



## The Nation's Medical Research Team: America's Medical Schools, Teaching Hospitals, and The National Institutes of Health

### **The National Institutes of Health: An Unrivaled Network of Researchers**

The NIH is the primary federal agency conducting and funding medical research to improve the public's health. With an annual budget of \$29 billion (FY07), the NIH budget supports:

- **Intramural Research** -- About 10 percent of the NIH budget funds research by nearly 6,000 scientists in its own laboratories, most of which are on the NIH campus in Bethesda, Md.
- **Extramural Research** -- Approximately 85 percent of the NIH's budget supports a total of nearly 50,000 competitive grants (including research project grants, research centers, and other types of grants) to more than 325,000 researchers at over 3,000 medical schools, teaching hospitals, universities, and other research institutions. Physicians and scientists at the nation's medical schools and teaching hospitals conduct more than half of the NIH's extramural research.
- The remaining NIH funds, about 5 percent, go to research management and support, cancer prevention and control, the National Library of Medicine, extramural construction, buildings and facilities, and the Office of the Director.

The nation's medical schools and major teaching hospitals are the research engines of the U.S. health system. As major centers of medical discovery, they are awarded more than half of all NIH grants to scientists across the country through its extramural research program.

For more than 60 years, the teamwork between the NIH and academic medicine has pioneered many of medicine's most remarkable advances, including life-saving vaccines; new and better treatments for diabetes, cancer, and heart disease; and advanced technology to improve quality of life, from artificial hips to minimally invasive techniques. Recent examples of this extraordinary collaboration include the identification of the gene for basal cell carcinoma – a form of skin cancer that affects about 750,000 Americans each year, the development of the first FDA-approved cardiac stent, and the discovery of the hormone resistin, which promotes type 2 diabetes and is resistant to insulin.

### **Better Health Care Through Teamwork**

With an annual budget of \$29 billion (FY07), the NIH is the primary source of federal funding for medical research. In 2006, the NIH invested over \$13 billion in research at U.S. medical schools and teaching hospitals, supporting the work of distinguished physicians and scientists. These researchers apply for NIH funding through a highly competitive peer-review process that identifies and funds only the most promising and highest-quality research. Today, the NIH receives more than 40,000 research project grant applications a year, with about one in five receiving support through its extramural research program.

Medical school and teaching hospital faculty who receive NIH grants can be divided into two groups:

- **Basic science**—typically Ph.D. and M.D. researchers who pursue laboratory research, teach medical students the basic sciences, and train graduate students.
- **Clinical science**—most often M.D. physician-scientists who conduct research with patients and healthy volunteers and who teach and train medical students and residents.

The advances pioneered in medical school laboratories are further developed and tested through clinical research programs. Some are funded by NIH grants at the nation's major teaching hospitals (hospitals affiliated with one of America's medical schools), while others are funded by pharmaceutical companies, medical device manufacturers, and other industries. Medical schools and teaching hospitals also frequently serve as sites for clinical trials to advance treatments for cancer, cardiovascular diseases, diabetes, and neurological and orthopedic disorders. Often, successful results from these research endeavors are further developed by private companies into commercial products, such as new drugs and diagnostic tests.

Patients are the ultimate beneficiaries of the collaboration between the NIH and the nation's medical schools and teaching hospitals. Because of their teamwork, the public has access to advances in medical research and the very best health care.

The nation's 125 medical schools and nearly 400 major teaching hospitals are the foundation of the nation's health care system. Together, they pursue their multiple missions to educate tomorrow's doctors and scientists, find tomorrow's cures and provide the most advanced patient care available today.

### **Training Tomorrow's Scientists**

Medical schools and teaching hospitals across the country also work with the NIH to prepare the next generation of biomedical researchers, individuals working to earn doctorates in scientific disciplines. Graduate programs at U.S. medical schools train more than half of all biomedical science Ph.D.'s. In 2005, approximately 32,000 students were enrolled in biomedical science graduate programs at the master's and doctoral level, with 6,368 Ph.D. degrees awarded in these disciplines.

Dual M.D./Ph.D. programs are an important example of the collaboration between the nation's medical schools and the NIH to train the nation's scientists. The start of this effort can be traced to 1964 when the NIH launched the Medical Scientist Training Program (MTSP) with funding to three medical schools. During the last decade, the budget for NIH research training increased, along with the number of training positions. Today, the NIH funds 933 training positions in 40 programs involving 45 degree-granting institutions.

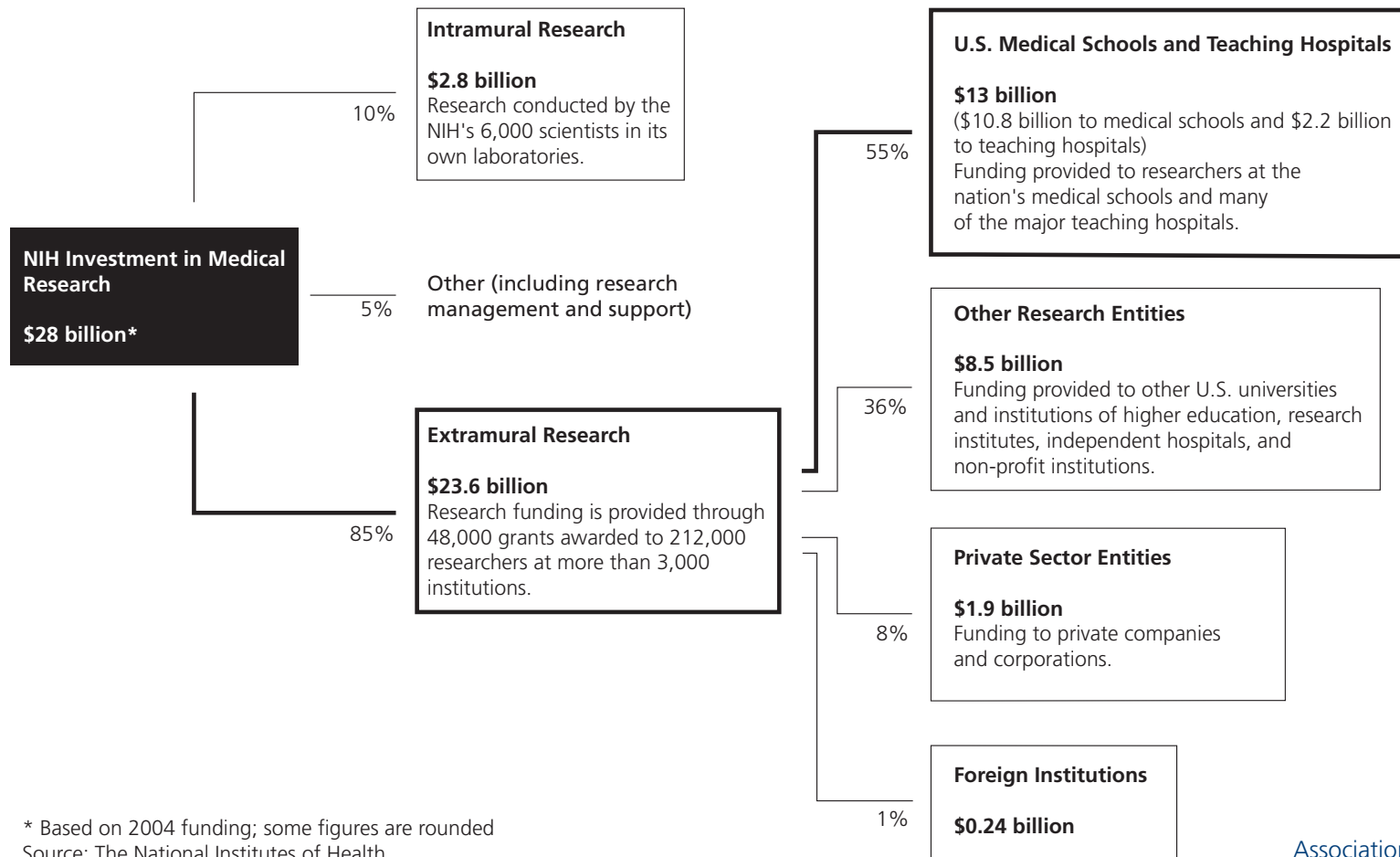
### **Improving Health, Saving Lives**

The collaboration between the NIH and the nation's medical schools and teaching hospitals has been enormously successful and remains essential to fulfilling the promise of medical research. It has been the driving force behind many of the medical breakthroughs achieved over the past 60 years. Because of this critically important teamwork, our nation stays at the forefront of progress in medical research that improves the public's health and provides hope to the millions of Americans who suffer from disease and disability.

To learn more about how medical schools, teaching hospitals, and the NIH are working together to fulfill the promise of medical research, go to [www.aamc.org/ftp](http://www.aamc.org/ftp).

## The NIH Investment in Medical Research

U.S. Medical Schools and Teaching Hospitals are Awarded More Than Half of All Extramural Funding



\* Based on 2004 funding; some figures are rounded  
Source: The National Institutes of Health

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## **Funding for the National Institutes of Health**

The National Institutes of Health (NIH) is the principal federal funder of medical research. The NIH budget is established through the Congressional appropriations process. Throughout its history, the NIH has enjoyed strong bipartisan support, regardless of which party controlled the Congress.

## **Authorization for NIH**

In the House of Representatives, NIH is within the jurisdiction of the House Energy and Commerce Committee and its Subcommittee on Health. In the Senate, the NIH falls within the purview of the Senate Health, Education, Labor and Pensions Committee. Although some NIH programs need periodic reauthorization, the Public Health Service Act provides a general, standing authorization for most of the NIH's programs.

## **Appropriations for NIH**

Funding for the NIH is contained in the annual Labor, Health and Human Services, Education and Related Agencies appropriations bill, developed by the House and Senate Labor, Health and Human Services, Education and Related Agencies Appropriations Subcommittees. Funding is divided among the NIH's institutes and centers through a collaborative process involving Congress, the Executive Branch, HHS, and NIH.

## **Competing for NIH funds**

Researchers at medical schools and teaching hospitals compete for much of this federal funding, which is available through the NIH's extramural research program. Physicians and scientists (known as "principal investigators") seeking financial support for a research project at their institution may apply for NIH funding, which is awarded in the form of grants, cooperative agreements, or research contracts. Grants, the largest category of funding, are available for one to five years. More than 40,000 funding applications are submitted

to the NIH each year. These applications are subject to a peer-review process, as mandated by law. A national pool of research scientists helps the NIH select which applications will be approved for funding. The review of grant applications is done on the basis of scientific and technical merit, and in consideration of the sponsoring NIH institute's program goals and available funds.

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## Teaming Up to Improve Health: NIH-Funded Advances by America's Medical Schools and Teaching Hospitals

For more than 60 years, the National Institutes of Health has teamed with the nation's medical schools and teaching hospitals to pioneer many of medicine's most remarkable advances, including life-saving vaccines; new and better treatments for diabetes, cancer and heart disease; and advanced technology to improve quality of life, from artificial hips to minimally invasive techniques.

Today, Americans are living healthier, longer lives thanks to NIH-supported research and the efforts of the nation's medical schools and teaching hospitals:

- Death rates from heart disease and stroke have been cut in half
- More and more Americans are surviving cancer, and
- Seniors are more active than ever before in their "golden years," with disability rates for people 65 years and older having dropped by 25 percent.

Here are some examples of NIH-funded research advances achieved at the nation's medical schools and teaching hospitals since 1990:

1990 Discovered that premature babies can be saved from blindness and vision complications by freezing part of the eye

**Oregon Health & Science University School of Medicine**

Basic science research on breast cancer cell proteins, leading to the development of the drug Herceptin®, effective in 20-30 percent of breast cancers

**University of Pennsylvania School of Medicine**

1992 Discovered the gene for Huntington's Disease, allowing the development of a screening test for families at risk

**Harvard Medical School, Massachusetts General Hospital**

Developed the Arrow LionHeart™ - the first wireless, electrically transmitted, implanted heart assist device to reach clinical trials

**Pennsylvania State University College of Medicine,  
Milton S. Hershey Medical Center**

- Determined that not all organ transplant recipients require costly lifelong anti-rejection drugs, radically changing the way organ rejection is managed  
**University of Pittsburgh School of Medicine**
- 1993 Pioneered new uses for MRI imaging technology to better understand the brain and disorders that affect it  
**University of Minnesota Medical School**
- 1994 Developed the first cardiac stent approved by the FDA for use in keeping coronary arteries open  
**University of Texas Medical School at San Antonio**
- 1995 Developed the first vaccine for cholera, now in clinical trials  
**Harvard Medical School**
- 1996 Identified the gene for basal cell carcinoma, a common form of skin cancer  
**Stanford University School of Medicine**
- 1998 Identified a gene for prostate cancer  
**Johns Hopkins University School of Medicine, University of Maryland School of Medicine, Fox Chase Cancer Center and the Mayo Clinic**
- Identified the protein that more reliably signals warning signs for cervical cancer, leading to an improved standardized screening test  
**University of California, Irvine, College of Medicine**
- Discovered that the drug tamoxifen decreases the incidence of breast cancer by almost 50 percent in women who have a higher risk of developing the disease National Surgical Adjuvant Breast and Bowel Project (lead researcher from **University of Pittsburgh School of Medicine**)
- 2000 Discovered a way to prevent chemotherapy-related hearing loss in children undergoing cancer treatment (nearly one-third of all children with cancer experience permanent hearing loss)  
**Oregon Health & Science University School of Medicine**
- Bioengineered corneal tissue to restore or improve vision in blind or visually impaired patients  
**University of California, Davis, School of Medicine**
- 2001 Discovered the genetic cause of myotonic dystrophy, the most common type of muscular dystrophy in adults  
**University of Minnesota Medical School**
- Discovered the hormone, “resistin” that promotes type-2 diabetes and is resistant to insulin  
**University of Pennsylvania School of Medicine**

2003 Determined that Americans at risk of developing advanced age-related macular degeneration can avoid vision loss by taking daily supplements of antioxidant vitamins and zinc

**Johns Hopkins University School of Medicine**

2004 Discovered a new, progressive neurological disorder affecting men over age 50 that causes tremors, balance problems and memory deficits

**University of California, Davis, School of Medicine; University of Colorado Health Sciences Center; RUSH-Presbyterian-St. Luke's Medical Center**

Designed a robotic, prosthetic arm controlled by the brain that promises to restore mobility to patients with paralyzing injuries or lost limbs

**University of Pittsburgh School of Medicine**

To learn more about medical firsts achieved in your state or local medical school and teaching hospital, go to the *Fulfilling the Promise* Web site ([www.aamc.org/ftp](http://www.aamc.org/ftp)) and click on life-saving innovations to access the AAMC's Discoveries and Innovations in Patient Care and Research Database.

## Medical Research: Saving Lives Through New Cures and Treatments

Americans have benefited from tremendous progress in medical research over the past 60 years. Today, people are living longer and healthier lives thanks in significant part to NIH-funded research conducted by physicians and scientists at the nation's medical schools and teaching hospitals. But even though reports of medical discoveries are in the news nearly every day, new cures, treatments, prevention approaches and diagnostics are actually the products of a long and arduous process.

### The Road to Discovery

There are four different categories of medical research that take place in laboratories and at the patient's bedside.

#### Basic Research Debunks Notion that Aging is Inevitable

Ten years ago, biochemist Cynthia Kenyon, Ph.D., found a way to double the lifespan of a microscopic roundworm—by manipulating a single gene. With support from NIH, Kenyon's team at the University of California at San Francisco has been using DNA microarray technology to trace all the genetic changes that flow from that single gene change. Because the same pathway affects the lifespan of fruit flies and mice, it's possible that it also affects the lifespan of humans. And these changes don't just delay aging, they postpone the diseases of aging, including Huntington's disease and cancer, as well. "The consequences are stunning," Kenyon says, "and if we can figure out a way to copy these effects in humans, we might all be able to live very healthy long lives."

#### Basic research

This type of research seeks to answer important biological questions like:

- How do cells talk to each other?
- How are genes regulated?
- Why does the body sometimes destroy its own tissues?

Basic research typically takes place in a laboratory. While it does not involve human subjects, human tissues or fluids may be used. Basic research often relies on studies in "model organisms" such as yeast, fruit flies or mice. Human cells contain the same molecular building blocks and pathways as those of most other living things, so researchers can learn a great deal about the way cells work by studying these simpler organisms.

Although these studies may not have an immediate impact on health, it is "untargeted," investigator-initiated basic research that most often has led to breakthroughs that transform our understanding of life's complex processes and provide the leads to new medicines, technologies and research tools. Examples of advances that grew out of basic research include: biotechnology; a variety of drugs used to treat conditions from cancer to AIDS; magnetic resonance imaging (MRI), which provides a different way of viewing the body's organs and tissues; and the polymerase chain reaction, a laboratory technique that is the basis of "DNA fingerprinting," which revolutionized criminal forensics. In general, about two-thirds of the grants NIH awards to outside scientists are for basic research.

### **Clinical Genomics Research Uncovers a Genetic Susceptibility to HIV/AIDS**

Sunil K. Ahuja, M.D., an infectious disease expert at University of Texas Health Science Center at San Antonio, wanted to know why some people infected with HIV do not suffer immune system damage. By studying the genetic make-up of more than 4,000 HIV-positive and -negative individuals, Ahuja and his colleagues found that people with more copies of a gene that fights HIV are less likely to become infected with the virus or to develop AIDS than people who have fewer copies of the gene. Their NIH-supported study was published in January 2005 and could lead to a screening test to determine individual susceptibility to HIV/AIDS and enable doctors to adapt treatment regimens or vaccine trials to the patient's needs. Ahuja collaborated on the research with Matthew J. Dolan, M.D. of the U.S. Air Force's Wilford Hall Medical Center and Brooks City-Base in San Antonio.

### **Clinical Research**

Many of the advances pioneered in medical school laboratories are then developed and tested at medical schools and their affiliated teaching hospitals through clinical research programs funded by NIH grants. Clinical research is made possible through the participation of people who volunteer to take part in scientific studies. Clinical trials and epidemiologic studies are two types of the important research that falls within this area.

*Clinical trials*, also called patient studies, usually aim to produce a therapy—a drug, or a new device or a vaccine, for example—that will slow, cure, or perhaps prevent a disease. These studies are usually done in three phases: Phase I clinical trials aim to find out whether a new experimental treatment is safe in people and to establish the best dose to test in larger studies; Phase II trials test the safety and efficacy of new medications, medical devices or surgical treatments; and Phase III trials test a new treatment or procedure compared to the current standard of care. These trials usually enroll large numbers of people and may be conducted in many teaching hospitals, doctors' offices, and clinics nationwide. Medical schools and teaching hospitals frequently serve as sites for clinical trials to advance treatment for an array of conditions, including cancer, cardiovascular diseases, diabetes, and neurological and orthopedic disorders.

*Epidemiologic studies* examine factors that influence distributions of diseases in population groups. Harvard Medical School, for example, is conducting several large, long-term population-based studies, including the NIH-funded Nurses' Health Study I and II. In these two studies, participants are surveyed every two years to gather information on diet, smoking, physical activity, medications, health screening behavior, as well as occurrence of cancer, cardiovascular disease, and other serious illnesses, such as diabetes, fractures, kidney stones, and pre-cancerous lesions. Important findings have come from these studies, including the effect of aspirin use on various cancers and the impact of fish diets and omega-three fatty acids on heart disease.

Approximately 37 percent of the NIH's extramural budget supports clinical research.

### **Translational Research Curtails Heart Disease Deaths**

Benefits from basic, clinical and epidemiologic research on heart disease include the development of cholesterol- and blood pressure- lowering drugs and prescriptions for changes in behavior (less dietary fat, no smoking, more exercise). Deaths from heart disease have dropped dramatically as a consequence. And the research continues. Seven years ago, cardiologist Paul Ridker, M.D., at Brigham and Women's Hospital, a teaching hospital in Boston, set a two-part goal: to provide evidence that inflammation produced by an immune-system reaction in the arteries caused heart attacks; and to devise a method for doctors to detect inflammation in their patients. In a series of landmark studies, Ridker's group revealed that serum C-reactive protein (CRP), an indicator of inflammation, could be used to detect and measure inflammation in the arteries as well as predict first-ever heart attacks and strokes. They also provided critical evidence that life-saving "statin" drugs not only lower cholesterol, but also lower CRP. Researchers at the Cleveland Clinic published results supporting that conclusion.

### **Translational Research**

This kind of research seeks to move basic research findings from the laboratory to patients and populations and speed up the back-and-forth exchange between basic and clinical science. Investigators at medical schools and teaching hospitals historically have been the chief agents in this type of research where observations are often first made at the patient's bedside, and then move to the laboratory "bench" where the mechanisms of disease are studied at a molecular or cellular level. The laboratory findings are then brought back to the bedside to improve patient care. This approach requires intense two-way collaborations between basic scientists and clinical researchers and a corps of physician-scientists who are expert in both laboratory science and medical care.

The National Cancer Institute's Specialized Programs of Research Excellence (SPOREs) initiative is an example of the federal government's expanding support for translational research. Most of the 60 SPOREs, which cover 14 different cancers, are located at medical schools, teaching hospitals, and affiliated cancer centers, such as Baylor College of Medicine, Johns Hopkins University School of Medicine, and Duke University Medical Center.

To learn more about how medical schools, teaching hospitals and the NIH are working together to fulfill the promise of medical research, go to [www.aamc.org/ftp](http://www.aamc.org/ftp).

## **Charting the Future: The NIH Roadmap**

The NIH Roadmap for Medical Research, launched in 2004 by NIH Director Elias Zerhouni, M.D., is a series of far-reaching initiatives that the agency will pursue over the next decade to reshape medical research for the most profound impact on human health. This plan was created with extensive input from NIH leadership and more than 300 nationally recognized leaders in academia, industry, government and the public. The Roadmap is focused on three broad themes: New Pathways to Discovery, Research Teams of the Future and Re-engineering the Clinical Research Enterprise.

The first theme is aimed at creating new libraries of critically important “research tools,” such as the crystal structures of biologically crucial proteins, images of brain functioning and small chemical models that can effect the way genes are expressed and cells function. The libraries will help researchers everywhere to understand better the complex biological systems that are orchestrated by our genes and identify promising “targets” for therapeutic development.

The second theme focuses on stimulating new ways of combining skills and scientific disciplines to promote greater collaboration among teams of researchers; a new Pioneer Award to inspire investigators to take on creative, unexplored avenues of research that have the

## Working Together to Transform Medical Research

Research advances have opened a new landscape of opportunities to understand human health and disease. With a burgeoning knowledge base, researchers at medical schools and teaching hospitals are working with the National Institutes of Health (NIH) to make the most of the knowledge gained and accelerate the pace of discovery.

Scientists are exploring the workings of the cell, molecule by molecule. They are devising more powerful research tools to answer questions they didn't dream of asking just five years ago. Interdisciplinary teams are bringing together the resources of diverse disciplines—biology, mathematics, engineering, and computer science—to move more quickly toward solutions to today's medical problems.

### **New Approaches**

The human body is an amalgam of complex, interacting biological systems that need to be better understood to stop disease and disability. Researchers are beginning to apply a systems approach to understand diseases, using new research strategies to integrate knowledge from biology, genetics and environmental studies. As a result, whole new areas of research have been born—genomics, proteomics, pharmacogenetics, nanomedicine—all aimed at understanding the workings of the body at the level of genes, proteins and other molecules, and developing ways to intervene in the disease process sooner and more effectively than is possible today.

### **A Better Tool Box**

Scientists are relying on sophisticated new tools such as powerful computers and mathematical models to decipher the vast amounts of data generated through basic research and clinical studies. With new imaging tools and techniques, researchers can detect single molecule events in living cells and scientists can dramatically increase resolution of images in real time. Medical schools and teaching hospitals are major participants in these efforts and have developed important imaging and genomics tools that have contributed to the accelerated pace of medical discovery. For example:

- The DNA microarray, developed in 1995 at Stanford University Medical School, lets scientists study thousands of genes at a time. These “DNA chips” are created with miniscule amounts of hundreds or thousands of gene sequences on a single microscope slide to reveal detailed snapshots of which genes are active inside the cell.

### The NIH Roadmap cont'd

potential to make extraordinary contributions; and novel partnerships that will bring together the public and private sectors to accomplish what neither can do alone.

The third theme undertakes the most important challenge identified in the NIH Roadmap process: exploring ways to transform basic science discoveries into preventive measures, diagnostics, drugs or treatments. Under this initiative, the NIH will establish better-integrated networks of academic centers, including medical schools and teaching hospitals, which work together on clinical trials and include community-based practitioners who care for large groups of patients. This area also focuses on efforts to expand the clinical research workforce by supporting the education and career development of young investigators from many disciplines, and inspiring them to join the teams needed to conquer illness and disease in this country. Recently, the NIH announced a major Roadmap initiative, through the National Center for Research Resources, to catalyze the reinvigoration of clinical translational sciences at the nation's medical schools and major teaching hospitals. The goal is to foster an academic "home" and the integrated resources needed to support and advance this discipline through the collaborative efforts of the NIH, medical schools and teaching hospitals.

The NIH Roadmap initiatives foster the efforts of scientists at medical schools, teaching hospitals and other institutions to develop the research tools of the future, to build the networks necessary to tackle the most complex questions in biology, and to make the next leaps in medical discovery.

For more information, go to:  
[www.nihroadmap.nih.gov](http://www.nihroadmap.nih.gov)

- In 2004, scientists at the University of Pittsburgh School of Medicine completed the first human studies of a new chemical that enables positron emission tomography or PET scanning to reveal the memory-stealing amyloid plaques that are the hallmark of Alzheimer's disease. This new technique should help researchers learn how and when the disease originates and to evaluate new therapies.
- In 1995, researchers at Johns Hopkins University School of Medicine in Baltimore, Maryland, developed a computer model that helps to predict how complicated proteins "fold," a technology that will help determine the function of newly discovered genes.
- In 1993, researchers at University of Minnesota Medical School were the first to use an imaging technique called functional MRI to localize thought processes in the brain.

### Team Science

Today's medical research, which relies so heavily on technology, calls for interdisciplinary teamwork. Scientists, engineers, and mathematicians are crossing traditional disciplinary lines to answer complex questions that no one field of study can address alone. Infrastructure is being put in place to enhance tool and data sharing across research areas and among researchers at different institutions with shared aims. Some examples:

- The Broad Institute in Cambridge, Massachusetts is a first-time collaboration by three institutions: Harvard Medical School and affiliated hospitals, Massachusetts Institute of Technology, and the Whitehead Institute for Biomedical Research to create and apply cutting-edge tools for genomics research to "propel the understanding and treatment of disease."
- The University of Texas Medical School in Houston will make available new facilities at its Functional Genomics and Proteomics Research Center to researchers and clinicians who treat patients at the University of Texas Health Science Center and Texas Medical Center. The center will provide core laboratories in various technologies and disciplines that identify how genes work, study the structure and function of proteins encoded by the human genome, and develop mathematical tools and models to analyze the genome.
- The NIH-supported Michigan Proteome Consortium is a partnership among the University of Michigan Medical School, Wayne State University Medical School, Michigan State University and Van Andel Research Institute to develop specialized laboratories in the fast-moving field of proteomics, the study of proteins and their functions.

To learn more about how medical schools, teaching hospitals and the NIH are working together to fulfill the promise of medical research, go to [www.aamc.org/ftp](http://www.aamc.org/ftp).

## Medical Firsts: Advances Pioneered at America's Medical Schools and Teaching Hospitals

The nation's medical schools and major teaching hospitals are the research engines of the U.S. health system. For more than a century, medical researchers at these institutions have worked to develop life-saving vaccines; create new and better treatments to fight such diseases as diabetes, cancer and heart disease; and pioneer new technology to improve the quality of life, from artificial joints to minimally invasive techniques. Following are just a few examples of the medical firsts achieved by the nation's medical schools and teaching hospitals.

To learn more about medical firsts achieved in your state or local medical school and teaching hospital, go to the *Fulfilling the Promise* Web site ([www.aamc.org/ftp](http://www.aamc.org/ftp)) and click on life-saving innovations to access the AAMC's Discoveries and Innovations in Patient Care and Research Database.

- 1960 First intensive care unit for newborns
- 1966 First successful pancreas transplant
- 1967 First successful liver transplant
- 1968 First successful bone marrow transplant
- 1968 First adult human heart transplant in the U.S.
- 1969 Development of an influenza vaccine, the first genetically engineered vaccine
  
- 1970s First telephone-based cancer help line
- 1972 First hospital-based comprehensive screening program for sickle cell anemia
- 1972 First implantable, rechargeable pacemaker for cardiac disorders
- 1973 First use of a laser to remove growths from the larynx
- 1974 First production of recombinant DNA, the seminal step in the creation of the biotechnology industry and the rejuvenation of the field of biology
- 1974 Development of positron emission tomography (PET), an advance in imaging technology
- 1975 First microcomputer-controlled implantable medical delivery system
- 1975 Identification and naming of Lyme disease
- 1976 First total shoulder replacement
- 1977 First human images with a magnetic resonance imager (MRI)
- 1977 Development of angioplasty
- 1978 First performance of radial keratotomy to correct myopia
- 1978 Development of an insulin infusion pump for diabetics

- 1979 First toll-free hotline for epilepsy information
- 1979 First use of the immunosuppressant drug cyclosporine, now standard therapy for organ-transplant patients
  
- 1980s Development of coronary angioplasty
- 1980 First acute spinal cord injury intensive care unit
- 1981 First successful surgery on a fetus in utero
- 1981 Establishment of the first Pediatric Trauma Center
- 1981 First successful human combined heart/lung transplant
- 1981 Development of the first artificial skin made from living human cells
- 1981 Descriptions and reports of the nation's first cases of AIDS
- 1981 Development of balloon angioplasty
- 1983 First performance of autologous bone marrow transplant for acute myeloid leukemia
- 1984 First successful pediatric heart transplant
- 1985 First Fetal Cardiovascular Center
- 1986 First hospital to initiate a lung transplantation program
- 1986 First use of lithotripsy to break up common duct gallstones
- 1988 First successful double-lung transplant
- 1989 First living-donor liver transplant, and in 1993, the first liver transplant from an unrelated living donor
- 1989 Identification of human umbilical cord blood as a suitable source for stem cell transplantation
  
- 1993 First Geriatric Research and Training Center
- 1993 First human gene therapy trial for cystic fibrosis
- 1993 First gene-therapy procedure on a newborn infant, correcting an inherited disorder of the immune system
- 1994 First use of functional MRI to provide rapid diagnosis of most strokes
- 1994 First gamete intrafallopian transfer for treatment of female infertility
- 1994 First human retinal cell transplant
- 1995 First implantable, artificial inner ear for treatment of deafness
- 1995 First deep brain stimulator implantation for the treatment of Parkinson's disease
- 1996 Development of computer-assisted stereotactic neurosurgery
- 1997 First use of gene therapy in cardiac disease in humans
- 1997 First stem cell transplant for active lupus
- 1997 First retinal transplant
- 1997 First transplant of human fetal tissue in patient with spinal cord injury
- 1998 First laryngeal transplant
- 1999 First hand transplant
  
- 2000 First quadruple transplant of four organs—a kidney, two lungs and a heart—from a single donor
- 2000 First bioengineered cornea transplant
- 2001 First implantable replacement heart that functions without a permanent attachment to a power source
- 2001 Discovery of stem cells within the pancreas that can generate insulin-secreting beta cells
- 2002 Development of a Rapamycin-coated stent, a breakthrough in the prevention of restenosis following cardiac catheterization
- 2003 First successful larynx reconstruction accomplished using tissue taken from patient's arm



## Advancing the Fight Against Cancer: America's Medical Schools and Teaching Hospitals

For more than a century, the nation's medical schools and teaching hospitals have worked to understand, treat and fight cancer. Critically important research support from the National Institutes of Health (NIH), and especially the NIH's National Cancer Institute, over the past 60 years has helped to catalyze these and myriad other scientific endeavors at institutions across the country.

This united front has resulted in millions more Americans surviving cancer. For example:

- Cancer survival has doubled over the past 20 years – currently there are 9 to 10 million cancer survivors.
- Almost eight out of 10 women with breast cancer are alive 10 years after their diagnosis.
- Today, the overall survival rate for men with testicular cancer is 96 percent.
- The five-year survival rate for children with cancer is now more than 75 percent.
- Today, more people are living with cancer than dying from it. In 1976, just half of all cancer patients survived more than five years after their diagnosis. Today, nearly two-thirds (64 percent) are alive five years after they learn they have the disease.
- Deaths rates for the four most common cancers—breast, lung, prostate, and colorectal—have been dropping since 1990.

Listed on these pages are a few of the many examples of the advances in cancer knowledge and treatments achieved by medical schools and teaching hospitals. NIH funding support for these discoveries—where known by the AAMC—is indicated below the appropriate listing. To learn more about these and other advances, go to [www.aamc.org/innovations](http://www.aamc.org/innovations).

2005

Discovered that women who have higher levels of an antibody to a protein called human mucin, or MUC1, are less likely to develop ovarian cancer. The findings may lead to a vaccine to prevent ovarian cancer.

**Brigham and Women's Hospital, MA**

**Dartmouth Medical School, NH**

**University of Pittsburgh School of Medicine, PA**

**NIH funded**

Developed first new breast cancer CT scanner to reach clinical testing in a generation. The new technology may have the ability to detect tumors much earlier than conventional mammography.

**University of California, San Diego, School of Medicine**

**University of California, Davis, School of Medicine**

**NIH funded**

2004

Discovered that a booster dose of a substance already found in the body appears to be a safe, non-toxic treatment for pancreatic cancer and shows signs of arresting pancreatic cancer cell growth in patients.

**Pennsylvania State University College of Medicine, PA**

**NIH funded**

Discovered mutations in a family of genes linked to more than a quarter of colon cancers as well as several other common cancers such as breast and lung cancer. This discovery revealed options for creating personalized therapies tailored for individual patients.

**Johns Hopkins University School of Medicine, MD**

**NIH funded**

2003

Discovered the first molecular therapy to target cancer-causing components and stop the infections process of the human papillomavirus (HPV). HPV is the major risk factor for developing cervical cancer.

**Pennsylvania State University College of Medicine, PA**

**NIH funded**

2000

Developed a polymer that enables medications to pass through cancer cell membranes and across the blood-brain barrier. This technology has great potential for improving treatment of a variety of cancers, especially those of the central nervous system.

**University of Nebraska Medical Center, NE**

**NIH funded**

1999

Discovered distinct genetic and cellular differences among B-cell chronic lymphocytic leukemia (CCL) patients that can predict clinical outcome. CLL is the most common U.S. adult leukemia. Doctors now know early whether to treat patients aggressively with chemotherapy.

**North Shore-Long Island Jewish Health System, NY**

**NIH funded**

1998

Identified for the first time an easily detectable protein that holds the key to more reliably warning women about early cell abnormalities in the cervix before cancer can develop.

**University of California, Irvine, School of Medicine, CA**

**NIH funded**

Pinpointed the site of the first gene for a major cancer located on the human X chromosome. The gene, for prostate cancer, may account for 20 percent of disease in families with a strong history of the cancer.

**Fox Chase Cancer Center, PA**

**Johns Hopkins University School of Medicine, MD**

**Mayo Medical School, MN**

**NIH funded**

Pioneered development of high-dose chemotherapy treatment for slow-growing cancers.

**University of Maryland School of Medicine, MD**

1997

Identified a tumor suppressor gene involved in a large percentage of brain, breast, and prostate cancers.

**Columbia University College of Physicians and Surgeons, NY**

1996

Isolated the gene for basal cell carcinoma, a form of skin cancer that affects about 750,000 Americans each year.

**Stanford University School of Medicine, CA**

**NIH funded**

Mapped the first specific prostate cancer gene to chromosome 1.

**Johns Hopkins University School of Medicine, MD**

**NIH funded**

1993

Identified a chemical in broccoli and other cruciferous vegetables that appears to inhibit the development of cancer.

**Johns Hopkins University School of Medicine, MD**

**NIH funded**

Identified a gene responsible for a widespread form of colon cancer.

**Johns Hopkins University School of Medicine, MD**

**NIH funded**

Discovered a genetic mutation that accounts for 60 percent of all cases of hereditary nonpolyposis colon cancer.

**Dana-Farber Cancer Institute, MA**

**Harvard Medical School, MA**

**Johns Hopkins University School of Medicine, MD**

**NIH funded**

1990

Unraveled the basic science behind the breast cancer drug Herceptin, which is effective in 20 to 30 percent of women with aggressive, early stage cases of breast cancer.

**University of Pennsylvania School of Medicine, PA**  
**NIH funded**

Early use of gene therapy to treat recurring brain tumors.

**University of Cincinnati College of Medicine, OH**

1988

Discovered the relationship between a certain gene and an aggressive form of breast cancer. Led to the development of an antibody called Herceptin, which can help about 60,000 women a year and is the first approved treatment designed to attack cancer by attacking the defective protein made by a defective gene.

**David Geffen School of Medicine at UCLA, CA**  
**NIH funded**

1985

Developed deoxycoformycin to cure hairy cell leukemia.

**Ohio State University College of Medicine and Public Health, OH**

1984

Created the "OncoMouse," a transgenic, highly cancer-prone mouse that offers important insights into human cancers.

**Harvard Medical School, MA**

1983

Performed nation's first autologous bone marrow transplant for acute myeloid leukemia.

**Dartmouth Medical School, NH**

1979

Identified human prostate-specific antigen and later developed the PSA blood test for prostate cancer.

**Roswell Park Cancer Institute, NY**

**University at Buffalo State University of New York School of Medicine & Biomedical Sciences, NY**

Identified the mechanism of action of Taxol, the first effective anti-cancer agent for use in the treatment of ovarian cancer.

**Albert Einstein College of Medicine of Yeshiva University, NY**

1977

Identified a cure for testicular cancer.

**Indiana University School of Medicine, IN**

1976

Discovered oncogenes, cancer-causing genes whose normal function has gone awry.

**University of California, San Francisco, School of Medicine, CA**  
**NIH funded**

1970s

Pioneered limb-saving surgery for osteogenic sarcoma, a fast-growing cancer most common in children.

**University of Florida College of Medicine, FL**

1968

Developed first use of ultrasound to detect prostate cancer.

**Wake Forest University Health Sciences (School of Medicine), NC**

1957

Synthesized the anti-cancer drug fluorouracil.

**University of Wisconsin Medical School, WI**

1951

Showed link between smoking and lung cancer.

**Wake Forest University School of Medicine, NC**

**University of Washington School of Medicine, WA**

1950

Published initial convincing evidence of relationship between cancer and cigarette smoking.

**University of Maryland School of Medicine, MD**

1947

First successful leukemia remission.

**Children's Hospital, MA**

**Harvard Medical School, MA**

1942

First use of chemotherapy as a cancer treatment.

**Yale-New Haven Hospital, CT**

1940s

First bone marrow transplant performed.

**University of Chicago Hospitals, IL**

1929

First successful use of hormone therapy to treat prostate cancer.

**University of Chicago Hospitals, IL**

1920s

Invented the oxygen tent and developed the Whipple procedure, a standard surgical technique to treat cancer of the pancreas.

**Columbia University College of Physicians and Surgeons, NY**

1853

Initial use of the microscope in America for diagnosis of cancer.

**University of Maryland School of Medicine, MD**

## Cancer Genomics Promises to Revolutionize Patient Care

When the National Cancer Act was passed in 1971, a diagnosis of cancer was considered a death sentence. Cancer was often diagnosed only after the disease was advanced, having spread to distant parts of the body—when it is most difficult to treat. Doctors had no way of knowing why a treatment might work for one patient but not for another.

For many cancers, treatments still involve surgery to remove the tumor, plus radiation or chemotherapy to kill any remaining cancer cells. Each can result in serious side effects. Many common chemotherapy drugs, for example, cause hair loss, severe nausea and dangerous drops in red and white blood cells. But tremendous progress in medical research—much of it done at U.S. medical schools and teaching hospitals with support from the National Institutes of Health (NIH) and especially, the NIH's National Cancer Institute (NCI)—has led to better and earlier detection of cancer, more targeted and effective treatment, and improved management of side effects.

Testicular cancer is a striking example of the great progress made. Men diagnosed with metastatic testicular cancer in the 1970s had a five percent cure rate. In 1977, researchers at the Indiana University School of Medicine developed a new chemotherapy regimen that boosted cure rates for the advanced form of this disease to 80 percent. Today, the overall five-year survival rate for testicular cancer is 96 percent.

Cancer still remains a formidable foe. Yet, breathtaking research within the field of cancer genomics has the medical community predicting revolutionary changes in the way cancer is understood, diagnosed and treated. Researchers are working to interrupt cancer at many stages—to prevent it from developing, eliminate it early when it does occur, and diminish its devastating effects.

While genetics is the study of single genes in isolation, genomics is the study of all the genes in the genome and the interactions among them and their environments. Cancer genomics has brought about a fundamental shift in the way scientists think about cancer. Cancers that appear on the surface to be the same disease, when analyzed for their “genetic fingerprint,” show important differences that determine how aggressive the cancer will be and how it will respond to certain treatments.

Using genomics technology, researchers are discovering the genetic causes of cancer. By focusing on the genes responsible for the growth and spread of various cancers, researchers can identify leads to future drug targets, and design new treatments to zero in on cancer cells without harming healthy tissue.

### Cancer Survival Rates are Increasing

- In 1976, just half of all cancer patients survived more than five years after their diagnosis. Today, closer to two-thirds (64 percent) are alive five years after they learn they have the disease.
- Deaths rates for the four most common cancers—breast, lung, prostate, and colorectal—began dropping in the late 1990s and continue to do so. Today, almost eight out of 10 women with breast cancer are alive 10 years after their diagnosis, according to data from the NCI.
- The five-year survival rate for children with cancer is now more than 75 percent—a vast improvement over the early 1960s, when childhood cancers were nearly always fatal.

## Prevention

Finding the genetic triggers of cancer gives scientists a chance to try to prevent the disease altogether.

- In 2005, NIH-supported researchers at multiple institutions worked together to show how women with higher levels of an antibody to a protein called human mucin, or MUC1, are less likely to develop ovarian cancer. The findings may lead to a vaccine to prevent ovarian cancer. The institutions involved in this important discovery included **Brigham and Women's Hospital in Boston, New Hampshire's Dartmouth Medical School and the University of Pittsburgh School of Medicine.**
- In 1997, researchers at the **Columbia University College of Physicians and Surgeons** in New York identified a tumor suppressor gene involved in a large percentage of brain, breast, and prostate cancers.
- At **Stanford University School of Medicine** in 1996, NIH funding helped researchers isolate the gene for basal cell carcinoma, a form of skin cancer that affects about 750,000 Americans each year.

## Diagnostics and Screenings

Diagnostic tools based on genomics will help doctors improve accuracy of cancer detection and lead to better screening tests.

- In 2002, NIH-supported researchers at the **Johns Hopkins University School of Medicine** identified a new genetic culprit that may serve as an early marker for prostate cancer and may also help identify new dietary or chemical means of preventing the disease. They used DNA microarray technology, first developed by **Stanford University School of Medicine** in 1995, to analyze more than 6,500 genes and found that one gene was overexpressed in prostate cancer. When they examined 168 prostate cancer tumors, more than 95 percent of the tumors showed overexpression of the gene, making it one of the most consistent biological markers known for prostate cancer.
- Researchers at the medical schools at **University of California campuses in San Diego and Davis** have worked collaboratively, with NIH support, to develop the first new breast CT scanner to reach clinical testing in a generation. This new technology may have the ability to detect tumors much earlier than conventional mammography and is easier on patients since it does not require compression of breast tissue.
- In 1998, NIH-funded research conducted at **University of California, Irvine, College of Medicine**, identified a protein that holds the key to more reliably warning women about early cell abnormalities in the cervix before cancer develops, leading to the development of an improved standardized screening test for cervical cancer.

## Prognosis

Cancer researchers are using genomics information to accurately predict which cancers are likely to spread aggressively and which cancers are most likely to respond to current therapies or require different approaches.

- Researchers at the National Surgical Adjuvant Breast and Bowel Project (led by a researcher from the **University of Pittsburgh Medical Center**) have developed a “recurrence score” for women with breast cancer that helps determine whether these women will need chemotherapy after surgery. The research suggests that almost half of the 50,000 U.S. women diagnosed annually with this form of the disease are at low risk of recurrence and can be spared chemotherapy and its harmful side effects. NSABP is a clinical trials cooperative group supported by the NCI.
- NIH-supported researchers at **Stanford University Medical School** used genetic profiling to identify tumors with gene expression signatures suggestive of active wound healing. The signature they found appeared early in the disease, persisted during treatment and predicted increased risk of metastasis and death in breast, lung, and gastric cancers. This research provides a possible link between cancer progression and wound healing and may be a powerful predictor of the clinical course of several common cancers.

### NIH-Supported Networks

U.S. medical schools and teaching hospitals play integral roles in several NIH-supported networks, including the NCI-supported Comprehensive Cancer Centers. Networks and consortia usually focus on the development or validation of new interventions, ranging from new therapies to genetic-risk counseling to outreach. More than 40 Comprehensive Cancer Centers exist today as unique venues for integrating laboratory, clinical and basic research with health care delivery. All but one is directly affiliated with medical schools and teaching hospitals, and together, they serve as a model of the collaboration between the NIH and the nation's medical schools and teaching hospitals.

The NCI's Specialized Programs of Research Excellence (SPOREs) initiative is an example of the federal government's expanding support for translational research. Most of the 60 SPOREs, which cover 14 different cancers, are located at medical schools, teaching hospitals and affiliated cancer centers. For example, the University of North Carolina SPORE in Breast Cancer's unique goals emphasize multidisciplinary translational research that encompasses the population, clinical, and basic sciences, and examines health disparities between African-American and Caucasian populations.

### Treatment

The ultimate goal of pharmacogenomics—the study of how genes affect the way people respond to medicines—is to tailor medicines to people's unique genetic make-ups. Several targeted drugs are already available, and were either developed at U.S. medical schools or tested in clinical trials through networks of medical schools and teaching hospitals around the country. For example:

- In 2004, **Pennsylvania State University College of Medicine** researchers found that a booster dose of a substance already found in the body appears to be a safe, non-toxic treatment for pancreatic cancer and shows signs of arresting pancreatic cancer cell growth in patients.
- In 2003, the Food and Drug Administration approved a new drug, Velcade, a potent new treatment for an often-fatal bone marrow cancer. The drug was developed based on research by scientists at **Harvard Medical School** who wanted to learn how, when and why cells destroy their own proteins. Their research identified a proteasome, a kind of garbage disposal that chews up abnormal or damaged proteins and can also control cell growth and affect other processes by destroying regulatory proteins. In working to develop drugs that will inhibit the proteasome, these researchers discovered one inhibitor, Velcade, that would block growth of cancer cells and shrink tumors in mice.
- In 1988, researchers at the **David Geffen School of Medicine at University of California, Los Angeles** discovered the relationship between a certain gene and an aggressive form of breast cancer, which led to the development of an antibody called Herceptin. Two years later, scientists at **University of Pennsylvania School of Medicine** unraveled the basic science behind Herceptin, which was added to the chemotherapy treatments for women who have aggressive, early stage breast cancer. Herceptin cut the risk of recurrence of the disease for these patients in half.

Genomics is moving us away from a one-size-fits-all model of patient care. Researchers are using genomic technology to gather a wealth of new information that should aid cancer diagnosis and ultimately therapy. Researchers also hope to pair genomics with imaging to monitor cancer at the molecular level, enabling earlier diagnosis and the ability to measure treatment effects before the cancers are clinically apparent, and make more timely treatment decisions.



### Alzheimer's Disease Centers

U.S. medical schools are home to the majority of the 34 National Institute of Aging-supported Alzheimer's Disease Centers (ADCs). These centers enable researchers to share data and collaborate to translate research advances into improved diagnoses and a possible cures for people with Alzheimer's. ADCs are located at these medical schools and institutions:

- Sun Health Research Institute/Arizona Consortium
- Boston University
- Case Western Reserve University
- Columbia University
- Duke University
- Emory University  
School of Medicine
- Harvard Medical School/  
Massachusetts General Hospital
- Indiana University  
School of Medicine
- The Johns Hopkins University  
School of Medicine
- Mayo Clinic
- Mount Sinai School of Medicine
- Northwestern University Feinberg  
School of Medicine
- New York University  
School of Medicine
- Oregon Health and Science  
University
- Rush Medical College of Rush  
University Medical Center
- Stanford University
- University of Alabama
- University of Arkansas  
College of Medicine
- University of California, Davis,  
School of Medicine
- University of California, Irvine,  
College of Medicine
- University of California,  
Los Angeles, David Geffen  
School of Medicine at UCLA

## Making Inroads into Alzheimer's Disease

Alzheimer's disease devastates the people who have it and their families. It robs individuals of their memories and causes progressive problems with language and behavior. It is the most common cause of dementia among people over age 65, affecting an estimated 4.5 million Americans, according to the National Institutes of Health (NIH).

The risk of developing Alzheimer's disease doubles every five years after age 65—and the disease is on the rise. Researchers at Rush-Presbyterian-St. Luke's Medical Center in Chicago estimate that the number of older people with Alzheimer's will dramatically increase as the population ages—rising to 13.2 million by 2050.

Until recently, the prognosis for patients with Alzheimer's was grim. President Ronald Reagan's slow demise from the disease spotlighted the private battle lost by so many Americans each year.

But the tide is turning on this disease, because of research supported by the NIH at U.S. medical schools and teaching hospitals. Scientists are working to delay the onset of Alzheimer's, slow its progress, and even prevent it altogether. Today, five drugs are available to help control symptoms of the disease.

Research on Alzheimer's disease supported by the NIH is divided into three broad, overlapping areas: causes/risk factors, diagnosis, and treatment/caregiving.

### Cause/Risk Factors

To thoroughly understand what causes Alzheimer's disease, scientists are delving into the basic biology of the aging nervous system, studying how nerve cells lose their ability to communicate with each other. Other investigators are studying factors that may play a role in disease risk.

- An intriguing finding by researchers at Washington University School of Medicine in St. Louis suggests that Alzheimer's disease may be due to abnormalities in the regions of the brain involved in the process of daydreaming by young, healthy people. The NIH-supported study was published in 2005.
- University of Rochester Medical Center researchers found in 2005 that a gene called *Meox2* is underactive in the brains of Alzheimer's patients. By restoring the gene's activity in human brain cells, the NIH-supported researchers stimulated new blood vessels and boosted the level of a protein that removes the toxins that build up in the brain tissue of Alzheimer's patients. These results have opened the door to testing this approach as a potential new treatment.

#### Alzheimer's Disease Centers cont'd

University of California,  
San Diego, School of Medicine  
University of California,  
San Francisco, School of Medicine  
University of Kentucky  
College of Medicine  
University of Michigan  
University of Pennsylvania  
School of Medicine  
University of Pittsburgh  
University of Southern California  
University of South Florida  
University of Texas, Southwestern  
Medical Center at Dallas  
Southwestern Medical School  
University of Washington  
Washington University  
School of Medicine

- Exercise slows development of Alzheimer's-like brain changes in mice, according to NIH-supported research published in 2005 at University of California, Irvine, College of Medicine.
- Loss of body mass over time appears to be strongly linked to older adults' risk of developing Alzheimer's disease, and the greater the loss, the greater the chance of a person developing the disease, according to a 2005 NIH-supported study at Rush University Medical Center.

#### Diagnosis

Most current treatments work best at the earliest stages of disease. A wave of research, therefore, has been aimed at early detection of Alzheimer's disease. With NIH support, researchers at medical schools and teaching hospitals around the country are looking for new markers and improving neuro-imaging technologies to identify the first brain changes that eventually result in Alzheimer's disease.

- In 1988, the University of Washington School of Medicine researchers developed, with NIH support, the Clinical Dementia Rating, used worldwide in the diagnosis of Alzheimer's disease.
- In 2004, NIH-supported researchers at the University of Pittsburgh School of Medicine discovered a novel tracer they could use with positron emission tomography (PET) to visualize amyloid plaques in individuals with Alzheimer's disease. This new technique should help researchers learn how and when the disease originates and to evaluate new therapies.
- Researchers at the New York University (NYU) School of Medicine used NIH support to develop a new computer program in 2005 to show that the region of the brain called the hippocampus is the very first region to be affected by Alzheimer's —years before symptoms occur.
- NIH-supported scientists from Northwestern University and Rush University Medical Center are using nanotechnology to develop a clinical test capable of diagnosing Alzheimer's in its earliest stages. They can identify miniscule amounts of a toxic protein in human cerebrospinal fluid—which is detectable before the memory-robbing plaques appear in the brain.

#### Treatment/Caregiving

Researchers are working hard to discover and develop therapies that may help treat symptoms or slow the progress of the disease. Many of these interventions are now being tested in clinical trials. Scientists and many health care professionals are also seeking better ways to help people with Alzheimer's disease and their caregivers cope with the decline in mental and physical abilities and the difficult behaviors that accompany the disease.

- In 1997, NIH-supported scientists at the University of California, Irvine, College of Medicine completed the first study to show that vitamin E and an anti-Parkinson's drug called selegiline can significantly delay the progress of Alzheimer's disease.

- In 2004, researchers at the University of South Carolina College of Medicine discovered a class of drugs that blocks activation of inflammatory cells, which may be used to treat Alzheimer's disease, multiple sclerosis, stroke and spinal cord injury.
- A 2004 NIH-supported study by researchers at the University of Miami School of Medicine and Mount Sinai Medical Center suggests that people with early Alzheimer's disease are more capable of learning than previously thought. They can still be taught to recall important information and better perform daily tasks.
- Researchers at the University of Minnesota Medical School in Minneapolis, with NIH support, were able to reverse memory loss in mice with significant brain degeneration for the first time. This 2005 breakthrough suggests that perhaps, in the future, the same process could be used for Alzheimer's patients.
- Short-term intensive counseling in conjunction with readily available support can significantly reduce the long-term risk of depression among husbands and wives caring for spouses with Alzheimer's disease, according to research from the NYU School of Medicine.

### **On the Horizon**

The research discoveries highlighted above are helping scientists focus on the key issues in the prevention, detection and treatment of Alzheimer's disease. Additional NIH-supported research currently underway at the nation's medical schools and teaching hospitals holds promise for future breakthroughs on this disease. For example:

- Misfolded proteins are implicated in several degenerative diseases, including Alzheimer's disease. Scientists at Yale University School of Medicine are studying mechanisms that help proteins fold into their active, functional state.
- Researchers at the University of Pennsylvania School of Medicine are using NIH support to develop drugs that bind to and stabilize microtubules, protein structures found within cells. Their research suggests that microtubule-stabilizing drugs may help correct the problems caused by clumped tau proteins in the nerve cells of mice and, as a result, could be used to treat Alzheimer's and other related diseases in humans.
- At Weill Medical College of Cornell University, scientists have encouraging evidence that antibodies derived from human plasma can capture the beta-amyloid protein in blood and may be able to improve patients' thinking abilities. Beta-amyloid is a central component of the senile plaque in the brains of Alzheimer's patients, and its toxicity against brain cells is believed to be a prime cause of the illness.

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/research/ftp](http://www.aamc.org/research/ftp)



## Understanding Aging, Combating Disease, Improving Life: America's Medical Schools and Teaching Hospitals

In the past century, life expectancy has nearly doubled. Today there are 35 million Americans age 65 and older. By 2030, this population group will likely double. More elderly Americans will present an array of health care and research challenges and opportunities in the decades to come.

Most notably, today, some 4.5 million Americans have Alzheimer's disease, the leading cause of dementia in people over the age of 65. By 2050, the number of Americans with Alzheimer's is expected to triple to an estimated 13.2 million people.

For more than 60 years, America's medical schools and teaching hospitals have teamed up with the National Institutes of Health (NIH) to improve the health of all Americans, throughout their lives. Their research efforts have resulted in important advances in understanding the normal process of aging and in better diagnoses, treatment and even prevention strategies for many of the diseases that affect the elderly, particularly Alzheimer's disease.

Listed on these pages are a few of the many examples of research progress by NIH-funded investigators and scientists at medical schools and teaching hospitals on aging, Alzheimer's, and other diseases that affect the elderly. To learn more about these and other advances, go to [www.aamc.org/innovations](http://www.aamc.org/innovations)

### **2005**

Researchers found that loss of body mass over time is related to older adults' risk of developing Alzheimer's disease. These findings, the first link discovered between body mass and Alzheimer's, established that the greater the loss of body mass, the greater the chance of a person developing the disease.

**Rush University Medical Center**

**NIH Funded**

Researchers identified changes in the blood platelets of Alzheimer's disease patients, indicating that platelets may serve a useful way to monitor drug efficacy in clinical trials.

**Univ. Texas Southwestern Medical Center/Gambro Center, TX**

**NIH Funded**

Researchers pinpointed the first major gene, called complement factor H (CFH), to determine an individual's risk for developing age-related macular degeneration (AMD). The gene is estimated to be responsible for 43 percent of the risk of AMD among older adults. The advance sheds light on the mechanisms underlying the disease and could lead to new avenues for treatment. It may also help to identify those at risk, earlier.

**Duke University School of Medicine**  
**Vanderbilt University Medical Center**  
**NIH Funded**

This year, for the first time in history, researchers at University of Minnesota Medical School were able to reverse memory loss in mice with significant brain degeneration. By turning off a specific gene, the mice's symptoms of dementia not only stopped, they were reversed.

**University of Minnesota Medical School**  
**NIH Funded**

#### **2004**

Amid ongoing efforts to find new drugs to treat Alzheimer's disease and related brain disorders, researchers at the University of Pennsylvania School of Medicine discovered that paclitaxel (Paxceed), a potent anticancer drug, increases the function of nerve cells in mice with neurodegeneration.

**University of Pennsylvania School of Medicine**  
**NIH Funded**

Researchers at the Medical University of South Carolina College of Medicine discovered a class of drugs that blocks activation of inflammatory cells, which may be used to treat conditions caused by inflammation of the brain or spinal cord, such as Alzheimer's disease, stroke, and multiple sclerosis.

**Medical University of South Carolina College of Medicine**  
**NIH Funded**

Researchers identified two new locations, and confirmed three previously known locations, in the human genome implicated in age-related macular degeneration, or progressive vision loss.

**University of Michigan Medical School**  
**University of Pennsylvania School of Medicine**  
**NIH Funded**

Researchers discovered a novel amyloid-imaging positron emission tomography (PET) tracer, called Pittsburgh Compound B (PIB). PIB will enable researchers to define the role of amyloid plaques in the development of Alzheimer's development and may someday help identify those at risk of the disease.

**University of Pittsburgh School of Medicine**  
**NIH Funded**

**2003**

Researchers identified a single gene, GSTO1, that influences the age at which individuals develop symptoms of Alzheimer's and Parkinson's diseases.

**Duke University School of Medicine**

**NIH Funded**

Scientists determined that Zoloft, a drug commonly used to treat depression, also improves quality of life and alleviates disruption in daily activities of Alzheimer's patients who also suffer from major depression.

**Johns Hopkins University School of Medicine**

**NIH Funded**

A patient at Weill Medical College of Cornell University received the first-ever gene therapy for Parkinson's disease.

**Joan and Stanford I. Weill Medical College of Cornell University**

**NIH Funded**

National Age-Related Eye Disease Study estimated that if every American at risk of advanced age-related macular degeneration took daily supplements of antioxidant vitamins and zinc, more than 300,000 people could avoid vision loss over the next five years.

**Johns Hopkins University School of Medicine**

**NIH Funded**

**2002**

Researchers uncovered a link between gait disorders and non-Alzheimer's dementia in older people. Seniors with neurological gait abnormalities were at increased risk—nearly two to one—for developing dementia.

**Albert Einstein College of Medicine of Yeshiva University**

**NIH Funded**

**2001**

Researchers found that the enzyme COX-2 causes mice to develop memory problems as they age, mimicking Alzheimer's disease. COX-2 is also linked to loss of brain cells in animal bodies, including Parkinson's and Lou Gehrig's diseases.

**Johns Hopkins University School of Medicine**

**NIH Funded**

**2000**

Researchers reported that memory loss from minor strokes deep in the brain could now be distinguished from that caused by mild Alzheimer's disease.

**University of California, Davis, School of Medicine**

**NIH Funded**

**1997**

Researchers found that different Alzheimer's disease genes cause the same problem in the mouse brain. The amyloid plaques that form in the brains of Alzheimer's disease patients are not the end products of the disease but the beginning of it.

**Johns Hopkins University School of Medicine**

**NIH Funded**

Researchers found that vitamin E and an anti-Parkinson's disease drug can significantly delay the progress of Alzheimer's disease. This finding was the first to show the impact of vitamin E on brain aging.

**University of California, Irvine, College of Medicine**  
**NIH Funded**

Scientists discovered why proteins fold properly, which may lead to treatments for diseases such as Alzheimer's, Huntington's, and Parkinson's—which are related to proteins that do not fold properly.

**Yale University School of Medicine**  
**NIH Funded**

**1996**

Researchers discovered that a glitch with the protein, presenilin, may be an early problem in inherited Alzheimer's disease.

**Johns Hopkins University School of Medicine**  
**NIH Funded**

Researchers developed a mouse model of Alzheimer's disease by inserting an Alzheimer's gene directly into the mouse's genetic material. The animal developed many of the same problems that patients with Alzheimer's disease experience.

**University of Minnesota Medical School**  
**NIH Funded**

**1995**

Scientists introduced the concept of geriatric syndromes as health conditions common among older adults that result from multiple coexisting impairments. For example, the problem of dizziness in elderly people is more often a result of multiple problems—described as a “geriatric syndrome”—than a symptom of a particular illness.

**Yale University School of Medicine**  
**NIH Funded**

**1993**

Researchers discovered that that Apolipoprotein E (ApoE) is a major genetic risk factor for Alzheimer's disease. People who inherit a version of the ApoE gene—the version known as E4—are at significantly increased risk for developing Alzheimer's disease later in life. E4 is related to half of all late onset Alzheimer's disease cases.

**Duke University School of Medicine**  
**NIH Funded**

**1988**

Investigators determine that falling, long considered an inevitable consequence of aging, is a diagnosable health condition that results from the effect of multiple impairments and diseases acting together.

**Yale University School of Medicine**  
**NIH Funded**

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/research/ftp](http://www.aamc.org/research/ftp)

## Influenza

While bird flu receives major attention, many forms of influenza, caused by a variety of flu viruses, threaten human health. In the United States more than 200,000 people are hospitalized and about 36,000 die from the flu and its complications every year. Scientists are concerned that a new flu virus will emerge in this century and cause a severe pandemic similar to the one in 1918, which killed 20 million people. For this reason, research institutions and health departments worldwide are cooperating to track flu outbreaks in humans and animals.

- Last year, researchers at **Mount Sinai School of Medicine of New York University** collaborated with other scientists to reconstruct the 1918 Spanish flu virus to learn more about the virus and predict future pandemics. They discovered that the drug Tamiflu protects mice against the Spanish flu, suggesting that humans could be protected as well.
- To make delivering flu vaccine easier, doctors at the **Virginia Commonwealth University Center for Drug Studies** in Richmond are developing an auto-injector.

## Infectious Diseases— Making Progress on a Perpetual Challenge

Infectious diseases are a perpetual threat to human health. Some, like polio and smallpox, are largely a memory in most countries because medical research produced lifesaving vaccines. But just as one infectious disease is conquered, a new one emerges—or an old enemy reappears. Most recently, bird flu has caused alarm among researchers and the public.

According to the 2004 *World Health Report* of the World Health Organization (WHO), infectious diseases accounted for about 26 percent of the 57 million deaths worldwide in 2002. Infectious diseases are the second-leading cause of death globally after cardiovascular disease, but the leading cause of death in infants and children. While deaths in the United States from infectious diseases declined markedly during the 20th century, influenza and pneumonia remain the 7th leading cause of death, according to the U.S. Centers for Disease Control.

The National Institutes of Health (NIH), principally through the National Institute of Allergy and Infectious Diseases (NIAID), supports research at the nation's medical schools and teaching hospitals to combat HIV/AIDS, influenza (including bird flu), malaria, tuberculosis, SARS, West Nile virus, viruses that cause fatal diarrhea in infants, and potential bioterror agents. Here are just a few examples of laboratory research and patient studies.

### Bird Flu

Bird flu, known as H5N1, is a highly contagious form of influenza spread by birds. It was first detected in humans in Southeast Asia in the late 1990s. As of early March, the WHO had confirmed 175 cases of avian flu in humans, with 96 reported deaths. U.S. medical schools and teaching hospitals are playing a critical role in the nation's preparations for a potential bird flu pandemic.

- An NIAID-supported network of seven medical schools and teaching hospitals is leading the NIH's effort to evaluate new vaccines for avian flu. Numerous clinical trials with this vaccine are currently being conducted in healthy adults, healthy seniors, and children. Preliminary results of the initial trial show promise that the vaccine is safe, and causes an immune response that will protect those vaccinated. The seven institutions are:

- \* **Baylor College of Medicine**
- \* **University of Cincinnati Children's Hospital Medical Center**
- \* **Saint Louis University Health Sciences Center**

### **Malaria and Tuberculosis**

Two other deadly diseases are receiving crucial attention from U.S. medical schools and teaching hospitals with NIH support—malaria and tuberculosis (TB). Malaria kills 1 million people around the globe each year—many of them children.

- In 2002, scientists at **Stanford University School of Medicine** were part of the team that sequenced the genomes of the most important malaria-causing parasite and of the main mosquito that carries the parasite. This information is being used to guide the design of effective drugs and vaccines.

Tuberculosis also remains a very serious global health problem. Even in the United States, 10 to 15 million people have latent infection, and 10 percent of them will develop active disease at some point in their lives.

- In 2003, scientists at the **University of California, Los Angeles School of Medicine** demonstrated that a new vaccine against TB provides more potent protection in guinea pigs than the current vaccine. Human studies are forthcoming.

- \* **University of California, Los Angeles, Center for Vaccine Research**
- \* **University of Maryland School of Medicine**
- \* **University of Rochester School of Medicine and Dentistry**
- \* **Vanderbilt University Medical Center**

- Last year, NIH-funded researchers at the **University of Pittsburgh School of Medicine** developed a novel viral vector method of producing vaccines in only six weeks, four to six times faster than usual. Reducing vaccine production time will help to curb disease outbreaks before they reach pandemic proportions. Using this method, a vaccine against avian flu was created, and preliminary animal testing has shown its efficacy in significantly reducing symptoms.
- Also backed by a grant from the NIAID, scientists at **Indiana University School of Medicine** are collaborating with **Purdue University's College of Agriculture and School of Veterinary Medicine** to study a harmless form of adenovirus as a transmitting agent for a vaccine to fight off highly virulent strains of the avian flu viruses.

### **HIV/AIDS**

In 1981, HIV/AIDS was an emerging disease just beginning to garner the attention of the scientific community. Today, approximately 40 million people throughout the world are infected with HIV—and 90 percent of new infections occur in developing countries. In Botswana, for example, one in three adults is infected. In 2004, 3 million people died from AIDS. HIV/AIDS continues to be a major threat in the United States as well, where 40,000 new infections occur every year.

One of the great triumphs of medical research is the development of potent antiretroviral drugs that have prolonged and improved the lives of people infected with HIV. Deaths in the United States have dramatically declined since the 1990s, when combination antiretroviral therapy was introduced. In 2004, 15,798 people died of AIDS in the United States—less than one-third the number of deaths in 1995. U.S. medical school researchers are working hard to end this worldwide scourge.

- In 2006, the NIH-sponsored Strategies for Management of Anti-Retroviral Therapy (SMART) study found that continuous antiretroviral therapy is superior to episodic therapy. This international HIV/AIDS trial was conducted through the NIH-supported Community Programs for Clinical Research on AIDS network of 318 clinical sites in 33 countries. Researchers at **Columbia University College of Physicians and Surgeons** served as members of the SMART study team.
- Supported by the NIH, researchers at the **Weill Medical College of Cornell University** recently found that a combination of microbicides successfully blocked vaginal transmission of a virus similar to SIV and HIV in non-human primates. Based on these results, a combination of microbicides could potentially provide a safe, effective and practical way to prevent vaginal transmission of HIV to women. The next step is to conduct clinical trials in humans to determine safety and optimal dosage.
- Individuals who have more copies of a gene that helps to fight HIV are less likely to become infected with the virus or to develop AIDS than those with fewer copies of the gene, according to a 2005 NIH-funded study by researchers at the **University of Texas Health Science Center and the Veterans Administration Center for AIDS**

### **A Sustained Commitment to Children**

A new vaccine to prevent rotavirus infections, the most common cause of fatality due to severe diarrhea and vomiting in infants and young children, is available in Europe, Latin America, and parts of Southeast Asia, and is expected to become available in the United States by 2008. This breakthrough discovery was the result of a 23-year partnership between Richard Ward, Ph.D., and David Bernstein, M.D., researchers at **Cincinnati Children's Hospital Medical Center**.

With NIH support, Ward and Bernstein did the necessary laboratory research and early clinical studies to devise a vaccine based on a weakened strain of the virus that produces an immune response and protection without causing illness. They found a commercial partner in Avant Immunotherapeutics, a necessary step to move the vaccine into large-scale clinical trials. After the vaccine was found to be effective and safe in very large studies involving more than 60,000 children worldwide, GlaxoSmithKline now manufactures the vaccine, called Rotarix, under a sublicense from Avant. It is anticipated that with widespread global immunization, this vaccine could prevent 50,000 hospitalizations in the United States and the loss of more than 600,000 lives worldwide each year.

**and HIV-1 Infection** in San Antonio. This discovery could lead to a screening test that identifies individuals who have a higher or lower susceptibility to HIV/AIDS, potentially enabling clinicians to adapt treatment regimens, vaccine trials, and other studies accordingly.

- In 1999, a joint U.S.-Uganda study, led by researchers at the **Johns Hopkins University School of Medicine** in Baltimore, found an inexpensive, simple, and effective drug regimen to reduce HIV transmission from an infected mother to her newborn. With support from the NIH, they found that a single dose of the antiviral drug nevirapine given to an HIV-infected woman and her infant within 72 hours of birth significantly reduced HIV transmission. This study has helped provide a viable and inexpensive strategy to prevent mother-to-child transmission in developing countries where HIV-infected mothers regularly practice breastfeeding.
- In an NIH-supported study in the early 1990s, **Emory University School of Medicine** scientists discovered two anti-HIV drugs, lamivudine and emtricitabine. Lamivudine is currently used by 80 percent of HIV-infected patients in the United States, as part of a combination therapy.

### **Bioterror Preparedness**

Since the 2001 anthrax attacks, the United States has become more cognizant of the potential for terrorist attacks using agents of bioterrorism. This heightened awareness has compelled the federal government to expand its biodefense research program. The NIAID has at least 50 major research initiatives underway involving NIH scientists, medical school researchers, and industrial partners.

- Within weeks of the 2001 anthrax attacks, **Harvard Medical School** scientists, funded by the NIH, discovered that small molecules they had created were able to prevent the bacteria's lethal toxin from entering cells. Researchers currently are using this technique to develop a potential therapy against anthrax.
- In 2005, NIAID completed a national network of 10 Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), to support research focused on countering threats from bioterror agents and emerging infectious diseases. Each center is working to develop next-generation treatments, vaccines, and diagnostic tools for diseases such as anthrax, plague, smallpox, tularemia, botulism, and West Nile virus. Several of the nation's medical schools are involved in these centers, including:

- \* **University of California, Irvine, School of Medicine**
- \* **University of Colorado School of Medicine**
- \* **Duke Medical Center**
- \* **Harvard Medical School**
- \* **University of Chicago Pritzker School of Medicine**
- \* **University of Maryland School of Medicine**
- \* **University of Massachusetts Medical School**
- \* **University of Texas Medical Branch, Galveston**
- \* **University of Washington School of Medicine**
- \* **Washington University School of Medicine, St. Louis**

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## Confronting Infectious Diseases— America's Medical Schools and Teaching Hospitals

Diphtheria, malaria, typhoid, polio, hepatitis C, HIV/AIDS, tuberculosis, SARS, smallpox, avian flu.

The list of infectious diseases that emerge and re-emerge challenges researchers, clinicians, and the public health community to continually develop more effective preventions and treatments. For decades, the National Institutes of Health (NIH) and America's medical schools and teaching hospitals have worked together to stop the spread of infectious diseases through new knowledge, better treatments, and life-saving vaccines.

Following are some recent examples of NIH-funded research advances achieved at the nation's medical schools and teaching hospitals to halt infectious diseases:

### 2006

Discovered how and where Listeria bacteria invade cells in the intestine. Listeria can cause potentially fatal infections in the blood or brain, or miscarriages in pregnant women. This discovery will enable scientists to develop better ways to protect against the disease.

**Stanford University School of Medicine**  
**NIH-funded**

### 2005

Discovered a genetic marker that may identify individuals at greater risk of life-threatening infection from the West Nile virus. Understanding who is susceptible to West Nile could help identify those most in need of a vaccine, when one is developed.

**Baylor College of Medicine**  
**University of Texas School of Public Health at Houston**  
**NIH-funded**

A novel 3-D imaging technique has revealed, for the first time, the brain damage inflicted by AIDS. However, it also showed that the antiretroviral drugs used to protect the immune system from HIV do not protect the brain, demonstrating the need for improved therapeutics.

**David Geffen School of Medicine at UCLA**  
**University of Pittsburgh School of Medicine**  
**NIH-funded**

Developed a novel viral vector method of producing vaccines in only six weeks – four to six times faster than usual. Reducing vaccine production time will help to curb disease outbreaks before they reach pandemic proportions. Using this method, a vaccine against avian flu was created, and preliminary animal testing has shown its efficacy in significantly reducing symptoms.

**University of Pittsburgh School of Medicine**  
**NIH-funded**

Developed an animal model of Lyme disease making it possible to conduct a study of how it affects the nervous system and to develop, patent, and obtain FDA/USDA approval of a diagnostic test now poised to replace the current diagnostic protocol used in humans.

**Tulane University Health Science Center**  
**NIH-funded**

Led a nationwide study that proved the safety and efficacy of an acellular vaccine for whooping cough (pertussis) in adults and adolescents.

**University of Rochester Medical Center**  
**NIH-funded**

Developed a DNA vaccine for *Chlamydia pneumoniae*. This vaccine may eliminate the organism from the respiratory tract and thereby reduce morbidity and mortality of diseases such as atherosclerosis, heart disease, chronic obstructive pulmonary disease, and asthma associated with infection by this organism.

**The University of Texas Health Center at Tyler**  
**NIH-funded**

## **2004**

Discovered new information about how viral proteins move between cells and alert the immune system, suggesting that a double-punch approach to vaccine design could lead to more effective vaccines.

**Pennsylvania State University College of Medicine**  
**NIH-funded**

Created an early detection method for respiratory syncytial virus, the major cause of hospitalization among children under 5. It detects viral particles in hours, not days.

**Vanderbilt University Medical Center**  
**NIH-funded**

Created a virtual computer model to visualize what happens in the lungs after the inhalation of the bacterium that causes tuberculosis. The computer simulation revealed new information about how the immune system is able to contain the spread of the bacteria that is normally impossible to see in humans or animals.

**University of Michigan Medical School**  
**NIH-funded**

In the largest comparison of AIDS treatments involving multiple drugs given together, researchers found that one specific combination was the most effective way to combat HIV. The “cocktail” included AZT, Efavirenz, and Zidovudine. Clinicians now know that the most effective way of treating HIV is while the virus is still vulnerable and before it takes its toll on the immune system.

**Stanford University School of Medicine**  
**NIH-funded**

Discovered that half of the HIV-positive patients in a small study were able to live medication-free for more than a year without developing AIDS-related illnesses. A reduced drug regime could provide some patients with a healthier quality of life and enable twice as many people to be treated for the same cost while being exposed to fewer toxic side effects from the drugs.

**Stanford University School of Medicine**  
**NIH-funded**

Led a national study of more than 1,000 participants that showed that a flu vaccine used in other parts of the world is also safe and effective in the United States.

**University of Rochester Medical Center**  
**NIH-funded**

**2003**

Discovered the role of T-helper cells in controlling infection by a tumor virus.

**Ohio State University College of Medicine and Public Health**  
**NIH-funded**

Proved that drugs aimed at preventing HIV transmission may be an effective way to reduce the incidence of HIV in places where the epidemic is rampant and where condom use is prohibited. Specifically, researchers discovered that vaginal transmission of the HIV virus among primates could be completely prevented when specific drugs were added to the vagina shortly before addition of the virus.

**Tulane University School of Medicine**  
**NIH-funded**

Created methods to replicate the hepatitis C virus in two human cell lines, enabling the development of novel therapies to treat chronic hepatitis C infection and ways to reduce the potential risk of developing liver cirrhosis and liver cancer.

**Tulane University School of Medicine**  
**NIH-funded**

Identified, using genomic and proteomic technology, all of the genes and proteins involved in anthrax infection, providing valuable new information for potential vaccine development and new targets for treatment.

**University of Michigan Medical School**  
The Institute for Genomic Research  
Scripps Research Institute  
**NIH-funded**

**2002**

Discovered a novel genetic trait that protects its carriers from the deadliest forms of malaria, while people without the trait are more likely to succumb to its fatal consequences.

**Duke University School of Medicine**  
**NIH-funded**

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## The Women's Health Initiative

The largest, most comprehensive study of postmenopausal women's health ever conducted in the United States, the Women's Health Initiative (WHI), was launched in 1991. It is supported by NHLBI to address the most common causes of death, disability, and impaired quality of life in postmenopausal women. These causes include heart disease, breast and colorectal cancer, and osteoporosis. It consisted of a set of clinical trials and an observational study, which together involved nearly 162,000 generally healthy women ages 50-79 enrolled at 40 clinical centers nationwide, many of which are U.S. medical schools and teaching hospitals. Some recent results:

- WHI's Dietary Modification Trial, reported in 2006, failed to find that a lower-fat diet provides a significantly beneficial reduction in women's risk for breast cancer, heart disease, stroke, or colorectal cancer in healthy postmenopausal women.
- Researchers from the WHI Calcium and Vitamin D Trial, whose lead investigators are at the Ohio State University Medical Center and the University at Buffalo State University of New York School of Medicine and Biomedical Sciences, reported in 2006 that calcium and vitamin D supplements in postmenopausal women have a modest benefit on bone mineral density and prevent hip fractures in certain groups, but do not prevent colorectal cancer or other bone fractures.

## Heart Disease in Women – Getting the Attention it Deserves

Overall U.S. death rates from heart disease have been cut in half since 1950, according to U.S. Vital Statistics. Yet heart disease remains the leading cause of death today. For women, heart disease presents a special challenge—one in three will die of heart disease. About 3 million American women have had a heart attack; two-thirds of those women did not make a full recovery. Research supported by the National Institutes of Health (NIH) and conducted at U.S. medical schools and teaching hospitals is making progress in determining the risk factors for heart disease, how these factors differ between women and men, and what diagnostic measures and treatments are most appropriate and effective for women.

The Framingham Heart Study—a long-term epidemiologic study launched in 1948, currently based at the Boston University School of Medicine, and supported by NIH's National Heart, Lung, and Blood Institute (NHLBI)—has identified numerous behaviors and conditions that increase women's risk of heart disease. Among the study's key findings:

- At menopause, a woman's heart disease risk starts to increase significantly.
- High blood pressure, smoking, a high level of LDL cholesterol or a low level of HDL cholesterol, obesity, physical inactivity, and diabetes all predispose women to develop heart disease.
- A diagnosis of diabetes in women increases the risk of having heart disease more so than it does for men. For example, the risk of heart attack is 150 percent greater in diabetic than nondiabetic women (but only 50 percent greater in diabetic men versus nondiabetic men).

Recent major multicenter research trials in women supported by NHLBI include the Women's Health Initiative (WHI) and the Women's Ischemia Syndrome Evaluation (WISE) study. For these large studies, investigators at U.S. medical schools, teaching hospitals, and other clinical centers recruit and follow individuals in various clinical trials and observational studies. Some important findings from NHLBI-supported research follow.

## The Women's Health Initiative cont'd

- The WHI Observational Study, which involved more than 40 academic medical centers, yielded important findings in 2003 on the effects of exercise on cardiovascular disease, breast cancer, and diabetes. Among the findings, exercise duration increases the degree of protection against heart disease, and walking is as effective as more vigorous exercise in protecting against breast cancer.
- The WHI Memory Study, whose principal investigator is at Wake Forest University School of Medicine, released results in 2003 indicating that women taking combination hormone therapy have twice the rate of dementia, including Alzheimer's disease, than women not taking the medication.

## Cause/Risk Factors

It has become clear that many factors influence a woman's risk of heart disease.

- In 2004, researchers from the Northwestern University Feinberg School of Medicine found that young women with two or more major heart disease risk factors (diabetes, high blood pressure, unhealthy cholesterol level, high body mass index, or smoking), screened between 1967 and 1973, were less likely to be alive in 2001 than their counterparts with none of these risk factors. Only 20 percent of the women in the study were classified as "low risk," demonstrating the urgent need to establish heart-healthy habits among women early in life.
- Stress hormone levels in working mothers rise each morning and stay high until bedtime, putting them at higher risk than other working women for health problems such as heart attack, according to a 1997 study by Duke University Medical Center researchers.
- Forty percent of African-American women in the Jackson Heart Study, based at the University of Mississippi Medical Center, have metabolic syndrome, as compared with 29 percent of men. The syndrome is characterized by a concurrence of several risk factors for heart disease—abdominal obesity, low HDL cholesterol, elevated triglycerides, high blood pressure, and abnormal blood sugar.
- To identify genes underlying heart attack, stroke, and other chronic diseases in the three generations of Framingham Heart Study participants, NHLBI and Boston University School of Medicine launched the Framingham Genetic Research Study in 2006.

## Diagnosis

Several recent studies have identified the need for improvements in the diagnosis of heart disease in women. Acknowledging the gender differences in heart disease, NHLBI Director Elizabeth G. Nabel, M.D., believes, "We must think out of the box when it comes to the evaluation and diagnosis of heart disease in women."

- The WISE study, led by researchers at Cedars-Sinai Medical Center in Los Angeles, reported in 2006 that heart disease goes undiagnosed in as many as 3 million women because cholesterol plaque may not build up into major blockages, as it does in men, but instead spreads evenly throughout the artery wall, eventually starving the heart muscle of its blood supply. As a result, some diagnostic tests reveal "clear" arteries, falsely indicating low risk.
- Johns Hopkins Medical Institutions researchers revealed in 2003 that the results of some exercise tests indicate a different prognosis for women than they do for men. An electrocardiographic finding of "ST-segment depression," indicating low blood flow to the heart muscle, may be an ominous sign in men, but is unrelated to increased risk in women. However, two measures of cardiovascular fitness—exercise capacity and heart rate recovery—are useful for predicting risk in women.

- High levels of C-reactive protein—an indicator of inflammation—are associated with an increased risk of developing high blood pressure in women, according to a 2003 study by researchers at Brigham and Women’s Hospital and Harvard Medical School, analyzing data from the NHLBI-supported Women’s Health Study. This suggests high blood pressure is, in part, an inflammatory disorder and that C-reactive protein can be a useful tool for identifying women who need to reduce their risk of high blood pressure.

### **Treatment and Prevention**

Over the past 50 years, the risk of dying of heart failure within 10 years after diagnosis dropped by about one-third for both women and men, according to a 2002 report from the Framingham Heart Study. Importantly, the incidence of heart failure has also decreased by about one-third among women (although it has changed very little for men), largely due to the availability of better drugs for controlling high blood pressure. In addition, many more patients survive a heart attack and return to normal activity within weeks thanks to medications that help control blood clotting, high blood pressure and high cholesterol, improvements in emergency care, and less invasive and more effective heart surgery.

But new findings are emerging in the treatment and prevention of heart disease in women.

- Researchers at Yale-New Haven Hospital determined that digoxin therapy for heart failure had different effects in women than in men. Although the drug reduced the hospitalization rate for men, it was linked to an increased risk of death for women taking the drug, compared with women taking a placebo.
- In 2002, the WHI estrogen-plus-progestin study was stopped when it was determined that participants were at an increased risk of heart attacks, breast cancer, stroke, and blood clots. It was determined that the risks involved in the use of these hormones outweighed the benefits—reduced risk of hip and other bone fractures, and colon cancer. These results significantly changed hormone therapy recommendations for postmenopausal women. Two years later, the WHI estrogen-alone study was halted after finding that participants were at an increased risk for stroke, yet the hormone had no significant effect on the risk of heart disease. The WHI Extension Study will follow WHI participants through 2010 to collect longer-term data on the effects of hormones on women’s health.

### **Outreach and Education**

A 2005 survey from the American Heart Association shows that more women are getting the message that heart disease is the primary cause of death in women. According to the survey, 55 percent of American women know that heart disease is the leading killer of women, up from 34 percent in 2000. Campaigns like NHLBI’s “The Heart Truth” are making a difference, and several medical school faculty are playing a role. In 2005, Anne Taylor, M.D., professor of cardiology at the University of Minnesota Medical School helped launch “The Heart Truth Women of Color Initiative” with First Lady Laura Bush and NHLBI’s Dr. Nabel. Susan K. Bennett, M.D., of George Washington University Medical Center in Washington, D.C., also serves as a medical spokesperson for “The Heart Truth” campaign.

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## Heart Disease: A Special Challenge for Women

Heart disease is the leading cause of death in the U.S. For women, it presents a special challenge:

- Heart disease kills one in every three women.
- Eighty percent of women ages 40-60 have one or more risk factors for heart disease.
- Three million American women have had a heart attack; two-thirds of those women did not make a full recovery.

U.S. medical schools and teaching hospitals, together with the National Institutes of Health (NIH), are working to reduce the number of heart disease-related deaths in women by identifying their unique risk factors and developing more effective methods to diagnose and treat heart disease in women.

The following examples of NIH-funded research advances achieved at the nation's medical schools and teaching hospitals hold promise for reducing the incidence of heart disease in women:

### **2006**

Found that heart disease goes undiagnosed in as many as 3 million women because cholesterol plaque may not build up into major blockages as it does in men, but instead spreads evenly throughout the artery wall, eventually starving the heart muscle of its blood supply. As a result, some diagnostic tests reveal "clear" arteries, falsely indicating low risk.

**Cedars-Sinai Medical Center**

**NIH funded**

Determined that calcium and vitamin D supplements in postmenopausal women have a modest benefit to bone mineral density and prevent hip fractures in certain groups, but do not prevent colorectal cancer or other bone fractures.

**Ohio State University Medical Center**

**University at Buffalo SUNY School of Medicine and Biomedical Sciences**

**NIH funded**

**2005**

Determined that the stress hormone, cortisol, causes fetal heart muscle cells to multiply faster than normal. A stressed mother's cortisol levels can cross the placenta and affect the fetus. This establishes that high stress in mother during pregnancy can lead to abnormal growth of the baby and increase its risk for heart disease.

**Oregon Health & Science University**  
**NIH funded**

Forty percent of African-American women in the Jackson Heart Study, based at the University of Mississippi Medical Center, were discovered to have metabolic syndrome, as compared with 29 percent of men. The syndrome is characterized by a concurrence of several risk factors for heart disease—abdominal obesity, low HDL cholesterol, elevated triglycerides, high blood pressure, and abnormal blood sugar.

**University of Mississippi Medical Center**  
**NIH funded**

**2004**

Discovered that the outcome of using cardiopulmonary resuscitation for cardiac arrest, in animal models, is gender dependent—female mice have a better outcome than male mice. Researchers also discovered that the outcomes could be modified by altering certain genes in mice.

**Oregon Health & Science University**  
**NIH funded**

Found that young women with two or more major cardiovascular disease risk factors (diabetes, high blood pressure, unhealthy cholesterol level, high body mass index, or smoking), screened between 1967 and 1973, were less likely to be alive in 2001 than their counterparts with none of these risk factors. Only 20 percent of the women in the study were classified as “low risk,” demonstrating the urgent need to establish heart-healthy habits among women early in life.

**Northwestern University Feinberg School of Medicine**  
**NIH funded**

**2003**

The results of some exercise tests indicate a different prognosis for heart disease in women than they do for men. An electrocardiographic finding of “ST-segment depression,” indicating low blood flow to the heart muscle, may be an ominous sign in men, but is unrelated to increased risk in women. However, two measures of cardiovascular fitness—exercise capacity and heart rate recovery—were deemed useful for predicting risk in women.

**Johns Hopkins Medical Institutions**  
**NIH funded**

Determined that high levels of C-reactive protein—an indicator of inflammation—are associated with an increased risk of developing high blood pressure in women. This suggests high blood pressure is, in part, an inflammatory disorder and that C-reactive protein can be a useful tool for identifying women who need to reduce their risk of high blood pressure.

**Brigham and Women's Hospital**  
**Harvard Medical School**  
**NIH funded**

Found that women taking combination hormone therapy have twice the rate of dementia, including Alzheimer's disease, than women not taking the medication.

**Wake Forest University School of Medicine**

**NIH funded**

**2002**

Researchers found that depression in elderly women is associated with an increased risk of heart failure. Women may have a stronger physiological response to depression than men, thereby significantly increasing their risk of heart failure.

**Emory University School of Medicine**

**Yale University School of Medicine**

**NIH funded**

Determined that digoxin therapy for heart failure had different effects in women than in men. Although the drug reduced the hospitalization rate for men, it was linked to an increased risk of death for women taking the drug, compared with women taking a placebo.

**Yale-New Haven Hospital**

**NIH funded**

**1997**

Identified a new compound that appeared to strengthen bones and improve cardiovascular health in the same way that natural estrogen does, while stopping the ability of estrogen to speed the growth of cancer in uterine cells.

**Duke University Medical Center**

**NIH funded**

Determined that even one child is enough to put working mothers at higher stress and at risk for health problems such as heart attack.

**Duke University Medical Center**

**NIH funded**

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#### Clinical Trials Network

NIDA's National Drug Abuse Clinical Trials Network serves 34 states plus the District of Columbia and Puerto Rico. Researchers test the effectiveness of new and improved interventions in real-life community settings with diverse populations. The network recently demonstrated the efficacy of an incentive-based method for cocaine and methamphetamine abstinence. The network also stands ready to help NIDA respond to emerging public health needs. Academic medicine institutions affiliated with this network include:

David Geffen  
School of Medicine at UCLA

Duke University  
School of Medicine

Johns Hopkins University  
School of Medicine

Medical University of South Carolina

New York University  
School of Medicine

Oregon Health & Science University

University of California,  
San Francisco, School of Medicine

University of Cincinnati  
College of Medicine

University of Colorado  
School of Medicine

University of Miami Miller  
School of Medicine

University of New Mexico  
School of Medicine

University of Pennsylvania  
School of Medicine

University of Pittsburgh  
School of Medicine

University of Texas Southwestern  
Medical Center at Dallas

University of Washington  
School of Medicine

Yale University School of Medicine

## Drug Use and Abuse: Fighting the Destructive Grip of Addiction

Addiction is a developmental disease that begins in childhood and adolescence and is influenced by a tangle of factors involving genes, environment, and an individual's age at first substance use. Whatever the addiction—cigarettes, alcohol, illicit or prescription drugs—groundbreaking research conducted at the nation's medical schools and teaching hospitals and supported by the National Institutes of Health (NIH), has made it clear that addiction is a chronic and relapsing disease, yet treatable.

In 2004, approximately 22.5 million Americans age 12 or older needed treatment for substance (alcohol or illicit drugs) abuse and addiction. Of those, only 3.8 million people received it. The medical and social consequences of an untreated drug addiction can be devastating. Tobacco use kills nearly half a million Americans each year. Other chemical addictions boost the risk for HIV/AIDS, tuberculosis, fetal abnormalities and illness, and can lead to increases in crime and violence—problems that can impact individuals, families, and entire communities.

The NIH, principally through its National Institute on Drug Abuse (NIDA), supports research at the nation's medical schools and teaching hospitals to better understand the disease of addiction and develop more targeted strategies for its prevention and treatment. Examples of progress from this research are described below.

#### Genetics/Cause

Genetic factors and combined genetic-environmental interactions are estimated to account for 40 percent to 60 percent of the variability in addiction risk. Several susceptibility genes have been found for alcohol dependence and nicotine addiction. For example:

- Scientists at Washington University School of Medicine conducted a genome-wide association study in 2006 and identified several novel genes involved in nicotine dependence.
- In 2004, researchers at the Johns Hopkins University School of Medicine found a protein, called Arc, which may be a culprit in drug addiction. The protein helps the brain retain memories for longer than an hour or two.
- In 1994, scientists at the Oregon Health & Science University were the first to clone the mammalian gene for the D2 dopamine receptor. Dopamine is a brain neurotransmitter that is thought to be essential to the brain's response to drugs like opiates and psychostimulants.

### **The Criminal Justice System**

A majority of prisoners (60 to 80 percent) in the U.S. criminal justice system were convicted on drug-related charges. Research demonstrates that providing treatment to these individuals decreases future drug use and criminal behavior. NIDA launched the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative in 2002 to bring new treatment models into the criminal justice system and improve outcomes for offenders with substance use disorders. Several of the nation's medical schools are involved in CJ-DATS, including:

David Geffen  
School of Medicine at UCLA  
University of Kentucky  
College of Medicine  
University of Miami Miller  
School of Medicine  
Virginia Commonwealth  
University School of Medicine

- Johns Hopkins University School of Medicine researchers reported in 2006 that men's brains show evidence of up to three times the amount of the brain chemical dopamine as women's brains when exposed to amphetamines. This is the first clinical study that explains why more men than women abuse amphetamines and could lead to tailored treatments for drug abuse and neurological diseases.

### **Brain Studies**

High-powered imaging techniques are revealing the harmful damage done by addiction. Recent scientific research provides overwhelming evidence that drugs interfere with normal brain functioning and have long-term effects on brain metabolism and activity. At some point, changes occur in the brain that can turn a drug abuse problem into an addiction. Those addicted to drugs suffer from a compulsive craving and often cannot quit using their drug of choice without professional help.

- In 2004, researchers at the David Geffen School of Medicine at UCLA used structural magnetic resonance imaging (MRI) and computational brain mapping to reveal structural abnormalities in the brains of chronic methamphetamine users.
- A 2005 study at the University of California, San Diego, School of Medicine showed that functional MRI might be used to predict relapse in substance-dependent individuals. A simple two-choice test correctly predicted 20 of 22 subjects who did not relapse and 17 of 18 subjects who did.

### **Prevention**

The best approach to reducing the tremendous toll of substance abuse is to stop the damage before it occurs. Each dollar invested in prevention achieves a savings of up to seven dollars in areas such as substance abuse treatment and criminal justice system costs, according to NIDA. The positive impact of prevention messages is reflected in current NIDA statistics. As of December 2006, recent use of illicit drugs in the United States has dropped almost one quarter (23.2 percent) since 2001 among 8th, 10th, and 12th graders.

- An NIH-supported prevention program called Life Skills Training, developed at Weill Medical College of Cornell University, combines teaching of drug and alcohol resistance skills with social and personal skills, such as assertiveness and goal setting. A 2006 long-term evaluation of the program found that young adults who went through the program in grades 7 through 9 were not only less likely to use drugs and alcohol, but were also less likely to exhibit behaviors that put them at high risk for contracting HIV/AIDS.
- ATLAS (Athletes Training and Learning to Avoid Steroids) and ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives) are two highly successful school programs for male and female athletes that address steroid abuse and drinking and driving. The programs leverage the influence of coaches and peer groups and have been adopted by schools in 29 states and Puerto Rico, and endorsed by Congress as exemplary prevention programs. Scientists at the Oregon Health & Science University developed both programs.

### **Treatment**

Addictions can be successfully treated, often with a combination of medication and behavioral therapy. Advances in pharmacogenomics are helping identify genetic factors that may predict which individuals may respond well to specific medications for addiction.

- Researchers at Yale University School of Medicine reported early success in 2005 with a vaccine that dulls cocaine's euphoric effects.
- In 2006, University of Pennsylvania School of Medicine scientists identified genetic variants that predict which patients are most likely to quit smoking using the drug bupropion and who will respond better to nicotine replacement therapy.
- In 2006, scientists at the Columbia University College of Physicians and Surgeons and the University of Pennsylvania School of Medicine collaborated to show the efficacy of a sustained-release, injectable drug called naltrexone as a treatment for opioid dependence.
- A 2005 study by researchers at the Johns Hopkins University School of Medicine indicated that providing incentives for patients leaving drug detoxification, such as rent payments, recreational activities, and job-skills training, leads to much higher short-term drug abstinence and large increases in days worked and wages.

**For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/research/ftp](http://www.aamc.org/research/ftp)**



## The Disease of Addiction

Nearly 4 million Americans a year receive treatment for substance abuse and addiction. Almost 20 million more need treatment but do not receive it.

U.S. medical schools and teaching hospitals, together with the National Institutes of Health (NIH), are working to better understand the disease of addiction and develop more targeted strategies for its prevention and treatment.

The following examples of recent NIH-funded research advances achieved at the nation's medical schools and teaching hospitals hold promise for individuals struggling with addiction:

### **2006**

Researchers discovered a key receptor for a brain chemical involved in addiction, obesity, and other neurological processes, the first study to find evidence for specific cocaine- and amphetamine-regulated transcript peptide receptor binding.

**Emory University School of Medicine**

Research in animals showed that vaccines against cocaine and methamphetamine are possible and effective. A vaccine to block the effects of these drugs in the brain may be a method of alleviating addiction.

**Baylor College of Medicine**

**Michael E. DeBakey Veterans Affairs Medical Center**

**Ben Taub General Hospital**

Repeat offenders of Driving Under the Influence (DUI) violations are much more likely to qualify for the classification of "drug dependence disorder" if their first DUI was before the age of 21. These offenders are also more likely to have adolescent onset of substance use disorders, reinforcing the importance of early intervention in adolescent drinking and substance use.

**Harvard Medical School**

**Cambridge Health Alliance**

Nicotine exposure at a young age may alter the brain's "hard-wiring" that occurs during adolescence and young adulthood. Researchers found that nicotine induces molecular and metabolic changes in the brain that result in nerve cell membrane breakdown, especially in men. This finding establishes a biological basis for previous observations that individuals who smoke early in life are more susceptible to addiction and to becoming life-long smokers than those who begin smoking later in life.

**University of Pittsburgh School of Medicine**

A population-based study on twins found that genetic factors may play an important role in a person's use/misuse of or dependence on illicit drugs like marijuana, opiates, and cocaine.  
**Virginia Commonwealth University School of Medicine**

In a study on monkeys, researchers discovered that RTI-336, a compound that mimics the effects of cocaine by inhibiting dopamine transporters, eliminates the need for self-administration of cocaine. This compound holds promise for effectively treating cocaine addiction. This finding will be tested in humans, beginning at two sites in 2007, as part of the National Institute on Drug Abuse's large-scale effort to move cocaine addiction treatments to human clinical trials as quickly as possible.  
**Emory University School of Medicine**

Pathological gamblers respond to treatment with a drug that negates the rush addicted gamblers feel and curbs their craving. Pathological gambling is a psychiatric condition in which gambling and the need to gamble cripples a person's ability to function.  
**University of Minnesota Medical School**

In the first clinical study to explain why more men than women abuse amphetamines, researchers found that amphetamines have a greater effect on men's brains than women's brains. Men's brains show evidence of up to three times the amount of the chemical activator dopamine as in women's brains when exposed to amphetamines.  
**Johns Hopkins University School of Medicine**

## **2005**

Researchers found that the anticonvulsant drug valproate reduces drinking (both frequency and quantity) in bipolar patients when combined with a patient's regular treatment program. Bipolar disorder with alcoholism is a common but difficult combination to treat.  
**University of Pittsburgh School of Medicine**

Women with a serious caffeine habit and a family history of alcohol abuse are more likely to ignore advice to stop using caffeine during pregnancy. This research validates caffeine dependence as a clinically significant phenomenon, particularly for pregnant women. It suggests genetic vulnerability reflected in a family history of alcoholism may be at the root of one's inability to stop caffeine use.  
**Johns Hopkins University School of Medicine**

## **2004**

People with mutation of the gene Epac are more likely to start smoking and become addicted to nicotine than people without the gene. A study of twins linked variants in the gene with an individual's tendency to become nicotine dependent.  
**Virginia Commonwealth University School of Medicine**  
**Wayne State University School of Medicine**

Researchers discovered a protein called Arc that may be a culprit in drug addiction. The protein contributes to long-term memory-based behaviors and helps the brain remember things for longer than an hour or two.  
**Johns Hopkins University School of Medicine**

Researchers discovered Mpdz, a gene that makes individuals susceptible to alcohol and barbiturate dependence.

**Oregon Health & Science University  
Oregon Veterans Administration Medical Center**

Some people may be born to smoke. For people with aggressive personalities, nicotine triggers significant brain activity in the areas that help control social response, thinking, and planning. Non-hostile people showed no brain activity increases at all to nicotine.

**University of California, Irvine, College of Medicine**

Researchers using structural magnetic resonance imaging and computational brain mapping revealed structural abnormalities in the brains of chronic methamphetamine users.

**David Geffen School of Medicine at UCLA**

Drug addiction affects men and women differently. Women develop more medical and employment problems and major depression, but fewer personality disorders than men.

**Johns Hopkins University School of Medicine**

**2003**

Researchers discovered a genetic variant, involving the endogenous opioid system that results in increased euphoria from alcohol. This endophenotype of alcoholism shows improved response to naltrexone treatment. This finding has the potential to be the first example of genomic medicine in psychiatry.

**University of Pennsylvania School of Medicine  
Philadelphia Veterans Affairs Medical Center**

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/ftp](http://www.aamc.org/ftp)

## The Osteoarthritis Initiative

To find new ways to prevent osteoarthritis and speed studies of new treatments, the NIH collaborated with private-sector sponsors and the Food and Drug Administration to launch the Osteoarthritis Initiative (OAI), a unique, long-term, public-private partnership to create a publicly available research resource to identify and evaluate biomarkers for osteoarthritis. With better biomarkers—including physical signs or biological substances in body fluids—scientists could diagnose the disease in its earlier stages and better monitor changes in joint health.

The OAI has 4,800 participants who are at high risk for knee osteoarthritis. The initiative includes four clinical centers and a data coordinating center, located at the following U.S. medical schools:

- **University of Maryland School of Medicine, Baltimore**
- **The Ohio State University College of Medicine, Columbus**
- **University of Pittsburgh School of Medicine**
- **Memorial Hospital of Rhode Island, Pawtucket**
- **University of California, San Francisco (data coordinating center)**

For more information about the OAI, go to [www.oai.ucsf.edu/datarelease/About.asp](http://www.oai.ucsf.edu/datarelease/About.asp).

## Osteoarthritis: A Debilitating and Progressive Disease

With Americans urged to exercise daily to ward off the diseases of aging and stem the growing epidemic of obesity, joint pain and stiffness can stand in the way of the best fitness plans. But for millions of older Americans who have the degenerative joint disease osteoarthritis (OA), even basic physical activities are a challenge.

Osteoarthritis, by far the most common form of arthritis, affects an estimated 21 million Americans. It is caused by a breakdown of cartilage—the smooth, elastic tissue that normally covers and cushions the ends of bones where they meet to form a joint. For many, the result is daily joint pain, stiffness, and disability. Osteoarthritis can occur in any joint but most often affects the hands, spine, knees, and hips. While medications can help control the pain of OA, nothing can stop the disease process. Once the damage has occurred, there is no effective way to repair the cartilage.

The National Institutes of Health (NIH), principally through its National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), supports research at the nation's medical schools and teaching hospitals to determine the underlying causes of OA and devise prevention and treatment strategies that can keep Americans active for a lifetime. Some important findings from NIH-supported research follow.

### Causes and Prevention

Risk for OA increases with age, and it is more likely to occur in people who are overweight or perform jobs or activities that place stress on particular joints. NIH-supported researchers are developing new strategies to better predict who is at risk of developing OA and preempt the joint degeneration that causes OA pain and disability.

- Men who suffer knee or hip injuries early in adult life are at greater risk for OA in these joints later in life compared with men who do not have such injuries, according to a 2000 study by researchers at **Johns Hopkins University School of Medicine**, the **University of Maryland School of Medicine**, and the **Veterans Affairs Medical Center**, all in **Baltimore**.
- In 2001, researchers at **MCP Hahnemann University School of Medicine, Philadelphia**, and the **University of Alabama at Birmingham School of Medicine** discovered a gene mutation that weakens collagen (a major component of cartilage) and causes it to break down more easily under stress.

- OA susceptibility increases when chondrocytes—cells in the body that maintain and repair cartilage—are damaged. Researchers at the **University of Iowa Hospitals and Clinics (Iowa City)** reported in 2006 that chondrocyte damage occurs with normal aging, but also from oxidative stress, which occurs with joint injury.
- Researchers at **Vanderbilt University Medical Center in Nashville, Tenn.**, are leading a 2007 study by six academic centers to determine the most important predictors that may lead to eventual OA in the knees of patients who undergo reconstructive surgery of a torn anterior cruciate ligament, an injury common in athletes.
- Smokers who have osteoarthritis have more severe joint pain and a greater degree of cartilage breakdown than nonsmokers with OA, according to a 2006 study by researchers at **Mayo Clinic College of Medicine** in Rochester, Minn. and **Boston University School of Medicine**.

### **Treatment**

NIH-supported scientists are currently working to improve existing treatments for OA. For example, surgical advances have made hip replacements safer for older adults, who have often had other conditions that made them ineligible for this procedure in the past. Longer-lasting materials are also making knee replacements a better option for younger, more active individuals. In addition, the NIH is investing in emerging areas of research at U.S. medical schools and teaching hospitals, including tissue engineering and regenerative medicine, to engineer new cartilage (sometimes from a patient's own tissue) that can support the damaged joint. The goal is to stop or slow OA, and one day hopefully eliminate the need for joint replacements.

- People aged 60 and older with osteoarthritis of the knee who exercise in moderation have less pain, reduced disability, and can improve their physical performance, according to a 1997 clinical study conducted at **Bowman Gray School of Medicine at Wake Forest University (Winston-Salem, N.C.)** and the **University of Tennessee (Memphis)**.
- By devising an animal model of vertebral disk compression and degeneration, researchers at the **University of California, San Francisco, Medical Center** have been working since 1998 to improve understanding of the cellular and molecular events of disk aging and degeneration, and enhance the feasibility of tissue engineering approaches to disk repair.
- Since 2001, researchers at **Duke University Medical Center (Durham, N.C.)** have been working on a three-dimensional fabric scaffold that could one day be used to patch damaged joint surfaces, allowing a patient's cartilage-forming stem cells (taken from his or her own fat tissue) to move in and repair the damage. The hope is that this approach will delay or even eliminate the need for joint replacement.
- Acupuncture can reduce pain and improve function in patients with knee OA, according to a 2004 study by researchers at the **University of Maryland School of Medicine**.

- **Case Western Reserve University School of Medicine (Cleveland)** scientists have been investigating factors that cause artificial joints to fail, and, in 2006, clarified the role of bacteria in the loosening of orthopaedic implants.
- OA patients who participate in exercise programs before receiving an artificial knee or hip are more likely to skip inpatient rehabilitation after surgery and go directly home instead, a much more cost-effective option, according to a 2006 study by researchers at **Harvard Medical School (Boston)**.

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## The Growing Importance of Bone Health

Diseases of the bones and joints, including osteoarthritis, osteoporosis, and similar conditions, affect millions of Americans every year. For osteoarthritis alone, the number of individuals at risk will increase dramatically by 2030 when an estimated 70 million Americans will be 65 or older.

U.S. medical schools and teaching hospitals, together with the National Institutes of Health (NIH), are working to better understand the many diseases and conditions that affect bone health, and find new and better prevention and treatment strategies.

The following examples of recent NIH-funded research advances achieved at these institutions hold promise for individuals suffering from, or at risk of developing, osteoarthritis and similar conditions:

### 2007

Older women who take a commonly prescribed class of antidepressants known as SSRIs lose bone mass more quickly than women who are not on the medication, new research shows. Serotonin transporters, which are found in bone, were inhibited by the SSRIs, a group of drugs that includes Prozac, Lexapro, Paxil, and Zoloft.

**University of Minnesota Medical School**

Researchers are hoping to discover the genetic triggers for rheumatoid arthritis, and thus potentially provide pathways to early diagnosis and treatment. Currently, the condition is not diagnosed until it is too advanced to treat effectively; available treatments address symptoms but do nothing to eradicate the disease.

**Rush University Medical Center**

Rheumatoid arthritis patients treated with the drug hydroxychloroquine (HCQ) were found to be as much as 77 percent less likely to develop diabetes as compared to those who never took the drug, according to a 20-plus-year study.

**University of Pittsburgh School of Medicine**

2006

Investigators have determined that calcium and vitamin D supplements in postmenopausal women have a modest effect on bone mineral density and prevent hip fractures in certain groups, but do not prevent other bone fractures.

**Ohio State University College of Medicine**  
**University at Buffalo The State University of New York School of Medicine and Biomedical Sciences**

The Osteoarthritis Initiative, a study of 5,000 people at risk of developing osteoarthritis of the knee, is providing unparalleled database images and clinical outcome information for researchers. Researchers hope the data will help facilitate osteoarthritis studies.

**Johns Hopkins University School of Medicine**  
**Memorial Hospital of Rhode Island**  
**University of Maryland School of Medicine**

Two popular nutritional supplements, glucosamine and chondroitin sulfate, do not reduce pain effectively in many patients with osteoarthritis of the knee, although the combination may be effective in patients with moderate to severe knee pain caused by other conditions. The study calls into question the daily use of these two over-the-counter supplements, which are heavily marketed as osteoarthritis pain relievers.

**Indiana University School of Medicine**  
**Johns Hopkins University School of Medicine**  
**University of Nebraska Medical Center**  
**University of Utah School of Medicine**

Researchers have discovered the gene that causes fibrodysplasia ossificans progressive, or FOP, a rare condition in which the body's muscles and connective tissue change to bone. The discovery may be relevant not only for FOP patients but for those with more common skeletal conditions like osteoarthritis.

**University of Pennsylvania School of Medicine**

The AIDS virus accelerates development of osteoporosis, according to a study on the condition. HIV augments the growth of bone-dissolving agents known as osteoclasts. The findings could lead to new anti-osteoporosis drugs.

**Columbia University College of Physicians and Surgeons**

Researchers found that even after accounting for the contribution of age, women with lower levels of the hormone estradiol had greater risk for subsequently developing knee osteoarthritis. Changes in naturally occurring sex steroid hormones such as estradiol (the primary estrogen in premenopausal and early perimenopausal women) may explain why knee osteoarthritis becomes more prevalent among women during midlife.

**University of Maryland School of Medicine**

2005

Data show that men with prostate cancer who were receiving hormone suppression therapy had up to 50 percent more bone fractures than men who were not receiving the therapy.

**University of Texas Medical Branch at Galveston**

Researchers determined several factors that affect bone health in middle-aged women. Quantitative relationships that play a role in the “calcium economy” of women at midlife include calcium absorption efficiency, calcium losses through urine and digestive juices, and certain hormonal changes.

**Creighton University School of Medicine**

**2004**

Research targeted a gene therapy that eliminated the genetic mutations associated with osteogenesis imperfecta, or brittle bone disease, in adult stem cells. This may result in new treatments for the relatively rare genetic disease.

**University of Washington School of Medicine**

A specific genetic variation more than doubles the risk for rheumatoid arthritis, a team of investigators found. This genetic variation also significantly increases risk for systemic lupus, type 1 diabetes, and autoimmune thyroid disease.

**North Shore-Long Island Jewish Health System**

**University of California, San Francisco, School of Medicine**

**University of Minnesota Medical School**

**2003**

Insights into cartilage development and maintenance may help promote understanding of how to prevent progressive cartilage loss in osteoarthritis patients. So-called cytokine-induced transcription or reproduction factors involved in cartilage development and homeostasis were also found to be expressed in the cartilage of osteoarthritis patients.

**Weill Cornell Medical College**

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## A Spectrum of Behaviors

Autism, or more specifically autism spectrum disorders (ASDs), range from a severe form, called autistic disorder, to a milder form, Asperger syndrome. In between is pervasive developmental disorder not otherwise specified (PDD-NOS). Other rare, very severe disorders included in (ASDs) are Rett syndrome and childhood disintegrative disorder (CDD). Rett syndrome occurs almost exclusively in girls and involves deteriorating behavior between 6 and 18 months. The child no longer responds to parents, loses the ability to speak, cannot control her feet, and wrings her hands.

The very rare condition called CDD occurs relatively late, between age 3 or 4, with a major decline in speech, social skills, and movement. CDD is also accompanied by loss of bowel and bladder control and often-times seizures and a very low IQ.

## Vaccines under Scrutiny

Many studies have examined whether there is a relationship between vaccines and autism. According to the Centers for Disease Control and Prevention (CDC), the weight of evidence indicates that vaccines are not associated with autism. However, the CDC is committed to protecting the health of children and identifying the biological and environmental causes of autism and other developmental disabilities, and will continue to study the role of vaccines.

## Autism: Unraveling the Mystery

Autism, a complex brain disorder, begins in the first three years of life and can persist into adulthood. Individuals with autism have problems communicating verbally and nonverbally, have limited or no social skills, and often engage in repetitive behaviors, such as rocking or twirling, which can lead to isolation.

Autism is a common name for a group of conditions, referred to collectively as autism spectrum disorders (ASDs). Symptoms vary from mild conditions, such as Asperger syndrome, to childhood disintegrative disorder, which is severely disabling.

An estimated 1 in 150 eight-year old children in the United States has an ASD, according to the Centers for Disease Control and Prevention. The risk is three to four times higher in boys than in girls. Currently, there is no cure and treatments are limited. However, with support from the National Institutes of Health (NIH), scientists at U.S. medical schools and teaching hospitals have made some remarkable research progress that has provided clues about how brain development goes awry in individuals with the disease, and how genes may play a role.

The NIH, principally through the National Institute of Mental Health (NIMH) and four other institutes (Neurological Disorders and Stroke, Deafness and Other Communication Disorders, Child Health and Human Development, and Environmental Health Sciences), supports research by medical schools and teaching hospitals on autism's causes, as well as detection and treatment strategies.

Some important findings from this NIH-supported research follow.

### What Causes Autism?

Both genetics and environment likely play a role in autism development. Recent studies suggest that several genes are involved. Many of the implicated genes control the communications pathways of the brain.

- In 2008, the Autism Consortium, a group of 14 Boston-area institutions, including **Harvard Medical School, Boston University Medical School, Beth Israel Deaconess Medical Center, and Children's Hospital Boston**, found a rare genetic variation on chromosome 16 that dramatically raises the risk of developing autism, opening new research targets for treating the disorder. The defect was inherited in some cases, but was more often the result of a random genetic accident.
- Scientists at **Johns Hopkins School of Medicine** have found a gene variation that may raise the risk of developing autism, especially when the variation is inherited from

### Autism Centers of Excellence

Thanks to crucial funding from the National Institutes of Health (NIH), the nation's medical schools and teaching hospitals are on the frontlines of autism research. On April 1, the NIH announced the latest awardees in the Autism Centers of Excellence program, designed to support studies covering a broad range of autism research areas. Three of the four award recipients are based at U.S. medical schools:

**Daniel Geschwind, M.D., Ph.D., David Geffen School of Medicine at UCLA:** Genetic risk factors among African Americans and whites.

**Diana Chugani, Ph.D., Wayne State University School of Medicine:** Can buspirone, a drug that stimulates serotonin production, promote normal brain growth and development in autistic children?

**Ami Klin, Ph.D., Yale University School of Medicine:** Eye-tracking technology for early detection of autism spectrum disorders, perhaps before symptoms emerge.

mothers rather than fathers. The gene, *CNTNAP2*, makes a protein that enables brain cells to communicate with each other through chemical signals and appears to play a role in brain cell development. In this 2008 study, researchers were able to link a specific variation in the protein's structure to autism.

- Two 2005 studies at **Vanderbilt University Medical Center** suggest that mutations in the gene regulating brain serotonin, a chemical necessary for communication between nerve cells, may be an autism risk factor. In 2008, these researchers determined how the mutation may block serotonin's activity.
- By age 2, children with autism show a generalized enlargement of their brains, according to a 2005 study of MRI scans by researchers at **University of North Carolina at Chapel Hill** and **Duke University medical schools**. In autistic children, the temporal lobe, where language is controlled, was enlarged, along with other parts of the brain. It is unclear whether the brain enlargement is a primary cause of autism or a downstream effect of another process occurring in the brain.
- In 2005, researchers at the **University of California (UC), Davis, School of Medicine** demonstrated that children with autism have different immune system responses than other children. The results provided important evidence that scientists may one day be able to diagnose autism through early biological changes, rather than the behavior-based diagnoses used today.

### Improving Diagnosis and Treatment

Researchers are looking for neurological or other biomarkers to enable earlier diagnosis and treatment. Most professionals agree on the importance of early intervention with highly structured, specialized programs. For serious behavioral disturbances, such as self-injury, aggression, hyperactivity, and tantrums, behavioral therapy (teaching children how to overcome anxiety and develop better social skills) and medications are the two main forms of treatment. Many people with autism continue to require a high level of support throughout their adult years.

- Risperidone, an antipsychotic medication, was effective and well tolerated in a 2002 placebo-controlled study for the treatment of serious behavioral disturbances associated with autistic disorder in children ages 5 to 17, according to research at **Yale University School of Medicine**. In 2006, the drug became the first medication approved by the Food and Drug Administration for the treatment of autism symptoms.
- Children with autism are often placed on restrictive diets in hopes of improving some symptoms. Researchers at **Cincinnati Children's Hospital Medical Center** collaborating with NIH investigators found in 2008 that dairy-free diets and unconventional food preferences could place boys with autism at a higher-than-normal risk for thinner, less dense bones when compared to a group of same-aged boys who did not have autism.

Several NIH-supported studies have been launched in the past year to improve treatments by taking advantage of new knowledge. For example, researchers are currently examining the use of an antibiotic minocycline in treating regressive autism. Children affected by this condition develop normally until about 18 months, when they lose speech and social skills. Research studies like the one at UC Davis School of Medicine referenced earlier, suggest that autism may be linked to changes in the immune system that cause inflammation in the brain. Minocycline has known anti-inflammatory effects. Others are determining the impact of chelation therapy, an unproven, though popular, treatment to remove heavy metals from the bloodstream. As scientists learn more about the origins of the disorder, more treatment options will be explored.

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## Understanding the Complexities of Autism

Approximately 1 in 150 eight-year-olds in the United States has autism or a closely related disorder. The risk for this complex brain disorder is three to four times higher in boys than in girls.

U.S. medical schools and teaching hospitals, together with the National Institutes of Health (NIH), are working to better understand autism and the milder autism spectrum disorders (ASDs) that affect so many children.

The following examples of recent NIH-funded research advances achieved at these institutions hold promise for children struggling with autism, as well as their parents and loved ones.

### 2008

#### **Children's Hospital Boston**

Premature infants born weighing less than 1,500 grams (approximately 3 pounds, 4 ounces) have an increased risk for showing early signs of autistic features. Researchers suggest that early autistic behaviors may be under-recognized in infants with very low birth weights, and early screening for signs of autism could be warranted for all preterm infants.

#### **Cincinnati Children's Hospital Medical Center**

Unconventional diets could put boys with autism and ASDs at a higher risk of having thinner, less-dense bones than boys of the same age who do not have these disorders. Researchers believe that boys with autism and ASDs are at risk for poor bone development for several reasons, including lack of exercise, reluctance to eat a varied diet, digestive problems, and diets that omit casein, a protein found in dairy products. Casein-free (nondairy) diets are thought by some to lessen the symptoms of autism.

#### **Johns Hopkins University School of Medicine**

A team of investigators found that a common genetic alteration appears to be associated with autism only when passed down to sons from their mothers. The alteration, which occurs in a gene called CNTNAP2, is one of the strongest and most common known genetic links to autism susceptibility. This discovery will help guide future studies on understanding autism.

#### **University of California, Davis, School of Medicine**

Researchers have identified endocrine dysfunction in children with early onset autism. Examining molecular biomarkers may prove valuable as early diagnostic tools, and provide insights into molecular characteristics in autistic children.

2007

**University of Texas Southwestern Medical Center**

After discovering two proteins involved in autism, researchers engineered mice with mutations in a gene for these proteins. These mice, the closest animal model to autism, exhibit poor social skills but increased intelligence, as do people with some forms of autism. The proteins, called neuroligins, link brain nerves together.

**Vanderbilt University Medical Center**

Few rapid screening tools are available that encompass the range of symptoms commonly occurring in autism. Researchers have developed and evaluated a screening checklist—the Parental Concerns Questionnaire (PCQ)—that can accurately identify symptoms of autism.

**Johns Hopkins University School of Medicine**

A landmark analysis of genomic data, released in 2007, provided the most detailed look thus far at genetic variation patterns in families with autism. The study included 1,250 autistic individuals and their siblings and parents from across the country.

**University of Pennsylvania School of Medicine**

Researchers analyzed different treatments prescribed for children with autism spectrum disorders who were enrolled in Medicaid in 2001, and examined factors associated with psychotropic, or mind-affecting, medication use. Study results determined that children with ASDs who were male, older, white, in foster care, or diagnosed with more than one psychiatric condition were more likely to have used psychotropic drugs; children in geographic areas with fewer white residents or greater urban density were less likely to use such medications.

2006

**Vanderbilt University School of Medicine**

Researchers have identified a genetic mutation that increases the risk of autism; the mutated gene is common in children with autism.

**Johns Hopkins University School of Medicine**

**University of Illinois at Chicago College of Medicine**

There is a common genetic alteration that leads to autism only when inherited by sons from their mothers. Findings from this research discovery were later replicated in one of the largest-ever group of autism samples ever studied.

**Arkansas Children's Hospital**

**University of Arkansas for Medical Sciences**

Scientists at the Autism Metabolic Genomics Laboratory discovered that many children with autism have low levels of glutathione, the major intracellular antioxidant and mechanism used to detoxify environmental contaminants.

2005

**University of North Carolina at Chapel Hill School of Medicine  
Duke University School of Medicine**

Results of MRI scans show that, by age 2, children with autism show a generalized enlargement of their brains. The temporal lobe, where language is controlled, was enlarged, along with other parts of the brain. It is not yet clear whether the enlargement is a primary cause of autism or a downstream effect of another process occurring in the brain.

**University of California, Davis, School of Medicine**

Children with autism have different immune system responses than nonautistic children. This discovery is important evidence that autism, currently defined primarily by distinct behaviors, may potentially be defined by distinct biologic changes as well.

**Vanderbilt University Medical Center**

The results of two research studies imply that mutations in the gene that regulates brain levels of serotonin may be a risk factor for autism. In individuals with autism, regulatory problems within the gene may disrupt serotonin signaling.

**University of Louisville School of Medicine**

Researchers found that individuals with autism have smaller and more numerous cortical minicolumns (structures that serve as the brain's microprocessors) than do individuals without autism.

2004

**Johns Hopkins University School of Medicine**

Scientists found new evidence that the brains of some autistic individuals show clear signs of inflammation, suggesting that autism may be associated with activation of the brain's immune system.

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/ftp](http://www.aamc.org/ftp)



## A Better Quality of Life for Stroke Victims

Stroke is the third-leading cause of death and a leading cause of long-term disability and cognitive decline in the United States, according to the Centers for Disease Control and Prevention. According to the American Stroke Association, more than 780,000 strokes occur each year in this country, or one stroke every 40 seconds.

U.S. medical schools and teaching hospitals, together with the National Institutes of Health (NIH), are working to find more effective treatments for stroke patients and to better understand how the brain recovers after a stroke.

The following examples of recent NIH-funded research advances achieved at these institutions hold promise for patients at risk for or recovering from a stroke.

### 2008

#### **University of New Mexico School of Medicine**

Researchers have developed a novel MRI imaging method to demonstrate blood-brain-barrier leakage in patients with vascular dementia. This is the first time such leakage has been sensitively quantified in these stroke patients.

#### **Emory University School of Medicine**

Experts have found that a new structural class of drugs, called glutamate receptor antagonists, is a potential treatment for the neurological degeneration associated with stroke. The new compounds are neuroprotective, yet free of the previous side effects of this class of drug.

#### **University of Arkansas for Medical Sciences**

Researchers created a mouse model to study the role of zinc in normal brain function and in neurological diseases in which the zinc-binding site of certain brain receptors—called NMDA receptors—was destroyed. This mouse model will help establish the zinc site of NMDA receptors as a novel target for developing new drug treatment for stroke and other brain diseases.

#### **University of New Mexico School of Medicine**

According to recent findings, treatment with normobaric oxygen or matrix metalloproteinase inhibitors may extend the time window available to treat stroke with clot-busting drugs, which can reverse or limit brain damage.

2006

**Emory University School of Medicine**  
**University of Alabama School of Medicine**  
**University of Florida College of Medicine**  
**University of North Carolina at Chapel Hill School of Medicine**  
**Wake Forest University School of Medicine**  
**Washington University School of Medicine**

Results of the “EXCITE” clinical trial—a multisite study of upper extremity rehabilitation for recent stroke victims—indicate that restraining a patient’s use of the “good” arm/hand while training the weak arm/hand for up to six hours daily for two weeks improved motion function.

**Emory University School of Medicine**

In clinical trials across more than 40 academic institutions, it was determined that a very low-fat diet with increased carbohydrates does not significantly reduce the risk of stroke, colorectal cancer, coronary heart disease, cardiovascular disease, or invasive breast cancer in postmenopausal women, although it does lower breast cancer incidence.

2004

**Medical University of South Carolina College of Medicine**

Researchers discovered a class of drugs that blocks activation of inflammatory cells, which may be used to treat conditions caused by inflammation of the brain or spinal cord—such as stroke, multiple sclerosis, Alzheimer’s disease, and spinal cord injury.

**Johns Hopkins University School of Medicine**

Research results indicate that exercise can lessen the effects of stroke, heart disease, and diabetes. Even a moderate program of physical exercise reduces risk factors such as high blood pressure, elevated blood glucose levels, abdominal fat, and abnormal cholesterol levels.

2003

**Pennsylvania State University College of Medicine**  
**University of Iowa Roy J. and Lucille A. Carver College of Medicine**

Computer algorithms can now quantify the geometry and hemodynamics of intracranial aneurysms from three-dimensional computer images. Preliminary data suggest that aneurysm shape may be a better predictor of potential rupture than aneurysm size.

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to: [www.aamc.org/ftp](http://www.aamc.org/ftp)

## Team Science

NIH has supported more than two dozen large phase 3 clinical trials to improve stroke care since the mid 1970s. As a result, today's stroke treatments are better and more cost effective. Several ongoing phase 3 studies, all multi-center trials, are recruiting patients to further improve options for stroke patients. The following are three examples:

- FAST-MAG is a study of intravenous magnesium sulfate initiated by paramedics in the field within two hours of symptom onset in acute stroke. The study is being coordinated by the **University of California, Los Angeles Medical Center**.
- The Albumin Therapy for Neuroprotection in Acute Ischemic Stroke (ALIAS) trial, headed by the **University of Miami School of Medicine**, is evaluating high-dose human serum albumin's ability to reduce tissue death in the brain, reduce swelling, and prevent brain damage after a stroke.
- The Insulin Resistance Intervention After Stroke (IRIS) trial is examining the effectiveness of a new approach to prevent recurrent stroke and heart attack among patients with a recent ischemic stroke or mini-stroke. The approach targets insulin resistance, a newly recognized cause of hardening of the arteries. Approximately 100 hospitals in the United States and Canada will be involved in the study with **Yale University School of Medicine** serving as the coordinating center.

## Speed Is Essential When Treating Stroke

A stroke can leave a once-vital adult unable to speak, lift a coffee mug, or walk unassisted. Each year, more than 780,000 Americans suffer strokes. Stroke causes more serious long-term disabilities than any other disease and is the third-leading cause of death in this country. While a stroke can occur at any age, the risk of stroke more than doubles each decade after age 55.

There are two types of stroke. The more common *ischemic* stroke is caused by a clot or a narrowing of the arteries that blocks a vessel supplying blood to the brain, a *hemorrhagic* stroke is caused by bleeding into or around the brain.

With support from the National Institutes of Health (NIH), principally through the National Institute of Neurological Disorders and Stroke (NINDS), scientists at U.S. medical schools and teaching hospitals are studying the genetics of stroke and stroke risk factors, and discovering new and better ways to help the brain repair itself and restore important functions. Their efforts have helped identify manageable risk factors and resulted in development of the only FDA-approved therapy for treating stroke that maximizes the potential for patient recovery. Because of this groundbreaking research, deaths from stroke have dropped more than 60 percent since the 1970s.

As in many neurological diseases, advances in treatment depend on an improved understanding of the underlying basic science. NINDS-funded basic research on the regulation of brain blood flow, brain cell death and protection, blood brain barrier, brain metabolism, inflammation, and the brain's mechanisms of repair after injury inform our present and future patient studies. Some recent findings from NIH-supported research follow.

### Risk and Prevention

The most important known risk factors for stroke are hypertension, heart disease, diabetes, and cigarette smoking. Researchers are studying these and other risk factors, including how genetics may play a role, to improve prevention. Finding ways to prevent a recurrence is also a critical research goal.

- Using magnetic resonance imaging, researchers at **Boston University School of Medicine** found that 10 percent of midlife adults had experienced a stroke without knowing it, raising their risk for future strokes and memory loss. The 2008 study showed that atrial fibrillation, or irregular heartbeat resulting in pooling of blood in the heart's two upper chambers and formation of blood clots, doubles the risk of a silent stroke.
- The Ischemic Stroke Genetics Study, whose lead researchers were at **Wake Forest University School of Medicine**, revealed in 2006 that individuals who suffer a stroke are more likely to have a severe one if they have a sibling who had a stroke.
- Aspirin is equivalent to warfarin (marketed under the brand name Coumadin) in preventing subsequent strokes, according to a 2005 study conducted at 59 medical centers. Researchers at **Emory University School of Medicine** who led the study also discovered that aspirin causes fewer and less serious side effects, costs less, and is easier to use.

- Fiber consumption may lower stroke risk and severity, according to a 2008 observational study by researchers at **Massachusetts General Hospital**. Of people who had recently had a stroke, those with the highest fiber intake had the best recovery outcomes.
- Exercise reduces the risk for stroke and other diseases, according to a 2004 study at **Johns Hopkins University School of Medicine**. Even a moderate program of physical exercise lowers risk factors such as high blood pressure, elevated blood glucose levels, abdominal fat, and high cholesterol levels.
- Results of the 2003 African American Antiplatelet Stroke Prevention Study, a large, multicenter trial led by researchers at **Rush Medical College**, showed treatment with aspirin is as effective as the anticlotting agent ticlopidine in preventing recurrent stroke. African Americans have about twice the risk of experiencing a stroke as whites.

### Emergency Treatment

Stroke is treated with medications and sometimes surgery. Treatment is most effective when administered as soon as possible after stroke onset, before irreparable brain damage occurs. NIH-funded research advances have transformed the outlook for stroke patients.

- Since 1996, t-PA (tissue plasminogen activator) has been the only FDA-approved therapy for acute ischemic stroke. The drug, when administered within three hours of ischemic stroke onset, breaks down blood clots and can greatly improve a patient's chance for a full recovery. In the 1980s, **University of Cincinnati College of Medicine** scientists led the first multicenter t-PA studies in the United States and established a protocol for quick diagnosis and treatment for stroke victims.
- A 2006 review of the economic benefits of phase 3 clinical trials by the **University of California, San Francisco Medical Center** found that the trial which indicated t-PA could prevent brain damage if used within the first three hours after a stroke had an estimated net benefit of more than \$6 billion over 10 years.
- The leukemia drug Gleevec (also known as imatinib) may improve stroke treatment, according to a 2008 study conducted with mice. The international clinical study, led by researchers at the **University of Michigan Medical School**, revealed that Gleevec reduced the bleeding caused by t-PA, and allowed for the administration of t-PA after the three-hour treatment window.
- Injection of a gene called kallikrein after the onset of stroke in rats protects against ischemic brain injury by inhibiting cell suicide and inflammation and promoting growth of new blood vessels and nerves in the brain, according to 2006 research conducted by the **Medical University of South Carolina College of Medicine**.

### Stroke Recovery

NIH-supported scientists are looking for new, more effective ways to aid brain repair following a stroke. Recent advances in imaging and rehabilitation have shown that the brain can rewire itself to compensate for a function lost as a result of a stroke. Researchers have found that after a stroke, a secondary wave of damage results from inflammation and toxic chemicals created by dying brain cells. They are working to develop neuroprotective agents that prevent this damage.

- Stroke patients who have lost use of one arm can regain significant function through a special training program, according to a 2006 multicenter study led by researchers at the **Emory University School of Medicine**. Constraint-induced movement therapy, which restrains the unaffected arm, effectively trains the patient to use the affected hand and arm.
- A 2007 randomized study at the **Indiana University School of Medicine** showed that a management program called "AIM" improved outcomes in patients with post-stroke depression. Thirty-nine percent of patients had complete remission from depression after 12 weeks of treatment. AIM consists of three steps: activating stroke survivors and their families to understand and accept depression diagnosis and treatment, initiating antidepressant medication, and monitoring treatment effectiveness.

For more information about how medical schools and teaching hospitals are fulfilling the promise of medical research, go to [www.aamc.org/research/ftp](http://www.aamc.org/research/ftp).