms and evidence of disease, we will have already banked materials. Once and for all we can begin to get insight into the very earliest stages of the disease, so that we can begin to pick out those people in the community who are most at risk. I think that's going to be a very important adjunct.

We have programs to look at the very earliest stages of the disease. We have programs looking at the disease as it currently exists, and then we have the programs at the end stages, where we are recreating the joint for those individuals who have had extensive joint destruction.

Senator HARKIN. Very good, I'll keep on top of this. We've been on it for several years, and I'm really interested in, again, pushing this ahead and advancing the early detection of that, and intervention on that program.

AUTISM

Dr. Schwartz, let's talk a little bit about autism. You didn't really cover that in your testimony, but we just had a hearing on that, and it was the first hearing we've had on this committee just looking at autism.

Anyway, you look at it, autism is almost epidemic right now. The increases over the last 2 years have been phenomenal, and the number of kids diagnosed with autism. Again, we're looking at things like, we know the earlier you get to it, there are certain interventional-type programs you can do that can lessen the effects of autism later on.

But, still, kids have autism. We don't know whether it's genetic or environmental, and it seems to be, in talking with CDC, maybe it's some genetic, maybe some environmental. Maybe the two feed off of each other. I'm wondering, what are you doing in your Department, what are you doing, looking at any environmental aspects of autism? Any correlative types of things that deal with autism and the environment?

Dr. SCHWARTZ. I agree with you entirely. I think a very important area of health research in the United States, with the changing patterns of disease. It looks like environment is playing an important role in terms of increasing the risk of developing disease, the patterns of disease, the severity of disease, or the type of disease that children are presenting with. Because we recognize that, we have been working in a very focused way to address this issue of autism. In fact, we've increased our funding from 2006 to 2007 from \$1.8 million to \$3.5 million in the area of autism.

We have a new study that we are funding at the University of California in Davis, UC Davis.

Senator HARKIN. Just stop right there a second. Okay, tell me again, how much you're spending this year, on autism?

Dr. SCHWARTZ. In 2007, \$3.5 million.

Senator HARKIN. That's all you're spending on looking at environmental aspects of autism? Is that what you're saying?

Dr. SCHWARTZ. That's correct.

Senator HARKIN. Out of \$637 million?

Dr. SCHWARTZ. That's correct. As I said, we have doubled the amount from 2006 to 2007.

Senator HARKIN. Okay, but I'm just wondering why we haven't been doing more before that. I'm always interested when people tell me they've doubled, or something's gone up by 100 percent, I always try to remember, and remind people that zero to 1 is an infinite increase. So, it depends on where you're starting from.

Dr. SCHWARTZ. In the climate of a flat budget, we have increased the investment in this area, because we recognize the importance of this. So, let me just tell you the things we're doing, and that we're planning to do, because I think it really gets at your questions which are, what will our investment be over the next several years, and how seriously do we take this disorder?

AUTISM RESEARCH

In terms of the \$3.5 million, we just initiated a very large, prospective study of children at risk of developing autism to try to identify the factors that pre-date the development of autism to understand the biological signals, and also the genetic factors, as well as the environmental exposures, that are related to the development of autism.

That's one thing. The second thing is that we're working with the Centers for Disease Control to make their panel of exposure meas-

urements, which constitutes about 150 biological exposure measurements, available to these long-term epidemiological studies to try to understand whether pesticides in the blood, or solvents, or metals in the blood are related to the risk of developing autism in these populations that have already been established.

The third thing that we have done is we recently helped develop a conference with the Institute of Medicine focusing on the environment and autism. Dr. Alexander was involved in that conference. Dr. Insel, Director of the National Institute of Mental Health, was also involved in that conference, and we identified several areas of potential collaborative activities in the area of autism that we want to pursue further. So, we're currently in discussions with the National Institute of Mental Health—one other thing, we are newly supporting this year are the Autism Centers of Excellence. One of those Centers will be supported by NIEHS. That will be in the 2008 budget, so that is not counted in the \$3.5 million.

Now, one of the areas we're developing in collaboration with the National Institute of Mental Health is to take our Environmental Health Science Centers and when they are co-localized with the Autism Centers of Excellence, we will provide extra support for those two areas of expertise, to collaborate effectively on how the environment is affecting autism.

Senator HARKIN. Okay. In a recent issue of Discover Magazine, I think there was a cover story on autism, yes, and it had an interesting map. This was of the State of Texas, and it had a map of the State of Texas, like three maps. One showed the number of reported cases of autism in young children. I think it was, maybe, 10 years ago. I could be off on that, but some time ago. The next map showed the use of, by county by county, it was a map of the counties of Texas. I think it was EPA data showing the amount of, levels of, I don't know if they were carcinogenic, but of different compounds in the environment that was, sort of, toxic. It had a lot to do with, I think, petrochemicals. It had a lot to do with pesticides, herbicides, a whole panoply of things, a whole bunch of things.

Then, the next map showed the increase in the rate of autism. You overlay that map and it is just amazing. It's just about the same. So again, this is your department, right?

Dr. SCHWARTZ. That is correct.

Senator HARKIN. It seems to me that you really ought to be really pushing the envelope on this to try to find these kind of patterns and getting more scientists involved and getting more grants. I don't know what the rate or what the kind of proposals that are coming in that actually get through the peer review process. I would be interested in knowing what percentage or how many of the peer reviewed client proposals that come through, requests that come through to study the environmental aspect of the impact on autism. How many of those are being granted?

Dr. SCHWARTZ. A great question.

Senator HARKIN. Is it 15, is it 20?

Dr. SCHWARTZ. We can provide that information to you.

[The information follows:]

SUCCESS OF NIEHS AUTISM GRANT APPLICATIONS

The NIEHS received eight research applications for projects focusing on autism in fiscal year 2006. Three of the proposals, or 37.5 percent, were funded. This percentage is substantially higher than the success rate of the overall NIEHS portfolio and demonstrates the Institute's commitment to autism research as a program priority.

Dr. SCHWARTZ. It is more than 20 percent. It's probably 30 or 40 percent. I think we are looking at this as a challenge and also an opportunity for the field of environmental sciences.

THIMEROSAL

Senator HARKIN. Are you looking, there was for some time this thought that Thimerosal was a leading cause. Medical professionals and researchers said that that's not the case. CDC basically testified that they did not think there was a correlation there, but there's other thoughts that it's the amount of vaccinations that are given to kids before the age of 2. Now, it's like 25 or 26 or something like that.

Do you know, Dr. Alexander?

IMMUNIZATIONS

Dr. ALEXANDER. If you add all the diseases together and the number of immunizations you get for each one of them, that's about the right ballpark.

Senator HARKIN. Somewhere between 20 and 30. I know my grandson, they're just wrestling with that right now, but this is something relatively new. I mean new in the last 20 years or so. We never did that before.

Dr. ALEXANDER. But, there's been no thimerosal in any of these vaccines for the last 5 years.

Senator HARKIN. Not the thimerosal, I'm just saying maybe it's the number of these and the cumulative effect it has. As you said, these are not just little adults. Everything is different in a baby and you're talking about giving between 20 and 30 immunizations between, before they're 2-years-of-age. There's some thought that maybe just the accumulation of that may have some affect on autism.

NATIONAL CHILDREN'S STUDY

Now again, I don't know and I don't know if any research is being done into that either through you or through you.

Dr. ALEXANDER. Let me tell you something that is about to be done. It's a payoff benefit from the National Children's Study that you made reference to earlier. NIEHS and EPA and CDC are joined with the NICHD and many other institutes in the planning for this study. One of the things that will be looked at as a key outcome is autism. With a prevalence of six per thousand, we will have 600 kids and 99,000 controls. So, we will have information on these children including DNA from both parents and the child and siblings, we will have prenatal exposures of the mom to a large number of environmental factors and toxins and substances and so forth. We will be sampling the child from birth with umbilical cord blood etc. and we will be following the environment that the child lives in, measuring environmental exposures. We will measure the

vaccinations and immunizations the child gets, the whole course of their medical history.

Senator HARKIN. Are you talking about the children study?

Dr. ALEXANDER. Yes.

Senator HARKIN. That longitudinal study?

Dr. ALEXANDER. Right, and that will be providing us with this information that there is no other source to get. It will all be obtained prospectively and we'll be able to analyze, not just one thing at a time, but we'll be able to analyze gene-environment interactions, the interactions between different environmental exposures and each other, and we will be able to look at that in relationship to family history.

You made reference earlier with Dr. Kirschstein as to whether there were genetic variations and susceptibility to things, this is one of the things we'll be able to look at in the National Children's Study with validity, because it's collected prospectively, and we have a large sample size of 100,000 children 200,000 parents.

Senator HARKIN. Okay, since we're on that—as you know, I've been a strong supporter of that, and we put the money in this year to continue that again. Where are we on this children's study? How far along are we in terms of identifying, fitting that 100,000 pool?

NCS STUDY PLAN

Dr. ALEXANDER. Okay, with the funding that you provided this year, the \$69 million that you added to the appropriations for 2007, we will be recruiting the first one-third of the 105 sites around the country who will be conducting the study. Those will be funded by September 30. That is \$32 million of the funds that you provided. The 7 Vanguard centers that have been funded for the last year and a half to start some of the piloting for this study will be funded with about \$20 million this year to markedly expand their efforts and get them ready, so that they can start to actually enroll subjects for the study, for the pilot phase by July 2008.

The following year, another third of the sites will be added, then the following year, another third. So, we will be actually starting the actual recruitment of the full study cohort in 2009, with a pilot cohort from the Vanguard sites in July 2008. We also will be using the funds to set up the sample repository center, the laboratories that are going to be doing the analyses, the informatics and data collections systems, all of which will be electronic, so that those funds are going to be put to good use in 2007.

Senator HARKIN. Well, that is encouraging, and we need to move ahead as aggressively as possible, and I would like to know from you if the funding levels are adequate to move it as aggressively as possible? I know these things—some of these things take time, and no amount of money can move some of these things, because you just have to set up the structures, and have to identify the people and that kind of thing. But I would like to know whether or not we can move more aggressively on that.

AUTISM RESEARCH

But I want to make the point that we shouldn't, Dr. Schwartz, that we—both Dr. Alexander—that we shouldn't have to just wait

10 or 15 or 20 years to get data and information from the children's study.

Dr. ALEXANDER. We will have all of the kids with autism diagnosed by age 3, so we don't have to wait 15 years. We'll be doing those analyses as quickly as we can have the data available.

Dr. SCHWARTZ. That is precisely why we're funding focused studies on the environment and autism today.

Senator HARKIN. Yes, that's my point, we can't just wait.

Dr. SCHWARTZ. We initiated a cohort study in October 2006—that's \$1.5 million each year to support a study that focuses on children at very high risk of autism, and looks at environmental causes of autism in relation to the development of the disorder.

Senator HARKIN. When you say environmental, that also might include immunizations?

Dr. SCHWARTZ. Absolutely, absolutely. Also thimerosal.

Senator HARKIN. But we don't use thimerosal any longer.

Dr. SCHWARTZ. So we do have studies. The thimerosal question is not completely a moot issue, and we have studies that are looking at the relationship between mercury and brain damage in primates and in animal models, and we're still in the process of doing that research.

Senator HARKIN. I thought it was a well-known fact that mercury in the bloodstream does affect the brain.

Dr. SCHWARTZ. It does affect the brain. The question is, does it affect the brain in terms of the risk of developing autism.

Senator HARKIN. I don't know the answer to that question, obviously. Okay, I just, again, need to keep—I want you to keep us up to speed, and keep my staff up to speed on what your Institute is doing in this area of autism.

Dr. SCHWARTZ. We can provide you that information.

[The information follows:]

NIEHS AUTISM RESEARCH

NIEHS is actively investigating possible environmental factors in autism risk, including studies of gene-environment interaction. These are some of the projects being funded:

- The NIEHS Center for Children's Environmental Health and Disease Prevention Research at the University of California (UC) Davis is building on its earlier finding of immune dysfunction in autism and is currently focusing on the interplay of immune, genetic and environmental factors in autism susceptibility.
- NIEHS is expanding support for continuation of enrollment in another large, ongoing study at UC-Davis (CHARGE) to provide the ability to detect gene-environment interactions in distinct subgroups of children.
- An epigenetic study of genes implicated in autism and their interactions with neurotoxicants is also being conducted at UC-Davis.
- NIEHS is funding a promising project at Johns Hopkins to develop a sensitive biomarker for the immunotoxic effects of mercury (and use it to compare families with and without autism).
- NIEHS helped to plan and conduct the recent Institute of Medicine workshop on *Autism and the Environment: Challenges and Opportunities for Research* to examine the most promising scientific opportunities for improving the understanding of potential environmental factors in autism.
- The NIEHS is contributing funding for the Autism Centers of Excellence. Some funds are being committed in fiscal year 2007, and a larger investment is planned for fiscal year 2008.
- NIEHS plans to fund a new 5-year prospective cohort study of pregnancies at high risk for autism beginning in fiscal year 2008.
- NIEHS is a contributor to the National Database for Autism Research (NDAR). The initial phase is focused on developing a clinical module which will serve as

a data repository for the ACE investigators. The plan is ultimately to expand the NDAR to other investigators and other types of autism research beyond clinical research. NIEHS contributed \$250,000 in fiscal year 2006.

ASTHMA RESEARCH

Senator HARKIN. Asthma—more and more kids getting asthma, it's amazing. But tracking with autism, what is going on? Why are so many kids getting asthma today, what's happening?

Dr. SCHWARTZ. Asthma is a classic example of a disease that is clearly increasing in prevalence, and our genetics are not changing to alter the risk of developing the disease, so the environment is contributing substantially to the risk of developing asthma. Environments like the environment in New Orleans, environments that are heavily contaminated with micro-organisms, are risky, environments for the development of airway inflammation. That is one of the reasons that we're studying that population very carefully, to try to identify ways in which we can intervene to decrease the risk of asthma.

Senator HARKIN. I can't tell you how many people I've talked to in the last several years that come up to me and, in different settings, and have said, "You know, I've never had allergies before I came to Washington, DC." That, a lot of people say that. There's something happening around here, I don't know what it is.

Dr. SCHWARTZ. There's a very interesting process that's occurring. There's definitely an interaction between airway inflammation that is caused by environmental pollutants, and the risk of developing allergic responses in the body. We're spending \$40 million a year on our asthma portfolio. So, this is something we're actively engaged in to try to understand how these air pollutants are altering—

Senator HARKIN. When you say asthma, that's allergies also, right?

Dr. SCHWARTZ. There is a non-allergic form of asthma as well. Individuals who work in the hog industry can develop asthma caused by microbial contamination alone without any allergic response. They develop the same exact symptoms and signs of asthma that someone who has allergic asthma.

HEALTH EFFECTS OF NOISE

Senator HARKIN. One other area I want to cover with you, Dr. Schwartz, before I leave you here is, you didn't cover it in your thing, and I want to know if your Institute covers this—noise. Noise, the environmental aspects of noise, and what it is doing to kids today, and all of us. The noise levels we're subjected to all of the time, whether it's jet aircraft, automobile noise, just the noise around, is phenomenal. Kids with those plugs in their ears, listening to their iPods, and you don't know what volume you've got them cranked up to, but I suspect the volume—the more the volume gets cranked up, the more they lose their hearing. They keep cranking it up all of the time. So, talk to me about what your Institute is doing in looking at the environmental aspects of noise, and its effect. Its behavioral effect, not just the effect on loss of hearing, maybe neurobiological types of effects it might have on an individual, are you looking at that?

Dr. SCHWARTZ. We have a relatively small portfolio in terms of noise, and the portfolio that we have in relation to noise relates to occupational or excessive environmental exposures to noise.

The Dr. Battey's institute.

Senator HARKIN. The National Institute on Deafness.

Dr. SCHWARTZ. They're looking at the pathophysiologic effects of noise.

Senator HARKIN. That's what he's looking at. I'm just talking about the environmental aspects, and how that impacts. Are you coordinating with them on that?

Dr. SCHWARTZ. Any time we have an opportunity to, we do. I don't know the specifics, and I can get that specific information back to you, in terms of what studies are being supported by NIEHS, and what studies are coordinated with the other institutes. I just don't have that information for you.

Senator HARKIN. Well, give us some information on what you're looking at in terms of noise, and what kind of research you're doing in terms of the effect of noise on our bodies, on our physiological things, and what happens with behavioral aspects of noise.

Again, I read these articles in Science magazine, I read about certain thoughts that a lot of this noise is causing people to behave in odd ways. Maybe altering brain patterns and brain waves. I don't know. I'm just saying there's some bits and pieces, some research in different places going on about this, and I don't know who, among all of your institutes out there, covers this. If it's not you—I don't know if it's Dr. Battey or not. I would like to find out that answer. But it seems to me it is an environmental aspect.

Dr. SCHWARTZ. I'll get you that information.

[The information follows:]

RESEARCH ON THE HEALTH EFFECTS OF NOISE EXPOSURE

Environmental noise is certainly a ubiquitous exposure and one that is understudied. A recent review¹ of the published literature underscores the difficulty of conducting this research. Both active coping strategies employed by noise-exposed people as well as subconscious physiological adaptation to noise complicate the ability to perform good studies. Furthermore, clinical expression of these stress reactions in the form of symptoms can take many years to occur. In reviewing the existing work, the authors state that:

"The evidence for effects of environmental noise on health is strongest for annoyance, sleep and cognitive performance in adults and children. Occupational noise exposure also shows some association with raised blood pressure. . . . The effects of noise are strongest for those outcomes that, like annoyance, can be classified under 'quality of life' rather than illness."

That said, the authors also recognize that "the interaction between people, noise and ill-health is a complex one," and that further study is needed. It may be that adaptation to noise carries its own health costs, or that noise can combine with other physiological or chemical stressors to lead to greater health impacts than noise exposure alone.

NIEHS has funded research in the past on effects of noise (with or without concomitant ototoxic chemical exposure) on hearing loss. Current research applications on noise exposure resulting in hearing loss are typically assigned to the National Institute on Deafness and Other Communication Disorders. NIEHS has also funded research looking at effects of noise-induced stress on intestinal disease and presence of reactive oxygen species in rats. No specific noise-related solicitations are planned in the current budget, but investigator-initiated grants would be welcomed and carefully considered. In addition, noise is an exposure category proposed for study in the

¹Stansfeld SA, Matheson MP, 2003. Noise pollution: non-auditory effects on health. *British Medical Bulletin* 68: 243–257.

National Children's Study, for which NIEHS has been a contributor of both funding and expertise through the planning phase.

Senator HARKIN. I'd like to kind of know who's looking over that.

AGE-RELATED EYE DISEASE STUDY

Dr. Sieving, you mentioned the AREDS Study. It showed that certain supplements, beta-carotene, Vitamin C, and E, and Zinc can slow the progression of AMD, macular degeneration. Well, okay, so that's useful once a person has been diagnosed with AMD, is that right? But how about before? Is there any evidence that these can help prevent a person from getting AMD in the first place? Also, direct yourself to the use of lutein, I don't know if you mentioned that or not, but is there not some scientific evidence that lutein acts as a preventative, or is there not?

Dr. SIEVING. Those are very interesting questions. As you have stated, the first AREDS study explored anti-oxidants, principally, Vitamins A, C, E, and some minerals. The design of the study—when you don't know what the answer will be, you have to design a question that will get you the first phase of it, and the first phase of the answer was to look at the conversion from early stage AMD to later stage AMD, and it was found that these factors—anti-oxidants—were effective in slowing, retarding that progression.

Senator HARKIN. When you said delay, by 25 percent, delay for how long? 1 year? 2 months? 5 years?

Dr. SIEVING. That would be the perspective you and I would have as the person taking it, in terms of delaying, or decreasing the conversion from one State to another. That is a population statement. So it is slowing the conversion rate. The actual delay in time is the more difficult question to get at.

Senator HARKIN. You're saying the 25 percent of the population had a delayed onset?

Dr. SIEVING. That's correct, yes.

Senator HARKIN. I still don't know how much of a delayed onset, or did it just vary?

Dr. SIEVING. The slope, as you look at time. The proportion of individuals who went on to develop AMD over this 5-year interval was about a 25 percent reduction. So, one can think in terms of years of putting off the conversion for some individuals. The study was not sensitive at the level of asking, is it going to help people who have not yet been identified or diagnosed with some early stage of AMD.

Senator HARKIN. Now, are these helpful in preventing, how about lutein?

Dr. SIEVING. The question of lutein is the subject of the next phase of this called AREDS 2. It's lutein, zeaxanthin and the fish oil, omega-3 fatty acid or fish oil, DHA. So, we hope that we will have an answer in a few years on your question of lutein.

[The information follows:]

LUTEIN RESEARCH

NCCAM has funded an exploratory study at the Johns Hopkins University to investigate the effects of lutein, an antioxidant that is part of the carotenoid family, to address retinitis pigmentosa, which is an eye disease that causes loss of night vision and peripheral vision, and, possibly blindness. Currently, NCCAM has no ongoing research on lutein.

Dr. SIEVING. There is the expectation, at least, in part of the practicing community of physicians, ophthalmologists, that lutein is beneficial in retarding the conversion to active vision loss from advanced AMD, and that's the reason for doing the study.

Senator HARKIN. Dr. Kirschstein, do you know if NCCAM is doing anything in that area?

Dr. KIRSCHSTEIN. I do not know. I will check on it, but I don't think so. I think Dr. Sieving, the Office of Dietary Supplements may also be doing some things, and of course, anything that they fund, would be in conjunction with NCCAM, or other ICS. They do not have the authority to fund grants.

GENE THERAPY

Senator HARKIN. Good point. Well, and also—I understand that more dogs have joined Lancelot.

Dr. SIEVING. Nearly 50.

Senator HARKIN. Nearly every year, I keep hearing they're now going to move into primates. And then I heard recently they were actually going to start doing this gene therapy in humans, where are we?

Dr. SIEVING. Well, I'm pleased to tell you, on the international world scale, we have crossed your threshold of moving it to people. There are four groups internationally, two in this country, one in France, one in England, considering the question of whether gene delivery into people will restore vision, will do something beneficial for vision. And the first of the groups to accomplish this is in London at the Institute of Ophthalmology. A scientist by the name of Robin Ali, who, I think it would now it would be 3 months ago, had done the injections of this gene construct called RPE 65, in two individuals to my knowledge. Looking forward in future attempts over the next 2 months, we can expect similar experiments to be done in Senator Specter's home State at the University of Pennsylvania. That study has been funded by the American people through the NIH National Eye Institute, and we will have a second opportunity to see whether there is benefit to doing this gene therapy in people.

Senator HARKIN. So again, just to make sure I understand this, a couple of people have already been, already agreed to undergo this gene therapy in London? This year you will have some more people who will be willing to undergo this, here in the United States?

Dr. SIEVING. That is correct. Just for the others around the table, the condition that is being treated is a form, a genetic form, of childhood blindness. In this case, the absence of an enzyme, genetic absence of an enzyme called RPE 65, the lack of that enzyme prevents the retina from responding to light, and hence, the individual has no vision, and is blind. When that was done in Lancelot, who you met, that dog has this RPE 65 deficiency, and by injecting the gene construct into that dog, the dog can now nearly play Frisbee with you, and can certainly walk the halls of Congress and look at you. That is an extremely exciting possibility.

As I think about opportunities to move forward on an experimental basis, on gene delivery as a concept in medicine, this is a designer circumstance to try.

Senator HARKIN. So, the first humans in the United States will be at the University of Pennsylvania, is that what you said?

Dr. SIEVING. Yes, it's a consortium between Pennsylvania and Florida.

Senator HARKIN. How many, do we know?

Dr. SIEVING. It will be a handful. The question the first time through is, one can think of this on two planes, one can think of the people who could potentially benefit, we hope they do, and it will be a small number. On the other side, this will be a big advance, like a moon shot to get a person to the moon—this is a big advance for the concepts and the validity of gene therapy, if these experiments are successful.

So, we're hoping.

Senator HARKIN. So, will this be publicized? I mean, I would be interested in finding out how soon after a person—and I don't even know the process, how many injections they have to have?

Dr. SIEVING. One.

Senator HARKIN. Just one? Just one? I thought it was a pattern you had to go through.

Dr. SIEVING. No, the delivery of genetic material is courtesy of a virus, an adenovirus. Once that virus introduces the gene into the cell, it persists there. In the case of Lancelot, Lancelot had one injection, now some 5 years ago, and this dog is still seeing. So, it would be one injection.

Senator HARKIN. How soon after that injection would we know whether or not it worked?

Dr. SIEVING. Well, in the mouse, the biology in the mouse says that within 60 days or fewer, the transfer of the gene into the cell and the activity in the cell can make this protein. So, it should be short order, it should be on the order of weeks to months.

Senator HARKIN. But you don't know when this is going to happen.

Dr. SIEVING. We have a good idea of when it will happen.

Senator HARKIN. Is it this summer?

Dr. SIEVING. We expect this summer. Obviously, for something like this, we are helping to take a close and careful look at the safety, getting the trial started, and the first outcome of the study will be announced as a safety outcome. If, in fact, the individual recovered some form of vision, that would be a bonus, and quite a delightful bonus.

Senator HARKIN. That's very informative. I appreciate that. We will be following that.

Dr. SIEVING. We will keep you informed, obviously.

Senator HARKIN. We'll follow that very closely.

READING FIRST

Dr. Alexander, I know time is running out, and I have to leave here in a few minutes, but I just wanted to go over one thing with you.

NICHD's involvement in a program called Reading First, a lot of congressional interest in this area. Education's Inspector General found the Department officials mismanaged the program, steered school contracts to publishers they favored away from others, flagrantly ignored Federal laws on maintaining local and State con-

trol of school curricula. Not me, that's the Inspector General of the Department of Education said that, and we've been looking into it.

As to be expected, the Education Inspector General focused mainly on the activities of the Education Department employees, but a former NICHD researcher named Reid Lyon also played a huge role in how Reading First was implemented. Lyon, a reading specialist, was the Chief of the Child Development and Behavior Branch under you. According to one news article, he said he spent more than half of his time between 2002 and 2004 on Reading First. E-mail showed that he frequently advised the Reading First Director Mr. Chris Doherty on how to run the program. He wasn't simply offering general advice, there were detailed discussions about how particular districts were using Reading First grants. We also know that Dr. Lyon wrote on numerous occasions to Margaret Spellings, the current Secretary of Education when she was Domestic Policy Advisor at the White House on this program.

Now, again, I can understand that an NIH researcher who's an expert on reading might occasionally be called upon by the Department of Education to offer some expert advice when they're called upon. But, I don't expect someone like that to spend more than half of his time trying to advise another agency on how to run their programs, it doesn't smell right, there's something wrong there.

Now, again, I know that Dr. Lyon is no longer there, he now works for a for-profit education company. That's fine, if he wants to be an advocate for that, that's what he should be. So, I would hope that the Chief of the Child Development and Behavior branch would have other things to do than like this.

So now, again, we have a replacement coming up. Has that replacement been named yet?

Dr. ALEXANDER. Yes.

Senator HARKIN. Oh, you do have a replacement?

Dr. ALEXANDER. For Dr. Lyon, as chief of that branch? Yes. Dr. Peggy McCardle. She's been in there as branch chief for almost 2 years.

Senator HARKIN. Two years? I didn't know that. Is this person spending more time, spending half his time on Reading First?

READING FIRST SCIENCE

Dr. ALEXANDER. No, I think she's spending virtually no time on it. Dr. Lyon's time when he was involved with this, was when he was on detail to the White House, and was not in charge of the branch. Basically, that was turned over to Dr. McCardle on an acting basis. I have no direct knowledge on what Dr. Lyon's interactions were, specifically. I know that he was called upon frequently by the Reading First program, and the Department of Education in other areas as well, for advice on the scientific basis for different types of approaches to reading instruction. The legislation related to Reading First required that the programs have demonstrated efficacy in a scientific fashion, of their effectiveness in being able to result in children learning to read in an effective way.

Much of the question that came to Dr. Lyon, in my understanding, was in terms of whether programs that were proposed for use in Reading First were, in fact, scientifically validated, research-based programs, and the advice that he provided was evaluating

the quality of the science that was done in evaluating those programs. Sometimes it was very weak science, weak to none. Other programs have been very thoroughly and rigorously evaluated, and to my knowledge, and what we really have the authority and authorization to do, was to provide information and advice as to the scientific validity of these programs. How rigorously have they been evaluated for their effectiveness as a teaching method? That was a requirement in order for them to be funded as part of Reading First.

So, that was the nature of the interaction, to my knowledge.

Senator HARKIN. Well, I know that, because I was very much involved in writing that law.

Dr. ALEXANDER. You were, indeed.

Senator HARKIN. In the other hat I wear on the other committee, and I had been following this very closely with my staff, and a number of these programs in a certain State were scientifically valid, they were passed, the scientific reviews and all of that. But a funding pattern emerged, that when these programs were evaluated and it all came down, that they had to use this one program, this one certain program, all of these things seemed to trace back, in many ways, to Dr. Lyon.

I thought that was an odd situation, that someone from NIH would be so heavily involved in trying to choose one over the other, when they were basically scientifically validated, and saying, "Well, yeah, they may be scientifically valid, they may all meet the scientific requirements, but this one is best." That is not—that was never, that should never have been his job.

That's sort of water over the dam, but I just, again, I hope that we don't go through that again. It was kind of disturbing to me to see that that had happened, and that is why I asked the question about the new replacement, which I didn't know was there, and how much they were spending. Like I said, I don't mind if they're called upon for expert advice, I mean, that's fine—that is what they should be doing. But it seemed like he went overboard in being involved in how this was being run.

SPINAL MUSCULAR ATROPHY

The last thing I wanted to cover with you is SMA. As you know, I've been very much involved with this ever since I first learned its leading genetic cause of death in small kids, and then how much we were looking at it, and you and I talked about this before, on SMA, and I've talked to Dr. Landis about it, also. I talked about this with Dr. Landis just a few weeks ago, there's some breakthrough work that NINDS is doing in this area.

But, you have funded, as I understand, two small grants on SMA in the past few years. Since it is a leading genetic cause of death to infants and toddlers, I think I would have expected that NICHD would take a larger role than it has thus far, so I'm just wondering, where are you in SMA research in the coming year?

Dr. ALEXANDER. Well, last year, we funded four grants, or parts of four grants, focusing largely on improving newborn screening, and developing the capability for doing newborn screening for the disorder, and we additionally funded two grants that came in, in response to our program announcement for developing new thera-

peutic approaches to disorders that could potentially be diagnosed by newborn screening.

The best progress we have to report is that in one of the grants, Dr. Tom Pryor at Ohio State has, in fact, developed a very successful approach to newborn screening for SMA. With the technology that he has, he's gotten samples from the filter paper blood spots like I just handed out to you, several hundred with SMA, several hundred carriers, and several hundred normals. They have 100 percent success in diagnosing every case of SMA, 100 percent success in identifying every carrier, 100 percent success in determining unaffected individuals.

He's also developed a methodology for incorporating this onto the luminex-bead system, which is one of the systems we're testing for new applicability. The SMA community is so excited and enthusiastic about this, that they've actually petitioned the Secretary's Advisory Committee on screening of infants and children for genetic disorders for inclusion of this in newborn screening regimens.

So, we are very excited about this approach, we think this is probably going to be the one that can be incorporated, it can be done in a very cost-effective way, and that we will have the newborn screening, and as the SMA advocacy groups point out, all of the evidence is that it is essential to begin treatment at birth, or as close to birth as possible. Because the moms protect the fetus during development, these babies are pretty much okay at birth. If we can get the treatment to them, and have an effective treatment, that is going to be key.

We also have two grants that are working on new treatment methodologies for this. There are two different approaches—one is to increase the production of a protein that doesn't work very well, another is to try and skip a codon, that is, blocking the formation of the normal proteins, so that we produce more normal protein. We're testing both of these, and we're hopeful that we're going to have, not just the prenatal diagnosis methodology, but a treatment methodology as well. That is where we are.

Senator HARKIN. That's good. That is good news. So that is what is going to be happening in the future.

Dr. ALEXANDER. Yes, we will continue with that.

Senator HARKIN. Now, I can't leave that without—one thing leads to another, don't you know? I learned about SMA and I get to learning about causes, and I meet with families, well then I start thinking about Fragile X Syndrome also, which is another one. Now I find out that's a leading cause of mental retardation, genetic cause of retardation. So, then I'm wondering, where are you going in that?

NEW APPROACH TO NEWBORN SCREENING

Dr. ALEXANDER. Similar story, we're working on newborn screening. We funded a grant several years ago, to develop and evaluate newborn screening for this condition, with the support of parents and advocacy groups. The test that we thought was going to work, didn't, another one that we thought was going to work didn't, we're now on a third approach to the newborn screening. This one looks like it's going to work, but we're still in the final testing for that.

That is the essential component for that grant, in order to be able to diagnose this in newborns.

In terms of therapy, we're farther away from that than we are, probably, with SMA. Although different approaches are being tried, we have nothing that looks real promising right now. But, the parent and advocacy groups still say we want to diagnose this in newborns, if at all possible, because we would like to be able to plan for these children, we'd like to intervene as early as possible with ancillary kinds of treatments, and we would like to know for our family planning purposes whether we have this problem, because these kids are often not diagnosed until 3, 4, 5, 6 years of age, and there's often another child born by then.

Senator HARKIN. Doesn't that, doesn't that gene just go through one parent or the other?

Dr. ALEXANDER. Yes, the mother.

Senator HARKIN. Okay, that's good information, that's good information. Okay, any last things before we all get out of here and go to lunch, or something like that? I want to thank all of you for coming down, it's been a good session. As I said, I always learn a lot of things at this, it's like being in class again.

So, I thank you very much. Thanks for all of your leadership, Dr. Alexander. Thanks for the SMA work you're doing, we appreciate that. You're going to get back to me on some of this stuff.

ADDITIONAL COMMITTEE QUESTION

There will be an additional question which will be submitted for your response in the record.

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

QUESTION SUBMITTED BY SENATOR TOM HARKIN

DOWN SYNDROME

Question. An estimated 350,000 Americans have Down syndrome. Yet the fiscal year 2008 proposed budget calls for spending just \$13 million on research concerning this condition—down 43 percent from the fiscal year 2003 level of \$23 million. Why has funding for Down syndrome research declined so dramatically?

Answer. The senator's funding figures for NIH-supported research on Down syndrome are correct. Although NICHD has the scientific lead on this issue, a number of other Institutes and Centers also contribute resources to address this condition. However, due to the competitive nature of the peer review process, the number of successful applications proposing research on Down syndrome has decreased, and thus funding contributed by ICs to such research has decreased.

However, research on Down syndrome is an important part of NIH's research portfolio. In fact, to facilitate research on Down syndrome across the NIH, NICHD took the lead in pulling together a working group of these ICs in 2006. NICHD, NINDS and NIA form the steering committee for the group, which has been meeting regularly with the goal of producing a NIH research plan for Down syndrome in the fall of 2007. In addition to compiling the NIH-funded research in this area, literature reviews are being conducted so that new research is complementary and not duplicative. The working group sponsored two major scientific meetings, in March 2007 and July 2007, to get input from that community, as well as from national constituency organizations representing individuals with Down syndrome and their families. Input on the plan, which will address strategies for basic and clinical research on the genetics of Down syndrome, its developmental consequences, and its impact on cognition and synaptic function, will be actively sought prior to its publication.

CONCLUSION OF HEARINGS

Senator HARKIN. So, thank you all very much, that concludes our hearings.

[Whereupon, at 12:07 p.m., Friday, June 22, the hearings were concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]