DEPARTMENTS OF LABOR, HEALTH AND HUMAN SERVICES, AND EDUCATION, AND RELATED AGENCIES APPROPRIATIONS FOR FISCAL YEAR 2012

WEDNESDAY, MAY 11, 2011

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

The subcommittee met at 9:59 a.m., in room SD–124, Dirksen Senate Office Building, Hon. Tom Harkin (chairman) presiding.

Present: Senators Harkin, Reed, Mikulski, Brown, Shelby, Kirk and Moran.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

STATEMENT OF DR. FRANCIS S. COLLINS, DIRECTOR

ACCOMPANIED BY:

HAROLD VARMUS, M.D., DIRECTOR, NATIONAL CANCER INSTITUTE

ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

SUSAN B. SHURIN, M.D., ACTING DIRECTOR, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

DR. GRIFFIN RODGERS, DIRECTOR, NATIONAL INSTITUTE OF DIABETES, DIGESTIVE AND KIDNEY DISEASES

OPENING STATEMENT OF SENATOR TOM HARKIN

Senator HARKIN. The Senate Subcommittee on Labor, Health and Human Services, and Education will now come to order.

First of all, Dr. Collins, welcome back to the subcommittee. We welcome also Dr. Harold Varmus, Director of the National Cancer Institute; Dr. Tony Fauci, Director of the National Institute of Allergy and Infectious Diseases; Dr. Griffin Rodgers, Director of the National Institute of Diabetes, Digestive and Kidney Diseases; and Dr. Susan Shurin, Director of the National Heart, Lung, and Blood Institute.

This subcommittee holds an appropriations hearing on the NIH budget every year, and every year I am both inspired by the dedication of the scientists who testify before us and proud that their accomplishments have made America the world leader in biomedical research. But in recent years, our Nation's status in that regard has been threatened. While China and Singapore make

massive investments in research, here in the United States we're pulling back.

The fiscal year 2011 appropriations bill that Congress passed last month cut NIH funding by $322 million below the fiscal year 2010 level. When you consider how much funding was needed to keep up with inflation, the cut was more like $1.3 billion, taking inflation into account.

We should be thankful that the result wasn't significantly worse. H.R. 1, the spending bill passed by the House majority, would have cut NIH funding by $1.6 billion or $2.6 billion if you counted inflation. Fortunately, the Senate rejected that plan.

But even the compromise bill that was ultimately signed in law will result in a success rate for NIH research grants, I'm told, of just 17 or 18 percent, meaning just one out of every six peer-reviewed application will be approved. And, again, I am informed that that is the lowest success rate on record for NIH.

What a dismal downturn from what Senator Specter and I, and others did back in the late 1900s and early 2000 when we doubled the funding of NIH and we got the success rate up, I think—if I'm not mistaken. You correct me, Dr. Collins—up in the 20–30 percent range, somewhere in there. And we thought we were on a path to continue that kind of a success rate. Now, it's down lowest on record.

And there is cause to fear even bigger cuts next year. The budget plan approved by the House last month would cut health funding by 9 percent in fiscal year 2012. If that plan were approved, severe reductions to NIH research would be unavoidable.

That doesn't make sense. Let's set aside for a moment any thoughts about the moral value of trying to improve people's health, and just look at the issue from a purely economic standpoint. NIH research is one of the best investments this country can make.

A study released yesterday by United for Medical Research concluded that in fiscal year 2010, NIH funding supported almost 500,000 jobs across country. And I always have to remind people that only a small percentage of that goes to NIH in Bethesda, Maryland. I want Senator Mikulski to know that. Most is awarded to researchers at academic institutions all over the United States.

Another study by Battelle examined the specific impact of the Human Genome Project, which was overseen, again, by Dr. Collins and completed in 2003. The Federal Government spent a total of $3.8 billion on this historic initiative. A lot of money, but the return on the investment is staggering. According to the Battelle study that $3.8 billion translated into an economic output of $796 billion between 1988 and 2010. And, of course, we'll be seeing benefits from the Human Genome Project for many more decades to come. In fact, when I was reading all of your testimonies last night, what struck me in each one of them there were references made back to genomic research in every single case of the institutes who are represented here.

So the lesson is clear. Biomedical research is one of the engines that drive our economy. If we want our economy to grow, both immediately and in the long term, that engine needs fuel. Drastically cutting NIH, as the House budget would force us to do, would be

a classic case of penny wise and pound foolish thinking. That, again, is just on the economic side.

On the human side, though, the great advances that have been made in cancer research and what we have done to lessen the threat of cancer—young kids now with leukemia are being cured at an almost 100 percent rate. Maybe that's not quite right, but pretty darn close, things that were unheard of just a few years ago. The advances that we're making in infectious diseases, unheard of 20 years ago when I first came on this subcommittee. Well, that's been 25 years ago, but great advances have been made. Just stark.

So, from the human standpoint, in helping people have better lives and overcoming some of the dreaded diseases that have plagued mankind for so long, on both fronts, biomedical research is the place to go and we ought not to be penny wise and pound foolish on that.

And so now I'll recognize my ranking member, Senator Shelby, for an opening statement.

STATEMENT OF SENATOR RICHARD C. SHELBY

Senator SHELBY. Thank you, Mr. Chairman. I appreciate you holding this hearing today to discuss the vital mission carried out by the National Institutes of Health.

We live in a world where there are thousands of debilitating and life-threatening diseases, all that could use additional funding for research and clinical trials.

I support Federal investment in basic biomedical research and development. Research carried out by the NIH and its network of 325,000 researchers at 3,000 institutions across the country serves the Nation with the goal of improving human health. As research becomes more expensive and private capital dries up, I believe it's critical to ensure support for translational research; that is, research that moves a potential therapy from development to the market.

The NIH has developed an interesting proposal with the establishment of the National Center for Advancing Translational Sciences, NCATS. NCATS is intended to fill the gap between advances in scientific understanding of disease and the process to turn new scientific insights into products. I believe the need for an entity to straddle the world's research and industry is clear.

In the private market, pharmaceutical companies will abandon drug development projects that are not initially successful, become too complex or do not provide a lucrative path forward.

For example, since 1949, there have only been two major drug discoveries in mental health—lithium and Thorazine. Sixty years later, researchers still do not know why these drugs actually work. Hundreds of genes have been shown to play roles in mental illness, too many for focused efforts by drug developers.

Therefore, many drug manufacturers have dropped out of the mental-health field. In particular, pharmaceuticals for rare and neglected disease are often ignored because private companies avoid this small market with little profit appeal leaving patients with no treatment options.

Even promising new drugs discovered through basic research often struggle during the translational stage of the process because

it's expensive, time consuming and prone to failure. These barriers inhibit both the scientists dedicated to improving health and the patients who ultimately need improved cures and care.

The question remains, however, as to whether NCATS is the right approach to solving the issue. Will NCATS be the right mechanism for taking valuable discoveries that the taxpayer has funded and giving it a greater opportunity to make it in the marketplace? As we review this proposal, we need to consider the fact that NIH is not a drug developer or an expert in the therapeutics world.

Dr. Collins, I would like to continue to work with you to make a thoughtful, informed decision regarding the NCATS. Unfortunately, the fiscal year 2012 budget request, I believe, does not provide adequate details on the reorganization.

It is May 11 and we've not received a budget amendment or specific structural details of an NCATS, a program NIH wants to implement by October 1. How can the subcommittee be expected to support a program that does not yet exist in budget documents?

I understand that the transition from basic research to clinical application requires interdisciplinary and multidisciplinary expertise. Research that aims to transform science is inherently difficult. If it were easy, the need for transformation would not exist.

NCATS may be the answer to solve this complex issue, but it also may not be. We don't know. Dr. Collins, I believe that NCATS is a matter that we should contemplate, but we must ensure that the steps forward are measured and in the best interests of all stakeholders, especially those who are in need of treatment and care.

I look forward to working with you and the chairman on this very important issue. Thank you.

INTRODUCTION OF WITNESS

Senator HARKIN. Thank you very much, Senator Shelby.

Now, welcome back to Dr. Collins.

Francis Collins was sworn in as the 16th Director of the National Institutes of Health in August 2009 after being unanimously confirmed by the Senate.

He is a physician geneticist noted for his discoveries of diseased genes and leadership, of course, of the Human Genome Project. Prior to becoming Director, he served as Director of the National Human Genome Research Institute at NIH.

Dr. Collins received his bachelor's degree from the University of Virginia, his Ph.D. from Yale and his M.D. from the University of North Carolina at Chapel Hill.

Dr. Collins, again, welcome, and first I want to say that your testimony, and all of the testimony of the Directors who are here, will be made a part of the record in their entirety.

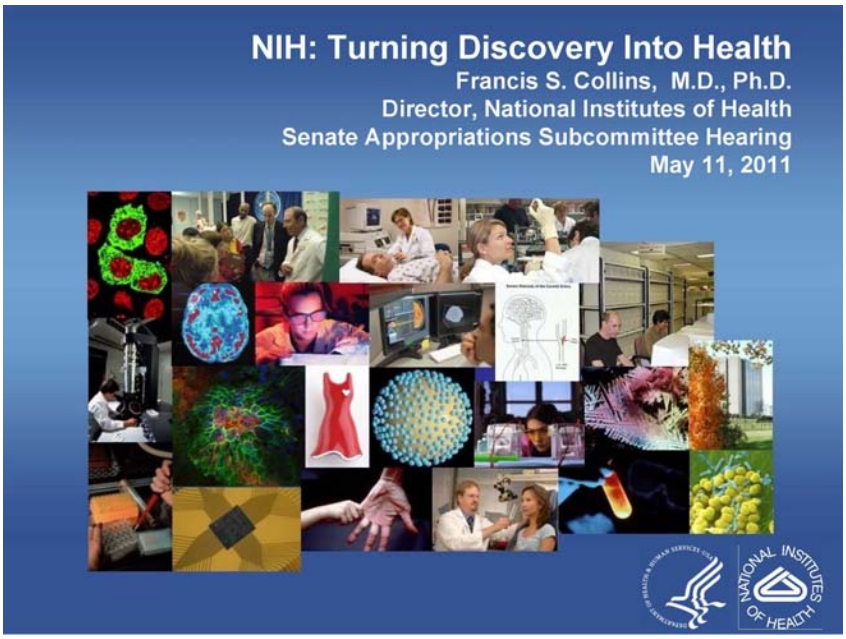
Again, due to time, Dr. Collins, we ask you to make a fairly comprehensive statement. I'm not going to get the clock going here, but if it goes too long and people start looking at me funny, then I'll probably ask you to close it out. But please take whatever time you need to give us an update on NIH and a concise summation of your written testimony.

SUMMARY STATEMENT OF DR. FRANCIS S. COLLINS

Dr. COLLINS. Well, thank you, Senator, and, Mr. Chairman, and distinguished members of the subcommittee, it's an honor to appear before you this morning, together with my colleagues, on behalf of NIH.

And I'll try not to talk so long that people start looking at you or looking at me, but I do have some things I really wanted to put in front of this distinguished subcommittee, because this is a very exciting time for biomedical research.

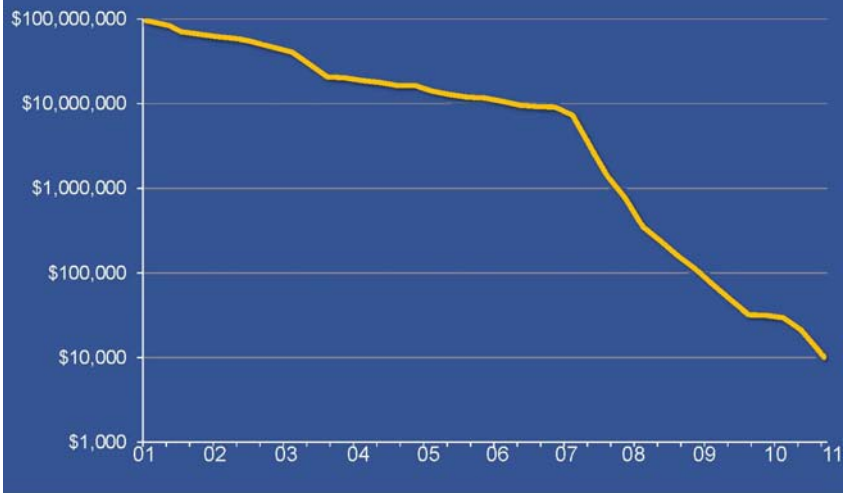
NIH is the largest supporter of biomedical research in the world, and we're here to present the President's budget request of $31.987 billion for fiscal year 2012.



NIH Investments in Innovation

- Accelerating Discovery Through Technology
- Applying Science to Prevention
- Enhancing U.S. Economy and Global Competitiveness
- Advancing Translational Sciences

Cost to Sequence a Human Genome 2001-2011



The Cancer Genome Atlas (TCGA)

- Cancer is a disease of the genome
- DNA mutations in vulnerable locations cause cells to grow uncontrollably
- TCGA is developing a comprehensive molecular atlas of the driving mutations in the 20 most common cancers
- This will ultimately revolutionize the diagnosis and treatment of cancer

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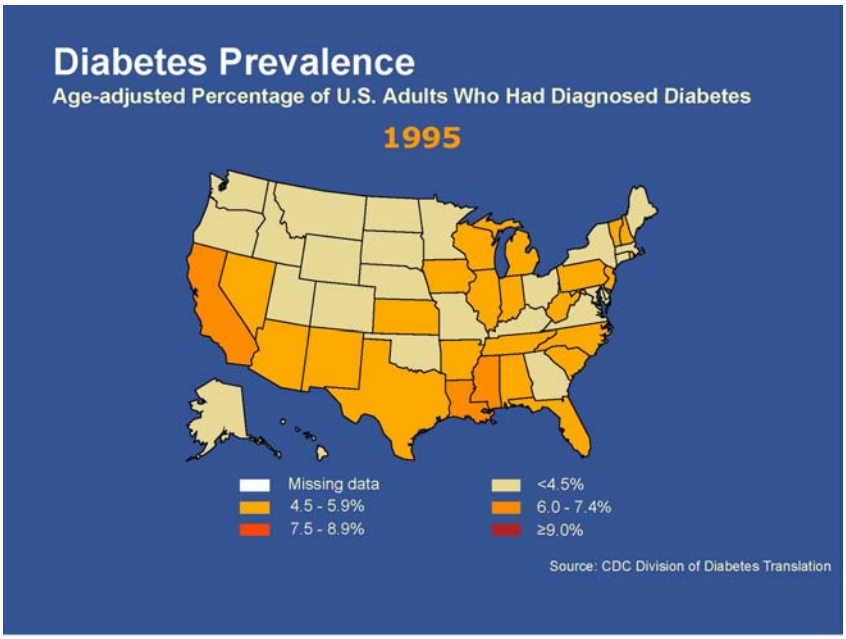
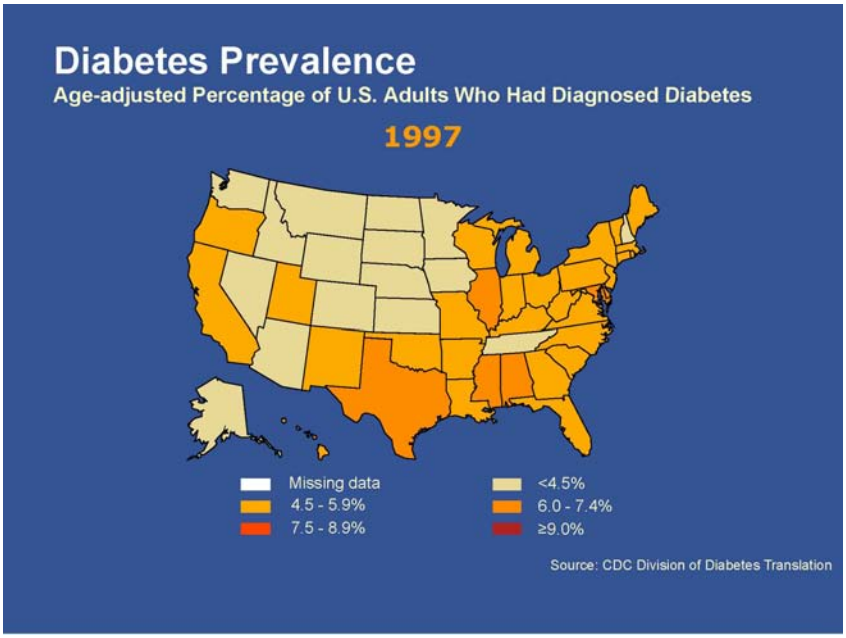

Diabetes Prevalence
Age-adjusted Percentage of U.S. Adults Who Had Diagnosed Diabetes
1995
Missing data
4.5 - 5.9%
7.5 - 8.9%
<4.5%
6.0 - 7.4%
≥9.0%
Source: CDC Division of Diabetes Translation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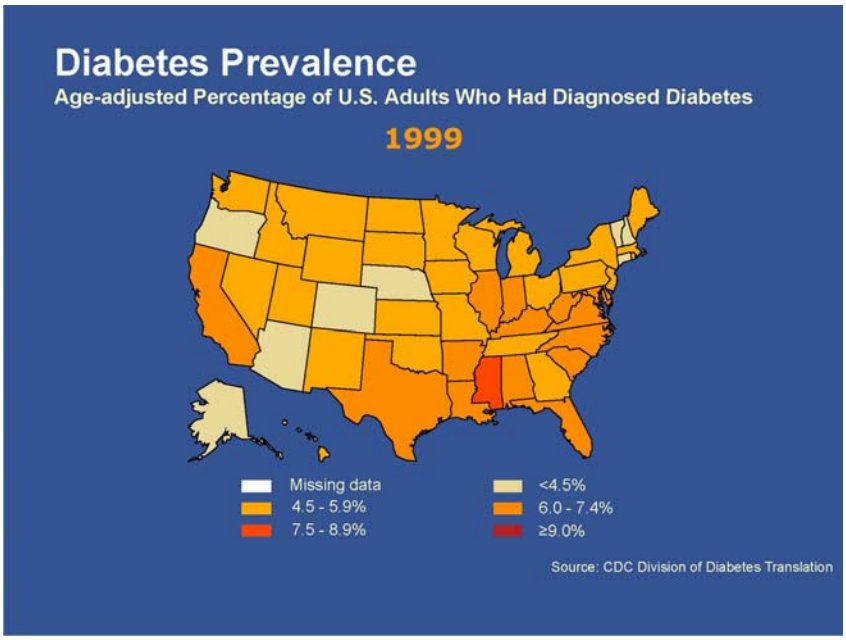
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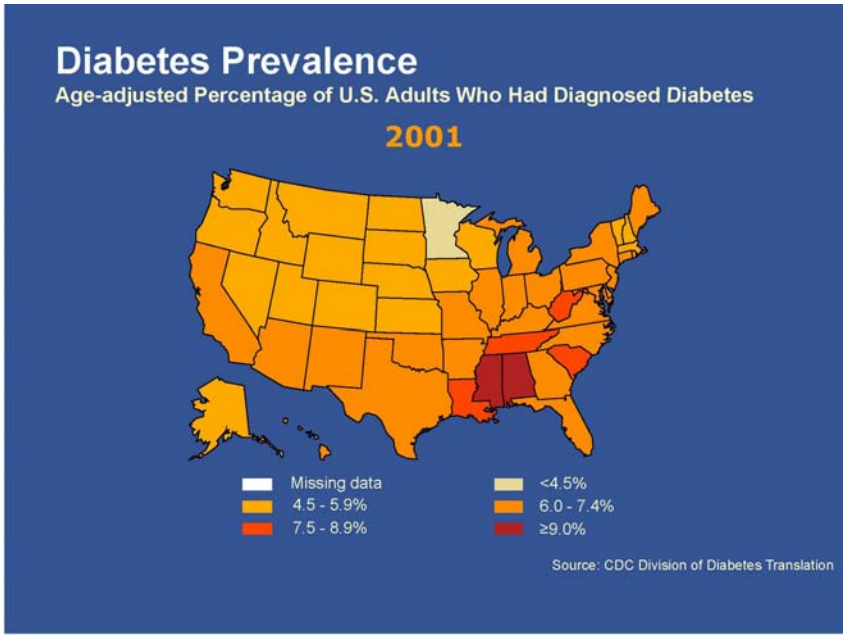
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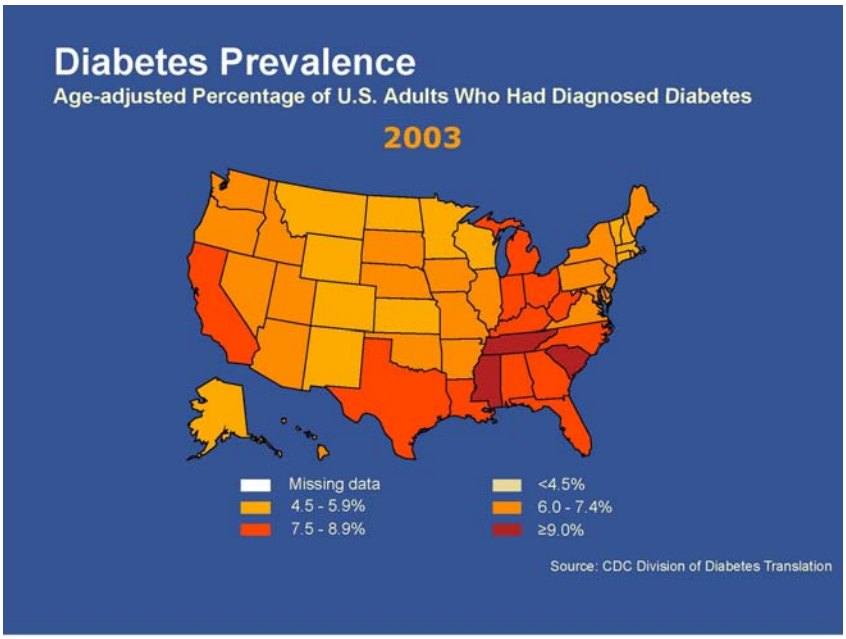
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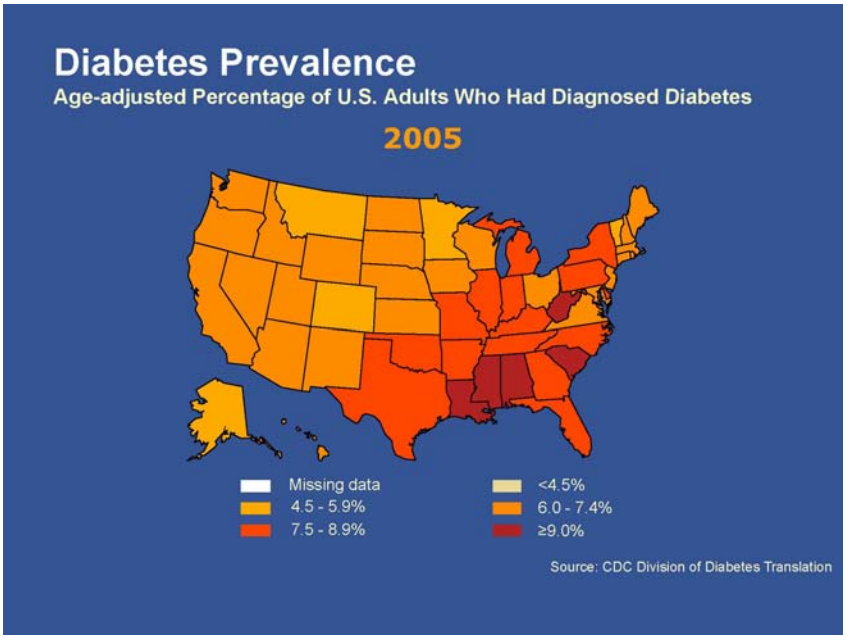
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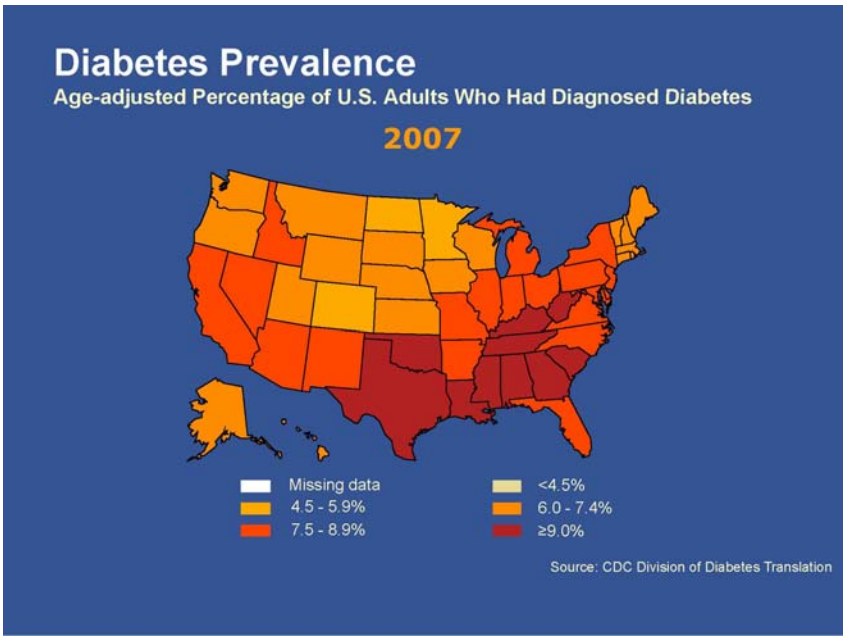
Diabetes Prevalence
Age-adjusted Percentage of U.S. Adults Who Had Diagnosed Diabetes
2007
Missing data
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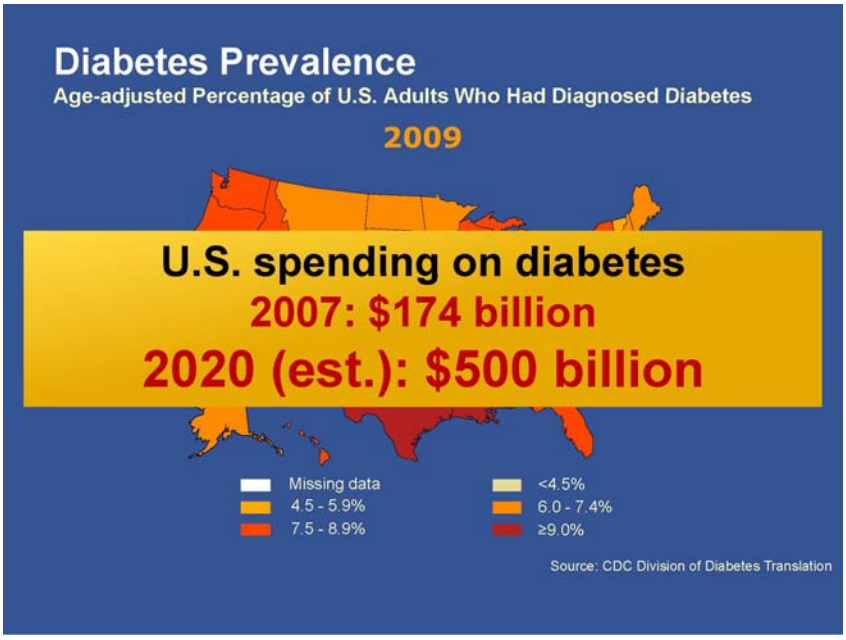
6.0 - 7.4%
≥9.0%
Source: CDC Division of Diabetes Translation


Diabetes Prevalence
Age-adjusted Percentage of U.S. Adults Who Had Diagnosed Diabetes
2009
U.S. spending on diabetes
2007: $174 billion
2020 (est.): $500 billion
Missing data
4.5 - 5.9%
7.5 - 8.9%
<4.5%
6.0 - 7.4%
≥9.0%
Source: CDC Division of Diabetes Translation

Diabetes Prevention Program (DPP) Trial

- Adults with "pre-diabetes"
- Exercised 30 minutes a day, lost 7% body weight, were aided by a coach
- **Reduced diabetes risk 58%!**
- Many partners now taking this program to 13 communities in 10 states; CMS exploring ways to extend to Medicare and Medicaid

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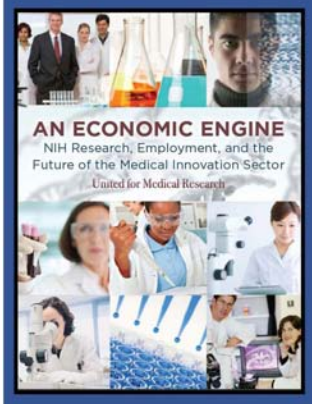
NIH's Contribution to U.S. Economic Growth and Global Competitiveness



NIH research funding supported an estimated 487,900 American jobs in 3000 institutions and small businesses in all 50 states…

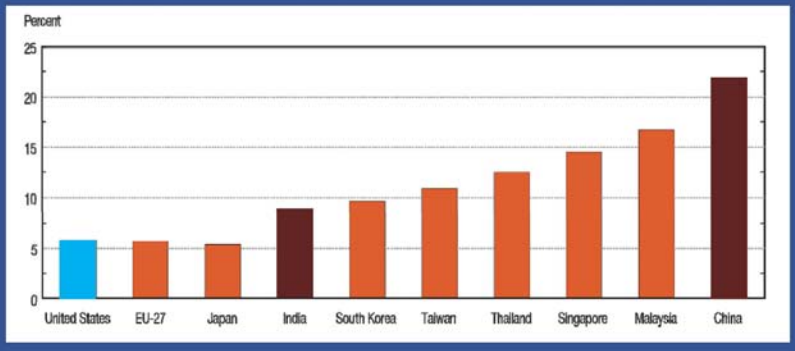
…EVEN WIDER IMPACT in its role as the foundation for the medical innovation sector…

…1 MILLION U.S. citizens employed…

…earning $84 BILLION in wages and salary…

…exporting $90 BILLION of goods and services.

Average annual growth of R&D expenditures for United States, EU-27, and selected Asia-8 economies: 1996–2007



Source: National Science Board, *Science and Engineering Indicators 2010*

Case Study in Competitiveness: The BGI Genome Center in Shenzhen, China

- BGI has procured technology to sequence >10,000 human genomes/year
- **This single Chinese institution now surpasses the DNA sequencing capacity of all U.S. genome centers combined**

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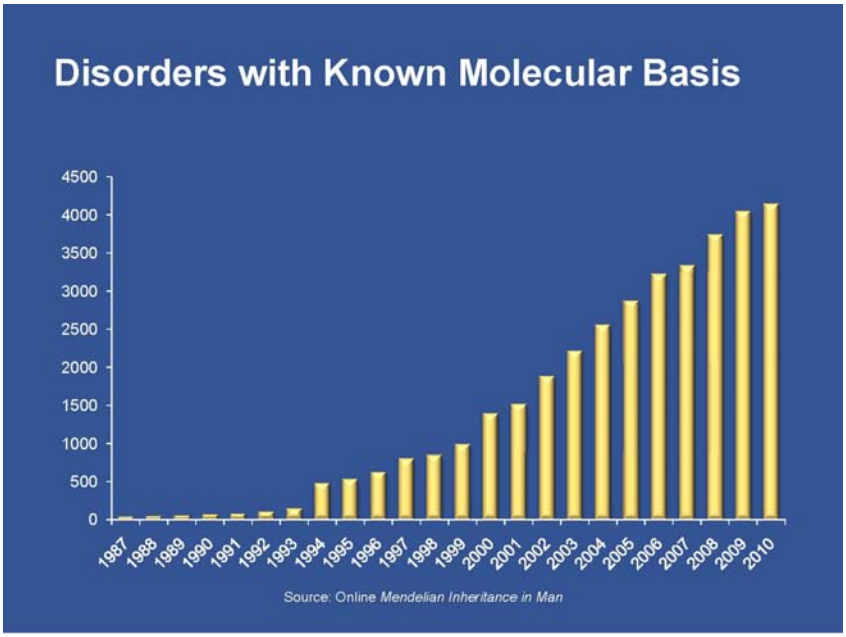
Disorders with Known Molecular Basis
4500
4000
3500
3000
2500
2000
1500
1000
500
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1987
1988
1989
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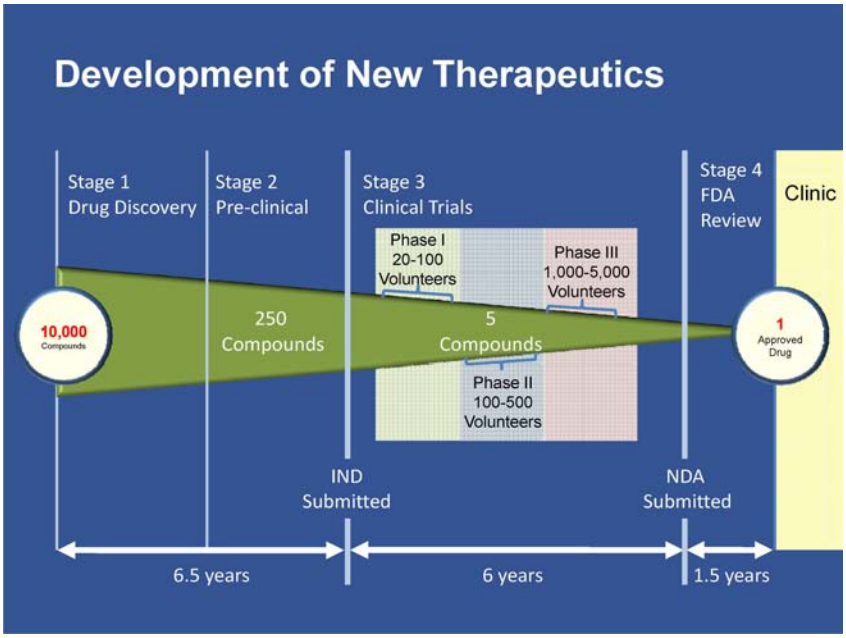
2010
Source: Online Mendelian Inheritance in Man


Development of New Therapeutics
Stage 1
Drug Discovery
Stage 2
Pre-clinical
Stage 3
Clinical Trials
Stage 4
FDA
Review
Clinic
Phase I
20-100
Volunteers
Phase III
1,000-5,000
Volunteers
10,000
Compounds
250
Compounds
5
Compounds
1
Approved
Drug
Phase II
100-500
Volunteers
IND
Submitted
NDA
Submitted
6.5 years
6 years
1.5 years

Creation of the National Center for Advancing Translational Sciences (NCATS)

To advance the discipline of translational science and catalyze the development, testing, and implementation of novel diagnostics and therapeutics across a wide range of human diseases and conditions.

NCATS will:

- Complement – not compete with – the private sector
- Facilitate – not duplicate – the translational research activities supported and conducted by the NIH Institutes and Centers
- Reinforce – not reduce – NIH's commitment to basic science research

NIH Investments in Innovation

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Nic's Story

Credits: Milwaukee Journal Sentinel, Amylynne Santiago Volker, Medical College of Wisconsin

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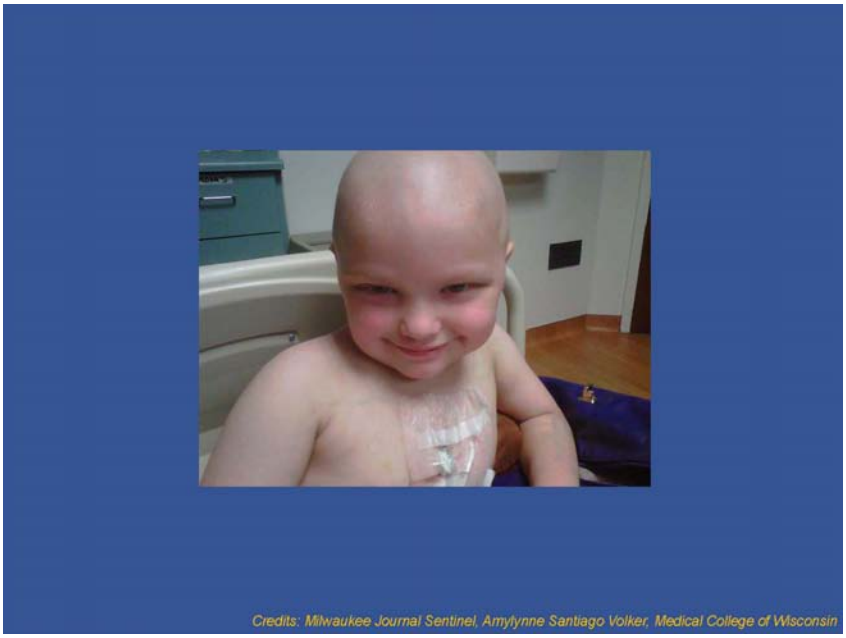
HAPPY MARROW DAY
NIC
Credits: Milwaukee Journal Sentinel, Amylynne Santiago Volker, Medical College of Wisconsin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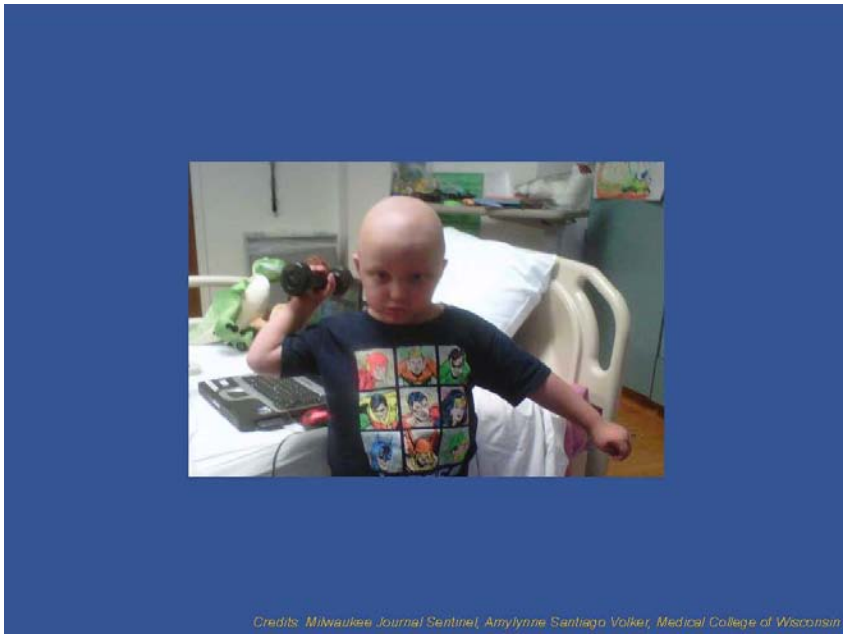
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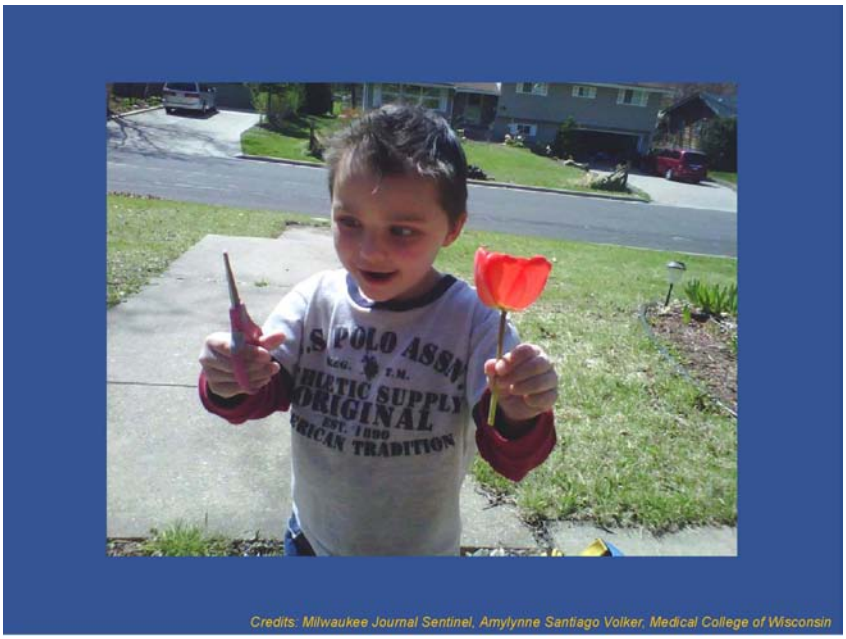
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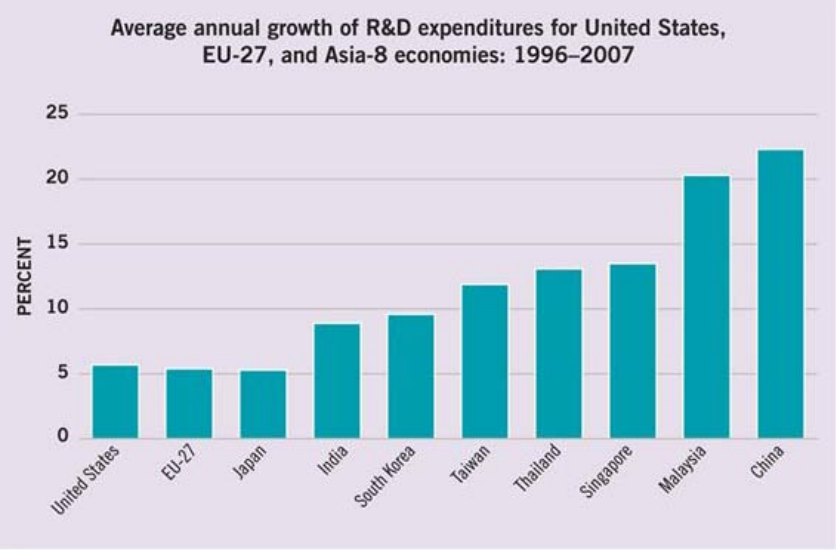
NIH
Turning discovery into health
U.S. Department of Health and Human Services

GLOBAL COMPETITIVENESS—THE IMPORTANCE OF U.S. LEADERSHIP IN SCIENCE AND INNOVATION FOR THE FUTURE OF OUR ECONOMY AND OUR HEALTH

The National Science Board's 2010 Key Science and Engineering Indicators, provide insight into how crucial decisions on R&D funding may affect our Nation's ability to thrive in an increasingly competitive and knowledge-driven global economy. While these trends apply not just to bimoedical reserch, but also to research in chemistry, physics, engineering, computer science, and many other fields, the conclusion of most observers is that the 21st century will be dominated by the life sciences, and the country that leads in this area will have much to gain. Unfortunatley, the United States, traditionally the dominant Nation in scientific resarch, has been slipping in leadership recently.

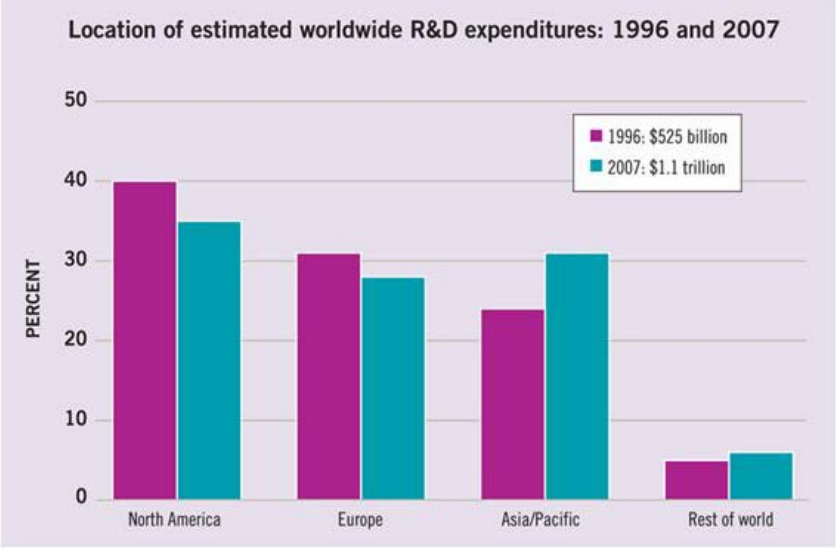
Losing Ground.—R&D investment growth rates are rising sharply in Asia.



SEI 2010: **Global Patterns of R&D Expenditures,** Chapter 4.

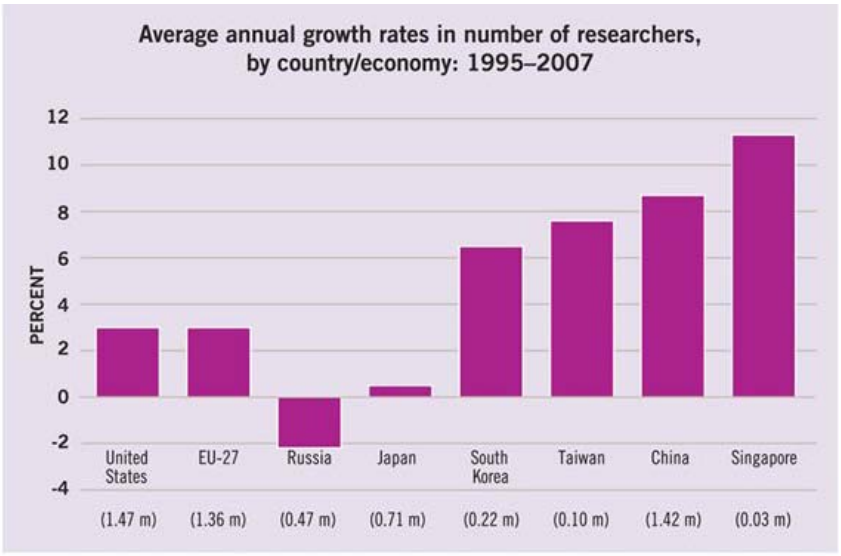
For example, China's growth rate is 4 times higher than the U.S. rate.

While the U.S. remains among the nations with the highest actual R&D expenditures, Asia is rapidly closing the gap.



SEI 2010: **Global Patterns of R&D Expenditures,** Chapter 4.

Employment Impact: The number of people engaged in scientific research in China has increased dramatically. In 2007, China had 1.42 million researchers, while the US had 1.47 million. In 2010, it is likely that China has surpassed the U.S. research workforce.

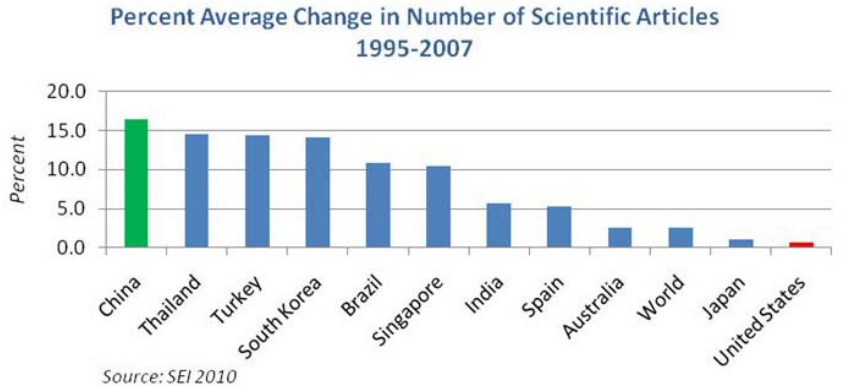


NOTE: Estimated number of researchers (in millions) is for 2007 and shown below country/economy. U.S. 2007 estimate based on long-term growth rate.

SEI 2010: **Global S&E Labor Force,** Chapter 3.

Knowledge Generation: The number of scientific articles published is a common measure of scientific productivity. The average increase in U.S. publications is significantly lower than for other key countries and also below the world average.

Meanwhile, China, Thailand, South Korea, and others show impressive growth rates.



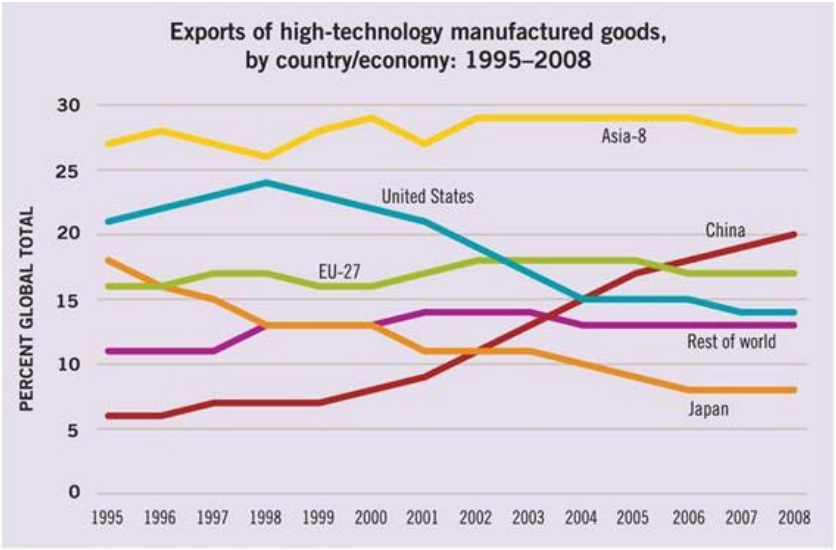
As a result of the previously mentioned trends, it is not surprising that the U.S. share of world publications has significantly decreased, and that China's share has grown.

Country/Region	Share of world articles (Percent)		Percent Change
	1998	2008	
United States	34	28.9	−5.1
EU	34.6	33.1	−1.5
China	1.6	5.9	4.3
Japan	8.5	7.8	−0.7
Asia-8	3.6	6.8	3.2

Source: SEI 2010

The number of times a scientific article is cited indicates its scientific impact. One could argue that emerging countries are publishing articles with limited impact. While this may be the case from certain perspectives, the aggregate number of citations indicates a worrisome plunge in the U.S. share of worldwide citations, which fell 8.6 percent from 1998 to 2008. In contrast, China and Asia-8 countries displayed a noticeable increase in their share of citations, rising 3.7 percent and 3.1 percent respectively over the same time period.

Economic consequences: Reducing R&D investments when other nations are rapidly increasing them has already had significant consequences on exports, which are an important component of the U.S. economy and well being of Americans.



NOTES: China includes Hong Kong. Excludes intra-EU trade.
SEI 2010: **Trade of High-Technology Goods,** Chapter 6.

IMPACTS ON U.S. ECONOMY

NIH is the largest funder and conductor of biomedical research in the world.

The NIH fiscal year 2011 budget is $31 billion—84 percent of which is awarded to the Nation's finest universities, institutes, and small businesses through a rigorous peer review process. Every State, along with almost every Congressional district, benefits.

NIH extramural program supports more than 40,000 competitive research grants and 325,000 research personnel at more than 3,000 universities, medical schools, and other research institutions in all 50 states, U.S. territories, and around the world.

Approximately 10 percent of the NIH budget funds nearly 6,000 scientists working at the NIH campus in Bethesda, in laboratories in Rockville and Frederick, Maryland, at Research Triangle Park in Raleigh, North Carolina, and at the Rocky Mountain Laboratories in Hamilton, Montana.

NIH spending increases business activity directly and indirectly: According to Families USA, each dollar of NIH award money generates about $2.21 of new business activity within 1 year, while each grant awarded by NIH generates about 7 jobs.

NIH-driven advances have not only had profound effects on the health and quality of life for all Americans, but also yielded economic gains. The percentage of elderly with chronic disabilities has declined (from 27 percent in 1982 to 19 percent in 2005). Since 1970, life expectancy in the United States has risen from 71 to 78 years. Economists estimate that these gains in life expectancy have been worth approximately $95 trillion.

The economic potential of NIH-fueled advances in improved treatments for disease is also clear in this projection: a reduction in cancer deaths by one percent has a present value to current and future generations of Americans of nearly $500 billion. A full cure would be worth approximately $50 trillion—more than three times today's GDP.

Advances in disease diagnosis also illustrate the health-related and economic benefits of NIH research: approximately $100 million in health care costs annually are being saved through the use of a genomic test that determines whether a particular type of breast cancer is likely to be cured by surgery and radiation or by chemotherapy. As a result of this test, thousands of women are being spared needless exposure to toxic therapies—and millions of dollars are being saved.

NIH is an engine of innovation—and a crucial support for the global competitive stature of the United States. In fiscal year 2010, NIH filed 289 U.S. patent applications (of which 141 were new applications). These are now included in a total of 3,186 NIH patent applications in the United States and abroad that were pending approval.

Key Facts on U.S. Competitiveness in the Global Research Arena

The United States still is the world leader in science and engineering research. But that leadership role is being challenged by China, India, and other nations as they recognize the economic, health, and social benefits of investing in R&D.

Over the past decade, R&D intensity has grown in Asia, but remained flat in the United States.

Growth of R&D expenditures in the United States averaged 5–6 percent annually from 1996–2007, lagging behind the worldwide average of 7 percent per year. In contrast, growth in most Asian nations exceeded the worldwide average, and China's R&D expenditures grew more than 20 percent annually from 1996–2007.

The United States share of high technology exports fell by one-third from 1996–2007. China's share more than tripled.

India exported $8.3 billion in pharmaceutical products and services in fiscal year 2009, up 25 percent from the previous year.

About 277,000 people, ranging from scientists and to production workers, are currently employed by pharmaceutical companies in the United States, a decline of 5 percent from 2008. More than 340,000 people work in India's pharmaceutical manufacturing industry in 2009—and the industry is projected to grow by 13 percent in 2010.

Between 1995 and 2007, the worldwide share of researchers working in China, Singapore, South Korea, or Taiwan rose from 16 percent to 31 percent.

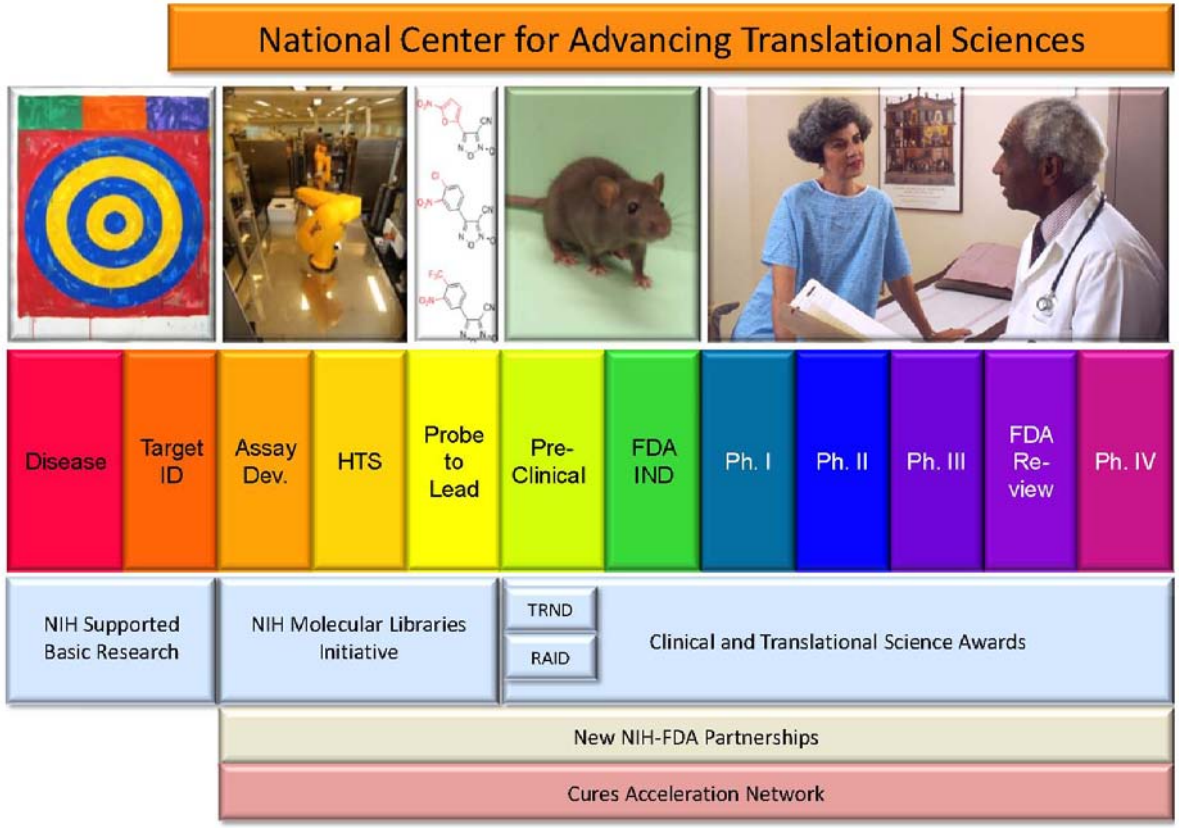
In 2007, the United States had 1.47 million people engaged in scientific research; China had 1.42 million—and it was generating R&D jobs at three times the rate of the U.S.

In the United States, the percentage of undergraduate students who major in science and engineering is 15 percent; in China, it is 50 percent.

In 1995, China ranked 14th in the world in the production of research publications. In 2008, it ranked second.

China's leading genome sequencing institute, BGI, is on track to sequence more than 10,000 human genomes a year. That would surpass the entire DNA sequencing output of the United States.

For more on how shifts in global research capacity are challenging the United States to actively focus on maintaining its competitive strength, go to http://www.nsf.gov/statistics/nsb1003/.


National Center for Advancing Translational Sciences
Disease
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Ph. III
FDA Re-view
Ph. IV
NIH Supported Basic Research
NIH Molecular Libraries Initiative
TRND
RAID
Clinical and Translational Science Awards
New NIH-FDA Partnerships
Cures Acceleration Network

HEALTH IMPROVEMENTS

In the last 25 years, NIH-supported biomedical research has directly led to human health benefits that both extend lifespan and reduce illnesses:

—*Prolonging Life and Reducing Disability*.—Our Nation has gained about 1 year of longevity every 6 years since 1990. A baby born today can look forward to an average lifespan of nearly 78 years—nearly three decades longer than a baby born in 1900. Not only are people living longer, they are staying active longer. From 1982 through 2005, the proportion of older people with chronic disabilities dropped by almost a third.

—*Heart Disease*.—NIH research has generated new techniques for heart attack prevention, effective drugs for lowering cholesterol and controlling blood pressure, and strategies for dissolving blood clots. As a result, the death rate for coronary disease is 60 percent lower—and for stroke, more than 70 percent lower—than during the era of World War II. Better treatment of acute conditions, better medications, and improved health-related behaviors—all made possible by NIH research—account for as much as two-thirds of this reduction.

—*Chronic Disability*.—From 1982–2004, the reported chronic disability among American seniors dropped nearly 30 percent. Health improvements from NIH research played a major role in this, including better prevention and treatment of heart attacks and strokes, advances in treatment of arthritis, and improved technologies for cataract surgery.

—*Age-Related Macular Degeneration (AMD)*.—Forty years ago there was little or nothing one could do to prevent or treat advanced AMD and blindness. Because of new treatments and procedures based on NIH research, 750,000 Americans who would have gone blind over the next 5 years instead will continue to have useful vision.

—*Breast Cancer*.—The 5-year survival rate for women diagnosed with breast cancer was 75 percent in the mid-1970s. Because of NIH-supported research, the 5-year survival rate has risen to over 90 percent.

—*Cervical Cancer*.—Cervical cancer is a deadly cancer in women. Due to groundbreaking NIH research, an FDA-approved vaccine (Gardasil) now is available to prevent the development of cervical cancer.

—*Colon Cancer*.—From 1974–1976, in an NIH-sponsored study, the 5-year survival for patients with colon cancer was 50 percent. In 2009, based on NIH-supported clinical trials using new diagnostics and treatments, a comparable patient group has a 5-year survival rate of over 70 percent.

—*Cochlear Implants*.—Because of NIH-supported research, children who are profoundly deaf but receive a cochlear implant within the first 2 years of life now have the same skills, opportunities, and potential as their normal-hearing classmates.

—*Type 1 Diabetes*.—Thirty to forty years ago, 30 percent of patients died within 25 years of a diagnosis of type 1 diabetes. Today, due to tight blood glucose control, heart disease and stroke in patient with type 1 diabetes have been reduced by over 50 percent.

—*Hepatitis B*.—In the mid-1980s, hepatitis B infection caused untreatable and fatal illness. Due to intensive vaccination programs based on NIH research, the rate of acute hepatitis B has fallen by more than 80 percent.

—*HIV/AIDS*.—In the 1980s, the diagnosis of HIV infection was a virtual death sentence. Due to antiviral drugs developed by NIH, today an HIV-positive 20-year-old can be expected to reach the age of 70.

—*Infant Health*.—In 1976, the infant mortality rate was 15.2 infant deaths per 1,000 live births. By 2006, that rate had fallen to 6.7 deaths per 1,000 live births. Much of this progress can be attributed to NIH research in the areas of neonatal care unit procedures and new drugs administered to women at risk for premature birth.

—*Childhood Leukemia*.—Survival rates for children with the most common childhood leukemia (acute lymphocytic leukemia) is now 90 percent.

ADVANCES IN KNOWLEDGE

NIH-funded research leads to thousands of new findings every year. These incremental advances and technological developments are the building blocks that ultimately yield significant improvements in health. Highlighted below are just a few of the many recent advances from NIH-supported research:

—*Studies find possible new genetic risk factors for Alzheimer's disease*.—Scientists have confirmed one gene variant and have identified several others that may be risk factors for late-onset Alzheimer's disease, the most common form of the disorder. In the largest genome-wide study, or GWAS, ever conducted in Alz-

heimer's research, NIH-supported investigators studied DNA samples from more than 56,000 study participants and analyzed shared data sets to detect gene variations that may have subtle effects on the risk for developing Alzheimer's. Until recently, only one gene variant, Apolipoprotein E-e4 (APOE-e4), had been confirmed as a significant risk factor gene for the common form of late-onset Alzheimer's disease, which typically occurs after age 60. In 2009 and 2010, researchers confirmed additional gene variants of CR1, CLU, and PICALM as possible risk factors for late-onset Alzheimer's. This newest GWAS confirms the fifth gene variant, BIN1, affects development of late-onset Alzheimer's. The genes identified by this study may implicate pathways involved in inflammation, movement of proteins within cells, and lipid transport as being important in the disease process.

—*NIH scientist advance universal flu vaccine*.—Significant progress was made toward the development of a universal flu vaccine that would confer longer term protection against multiple influenza virus strains. NIH-supported researchers have identified the regions of influenza viral proteins that remain unchanged among seasonal and pandemic strains. These findings will inform the development of influenza vaccines that might one day provide universal protection against the broad range of influenza strains. Such a universal influenza vaccine would provide broader protection against multiple flu strains and make yearly flu shots a thing of the past.

—*Early detection of cancer is critical to provide effective therapy*.—NIH-supported investigators recently reported the detection of a single metastatic cell from lung cancer in one billion normal blood cells. These circulating tumor cells (CTCs) may also be released into the bloodstream of patients with invasive but localized cancers. The presence of CTCs may be an early indicator of tumor invasion into the bloodstream long before distant metastases are detected. Identifying CTCs may be viewed as performing liquid biopsies, which can be especially advantageous for prostate cancer. Researchers plan to extend their work to develop a point-of-care microchip that would allow non-invasive isolation of CTCs from patients with many different types of cancer, to improve the management and treatment of this devastating disease.

—*Prenatal surgery reduces complications of spina bifida*.—NIH-supported scientists reported that a surgical procedure to repair a common birth defect of the spine, if undertaken while a baby is still in the uterus, greatly reduces the need to divert, or shunt, fluid away from the brain. The fetal surgical procedure also increases the chances that a child will be able to walk without crutches or other devices. The birth defect, myelomeningocele, is the most serious form of spina bifida, a condition in which the spinal column fails to close around the cord. The study, the Management of Myelomeningocele Study (MOMS), was stopped after the enrollment of 183 women, because of the benefits demonstrated in the children who underwent prenatal surgery. In spite of an increased risk for preterm birth, children who underwent surgery while in the uterus did much better, on balance, than those who had surgery after birth.

—*Progesterone reduces rate of early preterm birth in at risk women*.—Preterm infants are at high risk of early death and long term health and developmental problems including, breathing difficulties, cerebral palsy, learning disabilities, blindness and deafness. An NIH study found that progesterone gel reduces the rate of preterm birth before the 33rd week of pregnancy by 45 percent among women with a short cervix, which is known to increase the risk of preterm birth. Women with a short cervix can be identified through routine ultrasound screening, and once identified could be offered treatment with progesterone. In addition, infants born to women who received progesterone had a lower rate of respiratory distress syndrome than those in the placebo group.

—*Daily dose of HIV drug reduces risk of HIV infection*.—A daily dose of an oral antiretroviral drug, currently approved to treat HIV infection, was shown to reduce the risk of acquiring HIV infection by 43.8 percent among men who have sex with men. The findings, a major advance in HIV prevention research, came from a large international clinical trial supported by NIH. The study, titled "Chemoprophylaxis for HIV Prevention in Men" found even higher rates of effectiveness, up to 72.8 percent, among those participants who adhered most closely to the daily drug regimen. These new findings provide strong evidence that pre-exposure prophylaxis with an antiretroviral drug, a strategy widely referred to as PrEP, can reduce the risk of HIV acquisition among men who have sex with men, a segment of the population disproportionately affected by HIV/AIDS. Prophylactic antiretroviral therapy has already been proven to significantly reduce the transmission of HIV from a mother to a child during childbirth through breastfeeding.

—*Pocket-sized device makes medical ultrasound more accessible*.—NIH-supported research at General Electric supported the development of a low-cost, portable, high-quality ultrasonic imager. In the last year, this advance was extended even further with GE's production of "Vscan." This pocket-sized device makes medical ultrasound even more accessible and has enabled wireless imaging, patient monitoring, and prenatal care applications.

—*Lung cancer screening with CT scan reduces deaths*.—The National Lung Screening Trial found that screening with low-dose computed tomography (CT) can decrease lung-cancer deaths among current and former heavy smokers by 20 percent. Because of earlier identification of cancerous tumors, screening was found to reduce mortality from lung cancer, the most common cause of cancer deaths.

—*Nicotine vaccine shows promise in preventing tobacco addiction*.—Vaccines developed to combat drug addictions work by generating drug-specific antibodies that bind the drug while in the bloodstream and prevent its entry into the brain. A nicotine vaccine recently found to improve smoking quit rates is now in phase III trials to evaluate continued abstinence at 12 months.

—*Nanotechnology demonstrates advances in the realm of materials technologies*.—Carbon nanotubes have been used to deliver chemotherapeutic agents specifically to head and neck cancer cells, causing rapid death of the cancer cells, but leaving non-cancerous cells unharmed.

—*Certain lipid molecules that show promise in controlling pain could result in new treatments*.—Researchers have demonstrated in animal models that certain lipids called resolvins, which shut down inflammation, are more potent than morphine in controlling pain. Since these resolvins are normally found in the body, they are likely to be safe and non-addictive when used therapeutically. Additional research is under way to explore these compounds further and translate into new analgesics for pain management.

—*Combined treatment improves vision in patients with diabetic macular edema*.—A comparative effectiveness study for diabetic macular edema found that combined treatment with the drug ranibizumab and laser therapy was substantially better at improving vision in patients with diabetes than laser therapy alone, and better than laser therapy with a different drug (triamcinolone).

—*Scientists develop a system for making functional hair cells from stem cells, offering possible new treatment of deafness*.—In mammals, mechanically-sensitive "hair cells" in the inner ear, which are essential for both hearing and balance cannot regenerate when they die or are damaged. NIH supported scientists have used mouse embryonic stem cells as well as induced pluripotent stem cells and generated hair cells that respond to mechanical stimulation, offering a new avenue for the treatment of deafness.

—*Experimental medication lifts depression symptoms in people with bipolar disorder*.—NIH intramural researchers discovered that ketamine, an anesthetic medication, provides rapid and effective treatment for depressive symptoms among patients with bipolar disorders. While ketamine's side effects make it impractical for long-term use, this class of drugs may be invaluable for treating severe depressive symptoms in these patients during the weeks it usually takes for typical antidepressants to take full effect.

PROPOSED NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

NATIONAL INSTITUTES OF HEALTH

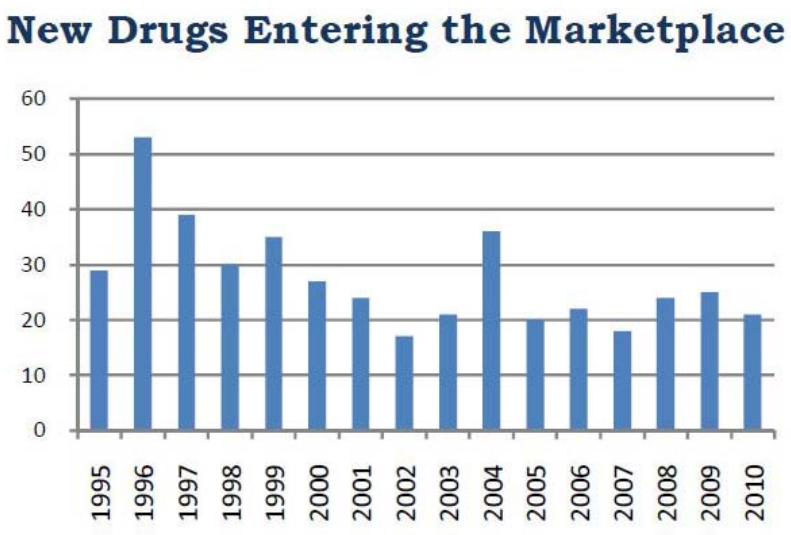
Rationale

The development of new diagnostics and therapeutics is widely recognized as a complex, costly, and risk-laden endeavor. Only a few of the thousands of compounds that enter the drug development pipeline will ultimately make it into the medicine chest.

MISSION

To advance the discipline of translational science and catalyze development and testing of novel diagnostics and therapeutics across a wide range of human diseases and conditions.

In recent years, there has been a deluge of new discoveries of potential drug targets, yet we still lack effective therapeutics for many conditions, especially rare and neglected diseases. A major problem is that the drug development pipeline is full of bottlenecks that slow the speed of development and add expense to the process. To address these challenges, the National Institutes of Health (NIH) has proposed establishing the National Center for Advancing Translational Sciences (NCATS).



Source: FDA

NCATS will study various steps in the drug development pipeline, identify bottlenecks amenable to re-engineering, and experiment with innovative methods to streamline the process. Promising therapeutic projects will be used to evaluate pipeline innovations.

NCATS will complement—not compete with— translational research being carried out elsewhere at NIH and in the private sector. In fact, through its mission to use the power of science to advance the entire discipline, NCATS will benefit all stakeholders, including academia, biotechnology firms, pharmaceutical companies, the Food and Drug Administration, and—most importantly—patients and their families.

Functions

NCATS will aim to improve the processes in the drug development pipeline by:
—experimenting with innovative approaches in an open-access model;
—choosing therapeutic projects to evaluate these innovative approaches; and

—promoting interactions to advance the field of regulatory science.

NCATS also will strive to catalyze the development of new drugs and diagnostic tests by:

—encouraging collaborations across all sectors;
—providing resources to enable therapeutic development; and
—enhancing training in relevant disciplines.

NCATS will:
—facilitate—not duplicate—other translational research activities supported by NIH;
—complement—not compete with—the private sector; and
—reinforce—not reduce—NIH's commitment to basic research.

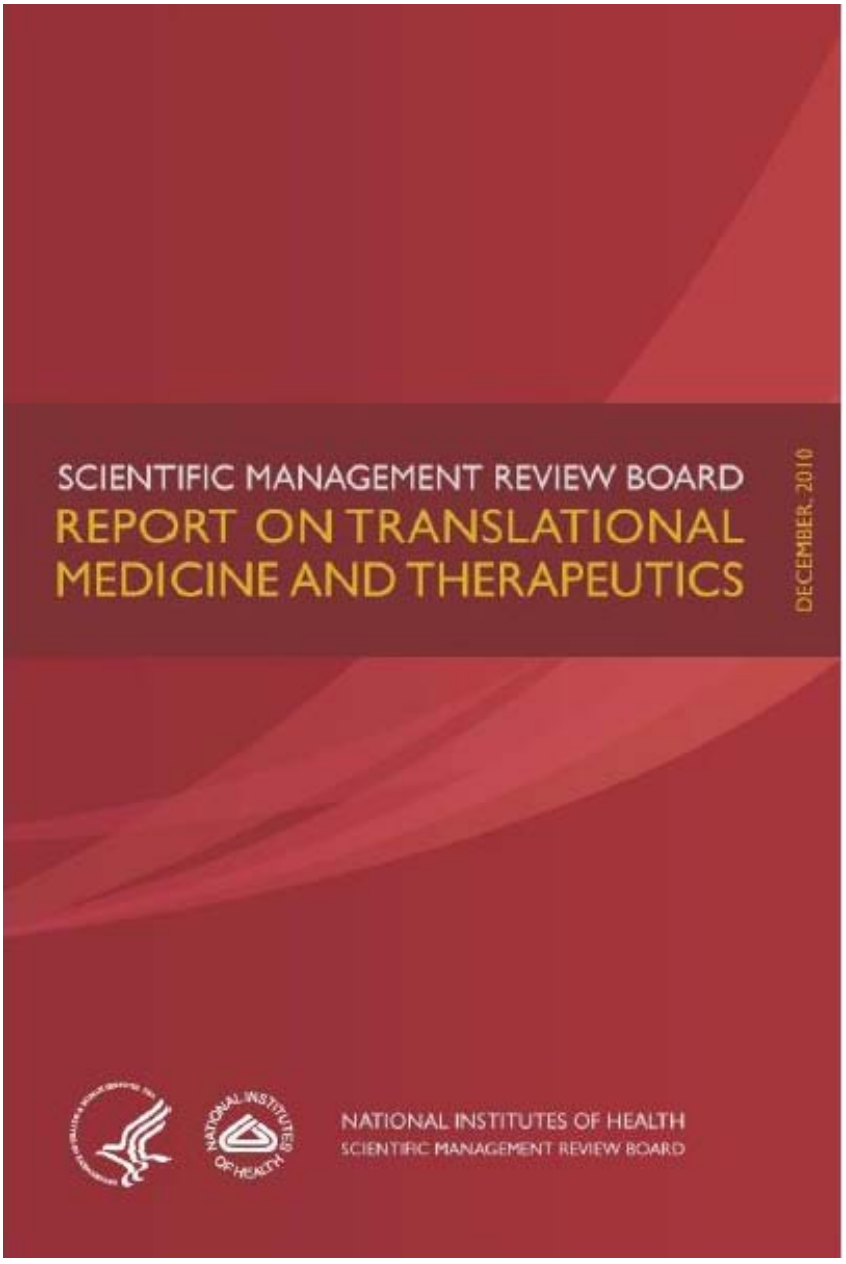
Programs

NCATS will be formed by pulling together these existing NIH programs: components of the Molecular Libraries initiative, Therapeutics for Rare and Neglected Diseases, Office of Rare Diseases Research, Rapid Access to Interventional Development, Clinical and Translational Science Awards, and FDANIH Regulatory Science. In addition, the Cures Acceleration Network will be part of NCATS if funds are appropriated for fiscal year 2012. Relocated programs will have their respective budgets transferred to the new center.

Background

On May 19, 2010, the NIH Director asked the NIH Scientific Management Review Board (SMRB) to:

—identify the attributes, activities, and functional capabilities of a translational medicine program for advancing therapeutics development; and
—broadly assess the NIH landscape for existing programs, networks, and centers for inclusion; and recommend their optimal organization.



On Dec. 7, 2010, the SMRB recommended the creation of a new translational medicine and therapeutics center. It also urged NIH to undertake a detailed analysis, through a transparent process, to evaluate the new center's impact on existing NIH programs.

Informed by the SMRB's recommendations, NIH initiated a planning process to establish NCATS. The NIH Director established three panels to guide and inform the process: the Institute and Center Directors' (ICD) NCATS working group, the

Advisory Committee to the Director (ACD) NCATS working group, and the NIH Clinical and Translational Science Awards (CTSA) Integration working group.

On Jan. 4, 2011, Dr. Collins charged the ICD working group with making recommendations on the mission, functions, and organizational design of NCATS. This panel presented its recommendations to Dr. Collins on Feb. 17, 2011. The ACD working group, which has been asked to provide high-level advice on how NCATS can best engage the private sector in translational science, met for the first time on Feb. 4, 2011. This distinguished panel of outside experts will report its findings to the ACD later this year.

The final working group, composed of leaders from across NIH, was formed in mid-March to ensure a smooth transition of the CTSA program into NCATS.

Next Steps

At every point along the way, NIH has sought input on NCATS from a broad and diverse array of stakeholders. In addition, NIH will continue to inform all stakeholders on new developments and seek their comments through our interactive web site Feedback NIH.

Pending approval from the Health and Human Services Secretary, the Office of Management and Budget, and the Congress, NCATS will be included in the fiscal year 2012 budget and be formally established on Oct. 1, 2011.

So in this brief statement today, I'd like to tell you about four innovative areas, and I'm going to show some pictures up on the screen in which NIH is investing in order to carry out its mission of turning discovery into health.

First, dramatic advances in technologies, including imaging, nanotechnology, computational biology, and, yes, genomics, have recently made it possible for scientists to understand the details of health and disease in breathtaking new ways.

Consider this curve, the cost to sequence a human genome. Look at the profound reduction over the past decade. In 2001, it cost about $100 million to sequence a single human genome. That cost now stands at about $10,000, and we anticipate it will be less than $1,000 within the next few years.

That advance will give many Americans access to far more personalized strategies for detecting, treating and preventing disease than are now available.

Those new technologies not only reduce the cost of doing science, but open up whole new frontiers in medicine. I'll tell you about one of those later in a story about a 6-year-old boy named Nic that I think you'll find quite compelling.

But, first, let's turn to the effects that this technology has had on our understanding of cancer. Cancer is a disease of the genome, comes about because of mutations in DNA.

Through a bold initiative, called the Cancer Genome Atlas, or TCGA, my colleague, Harold Varmus, and others are analyzing the DNA of tumors of hundreds of patients to identify comprehensively the genetic mutations associated with the specific cancers.

Brain and ovarian cancers were the first ones selected for study through TCGA and the results have been stunning. Knowing the molecular drivers of cancer gives us a chance to make much more accurate diagnoses, prognoses, and predictions of response to therapy. And in the longer run, this approach will lead to development of a new generation of targeted therapies, those magic bullets so dreamed of to treat this disease.

The plan for the next few years is ambitious. TCGA will sequence, characterize, and understand the genomes of 20 different types of tumors.

New treatments are wonderful. Effective prevention can be even better. NIH is dedicated to use the latest science to improve America's health today by identifying effective new strategies for disease prevention. The grave threat of diabetes is a compelling example of how we are doing this.

This map shows the prevalence of diabetes in the United States in 1995. As you can see from the color code, in most States, less than 5 percent of adults were affected, but watch what happened over just 15 years. Prevalence of diabetes has gone up rapidly in every State, and it now stands at 9 percent or more in many parts of the country.

The total costs of the disease, including medical care, disability and premature death, were an estimated $174 billion in the United States in 2007. If current trends continue, one in three U.S. adults will have diabetes by 2020, just 9 years from now, and the annual cost of care alone will have risen to a breathtaking $500 billion.

But my colleague, Grif Rodgers, and I can offer some hope. NIH spearheaded a landmark clinical trial on how to prevent type 2 diabetes. The Diabetes Prevention Program, or DPP, involved adults with pre-diabetes. That refers to a modest elevation of glucose in the blood foreshadowing much worse to come if nothing is done, but not yet frank diabetes.

The study participants were assigned personal coaches who encouraged them to exercise about 30 minutes a day and to make modest dietary changes resulting in an average weight loss of just 7 percent. This simple approach lowered the chance of full-blown diabetes by a whopping 58 percent, and that has been sustained for more than 10 years.

Building on these results, NIH has joined with the Centers for Disease Control and Prevention (CDC), the YMCA, Walgreens, United Health Care and other partners to bring this program to communities in 10 States. And we are now working with colleagues at CMS to explore how a similar program could be used to great advantage in Medicare and Medicaid.

Now, I'd like to turn your attention to another important contribution of NIH research already mentioned by the chairman, enhancing the economy and U.S. competitiveness worldwide.

NIH will be a key engine driving the U.S. economy in the 21st century. Many call this the century of biology. As mentioned, just yesterday, a new economic impact study published by United for Medical Research suggests that in fiscal year 2010 NIH research funding supported an estimated 487,900 American jobs at 3,000 institutions and small businesses across all 50 States of this Nation.

More than that, nearly 1 million U.S. citizens are employed by the industries and companies that make up this sector of the economy, earning $84 billion in wages and salary and exporting $90 billion of goods and services annually. But despite this impressive track record, our Nation today is at serious risk of losing its position as the world's research leader.

As you can see in this slide, which shows the percent growth of R&D expenditures on an annual basis, China and India and other countries have been steadily increasing their R&D expenditures by 10 percent or more per year, highlighting China and India there.

Whereas, the United States has been at a substantially lower level. China's growth rate is now four times greater than ours.

Let me give you a personal example of what this means. Last fall, when I visited the BGI Genome Center in Shenzhen, China, I saw an amazing facility built in just 3 years from an abandoned shoe factory that is capable of sequencing more than 10,000 human genomes a year.

The capacity of that one Chinese institution now surpasses the combined capacity of all genome sequencing centers in the United States. This critical area of scientific innovation, stimulated by the U.S.-led Human Genome Project, is now being developed more aggressively in China than it is here, a sobering story indeed, and one that I hope would inspire our Nation to redouble its efforts on the research front.

A final area I wish to highlight in which our Nation faces exceptional challenges, as well as exceptional opportunities, is this field of translational science which Senator Shelby has specifically highlighted in his opening statement. As a result of years of steadfast support of NIH research by Congress and the American people, we find ourselves in a paradoxical situation.

This graph shows we've seen a deluge of discoveries about the molecular basis of disease, both rare and common, which provide us with the power to identify more therapeutic targets than ever before; more than 4,000 diseases now having their molecular basis discovered, much of that in the last decade.

But there's a serious problem. The process of taking those basic discoveries to the point of clinical advances, as here demonstrated by a diagram showing you what happens in the development of new therapeutics, is far too slow—14 years on the average—and the failure rate is far too high—more than 98 percent. We clearly need a new approach to therapeutic development and a new partnership with the private sector.

So to meet this need, NIH is proposing the establishment of a new national center for advancing translational sciences or NCATS. NCATS will allow us to study the various steps in the development of diagnostics, devices and therapeutics, identify bottlenecks that might be reengineered and experiment with innovative methods to streamline this process.

Through this new center, we can work in an open-access model that will allow stakeholders, including industry and academia, to access and apply the innovations that are developed. NCATS will also advance the field of regulatory science by promoting interactions among the NIH, FDA, patient advocates, and pharmaceutical and biotechnology companies.

Importantly, NCATS will complement, not compete with, the private sector. This is not Bethesda Pharm. It will facilitate translational research being carried out elsewhere at the NIH, extensive translational work already going on by many of the 27 Institutes, including those represented at this table. And it will reinforce, not reduce, NIH's commitment to basic science, a foundational part of our mission.

Most importantly, though, by advancing discipline of translational sciences, NCATS will benefit patients and their families.

So, Mr. Chairman, members of the subcommittee, I've spoken today about the great promise of new technologies, how we're applying science to prevention, NIH's role in maintaining U.S. economy—world leadership, and the unique opportunity to pursue a new paradigm in translation.

Let me close by sharing the story of one little boy to show you what NIH research advances now allow us to do. So meet Nic Volker, a brave boy from Monona, Wisconsin.

Starting about the age of two, Nic developed a mysterious life-threatening disease that ravaged his body, making it impossible for him to eat normally and causing unimaginable pain and suffering.

At a loss to explain Nic's terrible affliction, researchers at the Medical College of Wisconsin decided to sequence Nic's DNA instruction book hoping to find an answer. After exacting work over several months, the researchers identified a misspelling of just one single letter in a little-studied gene called XIAP. Now, glitches in this gene had been associated with rare blood disorders, but not with intestinal symptoms. Based on this new insight, the research team had an idea that, as with the rare blood disorders, Nic's disease might be curable with a bone-marrow transplant.

Transplantation of cord blood cells from—stem cells from a matched donor occurred in July of last year. Although Nic is still receiving some immunosuppressant drugs to prevent rejection of the donated cells, his symptoms have largely disappeared, and, today, as you can see here, he can eat normally and vigorously.

What's more, he's now attending kindergarten, enjoying outings with his family and friends, signing up for a T–Ball team, and, this past Sunday, presenting his mother with a flower for Mother's Day. Nic has given us all a glimpse of the future.

PREPARED STATEMENTS

Thank you, Mr. Chairman. This concludes my formal remarks.

[The statements follow:]

PREPARED STATEMENT OF FRANCIS S. COLLINS, M.D., PH.D.

INTRODUCTION

Good morning, Mr. Chairman and distinguished Members of the Subcommittee. I am Francis S. Collins, M.D., Ph.D. and I am Director of the National Institutes of Health (NIH).

It is a great honor to appear before you today to present the administration's program level request of $31.987 billion for NIH in fiscal year 2012, and to discuss the contributions that NIH-funded biomedical research has made in improving human health. NIH is the largest supporter of biomedical research in the world, providing funds for more than 40,000 competitive research grants and more than 325,000 research personnel at more than 3,000 research institutions and small businesses across our Nation's 50 States. I also want to offer a vision of how NIH will catalyze innovation in basic and translational sciences, and will ensure future U.S. economic strength and global competitiveness.

On behalf of NIH and the biomedical research enterprise, I want to thank you as Members of the Senate for sparing NIH from deeper cuts in the final fiscal year 2011 continuing resolution (CR). We know that, even as Congress and the administration wrestled with cuts of more than 3 percent to the Labor-HHS portion of the CR, NIH received a 1 percent, or $321.7 million, cut from the fiscal year 2010 level, while other programs and functions were cut more deeply.

NIH's mission is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance human health, lengthen life, and reduce the burdens of illness and disability. I can report to you that NIH continues to believe passionately in that mission and works tirelessly to achieve it.

Due in large measure to NIH research, our Nation has gained about 1 year of longevity every 6 years since 1990. A child born today can look forward to an average lifespan of nearly 78 years—nearly three decades longer than a baby born in 1900. And not only are people living longer, but their quality of life is improving: in the last 25 years, the proportion of older people with chronic disabilities has dropped by almost one-third.

NIH research has enabled new techniques to prevent heart attacks, newer and more effective drugs for lowering cholesterol and controlling blood pressure, and innovative strategies for dissolving blood clots and preventing strokes. As a result, the U.S. death rate for coronary disease is 60 percent lower—and for stroke, more than 70 percent lower—than three generations ago. Better treatment of acute heart disease, better medications, and improved health-related behaviors—all underpinned by NIH research—account for as much as two-thirds of these reductions.

In recent years, largely as a result of NIH research, we have succeeded in driving down mortality rates for cancer in the United States. This progress comes despite the fact that cancer is largely a disease of aging and our population is growing older. Over the 15-year period from 1992 to 2007, cancer death rates dropped 13.5 percent for women and 21.2 percent for men. According to an American Cancer Society report released in July 2010, the continued drop in overall mortality rates over the last 20 years has saved more than three-quarters of a million lives.[1] And in cancers that strike children we have made near-miraculous progress—the 5-year survival rate for children with the most common childhood cancer, acute lymphocytic leukemia, is now 90 percent.[2]

I would also like to offer a shining example of the Senate's strong and consistent support of biomedical research at NIH by note that we are celebrating a significant anniversary. This year marks the 10th anniversary of the establishment of the Dale and Betty Bumpers Vaccine Research Center (VRC) at NIH. Groundbreaking research performed at the VRC is making great progress toward developing a universal flu vaccine that confers longer-term protection against seasonal and pandemic influenza strains.

Today, scientists have to make an educated guess about the make-up of the coming winter's influenza viruses. These educated guesses become the basis for the manufacture of each year's flu shot and mean that everyone has to be re-immunized in anticipation of next year's strain of flu. Recently, NIH scientists have identified pieces of influenza viral proteins that consistently appear among seasonal and pandemic flu strains. These findings raise the possibility that we might soon develop an influenza vaccine that provides near-universal protection against a broad range of current and future strains of influenza,[3] as well as make yearly flu shots a thing of the past. Most of this exciting work was performed at the VRC. Scientists at that same center are making important strides toward the development of the long-hoped-for vaccine against the human immunodeficiency virus (HIV), the cause of acquired immune deficiency syndrome (AIDS). While after so many frustrations, no one would want to predict success just yet, recent discoveries of VRC scientists about how to encourage production of neutralizing antibodies against HIV have provided renewed hope that this pressing problem may ultimately be solved.

NIH AND ECONOMIC GROWTH

Mr. Chairman and Members of the Subcommittee, I recognize that, given our Nation's fiscal situation, and the extraordinarily tough decisions that you will have to make about our Nation's finances, you need to be assured that NIH remains a worthwhile national investment. Even as you make these decisions and even as our country recovers from financial recession, I want to offer evidence that NIH and its research provide two strong and ongoing benefits to our economy.

First, NIH research spending has an impact on job creation and economic growth. A new economic impact study by United for Medical Research suggests that in fiscal year 2010, NIH research funding supported an estimated 487,900 American jobs, including researchers and spin-off employment.

Second, NIH research funding has a longer term impact in its role as the foundation for the medical innovation sector. Nearly 1 million U.S. citizens are employed by the industries and companies that make up this sector of the economy, earning $84 billion in wages and salary in 2008, and exporting $90 billion of goods and services in 2010. NIH support for biomedical research institutions catalyzes business ac-

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[1] http://pressroom.cancer.org/index.php?s=43&item=252.

[2] http://seer.cancer.gov/csr/1975__2008/browse__csr.php?section=28&page=sect__28__table.08.html.

[3] http://www.niaid.nih.gov/news/newsreleases/2010/Pages/UniversalFluVax.aspx.

tivity in other ways as well. Such institutions constitute reservoirs of skilled, knowledgeable individuals and, thereby, attract companies that wish to locate their operations within such "knowledge hubs."

For example, in the 1990s, Federal funding through research grants and the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs transformed the academic research environment and helped to launch new industrial sectors in Silicon Valley and elsewhere that are flourishing today. Federal funding has been crucial in stimulating the formation of start-up companies and collaborations among academia and the private sector in the development of innovative technology. A prime example is the company Affymetrix.

In the late 1980s, a team of scientists led by Stephen P.A. Fodor, Ph.D., developed methods for fabricating DNA microarrays, called GeneChips, using semiconductor manufacturing techniques, melded with advances in combinatorial chemistry to capture vast amount of biological data on a small glass chip. In 1992, the first of several NIH grants was awarded to Affymetrix; with this and an SBIR grant from the Department of Energy, Dr. Fodor was able to demonstrate proof of principle of using large arrays of DNA probes in genetic analysis. Affymetrix and similar companies are building the machine tools of the genomic revolution. In 2009, Affymetrix had annual revenue of $327 million and employed more than 1,100 people.

Furthermore, NIH research leads to better health outcomes that not only ease human suffering, but also produce an economic return. A 2006 study by Kevin Murphy and Robert Topel of the University of Chicago shows that a permanent reduction of 1 percent in cancer deaths has a present value to current and future generations of Americans of nearly $500 billion. The article states that if we were able to defeat cancer completely, such cures would be worth approximately $50 trillion—more than three times today's Gross Domestic Product.[4]

We face a similar economic threat from diabetes. If current trends continue, by 2050 as many as one in three U.S. adults will be diagnosed with diabetes.[5] Total costs of diabetes, including medical care, disability, and premature death, reached an estimated $174 billion in the United States in 2007.[6] According to analysis from the UnitedHealth Center for Health Reform & Modernization, more than 50 percent of Americans could have diabetes or pre-diabetes by 2020.[7] Furthermore, the center's analysis predicts diabetes and pre-diabetes will account for an estimated 10 percent of total healthcare spending by the end of this decade, at an annual cost of almost $500 billion.

But I can offer some hope. NIH spearheaded a landmark clinical trial on type 2 diabetes prevention that showed that people at high-risk for diabetes can dramatically reduce their risk of developing type 2 diabetes through modest exercise and dietary changes that achieve modest weight loss. Called the Diabetes Prevention Program (DPP), the clinical trial included 3,234 adults at high risk for developing type 2 diabetes, including those with a family history of diabetes, as well as other risk factors. One-third of these individuals participated in a lifestyle program that included exercise training and dietary change implemented under the guidance of lifestyle coaches. The DPP research team found that this approach lowered risk of diabetes by 58 percent.[8] The DPP trial also demonstrated that the cost of the lifestyle intervention was $3,540 per participant over 3 years, which was significantly offset by the lowering of other healthcare costs as lifestyle participants became healthier.[9] The cost effectiveness of the DPP has continued to be followed and 10-year results will be published in the near future. Building on these critically important results, NIH partnered with the Centers for Disease Control and Prevention (CDC) and more than 200 private partners, including the YMCA, Walgreens, and UnitedHealthcare, to bring these evidence-based lifestyle interventions to communities in Ohio, Indiana, Minnesota, Arizona, Oklahoma, New Mexico, New York, New Jersey, Connecticut, and Georgia. In addition, the DPP Lifestyle Intervention is being used by the Indian Health Service in a large demonstration project on many American Indian reservations.

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[4] Murphy, K.M., & Topel, R.H. (2006), The value of health and longevity. Journal of Political Economy, 114(5), 871–904.

[5] http://www.cdc.gov/media/pressrel/2010/r101022.html.

[6] CDC National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/pdf/ndfs__2011.pdf.

[7] http://www.unitedhealthgroup.com/hrm/UNH__WorkingPaper5.pdf.

[8] Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metiformin. N. Engl J Med 346:393–403, 2002.

[9] *Diabetes Care*. 2003 Jan;26(1):36–47.

INVESTING IN BASIC SCIENCE

At NIH, we have always put our greatest percentage of our resources into basic research. This is because the fundamental observations made today become the building blocks of tomorrow's knowledge, therapies, and cures. NIH's history has repeatedly demonstrated that significant scientific advances occur when new basic research findings, often completely unexpected, open up new experimental possibilities and therapeutic pathways. Historically, NIH has put more than 50 percent of its budget into basic research and the research discoveries that led to the 132 Nobel prizes won by our intramural and university scientists are evidence of the wisdom of this investment.

Basic research is precisely the type of work that the private sector, which must see a rapid return on invested capital, cannot afford to support. NIH provides the fundamental observations that pharmaceutical and biotechnology companies can turn into diagnostics, therapies, and devices that eventually reach patients. As the Congressional Budget Office put it, "Federal funding of basic research directly stimulates the drug industry's spending . . . by making scientific discoveries that expand the industry's opportunities for research and development." [10]

Because we simply cannot predict the next scientific revelation or anticipate the next opportunity, our basic research portfolio must be diverse. We set scientific priorities by considering a wide array of biomedical questions that we might try to answer. It is rather like facing a series of doors, some of which lead to vast treasures and others to much more modest payouts, without any sure way of knowing what lies behind any particular door. To improve our odds of striking scientific gold, we need a broad basic research portfolio that enables our Nation to open as many doors as our resources allow.

Not all disease or scientific problems are equally ripe for new advances, nor do such advances come at the same rate across the portfolio, no matter how pressing today's public health challenges are. We can only be sure that without a strong commitment to basic research today, the new knowledge of tomorrow will remain hidden behind those unopened doors and future therapies and cures will remain out of our reach.

Let me offer a few of the exciting insights that NIH's support of basic research have provided. On April 3, 2011, the online issue of Nature Genetics presented the findings by a team of NIH-supported scientists who had identified five new genetic variants that are risk factors for late-onset Alzheimer's disease, which is the most common form of the disorder. These findings doubled from 5 to 10 the number of gene variants that we know are associated with Alzheimer's disease.[11]

What is even more compelling is that these newly identified genes strongly implicate inflammation and high cholesterol as risk factors in the development of Alzheimer's disease. Although each of these newly identified genes increases a given individual's risk of developing the disease by no more than 10 to 15 percent, the unanticipated insight that cholesterol and inflammation are contributing factors opens up new research avenues to understand the disease process, and increases the likelihood that we can glimpse potential preventions or therapies.

NIH's commitment to basic research has also provided us with one of the most promising therapeutic strategies we have seen to date for the deadliest form of skin cancer, melanoma. Since 2002, we have known that many melanoma tumors exhibit a mutation in the BRAF gene and that this mutation might provide a target for therapeutic intervention. A team that included NIH-supported investigators used high-throughput screening in combination with structural biology, to identify compounds that inhibit the activity of the mutant form of the BRAF gene found in most melanomas, but have little effect on the BRAF gene found in normal cells. This basic cancer research supported by NIH contributed to the development of the drug PLX4032, a drug designed to inhibit the activity of a mutant form of the protein called BRAF. This is a powerful example of how support for basic research can be translated into therapeutic potential. In August 2010, Plexxikon, a small drug development company, announced that PLX4032, had elicited a positive response in more than 80 percent of melanoma patients in early phase clinical trials. PLX4032 caused the tumors in 24 of the 30 trial participants to shrink by at least 30 percent, while the tumors of two patients disappeared. Another clinical trial involving hundreds of participants across many institutions demonstrated that metastatic melanoma pa-

[10] Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, October, 2006, p. 3.

[11] Naj, A.C. et al. Common Variants of MS4A4/MSA6E, CD2AP, CD33 and EPHA 1 are associated with late-onset Alzheimer's Disease. Nature Genetics, EPUB April 3, 2011, and Holligworth, P., et al. Common variants at ABCA7, MS4A/MS4A4E, EPHA 1, CD33 and CD2Ap are associated with Alzheimer's disease. Nature Genetics. Epub April 3, 2011.S

tients treated with PLX4032 lived 6 to 8 months longer than those who had been given the chemotherapy drug dacarbazine, which is the current standard of care.

Whether it is with the hope of finding new ways to treat cancer, prevent Alzheimer's disease, or help people suffering from countless other rare and common conditions, we at NIH invest in basic research because of our conviction that it will benefit our Nation in the long term.

ADVANCING TRANSLATIONAL SCIENCE

NIH also has a longstanding commitment to translating fundamental knowledge into cures and therapies for human disease. It should not be surprising that NIH-supported science underpins many of the most transformative drugs and therapies that have benefited millions of Americans and people around the world, including statins to lower cholesterol and drugs to treat depression. In 2010, we conducted a trans-NIH inventory of therapeutics development activities and found more than 550 such projects, of which approximately 65 percent were pre-clinical and 35 percent were clinical research.

An analysis published in the February 10, 2011 issue of the New England Journal of Medicine (NEJM) underscores the depth and breadth of NIH's support for translational science that benefits patients.[12] The article's authors describe a new emphasis on "public sector research" that is almost exclusively supported or conducted by NIH, noting "the boundaries between the roles of the public and private sectors have shifted substantially since the dawn of the biotechnology era, and the public sector now has a much more direct role in the applied-research phase of drug discovery."

Drugs that represent a major advance in treatment or offer treatments for diseases for which no adequate therapy currently exists are granted "priority review" by FDA. According to the NEJM article, between 1990 and 2007, 20 percent of the FDA approvals of novel compounds granted priority review were given to drugs discovered by NIH. Examples include AZT for HIV/AIDS and the targeted leukemia therapy Gleevec. Over the past 40 years, 153 new FDA-approved drugs, vaccines, or new indications for existing drugs were discovered through work carried out by NIH-supported biomedical research institutions.

Despite NIH's historic and growing commitment to translational sciences, far more remains to be done. Millions of people still suffer from diseases, such as cancers and diabetes, for which we have no adequate treatments. There are nearly 7,000 rare diseases, yet we have therapies for fewer than 200 of them. This staggering public health need and attendant human suffering continues even as the pharmaceutical industry, beset by economic stress, is investing less in research and development, and the pool of venture capital needed by the biotech industry is drying up.

At the same time, a deluge of discoveries about the molecular basis of disease has been made possible by the sequencing of the human and many other genomes, as well as breathtaking advances in research technologies, such as high-throughput screening and bioinformatics. These discoveries reveal hundreds of tantalizing potential therapeutic targets. As the result of years of steadfast support of NIH research by Congress and the American people, we find ourselves in a paradoxical situation: we can uncover the molecular basis of common and rare diseases better than ever before and we can more readily identify therapeutic opportunities than at any point in history, but the pipeline through which these new therapeutic agents must pass is crimped and, in some places completely blocked.

Consequently, a new approach to therapeutic development, and a new partnership with the private sector, is needed. That is why we have proposed the establishment of NIH's new National Center for Advancing Translational Sciences beginning in fiscal year 2012.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES

As previously noted, NIH has a long and rich history of significant contributions to therapeutic development. In particular, the National Cancer Institute (NCI) and the National Institute for Allergy and Infectious Diseases (NIAID) have made major contributions over many years to the discovery of new treatments. However, now is the time to consider the therapeutic development process itself as a scientific problem that is ripe for innovation. The mission of the National Center for Advancing Translational Sciences (NCATS) will be to advance the discipline of translational science and catalyze the development and testing of novel diagnostics and thera-

[12] Stevens, Ashley J. et al. The role of public-sector research in the discovery of drugs and vaccines. New England Journal of Medicine, 364,:6, February 10, 2011.

peutics across a wide range of human diseases and conditions. NIH has no intention of entering the drug development arena that is rightly the province of private sector companies. Indeed, given that it costs in the range of $ 1.3 billion to $1.8 billion to bring one drug to market, it is clear that it would be impossible for NIH to compete with private industry.[13] What NCATS intends to do is advance the science of therapeutic development and determine if there are ways we can re-engineer the drug development pipeline; creating new approaches and methods that will benefit everyone interested in speeding the delivery of new medicines.

Today, the development of new diagnostics and therapeutics is a complex, costly, and risky endeavor. Only a few of the thousands of compounds that enter the drug development pipeline will ultimately make it into the medicine chest or to the patient's bedside. NCATS will study the various steps in the drug development pipeline, consult with the private sector to identify bottlenecks amenable to re-engineering, and experiment with innovative methods to streamline the process.

To offer one example of the kind of pipeline challenge we might address, new ideas about assessing the toxic potential of drug candidates using sophisticated cell-based methods, instead of animal toxicology testing, hold out the promise of revolutionizing this step in validating a new therapeutic agent—and such research can be catalyzed by NIH in ways that might otherwise not be possible.

NCATS will attack the bottlenecks in the drug development pipeline by experimenting with innovative approaches in an open-access model so that all stakeholders, ranging from industry to patients, will be able to access and apply its innovations. NCATS's open access operating framework will also advance the field of regulatory science by promoting interactions among the Food and Drug Administration (FDA), NIH, patient advocates, and pharmaceutical and biotechnology companies. NCATS will encourage collaboration across all sectors, provide resources to enable therapeutic development, and support and enhance training in the relevant translational science disciplines.

NCATS will complement—not compete with—translational research being carried out elsewhere at NIH and in the private sector. In fact, in pursuing its mission of using the power of science to advance the entire discipline of translational science, NCATS will benefit all stakeholders, including academia, biotechnology firms, pharmaceutical companies, the FDA, and—most importantly—patients and their families.

NCATS will pull together existing NIH programs such as the Therapeutics for Rare and Neglected Diseases program, the Office of Rare Diseases Research, the Rapid Access to Interventional Development program, the Clinical and Translational Science Awards, the FDA–NIH Regulatory Science grants program, and components of the Molecular Libraries initiative. These relocated programs will have their respective budgets transferred to or implemented by the new center. In addition, we are hopeful that funding for the new Cures Acceleration Network will be provided within the NCATS appropriation in fiscal year 2012. The intent of this innovative program and its exceptional DARPA-like flexibilities for supporting projects are a natural fit with NCATS.

Aside from the new funding requested in fiscal year 2012 for the Cures Acceleration Network, resources for NCATS will come from the combination of already existing and appropriated programs and so be budget neutral.

NCATS will bring the scientific method to bear on today's drug development process and aim to improve and speed the therapeutic development process of tomorrow.

CONCLUSION

This statement has provided you with a brief overview of NIH's past successes and future commitment to basic and translational sciences, along with a quick look at the important role that NIH plays in our domestic economy and U.S. global economic and scientific leadership.

But I would like to close my testimony today with an example that demonstrates the benefits to be reaped from our continuing pursuit of "personalized medicine." It is the story of one individual, 6-year-old Nic Volker of Monona, Wisconsin. Starting about the age of 2, Nic developed a mysterious, life-threatening disease that ravaged his intestines, making it impossible for him to eat normally and causing unimaginable pain and suffering. At a loss to explain this terrible, inflammatory condition, researchers and clinicians at the Medical College of Wisconsin decided to sequence Nic's entire exome, that is, all the parts of the genome that code for the proteins

[13] DiMasi, JA, Hansen RW, Grabowski HG. Extraordinary claims require extraordinary evidence. Journal of Health Economics 2005;24(5):1034–1044. Tonkens, R. An Overview of the Drug Development Process. The Physician Executive May-June 2005.

that become life's building blocks. After exhaustive work over a period of months, the researchers identified a mutation in Nic's XIAP gene. Such mutations had been associated with rare blood disorders, but not with bowel symptoms. Based on this new insight, the research team had an idea that, as with the rare blood disorders, Nic's disease might be curable with a bone marrow transplant.

NIH investment over the years in the sequencing of genomes—and the technologies associated with such sequencing—has put us at the threshold of "personalized medicine." Young Nic Volker is one of a handful of individuals who has crossed that threshold, and it was made possible because of years of research and development supported and performed by NIH.

Transplantation of cord-blood stem cells from a matched donor occurred in July of last year and, although Nic is still on immunosuppressant drugs to prevent rejection of the donated cells, his symptoms have largely disappeared and today he can eat normally. Hot dogs are his favorite!

The local newspaper, the Milwaukee Journal Sentinel, was so struck by the saga of Nic and his family that they devoted a series of articles to the little boy's struggles and therapy, coverage that included posting photos, videos, blogs, and many other resources to the web. The five Journal Sentinel journalists did such a good job that they were awarded the Pulitzer Prize for Explanatory Reporting on April 18. Now, that is truly putting a face on the promise of today's biomedical research, tomorrow's personalized medicine, and NIH's role in making this promise possible.

Thank you Mr. Chairman. This concludes my formal remarks.

PREPARED STATEMENT OF HAROLD VARMUS, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The fiscal year 2012 request includes $5,196,136,000 for NCI, which reflects an increase of $141,899,000 over the comparable fiscal year 2011 level of $5,054,237,000.

We now know that cancer is a collection of diseases reflecting changes in a cell's genetic makeup and thus its programmed behavior. Sometimes the genetic changes occur spontaneously or are inherited; sometimes they are caused by environmental triggers, such as chemicals in tobacco smoke, ultraviolet radiation from sunlight, or viruses. While cancers constitute an incredibly diverse and bewilderingly complex set of diseases, we have at hand the methods to identify essentially all of the genetic changes in a cell and to use that knowledge to rework the landscape of cancer research and cancer care, from basic science to prevention, diagnosis, and treatment. The funds in the President's budget for NCI represent a bold investment strategy critical for realizing that goal.

The emerging scientific landscape offers the promise of significant advances for current and future cancer patients, and for preventing cancer so that many never become cancer patients. And it offers scientists at the National Cancer Institute—and in the thousands of laboratories across the United States that receive NCI support—the opportunity to increase the pace of lifesaving discoveries dramatically.

In the past year alone, we have seen powerful examples of how research dollars have translated into concrete advances against cancer through basic science, prevention and early detection, and treatment.

Basic science.—In collaboration with NHGRI, the NCI is leading The Cancer Genome Atlas (TCGA), the largest and most comprehensive analysis of the molecular basis of cancer ever undertaken. TCGA aims to identify and catalog all of the relevant genetic alterations in many types of cancer. For instance, building on their recent reclassification of glioblastoma multiforme (GBM), an aggressive form of brain cancer, this year TCGA investigators discovered that about 10 percent of patients with one of the four subtypes of GBM are younger at diagnosis and live longer than patients with other subtypes of the disease, but their tumors are unresponsive to current intensive therapies. The molecular profile of this subtype offers new targets for developing drugs to treat this form of the disease more effectively. TCGA scientists are also preparing to publish similarly important findings about the major form of ovarian cancer in mid-2011 and are in the midst of analyzing nearly 20 other types of cancer.

Prevention and early detection.—NCI's intensive efforts to study and reduce the use of tobacco products have contributed to a sustained annual reduction in age-adjusted cancer mortality rates over the past decade and more. But current and former heavy smokers remain at high risk of developing lethal lung cancers, which are the leading cause of cancer mortality. In late 2010, NCI announced initial results from the National Lung Screening Trial, a large, multi-year randomized trial

that enrolled more than 53,000 subjects. Because early detection provides the potential to intervene at the earliest, most treatable stages of disease, thus reducing potentially difficult to treat outcomes seen in more advanced disease, current and former smokers who were screened with low-dose helical computed tomography were 20 percent less likely to die of lung cancer than were peers who received standard chest x-rays. These results provide the first clear demonstration that a screening procedure can be effective in reducing mortality from lung cancer—a finding that could save many lives among those at greatest risk. Over the course of the $240 million study, NLST investigators collected samples of early and advanced lung cancers from enrolled subjects, and these specimens will be invaluable for determining genetic alterations that may be used to predict which tumors are likely to progress to an advanced stage.

Cancer treatment.—The potential therapeutic impact of basic discoveries made by TCGA and other efforts in cancer genomics has been dramatically illustrated this year by the development of effective drugs against the most deadly form of skin cancer, melanoma. Almost a decade ago, studies of cancer genomes first uncovered a common mutation in a gene that encodes an enzyme called BRAF. Last year, early stage clinical trials at NCI-designated Cancer Centers of drugs targeted against the mutant BRAF enzyme showed that most melanomas with the relevant mutation regressed dramatically. Although tumor regression generally lasted less than a year, NCI-supported investigators have already pinpointed some causes of resistance to BRAF inhibitors, outlining a pathway to more sustained control of this lethal disease.

Another benefit of a prolonged and broad-based investment in cancer research has also been realized in the context of malignant melanoma this year, with the recent approval by the FDA of an antibody, ipilimumab, which extends the lives of patients with metastatic melanoma. Ipilimumab stimulates the immune system to act against cancer by blocking natural inhibitors of the immune response, an approach that would not be possible without a profound understanding of the immune system and one that promises to harness immunological tools against other cancers.

These examples of NCI's progress in understanding, treating, and detecting different forms of cancer illustrate what can be achieved at an accelerated pace with sustained investments across the cancer research spectrum, such as proposed under the President's budget. While those perspectives are only beginning to inform the American public's perception about cancer and its treatment, the downward trajectory of cancer deaths—reported by NCI and its partners in March—reflects real and sustained reductions over more than a decade for numerous cancers, including the four most common: breast, colorectal, lung, and prostate. We have identified proteins and pathways that different cancers may have in common and represent targets for new drugs for these and many other cancers—since so often research in one cancer creates potential benefits across others.

Additional progress against cancer also will require building these research advances into clinical treatments and diagnostic tools for better patient care and by our many connections with public and private sector partners. The Institute's investments in translational research are broad and deep, and will receive NCI's full energies, recognizing that the publicly announced proposal for reorganizing services that support translational science in general could give NIH additional focus in this important area.

REVITALIZING THE CANCER CLINICAL TRIALS SYSTEM

For today's new understandings of cancer biology to benefit cancer patients on a broad scale, they must be coupled with a modernized system for conducting cancer clinical trials. This system must enable clinical researchers across the Nation to acquire tumor specimens and conduct genetic tests on each patient, to efficiently analyze molecular changes in those samples, to manage and secure vast quantities of genetic and clinical data, and to identify subsets of patients with tumors that demonstrate changes in specific molecular pathways—pathways that can be targeted by a new generation of cancer therapies.

As part of its effort to transform the cancer clinical trials system, NCI asked the Institute of Medicine (IOM) in 2009 to review the Clinical Trials Cooperative Group Program. This program involves a national network of 14,000 investigators currently organized into nine U.S. adult Cooperative Groups and one pediatric cooperative group that conduct large-scale cancer clinical trials at 3,100 sites across the United States. The IOM report, issued in April 2010, noted that the current trials system—established a half-century ago—is inefficient, cumbersome, underfunded, and overly complex. Among a series of recommendations, the report urged that the existing adult cooperative groups be consolidated into a smaller number of groups,

each with greater individual capabilities and with new means to function with the others in a more integrated manner.

In December 2010, NCI announced its intent to begin consolidating the current nine adult cooperative groups into four state-of-the-art entities that will design and perform improved trials of cancer treatments, as well as explore methods of cancer prevention and early detection, enhance the ability of the cooperative groups to assess the molecular characteristics of individual patients' tumors, and study quality-of-life issues and rehabilitation during and after treatment. The sole pediatric cooperative group was created by consolidating four pediatric cooperative groups almost a decade ago, and that group will not be affected by the current consolidation effort.

PROVOCATIVE QUESTIONS

This has been a challenging and hopeful time for NCI to lead the Nation's cancer research program. Over the past two decades researchers have unraveled some of the damage that occurs in the genome of a cancer cell and how a cancer cell behaves in its local environment as a result of those changes. With this better understanding of cancer and recent technological advances in many fields, such as genomics, molecular biology, biochemistry, and computational sciences, progress has been made on many fronts, and a portrait has emerged for several cancers. With sustained and accelerated funding, and NCI's strong leadership in defining cancer research priorities, we can build upon today's cancer advances with provocative thinking by asking better questions.

To that end, NCI is asking researchers in various disciplines to pose and articulate "provocative questions" that can help guide the Nation's investment in cancer. Provocative questions may be built on older, neglected observations that have never been adequately explored, or on recent findings that are perplexing, or on problems that were traditionally thought to be intractable but now might be vulnerable to attack with new methods.

Many of these provocative questions are being asked—and answered—by young scientists who are early in their careers. The 2012 budget will support NCI's commitment to ensuring that an equitable share of our research grants will go to the young men and women, who are at the forefront of understanding cancer.

We are now reaping the rewards of investments in cancer research made over the past 40 years or more, even as we stake out an investment strategy to realize the potential we see so clearly for the future. The public has benefitted from past generous congressional stewardship of biomedical research funding; cancer research over the past four decades has provided the evidence required to lower the incidence and mortality of many kinds of cancer, to improve the care of cancer patients, and to establish the new understanding of cancer that is now beginning to revolutionize control of cancer throughout the world.

No matter what the fiscal climate, NCI will strive to commit the resources necessary to bring about a new era of cancer research, diagnosis, prevention, treatment, and survivorship.

Thank you for the opportunity to provide you this testimony, and I would be pleased to answer any questions you might have.

PREPARED STATEMENT OF SUSAN B. SHURIN, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). The fiscal year 2012 budget of $3,147,992,000 includes an increase of $80,903,000 over the comparable fiscal year 2011 level of $3,067,089,000.

The NHLBI provides global leadership for a research and education program to promote prevention and treatment of heart, lung, and blood diseases. Our vision is to enhance the health of all individuals and thereby enable them to enjoy longer and more productive lives. The Institute advances its objectives through an innovative program of excellent science that addresses urgent public health needs, capitalizes upon extraordinary opportunities, leverages strategic assets, balances and integrates basic and clinical research approaches, and calls upon the creativity, expertise, and dedication of thousands of scientists here and abroad. The American people have generously supported this work for many years, and tremendous progress has resulted.

This testimony highlights three areas of particular current emphasis: (1) genetics and genomics; (2) regenerative medicine; and (3) translational medicine.

GENETICS AND GENOMICS

NHLBI-funded gene-sequencing projects and genome-wide association studies have been extraordinarily productive. Scanning the genomes of more than 100,000 people from all over the world, scientists recently reported the largest set of genes yet discovered that underlie blood lipid variations known to be major risk factors for coronary heart disease. Altogether, the gene variants explain between one-quarter and one-third of the inherited portions of cholesterol and triglyceride measured in the blood. Of the variants, 59 had not been previously identified and thus provide new clues for developing effective medicines to combat heart disease. This exciting discovery follows upon similar research, reported in 2009, regarding another heart disease risk factor—hypertension. Using genomic analysis of over 29,000 participants from the Framingham Heart Study and other cohorts, an international research team identified a number of unsuspected genetic variants associated with systolic and diastolic blood pressure. Although hypertension has long been known to run in families and have a substantial genetic component, previous attempts to identify genes associated with blood pressure had met with only limited success. The new findings from both the lipid and the blood pressure studies illustrate the potential of large-scale genome-wide scans to identify genes that play roles in a complex disease of widespread public health importance.

Smaller-scale genome-wide scans are also providing valuable new information about less common disorders, such as thoracic aortic aneurysm and dissection—a condition that is often asymptomatic until an unpredictable catastrophic cardiovascular event occurs. Researchers comparing 418 patients with non-familial thoracic aneurysms to normal controls identified a number of genetic variants that appeared more frequently in the patients. Many of the variants exist in genes that are in some manner involved in contraction of smooth-muscle cells, suggesting that genetic variants governing smooth-muscle cell function are a potential target of predictive tests that could be developed in the future.

Although genome-wide scans and sequencing have identified many genetic variations that contribute to disease risk, much more research is needed to understand the mechanisms underlying gene disease associations. NHLBI is advancing this area by supporting a new program, Next Generation Genetic Association Studies, to investigate cells that have been reprogrammed into induced pluripotent stem cells to model heart, lung, and blood diseases and explore the functional consequences of genetic variation.

Another initiative, Getting from Genes to Function in Lung Disease, will support characterization of the function of lung-disease associated genes and their variants that have been identified through GWAS or other genetic approaches. Multidisciplinary teams will use a variety of experimental methods and tools to elucidate the mechanisms that contribute to diseases such as asthma, chronic obstructive pulmonary disease (COPD), sarcoidosis, and idiopathic pulmonary fibrosis and thereby generate knowledge that may lead to more effective ways to prevent and treat them. In fiscal year 2012, the Institute plans to solicit research projects to study two severe and poorly understood conditions that affect the lungs: The Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis program will conduct state-of-the-art genomic, microbiomic, and phenotypic studies with the goals of understanding the molecular and cellular bases of the diseases, facilitating classification of subtypes, and developing new drug therapies.

Because genome-wide scans are not well suited to discovery of extremely uncommon genetic variants, the Institute is pursuing other avenues to explore the contributions of infrequent variants to both common and rare diseases. A program planned for fiscal year 2012 in collaboration with the National Human Genome Research Institute, Life After Linkage: The Future of Family Studies, will use data from existing family studies to identify and characterize genes, including rare variants, that influence complex diseases. The potential success of such an approach is illustrated by a recent breakthrough resulting from a collaboration between the NHLBI intramural program and the NIH Undiagnosed Diseases Program. Researchers identified the genetic cause of a rare and debilitating vascular disorder, not previously explained in the medical literature, that involves severe arterial calcification. Analysis of DNA from members of three affected families revealed that the variant is in a gene responsible for a product that protects arteries from calcifying. It is hoped that this understanding of the underlying defect will enable discovery of improved treatment for the patients.

REGENERATIVE MEDICINE

Body components can malfunction because of inherent defects, catastrophic or accumulated damage, or senescence, and chronic disease is often the result. Restoring

healthy function via delivery of "replacement parts" and helping organs repair injury with functional tissue instead of scarring are high priorities of NHLBI. Recent progress gives much reason for optimism. For example, heart attacks cause permanent damage to heart muscle cells (cardiomyocytes) that renders them useless for pumping blood. Although cardiomyocytes cannot themselves be rejuvenated, NHLBI-supported scientists were able to induce other heart cells (fibroblasts) to become pluripotent stem cells that, in turn, were induced to become cells that looked and behaved much like cardiomyocytes. The finding suggests the possibility that fibroblasts—cells widely available throughout the body—could be directly reprogrammed into functional cells to treat or prevent heart failure and other adverse consequences of cell damage. Other NHLBI-supported researchers recently reported progress toward engineering lung tissue in a rat model, creating a scaffold populated with multipotent neonatal rat cells to produce a transplantable organ capable performing the fundamental lung function of gas exchange. The success of this study and others using cadaveric human lung tissue and immortalized cell lines suggests that such an approach might one day be beneficial for patients who are awaiting lung transplant.

NHLBI is making considerable investments to advance regenerative medicine research for cardiovascular, lung, and blood diseases. A collaborative solicitation with the National Institute of Biomedical Imaging and Bioengineering, New Strategies for Growing 3D Tissues, will support highly integrated, multidisciplinary research to improve understanding of how cells respond to their environment and how cell-communication systems that enable blood-vessel and organ development can be used to engineer 3D human cellular aggregates. Translation of Pluripotent Stem Cell Therapy for Blood Diseases will promote the development of technologies for translation of recent stem cell advances into treatments for sickle cell disease and other blood disorders. This new program will build upon the expertise, resources, and infrastructure of the ongoing NHLBI Progenitor Cell Biology Consortium, and it will encourage collaboration with two other Institute initiatives—Production Assistance for Cellular Therapies and the Gene Therapy Resource Program, which is slated for renewal in fiscal year 2012.

A major initiative planned for fiscal year 2012, Consortium of Lung Repair and Regeneration: Building the Foundation, will establish an interactive group of multidisciplinary teams to formulate and test innovative hypotheses about the mechanisms that control lung repair and regeneration. The program will seek to leverage innovative technologies such as tissue engineering, biomaterials and scaffolds, induced pluripotent stem-cell technology, cell-directed therapy, and humanized animal models that are not used widely in lung-regeneration research but are being applied to investigate regeneration and repair in other organ systems.

TRANSLATIONAL MEDICINE

NHLBI continues to place strong emphasis on translating basic science findings into better diagnostic, therapeutic, and preventive approaches and fostering their use in real-world clinical practice. A number of initiatives are supporting these efforts. For example, a program called Science Moving Towards Research Translation and Therapy (SMARTT) has been launched to facilitate transition of potential new therapies for heart, lung, and blood diseases from discovery in the lab to the testing needed to establish their safety and effectiveness in people. Pre-clinical development—that is, readying products for testing in humans—is the first step in turning discoveries into cures, but the processes involved can be expensive and baffling to academic scientists. Connecting academic researchers with industry, the SMARTT program will offer help with manufacturing, pharmacology and toxicology testing, pre-clinical and early-phase clinical study design, and administrative and regulatory matters.

The Translational Research Implementation Program, or TRIP, is intended to facilitate well-designed clinical trials in heart, lung, or blood diseases to demonstrate the safety and efficacy of promising interventions that have emerged from fundamental studies. Its initial phase, which began in fiscal year 2010, supported the planning of trials; the second phase will fund the most promising of them beginning in fiscal year 2012. A second new program will provide planning grants to establish the feasibility of pivotal clinical trials with a major focus on hemoglobinopathies such as sickle cell disease and thalassemia. Another solicitation, planned for fiscal year 2012, would provide an innovative mechanism for the development of clinical trials for hemostatic and thrombotic disorders, including access to expertise in clinical trial methodology and design through existing institutional resources.

Several exceptionally promising new translational efforts in lung diseases are also under way. Research Education in Sleep and Circadian Biology is promoting the use

of innovative educational tools and programs to accelerate the transfer of recent scientific advances and health knowledge in sleep and circadian biology into clinical and public-health practice. Renewal of a solicitation titled Utilization of a Human Lung Tissue Resource for Vascular Research will advance translational efforts in lung vascular disease, using previously collected biospecimens from patients with pulmonary hypertension. An initiative slated for fiscal year 2012 would support dosing and efficacy trials of promising but untested therapies for lung diseases, including agents that have already been approved for use in treating other diseases and combinations of common drugs with low toxicities, neither of which would be likely candidates for testing by industry. Such small proof-of-concept trials are vitally important for translating basic research advances into clinical research, providing a foundation for larger efficacy trials, and advancing understanding of disease processes.

PREPARED STATEMENT OF GRIFFIN P. RODGERS, M.D., M.A.C.P.

I am pleased to present the President's fiscal year 2012 budget request for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $1,837,957,000, which is $47,272,000 more than the comparable fiscal year 2011 level. Complementing these funds is an additional $150,000,000 also available in fiscal year 2012 from the Special Statutory Funding Program for Type 1 Diabetes Research. The NIDDK supports research on a wide range of common, chronic, costly, and consequential diseases and health problems that affect millions of Americans. These include diabetes and other endocrine and metabolic diseases; digestive and liver diseases; kidney and urologic diseases; blood diseases; obesity; and nutrition disorders.

UNCOVERING THE GENETIC AND ENVIRONMENTAL CAUSES OF DISEASE TO INFORM THERAPY AND PREVENTION

Unprecedented discoveries in genetics continue to lead the way toward the development of personalized treatments and prevention of devastating diseases and disorders. Scientists revealed that certain variants in the APOL1 gene may be responsible for the differential risk of developing kidney disease for African Americans. These variants also provide a degree of protection against African sleeping sickness, a degenerative and potentially fatal condition caused by a parasite that is endemic to Africa. This could explain why these variants are more commonly found in individuals of African descent, despite the increased risk of kidney disease they confer.

Many of the diseases within the NIDDK research mission result from the interaction between multiple genetic and environmental factors. Research on the human microbiome—the microorganisms associated with the body—has demonstrated that the composition of bacterial communities is determined mostly by their location on or in the body and varied between people. In a separate study, scientists reported that bacteria in the mouse gut contributed to changes in appetite and metabolism. Therefore, excess calorie composition and obesity may be affected by these bacterial populations. Researchers in The Environmental Determinants of Diabetes in Youth are using newly developed technologies to study the microbiome of children at high risk for developing type 1 diabetes and explore whether viral or bacterial-based treatments could be used to prevent or treat the disease. NIDDK will continue to capitalize on recent genetics and environment discoveries to transform prediction, prevention, diagnosis, and treatment of diseases within the Institute's mission.

IMPROVING PATIENT CARE THROUGH RESEARCH

Obesity is a major health epidemic in the United States, and it increases the risk for type 2 diabetes; kidney, heart, and liver disease; and other health issues. Therefore, efforts to curb this rising trend are vitally important. The NIDDK's HEALTHY study revealed that while a middle school-based intervention did not reduce obesity school-wide, it lowered the obesity rate in students with the highest risk for type 2 diabetes. This important result will inform future school-based efforts to reduce overweight and obesity in children. Research also shows that weight loss can improve the health of people with diabetes. NIDDK's Look AHEAD study showed that weight loss in overweight and obese people with type 2 diabetes can lead, with lower medication requirements, to long-term favorable effects on diabetes control and cardiovascular risk factors.

NIDDK continues to support efforts to test potential treatments for NIDDK-related diseases and disorders. Investigators demonstrated in a preliminary trial that

salsalate, an anti-inflammatory drug used for years to manage arthritis pain, can help people with type 2 diabetes control blood glucose levels. If the expanded trial is successful, it could lead to a safe and inexpensive way to treat the disease. Nonalcoholic steatohepatitis (NASH) is a form of fatty liver disease associated with overweight and can lead to liver cirrhosis and liver failure requiring a transplant. Currently, there are no specific, FDA-approved treatments for NASH. NIDDK scientists compared vitamin E, the insulin-sensitizing drug pioglitazone, and placebo for treatment of adult NASH, and reported promising improvements in response to 2-year therapy, especially for vitamin E.

It is important to compare available, effective treatments and combine this knowledge with a patient's history to identify the best option for treating an individual. A recent NIDDK study demonstrated that, on average, a lower blood pressure goal was no better than the standard goal at slowing progression of kidney disease among African Americans who had chronic kidney disease resulting from high blood pressure. However, the lower blood pressure goal did benefit patients who had protein in their urine, a sign of kidney damage. In light of the APOL1 results I described earlier, this and other findings suggest that genetic traits more common in African Americans may subtly alter the pathogenesis of kidney disease in this population, and new classes of drugs that target these pathways might be more effective in preventing the onset and progression of chronic kidney disease in these patients.

Millions of American women suffer from stress urinary incontinence, an underdiagnosed public health problem that is associated with diminished quality of life. An NIDDK trial demonstrated that two different surgical approaches were equally effective—although they had different side effects—in treatment for stress urinary incontinence, a major milestone in treatment for this condition. This information will enable women and their doctors to weigh more accurately the benefits and risks of available treatment options. In concert with identifying the best treatment options, NIDDK research aims to ensure that patients are able to take advantage of these results to improve their health and care.

DISSEMINATING RESEARCH RESULTS TO IMPROVE PUBLIC HEALTH

It is critical that the results of research reach the American public quickly and clearly to translate to real improvements in health. NIDDK supports a number of public health campaigns such as the National Kidney Disease Education Program, the Weight-control Information Network, a Celiac Disease Awareness Campaign, and the National Diabetes Education Program (NDEP).

Diabetes continues to be a growing worldwide public health concern; rising rates of obesity and an aging populance are driving the increasing prevalence of type 2 diabetes. There is hope, however: research has shown that it is possible to delay—or even prevent—the disease. The NIDDK's landmark Diabetes Prevention Program (DPP) was a tremendous success, demonstrating that loss of 5–7 percent of an individual's body weight—or treatment with the drug metformin—can delay type 2 diabetes. By eating less fat and fewer calories and doing moderate exercise, such as brisk walking, DPP participants were able to lose body weight and maintain the loss. These lifestyle changes worked particularly well for participants age 60 and older, and were equally effective for all participating ethnic groups and for both men and women.

To transfer the lessons of the DPP to the community level, NIDDK supports translational research, which included a trial of less costly delivery of the DPP intervention in YMCAs in group settings. The results have led CDC and private organizations to fund the intervention at more Ys and United Health Group to cover the cost for plan participants to use the intervention at Ys. Additionally, the NDEP is disseminating the good news from the DPP follow-up study that development of type 2 diabetes continued to be reduced 10 years after the intensive lifestyle change or treatment with metformin. NDEP has partnered with NIH's Office of Research on Women's Health to also raise awareness of the increased risk of type 2 diabetes for women who have a history of gestational diabetes.

GENERATING RESEARCH OPPORTUNITIES

The future of public health depends critically on the development of the next generation of scientists and the pursuit of scientific opportunities. NIDDK continues to vigorously support new investigators, and training and mentorship in biomedical research. NIDDK held its second annual New Investigators' meeting to enhance their ongoing research and spur future success. NIDDK also held its eighth annual workshop for the Network of Minority Research Investigators to encourage and facilitate participation of members of underrepresented racial and ethnic minority groups in the conduct of biomedical research in NIDDK-relevant fields. These new investiga-

tors will be poised to take advantage of a wealth of opportunities to improve the health of Americans; such opportunities have been identified by a number of recent strategic planning efforts undertaken by the NIDDK.

The development and application of new technologies will also improve patient care. Through support for small business innovation research grants and other efforts, NIDDK will foster cutting-edge research in this area. New technologies could facilitate analysis of organs, tissues and biological molecules, and, with mobile communication, help convey critical information quickly to patients and healthcare providers. This research would enhance our ability to monitor disease progression or how a therapy is working and would improve diagnosis of disease or risk, to enable earlier intervention.

In closing, Mr. Chairman, NIDDK will continue to emphasize my guiding principles: support a robust portfolio of investigator-initiated research; vigorously support clinical trials to identify better ways to prevent and treat disease; preserve a stable pool of new investigators; disseminate science-based knowledge from research through education programs; and foster research training and mentoring.

Thank you Mr. Chairman and members of the Committee for the opportunity to share with you a few highlights of NIDDK's research and outreach efforts to improve the health of Americans. I will be pleased to answer any questions you may have.

PREPARED STATEMENT OF ANTHONY S. FAUCI, M.D.

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $4,915,970,000, which is $144,100,000 more than the comparable fiscal year 2011 level of $4,771,870,000.

NIAID conducts and supports biomedical research to understand, treat, and prevent infectious and immune-mediated diseases, including HIV/AIDS; tuberculosis; malaria; influenza; emerging and re-emerging infectious diseases; asthma and allergies; autoimmune diseases; and the rejection of transplanted organs. NIAID makes a major investment in translational research, which seeks to accelerate the findings from basic research into healthcare practice. This decades-long commitment, together with NIAID's multidisciplinary collaborations with experienced as well as new investigators at academic centers, the private sector, and other governmental and non-governmental partners, continues to help improve domestic and global health through the development of diagnostics, therapeutics, and vaccines for infectious and immune-mediated diseases. I appreciate the opportunity to highlight just a few of our research successes and to describe some of our most promising research programs aimed at improving public health and quality of life.

GLOBAL HEALTH

NIAID has been a leader in both basic and clinical HIV/AIDS research ever since the disease emerged as a devastating public health crisis 30 years ago. In 2010, NIAID support for HIV/AIDS research resulted in landmark scientific advances in HIV prevention. The NIAID-supported iPrEx study demonstrated that a daily dose of an oral antiretroviral medication, a strategy known as pre-exposure prophylaxis or PrEP, was effective at reducing the risk of HIV acquisition among men who have sex with men. This finding was selected by the prestigious journal The Lancet as one of the top six medical discoveries in the world in 2010 and was named by Time magazine as the number one medical breakthrough in 2010. A second important study, and another of The Lancet's selections, CAPRISA 004, showed that a vaginal microbicide gel of an antiretroviral drug could give women a measure of protection against HIV infection. This important trial was funded by the U.S. Agency for International Development and carried out using a research infrastructure developed with NIAID support. In the area of HIV vaccine development, researchers in NIAID's intramural Vaccine Research Center and NIAID-funded extramural investigators discovered human antibodies that can block a wide range of HIV strains from infecting human cells in the laboratory and are now zeroing in on their precise mechanisms of action. Coupled with last year's success from the RV 144 HIV vaccine clinical trial conducted in Thailand, which found a "prime-boost" vaccine candidate to be safe and modestly effective in preventing HIV infection, NIAID is making important strides in developing a robust package of prevention modalities that can be used in combination. In addition, research supported under NIAID's new initiative, the Martin Delaney Collaboratory: Towards an HIV Cure, will provide insights into how HIV hiding places in the body—so-called "reservoirs"—are formed,

where they are located, how they are maintained despite effective antiretroviral therapy, and how they might be eliminated.

NIAID makes a significant investment in research on the co-infections and co-morbidities that often accompany HIV infection. Tuberculosis (TB) occurs in about one-third of HIV-infected individuals and is the leading cause of death in this group. The NIAID-sponsored CAMELIA study demonstrated that survival of untreated HIV-infected adults with weak immune systems and newly diagnosed TB can be prolonged by starting antiretroviral therapy 2 weeks after beginning TB treatment, rather than waiting the standard 8 weeks. This finding will help to optimize treatment strategies for people co-infected with HIV and TB and promises to save many lives in the developing world. A significant number of adults at risk for HIV infection are also at risk for hepatitis B and C infection. NIAID supports a robust research program to understand the pathogenesis of and immune response to hepatitis viruses and to develop novel therapeutics and vaccines against the diseases caused by these viruses.

In 2009, there were approximately 9.4 million TB cases and 1.7 million TB deaths globally according to the World Health Organization (WHO). NIAID has accelerated its TB research activities and is applying 21st century technology to a field that has lagged behind the study of other infectious diseases. NIAID supports the development of several promising TB vaccine candidates, and basic and clinical research has contributed to both new and repurposed therapeutic approaches and candidates. With NIAID support, researchers also have developed a tool for diagnosing TB that provides more specific, sensitive, and rapid results than currently available diagnostics.

In 2009, approximately 225 million cases of malaria resulted in more than 780,000 deaths, 90 percent of which occurred in Africa, according to WHO. More than a decade has passed since the newest class of antimalarial drugs, artemisinins, entered widespread use worldwide; unfortunately, malaria parasites are becoming increasingly resistant to these medications. There is a pressing need for new malaria therapies due to the constant threat of the emergence of drug resistance, which NIAID is addressing by supporting domestic and international research. For example, NIAID-supported researchers identified NITD609 as a promising antimalarial drug with a mode of action that differs from the current drugs used to treat malaria. NIAID-supported scientists also discovered a novel metabolic pathway of the malaria parasite Plasmodium falciparum that could lead to new drug targets. In 2010, NIAID established ten International Centers of Excellence for Malaria Research in malaria-endemic regions. In addition to research on HIV/AIDS, TB, and malaria, NIAID supports research devoted to better understanding, preventing, and treating other important diseases that cause a significant burden of illness and death globally, including neglected tropical diseases such as lymphatic filariasis, trachoma, and leishmaniasis.

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

NIAID continues its critical focus on advancing drugs, vaccines, and diagnostics from concept to product development to fight emerging and re-emerging infectious diseases. In response to the 2009 H1N1 influenza pandemic, NIAID played a key role in developing and testing the 2009 H1N1 influenza vaccines, and in assessing their safety and potential effectiveness in a variety of populations. NIAID researchers also made important strides in the development of broadly protective influenza vaccines. NIH intramural researchers in the Vaccine Research Center demonstrated that a "prime-boost" vaccine strategy could protect animals from infection with multiple strains of influenza. NIAID-supported scientists also determined that individuals infected with pandemic 2009 H1N1 influenza generated antibodies that neutralized many different influenza virus strains. This adds to the evidence base that a universal influenza vaccine may be possible, which would obviate the need to modify the influenza vaccine each season. NIAID-supported investigators also showed that vaccinating children against influenza protects the wider community, underscoring the public health importance of widespread vaccination with current and improved vaccines. The Lancet chose this study as its top scientific advance of 2010.

Building on the experience and challenges of the 2009 H1N1 influenza pandemic, the Department of Health and Human Services conducted a review of the Federal Government's efforts to develop medical countermeasures (MCMs) such as drugs and vaccines for public health emergencies, including bioterror attacks, culminating in a new vision for MCM development. As part of this vision, NIAID—in coordination with the Biomedical Advanced Research and Development Authority and the Department of Defense—will lead the Concept Acceleration Program to stimulate

the translation of new scientific concepts and discoveries to the development of MCMs for biodefense and emerging infectious diseases.

The dengue epidemic in Puerto Rico and dengue cases in Florida and Hawaii, as well as the cholera outbreak in earthquake-ravaged Haiti, demonstrate the importance of understanding the factors that contribute to disease emergence and re-emergence. NIAID dengue research includes basic research, vector biology, translational research, as well as the development of research tools, resources, and services. With NIAID support, scientists are developing several vaccine approaches for dengue. NIAID research on cholera spans basic research, genomics, studies of environmental and climactic factors, and the development of vaccines and therapeutics. An NIAID-supported study pinpointed the genetic lineage of the cholera microbe that is causing the epidemic in Haiti.

NIAID continues to support a robust basic, translational, and clinical research portfolio to address the public health issue of antibiotic resistance for key pathogens, including methicillin-resistant Staphylococcus aureus (MRSA) and Gram-negative bacteria. For example, NIAID scientists recently identified a toxin from a community-acquired strain of MRSA that could be a factor in the severity of MRSA infections. NIAID also supports research to preserve the effectiveness of currently used antibiotics, including studies to examine optimal treatment of community-acquired pneumonia and infections caused by Gram-negative bacteria such as Pseudomonas and Acinetobacter. NIAID-supported researchers settled a medical controversy by recently showing that antibiotics clearly reduce the severity and duration of acute middle-ear infections in toddlers that were diagnosed using consistent criteria.

IMMUNE-MEDIATED DISORDERS

NIAID is committed to furthering our understanding of the immunologic mechanisms underlying autoimmune diseases, asthma and allergic diseases, rejection of transplanted organs, and other immune-mediated disorders; and to translating this knowledge into new approaches for diagnosis, prevention, and treatment. In 2010, an NIAID-sponsored expert panel produced much-needed comprehensive guidelines for medical practitioners for the diagnosis and management of food allergy that will be helpful to clinicians across a range of medical specialties. NIAID also launched the Human Immunology Project Consortium to better understand the human immune system and how it reacts to infection or vaccination. The information gained from this effort will provide insights into the development of safer and more effective vaccines, including those for young children and the elderly. In addition, researchers in the NIAID Immune Tolerance Network demonstrated that Rituxan® is a safe and effective therapy for two forms of severe vasculitis, a rare and devastating disease of the blood vessels. These data were instrumental in the recent Food and Drug Administration-approval of Rituxan® for this indication, representing the first licensed treatment for this disorder in 40 years. Also, the NIAID Inner-City Asthma Consortium determined that the addition of Xolair® to NIH guidelines-based asthma therapy for young children and adolescents resulted in fewer asthma symptoms and severe asthma attacks.

CONCLUSION

For more than 60 years, NIAID has conducted and supported basic and clinical research on infectious and immune-mediated diseases leading to the development of vaccines, therapeutics, and diagnostics that have significantly improved the health and saved the lives of millions around the world. NIAID will continue to support the highest quality research with the aim of translating fundamental discoveries into improved public health.

PREPARED STATEMENT OF JOSEPHINE P. BRIGGS, M.D., DIRECTOR, NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health. The fiscal year 2012 budget includes $131,002,000, which is $3,399,000 more than the comparable fiscal year 2011 appropriation of $127,603,000.

The National Center for Complementary and Alternative Medicine (NCCAM) is the Federal Government's lead agency for scientific research on complementary and alternative medicine (CAM). CAM includes a group of diverse medical and healthcare interventions, practices, products, or disciplines that are not generally

considered part of conventional medicine (sometimes called Western or allopathic medicine). The boundaries between CAM and conventional medicine are not absolute; instead, they are constantly evolving: interventions such as hospice care or relaxation and breathing techniques in childbirth that were once considered unconventional are now widely accepted. Furthermore, there is growing interest in more integrative approaches that use both CAM and conventional interventions. For example, both the Departments of Defense [1] and Veterans Affairs are integrating select CAM modalities into treatments for pain, stress, and sleep disorders.

CAM is used by many in the United States, both in treating health problems and in promoting better health and well-being. Data from the 2007 National Health Interview Survey [2] (NHIS), developed under NCCAM leadership in collaboration with the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC), show that nearly 40 percent of adult Americans and 12 percent of children are using some form of CAM. The data also show that in 2007 out-of-pocket expenditures for CAM totaled $33.9 billion. While this amount accounted for only 1.5 percent of total healthcare expenditures, it was more than 11 percent of out-of-pocket expenditures. Finally, NHIS data indicate that a large portion of CAM use is best described as "self-care" in that it occurs outside of the framework of a relationship with a healthcare professional. The scope, associated costs, and self-care nature of CAM use in the United States reinforce the need to develop reliable, objective scientific evidence concerning the usefulness and safety—or lack thereof—of CAM interventions, and to ensure the public has access to accurate and timely evidence-based information.

NCCAM is shaping its research directions through our third strategic plan, which was developed with considerable input from our diverse stakeholder community and released in February 2011. The strategic plan, Exploring the Science of Complementary and Alternative Medicine (available at www.nccam.nih.gov), was built around three long-range goals aimed at improving the state and use of scientific evidence regarding the two major reasons for use of CAM in the United States—treating health problems and supporting or promoting better health and well-being. The three goals are to (1) advance the science and practice of symptom management; (2) develop effective, practical, personalized strategies for promoting health and well-being; and (3) enable better evidence-based decisionmaking regarding CAM use and its integration into healthcare and health promotion.

PAIN AND SYMPTOM MANGEMENT

CAM approaches, as treatments for health problems, are used most often to manage symptoms such back or neck pain, arthritic or other musculoskeletal pain, headache, and insomnia. These are all difficult problems and there is broad agreement that existing options are less than fully satisfactory for many patients. For example, chronic back pain is, by far, the most frequent health problem for which Americans turn to CAM. They might try CAM approaches after exhausting other options such as opioids, injections, surgery, or physical therapy. More often, however, they pursue CAM treatment options, including spinal manipulation, yoga, acupuncture, and massage, in conjunction with conventional approaches. Individuals suffering from chronic pain conditions, their healthcare providers, and health policymakers all need better evidence regarding the value and safety of these complementary and integrative approaches in alleviating pain, and in improving quality of life.

To address this critical need, NCCAM is intensifying its focus on determining whether and how CAM interventions add value to existing approaches and on understanding their biological mechanisms. In order to advance the science and practice of symptom management, NCCAM plans to support Centers of Excellence for Research on CAM for Pain in fiscal year 2011. NCCAM is also working with our colleagues at the Department of Defense to explore ways that CAM mind and body approaches can be used in integrative approaches to treat pain, stress disorders, and other symptoms. For example, we recently sponsored a joint workshop on acupuncture for the treatment of acute pain. We are also investigating potential collaborations with the Department of Veterans Affairs to advance CAM research and to maximize our investments in bringing relief to our wounded warriors.

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[1] Pain Management Task Force Final Report: *Providing a Standardized DOD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and Their Families*, Office of the Army Surgeon General, Department of Defense, May 2010.

[2] Nahin RL, Barnes PM, Stussman BA, et al. *Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007*. CDC National Health Statistics Report #18. 2009.

STRATEGIES FOR PROMOTING HEALTH AND WELL-BEING

It is generally accepted and well established that sustaining healthy behaviors (e.g., good eating habits and regular physical exercise) and modifying unhealthy behaviors (e.g., smoking) reduce risks of major chronic diseases. Many CAM and integrative medicine practitioners and disciplines employ various interventions (e.g., meditation or yoga) to help motivate people to adopt and sustain health-seeking behaviors, or to encourage dietary practices (sometimes grounded in traditional medical systems) that incorporate a healthy food philosophy. Newly emerging evidence suggests that CAM use may be associated with greater degrees of health-seeking behavior. While causal relationships between CAM use and healthy behavior have not been established, the claims and preliminary data deserve investigation given the formidable public health challenges in motivating behavior change. Research is needed to explore, clarify, and examine the hypothesis that certain CAM approaches or practices can, in fact, be useful in encouraging better self-care, an improved personal sense of well-being, and a greater commitment to a healthy lifestyle.

CAM RESEARCH CHALLENGES

Given the scope and self-care nature of CAM use by Americans, NCCAM remains committed to supporting rigorous research that will address the need for scientific evidence to help the public and their healthcare providers make better-informed decisions about CAM use. For example, herbal medicines, dietary supplements, and other CAM natural products are readily available to and purchased by consumers, but evidence regarding usefulness of many does not exist. In addition, some people believe that herbal medicines, dietary supplements, and other CAM natural products are inherently healthier or safer than drugs. In fact, there are ongoing concerns about safety, including the presence of contaminants or adulterants (e.g., conventional drugs) in some CAM natural products, and the potential of toxic interactions with drugs or other natural products.

Clinical research to address these needs will remain a cornerstone of the CAM research enterprise, but these studies are complex, expensive, and time-consuming. NCCAM's strategic approach is to ensure that clinical trials of CAM natural products are based on a scientifically sound hypotheses and methods that are grounded in basic mechanistic and translational research. This foundation facilitates design of maximally informative clinical trials that include measures of biological effect relevant to the hypothesis (e.g., biomarkers or surrogate markers), as well as measures of clinical outcomes.

Investigators studying mind and body interventions face other scientific challenges in designing rigorous research that will address the questions of greatest importance to consumers, providers, and healthcare policymakers. These include identifying relevant study endpoints and defining appropriate experimental designs to test interventions. To address such challenges, NCCAM recently collaborated with several NIH ICs to sponsor a workshop on control and comparison groups for studies of non-pharmacological interventions.[3]

CONCLUSION

As established in its third strategic plan, NCCAM is focusing the Center's efforts and resources on two compelling areas of public health need: better strategies for managing symptoms such as chronic pain, and better strategies for promoting health and well-being. In both areas there exist promising scientific opportunities for research on CAM interventions to contribute to real and meaningful progress in addressing common and vexing individual and social problems, and in developing more integrative approaches to healthcare and the support of healthy behaviors and lifestyles.

Finally, NCCAM's plan looks to a vision in which scientific evidence informs decisionmaking by the public, by healthcare professionals, and by health policymakers regarding CAM use. NCCAM will continue its multi-pronged efforts to provide world-class information about the safety and usefulness of CAM interventions to consumers, and to foster dialogue about CAM use between patients and their healthcare providers. In addition, a new online resource, tailored to the needs of healthcare professionals, is being launched on the NCCAM website. It includes information on the safety and efficacy of a range of CAM practices, and was developed in response to providers' needs for an evidence-based, one-stop resource to help answer their patients' questions on CAM.

[3] NCCAM Workshop on Control/Comparison Groups for Trials of Non-Pharmacologic Interventions, April 26, 2010.

PREPARED STATEMENT OF BARBARA M. ALVING, M.D., DIRECTOR, NATIONAL CENTER FOR RESEARCH RESOURCES

Mr. Chairman and Members of the Committee: It is a privilege to present to you the President's budget request for the National Center for Research Resources (NCRR) programs for fiscal year 2012. The fiscal year 2012 budget of $1,297,900,000 includes an increase of $41,225,000 over the comparable fiscal year 2011 level of $1,256,675,000. Funding priorities for fiscal year 2012 include the continued support and refinement of the Clinical and Translational Science Award program, which will reach its targeted number of 60 consortium members later this year. Funds will also sustain the range of activities supported by the Center's other major programs, including the Research Centers in Minority Institutions, the Institutional Development Awards, the National Primate Research Centers, and the Biomedical Technology Research Centers.

By uniting innovative research teams with the power of shared resources across the Nation, NCRR programs provide laboratory scientists and clinical researchers with the tools and training they need to understand, detect, treat, and prevent a wide range of diseases through clinical and translational research. NCRR's diverse yet interconnected NCRR programs enable the research of more than 30,000 NIH-funded investigators nationwide by providing the resources, tools, and networking connections.

This statement is submitted with the recognition of a publically announced proposal for reorganization that would result in dissolution of NCRR and the transfer of programs to other NIH ICs and Offices.

BUILDING CLINICAL AND TRANSLATIONAL RESEARCH CAPABILITIES

NCRR's Clinical and Translational Science Award (CTSA) program is transforming biomedical research by building national clinical and translational research capacity to speed the translation of laboratory discoveries into better treatments for patients. Launched in 2006, the CTSA program is a national clinical and translational research consortium which now includes 55 medical research institutions in 28 States and the District of Columbia. The consortium supports research by disseminating clinical research informatics tools, forging new partnerships with healthcare organizations, and expanding outreach to minority and medically underserved communities. The first cohort of CTSAs, now re-competing for their next 5 years of funding, have pushed scientific discoveries toward novel and promising treatments that enable healthcare reform and more cost-effective treatments. For instance, research conducted at the University of California, San Francisco's CTSA found that reducing salt intake by just a half teaspoon per day could help Americans significantly improve their heart health, reduce a number of heart-related deaths and potentially save millions in healthcare costs. The findings influenced the Food and Drug Administration's decision to limit the amount of salt in prepared foods and helped support the CDC's salt reduction campaign.

Importantly, the CTSA consortium serves as a communications hub that ensures sharing among sites and accelerates adoption of best practices for clinical and translational research. The CTSAs are building biomedical research capability by generating new tools and resources, such as ResearchMatch.org, a Web-based national recruitment registry which matches volunteers with clinical studies seeking participants, and the CTSA Pharmaceutical Assets Portal, a public-private collaboration enabling scientists to learn more about existing compounds that are not being actively developed and might be repurposed to treat other types of diseases.

ENERGIZING RESEARCH COMMUNITIES

NCRR programs support new investigators and promote new ideas through innovative networking collaborations, partnerships, training, and career development for clinical and translational scientists. Members of the Institutional Development Award (IDeA) program, which supports rural and underserved communities, developed the Network of IDeA-funded Core Laboratories (NICL) to address common challenges of NCRR-funded core laboratories. NICL addresses, develops and disseminates sustainable business models for efficient core operations and expands access to advanced core resources and expertise. Now extended to other NCRR programs, NICL supports, encourages, and facilitates resource sharing and collaboration among NCRR-funded cores and shared-resource facilities. NCRR programs are also energizing the research community with the world's first physician-scholar training program on wireless healthcare research, launched through a partnership between The Scripps Translational Science Institute (STSI) CTSA and the wireless

telecommunications company Qualcomm. STSI is positioned to become an invaluable resource for this emerging, high-impact field of research.

ADVANCING INNOVATIVE BIOMEDICAL TECHNOLOGIES

The Biomedical Technology Research Centers (BTRCs) program is producing leading edge technologies to accelerate discoveries that help researchers who are studying virtually every human disease. At the Resource for Magnetic Resonance and Optical Imaging at the University of Pennsylvania, researchers are working closely with clinicians to improve patient care by developing and promoting ready access to imaging tools with the goal of translating novel approaches for imaging blood flow through brain tissue and other organs.

NEW AND BETTER TREATMENTS THROUGH ANIMAL MODELS

The National Primate Research Center (NPRC) program advances research and knowledge in HIV and AIDS, as well as in numerous other diseases. The NPRCs have a close relationship with the CTSAs; one example is the collaboration between the New England NPRC and the Harvard CTSA. The two are jointly examining the observation that insulin resistance appears to be a predictor of dementia utilizing a monkey model of insulin resistance and an analysis of high-field MRI scans in the monkey model conducted by the Harvard CTSA investigators who have expertise with MRI in humans. NCRR continues to supply the research community with animal models and resources. Through the Link Animal Models to Human Disease Initiative (LAMHDI), a Web-based resource, investigators can identify and locate useful animal models that are essential to their research in treatments for human disease.

EXPANDING RESEARCH CAPABILITIES TO ADDRESS HUMAN HEALTH

Through the IDeA and Research Centers in Minority Institutions (RCMI) programs, biomedical research capacities across the Nation are expanding into States with historically low NIH funding and are having a direct impact on human health. One example is from the National Center for Genome Resources in New Mexico, home of the DNA sequencing and bioinformatics core for the New Mexico IDeA Networks of Biomedical Research Excellence (INBRE). Scientists used innovative whole-genome sequencing and expression analyses to study Multiple Sclerosis (MS) in identical twins resulting in the first published genome sequences of female twins or individuals with autoimmune disease. It is also the first systematic comparison of genomes in identical twins, including epigenetic markers and expression profiles. Another study from the New Mexico INBRE used next-generation sequencing methods to develop a pre-conception genetic test for 500+ mutations known to increase the risk of numerous rare diseases in children of carriers.

Another illustrative example is a pilot study, initiated by the RCMI Translational Research Network, to study the effect of Vitamin D on cardiovascular disease risk factors in African Americans. This study is important because racial/ethnic minorities, especially African Americans, continue to suffer a disproportionate burden of cardiovascular disease. African Americans also tend to have low levels of Vitamin D and these low levels have been associated with cardiovascular disease risk. Supplementation with Vitamin D may be an accessible and affordable intervention.

PROVIDING A CATALYST FOR RESEARCH COLLABORATION

Grantee institutions are adopting research networking tools as a step toward national networking of people, resources, and data on the web. The VIVO project, which is an initiative to enable national networking of scientists and resource discovery, is driving the network with availability of linked open data about scientists and their work. The potential will be realized through their commitment to publish data on the web so the information is more easily discoverable and connections with other open linked data can be made. VIVO is an open source semantic web application linking information automatically from institutional and public systems of record to provide detailed profiles of scholars and researchers. The power of this semantic web approach is the ability for creative visualization of connections not previously possible between diverse types of information and data.

This brief overview of NCRR's programs demonstrates our continuing commitment to accelerating clinical and translational research. NCRR will continue to advance research through partnerships among its programs, other Institutes and Centers at the NIH, and with other Federal and non-Federal agencies to advance training and translational research opportunities.

PREPARED STATEMENT OF PAUL A. SIEVING, M.D., PH.D., DIRECTOR, NATIONAL EYE INSTITUTE

Mr. Chairman and Members of the Committee:I am pleased to present the President's budget request for the National Eye Institute (NEI). The fiscal year 2012 budget of $719,059,000 includes an increase of $18,832,000 over the fiscal year 2011 appropriation level of $700,227,000. 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.

TECHNOLOGIES TO ACCELERATE DISCOVERY

The causes of common diseases are complex in that there are potentially many different environmental factors and genetic variants that can contribute to disease. New technologies such as genome-wide association studies (GWAS) allow investigators to scan the genomes of patients to identify genetic risk variants for common diseases. Individually, each of these variants may only contribute to a small percentage of cases, so GWAS require many subjects to identify low frequency risk variants. In the largest GWAS study in vision research to date, NEI investigators recently sequenced DNA from over 18,000 patients and control subjects and identified three new genes associated with age-related macular degeneration (AMD), the most common cause of vision loss in older Americans. Two of these genes are involved with high-density lipoprotein cholesterol metabolism, implicating a new biochemical pathway involved in the pathogenesis of AMD. These findings will allow researchers to better understand the disease mechanisms underlying AMD and develop therapies that address the root cause of vision loss. Glaucoma is another heritable blinding disease where the genetic underpinnings are poorly understood. The NEI Glaucoma Human Genetics Collaboration, a consortium of clinicians and geneticists at 12 institutions throughout the United States dedicated to identifying the genetic factors associated with glaucoma is conducting a large-scale GWAS that involves scanning 5,000 DNA samples. The consortium is using state-of-the-science technology to sequence the exome, the full complement of protein coding regions in the human genome, in a subset of patients. The data from these DNA samples are expected to be available to the vision research community in 2011.

TRANSLATIONAL SCIENCES AND THERAPEUTICS DEVELOPMENT

Positive results of ongoing, pioneering clinical trials of gene therapy for Leber congenital amaurosis, a severe, early onset retinal disease, have encouraged applications of this approach to many other eye diseases. In the past year, NEI investigators demonstrated proof-of-concept of gene therapy using animal models of AMD, achromatopsia, Leber's hereditary optic neuropathy, retinitis pigmentosa, and red-green color blindness. Previous work with animal models established the utility of gene therapy in juvenile retinoschisis, optic neuritis, and Stargardt disease. These studies now allow investigators to conduct the pre-clinical work necessary to pursue regulatory approval for clinical trials. In addition, novel gene delivery systems, such as the use of nanoparticles, have shown promise in animal models. Such vectors will be helpful in expanding the reach of gene therapy to target a variety of ocular tissues such as retinal ganglion cells and the light-sensitive photoreceptor cells.

ENHANCEMENT OF EVIDENCE-BASE FOR HEALTH CARE DECISIONS

For treating the blinding ("wet") form of advanced AMD, monthly ocular injections of a drug, Lucentis, was approved in 2007 by the FDA. This was the first effective treatment that not only stopped progression of the disease, but also improved vision for many patients. Lucentis blocks formation of new, but abnormal blood vessels that leak fluid into the central part of the retina that is responsible for keen vision. It was developed from another inhibitor of blood vessels, Avastin, which since its approval in 2004, has been used to block new vessels that form to nourish growth of some cancers. Even before final FDA approval of Lucentis, ophthalmologists began using Avastin "off-label" for treating AMD, and today, most AMD patients receive Avastin. Given the lack of data regarding the effectiveness of Avastin for AMD treatment, in 2007, the NEI had an obligation to patients and clinicians to compare the two drugs and to evaluate whether the drugs could be used less frequently as needed—called PRN—rather than monthly as originally approved for Lucentis. Visual acuity improvement was virtually identical (within one letter difference on an eye chart) for either drug when given monthly. When each drug was given PRN, there also was no difference between drugs. For PRN dosing, patients required four to five fewer injections per year compared to monthly treatment and still had substantial gains in vision.

Lucentis was also studied in a comparative effectiveness trial for diabetic macular edema (DME), a common sight-threatening complication of diabetes in which fluid from leaky blood vessels causes the retina to swell. For the past 25 years, DME has been treated with a laser to destroy abnormal blood vessels. Although laser therapy slows disease progression, the effects are temporary, and repeated treatments can damage healthy retinal tissue and impair vision. In recent years, ophthalmologists have been supplementing laser treatment with ocular injections of either Lucentis, a drug that prevents blood vessel growth, or triamcinolone, a corticosteroid to reduce inflammatory complications. An ongoing clinical trial comparing the safety and efficacy of these two drugs is being conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), a public-private partnership funded by NEI, the Type 1 Diabetes Funding Program, and industry collaborators. After 1 year, Lucentis plus laser treatment was superior in both safety and efficacy compared to triamcinolone plus laser or to laser alone. This landmark clinical trial identified the first new safe and effective treatment regimen for DME in more than two decades. In addition, the study demonstrated that intravitreal triamcinolone, which had been used in 60 percent of patients with DME, had significant side effects (cataract and glaucoma) and was not better than laser alone. These results are already being used by community ophthalmologists to greatly improve the vision and quality of life for people living with diabetes.

Treatment of cataracts in infants is challenging for pediatric ophthalmologists and parents. Replacing the opaque lens with an artificial lens is critical to prevent permanent loss of vision in the eye. After removing the cataract, contact lenses have been the preferred method to overcome the loss of the natural lens. However, it is difficult and stressful for parents to insert a contact lens into an infant's eye. Removing the cataract and surgically implanting a transparent intraocular lens (IOL) in adults is common but had not been fully characterized in infants. An NEI-supported clinical trial found no difference in visual acuity with contact lenses compared to IOLs 1 year after cataract removal. However, IOLs caused significant numbers of surgical complications. Based on these results, the use of contact lenses is considered the safest effective treatment for infants with cataract.

NEW INVESTIGATORS, NEW IDEAS

The increasingly quantitative nature of the biomedical sciences and the explosive growth of genomic, transcriptomic, proteomic, metabolomic, neurophysiological and clinical data require that investigators work at the interface of biology and computational sciences. The NEI is committed to developing the next generation of vision researchers and has expanded its institutional training grant program with a program in ocular statistical genetics at several universities. This program will partner researchers with expertise in mathematics, modeling, and computation, fields that are not usually affiliated with ocular research, with researchers in all areas of vision science to provide state-of-the-art training for a new breed of researchers.

PREPARED STATEMENT OF ERIC D. GREEN, M.D., PH.D., DIRECTOR, NATIONAL HUMAN GENOME RESEARCH INSTITUTE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for the National Human Genome Research Institute (NHGRI). The proposed fiscal year 2012 budget is $524,807,000, an increase of $13,749,000 from the comparable fiscal year 2011 level of $511,058,000.

This is an exciting time for biomedical research in general and for genomics research in particular. NHGRI investments in the development of genomic technologies and their application are generating innovative and powerful approaches to address a diverse array of biological and biomedical questions. In early 2011, after 2-plus years of rigorous consultation and planning, NHGRI published a new strategic plan for the field of genomics in the premiere scientific journal Nature. This comprehensive strategic vision describes the next key steps in the herculean journey to decipher the secrets within our genetic code and to use those discoveries to empower health practitioners and patients in a fashion that leads to improved human health. The strategic plan also challenges the broader biomedical community to anticipate the scientific and non-scientific achievements that will be necessary to implement cost-effective and accessible genomics-based medical care (i.e., genomic medicine).

ENABLING RESEARCH

Basic research lays the foundation for understanding the functional features within our genome and how disruptions in them can lead to disease. In fact, the knowledge gained from basic genomic investigations enables scientists and clinical investigators from other disciplines to pursue translational research programs to understand particular biological pathways or address disease-specific questions. The ENCyclopedia of DNA Elements (ENCODE) project and the related model organism ENCODE (modENCODE) project are moving forward effectively toward their goals of finding all the functional elements in the human genome, as well as in the genomes of organisms that serve as important models for human biology.

To stimulate and accelerate multi-disciplinary research, NHGRI has funded several Centers of Excellence in Genomic Science (CEGS). In addition to pursuing cutting-edge genomics research questions, these centers are associated with rigorous training programs that focus on groups under-represented in biomedical research. Such efforts aim to reinvigorate the biomedical research community by engaging diverse expertise and fostering the development of versatile young scientists.

The unprecedented decreases in the cost of DNA sequencing resulting from the NHGRI-stimulated technology development efforts are moving us steadily closer to the reality of using genome sequencing as a routine part of clinical care. However, even with the three-to-four orders-of-magnitude drop in DNA sequencing costs that has occurred, sequencing an entire human genome remains too expensive for the kind of human research studies needed to dissect the small genetic differences between individuals that contribute to increased risk for common diseases, such as cancer, heart disease, and asthma, because such work often requires the study of thousands or tens of thousands of individuals. To this end, NHGRI continues to push forward technology-development initiatives, such as the $1,000 Genome program, to develop novel and even more cost-effective DNA sequencing methods. Concurrently, the NHGRI-funded large-scale sequencing centers continue to use innovative approaches for improving available DNA sequencing technologies. These efforts are projected to result in a substantial drop in the cost of generating a human genome sequence—to less than $25,000 by the end of fiscal year 2011 and less than or equal to $15,000 by the end of fiscal year 2012.

To develop an appropriately broad catalog of information about the variation within the genomes of different individuals across the world, NHGRI continues to contribute substantially to the international 1000 Genomes Project. In addition, on behalf of NIH, NHGRI led the effort to launch a research partnership with the Wellcome Trust, called the Human Heredity and Health in Africa (H^3Africa) Initiative. This new effort seeks to stimulate research within African laboratories to enable leading-edge genomic studies to be conducted across the continent. The knowledge gained through a deeper understanding of genomic variation in African populations will not only lead to improved abilities to study genetic diseases in those populations, but will enhance our understanding of the complex interplay between environmental and genetic factors that influence disease susceptibility and drug responses in many diverse populations.

BUILDING A FRAMEWORK FOR TRANSLATION

Building on the tools and knowledge created by these and other basic research programs, the joint NHGRI-National Cancer Institute (NCI) project, The Cancer Genome Atlas (TCGA), is providing important new insights into some of the most vexing forms of malignancy, including brain cancer and, more recently, acute myeloid leukemia and ovarian cancer. Results from TCGA and associated cancer genomics studies by NHGRI-funded investigators point to new therapeutic targets and, as recently reported in the Journal of the American Medical Association, demonstrate the potential for more precise modes of cancer diagnosis and treatment. As a flagship program for NIH translational research activities, TCGA is expanding its efforts and will focus on an additional 20 major cancers over the next 5 years.

Beginning in fiscal year 2012, NHGRI will expand its large-scale genome sequencing and analysis portfolio to include centers that target the study of rare, single-gene (Mendelian) disorders using cutting-edge genomic technologies. Rare disease research already is benefiting from the new genomic technologies. For example, the causative genes for a pair of developmental disorders were discovered recently: Miller syndrome, which affects the development of the face and limbs, and Kabuki syndrome, which affects facial and cognitive development. These two discoveries represent the "tip of the iceberg" with respect to the identification of altered genes that result in rare diseases, as reports of such discoveries are published in the scientific literature almost weekly. Another new NHGRI initiative in fiscal year 2012 will

pilot the use of genome sequencing in clinical care settings, an important step towards implementing genomic medicine.

Complementing the genome sequencing initiatives, the NIH Therapeutics for Rare and Neglected Diseases (TRND) program, which is currently administered by NHGRI, aims to innovate and accelerate the drug development pathway for rare and neglected diseases. As the TRND pilot projects move toward their initial milestones, the first full-scale project portfolio will be launched in collaboration with external and internal partners. Likewise, the NIH Chemical Genomics Center (NCGC) continues to serve as a national resource for the generation of novel chemical "leads" to spur inventive directions in candidate drug and biological assay identification. This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences (NCATS).

EARLY OPPORTUNITIES FOR GENOMIC MEDICINE

The clinical promise of genomics requires strong foundational knowledge about the structure and biology of genomes as well as the biology of disease. Increasingly, genomics will be used to advance medical science and to improve the practice of medicine.

Cancer genomics (as previously discussed) and pharmacogenomics (or genomically guided medication prescription) are anticipated to be leading-edge examples of genomic medicine. Successes of the latter include the use of genomic information for making decisions about administering the antiretroviral drug abacavir, now the standard of care for HIV-infected patients. Other promising examples of pharmacogenomics involve the use of patient genomic information to target the application and dose of tamoxifen to treat breast cancer, clopidogrel to treat cardiovascular disease, and the blood-thinner warfarin. For cancer genomics, it is expected that genomic profiling of tumors will become increasingly routine for making decisions about treatment strategies.

Major advances in the study of common, genetically complex diseases also have been seen recently. Over the past 5 years, more than 4,000 validated associations have been made between a genomic region and a common disease (or another specific trait). Studies that identify and provide evidence to support the value-added connections between genetic factors and observed phenotype (physical traits, clinical symptoms, etc.) require substantial investments in time, funding, and resources, but are fundamental to translating genomics investments into clinical applications. One such initiative, the Electronic Medical Records and Genomics (eMERGE) Network, aims to advance the efficiency of this scientific approach. This program will enter its second phase in late fiscal year 2011, during which it will not only link patients' DNA to their electronic medical record information, but also will explore the challenges of using the information to inform clinical care in a respectful, responsible manner.

The new NHGRI strategic plan identified several critical cross-cutting elements that are integral to navigating successfully the path to genomic medicine: bioinformatics and computational biology, education and training, and the continued study of the societal implications of genomics. The major bottleneck in genome science is no longer data generation; rather, it is the computational analysis of data. Beyond the research setting, the public, and especially healthcare providers, need to become much more conversant in genomics. To help address the needs of healthcare professionals, NHGRI has launched online tools to support genetic and genomic training in health professional education programs, including bilingual case studies.

Moving forward, translating basic genomic knowledge to improve human health will continue to rely on innovative technology development, large-scale collaborative and, increasingly, multi-disciplinary efforts, and robust attention to the societal implications of genomic advances. Demonstrating utility and feasibility will be critical for widespread adoption of genomic medicine; the thresholds for defining benefit and harm will vary across stakeholders and cultural perspectives. However, overcoming the challenges that accompany such a paradigm-changing venture is within reach. The research and related programs that NHGRI will pursue over the next year will continue to lay the groundwork for an era where individualized genomic medicine will become a reality, and the original promise of the Human Genome Project will be fulfilled.

PREPARED STATEMENT OF RICHARD HODES, M.D., DIRECTOR, NATIONAL INSTITUTE ON AGING

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute on Aging (NIA) of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $1,129,987,000 which is $30,450,000 more than the comparable fiscal year 2011 appropriation of $1,099,537,000.

The National Institute on Aging leads the national effort to understand aging and to identify and develop interventions that will help older adults enjoy robust health and independence, remain physically active, and continue to make positive contributions to their families and communities. We support a comprehensive portfolio of genetic, biological, clinical, behavioral, and social research related to the aging process, healthy aging, and diseases and conditions that often increase with age. We also carry out the crucial task of training the next generation of researchers who specialize in understanding and addressing the issues of aging and old age.

Approximately 39 million people age 65 and older live in the United States, and data from the Federal Interagency Forum on Aging-Related Statistics indicate that their numbers will double within 25 years. In less than 50 years, the number of "oldest old"—people ages 85 and older—may quadruple. As record numbers of Americans reach retirement age and beyond, profound changes will occur in our economic, healthcare, and social systems.

TRANSLATIONAL SCIENCES AND THERAPEUTICS DEVELOPMENT

NIA supports a comprehensive portfolio of research that builds upon basic discovery to develop new preventive, diagnostic, and therapeutic interventions for age-related diseases and conditions. For example, investigators with the Alzheimer's Disease Neuroimaging Initiative (ADNI) have found that changes in the structure of the hippocampus, a brain area important to learning and memory, may reflect disease progression and effectiveness of potential treatments, and have established biomarker and imaging measures that may predict risk for cognitive decline and conversion to dementia. Clinical, imaging, and biological data from ADNI are available to qualified investigators around the world; over 1,700 researchers have signed up for access to the ADNI database, and global collaborations have resulted in over 170 published scientific papers since 2004.

NIA-supported research to identify Alzheimer's disease (AD) biomarkers and gain a deeper understanding of the disease's pathology and clinical course has made possible the first revision of the clinical diagnostic criteria for AD in 27 years through a joint effort of the NIA and the Alzheimer's Association. Unlike the criteria that doctors and researchers have been using since 1984, the updated guidelines cover the full spectrum of the disease as it gradually changes over many years, from the earliest preclinical stages before symptoms are apparent through mild cognitive impairment (MCI) and advanced dementia. The new guidelines also address the use of imaging and biomarkers to determine whether changes in the brain and body fluids are due to AD.

Even under the new guidelines, however, diagnosis of AD remains complex. NIA intramural investigators are working toward development of an accurate, noninvasive, inexpensive blood test for AD. Last year, they found that the amount of a protein called clusterin in the blood of AD patients reflected the severity of disease, predicted the progression of memory impairment, and may predict brain amyloid burden long before the patient develops memory problems. These findings were recently replicated by independent researchers, and research is ongoing in this promising area.

A continuing translational research success story for NIH is the ongoing development of the compound exendin-4. NIA intramural investigators originally developed exendin-4 as a treatment for type 2 diabetes, but have since found that exendin-4 may act as a neuroprotective agent in animal models, and they are now conducting a phase II/III clinical trial of the compound in patients with MCI and early AD. NIA also supports over 40 drug discovery and development projects through our AD Translational and Drug Discovery Initiative, including a number of AD pilot clinical trials.

Other NIA-supported researchers are pursuing the development of interventions that will delay disease and dysfunction and even extend lifespan. Investigators with the innovative Interventions Testing Program found that the drug rapamycin, used to help prevent rejection of transplanted organs in humans, extended life span in middle-aged mice, and more recently demonstrated that the drug exerts beneficial effects early in life. Rapamycin inhibits the mTOR pathway, which helps regulate cell growth and proliferation. Building upon these findings, in 2010 NIA began solic-

iting research to identify and characterize molecular targets within the mTOR pathway with potential to impact health span and lifespan.

NIA also partners with other agencies and organizations on translational initiatives. For example, with the Administration on Aging, NIA has established an initiative to support development of evidence-based interventions, programs, policies, practices, and tools that can be used by community-based organizations to help elderly individuals remain healthy and independent in their own homes and communities. NIA is also joining "ambassadors" from organizations interested in the health and well-being of older people to promote Go4Life, our new exercise and physical activity website (www.nia.nih.gov/Go4Life.)

TECHNOLOGIES TO ACCELERATE DISCOVERY

New GWAS (genome-wide association study) technologies are transforming our understanding of the origins of disease and disability by facilitating rapid comparisons of the full genomes of thousands of individuals. This research may lead to the identification of novel disease pathways that can be targeted to develop new treatments. In the largest GWAS ever conducted in AD research, scientists with the AD Genetics Consortium found that a previously unconfirmed gene variant, BIN 1, affects development of late-onset AD and identified four additional genetic variants significant for the disease. The genes identified by this study may implicate pathways involved in inflammation and the movement of proteins and lipids both within and between cells as being important in the disease process. In a another large GWAS, NIA intramural researchers joined an international research consortium to confirm six previously identified genes for Parkinson's disease and identify five new genes or loci (an area on the chromosome where a gene is thought to be located).

A new NIA-supported initiative is underway to develop technologies to better understand the life span and fate of cells in various tissues of aged mammals. In these studies, cells are permanently marked at a specific point in the organism's life and those marked cells are followed to determine their fate and traits over time. These studies will provide important insights into aging at the cell and tissue levels.

USING SCIENCE TO INFORM HEALTH CARE REFORM

Research that will lead to the identification of more effective and less expensive clinical interventions is a high priority for NIA, particularly through a broad portfolio of comparative effectiveness research (CER). A major CER effort has been NIA's administration, on behalf of the Agency for Health Care Research and Quality and the Office of the DHHS Secretary, of an initiative identifying ways that principles of behavioral economics could be used to encourage healthcare providers to incorporate findings from CER studies into their practices. Other ongoing CER studies include a randomized trial of behavioral economic interventions to reduce risk of cardiovascular disease; a study comparing various motivators to increase HIV screening; and a study comparing the effects of an intensive exercise program vs. stretching and range of motion exercises on ambulation in hip fracture patients.

Surprisingly little definitive evidence exists on the impact insuring the uninsured has on their health-related behaviors (including healthcare usage) and outcomes. However, NIA-supported investigators are currently taking advantage of a remarkable opportunity to develop such evidence. For a brief period in 2008, Oregon opened a waiting list for enrollment in its previously closed public health insurance program for certain low income adults, and then offered randomly selected people the opportunity to enroll. By comparing individuals who obtained health insurance through this program with otherwise eligible individuals who were not selected in the "insurance lottery," the investigators are assessing the impact of insurance on healthcare usage and health outcomes, including the differing impacts on different groups. Understanding the consequences of health insurance coverage will be central to evaluating proposals to expand or modify health insurance coverage in the United States.

Recently, NIA-supported investigators studying older populations in the United States, England, and 11 European countries found that retirement prior to age 65 was associated with a significant decline in cognitive performance. The investigators suggest that this may be in part because for many people retirement leads to a less stimulating daily environment, and the prospect of retirement reduces the incentive to engage in mentally stimulating activities on the job. It is possible (although not yet proven) that the recent trend of American workers delaying retirement may eventually lead to improved cognitive performance in this group.

NEW INVESTIGATORS, NEW IDEAS

As the American population grows older, the need for healthcare professionals who specialize in the unique needs of older individuals is becoming ever more urgent. To address this increase in demand effectively, we must foster the development of physician-scientists whose research will lead to improved care and more effective treatment options for older patients with complex medical conditions. Recently, NIA established the Grants for Early Medical/Surgical Subspecialists' Transition to Aging Research (GEMSSTAR) program to support physicians who seek to become clinician-scientists in geriatric aspects of their subspecialty. We anticipate supporting 18 to 20 emerging physician-scientists in this program.

Once again, thank you. I welcome your questions.

PREPARED STATEMENT OF ROGER I. GLASS, M.D., PH.D., DIRECTOR, FOGARTY INTERNATIONAL CENTER

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget for the Fogarty International Center (FIC). The fiscal year 2012 budget of $71,211,000 reflects an increase of $1,835,000 over the comparable fiscal year 2011 appropriation of $69,376,000.

When it comes to global health, there is no "them"—only "us."[1] In an increasingly interdependent world, the United States and nations around the globe share diseases, as well as the burden that these diseases inflict on healthy people. In fact, the interests of the American people are well-served when the United States promotes global health, as healthy nations are more likely to succeed in economic development and enjoy political stability. In addition, Americans have a strong humanitarian tradition and have long supported efforts to improve the health of people around the world. The U.S. Government (USG) has recognized these realities, and has made global health a national priority. For these investments to yield the maximum benefit however, U.S. and foreign scientists must work together to generate the scientific evidence that will inform how best to allocate resources. These researchers will contribute the necessary local expertise and knowledge to thwart pandemics and fight diseases that prevent societies from achieving their full potential. They will also empower nations to more effectively improve the health of their own populations. The Fogarty International Center plays a unique role at the National Institutes of Health (NIH) and in the USG by supporting the development of global health research expertise in the United States and abroad.

NEW INVESTIGATORS, NEW IDEAS

Research advances are more likely occur when investigators study diseases onsite to develop health interventions that are responsive to local and international priorities. Therefore, Fogarty supports long-term research and training partnerships between United States and low- and middle-income country (LMIC) research institutions, which has resulted in the training of more than 5,000 researchers—many of whom contribute to major scientific advances. For example, the first results from a large clinical trial testing candidate microbicides that use anti-retrovirals (ARVs) found that the incorporation of an ARV into a vaginal gel was more than 50 percent protective against HIV infection when used as directed. This advance is a key step toward empowering women with a safe and effective HIV prevention tool. Notably, six of the study's authors are current or former Fogarty-sponsored trainees.

To increase the pool of physicians who have the necessary skills to conduct robust and critical health research, and to support country-driven efforts that enhance the sustainability of gains made under PEPFAR, Fogarty is also administering a major new program called the Medical Education Partnership Initiative (MEPI)—a joint effort of the Office of the Global AIDS Coordinator, HRSA, DOD, USAID, CDC, and NIH. MEPI supports institutions in Sub-Saharan African countries and their U.S. partners to develop new models of medical education, and to strengthen the ability of medical students and faculty to conduct research that responds to the health needs of their countries.

Non-communicable diseases—such as heart disease, stroke, cancer, and diabetes—are in fact the leading causes of worldwide mortality, accounting for 60 percent of all deaths. According to the World Health Organization, 80 percent of this burden is in LMICs, where these diseases affect people disproportionately during their most economically productive years. Fogarty is addressing this challenge through its expanded program on Chronic, Non-Communicable Diseases and Disorders across the

[1] Global Health Council, Washington, DC.

Lifespan, which will support training of in-country scientists to conduct research on these diseases. Given the high burden of non-communicable diseases in the United States, knowledge gained from these research activities can inform domestic efforts to prevent and treat these diseases—particularly in low-resource settings.

Fogarty also supports the training of U.S. investigators to conduct global health research and actively engage in international scientific collaborations. These investments directly respond to the overwhelming demand for global health opportunities on university campuses across the United States, and are helping early career scientists to build long-term relationships and acquire skills that will help to ensure that the United States continues to be a global leader in health innovation.

ENHANCEMENT OF EVIDENCE BASE FOR HEALTH CARE DECISIONS

There is a tremendous gap between scientific advances and health outcomes in the developing world. Therefore, there is an urgent need to bridge the gap between what we know and what we do. Fogarty has expanded support for research training in implementation science, which generates knowledge and methods to better integrate research findings and proven health interventions into health policy and practice.

For example without a significant shift in global prevalence patterns, smoking is projected to cause roughly 8 million deaths annually by 2030; notably, more than 80 percent of these deaths will occur in LMICs. Fogarty's International Tobacco and Health Research and Capacity Building Program addresses the critical role of research and local research capacity in reducing the global burden of tobacco consumption and the need to generate a solid evidence base that can inform effective local tobacco control strategies and health policies. The program supports epidemiological and behavioral research, as well as prevention, treatment, communications, implementation, health services and policy research. In Delhi, India, researchers are testing the efficacy and cost-effectiveness of a community-based behavioral intervention for tobacco cessation among youth living in low-income communities. Such studies can inform efforts to curb adolescent smoking in the United States—particularly in resource-poor settings.

Another example is Fogarty's International Implementation, Clinical, Operational, and Health Services Research Training Award for AIDS and Tuberculosis program, which supports training of scientists and health professionals in developing countries to conduct research-related to implementation of prevention, care and treatment interventions for HIV and/or TB. Researchers supported by this program recently made a significant discovery regarding the treatment of patients with both HIV/AIDS and TB. In these resource-limited settings, a high proportion of patients begin antiretroviral therapy (ART) while on TB treatment, and paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB–IRIS) is a frequent complication of the ART. To address this disease management challenge, investigators in South Africa found that a 4-week course of prednisone reduced the need for hospitalization and therapeutic procedures, and hastened improvements in symptoms, performance, and quality of life—all without excess adverse events.

Fogarty has also partnered with the Bill and Melinda Gates Foundation and the Foundation for NIH on a study that examines the relationship between malnutrition and intestinal infections, and also the consequences of these conditions on various aspects of child health and development. Investigators across multiple international research sites seek to facilitate the design of more targeted, cost-effective interventions that will reduce the burden of child morbidity and mortality from diarrheal diseases. One area of focus is the impact of malnutrition, along with damage to the gut (from repeated and persistent episodes of diarrheal disease), on the effectiveness of childhood vaccines. In many low-resource settings, the immunity conferred by various vaccines is significantly lower than in high-income countries. A better understanding of the links between nutrients and the health and function of the intestinal immune system will likely lead to the development of targeted and modified vaccine formulations and delivery strategies (e.g., dosing, schedules) for improved control of intestinal infections.

TECHNOLOGIES TO ACCELERATE DISCOVERY

With increasing globalization, the need to monitor, diagnose and respond to epidemics has risen dramatically. Since 1998, Fogarty has supported partnerships between the United States and LMIC research institutions to increase the capacity of biomedical scientists to design, access and use modern information technology in support of health sciences research. These partnerships are training biomedical and behavioral scientists, engineers, clinicians, librarians, and other health professionals to access, manage, analyze, and share biomedical information electronically. They

are also training individuals who will be capable of developing new informatics applications. This will increase the ability of local scientists and institutions to conduct multi-site clinical trials and perform international disease surveillance and prevention programs. Several Fogarty-supported informatics projects have now reached new levels of maturity, expanding to form regional networks and leveraging tools and lessons learned to benefit more researchers. For example, a program in Brazil is sharing its materials with Mozambique, where Portuguese is also the national language. Researchers in Peru are building a Latin American training network, and a university in South Africa is forming a consortium to strengthen biomedical informatics throughout Africa.

TRANSLATIONAL SCIENCES AND THERAPEUTICS DEVELOPMENT

Fogarty's International Cooperative Biodiversity Groups program supports natural products drug discovery and ethnomedical and botanicals research. Investigators supported by this program are generating new and exciting leads from natural products that may result in new therapeutics for a range of diseases. For example, a promising new weapon in the war against malaria may come from seaweed found in Fiji, as discovered by Fogarty grantee Dr. Julia Kubanek, a chemical ecologist at the Georgia Institute of Technology. She and her team discovered that a type of red algae in Fiji has strong anti-malarial properties. Animal studies have begun to further explore the compound's potential as a new therapeutic.

In conclusion, to effectively confront complex health issues that transcend national boundaries, more scientific collaborations must be developed and strengthened. Deep regional expertise enables Fogarty to facilitate these scientific collaborations. In the context of advancing science and health, Fogarty seeks opportunities to bridge differences between countries that might otherwise not engage and to build trust by encouraging scientists from around the world to work together to address shared health challenges. These partnerships promote goodwill, stability and peace, and effectively harness science for diplomacy. As the world continues to become more interdependent, international scientific partnerships will play a critical role in building bridges and in improving health for people worldwide. Working in partnership with rest of the NIH, Fogarty's unique programs will continue to enable scientists in the United States and abroad to work together to tackle the most pressing and complex health challenges of our time.

PREPARED STATEMENT OF DR. KENNETH WARREN, PH.D., DIRECTOR, NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute on Alcohol Abuse and Alcoholism (NIAAA), of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $469,197,000 for the NIAAA, which reflects an increase of $11,304,000 over the fiscal year 2011 level of $457,893,000, comparable for transfers proposed in the President's request.

ALCOHOL AND HEALTHCARE—TRANSFORMING THE LANDSCAPE

NIAAA-supported research is leading to dramatic changes in the understanding of alcohol-related problems and their prevention and treatment across the lifespan. By translating this research into new and better prevention and treatment approaches we have the ability to reduce the heathcare burden due to alcohol and enhance the well-being of individuals, their families, and society-at-large.

SCOPE OF THE PROBLEM

According to the World Health Organization, alcohol is among the ten leading causes of death and disability worldwide; and according to the Centers for Disease Control and Prevention (CDC), alcohol is also a major cause of preventable death and disability in the United States. As the United States. implements healthcare reform, it is important to recognize that alcohol misuse costs our Nation an estimated $235 billion annually.[1]

The consequences of alcohol misuse can affect both drinkers and those around them at all stages of life. NIAAA's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) estimates that almost 18 million people in the United States. ages 18 and older suffer from alcohol abuse or dependence (collectively known as alcohol use disorders, AUDs). The highest prevalence of alcohol depend-

[1] Rehm J, et al. The Lancet 373(9682): 2223–2233, June 27, 2009–July 3, 2009.

ence, which encompasses a broad spectrum of disease ranging from a single episode of a few years duration to a chronic relapsing disorder, occurs among 18–24 year olds. Of note, more than 85 percent of individuals with an AUD do not have another drug use disorder. Returning war veterans represent a particularly vulnerable population for developing AUDs that co-occur with Post Traumatic Stress Disorder (PTSD) and other mental health problems. Chronic, heavy alcohol use can damage tissues and organs, most notably in the brain, liver, heart, pancreas, and esophagus. According to the CDC, in 2007, alcoholic liver disease accounted for over 14,000 deaths and in 2008 was responsible for nearly 20 percent of U.S. liver transplants.

Alcohol misuse can also have second hand effects, both direct effects of alcohol exposure such as damage to the developing embryo due to drinking by the pregnant mother, as well as indirect effects experienced by individuals other than the drinker such as car crashes, sexual assault, and violence. According to an analysis of NIAAA's NESARC, one in four children grow up in a household where alcohol is a problem, putting them at risk for short and long-term adverse physical and psychological health outcomes.

Research to Practice

NIAAA-supported research is increasing our understanding of how to identify and address alcohol-related problems across the lifespan. Research shows that early identification and intervention are key to reducing future health problems and can dramatically reduce healthcare and other costs for individuals who misuse alcohol and those around them.

The Value of Screening and Brief Intervention

The medical and economic value of screening and brief intervention (SBI) to identify and address high risk drinking behavior early has been well documented. In fact, according to an analysis in the American Journal of Preventive Medicine, SBI for alcohol misuse was ranked similarly in cost-effectiveness to screening for colorectal cancer and hypertension, and to influenza immunization. Using NIAAA's A Clinician's Guide: Helping Patients Who Drink Too Much, SBI can be performed efficiently and effectively by primary care clinicians. By intervening early, providers are able to offer their patients more appealing, accessible options to address their alcohol problems, options that are less resource intensive and less expensive than those needed to treat more severe forms of dependence. For individuals who want to assess and address their drinking behavior on their own, NIAAA has developed an interactive Web site and booklet, Rethinking Drinking, http://rethinkingdrinking.niaaa.nih.gov. These tools offer evidence-based information about risky drinking patterns, the alcohol content of drinks, and the signs of an alcohol problem, along with other resources to help people who choose to cut back or stop drinking. Tools such as Rethinking Drinking may benefit those who could ultimately recover from dependence without treatment by decreasing the severity and duration of dependence. For others it may provide the motivation to seek professional help.

Underage and College Drinking

According to the Substance Abuse and Mental Health Services Administration, more than one-fourth of 16–17 year olds drank in the past 30 days, and 17 percent engaged in binge drinking, i.e. drinking more than five drinks on an occasion. For 18–20 year olds, over one-third engaged in binge drinking in the past 30 days. According to The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking, each year underage drinking results in the death of about 5,000 people under the age of 21 from alcohol-related injuries. This number is equivalent to the incoming freshman class at Virginia Tech, and greater than the total student body at the United States Naval Academy. Given the widespread use of alcohol and high prevalence of binge drinking by children and adolescents, and the link between early alcohol use and later problems including alcohol dependence, it is important to identify children and adolescents who are at high risk for alcohol use and/or alcohol use disorders. NIAAA will soon release an easy to use two question screener and guide for pediatricians and other clinicians who provide medical care to children and adolescents. This empirically based screening instrument is devised to identify children at elevated risk for using alcohol as well as those who have already begun to experiment or are more heavily involved with alcohol. In addition to identifying individuals who need any level of intervention, health practitioners can also use the screening process to provide information to patients and their parents about alcohol's effects on the developing body and brain. In collaboration with other Federal and non-Federal partners NIAAA will implement and evaluate the new guide.

Alcohol use is also a serious public health and safety problem among college students with adverse consequences that range from poor academic performance to al-

cohol poisoning. NIAAA has an ongoing research focus on reducing college drinking and its consequences. Research encompasses both individual approaches, such as screening and brief intervention in college health centers, and environmental approaches including studies on college and community policies. NIAAA has also established a College Presidents Working Group to advise the Institute.

Exploiting Technology to Improve Treatment

For those who need treatment, NIAAA seeks to provide more and improved options. Individuals experience alcohol differently, for some it provides almost immediate euphoria, others can drink much higher quantities yet feel relatively little effect. Both types may be at risk for developing alcohol dependence. Clinical trials with alcohol dependent patients testing a variety of medications suggest that, just as their physiological response to alcohol differs, so too does their response to a specific treatment; and genes appear to be responsible, at least in part, for these differences. Given that alcohol dependence is a complex disorder influenced by multiple genes, along with the evidence that specific treatments only work for subsets of individuals, NIAAA continues to seek additional medications that target different molecules and pathways in the brain. A number of medications currently prescribed for other indications are being evaluated as pharmacotherapies to reduce heavy drinking including: the mood stabilizing drug quetiapine, the antiepileptic drug levetiracetum, the smoking cessation drug varenicline and the anti-nausea drug ondansetron. Recently, clinical trials with ondansetron revealed that individuals with specific variations in a gene which encodes the serotonin transporter respond better to treatment than individuals without these variants. Similarly, individuals with a specific variant in the mu opioid gene respond better to the FDA-approved alcohol dependence treatment naltrexone than those lacking the variant. The identification of additional medications, along with the knowledge of what works for whom, will soon make personalized treatment for alcohol dependence a reality. NIAAA's efforts to make testing of compounds more efficient, its active role in engaging the pharmaceutical industry in concert with its willingness to test novel compounds, and its work with the FDA to improve guidelines and methodology for alcohol clinical trials have greatly accelerated the pace of medications development for alcohol dependence.

In parallel, NIAAA is exploiting technological advances in genomics to determine the multiple underlying genetic signatures that contribute to the range and severity of alcohol use disorders. As part of the next NIAAA NESARC, DNA samples will be collected from an estimated 46,000 people for use in genome-wide association analyses. The level and complexity of information derived from new, large-scale, comprehensive genomic studies will facilitate our ability to correlate genetic make-up with subtypes of alcohol dependence improving our ability to match patients with treatments.

Treating the medical consequences of heavy chronic drinking is also a priority. For example, currently liver transplantation is often the only viable option for treating advanced liver disease but it is a prolonged, expensive and risky process only available to patients who maintain abstinence. To expand treatment options, NIAAA is supporting studies to test a number of compounds that target progressive stages of liver disease including fatty liver and liver fibrosis. In addition, seminal research is providing a better understanding of why some individuals develop liver cirrhosis whereas others who consume similar amounts of alcohol do not. Over-activation of the body's natural repair mechanisms may actually promote liver disease, suggesting new targets for prevention and treatment of alcoholic and non-alcoholic liver disease.

PREPARED STATEMENT OF STEPHEN I. KATZ, M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $547,891,000 which is $14,002,000 more than the comparable fiscal year 2011 appropriation of $533,889,000.

INTRODUCTION

NIAMS addresses diseases that affect individuals of all ages, of all racial and ethnic backgrounds, and across all economic strata; many disproportionately affect women and minorities. Some are rare disorders, but many are very common, and all have a major impact on the quality of people's lives. Twenty-five years of

NIAMS-funded research has contributed greatly to a variety of new treatment and prevention strategies that are reducing the burden the diseases place on individuals, their families, and society.

LEVERAGING BASIC SCIENCE TO IMPROVE PATIENT CARE

NIAMS research has been the basis for the development and testing of many new medications, including biologic therapies for autoimmune diseases. The newly approved drug belimumab, the first lupus treatment to receive U.S. Food and Drug Administration approval in over 50 years, interferes with a molecule that NIAMS-funded researchers showed to be involved in the immune dysfunction that characterizes this disorder. Other, more recent basic research results suggest another existing drug, omalizumab, may prevent lupus-associated kidney damage. NIAMS investigators in Bethesda, Maryland, are planning to start testing the drug's safety for lupus patients soon.

Basic research into disease mechanisms also is explaining why some therapies do not work as well as expected. In 2003, investigators were baffled when two NIAMS-funded clinical trials showed that combining two medications (a bisphosphonate and parathyroid hormone) that each improve bone mass and prevent fractures did not help people any more than either drug did individually. Eight years later, research into the mechanisms by which bisphosphonates preserve bone revealed that they interfere with parathyroid hormone's bone-forming activity. This discovery can help physicians choose drug regimens that are best for their patients.

DEVELOPING TOOLS TO DIAGNOSE AND MONITOR DISEASE

Improvements in bone health have underscored the importance of identifying which of the 40 million Americans [1] who have low bone mass are most likely to break a bone. Several large, NIAMS-funded studies have indicated that spine fractures predict both future spine fractures and debilitating hip fractures. Researchers recently published evidence that women who have mild spine defects may also be at risk of hip fractures and could benefit from lifestyle changes or drugs that prevent bone deterioration. However, the ability to distinguish between deformities related to fragile bones and those from other causes is critical. If imaging tools that are under development can make this distinction, clinicians will be better able to predict patients' risk and monitor responses to therapies. Also, the new tools potentially could reduce the cost of clinical trials by allowing investigators to assess a medication's effects relatively quickly.

Other researchers are testing whether a specific type of magnetic resonance imaging can predict worsening of knee arthritis. Preliminary work—using images that are available to the research community through a public-private partnership supported by the NIH and various companies—is promising. If confirmed, clinicians could use the technology to identify patients whose knee cartilage is likely to rapidly deteriorate due to osteoarthritis. Moreover, like the imaging tools mentioned above, the discovery and validation of structural changes that researchers can visualize could lead to shorter, more efficient trials of promising disease-modifying agents that may help the more than 27 million Americans [2] who have osteoarthritis pain in their knees or other joints.

Many diseases within the NIAMS mission involve pain, fatigue, and other difficult-to-measure symptoms. A test to quantify changes in these parameters could enhance clinical outcomes research and, ultimately, clinical practice. NIAMS is one of several NIH components engaged in the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative to develop such a tool. In addition to managing PROMIS on behalf of the NIH, NIAMS encourages researchers to use the resource. For example, NIAMS is funding a study to test questions for fibromyalgia patients, along with information collected through PROMIS, for development of disease-specific measures that allow investigators and healthcare providers to monitor patients more effectively.

APPLYING GENETICS, GENOMICS, AND OTHER CUTTING-EDGE RESEARCH TO NEW TREATMENTS

Researchers have been trying to determine for decades if pain and itch send different signals to the brain. Difficulties distinguishing the two symptoms at molecular and cellular levels had hindered this effort, but a group of NIAMS investigators finally identified an itch-specific molecule. Their work also illuminated a previously

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[1] Looker AC, et al. J Bone Miner Res. 2010 Jan;25(1):64–71. PMID: 19580459.

[1*] Lawrence RC, et al. Arthritis Rheum. 2008 Jan;58(1):26–35. PMID: 18163497.

elusive mechanism by which the itch message travels through the spinal cord to be perceived by the brain. Such a discovery should pave the way for studies into how chronic itch develops, and make it possible, for the first time, to design better treatments.

Research is providing hope to patients with epidermolysis bullosa (EB), a group of rare, inherited blistering skin conditions. When investigators repaired the genetic defect in an EB patient, NIAMS-funded scientists wondered if gene therapy might also work for another form of the disease. The strategy seemed promising in a mouse model of recessive dystrophic EB (characterized by large, painful blisters, open wounds, and early death due to cancer). A first-in-human clinical trial will begin this year.

NIAMS also is funding a Phase I clinical trial that suggests that a different gene transfer approach may correct the molecular defect underlying type-2 limb-girdle muscular dystrophy (LGMD–2D). The study, supported through one of the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, demonstrated that the procedure could safely produce the corrected protein for at least 6 months. The data provide a framework that investigators can use when designing subsequent LGMD–2D clinical trials. Furthermore, researchers can leverage the study's findings about immune responses as they develop gene-based therapies for other diseases.

In the past 12 months, muscular dystrophy researchers also have made considerable progress toward understanding the genetic underpinnings of facioscapulohumeral muscular dystrophy (FSHD). Prior findings from an NIH-funded FSHD patient registry showed that the disease is associated with a shorter-than-normal series of repeated genetic sequences. Recent technologic advances enabled researchers to identify a genetic pattern within these sequences in FSHD patients. This discovery, combined with findings that the defects cause FSHD by activating a gene and allowing its product to accumulate in muscle, are enabling new directions that will accelerate progress. For example, researchers can now engineer animal models of the disease, something that they could not do without a basic understanding of the genes involved.

Like FSHD, many health problems are influenced by complex genetic factors. Over the last few years, the ability of genome-wide association (GWAS) approaches to identify gene variants related to disease risk has matured from an intriguing concept to a widely used scientific tool. These analyses can require thousands of patients, and often entail data sharing among NIAMS-funded researchers and scientists around the globe.

An international GWAS team including researchers at the NIH Clinical Center showed that a gene involved in the body's immune response underlies a person's susceptibility to a painful, inflammatory condition called Behcet's disease, which primarily affects people of Asian, Middle Eastern, Turkish, or European descent. The gene linked to Behcet's disease is associated with other conditions for which treatments exist or are being developed. Because of this connection, therapies might be available sooner than if the investigators had found a completely new disease mechanism.

In the past year, other genetic studies uncovered additional, shared links among diseases. Investigators discovered that rare variants of a gene encoding the enzyme sialic acid acetylesterase are associated with rheumatoid arthritis and type 1 diabetes, and may play a role in other autoimmune diseases. Likewise, researchers leveraging the NIAMS-sponsored National Alopecia Areata Registry found that genes associated with rheumatoid arthritis and type 1 diabetes are linked to the development of alopecia areata, a disease in which the body's immune system attacks the hair follicles and causes hair loss. As with Behcet's disease, the possibility of a common mechanism is particularly exciting because drugs under development for other diseases might also be effective against alopecia areata.

GWAS also holds promise for understanding the genetic differences that give rise to more common diseases, such as osteoporosis. The NIAMS dedicated funds from the American Recovery and Reinvestment Act of 2009 toward developing a resource that investigators can use to identify molecular changes that influence bone health. The discovery of gene variants that protect against osteoporosis or increase a person's risk of having low bone mass is likely to suggest targets that researchers can pursue when exploring new ways to prevent fragility fractures. Moreover, investigators could use genetic markers to identify appropriate participants for clinical trials. Data from this effort is likely to be available to the wider research community at the end of this year.

CONCLUSION

Twenty-five years ago, a few months after Congress passed the Health Research Extension Act of 1985 (Public Law 99–158), the NIH established the NIAMS. Over the past two and one-half decades, the increased emphasis on research on arthritis and musculoskeletal and skin disorders has benefited nearly every household in our Nation. We are proud of the scientific advances that our researchers have made toward helping people who have diseases of the bones, joints, muscles, and skin, and are excitedly looking forward to the discoveries they will make in the future.

PREPARED STATEMENT OF RODERIC I. PETTIGREW, PH.D., M.D., DIRECTOR, NATIONAL INSTITUTE OF BIOMEDICAL IMAGING AND BIOENGINEERING

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH). The fiscal year 2012 budget is $322,106,000, which is $8,573,000 more than the fiscal year 2011 appropriation of $313,533,000. This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences and reallocate the remaining portions of the National Center for Research Resources to other parts of NIH, including NIBIB.

The mission of NIBIB is to improve human health by leading the development and accelerating the application of biomedical technologies. NIBIB invests resources in scientific and technological research opportunities at the convergence of the quantitative and life sciences, and in training the next generation of researchers. The Institute is at the forefront of translating scientific advances into engineered medical solutions. Ultimately, NIBIB seeks to realize innovations that address healthcare challenges, reduce disease mortality and morbidity, and enhance quality of life. To accomplish this goal, NIBIB continues to fund bold and far-reaching projects that facilitate discovery and translate basic science into new and better healthcare.

TRANSLATIONAL SCIENCE AND THERAPEUTICS DEVELOPMENT

Biodegradable Home-Based Vaccination System.—Influenza is a major cause of morbidity and mortality worldwide. Despite vaccination campaigns, the CDC attributes 36,000 deaths and 226,000 hospitalizations per year in the United States to influenza, with an associated cost of approximately $100 billion per year. The number of cases could be greatly reduced if more people were vaccinated and if the vaccine was more effective. Researchers at the Georgia Institute of Technology are addressing both issues by developing a bio-dissolvable micro-patch that will allow people to vaccinate themselves. The patch is painless, has an application time of just seconds, has no biohazardous waste, does not require refrigeration for storage, and develops an enhanced immune response to flu. The patch combines cutting edge technology and user-friendly simplicity to address this significant public health problem.

Noninvasive Image-Guided Therapy: Focused Ultrasound.—NIBIB supports research to develop and promote innovative image-guided therapies. One of these technologies is High-Intensity Focused Ultrasound (HIFU). HIFU is a non-invasive, image-guided and controlled new therapy delivery system which consists of a highly focused beam of high-intensity ultrasound that is capable of ablating tissue in a targeted region of the body, without harming surrounding tissues. Researchers are combining magnetic resonance imaging and HIFU to form an image-guided therapy delivery system for non-invasive tumor ablation, which can either replace or complement surgery or radiation therapy. In addition, transcranial transmission of HIFU can also induce the opening of the blood-brain barrier, which allows delivery of drugs directly to specific locations in the brain. HIFU for treatment of uterine fibroids is now an FDA-approved clinical procedure. These developments could revolutionize surgery, cancer therapy and the delivery of therapeutic agents in new targeted approaches.

Regenerative Medicine for Wounded Warriors.—The NIBIB is the lead NIH institute for participation in the U.S. Military's signature Armed Forces Institute for Regenerative Medicine (AFIRM), now in its third year. AFIRM is a multi-institutional, interdisciplinary network to develop advanced treatment options for our wounded servicemen and women. Researchers are addressing many severe medical conditions including burns, compartment syndrome, complex craniofacial injuries, limb/digit salvage, and wound healing.

TECHNOLOGIES TO ACCELERATE DISCOVERIES

Monitoring Tumor Cells and Cancer Biology.—NIBIB Quantum Grant investigators have successfully developed a test capable of detecting a single cancer cell among the billions of normal cells in a blood sample. The microchip device, known as the HB-Chip (after the micro herringbone pattern on the chip surface), enables the isolation of rare circulating tumor cells that may be the source of cancer metastasis. Subsequent molecular characterizations of these cells have led to the discovery of several subtypes of prostate, breast, and lung cancer. These subtypes serve as the basis for customized cancer treatments that are tailored to specific patients. The isolation and characterization of circulating tumor cells has the potential to revolutionize the management of care in cancer patients. Recently, Johnson & Johnson announced a partnership with the researchers at Massachusetts General Hospital to further develop and market this blood test. "Stand Up to Cancer," an organization focused on translational cancer research, is supporting four leading cancer centers to launch clinical trials using the HB-Chip to determine the sensitivity and specificity of the device for various cancers.

Global Technologies for Disease at the Point of Care.—NIBIB has partnered with the Department of Biotechnology and the Ministry of Science and Technology in India to support the development of low-cost diagnostic and therapeutic technologies that will be used in underserved communities worldwide. As the prevalence of chronic diseases in low-resource settings increases, PATH (Program for Appropriate Technology in Health, a nonprofit organization that improves the health of people around the world) is working on new initiatives to tackle diabetes. NIBIB-supported researchers are evaluating cost-effective technologies to monitor and screen for gestational and type 2 diabetes in India. These technologies are also applicable to rural and low resource settings in the United States and can lead to more effective interventions and therapies.

In the United States, about 500 mothers die every year during childbirth, and in Africa, childbirth-related deaths are nearly 300,000 annually. Many of these deaths could be prevented if these populations had ready access to ultrasound exams, which identify mothers at high risk for birth complications. In addition, cardiovascular disease and abdominal illnesses could be broadly monitored and managed with wide access to ultrasound exams. NIBIB has supported the successful development by GE of a hand-held battery powered portable ultrasound system (VSCAN™) that costs approximately $8,000 but has the features of a conventional hospital or office based system costing approximately $200,000. The broad goal is to make ultrasound imaging as available as stethoscopes, to facilitate earlier detection and monitoring response to therapies.

TECHNOLOGIES TO IMPROVE EVIDENCE-BASED CLINICAL DECISIONS

Patients routinely receive their healthcare at multiple locations ranging from physician's offices to major medical centers. For optimal care, medical records and medical imaging studies must be readily available at different sites. To address the need for sharing of images and to enhance the adoption of evidence and comparative effectiveness in clinical decisions, NIBIB has funded several coordinated projects.

Patient Controlled Web-Based Access and Sharing of Medical Images.—A contract with the Radiological Society of North America (RSNA) includes five academic institutions: UCSF, University of Maryland, Mayo Clinic, University of Chicago, and Mount Sinai. Two additional grants provide support to Wake Forest University and the University of Alabama at Birmingham. Each of these projects is developing an approach to patient-controlled medical image sharing systems for secured image sharing among radiologists and clinicians across organizational boundaries. The project at Wake Forest University has a special focus on image sharing in rural and under-served areas. Validation testing of patient health records that can accept images with the appropriate controls and privacy safeguards has begun and will start enrolling patients in the near future.

On Line Decision Support Systems.—NIBIB is providing resources to the Brigham and Women's Hospital and the Massachusetts General Hospital to implement information technology systems that include clinical decision support capability. These systems enable the care providers to make clinical decisions that are based on the best available evidence and the patient's comprehensive medical data set, including clinical images.

NEW INVESTIGATORS, NEW IDEAS

Nanoparticles for Improved Drug Delivery: Overcoming the Mucus Barrier.—The delivery of bioactive molecules to target tissues can significantly improve drug effec-

tiveness while reducing side effects by concentrating medicine at selected sites in the body. While the barrier properties of mucus provide protection against infection and other potentially toxic particles, they also have thwarted efforts to achieve uniform and sustained drug delivery to mucosal surfaces, and have likely prevented successful delivery of genes that could potentially treat fatal diseases, such as cystic fibrosis. The work of NIBIB grantee Dr. Justin Hanes at Johns Hopkins University seeks to understand the properties of mucosal barriers and use this knowledge to guide the development of polymeric nanoparticulate carriers capable of more efficient drug and gene delivery to the respiratory tract, female reproductive tract, gastrointestinal tract, surface of the eye, and other mucosal tissues for improved therapies. The delivery of bioactive molecules to target tissues can significantly improve drug effectiveness while reducing side effects by concentrating medicine at selected sites in the body.

Robotic Prostheses for Amputees.—Despite significant technological advances over the past decade, state-of-the-art transfemoral prostheses are unable to provide power for joint motion. The absence of joint power significantly impairs the ability of these prostheses to restore many locomotive functions, including walking upstairs and up slopes, running, and jumping, all of which require significant net positive power at the knee joint, ankle joint, or both. Dr. Michael Goldfarb, an NIBIB Edward C. Nagy Young Investigator, recently reported the development of the first robotic transfemoral prosthesis with fully powered knee and ankle joints. The device allows above-the-knee amputees to walk 25 percent faster with less energy than is expended with conventional prosthetics and provides increased balance, agility, and recovery reflexes to prevent falls. In April, Freedom Innovations announced a worldwide licensing agreement for exclusive rights to commercialize this device.

The Institute's emphasis on interdisciplinary approaches to biomedical research has provided unprecedented opportunities for collaborations among the life and physical scientists leading to advances in biology and medicine through the quantitative, physical sciences, and engineering perspective, as well as the development of technologies that reflect the translation of biological mechanisms. These advances will produce remarkable improvements in the health of individuals around the world.

PREPARED STATEMENT OF ALAN E. GUTTMACHER, M.D., DIRECTOR, EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of $1,352,189,000. This reflects an increase of $35,466,000 over the fiscal year 2011 level of $1,316,723,000.

In my short time as NICHD Director, the breadth and importance of the Institute's mission have already impressed me. Our research changes clinical practice and improves health for many people, particularly those who may be under-represented in medical research—pregnant women and their offspring; adolescents; and people with intellectual, developmental, and physical disabilities. Our research shows that even simple approaches can have significant impact. For example, a recent study found that an inexpensive program teaching newborn care to Zambian midwives reduced deaths in the first week of life by 40 percent. Today, I would like to highlight a few other examples of NICHD's recent progress toward improving health, and describe a new effort to position our research to continue to contribute to a healthier Nation and world.

IMPROVING HEALTHCARE FOR WOMEN AND CHILDREN

Thanks partly to NICHD research, Centers for Disease Control and Prevention (CDC) data show that the preterm birth rate in the United States declined for the second year in a row in 2008. Still, 12 percent of all pregnancies end in preterm birth, a leading cause of infant death in our country. Preterm infants have greater risk for breathing problems, life-threatening infections, cerebral palsy, and developmental disabilities. In recent years, NICHD research showed that treating pregnant women with a prior history of preterm birth with a type of progesterone reduced their risk of another preterm delivery. Now, a new study shows that a vaginal gel containing another type of progesterone substantially reduces the risk of premature delivery in women with a short cervix. With adoption of such treatments, the preterm birth rate should drop further.

Spina bifida, which occurs when the fetal spinal column does not close properly, affects nearly 1,500 U.S. infants a year, according to the CDC. The most common and severe form of spina bifida, myelomeningocele, can cause paralysis, problems

with nerve function, and brain damage. Recently, the NICHD reported an important trial, the Management of Myelomeningocele Study (MOMS). MOMS researchers compared standard surgical repair of the spinal cord after birth to repair while the fetus is in utero. They found that repairing the spinal cord in the womb greatly reduced risk of death and the need to divert fluid from the brain. It also doubled the chance of walking and improved later motor and cognitive development. Infants undergoing prenatal surgery, however, were also more likely to be born preterm, and their mothers more likely to experience a uterine tear in childbirth. While researchers continue to study this specialized surgery, the initial findings promise to improve the quality of life for thousands of children.

New findings also can improve healthcare for women: NICHD researchers recently showed that women's cholesterol levels correspond with monthly changes in estrogen levels. On average, the total cholesterol level of the women studied varied 19 percent over the course of the menstrual cycle. Although previous data showed that estrogen-containing oral contraceptives or menopausal hormone therapy could affect cholesterol levels, this was the first study to show conclusively that the cyclical levels of naturally occurring hormones have similar effects. This natural variation suggests that clinicians should consider the phases of a woman's monthly cycle when evaluating her cholesterol levels and before prescribing treatment to help protect women against heart disease.

NEW TECHNOLIGES ADVANCE HOPE FOR AUTISM AND PARKINSON'S

Autism spectrum disorder (ASD) encompasses a range of conditions involving impaired social interactions and communication, atypical behaviors, and health problems. While ASD is known to have genetic components, researchers have not identified a consistent pattern of variant genes. In fact, dozens of gene variants, along with other factors, are now linked with ASD, complicating, but also advancing, our understanding of the condition and ability to develop new treatments. Using advanced imaging technology, NICHD-supported researchers identified a gene that impairs communication between parts of the brain. Additional genetic studies may reveal ASD subtypes and how certain genes function and interact with each other. This research could help individualize treatments based on a child's genetic profile. New technologies also hold promise for other neurologic conditions, such as Parkinson's disease, which results from a loss of brain cells that help coordinate movement. NICHD-supported researchers injected stem cells from the endometrium (lining of the uterus) into the brains of mice with a laboratory-induced form of the disease. These new cells took over the function of the brain cells eradicated by Parkinson's. This is the first time that scientists showed endometrial stem cells could assume the properties of the tissue into which they were transplanted. Since endometrial stem cells are widely available, this suggests that women with Parkinson's disease might serve as their own stem cell donors, or healthy endometrial stem cells might be stored and later matched to individuals with the disease.

TRANSLATING SCIENCE TO ADVANCE REHABILATION

Applying basic scientific findings to clinical problems can help scientists develop new diagnostics or therapeutics for many conditions. For instance, NICHD researchers seeking to understand how the vitamin folate is metabolized found that the vitamin appears to promote healing in rats with damaged spinal cord tissue. Up to 20,000 people yearly suffer a spinal cord injury, and about 200,000 people currently live with such injuries, according to the National Center for Injury Prevention and Control. Folate, a B vitamin that naturally occurs in leafy green vegetables and other foods, plays an important role in early embryonic brain and spinal cord development. Further translational studies on folate could lead to new techniques to help regenerate nerve fibers and heal damaged nervous system tissue.

THE NATIONAL CHILDREN'S STUDY (NCS)

The NCS is designed to examine the effects of genetic factors and a broad range of environmental factors such as physical environment and family, community, and cultural influences on the development and health of children in the United States over time. The NCS will yield a rich repository of environmental and genetic/genomic data and biospecimens that can be mined by scientists for years to come and help answer questions concerning the earliest origins of health and disease. Over the past year, the NCS has been in a pilot phase, known as the "Vanguard Study," enrolling about 650 children in 37 sites as of February 2011. Three separate recruitment strategies are being tested to optimize participation and cost management. During the coming year, a range of experts will review ongoing findings, al-

lowing staff to develop, by late summer 2011, evidence-based cost-estimates and recommendations for the initial phase of the Main Study.

VISION FOR THE FUTURE

The NICHD has embarked on crafting a vision for the future that inspires the institute and its partners to achieve critical scientific goals and meet pressing public health needs. In early 2011, in a series of workshops, we asked leading scientific and health experts to identify what the scientific future should look like in 10 years and what knowledge must be obtained to reach these new frontiers. We focused on such areas as plasticity, development, cognition, behavior, reproduction, pregnancy and pregnancy outcomes, developmental origins of health and disease, environment, and diagnostics and therapeutics. Resultant white papers are posted on our website for additional public comment. In June, we will assemble another diverse group of experts to refine these concepts and identify those that are most promising. We will publish the final vision document by early 2012, helping to ensure that NICHD addresses the most important science for the Nation's women, children, families, and individuals with special needs.

Mr. Chairman and members of the Committee, thank you for your continued support of NICHD's important work. I would be pleased to respond to any questions.

PREPARED STATEMENT OF NORA VOLKOW, M.D., DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute on Drug Abuse (NIDA). The fiscal year 2012 budget of $1,080,018,000 includes an increase of $30,377,000 over the comparable fiscal year 2011 level. The following statement updates NIDA's scientific progress in addressing drug abuse and addiction. These public health problems cost our society more than $600 billion annually in health- and crime-related costs and losses in productivity, not to mention incalculable personal and social devastation (ONDCP 2004; Rehm et al. 2009; CDC 2007). NIDA has crossed a threshold into a new research era, unprecedented in its scope, and transformative in its prevention, treatment, and policy implications for substance use disorders (SUDs).

RETURN ON INVESTMENT: TECHNOLOGIES TO SPEED DISCOVERY

New technologies and scientific breakthroughs continue to generate actionable information about the genetics, chemistry, and circuitry of the human brain. This knowledge has dramatically enhanced our understanding of the underlying vulnerabilities and the long-term effects of addiction on neurophysiology and behavior. Continuing advances in DNA sequencing and analytical tools have transformed the landscape of genomic exploration. For example, we can now engage in high resolution and accurate sequencing of vast genomic tracts, from many different individuals, to systematically search for and identify addiction risk variants, which may open up new targets for medications. Also, we are dissecting the epigenetic processes that can affect gene expression through persistent but reversible changes. Epigenetics research has started to help explain the deleterious impact of known environmental risk factors, like poverty or chronic stress, on vulnerability for SUDs. The burgeoning availability of genetic, epigenetic, and environmental data heralds new opportunities for translational applications. NIDA is committed to optimizing this potential through harmonization efforts that help ensure the comparability of pooled data.

Harmonized databases are crucial for individualized medicine. This is clear in the genomics field, but also in the emerging field of globally connected biomarkers, or the "human connectome," and for brain imaging. NIDA is supporting research to develop biomarkers to screen for drug exposure and addiction vulnerability that would be more accurate, reliable, and sensitive than current tests (i.e. bodily fluids, hair, questionnaires) and would help transform the way SUDs are identified and treated.

Other innovations, such as wireless remote sensing and virtual technologies, offer opportunities for transforming how prevention messages, real-time monitoring, and even some treatment modalities are delivered to the public. Having real-time, objective measures of drug use could have a huge impact on SUD treatments. One example is remote physiological monitoring (RPM), a rapidly evolving form of telemedicine that can track patients' health status (e.g., heart rate, blood pressure, skin temperature, and glucose levels) remotely, using devices that can store and transmit the results in real-time. NIDA is supplementing studies on the use of RPM for moni-

toring drug use to evaluate the effects of treatment interventions and their relationship to clinical outcomes. Such data could support the establishment of non-abstinence endpoints, which in turn could inform the Food and Drug Administration (FDA) addiction medications approval process.

EMERGING PSYCHOACTIVE THREATS TO PUBLIC HEALTH

The past few years have witnessed several alarming trends, particularly prescription drug abuse. Although opioid analgesics are among the most effective medications for pain management, they are also associated with serious and growing public health problems, including drug abuse, addiction, and overdose deaths. The Substance Abuse and Mental Health Services Administration reports a six-fold increase in treatment admissions for opioid analgesics, from nearly 20,000 in 1998 to about 120,000 in 2008, while the Centers for Disease Control and Prevention acknowledge that unintentional poisonings involving opioid analgesics have more than tripled from 1999 through 2007, exceeding the total number of deaths involving heroin and cocaine. These trends illustrate the challenge of balancing access to critical medications for those who need them and preventing their abuse, particularly when the public does not perceive their dangers and has much greater access to them from a decade-long surge in availability. In 2009, 202 million opioid prescriptions were dispensed in the United States making opioids the most prescribed class of medications. NIDA is committed to helping reverse this trend by providing information on the patterns and motivations behind their abuse, sponsoring research on developing pain medications with less abuse potential, and creating curricula to minimize diversion through better prescribing practices.

Lingering public misperceptions, particularly among youth, continue to hinder our marijuana prevention efforts. The latest Monitoring the Future survey of 8th, 10th, and 12th graders reveals that daily marijuana use is up for all grades. These teens are not only at higher risk of becoming addicted, but they are functioning below optimal level at a time when their future depends on peak cognitive performance. Why is this happening now? We do not know for sure, but it is reasonable to infer that the public debates surrounding medical marijuana have increased confusion and lowered the perception of risk, an important factor in curtailing use.

Meanwhile, new drugs routinely emerge and gain rapid notoriety thanks to the Internet. Recent examples include "bath salts" and "spice," which are synthetic stimulants and cannabinoids, respectively.

IMPROVING PUBLIC HEALTHCARE—DELIVERY AND PERFORMANCE

NIDA will continue to leverage our knowledge base into better strategies for battling addiction. To further this goal, NIDA takes advantage of collaborative research infrastructures designed to deploy proven strategies rapidly and effectively. For example, NIDA's Drug Abuse Treatment Clinical Trials Network (CTN) tests evidence-based treatments in community settings with diverse patient populations, optimizing the utility and cost-effectiveness of treatments and fostering their adoption. Similarly, NIDA's Criminal Justice-Drug Abuse Treatment Studies (CJ–DATS) network promotes multilevel collaborations to bring proven treatment models into the criminal justice system, disproportionately affected by both drug abuse and HIV. These infrastructures allow for the broad testing of promising new strategies. One example, called "Seek, Test, and Treat," has great potential to improve the public health by expanding access to HIV testing and treatment, and ultimately reducing HIV spread.

Another cornerstone of our strategy is to engage physicians as "frontline" responders to patient substance abuse, providing the science-based tools they need to identify potential substance abuse in their patients and offering better options for treatment. Recent research shows, for example, that compared with methadone, buprenorphine results in fewer neonatal abstinence symptoms among babies born to opioid-addicted mothers, and is associated with decreased hospital stays and thus, costs. To bolster education in the treatment of pain, NIDA is leading a multi-Institute effort to create Centers of Excellence (CoEs) to develop curricula for medical students, nurses, resident physicians, and others. Part of our NIDAMED physician outreach initiative, CoEs have also developed and are helping to disseminate substance abuse training curricula, woefully neglected in most medical training. NIDA continues to encourage physician screening of drug abuse with the help of a Web-based interactive screening tool that generates clinical recommendations. The broad availability of these resources is an important step toward integrating substance abuse screening, brief intervention, and referral to treatment (SBIRT) into medical care, which will enable better healthcare decisions and outcomes.

TRANSLATION—THERAPEUTICS DEVELOPMENT

To help those affected by the disease of addiction, we need to expand the pharmacological and behavioral tools available to treat SUDs. Thus, medications development is one of the main areas that benefits from new discoveries. For example, the century-old practice of vaccination has recently been found to be a viable approach for treating addiction. In this case, the body itself is coaxed to produce antibodies that bind a drug while still in the bloodstream, blocking its psychoactive effects in the brain. Already, a nicotine vaccine that reduces craving and withdrawal symptoms is in advanced stages of development and will be market-ready following approval by the FDA. Another strategy has been the development of long-acting, or depot, formulations of medications that serve to overcome poor compliance. One example is Vivitrol, an extended-release opioid antagonist (naltrexone), recently FDA-approved for treating opioid addiction. NIDA is now testing the use of depot medications in high-risk groups, such as criminal justice offenders, and in regions of the world that have high rates of HIV infection and are resistant to treatment with opioid agonist medications.

In parallel, NIDA is supporting research on drug combinations, an effective strategy for treating many diseases (e.g., HIV/AIDS, cancer) and one starting to show success with addiction. For example, the combination of lofexidine (a hypertension medication) and marinol (a synthetic form of marijuana's THC) shows promise in treating withdrawal symptoms among marijuana-addicted individuals. Early results also suggest that a buprenorphine-naltrexone combination could be effective in treating cocaine addiction.

NEW INVESTIGATORS, NEW IDEAS

To help sustain our commitment to the next generation of biomedical research scientists, NIDA supports multiple training initiatives at various career levels and areas of need (e.g., physician scientists, computational neuroscience, and medicinal chemists). Examples include efforts aimed at mentoring minority investigators and international HIV/AIDS researchers, as well as multi-Institute training programs. To identify and encourage the next generation of addiction scientists, NIDA also awards special prizes at the annual Intel International Science and Engineering Fair to high school students whose projects exemplify excellent achievement in addiction science.

In closing, NIDA pledges to continue to tackle the emerging and significant public health needs related to drug abuse and addiction, taking advantage of unprecedented scientific opportunities to close the gaps in our knowledge base and develop and disseminate more effective strategies to prevent and treat drug abuse and addiction.

PREPARED STATEMENT OF JAMES F. BATTEY, JR., M.D., PH.D., DIRECTOR, NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS

Mr. Chairman and Members of the Subcommittee: I am pleased to present the President's budget request for the National Institute on Deafness and Other Communication Disorders (NIDCD) of the National Institutes of Health (NIH). The fiscal year 2012 NIDCD budget of $426,043,000 includes an increase of $11,244,000 over the comparable fiscal year 2011 appropriation of $414,799,000. This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences (NCATS).

The NIDCD conducts and supports research and research training in the normal and disordered processes of hearing, balance, smell, taste, voice, speech, and language. Our Institute focuses on disorders that affect the quality of life of millions of Americans in their homes, workplaces, and communities. The physical, emotional, and economic impact for individuals living with these disorders is tremendous. NIDCD continues to make investments to improve our understanding of the underlying causes of communication disorders, as well as their treatment and prevention. It is a time of extraordinary promise, and I am excited to be able to share with you some of NIDCD's ongoing research and planned activities on communication disorders.

AFFORDABLE HEARING HEALTHCARE

Hearing loss is a serious public health issue and has significant social and economic impacts. Approximately 17 percent of American adults, or 36 million individuals, report a hearing loss, and only about one in five of those individuals who could

benefit from a hearing aid wears one. Additionally, hearing healthcare and hearing aids are only rarely covered by health insurance, and are not covered by Medicare. A recent industry survey found that the average cost per hearing aid to an individual is $1,600, and for many, the cost is much higher. Hearing aids are also consumable devices, often requiring replacement every 4–6 years, and frequent battery replacement. This makes hearing aids potentially the third highest cost item for an individual, following just behind the purchase of a home and car. In 2009, NIDCD sponsored a workshop, Accessible and Affordable Hearing Health Care for Adults with Mild to Moderate Hearing Loss, to examine the factors that contribute to hearing healthcare access, affordability, and usage; and to develop a set of research objectives which could be explored in the future. Based on the recommendations, NIDCD published several targeted research initiatives for hearing healthcare: to explore new approaches that could lead to improved access, assessment, and intervention; to develop methods to determine the success of new or improved approaches; and to create small business technologies to improve access for underserved patients. The research supported through these and other NIDCD-sponsored efforts will enhance the evidence-base for hearing healthcare decisions, and provide a strong research base for future policy decisions related to affordable hearing healthcare.

TINNITUS

Tinnitus—a perceived ringing, buzzing or roaring in the ears—is a major public health concern, affecting more than 25 million American adults. It can range in severity from a mild condition, requiring no medical intervention, to a severe debilitating disease with significant physical, emotional, and economic impacts. The Department of Veterans Affairs reports tinnitus as the most prevalent service-connected disability for veterans receiving disability compensation. More than 744,000 veterans received service-connected disability compensation for tinnitus in fiscal year 2010, presenting a significant cost burden for the Nation. Past research has shown that tinnitus is often associated with hearing loss; however, little is known about the specific neural dysfunctions that lead to the disorder. There are also limited treatment options available, and their effectiveness varies widely. In response to this need, NIDCD is supporting a strong research portfolio on tinnitus. In 2009, NIDCD sponsored a research symposium, Brain Stimulation for the Treatment of Tinnitus, to explore the potential translation of existing brain stimulation technologies for the treatment of tinnitus. Recently, NIDCD supported scientists have demonstrated that stimulation of the vagus nerve (a large nerve that runs from the head to the abdomen) with an implantable electrode, in combination with the playing of tones, is able to "reset" the brain, eliminating tinnitus in a rat model of the disease. (Vagus nerve stimulation is already in use for the treatment of epilepsy and depression in more than 50,000 individuals). By varying the tones played and the co-stimulation of the vagus nerve, scientists were able to abolish the tinnitus sensation and restore the normal function of the brain. These exciting findings are the first demonstration of a treatment that specifically erases the tinnitus, rather than simply masking the sound or providing coping mechanisms for the individual. Scientists are now working to translate these findings from the animal model into a novel therapeutic strategy for people with severe tinnitus.

VESTIBULAR PROSTHESIS

Based on the recent 2008 National Health Inventory Survey, Balance and Dizziness Supplement, about 15.5 percent of U.S. adults, or about 33.6 million individuals, reported they had a problem with dizziness or balance in the past 12 months. Balance disorders are one of the reasons older people fall, and falls and fall-related injuries, such as hip fracture, can have a serious impact on an older person's life. One balance disorder which has been particularly difficult to treat is Ménière's disease. This disorder causes severe dizziness (vertigo), tinnitus, hearing loss, and a feeling of fullness or congestion in the ear. NIDCD estimates that approximately 615,000 individuals in the United States are currently diagnosed with Ménière's disease and that 45,500 cases are newly diagnosed each year. While many individuals are able to manage the symptoms associated with Ménière's disease through diet, drugs, or surgery, up to 2 in 10 do not find adequate relief from their symptoms after exhausting all treatment options. NIDCD-supported scientists are working to adopt cochlear implant technologies to produce a vestibular implant that could counteract vertigo attacks that persist despite other treatments. Scientists have already demonstrated the ability of a vestibular implant to induce, and provide recovery from, vertigo attacks in animal models of Ménière's. Most recently, scientists have translated this technology to humans and performed their first implantation into an

individual. While clinical trials are still several years away, this recent breakthrough provides hope to many for whom traditional treatments have failed.

STUTTERING

The popularity of the recent Academy Award winning movie, "The King's Speech," has brought to light the communication challenges faced by approximately 3 million Americans each day. Stuttering can affect individuals of all ages, but occurs most frequently in young children between the ages of 2 and 6, with boys 3 times more likely than girls to stutter. Most children, however, outgrow their stuttering, and it is estimated that less than 1 percent of adults stutter. For those individuals who continue to stutter into adolescence and adulthood, there are limited treatment options. NIDCD supports a research portfolio on stuttering to understand the underlying genetic, neurologic, and physiologic causes of stuttering, to predict which children will continue to stutter, and to develop novel and effective therapies for treatment of stuttering. Recently, NIDCD intramural scientists pinpointed the first specific genes that underlie stuttering. Building on previous studies which identified a genetic region linked to stuttering, and harnessing new technologies in genetic sequencing, the researchers found mutations in three genes important in the recycling of cellular breakdown products inside cells. Different mutations in two of these genes are related to severe metabolic disorders, called mucolipidosis II and III, which cause joint, skeletal, heart, liver, and other health problems, including speech problems. The findings may result in the development of new drug therapies for individuals who stutter.

OLFACTORY DEFICITS EARLY WARNING OF ALZHEIMER'S DISEASE

For several years, it has been know that individuals with Alzheimer's disease (AD) often exhibit an impaired sense of smell (olfaction), making a smell screening test an attractive opportunity for development as a biomarker of disease. However, it was not known why AD impacts olfaction. Recently, NIDCD-supported scientists used a mouse model of AD to identify pathological changes in the olfactory system very early in the animals' lives, indicating a sensitivity of the olfactory system to this type of damage. These changes manifested well in advance of the onset of changes in other areas of the brain involved in memory, and were predicted by the animals' performance on a smell discrimination task. In addition, NIDCD-supported scientists have used brain imaging of humans to examine changes in brain activity during smell discrimination tasks. These imaging studies have identified a significant blunting of response in individuals with AD. Both of these discoveries could lead to new, non-invasive tools to enhance the early diagnosis of AD, and better inform healthcare decisions for affected individuals.

NEW STRATEGIC PLAN FOR NIDCD

NIDCD has initiated the development process for a new Strategic Plan. In March 2011, NIDCD convened a series of working groups of scientific experts in the smell and taste; voice, speech, and language; and hearing and balance fields to advise us on emerging scientific opportunities in four priority areas: understanding normal function of communication systems; understanding diseases and disorders of communication systems; improving diagnosis, treatment, and prevention of communication disorders; and accelerating translation of research findings into practice. In addition, we remain committed to continuing our leadership in fostering the development of new investigators in the communication sciences. Our staff is currently working to compile these priority areas into a document that will guide our research investments from fiscal year 2012 through 2016. A draft will be made available for public comment later this year and we anticipate publication of our new Strategic Plan in January 2012.

Mr. Chairman, I would like to thank you and Members of this Subcommittee for giving me the opportunity to present examples of recent research progress and to highlight some programs made possible through your support of the NIDCD.

PREPARED STATEMENT OF DR. A. ISABEL GARCIA, D.D.S., M.P.H., DIRECTOR, NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

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 2012 budget request for NIDCR is $420,369,000, which reflects an increase of $11,113,000 over the

fiscal year 2011 enacted level of $409,256,000 comparable for transfers proposed in the President's request.

The NIDCR goal of improving the Nation's dental, oral, and craniofacial health is an ambitious one. It demands that we address the wide array of diseases and conditions that affect the oral cavity and craniofacial structures, including diseases such as dental caries (tooth decay) and periodontal diseases that are endemic in the United States, as well as birth defects such as cleft lip and palate, chronic oral-facial pain conditions, oral and pharyngeal cancers, and oral manifestations of systemic diseases, such as Sjögren's syndrome, diabetes, and HIV infection. NIDCR is committed to identifying effective preventive, diagnostic, and treatment approaches for these diseases and conditions. Today, I will describe how we are investing in basic discovery and preclinical studies across these myriad areas and applying new knowledge to the development of clinical trials and studies in humans.

ACCELERATING BASIC DISCOVERY

Joshua Lederberg, who shared the 1958 Nobel prize for discovering that bacteria can mate and exchange genes, once quipped about microbes that "you know one when you see it." The problem, he explained, is that microbes were largely "invisible" and noticed only after their damage had been wrought. NIDCR-supported researchers and others recently identified—made "visible"—more than 600 distinct microbial species as residents of the human mouth. NICDR scientists are also systematically exploring how the individual bacterial species assemble into biofilms. Biofilms are the living, mat-like microbial communities found on many parts of the human body, including our teeth and gums, and play a major role in the development of dental and oral disease.

Microbial biofilms can form on any surface, including on medical devices, and are implicated in more than 80 percent of human infections. The oral cavity offers tremendous potential both as a diagnostic window and an easily accessible model for research aimed at understanding the host of bacteria associated with biofilm-mediated disease throughout the body. Researchers now possess the tools to extract a biofilm sample and determine the identities of most of its microbial inhabitants.

Recently, NIDCR grantees devised a new fluorescent imaging system that successfully distinguished among 28 oral microbes within a single field of view and that soon will be able to distinguish among at least 100, providing spatial analysis in three dimensions. Enhanced imaging of the oral biofilm will accelerate discovery in studies of biofilm formation, organization, and composition and thus the keys to their control. This structural understanding will form the basis for research aimed at development of tools to combat oral and other infectious diseases and improve health.

An NIDCR grantee and colleagues recently performed a novel type of systematic genetic analysis to better elucidate microbial behavior. The researchers collected over 4,000 mutant bacterial strains and tested them in 324 different environmental conditions. Pulling all the data together, the scientists gained a fuller understanding of the functional molecular networks governing bacterial response. They also gleaned new information about a gene involved in antibiotic resistance and the synergy of three common antibiotic drugs.

Both of the exciting advances described above were spearheaded by young investigators on NIDCR training grants, offering prime examples of the vital importance of continuing to support new investigators and new ideas. NIDCR is committed to developing and strengthening the workforce of researchers that can leverage the latest tools of discovery and are dedicated to solving urgent problems in oral, dental and craniofacial health. To enhance this critical pipeline further, NIDCR continues to create innovative new training and career programs, such as a new transition path for clinical researchers, as well as an initiative to catalyze the formation of multidisciplinary teams led by new investigators researching temporomandibular disorders and orofacial pain.

TRANSLATING BASIC SCIENCE INTO IMPROVED PUBLIC HEALTH

Advances in studying oral microbial communities have the potential for rapid impact on research for new, more personally targeted, clinical treatment. A team of NIDCR-supported scientists recently reported that a microbe called Scardovia wiggsiae appears to be linked with severe forms of early childhood caries (ECC), the most prevalent chronic childhood disease in the United States. For decades, the oral bacterium Streptococcus mutans has been singled out as the primary pathogen involved in ECC. The scientists found that S. wiggsiae often was present in children with decayed teeth in the absence of S. mutans. The discovery of this bacterium's

role in ECC offers a future target in efforts to identify children at risk and to prevent or stop progression of this disease before it leads to destruction of the teeth.

The burden of craniofacial, oral, and dental disease, particularly untreated disease, falls heaviest on lower socioeconomic status (SES) groups, which include disproportionately large numbers of racial and ethnic minorities. Researchers, including those at the five NIDCR-supported Centers for Research to Reduce Disparities in Oral Health, continue working to identify creative, practical approaches to deal with pressing oral health issues, including ECC and oral and pharyngeal cancer. These approaches must be inexpensive, easily applied, and readily tailored to meet individual and community needs. Three of these Centers recently initiated clinical trials to test new interventions to prevent ECC among American Indian and Hispanic children and in residents of public housing. Children in low SES families are particularly vulnerable to ECC's painful and costly impact. Three additional trials will launch in fiscal year 2012.

ENHANCING THE EVIDENCE BASE FOR ORAL HEALTH CARE

Tackling real-world clinical issues and generating evidence that will be of immediate value to practitioners and patients is the central goal of the NIDCR-supported dental Practice-based Research Networks (PBRNs). Conducting research in dental practices draws on the experience and insight of practicing clinicians to help identify and frame research questions. Because PBRN studies address practice-based problems, their results tend to be more quickly translated into daily clinical care.

Leveraging the infrastructure of established dental practices for conducting PBRN studies also can be a powerful and cost-effective means to conduct clinical research. For example, the past decade brought reports that people who take bisphosphonates, a class of drug prescribed for osteoporosis or to treat the bone-wasting effects of cancer, can develop osteonecrosis (bone death) of the jaw, or ONJ. To address the problem, the three regional PBRNs, taking advantage of their presence in practices spanning multiple States, teamed up to carry out a collaborative study on ONJ. The study results, published in 2010, confirmed that bisphosphonate use is a risk factor for ONJ, and provided additional important evidence to guide clinicians in their treatment of this challenging condition.

In fiscal year 2012, NIDCR will launch a new National Dental PBRN. This single network, more national in scope and more representative of a greater variety of practice settings, will provide a framework to study and improve the delivery of oral care and will build upon the collaboration among the regional networks that was crucial to the successes to date. Critical to this effort is an improved capacity to collect data electronically. Using an adaptable electronic platform for enhanced connectivity, data sharing, and communication within and between networks will help providers conduct research effectively and efficiently and strengthen the PBRN enterprise.

DEVELOPING NEW CLINICAL TREATMENTS

Each year, about 400,000 people worldwide are diagnosed with cancer in the head and neck region. In an effort to identify new treatments and improve the stagnant 5-year survival rate that hovers only slightly above 50 percent, NIDCR scientists focused their research on the immunosuppressive drug rapamycin. This research is now moving from the basic and preclinical phases, which included studies in an NIDCR-developed mouse model, to clinical studies. By fiscal year 2012, scientists will be recruiting subjects for a clinical trial to assess rapamycin's safety and efficacy in humans.

Research is also needed to combat harmful treatment side effects for head and neck cancers. Many patients with head and neck cancers will receive radiation therapy, which has the significant long-term side effect of xerostomia (dry mouth). The salivary glands, damaged by the radiation used to kill nearby tumor cells, can become less permeable to the fluid that naturally flows through them and yield less saliva, or stop working altogether. Many functional and quality-of-life problems occur when oral tissues are deprived of saliva's protective properties, including difficulty chewing and swallowing, burning mouth, and greater risk of dental caries and oral fungal infections. Despite continuing efforts to eliminate this problem, many patients continue to suffer.

Moving from bench to bedside, NIDCR scientists began the first gene-transfer study in people with radiation-induced xerostomia. The transferred gene, Aquaporin-1, encodes a protein that conveys fluid by forming pores, or water channels, in the cell membrane. The study assesses whether the transferred gene will open water channels in the duct cells, allowing the rapid movement of water through the duct. In fiscal year 2012, NIDCR will issue an initiative to stimulate

additional research on restoring damaged salivary gland structure and function to complement this important clinical advance.

As these highlights illustrate, NIDCR has made a strong commitment to advancing oral health science through efforts in the laboratory, in training sites, in dental practices, and in the community. This investment is providing new tools and scientific approaches that may greatly accelerate the next breakthroughs in oral health research. NIDCR will continue to support research that provides new and exciting leads that can translate into better ways to prevent, diagnose, and manage oral, dental, and craniofacial diseases and disorders. In so doing, NIDCR seeks to improve the oral health of the Nation.

PREPARED STATEMENT OF LINDA S. BIRNBAUM PH.D., D.A.B.T., A.T.S., DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES AND HEALTH SERVICES

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $700,537,000; an increase of $17,400,000 over the comparable fiscal year 2011 enacted level of $683,137,000, comparable for transfers proposed in the President's request.

INTRODUCTION

Good health is vitally important for all Americans, and it depends on a clean and safe environment. Currently, our healthcare system expends huge resources controlling a variety of diseases and dysfunctions that are known to be at least partially connected with environmental exposures: asthma, cancer, developmental disabilities, neurological/cognitive deficits, heart attack, and many others. Preventing these diseases through prevention of adverse environmental exposures could make an enormous difference in reducing healthcare costs. At NIEHS, and through NIEHS-funded projects in research institutions across the United States, we are bringing all the tools of biomedical science to bear on the fundamental questions of the effects of environmental exposures to toxic substances on biological systems. Environmental health science is advancing at a tremendous rate and new tools—genetics, genomics, proteomics, metabolomics, informatics, and computational biology, just to name some of these new disciplines—give us new insights on how environmental effects happen in our bodies. They also point the way toward technologies and testing procedures to provide better and more timely information for the use of our agency partners who are responsible for policy decisions and regulations.

ADVANCES IN TOXICOLOGY AND EXPOSURE ASSESSMENT

With our rapidly increasing understanding of the subtleties of biological effects of environmental exposures, we are moving toward a new kind of toxicological testing that is less expensive and time-consuming than our current methods, and also gives us an improved understanding of the actual effects on humans. Toxicology is becoming a more powerful predictive science focused on making target-specific, mechanism-based, biological observations. Alternative assays are targeting the key pathways, molecular events, and processes linked to disease or injury and incorporating them into a research and testing framework. Our National Toxicology Program (NTP) at NIEHS is laying the foundation for this new testing paradigm in partnership with the National Human Genome Research Institute, the Environmental Protection Agency, and the Food and Drug Administration. We are using quantitative high-throughput screening assays to test a large number of chemicals. The resulting data are being deposited into publicly accessible relational databases. Analyses of these results will set the stage for a new framework for toxicity testing.

The NIEHS-led Exposure Biology Program (EBP), part of the NIH Genes, Environment and Health Initiative, has resulted in the development of dozens of new technological advances for personalized measurement of environmental exposures. At a recent workshop, EBP investigators presented their prototypes: miniaturized personal monitors for black carbon and other air pollutants; a wearable nanosensor array for real-time monitoring of exposure to diesel and gasoline exhaust; a personal aerosol sensor platform to link children's exposures to asthma severity; personal exposure assessment systems for chemical toxicants; gene expression biomarkers of airway response to tobacco exposure; and biomarkers of organophosphate-linked proteins. One prototype of a continuously operating wearable badge that provides real-time measurements of chemical toxicants has attracted subsequent R&D funding from the Department of Defense to develop this model for use by military personnel.

Others are being moved into validation studies as a next step toward their deployment in environmental health research.

EPIGENETICS, ENDOCRINE DISRUPTERS, AND ENVIRONMENTAL HEALTH

Our understanding of chemical toxicity has been challenged by the new science of epigenetics, which is the study of changes to the packaging of the DNA molecules that influence the expression of genes, and hence the risks of diseases and altered development. Studies indicate that exposures that cause epigenetic changes can affect several generations.[1] This new understanding heightens the need to protect people at critical times in their development when they are most vulnerable. NIEHS is making key investments in understanding basic epigenetic processes and how they are influenced by environmental factors. Recently, some of this work has provided a critical resource for understanding and characterizing properties of human induced pluripotent stem cells.[2] The development of pluripotent stem cells shows promise for research and clinical applications in lieu of embryonic stem cells, but many questions remain to be answered about their structure, utility, and safety. NIEHS-funded investigators have established genome-wide reference maps of DNA methylation (an epigenetic marker) and gene expression in previously derived human embryonic cell lines and human iPS cell lines, to assess their epigenetic and transcriptional similarity and predict their differentiation efficiency. A separate report by another NIEHS-funded group reported "hotspots" of aberrant epigenomic reprogramming in human iPS cells.[3] There are still many questions about the role of these important epigenetic processes which will need to be answered before iPS cells can be confidently used in research and therapy.

Related to the field of epigenetics is the key concept of "windows of susceptibility." Research shows that the developmental processes that occur at fetal and early life stages are especially vulnerable to disruption from relatively low doses of certain chemicals.[4] [5] [6] We first saw this in the case of lead and other metals, such as mercury and arsenic, which we learned decades ago could harm neurological development as a result of fetal and childhood exposures. This concept also applies to hormonally active agents which disrupt the endocrine system. This is an active area of our research program. For example, NIEHS and NTP are funding important studies to fill the gaps in our knowledge about bisphenol A (BPA), a widely distributed compound used in plastics, can linings, thermal paper, and more. NTP's Center for Evaluation of Risks to Human Reproduction determined that there was "some concern" about effects to the brain, behavior, and prostate gland in fetuses, infants, and children exposed to BPA.[7] NIEHS is now supporting an aggressive research effort to fill the research gaps in this area, especially concerning BPA effects on behavior, obesity, diabetes, reproductive disorders, development of prostate, breast and uterine cancer, asthma, cardiovascular diseases and transgenerational or epigenetic effects.

Any consideration of important public health issues in the United States. has to include obesity. Environmental exposures are beginning to be implicated in the obesity epidemic.[8] [9] NIEHS is supporting research on the developmental origins of obesity and the theory that environmental exposures during development play an important role in the current epidemic of obesity, diabetes, and metabolic syndrome. There are data showing weight gain in adult rats and mice following developmental exposure to a number of different chemicals, such as tributyltin compounds,[10] which

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[1] Anway MD, Cupp AS, Uzumcu M, Skinner MK (2005) Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308:1466–1469.

[2] Bock C, Kiskinis E, Verstappen G, et al. (2011) Reference maps of human ES and iPS cell variation enable high-throughpu characterization of pluripotent cell lines. Cell 144(3):439–52.

[3] Lister R, Pelizzola M, Kida YS, et al. (2011) Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. Nature 471(7336):68–73.

[4] Rogan WR, Ragan NB (2003) Evidence of effects of environmental chemicals on the endocrine system in children. Pediatrics 112:247–252.

[5] Dolinoy DC, Weidman JR, Jirtle RL (2007) Epigenetic gene regulation: Linking early developmental environment to adult disease. Reproductive Toxicology 23:297–307.

[6] Committee on Environmental Health, American Academy of Pediatrics (1999) Pediatric environmental health, 2nd edition, pp 9–23.

[7] http://www.niehs.nih.gov/news/media/questions/sya-bpa.cfm See "What does some concern mean?".

[8] Grun F, Blumberg B (2009) Endocrine disrupters as obesogens. Mol Cell Endocrinol 304:19–29.

[9] Verhulst SL, Nelen V, Hond ED, Koppen G, Beunckens C, Vael C, Schoeters G, Desager K (2009) Intrauterine exposure to environmental pollutants and body mass index during the first 3 years of life. Environ Health Perspect 117:122–126.

[10] Iguchi T, Watanabe H, Ohta Y, Blumberg B (2008) Developmental effects: oestrogen-induced vaginal changes and organotin-induced adipogenesis. Int J Androl 31:263–268.

have been termed "obesogens" by some researchers. A groundbreaking workshop on environmental factors in obesity and diabetes was sponsored by NIEHS in January 2011. Many research gaps still need to be filled, but if these early research results are confirmed, we may find it more useful to expand our approach to fighting obesity to include not just educating about diet and lifestyle but also reducing early life exposure to these "obesogenic" chemicals that might be setting the stage for us to gain weight later in life.

PLANNING FOR THE FUTURE

NIEHS recently began work on the development of a new Strategic Plan to set goals for guiding our research investments over the next 5 years. Our process is designed to bring in information and perspectives from a wide variety of sources: community members, advocacy groups, agency partners, and scientists from all disciplines.

In summary, understanding the connection between our health and our environment, with its mixture of chemicals, diet and lifestyle stressors, is a complex and intricate scientific endeavor. At NIEHS, we remain committed to leading the evolution of the field of environmental health sciences to meet emerging public health challenges.

PREPARED STATEMENT OF THOMAS R. INSEL, M.D., DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute of Mental Health (NIMH) of the National Institutes of Health (NIH). The fiscal year 2012 NIMH request of $1,517,006,000 includes an increase of $40,981,000 over the fiscal year 2011 appropriated level of $1,476,025,000. In my statement, I will underscore the impact that mental disorders have on public health in the United States; outline examples of NIMH's strategies for reducing the burden associated with mental disorders; and, highlight examples of research activities that are advancing us toward this goal. I submit this statement with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences.

PUBLIC HEALTH BURDEN OF MENTAL ILLNESS

NIMH's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. The burden of mental illness is enormous. In 2009, an estimated 11 million American adults (approximately 1 in 20) suffer from serious mental illness.[1] According to the World Health Organization, mental disorders are the leading cause of medical disability in the United States and Canada.[2] In contrast to many other chronic medical conditions, mental disorders typically begin at an early age, usually before the age of 30. Mental disorders, such as schizophrenia, depression, and bipolar disorder, are increasingly recognized as the chronic medical illnesses of young people.

The annual economic costs of mental illness in the United States are enormous. The direct costs of mental health treatment represent an estimated 6.2 percent of all healthcare spending,[3] which, according to the Centers for Medicare and Medicaid Services, totals 15.8 percent of the gross domestic product. Indirect costs, which include all non-treatment-related costs such as Social Security disability payments, lost earnings, and incarceration, account for an even greater expense than the direct costs associated with mental healthcare. A conservative estimate places the total direct and indirect costs of mental illness at well over $300 billion annually.[4]

NIMH's mission is not merely to reduce the symptoms and disability associated with mental disorders, but to promote recovery, to extend healthy life, and ulti-

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[1] SAMHSA. *Results from the 2009 National Survey on Drug Use and Health: Mental Health Findings* (Office of Applied Studies, NSDUH Series H–39, HHS Publication No. SMA 10–4609). Rockville, MD; 2010.

[2] The World Health Organization. The global burden of disease: 2004 update, Table A2: Burden of disease in DALYs by cause, sex and income group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008.

[3] Mark TL, et al. *National Expenditures for Mental Health Services and Substance Abuse Treatment*, 1993–2003. SAMHSA Publication No. SMA 07–4227. Rockville, MD: SAMHSA, 2007.

[4] Insel TR. Assessing the economic cost of serious mental illness. Am J Psychiatry. 2008 Jun;165(6):663–5.

mately, to discover preventive interventions. In the year ahead, NIMH will work toward this mission by fostering and facilitating a collaborative approach across the spectrum of mental health research approaches—from discovery to dissemination—to make a positive change in the lives of people with mental disorders and their families.

TECHNOLOGIES TO ACCELERATE DISCOVERY

Funding from the American Recovery and Reinvestment Act of 2009 has enabled NIMH to support infrastructure development that will provide a framework for future discoveries. One large, collaborative project that promises to provide researchers with an invaluable reference tool is the Transcriptional Atlas of Human Brain Development. This atlas is mapping when and where genes are switched on and off during normal brain development, because to understand disorders, scientists must first understand what the normal patterns of gene expression are during development. The atlas will contain data from 16 brain regions at 11 developmental stages—ranging from embryonic development to mid-adulthood. These maps will highlight differences between prenatal and postnatal brains, changes across adolescence, and unique patterns of gene expression that only occur during development. The first maps from the atlas were released this year and will form the foundation for future maps and releases.

TRANSLATIONAL SCIENCES AND THERAPEUTICS DEVELOPMENT

NIMH-funded researchers are working to translate discoveries from basic science into targeted, rapidly acting therapeutics. Current antidepressant medications and cognitive behavioral therapies often require 6 to 8 weeks to have an effect. Previous NIMH research has shown that the drug ketamine can reduce depression, including thoughts of suicide, within 6 hours. However, long-term use is associated with side effects, and the mechanism by which ketamine works remained unclear, until NIMH-funded researchers made a significant discovery in 2010. They identified how the brain responds to ketamine, as well as the molecular mechanism for this rapid response—the rapid activation of an enzyme, mTOR, which regulates cell growth, proliferation, and survival. The discovery of this cellular mechanism today helps point the way to developing practical, rapid-acting treatments for depression tomorrow.

In tandem with this cutting-edge discovery-to-treatment research, NIMH is looking into ways to personalize and optimize current treatments for depression. While effective interventions do exist, there is considerable variation in individual treatment outcomes. The Establishing Moderators/Mediators for a Biosignature of Antidepressant Response in Clinical Care (EMBARC) study is working to develop a collaborative approach among researchers who are focusing on biological indicators (biomarkers) of depression. EMBARC researchers hope to identify a standard set of biomarkers and other measures that can be used to predict which interventions will produce the best treatment outcomes for an individual. Taken together with our advancing knowledge of ketamine, we can say with confidence that rapid, personalized, and effective treatments for depression are close at hand.

ENHANCEMENT OF EVIDENCE-BASE FOR HEALTHCARE DECISIONS

NIMH's basic and translational research will improve U.S. public health only when they lead to improved mental healthcare. To improve the outcomes for people suffering from schizophrenia, NIMH is funding the Recovery After an Initial Schizophrenia Episode (RAISE) project—a large-scale clinical trial designed to alleviate the long-term disability associated with schizophrenia by intervening as early as possible after the first onset of symptoms, so that people with the disorder can lead more productive, independent lives. RAISE addresses the effectiveness of providing early, sustained, and integrated care to improve health and life functioning outcomes, and develops strategies to facilitate implementation of successful, cost-effective early interventions in the U.S. healthcare system. RAISE incorporates features necessary for rapid dissemination into community settings, thus accelerating the transition from research to practice.

NIMH has also launched the Mental Health Research Network to encourage scientific collaboration among nine established research centers that are based in integrated, not-for-profit healthcare systems. These systems provide care coverage to a diverse population of 10 million people in 11 States, and they share rich and compatible data resources to support a range of effectiveness research. Researchers have begun to use this network to address vital issues, including the development of a geographically and ethnically diverse autism research registry; a pilot study for a

new type of therapy for postpartum depression; and, a longitudinal analysis of how suicide warning labels on antidepressants affect later suicidality among youth.

NEW INVESTGATORS, NEW IDEAS

The future of discovery and translational research lies in the next generation of mental health researchers. NIMH's Biobehavioral Research Awards for Innovative New Scientists (BRAINS) program provides support to early stage investigators to foster innovative research aimed at critical gaps identified by the NIMH Strategic Plan. NIMH also recognizes the importance of ensuring that our workforce reflects the diversity of backgrounds and perspectives that has made the United States a source of innovation. NIMH is leading an NIH Blueprint for Neuroscience initiative to enhance diversity in neuroscience through undergraduate research education experiences, and has established a supplemental funding program to provide underrepresented minority scholars with mentored research training in strong institutional training programs.

WORKING COLLABORATIVELY TO COMBAT SUICIDE

NIMH is committed to collaborating with other Federal agencies and private partners to hasten the development of interventions and to facilitate their widespread use by those most in need. As an example, NIMH has been concerned by the high rate of suicide among our Nation's military personnel, and has partnered with the Army to conduct the Study to Assess Risk and Resilience of Service Members (Army STARRS)—the largest mental health study of military personnel ever conducted. Early examination of Army STARRS data has begun to reveal potential predictors of risk for suicide among soldiers. Researchers plan to analyze additional historical data and new survey data collected by Army STARRS to confirm and expand upon these findings.

Suicide among civilians is also of significant concern. Approximately 34,500 American lives are lost to suicide each year, nearly twice the number lost due to homicide, making it the 10th leading cause of death in the United States.[5] [6] To combat this issue, under the leadership of the Substance Abuse and Mental Health Services Administration, NIMH joined the Army, the Centers for Disease Control and Prevention, other NIH Institutes, and private partners to form the National Action Alliance for Suicide Prevention. NIMH is spearheading a Research Prioritization Taskforce on behalf of the Action Alliance to develop a strategic research agenda that could reduce suicide-related mortality by 20 percent in 5 years, or 50 percent in 10 years, if fully implemented.

Successfully combating mental disorders requires collaboration across multiple levels of society; Federal agencies, the research community, private industry, and the individuals and families affected each day. Despite the tremendous burden of mental disorders, NIMH is up to the challenge of bringing all stakeholders to the table, harnessing scientific advances, and directing the next generation of research to improve the lives of people affected by mental disorders.

PREPARED STATEMENT OF JOHN RUFFIN, PH.D., DIRECTOR, NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES

Mr. Chairman and Members of the Committee: I am pleased to present the President's budget request for the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health (NIH). The fiscal year 2012 budget of $214,608,000 includes an increase of $5,073,000 over the fiscal year 2011 comparable appropriation level of $209,535,000.

This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences and reallocate the remaining portions of the National Center for Research Resources to other parts of NIH, including NIMHD.

INTRODUCTION

Health disparity is an issue of immense proportions with health, economic, social and environmental impact for the Nation. Disparities in the burden of illness and

[5] CDC, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System.

[6] U.S. Department of Justice, Federal Bureau of Investigation. (September 2009). Crime in the United States, 2008.

premature death experienced by racial and ethnic minorities, low-income, and rural populations, apply to a broad spectrum of disease types. Evidence-based research reveals that health disparities are the result of interacting factors that may be genetic, biological, environmental, social, economic, or psychological in nature. The causes of and solutions to health disparities are multidimensional and require multidimensional approaches to improve health and eliminate the disparities.

Health disparities have had a longstanding economic burden on the healthcare system. The Affordable Care Act (ACA) included several provisions aimed at mobilizing the Nation around actions to confront health disparities in order to overcome the multiple barriers faced by underserved communities in obtaining quality healthcare. One provision in the ACA re-designated the National Center on Minority Health and Health Disparities (NCMHD) at the NIH to an Institute—named the National Institute on Minority Health and Health Disparities. The NIMHD was created to strengthen the base for the acceleration of scientific discovery already initiated by the predecessor organization, the NCMHD, to understand health disparities and to identify and implement strategies to eradicate them across the Nation. In accordance with the Affordable Care Act, NIMHD is charged to plan, review, coordinate, and evaluate minority health and health disparities research activities conducted by the NIH Institutes and Centers (ICs). As health disparities transcend many diverse areas of biomedical science and public health, this work must involve all of the NIH ICs, and numerous Federal Government and non-Federal Government partners.

BUILDING ON A DECADE OF PROGRESS

During the past decade, under the aegis of the NCMHD, the NIMHD launched its congressional mandates, and established new programmatic initiatives and partnerships, allowing it to create the infrastructure required to be at the cutting edge of scientific discovery through its independent programs and support for collaborative research, research infrastructure development, and outreach projects with partners within the NIH, HHS, and beyond.

The foundation of the NIMHD's research portfolio is the NIMHD Exploratory and Comprehensive Centers of Excellence (COE) programs. Research in the COEs spans the wide array of diseases, health conditions, and complex non-biological factors contributing to health disparities. Translational research and the development of appropriate health interventions is a particular strength of the NIMHD COEs. The NIMHD University of Puerto Rico-Cambridge Health Alliance Research Center of Excellence has focused its research on Latino health and healthcare disparities, specifically mental disorders, substance abuse and asthma. This COE has generated and tested models aimed to improve health service delivery to eliminate these disparities. This includes multi-level interventions at the provider, individual/family and policy levels to reduce health services disparities and has provided invaluable data to understand the magnitude of substance abuse treatment disparities and the social and economic burden of these disparities.

In addition, NIMHD COEs have assisted in emergency response to disasters with health disparities implications such as Hurricane Katrina in 2005, and the Haiti earthquake in 2010. NIMHD COEs responded to the Haitian earthquake crisis with assistance to Haitian communities in south Florida and beyond the borders of the country. These efforts have improved the understanding of the global nature of health disparities.

To effectively conduct research, individuals, institutions and organizations must have the capacity and access to the resources that are necessary to conduct research. NIMHD is a leader in advancing the NIH efforts to increase the number of underserved populations represented in science and medicine. The NIMHD Health Disparities Research and the Clinical Research for Individuals from Disadvantaged Backgrounds Loan Repayment Programs (LRP) have supported more than 2,300 individuals representing multiple disciplines through loan repayment of educational loans. More than 60 percent of the LRP scholars represent racial/ethnic minority populations. The program has incentivized the pursuit of a scientific or health disparities research career and many former LRP recipients have been successful in competing for other NIH grants. Also, NIMHD offers the opportunity for LRP recipients to transition into becoming independent investigators through its Disparities Research and Education Advancing our Mission (DREAM) program in its Intramural Research Program (IRP). During their 2-year appointment at the NIH conducting research on health disparities, the DREAM fellows work with mentors within the NIH Intramural Research Program across different NIH Institutes and Centers. After the 2-year period, the DREAM fellows have the option of returning to

their originating academic institution or to a health disparity community to further hone their research skills and complete the final 3 years of the program.

In addition, programs such as the Research Centers in Minority Institutions and the new NIMHD Science Education Initiative which focuses on promoting science education and increasing the pool of individuals from health disparity populations in the science field starting from kindergarten through the post-doctoral level, will play a key role in advancing the NIMHD's activities in this area.

There is growing interest in scientific research including health disparities research at academic institutions throughout the Nation. However, many institutions have limited or no current capacity to conduct scientific research. Recognizing the variance in capacity among institutions of higher education, the NIMHD has invested considerable resources in the enhancement of research infrastructure and capacity of less research-intensive institutions through programs such as the NIMHD Building Research Infrastructure and Capacity (BRIC) program. Over time, the BRIC awards have been instrumental in transforming the abilities of some institutions to conduct health disparity research. For example, San Francisco State University (SFSU) through the development of shared research facilities has resulted in the publication of approximately 70 research articles on a variety of scientific topics, 76 SFSU students have entered highly competitive Ph.D. programs, and BRIC-supported faculty have received more than $13 million in support to conduct health disparity research. Importantly, BRIC support has provided a strong base for institutions to expand their graduate level educational programs to include new doctorate opportunities to advance health disparities research, as well as the development of NIMHD Centers of Excellence.

A NEW ERA IN THE FIGHT AGAINST HEALTH DISPARITIES

The next decade will focus on bridging persistent gaps in health disparities, sustaining effective investments, and developing and adapting innovative approaches to health disparities. NIMHD will lead the development, implementation and evaluation of the agency's health disparities research agenda in collaboration with the other NIH Institutes and Centers. Research on minority health and health disparities, research capacity-building and outreach/information dissemination priorities across the NIH will emphasize areas such as: translational research, genetics and biological factors, global health, social determinants of health, behavioral and social sciences, innovative health technologies, developing a diverse scientific workforce, health informatics capacity, public-private partnerships, social networking, and diverse participation in clinical trials.

NIMHD will advance this health disparities research agenda through translational research and dissemination of research findings for the benefit of clinical practice and health disparity communities. Community and population health intervention studies that map social, economic and environmental determinants will provide greater insight into the underlying causes of health disparities. In addition, primary care and prevention research to inform healthcare reform, improve healthcare quality, reduce costs and ultimately improve health outcomes for health disparity populations will be examined.

In today's culturally diverse and technologically advanced society, the construction of health messages that do not consider culture, history, environments, or literacy levels of certain health disparity communities can result in the inability of those communities to receive health information. NIMHD is committed to supporting and developing vehicles to translate and deliver research findings and health information to health disparity communities in a culturally and linguistically appropriate manner.

CONCLUSION

While many health disparities concerns of the past decade remain pervasive, the NIMHD sees opportunities to accelerate the pace of scientific discovery and translation. Within the context of the NIH and HHS priorities for eliminating health disparities, the NIMHD will intensify and diversify its research focus to elucidate the Nation's understanding of health disparities. Research strategies must continue to be innovative and the results of this research must reach the community at a faster pace. The NIMHD is committed to strengthening its research efforts to realize these goals.

PREPARED STATEMENT OF STORY C. LANDIS, PH.D., DIRECTOR, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for NINDS. The fiscal year 2012 budget is $1,664,253,000. Our mission is to reduce the burden of neurological disorders through research. NINDS research has improved diagnosis, prevention, and treatment, but the best of medical science is still far from optimal for most nervous system disorders. Fortunately, advances in understanding the brain and its disorders are providing extraordinary opportunities for progress.

ENHANCING THE EVIDENCE BASE FOR MEDICAL DECISIONS

U.S. Centers for Disease Control and Prevention statistics show that from 1997 to 2007 the stroke death rate in the United States decreased 34.3 percent, and the number of stroke deaths declined 18.8 percent, which translates to thousands of lives saved and thousands with reduced disability every year. For decades, NINDS clinical trials have contributed to this trend by providing evidence that enables physicians to choose the best stroke prevention interventions according to each person's risk factors. In April, NINDS stopped a stroke prevention clinical trial early because the results were already clear[1]. The trial included patients at high risk because of a prior non-disabling stroke and severe narrowing of arteries to the brain. Angioplasty combined with stenting, which opens clogged arteries with a tiny balloon and inserts a device to prop them open, plus aggressive medical therapy led to a higher risk of stroke than the medical therapy alone. Another recent NINDS clinical trial showed that a procedure using stents is as safe and effective in preventing stroke as carotid endartarectomy, a more invasive surgical procedure to clear arteries, in people with certain risk factors.[2] Follow up to monitor longer term results is continuing for both trials. NINDS clinical trials are similarly guiding treatment for other diseases. A recent clinical trial showed that an older drug, ethosuximide, may be the best first drug to test to prevent seizures with minimum side effects in children with absence epilepsy, providing much needed guidance for treating this common disorder[3]. An NINDS-Department of Veterans' Affairs trial showed that surgical implantation of deep brain stimulators (DBS) can yield better movement and quality of life than drug treatment for people with advanced Parkinson's disease, and more recent results of this trial provided information about choosing the best site in the brain to implant electrodes for each patient[4]. NINDS currently supports 32 multi-site clinical trials to test the safety and effectiveness of interventions in stroke, epilepsy, traumatic brain injury, multiple sclerosis, muscular dystrophy, and other diseases, and more than 120 earlier phase trials that are essential steps toward large efficacy trials.

ADVANCING TRANSLATIONAL SCIENCE

Since long before the term "translational" became common, NINDS has pushed development of basic science advances into drug, biologic, and device therapies. The first enzyme therapy for inherited metabolic diseases, several drugs for epilepsy, the first emergency treatment for stroke, and pioneering technology for devices that replace lost nervous system function are among advances that NINDS translational research made possible. Often, industry capitalizes on NIH basic science findings to develop a new therapy. However, rare diseases, bold new therapeutic strategies, and new uses for existing drugs are all challenges that NINDS is more likely than industry to take on. This is especially so now because drug companies, citing the extraordinary challenges of brain research, are reducing programs to develop nervous system drugs[5].

NINDS launched the Cooperative Program in Translational Research in 2003 to exploit increasing opportunities from neuroscience research. This program supports teams of academic and small business investigators to carry out milestone-driven, preclinical therapy development for a broad range of neurological disorders. The

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[1] http://www.nlm.nih.gov/databases/alerts/intracranial_arterial_stenosis.html.

[2] Brott TG et al. Stenting Compared to Endarterectomy for Treatment of Carotid Artery Stenosis, New England Journal of Medicine 363:11–23 2010.

[3] Glauser et al. Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy. New England Journal of Medicine. 362:790–799 2010.

[4] Weaver F. et al. Best Medical Therapy versus Bilateral Deep Brain Stimulation for Patients with Advanced Parkinson's Disease: A Randomized Controlled Trial. JAMA 301:63–73 2009; Follett et al. Pallidal versus Subthalamic Deep Brain Stimulation for Parkinson's Disease. New England Journal of Medicine 362:2077–91 2010.

[5] "R&D Cuts Curb Brain-Drug Pipeline," The Wall Street Jounal, March 27, 2011.

first candidate therapies from this program have moved into clinical testing for disorders including stroke, Batten disease, and muscular dystrophy.

Several NINDS programs meet special translational needs for particular diseases. Among these are the Anticonvulsant Screening Program, the Specialized Centers of Translational Research in Stroke (SPOTRIAS), the Udall Centers of Excellence in Parkinson's Disease, and the Wellstone Centers for Muscular Dystrophy Research. NINDS chose spinal muscular atrophy (SMA) as the disease to pilot another innovative approach to drug development. With experts from academia, industry, and FDA, the SMA Project designed a drug development plan and is implementing the plan through a "virtual pharma" organization that engages resources via contracts. Promising drug candidates are now in advanced pre-clinical testing, and the Project is working toward certification for a clinical trial in 2012. Building on the SMA Project strategy, NINDS is leading the NIH Blueprint for Neuroscience in a larger scale Grand Challenge on Neurotherapeutics. The challenge goal is to develop truly novel drugs that will transform the treatment of nervous system diseases. The NINDS Intramural Research Program, which has a long record of therapy development, is also accelerating translational research under a new Clinical Director. NINDS translational programs work closely with all of the NIH-wide programs and resources that will become part of the National Center for Advancing Translational Sciences (NCATS), and will certainly benefit from NCATS programs to catalyze translational research.

Because novel therapies for several neurological diseases are moving toward readiness for clinical testing, NINDS is developing a multi-site clinical network to improve the speed and effectiveness of the early steps in clinical testing of novel therapies for neurological disorders. Better early phase testing will increase the likelihood of success in larger and more expensive phase III clinical trials of effectiveness. This network will test promising interventions, whether they arise from academia, foundations, or industry, and will engage expertise much greater than the Institute could dedicate to separate networks for each of the many neurological diseases. This is especially important for rare disorders, including pediatric diseases. A project to validate biomarkers for SMA will be among the network's first studies.

Another major clinical initiative will develop and validate biomarkers for Parkinson's disease, that is, measurable indicators of the disease process. Biomarkers research, which NINDS supports for many disorders, exemplifies another way that NINDS programs can catalyze both NIH and industry therapy development efforts. With biomarkers for neurodegenerative disorders, clinical trials can determine in months, rather than years, whether drugs are slowing the progression of disease and understand why a new treatment worked or did not. Better biomarkers can reduce the cost of research and speed the development of better treatments in NIH and industry.

ACCELERATING PROGRESS THROUGH TECHNOLOGY

An extraordinary array of technologies has accelerated progress in neuroscience. These range in scale from imaging activity of the thinking human brain as people carry out complex tasks, to understanding atom by atom how molecules control electrical activity in brain cells. This year research demonstrated the power of whole genome sequencing to understand Charcot-Marie-Tooth disorder, a peripheral nerve disease [6]. This is a harbinger of personalized genomics for many diseases. Next generation genomics research is underway for several neurological disorders. A "Center without Walls" will bring together the best possible team, regardless of geography, to apply advanced genomics to epilepsy. On another technological frontier, ARRA enabled NINDS to accelerate research on induced pluripotent stem cells (iPSC's) that can be derived from patients with Parkinson's, Huntington's, ALS, epilepsy, and other disorders. A spate of new technologies, from methods that label nerve cells with more than a hundred different colors, to computerized three-dimensional reconstruction of intricate nerve cell circuits, to techniques that control the activity of individual nerve cells with light, are arming neuroscientists to meet the longstanding challenge of understanding how circuits of nerve cells underlie memory, perception, complex movement, and other higher brain functions. This has implications for understanding autism, epilepsy, Parkinson's, Alzheimer's, and many other diseases.

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[6] Lupski JR et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. New England Journal of Medicine 362:1181–91 2010.

ENCOURAGING NEW INVESTIGATORS AND NEW IDEAS

When progress against disease is not forthcoming, a gap in basic understanding of the normal brain or the disease process is often the cause. Physicians and scientists across academia and industry agree that basic research propels long-term progress against disease. The insight and ingenuity of the research community is the key. Supporting a vigorous scientific community and investigator-initiated research are thus high priorities throughout NINDS programs and policies. To encourage innovative research, for example, the EUREKA (Exceptional Unconventional Research Enabling Knowledge Acceleration) program complements the NIH Pioneer Awards, New Innovator Awards, and Transformative R01's, all of which support neuroscientists. To prepare the next generation of neuroscientists, NINDS training and career development programs are tailored to the needs of basic and clinical researchers, and funding policies favor early stage investigators. NINDS encourages cooperative research and promotes sharing through several programs. Examples include the Common Data Elements program, Human Genetics Resource Center, consortia on induced pluripotent stem cells, disease centers programs, and other grants to multi-investigator teams. NINDS is improving programs on workforce diversity and health disparities based on guidance from an external review and planning process that was completed in 2011.

CONCLUDING REMARKS

Neurological disorders present formidable challenges. Nonetheless, prospects for progress have never been more encouraging because of progress in understanding the nervous system and its diseases at every level from molecules through the working human brain. NINDS is aggressively pursuing better prevention and treatment with a balance of basic, translational, and clinical research, supported through investigator-initiated and priority-targeted programs.

PREPARED STATEMENT OF PATRICIA A. GRADY, PH.D., RN, FAAN, DIRECTOR, NATIONAL INSTITUTE OF NURSING RESEARCH

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Institute of Nursing Research (NINR) of the National Institutes of Health (NIH). The fiscal year 2012 budget includes $148,114,000 which is $3,857,000 more than the comparable fiscal year 2011 appropriation of $144,257,000.

INTRODUCTION

I appreciate the opportunity to share with you some of the exciting areas of research that we support at the National Institute of Nursing Research (NINR). As you know, a unique combination of societal trends challenges our Nation's health, including an aging population, increased chronic illness and obesity rates, and shortages in the healthcare workforce. At NINR, we address these issues by supporting research across the life span that: builds the scientific foundation for clinical practice; improves quality of life through managing and easing symptoms of illness; promotes health and prevents disease through biological and behavioral interventions; and enhances end-of-life and palliative care. We also seek to ensure future discoveries by training the next generation of nurse scientists. NINR's emphasis on clinical research and training places NINR in a position to make major contributions to trans-NIH initiatives to enhance the evidence-base for healthcare decisions, promote translational research, and support new investigators and new ideas. NINR was established 25 years ago, in 1986, as the National Center for Nursing Research. This year, we are commemorating our 25th anniversary through a series of scientific outreach events to celebrate our longstanding emphasis on translating science to improve health and clinical practice. In our first event, a scientific symposium entitled "Bringing Science to Life," some of our distinguished scientists presented cutting edge research on topics as varied as: the role of sleep in health and safety; managing chronic illness in racially/ethnically diverse groups; testing interventions to educate and support parents with premature infants; and understanding the biological underpinnings of muscular dystrophy. This Anniversary is an opportunity to review what NINR science has accomplished, and more importantly, to envision and plan the next phase of evidence-based research to meet future health and healthcare needs, challenges, and priorities. As we look forward to the next 25 years, we are confident that NINR-supported science will play an ever-increasing role in addressing the most pressing issues facing our Nation's health. I would, next, like to share

with you some examples of the research that we support and how it improves quality of life.

CHILDHOOD AND ADOLESCENCE: RISK AND RESILIENCE

From birth through young adulthood, children and adolescents face many health challenges and also demonstrate incredible resilience. NINR supports research to promote positive outcomes for children and families facing a myriad of challenges. For example, chronic health conditions in children, such as diabetes, arthritis, and obesity, pose challenges for the entire family and require sustained attention to treatment adherence and health assessment. NINR-funded scientists have made advances both in understanding the family's role in children's health and in improving assessment strategies. One study found that although parents detected significant pain in their child following the child's surgery, they tended to under-treat it, suggesting that educating parents about pain management may be beneficial. Another study found that screening children's waist circumference, which can be easily implemented in schools, identifies more cases of high blood pressure than the usual measure of body mass index alone. A current initiative led by NINR aims to improve self-management of chronic illness in children. An increasing challenge later in childhood comes from HIV, with adolescents and young adults comprising one-third to one-half of new infections in the United States,[1] despite numerous prevention campaigns. Moreover, adolescents from racial/ethnic minority groups are disproportionately affected.[2] A new NINR initiative supports projects to examine psychosocial, cognitive, and neurological predictors of HIV/AIDS risk decisionmaking in adolescents. This research will provide an evidence-base to guide future culturally and developmentally relevant interventions to prevent HIV/AIDS.

CHALLENGES AND CHANGES IN AN AGING POPULATION

The population of our Nation is aging rapidly, due in large part to increased longevity and the aging of the baby boomers. These changes are giving rise to significant challenges, resulting in a need for: improved strategies to manage co-occurring chronic illnesses; better interventions to support family caregivers; and new ways to address health disparities and meet the needs of an elderly population that is more racially and ethnically diverse than ever before. One pressing challenge is the increase in the number of older adults with multiple chronic illnesses, such as heart disease, diabetes, and arthritis. Such older adults have complex care needs, face long-term self-management of illness, and may experience poor coordination of care in the community. In a recent NINR-supported Nurse Coordinated Care Intervention, advanced practice nurses developed individualized care plans for older adults, which included family members and ongoing follow-up care. The intervention improved health outcomes and reduced costs of care for Medicare patients. A new NINR initiative, that benefits not only older adults but individuals across the life span, supports research that translates basic genomic science to clinical practice with the goal of preventing and alleviating symptoms of chronic illness. Such efforts have the potential to improve quality of life for older adults and families. Another challenge is Alzheimer's disease (AD), which is incurable, affects up to 5.1 million Americans, and is expected to dramatically increase in incidence by the year 2030.[3] NINR is addressing the quality of care for AD patients, and the quality of life of, and burden on, family caregivers. For example, researchers funded by NINR and the National Institute on Aging (NIA) developed an intervention to teach caregivers about AD, stress management, and maintaining their own health. The intervention showed promising improvements in emotional, mental, and physical health in racially diverse groups.

END OF LIFE: SUPPORTING INDIVIDUALS AND FAMILIES

As a society we are living longer lives than ever before; however, we are also more likely to die from chronic and sometimes painful illnesses[4] that require families to make complex decisions about life and death issues, often without adequate support and information. As the lead NIH Institute on issues related to end-of-life research, NINR supports research leading to evidence-based end-of-life and palliative care

[1] National Institute for Child Health and Human Development. AIDS/HIV. 2008.
[2] Centers for Disease Control and Prevention. 2008. HIV/AIDS among youth.
[3] National Institute on Aging. 2009 Progress report on Alzheimer's disease: Translating new knowledge.
[4] Centers for Disease Control and Prevention and The Merck Company Foundation. The state of aging and health in America 2007. Whitehouse Station, NJ: The Merck Company Foundation; 2007.

that ultimately assists individuals, families, and healthcare professionals in alleviating symptoms, planning for end-of-life decisions, and promoting psychological, social, spiritual, and physical well-being. NINR's Office of Research on End-of-Life Science and Palliative Care, Investigator Training, and Education coordinates research, training, and educational efforts in end-of-life and palliative care science. One NINR-supported study recently examined the effectiveness of a program to communicate patient preferences for end-of-life decisions to clinicians. Compared to traditional practices such as Do-Not-Resuscitate orders, the program led to fewer unwanted life-sustaining treatments without affecting quality of remaining life. In addition, a new NINR initiative begun in 2011 will support research to address issues related to end-of-life and palliative care for individuals with chronic illness who also experience life-threatening acute illness. Finally, on August 10–12, 2011, NINR, with support from partners across the NIH, will convene a forum entitled "The Science of Compassion: Future Directions in End-of-Life and Palliative Care." This forum is intended to energize and mobilize end-of-life and palliative care research and to draw attention to the end-of-life and palliative care processes, the care options available to patients and their families, and the obligations of health service communities to address these complex needs.

TRAINING THE NEXT GENERATION OF SCIENTISTS

NINR places strong emphasis on equipping the next generation of scientists with the necessary skills to conduct research that improves the Nation's health. In light of the societal trends that will characterize the coming decades, NINR recognizes that tomorrow's nurse scientists need to be trained in rigorous, innovative, and interdisciplinary research that reaches diverse individuals, families, and communities. NINR supports young scientists and junior and senior scholars through grant funding, fellowships, and career development awards. NINR also offers an intensive summer training program, the Summer Genetics Institute, to improve research and clinical practice among graduate students and faculty by providing a foundation in molecular genetics. Additionally, our Pain Boot Camp, held for the first time in 2010, is a 1-week research intensive program where participants learn innovative pain research methodology from nationally and internationally known scientists. NINR's efforts to invest in new investigators and new ideas are critical investments in preparing a nursing workforce to address the healthcare challenges of the coming years.

FUTURE DIRECTIONS IN NURSING SCIENCE

Nursing science is at the forefront of efforts to improve health and healthcare practice. NINR is currently formulating its new strategic plan and will continue its focus on the unique social, cultural, societal, genetic, and biological factors that contribute to disease prevention, health promotion, and self-management of illness. We look forward to the next 25 years in which nursing science, focused on individuals, patients and families, will make critical contributions to improving healthcare practice and quality of life across the disease spectrum and across the lifespan. Thank you, Mr. Chairman. I will be happy to answer any questions that the Committee might have.

PREPARED STATEMENT OF DONALD A.B. LINDBERG, M.D., DIRECTOR, NATIONAL LIBRARY OF MEDICINE

Mr. Chairman and Members of the Committee: I am pleased to present the President's fiscal year 2012 budget request for the National Library of Medicine (NLM) of the National Institutes of Health (NIH). The fiscal year 2012 NIH request includes $387,153,000 for NLM, which is $24,420,000 more than the comparable fiscal year 2011 NLM appropriation of $362,733,000.

As the world's largest biomedical library and the producer of internationally trusted electronic information services, NLM delivers trillions of bytes of data to millions of users every day. Many who begin a search in Google, another search engine, or a mobile "app" actually receive health information from an NLM website. Now in its 175th year, NLM is a key link in the chain that makes the results of biomedical research—DNA sequences, clinical trials data, toxicology and environmental health data, published scientific articles, and consumer health information—readily available to scientists, health professionals, and the public worldwide. A leader in biomedical informatics and information technology, NLM also conducts and supports leading-edge informatics research and development in electronic health records, clin-

ical decision support, information retrieval, advanced imaging, computational biology, telecommunications, and disaster response.

NLM's programs and services directly support NIH's four key initiatives. The Library organizes and provides access to massive amounts of scientific data from high throughput sequencing; assembles data about small molecules to support research and therapeutic discovery; provides the world's largest clinical trials registry and results database; and is the definitive source of published evidence for healthcare decisions. Research supported or conducted by NLM underpins today's electronic health record systems. The Library has been the principal funder of university-based informatics research training for 40 years, supporting the development of today's leaders in informatics research and health information technology. NLM's databases and its partnership with the Nation's health sciences libraries deliver research results wherever they can fuel discovery and support health decisionmaking.

RESEARCH INFORMATION RESOURCES

NLM's PubMed/MEDLINE database is the world's gateway to research results published in the biomedical literature, linking to full-text articles in PubMed Central, including those deposited under the NIH Public Access Policy, and on publishers' websites, as well as connecting to vast collections of scientific data. Through its National Center for Biotechnology Information (NCBI), NLM is a hub for the international exchange and use of molecular biology and genomic information, with databases accessed by more than 2 million users daily. NCBI meets the challenge of organizing, analyzing, and disseminating scientific research data with more than 40 integrated databases and analysis tools that enable genomic discoveries in the 21st century. These databases are fundamental to the identification of important associations between genes and disease and to the translation of new knowledge into better diagnoses and treatments. Resources such as dbGAP and the upcoming Genetic Testing Registry (GTR) create a bridge between basic research and clinical applications. dbGaP links genotype and phenotype information from clinical studies to identify genetic factors that influence health and serves as the public repository for data from genome wide association studies (GWAS) supported by NIH and other research funders. The GTR will be a central source for healthcare providers and patients to find detailed information about genetic tests and the laboratories that offer them.

NLM also stands at the center of international exchange of data about clinical research studies. NLM's Lister Hill National Center for Biomedical Communications builds ClinicalTrials.gov, the world's largest clinical trials database, including registration data for more than 106,000 clinical studies with sites in 174 countries. ClinicalTrials.gov has novel and flexible mechanisms that enable submission of summary results data for clinical trials subject to the Food and Drug Administration Amendments Act of 2007. To date, summary results are available for about 3,400 completed trials of FDA-approved drugs, biological products, and devices—providing a new and growing source of evidence on efficacy and comparative effectiveness.

HEALTH DATA STANDARDS AND ELECTRONIC HEALTH RECORDS

Electronic health records with advanced decision-support capabilities and connections to relevant health information will be essential to achieving personalized medicine and will help Americans to manage their own health. For 40 years, NLM has supported seminal research on electronic health records, clinical decision support, and health information exchange, including concepts and methods now used by MicroSoft Health Vault and Google Health. As the central coordinating body for clinical terminology standards within HHS, NLM works closely with the Office of the National Coordinator for Health Information Technology (ONC) to facilitate adoption and "meaningful use" of electronic health records (EHRs). NLM supports, develops, and disseminates key data standards for U.S. health information exchange in ONC's criteria for certification of electronic health records. NLM is actively engaged in research on Next Generation EHRs, while also developing tools and frequently used subsets of large terminologies to help EHR developers and users implement health data standards right now. Most recently, NLM released MedlinePlus Connect, which allows application developers to establish direct links from a patient's view of his or her EHR to high quality health information relevant to that person's specific health conditions, medications, and (coming soon) recent tests.

INFORMATION SERVICES FOR THE PUBLIC

This new EHR connection builds upon NLM's extensive information services for patients, families and the public. The Library's MedlinePlus website provides integrated access to high quality consumer health information produced by all NIH com-

ponents and HHS agencies, other Federal departments, and authoritative private organizations and serves as a gateway to specialized NLM information sources for consumers, such as the Genetic Home Reference and the Household Products database. Available in English and Spanish, with selected information in 40 other languages, MedlinePlus averages well over 600,000 visits per day. Covering nearly 900 health topics, MedlinePlus has interactive tutorials for persons with low literacy, an illustrated medical encyclopedia, surgical videos and links to the scientific literature in PubMed. Mobile MedlinePlus, also in both English and Spanish, reaches the large and rapidly growing mobile Internet audience.

The NIH MedlinePlus quarterly magazine is an outreach effort made possible with support from many parts of NIH and the Friends of the NLM. Like MedlinePlus itself, the magazine is free and contains no advertising. It is distributed to the public via physician offices, community health centers, libraries and other locations and has a readership of up to 5 million nationwide. Each issue focuses on the latest research results, clinical trials and new or updated guidelines from the 27 NIH Institutes and Centers. A Spanish/English version, NIH MedlinePlus Salud, launched with support from the National Alliance for Hispanic Health and the National Hispanic Medical Association, addresses the specific health needs of the growing Hispanic population and showcases the many Hispanic outreach efforts and relevant research results funded by the NIH.

To be of greatest use to the widest audience, NLM's information services must be known and readily accessible. The Library's outreach program, with a special emphasis on reaching underserved populations, relies heavily on the more than 6,300-member National Network of Libraries of Medicine (NN/LM). The NN/LM is a network of academic health sciences libraries, hospital libraries, public libraries and community-based organizations working to bring the message about NLM's free, high-quality health information resources to communities across the Nation.

DISASTER INFORMATION MANAGEMENT

Events of the past year, such as the *Deepwater Horizon* oil spill and the earthquake, tsunami, and radiation event in Japan, demonstrated yet again the importance of rapid, organized response to natural disasters and other emergencies. NLM has a long history of providing health information to prepare for, respond to, and recover from disasters and has tools and advanced information services designed for use by emergency planners, responders and managers. Through its Disaster Information Management Resource Center, NLM builds on proven emergency backup and response mechanisms within the National Network of Libraries of Medicine to promote effective use of libraries and disaster information specialists in disaster preparedness and response. NLM also conducts research on new methods for sharing health information in emergencies as its contribution to the Bethesda Hospital Emergency Preparedness Partnership, a model of private-public hospital collaboration for coordinated disaster planning. NLM partners with the Pan American Health Organization (PAHO) and other bodies in the Latin American Network for Disaster and Health Information to promote capacity-building in the area of disaster information management.

Within 2 days of the gulf oil spill, NLM launched a web page focused on the potential effects of oil on human health, which quickly became a highly regarded resource for evidence-based information by Federal, State, and local agencies and communities. NLM continued to support information needs in Haiti, including onsite assistance to PAHO in setting up a system for collecting information from cholera treatment centers. The Radiation Emergency Medical Management (REMM) tool, previously developed by NLM, the HHS Office of the Assistant Secretary for Preparedness and Response, CDC and NCI, was deployed in Japan, via the web and on mobile devices, to assist with assessing and managing the health effects of radiation. NLM also activated the Emergency Access Initiative, a partnership with publishers and medical libraries which provides free temporary access to key electronic medical journals and books when disasters interrupt regular health information services, and provided practical advice to Japanese libraries and archives on rescuing water-damaged books and documents.

In summary, NLM's information services and research programs serve the Nation and the world by supporting scientific discovery, clinical research, education, healthcare delivery, public health response, and the empowerment of people to improve personal health. The Library is committed to the innovative use of computing and communications to enhance public access to the results of biomedical research.

PREPARED STATEMENT OF JACK WHITESCARVER, PH.D., DIRECTOR, OFFICE OF AIDS RESEARCH

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for the trans-NIH AIDS research program, which is $3,159,531,000. This amount is an increase of $100,254,000 over the fiscal year 2011 enacted level. It includes the total NIH funding for research on HIV/AIDS and the wide spectrum of AIDS-associated malignancies, opportunistic infections, co-infections, and clinical complications; intramural and extramural research; research management support; research centers; and training. It also includes a transfer of approximately $27 million to the HHS Office of the Assistant Secretary of Health to foster collaborations across HHS agencies and finance high priority initiatives in support of the President's National HIV/AIDS Strategy.

THE AIDS PANDEMIC

Nearly 30 years since the recognition of AIDS and the identification of HIV as its causative agent, the HIV/AIDS pandemic remains a global scourge. UNAIDS reports that in 2009, more than 33 million people were estimated to be living with HIV/AIDS; 2.6 million were newly infected; and 1.8 million people died of AIDS-related illnesses. The majority of cases worldwide are the result of heterosexual transmission, and women represent more than 50 percent of HIV infections worldwide. More than 1,000 children become infected each day, most of them as newborns. More than 25 million men, women, and children worldwide have already died.

In the United States, CDC reports that more than 1.1 million people are estimated to be HIV-infected; approximately 56,300 new infections occur each year; and someone is infected with HIV every 9½ minutes. HIV/AIDS continues to be an unrelenting public health crisis, disproportionately affecting racial and ethnic populations, women of color, young adults, and men who have sex with men. The number of individuals aged 50 years and older living with HIV/AIDS is increasing, due in part to antiretroviral therapy, which has made it possible for many HIV-infected persons to live longer, but also due to new infections in individuals over the age of 50.

NIH AIDS RESEARCH PROGRAM

To address this pandemic, NIH has established the most significant AIDS research program in the world, a comprehensive program of basic, clinical, translational, and behavioral research in domestic and international settings—a multi-disciplinary, global research program carried out by every NIH institute and center in accordance with their mission. This diverse research portfolio requires an unprecedented level of trans-NIH planning, scientific priority-setting, and resource management. The Office of AIDS Research (OAR) was authorized to plan, coordinate, evaluate, and budget all NIH AIDS research, functioning as an "institute without walls," to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently.

NEW SCIENTIFIC ADVANCES AND OPPORTUNITIES

The past year has been a significant one for AIDS research. The NIH investment in the priority areas of HIV prevention research and in basic science over the past several years has resulted in important progress in critical areas of the NIH AIDS research program. Recent research advances by NIH intramural and extramural investigators have opened doors for new and exciting research opportunities in the search for strategies to prevent, treat, and ultimately cure HIV infection. These advances include:

Technologies to accelerate discovery—

—*Vaccines*.—A team of scientists led by researchers at the NIAID Vaccine Research Center discovered two potent human antibodies that can stop more than 90 percent of known global HIV strains from infecting human cells in the laboratory and determined the structural analysis of how they work. The novel techniques used in this research may accelerate HIV vaccine research as well as the development of vaccines for other infectious diseases. An HIV vaccine clinical trial conducted in Thailand by NIH and the Department of Defense demonstrated the first indication of a modest but positive effect in preventing HIV infection. The trial marked the first step in proving the concept that a vaccine to prevent HIV infection is feasible.

—*Microbicides*.—For the first time in nearly 15 years of research, scientists discovered a vaginal microbicide gel that gives women a level of protection against

HIV infection. The study, sponsored by USAID and conducted by the Centre for the AIDS Programme of Research in South Africa (CAPRISA), found that the use of a microbicide gel containing the antiretroviral drug tenofovir resulted in 39 percent fewer HIV infections compared with a placebo gel. NIH provided substantial support and resources to establish the infrastructure and training for CAPRISA. Ongoing and future NIH clinical trials will build on these study results with the goal of bringing a safe and effective microbicide to licensure.

—*Basic Science*.—This past year, using genome-wide association studies, NIH-sponsored researchers made an important discovery related to the genetics of an individual's immune system. These genes appear to be involved in the control of HIV disease progression among a group of individuals considered "elite controllers," who have been exposed to HIV over an extended period, but whose immune systems have controlled the infection without therapy and without symptoms. These findings will contribute to the development of potential HIV prevention strategies.

Translational sciences and therapeutic development.—New lymphoma regimens have been developed that can be tailored to specific tumor types. This development has markedly improved the therapeutic outcome and survival of patients with AIDS-related lymphoma. In addition, progress in both basic science and treatment research aimed at eliminating viral reservoirs has been significant enough that scientists are now, for the first time, planning to conduct research aimed at a cure. NIH has announced several initiatives to generate new ideas for curing HIV infection through domestic and international partnerships among government, industry, and academia.

Enhancement of evidence-base for healthcare decisions.—In the critical area of treatment as prevention, two recent studies have demonstrated the effectiveness of new multi-drug antiretroviral regimens for the prevention of mother-to-child-transmission of HIV during pregnancy and breastfeeding. In addition, a large international NIH clinical trial provided strong evidence that the use of pre-exposure prophylaxis (PrEP), that is, the use of antiretroviral treatment before exposure to prevent infection, can reduce risk of HIV acquisition in men who have sex with men. Additional and continued research is needed to determine whether PrEP will be similarly effective at preventing HIV infection in other at-risk populations and assist healthcare workers in providing these potential options.

TRANS-NIH PLAN AND BUDGET

These advances, while preliminary and incremental, provide the groundwork for further scientific investigation and the building blocks for the development of the trans-NIH AIDS strategic Plan, developed by OAR in collaboration with both government and non-government experts. The priorities of the strategic Plan guide the development of the trans-NIH AIDS research budget. OAR develops each IC's AIDS research allocation based on the Plan, scientific opportunities, and the IC's capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration. The priorities of the Plan will establish the biomedical and behavioral research foundation necessary to implement the major goals of the President's National HIV/AIDS Strategy and to implement the NIH Director's themes.

FISCAL YEAR 2012 SCIENTIFIC PRIORITIES

A growing proportion of patients receiving long-term antiretroviral therapy (ART) are demonstrating treatment failure, experiencing serious drug toxicities and side effects, and developing drug resistance. Recent studies have shown an increased incidence of malignancies, as well as cardiovascular and metabolic complications, and premature aging associated with long-term HIV disease and ART. NIH research will address the need to develop better, less toxic treatments and to investigate how genetic determinants, sex, gender, race, age, pregnancy status, nutritional status, and other factors interact to affect treatment success or failure and/or disease progression.

NIH-funded research is needed to address the causes of HIV-related health disparities, their role in disease transmission and acquisition, and their impact on treatment access and effectiveness. These include disparities among racial and ethnic populations in the United States; between developed and resource-constrained nations; between men and women; between youth and older individuals; and disparities based on sexual identity. In addition, specific fiscal year 2012 research priorities include: biomedical and behavioral research focused on the domestic AIDS epidemic, particularly in racial and ethnic populations of the United States; research to build on important research advances in prevention research in the past

year in the areas of microbicides, vaccines, and treatment as prevention; research to prevent and treat HIV-associated co-morbidities, malignancies, and clinical complications; research to address the complex issues around AIDS and aging; research to better understand the issues of adolescents and AIDS; basic and therapeutic research focused on elimination of viral reservoirs leading toward a cure; genetic studies to delineate the genetic basis for immune responses to HIV and to sequence HIV-associated tumors; and research on feasibility, effectiveness, and sustainability required for the scale-up and implementation of interventions in communities at risk.

SUMMARY

The OAR has utilized its authorities to shift AIDS research program priorities and resources to meet the changing epidemic and scientific opportunities. This investment in AIDS research has produced groundbreaking scientific advances. AIDS research also is helping to unravel the mysteries surrounding many other cardiovascular, malignant, neurologic, autoimmune, metabolic, and infectious diseases as well as the complex issues of aging and dementia. Despite these advances, however, AIDS has not been conquered, and serious challenges lie ahead. The HIV/AIDS pandemic will remain the most serious public health crisis of our time until better, more effective, and affordable prevention and treatment regimens are developed and universally available. NIH will continue its efforts to prevent, treat, and eventually cure AIDS.

Thank you for your continuing support for our efforts.

PREPARED STATEMENT OF LAWRENCE A. TABAK, D.D.S., PH.D., PRINCIPAL DEPUTY DIRECTOR, NATIONAL INSTITUTES OF HEALTH

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for the Office of the Director (OD). The fiscal year 2012 budget includes $1,298,412,000; an increase of $132,451,000 over the comparable fiscal year 2011 enacted level of $1,165,961,000, comparable for transfers proposed in the President's request.

The OD promotes and fosters NIH research and research training efforts in the prevention and treatment of disease through the oversight of the Intramural Research program and through coordination of program offices responsible for stimulating specific areas of research throughout NIH to complement the ongoing efforts of the Institutes and Centers. The OD also develops policies in response to emerging scientific opportunities employing ethical and legal considerations; maintains peer review policies; provides oversight of grant and contract award functions; coordinates information technology across the Agency; and coordinates the communication of health information to the public and scientific community. Moreover, the OD provides the core management and administrative services, such as budget and financial management, personnel, property, and procurement services, ethics oversight, and the administration of equal employment policies and practices.

The principal OD offices providing these activities include the Offices of Extramural Research, Intramural Research, Science Policy, Communications and Public Liaison, Legislative Policy and Analysis, Equal Opportunity and Diversity Management, Financial Management, Budget, Management, Human Resources, Chief Information Office, and the Executive Office. This request contains funds to support the functions of these offices as will be outlined in the Program, Project and Activities Table which follows.

The statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences and reallocate the remaining portions of the National Center for Research Resources to other parts of NIH, including the OD.

DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES (DPCPSI)

The DPCPSI mission includes identifying the most compelling scientific opportunities, emerging public health challenges, and scientific knowledge gaps that merit further research or would otherwise benefit from strategic coordination and planning across the Agency. DPCPSI provides key support of research that is consistent with the NIH Director's Themes. The Division is comprised of the Office of AIDS Research, Office of Research on Women's Health, Office of Behavioral and Social Sciences Research, Office of Disease Prevention, Office of Medical Applications of Research, Office of Dietary Supplements, Office of Rare Diseases Research, and the

Office of Strategic Coordination (OSC). The OSC is responsible for the oversight and management of the NIH Common Fund. The Division is responsible for agency-wide effort in portfolio analysis and also manages NIH-wide evaluation and performance activities, including the Evaluation Set-Aside program and the Government Performance and Results Act plans and reports. The fiscal year 2012 budget for DPCPSI/Office of the Director is $8,401,000. Descriptions of the eight programmatic offices within DPCPSI, and their separate budgets, follow.

THE OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) plays a unique role at NIH, establishing a plan for the AIDS research program. OAR coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. OAR's response to the AIDS epidemic requires a unique and complex multi-institute, multi-disciplinary, global research program. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently, allowing NIH to pursue a united research front against the global AIDS epidemic. The fiscal year 2012 budget for OAR is $65,760,000.

THE OFFICE OF RESEARCH ON WOMEN'S HEALTH

The Office of Research on Women's Health (ORWH) mission is to enhance and expand research supported by the NIH to adequately address women's health. This is done by identifying gaps in knowledge, and collaborating with the ICs to stimulate and support innovative research including interdisciplinary scientific approaches to women's health and studies of sex and gender differences in health and diseases. ORWH continues to lead efforts to ensure adherence to policies for the inclusion of women and minorities in clinical research The fiscal year 2012 budget for ORWH is $43,811,000.

THE OFFICE OF BEHAVIORAL AND SOCIAL SCIENCES RESEARCH

The Office of Behavioral and Social Sciences Research (OBSSR) was established by Congress to stimulate behavioral and social science research at NIH and to integrate it more fully into the NIH research enterprise. The Office furthers the NIH mission by emphasizing the critical role that behavioral and social factors play in health, healthcare, and well-being. The Office supports the activities of the NIH Basic Behavioral and Social Science Opportunity Network, a trans-NIH initiative to expand the agency's funding of basic behavioral and social sciences research. The fiscal year 2012 budget for OBSSR is $27,949,000.

THE OFFICE OF DISEASE PREVENTION

The primary mission of the Office of Disease Prevention (ODP) is to stimulate disease prevention research across the NIH and to coordinate and collaborate on related activities with other Federal agencies as well as the private sector. The fiscal year 2012 budget for ODP is $1,400,000. The Office of Medical Applications of Research (OMAR), Office of Dietary Supplements (ODS), and Office of Rare Diseases Research (ORDR) are within the ODP organizational structure.

The Office of Medical Applications of Research (OMAR) mission is to work with NIH Institutes, Centers, and Offices to assess, translate and disseminate the results of biomedical research that can be used in the delivery of important health interventions to the public. The fiscal year 2012 budget for OMAR is $4,877,000.

The Office of Dietary Supplements (ODS) promotes study of the use of dietary supplements by supporting investigator-initiated research, and through other major mechanisms. The fiscal year 2012 budget for ODS is $28,691,000.

The Office of Rare Diseases Research (ORDR) supports activities that stimulate research on rare diseases by collaborating with the research institutes, research investigators, patient advocacy groups, the pharmaceutical industry, and Federal regulatory and research agencies. The fiscal year 2012 budget for ORDR is $18,423,000.

THE OFFICE OF STRATEGIC COORDINATION AND THE COMMON FUND

The Office of Strategic Coordination (OSC) facilitates strategic planning and management of Common Fund-supported programs by working with groups of staff from across the NIH to develop and implement each individual program while providing central management for the Common Fund as a whole. The NIH Common Fund was enacted into law by Congress through the 2006 NIH Reform Act to support cross-cutting, trans-NIH programs that require participation by at least two NIH Insti-

tutes or Centers (ICs) or would otherwise benefit from strategic planning and coordination. The Common Fund provides limited-term funding for new programs that are intended to catalyze research in the ICs through the development of cross-cutting resources, technologies, and data sets. Common Fund programs do not address any particular disease or condition, but rather, are designed to be broadly relevant. The fiscal year 2012 budget for the Common Fund is $556,890,000.

THE OFFICE OF SCIENCE EDUCATION

The Office of Science Education (OSE) develops science education programs, instructional materials, and career resources that serve our Nation's science teachers, their students (kindergarten through college), and the public. OSE's activities are an important component to the overall Agency effort to achieve the NIH Director's goal to reinvigorate and empower the biomedical research community and enhance America's competitiveness in the global economy. The OSE creates programs to improve science education in schools (the NIH Curriculum Supplement Series) that stimulate interest in health and medical science careers (LifeWorks Web site); and advance public understanding of medical science, research, and careers; and advises NIH leadership about science education issues. The OSE website is a central source of information about available education resources and programs. http://science.education.nih.gov. The fiscal year 2012 budget for OSE is $4,120,000.

LOAN REPAYMENT AND SCHOLARSHIP PROGRAMS

The Office of Intramural Training and Education administers the NIH Intramural Loan Repayment and Undergraduate Scholarship Programs (UGSP). The Loan Repayment Programs (LRPs) seek to recruit and retain highly qualified physicians, dentists, and other health professionals with doctoral-level degrees. These programs offer financial incentives and other benefits to attract highly qualified physicians, nurses, and scientists into careers in biomedical, behavioral, and clinical research as employees of the NIH. The NIH UGSP offers competitive scholarships to exceptional college students from disadvantaged backgrounds that are committed to biomedical, behavioral, and social science health-related research careers at the NIH. The fiscal year 2012 budget is $7,653,000 for the Intramural Loan Repayment and Undergraduate Scholarship Programs.

I am happy to answer any questions you may have about the OD's programs and activities as well as our plans for the upcoming year.

PREPARED STATEMENT OF JEREMY M. BERG, PH.D., DIRECTOR, NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Mr. Chairman and Members of the Committee: I am pleased to present the fiscal year 2012 President's budget request for the National Institute of General Medical Sciences (NIGMS). The fiscal year 2012 budget request includes $2,102,300,000, an increase of $70,263,000 above the fiscal year 2011 appropriation of $2,032,037,000, which has been adjusted comparably to reflect NIH proposed transfers. This statement is submitted with the recognition of the Department's notification to the Congress of an NIH reorganization that would establish a new National Center for Advancing Translational Sciences and reallocate the remaining portions of the National Center for Research Resources to other parts of NIH.

Since the mid-20th century, NIGMS has played a leading role as NIH's "basic research institute." Spanning a broad spectrum, the Institute's mission supports discovery ranging from how cells work to how diseases affect communities across towns, nations, and countries. NIGMS-supported scientists probe the unknown to solve mysteries about fundamental life processes. This effort goes well beyond the need to satisfy innate curiosity; answering basic research questions such as how bacterial and human cells divide, move, and communicate has increased our knowledge about infections, cancer, birth defects, and heart disease in ways that would have been difficult to achieve with more directed studies. Other ongoing NIGMS research investments, such as in chemistry, continue to provide tangible benefits to society and our economy. This past year, an NIGMS-supported scientist shared a Nobel Prize for his discovery of a ground-breaking chemistry method that is used routinely in the pharmaceutical, electronic and agricultural industries.

Continued investment in basic research is vital because many of today's therapies, although effective, nevertheless have significant limitations. Treatments that are applied after the onset of serious illness—kidney transplants and dialysis, bypass surgery for coronary artery disease, surgical removal of tumors—though often lifesaving, are still not optimal. Treating disease before such interventions are needed

would likely improve both outcomes and quality of life. Basic biomedical and behavioral research has the power to move treatments in this direction, and in the coming years, emerging biotechnology and nanotechnology tools will give researchers unprecedented precision to detect and derail disease at its earliest stages.

TECHNOLOGIES TO ACCELERATE DISCOVERY

Basic research on stem cells remains one of the most rapidly advancing areas of biomedicine, in large part because of the knowledge base scientists already have about how cells behave and change. NIGMS-supported research on stem cells continues to provide hope that these multitalented cells will find use in customized therapies for a range of conditions. In the near term, stem cells are providing researchers powerful tools for understanding diseases and developing drugs to treat them. This past year, NIGMS-funded researchers made important progress on several fronts:

—Stem cell research pioneer James Thomson, D.V.M., Ph.D., created a powerful tool to trace the individual steps in a deadly cancer by turning the clock back on blood cells from a person with leukemia.

—Chemist Laura Kiessling, Ph.D., developed an inexpensive and simple synthetic culture system for growing embryonic stem cells in the laboratory.

—NIH Director's New Innovator Awardee Alysson Muotri, Ph.D., used cells from a person with Rett syndrome to create a cellular model of autism.

Another area showing great promise is molecular diagnosis. This past year, NIH Director's Pioneer Awardee Thomas Kodadek, Ph.D., applied a unique and creative strategy that conducts an "immune surveillance" of human blood to look for early signs of disease before symptoms appear. To date, he has obtained exciting evidence that Alzheimer's disease may be detectable by this approach, and he has licensed the technology to further its development and application.

The study of systems—of cells, organs, and diseases—is an important area of basic discovery within the NIGMS mission. In 2010, the Institute grew its support of systems biology by adding two new National Centers for Systems Biology. All 12 centers integrate approaches from engineering, genomics, and systems and synthetic biology to identify principles and architectural features involved in common cellular behaviors, including the response to disease-causing microorganisms, poisons, and metabolic imbalances.

Computer modeling is a key element of all systems biology, and a central aspect of the NIGMS-led Models of Infectious Disease Agent Study (MIDAS). This international effort continues to add new research expertise to increase its capacity to simulate disease spread, evaluate different intervention strategies, and help inform public health officials and policymakers. This past year, two MIDAS findings are worth highlighting:

—One MIDAS study used computer modeling to analyze the spread of H1N1 flu in a Pennsylvania elementary school. The researchers collected extensive data from seating charts, school timetables, bus schedules, nurse logs, attendance records and questionnaires. The findings indicated that transmission occurs mostly through girl-to-girl and boy-to-boy interactions and that sitting directly next to a child with the flu does not raise a child's risk of getting it.

—In another MIDAS study, researchers learned that the Haiti cholera outbreak that followed that Nation's colossal earthquake in 2010 could have been blunted with the use of a mobile stockpile of oral cholera vaccine.

TRANSLATIONAL SCIENCES AND THERAPEUTICS DEVELOPMENT

Since the landmark discovery of the structure of DNA in the 1950s, our increasing knowledge of how all living things share a basic set of working parts has catalyzed progress in biomedicine. Large-scale efforts to scan and compare genomes are teaching scientists about individual differences in DNA scripts that predispose us to disease. However, such sequence information is only useful if it can be properly interpreted. NIGMS has been at the forefront of supporting research that facilitates this interpretation, leading to numerous discoveries that have revealed new, unforeseen mechanisms by which DNA information is made operational.

As one example, the NIGMS Protein Structure Initiative (PSI) has been creating knowledge and providing tools to researchers for more than 10 years. This past year, NIGMS enhanced this signature effort by launching PSI:Biology, a new program that supports research partnerships between groups of biologists and high-throughput structure determination centers to solve medically important problems. Already this investment is bearing fruit, yielding new structures that show how the largest class of drug receptors functions.

Another example is a pilot study by an individual scientist that searched systematically for environmental factors—nutrients, chemicals and toxins—that may be linked to diabetes. Based conceptually on the Genome-Wide Association Studies approach, Atul Butte, M.D., Ph.D., developed a new technique he calls Environment-Wide Association Studies. In this method, he considered many different factors at once, using health survey data from the U.S. Centers for Disease Control and Prevention, which led him to identify 266 environmental factors linked to type 2 diabetes. This example highlights the tremendous potential benefits of integrating existing data sources and asking the right questions.

ENHANCEMENT OF EVIDENCE BASE FOR HEALTHCARE DECISIONS

Although medicines have been revolutionary in humankind's ability to stay healthy, we now know that people having widely varying responses to the drugs they take to heal their various ills. NIGMS has been a long-time supporter of pharmacogenomics, the study of how our DNA influences the way we respond to medications. This area of research is an especially important focus in our country today, as the baby-boom generation gets older and is more likely to take multiple medicines routinely. NIGMS leads the trans-NIH Pharmacogenomics Research Network (PGRN), a nationwide collaborative of scientists looking for clues to inherited variability in the response to medicines used to treat heart disease, asthma, cancer, depression and addiction.

This past year, two new groups joined the network, adding rheumatoid arthritis and bipolar disorder as new focus areas. Over the next 5 years, the PGRN plans to expand to pursue cutting-edge DNA sequencing methods and statistical analysis, as well as to perform pilot studies to learn about medication response from de-identified medical records in healthcare systems. Furthermore, previous PGRN-based discoveries are now moving further into clinical application with evidence accumulating on improved outcomes and lower costs.

NEW INVESTIGATORS, NEW IDEAS

Biomedical and behavioral research is a human endeavor, and NIGMS has a long-standing commitment to supporting and sustaining the people behind the research. Creativity comes from the sparks of individual minds, and thus the Institute has always adhered to the principle that a healthy workforce is an essential ingredient for good science that leads to better health for all.

Science and the conduct of research continue to evolve, though, as do workforce needs. It is our responsibility to stay attuned to these new needs and opportunities. In 2010, NIGMS launched a process to examine its activities and general philosophy of research training—to assure that all of the Institute's activities related to the training of scientists are aligned with our commitment to build an excellent, diverse research workforce to help achieve the NIH mission, now and in the long term.

NIGMS gathered data and input from the scientific community through a series of regional meetings across the country, as well as through other means of electronic communication including a webinar, online postings, and comment submissions via e-mail. The resulting plan, Investing in the Future, the NIGMS Strategic Plan for Biomedical and Behavioral Research Training, was released in early 2011.

A key focus of this plan is the importance of putting the needs of trainees first—by focusing on mentoring, career guidance, and diversity. The plan also affirms the Institute's strong assertion that there are multiple avenues in which a well-trained scientist can make meaningful contributions to society. These include research careers in academia, Government, or the private sector, as well as careers centered on teaching, science policy, patent law, communicating science to the public, and other areas.

In closing, and on the cusp of my departure from Federal service, I want to note how proud I have been to play a role in furthering the basic research that has had such a profound effect on the health and well-being of our Nation. I will treasure the time and effort spent leading the fine institution that is NIGMS.

AVERAGE COST OF RESEARCH PROJECT GRANTS

Senator HARKIN. Well, thank you, Dr. Collins. Very poignant ending for your testimony.

We will now begin a round of 5-minute questions.

Dr. Collins, in addition to drastically cutting NIH funding, the House Appropriations bill would have required NIH to fund a min-

imum number of new competing research grants and put a ceiling on the average cost to them.

I have a letter here from a number of different entities—American Association for Cancer Research, American Medical Colleges, American University—a whole list of different people who've written us a letter saying that this would really hamper the ability of NIH to fund the best, the most innovative, the brightest by putting a cap on it. Now, you have to fund so many and you have to—I think it was 9,000—and then they put a cap on it of, I think, $400,000, if I'm not mistaken.

Again, I'd like you to speak to that. We've been down this road before over the last 25 or 30 years that I've been on this subcommittee, in saying that NIH really ought to do this on a peer-reviewed basis. Some of the projects cost more, some cost less, but to limit it and then to say you have to do so many, takes away the ability to really do a good peer-reviewed systematic approach to this.

I would like you to respond to that and what that would mean to NIH if, in fact, we were to set a limit on how much and to mandate that you have to fund at least so many grants.

Dr. COLLINS. Senator, I appreciate the question. This is a very serious issue and you've set it up quite well in terms of what the risks might he here.

Certainly, that feature of the language that was part of H.R. 1 was deeply troubling to those of us at NIH, because, as you have just said, the goal of all of us who tried to carry out our responsibilities to support the very best biomedical research is to utilize the tools of peer review, to seek advice from the scientific community and our advisory councils about how best to utilize the resources that the taxpayers, through this Congress gives to us.

The idea that we would have to manage that enterprise in an arbitrary way to try to hit a certain number of grants, and particularly to try to hit some average cost of a new and competing grant could potentially seriously interfere with the flexibility that we believe is necessary for the best science to be supported.

For instance, clinical trials tend to be more expensive. Would this kind of a limit on the average costs of a new and competing grant find its way into conversations about, well, maybe we should do fewer clinical trials and more grants that happen to be inexpensive, like conference grants? That would be, I think, a serious intrusion into the ways in which, really, scientific decisions should be made.

So I agree with you that that particular kind of way of tying NIH's hands would be very unfortunate. Given all of the scientific opportunities that we have right now, we should be able to pursue them in a way that represents the best decisions and not managed in this sort of arbitrary way by trying to hit certain numerical grant limits.

DIABETES

Senator HARKIN. I appreciate that.

Dr. Rodgers, on diabetes, I think we saw that chart there about moderate changes in diet and exercise resulting in a huge decrease in the incidence of the disease. I had 71 percent and the chart said 58 percent, so I have to figure out why there's a difference here.

When you testified a few years ago on this, you said you would be undertaking a follow-up study to see whether these could be sustained over time. What's happened?

Dr. RODGERS. That's correct, Senator, and thanks for the question.

First of all, the 71 percent, even though the average improvement in terms of a reduction with that intensive lifestyle modification was 58 percent for all comers, among the people over 60 years of age, it was 71 percent. So they really enjoyed the best benefit of all of the subsets of the patients studied.

Now, the initial trial, the diabetes prevention trial, was published in 2002, and, at that point, the reduction was 58 percent for intensive lifestyle, 31 percent for a drug, metformin.

But, more recently, the 10-year follow-up, which is what I was referring to at that hearing, was just published in the Lancet in 2009, and that shows, as Dr. Collins mentioned, a durable effect out 10 years. These patients who engaged in the intensive lifestyle still showed a reduction of their going on to develop diabetes, and the patients, in fact, who were on the metformin also continued to show an improvement.

Senator HARKIN. Very good.

Now, my 5 minutes is up, but I have other questions for other people here. I'll do that on my second round.

Senator Shelby.

NCATS BUDGET AMENDMENT

Senator SHELBY. Thank you, Mr. Chairman.

Dr. Collins, I'm going to get back into NCATS for a minute. I think it's very important, and I think it has great promise.

I think that NCATS proposal requires thoughtful consideration to the effect that it will have on NIH, the extramural research community and the private pharmaceutical market. You've alluded to this a little.

As I stated, I remain concerned that this announcement was made in December, yet we don't have some details before the subcommittee yet.

The reorganization will impact all of NIH's 27 Institutes and Centers and will shift at least $1.3 billion. I believe the subcommittee needs to review such a proposal, especially one that has such a potential impact on the NIH community.

My question is when will we receive some more details that we can renew—for the staff and the subcommittee—or do you have a timeline? I know it's a difficult transition.

Dr. COLLINS. Senator, it's a very fair question, and I had certainly hoped that by the time of this hearing we would have been able to provide the full details about the budgetary consequences of standing up this new and exciting new center.

It is a complicated process. The recommendation to do this came forward from my Scientific Management Review Board last December 7.

Rather than putting this off until fiscal year 2013, which I thought would really have wasted an opportunity, we decided we would try to move as quickly as possible. Although some people said, "Hey, this is the Government. You can't possibly do that by

October", well, they used to say that about the Genome Project. So I decided that we could, and we should, because this is the best way to move the science forward.

But, of course, what this means is taking a number of components that already exist in various institutes and in the common funded NIH and moving them together into this new synergistic entity. That's important to point out.

Actually, what we're talking about is not to create new budgetary implications, with the one exception of the Cures Acceleration Network, which is in the President's fiscal year 2012 budget at $100 million, and which we hope this subcommittee and others will see fit to support, because it'll give us some flexibilities in terms of how we manage the budget that we would dearly love to have.

But the other pieces of NCATS are basically derived from existing programs that are moved together in a way that are going to be highly complementary and synergistic.

We needed, of course, to consult with our communities, with our constituencies, and, as we figured out how to do the shifting right down to every employee to make sure that the programs were encouraged and nurtured, we had to be sure we had that right.

We are at the point now where we believe we have that together. It needs, of course, to be reviewed by the Department of Health and Human Services (HHS) and Office of Management and Budget (OMB) experts. We hope to get that to you, Senator, in the fairly near future, within, certainly, the next few weeks and, hopefully, a very few weeks.

COST OF DE-RISKING PHARMACEUTICALS

Senator SHELBY. Dr. Collins, you've also described the NCATS mission as one of what you call de-risk—that moves basic scientific discoveries beyond the lab to a point where the private pharmaceutical market feels confident enough to jump in.

What is the policy or what would you think the policy would be if a selected project is successfully de-risked, but no companies produce the drug or medical product? I know you've thought about that.

Dr. COLLINS. And, indeed, I should point out that this is an activity which NIH has been engaged in for some long periods of time, and my colleagues, particularly from the National Cancer Institute (NCI) and National Institute of Allergy and Infectious Diseases (NIAID), have been supporting this kind of translational effort in always looking for a commercial partner at the earliest moment in order to be able to carry a project through to completion and limit the amount of dollars that the taxpayers have to cover.

I would say projects that get undertaken at this point need to think about that from the very beginning. There will be instances perhaps where no commercial partner can be found, even all the way through to the end of a phase III trial, but they will be rare indeed, because those are very expensive enterprises.

But for very rare diseases, where the economic incentives are simply going to be very limited, and especially if one is in a circumstance where you could conduct such a clinical trial by repurposing a drug that's already been approved for something

else, then NIH may very well find it worthwhile to undertake that effort.

But you're quite right to point this out. We have to get the balance——

HEALTH PREPAREDNESS AND OBESITY

Senator SHELBY. Absolutely.

Just want to touch on health disparities. You got into it a little. Health disparities most often associated with the ethic population persist in rural United States. Stroke, diabetes, kidney disease and cancer are all more prevalent in both the African-American community as well as the South.

One of the root causes to health disparity is the obesity epidemic that is rampant in our Nation. You pointed it out in your slides. Southern States have the highest rates in the Nation.

My question is should we be looking for a new paradigm that broadly addresses this critical national issue at multiple levels for molecules to behavior to policy? You touched on it with your slide. And how can NIH help the American people meet that challenge?

Dr. COLLINS. So, Senator, I really appreciate the question because this is an enormous public-health challenge for all communities, but particularly so for certain underserved communities.

I'm going to turn to my colleagues, Dr. Rodgers and Dr. Shurin, who lead the Obesity Task Force at NIH, who are just putting forward a new research plan that's quite exciting.

Dr. RODGERS. Thank you, Senator.

Because of the extreme importance of this project, and particularly the recognition that obesity is occurring much more frequently in children in this country, we've also asked Dr. Collins for his permission to have the Director of the Child Health Institute on board as a co-chair of this obesity research task force.

As Dr. Collins indicated, we just put out this last month a strategic plan which highlights a blueprint for research in these critical areas related to prevention and potential treatment of obesity, particularly in health disparities or in certain ethnic and racial groups, in older adults, in young children.

And it recognizes the fact that obesity is a multifaceted problem, and, therefore, you need multifaceted solutions, including behavioral, medical, surgical and others.

Senator SHELBY. How important is behavioral here——

Dr. RODGERS. Behavioral research is extremely important. For example, we know that for childhood obesity just decreasing screen time, the amount of time kids are in front of the television, the computer, video games can greatly reduce the risk. Increasing physical activity is another important component to this.

Let me turn to my colleague, Dr. Shurin, who actually has a very active program involving children.

Dr. SHURIN. Thank you, Senator. We share your very deep concerns about this.

One of the things that Dr. Rodgers and I have done is to convene a group, a collaborative on obesity with the CDC and the Department of Agriculture with the support of the Robert Wood Johnson Foundation, which has a particular interest in childhood obesity.

So we have a multifaceted research program. Much of it is community-based research, but it also ties in to many biologically and behaviorally oriented research programs really looking at the factors that impact obesity.

As Dr. Rodgers has said, we've got several studies now which show a very profound influence of screen time. Physical activity is at least as important as diet, but dietary issues are obviously of major importance. And we have a very rich portfolio of research projects looking at what are the most effective interventional strategies.

Many of these are site-based, worksite-based and school-based programs. I think one of the things that's particularly important is that many of the projects that we get into which look very promising don't actually pan out. It's very helpful for us to know what doesn't work, so we can really be fairly aggressive in pursuing the ones that do.

The impact of policy changes, the engagement of the food industry and of preventive health services we think are particularly important. We initiated a program called We Can, which is ways of enhancing childhood activity and nutrition, which we have now several thousand community partners aimed very heavily at reducing screen time and increasing physical activity and focusing very heavily on dietary activities.

We have several collaborations with the food industry, with several partners in the food industry which have become increasingly responsive, but we think that there are probably going to have to be some policy approaches that will have an impact on this, that simply relying on individual choices is not going to be sufficient.

Senator SHELBY. Thank you. Thank you, Mr. Chairman.

Senator HARKIN. Thank you. In keeping with the subcommittee's policy in order of appearance here at the subcommittee be Senator Reed, Senator Moran, Senator Mikulski, Senator Brown.

Senator Reed.

GLOBAL COMPETITIVENESS

Senator REED. Thank you very much, Mr. Chairman, and thank you, doctors.

Dr. Collins, just a quick point, that Chinese facility that you mentioned to is supported by the Chinese Government or do we know?

Dr. COLLINS. Interesting. It is partly supported by the Government, but they actually have put this in place by taking out a bank-supported loan to allow them to purchase 128 of these——

Senator MIKULSKI. They didn't get it here.

Dr. COLLINS. Senator Mikulski is correct. It was not at an American bank. And they have purchased 128 of these sequencing machines, the largest collection in the world, and they are quite confident that the value economically will fully justify the cost of buying the machines.

They've also hired about 4,000 of the smartest young scientists that I've ever seen in one place from all over China who are in their 20s and who are prepared to change the world and probably are going to.

And we should celebrate that. I don't mean in any way to say I think this is a bad thing, but it worries me to see that China has taken that kind of initiative and we have not.

Senator REED. But the financing might be considered quasi private and public together, but this is clearly an initiative at the highest levels of the Chinese Government to get this done.

Dr. COLLINS. Yes.

Senator REED. And we are at this debate here in the United States about what we will commit as a Government to not only the genome sequencing, but so many of the innovative proposals you've talked about.

Dr. COLLINS. That's correct——

NIC VOLKER TREATMENT DETAILS

Senator REED. Just want to clarify that.

I thought also, joining the chairman, that the poignant story of Nic—I wonder did he or his doctors avail themselves to the National Cord Blood Registry, CDC's the MATCH? Was that a——

Dr. COLLINS. I don't know in terms of where his stem cell transplant came from. I can find that out for you, Senator.

PEDIATRIC RESEARCH

Senator REED. But that's an initiative that Senator Hatch and I worked on and I hope it contributed to that great story.

[The information follows:]

NIC AND THE NATIONAL BLOOD CORD REGISTRY

David A. Margolis, M.D., professor of pediatrics and director of the Bone Marrow Transplant Program at the Children's Hospital of Wisconsin, said, "Our donor coordinator says 'Yes. If it were not for the National Marrow Donor Program, and the single access that it provides, the search (for Nic's cord blood stem cell donor) would have been more difficult, time consuming, and may not have yielded the same results.'"

Senator REED. But this raises a larger question, then, in terms—that I have with respect to the amount of resources going to pediatric research. You've cited several examples. Dr. Rodgers, Dr. Shurin have talked about, you know, the research you're doing in children's obesity, et cetera.

For example, I'm told that only about 4 percent of the funds in the National Cancer Institute are for pediatric cancers. That might be good news, because it might represent that it's a relatively healthy population, but just generally a sense do you think we're making the right allocation of resources to pediatric research?

If we're not, are there structural issues; that is, is the peer-based review tilted toward adult experts rather than pediatric experts? Any comments I'd appreciate.

Dr. COLLINS. Well, quickly, and then I'll ask Dr. Varmus to address the pediatric oncology issue, but we have an entire Institute at NIH, the National Institute of Child Health and Human Development, which has as its major focus pediatric research and which certainly is a place of a great deal of interest and excitement right now because there are so many promising developments in childhood illness.

We also are investing in a very large national project, an unprecedented one, the National Children's Study, which will enroll 100,000 kids beginning even before conception through pregnancy and up to age 21 in order to comprehensively collect the kind of information about environmental exposures and genetics that may shed light on diseases like autism and diabetes that have continued to vex us.

I would say, yes, there's a lot of investment. Could there be more? You bet there could, but that would probably be true in virtually every area that we're looking at. With these 17 to 18 percent success rates that were mentioned by the chairman, we are clearly not able to support a lot of great science that we'd like to support.

Senator REED. Before Dr. Varmus, I must say that Brown University Medical School is participating along with Women and Infants Hospital, and Dr. Rodgers is their commencement speaker, because he's one of the most illustrious Brown University medical graduates in the history of the program. I had to put that in the record. Forgive me, Dr. Collins.

Dr. Varmus.

Dr. VARMUS. Senator Reed, thank you very much, and I appreciate your honoring my colleague, Dr. Rodgers.

You're correct that the amount of money we specifically identify as being devoted to pediatric cancer research is about 4 percent of our budget, which is about $200 million a year, but, of course, a great deal of other funding that we're involved in addresses cancer more generally and is applicable to pediatric problems.

Let me say a few words more broadly about pediatric cancer. Chairman Harkin alluded to the fact that we do cure most patients with leukemia. Pediatric cancers, in general, are much more effectively treated, whether they're brain tumors or neuroblastomas or Wilms tumor or leukemias, but, nevertheless, there still is an increased incidence of childhood cancers over the last several years by about 30 percent, but a continuing decline in mortality.

Nevertheless, mortality figures do not tell us the whole story. There are severe consequences of being treated for cancer at an early age—developmental defects, loss of mental capacity in some individuals, and, of course, a very high incidence of second tumors, particularly in survivors' 20s and 30s.

We're trying to address these problems in a variety of ways. We're trying to understand the cancers more profoundly with some of the genomic-sequencing techniques that Dr. Collins alluded to.

We, in fact, have spent Recovery Act money on a new project to study pediatric cancers in great detail. And we have new therapeutic maneuvers that are based on more targeted, bullet-specific drugs and antibodies that have been very effective in reducing mortality rates in neuroblastoma and leukemias with therapies that are less toxic.

We have paid a lot of attention to the survivors of pediatric cancer. We have a nationwide survivors study for pediatric cancer that has enrolled over 20,000 patients in roughly 37 different centers. So with these and other projects, we think we're making a pretty good effort to control the consequences of treatment of pediatric cancer and to do a better job in treating pediatric cancers in a less toxic manner.

But you're correct, we could do more, but, as you know, we have budget constraints this year. It's unlikely that we'll see a very significant increase in that domain or any other in the coming year.

BIOMEDICAL RESEARCH RESOURCES AND WORKFORCE

Senator REED. Thank you very much. Thank you, gentlemen. Thank you, Dr. Shurin. Thank you, Mr. Chairman.

Senator MORAN. Chairman Harkin, thank you.

Dr. Collins and your colleagues, fellow doctors, I appreciate the opportunity to have this conversation with you this morning.

This is a beginning course for me. I have 4 months of being a United States Senator and being a member of this subcommittee, but I'm excited about joining Senator Harkin and Senator Shelby and my colleagues here.

I think medical research is a huge component of the future of our country. I think it matters greatly, and I commend you for your efforts to date.

In my healthcare reform bill, we would support medical research in a dramatic way. I think it's a cost-saving measure. It's about saving people's lives, improving the quality of their life. And so from an economic—as you point out—but also from a personal, humanitarian point of view, what we do here in this subcommittee and what you do at NIH matters greatly.

And I would welcome the opportunity to become better acquainted with NIH, its personnel, its mission. Maybe the people in the rows behind you—I want my doctors out there doing the research, but I'm happy to have others at NIH devote some time to educating me so that I can better understand how we can advance the cause of medical research here in the United States.

I would ask first if there is something missing. We're here in an appropriations subcommittee, but other than money, is there something missing at NIH or here in our country, in the United States, that makes it much more difficult or makes it difficult for you to reach the goals that you outlined for us today or is this just a financial issue, how many dollars do we devote? What are the other, if any, impediments toward success?

Dr. COLLINS. Well, Senator, I appreciate the question and certainly appreciate your strong statement of support, and you are most welcome to come and visit us at NIH. We'd love to host you for a visit and show you some of the things that are going on in the laboratories and in the clinical center, the largest research hospital in the world, that's up there in Bethesda.

Senator MORAN. Thank you.

Dr. COLLINS. But as you know, most of the money that NIH sends out in grants goes to the 50 States, including Kansas, and we're very proud of the research that's going on there in your State.

Senator MORAN. Thank you.

Dr. COLLINS. In terms of other things that potentially are barriers, certainly we do not have what I would call a vigorous pipeline of young scientists coming into our field, and part of that is the sad state of K through 12 science education in this country, which has certainly, by any measure, slipped badly over where it

used to be back in the—30 or 40 years ago in the sort of post-Sputnik arena where science education was really emphasized.

Now, in many schools, it is unfortunately quite rudimentary, and I think we lose, therefore, the chance to capture young people's imagination that science would be a place they wanted to spend their own careers. And that means we have fewer American-born individuals who are clamoring to come in to our laboratories and make the next great discoveries.

We have lots of interest from individuals born in other countries to do that, but that interest has actually declined a bit as more opportunities are present in their own countries.

Some of them, certainly in large numbers, still come to train in our universities, but they often now go back to their original homes and carry out research instead of staying in the United States. And some of our visa practices have not helped in that regard in terms of making such talented scientists from other countries feel less welcome than we wish they were.

It seems to me that would be a very important area for us to, again, try to get right, because it is to our advantage to recruit such individuals—and our universities are still seen as the very best in the world—to come and do their research, but then for us to also be able to capture their talents in an ongoing way I think would be a great advantage. That is just one of the areas.

But, frankly, the major concern that I think we have is just the lack of sufficient resources to chase down all of the great ideas that are now potentially possible.

INTERDISCIPLINARY RESEARCH

Senator MORAN. I appreciate that answer and look forward to finding solutions in that regard and understand now the importance you place upon the resources.

I did visit the University of Kansas last week and one of the research facilities there, the Molecular Libraries Program, and I'm very interested in what the ranking member pursued in regard to NCATS.

And when I heard your testimony today, my assumption is that this will take a lot of different kinds of scientists engaged in this effort, and I guess an initial question would be what steps would you anticipate being taken to ensure that the best of American science in as many areas will have that opportunity to contribute to this new program?

Dr. COLLINS. Well, a very appropriate point. It will take an interdisciplinary effort of a considerably revolutionary sort.

It means bringing together biologists and chemists—as no doubt you saw at the Molecular Libraries Program in Kansas—along with computational experts, structural biologists who can actually figure out the shape of molecules and figure out which shapes fit together in a way that might make a particular drug work, immunologists who can help us with monoclonal antibody development, engineers who can work on devices that will be the next generation of what we need for all manner of medical applications, and those disciplines traditionally haven't had such an easy time talking to each other, and one of our goals through this program and many others is to do that.

Maybe this is also partly in answer to your first question about what are some of the barriers. In some way our own traditional disciplines have presented some of that problem, although I think those barriers are coming down.

Clearly, there's a lot of excitement—and I suspect you perceived that in your visit to the Kansas center—about the potential here of bringing those disciplines together with these new comprehensive sciences to enable academic investigators to play a larger role in reengineering this broken pipeline to try to make it possible to come up with therapeutics and devices and diagnostics in a shorter time period.

This resonates with me for the same kind of feeling I had about the Genome Project 20 years ago. It was controversial then, too, of course. A lot of people wondered whether this was biting off more than the Government could chew, but it recruited into the effort some of the best and brightest minds of that generation because they could see the potential.

I think that same atmosphere is beginning to appear in translational science, and I suspect once we have the programs in place it will not be hard to recruit some really brilliant minds to play a role in this.

Harold, did you want to add to that?

Dr. VARMUS. I think it might be important to reassure you, Mr. Moran, about the effort that's being made in translational research across the institutes.

As Francis alluded to in his testimony, a great deal of work—interdisciplinary work, indeed—has gone on in the Institutes and will continue to go on, while NCATS provides a catalytic advantage to the efforts that we're making by providing new methodologies, ways to analyze how translational research is done, some core facilities.

But, as you probably know from going to your cancer center at the University of Kansas, that there is a lot of translational research going on there, and that's done by interdisciplinary teams.

So all of us at the NIH are engaged in this process and we've had a lot of experience in gathering multidisciplinary teams over the last decade or so to do this kind of work.

Senator MORAN. So it's not new and we know it can be done. It's being done today.

Dr. VARMUS. But we're all engaged in the process, and it's not going to fall solely on the head of NCATS.

Senator MORAN. And, unfortunately, I'm on the social science in my education and I detect that the same thing may be there between chemistry and biology as there is between history and political science.

Dr. VARMUS. Well, there could well be. Yes——

Senator MORAN. But I appreciate that, and I did see the enthusiasm. That was perhaps the takeaway of my visit is the excitement that is there and the belief in the potential of what can be accomplished.

Dr. VARMUS. Yes.

Senator MORAN. It's very appealing to me.

Dr. COLLINS. Dr. Fauci wants to add something.

Dr. FAUCI. There is one other thing that sometimes gets misunderstood. We mention—and Dr. Varmus mentioned also that there's a lot of translational research going on.

What the center is going to be directing itself at is to really advance what we call the discipline of translational research, in other words, to help us to do more innovative ways of approaching translational research. So translational research goes on to the tune of many billions of dollars at the NIH, mostly in the big Institutes, but some of the smaller Institutes also.

What we want to do is advance the discipline of how it's done, making it a 21st century approach toward translational research as opposed to relying on many of the methodologies that have been good, but that we think we can do better on. That's what it's really all about, putting forth the discipline and improving the discipline of translational research.

Senator HARKIN. Thank you. Thank you, Senator Moran.

Senator Mikulski.

SUPPORT OF NIH

Senator MIKULSKI. Thank you very much, Mr. Chairman. I'm very proud of the fact that NIH is located in the State of Maryland. And for more than 25 years, I've visited NIH regularly, and every time I come, my eyes pop with wonder, my heart beats with excitement and I just—one of the reasons I wanted to be here today was to tell you and all of the people who work at NIH how proud I am of you, and how America ought to be proud of you.

Dr. Collins, you did path-breaking pioneering work when mapping the genome. And we were in a race. You had another competitor down the street. You broke the code and we invented—not only mapped the code, but came up with new fields called computational biology, bioinformatics, new exciting careers that help both us in particularly the private sector be able to come up with new products.

And, Dr. Fauci, you, what you've done. You were the guy who broke the AIDS code. You were the guy that came here when we were gripped in fear and near panic when we were shut down due to anthrax and we had no place to turn in our United States Government for information, but we turned to you and you kept us on the right path, so that we could keep the doors of the Capitol——

Dr. Varmus, a former head of NIH. You know, NIH Directors don't leave. They leave legacies, and then they come back to create new ones, and we're so glad to see you. And we note that when you were at Sloan-Kettering you had a lot of other zeros behind your compensation package, which says something about why you came back.

And to Dr. Rodgers and Dr. Shurin, who also was educated at Hopkins, we're just glad to see you.

And, Mr. Chairman, and what they do is the work that helps us manage the biggest budget busters in our healthcare budget—diabetes, heart disease, the chronic conditions that lead to chronic problems in the way we live, in the way we have to fund healthcare.

So I wanted to be here today to say for all the people work at the institutes, all the people work at the various offices, all the lab

techs, the security guards, the fire department, we're really proud of you.

So having said that, I want to make sure we help NIH be NIH. So I want to stick to the basic mission in addition to these exciting new ideas.

Dr. Collins, how many research grants did NIH fund last year, and how many requests did you get for funding? In other words, what is the funding gap, and particularly not only with the tried and true research, but also with those promising young, maybe more upstart type thinking?

Dr. COLLINS. So in fiscal year 2010, we funded approximately 9,300 research grants. The success rate in fiscal year 2010 came out at just about 20 percent; that is, one out of five that were able to be supported.

With the fiscal year 2011 budget now in front of us, now that it's been decided, we won't do that well, because, of course, as you know, after the dust all settled, we ended up with a 1-percent cut of $320 million, although I really want to express my appreciation——

Senator MIKULSKI. So that's what one percent means, $320 million?

Dr. COLLINS. That's correct. But I do want to express my appreciation to members of this subcommittee, because I know there was a great deal of debate about exactly where the dust would all settle out, and certainly many of the proposals were vastly worse than this, and I know many people really went to bat for NIH, and we appreciate that enormously.

But we do believe that in fiscal year 2011—with some uncertainty in the number, because we don't actually know how many grants we will receive, and, of course, we're talking about a proportionality here—that the success rate will fall to approximately 17 to 18 percent, and that will be the lowest in history.

We will do our best to try to manage the resources that we've got, and we've made a number of adjustments to try to keep that number——

Senator MIKULSKI. But for every one grant that you can fund, let's even go to before fiscal 2011, how many are unfunded?

Dr. COLLINS. So it would be five out of the six. If you have six grants in front of you, we're going to fund one of them and five of them are going to go begging.

WORKFORCE PIPELINE

Senator MIKULSKI. All of which are quite promising.

Now, let's go to much is made about recruiting young people into science, and we want a lot of initiatives in that, but young people follow opportunity. So when we look at your internship, your fellowship program, both for high school, undergraduates and so on, again, how many students can you have come in to NIH? And how many—In other words, how many can you take and how many apply? What's the enthusiasm gap here?

Dr. COLLINS. Well, there is enormous enthusiasm. Certainly, we run a number of internship programs on the NIH campus. We have a program for high school students and college students who come and spend 10 weeks in the summer. That is always oversubscribed

by at least a factor of five in terms of the number of slots that we have available and the space that's in the labs.

We also have a program for individuals who are finishing college, who are really interested in science, but they're not sure whether they want to go to graduate school or medical school. They come and spend 1 year, sometimes 2 years doing full-time research in the lab.

I have three of those students in my lab right now. They're enormously energized, excited about what they're doing, and they go on to do great things. This is a really important program.

But there again, the number of applications we have for that so-called post bac program is at least four or five times greater than the number of slots that we have available to offer.

Senator MIKULSKI. So while we're busy—You know, we like to pound our chest and come up with all kinds of things in education to encourage people for science, but our young people are going in it, but they need opportunity, both in the public as well as in the private sector.

Dr. COLLINS. So, Senator, I've just set up, as part of my advisory committee to the Director, a working group to look at our workforce issues, and I've asked Dr. Shirley Tilghman, the president of Princeton, to co-chair that, because I think we need a better handle on what the supply-and-demand issues are in terms of the biomedical research workforce.

We want to be sure that we're looking forward with a clear eye toward all of the different pathways that are going to need well-trained, doctoral-level biomedical researchers and that we, NIH, as a major source of training support are appropriately tuning our programs so that we have the numbers right in terms of how many people we are bringing in and what kinds of careers we're preparing them for.

EFFECTS OF A GOVERNMENT SHUTDOWN

Senator MIKULSKI. Well, I think this would be enormously useful to this subcommittee, Mr. Chairman, because, as you know, this is a topic—a big public-policy topic they ponder all of the time.

My last just comment or question is with all the talk of the shutdown and during H.R. 1, a cut to the National Cancer Institute, which was stunning to many people, including me, what is the morale at NIH now that they thought that they might be sent home and told that they were non-essential and the cuts might be coming?

I mean, I must say both the chairman and the ranking member were enormously supported to minimize the disaster, but it was not a victory.

Dr. COLLINS. So I would say this was a very difficult period to go through. We were required, of course, in preparation for what appeared to be a very high likelihood of a shutdown, to define how we would manage that, and that meant defining which particular employees were considered essential and which were excepted, was the term that was used, and which were non-excepted.

And, of course, those who were involved in patient care or management of animals couldn't very well just not come to work, but

others were told, "I'm sorry. If there is a shutdown, you can't come to work."

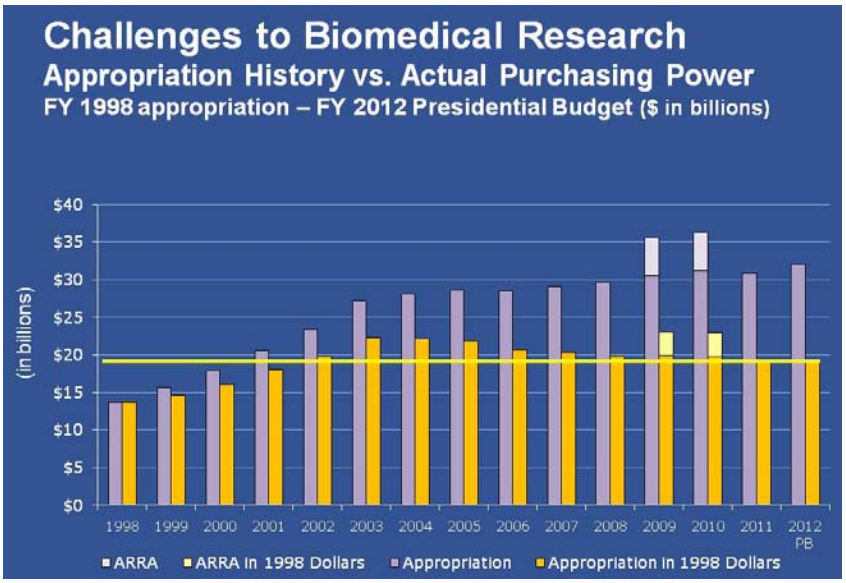
Think about how that feels if you're a post-doctoral fellow who's in the middle of an experiment that you've been working on for 2 or 3 weeks and has another couple of weeks to go and you're being told, "I'm sorry. You're not allowed to come to work tomorrow if the Government shuts down." It did have a very significant effect. People were quite shaken up by that.

I think people are—in the aftermath of that—feeling a little uncertain about what it's like to work in this environment and hoping that we won't face that again. But, again, I think everybody understands these are terribly, terribly difficult times for our country.

INFLATION EFFECTS ON PURCHASING POWER

I just want to show you one image because I think it might be actually useful.

[The information follows:]



Senator MIKULSKI. Okay. I'm going to just—chairman regulate the time, but I'm fine with it, but if that's okay with the chairman.

Dr. COLLINS. It'll take 1 second. This is basically why we are in such a crunch.

Senator MIKULSKI. Well this is a terrific slide.

Dr. COLLINS. So this is—this shows——

Senator MIKULSKI. It's more like the way my heart went up during the shutdown mode.

Dr. COLLINS. So in blue, you see the appropriations for NIH going back to 1998. You see the doubling that happened between 1998 and 2003, and then you see that since 2003 the NIH budget has been much more in a flat trajectory.

But in yellow, you see the effects of inflation, the biomedical research and development index, which has been eating away at our

buying power since 2003, placing us now, even with the President's budget, in the range of what we were at 2001. So we're sort of where we were 10 years ago.

You see the Recovery Act dollars there in 2009 and 2010, which were a wonderful boost to the scientific community, but, of course, that was 2-year money.

That is why the success rates are now dropping to where they are. It's all pretty much clear what the consequences would be once one considers what's happened to buying power for research.

Senator MIKULSKI. Thank you. Mr. Chairman, thank you.

Senator HARKIN. Senator Mikulski.

Senator MIKULSKI. You are the genius club. I mean, you really are. So thank you.

Dr. COLLINS. Thanks.

Senator HARKIN. Senator Brown.

NEW INVESTIGATORS

Senator BROWN. Thank you, Mr. Chairman. And I've always so enjoyed having panels from NIH, some of the smartest people in the country, especially those who used to teach in Cleveland, Dr. Shurin.

But thank you. I mean, it really is illuminating and we thank you so much for your service. This is such an example of public service and why government matters.

And when I hear some of the know-nothings that hold jobs like we hold say that the Government is broke and that Government can't function and Government doesn't contribute anything and Government doesn't create jobs, you know, I think about the special forces. Those were Government employees that were in Abbottabad, but I think primarily of what NIH does and what you contribute to public health and to wealth of our country.

I want to take up on what Senator Mikulski said, and Dr. Collins' response, on the one out of five grants. I was in the House, ranking Democrat on the subcommittee back when we actually wanted to fund public health bipartisanly in this country 15 years ago, doubled the budget at NIH.

And I remember in those days those numbers that some of your predecessors—well, some of you and some of your predecessors—would cite, now that we fund one out of five grants or one out of six grants. It's gotten a bit worse than what Senator Mikulski said.

The other part of that story that I remember is the young researchers that you are always looking to attract when you teach at med schools and you counsel people and you mentor people, those are the least likely to be the one out of five that gets the grants—or the one out of six—because my understanding is that people that have done these grants over time kind of know how to win the grants better than the young, bright researcher also applying for the grant. So the numbers, in some sense, among younger, hungry researchers are even worse, the ratios, and too many of these young people leave the field.

And I think that's, to me, the most compelling reason that this fervor to cut budgets as—we need to address our budget deficit, but we're creating terrible deficits in young scientists and terrible deficits in the public body of knowledge, I just want to say.

COST OF PHARMACEUTICALS

Let me go—two issues I want to talk briefly about. One is the issue of the Makena drug, the progesterone that was developed over time into a—produced by compounding pharmacies as you know, has made a huge difference, provable huge difference, clinically trialed—if that's a verb or adverb—huge difference in preventing early birth, pre-term births.

We know what this KV Pharmaceuticals in St. Louis did. We also know that you at NIH have invested $21 million on now four clinical trials, in the midst of the fourth one and still investing in this and finding, I think, more indications, perhaps, to use this drug, this progesterone, this compounded pharmacy drug.

Well, just give me your thoughts, briefly, if you would, how do we prevent this from happening? The Food and Drug Administration (FDA) has stepped in and done something pretty unusual and pretty gutsy by saying they're not going to enforce the cease-and-desist order on compounding pharmacies.

So when I talk to obgyns and visit hospitals—I was at University Hospitals yesterday in Cleveland—2 days ago—talking about they're still compounding it, still producing this.

When taxpayers invest in this and it's clearly a drug in the public interest and one company can get exclusivity for 7 years, while you continue to do these clinical trials expanding—in a sense expanding their market on this fourth clinical trial you're doing—and I know this cuts across FDA, HHS as a whole and you and CDC and all, but what do we do about this?

Dr. COLLINS. Well, Senator, I think you spoke out quite strongly about the Makena situation and I think brought a lot of attention to a circumstance that really was deeply troubling, that a drug—let's just call it 17P—that was previously available and compounded by pharmacists and then was put into a clinical trial, ultimately ended up, after FDA approval and orphan-drug status, going up in cost from something that cost $10 or $20 to something that costs $1,500.

We were also deeply alarmed to see that and quite pleased to see FDA step in and say they were not going to go after pharmacists that continued to provide the compounded material.

And that, by the way, also, and along with your strong statements and that from some of the professional groups, did cause KV Pharmaceuticals to drop their costs, but still at a much higher level than they were in the old days.

NIH has its hands a bit tied in this situation. Back in the 1990s, when Harold Varmus was NIH Director, we had a big discussion about whether drugs that NIH plays a role in developing should have some sort of reasonable pricing clause attached to any kind of licensing that we would do to a company.

And while that might have seemed like a way to avoid another kind of Makena outcome, it was a poison pill for any serious relationship that NIH would have with a company. No company in this country or elsewhere would be interested in a partnership with NIH under those circumstances.

What we can do is to make sure that if profits ensue and NIH has made a contribution to that, in terms of genuine intellectual

property discoveries, that there should be royalty sharing on that basis.

But when it comes to setting the price, as KV did, even though we supported the clinical research, we are probably not the agency in a position to be able to do something to step in and interfere with their pricing decision.

It was the public outcry, your outcry, Representative DeLauro, the professional societies that I think actually turned the tide.

Senator BROWN. But that outcry only brought the price from $1,500 multiplied times 20, with 20 weeks of treatment, as you know——

Dr. COLLINS. Yes.

Senator BROWN [continuing]. $1,500, $30,000, when it was 20 times $10 or $20—depending on the compounded pharmacy's charge—down to $690. So the outcry worked with FDA. The outcry barely worked with KV.

But is there a way to sort of cross the—I understand that you don't want to engage in partnering and price-setting and all that, but—or maybe you do—but when a company so overreaches like this, it was such an affront to the public interest, if there's a way, sort of across help agencies we could find some solutions or——

I mean, Dr. Hamburg was in here and she said, well, you know, FDA didn't do this. She wasn't defensive at all, but then FDA did something. This was before they made that decision.

But I just will follow up with you, but I'd like to see if there's a way to——

CANCER CLUSTERS

My other question—I'm sorry to go over the 5 minutes, Mr. Chairman—Dr. Varmus, you had talked about pediatric cancers and Senator Reed had asked you about that.

There's a cancer cluster in Clyde, Ohio, where many, many children, under 12 in most cases, have developed cancer, and I know you see these. There are four or five believed to be cancer clusters. I don't know if that's a particular medical term, but is certainly what we talk about.

What is NIH's role in sort of examining these, exploring these, finding out the environmental cause, if it is that, as I presume—I guess I presume it is. What is your role in that?

Dr. VARMUS. Well, we do investigate that. We have a Division of Epidemiological Cancer Research that will look at these clusters to ascertain whether or not the cluster is real. Because, as you might expect, if cancers are distributed in their frequency across the country, there are going to be some places that just, by chance, have a particularly high or particularly low incidence, and there are several classical examples of clusters that turned out only to be arithmetic aberrations, but without any clear indication of causes.

On the other hand, there have been clusters of cancers that are linked to certain practices or to exposure to industrial mutagens, and we would go in with collaboration with the National Institute of Environmental Health Sciences and try to ascertain what might be a precipitating cause.

So we do have a role and we would—I don't know about the one you're citing, but we can certainly look into it and report back to you on what——

Senator BROWN. We have talked to NIH overall, but we will specifically talk to you.

Thank you, Mr. Chairman.

[The information follows:]

CLYDE, OHIO CANCER CLUSTER

State and Federal Responses to Cancer Cluster Reports.—State and local health departments respond to cancer cluster reports and provide the first level of response and review of the most current local data for the area. If needed, these local health departments can request assistance from Federal agencies, including the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP) of the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substances and Disease Registry (ATSDR), and the U.S. Environmental Protection Agency (EPA). CDC's role in investigating potential cancer clusters is to provide technical assistance to States at their request as they conduct their investigations. In State cancer registries, States have the data needed to determine whether a cluster exists.

National Cancer Institute (NCI).—NCI does not investigate anecdotal clusters of individual cancer cases in neighborhoods, but rather clusters of counties with elevated rates as part of the geographic mapping strategy to identify and investigate high-risk populations for etiologic insights. However, upon occasion NCI's Division of Cancer Epidemiology and Genetics (DCEG) may be called upon to consult with local and State health officials and CDC experts as they investigate purported cancer clusters.

DCEG's research portfolio includes analysis of cancer treands in human populations, and DCEG investigators conduct studies both within the U.S. and around the world where the incidence of certain cancers is significantly higher than might be expected. Examples of such investigations include lung cancer in coastal communities in the U.S., which was linked to asbestos exposure in ship yards, and oral cancer in women in the rural south, which was linked to smokeless tobacco use. DCEG researchers are currently investigating the reasons for the very high rates of bladder cancer in northern New England; they will soon be reporting data from this effort. They are also conducting a study to explore the elevated rates of Burkitt's lymphoma in regions in Africa.

Regarding the Clyde, Ohio Investigations.—It is our understanding that there was a multi-year analysis of a suspected cancer cluster in Clyde, Ohio by the Ohio Department of Health (ODH). Both CDC and ATSDR provided technical assistance to the State officials over the course of the multi-year assessment. While NCI has not received any reports or conclusions, it is our understanding that the assessment's final conclusion was that the data were inconclusive and there was no cancer cluster identified. These Federal public health agencies are continuing their collaboration with ODH and are available to provide support as needed.

FLU VACCINE

Senator HARKIN. Thank you, Senator Brown.

Dr. Fauci, for years, you've been here, year after year, and we've talked about flu vaccines, and, some time ago, I remember you talked about progress being made toward a—perhaps a universal type flu vaccine. You mentioned it in your written statement, which I read last night. Again, how close are we?

Dr. FAUCI. Well, I can't give you an exact time in years, because every time a vaccinologist does that, he or she gets burned. So I'll refrain from that, but I can tell you that we clearly are considerably closer than when I spoke to you last time at a hearing when we were talking about the possibility of getting away from that very frustrating situation where each year you have to hopefully guess right, and we do most of the time, but not all the time.

But even more importantly, when we're faced with a pandemic flu like we were with the 2009 H1N1, when we made a vaccine

after isolating the virus, but the production issues were such that by the time we got enough to distribute, unfortunately, the pandemic had already peaked. Fortunately for us, it was a relatively mild one, but that's not going to happen all the time.

So what's happened in the last year since we spoke, Mr. Chairman, is that there have been a number of experiments that have been conducted both at the NIH and by our grantees and contractors, which have really identified components of the influenza virus that the body generally does not make a very good response to readily, and that part of the virus is the one that would give you protection against virtually all strains.

And one of the reasons is is that it's sort of hidden from the view of the immune system. The thing that the immune system sees really clearly is the part of the virus that changes from season to season, and that really changes a lot when you get a pandemic. There's a part of the virus that the body can make an immune response to that it doesn't usually see very well.

So what investigators have done, in a very simple way, is that to put that particular component of the virus in a form that the body would see it much more sharply and clearly. This has been done in animal models and proven to be inducing responses that are good against decades of changes of influenza.

And, now, those studies are being done in what we call phase I trials in humans, and the early work indicates that, clearly, it looks quite safe, and, second, it is inducing responses that span multiple years.

So I believe it's really just a matter of time. As you know, clinical trials, when you want to prove safety and efficacy over a period of time, naturally would take years, but it's on a track that I believe it's going to happen. I don't think it's going to be a question of if. It's going to be a question of when. So we're really quite excited about it.

And that's a very good example of that transition from fundamental basic research observations on molecules and their confirmation and how that ultimately gets translated into something that, if successful, is going to have enormous public health benefit.

Senator HARKIN. Well it would. I mean, the amount of just savings alone on annual flu shots would be incredible, aside from the fact that you wouldn't—I would, from what I understand is if this was really developed, the threat of pandemics would not be as large as they are now either.

Dr. FAUCI. The ultimate goal is to have on the shelf, ready for utilization a vaccine that does have the universal characteristics to it, so that if you do get a change with a pandemic, that you can actually have that particular virus be covered by it.

So we'd like to get it to the form—I don't think it's going to be perfectly this way, Mr. Chairman, but it's going to be close. I don't think it's going to be one flu vaccine and that's it for the rest of your life.

It'll probably be having to be given every several years to continue to boost the immune system, but we would like to be the way we are, for example, with measles or hepatitis or polio, where you just make a lot of it, you have it available and when you need it,

you deploy it, as opposed to having to play catch up every single time a new virus emerges.

MEDICAL MILESTONES

Senator HARKIN. Very good.

Dr. Varmus, in 2001, Gleevec was on the cover of all our national news magazines, talked about it being the magic bullet that would herald in a new age in the war against cancer. For the first time, we had a drug that specifically targeted a known cancer gene. It took this deadly blood disease, turned it into a chronic, but survivable condition.

We were told that Gleevec was the promise of the future. We talked about it in our subcommittee hearings at that time, but that was 10 years ago. We haven't had any other Gleevecs. What's happened? How come no more Gleevecs?

Dr. VARMUS. Well, I wouldn't characterize it quite that way, Senator. Gleevec remains the poster child for targeted therapy.

Senator HARKIN. Yes.

Dr. VARMUS. And just to give you a brief update, it's used not only for the treatment of chronic myeloid leukemia, the leukemia you heard about, it's used for the treatment of several other diseases in which potential targets for the drug are mutated, and that includes gastrointestinal stromal tumors, a number of other blood diseases, and, indeed, a few other diseases in a few cases in which certain genes are known to be mutated as a result of analysis of the genome of those cancers.

Moreover, it's recently been shown that we can deal with drug resistance, a common problem in cancer therapy, by using drugs closely related to Gleevec but not identical to it and to treat patients who become resistant to Gleevec.

Second, it's been shown recently that a person in their 40s or 50s who develop—leukemia now have a normal life expectancy, which was previously 5 years. That's a dramatic change and it shows that the efficacy of Gleevec has been sustained over the last 10 years, and, actually, the evidence that it's effective is only strengthened.

There are a number of other targeted therapies. They tend to work quite well initially. Patients become—their tumors become resistant to therapy. Let me give you a couple of examples.

One happens to involve my own work on lung cancer, which is a significant percentage, perhaps 10 percent, of cancers have mutations in some specific genes against which we have effective inhibitors, but, generally speaking, within 1 year or so, on average, patients become resistant to those drugs. We don't have good therapies to counter the tumors that are resistant.

Recently, in the case of a disease called metastatic melanoma, a disease that is secondary to finding a skin tumor, but the tumor has spread to the liver, bones, and other sites, it's been found as recently as 7 or 8 years ago, that about 60 percent of those cancers have a mutation in a specific gene against which an inhibitor has been developed.

It's extremely effective, again, in inducing remissions in a fairly non-toxic way. This is, again, an orally available drug that promotes a dramatic regression in the size of tumors.

There are two drugs that do this. They are very likely soon to be approved by the FDA. They don't cause persistent regressions, but there's every reason to hope that additional drugs will be on the way to help counter drug resistance.

So I would say that we've had a number of other targeted therapies. They have not, in general, been quite as dramatic as Gleevec, but most of us who are working in this area are quite optimistic about a number of new drugs, some of which I haven't mentioned, that are in the pipeline.

Senator HARKIN. That drug you mentioned about metastatic melanoma, you mentioned it in your written testimony.

Dr. VARMUS. Correct.

Senator HARKIN. What's the name of the drug? I forget——

Dr. VARMUS. Well, there are two things that I mentioned in my testimony, Senator, first was these so-called inhibitors of BRAF. These drugs are not yet on the market. One comes from Flexicon, one from GlaxoSmithKline (GSK).

Senator HARKIN. Yes.

Dr. VARMUS. There's also a new immunotherapy called ipilimumab, which has been approved by the FDA. That's not the same kind of targeted therapy, but it's a dramatic development, because it's one of the first immunological approaches.

There are others, but this is one of the first that actually displays how we can manipulate our understanding of the immune system to galvanize the response of the immune system against a variety of cancers, including melanoma.

Senator HARKIN. But I can't even pronounce that word, ipilimumab?

Dr. VARMUS. Ipilimumab.

Senator HARKIN. Thank you very much.

Dr. VARMUS. Yes, I'm not responsible for that, Senator. It would not have been my choice. Ipi for short.

Senator HARKIN. It seems to me this is about as important as Gleevec. I mean, this attacks metastatic melanoma in later stages.

Dr. VARMUS. Correct.

Senator HARKIN. And this has always been a death sentence before.

Dr. VARMUS. As does the drug that inhibits the BRAF mutation. But ipilimumab does not work in all cases, but does prolong life significantly in a very substantial 15 to 30 percent of patients who have metastatic melanoma. It is a major development, no question about it.

One of the open questions is why do a certain subset of patients with this disease respond and others not respond.

There are other inhibitors of the so-called brakes on the immune system that are in development, and I think may be combined with ipilimumab or used as an alternative when ipilimumab doesn't work.

So we're quite optimistic after many years of trying to manipulate the immune system that we have some very serious handles on how the immune system works that we can use in cancer therapies.

Senator HARKIN. Very good. Thanks, Dr. Varmus.

Recognize Senator Shelby, then I see Senator Kirk has joined us. I'll go to Senator Kirk next.

ACADEMIA-INDUSTRY COLLABORATION TO REPURPOSE DRUG COMPOUND

Senator SHELBY. Thank you.

Dr. Collins, repurposing drugs, you alluded to that earlier. As we have searched for treatments, as you do, and others, investigators, to the healthcare challenges, one of the clear ways that some people believe we can continue drug development is by finding new uses for drugs that were discontinued or halted mid-development. By leveraging existing compounds, researchers in industry can develop and have new, novel treatments for patients.

It's my understanding that the NIH recently held a roundtable discussion regarding rescuing and repurposing compounds. Seems like that's an ideal opportunity for academia to team with industry to bring treatments to patients faster. Could you expand on that? What are you doing here and how?

Dr. COLLINS. I'd be happy to, Senator, because this is a really exciting potential area to speed up the process of developing new treatments for diseases that currently lack effective interventions, and it's another example of the kind of thing that NCATS will be able to catalyze just by its convening power.

Yes, we did have this meeting just about 10 days ago. We invited major leaders from pharmaceutical and biotech industries to meet with NIH investigators, with academic experts and to ask the question: Are there in fact, already sitting in medicine bottles or in freezers of companies that have tried various compounds and abandoned them along the way opportunities to take molecules about which we already know a lot and find a new use for them?

Senator SHELBY. Do you have any examples or is it too early?

Dr. COLLINS. We have some very striking examples. Maybe I'll even ask Dr. Shurin to tell the example of Marfan syndrome. So let me set this up.

Marfan syndrome is a genetic condition caused by a single glitch in a gene called fibrillin and is characterized by very tall stature, and, unfortunately, by a high risk of an aortic dissection, which is often fatal. So Flo Hyman, the volleyball star, died suddenly because of that condition, and it's not that rare.

And many of us thought, well, we'll never come up with a therapy for that in the next 50 years, because it's too rare for there to be much economic interest, but something pretty interesting happened. Do you want to tell that story?

Dr. SHURIN. One of our investigators at Johns Hopkins, Dr. Hal Dietz, discovered that a drug, losartan, which is used for blood pressure—it's an approved drug—actually cures Marfan syndrome, not only in the test tube, but also in mice.

And so we were able, using our existing Pediatric Heart Network, to rapidly launch a clinical trial. We had the first patient enrolled about 5 months after we had opened the trial and, working very closely with the Marfan Foundation, have been able to complete enrollment.

The results are not yet fully available. The trends are looking very good, and we've been very excited by this. But the ability to

do this with the cooperation of the drug manufacturer and the patient advocacy groups has been really quite spectacular.

Dr. COLLINS. So that's an example.

My own lab works on a disease called Progeria, the most dramatic form of premature aging. These kids age about seven times the normal rate and usually die by age 12 or 13 of heart attack or stroke.

By discovering the genetic cause of that disease, understanding the pathway that's involved, it became clear that a drug class developed for cancer might actually turn out to be beneficial in this premature-aging disease.

They've just completed a 2-year clinical trial on kids with Progeria using this supposed cancer drug, and while the results are not yet published, I'm hearing very encouraging noises. So it's repurposing a very different idea of what that drug would be used for for a new application.

I am sure that if we had a systematic way of trolling the landscape to identify other such opportunities there would be lots more.

INTER-AGENCY COLLABORATIONS

Senator SHELBY. Dr. Collins, dealing with NIH–FDA collaboration, which is, I think, is very important, what do you think would be the best results to come from increased NIH–FDA collaboration? Are there topics in particular that you're working on with the NIH and partnering there to move—I assume moving drugs to market and getting them approved safely is very important.

Dr. COLLINS. Commissioner Margaret Hamburg and I have been meeting for now almost 2 years to talk about ways that our agencies could work more closely together. And she is a strong advocate, and I share that same view with her, that regulatory science—that is, applying science to how reviews are done of drugs and devices—is very much a possible solution to the current logjam of trying to get products through that pipeline.

Senator SHELBY. We would all benefit from that, wouldn't we?

Dr. COLLINS. We would, indeed.

And so she and I have together started a regulatory science research program. We formed a leadership council between the two of us which involves the senior leadership of both of our agencies. We've identified six areas that we think are particularly ripe for progress, such things as how do you do toxicology more efficiently? How do you deal with combination therapies like Dr. Varmus was mentioning may be necessary for cancer when, in fact, that's hard to review. You have to come up with new ways to look at that.

And I think together, working as sister agencies, we can make progress that neither of us could have done alone, and we're totally committed to making that happen.

Senator SHELBY. How do you collaborate with CDC?

Dr. COLLINS. Oh, quite intensively.

Senator SHELBY. I know you do.

Dr. COLLINS. Tom Frieden, the head of CDC, and I were on the phone yesterday, and that happens regularly, about areas of shared interest, and that includes global health as well as domestic issues.

He and I have exchanged people by going back and forth to look at shared projects. We obviously work very closely in the area of infectious disease.

Maybe Dr. Fauci would want to make a comment about your relationship with CDC, because it's so important.

Dr. FAUCI. Yes. We have very strong and long-standing collaborations, particularly in the arena of global health with the emphasis on infectious diseases, even though global health certainly encompasses more than just infectious diseases.

An example of that is we share some of our sites. The CDC has epidemiological sites and posts for surveillance of disease. We are now incorporating many of those sites in our clinical trials of drugs, so many of the trials that take place are really strong collaborations between the CDC and the NIH, and that's worked very well.

CYSTIC FIBROSIS

Senator SHELBY. Dr. Collins, I enjoyed seeing you last night, and you know better than anybody that they've come out with a new drug in the treatment of lupus for many things. That's a breakthrough of many, many years.

What about cystic fibrosis? Where are you in this area? I know you've done a lot of research in that area, too.

Dr. COLLINS. Senator, I appreciate the question. I enjoyed the experience of chatting with you last night at the Lupus Foundation of America event. And they are very excited, and justifiably so, at the approval of Benlysta, this first drug for lupus in a long time.

Cystic fibrosis is an area of intense interest for me, because I was part of the team that found the cause of that in 1989, and that has now, finally, after many years of struggle, led to a very exciting time therapeutically.

So just in the last few months, a drug developed using this same approach to try to identify small molecules, the same kind of thing that Senator Moran was seeing in Kansas, this, in this case, done as a partnership with a company called Vertex, found a molecule which goes by a not terribly friendly name, VX–770, which, in fact, for that category of patients with cystic fibrosis who have a particular mutation in the gene, appears to be highly effective, and taken over the course of just a month improves lung function. It reduces the sweat chloride, which has been the diagnostic hallmark of cystic fibrosis——

Senator SHELBY. This has been out how long now?

Dr. COLLINS. This is still in clinical trials. It hasn't yet been approved by the FDA, but the phase III trial results look extremely promising.

Senator SHELBY. That would herald, if it were approved by FDA—It's in clinical trials now.

Dr. COLLINS. That would be an enormous step forward.

Senator SHELBY. A huge breakthrough, hopefully, for cystic fibrosis.

Dr. COLLINS. Now, the down side is that this particular drug is only likely to be effective in that subset of patients with cystic fibrosis who have a particular mutation in the cystic fibrosis gene. The common mutation would not necessarily respond to this drug. You wouldn't expect it would.

There is another drug in the pipeline a few steps behind, VX–809, which is targeted toward the common mutation. We all have high hopes that that will turn out to be just as effective, but we have to wait and see what the clinical trials show.

Senator SHELBY. But it holds promise for the people with cystic fibrosis and their families.

Dr. COLLINS. I've been in this field for 25 years. I've not seen more excitement and hope about a therapeutic intervention in that whole time until now.

Senator SHELBY. Thank you.

Senator HARKIN. Thank you.

Senator Kirk.

HEALTHCARE SPENDING POLICY OPTIONS

Senator KIRK. Thank you, Mr. Chairman, and I'm sort of overawed to see this group here. I followed in the Congress Congressman John Porter, very much a supporter of NIH and Research!America.

And, to me, it's interesting, in these times of deficits and debt in which the largest bond purchaser in America, Pimco, has now divested itself of all U.S. Treasury securities, because he's worried about the long-term future of us being able to borrow money.

I just met with one of the Chinese top officials in meeting Secretary Clinton, and they also talked about how they were making moves to leave U.S. debt.

And so it's—over the long term, I wonder how we might be able to borrow the kind of monies that are being thought of.

With these kind of limitations, you wonder, then, what direction you take with regard to healthcare policy. And there are obviously two main directions, if the Government is to support it, and that is to subsidize care or to subsidize research.

Now, in subsidizing care, I guess the rough numbers are Medicare is now $370 billion and Medicaid is $300 billion. So that's very, very expensive now and growing quite rapidly, but $670 billion in the subsidizing care path.

In the subsidizing research, NIH comes in at $26 billion, and yet I think offers a much brighter future of a virtuous cycle of better and better patient outcomes, faster and faster innovation and dramatic reversals in disease outcomes, as we've seen in several cancers or, for example, in juvenile diabetes.

And so in a resource-constrained area—and I think either the Congress is going to make budget cuts or the bond market is going to make budget cuts to the Federal budget—you then say do we double down on subsidizing care or do we continue on the funding research side, and because this also has a huge economic benefit to the United States, I very much favor NIH, where I worry about the long-term sustainability of other parts of the budget.

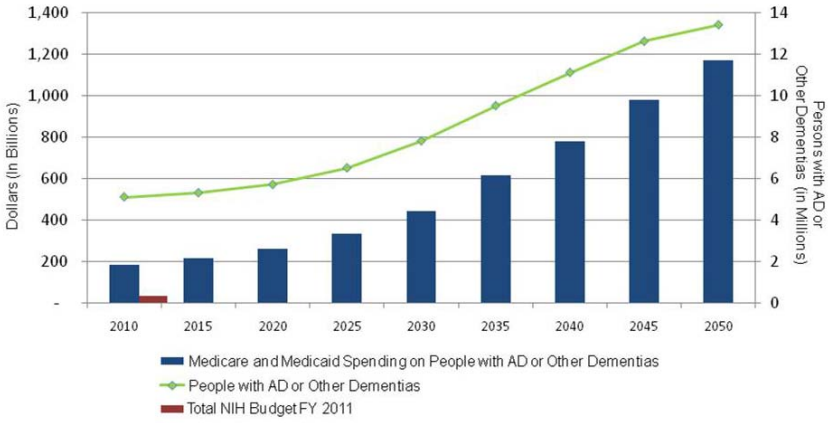
So let me ask you somewhat of a theological question on how we move forward in this environment, which is the President's healthcare bill set up an independent payment advisory board to ration care and basically to deny care in several areas. Its goal, I think, over time will be to replicate the power and authority of the British NIH's NICE rationing board.

Have we thought about NIH's relationship to IPAB and how we would advise the people who would be denying care under Medicare how they would keep up with medical research and technology?

Dr. COLLINS. So these are difficult questions indeed, Senator. NIH's role as the prime supporter of biomedical research is to provide the evidence that is necessary for making wise healthcare decisions, but, obviously, those decisions depend on more than just the scientific evidence. They also depend on how society wants to expend its resources.

But I think we can help in substantial ways with the very frightening cost curve that otherwise faces us. If you'll permit me, I'd just like to show you one example of the kind of looming problem that we have in front of us if nothing is done.

Projected Medicare and Medicaid Spending on Persons with Alzheimer's Disease or Other Dementias



Source: Alzheimer's Study Group, *A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group* (March 2009); Alzheimer's Association, *2009 Alzheimer's Disease Facts and Figures* (March 2009).

This curve shows you for one disease, Alzheimer's disease, what we are currently spending, which in 2010 is about $180 billion, and which by the projections that many people have made, if nothing is done, if research is unsuccessful or not supported, will rise to more than $1 trillion just for that one disease in 2050, and the number of effected individuals at that point will be in the neighborhood of 13 million. One disease.

And, yet, at the present time, our investments in research on Alzheimer's disease fall somewhat less than $1 billion. So, clearly, we feel a great responsibility to move that curve in a different direction. If we could even come up with a therapeutic approach that would slow the onset of disease, delay it by 5 years, you could cut these costs almost in half, and, obviously, something more dramatic would have an even more beneficial effect. That's what we see as our mission——

Senator KIRK. I'm just wondering—My time has run out, but if we—I think IPAB's future depends on the presidential election. Should the President prevail, then IPAB and the healthcare bill is with us. Should the President be defeated, I think that much of the healthcare bill will be wiped out and IPAB with it.

But on the potential that the President is reelected, have you thought about—because what I'm worried about is IPAB will become an incredibly bureaucratic, stultified organization. It will review diseases and protocols, but the danger is that they will be working on heart disease and a breakthrough comes in cancer that revolutionizes research and they will not have the bureaucratic means to switch and then advise for a new payment. And we have such a pace of innovation that a huge state bureaucracy inevitably will slow down and be unable to keep pace with medical innovation.

In fact, I would actually argue it probably will kill a lot of medical innovation as it locks in payment methodologies the way Medicare has.

But have you begun to think about how you might relate to this new bureaucracy?

Dr. COLLINS. Well, again, Senator, I think our best answer to that is to do the rigorous research that actually not only tries new therapeutic approaches, but also does comparisons, when there's more than one alternative, to see what works, and then to do what we do routinely, and which we believe is a strong part of our job, is to make that data immediately available, publish it, make sure it's propagated so that nobody is left in the dark about knowing what the results have been.

And then I guess I'm just enough of an optimist to think if the data is there and if it's compelling, it'll be hard to ignore. But I hear your concern.

Senator KIRK. I would just simply finish up by saying should IPAB not survive—I hope it doesn't, but should it survive I think we might want to think about a more formal data transmission between NIH and IPAB, because, otherwise, IPAB, I think, will rapidly cause Medicare to fall behind technology and innovation.

Thank you, Mr. Chairman.

Senator HARKIN. Senator Moran.

EFFECTS OF RESEACH ON HEALTHCARE COSTS

Senator MORAN. Mr. Chairman, thank you again.

Dr. Collins, perhaps my question is in ways related to the Alzheimer's chart you just showed, which was a request that do you have information to substantiate my suggestion or a belief that money spent on biomedical research results in cost savings in healthcare? Is there that kind of science-based fact that substantiates my feelings?

Dr. COLLINS. So those are complex economic analyses, and even economists will tend to disagree with each other about the right way to do it. Let me just cite a couple of figures, though.

If you look, for instance, at heart disease, what's happened in the last 40 years, Dr. Shurin will tell you we've seen a 60-percent drop in mortality from heart attack during those 40 years. The cost of that, if you average it out per American per year, in terms of the

research that led to those advances, beginning with the Framingham Study, going through with the development of understanding about cholesterol and ultimately the development of statins, was about $3.70 per American per year, the cost of a latte, and not even a grande latte, that would be a tall, I think.

So and if you add up the economic benefits that have resulted from the increase in longevity that have occurred between 1970 and 2000, I am told credible economists believe that adds up to $91 trillion. Michael Milken, in a recent editorial in The Wall Street Journal runs through a lot of those figures and they seem to be cited by reasonable experts.

If we were to diminish the frequency of cancer by just one percent—and that's actually happening each year. Each time the frequency of cancer goes down by 1 percent, economists say that's saving our country $500 billion in terms of economy that is sustained as a result of having those people with us. So the return is enormous.

I could cite you specific examples of new technologies, but the big picture is quite compelling.

RARE AND NEGLECTED DISEASES

Senator MORAN. Well, I'm not surprised by that. It would be very helpful to have that—I don't like the word sound byte, but that phrase that says for every dollar spent, here's what we're able to save in otherwise spending on healthcare.

Let me go back to something more specific and just ask you to elaborate upon the value of academic and nonprofit research institutions' role in developing therapies and treatments for rare and neglected diseases through NCATS, as you propose, and through your therapeutic and rare neglected disease program that you already have.

I mean, is this something that you envision as having a significant role in the future as you develop NCATS are these neglected diseases?

Dr. COLLINS. Indeed. And, in fact, the 27 Institutes and Centers at NIH have been engaged in such efforts for rare and neglected diseases for some time.

We expect that the advent of NCATS serving as a hub of this activity will further encourage that and hopefully contribute innovations that will result in more rapid progress and also a lower failure rate.

The TRND Program, Therapeutics for Rare and Neglected Diseases, which the Congress authorized 2 years ago, is specifically devoted to identifying projects that might otherwise sit there untouched, where there's a real promise in taking a therapeutic and moving it into the preclinical space, which is often called the Valley of Death, because that's where often good projects go to die.

Take example sickle-cell disease. There's a TRND Program right now pursuing an interesting therapeutic for sickle-cell disease originally identified at a university, Virginia Commonwealth University, then licensed out to a biotech company, AESRX.

The biotech company carried it to a certain level and then ran out of money, and venture capital is hard to find these days unless

you have something that's going to result in profits within a couple of years.

So the company has now partnered with the NIH to move this forward. The preclinical studies look very good. This will, as I understand it, be submitted to the FDA for an IND application later this year, and clinical trials may well get under way within 1 year at our NIH Clinical Center.

If this were successful, this would be a radical new approach to sickle-cell disease. The way this molecule works is unlike anything that's been tried for this disease before.

And while this is certainly a neglected and relatively rare disease, it still affects tens of thousands, hundreds of thousands of individuals in this United States and many more across the world. So it's a good example of a way in which NIH may be able to assist in the current scientific environment to move projects forward that otherwise would have languished.

Senator MORAN. Thank you very much. Mr. Chairman, thank you. And let me express my gratitude to all of you for your public service.

Senator HARKIN. Well, I want to thank you all for being here, again, for another enlightening session.

ADDITIONAL COMMITTEE QUESTIONS

I have some other questions I won't propound now, but I'll submit those in writing, and the record will remain open for a week for other Senators to submit further questions or statements.

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

QUESTIONS SUBMITTED BY SENATOR TOM HARKIN

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM) ADVISORY COUNCIL

Question. The statute for the NCCAM stipulates that of the 18 appointed members of the Center's Advisory Council, 9 must be practitioners licensed in one or more of the major systems with which the Center is concerned, and at least three shall represent the interests of individual consumers of complementary and alternative medicine. Is the NCCAM meeting this requirement? Of the four new members announced on June 6, 2011, how many meet one of the two categories described above?

Answer. The composition of the National Advisory Council for Complementary and Alternative Medicine meets the statutory requirements concerning membership. Collectively, its membership includes the expertise required for it to carry out its requirements to provide second level peer review and other advice across the broad and varied spectrum of clinical practice and scientific disciplines which fall under the Center's mandate.

On Friday, June 3, 2011, four new members joined the NCCAM Advisory Council. Brian M. Berman, MD, LAC, is a licensed physician and acupuncturist. James Lloyd Michener, MD, is professor and chairman of the Department of Community and Family Medicine and Director of the Duke Center for Community Research. Dr. Michener also represents the interests of individual consumers of complementary and alternative medicine (CAM). Daniel C. Cherkin, Ph.D., is an epidemiologist and highly experienced clinical researcher who has conducted a number of major studies that have provided evidence for benefit of CAM therapies (including chiropractic manipulation, acupuncture, and massage) for low back pain. David G.I. Kingston, Ph.D., is a widely respected natural products chemist whose research focuses on the chemistry of biologically active natural products and the discovery of new therapies for cancer and malaria from plants.

THE NCCAM RESEARCH SUCCESSES

Question. Under the statute that created the NCCAM, the general purposes of the Center include "identifying, investigating, and validating complementary and alternative treatment, diagnostic and prevention modalities, disciplines and systems." Please identify all instances in the past 10 years in which the NCCAM-supported research has validated complementary and alternative treatment, diagnostic and prevention modalities, disciplines and systems.

Answer. The NCCAM is strongly committed to the highest standards of evidence-based medicine. Validating health interventions is a process that begins with evidence developed in peer-reviewed basic and clinical research. Next, the evidence from multiple studies is collectively assessed through formal systematic review methods. Finally, if these earlier steps indicate sufficient usefulness and safety, professional organizations and health policy makers undertake the development of guidelines and recommendations regarding use and clinical practice. This process, collectively referred to as evidence-based medicine, entails assimilation of the body of scientific evidence; almost never does a single study result in consensus that an intervention is valid.

Eleven years ago, when the NCCAM was created, there was no significant evidence-base on the biological properties, safety, and efficacy of the vast majority of CAM modalities. The Center's first decade was therefore focused on the conduct and support of basic and applied research that addressed this lack of scientific information. The results of that investment now include an emerging evidence base that is dramatically stronger in terms of both quality and quantity. Basic research and clinical trials, large and small, have yielded results—both "positive" and "negative"—regarding the effects, efficacy, safety, and in some cases, promise regarding CAM interventions.

Critically, sufficient evidence regarding some CAM interventions has now been developed to permit informative evidence-based analyses and systematic reviews by independent organizations (e.g., the Cochrane Collaboration) using the rigorous standards of evidence-based medicine. Indeed, such analyses now point increasingly toward clinically helpful conclusions regarding usefulness and safety—or lack thereof—of specific CAM interventions and practices.

Notably, the expanding evidence base now includes a large body of science that points toward specific, very promising opportunities to improve healthcare and health promotion using CAM-inclusive strategies. These opportunities are reflected directly in the NCCAM's recently-released third strategic plan. Important examples include the following:

Mind and Body Practices

—Developing better, comprehensive strategies for management of chronic back pain and defining the roles of acupuncture, spinal manipulation, and massage in those strategies
—Exploring the role of specific promising CAM practices or disciplines (e.g., meditation, yoga, or acupuncture) in developing better strategies for alleviating symptoms (e.g., chronic pain, stress) or in promoting healthier lifestyles
—Exploring the associations between well-characterized pathways of pain processing and acupuncture analgesia or the placebo response
—Exploring the associations of major pathways of cognitive processing and emotion regulation by meditative practices
—Studying the influence of the provider-patient/client interaction, context effects, and the placebo response on outcomes of CAM interventions

Natural Products

—Studying the molecular targets and biological effects of potentially beneficial small molecules that are constituents of natural products or diet (e.g., quercetin, curcumin, or other polyphenols and flavonoids)
—Defining the anti-inflammatory actions of omega-3 fatty acids
—Employing state-of-the-art tools and technologies to study the effects of probiotics on the human microbiome
—Developing evidence regarding the safety profile of certain widely used natural products, including interactions with drugs and other herbals or dietary supplements

The growing evidence base is clearly influencing professional practice guidelines of mainstream professional medical societies, and the practice of integrative medicine. Complementary and alternative therapies are increasingly being accepted and integrated into conventional healthcare systems. For example, recent data show that approximately half the hospices in the United States and 9 out of 10 Department of Veterans Affairs facilities offer some complementary or alternative therapies. The

Consortium of Academic Health Centers in Integrative Medicine, an organization of integrative medicine departments at academic medical centers, has grown from 11 members in 2002 to 43 members in 2011. Medical societies such as the American College of Physicians, the American Academy of Pediatrics and the American Academy of Family Physicians have formulated policies regarding complementary therapies and offer educational material about these forms of treatment. The Departments of Defense and Veterans Affairs are also actively pursuing care and research initiatives that include various CAM interventions in treatment and prevention of problems such as chronic pain and post-traumatic stress disorder afflicting our wounded warriors.

In the appendices, we have included a status report on the process of validation of selected interventions. In Appendix A, we present examples of specific complementary and alternative interventions for which a sufficient number of individual studies exist for systematic reviews to conclude the interventions appear to offer benefit. In Appendix B, we list numerous additional examples of individual NCCAM-supported studies that provide preliminary evidence of benefit in other indications. We feel it important to provide both types of information in addressing the subcommittee's specific questions because the processes of evidence-based validation of health practices and decisionmaking regarding their use are iterative, and draw on a variety of such sources rather than merely single studies.

APPENDIX A: THE STATUS OF THE EVIDENCE BASED REVIEWS AND PROFESSIONAL GUIDELINES FOR SELECT COMPLEMENTARY AND ALTERNATIVE THERAPIES

The examples of systematic reviews and professional assessments cited here all include evidence derived from clinical and mechanistic research supported by the NCCAM. As is true with the evidence in most areas of healthcare, there continues to be controversy about some of these conclusions, and not all systematic reviews come to the same conclusions.

Role of Complementary Therapies in the Management of Chronic Low Back Pain

Management of chronic low back pain is a critical challenge for our healthcare system and a major driver of healthcare costs. Complementary interventions are increasingly being integrated into the care of chronic back pain patients, and there is substantial recognition, supported by findings from the NCCAM research, that complementary therapies, particularly chiropractic and osteopathic spinal manipulation, massage, acupuncture, and meditative exercise forms such as yoga, can make important contributions to improved outcomes for patients. Many systematic reviews have assessed these therapeutic approaches. The Joint Clinical Practice Guideline for low back pain, developed by the American College of Physicians and the American Pain Society, reflects the strength of this evidence base and the emerging professional consensus for the value of the incorporation of complementary approaches. To quote directly from the summary:

"For patients who do not improve with self-care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits-for acute low back pain, spinal manipulation; for chronic or sub-acute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation."—Joint Clinical Practice Guideline, American College of Physicians and American Pain Society. Annals of Internal Medicine, 2007: 147,478.

Nevertheless, there is also a consensus among healthcare providers, both conventional and complementary, that, current approaches are not satisfactory for many patients suffering with back pain. Moving forward, a major area of emphasis for the NCCAM, as described in the NCCAM's 2011 Strategic Plan, will be improving management of chronic back pain. Research is needed to optimize complementary therapies, to understand better who benefits from them, and to develop better systems of integrated care that improve real world application of these helpful therapeutic techniques.

Role of Natural Products in Promotion of Health and Wellness

The NCCAM's natural product research portfolio, carefully assessed during our strategic planning process, has yielded many important lessons that will guide us moving forward. Fundamental scientific understanding of potential beneficial mechanisms of many dietary supplements and natural products has increased markedly, with some notable examples described below. New high-throughput technologies and modern genomic tools have created important new scientific opportunities. We have learned much about the challenges of translation of these findings to clinical efficacy research. The future emphasis, as described in our strategic plan and strongly sup-

ported by both academic investigators and leaders of the botanical and dietary supplement industry, is on the development of strong biological mechanistic hypotheses, sensitive biological signatures of effect, and carefully optimized trial designs.

A few examples of the independent systematic reviews that have provided validation of the potential value of natural products or other dietary supplements are as follows:

—*Fish Oil for the Prevention of Cardiovascular Disease*.—"Dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events."—Clinical Cardiol. 2009: 32, 365.

—*Melatonin for the Prevention and Treatment of Jet Lag*.—"Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe."—Cochrane Database Syst Rev 2002: 1520.

—*Probiotics for Prevention of Necrotizing Enterocolitis in Preterm Infants*.—"Enteral supplementation of probiotics prevents severe necrotizing enterocolitis and all cause mortality in preterm infants."—Cochrane Database Syst Rev 2008: 5496.

—*Prebiotics and Probiotics for Hepatic Encephalopathy*.—"The use of prebiotics, probiotics and synbiotics was associated with significant improvement in minimal hepatic encephalopathy."—Ailment Pharmacol Ther 2011: 33.

—*Probiotics for Acute Infectious Diarrhea*.—"Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea."—Cochrane Database Syst Rev 2010: 3048.

—*Zinc for the Common Cold*.—"Zinc administered within 24 hours of onset of symptoms reduces the duration and severity of the common cold in healthy people."—Cochrane Database Syst Rev 2006: 1364.

Role of Complementary Therapies in the Management of Pain and Other Troublesome Symptoms

Concern is often voiced that the processes of evidence-based medicine could not accommodate the evidence emerging from research on many complementary therapies. In fact, this is a challenge common to evaluation of the evidence of many nonpharmacological interventions, including psychotherapy and surgery. The NCCAM's strategic plan addresses this challenge by calling for increased use of outcomes and effectiveness research methodology, and collaboration with experts who work in other fields facing similar challenges. Nonetheless, several examples are provided below which illustrate that rigorous research on these complicated therapies is possible and can meet the exacting standards of evidence-based review.

—The Cochrane Collaborative has reviewed the evidence that acupuncture may provide benefit for migraine prophylaxis and for treatment of tension-type headache, and concluded that it has value in both situations.—Cochrane Database Syst Rev 2009: 1218, Cochrane Database Syst Rev 2009: 7587.

—The Cochrane Collaborative has reviewed the evidence that acupuncture may be useful for postoperative nausea and vomiting, as well as for nausea and vomiting which has been induced by cancer chemotherapy. Systematic reviews conclude benefit in both cases.—Cochrane Database Syst Rev 2009, 3281, National Cancer Institute, PDQ summary.

—A systematic review published in the British Journal of Anesthesia concluded that perioperative acupuncture is a useful adjunct for acute postoperative pain management.—Br. J Anaesth 2008: 101, 151.

APPENDIX B: THE NCCAM-SUPPORTED STUDIES THAT CONTAIN EVIDENCE OF VALUE OF CAM

Listed below are the NCCAM-supported studies, which contain evidence of the value of CAM. Consistent with the priorities of the NCCAM's strategic plan, these findings are grouped into three major categories: Mind and Body Interventions; Natural Products Interventions; and Population-Based Research. Within each category, the findings are listed in reverse chronological order by the publication date.

Mind and Body Interventions

Chronic Pain

Review of CAM Practices for Back and Neck Pain Shows Modest Benefit.—According to a recent review published by the Agency for Healthcare Research and Quality, the benefits of complementary and alternative therapies for back and neck pain—such as acupuncture, massage, and spinal manipulation—are modest in size but provide more benefit than usual medical care. While these effects are most evident following the end of treatment, the authors of the report noted that very few

studies looked at long-term outcomes. Back and neck pain are important health problems that affect millions of Americans, and back pain is the most common medical condition for which people use complementary and alternative medicine (CAM). They noted that more well-designed studies are needed to draw more definitive conclusions regarding the benefits of CAM therapies for pain. http://nccam.nih.gov/research/results/spotlight/100110.htm.—AHRQ Publication No. 10(11)E007. Rockville, MD: Agency for Healthcare Research and Quality. October 2010.

Tai Chi May Benefit Patients With Fibromyalgia.—Fibromyalgia is a disorder characterized by muscle pain, fatigue, and other symptoms. Researchers, funded in part by the NCCAM, evaluated the physical and psychological benefits of tai chi (which combines meditation, slow movements, deep breathing, and relaxation) in 66 people with fibromyalgia. The participants were assigned to one of two groups: an attention control group that received wellness education and practiced stretching exercises, or a tai chi group that received instruction in tai chi principles and techniques and practiced 10 forms of Yang-style tai chi. Compared with the attention control group, the tai chi group had a significantly greater decrease in total score on the Fibromyalgia Impact Questionnaire at 12 weeks. In addition, the tai chi group demonstrated greater improvement in sleep quality, mood, and quality of life. Improvements were still present at 24 weeks. No adverse events were reported. The researchers concluded that these findings support previous research indicating benefits of tai chi for musculoskeletal pain, depression, and quality of life. The underlying mechanisms are unknown, and the researchers noted that larger, longer term studies are needed to evaluate the potential benefits of tai chi for patients with fibromyalgia. http://nccam.nih.gov/research/results/spotlight/081810.htm.—New England Journal of Medicine. 2010;363(8):743–754 and 783–784.

Analysis of National Survey Reveals Perceived Benefit of CAM for Back Pain.—According to an analysis of the 2002 National Health Interview Survey, approximately 6 percent of U.S. adults used complementary and alternative medicine (CAM) to treat their back pain during the previous year. The data from this analysis also revealed that a majority (60 percent) of survey respondents who used the most common CAM therapies for back pain perceived "a great deal" of benefit. The most common CAM therapies used for back pain—in descending order of perceived benefit—were chiropractic (66 percent), massage (56 percent), yoga/tai chi/qi gong (56 percent), acupuncture (42 percent), herbal therapies (32 percent), and relaxation techniques (28 percent). The specific factors associated with a greater perception of benefit from CAM use were having an improved self-reported health status, and using CAM because "conventional medical treatment would not help." Back pain is the most common medical condition for which people use CAM, and these data give more insight into the use and perceived benefit of CAM therapies for this condition. The researchers suggested that this analysis demonstrates the need for future studies that include both self-reported outcomes and observer-based performance measures of patients using CAM therapies for back pain. http://nccam.nih.gov/research/results/spotlight/060110.htm.—Journal of the American Board of Family Medicine. 2010;23(3):354–362.

Study of Spinal Manipulative Therapy for Neck-related Headaches Reports Findings on Dose and Efficacy.—Previous research suggests that spinal manipulative therapy (SMT) may be helpful for various types of chronic headaches, including cervicogenic headache (CGH), which is associated with neck pain and dysfunction. This randomized controlled trial evaluated the dose (number of treatments) and relative efficacy of SMT in a group of 80 patients with chronic CGH. Compared with massage, participants receiving SMT had greater improvements in CGH-related pain and disability, lasting to 24 weeks. These differences were clinically important and statistically significant. The dose effects of SMT treatments (i.e., differences between 8 and 16 treatments) were small but significant. The mean number of headaches reported by SMT subjects decreased by more than half during the study. The researchers concluded that their findings support SMT as a viable option for treating CGH, but also point out that these findings should be considered preliminary. They suggest additional research to determine whether SMT results for patients with CGH are affected by treatment intensity and duration, use of other therapies, lifestyle changes, and an integrative care approach. http://nccam.nih.gov/research/results/spotlight/041310.htm.—Spine Journal. 2010;10(2):117–128.

Preliminary Trial Finds Possible Benefits of Osteopathic Treatment for Back Pain During the Third Trimester of Pregnancy.—Most pregnant women experience low-back pain, which often is associated with sleep disturbance and can affect daily activities. Researchers investigated the effects of osteopathic manipulative treatment on back pain during the third trimester of pregnancy. They found that back-specific functioning deteriorated significantly less in the osteopathic manipulative treatment group than in the usual care or usual care with sham treatment groups. Although

the results of this preliminary study suggest that osteopathic manipulation may have benefits for back-specific functioning, but not pain, in the third trimester of pregnancy, larger trials are needed before definitive conclusions can be drawn about its efficacy or effectiveness for this purpose. http://nccam.nih.gov/research/results/spotlight/032210.htm.—American Journal of Obstetrics and Gynecology. 2010;202(1):43.e1–43.e8.

Tai Chi May Benefit Older Adults With Knee Osteoarthritis.—Knee osteoarthritis (OA) is an increasing problem among older adults, causing pain, functional limitations, and reduced quality of life. Researchers conducted a long-term, randomized, controlled trial comparing tai chi and conventional exercise in a group of 40 adults (mean age 65) with symptomatic knee OA. The tai chi group learned and practiced Yang-style tai chi, modified slightly to eliminate excess stress on the knees. The control group received wellness education and did stretching exercises. Compared with the control group, tai chi patients had greater improvement in measures of pain, physical function, self-efficacy (belief in one's own abilities), depression, and health-related quality of life. Although most differences between the two groups were statistically significant only at 12 weeks, the differences for self-efficacy and depression remained statistically significant at 24 and 48 weeks. No serious adverse events were reported. The researchers recommend additional studies of biologic mechanisms and approaches of tai chi, so its benefits can be extended to a broader population. http://nccam.nih.gov/research/results/spotlight/011510.htm.—Arthritis & Rheumatism. 2009;61(11):1545–1553.

Iyengar Yoga for Chronic Low-back Pain Shows Promising Results.—Researchers conducted a clinical trial to evaluate the effects of Iyengar yoga (a popular style of yoga that uses props to help support the body during postures) on chronic low-back pain. They found that compared with the control group, the yoga group had significantly greater reductions in functional disability, pain, and depression, at weeks 12 and 24 and at the 6-month followup. There were no significant differences in pain medication usage between the groups; however, there appeared to be a trend toward decreased usage in the yoga group. The researchers concluded from their results that yoga decreases functional disability, pain, and depression in people with chronic low-back pain. However, they noted potential limitations of their study (e.g., heavy reliance on self-report instruments, and differential demands on yoga vs. control groups in terms of attention and group support) and suggest design considerations for future research. http://nccam.nih.gov/research/results/spotlight/112409.htm.—Spine. 2009;34(19):2066–2076.

Managing Low-Back Pain: an Evidence-Based Approach for Primary Care Physicians.—A physician's response to a patient with low-back pain (LBP) should take into account psychological and social factors as well as physical symptoms, according to an article that looked at two case studies in light of evidence-based clinical guidelines developed by Roger Chou et al. for the American Pain Society and the American College of Physicians. The article's authors, recommend a measured approach to the use of imaging (x-rays and MRI/CT scans) and medication. The authors outline considerations in evaluating each patient and choosing action steps. The authors also noted that most people with chronic LBP will not become pain free. Physicians can help patients have a realistic outlook that focuses on improving functioning in addition to reducing pain. http://nccam.nih.gov/research/results/spotlight/040209.htm.—Journal of Family Practice. 2009;58(4):180–186.

Study Finds Benefits of Therapeutic Massage for Chronic Neck Pain.—In a research study, 64 adults with neck pain persisting for at least 12 weeks were randomly assigned to receive either massage or a self-care book. The massage group had up to 10 treatments over a 10-week period, provided by licensed practitioners who used a variety of common Swedish and clinical massage techniques and also made typical self-care suggestions. After 10 weeks, the massage group was more likely than the self-care-book group to have clinically significant improvement in function and symptoms. At 26 weeks, the massage group tended to be more likely to report improvement in function but not in specific symptoms. For both function and symptoms, mean differences between the two groups were strongest at 4 weeks and not evident by 26 weeks. At all followup points, the massage group was more likely than the self-care-book group to report global improvement ratings of "better" or "much better." At 26 weeks, medication use had increased 14 percent for the self-care-book group but had not changed for the massage group. The researchers concluded that therapeutic massage is safe and may have benefits for treating chronic neck pain, at least in the short term. They recommended studies to determine optimal massage treatment, as well as larger, more comprehensive studies to follow patients for at least 1 year. http://nccam.nih.gov/research/results/spotlight/051809.htm.—Clinical Journal of Pain. 2009;25(3):233–238.

Massage Therapy May Ease Pain and Improve Mood in Advanced Cancer Patients.—Researchers investigated the benefits of massage versus simple touch therapy (placing both hands on specific body sites) in patients with advanced cancer. This multisite study—conducted at 15 U.S. hospices in the Population-based Palliative Care Research Network—included 380 participants with advanced cancer who were experiencing moderate-to-severe pain. Results of the study showed that both the massage and simple touch therapy groups experienced statistically significant improvements in pain relief, physical and emotional distress, and quality of life. Immediate improvement in pain and mood was greater with massage than with simple touch; however, sustained effects of these therapies were not observed. The researchers concluded that massage therapy may provide some immediate relief for patients with advanced cancer. They also suggest that simple touch, which can be provided by family members and volunteers, may benefit these patients. http://nccam.nih.gov/research/results/spotlight/110608.htm.—Annals of Internal Medicine. 2008;149(6):369–379.

Study Points to Cost-effectiveness of Naturopathic Care for Low-Back Pain.—Researchers who studied treatment alternatives for low-back pain in a group of 70 warehouse workers found that a naturopathic approach (incorporating a range of treatment options—acupuncture, exercise and dietary advice, relaxation training, and a back-care booklet) was more cost-effective than the employer's usual patient education program. Both the workers and the employer benefited from the naturopathic approach, which was associated with better health-related quality of life, less absenteeism, and lower costs for other treatments and pain medication. The study consisted of workers ages 18 to 65 who had experienced low-back pain for at least 6 weeks. The workers were randomly assigned to receive naturopathic care or patient education visits over a 3-month period. The 30-minute, onsite visits were conducted semiweekly (naturopathic) or biweekly (patient education). The researchers conclude that naturopathic care is more cost-effective than a patient education program in treating low-back pain. They also recommend further studies of the economic impact of naturopathic medicine, particularly to address the limitations of their evaluation. http://nccam.nih.gov/research/results/spotlight/070708.htm.—Alternative Therapies in Health and Medicine. 2008;14(2):32–39.

Acupuncture Relieves Pain and Improves Function in Knee Osteoarthritis.—Acupuncture provides pain relief and improves function for people with osteoarthritis of the knee and serves as an effective addition to standard care, according to a landmark study. The researchers enrolled 570 patients with osteoarthritis of the knee, aged 50 and older, to receive one of three treatments: acupuncture, simulated acupuncture (procedures that mimic acupuncture, sometimes also referred to as "placebo" or "sham"), or participation in a control group. The control group followed the Arthritis Foundation's self-help course for managing their condition over 12 weeks. Participants in the actual and simulated acupuncture groups received 23 treatment sessions over 26 weeks. All study participants continued to receive standard medical care from their primary physicians, including anti-inflammatory medications and opioid pain relievers. At the start of the study, participants' pain and knee function were assessed using standard arthritis research survey instruments and measurement tools. After 26 weeks participants in the acupuncture group had a 40 percent decrease in pain and a nearly 40 percent improvement in function compared to their assessments at the start of the study. Findings from this study begin to shed more light on acupuncture's possible mechanisms and potential benefits, especially in treating painful conditions such as arthritis. http://nccam.nih.gov/research/results/spotlight/052504.htm.—Annals of Internal Medicine. 2004;141(12):901–910.

Stress/Anxiety

Long-term Yoga Practice May Decrease Women's Stress.—Research has shown that women who practice hatha yoga (a common type of yoga involving body postures, breath control, and meditation) regularly recover from stress faster than women who are considered yoga "novices." The research also showed that yoga may boost the mood of both yoga experts and novices. The researchers found that the novices' blood had 41 percent higher levels of the cytokine interleukin-6 (IL–6) than those of the experts. IL–6 is a stress-related compound that is thought to play a role in certain conditions such as cardiovascular disease and type 2 diabetes. In addition, the novices' levels of C-reactive protein, which serves as a general marker for inflammation, were nearly five times that of the yoga experts. Experts had lower heart rates in response to stress events than novices. The researchers suggested that this study offers insight into how yoga and its related practices may affect health. Regularly performing yoga could have health benefits, which may only become evident after years of practice. http://nccam.nih.gov/research/results/spotlight/051510.htm.—Psychosomatic Medicine. Feb 2010;72(2):113–121.

A Form of Acupuncture May Help in Opioid Addiction.—Transcutaneous electric acupoint stimulation (TEAS), a form of acupuncture that uses skin electrodes to apply electrical stimulation at different points on the body, may help people addicted to opioid drugs. This study, supported in part by the NCCAM, also suggests that combining this technique with prescribed drugs that ease withdrawal symptoms may improve other outcomes for people addicted to opioids. Further, participants who received active TEAS were more than two times less likely to have used any drugs than those who received simulated TEAS. In addition, patients in the active TEAS group reported they were less bothered by pain and that they experienced greater improvements in overall health. However, the researchers noted that drug abstinence may have contributed to these improvements. The researchers noted several limitations of this study, including a small number of participants and brief duration of treatment. Despite these limitations, they suggested that additional studies with larger, more diverse populations and longer treatment durations are needed. http://nccam.nih.gov/research/results/spotlight/010410.htm.—Journal of Substance Abuse Treatment. 2010;38(1):12–21.

Transcendental Meditation Helps Young Adults Cope With Stress.—A study found that Transcendental Meditation (TM) helped college students decrease psychological distress and increase coping ability. For a group of students at high risk for developing hypertension, these changes also were associated with decreases in blood pressure. Compared with controls, the TM group had significant improvement in total psychological distress, anxiety, depression, anger/hostility, and coping ability. Changes in psychological distress and coping paralleled changes in blood pressure. According to the researchers, these findings suggest that young adults at risk of developing hypertension may be able to reduce that risk by practicing TM. The researchers recommend that future studies of TM in college students evaluate long-term effects on blood pressure and psychological distress. http://nccam.nih.gov/research/results/spotlight/051410.htm.—American Journal of Hypertension. Dec 2009;22(12):1326–1331.

Mantram Instruction May Help HIV-positive Individuals Handle Stress.—Repeating a mantram (also known as a mantra—the practice of silently focusing on a spiritual word or phrase frequently throughout the day)—may help HIV-positive individuals develop coping skills and reduce anger. Researchers analyzed the effects of a group-based mantram training program, based on data from a study involving 93 HIV-positive individuals. After the 5-week intervention, the mantram group reported a significant increase (25 percent on average) in use of positive reappraisal coping (handling stressful situations by focusing on positive aspects), while the control group reported a significant decrease. At a 22-week followup, anger levels had decreased in the mantram group (13 percent on average) but not in the control group. According to the researchers, these findings suggest that repeating a mantram may help HIV-positive individuals examine stressful situations in a more nonjudgmental and accepting way, reducing the likelihood of an angry response. This is significant because reducing reactive anger may help individuals preserve supportive social relationships as well as maintain adherence to antiretroviral treatments. The researchers suggested additional studies to explore the effects of mantram on attention, cognitive processing, and acceptance-based responding. http://nccam.nih.gov/research/results/spotlight/010609.htm.—International Journal of Behavioral Medicine. 2009;16(1):74–80.

Stress Management Interventions May Enhance Immune Function in People With HIV.—Stress management interventions may help to improve immune function and coping skills in HIV-positive individuals. Researchers assessed three interventions: cognitive-behavioral relaxation training (physical and mental relaxation techniques and active coping skills); focused tai chi training (exercises for balance, breathing, posturing and movement, and relaxation); and spiritual growth (discussions and personal journals to enhance spiritual awareness). None of the intervention groups differed from controls on measures of HIV-related psychological distress, quality of life, and health status, or on physiological stress response (cortisol levels). However, compared with controls, all three treatment groups had significant increases in lymphocyte proliferation (production of white blood cells), indicating enhanced immune function. The researchers noted the potentially important clinical implications of this finding. They recommend additional research to examine specific effects of stress management interventions in people with HIV. http://nccam.nih.gov/research/results/spotlight/060208.htm.—Journal of Consulting and Clinical Psychology. 2008;76(3):431–441.

Acupuncture May Help Symptoms of Post-traumatic Stress Disorder.—A pilot study shows that acupuncture may help people with post-traumatic stress disorder. Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop after exposure to a terrifying event or ordeal in which grave physical harm occurred or

was threatened. Traumatic events that may trigger PTSD include violent personal assaults, natural or human-caused disasters, accidents, or military combat. Researchers conducted a clinical trial examining the effect of acupuncture on the symptoms of PTSD. The researchers analyzed depression, anxiety, and impairment in 73 people with a diagnosis of PTSD. The participants were assigned to receive either acupuncture, group cognitive-behavioral therapy, or were put on the wait list as a control group. The people in the control group were offered treatment or referral for treatment at the end of their participation. The researchers found that acupuncture provided treatment effects similar to group cognitive-behavioral therapy; both interventions were superior to the control group. Additionally, treatment effects of both the acupuncture and the group therapy were maintained for 3 months after the end of treatment. The limitations are that the study consisted of a small group of participants that lacked diversity and that the results do not account for outside factors that may have affected the treatments' results. http://nccam.nih.gov/research/results/spotlight/092107.htm.—The Journal of Nervous and Mental Disease, June 2007.

Self-hypnosis Beneficial for Women Undergoing Breast Biopsy.—Researchers have found that women who used self-hypnosis during a type of core needle breast biopsy experienced anxiety relief and reduced pain when compared with standard care. A large core needle breast biopsy is usually an outpatient procedure that limits the use of anesthetic. Women having this procedure often experience anxiety because of the possibility of a cancer diagnosis in addition to the anxiety that patients typically experience during a medical procedure. In this randomized, controlled trial researchers recruited 236 women who were randomly assigned to receive standard care, structured empathic attention from a research assistant, or guided self-hypnotic relaxation during the biopsy. The study found that both self-hypnosis and empathic attention reduced pain and anxiety during the procedure. Self-hypnosis provided greater anxiety relief than empathic attention. Neither intervention increased procedure time or significantly increased cost. As a result, the researchers suggest that self-hypnosis appears attractive for outpatient pain management. http://nccam.nih.gov/research/results/spotlight/122606.htm.—Pain, December 2006.

Basic and Translational Research

Basic and translational research provides important insights into how CAM interventions can benefit human health. For example, animal studies help to identify biomarkers or signatures of biological effects that can be applied to future studies in humans.

Mindfulness Meditation is Associated With Structural Changes in the Brain.—Practicing mindfulness meditation appears to be associated with measurable changes in the brain regions involved in memory, learning, and emotion, according to a research study that compared brain images of participants who participated in a mindfulness-based stress reduction program with those who did not. Specifically brain images in the meditation group revealed increases in gray matter concentration in the left hippocampus, which is an area of the brain involved in learning, memory, and emotional control, and is suspected of playing a role in producing some of the positive effects of meditation. The researchers concluded that these findings may represent an underlying brain mechanism associated with mindfulness-based improvements in mental health. Additional studies are needed to determine the associations between specific types of brain change and behavioral mechanisms thought to improve a variety of disorders. http://nccam.nih.gov/research/results/spotlight/012311.htm.—Psychiatry Research: Neuroimaging. 2011;191(1):36–43.

Study Examines the Effects of Swedish Massage Therapy on Hormones, Immune Function.—Massage is used for many health purposes, but little is known about how it works on a biological level. This study examined the effects of one session of Swedish massage therapy—a form of massage using long strokes, kneading, deep circular movements, vibration, and tapping—on the body's hormonal response and immune function. Researchers randomly assigned 53 healthy adults to receive one session of either Swedish massage or light touch (in which the therapist used only a light touch with the back of the hand). The researchers found that participants who received Swedish massage had a significant decrease in the hormone arginine-vasopressin (which plays a role in regulating blood pressure and water retention) compared with those who were treated with light touch. Study data, although preliminary data, led the researchers to conclude that a single session of Swedish massage produces measurable biological effects and may have an effect on the immune system. However, more research is needed to determine the specific mechanisms and pathways behind these changes. http://nccam.nih.gov/research/results/spotlight/090110.htm.—The Journal of Alternative and Complementary Medicine. 2010;16(10):1–10.

Electroacupuncture Relieves Cancer Pain in Laboratory Rats.—Electroacupuncture (acupuncture combined with electrical stimulation) has been used to treat cancer pain; however, the existing data on its efficacy and how it works are unclear. Researchers investigated the effects of electroacupuncture on cancer pain in rats and also looked at the underlying biomechanisms. The results showed that compared with the sham control, electroacupuncture significantly reduced cancer-induced bone pain. The researchers also examined the rats spinal cords to see whether electroacupuncture affected chemical processes thought to play a role in pain. They found that compared with the sham control, electroacupuncture inhibited up-regulation of two substances involved in these processes: spinal cord preprodynorphin mRNA and dynorphin. In a separate experiment, they found that injection of an antiserum against dynorphin also inhibited cancer-induced pain in the rats. The researchers concluded that electroacupuncture eases cancer pain in rats, at least in part by inhibiting spinal dynorphin. They note that their findings support the clinical use of electroacupuncture in the treatment of cancer pain. http://nccam.nih.gov/research/results/spotlight/040109.htm.—European Journal of Pain. 2008;12(7):870–878.

Brain-Imaging Study Explores Analgesic Effect of Acupuncture.—Researchers used two imaging technologies—functional magnetic resonance imaging (fMRI) and positron emission tomography (PET)—to investigate how specific areas of the brain might be involved in acupuncture analgesia. The imaging results showed acupuncture-related changes in both of the brain's pain networks: the lateral network, which is associated with sensory aspects of pain perception, and the medial network, which is associated with affective aspects. However, the fMRI and PET results pointed to different areas in these networks, with one exception: both imaging technologies showed changes in the right medial orbitofrontal cortex—an indication that this area of the brain may be important in acupuncture analgesia. The researchers note that their preliminary findings demonstrate that imaging studies using more than one imaging technique have potential for clarifying the neural mechanisms of acupuncture. They point out that similar studies with much larger samples might reveal other areas of the brain where fMRI and PET results converge. http://nccam.nih.gov/research/results/spotlight/121208.htm.—Behavioural Brain Research. 2008;193(1):63–68.

Green Tea May Help Protect Against Rheumatoid Arthritis.—Investigators examined the effects of green tea polyphenols on rheumatoid arthritis (RA) by using an animal (rat) model. The animals consumed green tea in their drinking water (controls drank water only) for 1 to 3 weeks before being injected with heat-killed Mycobacterium tuberculosis H37Ra to induce arthritis. The researchers found that green tea significantly reduced the severity of arthritis. They suggest that green tea affects arthritis by causing changes in various arthritis-related immune responses—it suppresses both cytokine IL–17 (an inflammatory substance) and antibodies to Bhsp65 (a disease-related antigen), and increases cytokine IL–10 (an anti-inflammatory substance). Therefore, they recommend that green tea be further explored as a dietary therapy for use together with conventional treatment for managing RA. http://nccam.nih.gov/research/results/spotlight/120808.htm.—The Journal of Nutrition. 2008:138(11):2111–2116.

Electroacupuncture May Help Alcohol Addiction.—Researchers examined the effects of electroacupuncture on alcohol intake by alcohol-preferring rats. After being trained to drink alcohol voluntarily and then subjected to alcohol deprivation, the rats received either electroacupuncture or sham electroacupuncture, and their alcohol intake was monitored after the intervention. Some rats were also pretreated with naltrexone (a drug that blocks the effects of opiates), so researchers could look for evidence that opiate mechanisms are involved in electroacupuncture's effects. The results showed that electroacupuncture reduced the rats' alcohol intake. The researchers also found that injecting the rats with naltrexone blocked the effect of electroacupuncture on alcohol intake-an indication that this effect may be through the brain's opiate system. On the basis of their findings, the researchers recommend rigorous clinical trials to study the effects of electroacupuncture in alcohol-addicted people. They also recommend further investigation of how electroacupuncture affects the brain. http://nccam.nih.gov/research/results/spotlight/022609.htm.—Neurochemical Research. 2008;33(10):2166–2170.

Lifestyle Changes May Affect Cell-level Processes Related to Disease.—Disease risk, progression, and premature mortality—in many types of cancer and in cardiovascular and infectious diseases—have been linked to telomeres, which are protective DNA-protein complexes that keep cells genetically stable. The cellular enzyme telomerase is an important part of the body's maintenance system for these essential complexes. In a pilot study researchers investigated the effects of lifestyle changes on telomerase levels in 24 men with low-risk prostate cancer. The partici-

pants underwent a comprehensive lifestyle modification that included: improved nutrition, moderate aerobic exercise, stress management, and increased social support. After 3 months, the study participants' telomerase activity had increased 29.8 percent. Decreases in psychological distress and low-density lipoprotein (LDL) cholesterol were associated with the increase in telomerase activity. This is the first longitudinal study to suggest that lifestyle modifications (or any intervention) might significantly increase telomerase activity. The researchers emphasize that additional research is needed and recommend larger randomized controlled trials to confirm the findings. http://nccam.nih.gov/research/results/spotlight/100908.htm. The Lancet Oncology. Published online September 16, 2008.—Journal of Immunology. 2007;179(6):4249–4254.

New Research Gives Insight Into How Acupuncture May Relieve Pain.—In the first study of its kind, researchers evaluated the effects of acupuncture on brain activity following active stimulation. The researchers used functional magnetic resonance imagery (fMRI) to monitor brain activity in 15 healthy adults before and after true acupuncture and sham acupuncture. The procedure lasted 150 seconds, and the rest period was 5.5 minutes. Analysis of the fMRI images showed that following true acupuncture—but not sham—there were increased connections among the parts of the brain involved in the perception and memory of pain. The subjects also reported stronger sensations with true acupuncture than with sham. The researchers concluded that acupuncture changes resting-state brain activity in ways that may account for its analgesic and other therapeutic effects. http://nccam.nih.gov/research/results/spotlight/111408.htm.—Pain. 2008;136(3):407–418.

Prostate Genes Altered by Intensive Diet and Lifestyle Changes.—A pilot study suggests that intensive lifestyle and diet changes may alter gene expression (the way a gene acts) in the prostate—possibly affecting the progression of prostate cancer. This pilot study included a group of 31 men with low-risk prostate cancer. These men declined immediate surgery, hormonal therapy, or radiation, and participated in an intensive 3-month nutritional and lifestyle intervention while researchers monitored their tumor progression. The men stuck to a low-fat, plant-based diet and took dietary supplements including fish oil, selenium, and vitamins C and E. They also participated in stress management activities, did moderate aerobic exercise, and attended group support sessions. The researchers found that there were changes in the men's RNA following the lifestyle and diet modifications. Certain RNA transcripts that play a critical role in tumor formation had "up-regulated" (increased) and others "down-regulated" (decreased). The researchers concluded that intensive nutrition and lifestyle changes may alter gene expression in the prostate. They believe that understanding how these changes affect the prostate may lead to more effective prevention and treatment for prostate cancer, and recommend larger, randomized controlled trials to confirm the results of this pilot study. http://nccam.nih.gov/research/results/spotlight/100808.htm.—Proceedings of the National Academy of Sciences of the United States of America. 2008;105(24):8369–8374.

Meditation May Increase Empathy.—Previous brain studies have shown that when a person witnesses someone else in an emotional state—such as disgust or pain—similar activity is seen in both people's brains. This shows a physiological base for empathy, defined as the ability to understand and share another person's experience. Now, research using advanced brain images (functional magnetic resonance imaging) have shown that compassion meditation—a specific form of Buddhist meditation—may increase the human capacity for empathy. In the study, researchers compared brain activity in meditation experts with that of subjects just learning the technique (16 in each group). They measured brain activity during meditation and at rest, in response to sounds designed to evoke a negative, positive, or neutral emotional response. The researchers found that both the novice and the expert meditators showed an increased empathy reaction when in a meditative state. However, the expert meditators showed a much greater reaction, especially to the negative sound, which may indicate a greater capacity for empathy as a result of their extensive meditation training. An increased capacity for empathy, the authors say, may have clinical and social importance. The next step, they add, is to investigate whether compassion meditation results in more altruistic behavior or other changes in social interaction. http://nccam.nih.gov/research/results/spotlight/060608.htm.—PLoS ONE [online journal], 2008.

Meditation May Make Information Processing in the Brain More Efficient.—"Attentional-blink" occurs when two pieces of information are presented to a person in very close succession, and the brain doesn't perceive the second piece of information because it is still processing the first. Researchers attempted to determine if intensive mental training through meditation could extend the brain's limits on information processing, reducing "attentional-blink." Two groups of people—17 expert meditators and 23 novices—were compared to see if either was better at recognizing two

pieces of information shown in quick succession. The participants were tested at the beginning and end of a 3-month period. For the intervening 3 months, the meditation practitioners participated in a retreat, during which they meditated for 10–12 hours a day. The novices participated in a 1-hour meditation class, and were asked to meditate for 20 minutes a day for the week before each test. The researchers found that intensive training did reduce "attentional-blink." The participants who had gone through the mental training were more likely to perceive both pieces of information instead of just the first because the brain used fewer resources to detect the first piece of information—leaving more resources available to detect the second. The researchers also note that this study supports the idea that brain plasticity, or the ability of the brain to adapt, exists throughout life. http://nccam.nih.gov/research/results/spotlight/082307.htm.—PLOS Biology, June 2007.

Quality of Life and Other Factors

Quality of Life and Safety of Tai Chi and Green Tea Extracts in Postmenopausal Women.—For postmenopausal women with osteopenia (low bone mineral density), practicing tai chi and/or taking green tea polyphenols appears to be safe. Further, practicing tai chi by itself or in combination with green tea polyphenol supplements may improve quality of life; however, taking green tea supplements by themselves has no significant improvement in quality of life. The researchers noted that this is the first placebo-controlled, randomized study to evaluate the safety of long-term use of green tea supplements in postmenopausal women. Based on these findings, the researchers concluded that green tea polyphenols at a dose of 500 mg daily for 24 weeks, alone or in combination with tai chi, appears to be safe in postmenopausal women with low bone mineral density. http://nccam.nih.gov/research/results/spotlight/121410.htm.—BMC Complementary and Alternative Medicine. 2010;10(1):76. [Epub ahead of print]

Tai Chi and Qi Gong Show Some Beneficial Health Effects.—A review of scientific literature suggests that there is strong evidence of beneficial health effects of tai chi and qi gong, including for bone health, cardiopulmonary fitness, balance, and quality of life. Both tai chi and qi gong (also known as qigong) have origins in China and involve physical movement, mental focus, and deep breathing. Researchers analyzed 77 articles reporting the results of 66 randomized controlled trials of tai chi and qi gong. The studies involved a total of 6,410 participants. Of the many outcomes identified by the reviewers, current research suggests that the strongest and most consistent evidence of health benefits for tai chi or qi gong is for bone health, cardiopulmonary fitness, balance and factors associated with preventing falls, quality of life, and self-efficacy (the confidence in and perceived ability to perform a behavior). The reviewers concluded that the evidence is sufficient to suggest that tai chi and qi gong are a viable alternative to conventional forms of exercise. http://nccam.nih.gov/research/results/spotlight/071910.htm.—American Journal of Health Promotion. 2010;24(6):e1–e25.

Hypnosis May Reduce Hot Flashes in Breast Cancer Survivors.—Researchers investigated the effects of hypnosis on hot flashes among women with a history of primary breast cancer, no current evidence of detectable disease, and at least 14 hot flashes per week over a 1-month period. Sixty women were assigned to receive either hypnosis (weekly 50-minute sessions, plus instructions for at-home self-hypnosis) or no treatment. The women who received hypnosis had a 68-percent reduction in self-reported hot flash frequency/severity and experienced an average of 4.39 fewer hot flashes per day. Compared with controls, they also had significant improvements in self-reported anxiety, depression, interference with daily activities, and sleep. The researchers concluded that hypnosis appears to reduce perceived hot flashes in breast cancer survivors and may have additional benefits such as improved mood and sleep. They recommend long-term, randomized, placebo-controlled studies to further explore the benefits of hypnosis for breast cancer survivors. The researchers are currently conducting a randomized clinical trial with 200 participants. http://nccam.nih.gov/research/results/spotlight/102308.htm.—Journal of Clinical Oncology. Published online September 22, 2008.

Tai Chi May Help Heart Failure Patients Sleep Better.—People with heart failure may benefit from practicing tai chi, according to researchers who analyzed sleep in 18 patients with chronic heart failure. All patients were on maximal medical therapy. The patients were assigned into one of two groups: a usual care group (the control) that received medication and diet/exercise counseling, or a tai chi group that received usual care plus 12 weeks of tai chi training. Compared with the usual care group, the tai chi group had significant improvements in sleep stability. The tai chi group also demonstrated significant quality-of-life improvements over the usual care group. The researchers concluded that a 12-week tai chi exercise program may help heart failure patients sleep better. They noted that it remains to be determined if

any single component of tai chi—meditation, relaxation, or physical activity—may be responsible for the observed benefit. They suggested further research to better understand the mechanisms of tai chi's effects on sleep should include more conventional sleep testing to document sleep stages and patterns of sleep disruption. http://nccam.nih.gov/research/results/spotlight/072508.htm.—Sleep Medicine. 2008;9(5):527–536.

Tai Chi Chih Improves Sleep Quality in Older Adults.—Researchers conducted a randomized controlled trial to determine whether tai chi chih could improve sleep quality in healthy, older adults with moderate sleep complaints. In the study, 112 individuals aged 59 to 86 participated in either tai chi chih training or health education classes for 25 weeks. Participants rated their sleep quality based on the Pittsburgh Sleep Quality Index, a self-rate questionnaire that assesses sleep quality, duration, and disturbances. The results of the study showed that the people who participated in tai chi chih sessions experienced slightly greater improvements in self-reported sleep quality. The researchers concluded that tai chi chih can be a useful nonpharmacologic approach to improving sleep quality in older adults with moderate sleep complaints, and may help to prevent the onset of insomnia. http://nccam.nih.gov/research/results/spotlight/031109.htm.—Sleep. 2008;31(7):1001–1008.

Acupuncture Shows Promise in Improving Rates of Pregnancy Following IVF.—A review of seven clinical trials of acupuncture given with embryo transfer in women undergoing in vitro fertilization (IVF) suggests that acupuncture may improve rates of pregnancy. An estimated 10 to 15 percent of couples experience reproductive difficulty and seek specialist fertility treatments, such as IVF. According to researchers who conducted the systematic review, acupuncture has been used in China for centuries to regulate the female reproductive system. With this in mind, the reviewers analyzed results from seven clinical trials of acupuncture in women who underwent IVF to see if rates of pregnancy were improved with acupuncture. The studies encompassed data on over 1,366 women and compared acupuncture, given within 1 day of embryo transfer, with sham acupuncture, or no additional treatment. The reviewers found that acupuncture given as a complement to IVF increased the odds of achieving pregnancy. According to the researchers, the results indicate that 10 women undergoing IVF would need to be treated with acupuncture to bring about one additional pregnancy. The results, considered preliminary, point to a potential complementary treatment that may improve the success of IVF and the need to conduct additional clinical trials to confirm these findings. http://nccam.nih.gov/research/results/spotlight/020808.htm.—British Medical Journal. Published online February 2008.

Tai Chi May Help Maintain Bone Mineral Density in Postmenopausal Women.—Tai chi may be a safe alternative to conventional exercise for maintaining bone mineral density (BMD) in postmenopausal women. Bone mineral density is one of the key indicators of bone strength and low BMD is associated with osteoporosis. Exercise is an important component of osteoporosis prevention and treatment. Researchers conducted a systematic review of research looking at the effect of tai chi, a mind-body practice that originated in China, on BMD. They found that tai chi may be an effective, safe, and practical intervention for maintaining BMD in postmenopausal women. The authors further note that the benefits of tai chi appeared similar to those of conventional exercise. However, tai chi may also improve balance, reduce fall frequency, and increase musculoskeletal strength. They note that the evidence is preliminary because the research they reviewed was of limited scope and quality, but enough evidence of effectiveness exists to warrant further research. http://nccam.nih.gov/research/results/spotlight/081407.htm. Archives of Physical Medicine and Rehabilitation, May 2007.

Tai Chi Boosts Immunity to Shingles Virus in Older Adults.—Tai chi, a traditional Chinese form of exercise, may help older adults avoid getting shingles by increasing immunity to varicella-zoster virus and boosting the immune response to varicella vaccine. The study is the first rigorous clinical trial to suggest that a behavioral intervention, alone or together with a vaccine, can help protect older adults from the varicella virus, which causes both chickenpox and shingles. The randomized, controlled trial included 112 healthy adults ages 59 to 86. Each person took part in a 16-week program of either tai chi or health education with 120 minutes of instruction weekly. After the tai chi and health education programs, with periodic blood tests to determine levels of varicella virus immunity, people in both groups received a single injection of the chickenpox vaccine, VARIVAX. Nine weeks later, the investigators assessed each participant's level of varicella immunity and compared it to immunity at the start of the study. Tai chi alone was found to increase participants' immunity to varicella, and tai chi combined with the vaccine produced a significantly higher level of immunity, about a 40 percent increase, over the vaccine alone. The study also showed that the tai chi group's rate of increase in immu-

nity over the course of the study was double that of the health education group. Finally, the tai chi group reported significant improvements in physical functioning, bodily pain, vitality and mental health. http://nccam.nih.gov/research/results/spotlight/040607.htm.—Journal of the American Geriatrics Society, April 2007.

Study Compares Year-long Effectiveness of Four Weight-loss Plans.—The very low carbohydrate diet known as the Atkins diet may contribute to greater weight loss than higher carbohydrate plans without negative effects such as increased cholesterol. The study consisted of 311 premenopausal women, all of whom were overweight or obese who were randomly assigned to 1 of 4 diets. Each of the diets used were selected for their different levels of carbohydrate consumption: the Atkins diet, the Zone diet, the LEARN diet and the Ornish diet. Participants in each group received books that accompanied their assigned diet plan, and attended hour-long classes with a registered dietitian once a week for the first 8 weeks. The researchers recorded body mass index (BMI); percent body fat; waist-hip ratio; as well as metabolic measures such as, insulin, cholesterol, glucose, triglyceride, and blood pressure levels. The Atkins diet group reported the most weight loss at 12 months with an average loss of just over 10 pounds. They also had more favorable overall metabolic effects. Average weight loss across all four groups ranged from 3.5 to 10.4 pounds. The authors note that "even modest reductions in excess weight have clinically significant effects on risk factors such as triglycerides and blood pressure." http://nccam.nih.gov/research/results/spotlight/030607.htm.—Journal of the American Medical Association. March 2007.

Natural Products Interventions

Treatment or Enhancement of Treatment

New Approach for Peanut Allergy in Children Holds Promise.—Currently, there are no treatments available for people with peanut allergy. A new treatment may be a safe and effective form of immunotherapy for those children. The double-blind, placebo-controlled study investigated the safety, clinical effectiveness, and immunologic changes with sublingual immunotherapy—a treatment that involves administering very small amounts of the allergen extract under a person's tongue. Though these findings are promising, more study is needed to determine whether sublingual immunotherapy can increase long-term tolerance to peanuts in children with peanut allergy. http://nccam.nih.gov/research/results/spotlight/022011.htm.—The Journal of Allergy and Clinical Immunology. 2011.

Magnesium Supplements May Benefit People With Asthma.—Some previous studies have reported associations between low magnesium consumption and the development of asthma. This study provides additional evidence that adults with mild-to-moderate asthma may benefit from taking magnesium supplements. Researchers found that participants who took magnesium experienced significant improvement in lung activity and the ability to move air in and out of their lungs. Those taking magnesium also reported other improvements in asthma control and quality of life compared with people who received placebo. The researchers noted that this study adds to the body of research that shows subjective and objective benefits of magnesium supplements in people with mild-to-moderate asthma. http://nccam.nih.gov/research/results/spotlight/021110.htm.—Journal of Asthma. 2010;47(1):83–92.

Study Shows Chamomile Capsules Ease Anxiety Symptoms.—Researchers conducted a randomized, double-blind, placebo-controlled trial to test the effects of chamomile extract in patients diagnosed with mild to moderate generalized anxiety disorder (GAD). Researchers used the Hamilton Anxiety Rating (HAM–A) and other tests to measure changes in anxiety symptoms over the course of the study; dosage adjustments were based on HAM–A scores. Compared with placebo, chamomile was associated with a greater reduction in mean HAM–A scores—the study's primary outcome measure. The difference was clinically meaningful and statistically significant. Chamomile also compared favorably with placebo on other outcome measures (although the differences were not statistically significant), and was well tolerated by participants. These results suggest that chamomile may have modest benefits for some people with mild to moderate GAD. As this was the first controlled trial of chamomile extract for anxiety, the researchers note that additional studies using larger samples and studying effects for longer periods of time would be helpful. They also point out that other chamomile species, preparations (e.g., extracts standardized to constituents other than apigenin), and formulations (e.g., oil or tea) might produce different results. http://nccam.nih.gov/research/results/spotlight/040310.htm.—Journal of Clinical Psychopharmacology. 2009 Aug;29(4):378–382.

Study Indicates Cranberry Juice Does Not Interfere With Two Antibiotics Women Take for Recurrent Urinary Tract Infections.—Cranberry juice, a popular home remedy for urinary tract infections (UT), is often taken along with low-dose antibiotics as a preventive measure. Because little is known about the potential of cranberry

juice to interact with drugs, researchers studied cranberry's effects on two antibiotics frequently prescribed for UTI: amoxicillin and cefaclor. The data showed that cranberry juice did not significantly affect either antibiotic's oral absorption or renal clearance (i.e., how completely the body processed the drugs in the intestine and kidneys). Absorption took somewhat longer with cranberry juice, but the delay was small, and the total amount of antibiotic absorbed was not affected. Based on these results, the researchers concluded that cranberry juice cocktail, consumed in usual quantities, is unlikely to change the effects of these two antibiotics on UTIs. They noted that the same may or may not be true of other antibiotics, or when people who take antibiotics also drink a large quantity of concentrated cranberry juice. http://nccam.nih.gov/research/results/spotlight/081009.htm.—Antimicrobial Agents and Chemotherapy. 2009 Jul;53(7):2725–32.

Traditional Chinese Herbs May Benefit People With Asthma.—Scientists reviewed research evidence on traditional Chinese medicine (TCM) herbs for asthma, focusing on studies reported since 2005. They determined that preliminary clinical trials of formulas containing Radix glycyrrhizae in combination with various other TCM herbs have had positive results. Laboratory findings on TCM herbal remedies suggest several possible mechanisms of action against asthma, including an anti-inflammatory effect, inhibition of smooth-muscle contraction in the airway, and modulation of immune system responses. http://nccam.nih.gov/research/results/spotlight/061609.htm.—Journal of Allergy and Clinical Immunology. 2009;123(2):297–306.

A Review of St. John's Wort Extracts for Major Depression.—Researchers reviewed the scientific literature on St. John's wort for major depression and analyzed findings from randomized, double-blind studies comparing St. John's wort extracts with placebo and standard antidepressants. The researchers reviewed a total of 29 studies in 5,489 people. The studies came from a variety of countries, tested several different St. John's wort extracts, and mainly included people with minor to moderately severe symptoms of depression. According to this literature review, St. John's wort extracts appeared to be superior to placebo, were as effective as standard antidepressants, and had fewer side effects than antidepressants. However, the findings from studies in German-speaking countries were disproportionately favorable, possibly because some subjects had slightly different types of depression, or because some of the small studies were flawed and overly optimistic in reporting their results. The authors noted the need to investigate the reasons for the differences between study findings from German-speaking countries and those from other countries. http://nccam.nih.gov/research/results/spotlight/120908.htm.—Cochrane Database of Systematic Reviews. 2008 8;(4):CD000448.

Study Suggests Vitamin E May Help People With Asthma.—A form of vitamin E (gamma-tocopherol) commonly found in foods may be a useful additional treatment for asthma, according to preliminary research. Researchers investigated the biological activity of a gamma-tocopherol supplement in asthma patients. The researchers gave a daily dose of a vitamin E preparation rich in gamma-tocopherol to 16 volunteers. Eight healthy volunteers and eight volunteers with allergic asthma received one supplement daily during the first week, followed by a week with no treatment, and then two supplements daily for another week. They found similar results for both doses—the vitamin E supplements prevented inflammation and decreased oxidative stress without any adverse health effects. This research was an initial step in extending previous findings of gamma-tocopherol's anti-inflammatory effects in animals. Further research on vitamin E in patients with asthma is under way. http://nccam.nih.gov/research/results/spotlight/070208.htm.—Free Radical Biology & Medicine. 2008;45(1):40–49.

Omega-3 Fatty Acids May Be Helpful in Psychiatric Care.—Omega-3 fatty acids may hold promise for use in psychiatry, particularly for depression and bipolar disorder. Researchers conducted a meta-analysis of research looking at omega-3 fatty acid supplements as treatments for psychiatric conditions, such as depression, bipolar disorder, schizophrenia, dementia, and attention-deficit hyperactivity disorder. Omega-3 fatty acids are essential nutrients that the body cannot make on its own, so they must come from food sources. The richest source of these fatty acids is fish and seafood, but they can also be found in flaxseeds and some eggs. The authors suggest that omega-3 supplements may be helpful for people with depression or bipolar disorder as a complement to standard care. However, they were unable to determine benefits for other conditions such as schizophrenia and dementia. They also "strongly recommend that patients with psychiatric disorders should not elect supplementation with omega-3 fatty acids in lieu of established psychiatric treatment options." They further recommend studies to look at how the nutrient may work, and large trials to conclusively determine the utility of omega-3 fatty acids in psychiatric care. http://nccam.nih.gov/research/results/spotlight/121506.htm.—Journal of Clinical Psychiatry, December 2006.

Polyunsaturated Fatty Acids for Depression.—Omega-6 and omega-3 fatty acids (also called PUFAs, short for polyunsaturated fatty acids) are among the CAM therapies used with the intent to help symptoms of depression. A team reviewing the evidence found five randomized controlled trials to be of sufficient quality for review, although all were small and of short duration. All but one of these trials found some improvement from using PUFAs for symptoms of depression, particularly from omega-3 fatty acids. The authors concluded that while the evidence to support using PUFA supplements as a treatment for depression is not strong, enough potential exists to merit further research. http://nccam.nih.gov/research/results/spotlight/050106.htm.—Journal of Affective Disorders, May 2006.

Disease Prevention

Ginkgo Does Not Shield Seniors' Hearts, But It May Protect Their Leg Arteries.—While findings from the Ginkgo Evaluation of Memory (GEM) study show that the herbal supplement Ginkgo biloba did not prevent heart attack, stroke, or death in a group of older adults, the herb may reduce the risk of developing peripheral arterial disease (also known as peripheral vascular disease), a painful and potentially life-threatening condition affecting blood circulation in the legs, arms, stomach, and kidneys. Of the 35 cases of peripheral arterial disease observed in the study, 23 patients received placebo and 12 patients received ginkgo, a difference that was statistically significant. The researchers reported that this finding was consistent with European studies that reported improvements in patients with peripheral arterial disease who received ginkgo versus placebo. But, due to the small number of patients in whom this was seen, the researchers suggest larger trials to evaluate the herb before they would recommend it as a treatment for peripheral arterial disease. This study was a planned secondary outcome of the GEM study. http://nccam.nih.gov/research/results/spotlight/052110.htm.—Circulation: Cardiovascular Quality and Outcomes. 2010;3(1):41–47.

Chinese Herbal Medicine May Benefit People With Pre-Diabetes.—In China and other Asian countries, Chinese herbal medicines have long been used to prevent or delay the onset of diabetes, and there is anecdotal evidence regarding efficacy for this purpose. A recent review, funded in part by the NCCAM, examined related clinical trials to see whether scientific evidence supports recommending Chinese herbal medicine as a treatment option for people with pre-diabetes. The review looked at 16 clinical trials involving 1,391 participants with pre-diabetes, 15 different herbal formulations, and various comparisons (i.e., lifestyle modification, drug interventions, placebo). Analysis of data from eight trials that included lifestyle modification as a comparison found that lifestyle modification combined with Chinese herbs was twice as effective as lifestyle modification alone in normalizing blood sugar levels. Participants who received herbal formulations were also less likely to develop full-blown diabetes during the study period. Due to limitations among the studies reviewed, the reviewers concluded that while their findings are promising, further, well-designed trials are needed to clarify the potential role of Chinese herbal medicines in glucose control and diabetes prevention. http://nccam.nih.gov/research/results/spotlight/110309.htm.—Cochrane Database of Systematic Reviews. 2009(4):CD00066690.

Red Yeast Rice May Help Patients With High Cholesterol Who Cannot Take Statin Drugs.—In light of previous findings that red yeast rice can reduce levels of low-density lipoprotein (LDL, or "bad" cholesterol), researchers investigated the effects of this supplement in patients with high cholesterol and a history of statin-associated myalgia (SAM). Compared with placebo, red yeast rice significantly decreased blood levels of LDL and total cholesterol over a 24-week period, without increasing the incidence of myalgia. Red yeast rice did not significantly affect levels of high-density lipoprotein (HDL, or "good" cholesterol), triglycerides, weight loss, or pain severity. This was the first randomized, double-blind, placebo-controlled trial to evaluate red yeast rice in patients who cannot take statin drugs because of muscle pain. The results suggest that red yeast rice may be a cholesterol-lowering alternative for these patients, but additional, larger studies are needed to establish long-term safety and efficacy. The researchers also suggest studies to compare red yeast rice directly with statins and to explore the role of lifestyle change therapy. http://nccam.nih.gov/research/results/spotlight/071709.htm.—Annals of Internal Medicine. 2009;150(12):830–839.

Flaxseed Reduces Some Risk Factors of Cardiovascular Disease.—Flaxseed is rich in alpha linolenic acid (ALA), a plant-based omega-3 fatty acid, as well as fiber and lignans (phytoestrogens), making it a possible functional food for reducing cardiovascular risk factors. A double blind, randomized, controlled clinical trial by researchers explored the effects of flaxseed on various cardiovascular risk factors in adults. Researchers found that flaxseed positively affected lipoprotein A and insulin

sensitivity. They also found a modest but short-lived lowering effect in participants' LDL ("bad") cholesterol levels. However, the researchers also noted that flaxseed significantly lowers HDL ("good") cholesterol levels in men, although not in women. There were no changes noted in markers of inflammation or oxidative stress. The authors suggest that additional investigation of the HDL lowering effect among men may be warranted. http://nccam.nih.gov/research/results/spotlight/062308.htm.—Nutrition, 2008.

Basic and Translational Research

Basic and translational research provides important insights into how CAM interventions can benefit human health. For example, animal studies help to identify biomarkers or signatures of biological effects that can be applied to future studies in humans.

Laboratory Study Suggests Potential Anti-cancer Benefit of White Tea Extract.—White tea extract increased a specific type of cell death in laboratory cultures of two different types of nonsmall cell lung cancer cells, indicating that the tea may have an anti-cancer effect. Although white tea comes from the same plant as green and black teas (Camellia sinensis), white tea goes through much less processing, resulting in a higher concentration of polyphenols. This study, for the first time, showed the roles of the PPAR-gamma and 15-LOX signaling pathways in white tea-induced apoptosis. (A reduction in PPAR-gamma in a tumor is linked to poor prognosis in patients with lung cancer.) The researchers also compared green tea extract with white tea extract and found that white tea extract was significantly more effective in increasing certain RNA transcripts (e.g., PPAR-gamma) that play a critical role in cell death. They noted, however, that the components in white tea extract that may be responsible for this outcome are not yet known. They noted that the findings from this preliminary study provide an important basis for more investigation of the anti-cancer properties of white tea extract and whether it may help prevent the development of lung cancer. http://nccam.nih.gov/research/results/spotlight/092110.htm.—Cancer Prevention Research. 2010;3(9):1132–1140.

Laboratory Study Shows Turmeric May Have Bone-Protective Effects.—Turmeric—an herb commonly used in curry powders, mustards, and cheeses—may protect bones against osteoporosis. This study, which used an animal (rat) model of postmenopausal osteoporosis, builds on previous laboratory research examining turmeric's anti-arthritic properties. Funded in part by the NCCAM, the study tested two turmeric extracts containing different amounts of curcuminoids—(components of the herb) in female rats whose ovaries had been surgically removed (ovariectomy—a procedure that causes changes associated with menopause, including bone loss). Tests showed that while nonenriched turmeric extract did not have bone-protective effects, curcuminoid-enriched turmeric extract prevented up to 50 percent of bone loss, and also preserved bone structure and connectivity. Other physiological changes associated with ovariectomy (weight gain and shrinking of the uterus) were unaffected—an indication that the bone-protective effects did not involve an estrogen-based chemical pathway. The researchers concluded that turmeric may protect bones, but that the effect depends on the amount of curcuminoids present. However, they emphasized that clinical research is needed to evaluate the use of turmeric-derived curcuminoid products to guard against osteoporosis in humans. http://nccam.nih.gov/research/results/spotlight/093010.htm.—Journal of Agricultural and Food Chemistry. 2010;58(17):9498–9504.

Effects of Milk Thistle Extract on the Hepatitis C Virus Lifecycle.—A laboratory study suggests that silymarin—an extract from the milk thistle plant—has multiple effects against the lifecycle of the hepatitis C virus. Hepatitis C is a chronic (long lasting) disease that primarily affects the liver and is often difficult to cure. This study examined the antiviral properties and mechanisms of silymarin on cultured (grown in a lab) human liver cells infected with the virus. By analyzing the interactions between silymarin and the virus, the researchers observed that silymarin prevented the entry and fusion of the hepatitis C virus into the target liver cells. They also found that silymarin inhibited the ability of the virus to produce RNA (a chemical that plays an important role in protein synthesis and other chemical activities of the cell), interfering with a portion of the virus's lifecycle. These findings build on previous research of silymarin's antiviral and anti-inflammatory properties and provide more information about the potential mechanisms involved in silymarin's antiviral actions. Further research, particularly in clinical trials, is needed to determine if silymarin could be a safe and effective supplement for treating hepatitis C in humans. http://nccam.nih.gov/research/results/spotlight/061610.htm.—Hepatology. 2010;51(6):1912–1921.

Fish Oil Enhances Effects of Green Tea on Alzheimer's Disease in Mice.—Fish oil, when combined with epigallocatechin-3-gallate (EGCG—a polyphenol and anti-

oxidant found in green tea), may affect chemical processes in the brain associated with Alzheimer's disease. This study, which used an animal (mouse) model of Alzheimer's disease, builds on previous research linking the disease to peptides (amino acid chains) called beta-amyloids and laboratory studies suggesting that EGCG decreases memory problems and beta-amyloid deposits in mice. Researchers found that the mice fed the combination of fish oil and EGCG had a significant reduction in amyloid deposits that have been linked with Alzheimer's disease. Upon examination of blood and brain tissues of the mice, the researchers found high levels of EGCG in the mice that were fed the combination of fish oil and low-dose EGCG compared with those fed low-dose EGCG alone. A possible explanation, according to the researchers, is that fish oil enhances the bioavailability of EGCG—that is, the degree to which EGCG was absorbed into the body and made available to the brain. This effect, in turn, may contribute to the increased effectiveness of this combination. Further research is necessary, however, to determine if the combination of fish oil and EGCG affects memory or cognition, and whether it might have potential as an option for people at risk of developing Alzheimer's disease. http://nccam.nih.gov/research/results/spotlight/031610.htm.—Neuroscience Letters. 2010;471(3):134–138.

Laboratory Study Suggests Potential Anti-Cancer Benefit of Ginseng.—American ginseng (Panax quinquefolius) extract caused laboratory cultures of colorectal cancer cells to die, indicating that the herb may have an anti-cancer effect. Although results from the study suggest that combining ginseng with antioxidants such as vitamin C may potentially enhance this effect, there is no evidence yet that this laboratory research can be extended to treatments in people. Researchers treated two types of colorectal cancer cells with steamed American ginseng root extract. This caused damage to the cells' mitochondria, the internal structures that are involved with energy production, and led to apoptosis (cell death). It also increased levels of reactive oxygen species (ROS)—a byproduct of the processes in which cells use and break down oxygen (increased levels of ROS can either bring on cell death or activate the survival pathways that protect against it). Whether ROS acts to induce cell death or survival in response to ginseng depends on the specific biochemical pathways that are activated, and how this happens remains unknown. Further studies are needed. The researchers also noted the need for additional investigations to test whether combining ginseng and antioxidants might help prevent the development of colorectal cancers. http://nccam.nih.gov/research/results/spotlight/032510.htm.—Cancer Letters. 2010;289(1):62–70.

Mouse Study Shows Green Tea Polyphenols May Repair DNA Damage Caused by Ultraviolet (UV) Radiation.—Antioxidants found in green tea may help repair DNA damage caused by sun exposure, according to a recent study in mice. Exposure to UV radiation can damage DNA and, in turn, trigger suppression of the immune system—a risk factor for developing skin cancer. The study, funded in part by the NCCAM, examined the effects of polyphenols from the leaves of the green tea plant, which are thought to fight free radicals (highly unstable molecules that can damage cells) and have anticarcinogenic activity. Compared with the control group, the mice treated with green tea polyphenols had reduced immunosuppression from the UV radiation. This same group of mice also showed more rapid repair of DNA damaged by UV radiation. Further, the study showed that green tea polyphenols increased the levels of some nucleotide excision repair genes, which allow for DNA repair. The researchers noted that this study is the first to show that preventing skin cancer with green tea polyphenols in water may be due to the blocking of UV-induced immunosuppression in mice. More studies are needed to determine if green tea has any potential chemopreventive effect on skin cancer in people. http://nccam.nih.gov/research/results/spotlight/022110.htm.—Cancer Prevention Research. 2010;3(2):179–189.

Cinnamon Bark and Ginseng in Herbal Formulas Increase Life Span of Roundworms.—Researchers used a roundworm that has some genetic and biochemical similarities to humans to examine complex herbal preparations thought to combat adverse effects of aging. The worms, called Caenorhabditis elegans, or C. elegans, have a brief life span (about 20 days). The researchers assessed two traditional Chinese multiherbal formulas—Huo Luo Xiao Ling Dan (HLXL), taken for chronic inflammatory pain (e.g., joint pain from arthritis); and Shi Quan Da Bu Tang (SQDB), taken to reduce fatigue and improve general wellness. They found that cinnamon bark, a component of both formulas, increased the worms' life span. Of all the individual components tested, two significantly prolonged life span: Cinnamomum cassia bark (present in both formulas) and Panax ginseng root (present in SQDB only). In light of these findings, the researchers concluded that C. elegans is a valid model for evaluating complex herbal preparations and may provide insight for future studies on longevity-promoting herbs. http://nccam.nih.gov/research/results/spotlight/052510.htm.—PLoS ONE [online journal]. 2010;5(2):9339.

Laboratory Study Explores Anti-HIV Potential of Palmitic Acid.—In a laboratory study, a fatty acid from seaweed reduced the ability of HIV-1 viruses to enter immune system cells. Researchers evaluated palmitic acid (from Sargassum fusiforme, a type of seaweed that grows off the coasts of Japan and China) to see if palmitic acid reduced the ability of HIV-1 viruses to enter CD4+ T-cells (white blood cells that are HIV-1's main target). Palmitic acid blocked both X4-tropic and R5-tropic viruses, the HIV viruses that use a particular receptor (X4 or R5) to enter a cell. In addition, the study's findings showed that palmitic acid protected other cells against HIV-1, reducing X4 infection in primary peripheral blood lymphocytes and R5 infection in primary macrophages (white blood cells). In all cases, the extent of the blocking effect depended on the concentration of palmitic acid, and most cells remained viable (alive) after treatment. The researchers noted that understanding the relationship between palmitic acid and CD4 may lead to development of an effective microbicide product for preventing sexual transmission of HIV. http://nccam.nih.gov/research/results/spotlight/121409.htm.—AIDS Research and Human Retroviruses. 2009;25(12):1231–1241.

Study Uses Rat Liver Cells To Explore Cholesterol-Lowering Mechanisms of Tea.—There is evidence that tea consumption can reduce the risk of cardiovascular disease, apparently by lowering cholesterol levels in the blood. Researchers examined extracts from both green tea and black tea, as well as some components of green tea, for their effects on the synthesis of cholesterol in liver cells from rats. The study's finding that black tea was more effective than green tea in decreasing cholesterol synthesis in rat liver cells was unexpected, as was the finding that EGCG alone was less effective than whole green tea. Additional research may reveal more about the cholesterol-lowering mechanisms of both kinds of tea. http://nccam.nih.gov/research/results/spotlight/040510.htm.—Journal of Nutritional Biochemistry. 2009 Oct;20(10):816–822.

Evidence in Mice May Spur More Research on Fish Oil and Curcumin for Alzheimer's Disease.—A popular dietary supplement and a curry spice may affect Alzheimer's disease—related chemical processes in the brain, according to research findings. This study, which used an animal (mouse) model of Alzheimer's disease, builds on previous research linking the disease to peptides (amino acid chains) called β-amyloids and to defective insulin-processing by the brain. A particular β-amyloid, Aβ–42, is associated with Alzheimer's disease. Funded in part by the NCCAM, the study looked at two dietary supplements: fish oil rich in the omega-3 fatty acid docosahexaenoic acid (DHA); and curcumin, a component of turmeric. Researchers fed the Alzheimer's disease—model mice a regular or fatty diet; some of the mice also received fish oil and/or curcumin. They found that the high-fat diet increased Alzheimer's disease—related chemical processes in the brain, and that fish oil and curcumin, alone or in combination, counteracted this effect. DHA and curcumin also protected cognitive performance for mice on the high-fat diet—i.e., how well the mice remembered a maze. http://nccam.nih.gov/research/results/spotlight/070109.htm.—Journal of Neuroscience. 2009;29(28):9078–9089.

Animal Study Shows Connection Between Vitamin E, Lung Inflammation, and Asthma.—Citing study results in mice, researchers reported for the first time that the form of vitamin E found primarily in food (gamma-tocopherol) increased lung inflammation in induced asthma, while the form of vitamin E found primarily in dietary supplements (alpha-tocopherol) reduced inflammation. The researchers found that compared with placebo, alpha-tocopherol significantly reduced inflammation while gamma-tocopherol significantly increased inflammation. The researchers also found that the mechanism by which both forms of vitamin E work involves the regulation of endothelial cell signals during leukocyte (white blood cell) recruitment—a process that occurs during inflammation. Endothelial cells line the inner walls of blood vessels. The researchers concluded that the opposing activities of the two common forms of vitamin E on inflammation found in this study are consistent with the contradictory outcomes of vitamin E on asthma in previous clinical trials. They also noted that the information gained from this study could have a significant impact on designing and interpreting future clinical studies on vitamin E. http://nccam.nih.gov/research/results/spotlight/041109.htm.—The Journal of Immunology. 2009;182(7):4395–4405.

Researchers Investigate Anti-inflammatory Effects of Pineapple Extract.—Previous research indicates that bromelain—an enzyme extracted from pineapple stems—may help inflammatory conditions such as allergic airway disease. Bromelain's anti-inflammatory effects have been attributed to its ability to alter the activation and expansion of the immune system's CD4+ T cells (a type of lymphocyte). To better understand the processes involved, the NCCAM-funded researchers conducted in vitro experiments with mouse cells, using bromelain derived from a commercially available, quality-tested product. The results show that bromelain reduces CD25 (a

protein involved in inflammation) expression via proteolytic (enzymatic) action, in a dose- and time-dependent manner. The researchers' analysis of the mechanism involved found that bromelain apparently splits CD25 from the CD4+ T cells, and that the T cells remain functional—i.e., they can still divide—after bromelain treatment. The researchers concluded that the novel mechanism of action demonstrated in their experiment explains how bromelain may exert its therapeutic benefits in inflammatory conditions. http://nccam.nih.gov/research/results/spotlight/080309.htm.—International Immunopharmacology. 2009;9(3):340–346.

Grape Seed Extract May Help Neurodegenerative Diseases.—In light of previous studies indicating that grape-derived polyphenols may inhibit protein misfolding, researchers examined the potential role of a particular grape seed polyphenol extract (GSPE) in preventing and treating tau-associated neurodegenerative disorders. The results of their in vitro study showed that GSPE is capable of interfering with the generation of tau protein aggregates and also disassociating preformed aggregates, suggesting that GSPE may affect processes critical to the onset and progression of neurodegeneration and cognitive dysfunctions in tauopathies. The researchers concluded that their laboratory findings, together with indications that this GSPE is likely to be safe and well-tolerated in people, support its development and testing as a therapy for Alzheimer's disease. http://nccam.nih.gov/research/results/spotlight/031209.htm.—Journal of Alzheimer's Disease. 2009;16(2):433–439.

Chinese Herbal Formula Shows Anti-Arthritis Effects in Animal Study.—Researchers analyzed the effects of a modified version of the classic Chinese formula Huo Luo Xiao Ling Dan (HLXL) in an animal (rat) model of adjuvant arthritis, which shares some features with human rheumatoid arthritis. The researchers induced adjuvant arthritis in male rats by injecting them with a complete Freund's adjuvant solution containing heat-killed Mycobacterium tuberculosis. On days 16 to 25, the rats were given a daily oral dose of either a quality controlled, 11-herb HLXL preparation or liquid only. Compared with controls, the HLXL-treated rats had significantly decreased arthritis symptom scores; reduced paw edema; and lower TNF-α and IL-1β levels. No adverse effects were observed. Based on their results, the researchers concluded that this HLXL formula may have benefits for treating arthritis and related inflammatory disorders. http://nccam.nih.gov/research/results/spotlight/071609.htm.—Journal of Ethnopharmacology. 2009;121(3):366–371.

Echium Oil Reduces Triglyceride Levels in Mice.—In light of previous research indicating that oil from the seeds of the Echium plantagineum plant can lower triglycerides in people, researchers used an animal model—mice with mildly elevated triglyceride levels—to investigate how echium oil achieves this effect. The researchers fed the mice diets supplemented with either echium oil, fish oil, or (as a control) palm oil. They found that both echium and fish oils had the following effects: reduced triglycerides in blood plasma and the liver; enriched EPA in plasma and the liver—echium less so than fish oil; and "down-regulated" (decreased the expression of) several genes involved in synthesis of triglycerides in the liver. The researchers concluded that echium oil may provide a botanical alternative to fish oil for reducing triglycerides. http://nccam.nih.gov/research/results/spotlight/022509.htm.—Journal of Nutritional Biochemistry. 2008;19(10):655–663.

Laboratory Study Shows Black Cohosh Promotes Bone Formation in Mouse Cells.—Results of laboratory research are the first to indicate that extracts of the herb black cohosh (Actaea racemosa) may stimulate bone formation. Researchers added an extract of black cohosh to a culture of bone-forming mouse cells. The researchers observed that a high dose (1,000 ng/mL) of the extract suppressed the production of these bone-forming cells, yet a lower dose (500 ng/mL) significantly increased the formation of bone nodules. When the cells were treated with a protein whose molecules attach to estrogen receptors in place of estrogen, this effect on bone nodule formation disappeared. Thus, the researchers suggest that ingredients within black cohosh contain a component that acts through estrogen receptors. The researchers concluded that their results provide a scientific explanation at the molecular level for claims that black cohosh may protect against postmenopausal osteoporosis. They also noted that studying extraction methods and identifying black cohosh's active components may make it possible to develop new ways to prevent and treat this condition. Although results from the study suggest that black cohosh may have potential implications for the prevention or treatment of postmenopausal bone loss, there is no evidence yet that this laboratory research can be extended to treatments in people. http://nccam.nih.gov/research/results/spotlight/090408.htm.—Bone. 2008;43(3):567–573.

Pomegranate Extract May Be Helpful for Rheumatoid Arthritis (RA).—RA is an autoimmune disease characterized by joint pain, stiffness, inflammation, swelling, and sometimes joint destruction. The pomegranate has been used for centuries to treat inflammatory diseases, and people with RA sometimes take dietary supple-

ments containing a pomegranate extract called POMx. However, little is known about the efficacy of POMx in suppressing joint problems associated with RA. Researchers used an animal model of RA—collagen-induced arthritis (CIA) in mice—to evaluate the effects of POMx. They found that POMx significantly reduced the incidence and severity of CIA in the mice. The arthritic joints of the POMx-fed mice had less inflammation, and destruction of bone and cartilage were alleviated. Consumption of POMx, the researchers also concluded, selectively inhibited signal transduction pathways and cytokines critical to development and maintenance of inflammation in RA. Although previous studies of POMx found cartilage-protective effects in human cell cultures, this is the first study to observe positive effects in a live model. The researchers note that the data from this study suggest the potential efficacy of POMx for arthritis prevention, but not for treatment in the presence of active inflammation; future studies will address disease-modifying effects of POMx. They also note that clinical trials are needed before POMx can be recommended as safe and effective for RA-related use in people. http://nccam.nih.gov/research/results/spotlight/120508.htm.—Nutrition. 2008;24(7—8):733–743.

Two Studies Explore the Potential Health Benefits of Probiotics.—In two studies, researchers investigated how probiotics may have a role in treating gastrointestinal illnesses, boosting immunity, and preventing or slowing the development of certain types of cancer. In one study, researchers investigated how Lactobacillus reuteri ATCC PTA 6475 might work to slow the growth of certain cancerous tumors. Their study documented the molecular mechanisms of the probiotic's effects in human myeloid leukemia-derived cells—i.e., how it regulates the proliferation of cancer cells and promotes cancer cell death. The researchers noted that a better understanding of these effects may lead to development of probiotic-based regimens for preventing colorectal cancer and inflammatory bowel disease. In another study, researchers looked at whether Lactobacillus acidophilus might enhance the immune-potentiating effects of an attenuated vaccine (a vaccine prepared from a weakened live virus) against human rotavirus infection—the most common cause of severe dehydrating diarrhea in infants and children worldwide. The investigators' tests on newborn pigs found that animals given both a vaccine and the probiotic had a better immune response than the animals given the vaccine alone. The researchers concluded that probiotics may offer a safe way to increase the effectiveness of rotavirus vaccine in humans. In both studies, the investigators called for additional research into the mechanisms behind the health-related effects of probiotics. http://nccam.nih.gov/research/results/spotlight/110508.htm.—Cellular Microbiology. 2008;10(7):1442–1452.—Vaccine. 2008;26(29—30):3655–3661.

Research Shows Promise of Pineapple Extract for Inflammatory Bowel Disease (IBD).—IBD, including Crohn's Disease (CD) and ulcerative colitis (UC), are characterized by inflammation of the gastrointestinal tract. Researchers have found that bromelain—an enzyme derived from pineapple stems—might be able to reduce inflammation in IBD. Researchers recruited patients with a confirmed diagnosis of CD or UC as well as a normal, non-IBD control group. In total, this pilot study recruited 51 participants: 8 controls, 20 with UC, and 23 with CD. To assess the effect of a bromelain preparation on the production of cytokines, colon biopsies obtained from patients with UC, CD, and normal controls were treated in the lab (in vitro) with bromelain. The researchers report that bromelain reduced production of several proinflammatory cytokines and chemokines that are elevated in IBD and play a role in the progression of IBD. The authors conclude that bromelain treatment could potentially benefit IBD patients if similar changes also occur when colon tissues are exposed to bromelain inside the body. The researchers also suggest that additional research is needed to understand how bromelain influences chemokine and cytokine production. http://nccam.nih.gov/research/results/spotlight/070108.htm.—Clinical Immunology (2008) 126, 345–352.

Grape Seed Extract May Help Prevent and Treat Alzheimer's.—Emerging research shows a correlation between red wine consumption and reduced risk of Alzheimer's disease-type cognitive decline. Researchers found that grape seed-derived polyphenolics—similar to that in red wine—significantly reduced Alzheimer's disease-type cognitive deterioration in mice. Researchers conducted experiments in mice with Alzheimer's disease to see if a highly purified polyphenolic extract from Vitis vinifera (cabernet sauvignon) grape seeds, could affect Alzheimer's disease-type cognitive deterioration. The mice received 5 months of either water containing grape seed extract or water alone as a placebo treatment. The mice were then given behavioral maze tests to determine cognitive function and brain tissue samples were tested to determine evidence of disease. The researchers found that mice treated with grape seed extract had significantly reduced Alzheimer's disease-type cognitive deterioration compared to the control mice. This is due to the prevention of a molecule called amyloid forming in the brain that has been shown to cause Alzheimer's

disease-type cognitive impairment. http://nccam.nih.gov/research/results/spotlight/062408.htm.—The Journal of Neuroscience. 2008. 28(25);6388–6392.

Chinese Herbal Formula May Be Helpful for Peanut Allergies.—A study in mice shows that a Chinese herbal formula may help prevent dangerous reactions to peanuts. Peanut allergies affect as many as 6 percent of young children and are a major cause of anaphylaxis—a severe allergic reaction with respiratory symptoms that can be fatal. Researchers conducted experiments in mice with established peanut allergies to see if a formula of nine Chinese herbs, called FAHF–2, could reduce sensitivity to peanuts. The peanut-sensitive mice received 7 weeks of oral treatment with FAHF–2 or water as a placebo treatment. The mice were then exposed to peanuts at 2 different times to see if they would have anaphylactic reactions. The researchers found that FAHF–2 completely protected the mice from a dangerous reaction on both occasions—showing that protection lasted at least 4 weeks after the treatment finished. The mice treated with the placebo (water) had anaphylactic reactions. The researchers note that the protection of FAHF–2 may result from a shift in the immune balance away from the allergic response. http://nccam.nih.gov/research/results/spotlight/012908.htm.—Clinical and Experimental Allergy, June 2007.

Turmeric and Rheumatoid Arthritis Symptoms.—More than 2 million Americans suffer from rheumatoid arthritis (RA), a condition in which the body's immune system attacks the joints, causing pain, swelling, stiffness, and loss of function. The herb turmeric has been used for centuries in Ayurvedic medicine (a whole medical system that originated in India) as a treatment for inflammatory disorders, including RA. To study the effects of turmeric, researchers created symptoms in rats that mimic those of RA in humans. In a series of experiments, they treated the rats with different preparations and dosages of turmeric extracts. The results, measured in terms of joint swelling, suggested that an extract containing only curcuminoids (a family of chemicals that is the major component of turmeric) may be more effective for preventing RA symptoms than a more complex extract containing curcuminoids plus other turmeric compounds. They also noted that the curcuminoids-only formulas appeared safer and more effective at lower doses. Also, the researchers found that the compounds had greater effectiveness when the rats were treated before instead of after the onset of inflammation. The authors identified a need for well-designed preclinical and clinical studies to look further into turmeric for anti-inflammatory use. http://nccam.nih.gov/research/results/spotlight/030106.htm.—Journal of Natural Products, March 2006.

Other Research

Botanicals May Help Conditions Associated With Aging.—To evaluate the effectiveness of botanicals in relation to conditions such as high blood pressure, cardiovascular disease, cognitive decline, insulin resistance, and excess fats in the blood, researchers conducted a literature review and examined studies from their own laboratory. The researchers looked at effects of dietary soy; soy isoflavones (daidzein and genistein); grape seed extract, which has a high concentration of polyphenols; and puerarin, an isoflavone found in kudzu. The literature review found that soy seemed to lower blood pressure in men and postmenopausal women, help protect against cardiovascular diseases (including heart disease and atherosclerosis), and benefit people with diabetes. The researchers' own animal studies found that soy isoflavones protected against salt-sensitive hypertension in male rats and in female rats whose ovaries had been removed (OVX); grape seed extract reduced blood pressure and improved cognitive functioning in OVX female rats; and puerarin improved glucose control in male mice. The researchers concluded that the botanical compounds reviewed appear to have beneficial effects in animal models of disease (soy also has shown benefits in humans), and that the compounds may be more effective in relation to cardiovascular, metabolic, and cognitive function than for menopausal symptoms. They recommended that the compounds' safety and mechanisms of action should be carefully tested in the context of the disease status of potential users. http://nccam.nih.gov/research/results/spotlight/121008.htm.—Gender Medicine. 2008; 5(suppl A):76S–90S.

Botanical Research Centers Featured in American Journal of Clinical Nutrition.—The February 2008 issue of the American Journal of Clinical Nutrition features eight articles from the NIH Botanical Research Centers Program, which is co-funded by the NIH Office of Dietary Supplements and the NCCAM. The articles highlight different areas related to the Centers' research into botanical use, safety, and efficacy. They include evaluation of botanicals for improving health; technologies and experimental approaches to evaluating botanicals; botanicals and metabolic syndrome; echinacea in infection; botanicals for age-related diseases; ways in which botanical lipids affect inflammatory disorders; botanicals to improve women's health; and ensuring botanical dietary supplement safety. The Botanical Centers are in-

tended to advance research activities in plant identification, as well as preclinical research and early phase clinical studies. Each Center has a broad interdisciplinary research program that focuses on collaborative activities. Each of the Centers was created with a high potential for translating findings into public health benefits. http://nccam.nih.gov/research/results/spotlight/042308.htm.—American Journal of Clinical Nutrition, 2008. Volume 87, Number 2, 463.

Population-based Research

Cancer Survivors Are More Likely Than General Population To Use CAM, According to National Survey Analysis

A recent analysis of the 2007 National Health Interview Survey revealed that cancer survivors are more likely to use complementary and alternative medicine (CAM) compared with the general population. Cancer survivors are also more likely to use CAM based on a recommendation by their healthcare providers and to talk to their healthcare providers about their CAM use. Although cancer survivors communicated more about their CAM use than the general population, the study authors emphasized the overall need for improving communication between patients and providers about CAM use to help ensure coordinated care. http://nccam.nih.gov/research/results/spotlight/032011.htm.—Journal of Cancer Survivorship: Research and Practice. 2011;5(1):8–17.

Analysis of National Survey Shows CAM Use in People With Pain or Neurological Conditions

According to an analysis of the 2007 National Health Interview Survey, approximately 44 percent of American adults with pain or neurological conditions, compared to about 33 percent of people without those conditions, used complementary and alternative medicine (CAM) during the previous year. The most common CAM therapies used by people with these conditions were mind-body therapies (25 percent), such as deep breathing exercises, meditation, and yoga; biologically based therapies (21 percent), such as herbal therapies; manipulative and body-based therapies (19 percent), such as massage and chiropractic care; and alternative medical systems (4 percent). In addition, respondents with pain or neurological conditions indicated that they used CAM because conventional treatment did not work (20 percent vs. 10 percent) and was too expensive (9 percent vs. 4 percent). The researchers noted that this analysis demonstrates the need for more robust studies on the efficacy of CAM therapies for people with these conditions. http://nccam.nih.gov/research/results/spotlight/111010.htm.—Journal of Neurology. 2010;257:1822–1831.

Study Asks Adolescents With Inflammatory Bowel Disease About Use of Complementary and Alternative Medicine (CAM) Mind-body Therapies

This study found that many adolescents with inflammatory bowel disease are currently using or would consider using CAM—specifically mind-body therapies such as relaxation and guided imagery—to help manage their symptoms. This disease is actually a group of disorders (including Crohn's disease and ulcerative colitis) that cause inflammation of the intestines. The physical and emotional problems associated with irritable bowel disease in adolescents often affect quality of life. The researchers noted that their findings provide groundwork for future studies to determine the effect of CAM therapies on health outcomes in adolescents with inflammatory bowel disease. http://nccam.nih.gov/research/results/spotlight/031110.htm.—Inflammatory Bowel Disease. 2010;16(3):501–506.

Certain Categories of Complementary Therapies Appear To Benefit Older Adults

According to a recent analysis of data from the 2002 National Health Interview Survey and the 2003 Medical Expenditure Panel Survey, use of biologically based therapies (e.g., herbs or megavitamins) and manipulative/body-based therapies (e.g., chiropractic or massage) may be associated with better health outcomes among individuals age 55 years and older. The analysis showed a statistical association between ability to function and use of biologically based therapies and manipulative/body-based therapies. The researchers concluded that some categories of complementary therapies may be more beneficial than others for older adults. They cautioned that these findings should not be interpreted as evidence for the efficacy of specific therapies. Although the findings indicate that the use of certain kinds of CAM therapies is associated with better health outcomes for older adults, only clinical trials can determine the efficacy of specific therapies. The researchers also noted that this is the first longitudinal assessment (analysis of data collected from the same people at different points in time) of possible connections between com-

plementary therapy use and health outcomes in a national sample of older adults. They recommended additional population-based research in this area. http://nccam.nih.gov/research/results/spotlight/070810.htm.—Journal of Alternative and Complementary Medicine. 2010;16(7):701–706.

Many Older People Use Both Prescription Drugs and Dietary Supplements

Researchers analyzed the use of prescription drugs and dietary supplements in a sample of 3,070 people aged 75 and older. The data had been gathered during the Gingko for the Evaluation of Memory (GEM) study, a clinical trial that examined the effects of Gingko biloba on the development of dementia. Nearly 75 percent of the GEM study participants took at least one prescription drug and one dietary supplement. Approximately 33 percent used three or more prescription drugs and three or more supplements. Furthermore, 10 percent of the participants combined five or more prescription drugs with five or more dietary supplements. Although supplements were taken along with all types of prescription drugs, individuals using prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), thyroid drugs, and estrogens were more likely to use dietary supplements. Individuals who used prescription drugs for high blood pressure and diabetes were less likely to use dietary supplements. Based on these data, they recommend that patients discuss dietary supplement use with their healthcare providers. In addition, the researchers emphasized the need for further investigations to better define the clinical importance of interactions between drugs and supplements. http://nccam.nih.gov/research/results/spotlight/071509.htm.—Journal of the American Geriatric Society. 2009;57(7):1197–1205.

Translating CAM Research Results Into Clinical Practice: Results From a National Survey of Physicians and CAM Providers

In an initial investigation of the potential for information from CAM research to influence clinical practice, a 2007 national survey asked acupuncturists, naturopaths, internists, and rheumatologists about their awareness of CAM clinical trials, their ability to interpret research results, and their use of research evidence in decisionmaking. The survey focused on awareness of two major NCCAM-funded clinical trials that studied acupuncture or glucosamine/chondroitin for osteoarthritis of the knee. Fifty-nine percent of the 1,561 respondents were aware of at least one of the two clinical trials but only 23 percent were aware of both trials. The acupuncture trial was most familiar to acupuncturists and rheumatologists, the glucosamine/chondroitin trial to internists and rheumatologists. Overall, awareness was greatest among rheumatologists and those practicing in institutional or academic settings. All groups regarded clinical experience as "very important" in their decisionmaking, although CAM providers were more likely to rate it "most important." Physicians were much more likely than CAM providers to consider research results very important or "very useful" in their clinical decisionmaking. The survey team concluded that CAM research has the potential to make a difference in both conventional and alternative medicine clinical practice. They recommend concerted efforts to better train all clinicians in interpretation and use of evidence from research studies, and to improve the dissemination of research results. http://nccam.nih.gov/research/results/spotlight/041309.htm.—Archives of Internal Medicine. 2009;169(7): 670–677.

National Survey Reports on CAM Use by Adults and Children

The 2007 The National Health Interview Survey (NHIS) found that approximately 38 percent of adults and 12 percent of children use some form of CAM. Among both adults and children, the most commonly used CAM therapy is nonvitamin/nonmineral natural products; fish oil/omega-3 is the most popular natural product for adults, while echinacea is the most popular for children. Back pain is by far the most common condition prompting adults to use CAM. Among children, back or neck pain is the most common reason for using CAM, followed closely by head/chest colds. The 2002 NHIS also included a supplement on CAM use by adults. Overall usage among adults in 2002 (36 percent) was about the same as in 2007. Since 2002, usage has increased for some therapies, including deep breathing, meditation, massage, and yoga. Adult use of CAM for head/chest colds showed a marked decrease between 2002 and 2007. The 2007 survey was the first to ask about CAM use by children. http://nccam.nih.gov/research/results/spotlight/123108.htm.—CDC National Health Statistics Report #12. 2008.

New Findings on Sleep Disorders and CAM

Based on a national survey, the NCCAM scientists found that over 1.6 million American adults use some form of CAM to treat insomnia or trouble sleeping. The authors key findings are:

—More than 17 percent of adults reported insomnia or trouble sleeping in the past 12 months. In this group, 4.5 percent used some form of CAM to treat these problems.
—The CAM users were most likely to use biologically based therapies (nearly 65 percent), such as herbal therapies, or mind-body therapies (more than 39 percent), such as relaxation techniques. Most who used these two types of therapies said they were at least somewhat helpful for insomnia or trouble sleeping.

http://nccam.nih.gov/research/results/spotlight/090106.htm.—Archives of Internal Medicine, September 2006.

CAM Use High Among Adolescents

Researchers conducting the first national survey of CAM use among adolescents in the United States analyzed responses from 1,280 adolescents aged 14 to 19. They found that 79 percent had used at least one form of CAM during their lifetime and that females used CAM more than males. Among all participants, almost 30 percent had used one or more dietary supplements, and almost 10 percent had used supplements along with prescription medications in the preceding month. Many of the supplements the teens reported using were related to attempts to change body shape (e.g., creatine and weight-loss products). The authors urged that healthcare providers be aware of CAM and dietary supplement use by their adolescent patients, because of the lack of standardization in supplements, as well as their potential for safety risks and interactions with prescription medications.http://nccam.nih.gov/research/results/spotlight/040106.htm.—Journal of Adolescent Health April 2006.

More Than One-third of U.S. Adults Use Complementary and Alternative Medicine, According to a 2002 Government Survey

According to the 2002 National Health Interview Survey (NHIS), 36 percent of U.S. adults use some form of CAM. The most commonly used form of CAM was natural products (such as herbs and other botanicals). Other popular CAM therapies included deep breathing, meditation, chiropractic care, yoga, massage, and special diets. Echinacea was the most commonly used natural product. CAM was most often used to treat back pain, colds, neck pain, joint pain, and anxiety or depression. The survey also revealed variations in CAM use by population subgroups. For example, CAM use overall was more common among women, people with higher education, people who had been hospitalized in the past year, and former smokers (compared to current smokers or those who had never smoked). The authors noted that the information from this survey is a foundation for future studies of CAM as it relates to health and disease among population subgroups. http://nccam.nih.gov/research/results/spotlight/050810.htm.—CDC Advance Data Report #343. 2004.

THE NCCAM RESEARCH APPROACHES

Question. Individualized therapies that involve multiple approaches often do not lend themselves to traditional double-blind studies but are frequently used in integrative medicine. Please describe work that the NCCAM is doing to support research on these kinds of treatments.

Answer. The NCCAM recognizes that assessing some of the individualized therapies used in integrative medicine in double-blind studies is challenging. Similar challenges confront other disciplines of healthcare research that employ individualized or multifaceted interventions, complex procedures, or system approaches (e.g. cognitive-behavioral therapy, surgery, or behavior change strategies). There is broad interest within the biomedical and behavioral research communities in applying effectiveness and outcomes approaches and pragmatic trial designs to such questions.

Addressing this challenge is a high priority for the NCCAM as evidenced by its inclusion as one of our strategic plan objectives: to "develop research examining the contributions of specific promising CAM approaches to better treatment and health promotion using the real-world methods and tools of the disciplines of observational, outcomes, health services, and effectiveness research." These methods and approaches also offer potential to address the challenges of conducting CAM research that reflects practice in the real world.

Health provider networks, practice-based clinical research networks, and integrative medicine practices provide important venues in which to develop real-world evidence across a broad array of outcome measures regarding the effects and effectiveness of CAM approaches and their integration into strategies for treatment and health promotion. Practice-based research provides an important setting in which to study the complex interplay of intervention, the patient-provider relationship, and other important contextual and environmental factors involved in healthcare and health promotion. Indeed, many CAM and integrative care practices actively seek to employ these factors. Population-based and practice-based research strate-

gies also offer great potential for developing evidence regarding the effectiveness of CAM-related interventions in engaging individuals in health-promoting behaviors and practices.

The NCCAM is pursuing these approaches in the context of CAM and integrative medicine practice through collaboration with experts who confront similar challenges and opportunities. For example, the NCCAM is working with our colleagues at the Departments of Defense and Veterans Affairs to explore ways that CAM mind and body approaches can be used in integrative approaches to treat pain, stress disorders, and other symptoms. Further, the NCCAM has released a funding opportunity announcement to foster development of CAM research methodology titled, "Translational Tools for Clinical Studies of Mind/Body and Manual Therapy CAM Interventions." It will "encourage the development of improved research methodology to study safety, efficacy, and clinical effectiveness of mind-body interventions."

Additionally, the NCCAM has substantially increased its investment in research which advances our understanding of the usefulness of CAM interventions in real world settings. For example, in one promising study being funded by the NCCAM at the Mount Sinai School of Medicine, researchers are studying methods to utilize all available information regarding CAM treatments in patients with HIV. By utilizing randomized controlled trials along with observational studies, expert judgment and other types of data, they seek to develop a clinical prediction model to determine which CAM interventions are beneficial. Another study, this one at Brigham and Women's Hospital, is looking at the effectiveness of an integrative healthcare team at improving outcomes for chronic low back pain by focusing on observational data. These are just two examples of studies funded by the NCCAM that go beyond traditional double-blind studies by using real world data to support CAM research.

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS) AND PREVENTATIVE MEDICINE

Question. One goal of the NCATS is to accelerate the process by which scientific discoveries are turned into treatments and cures—moving discoveries more quickly through the "valley of death" or the time between discovery and available cures. In particular, the NIH has indicated that the NCATS would focus on the drug development pipeline with a hope of understanding and addressing the reasons that so many drugs fail in development. Meanwhile, research has increasingly shown how a healthy lifestyle, exercise or better nutrition can help prevent the onset of disease or the use of expensive medicines or treatments. Will translational research that focuses on prevention or disease control through lifestyle changes be incorporated into the new vision for the NCATS? If so, how? Or will the NCATS focus exclusively on drug development?

Answer. As you point out, the prevention of diseases as well as their successful treatment may often require behavioral and lifestyle interventions or strategies. As such, a clear understanding of, and further research into, the role of behavioral and lifestyle factors in human health will be critical to the NCATS' success in catalyzing the development of new strategies to address human health and disease. The NCATS will support research to generate new methods and approaches aimed at accelerating the development, testing, and implementation of diagnostics, therapeutics, and prevention strategies. The NCATS prevention and behavioral research will be coordinated with the related work of the other NIH Institutes and Centers as well as with the Office of Disease Prevention and the Office of Behavioral and Social Sciences Research and carried out in part through the 60 institutions with Clinical and Translational Science Awards.

BUDGETARY CONSTRAINTS ON UNIVERSAL FLU VACCINE

Question. The NIH-supported scientists are making significant progress toward developing a universal flu vaccine that would confer longer term protection against multiple influenza virus strains and make yearly flu shots a thing of the past. What would be the impact on public health if research on the universal flu vaccine were delayed or scaled back due to budget constraints at the NIH?

Answer. The costly and time-consuming annual process of manufacturing, distributing, and administering millions of doses of seasonal influenza vaccine would become obsolete if researchers could design a vaccine that provides protection against a broad range of influenza strains over multiple influenza seasons. One strategy to overcome the need for a yearly influenza vaccine is to develop a vaccine against the common components of the influenza virus that do not change from year to year or from strain to strain. Recently, researchers supported by the National Institute of Allergy and Infectious Diseases (NIAID) have made significant breakthroughs in

identifying the specific parts of influenza viral proteins that are unchanged among both seasonal and pandemic strains. So-called "universal" influenza vaccines that capitalize on these findings might one day provide protection against the broad range of viruses arising from seasonal antigenic drift (minor changes) and pandemic antigenic shift (major changes) that are the hallmark of influenza viruses.

The NIAID is supporting a number of research projects to develop a vaccine that induces a potent immune response to the common elements of the influenza A virus that undergo very few changes from season to season and from strain to strain. Conserved internal proteins of the virus such as the M2 protein and conserved regions of the influenza envelope protein hemagglutinin (HA) have been identified as promising vaccine targets. For example, the NIAID-supported researchers found that a vaccine based on the M2 protein of H5N1 avian influenza virus elicited strong immune responses in mice. The HA protein of influenza virus, which is the protective antigen of the virus, has both a "head" region and a "stem" region. The NIAID-funded researchers recently generated a novel form of HA that elicited broadly cross-reactive antibodies against the stem region of a number of divergent seasonal and pandemic influenza subtypes and provided protection against disease in mouse challenge studies. In addition, the NIAID intramural researchers in the Vaccine Research Center demonstrated that a "prime-boost" vaccine strategy based on conserved regions of the HA protein could protect animals from infection with multiple strains of influenza that had been prevalent over many years. This "prime-boost" vaccine strategy involves first priming the immune system with a vaccine containing the DNA of an influenza surface protein (HA) and then administering a second vaccine made from a seasonal influenza virus or from a weakened cold virus, to amplify the immune response generated by the first vaccine.

Budget reductions could adversely affect the NIAID's ability to continue support of these activities in a robust and timely manner. Funding cuts could delay the development of new candidate vaccines for universal influenza and improved vaccines for seasonal influenza, as well as delay initiation of clinical trials necessary to test these vaccines. However, if budget reductions do materialize, the NIH would have to reevaluate its research priorities, and thus, the specific research areas to be impacted by such reductions would be determined at that time.

BUDGETARY CONSTRAINTS ON VACCINE RESEARCH

Question. What other types of vaccine research underway at the NIH might also have to be delayed or scaled back due to budget constraints?

Answer. Vaccines provide a safe, cost-effective, and efficient means of preventing illness, disability, and death from infectious diseases. The NIH is recognized as a worldwide leader in basic immunology research that underpins all vaccine development, and conducts or supports preclinical and clinical research on a broad spectrum of new and improved vaccine candidates. Recent progress in global vaccine research—from the RV 144 trial in Thailand that demonstrated that an HIV vaccine regimen provided a modest preventive effect, to the NIH-sponsored research advances that may unlock neutralizing antibody targets for a range of infectious diseases—highlights the need for a robust vaccine research portfolio at the NIH to pursue these and other advances in the field. A reduction in vaccine research funding at the NIH could slow the pace of ongoing efforts to develop new tools to prevent infectious diseases and could erode our ability to capitalize on scientific progress toward the development of vaccines.

HIV vaccine research activities that could be slowed by reduced funding levels include the conduct of additional and important Phase IIb trials that are planned to further assess and improve upon the results of the RV144 HIV vaccine trial, especially in other risk groups and in countries other than Thailand. Reduced funding could also undermine other important HIV vaccine trials. For example, investigators conducting the HIV Vaccine Trials Network (HVTN) 505 trial would likely be unable to expand the study to include 2,200 participants at 21 sites in 18 U.S. cities in order to assess whether the candidate vaccine regimen can prevent HIV infection and/or reduce viral load. Decreased funding could also limit the NIH's ability to support efforts to identify other promising HIV vaccine candidates, and curtail our ability to test those candidates that hold the most promise and advance them into clinical trials. Again, however, specific research areas that may be impacted by budget reductions are subject to priority assessments and cannot be precisely predetermined.

In addition to research to develop an HIV vaccine, the NIH is also supporting vaccine research across a range of other globally important diseases, including dengue, pandemic influenza, malaria, and tuberculosis, as well as diseases that might occur as a result of acts of bioterrorism. A reduction in funding could force the NIH to

scale back efforts across many of its infectious disease research programs. Potential adverse effects include a reduced ability to support preclinical product development, which is intended to assist companies and academic investigators in developing essential products to prevent and treat infectious diseases. Reduced funding levels could limit the development of new and improved preclinical products required to confront and keep pace with emerging and re-emerging infectious diseases, including a planned array of vaccine-related product development services. Funding constraints could also adversely affect clinical research efforts at the NIH, limiting our ability to support clinical trials designed to assess influenza and malaria vaccines, and slowing the progress of trials. Finally, budget constraints could result in significant delays in advancing research projects focused on the development of next-generation vaccines for biodefense purposes.

GUIDANCE FOR USE OF CLASS B CATS

Question. On March 18, the NIH released guidance on its plan to transition from the use of USDA Class B dogs to other legal sources (Notice NOT–OD–11–055). Why is there no mention of cats? The transition plan, as the NIH notes, is in accordance with the National Academy of Sciences report, Scientific and Humane Issues in the Use of Random Source Dogs and Cats in Research. The NIH notice also quotes from Senate report language regarding research on both dogs and cats, but the mention of cats was excised from the quotation. Does the NIH plan to issue a separate guidance dealing with cats?

Answer. The NIH believes that sufficient numbers of cats currently are available through Class A vendors to support the needs of the NIH-supported research. Therefore, no plan for phase out is needed nor a plan for developing sufficient animals from Class A vendors. At present, the NIH has no plans to issue separate guidance dealing with cats.

LUPUS RESEARCH

Question. How are the different NIH Institutes NIAID, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), General Medicine, among others) working together to increase support for research on lupus? How will the new Translational Center work to address diseases like Lupus that cross multiple Institutes?

Answer. Lupus is an autoimmune disease that affects the lives of many Americans. Ninety percent of Americans with lupus are women. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

A wide range of basic, translational, and clinical research on lupus is being supported by many of the Institutes, Centers, and Offices at the NIH. Highlights of collaborative efforts include:

—The Lupus Federal Working Group, established on behalf of the Department of Health and Human Services (HHS) Secretary by the NIH, facilitates collaboration among the NIH components, other Federal agencies, voluntary and professional organizations, and industry groups with an interest in lupus. The group is coordinated by the NIAMS and includes participation from nine other NIH Institutes and Centers.

—The NIAID chairs the NIH Autoimmune Diseases Coordinating Committee, established by the Congress in fiscal year 1998 to increase collaboration and facilitate coordination of autoimmune diseases research among 21 NIH Institutes and Centers (ICs), other Federal agencies, and private health and patient advocacy groups.

—In September 2010, the NIAMS, the National Cancer Institute (NCI), the NIAID, and the NIH Office of Research on Women's Health (ORWH) hosted a 2-day scientific meeting in Bethesda, Maryland, "Systemic Lupus Erythematosus: From Mouse Models to Human Disease and Treatment." Clinicians and basic scientists from a variety of disciplines came together to discuss the clinical and molecular similarities and differences seen in human disease and animal models. Participants also discussed advances in lupus genetics, challenges and advances in the treatment of lupus, and emerging areas warranting further study.

—The Autoimmunity Centers of Excellence (ACEs), sponsored by the NIAID, the NIDDK, the NIAMS, the National Institute of Neurological Disorders and Stroke (NINDS), and the ORWH, conduct collaborative research on autoimmune

diseases, including lupus. This research includes clinical trials of immunomodulatory therapies and associated studies to understand the mechanism of disease and therapeutic effects.

—The Human Leukocyte Antigen (HLA) Region Genomics in Immune-Mediated Diseases Consortium, a cooperative research group sponsored by the NIAID and the NINDS, focuses on defining the association between variations in the HLA genetic region and immune-mediated diseases, including lupus.

—The Cooperative Study Group for Autoimmune Disease Prevention, sponsored by the NIAID, the NIDDK, and the Juvenile Diabetes Research Foundation International, focuses on research for the prevention of human autoimmune diseases, including lupus. Projects include the creation of improved models of disease pathogenesis and therapy to better understand immune mechanisms that will provide opportunities for prevention strategies.

—The NIDDK and the NIAMS organized an April 2010 meeting, "Novel Therapies to Enhance ESRD (End Stage Renal Disease) Patient Survival," which included a session on "Lessons for Nephrologists from Lupus." The NIDDK is planning a meeting in mid-2012 that will focus on glomerular disease, including that arising from lupus.

—The NIDDK-supported Chronic Kidney Disease Biomarkers Consortium—which seeks to discover and validate biomarkers for chronic kidney disease—is assessing inflammatory mediators as biomarkers for progression of kidney disease in patients with lupus who have had kidney biopsies. The Consortium will cross-validate its findings using a variety of patient cohorts, including those funded by the NIDDK (such as the Chronic Renal Insufficiency Cohort) and other ICs (such as the Atherosclerosis Risk in Communities Study, funded by the NHLBI).

The proposed NIH NCATS has been designed to catalyze the development of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of conditions, including diseases such as lupus. The NCATS will encourage collaborations across all sectors, provide resources to enable therapeutics development, and support and enhance training in the relevant translational science disciplines.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) RESEARCH

Question. COPD is the third leading cause of death in the United States, killing approximately 141,075 Americans annually. Despite the growing burden of COPD, the United States does not currently have a comprehensive public health action plan on the disease. What activities are the NIH currently conducting on COPD and what is missing from the Federal response? Would a Federal action plan on COPD provide insights on how we could better address this leading killer?

Answer. The NHLBI—the NIH component with primary responsibility for lung diseases—supports a wide range of research and education activities on COPD. Its programs include basic science and animal studies of underlying disease mechanisms; clinical studies of COPD risk factors, genetics, molecular and cellular defects, disease progression, and co-morbidities; translational studies of pathways and drugs that may lead to better treatments; clinical trials; comparative effectiveness research; and public and professional educational programs to increase awareness of COPD and knowledge about its symptoms, diagnosis, and treatment. Several other NIH components, including the NCI, the National Institute on Aging (NIA), the National Institute on Drug Abuse (NIDA), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of General Medical Sciences (NIGMS), and the National Institute of Nursing Research (NINR), also support research relevant to COPD. For example, the NCI and the NHLBI are collaborating on an investigation of lung cancer and COPD. The NHLBI also cooperates with a number of other Federal agencies on this disease. The NHLBI Long Term Oxygen Treatment Trial is carried out in collaboration with CMS. The FDA collaborates with the NHLBI in a program called SPIROMICS, which is performing extensive molecular and clinical phenotyping of subjects with COPD to indentify biomarkers and characterize the heterogeneity in the patient population. VA Medical Centers participate in a number of the NHLBI clinical trials in COPD. The CDC is a partner in the NHLBI's COPD Learn More Breathe Better national public health education campaign. The NHLBI—CDC collaboration has led to the introduction of a module on COPD in the Behavioral Risk Factor Surveillance System Survey and to a recently released public health strategic framework for COPD prevention. Investigators supported jointly by the NHLBI and the AHRQ are setting up a large registry for comparative effectiveness research. Finally, the reports of the Surgeon General

on the health effects of smoking are a constant guide for the NHLBI programmatic directions for COPD.

These examples illustrate the extent and diversity of existing Government programs related to COPD, the cooperative and complementary interactions among Federal agencies in this area, and the central role that the NHLBI plays in the Government's efforts to control this disease. The NHLBI will continue to provide strong leadership for research and education activities to address this growing public health epidemic in collaboration with other components of the Federal Government. In particular, the NHLBI plans to host a forum of representatives from Federal Government agencies in fiscal year 2012 to share information regarding current activities related to COPD and to discuss opportunities for increasing cooperation among stakeholders and enhancing effectiveness of the Federal response to this debilitating and deadly disease. Whether a Federal action plan should be developed will almost certainly be a topic of discussion at the forum.

CLINICAL TRIALS COOPERATIVE GROUP PROGRAM REORGANIZATION IMPACT ON THE GYNECOLOGICAL COOPERATIVE GROUP

Question. The Institute of Medicine (IOM) of the National Academies was asked by the National Cancer Institute (NCI) to review the Institute's Clinical Trials Cooperative Group Program. One of the recommendations from that report is a reorganization of the Cooperative Group Structure that would entail restructuring and consolidating some of the cooperative groups. We understand that the reorganization may merge the Gynecological Cooperative Group (GOG) with the NSABP (National Surgical Adjuvant Breast and Bowel Project) and the RTOG (Radiation Therapy Oncology Group). Gynecological cancers are generally diagnosed by gynecologists and the GOG is the only cooperative group that studies gynecological cancers. Is our understanding of the reorganization plan for the GOG correct and, if so, what is the rationale for the planned merger of the GOG with these other groups? What is the scientific basis for it? If not, what is the current plan for the GOG? In general, what has been the process for making these reorganization decisions, what are the primary considerations and what is the timeframe and next steps for finalizing the reorganization decisions?

Answer. For more than 50 years, the NCI has supported a standing infrastructure—the NCI Cooperative Group Program—to conduct large scale cancer clinical trials across the Nation, with successful completion of many important trials that have led to new treatments for cancer patients. Over time, however, oncology has evolved into a more molecularly based discipline including genetic sub-classification of tumors and individualized treatments. Accordingly, the NCI must ensure that the Cooperative Groups are optimally situated and well-prepared to continue to design, enroll and complete state-of-the-art trials for cancer patients.

In 2009, the NCI commissioned the Institute of Medicine to review the Cooperative Group Program in order to gather independent and expert perspectives on the state of cancer clinical trials and to obtain advice about improvements in the NCI Cooperative Group Program. The IOM report "A National Cancer Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program" was issued in April 2010. The report called for a series of changes to the clinical trials program, including restructuring and consolidation of the adult Cooperative Groups.

Transforming the NCI's Cooperative Group System into a highly integrated National Clinical Trials Network is one of the Institute's major initiatives. Enhancing the scientific basis for the clinical trials that the NCI supports is essential if marked improvements in cancer diagnosis, prevention, and therapy are to continue unabated. The increasing need for molecular screening of large patient populations to define categories appropriate for intervention provides an important rationale for consolidating the NCI-supported clinical research groups into a coordinated network. Furthermore, the NCI's commitment to strategic consolidation includes the requirement for a shared, and standardized, clinical trials data management IT infrastructure, for a facile process by which the phase III clinical trials portfolio is prioritized, and for the conduct of clinical investigations that are multimodal in nature, and involve understudied and underserved patient populations. The NCI's restructured clinical trials network, as envisioned, will be organized to move such studies forward both efficiently and with the necessary resources to conduct correlative scientific investigations capable of increasing the potential of these trials to change current medical practice.

In addition to the ability to screen large patient populations, a coordinated network of a smaller number of consolidated Cooperative Groups will be better able to prioritize specific trials across all disease areas and to efficiently develop and complete multicenter trials. Consolidation will also enable optimal use of crucial bio-

specimens from the NCI-supported clinical trials. Finally, consolidation will address current disincentives to study less common diseases or to enroll patients to another Cooperative Group's trials.

The NCI began a discussion with the Cooperative Group Chairs in November 2010 about changes to the Group structure and has participated in multiple discussions with the public. Throughout the process, the NCI has been—and remains—committed to having an open dialogue about changes to the Cooperative Group Program. The NCI has not dictated mergers among groups and instead has encouraged groups to voluntarily consolidate on their own. The Gynecological Oncology Group (GOG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), and the Radiation Therapy Oncology Group (RTOG) have entered negotiations about consolidation, and as background for those discussions, the NCI program leadership met with the GOG Chair in May 2011 to discuss GOG concerns and to provide assurances that funding for gynecological cancers will be protected. The NCI expects that consolidation will greatly strengthen the overall program and will provide each of the consolidated Cooperative Groups with unique capabilities and a greatly expanded network of clinical sites to recruit patients for trials across the entire program.

Since December 2010, the NCI has been gathering input from stakeholders and the cancer community about the plans to restructure the program. The comment period will close in July 2011, at which point the NCI will develop a concept proposal about the new structure and proceed with the NCI leadership review and presentation to the Board of Scientific Advisors in November 2011. The Funding Opportunity Announcement for the new Clinical Trials Program will be developed over the next several months, and released in July 2012. Applications will be accepted in November 2012 and reviewed over the next few months, with the consolidated Cooperative Groups being funded in fiscal year 2014.

CREATION OF SUAA

Question. Based on recommendations from the Scientific Management Review Board, the NIH has been considering the formation of a single institute that would be devoted to research related to substance use, abuse and addiction. The focus at the NIH seems to have turned away from this reorganization as attention has shifted to the creation of the NCATS. Is the NIH still considering the formation of this institute and, if so, what is the latest thinking on the creation of such an institute? What is the process and timeframe for making a decision and developing a plan?

Answer. The NIH is actively considering the formation of a single Institute that will focus on substance use, abuse, and addiction-related research. After receiving the SMRB recommendations, Dr. Collins formed a Task Force of scientific experts to begin a comprehensive review of the NIH substance use, abuse, and addiction research portfolio. The Task Force has met with subject matter experts from across the NIH to gain a better understanding of the breadth and diversity of NIH's substance use, abuse, and addiction portfolio. This review has made it clear that this portfolio is very complex and taken together with the administrative steps that would be required to implement a reorganization of this magnitude, we determined that additional time would be advantageous. Additionally, during the last few months, many stakeholders have requested additional input into the development of the scientific plan for the new Institute.

The NIH will continue to analyze our substance use, abuse, and addiction portfolio to provide a framework for a new proposed Institute. We will also develop a new scientific strategic plan to provide a framework for substance, use, abuse, and addiction-related research at NIH. This scientific strategic plan will be directed by the relevant Institute or Center Directors and will include extensive consultation with stakeholders, including scientists, patients, and the community, in addition to soliciting information from the Advisory Councils of the potentially affected Institutes and Centers. It is our intent to release the portfolio integration plan and the scientific strategic plan in the fall of 2012 for public comment, obtaining the Secretary's formal approval in December 2012 with the ultimate goal of notifying Congress through inclusion in the proposed reorganization in the fiscal year 2014 President's budget and standing up the new Institute at the beginning of fiscal year 2014 (October 1, 2013).

USE OF CHIMPANZEES IN BIOMEDICAL RESEARCH

Question. In response to a request from the NIH, the Institute of Medicine (IOM) is conducting a study on the use of chimpanzees in biomedical and behavioral research. The study will assess the current and anticipated uses of chimpanzees in the NIH research and determine whether chimpanzees are and will be necessary for

research needed to advance public health. The IOM is expected to release the report by the end of this year, in December 2011. Some interest groups have suggested that a moratorium be put in place on new funding for invasive research using chimpanzees pending the release of the IOM report. What would be the impacts of this type of temporary moratorium on the NIH research?

Answer. NIH appreciates the Senator's continued interest in the use of chimpanzees in research. As you know, chimpanzees have been used in important research such as key studies on hepatitis, malaria, and vaccine research. The Senator wisely requested that NIH initiate an in-depth analysis to be performed by the Institute of Medicine (IOM) to assess the scientific need for the continued use of chimpanzees in biomedical research. The NIH has followed this advice and anticipates a thoughtful analysis and rigorous review that will be a valuable input as NIH charts the future course for the use of chimpanzees in research.

In the interim, while the IOM study is ongoing, we believe it would be unwise to make any abrupt changes in our primate research programs.μ Therefore, we think it best to await the IOM report before making decisions that could have potentially far reaching implications.

QUESTIONS SUBMITTED BY SENATOR DANIEL K. INOUYE

THE NATIONAL INSTITUTES OF HEALTH (NIH) RESEARCH SUPPORT TO HAWAII ACADEMIC INSTITUTIONS

Question. Over the years the subcommittee has urged the NIH to pay particular attention to developing a cadre of scientific investigators from rural America and in the case of Hawaii, from the neighbor islands. This month the College of Pharmacy at the University of Hawaii at Hilo will graduate its first class and I appreciate the ongoing efforts by the leadership of several of your Institutes to ensure that basic research infrastructure will be made available for their faculty and students. In order to attract the next generation of scientists, it is absolutely necessary that they be exposed to caring mentors and the joy of scientific inquiry in their early academic years. Those of us who represent rural America appreciate how difficult it can be to provide this critical nurturing experience, especially when bright high school students and undergraduate students have to face significant transportation barriers, such as exist in an island State. At this time, I would appreciate receiving a report detailing the extent to which your Institutes have been able to provide scientific resources to Hawaii, and particularly to the educational campuses on the various islands.

Answer. The NIH has provided considerable support to Hawaii in an effort to ensure that Native Hawaiian and other Pacific Islanders have access to the clinical benefits of the NIH research. While research and training investments represent the majority of the NIH support to institutions in Hawaii, technical assistance to Hawaiian institutions has also been important. Periodically over the past decade, the NIH through the Office of Policy for Extramural Research Administration (OPERA) has provided workshops in Hawaii on the topics of the NIH policies, grant writing skills, and human subjects research issues including adverse event reporting, vulnerabilities of pediatric populations, and cultural issues involving Native Hawaiians participating in research studies. Also, the Office of Laboratory Animal Welfare (OLAW) presented several comprehensive overviews of the laws, regulations, and policies that govern the humane care and use of laboratory animals.

The breadth of the research enterprise in Hawaii is quite impressive. In fiscal year 2010, more than 17 of the 27 NIH Institutes and Centers have provided support for academic institutions to conduct research activities ranging from basic biomedical science to behavioral interventions. For example, Chaminade University has a National Institute on Minority Health and Health Disparities (NIMHD) Building Research Infrastructure and Capacity grant which supports renovations, research training, student academic enrichment programs, and junior faculty career development activities. The University of Hawaii Hilo has received funding from the National Institute on Drug Abuse (NIDA) for the mentoring of clinical investigators and to conduct patient-oriented mental health services research, including post-traumatic stress disorder. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is supporting a project to develop research capabilities in the area of substance use and indigenous youth populations (e.g., Native Hawaiian) at Hawaii Pacific University.

The University of Hawaii Manoa plays a pivotal role since it has the most robust research enterprise of all the Hawaiian institutions of higher education. They have received over 70 NIH awards over the past year. The NIMHD Center of Excellence,

Partnerships for Cardiometabolic Disparities in Native and Pacific Peoples, has a focus on cardiometabolic health and eliminating health disparities among Native Hawaiians and other Pacific Islanders including Filipinos, Samoans, and Tongans. The Cancer Research Center of Hawaii is an NCI-designated Clinical Cancer Center and is the only such institution in the State of Hawaii. Moreover, the University of Hawaii Manoa Research Centers in Minority Institutions (RCMI) Multidisciplinary and Translational Research Infrastructure Expansion in Hawaii serves as the integrated "home" for clinical and translational science in the State of Hawaii. In addition, Hawaiian small business concerns have received NIH support for innovative ideas to improve health through the NIH Small Business Innovative Research and Small Business Technology Transfer programs. For example, Hawaii Biotech is taking the knowledge gained through its dengue fever and West Nile virus vaccine programs and applying it to tick-borne encephalitis. This project, Recombinant Subunit Vaccine for Tick-Borne Encephalitis, addresses an important unmet biodefense need within the United States since there is no registered tick-borne encephalitis vaccine.

The NIH is pleased to be able to support biomedical research and student training programs to help further the health of Native Hawaiians and other Pacific Islanders. Recent discussions between the NIH Deputy Director and several faculty at the University of Hawaii Hilo may help identify additional gaps that could be filled through the NIH-University partnerships.

Below is a list of all the NIH awards to Hawaiian institutions in fiscal year 2010.

FISCAL YEAR 2010 HAWAII NIH AWARDS

Organization name	Grant number	Institute/center	Project title
CARDAX PHARMACEUTICALS, INC.	4R44AA018922–02	NIAAA	Heptax for Alcoholic Liver Disease
CHAMINADE UNIVERSITY OF HONOLULU	1P20MD006084–01	NIMHD	Chaminade University BRIC Project
EAST-WEST CENTER	5R01HD042474–06	NICHD	Innovations in Early Life Course Transitions
HAWAII BIOTECH, INC.	5R44AI055225–04	NIAID	Recombinant Subunit Vaccine For Tick-Borne Encephalitis
HAWAII PACIFIC UNIVERSITY	3K01DA019884–04S1	NIDA	Ecological Factors and Drug Use of Native Hawaiian Youth
HAWAII PACIFIC UNIVERSITY	5K01DA019884–05	NIDA	Ecological Factors and Drug Use of Native Hawaiian Youth
KUAKINI MEDICAL CENTER	5U01AG017155–10	NIA	Epidemiology of Aging and Dementia—Autopsy Research
KUAKINI MEDICAL CENTER	5U01AG019349–09	NIA	Epidemiology of Brain Aging in the Very Old
KUAKINI MEDICAL CENTER	3R01AG027060–04S1	NIA	Defining the Healthy Aging Phenotype
NEUROBEHAVIORAL RESEARCH, INC	5R01AA013659–08	NIAAA	Brain Morbidity in Treatment—Naive Alcoholics
NEUROBEHAVIORAL RESEARCH, INC	5R01AA016944–03	NIAAA	Long-Term Abstinence Clinical Issues and CNS Disinhibition
NEUROBEHAVIORAL RESEARCH, INC	5R01AA016303–04	NIAAA	Effects of heavy alcohol abuse on adolescent brain structure and function
PACIFIC HEALTH RESEARCH INSTITUTE	5U10NS044448–08	NINDS	Parkinson's Disease Neuroprotection Trial: Hawaii Center
PACIFIC HEALTH RESEARCH/EDUCATION INST	3U10NS044448–09S1	NINDS	Parkinson's Disease Neuroprotection Trial: Hawaii Center
PACIFIC HEALTH RESEARCH/EDUCATION INST	3R01NS041265–10S1	NINDS	Risk Factors for Pathologic Markers of Parkinson Disease
PACIFIC HEALTH RESEARCH/EDUCATION INST	6U10NS044448–09	NINDS	Parkinson's Disease Neuroprotection Trial: Hawaii Center
PACIFIC HEALTH RESEARCH/EDUCATION INST	1R01DK089347–01	NIDDK	Reducing Cost-Related Medication Nonadherence in Persons with Diabetes
PANTHERA BIOPHARMA, LLC	5U01AI078067–03	NIAID	Antidotes to Anthrax Lethal Factor Intoxication
PAPA OLA LOKAHI	3U01CA114630–05S3	NCI	IMI HALE NATIVE HAWAIIAN CANCER NETWORK
PAPA OLA LOKAHI	1U54CA153459–01	NCI	IMI HALE NATIVE HAWAIIAN CANCER NETWORK
PAPA OLA LOKAHI	3U01CA114630–05S4	NCI	IMI HALE NATIVE HAWAIIAN CANCER NETWORK
QUEEN'S MEDICAL CENTER	5R01GM063954–08	NIGMS	Molecular and functional properties of the TRPM2 catioin channel
QUEEN'S MEDICAL CENTER	5R21CA139687–02	NCI	Treatment Effects on Tumor 18F-Choline Metabolism in Advanced Prostate Cancer
QUEEN'S MEDICAL CENTER	5R01GM080555–03	NIGMS	Molecular components of the store-operated CRAC channel
UNIVERSITY OF HAWAII AT HILO	5K24MH074468–05	NIMHD	Mentoring/Career Development in PTSD Services Research
UNIVERSITY OF HAWAII AT MANOA	2P20RR016467–09A1	NCRR	INBRE II: Hawaii Statewide Research & Education Partnership (HSREP)
UNIVERSITY OF HAWAII AT MANOA	3R01NS063932–03S1	NINDS	HIV and Global Drug Therapies: Peripheral Neuropathy Complications and Mechanisms
UNIVERSITY OF HAWAII AT MANOA	5R01NS053345–05	NINDS	HIV-1 Proviral DNA and Monocyte Phenotype in Relation to Neurocognitive Function
UNIVERSITY OF HAWAII AT MANOA	5U54NS056883–04	NINDS	Imaging Studies in Neurotoxicity and Neurodevelopment
UNIVERSITY OF HAWAII AT MANOA	5R01NS063932–03	NINDS	HIV and Global Drug Therapies: Peripheral Neuropathy Complications and Mechanisms
UNIVERSITY OF HAWAII AT MANOA	5R01NS053359–04	NINDS	HIV-1 Specific Immune Responses in Thai Individuals with HIV Dementia
UNIVERSITY OF HAWAII AT MANOA	5P20NR010671–04	NINR	Center for 'Ohana Self-Management of Chronic Illnesses Hawaii (COSMCI0): Building
UNIVERSITY OF HAWAII AT MANOA	5R01MH081845–02	NIMH	The Genetic Control of Social Behavior in the Mouse
UNIVERSITY OF HAWAII AT MANOA	5R01MH079717–02	NIMH	Modeling monocyte and macrophage based gene therapy for neuroAIDS
UNIVERSITY OF HAWAII AT MANOA	1R01EB011517–01	NIBIB	Spectral Spatial RF Pulses for Gradient Echo fMRI
UNIVERSITY OF HAWAII AT MANOA	5R24MD001660–06	NIMHD	PILI 'Ohana Project: Partnerships to Overcome Obesity Disparities in Hawai'i

FISCAL YEAR 2010 HAWAII NIH AWARDS—Continued

Organization name	Grant number	Institute/center	Project title
UNIVERSITY OF HAWAII AT MANOA	5R01CA115614–04	NCI	Physical Activity in Women with Infants
UNIVERSITY OF HAWAII AT MANOA	1U13HD063139–01	NICHD	Community-Based Capacity Building: Academic-Community Partnerships Using Partici
UNIVERSITY OF HAWAII AT MANOA	5G11HD054969–04	NICHD	Office of Research Development (EARDA)
UNIVERSITY OF HAWAII AT MANOA	5F32HD055000–03	NICHD	Origins of neuronal patterning in animal development
UNIVERSITY OF HAWAII AT MANOA	2T34GM007684–29A1	NIGMS	Minority Access to Research Careers
UNIVERSITY OF HAWAII AT MANOA	1R01GM093116–01	NIGMS	Gene regulatory network evolution and the origin of biological novelties
UNIVERSITY OF HAWAII AT MANOA	1P41GM094091–01	NIGMS	Accessing Cyanobacterial Chemical Diversity: A Unique Natural Product Library
UNIVERSITY OF HAWAII AT MANOA	5R01GM083158–03	NIGMS	Transposon Based Mammalian Transgenesis and Transfection
UNIVERSITY OF HAWAII AT MANOA	1R01GM088266–01A1	NIGMS	RSK–2 regulates integrin-mediated adhesion and migration
UNIVERSITY OF HAWAII AT MANOA	1K01DK090091–01	NIDDK	Neighborhood Characteristics and Diabetes Incidence in the Multiethnic Cohort Stu
UNIVERSITY OF HAWAII AT MANOA	5R25DK078386–04	NIDDK	High School Students STEP–UP To Biomedical Research
UNIVERSITY OF HAWAII AT MANOA	5R01DK079684–04	NIDDK	Multimedia intervention to motivate ethnic teens to be designated donors
UNIVERSITY OF HAWAII AT MANOA	3U10CA063844–17S1	NCI	Hawaii Minority-Based Clinical Community Oncology Program
UNIVERSITY OF HAWAII AT MANOA	5P01CA114047–05	NCI	Pathogenesis of mesothelioma
UNIVERSITY OF HAWAII AT MANOA	5R01CA058598–12	NCI	Collaborative Genetic Study of Ovarian Cancer Risk
UNIVERSITY OF HAWAII AT MANOA	5R01CA120799–04	NCI	Testing Alternative Stage Models of Smoking Cessation: An Intervention Study
UNIVERSITY OF HAWAII AT MANOA	5R37CA054281–18	NCI	Multiethnic Cohort Study of Diet and Cancer
UNIVERSITY OF HAWAII AT MANOA	1R03CA150041–01	NCI	Urinary Estrogen Metabolites in a 2-year Soy Trial Among Premenopausal Women
UNIVERSITY OF HAWAII AT MANOA	3U54CA143727–02S1	NCI	University of Guam/Cancer Research Center of Hawaii Partnership (1 of 2)
UNIVERSITY OF HAWAII AT MANOA	3P30CA071789–12S9	NCI	Cancer Research Center of Hawaii
UNIVERSITY OF HAWAII AT MANOA	3P30CA071789–12S8	NCI	Cancer Research Center of Hawaii
UNIVERSITY OF HAWAII AT MANOA	5U24CA074806–12	NCI	The Colon Cancer Family Registry: Hawaii
UNIVERSITY OF HAWAII AT MANOA	1R01CA153154–01	NCI	Self-Control as a Moderator for Effects of Mass Media on Adolescent Substance Use
UNIVERSITY OF HAWAII AT MANOA	3U24CA074806–11S1	NCI	The Colon Cancer Family Registry: Hawaii
UNIVERSITY OF HAWAII AT MANOA	7R01CA124687–03	NCI	The Sphingolipid Pathway in Colon Cancer Chemoprevention
UNIVERSITY OF HAWAII AT MANOA	2U10CA063844–17	NCI	Hawaii Minority-Based Clinical Community Oncology Program
UNIVERSITY OF HAWAII AT MANOA	5R21AT004844–02	NCCAM	Mechanisms by which selenium influences T helper cells during immune responses
UNIVERSITY OF HAWAII AT MANOA	5R21AT005139–02	NCCAM	Exploratory Studies on the Anti-Breast Cancer Function of Bamboo Extract
UNIVERSITY OF HAWAII AT MANOA	7R01AI054128–06	NIAID	Mechansim of activation of innate immunity by ISS–DNA
UNIVERSITY OF HAWAII AT MANOA	5R01AI075057–03	NIAID	Intraspecies Transmission and Infectivity of Insectivore-Borne Hantaviruses
UNIVERSITY OF HAWAII AT MANOA	5R01AI071160–04	NIAID	Malarial Immunity in Pregnant Cameroonian Women
UNIVERSITY OF HAWAII AT MANOA	1R01AI089999–01	NIAID	Selenoprotein K modulates calcium-dependent signaling in immune cells
UNIVERSITY OF HAWAII AT MANOA	5R01AI074554–03	NIAID	Global HIV Drug Therapies and Mitochondrial Complications and Mechanisms
UNIVERSITY OF HAWAII AT MANOA	5U01HG004802–03	NHGRI	Epidemiology of Putative Causal Variants in the Multiethnic Cohort
UNIVERSITY OF HAWAII AT MANOA	5R01DA021146–04	NIDA	RGR-based motion tracking for real-time adaptive MR imaging and spectroscopy
UNIVERSITY OF HAWAII AT MANOA	5R01DA021856–04	NIDA	The Project Success Model: Evaluation of a Tiered Intervention

UNIVERSITY OF HAWAII AT MANOA	5K02DA020569–05	NIDA	Parallel MRI for Substance Abuse Research
UNIVERSITY OF HAWAII AT MANOA	5K23DA020801–05	NIDA	Neurodevelopment of Methamphetamine Exposed Children
UNIVERSITY OF HAWAII AT MANOA	5R01DA019912–04	NIDA	Parallel MRI for High Field Neuroimaging
UNIVERSITY OF HAWAII AT MANOA	5K24DA016170–07	NIDA	Neuroimaging and Mentoring in Drug Abuse Research
UNIVERSITY OF HAWAII AT MANOA	1R24DA027318–01	NIDA	Factors for enhanced neurotoxicity in methamphetamine abuse in HIV infection
UNIVERSITY OF HAWAII AT MANOA	5K01DA021203–04	NIDA	Impact of Marijuana Exposure on Brain Maturation
UNIVERSITY OF HAWAII AT MANOA	3R25RR024281–03S1	NCRR	Pacific Education and Research for Leadership in Science (PEARLS)
UNIVERSITY OF HAWAII AT MANOA	5P20RR024206–03	NCRR	Institute for Biogenesis Research: COBRE
UNIVERSITY OF HAWAII AT MANOA	5P20RR016453–09	NCRR	COBRE: Center for Cardiovascular Research
UNIVERSITY OF HAWAII AT MANOA	5R25CA090956–08	NCI	Nutritional & Behavioral Cancer Prevention in a Multiethnic Population
UNIVERSITY OF HAWAII AT MANOA	5R01CA126895–03	NCI	Whole Genome Scan for Modifier Genes in Colorectal Cancer
UNIVERSITY OF HAWAII AT MANOA	5R01CA129063–03	NCI	Inflammation and Innate Immunity Genes and Colorectal Cancer Risk
UNIVERSITY OF HAWAII AT MANOA	5R03CA135699–02	NCI	A pooled analysis of mammographic density and breast cancer risk
UNIVERSITY OF HAWAII AT MANOA	5R01CA140636–02	NCI	Characterizing Mitochondrial DNA Susceptibility to Breast, Colorectal, and Prosta
UNIVERSITY OF HAWAII AT MANOA	5R01CA080843–09	NCI	Effects of Soy on Estrogens in Breast Fluid and Urine
UNIVERSITY OF HAWAII AT MANOA	5U54CA143727–02	NCI	University of Guam/Cancer Research Center of Hawaii Partnership (1 of 2)
UNIVERSITY OF HAWAII AT MANOA	5K23HL088981–03	NHLBI	Cardiovascular autonomic function in HIV virologic failure
UNIVERSITY OF HAWAII AT MANOA	5R01HL095135–03	NHLBI	Role of Oxidative Stress and Inflammation in HIV Cardiovascular Risk
UNIVERSITY OF HAWAII AT MANOA	1R01HL098423–01A1	NHLBI	Role of mTOR in the diabetic heart
UNIVERSITY OF HAWAII AT MANOA	5UH1HL073449–07	NHLBI	University of Hawaii Research Scientist Award in Molecular Cardiology
UNIVERSITY OF HAWAII AT MANOA	5R21HL087289–02	NHLBI	Pseudoxanthoma elasticum: Elastic fibers alterations and characterization of seru
UNIVERSITY OF HAWAII AT MANOA	5R01HL081863–05	NHLBI	Rho kinase in immune-mediated atherosclerosis
UNIVERSITY OF HAWAII AT MANOA	5R01AI068525–05	NIAID	Role of macrophages in HIV Lipoatrophy
UNIVERSITY OF HAWAII AT MANOA	5G12RR003061–25	NCRR	Research Outcomes Accelerating Discoveries for Medical Applications and Practice
UNIVERSITY OF HAWAII AT MANOA	1R01HD060722–01A1	NICHD	Contribution of Sperm Nucleus to Paternal DNA Replication
UNIVERSITY OF HAWAII AT MANOA	5R21AG032405–02	NIA	A Needle in a Haystack: New approaches to Alzheimer's Drug Discovery from Natural
UNIVERSITY OF HAWAII AT MANOA	2P20RR018727–06A1	NCRR	Pacific Center for Emerging Infectious Diseases Research
UNIVERSITY OF HAWAII AT MANOA	5P20MD000173–09	NIMHD	Partnerships for Cardiometabolic Disparities in Native and Pacific Peoples
UNIVERSITY OF HAWAII AT MANOA	5R01GM057873–11	NIGMS	Cyclopentannelation in Total Synthesis
UNIVERSITY OF HAWAII AT MANOA	1U54RR026136–01A1	NCRR	RCMI Multidisciplinary And Translational Research Infrastructure EXpansion Hawaii
UNIVERSITY OF HAWAII AT MANOA	5R25RR024281–03	NCRR	Pacific Education and Research for Leadership in Science (PEARLS)

THE NATIONAL INSTITUTE OF NURSING RESEARCH (NINR) SUPPORT FOR END-OF-LIFE CARE AND HEALTH DISPARITIES RESEARCH

Question. The NINR will soon be celebrating its 25th anniversary. The late Senator Quentin Burdick and I were active in establishing the original Center and I am confident he would share my enthusiasm for how nicely it has matured over the years. At this time I would appreciate an update on the extent to which the NINR has been able to co-fund various initiatives with other NIH Institutes, particularly in the areas of end-of-life issues and racial and geographical disparities.

Answer. Improving palliative and end-of-life care and eliminating health disparities are critical components of the NINR's research mission. Consistent with this mission, as well as the Institute's longstanding practice of extensive collaboration with other NIH ICs, the NINR co-funds numerous scientific efforts with other ICs focused on these two important topics.

As the lead NIH Institute on issues related to end-of-life care research, the NINR, with support from partners across the NIH, will convene a forum on August 10–12, 2011, entitled "The Science of Compassion: Future Directions in End-of-Life and Palliative Care." A part of the NINR's 25th Anniversary commemoration, this forum is intended to energize and mobilize palliative and end-of-life care research and to draw attention to palliative and end-of-life care processes, options available to patients and their families, and the healthcare community's obligation to address these complex needs. This event is co-sponsored by the following NIH partners: National Institute on Aging (NIA), Office of Rare Diseases Research, Office of Research on Women's Health, National Center for Complementary and Alternative Medicine, and the NIH Clinical Center Department of Bioethics.

In addition, the NINR and the NIH Common Fund recently awarded $7.1 million in funding provided by the American Recovery and Reinvestment Act to support a Palliative Care Research Cooperative (PCRC), a multi-institution effort to conduct collaborative research on palliative and end-of-life care. The PCRC will bring together experienced, multidisciplinary investigators to facilitate innovative, high-impact, clinically useful palliative care research to inform practice and health policy. The PCRC will address challenges associated with conducting research with individuals with life-limiting conditions, and could lead to significant improvements in the evidence base for palliative and end-of-life care.

NINR also collaborates with other ICs to support basic, clinical, and translational research to address health disparities across the life span. The NINR currently co-funds an initiative focused on reducing health disparities in minority and underserved children, including children from: racial/ethnic minority groups; rural and low-income populations; and geographically isolated locations. The NINR, and other Institutes, have supported various important projects under this initiative. For example, the NINR-supported investigators are testing interventions to improve the well-being of African American, Hispanic, and White families where grandmothers are raising grandchildren. These custodial grand-families are at high risk for psychological difficulties and limited access to needed services. This initiative is co-funded with the following NIH Institutes: National Institute of Child Health and Human Development; National Heart, Lung, and Blood Institute; National Institute on Alcohol Abuse and Alcoholism; and the National Institute on Deafness and Other Communication Disorders.

Additionally, researchers funded by the NINR and the NIA developed the Resources for Enhancing Alzheimer's Caregivers Health (REACH) II program which teaches caregivers about Alzheimer's disease, managing stress, and maintaining their own health. In a large sample of African American and White caregivers for Alzheimer's patients, those in the REACH II intervention reported better physical, emotional, and overall health and had lower scores for depression which contributed to reducing caregiving burden. To address the need for support of caregivers, particularly in racially/ethnically diverse families, multiple efforts across the Federal Government are currently underway to implement REACH in the community.

HEALTH MESSAGES FOR THE NATIVE HAWAIIAN POPULATION

Question. According to the fiscal year 2012 NIH CJ, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) "supports a robust information dissemination and outreach program to distribute research-based information to the public, patients, and their healthcare providers." The NIAMS supported National Multicultural Outreach Initiative "is creating a sustainable network of partners to assist in the development and dissemination of health messages and materials for racial and ethnic minority populations." The Initiative will focus its efforts on reaching many different minority/ethnic populations including Native Hawaiians. "Working with existing NIAMS partners, the Institute will develop research-based

self-care messages and products, and ensure their distribution through trusted health and multicultural community channels. The NIAMS implemented critical phases of the Initiative in fiscal year 2011, namely, the development and pretesting of culturally and linguistically appropriate health messages and materials through audience research."

The NIAMS and its National Multicultural Outreach Initiative are supporting the development of health messages for racial and ethnic minority populations. What types of health messages are being developed and tested for the Native Hawaiian population?

Answer. In fiscal year 2011, the NIAMS completed qualitative research with members of multicultural communities, including Native Hawaiians, to help inform the development of culturally appropriate and useful health education products for adults with medical conditions affecting the bones, joints, muscles, and skin. The NIAMS conducted a total of 18 focus groups (2 with Native Hawaiians), and 20 in-depth interviews (2 with Native Hawaiians) to gather feedback from individuals on preferences for different message concepts and formats for communicating health messages. The information gleaned from this audience research will enable the development of tailored products that raise awareness about the availability of reliable, research-based health information and resources from the NIAMS and partner organizations to help patients and their families manage their conditions.

The NIAMS National Multicultural Outreach Initiative relies on the guidance and input from its working groups for the development and dissemination of health messages and products. These groups are comprised of national experts from multicultural communities, and include representation from the Native Hawaiian community.

THE NATIONAL INSTITUTE ON MINORITY HEALTH AND HEALTH DISPARITIES (NIMHD) CENTERS OF EXCELLENCE (COE) IN HAWAII

Question. The fiscal year 2012 congressional justification states that the NIMHD has supported 91 COE sites in 35 States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. According to the CJ, the "types of institutions are diverse and include Historically Black Colleges and Universities, Hispanic-Serving Institutions, Tribal Colleges and Universities, Alaskan Native, and Native Hawaiian Serving Institutions." In fiscal year 2010, the 51 active COEs conducted transdisciplinary research on high priority diseases/conditions including "cardiovascular disease, stroke, cancer, diabetes, HIV/AIDS, infant mortality, mental health, and obesity that disproportionately affect racial/ethnic minority and other health disparity populations."

Is the NIMHD currently supporting a COE at a Native Hawaiian Serving Institution? What high priority diseases or conditions are the focus of research at a COE in a Native Hawaiian Serving Institution?

Answer. The NIMHD COE represent a scientific platform for innovative research projects, research training, and effective community engagement to address the health status of health disparity populations. The NIMHD has provided funding for a COE at the University of Hawaii Manoa since September 2002. This COE, Partnerships for Cardiometabolic Disparities in Native and Pacific Peoples, is a regional focal point for improving cardiometabolic health and eliminating health disparities among Native Hawaiians and other Pacific Islanders, including Filipinos, Samoans, and Tongans.

The primary focus of the COE is obesity and diabetes which are known risk factors for cardiovascular disease. Eighty-two percent of Native Hawaiians are overweight or obese, which is considerably higher than the national average of 53 percent. Pacific Islander women with diabetes have a higher risk of myocardial infarction. Through dedicated efforts over the years, Partnerships for Cardiometabolic Disparities in Native and Pacific Peoples has made significant contributions to the improvements in the health of Native Hawaiians and other Pacific Islanders.

In addition, supplemental funding was provided in July 2010 to support the establishment of the Comparative Effectiveness Research Approaches to Eliminate Cardiometabolic Disparities initiative as part of the COE. The intent of the project is to train researchers in comparative effectiveness research, to conduct innovative research, to establish diabetes and cardiometabolic disease registries, and to disseminate research results to communities with health disparities in Hawaii.

HEREDITARY ANGIODEMA RESEARCH SUPPORT

Question. Dr. Collins, I would like to thank you for your leadership of the National Institutes of Health, including its continuing emphasis on rare diseases. As you are aware, the NIH provides critical opportunities for research surrounding or-

phan conditions which otherwise may not have an opportunity for significant research. Recently, constituents and members of the U.S. Hereditary Angioedema Association (USHAEA), based in Honolulu, brought to my attention the absence of Federal support since 2009 for hereditary angioedema (HAE) research. I would appreciate receiving a report on why funding for this disease was eliminated and what your efforts are toward reinvigorating hereditary angioedema research support.

Answer. HAE is a rare genetic disorder. HAE patients suffer from swelling of the hands, feet, abdomen, face and/or throat. Especially the latter is a major medical emergency that may be fatal. Estimates for the prevalence of HAE range from 1 in 10,000 to 1 in 50,000 people in the United States.

In 2009, a number of research projects focusing on hereditary angioedema came to a natural end. For example, the most extensive project, sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, C1 Inhibitor Gene and Hereditary Angioneurotic Edema, was last funded in 2008 after 23 years of research and concluded in 2010. The Principal Investigator did not apply for renewed funding for this project.

The National Center of Research Resources (NCRR) funded Mount Sinai General Clinical Research Center project: CHANGE Trial (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy): Open-Label Safety/Efficacy Repeat Exposure Study of C1 Esterase Inhibitor (Human) in the Treatment of Acute Hereditary Angioedema (HAE) Attacks participant visits ended in March 2009 and closed in September 2009. The results were published in the NEJM in August 2010 (PMID 20818886). Currently, the NCRR-funded Mount Sinai Clinical and Translational Science Award supports the Phase III Randomized Double Blind, Placebo controlled Multicenter Study of Icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema.

The NCRR General Clinical Research Center at the University of Texas Medical Branch at Galveston (UTMB) conducted the Randomized, Placebo-Controlled, Double-blind Phase II Study of the Safety and Efficacy of Recombinant Human C1 Inhibitor for the Treatments of Acute Attacks in Patients with Hereditary Angioedema. The study ended in May 2009.

The NCRR-funded University of Texas Medical Branch at Galveston (UTMB) Clinical and Translational Science Award represents an additional site which conducted the Phase III Randomized Double-Blind, Placebo-Controlled Multicenter Study of Icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema (HAE). This study was completed in May 2011.

Currently, we also are supporting three training grants with projects investigating HAE, two from National Institute of Allergies and Infectious Diseases and one from the National Heart, Lung, and Blood Institute. These training grants are critical since they train the next generation of investigators. The trainees are expected to continue their careers with a research emphasis on HAE. The NIH would welcome the opportunity to support meritorious research studies focusing on hereditary angioedema (HAE).

To stimulate future research activities and applications we would encourage investigators and advocates of HAE research to submit an application for a scientific conference grant. In addition to helping to identify research opportunities and needs and develop a research agenda and research priorities for HAE, such a conference could create significant research interest in this particular rare disease. The Office of Rare Diseases Research (ORDR), collaborating with other NIH research institutes, would be pleased to confer with the U.S. Hereditary Angioedema Association (U.S. HAEA) and interested research investigators about your concerns.

CANCER PREVELANCE AND RESEARCH IN HAWAII

Question. Over the years the NCI has systematically invested in research activities targeting the unfortunately high incidence of cancer among my State's Native Hawaiian population. At one point the NCI researchers reported that Native Hawaiian women had the highest incidence of breast cancer in the world. I am confident that progress has been made and would appreciate a report describing the NCI's future plans for targeting the special needs of these indigenous people.

Answer. The NCI funds research that focuses on Native Hawaiian, other Pacific Islander, and Asian American populations. These studies are supported to illuminate the causes of cancer in these populations; to improve screening rates so that when cancer appears, it can be treated at an early stage; to increase knowledge about treatment options so that patients and their physicians can make more informed choices about their care; to fund registries, surveys, and reports that generate the latest statistics and inform researchers, policy makers, and the public; to

support cohorts that provide a population base from which to conduct important future research, and ultimately to prevent cancers in these populations.

Current Efforts

The NCI's Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and National Lung Screening Trial (NLST) studies, with more than 200,000 participants, include programs in Hawaii and from diverse ethnic populations. At the Pacific Health Research and Education Institute in Honolulu, of the 13,200 study participants in Hawaii, approximately half were Asians (5,553) and Native Hawaiians and other Pacific Islanders (1,053).

In the area of clinical trial recruitment of minorities, the University of Hawaii Minority-Based Community Clinical Oncology Program (MB–CCOP), funded since 1994, provides access to the NCI clinical trials in cancer prevention, treatment, and control to both children and adults.

The NCI Community Network Program (CNP) Centers address disparities at the community level with outreach, research, and training. Two CNPs are oriented to Pacific Islanders (Imi Hale and Weaving an Islander Network for Cancer Awareness, Research and Training, or WINCART) and two other CNPs are focused on underserved Asians (Asian American Network for Cancer Awareness, Research, and Training, or AANCART, and the Asian Community Cancer Health Disparities Center, or ACCHD).

National Outreach Program (NOP) supported by the Imi Hale Native Hawaiian Cancer Network is designed to reduce cancer incidence and mortality among Native Hawaiians by maintaining and expanding an infrastructure that:

—Promotes cancer awareness within Native Hawaiian communities;
—Provides education and training to develop Native Hawaiian researchers; and
—Facilitates research that aims to reduce cancer health disparities experienced by Native Hawaiians.

The Imi Hale Native Hawaiian Cancer Network made progress toward reducing cancer incidence and mortality among Native Hawaiians through a project, "Woman to Woman-Micronesians United Lay Educator Program" for Native Hawaiians focused on increasing breast and cervical cancer screening. Six months of outreach activities resulted in screening of 150 women. CNP-Southern California developed culturally tailored educational resources specifically for Native Hawaiians and the Marshallese, in colorectal cancer screening, which resulted in a library of culturally relevant resources. In addition to these primary efforts, the CNP Native Hawaiian trainees have submitted 40 grant applications and a total of 12 were ranked high enough for funding.

Imi Hale has a dedicated Community Health Educator, who seeks to bridge the gap between the community and the research community by developing culturally tailored cancer information. For instance, to help women learn to do self-breast exams to detect lumps early, Imi published Breast Health Shower Cards in nine languages. In terms of breast cancer education, Imi Hale has produced a DVD entitled "A Journey of Hope: When a Young Woman Gets Cancer." Seeking creative ways to educate women about breast cancer, Imi Hale created a breast cancer computer game (http://imihale.org/game/click__to__start.html). In addition, a series of brochures for Native Hawaiian breast cancer survivors called "Talking Story Booklets" has been developed. The outreach component works closely with such partners as the five Native Hawaiian healthcare Systems positioned on five islands.

—Imi Hale Clinical partners include: Community Health Centers serving Native Hawaiian clients, the Queen's Cancer Center and other hospitals, and the State-contracted Breast and Cervical Cancer Control Programs; and
—Imi Hale Community partners include: Association of Hawaiian Civic Clubs, Hawaii State Tobacco Coalition, Office of Hawaiian Affairs, and other community agencies.

A Comprehensive Partnership to Reduce Cancer Health Disparities Program between the University of Hawaii Cancer Center (UHCC) and the University of Guam (UOG) have an NCI-funded partnership with the aim of enhancing the awareness of cancer and cancer prevention and ultimately reducing the impact of cancer on the population in Hawaii, the Territory of Guam and the other U.S.-associated Pacific Island territories. The partnership supports projects designed to develop culturally appropriate guidelines for tobacco use prevention and cessation in youth with the underlying hypothesis that interventions to prevent tobacco use are more likely to succeed if they conform to culturally relevant guidelines developed with the active participation of the target youth themselves. The long-term goal of the community-based participatory outreach program is to engage the community as equal partners in tobacco control and cancer prevention research. The partnership also supports investigator-initiated cancer research projects that address different aspects of cancers

in Hawaii and Guam including the development of protocols for studying oral precancerous lesions and other health risks among betel nut users in Hawaii, the Territory of Guam and the other U.S.-associated Pacific Island territories.

The NCI Community Cancer Centers Program (NCCCP) is designed to create a community-based cancer center network to support basic, clinical and population-based research initiatives, addressing the full cancer care continuum—from prevention, screening, diagnosis, treatment, and survivorship through end-of-life care. The NCCCP pilot has added the Queen's Medical Center, Honolulu, Hawaii (The Queen's Cancer Center) to its 30 hospital network.

Future Research

The NCI will be launching a program to foster evidence-based research, data collection, and analysis within Asian American and Pacific Islander (AAPI) populations and subpopulations through a unique collaboration with the University of Guam, the University of Hawaii, the Pacific Regional Central Cancer Registry, and the Pacific Island Cancer Council. The NCI developed the Health Information National Trends Survey (HINTS) to monitor changes in the rapidly evolving field of health communication by collecting data across the Nation. The HINTS-Guam program will pilot test a localized survey instrument geared specifically to AAPI populations and subpopulations, including Chamorros and other Pacific Islanders living on Guam. Data collected from this survey will increase understanding of cancer information seeking, experiences, and behaviors (prevention, screening, treatment, etc.) among AAPI populations. Discussions have also begun on a HINTS pilot project to be conducted in Hawaii.

KIDNEY DISEASE AND DIABETES RESEARCH IN HAWAII

Question. It has recently come to my attention that my State's Filipino population has an extraordinarily high incidence of kidney disease. Similarly, several ethnic groups in Hawaii (including Native Hawaiians) have been found to have high incidences of diabetes. Accordingly, I would appreciate receiving a report on your efforts to develop initiatives targeting these populations, and particularly those which would stress prevention and perhaps diet.

Answer. Data show that Filipinos in Hawaii seem to have a disproportionate burden of kidney disease. The NIDDK is naturally very concerned about kidney disease in Hawaiians, including the health disparity in the Filipino population, and has several initiatives in place to address the problem. First, our National Kidney Disease Education Program (NKDEP) provides materials that can be used in Hawaii's high risk populations. The NKDEP's materials aim to raise awareness of the seriousness of kidney disease, the importance of testing those at high risk (those with diabetes, high blood pressure, or a family history of kidney failure), and the availability of treatment to prevent or slow kidney failure. NKDEP's extensive new offerings on dietary intervention in chronic kidney disease for providers and patients would be particularly useful.

The National Diabetes Education Program (NDEP) is sponsored by the NIDDK and Centers for Disease Control and Prevention (CDC) and includes more than 200 partners working together to improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes, a leading cause of kidney disease. The NDEP has a major focus on Asian Pacific Islanders; it has translated educational materials into Tagalog, one of the languages spoken in the Fillipino population. These materials address both prevention of diabetes and prevention of complications such as kidney disease. The University of Hawaii is a site for the Diabetes Prevention Program Outcomes Study, which recently reported data showing durability of effect of lifestyle intervention and the drug metformin at preventing or delaying onset of type 2 diabetes at 10 years follow-up.

People whose disease progresses to kidney failure can be treated with a kidney transplant, though limitations on available donor organs is a chronic problem. The NIDDK's "Minority Organ Donation Program" initiative supports an investigator at the University of Hawaii, Dr. Cheryl Albright, whose research focuses on educating Filipino high school students about signing up (on drivers' licenses) to donate organs. Students from Honolulu and other smaller Islands (including rural areas) are participants. The grant is in the fourth year and results are quite encouraging. The Filipino community is very interested in kidney transplants, and participated in the original National Minority Organ and Tissue Transplant Education Program (http://mottep.org/) to rally the community around kidney donation from relatives and friends.

In another initiative, the NIDDK, in collaboration with the CDC and the Indian Health Service, has funded eight Tribal Colleges and Universities in the initiative "Diabetes Education in Tribal Schools." This effort developed supplemental cur-

ricula, to be used in K–12 schools in American Indian and Alaska Native communities, about prevention and better management of diabetes, the most common cause of kidney failure. Although the cultural content is directed primarily toward American Indians, some Hawaiian schools participated in piloting the curricula. The project is completed and the curricula are being fielded in tribal schools. Also, the curricula were distributed to and currently are being used in Hawaiian schools, primarily on the Big Island of Hawaii.

STROKE DISPARITIES IN THE UNITED STATES

Question. I am concerned that stroke apparently remains the number two killer in the United States and a major cause of disability. In addition, stroke affects some segments and regions of our population more than others. I understand that the State of Hawaii ranks 20 out of 52 highest in our Nation for age-adjusted stroke deaths. Death rates from a certain type of stroke (intracerebral hemorrhage) are higher among Asians/Pacific Islanders than among Whites. More than 20 percent of Native Hawaiians or other Pacific Islanders have high blood pressure, a leading risk factor for stroke. Yet, the NIH invests only 1 percent of its budget on stroke research. What is your Institute doing to address the disparities that exist in stroke burden among different cultural and racial populations in the United States?

Answer. Stroke research at the NIH is comprehensive and includes research on basic disease mechanisms; epidemiology studies to assess stroke risk, occurrence and outcomes in the population; clinical research to develop effective prevention and acute treatment approaches; and development of strategies for improving recovery and rehabilitation in stroke patients. Clinical research in stroke is particularly a high priority at the National Institute of Neurological Disorders and Stroke (NINDS)—approximately 50 percent of its large Phase III trials are on stroke.

The NINDS also supports major research initiatives aimed at better defining stroke risk, incidence and outcomes in the United States and among different subpopulations. Collections of population-based data help identify and explain health disparities in stroke, and inform the development of preventive interventions that target high risk populations.

—In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, investigators are exploring the geographical and racial influences on stroke risk in a cohort of about 30,000 individuals, about half of whom live in the "stroke belt" region of the Southeastern United States. This large study has produced over 70 publications that have led to a better understanding of disparities in stroke in the United States. Data generated from this study continue to help researchers pinpoint why the stroke rate is higher in this region, and among African Americans, and to develop targeted strategies for intervention. Recent data from REGARDS indicated that overall time spent in the stroke belt is more predictive of hypertension—a powerful risk factor for stroke—than is current residence in the stroke belt. Data from the REGARDS study have also revealed that stroke survivors were more likely to have unrecognized hypertension and diabetes.

—The Stroke Disparities Program is a multi-component program to address major stroke challenges in the African American community. The three projects in this program include:

  —an intervention strategy to increase stroke knowledge and reduce the time from symptom onset to hospital arrival (ASPIRE);

  —an intervention utilizing navigators for secondary stroke prevention that targets adherence to poststroke care (PROTECT DC); and

  —an observational imaging study to better understand racial and ethnic differences in risk, occurrence and outcomes of small brain hemorrhages (DECIPHER).

—The NOrthern MAnhattan Study (NOMAS) investigators have been following a cohort of stroke-free adults, including whites, African Americans and Caribbean Hispanics in a Northern Manhattan community. Researchers are collecting imaging, biological and neuropsychological data to evaluate the relationship between biological and imaging predictors for stroke, heart attack and death, as well as cognitive decline. Using these markers in combination with other factors such as diet, alcohol use, smoking, and history of peripheral vessel disease, investigators are developing risk factor and cognitive ability assessment tools. Genetic studies involving this and other cohorts, have suggested that there may be genetic susceptibilities underlying left atrium size and atherosclerosis of the carotid arteries that contribute to stroke.

—BASIC (Brain Attack Surveillance in Corpus Christi) investigators are comparing trends in recurrent stroke, as well as functional and cognitive outcomes

following stroke, in 5,000 non-Hispanic whites and Mexican Americans in Corpus Christi, Texas. Data from this study have shown that Mexican Americans with atrial fibrillation are more likely to have recurrent strokes than whites, and the strokes are more likely to be severe. The investigators are also exploring associations between biological and social stroke risk factors, and recently found, for example, that the density of fast food restaurants was associated with neighborhood stroke risk.

—Ethnic and Racial variation in Intracerebral Hemorrhage (ERICH), a study that was initiated in 2010, will identify differences in intracerebral hemorrhage (ICH) risk factor distribution and outcomes by race and ethnicity. This project will compare 3,000 cases of ICH, among African Americans, Hispanics and non-Hispanic whites, to 3,000 demographically matched controls in order to identify differences in risk factor distribution and ICH outcome by race, ethnicity and location of ICH and to determine differences in imaging characteristics among African Americans and Hispanics compared to whites. The investigators will also collect DNA in order to combine with other cohorts to perform a genome-wide association study (GWAS) to identify genes that affect risk of ICH in whites, African Americans and Hispanics.

—The Alaska Native Stroke Registry (ANSR) is a population-based surveillance study on the epidemiology of stroke in Alaska Natives. Comprehensive assessment of the stroke epidemiology, vascular risk factors, cultural understandings of vascular health and lifestyle, and structural barriers to risk reduction strategies has informed the development of a community level prevention intervention pilot program that aims to reduce the burden of stroke in the Alaska Native population.

QUESTIONS SUBMITTED BY SENATOR HERB KOHL

COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENTS TRIALS

Question. The National Institutes of Health (NIH) recently released results of the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), which found that Lucentis and off-label Avastin are similarly efficacious at treating neovascular age-related macular degeneration (wet AMD). Now that the CATT study is released, what is the NIH going to do with the results? The taxpayers spent millions of dollars on the CATT study to determine the comparative effectiveness of the drugs. I believe the trial results ought to be actionable.

Answer. The National Eye Institute (NEI) recognizes its responsibility to fund and conduct scientifically valid clinical research and to disseminate the study results to the professional clinical community and the public.

We collaborate extensively with ophthalmic organizations to apprise their members of CATT results. In particular, outreach to professional groups was the most effective and efficient means of reaching the clinical ophthalmic community regarding CATT findings. For example, the American Academy of Ophthalmology (AAO) has 30,000 member ophthalmologists who are the primary eye care professionals that treat wet AMD. The NEI worked with AAO to disseminate CATT results through the AAO's Website, newsletters, press releases, and its upcoming annual meeting. Additionally, the AAO Executive Director has written extensively to the membership in support of CATT. We will continue to work with AAO as they develop "preferred practice plans" for the treatment of wet AMD. The Association for Research in Vision and Ophthalmology (ARVO) is a 12,500 member eye research organization comprised of clinicians and investigators. CATT investigators presented their results at ARVO's annual meeting in May 2011. These two organizations will continue to provide information and guidance to their members about CATT so that the results can inform clinical care decisions.

The NEI is also working to inform the public about the CATT findings. The release of the study was accompanied by an extensive media outreach campaign. For example, the NEI hosted a news briefing for journalists where the NEI Director and CATT investigators presented study findings and fielded questions from more than 60 media outlets. Supplemental background video footage was made available to broadcast outlets. A press release was also distributed widely to media outlets. The NEI generated robust media coverage for CATT, coverage that has been intense and more widespread than for other recent studies (see accompanying table), despite media competition from the royal wedding and the death of Osama Bin Laden. As follow-up to the initial media coverage, the NEI distributed CATT results to members of the National Eye Health Education Program (NEHEP), a partnership of 60 public and private organizations dedicated to eye health education. This program

provides the NEI with direct access to community-based public health education efforts, and we are preparing an NEI webpage devoted to CATT along with a brochure including public health information about CATT.

Of note, the May publication of CATT reported on first year results. The second year results will be published in the spring of 2012. At that time, the NEI will repeat its efforts with professional organizations and the media to disseminate CATT results.

NEI CLINICAL TRIAL MEDIA COVERAGE

Study name	Impressions (millions) [1]	Number of original news stories	Pick-up of original news stories [2]
CATT.—Comparison of AMD Treatment Trials (2011)	296	157	234
ETROP.—Early Treatment for Retinopathy of Prematurity Study (2010)	257	20	138
DRCR–DME.—Ranibizumab plus laser therapy for diabetic macular edema (2010)	232	42	29
ACCORD.—Action to Control Cardiovascular Risk in Diabetes Eye Study (2010)	8	9	([3])
GWAS–AMD.—Genome-wide association study genes associated with AMD (2010)	16	13	6
LALES.—Los Angeles Latino Eye Study (2010)	3	7	([3])
Myopia.—Increased pevalence of myopia in United States (2009)	158	76	([3])
SCORE.—Standard Care vs. Corticosteroid for Retinal Vein Occlusion (2009)	150	27	79
LCA.—Leber Congenital Amaurosis (2009)	155	32	37
CITT.—Convergence Insufficiency Treatment Trial (2008)	44	117	183
CDS.—Cornea Donor Study (2008)	63	118	74
AREDS2.—Age Related Eye Disease Study 2 (2006)	17	92	([3])

[1] *Impressions.*—Number of people exposed to the news story in print, online, or on television based on expected readership or viewers.

[2] *Pick-up.*—When an original story is reprinted in another outlet (i.e., an Associated Press article is printed in The Washington Post), it is counted as a pick-up.

[3] Not applicable.

Question. How does the NIH share this information with other agencies within the Federal Government?

Answer. In the preparation for the release of CATT, the NEI held a teleconference with relevant Department of Health and Human Services (HHS) agencies (FDA, CMS, CDC, and AHRQ) to inform them of CATT results and to coordinate the HHS response to media. In accordance with standard HHS and NIH operating procedures, the NEI distributed a draft press release for clearance within DHHS and responded to various issues prior to approval for release. This effort helped ensure a coordinated HHS response to CATT. Since this initial interaction, both the NEI staff and CATT leadership have been contacted by CMS staff to discuss the implications of the CATT study results.

Question. Has the NIH's National Eye Institute considered what effect, if any, the CATT study might have on future physician prescribing behavior regarding Lucentis vs. off-label Avastin to treat wet AMD?

Answer. Avastin, which inhibits the formation of new blood vessels, was approved by the FDA in 2004 for the treatment of colon cancer. Avastin is effective as an anticancer agent because inhibiting the blood supply to tumors inhibits their growth. Since wet AMD is due to leakage from new, abnormal blood vessels, ophthalmologists began trying Avastin off-label to treat this form of AMD in 2006 on the basis of both the cancer data and clinical trial results for Lucentis during the FDA approval process. At that time, Avastin off-label was the only available treatment for wet AMD that led to improvement in vision.

The vast majority of patients treated for wet AMD participate in Medicare. After Lucentis was FDA-approved in 2007, most ophthalmologists continued to use Avastin because the cost was significantly lower than for Lucentis and because a number of reported cases demonstrated Avastin efficacy that appeared similar to that reported in the Lucentis clinical trials. Last May, Dr. Ross Brechner and colleagues (Centers for Medicare and Medicaid Services) and Dr. Phillip Rosenfeld (Bascom Palmer Eye Institute, University of Miami) published an analysis of Medi-

care claims for wet AMD during 2008.[1] They found that 64.4 percent of patients received Avastin and 35.6 percent received Lucentis and concluded that despite its off-label designation, intravitreal Avastin is currently standard-of-care treatment for wet AMD. Medicare payments totaled $536.6 million for Lucentis and $20.3 million for Avastin.

CATT was a very tightly controlled, well-designed study, which compared the two drugs in more than 1,100 patients. The exceptionally wide dissemination of CATT results means that the retinal specialists who treat AMD and the patients they care for are undoubtedly well aware of the equivalence. As such, an increase in the number of patients receiving Avastin as first line therapy is to be expected. Careful monitoring of use of the drugs by CMS is expected.

Importantly, some patients with wet AMD respond better to Avastin, while others to Lucentis. In practice, if one is ineffective, the other may be tried. The fact that more than one drug is available is beneficial and allows ophthalmologists and patients treatment choices.

QUESTIONS SUBMITTED BY SENATOR MARY L. LANDRIEU

INTERIM STATUS OF IDeA PROGRAM

Question. Scientists have expressed their concern about programs that have been placed before under "interim" status and tend to lose direction and in some cases have disappeared. I am particularly concerned about the Institutional Development Award (IDeA) Program, which is so important to Louisiana. What is the reason for placing a program that serves 23 States and Puerto Rico on an interim status?

Answer. The IDeA Program has not been placed in an interim status. Under the proposed creation of the National Center for Advancing Translational Sciences (NCATS), we considered moving the program to a new unit called the Office of Research Infrastructure Programs within the Office of the Director, Division of Program Coordination, Planning, and Strategic Initiatives. However, following extensive consultation and feedback from multiple stakeholders, including grantees, professional organizations, and the public, we concluded that the IDeA program is most closely aligned scientifically and programmatically with the mission and goals of the National Institute of General Medical Sciences (NIGMS). Therefore, the National Institutes of Health (NIH) intends on moving the IDeA program and the IDeA program staff to the NIGMS. We are confident the program will flourish as a vital component of the NIGMS.

PLACEMENT OF NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR) PROGRAMS

Question. For many years the programs housed at the NCRR have worked synergistically to serve the IDeA community. Can this synergy continue by placing these programs under a single NIH institute?

Answer. There is no reason why synergies established between IDeA and other NCRR programs will not continue to flourish at both the national level through programmatic communication and collaboration across institutes and centers and at the local level through institutional collaborations and interactions. Fostering collaborative research networks is an inherent part of the IDeA mission, and it excels at establishing connections and linkages. IDeA institutions currently collaborate with grantees of the Research Centers in Minority Institutions (RCMI) program as well as the Science Education Partnership Award Program (SEPA). The NIH encourages such collaborations, and they will continue.

PLACEMENT OF IDeA WITHIN THE NATIONAL INSTITUTE OF MINORITY HEALTH DISPARITIES (NIMHD)

Question. It has been made public that some institute directors who have been approached to house IDeA programs have voiced reservations about housing these programs in their institutes based on their programmatic mission and staffing needs. We also know that the Advisory Council for the NIMHD has enthusiastically endorsed the idea of placing these programs in the NIMHD. Have you considered the possibility of placing these programs under the management of the NIMHD?

Answer. An NIH National Center for Research Resources (NCRR) Task Force, charged with identifying the optimal new home for the IDeA program, considered a range of options, including its placement within the NIMHD. After careful anal-

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[1] Brechner, R. J, P. J. Rosenfeld, J. D. Babish, and S. Caplan. Pharmacotherapy for Neovascular Age-Related Macular Degeneration: An Analysis of the 100 percent Medicare Fee-For-Service Part B Claims File. *American Journal Ophthalmology 151:887–895, 2011.*

ysis, fact-finding, and consultation, the Task Force recommended that this program be transferred to the National Institute of General Medical Sciences (NIGMS). The IDeA program fosters health-related research and enhances competitiveness of investigators at institutions located in States in which the aggregate success rate for applications to the NIH has been historically low. By its nature, the program extends beyond traditional capacity building in supporting research projects that are designed to strengthen future investigator-initiated research applications, most of which are focused on addressing basic science questions. The NIGMS has a basic science focus as well as a longstanding focus on institutional capacity building and career development. Given these synergies, the Task Force determined that the mission of the IDeA program is most closely aligned with the mission of the NIGMS and that the NIGMS would be the optimal new home for the IDeA Program.

THE CLINICAL AND TRANSLATIONAL SCIENCE AWARDS (CTSAS) AND THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Question. With the final five CTSAs expected to be announced in the near future, I have a couple of questions for Dr. Collins on this program's future direction now that it is being moved to the new NCATS.

Because the NCATS is primarily focused on drug development, what will become of the community research and integration aspect of the CTSAs' mission? Will community involvement continue to be a central focus of this program?

The CTSAs represent translational research across the country, but there are no centers in the gulf south—an area with significant health needs that would benefit greatly from a CTSA and could contribute much to the network of centers. Is geographic distribution considered as CTSA sites are being selected?

Answer. The mission of the NCATS will be to catalyze the development of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. In addition to strengthening and streamlining the therapeutics development process, the NCATS will support research aimed at accelerating the development, testing, and implementation of products and techniques, including diagnostics, drugs, biologics, medical devices, and behavioral interventions, for the diagnosis, treatment, and prevention of disease. The CTSAs possess the requisite expertise across the full spectrum of translational research, and they will be integral to the success of the NCATS. The involvement of research sites across the Nation and the study of the integration of research findings at the community level will continue to be an important focus of the CTSA program.

Institutions with CTSAs that are either close to or interact with communities and populations along the Gulf include the University of Texas Medical Branch in Galveston and the University of Alabama in Birmingham. The CTSA at the University of Texas Health Sciences Center at Houston serves gulf communities through its strong connections to UT's Brownsville campus.

With regard to the selection of the CTSA sites, NCRR has used the peer review process to establish priority scores to guide funding decisions. All applications, together with their priority scores, were then reviewed by the National Advisory Research Resources Council, which is able to make recommendations, where needed, concerning geographic distribution. Going forward, scientific merit will continue to be the principal selection criterion, and considerations of program relevance and public health need will be factored in at subsequent levels of review.

GEOGRAPHIC DISTRIBUTION OF SMALL BUSINESS INNOVATIVE RESEARCH (SBIR) GRANTS

Question. As one of the largest funders of SBIR grants, can you tell me what the NIH is doing to ensure that there is a more balanced portfolio and increased participation from States that have traditionally received a small number of SBIR grants?

Answer. The NIH prioritizes SBIR and Small Business Technology Transfer (STTR) outreach to States that historically have submitted a small number of SBIR applications and/or have lower success rates than the overall SBIR/STTR success rates. Each year, we hold an annual SBIR/STTR conference, this year on the NIH's campus in Maryland, but in past years in Ohio, Nebraska, Nevada, Georgia, and North Carolina. We also participate in direct one-on-one contact with current and potential applicants/grantees in several national, State, and regional SBIR events per year. Currently in fiscal year 2011, the NIH staff have already attended, presented, or participated on the SBIR program in Arizona, California, Florida, Kansas (via webinar), Kentucky, Maine, Maryland, Michigan, Missouri, Nebraska, New York, Virginia, Washington, DC, and Wisconsin. On the horizon is an event in Louisiana. These conferences attract attendees from across the country, and offers attendees an opportunity for one-on-one consultations with the NIH SBIR/STTR

program, review and grants management staff. In addition, there are a number of other conferences/meetings in which the NIH offers consultation to SBIR/STTR applicants and similar outreach is conducted by the individual NIH Institutes and Centers. In all venues, the NIH educates as many current and potential applicants/grantees as possible about the SBIR program.

In addition to these in-person opportunities, the NIH staff are available to provide assistance to all applicants from concept development through grant life-cycle by phone, email, webinars, and our Web sites. SBIR funding decisions ultimately are made at the NIH Institute level and are based on scientific merit (as determined by our two level peer-review system), available funding, and programmatic priority. Information about all NIH grant awards, including State location, can be accessed through our RePORTER Web site at http://projectreporter.nih.gov/reporter.cfm.

ANTIVIRAL DEVELOPMENT FOR FLU

Question. Discussions regarding the prevention of a flu pandemic frequently focus on vaccine development, but it is my understanding that effective management of influenza will require the continued development of new antiviral drugs. I was pleased to learn that the National Institute of Allergy and Infectious Diseases (NIAID) recently held a workshop on the influenza antiviral research pipeline. Are we making progress in the development of antiviral drugs for influenza and does the NIAID have plans for any new initiatives in this area?

Answer. In March 2011, the NIAID held the Influenza Antiviral Research Pipeline Workshop, which brought together stakeholders from a variety of sectors including academia, business, and government. Discussions focused on the state of influenza antiviral research and spanned all aspects from discovery to advanced clinical development. Workshop proceedings will be posted on the NIAID Web site in the near future.

Currently, there are four drugs licensed to treat influenza: oseltamivir (Tamiflu®), zanamivir (Relenza®), rimantadine (Flumadine®), and amantadine (Symmetrel®). Ongoing NIAID efforts in influenza drug development include combination studies with licensed and experimental drugs, studies of the safety of antiviral drugs in infants and children, studies of broad-spectrum antivirals, studies of antibody therapeutics, and evaluation of novel drug targets. For example, the NIAID also supports in vitro and in vivo antiviral screening and other preclinical services to identify new antiviral candidates. In fiscal year 2010, more than 100,000 compounds were evaluated by high-throughput screening assays against multiple influenza A strains, and several hundred compounds were tested for their efficacy against influenza in animal models. Also, the NIAID is supporting the preclinical and clinical development of a novel antiviral drug candidate; a safety study has been completed and a Phase II clinical trial is ongoing.

To meet the need for effective influenza management strategies, the NIAID will continue to support a robust influenza antiviral research portfolio, including discovery of drug targets, identification of compounds with novel mechanisms of action, and clinical studies to evaluate promising drug candidates.

STROKE IN WOMEN

Question. My State of Louisiana lays in the Stroke Belt, a group of Southeastern States where stroke death rates are the highest in our Nation. I am concerned about the seriousness of stroke, particularly among women who account for 61 percent of stroke fatalities. Please tell this subcommittee what studies the NIH is conducting to combat stroke in women, including prevention and rehabilitation efforts. In addition, please highlight planned activities in these areas.

Answer. The National Institute of Neurological Disorders and Stroke (NINDS) supports a large and broad portfolio of stroke research that includes numerous efforts to better understand and address the substantial burden that stroke places on women.

The NINDS supports multiple research studies on the physiological basis for gender-related differences in stroke risk and outcomes. One study funded by the NINDS and the National Heart, Lung, and Blood Institute (NHLBI) will follow a cohort of women to identify biological and physiological markers associated with ischemic stroke, and to establish which of those are influenced by sex hormones or menopausal status. This study will inform future development of gender-specific predictors for stroke risk. In another study, investigators will explore how biological functions programmed by sex-specific chromosomes are related to gender differences observed in cell death pathways activated by a stroke. The NINDS also funds a study to investigate the role of estrogen receptors in gender-related differences in incidence of stroke associated with cardiovascular surgical procedures.

The NINDS supports a number of surveillance studies that aim to illuminate differences in stroke knowledge, risk and outcomes among different sub-populations, including women, in order to inform development of tailored prevention intervention strategies. For example, the Reasons for Geographical and Racial Differences in Stroke Study (REGARDS) is a large cohort of more than 30,000 participants, more than half of whom are women. This comprehensive assessment of disparities in stroke risk and incidence is one of the largest longitudinal cohort studies of African Americans and the only national study of the epidemiology of cognitive change. The large representation of women in this important population-based study is significant as it allows for data analyses of gender-specific differences, as well as among different racial populations. For example, a recent publication from this study revealed that markers for inflammation led to more accurate vascular disease risk stratification, particularly in blacks and women, since they are at higher risk for increased levels of this marker. Studies from REGARDS will continue to improve our understanding of differences in stroke risk among a diverse U.S. population.

The NINDS supports a large number of clinical studies to improve acute management and long-term outcomes in stroke. All of the NIH-funded clinical trials are required to set and justify target enrollment by race, ethnicity, and gender and to report on enrollment progress. Approximately half of the participants in all of the NINDS-supported stroke clinical trials are women so that data can be analyzed for gender-specific differences. These trials are investigating new approaches to treat acute stroke and brain hemorrhage, to reduce brain damage due to stroke and to improve rehabilitation strategies, which will provide all patients, including women, and their physicians with more therapy options and a better chance of survival and recovery after a stroke.

The NINDS is embarking on a new stroke planning effort in 2011 to update research progress and activities in response to prior research recommendations, and to identify a specific set of high priority areas for advancing stroke research over the next 5–10 years. The planning effort will specifically address stroke prevention, treatment, and recovery in subpopulations, with a special emphasis on women and gender differences. Recommendations from this planning effort will inform future NINDS research investment and activities related to stroke in women.

NCI PRIORITIES

Question. Dr. Varmus, you have stated a desire for the NCI to continue to fund as many grants as in previous years, even if this means cuts in other areas, such as the Cancer Center program. Could you tell us a bit more about your plans and priorities for the institute and possible changes on the horizon?

Answer. Cancer is a complex disease requiring many approaches to make progress. It is important to fund as many meritorious grants as we possibly can within the resources we are given, because individual grants allow us to pursue new ideas effectively. We will be finding savings across the Institute by taking money away from routine administrative expenses, making cuts to the intramural and Cancer Centers programs, and by conducting reviews of large programs and cutting where possible. This will allow us to achieve acceptable grant levels and to protect certain imperatives.

In addition, realignment of the clinical trial cooperative groups, as recommended by the Institute of Medicine report in 2010, will improve the efficiency of the overall system and enable the cooperative groups to conduct state of the art oncology research more consistently. Funding for this effort is a priority for the NCI. A second imperative is maintaining the pace of work on cancer genomics. The Cancer Genome Atlas (TCGA), a project undertaken by the National Cancer Institute and the National Human Genome Research Institute to gain an understanding of the molecular basis of cancer, has already produced results in brain cancer and ovarian cancer. The rate of discovery is dependent on the level of funding. Therefore, we place a high priority on protecting funding for this project and other meritorious efforts in cancer genomics. As TCGA is expanded to include many cancer types, the ultimate goal is to ensure that genetic information is applied to prevention, diagnosis, and treatment of cancer in clinical practice.

QUESTIONS SUBMITTED BY SENATOR RICHARD J. DURBIN

ECONOMIC BENEFITS OF BIOMEDICAL RESEARCH

Question. According to a recent Families USA report, every $1 investment in medical research stimulates $2.43 in business activity—such as support staff, supplies, food services, and building development. Are you aware of other studies that at-

tempt to quantify the local impact of the Federal investment in medical research? Are there any efforts underway at the NIH to capture the return-on-investment that taxpayers receive as a result of the Federal commitment to research?

Answer. To the best of our knowledge, there are two comprehensive published studies that attempt a quantification of the economic effects of the NIH spending at the State level, both supported by research advocacy groups. Both studies rely on the Regional Input-Output Modeling System (RIMS II), developed by the Bureau of Economic Analysis at the Department of Commerce. RIMS II measures, at a State level, the economic multiplier effect generated by local demand. National aggregate averages are extrapolated from State data.

The first report was released in June 2008 by Families USA and was titled "In your own backyard."[1] The report found, among other things, that in fiscal year 2007, the NIH funding supported more than 350,000 jobs that generated wages in excess of $18 billion in the 50 States. The average wage for these jobs was $52,000. It also found that $1 spent by the NIH funding generates $2.21 of business activity at the State level. This $2.21 figure is an average; individual States may vary (e.g., in Illinois, the figure is $2.43.)

More recently, in May 2011, the organization "United for Medical Research" released a report, titled: "An Economic Engine. NIH Research, Employment and the Future of the Medical Innovation Sector."[2] The report draws three conclusions: the NIH extramural research is an important source of income and employment around the country; the complementary relationship between public NIH investment and private industry development is critical to the health and well-being of our Nation; and the U.S. medical innovation sector is facing increasing challenges in maintaining America's competitiveness and position as the world leader in medical research. The report found that in fiscal year 2010, the NIH directly and indirectly supported nearly 488,000 jobs and produced $68 billion in new economic activity and that $1 of the NIH investments generated, on average, $2.60 of business activity, at the national level.

The NIH has worked closely with experts in the field of labor and health economics and R&D evaluation on several projects. One of the studies found that a one dollar increase in the NIH funding leverages an additional 35 cents in funding from non-Federal sources.[3]

Another study determined that 33 percent of all drugs approved by FDA and 58 percent of approved priority review new molecular entities (which tend to be the most innovative drugs) cite an NIH-funded publication or an NIH patent.[4]

Another study showed that multinational companies in the pharmaceutical sector tend to locate their R&D facilities next to hubs of skilled workers. This finding underscores the importance of the NIH investments in sustaining a strong research infrastructure system in the United States and avoiding the loss of private sector investments in R&D that could be moved abroad.[5]

Another study, Economic Impact of the Human Genome Project (http://www.battelle.org/publications/humangenomeproject.pdf), which was commissioned by the Life Technologies Foundation and prepared by the Battelle Technology Practice Foundation, assessed the benefits of the Federal investment of the Human Genome Project (HGP). Finding that the benefits are widespread and increasing over time, the report cites among other factors, the production of 3.8 million job-years of employment (one job-year for each $1,000 invested) and the generation of personal income (wages and benefits) exceeding $244 billion over the last 7 years, an average of $63,700 per job-year.

With regard to whether there are other efforts underway at the NIH to capture the return-on-investment that taxpayers receive as a result of the Federal commit-

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[1] FamiliesUSA. (2008). *In Your Own Backyard: How NIH Funding Helps Your State's Economy*. Washington, DC. Retrieved December, 2008 from http://www.familiesusa.org/issues/global-health/publications/in-your-own-backyard.html.

[2] Ehrlich, E. (2011). United for Medical Research from http://www.unitedformedicalresearch.com/wp-content/uploads/2011/05/UMR__Economic-Engine.pdf.

[3] Blume-Kohut, M., Kumar, K. B., & Sood, N. (2008). *The Impact of Federal Funding on University R&D*. Retrieved November 7, 2009 from http://www.rand.org/labor/seminars/brown__bag/pdfs/2008__sood.pdf

[4] Lichtenberg, F. R., & Sampat, B. (2011). What are the respective roles of the public and private sectors in pharmaceutical innovation? *Health Affairs, 30*(2), 332–338.

[5] Thursby, J. G., & Thursby, M. C. (2009). *Is the US a Target of R&D Globalization? Location, Type and Purpose of Biomedical Industry R&D in New Locations*: NBER. Report prepared for the NIH Office of Science Policy Analysis.

ment to research, the NIH is also participating in the STAR METRICS Project.[6] [7] STAR METRICS is a collaboration between Federal science agencies and research institutions to document how Federal science investments support knowledge creation, economic growth, workforce development and a broad range of societal outcomes. The program's goal is to build a data infrastructure that will bring together inputs, outputs, and outcomes from a variety of sources in as open a fashion as possible.

STAR METRICS has two levels and the NIH participates in both. Level I documents the initial effect of S&T investments on employment using administrative records from research institutions. This approach goes beyond the RIMSII model, capturing the actual, rather than estimated, number of jobs supported. Level II builds on Level I by connecting sources of funding, recipients of funding, interactions among scientists (in both the public and private sector) and the products of research over time ranging from the most proximal (such as meeting presentations and publications) to more distal (such as the development of a new drug).

CONGENITAL HEART DISEASE (CHD)

Question. Congenital Heart Disease (CHD) is one of the most prevalent birth defects in the United States and a leading cause of birth defect-associated infant mortality. Due to medical advancements more individuals with congenital heart defects are living into adulthood. Please provide an update of research within the NIH, particularly the National Heart, Lung, and Blood Institute (NHLBI) related to congenital heart defects across the life-span. The healthcare reform law included a provision, which I authored, that authorizes the CDC to track the epidemiology of congenital heart disease, with an emphasis on adults with CHD and expanding surveillance. If adequately funded, how could a population-surveillance system for adults with CHD support the NIH's ability to investigate CHD across the life-course and across subgroups?

Answer. The NIH supports research on CHD across the lifespan. For example, as part of its Pediatric Heart Network, the NHLBI is following participants in an earlier study of the Fontan surgical procedure to assess functional health status, neurocognitive performance, and transitions from pediatric care to adult care for CHD. Through its Bench-to-Bassinet program, the NHLBI is examining the genetic causes of CHD and the effects of genetic variation on the long-term clinical outcomes of affected children as they grow older. The NHLBI also funds a research partnership between the Adult Congenital Heart Association and the Alliance of Adult Research in Congenital Cardiology that seeks to improve care delivery and long-term outcomes for adults with CHD and also to inform research designs for studies in adults. Through its Pumps for Kids, Infants, and Neonates (PumpKIN) program the NHLBI supports development of pediatric devices for congenital heart disease. In addition, an investigator-initiated project seeks to develop a blood pump for patients who have undergone the Fontan surgery. Patients who have had the surgery experience significant morbidity due to diminished blood flow, especially as they grow into adulthood, and a device to assist blood flow could dramatically improve care.

An adequately funded population-surveillance system for adults with CHD could facilitate the NIH research. The surveillance data would help the NIH ensure that its research efforts address the full range of heart conditions, risk factors, and complications across the lifespan; provide the potential to link genetic and other biological information; permit monitoring of the effectiveness of new preventive and therapeutic strategies; and identify a potential pool of patients who could benefit from participation in various research activities. However, funding was not provided for this provision in the Affordable Care Act, and no funds have been requested within the budget for the Centers for Disease Control and Prevention to implement it.

THE CANCER GENOME ATLAS

Question. The National Cancer Institute is making tremendous progress with the Cancer Genome Atlas (TCGA) in sequencing cancer genomes and then using scientific discoveries to further specific fields of cancer research. What is the status of the TCGA gastric cancer project? Specifically, the pilot project to utilize contiguous biopsies to sequence the genome for the diffuse gastric cancer subtype? How will the NCI utilize these groundbreaking discoveries to further the field of gastric

[6] https://www.starmetrics.nih.gov/.

[7] Lane, J., & Bertuzzi, S. (2011). Research funding. Measuring the results of science investments. *Science, 331*(6018), 678–680.

cancer research? What other initiatives and steps is the NCI taking to investigate gastric cancer?

Answer. TCGA staff and extramural researchers have been steadily working on identifying, collecting, and assessing the quality of gastric cancer biospecimens for inclusion into TCGA's genotyping and molecular characterization pipeline. However, due to the difficulty in obtaining qualifying biospecimens from patients with diffuse gastric cancer, the NCI began to explore a pilot project for collection of diffuse gastric cancer biospecimens. The challenges involved in this pilot project of multiple gastric biopsies was discussed in detail in May 2011 when the NCI hosted a workshop on gastric and esophageal cancer, bringing together a group of international experts to explore and discuss the basic biology, epidemiology, and clinical research aspects of these cancers across the world. There was tremendous interest in the pilot study from the gastric cancer researchers, and in June 2011 the NCI approved TCGA to proceed with the pilot study to collect biospecimens on a small number of diffuse gastric cancers from the United States. The extent of the project will depend on the cost per case and the number of centers willing to participate. We are hopeful that analysis of these biospecimens will yield valuable information that will stimulate novel research approaches for this challenging disease and will lead to advances in the prevention, diagnosis, and treatment of diffuse gastric cancer.

In addition to the TCGA-related efforts, an NCI Genome-Wide Association Study (GWAS) on gastric adenocarcinoma and esophageal squamous cell carcinoma has already revealed a common cancer susceptibility region at PLCE1, and the NCI is funding follow-up mechanistic studies on the effect of the gene variations in this location. A second GWAS will be conducted in a mostly Caucasian cohort to provide further clues about susceptibility regions and whether they differ between populations that experience different rates of gastric cancer. The NCI also funds broad based research at four Gastrointestinal Cancer Specialized Programs of Research Excellence (SPOREs), two of which include a focus on esophageal cancers.

EOSINOPHILIC-ASSOCIATED DISORDERS RESEARCH

Question. Eosinophilic-associated disorders were identified in the last decade. Consequently many people go undiagnosed for years, due to lack of information and awareness about these diseases. Please describe current efforts at the NIH, particularly the National Institute for Allergy and Infectious Diseases (NIAID) to investigate eosinophilic-associated disorders. Last year, the Senate budget included report language urging the NIAID to convene a working group to develop a research agenda aimed at improving the diagnosis and treatment of eosinophilic-associated disorders. What strides are the NIH and the NIAID making to develop a research agenda focused on these conditions?

Answer. As the lead institute at the NIH responsible for research on immunologic and allergic disorders, the NIAID is committed to research to better understand the mechanisms that mediate tissue injury when eosinophils accumulate, including eosinophilic gastrointestinal disorders, a group of recently recognized allergic diseases associated with the production of IgE antibodies and other immune responses to food. The NIAID works closely with other NIH Institutes and Centers supporting research on eosinophilic disorders. Although these collaborations and communications do not occur through a formal working group or a predetermined research agenda, they have led to jointly sponsored workshops and research initiatives on eosinophilic disorders. In fiscal year 2012, the NIH, with the NIAID as the lead, will establish a working group with participation by relevant NIH Institutes and Centers, to develop a trans-NIH strategy to improve the diagnosis and treatment of eosinophilic disorders.

As part of its overall research agenda on immunologic and allergic diseases, the NIAID pursues research on eosinophilic disorders through a variety of efforts and collaborations. For example, the Consortium of Food Allergy Research (CoFAR), cofunded with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and renewed in fiscal year 2010, develops new approaches to treat and prevent food allergy. A new CoFAR project is examining the genetic aspects of eosinophilic esophagitis. The NIAID Asthma and Allergic Diseases Cooperative Research Centers (AADCRC) support basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, including food allergy and anaphylaxis. Many of these disorders are associated with eosinophilia. In addition, the NIAID-supported investigators are conducting a pilot clinical trial to determine the efficacy of swallowed glucocorticoids for the treatment of eosinophilic esophagitis, and developing novel noninvasive diagnostic tools for eosinophilic gastrointestinal diseases to reduce the number of endoscopies and biopsies that are currently performed. Also, on behalf of more than 30 professional orga-

nizations, Federal agencies, and patient advocacy groups, including the American Partnership for Eosinophilic Disorders, the NIAID coordinated the development of Guidelines for the Diagnosis and Treatment of Food Allergy in the United States. This document includes clinical practice guidelines for the diagnosis and management of eosinophilic esophagitis associated with food allergy. The guidelines were published in the December 2010 issue of the Journal of Allergy and Clinical Immunology and can be accessed at: http://www.ncbi.nlm.nih.gov/pubmed/21134576.

The NIAID will continue its commitment to research and trans-NIH research collaborations on eosinophilic disorders to understand the mechanisms that mediate tissue injury when eosinophils accumulate. As part of this effort, in fiscal year 2011, the NIAID will recompete the AADCRC program.

QUESTIONS SUBMITTED BY SENATOR MARK PRYOR

EXTRAMURAL RESEARCH BUDGET

Question. What percentage of the NIH's funding leaves the greater Washington, DC area and goes to medical research in States and local communities?

Answer. In fiscal year 2010, the NIH awarded 82 percent ($25.6 billion of $31.2 billion) of its budget to more than 3,000 institutions and organizations across the United States, as well as several other countries throughout the world, 71 percent ($22.1 billion) in grants and 11 percent ($3.5 billion) in research and development contracts. The percentage of the fiscal year 2011 budget devoted to extramural research is also expected to be approximately 82 percent. An overview of the NIH funding allocations by Institute and Center in fiscal year 2010, fiscal year 2011, and the fiscal year 2012 budget is available at: http://officeofbudget.od.nih.gov/pdfs/FY12/COPY%20of%20NIH%20BIB%20Chapter%202-9-11-%20FINAL.PDF.

PERSONALIZED MEDICINE AS A PRIORITY

Question. As you well know, we are currently in a very difficult economic time. The Congress is in the process of making many decisions related to addressing the Nation's budget problems. We are considering many ways to control our costs and minimize additional debt, but at the same time, we have to prioritize and ensure that important programs are adequately funded. Having said that, do you believe advances in personalized medicine could be threatened should the Congress enact cuts to the NIH's budget?

Answer. Through the application of genomic research and high-throughput technologies, breakthroughs in our understanding of the causes of many diseases and the identification of new targets and pathways for the development of new therapeutics are within reach. For example, a decade ago, diagnosis of cancer was based on the organ involved and treatment depended on broadly aimed therapies that often greatly diminished a patient's quality of life. Today, research in cancer biology is moving treatment toward more effective and less toxic therapies tailored to the genetic profile of each patient's cancer. The NIH research is also identifying genetic markers that can predict whether an individual will respond well to a particular medication or will be at risk of having an adverse reaction. The NIH-funded researchers are also uncovering information about genes and the environment that will help point the way toward more personalized, targeted treatments for other diseases. The new National Center for Advancing Translational Sciences (NCATS) will provide the infrastructure and technologies to bring these critical basic discoveries to fruition through new diagnostics and therapeutics. Significant budget cuts could threaten the NIH's ability to continue to support these advances. However, the specific research areas that would be affected in the event that budget cuts materialize cannot be determined now since the NIH would need to re-evaluate its research priorities.

QUESTIONS SUBMITTED BY SENATOR RICHARD C. SHELBY

REORGANIZATION OF NCRR PROGRAMS

Question. There remain concerns within the Congress and the research community with the decision to eliminate the National Center for Research Resources (NCRR). Can you explain the rationale behind this decision and where the National Center for Research Resources' assets will be moved?

Answer. With the decision to move the Clinical And Translational Science Awards (CTSAs) into the proposed National Center for Advancing Translational Sciences (NCATS), it was necessary to consider the impact of its transfer on NCRR and

whether there were long-range benefits that could be achieved by relocating its remaining programs within other NIH components. A task force was formed to determine if the remaining programs should be kept in a separate organization or if there was an opportunity for greater scientific synergies by moving the remaining programs to other NIH components. The task force was guided by the following considerations and principles in developing its recommendations:

—The scientific synergies that could be achieved by placing the NCRR program in adjacency to existing (or in the case of the NCATS, proposed) portfolio/mission of the recipient IC versus the existing synergies among the NCRR programs.

—The "goodness of fit" for the NCRR program within the recipient IC versus the negative effects of adding a program that is disproportionately large and/or not well aligned to the recipient IC's current (or in the case of the NCATS, proposed) mission.

—The level of disruption to long-standing NCRR programs led by dedicated NCRR staff versus the disruptive innovation from reassigning NCRR staff to enable interactions with new colleagues and/or new programs.

The Task Force agreed with the SMRB recommendation that the CTSAs be placed in the proposed Center. The Task Force then determined that the greatest scientific synergies could be achieved by placement of the remaining programs to other components of the NIH. The Research Centers in Minority Institutions (RCMI) program was proposed for placement in the National Institute for Minority Health and Health Disparities; the Institutional Development Award (IDeA) program was proposed for placement in the National Institute for General Medical Sciences (NIGMS); the Imaging and Point-of-Care Biomedical Technology Research Center (BTRC) grants, and Biomedical Imaging, and Point-of-Care research grants for Technology Research and Development were proposed for placement in the National Institute of Biomedical Imaging and Bioengineering; the remaining BTRCs and all other research grants for Technology Research and Development, and the BIRN network grants were proposed for placement in the NIGMS; the Gene Vector Repository was proposed for placement in the National Heart, Lung, and Blood Institute; and the Comparative Medicine Program, Extramural Construction and Animal Facilities Improvement, Shared and High-End Instrumentation, and Science Education Partnership Awards (SEPA) were proposed for placement in a new Office of Research Infrastructure Programs in the Division of Program Coordination, Planning, and Strategic Initiatives in the Office of the Director.

The Task Force implemented a transparent process to collect and consider input from a wide range of internal and external experts, as well as stakeholders ranging from members of the public to members of the extramural research community. As the deliberations progressed, the NIH made information available to the public through a feedback page available on its website. The final Task Force recommendations were accepted by the NIH Director and the Secretary, and transmitted to the House and Senate Appropriations Committees in a letter dated June 6, 2011. Additional budget details on the reorganization were provided to the subcommittees on June 23, 2011.

BASIC AND APPLIED RESEARCH BALANCE

Question. How do you balance the NIH's goals in research aimed at knowledge generation (basic research) versus translation of that knowledge toward cures and improving human health (applied research)? Will the NCATS help to achieve a better balance?

Answer. Basic research advances knowledge of fundamental biological processes and elucidates the molecular underpinnings of human health and disease. Basic research makes it possible to understand the causes of disease onset and progression and opens up new avenues for developing new and improved diagnostics, therapeutics, and preventive strategies. Realizing the benefits of fundamental biomedical discoveries depends on the translation of that knowledge into strategies and products that treat disease and sustain and improve health. It is important to understand that "basic" and "translational" research are inherently interrelated and comprise a cyclical process. There are important feedback loops between the fields so that advances in one ultimately yield new avenues for scientific inquiry and discovery in the other. Breakthroughs in our understanding of therapeutic targets and pathways also stimulate new avenues for basic scientific inquiry. By studying the process of developing new therapeutics and diagnostics in an open access environment, the NCATS will ultimately catalyze the cycle of discovery in order to advance public health.

From a funding standpoint, 54 percent of the NIH budget is devoted to basic research and 46 percent to applied research, a ratio that has not varied appreciably for decades. The NIH does not intend to shift resources currently devoted to basic research to fund translational research. The NCATS will be formed through the realignment of existing translational research programs and, as such, will not affect the balance of basic and applied research supported by the NIH. It will certainly use discoveries made through basic research to advance its work while also providing important insights for basic scientists to pursue.

MOLECULAR LIBRARIES PROGRAM AS PART OF THE NCATS

Question. Dr. Collins, can you discuss the NIH Roadmap Molecular Libraries Probe Production Center Network component of the NCATS. I understand that this national network of centers provides for the first time a sophisticated infrastructure for drug discovery to the academic and nonprofit research community. What role will this program play in the NCATS going forward?

Answer. The NIH Molecular Libraries Probe Production Center Network (MLPCN), a component of the NIH Molecular Libraries Program (MLP), is a collaborative research network that enables the generation of effective and useful small molecule chemical probes for the entire biomedical research community. Through support from the NIH Common Fund, the MLPCN offers biomedical researchers access to large-scale screening capacity, along with medicinal chemistry and informatics needed to convert the large number of active compounds identified by high-throughput screening into useful probes for studying the functions of genes, cells, and biochemical pathways. Traditionally, these resources and associated expertise have resided exclusively within the private sector.

By providing early stage chemical compounds to the biomedical research community, the NIH anticipates that the components of the MLP can further enable researchers in both the public and private sectors to validate new drug targets, which could then move into the drug-development pipeline. This is particularly true for rare diseases, which may not be attractive for development by the private sector. For this reason, several components of the Common Fund's MLP are transitioning to be funded and managed through the NCATS. These include the Small Molecule Repository, Cheminformatics/PubChem, and the NIH Chemical Genomics Center (NCGC), an intramural high-throughput screening Center. The Common Fund will continue to provide support for the Chemical Diversity technology development program, the Imaging Probe Database, and the extramural Specialized Screening Centers.

THE NIH, ACADEMIA, AND INDUSTY RELATIONSHIP

Question. Much of the country's translational research has been within the pharmaceutical industry and the biotechnology community. Can you elaborate on the relationship between the NCATS and these entities? Is there a change in roles in academia and the commercial world?

Answer. The process of translating fundamental knowledge into new or better clinical applications is an exceedingly complex, costly, and risk-laden endeavor. Moreover, the average length of time from target discovery to FDA approval of a new drug is 14 years and the failure rate exceeds 95 percent, i.e., fewer than one out of twenty projects that enter the drug development pipeline will result in a new FDA-approved product. At the same time, recent progress in genomics, biotechnology, and other fields of biomedical research has advanced the potential for development of new diagnostics and treatments for a wide range of diseases, opening a wide door of opportunity in translational science.

There is a growing recognition on the part of all those involved in translational medicine that the current model for development is not sustainable and that novel partnerships and collaborations are critical to progress. The NIH is uniquely positioned to help bring about the changes by complementing the translational efforts of each sector. To achieve this goal, the NCATS will bring together resources and skilled scientists to study the steps in the therapeutics development and implementation process, consult with experts in academia and the biotechnology and pharmaceutical industries to identify bottlenecks in the processes that are amenable to reengineering, and develop new technologies and innovative methods for streamlining the processes. Cross-sector collaborations will be an essential part of how the NCATS operates.

FUTURE OF R01 FUNDS

Question. Will the establishment of the NCATS result in the loss of R01 funds?

Answer. No. Funds for research project grants will not be affected by the establishment of the NCATS, which is being created by realigning several existing NIH translational research programs. The NCATS will stimulate the pursuit of new avenues of scientific inquiry by facilitating and complementing translational research efforts carried out elsewhere at the NIH. It will not diminish the agency's commitment to basic science. Moreover, the NIH requested an additional $100 million for the operation of the Cures Acceleration Network within the NCATS, some of which would be used for research project grants.

PROCESS INNOVATION AND THE NCATS

Question. Dr. Collins, you have stated that "process innovation" is an important component of the NCATS. Can you explain what this is and why it is important? How will process innovation relate to individual disease-focused projects the NCATS may do?

Answer. Process innovation involves studying the therapeutics development process with the goal of developing new approaches and technologies that can strengthen and streamline the development pipeline itself. By approaching the development pipeline as a scientific question, the NCATS will identify bottlenecks in the processes that are amenable to re-engineering and develop new technologies and innovative methods for improving and advancing the discovery, testing, and implementation of new therapeutics. Among the specific developmental steps that may be addressed are target validation, preclinical toxicology testing, clinical trial design, and drug rescue and repurposing. In order to evaluate these innovations and new approaches, the NCATS will undertake targeted therapeutics development and implementation projects that may have relevance to individual disease-focused projects.

REORGANIZATION OF THE COMPARATIVE MEDICINE PROGRAM

Question. I have heard from several elite schools of medicine, including Stanford, MIT, UAB, and Auburn that splitting the components of the National Center for Research Resources' Comparative Medicine program into different administrative entities would have a negative impact on the NIH's critical scientific infrastructure. Dr. Collins, can you address their concerns and share with the subcommittee a solution to ensure components of the Comparative Medicine program remains intact and together within the new organizational structure?

Answer. Initially, we had considered a number of options with regard to the placement of the programs within the Division of Comparative Medicine, including dividing them among relevant institutes and centers. However, following extensive consultation with multiple stakeholders, including grantees, professional organizations, and the public, we concluded that it was important to keep the programs within the Division of Comparative Medicine together because of their intrinsic uniqueness and synergies. As such, the Division of Comparative Medicine is to be transferred in its entirety to the new Office of Research Infrastructure Programs in the Division of Program Coordination, Planning, and Strategic Initiatives within the Office of the Director.

BROADENING THE IDeA PROGRAM

Question. The National Center for Research Resources' Institutional Development Award program broadens the geographic distribution of the NIH funding for biomedical and behavioral research. It is my understanding that the goal of the program is to expand biomedical research capabilities to areas that currently lack it through research and infrastructure funding opportunities and faculty development.

In its entirety, Alabama is a significant recipient of the NIH funding, mainly due to the research funding received by its two medical schools. While they provide great benefit to my State and Nation through medical breakthroughs and economic investment, I am concerned that their success puts other Alabama institutions at a competitive disadvantage with similar institutions in IDeA-eligible States.

Has the NIH considered ways to include institutions in this program from non-IDeA eligible States? If not, are there other avenues within the NIH that could serve a similar role to IDeA for schools in States where one or two universities' significant NIH funding limits their access to preliminary support?

Answer. The current authorization language for the IDeA program limits participation in the program to institutions located in States with low aggregate success rates for obtaining NIH funding or States that do not attain a particular level of support from the NIH. It does not allow for participation by institutions from States with high success rates or States that receive substantial support from the NIH. In 2008, a working group of NCRR's advisory council, which was formed to review the eligibility criteria for the IDeA program, explored whether it would be possible to

base eligibility on institutional or regional success rates. The group was unable to identify an alterative approach that met the intent of the law.

In States that are not eligible for IDeA, institutions with limited NIH funding are encouraged to participate in are encouraged to apply for Academic Research Enhancement Awards (AREA) http://grants.nih.gov/grants/funding/area.htm which supports projects in the biomedical and behavioral sciences conducted by faculty and students in health professional schools, and other academic components that have not been major recipients of the NIH research grant funds. In addition, institutions could try to increase the NIH grant support by partnering with institutions with more significant NIH funding. Such partnerships can help build the experience and capacity necessary to successfully compete independently for the NIH funding in the future.

GULF OIL SPILL HEALTH EFFECTS RESEARCH

Question. According to the NIH press statement, of the 40 known oil spills in the past 50 years, the health effects have been studied from only eight of those spills. I am pleased to see the NIH will begin to review health effects of people impacted by the Deepwater Horizon oil spill in the Gulf of Mexico. It is critical to understand how being exposed to the oil and the dispersants may have affected the health of cleanup workers and volunteers. Could you discuss how this study will be conducted and what you are hoping the GULF Study will help us learn?

Answer. The Gulf Long-term Follow-up Study (GuLF STUDY) will help determine if oil spills and exposure to crude oil and dispersants affect physical and mental health. The National Institute of Environmental Health Sciences (NIEHS) is leading this research. A major facet of the study is to compare the health of clean-up workers and others who did not do clean-up work to learn if health problems are more common in workers. GuLF STUDY researchers will also examine other factors that may explain why some people are more likely than others to get sick and how stress affects health. The NIEHS will send approximately 90,000 invitation letters to people to be included in the study. Of this group it is expected that 55,000 will be enrolled and complete telephone interviews. Participants will be interviewed about their oil-spill clean-up jobs, demographic and socioeconomic factors, occupation and health histories, and current health, including stress and mental health. About half of the cohort will be asked to complete a brief clinical examination in their home. The home exam will include additional health questionnaires and collection of biological samples, such as blood and urine, and environmental samples, e.g., house dust. The exam will include basic clinical measurements such as height, weight, blood pressure and tests of lung function. The home exams will largely target workers residing in the four most affected Gulf States—Louisiana, Mississippi, Alabama, and Florida). All cohort members will be followed for development of a range of health outcomes. Follow-up of the entire cohort is initially planned for 10 years, with extended follow-up possible depending upon scientific and public health needs and the availability of funds.

GuLF STUDY researchers are hoping to learn if exposure to constituents of oil, dispersants, and oil-dispersant mixtures during oil spill clean-up is associated with adverse health effects, particularly respiratory, neurological, hematologic, and mental health. In addition, this research is anticipated to reveal biomarkers of potentially adverse biologic effects associated with oil spill-related exposures. Results of the study will provide further insight into how stress and job loss can affect health, including mental health. Overall, the findings may influence long-term public health responses in Gulf communities or responses to other oil spills in the future.

CYSTIC FIBROSIS RESEARCH

Question. In February, the NIH announced that federally funded research led to the development of a very promising therapy that targets the genetic defect that causes Cystic Fibrosis. How will the fiscal year 2012 NIH budget request support additional research on Cystic Fibrosis?

Answer. Cystic fibrosis (CF) research continues to be a high-priority area. The NIH estimates the fiscal year 2012 budget request would support about $88 million for CF research, ranging from basic science studies through clinical trials. The results of our prior investments have provided enormous benefit to affected patients. Whereas years of life expectancy for children born with CF could once be counted on the fingers of one hand, today average survival is 37 years and some patients live into their 50s and beyond. Evidence-based improvements in nutrition, infection control, and symptom management have substantially enhanced the quality of life of affected persons. Newborn screening for cystic fibrosis, now universal in the United States, is not only enabling early interventions but also providing unprece-

dented opportunities for effective translation of new research advances into clinical practice.

With improved understanding of CF biology, advances in experimental methods, and growing availability of new targets for interventions, we anticipate that CF research will be especially productive in the next few years and that tangible improvement in patient outcomes will follow. The recent NHLBI workshop "Future Research Directions in the Pathogenesis, Treatment, and Prevention of Early Cystic Fibrosis Lung Disease" identified a number of important topics for future research that can be pursued as funding permits. They include work with animal models to understand how early lung disease develops, identification of genetic and environmental factors that modify the manifestations and course of CF, examination of the role of mutant CFTR (the defective gene product in CF) in airway growth and development, and exploration of the mechanisms that underlie CF-related diabetes and liver disease. The NIH will continue to adjust its research portfolio in CF to ensure that needs and opportunities for advancing research are addressed.

THE NIH–FDA COLLABORATIONS

Question. The development of treatments for diseases, especially rare diseases, is an expensive and lengthy process. A very small percentage of potential medicines even make it to the clinical research stage, let alone to FDA review. What can the NIH do to reduce some of the regulatory requirements that both slow the pace and increase the cost of medical research, but that add little meaningful accountability?

Answer. The NIH is taking a multi-pronged approach to promote efforts to address unnecessary, inconsistent, and duplicative regulatory requirements. We work closely with FDA and the Office for Human Research Protections to enhance the consistency of regulations governing clinical research. Through the NIH–FDA Joint Leadership Council, we are working with FDA to help ensure that regulatory considerations are a component of scientific research at all phases of development and they are informed by the most current science and technologies. Such efficiencies along with targeted support for the development of novel technologies including new and improved preclinical toxicology approaches for testing safety should quicken the pace and reduce the human-related costs of medical research. The proposed National Center for Advancing Translational Sciences will be focused on studying diagnostics and therapeutics development, testing, and implementation; identifying bottlenecks amenable to re-engineering; and formulating innovative methods to streamline the process.

CLINICAL TRIAL PROCESS

Question. One of the priorities of the Joint NIH–FDA Leadership Council is to optimize and maximize data from clinical trials. Would you consider working with the FDA to grant greater flexibility regarding the approval of orphan drug therapies on the basis of a single, well-designed trial?

Answer. The FDA and the NIH have complementary roles and functions—the NIH supports and conducts biomedical and behavioral research and the FDA ensures the safety and effectiveness of medical and other products. The NIH does not share regulatory authorities with the FDA, i.e., we do not make decisions about regulatory pathways or the approvability of investigational products. However, we certainly have common goals and are working closely in a number of ways to address issues related to therapeutics development and regulatory science. As you noted, the agencies are working at the leadership level through the NIH–FDA Leadership Council, formed in 2010, to help ensure that regulatory considerations form an integral component of biomedical research planning and that the latest science is integrated into the regulatory review process. The challenges associated with the development and review of therapies for rare and neglected diseases, such as the availability of alternative regulatory pathways for trials of rare diseases and the level of scientific evidence needed for approval of a new orphan therapy, are among the specific topics of mutual interest. We also collaborate closely on issues associated with the development of new cancer diagnostics and therapeutics through an interagency oncology task force and, in accord with the provisions the Best Pharmaceuticals for Children Act, to advance the development of preclinical and clinical methodologies that provide optimal approaches for treating diseases in childhood. We believe all of these efforts can go a long way toward achieving our common goal of advancing public health by promoting the translation of basic and clinical research findings into medical products and therapies.

QUESTIONS SUBMITTED BY SENATOR THAD COCHRAN

TRANSFER OF THE IDeA PROGRAM TO THE NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES (NIGMS)

Question. The NIH has proposed the elimination of the National Center for Research Resources (NCRR). I am particularly concerned that this elimination will affect the Institutional Development Award (IDeA), which has benefitted my home State of Mississippi. Under the proposal, the IDeA program will be moved to the National Institute of General Medical Sciences. There have been concerns expressed that the IDeA program should not be placed in an Institute with a defined constituency. Dr. Collins, can you elaborate on the decision process for moving IDeA to the National Institute of General Medical Sciences? Why do you think this is the best Institute to house the IDeA program?

Answer. The IDeA program fosters research and enhances the competitiveness of investigators at institutions located in States in which the aggregate success rate for applications to the NIH has historically been low. By its nature, the IDeA program extends beyond traditional capacity building in supporting research projects that are designed to strengthen future investigator-initiated research applications, most of which are aimed at addressing basic science questions. The National Institute of General Medical Sciences (NIGMS) has a basic science mission as well as a longstanding focus on institutional capacity building and career development. Given these synergies, the NIGMS was determined to be the optimal new home for the IDeA program. The NIH reached this conclusion based on a careful analysis of existing NCRR programs as well as extensive consultation with stakeholders across the scientific community and input from the NIH Institutes and Centers, including NCRR leadership and staff.

JACKSON HEART STUDY IMPACTS

Question. African Americans are more likely to be diagnosed with coronary heart disease, and they are more likely to die from heart disease. Due to this greater prevalence, the Jackson Heart Study is exploring the reasons for this disparity and uncovering new approaches to reduce it. Can you discuss the impacts this study will have?

Answer. The goals of the Jackson Heart Study (JHS) are to determine the roles of established risk factors such as obesity, dyslipidemia, and high blood pressure in the development and progression of cardiovascular disease (CVD) and to identify factors related to the emergence of such risk factors. Moreover, the study seeks to shed light on the contributions of sociocultural factors (e.g., stress, racism, discrimination, and coping strategies) and familial/hereditary factors, genetic variants, and gene—environment interactions to the development of CVD and its risk factors. Based on our experience with other NHLBI-funded epidemiological studies of CVD such as the Framingham Heart study, we expect the JHS to provide important information that will help researchers to generate new hypotheses and design studies to test interventions to prevent CVD. Ultimately, we expect the results of the JHS to benefit not only Mississippians but also African Americans beyond the participants in the study.

The JHS also seeks to build research capabilities in minority institutions, address the critical shortage of minority investigators in epidemiology and prevention, and reduce barriers to dissemination and use of health information in a minority population. The JHS educational and community outreach components are very strong; consequently, the research findings will be efficiently disseminated among participants. The JHS training component continues to provide outstanding opportunities to inspire, motivate, and educate students to become research leaders and to study and disseminate important findings on prevention of CHD.

STAFFING THE JACKSON HEART STUDY

Question. The Jackson Heart Study is the largest epidemiologic investigation of Cardiovascular Disease among African Americans in the United States. The National Heart Lung and Blood Institute opened a field office in Jackson to provide scientific investigators and support staff to the study. It is my understanding that this one-person office will soon have no staff due to the staffer leaving Jackson. I am concerned that the National Heart Lung and Blood Institute may not fill the position quickly which would result in an adverse effect on the Jackson Heart Study. It is vital that the field site maintain strength to support scientific research at the Jackson Heart Study. Dr. Collins, can I have your assurance that the National Heart Lung and Blood Institute will replace this position in a timely manner?

Answer. At present, the National Heart, Lung, and Blood Institute (NHLBI) medical officer stationed at the Jackson Heart Study site plans to remain there indefinitely. Should the position become vacant in the future, the NHLBI would promptly pursue recruitment via standard competitive procedures.

GEOGRAPHIC HEALTH DISPARITIES FOR STROKE AND OBESITY

Question. Health disparities are persistent across ethnic populations as well as geographically. Geographic isolation, socioeconomic status, and health risk behaviors contribute to health disparities in these rural communities. Mississippi is part of the "Stroke Belt" and has the highest rate of obesity in the Nation. Both of these issues are persistent problems in the rural South, with 10 out of 11 States with the highest rates of obesity being in the South. Dr. Collins, how is the NIH addressing the geographic issues associated with many of the most serious diseases affecting our Nation?

Answer. The NIH supports a broad portfolio of research to understand the complex factors that contribute to obesity, stroke, and related health problems, and to develop and evaluate prevention and treatment strategies for diverse populations.

The Look AHEAD clinical trial, supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and other NIH components, is determining whether lifestyle intervention improves health in overweight/obese people with type 2 diabetes, and in particular the impact of the intervention on the incidence of cardiovascular events, including stroke, heart attack, hospitalized angina, and cardiovascular-related death. For the first four years of this long-term study, participants in the lifestyle intervention group lost more weight and improved their blood pressure, fitness, glucose control, and good cholesterol, with less use of medication, compared with those in the control group. Look AHEAD includes sites across the country, including in Alabama, Louisiana, and Tennessee.

A major National Institute of Neurological Disorders and Stroke (NINDS)-funded epidemiological study related to the "Stroke Belt" is the REGARDS study (REasons for Geographic and Racial Differences in Stroke) in which investigators are exploring the geographical and racial differences in stroke risk in a cohort of about 30,000 individuals, about half of whom reside in the Stroke Belt region of the United States. This study also includes measures of functional cognitive decline, which may be a risk factor for stroke as well as a marker for unrecognized stroke. Data generated from this study has led to more than 70 publications, and will continue to help researchers pinpoint the reasons that the stroke death rate is higher in this region, and among African Americans, and to develop targeted strategies for intervention. Recent data from REGARDS indicated that overall time spent in the Stroke Belt is more predictive of hypertension—a powerful risk factor for stroke—than is current residence in the Stroke Belt. Data from the REGARDS study have also revealed that stroke survivors were more likely to have unrecognized hypertension and diabetes.

To improve stroke care utilization and patient outcomes among vulnerable populations, the NINDS also invests in research to increase stroke awareness and reduce the time from symptom onset to hospital arrival, so that patients can be evaluated and treated in a timely manner.

In one such study, a novel behavioral intervention will be tested in which children in high risk, minority communities are taught through Hip Hop Stroke (stroke rap songs and animated musical cartoons) to recognize and act on the five cardinal stroke symptoms and the importance of early treatment, with the hopes that they will communicate this information to their parents. Preliminary pilot data indicated that 74 percent of children communicated the material to their parents, which significantly improved their stroke knowledge.

In the SWIFT (Stroke Warning Information and Faster Treatment) study, a culturally sensitive educational intervention focused on improving knowledge retention and time of arrival to the emergency department has been tested in minority communities. The outcome and results of this study are currently under review in a major medical journal.

The ASPIRE program (Acute Stroke Program of Interventions addressing Racial and Ethnic disparities) is currently testing strategies to overcome community/sociocultural and system barriers to stroke treatment with the goal of increasing the number of stroke patients treated with the clot-busting drug, tissue plasminogen activator (tPA), in six Washington, DC, hospitals.

Ten years ago, the NINDS convened a Stroke Progress Review Group (SPRG) to identify and prioritize scientific opportunities in stroke research. In 2011, the NINDS will embark on a new stroke planning and evaluation effort, which will identify a specific set of high priority areas for advancing stroke research over the

next 5–10 years. The topic of health disparities in stroke will be included as a cross cutting topic in this effort.

CARDIOVASCULAR DISEASE RESEARCH

Question. Cardiovascular Disease is the leading cause of death in Mississippi, accounting for more than 40 percent of all deaths. In 2004, the State of Mississippi implemented a 10-year plan to address Cardiovascular Disease risk factors in a two-fold approach: prevention of potential risk factors and management of existing risk factors. In addition, the Jackson Heart Study is the largest investigation of causes of Cardiovascular Disease in an African-American population. While both initiatives are good starts to addressing this health issue in my home State, Cardiovascular Disease is the number one killer in the United States and we need comprehensive research to fight the disease nationwide. What plans do you have to increase research in the area of Cardiovascular Disease?

Answer. The NHLBI is committed to supporting a comprehensive research program on the causes, prevention, diagnosis, treatment, monitoring, and management of cardiovascular disease (CVD). We invest 63 percent of the NHLBI extramural budget in CVD research, and we intend to continue that high level of support. This year, the Institute has launched a number of new projects, including two major clinical trials:

—The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) addresses management of patients with stable coronary heart disease who have substantial ischemia on a cardiac stress test. The trial will evaluate whether an invasive approach (performing an angiogram and then opening or bypassing any blockages with stents or surgery) plus optimal medical therapy is better than optimal medical therapy alone in forestalling CVD events. Quality of life and cost-effectiveness will also be assessed.

—The Cardiovascular Inflammation Reduction Trial (CIRT) addresses cardiovascular disease risk reduction in heart-attack survivors with persistently high levels of C-reactive protein, an indicator of inflammation. The trial will evaluate whether a very low dose of the anti-inflammatory drug methotrexate reduces rates of recurrent heart attack, stroke, and cardiovascular death. Several other conditions that have an inflammatory basis, such as diabetes, venous thromboembolism, and atrial fibrillation, will also be assessed.

The NHLBI has responsibility for cardiovascular, lung, and blood diseases that affect millions of people worldwide. We will continue our longstanding emphasis on the support of a balanced research portfolio that addresses the many public health needs and scientific opportunities that fall within our mandate.

QUESTIONS SUBMITTED BY SENATOR LAMAR ALEXANDER

REORGANIZATION OF NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR) PROGRAMS

Question. In my State of Tennessee, the largest single Federal grant at one of the State's largest medical research institutions is a Clinical and Translational Science Award (CTSA), for $40 million. How will this program and others like it be affected by the dissolution of the NCRR, and the creation of the National Center for Advancing Translational Sciences (NCATS)?

Answer. The NIH is committed to supporting each program currently housed within the NCRR; the proposed reorganization will not adversely affect the individual programs. Indeed, a careful programmatic evaluation concluded that important scientific synergies could be gained by moving NCRR programs to other NIH components with adjacent scientific missions. Staff responsible for administering and directing these programs will transfer with their respective programs to ensure continuity and oversight. With regard to the Clinical and Translation Science Awards (CTSA) program specifically, it is to be transferred to the proposed National Center for Advancing Translational Sciences (NCATS). The transfer was recommended by the NIH Scientific Management Review Board, a congressionally-mandated advisory committee to the NIH Director, and further supported by an internal NIH task force charged with assessing the optimal location for NCRR programs. The task force's analysis confirmed that the goals of the CTSA program were in close alignment with those of the new center. Decisions regarding the selection of individual CTSAs will continue to be made based upon each proposal's scientific merit and program relevance.

CTSA PROGRAM MISSION

Question. Given the established focus of the NCATS on drug development, will the CTSA's continue to be able to build on the programs of training, career development for young investigators, research informatics, community engagement and clinical research infrastructure?

Answer. The focus of the NCATS is to develop new and innovative approaches to conducting research across the therapeutic development pipeline, in the context of strengthening and streamlining the process itself. The CTSAs have the infrastructure and diverse expertise that supports translational research, including training and career development for the next generation of clinical investigators, informatics, and community engagement, and they will be integral to fulfilling the NCATS mission. The CTSAs are making important contributions in transforming translational research across the country, and the NIH is committed to building upon the program's successful efforts. Ensuring that the pipeline of new investigators is sufficiently equipped to tackle the challenges associated with translational science through training and mentoring is an inherent part of the NCATS mission and will continue to be an essential component of the CTSAs.

PERSONALIZED MEDICINE

Question. Physicians and researchers in Tennessee are investing a great deal in the science of personalized medicine. Can you tell us what the term "personalized medicine" means to you, and what role you see for the NIH?

Answer. The concept of "personalized medicine" is based on the idea that one size does not fit all when it comes to the practice of medicine. Knowledge gathered from basic research and clinical studies have demonstrated that individuals are highly unique in their susceptibility to disease, reaction to medical treatments, and response to environmental and social factors. More than ever before, and largely thanks to research supported by the NIH, we now have the tools to understand, describe, and quantify these biological differences as well as the power to better predict which available treatments are optimal for certain patients and to design rationale-based new targeted-based therapies.

The NIH will continue to play a pivotal role in the advancement of personalized medicine. For example, our support for pharmacogenomics research will advance understanding of the predictive roles and influences of genes in drug response. Findings from such research can help identify the right drug for the right patient at the right time. Increasingly, this information will help doctors calculate dosages that match a person's unique physiology. Pharmacogenomic information already is contained in approximately 10 percent of FDA-approved drug labels, helping to prevent the inappropriate use of diagnostics and therapies. Pharmacogenomic knowledge can also reduce the financial, emotional, and physical costs associated with the current trial-and-error based approach to treatment. Knowing each patient's DNA sequence is expected to add efficiencies and new research capabilities to current endeavors. As such, we are also fostering technological advances that are expected to bring down the cost of sequencing an individual genome to under $1,000. These advances will help make genetic analysis a routine part of medical care and a revolutionary factor in approaches to basic research and practice.

DNA DATABANKS

Question. Several major research institutions are creating databanks that allows researchers to access a large collection of human DNA. How does the NIH also plan to build on the mapping of the human genome by optimizing unique resources such as this?

Answer. In support of its mission to improve public health through research, the NIH has a longstanding policy of making data publicly available from the research that it funds. The NIH recognizes that data sets are not only valuable for addressing the questions that the experiments that generated them were designed to ask, but also can be powerful resources when combined with other data sets or used to answer other scientific questions. This is particularly true of DNA data sets that consist of information across the full sequence of the human genome. Consequently, building on the data sharing practices that characterized the Human Genome Project, the NIH launched research programs to stimulate the creation of genomic resources and created policies and tools for facilitating the sharing of genomic data to capitalize on the databanks created by other institutions with or without the NIH funding.

For example, under the leadership of the National Human Genome Research Institute (NHGRI) the International HapMap Project used the reference human ge-

nome sequence to build a comprehensive map (database) of the variation within human DNA sequences, so that "spelling" differences in the DNA code of those with disease and those without disease could be identified and studied. The 1000 Genomes Project is now capitalizing on technological advances to extend and deepen the HapMap data. All data from each of these projects are publicly available to any investigator through the web with regular updates as new data are generated.

In addition, to leverage the infrastructure and databank resources created at other research institutions, the NIH has introduced funding programs, such as the NHGRI-supported Electronic Medical Records and Genomics (eMERGE) Network. This consortium of U.S. medical research institutions has the primary goal of developing, disseminating, and applying approaches to research that combine existing DNA biorepositories with electronic medical record (EMR) systems for large-scale, high-throughput genomic research. eMERGE Network institutions use their own databanks (e.g., Vanderbilt University's BioVU DNA databank) for this program, but all data are shared through an NIH database, the database of Genotypes and Phenotypes (dbGaP), which provides centralized and consistent access to researchers around the globe. Importantly, dbGaP includes not only eMERGE data, but data from studies across the disease spectrum. Extremely rich databanks from studies such as the Framingham Heart Study, The Cancer Genome Atlas, and many other projects reside within dbGaP, enabling many more investigators to analyze the data as independent or combined data sets. The standardization of access supported by the NIH facilitates cross-study analyses, enables expansion of the study design beyond the initial research focus of the individual databanks, and increases the statistical power to identify the genetic contributors to common diseases that create substantial public health burden. And, importantly, all of these benefits are achieved through robust data sharing policies intended to protect the interests of the research participants who contribute their personal information to the individual databanks.

INDUSTRY INVESTMENT IN GENOME SEQUENCING

Question. How does private investment in genome sequencing help to leverage the Federal investment of genomic research through the NIH funding?

Answer. The sequencing of the human genome has rightly been regarded as one of the most important scientific undertakings of the modern era. The NIH's investment in genomics has been, and continues to be wide-ranging, from basic research to uncover and understand the structure of our genome to translational science aimed at using a patient's DNA code to tailor treatment. Enabling all of this research are innovative new tools for DNA sequencing that have precipitated a drop in the cost of sequencing an individual genome from hundreds of millions of dollars to $15,000 or less.[2] In the process, an entire industry of genomics-focused companies has been created, one that, according to a recent study conducted by Battelle Technology Partnership Practice, has generated an economic contribution of almost $800 billion since the start of the Human Genome Project.[3] [4]

The field of genomics has benefited from a combination of public and private investment. During the course of the last 10 years, the National Human Genome Research Institute's Genome Technology Program has provided support for the development of almost all of the currently commercialized, as well as several yet-to-be-commercialized or emerging, sequencing technologies. Private investment during and since that initial period of the NIH support has and will continue to bring these innovative advances to the market. Newer and increasingly cheaper sequencing machines and reagents have increased both capacity and productivity, enabling the NIH grantees to answer more research questions in the same period of time and for the same cost as previously. Illumina and Life Technologies, for example, have now developed smaller and less expensive sequencing machines that are bringing DNA sequencing within reach of single-investigator research labs. Affordable access to these technologies will greatly amplify the number of researchers that can employ genomic sequencing within their research plans, expanding the benefit of the Federal investment in genomic sequencing into yet more basic, translational, and clinical research domains. Companies like Illumina and Complete Genomics are also offering sequencing services that the NIH-funded researchers have used to great ef-

[2] Additional information on sequencing costs is available at http://www.genome.gov/27541954.
[3] http://www.battelle.org/publications/humangenomeproject.pdf.
[4] Additional information on the economic impact of the human genome project is available at http://www.genome.gov/27544383.

fect, such as the discovery last year of the causative genes behind rare disorders like Miller syndrome, something that had eluded science until now.[5]

QUESTIONS SUBMITTED BY SENATOR LINDSEY GRAHAM

EOSINOPHILIC DISORDERS WORKING GROUP

Question. I have heard from individuals in my State about the enormous challenges to children with eosinophilic disorders and their families. I understand that these conditions are often misdiagnosed and there is no cure for these children, many of whom suffer from extreme pain and are unable to eat normal food. This subcommittee has asked that the NIH convene a working group on this topic. When will this group meet and when can we expect to have a report of the group's recommendations?

Answer. Eosinophilic gastrointestinal disorders (EGID) are a group of diseases characterized by a wide variety of gastrointestinal symptoms including abdominal pain, swallowing problems, food impaction (food lodged or wedged in the esophagus), vomiting, diarrhea, growth impairment and bleeding. EGIDs are associated with increased numbers of eosinophils, a type of white blood cell, in the gastrointestinal lining. The most common EGID, eosinophilic esophagitis, is characterized by inflammation and accumulation of eosinophils in the lining of the esophagus. This disease and other EGIDs are diagnosed by a patient's clinical history plus endoscopy with biopsy.

As the lead Institute at the National Institutes of Health (NIH) responsible for research on immunologic and allergic disorders, the National Institute of Allergy and Infectious Diseases (NIAID) works closely with other NIH Institutes and Centers supporting research on eosinophilic disorders. Although these collaborations and communications do not occur through a formal working group or a predetermined research agenda, they have led to jointly sponsored workshops and research initiatives on eosinophilic disorders. In fiscal year 2012, the NIH, with the NIAID as the lead, will establish a working group with participation by relevant NIH Institutes and Centers, to develop a trans-NIH strategy to improve the diagnosis and treatment of eosinophilic disorders.

As part of its overall research agenda on immunologic and allergic diseases, the NIAID pursues research on eosinophilic disorders through a variety of efforts and collaborations. For example, the Consortium of Food Allergy Research (CoFAR), cofunded with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and renewed in fiscal year 2010, develops new approaches to treat and prevent food allergy. A new CoFAR project is examining the genetic aspects of eosinophilic esophagitis. The NIAID Asthma and Allergic Diseases Cooperative Research Centers (AADCRC) support basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, including food allergy and anaphylaxis. Many of these disorders are associated with eosinophilia. In addition, the NIAID-supported investigators are conducting a pilot clinical trial to determine the efficacy of swallowed glucocorticoids for the treatment of eosinophilic esophagitis, and developing novel noninvasive diagnostic tools for eosinophilic gastrointestinal diseases to reduce the number of endoscopies and biopsies that are currently performed. Also, on behalf of more than 30 professional organizations, Federal agencies, and patient advocacy groups, including the American Partnership for Eosinophilic Disorders, the NIAID coordinated the development of Guidelines for the Diagnosis and Treatment of Food Allergy in the United States. This document includes clinical practice guidelines for the diagnosis and management of eosinophilic esophagitis associated with food allergy. The guidelines were published in the December 2010 issue of the Journal of Allergy and Clinical Immunology and can be accessed at: http://www.ncbi.nlm.nih.gov/pubmed/21134576.

The NIAID will continue its commitment to research and trans-NIH research collaborations on eosinophilic disorders to understand the mechanisms that mediate tissue injury when eosinophils accumulate. As part of this effort, in fiscal year 2011, the NIAID will recompete the AADCRC program.

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[5] http://www.sciencemag.org/content/328/5978/636.

QUESTION SUBMITTED BY SENATOR JERRY MORAN

BUDGETARY EFFECTS ON THE NCI PROGRAMS

Question. Dr. Collins, I recently visited the University of Kansas and was given a tour of the University's drug discovery, delivery, and development operation. This visit helped demonstrate to me not only the many elements that will become part of the application by the University for National Cancer Institute (NCI) comprehensive cancer center designation, but also the impressive role that the NCI's cancer centers play across the Nation. This network of centers drives basic research, brings individuals into clinical trials, and, most importantly, leads to the development of new treatment advances that will change the course of cancer for all Americans and individuals across the globe.

While I understand that the University of Kansas' application for the NCI designation will be determined on its scientific merits, can you please explain how the NCI cancer center program will be affected by the proposed budgets of the NIH and the NCI?

Additionally, considering possible scenarios for the fiscal year 2012 budget, what will the effects of such scenarios be on current NCI programs and on the prospect for funding the review of new applications?

Answer. The the NCI-designated Cancer Centers are an important part of the NCI's research portfolio, and they play a unique and valuable role in providing cutting-edge cancer care and access to the NCI-sponsored clinical trials across the country. The final fiscal year 2011 appropriation has already necessitated a 5 percent reduction in funding below fiscal year 2010 for the cancer centers, and it is difficult to predict how they will be affected by the resolution of the fiscal year 2012 budget.

The NCI's first priority must be to preserve funding for Research Project Grants (RPGs). Ensuring support for as many new RPGs as possible will enable investigators, especially new investigators, to pursue novel ideas that will preserve the pipeline of innovative cancer research. This year, nearly every NCI program budget has had to be trimmed in order to award adequate, though reduced, number of new RPGs.

SUBCOMMITTEE RECESS

Senator HARKIN. Is there anything else that any one of you would like to state for the record now? If not—Yes.

Dr. COLLINS. Well, Senator, I'd just like to thank you and this subcommittee for your steadfast support for biomedical research.

All of us involved in this enterprise sitting here at this table, and many others who are not at the table, but who are engaged every day in this effort to try to find interventions for people with disease appreciate your support and your strong voice that, even in difficult times, medical research is basically a societal good.

I think a society ultimately will be judged by the ways in which, even in difficult times, priorities are chosen.

We think, in terms of alleviating suffering as well as encouraging our American competitiveness and our economic growth, that what we are able to do through NIH is a very good story indeed, but we appreciate the fact that you have convened this hearing and given us a chance to tell some of that story.

Senator HARKIN. Well, thank you very much, Dr. Collins, and I can just reciprocate then I'll join all my colleagues in thanking you and all of you and all your colleagues at the NIH, all the Directors, the people who work there, and through you the whole network of researchers, young and old, some of who have just come on, some who have been there for many years, to thank you for your outstanding public service. All of you, every single person engaged in NIH, thank you.

The subcommittee will stand recessed.

[Whereupon, at 11:45 a.m., Wednesday, May 11, the subcommittee was recessed, to reconvene subject to the call of the Chair.]