

# Selected Research Advances of NIH

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NIH has trained a host of scientists in its intramural programs and supported the training of hundreds of thousands of scientists at universities and medical schools around the country through research grants. These scientists have gone on to become leaders in biomedical research at universities and companies around the country, fueling a great many advances in the understanding and treatment of human diseases. What follows is only a sampling of the scientific advances supported by NIH in the past years. The most recent Research Advance is now linked to the current [NIH Research Matters](#)

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2014

### Clinical Advances

#### Ebola Research

The 2014 Ebola outbreak in West Africa is the largest such outbreak in history. More than 17,000 cases and 6,000 deaths have been reported. NIH-funded scientists [used genomic sequencing technologies](#) to identify the origin and track transmission of the Ebola virus in the current outbreak. Other NIH-funded researchers [used computer model projections](#) to provide insight into the dynamics of the outbreak. NIH has also intensified efforts to [develop a protective vaccine](#). The vaccine was tested at the NIH Clinical Center, which also provided state-of-the-art care to a nurse who had contracted the Ebola virus.

#### Paralyzed Men Regain Movement With Spinal Stimulation

Four young men paralyzed below the chest because of spinal cord injuries were able to regain control of some movement after receiving an experimental spinal stimulation therapy from a team of NIH-funded researchers. If confirmed in larger studies, this type of treatment may one day improve outcomes for people living with paralysis.

#### Adult Health Improved by Early Childhood Programs

An early childhood program (birth through age 5) has been shown to bring higher academic achievement and career benefits later in life. According to a follow-up NIH-funded study, it can also help prevent disease. By their mid-30s, those who'd participated in the program—especially males—had significantly fewer risk factors for cardiovascular and metabolic diseases compared to a control group.

#### Nurse Staffing, Education Affect Patient Safety

Patient deaths in hospitals might be reduced by easing nurses' workloads and emphasizing education in hiring, an NIH-funded study suggested. Researchers estimated that each additional patient in a nurse's workload increased the likelihood of a patient dying. An increase in nurses with bachelor's degrees lowered the likelihood of patient death. These findings can help administrators make informed staffing decisions.

#### Clinical Exome Sequencing Detects Disease-Causing Glitches

In 2 NIH-supported studies, a fast, powerful technique called whole-exome sequencing provided a molecular diagnosis for about 1 in 4 people suspected of having a genetic disorder. Whole-exome sequencing focuses only on the DNA in the 1% of the human genome that codes for proteins, in contrast to the whole genome. The new tool may help doctors pinpoint the underlying causes of many rare and hard-to-diagnose genetic conditions.

#### Gene Therapy Used to Treat Hemophilia

Hemophilia is a rare bleeding disorder in which blood doesn't clot normally. The primary treatment for people with severe hemophilia B is frequent injections of factor IX, a protein that helps blood clot, for a lifetime. An experimental gene therapy with the human factor IX gene improved symptoms for as long as 4 years in men with severe hemophilia. The NIH-funded study shows the potential for gene therapy as a safe, effective approach.

#### Study Points to Possible Blood Test For Memory Decline, Alzheimer's

Many experts believe that successful treatment of Alzheimer's disease will depend on early intervention before symptoms appear, but there isn't yet any sure way to detect that stage. NIH-funded researchers identified a set of 10 compounds in the blood that might be used to distinguish older adults at risk for developing memory deficits or Alzheimer's disease. More research is needed to confirm the findings, but the study suggests one possible approach.

#### Stem Cell Transplant Reverses Sickle Cell Disease in Adults

There is no widely available cure for the inherited blood disorder sickle cell disease. Some children have been successfully treated with blood stem cell, or bone marrow, transplants. This approach was thought to be too toxic for adults. NIH researchers successfully treated adults with severe sickle cell disease using a modified stem cell transplant approach that doesn't require extensive immune-suppressing drugs. Further follow-up and testing will be needed to assess the therapy.

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## PROMISING MEDICAL ADVANCES

#### An Atlas of the Developing Human Brain

The structure and function of the human brain is guided by gene expression patterns during prenatal development. NIH-supported scientists detailed the first comprehensive 3-D atlas of gene expression in the developing human brain. The resource will help reveal the early roots of brain-based disorders such as autism and schizophrenia.

#### Revealing The Human Proteome

In 2003, the Human Genome Project created a draft map of the human genome—all the genes in the human body. In 2014, NIH-funded researchers completed a draft map of the human proteome—the set of all proteins in the human body. The accomplishment will help advance a broad range of research into human health and disease.

### Cool Temperature Alters Human Fat and Metabolism

Humans have several types of fat. White fat stores extra energy. Brown fat burns chemical energy to create heat and help maintain body temperature. NIH-funded researchers found that men exposed overnight to a cool temperature in a carefully controlled environment for a month had an increase in brown fat with corresponding changes in metabolism. The finding hints at ways to alter the body's energy balance to treat conditions such as obesity and diabetes.

### Isolated Cancer Cells May Lead to Personalized Treatments

Cells shed from tumors enter the bloodstream in very low numbers and circulate through the body. These cells can take root elsewhere, causing the spread of the cancer to other organs. Scientists supported by NIH used a novel microchip-based method to isolate and grow tumor cells circulating in blood. The technique provides an opportunity to test treatments on tumor cells, an important step toward personalizing cancer therapy.

### Preserving Livers for Transplantation

Liver transplantation is the only available treatment for severe liver failure. Livers can currently be preserved outside the body for up to 24 hours. NIH-funded scientists were able to increase the time that rat livers can remain viable outside the body to several days. If the approach succeeds in humans, it could aid organ transplant efforts.

### Developing Insulin-Producing Cells to Treat Diabetes

Diabetes is a disorder in the use of glucose, a sugar that serves as fuel for the body. One strategy to treat diabetes is to replace the damaged cells that normally make insulin, which triggers cells to take up sugar from the blood. NIH-supported researchers designed a protocol to transform human stem cells into beta cells that produce insulin and respond to glucose. The finding could lead to new stem cell-based therapies to treat diabetes.

### Development of Antibiotics to Treat Tuberculosis

Tuberculosis (TB) is a contagious disease caused by infection with *Mycobacterium tuberculosis* bacteria. It's a leading cause of disability worldwide and results in 1.3 million deaths per year. An international team of NIH-funded researchers designed and tested a class of new antibiotics to treat TB. The work represents an initial step in developing therapies to combat drug-resistant forms of the disease.

### Comparative Genomics

Researchers often turn to model organisms in order to understand the complex molecular mechanisms of genome function. By analyzing the genomes of humans, flies, and worms, NIH-funded scientists uncovered many common, key features. The findings offer insights into embryonic development, gene regulation, and other biological processes that are vital to human biology and disease. The mouse in particular has long been used to gain insights into gene function, disease, and drug development. An international group of researchers funded by NIH gained insights into how similarities and differences between mice and people arise from their genomes. The findings will help scientists better understand how and when mouse models can best be used to study human biology and disease.

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## Insights from the Lab

### Method Can Target Specific Microbes

NIH-funded scientists designed a way to target and destroy specific DNA sequences in microbes, thus removing harmful bacterial genes. The team took advantage of a system called the CRISPR-Cas immune system, which bacteria use to protect themselves against invaders. The researchers modified the system to target genetic sequences associated with bacterial virulence or antibiotic resistance. The approach could be used to develop therapies against pathogenic bacteria, including those resistant to multiple antibiotics.

### Engineering Cartilage

Replacing cartilage lost in conditions such as osteoarthritis is a major goal in tissue engineering. Researchers supported by NIH developed a 3-D scaffold that guides the development of stem cells into specialized cartilage-producing cells. The approach could allow for the creation of orthopedic implants to replace cartilage, bone, and other tissues. Such implants could restore function immediately and allow development of natural tissue replacement.

### Expanding the Genetic Alphabet

Synthetic biology aims to redesign natural biological systems for new purposes. Scientists funded by NIH created the first living organism that can grow and reproduce using DNA base pairs that aren't found in nature. The achievement is a major step toward retooling nature to create novel therapeutics and nanomaterials.

### Stem Cells Form Light-Sensitive 3-D Retinal Tissue

Researchers supported by NIH induced human stem cells to form cup-like 3-D structures in a sequence of events that mimicked what occurs in the retina during human development. The structures developed layers containing all the major cell types normally found in the retina. The 3-D retina structure also responded to light. The finding may aid the study of eye diseases and potential new therapies.

### Discriminating Touch

The molecular mechanisms of how cells sense mechanical forces and send nerve signals to the brain are poorly understood. Two NIH-funded research teams revealed how cells in skin detect fine detail and texture. The findings may help scientists understand how aging and certain diseases can reduce our ability to sense touch. They could also lead to new approaches to restore the sense of touch.

### Structural States of a Brain Receptor Revealed

NIH scientists determined the structure and movement of the glutamate receptor, a protein in nerve cells involved in learning and memory. Problems with glutamate receptor function are thought to play a role in many disorders, including autism, schizophrenia, depression, Parkinson's disease, and some types of cancer. The finding provides a better understanding of how the receptor works and may aid in the development of therapies that target the receptor.

### Diet Affects Autoinflammatory Disease Via Gut Microbes

In autoinflammatory diseases, the innate immune system—the body's rapid first line of defense against infection—becomes activated and triggers inflammation. An NIH-funded study in mice revealed that diet-induced changes to intestinal bacteria can influence susceptibility to autoinflammatory disease. The results could help guide new approaches to treat autoinflammatory diseases in susceptible people.

### [Immune Cells in Heart Help it Mend](#)

The heart of a newborn has a much greater capacity for repair than that of an adult. A team of NIH-funded scientists thought this might be due to different populations of macrophages, a type of immune cell found in tissues such as the heart. The researchers discovered that the hearts of mice have distinct macrophages that play a key role in recovery from damage. The findings suggest that potential treatment strategies for heart failure might target macrophages.

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2013

## Clinical Breakthroughs

### **Malaria Vaccine Found Safe and Protective**

Malaria kills hundreds of thousands of people each year, most of them young children in Sub-Saharan Africa. While scientists have made significant gains in understanding, treating, and preventing the disease, a vaccine has remained elusive. NIH researchers reported that a candidate malaria vaccine is safe and protected against infection in an early-stage clinical trial.

### **Gene Variants Predict Response to Breast Cancer Drugs**

Women at risk for breast cancer may take certain types of medications that reduce the chance of developing the cancer. But in rare cases, the drugs can cause dangerous side effects. Many women decide that the chance of success doesn't outweigh the risks. An international research team, with NIH support, found genetic variations that can be used to identify women who are most likely to benefit from this potentially life-saving strategy—and who should avoid it.

### **Urine Test Detects Kidney Transplant Rejection**

After a kidney transplant, patients must take medications with toxic side effects to keep their immune system from attacking the new organ. If doctors could track rejection status over time, they could adjust drug doses for more effective treatment. NIH-funded researchers found that certain molecules in urine can provide an early sign of transplant rejection. The test could allow doctors to act early to protect transplanted kidneys.

### **Technique Directs Immune Cells to Target Leukemia**

When adult patients with B-cell acute lymphoblastic leukemia have remission followed by relapse, the prognosis is poor. An NIH-funded team used a type of targeted immunotherapy to induce remission in 5 patients with this aggressive form of leukemia. The early results of the ongoing trial highlight the potential of this approach.

### **Medical Management Best to Prevent Second Stroke**

After a stroke, treatment for patients at high risk for a second stroke typically involves a medical program that includes blood-thinning medications and control of blood pressure and cholesterol. In hopes of improving the odds, doctors over the past decade began to also use an intracranial artery stent. An NIH-funded clinical trial confirmed earlier findings that stenting adds no benefits over aggressive medical treatment alone for most of these patients.

### **Genetic Testing Doesn't Improve Warfarin Dosing**

Warfarin is often prescribed to prevent blood clots in people with certain conditions. But determining the best dose can be tricky. Too much can cause excess bleeding; too little can lead to dangerous clots. Past research suggested that adding genetic data to clinical information would improve initial dosing. But an NIH-funded study contradicted that result, highlighting the importance of using clinical trials to assess the role of genetics in optimizing treatments.

### **Eye Contact Declines in Young Infants with Autism**

Autism symptoms first appear during early childhood, and a definitive diagnosis can often be made by 2 years of age. Scientists have long been searching for ways to identify the condition at even younger ages, since outcomes tend to be better with earlier intervention. NIH-funded researchers found evidence that infants later diagnosed with autism show a steady decline in eye contact beginning as young as 2 months of age.

### **Duration of Obesity May Affect Heart Disease**

Past research has linked obesity to heart disease risk. But few studies have examined how the duration of obesity affects heart disease. NIH researchers found that how long a young adult is obese may affect that person's heart disease risk in middle age. The finding suggests that not only preventing but also delaying the onset of obesity can help reduce heart disease later in life.

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## Promising Medical Advances

### **Insights into Brain Injury**

Concussions can have serious and lasting effects. However, the specific damage that occurs in affected brain tissue hasn't been well understood. A study by NIH researchers provided insight into the damage caused by mild traumatic brain injury and suggested approaches for reducing its harmful effects.

### **Genomic Analysis of Endometrial Tumors**

Pathologists currently classify endometrial tumors by examining tissue under a microscope. A comprehensive genomic analysis of nearly 400 endometrial tumors revealed 4 novel endometrial tumor subtypes and also found similarities to other cancers. The findings, by an NIH-funded research network, suggest that genomic classification of endometrial tumors could help guide treatment strategies.

### **Common Genetic Factors Found in 5 Mental Disorders**

Autism, attention deficit hyperactivity disorder (ADHD), bipolar disorder, major depression, and schizophrenia were traditionally thought of as distinct mental disorders. However, their symptoms can overlap, making it difficult to distinguish between them. An international research consortium funded by NIH discovered that these disorders share certain genetic glitches. The finding may point to better ways to diagnose and treat these conditions.

### **Vaccine Clears Away Monkey AIDS Virus**

HIV, which causes AIDS in people, and the similar monkey virus SIV are thought to cause permanent infections in the body. Current therapies can control but not eliminate the virus. In an NIH-funded study, an experimental vaccine triggered a lasting immune attack in monkeys that eliminated all traces of SIV infection after a year or more. The finding points to a new strategy in the search for an effective AIDS vaccine.

### **The Human Microbiome**

The human body hosts trillions of microbes. We're now gaining a better understanding of the many roles that microbial communities and their genes—collectively known as the microbiome—play in human health and disease. NIH-funded scientists surveyed all the [fungi living on human skin](#). They uncovered links between gut microbes and [rheumatoid arthritis](#); discovered interactions among diet, gut microbes, and both [heart disease](#) and [obesity](#); and found that microbes may also influence the effectiveness of [cancer therapy](#) and [gastric bypass surgery](#).

### **Method Quickly Assesses Antibiotics**

Decades of widespread antibiotic use have encouraged the spread of bacteria with resistance to multiple antibiotics. To combat these multidrug-resistant bacteria, researchers have been searching for new classes of antibiotics that work by different mechanisms than current drugs. NIH-funded scientists developed an innovative method to quickly identify antibiotics that can treat multidrug-resistant bacteria—and reveal how these bacteria-killing medications work.

### **Strategy May Improve Survival after Shock**

Shock is a life-threatening condition in which blood pressure drops and not enough blood and oxygen can get to organs. Inflammation has been strongly linked with shock, and past research suggests that this inflammation involves the digestive system. An NIH-funded study of rats found that blocking digestive enzymes in intestines increases survival, reduces organ damage, and improves recovery after shock. The approach may lead to new therapies to improve patient outcomes.

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## **Insights from the Lab**

### **Seeing Into the Brain**

Scientists seeking to understand the brain's fine structure and connections have been faced with tradeoffs. To examine deeply buried structures, they had to cut brain tissue into extremely thin sections. This deforms the tissue and makes it difficult to study brain wiring and circuitry. NIH-funded scientists developed a new technique to preserve the brain's 3-D structure down to the molecular level with a hydrogel. It allows for study of the brain's inner workings at a scale never before possible.

### **Structure of a Potential Diabetes Drug Target**

People with diabetes have difficulty maintaining blood glucose levels. The hormones insulin and glucagon are used by the body—and also used as medications—to help keep blood glucose in a safe range. An international team of researchers, funded in part by NIH, determined and analyzed the structure of the human glucagon receptor. The results may aid in the development of drugs for diabetes and other metabolic disorders.

### **How Sleep Clears the Brain**

Sleep is important for storing memories, and also has a restorative function. Sleep helps reasoning, problem-solving, and other functions. However, the mechanisms behind these benefits have been unknown. An NIH-funded study in mice suggests that sleep helps restore the brain by flushing out toxins that build up during waking hours through a special series of channels in the brain.

### **Technique Forms Working Inner Ear Cells**

Specialized cells in the inner ear detect head movements, gravity, and sound. Researchers know the general scheme of inner ear development, but deeper knowledge will be critical for developing novel therapies for hearing loss and balance disorders. Using an innovative 3-D culture system, NIH-funded researchers were able to coax mouse embryonic stem cells to form complex cells and structures seen in the inner ear.

### **Study Reveals New Targets for Parkinson's Disease**

Defects in mitochondria, our cells' biological power plants, have been associated with certain neurological disorders, including Parkinson's disease, Charcot-Marie-Tooth syndrome, and the ataxias. NIH scientists used a novel approach, involving a protein tied to Parkinson's disease, to identify dozens of genes that may contribute to disorders that involve mitochondria.

### **Therapeutic Nanoparticles from Grapefruit Juice**

Nanoparticles are emerging as an efficient tool for drug delivery. Microscopic pouches of synthetic lipid can protect drug molecules within the body and deliver them to specific cells. However, these nanoparticles pose obstacles, including potential toxicity, environmental hazards, and large-scale production costs. NIH-funded researchers made nanoparticles from grapefruits and used them to deliver targeted drugs to treat cancer in mice. The technique may prove to be a safe and inexpensive alternative.

### **Understanding How We Speak**

Speech disorders, such as stuttering, affect roughly 5% of children by the first grade. The underlying causes of most speech disorders, however, aren't well understood. The process of speaking is one of the most complex actions humans perform. Scientists funded by NIH revealed the patterns of brain activity that produce human speech. The research may one day lead to new methods for treating speech disorders.

### **Scientists Recode Organism's Genome**

Living microbes can quickly and reliably produce proteins, the building blocks of the cell. This ability has long been harnessed to produce conventional proteins, such as insulin, for medical use. Synthetic biology seeks to redesign natural biological systems for new purposes. NIH-funded researchers developed a method to recode a bacterium's genome to incorporate synthetic non-standard amino acids into its proteins. The technique can potentially turn microbes into efficient living factories that make novel compounds.

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2012

## **Clinical Breakthroughs**

### **How Often Should Women Have Bone Tests?**

Experts recommend that older women have regular bone density tests to screen for osteoporosis. But it had been unclear how often to repeat the tests. An NIH-supported study of nearly 5,000 women reported that patients with healthy bone density on their first test might safely wait 15 years before getting rescreened. These findings can help guide doctors in their bone screening recommendations.

### **Hope for Beating Egg Allergy**

Small daily doses of egg powder might help children with egg allergy to eat the food safely. An NIH-funded study showed that most children could eat eggs while receiving the experimental therapy. Some could continue eating eggs even after the treatment ended. Although promising, this approach is still in development and shouldn't be tried at home.

### **Fending Off Cardiovascular Disease**

An NIH-supported study of data from over a quarter of a million people confirmed that high blood pressure and other traditional risk factors for cardiovascular disease substantially raise the chance of major cardiovascular events like heart attack or stroke over the course of a lifetime. The finding reinforces the importance of controlling these risk factors.

### **Thought-Control Gives Paralyzed People Helping Hand**

Paralyzed patients were able to reach and grasp objects by controlling a robotic arm with their thoughts. NIH-funded researchers taught 2 patients who were paralyzed by stroke—a 58-year-old woman and a 66-year-old man—to mentally control a robotic limb. The advance may help restore some independence and improve quality of life for people who've lost use of their limbs.

### **Using Autoinjectors to Treat Seizures**

Drug delivery into muscle using an autoinjector—akin to the EpiPen that treats serious allergic reactions—can quickly and effectively stop prolonged epileptic seizures. The finding, funded primarily by NIH, offers first responders a safe and fast therapeutic tool during an emergency. Autoinjectors may also provide quick therapy during a widespread crisis, such as a chemical or biological attack.

**Improved COPD Detection** An experimental technique developed with NIH support can distinguish between different types of chronic obstructive pulmonary disease (COPD) and track disease progression. The method could allow for more accurate diagnoses and lead to more effective treatments for COPD.

### **Diabetes Prevention A Good Investment**

Researchers supported primarily by NIH found that programs to prevent or delay type 2 diabetes make sound economic sense. Despite the money spent on these interventions, they lower overall medical care costs and improve quality of life. Diabetes currently costs the nation an estimated \$174 billion per year, including \$116 billion in medical expenses and \$58 billion in indirect costs like disability and work loss.

### **How Sulfa Drugs Work**

Scientists finally found out how sulfa drugs—the first class of antibiotics ever discovered—work at the molecular level. The NIH-supported finding offers insights into designing more robust antibiotic therapies that also avoid side effects and other problems associated with sulfa drugs.

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## **Promising Medical Advances**

### **Egg-Producing Stem Cells Found in Women**

Researchers long believed that women are born with a fixed number of young egg cells, or oocytes, that must last through their reproductive years. NIH-supported scientists were able to isolate egg-producing stem cells from the ovaries of women and observe these cells giving rise to oocytes. The finding may point the way toward improved treatments for female infertility.

### **Antibodies Protect Against Range of Flu Viruses**

Scientists isolated antibodies that protect mice against a variety of lethal influenza B viruses. One of them also guards against influenza A viruses. A universal influenza vaccine—one effective against multiple strains for several years—would have an enormous impact on public health. This NIH-funded accomplishment points the way toward approaches to combat all influenza A and B viruses.

### **Retinal Device Restores Sight in Mice**

Researchers funded by NIH developed a new prosthetic technique that can restore vision to blind mice. The approach could potentially be further developed to improve sight in blind people.

### **Clues to Emerging Drug-Resistant Malaria**

Malaria kills more than a half million people and infects over 200 million each year. An international team of scientists reported that a first-line treatment for malaria is losing its effectiveness in parts of Asia. They also found regions of the parasite's genome that seem to underlie its drug resistance. The NIH-supported studies may offer clues to help block the spread of hard-to-treat malaria.

### **Organ Transplants Without Life-Long Drugs**

An experimental method allowed kidney transplant recipients to eventually stop taking harsh immune-suppressing medications, even though they'd received mismatched organs. The findings from this NIH-supported study may one day reduce the need for anti-rejection drugs and lead to more options for patients awaiting organ transplants.

### **Implanted Heart Cells Stifle Irregular Rhythms**

Heart cells derived from human stem cells can protect injured guinea pig hearts against abnormal rhythms, according to a study partly funded by NIH. Similar heart cell transplants might one day hold promise for treating damaged human hearts.

### **Gene Therapy Restores Sense of Smell in Mice**

Mice that were unable to smell from birth gained the ability to smell when NIH-funded researchers used gene therapy to regrow structures called cilia on cells that detect odor. The approach might one day lead to treatments for related human genetic disorders.

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## **Insights from the Lab**

### **Finding Treasure in "Junk" DNA**

A worldwide research consortium created a view of the human genome that extends well beyond our genes. The NIH-funded ENCODE project involved over 1,600 sets of experiments on 147 types of tissue. Scientists catalogued many aspects of gene regulation that can affect function. The project's ultimate goal is to identify all functional elements in the human genome, including genes and the DNA in between.

### **The Healthy Human Microbiome**

The human body is host to trillions of microbes. Most are beneficial, but some can cause illness. NIH-funded investigators are using genomic techniques to study these microbial communities and their genes—collectively known as the microbiome. In a series of reports, scientists from nearly 80 institutions described 5 years of research that offers insights into how our microbes affect human health.

### **New Brain Cleaning System Discovered**

NIH-funded scientists discovered a system of tiny channels in the mouse brain that seem to quickly and efficiently remove waste products. Malfunction of this “glymphatic system” slows the clearance of amyloid beta, a brain protein that builds up in patients with Alzheimer’s disease. The finding may lead to new ways of treating neurodegenerative disorders.

### **Rare Immune Cell Involved in Multiple Sclerosis**

Patients with multiple sclerosis (MS) have elevated levels of an unusual immune cell called lymphoid tissue inducer, NIH-funded researchers reported. Patients receiving an experimental MS drug (daclizumab) proved to have lower numbers of these cells, and additional evidence linked the cells to MS-related brain inflammation. Lymphoid tissue inducer cells may be a promising target for future therapies.

### **Stabilizing Vaccines and Antibiotics With Silk**

NIH-supported researchers developed a way to use silk to store and distribute vaccines and antibiotics without having to keep them cold. Refrigeration can account for up to 80% of the cost of vaccines. The new silk-based film helps stabilize vaccines and drugs stored for months at warmer temperatures. The technique could lower costs and help expand the use of these lifesaving medical tools around the world.

### **Complex Brain Has Simple Grid Structure**

A landmark NIH-funded study showed that nerve fibers in the brain aren’t just a tangle of overlapping wires. Rather, they form a highly structured 3-D grid, with nerve pathways running parallel to each other and crossing each other at right angles. The finding is part of a larger effort called the Human Connectome Project, which is mapping connections between the brain’s 100 billion neurons.

### **Molecular Effects of Social Stress**

Social rank has broad effects on gene regulation, especially in the immune system, according to a study in rhesus macaques. By studying social groups of female monkeys, NIH-funded scientists identified nearly 1,000 genes whose expression levels varied with social hierarchy. The results provide insight into the long observed links between social stress and physiology.

### **Looking Inside Viruses**

Cryo-electron microscopy uses radiation to look at the surfaces of viruses, but radiation can destroy the tiny structures within. NIH-supported scientists turned the problem of radiation damage into an asset by taking and then superimposing many “snapshots” of viruses under increasing doses of radiation. They used the technique to clearly visualize the inner structure of a virus. The method may yield insights that suggest new therapeutic strategies.

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2011

## **CLINICAL BREAKTHROUGHS**

### **Less Invasive Surgery Just as Effective for Some Breast Cancer Patients**

When breast cancer has spread to nearby lymph nodes, many doctors believe that removing several more nodes provides better treatment. But an NIH-funded study found no difference in survival rates 5 years after surgery, whether patients had had about 2 or more than 10 lymph nodes removed. The finding may change the way early-stage breast cancer is treated in some patients.

### **Treating HIV Early Prevents Transmission**

Treating HIV-positive patients with anti-retroviral therapy early—before their T-cell counts start to drop—can significantly lower the risk of transmitting HIV. In a large NIH-funded clinical trial, researchers selected over 1,700 couples from around the world in which one partner was HIV-positive. Half the HIV-positive patients started anti-retroviral therapy immediately, while the other half received standard clinical treatment. Early therapy reduced the rate of HIV transmission by 96%.

### **Less Medication Effective for Wheezing Preschoolers**

Recurrent wheezing in children at risk for developing asthma can be controlled using far less medication by giving higher doses of an inhaled corticosteroid only as needed instead of lower doses every day. In an NIH-funded study, researchers found no significant differences in symptoms or number of doctor visits, but the children who took medication intermittently received one-third the total medication of those on a daily regimen.

### **DNA Primer Boosts Antibodies Against Avian Flu**

Avian flu-fighting antibodies rose significantly in adults who received a DNA “primer” vaccine followed by an avian flu shot. In an NIH study, people given the primer, followed 6 months later with an inactivated H5N1 vaccine, had 4 times the amount of antibody of those who received 2 vaccine doses. The technique holds promise for blocking several strains of influenza.

### **Saliva Testing Catches CMV Infection in Newborns**

A saliva sample from a newborn can be used to quickly and effectively detect cytomegalovirus (CMV) infection, a major cause of hearing loss in children. NIH-funded researchers, using a common technique called polymerase chain reaction, found CMV in liquid saliva samples in 100% of cases identified by the current standard. Better screening might lead to earlier treatment for affected babies.

### **Insulin Nasal Spray Shows Promise for Alzheimer’s Disease**

A small NIH-funded clinical trial found that daily doses of an insulin nasal spray can slow memory loss and preserve thinking skills in people with mild to moderate Alzheimer’s disease. Patients given either a 20 IU (international units) or 40 IU dose of insulin directly to the nose showed improvement in general function, and those given the lower dose also showed improved memory.

### **Treatment Helps With Kidney Transplants**

About 1 in 3 candidates for kidney transplantation has a condition that causes their bodies to immediately reject transplanted organs. In an NIH-funded study, transplant patients underwent several rounds of plasmapheresis, a process that removes transplant-reactive antibodies from the blood, and received an “incompatible” organ. The patients had an 80% survival rate after 8 years, significantly higher than those who waited for a compatible transplant. The technique could lead to thousands more kidney transplants every year.

### **Trial Restores Movement to Paralyzed Man's Legs**

Specialized physical therapy and electrical stimulation to the spine enabled a man with a spinal cord injury to stand and move paralyzed muscles. After 2 years of physical therapy alone, doctors supported by NIH implanted electrodes in the paralyzed man's spinal cord. With electrical stimulation from the electrodes, the patient now has control of previously paralyzed muscles below the site of injury.

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## **PROMISING MEDICAL ADVANCES**

### **Why Nicotine is a Gateway Drug**

An NIH-funded study in mice showed how tobacco products may act as gateway drugs, opening the door for cocaine use. Researchers found that mice given nicotine for 7 days had specific changes in the brain that also occur with cocaine addiction. Mice with these changes had stronger reactions to subsequent cocaine use. The finding hints that lowering smoking rates might help reduce cocaine abuse.

### **Blood DNA Test Detects Heart Transplant Rejection**

A new type of test that detects “foreign” DNA in a patient's bloodstream may provide early clues to organ rejection. Using blood samples from 17 heart transplant recipients, NIH-funded researchers found that the test could identify increases in the amount of free-floating transplant DNA during rejection episodes even before a standard biopsy test indicated rejection. This technique could offer an alternative to the expensive and invasive biopsies now used to detect transplant failure.

### **Antibodies Protect Against HIV in Mice**

Researchers devised a technique in mice that, with a single injection, protects the immune cells that HIV targets. NIH-funded scientists created a virus that expresses high levels of an HIV-neutralizing antibody. When injected into the muscles of special mice carrying human T-cells, the virus produced antibodies that prevented HIV from infecting the T-cells. With further development, the approach may one day prove effective at protecting people from HIV infection.

### **Parkinson's Protein May Regulate Fat Metabolism**

New NIH research suggests that Parkin, a protein linked to some cases of early-onset Parkinson's disease, regulates how cells in our bodies take up and process dietary fats. Mice lacking the Parkin gene didn't gain weight, even with age or a high-fat diet. These mice had lower levels of certain fat-transport proteins, which might affect the health of highly active neurons. Blood cells from patients enrolled at the NIH Parkinson's Clinic showed a similar pattern.

### **Targeted Light Therapy Destroys Cancer Cells**

NIH scientists developed a noninvasive technique that uses light to wipe out cancerous cells in mice without harming surrounding tissue. The researchers coupled a near-infrared fluorescent dye to cancer-specific antibodies. In mice, the antibodies bound to tumors. Near-infrared light, which can pass through an inch of tissue, then activated the dye and killed the cancer cells. This novel method might eventually be used to treat tumors in humans.

### **Tinnitus Cure May Lie in the Brain**

Scientists were able to eliminate tinnitus—a persistent ringing in the ears—in rats. Rats with noise-damaged hearing display tinnitus-like symptoms. NIH-funded researchers used nerve stimulation, paired with a series of tones above and below the pitch of the tinnitus ringing, to retrain the rats' brains. After the treatment, the rats no longer showed any tinnitus symptoms, suggesting that the ringing in their ears was permanently gone. The finding gives hope for a future tinnitus cure in humans.

### **Fungi Developed to Fight Malaria in Mosquitoes**

A genetically engineered fungus could help prevent malaria transmission. NIH-funded researchers modified a naturally occurring fungus to kill the malaria parasite inside infected mosquitoes. The modified fungus significantly reduced both the number of infected mosquitoes and the number of parasites in each mosquito still infected, but didn't kill the mosquitoes themselves. The advance might offer a new line of defense for combating a disease that affects nearly 300 million people worldwide.

### **Gene Therapy Helps Patients with Hemophilia**

Scientists reported that a single dose of an experimental gene therapy boosted production of a missing blood-clotting factor in people with hemophilia. In an NIH-funded study, 6 patients with severe hemophilia received infusions of a modified virus carrying a normal gene for the blood-clotting factor. After treatment, all the patients had higher levels of the factor in their blood, and 4 of the 6 patients no longer needed regular infusions of the blood-clotting factor to treat bleeding.

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## **INSIGHTS FROM THE LAB**

### **Sleep-Deprived Neurons Caught Nodding Off**

A new study gave insight into the roots of sleepiness. When NIH-funded researchers deprived rats of sleep, they caught neurons in the thinking part of the animals' brains taking catnaps. The longer the rats were awake, the more neurons they saw having brief “off” periods, which was linked to more difficulty touching a target. The study suggests that lowered performance in tired people might be due to neurons nodding off.

### **New Uses for Existing Medicines**

In a novel approach, researchers used computers and genomic data to find new applications for existing FDA-approved drugs. Computer algorithms correctly paired diseases with their current treatments, and also found new disease-drug pairs. Two of these drugs were tested in rodent models and effectively treated the paired disease. This new method represents a major step forward in drug discovery.

### **The Benefits of Being a Beta Male**

In male baboons, higher social rank generally brings lower stress. But a 9-year NIH-funded study of 125 baboons found an exception: the highest-ranked males had higher stress levels than second-ranking males. The researchers found that the top-ranked males spent significantly more energy guarding fertile females and behaving aggressively toward other males. The finding suggests that life at the very top can be more costly than previously thought.

### **Autism Blurs Distinctions Between Brain Regions**

An analysis of gene expression in the brain suggested that autism blurs the molecular differences that normally distinguish different brain regions. In an NIH-funded study, researchers found that of the hundreds of genes expressed at different levels between the frontal and temporal cortices in normal brains, only 8 genes were expressed differentially in brains from people with autism. The finding may point to a common molecular basis for autism spectrum disorders.

### **Study Undermines XMRV Connection to Human Disease**

The retrovirus previously tied to prostate cancer and chronic fatigue syndrome is unlikely to be responsible for either, according to an NIH study. Scientists found that the original patients and early patient tissue samples didn't contain XMRV, while later samples grown in the lab did carry the virus. The link to human disease was apparently due to contamination of samples while the tissues were grown in mice.

### **Gene Linked to Optimism and Self-Esteem**

Why can some people weather difficult times with little trouble while others crumble? An NIH-funded study suggested that the answer lies—at least in part—in your genes. Scientists found that people with 1 or 2 copies of a variant *OXTR* gene were less optimistic, had lower self-esteem and felt less control over their environment than those with 2 copies of a different variant. The gene is likely one of many that affect psychological resilience.

### **Survival Tactics of a Common Gut Microbe**

Scientists discovered how a common gut bacterium sends a “do not attack” signal to the immune system. Using mice with only one type of microbe in their intestines, the NIH-funded researchers found that a friendly gut bacterium uses a molecule called Polysaccharide A to activate certain cells in the mouse intestine. Those cells then turn down the immune response. The finding helps explain how our bodies distinguish between harmful microbes and those essential for health.

### **Genome Comparison Casts Light on Dark Areas of DNA**

A massive NIH-supported effort to sequence and compare 29 mammalian genomes shed new light on the “dark matter” of the genome, the over 98% of DNA that doesn't code for proteins. Scientists found that 5% of the genome is more similar than expected, or “constrained” by evolution. The study revealed previously undiscovered DNA segments that code for RNA and protein, and millions of other elements that may control gene expression.

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2010

## **Clinical Breakthroughs**

### **Alzheimer's Disease Signature Seen in Spinal Fluid**

Levels of 2 proteins in cerebrospinal fluid might be used to identify people with Alzheimer's disease before they show clinical symptoms. A distinct Alzheimer's signature—reduced levels of a specific beta-amyloid protein and increased levels of a phosphorylated tau protein—was found in 90% of Alzheimer's patients and 72% of people with mild cognitive impairment. The NIH-funded finding could open new opportunities for developing Alzheimer's therapies.

### **New Test Detects TB in Less than 2 Hours**

An automated test, developed with NIH support, rapidly and accurately detected tuberculosis and drug-resistant TB bacteria. In a study of 1,730 patients, the test identified 98% of all confirmed TB cases in less than 2 hours and up to 90% of TB cases that were missed by a more common diagnostic method. The finding could pave the way for earlier diagnosis and more targeted treatment of this sometimes-deadly disease..

### **Gene Variants Tied to Poor Outcomes with Heart Drug**

Clopidogrel, a widely prescribed anti-clotting drug, was known to be less effective for heart patients with 2 copies of a variant gene, or up to 4% of the population. An NIH-funded study showed that patients with just 1 variant—another 26% of the population—may also be at risk. The finding advances our understanding of how to tailor medications based on genetic makeup.

### **Immunotherapy Boosts Pediatric Cancer**

A new antibody-based therapy prompted an immune system attack on tumor cells and significantly improved the survival rates of children with neuroblastoma, a deadly nervous system cancer. In an NIH-funded study of 226 children with neuroblastoma, the new immunotherapy plus standard therapy raised the survival rate to 66%, compared to 46% for those receiving standard therapy. The study was stopped early because of the positive results.

### **Patient's Whole Genome Reveals Disease and Medication Risks**

By evaluating the entire genome of a 40-year-old man, scientists pinpointed gene variants linked to cardiovascular disease and several other conditions in the man's family, as well as diseases not known to be in his family. Some variants predicted the man's likely responses to common medications, including certain heart medications. This NIH-funded study provides a glimpse into how whole-genome sequencing might one day be used in the clinic.

### **Daily Drug Reduces Risk for HIV Infection**

A pill that's currently used to treat HIV infection can also greatly reduce the risk of acquiring HIV among at-risk men, according to an NIH-funded study. The clinical trial enrolled nearly 2,500 men who have sex with men. Men who received a daily antiretroviral tablet were 44% less likely to acquire HIV infection during the study than those receiving placebo pills. The finding represents a major advance toward HIV prevention.

### **Best Treatment Differs for Kids With Asthma**

Most children who have trouble controlling their asthma with low-dose inhaled corticosteroids show improvement by increasing the dose or adding another medication, an NIH-funded study reported. However, the best option differed for each child. The clinical study of over 150 children identified characteristics, such as ethnicity, that raise the likelihood of one treatment working better than another. The finding highlights the need for a personalized approach to treating pediatric asthma.

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## PROMISING MEDICAL ADVANCES

### Progress on a Universal Flu Vaccine

NIH researchers developed a method to generate antibodies that attack a diverse array of influenza viruses in animals. The success moves scientists closer to a universal flu vaccine—one that protects against multiple viral strains for several years. After receiving a vaccine that targets a particular viral protein, followed by a booster shot, animals produced broadly neutralizing antibodies. Most were protected from death after exposure to the deadly 1934 flu virus.

### The Health Benefits of Cutting Salt

A computer model of heart disease in U.S. adults suggested that reducing salt intake by 3 grams per day could cut the number of new cases of coronary heart disease each year by as many as 120,000, stroke by 66,000 and heart attack by nearly 100,000. It could also prevent up to 92,000 deaths and save up to \$24 billion in health care costs a year, the NIH-funded researchers estimated.

### Stem Cells Used to Create Cells to Study Heart Condition

Researchers made stem cell lines by reprogramming skin cells from patients with LEOPARD syndrome, a rare developmental disorder. The scientists coaxed the cells to become heart cells that had features seen in LEOPARD syndrome. These cell lines may now help researchers identify compounds that can reverse the characteristics of LEOPARD syndrome. The accomplishment is a major step toward using stem cells to model disease pathways and test potential treatments.

### Where Kids Get Their Empty Calories

Nearly 40% of the energy consumed by 2- to 18-year-olds comes in the form of "empty" calories, according to a study by NIH scientists. Half of those empty calories come from the solid fats and added sugars in just 6 sources: soda, fruit drinks, dairy desserts, grain desserts, pizza and whole milk. Experts recommend that kids limit their intake of empty calories to 20% or less of their total calories.

### First Genes Tied to Stuttering

NIH researchers and their colleagues identified 3 genes as a source of stuttering—the first time specific mutations have been tied to this speech disorder. Nearly 10% of people who stutter may have mutations in 1 of the 3 genes. The study of volunteers from 3 countries found that the genes may be linked to a glitch in cell metabolism, which could point to new approaches for treatment.

### How Light Boosts Migraine Pain

An NIH-funded study of blind patients showed how light might intensify headache pain. Light exposure worsened migraine pain in blind patients who couldn't perceive images but whose eyes could detect some light, even if they weren't aware of it. Light had no effect on migraine patients who were totally blind. The finding, which suggests that light-sensing, non-image-forming eye cells may help trigger migraines, could lead to new approaches for calming light-induced headaches.

### Preventing Bacterial Infections from Medical Devices

NIH scientists identified a protein that helps bacteria break away from medical devices like catheters and spread throughout the body. By treating mice with antibodies that block the protein, the researchers prevented the bacterium *Staphylococcus epidermidis* from spreading from a catheter to most other organs. The finding gives insight into how complex bacterial communities called biofilms cause disease and opens up new avenues for curbing biofilm-related infections.

### Cholesterol Genes Tied to Age-Related Macular Degeneration

By analyzing the genomes of more than 18,000 people, NIH-funded scientists identified 3 new genes associated with the blinding eye disease age-related macular degeneration (AMD). Two of the genes are involved in the cholesterol pathway—a formerly unknown biological mechanism for AMD disease development. The finding raises the possibility that new treatment or prevention approaches might target these genes or pathways.

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## INSIGHTS FROM THE LAB

### Structure of Receptor Involved in Cancer, HIV Infection

NIH-funded scientists determined the 3-dimensional structure of a protein involved in HIV infection and many forms of cancer. Using X-ray crystallography, the scientists captured snapshots of the protein, called CXCR4, bound to molecules that inhibit its activity. The images reveal how CXCR4 molecules form closely linked pairs, with inhibitors bound to their sides. The accomplishment could point to ways of locking out HIV and stalling cancer's spread.

### Making a Lung Replacement

NIH-funded researchers made transplantable lung grafts for rats. The team built on recent advances in decellularization—the process of removing cells from a structure but leaving the architecture of the original tissue intact. The scientists showed that the engineered lungs functioned in the animals. They were also able to decellularize human lung segments while preserving their architecture. The study could pave the way for the development of an engineered human lung.

### Controlling Computers with Your Mind

A brain-computer interface let people control pictures on a computer screen by activating just a few brain cells. NIH-funded scientists monitored brain cell activity via wires that sent information from patients' brains to a computer. In a simple computer game, participants were able to use their thoughts to control the images on the monitor nearly 70% of the time. The findings shed light on how single brain cells contribute to attention and conscious thought.

### Gut Bacteria May Influence Metabolic Syndrome

An NIH-funded study suggested that gut microbes, along with part of the immune system, may contribute to metabolic syndrome. Mice lacking an important immune receptor grew heavier than control mice and developed several features of metabolic syndrome. When gut microbes from these mice were transplanted into control mice, the recipient mice overate, became obese and diabetic. The next step will be to explore how gut microbes affect people's eating behavior.

### Coaxing the Body's Cells to Repair Damaged Joints

NIH-supported scientists developed a technique to regenerate damaged leg joints in rabbits. The researchers created porous scaffolds in the shape of leg bone tips and added a gel to aid cartilage development. By 3 to 4 weeks after surgery, the rabbits could move around almost as well as normal rabbits. Within 4 months, both bone and cartilage had regenerated. The accomplishment could point the way toward joint renewal in humans.

### Neanderthal Genome Sequenced

An international research team, including NIH scientists, produced the first whole-genome sequence of the Neanderthal genome—the closest evolutionary relative to humans. Neanderthal DNA is 99.7% identical to present-day human DNA and 98.8% identical to chimpanzee DNA. Present-day human DNA is also 98.8% identical to chimpanzee. The analysis suggests that up to 2% of the genome of present-day people outside of Africa originated in Neanderthals or their ancestors.

### Silk Helps Make Ultrathin Brain Interface

NIH-funded scientists developed ultrathin flexible implants made with a silk base that dissolves once it makes contact with the brain, allowing the electrode array to collapse into the brain's grooves and stretch over its rounded surfaces. The ultrathin implants can record brain activity more faithfully than thicker implants. The new technology allows for closer interaction between machines and living tissue, paving the way for more advanced implantable devices.

### Stress Hormone Causes Epigenetic Changes

Researchers found that chronic exposure to a stress hormone altered DNA in the brains of mice, prompting changes in gene expression. NIH-supported scientists found that giving mice a stress hormone caused epigenetic modifications—changes to DNA that don't alter sequences but influence gene expression—to a gene that has been tied to posttraumatic stress disorder and mood disorders in people. The finding provides clues into how stress might affect behavior.

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2009

## DISEASE PREVENTION, DIAGNOSIS, AND TREATMENT

### Weight Loss Depends on Less Calories, Not Nutrient Mix

Heart-healthy diets that reduce calorie intake—regardless of differing proportions of fat, protein or carbohydrate—can help overweight and obese adults achieve and maintain weight loss, according to an NIH-funded study. Over 800 adults were assigned to 1 of 4 diets that reduced their calorie intake and contained various levels of fat, protein and carbohydrate. All 4 groups achieved similar weight loss after 6 months and also after 2 years.

### Cocaine Vaccine Shows Promise for Treating Addiction

An experimental anti-cocaine vaccine significantly reduced cocaine use in a clinical trial. This NIH-funded study was the first successful demonstration of a vaccine against an illegal drug of abuse. The vaccine stimulates the production of antibodies that attach to cocaine molecules and prevent them from crossing the blood-brain barrier, thereby inhibiting or blocking cocaine-induced euphoria. Participants with the highest antibody levels had the greatest reductions in cocaine use.

### Gene Therapy Shows Promise for Eye Condition

Three young adults who received gene therapy for a blinding eye condition remained healthy and maintained visual gains one year later, NIH-supported researchers reported. One patient also noticed a visual improvement that helped her perform daily tasks. This is a promising advance for patients with Leber congenital amaurosis (LCA), an inherited disorder with no approved treatment. The results also demonstrate the clinical potential of gene therapy for treating inherited blindness.

### Acupuncture-Like Treatments Improve Low Back Pain

Patients with low back pain who had acupuncture improved more than those who got typical medical care, an NIH-funded study found. But surprisingly, "imitation" acupuncture—which used toothpicks to stimulate acupuncture points but didn't break the skin—brought as much improvement as the real thing. The finding raises questions about how acupuncture relieves pain.

### Deep Brain Stimulation Curbs Parkinson Symptoms

NIH-funded scientists reported that deep brain stimulation improves quality of life for Parkinson's patients and leads to more daily hours without troubling movement symptoms than standard medical care. But on the down side, brain stimulation also carries a greater risk of serious adverse events, such as infection from the surgery. This clinical study of 255 patients with advanced Parkinson's disease was the largest of its kind to date.

### Genetic Tests Help Optimize Doses of Blood-Thinning Drug

The widely prescribed blood-thinning drug warfarin (Coumadin) can help prevent blood clots that lead to heart attack, stroke or even death in certain patients. But determining the proper dosage for each patient can be difficult. An NIH-funded clinical trial showed that genetic tests can help doctors fine-tune warfarin dosing for individual patients. The findings may eventually help prevent the life-threatening dangers of improper dosing.

### Vitamin C May Reduce Gout Risk

An NIH-funded study linked higher vitamin C intake with a lower risk of gout. Vitamin C supplements, the results imply, may help to prevent this condition, which develops when uric acid crystals accumulate in joints to cause swelling and pain. Researchers looked at nearly 47,000 men who did not have gout at the start. After 20 years, those with more vitamin C intake were least likely to have gout.

### Neighborhood Food Options Linked to Obesity in Big Apple

Nearly one-third of adults nationwide are obese. One contributing factor may be the "built environment"—that is, access to stores that sell healthy foods and to resources that support physical activity. An NIH-funded study looked at data on over 13,000 residents of New York City. The scientists showed that ready access to healthy food outlets such as supermarkets and natural food stores was significantly linked to reduced weight status.

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## PROMISING MEDICAL ADVANCES

### Overlooked "Brown Fat" Tied to Obesity

Babies have a type of fat called brown fat, but scientists thought it disappeared by adulthood. NIH-funded researchers showed that not only do adults have it, but it may be important to weight control. Brown fat burns up chemical energy to create heat. Whole-body scans of about 2,000 adults found that the less brown fat tissue they had, the higher their body mass index tended to be.

### **Autism Tied to Genes That Influence Brain Cell Connections**

NIH-funded research teams identified several genetic factors that affect the risk of autism spectrum disorders. The scientists used genome-wide association studies, which involve scanning genomes — entire sets of DNA — to find small differences between people who have a disorder and people who don't. Understanding how these genetic variations affect brain development will suggest new strategies for diagnosing and treating autism spectrum disorders.

### **Time of Day Can Be Critical in Chemotherapy**

The time of day that chemotherapy drugs are taken is already known to affect the drugs' effectiveness and side effects. NIH-funded researchers uncovered the reason: the body's ability to repair DNA damage fluctuates with the time of day. The results show that it might be possible to take advantage of the body's circadian rhythms to develop better methods of hitting cancer cells when they're least able to recover.

### **Virus Linked to Chronic Fatigue Syndrome**

Chronic fatigue syndrome is a debilitating disease that affects millions of people in the United States, but no specific cause has yet been identified. A team of scientists at NIH and the Cleveland Clinic detected the DNA of a retrovirus called XMRV in the blood of patients with chronic fatigue syndrome. The discovery raises the possibility that the virus may be a contributing factor in the disorder.

### **How Ozone Harms Lungs**

Ozone is a common urban air pollutant that can irritate the airways and cause wheezing. The mechanisms responsible for ozone's effects have been poorly understood. NIH researchers discovered that a sugar called hyaluronan is responsible for causing the airways to narrow and become irritated in the presence of ozone. The finding suggests new targets for treating wheezing, coughing and shortness of breath.

### **Technique Blocks a Conditioned Fear in Humans**

NIH-funded researchers developed a way to erase a fear memory in rats without using drugs. Some of their colleagues then used the technique to selectively block a conditioned fear memory in humans. The advance represents a safe, easily implemented way to prevent the return of a fearful memory. It may one day lead to improved therapies for the treatment of anxiety disorders such as post-traumatic stress disorder.

### **Monkey DNA Swap May Block Mitochondrial Disease**

Most of our DNA is in the nuclei of our cells. But tiny structures called mitochondria in cells also contain some DNA. Defects in mitochondrial DNA cause several rare and deadly disorders. NIH-funded researchers developed a technique for exchanging DNA between egg cell nuclei while leaving mitochondria behind. The technique led to the birth of 4 healthy monkeys. The method may one day provide new options for preventing or treating mitochondrial disorders.

### **Lack of Sleep Linked to Alzheimer's Plaques in Mice**

People with Alzheimer's disease often have trouble sleeping. A new study suggested that sleep problems may actually contribute to the disease. Alzheimer's disease is marked by dense "plaques"—made mostly of a protein called amyloid-beta—forming between brain cells. NIH-funded researchers found that disrupted sleep can lead to buildup of these plaques in mice. Amyloid-beta levels in both mice and people naturally fluctuate, they discovered, rising while awake and falling during sleep.

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## **INSIGHTS FROM THE LAB**

### **Catching Flu's Drift**

Influenza viruses evade the immune system by constantly changing the shape of their outer proteins. New findings by NIH researchers yielded insights into the evolutionary forces that drive this shape shifting, or antigenic drift. If their model is correct, vaccinating more children against influenza could slow the rate of antigenic drift and extend how long seasonal flu vaccines remain effective.

### **Reprogrammed Human Stem Cells Clear Another Hurdle**

Researchers funded by NIH developed a technique in which the genes used to reprogram human cells and give them the versatility of embryonic stem cells can be cleanly removed afterward. This advance could open doors to innovative therapies in the future, where people's own cells might be reprogrammed and used to repair damaged tissues and organs.

### **Landmark Studies Look at Genetics of Africans, Indians**

By analyzing genetic variation in people across Africa—and those of African descent around the world—NIH-funded researchers teased apart the complex evolutionary history of Africans and African Americans. A separate study reconstructed the ancestry of people across India. In addition to revealing important human population history, these studies set the stage for future research into the genetic and environmental risk factors for disease and drug response.

### **Understanding a Common Cold Virus**

Rhinoviruses are a major cause of the common cold and may contribute to about half of asthma flare-ups. NIH-funded researchers completed sequencing the genomes of all the known rhinovirus types. These results provide a framework for tracking the movement and evolution of new viruses, and could prove valuable for developing medications and vaccines to combat the viruses in the future.

### **Wide Variety of Bacteria Mapped Across the Human Body**

By analyzing bacterial communities in and on several people, scientists have begun to create an atlas of bacterial diversity that documents the different types of microbes that thrive in distinct regions of the human body. The NIH-funded investigators found wide variability in bacterial communities on each person and between people. The results set the stage for determining how changes in bacterial communities help to cause or prevent disease.

### **Insights into How HIV Evades Immune System**

Vaccines typically work by triggering the immune system to produce antibodies that help to beat infections. But most antibodies can't latch onto and neutralize the human immunodeficiency virus (HIV). An NIH-led research team discovered how the virus resists these antibodies. Their insights into how antibodies bind the virus may help bring researchers closer to creating an effective HIV vaccine.

### **Alcohol's Site of Action Revealed**

Scientists knew that a membrane channel in brain cells was somehow activated by ethanol, the type of alcohol found in alcoholic beverages. An NIH-funded study finally provided a molecular explanation for how alcohol produces its pleasant and intoxicating effects. The scientists showed that alcohol directly interacts with a specific nook of a channel protein. The breakthrough could lead to new treatments for alcohol abuse and dependence.

### **Scientists Detect Key Proteins Needed for Ovulation**

Ovulation—the release of a mature egg from an ovary—results from a complex series of biochemical events that aren't fully understood. NIH-funded researchers have identified 2 proteins that are essential for ovulation in mice. The finding not only advances our understanding of ovulation; it may one day lead to new treatments for infertility as well as new ways to prevent pregnancy by blocking release of the egg.

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2008

## **DISEASE PREVENTION, DIAGNOSIS, AND TREATMENT**

### **Dietary Supplements Fail to Prevent Prostate Cancer**

Two large NIH-funded clinical trials found that taking vitamin E, vitamin C or selenium does not reduce the risk of prostate cancer or other cancers in older men, as some previous studies had suggested. The results highlight the fact that dietary supplements can sometimes seem beneficial in small observational studies, but large, carefully controlled trials are needed to test whether they really live up to their hoped-for benefits.

### **Intensive Blood Sugar Control in Type 2 Diabetes**

People with type 2 diabetes need to keep their blood sugar from getting too high. But a large NIH-funded clinical trial found that tighter control isn't always better. A therapeutic strategy designed to aggressively control blood sugar in adults with diabetes who are also at high risk for cardiovascular disease not only failed to reduce the risk of major cardiovascular events; it actually raised patients' risk of death.

### **Smokers Band Together and Quit Together**

Spouses, friends, siblings and co-workers usually decide to light up or stub out their cigarettes for good around the same time, an NIH-funded study found. Married couples seemed to exert the greatest influence on each other. When one spouse quit smoking, the other's likelihood of smoking dropped by nearly 70%. A better understanding of how social ties affect smoking behavior may lead to more effective ways to prevent or reduce smoking.

### **DTreatment Lowers Preterm Infants' Risk for Cerebral Palsy**

Preterm infants born to mothers receiving intravenous magnesium sulfate—a common treatment to delay labor—are less likely to develop cerebral palsy than those whose mothers don't receive it, according to NIH-supported research. The study, involving more than 2,200 pregnant women, is the largest, most comprehensive effort to date to examine the link between the often-used drug and cerebral palsy.

### **Laser Treatment Best for Diabetic Macular Edema**

Traditional laser therapy proved more effective than newer steroid injections for treating people with diabetes who have abnormal swelling in the eye, a condition called diabetic macular edema. About 700 patients were studied in the NIH-funded clinical trial, which showed that laser therapy protected against vision loss and had far fewer side effects than the corticosteroid treatments.

### **Wide Waists Boost Mortality Risk**

Even if your weight is in the normal range, your risk of death increases if your waist is wide, according to research by NIH scientists. The investigators studied nearly a quarter-million people over age 50. Those with the largest waists had about a 25% higher mortality risk than those with a normal-sized waist. Normal-weight people with large waists had a 20% higher risk of death than those with both a normal weight and waist size.

### **Children's Physical Activity Drops from Age 9 to 15**

Physical activity levels sharply declined in a large group of American children between the ages of 9 and 15, according to a long-term study by NIH-supported scientists. At ages 9 and 11, more than 90% of the children met recommended activity levels—at least 60 minutes of physical activities most days of the week. By age of 15, however, only 31% met the recommended level on weekdays, and only 17% on weekends.

### **Increased Allergen Levels in Homes Linked to Asthma**

A little housecleaning may help to reduce asthma symptoms in people who have both asthma and allergies, suggests a study by NIH scientists and their colleagues. A survey of more than 2,500 people showed that allergy-triggering substances, called allergens, were common in most homes. Households with asthmatic people were more likely to have higher levels of multiple allergens, including those from dog, cat, mouse and dust mite.

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## **PROMISING MEDICAL ADVANCES**

### **Gene Variations Linked to Kidney Disease in African Americans**

For the first time, researchers have identified genetic variations that are strongly associated with certain kidney diseases that disproportionately affect African Americans. The results of this NIH-funded research may eventually lead to new therapies or diagnostic tools to identify people at higher risk various types of kidney disease.

### **Artificial Connections Restore Movement to Paralyzed Limbs**

For the first time, scientists have shown that a direct artificial connection from the brain to muscles can restore wrist movement in monkeys whose arms have been temporarily anesthetized. The results of this NIH-funded study have promising implications for prosthetic design, although clinical applications are still probably at least a decade away.

### **Genome-Wide Studies Shed Light on Several Disorders**

In 2008, NIH-funded scientists identified genetic variations that put people at risk for several common and complex disorders, including breast cancer, gout, lung cancer, schizophrenia, glioblastoma and blood cholesterol and lipid levels. Their successes relied on genome-wide association studies (GWAS), which scan the genomes of large numbers of people to find genetic variations associated with a particular disease. By analyzing hundreds or thousands of genomes, GWAS analyses can detect infrequent but significant links to disease that might be obscured in smaller studies. One NIH-funded GWAS even examined the genetic make-up of smokers. The results suggested that certain genetic variants can affect smokers' chances for successful quitting and may also help determine which type of treatment would be most likely to help them quit.

### **Quick New Method Makes Human Antibodies that Fight Flu Virus**

Researchers devised a fast new technique for producing human monoclonal antibodies (mAbs) that can roam the bloodstream to target and destroy infectious microbes. Using the new method, NIH-funded scientists created fully human influenza-fighting antibodies in a matter of weeks, rather than the months typically needed to generate mAbs.

### **Fat Cell Numbers in Teen Years Linger for a Lifetime**

After your teen years, the number of fat cells in your body probably stays the same for the rest of your life, even if you gain or lose weight, according to an NIH-funded study. The fat cells simply get bigger or smaller as your weight changes. The findings may help to explain why it can be so hard for some people to drop pounds and keep them off.

### **Newly Identified Compounds Can Block Parasitic Worms**

NIH-supported scientists identified a molecule that holds promise for treating schistosomiasis, a sometimes-deadly disease that afflicts more than 200 million people worldwide. The new compound, called furoxan, can destroy all 3 major species of the microscopic parasitic worms that cause schistosomiasis in humans. Furoxan also blocked all stages of the *Schistosoma* worm's development in infected mice.

### **Learning How Cold Sore Viruses Hide**

Once you've been infected with a herpesvirus, like the virus that causes cold sores, it takes up permanent residence in your body, hiding quietly in your nerve cells until the next outbreak. NIH-funded scientists discovered tiny molecules, called microRNAs, that seem to help the cold sore virus stay inactive and protected. The finding may eventually lead to new strategies for treating persistent herpesvirus infections.

### **Map of Structural Variation in the Human Genome**

NIH-funded researchers produced the first sequence-based map of "structural" variations in the human genome, including gains, losses and rearrangements of long stretches of DNA. Structural variations have already been linked to HIV susceptibility, coronary heart disease, schizophrenia and autism. The map will help researchers better understand how these variations contribute to human health and disease.

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## **INSIGHTS FROM THE LAB**

### **Novel Type of Antibody Inhibits HIV Infection**

NIH scientists identified a small antibody fragment that's highly effective at neutralizing the human immunodeficiency virus (HIV). The antibody strongly binds to different versions of the HIV envelope protein and prevents a wide range of HIV strains from entering immune cells. The finding may ultimately lead to new therapies against HIV and other viruses.

### **Making "Safer" Stem Cells**

NIH-funded scientists developed a new technique that converts adult cells into versatile stem cells that can grow into a wide variety of cell types. This approach uses a common cold virus to insert 4 transformative genes into mouse cells. The new method sidesteps the cancer-causing potential of a previously developed technique, which used a different kind of virus to deliver the stem cell-generating genes.

### **Rethinking Metastasis**

Most cancer deaths result from metastasis, the spread of cancer from a tumor to other parts of the body. Researchers have long thought that metastasis comes at a late stage of cancer. NIH-funded studies of genetically altered mice now suggest that metastasis may start long before that. Normal cells may travel to other parts of the body early in the cancer process and then later become malignant.

### **Human Genes Associated With West Nile Virus Infection**

Since West Nile virus first appeared in the United States a decade ago, it's become a seasonal epidemic that flares up each summer. Unfortunately, our understanding of the virus on a molecular level has been limited. A study by NIH-funded scientists identified over 300 human genes that play a role in West Nile virus infection. The findings reveal several potential targets for antiviral therapies.

### **Metabolic Network Finds Disease Links**

By building an extensive computer network of molecular relationships, NIH-funded researchers uncovered completely unexpected connections between diseases. The metabolic disease network pinpointed 193 pairs of diseases that are metabolically linked and tend to occur together. This research broadens the study of disease by moving beyond single genes to consider multiple genes or proteins at the same time.

### **Adding "Color" to MRI**

NIH researchers and their colleagues have figured out how to add the equivalent of color to MRI. The scientists engineered different microscopic magnetic particles that give off distinct signals in an MRI scan. Computers can convert these signals into a rainbow of colors. With further development, the technique may produce MRI scans that better distinguish between the body's internal structures and cell types.

### **Immune Cells Help Tropical Parasites Evade Death**

Tiny parasites that cause the tropical disease leishmaniasis may take advantage of the body's initial defenses by hiding and surviving inside the fast-acting immune cells sent to devour them, according to a study by NIH scientists. The research provides a new view of the earliest stages of *Leishmania* infection, which affects about 12 million people worldwide.

### **Cholesterol Drug Makes Staph More Vulnerable**

NIH-funded researchers discovered that an experimental cholesterol-fighting drug may also prove useful as an antibiotic that beats back staph infections. The scientists showed that the cholesterol drug can strip *Staphylococcus aureus* bacteria of their golden color, weakening bacterial defenses and making them more susceptible to killing by the immune systems of mice.

Prepared by Vicki Contie

Edited by [Harrison Wein, Ph.D.](#)

December 2008

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## DISEASE PREVENTION, DIAGNOSIS, AND TREATMENT

### Established Drug Bests Newcomer in Treating Female Infertility

Researchers reported that infertility arising from polycystic ovary syndrome (PCOS) is better treated with an established ovulation-inducing drug (clomiphene) than with an increasingly popular alternative (metformin). The NIH-funded study was the largest, most comprehensive effort to date comparing the 2 drugs' abilities to promote pregnancy in women with PCOS, a hormonal disorder that affects about 1 in 15 women and is the leading cause of infertility.

### Inhaled Steroids Best Treatment for Children With Asthma

An NIH-funded study tested the effectiveness and safety of 3 different asthma medicines in nearly 300 school-age children. The scientists found that inhaled corticosteroids are the most effective initial daily therapy for children with mild to moderate persistent asthma.

### MRI Increases Detection of Second Cancer in Opposite Breast

When a woman is newly diagnosed with cancer in one breast, there's up to a 10% chance that clinical exams and mammography will miss a tumor growing in the opposite breast. An NIH-funded study found that magnetic resonance imaging (MRI) can help to detect these overlooked cancers in the opposite breast at the time of initial diagnosis, which may also lead to earlier treatment.

### Depressed Adolescents Respond Best to Combination Treatment

A major clinical trial found that a combination of antidepressant medication and "talk therapy," or psychotherapy, appears to be more effective for treating teens with major depressive disorder than medication or psychotherapy alone. The NIH-funded study enrolled 439 adolescents who had major depression. At both 4 months and 9 months after therapy began, response rates to the combination treatment significantly outpaced the 2 single-treatment approaches.

### Lower Sodium Decreases Long-Term Cardiovascular Risk

Several studies had already shown that lowering your salt intake helps to prevent high blood pressure, or hypertension. But a new NIH-funded analysis found that less sodium can also prevent heart disease. The researchers examined clinical trial data from studies of more than 3,000 adults with pre-hypertension. Men and women who reduced their salt intake had a 25% lower risk of total cardiovascular disease over the next 10 to 15 years.

### Diagnosing Autism Spectrum Disorder

Autism is rarely diagnosed before 3 years of age, but the sooner it is identified and treated the better the outcome for the child. NIH-supported scientists found that it's possible to detect autism in some children as young as 14 months of age, the earliest the disorder has ever been diagnosed. In other children, definite signs of autism can be seen by about 2, the researchers said. Their diagnoses were based on close assessment of the children's social and communication skills.

### Vaccine Shows Promise in Preventing Hepatitis E

An experimental vaccine—originally created and tested over the past 2 decades by NIH scientists—appears safe and effective in preventing hepatitis E, a sometimes-deadly viral disease prevalent in developing countries. A clinical trial involving nearly 2,000 healthy adults in Nepal, where the virus is widespread, found that the vaccine was nearly 96% effective in preventing hepatitis E during a follow-up period of about 2 years.

### Treating Depression in Patients with Bipolar Disorder

Patients with bipolar disorder have severe mood swings between mania and depression. Treatment typically involves mood-stabilizing drugs like lithium or valproate. Two separate reports—both part of a large-scale NIH-funded study of bipolar disorder—looked at how well patients with depression responded when additional treatments were added to their mood-stabilizing therapy. One found that adding an antidepressant medication was no more effective than a sugar pill in reducing depression. ([NIH press release](#) | [PubMed](#)). The other reported that patients tended to get well faster and stay well if they received intensive psychotherapy for several months.

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## PROMISING MEDICAL ADVANCES

### Soaking Up Toxic Protein to Stop Alzheimer's Disease

Scientists used a variant version of a protein called sLRP to soak up a toxic protein from the bloodstream and prevent its buildup in the brains of mice. The toxic protein, called amyloid-beta, forms dense deposits in the brain called plaques that have been linked to the symptoms of Alzheimer's disease. The NIH-funded researchers studied a strain of mice known to develop Alzheimer-like symptoms. Mice treated with the sLRP variant protein had improved learning and memory, and amyloid-beta plaques in their brains were reduced by about 90%.

### New Risk Factors Identified for Type 2 Diabetes

A collaborative effort by 3 international research teams uncovered new clues about why some people develop type 2 diabetes and others don't. The research relied on a relatively new method, called a genome-wide association study, which rapidly and cost effectively analyzes and compares genetic differences between people with and without specific illnesses. The scientists identified 4 new genetic risk factors for type 2 diabetes and confirmed 6 other genetic variants previously associated with the disease.

### Gene Variants That Help Control HIV Infection

The first genome-wide association study of an infectious disease, conducted by an international group of researchers and funded in part by NIH, offered a new understanding of why some people can suppress virus levels following HIV infection. The scientists identified several genetic variants associated with the amount of virus, or viral load, in a patient's bloodstream. Other variants were linked to disease progression. The findings provide new avenues for developing vaccines and improved therapies to fight HIV infection.

### Second-Generation Map of Human Genetic Variation

The International HapMap Consortium published analyses of its second-generation map of human genetic variation, which contains more than 3.1 million genetic variants—3 times the number reported in the initial HapMap of 2005. The new HapMap includes DNA data from 4 diverse populations, based in Nigeria, China, Japan and Utah in the United States. The improved HapMap will help researchers find DNA variants that influence the risk of disease and other traits.

### Lack of Sleep Disrupts Brain's Emotional Controls

Experience tells us that sleepless nights can lead to overwrought emotions. Now NIH-funded scientists have a better understanding of why this occurs. Their imaging studies showed that lack of sleep can lead to greater activation of the brain's emotional centers and disrupt the brain circuits that tame emotional responses. The findings suggest that sleep restores the brain's emotional circuits and prepares people for the next day's challenges and social interactions.

### **HIV's Potential Weak Spot**

Scientists identified a tiny, unchanging region on an AIDS virus protein that may be the key to neutralizing the virus. A multi-site research team, including NIH scientists, used X-ray crystallography to take detailed 3-D snapshots of an antibody grabbing onto this stable viral region, which HIV uses to latch onto and infect T cells. The discovery of this potential viral weak spot could have a profound impact on the development of an AIDS vaccine.

### **Predicting Future Bird Flu Mutations**

To foretell how the avian flu virus might one day jump from birds to humans, NIH scientists have been looking at the molecular shapes of viral molecules to see how they latch onto cells. They found that just 2 mutations to the viral H5 protein could change the shape in a binding region and make it easier for the avian H5N1 virus to latch onto human cells. These studies could help researchers prepare vaccines and therapies against deadly flu viruses before they mutate and begin to spread in the human population.

### **Stem Cell Treatment Repairs Damaged Rat Hearts**

NIH-funded researchers developed a procedure for repairing damaged rat hearts by using cells generated in a dish from human embryonic stem cells. When the human-derived cells were implanted into the damaged hearts of rats, new heart muscle was incorporated into the heart tissue within a month. Further testing showed that the treatment thickened the heart's walls and improved their ability to contract. The accomplishment brings scientists a step closer to a treatment for people who have had heart attacks.

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## **INSIGHTS FROM THE LAB**

### **Versatile Human Stem Cells Created Without Embryos**

By modifying only 4 genes in human skin cells, NIH-supported researchers found that they could "reprogram" the cells to give them the characteristics of embryonic stem cells. This major advance could open doors to innovative therapies in the future, where people's own cells might be reprogrammed and used to repair their damaged tissues and organs. The breakthrough might also eventually put to rest the ethical controversy surrounding stem cells.

### **Embryonic Stem Cell Milestone Achieved in Primates**

Researchers achieved a major milestone in embryonic stem cell research, isolating embryonic stem cells for the first time from a cloned primate embryo. The scientists, funded by NIH, showed that the stem cells could turn into heart or nerve cells in the laboratory and had other characteristics of established embryonic stem cell lines. The technique, if developed in humans, could potentially be used to make personalized stem cells to treat diseases without worry of rejection by the patient's immune system.

### **Tracking Neural Progenitor Cells in the Human Brain**

Scientists developed the first noninvasive technique for detecting neural progenitor cells in the living human brain. Neural progenitor cells give birth to neurons and other types of brain cells. This new imaging method may eventually point to improved treatments and diagnostics for a host of brain-related disorders, including depression, Parkinson's disease and brain tumors.

### **Structure of Common Drug Target Unveiled**

More than 40 years after beta blockers were first used clinically, NIH-funded scientists finally got a close-up, 3-dimensional look at the drugs' molecular target: the 2-adrenergic receptor. The receptor is one of a family of proteins called G protein-coupled receptors (GPCRs), which carry signals across the cell membrane. GPCRs control critical bodily functions, several of our senses and the action of about half of today's pharmaceuticals. Better understanding of the receptor's molecular shape promises to help speed the discovery of new drugs and illuminate many aspects of human health and disease.

### **Brain Connections Revealed**

Using a clever genetic trick to generate dozens of different colors, NIH-supported researchers visualized hundreds of cells and their connections to each other in the brain. The scientists developed DNA constructs, which they call "Brainbows," that randomly rearrange themselves to activate genes for different-colored fluorescent proteins. When the researchers created transgenic mice with Brainbows, individual neurons in the brain had distinctive colors, allowing them to accurately trace specific cells and their interactions with each other. This new tool will help scientists better understand how the brain and nervous system work.

### **Monkey Genome Gives Insight into Humans**

An international team of more than 170 scientists sequenced the genome of the rhesus macaque monkey and compared it to both the chimpanzee and human genomes. Their analysis revealed that the 3 primate species share about 93% of their DNA. The team also identified nearly 200 genes that appear to play key roles in differences between the species. These include genes involved in hair formation, the immune response and cell communication.

### **Proteins Pair to Form Crucial Hearing Structure**

NIH scientists and their collaborators identified 2 proteins that appear to pair up at the precise location in the ear where sound vibrations are turned into electrical signals. The investigators also showed that a known deafness-causing mutation seemed to disrupt interactions between the 2 proteins, called cadherin 23 and protocadherin 15. The findings may eventually help scientists develop more precise treatments for hearing loss, a condition that affects more than 32 million people in the United States alone.

### **Genetically Altered Mice See a More Colorful World**

By giving mice the gene that allows people to see red hues, scientists created rodents that can see a wider range of colors. Mouse eyes normally have only 2 types of light-detecting photoreceptors, sensitive to blue and green light. NIH-funded scientists created genetically engineered mice that also had photoreceptors for red light, which are found in most primates. Tests showed that the altered mice could perceive different colors better than normal mice. The study suggests that the brains of mammals can quickly adapt to new sensory information. It also provides clues to the evolution of color vision.

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2006

## **DISEASE PREVENTION, DIAGNOSIS, AND TREATMENT**

### **First Vaccine To Prevent Cervical Cancer**

An NIH-funded scientific quest spanning nearly two decades ultimately led to U.S. Food and Drug Administration approval for a vaccine to prevent cervical cancer, a disease that claims the lives of nearly 4,000 women in the United States each year. The genetically engineered vaccine—the first vaccine ever approved for use against cancer—protects against infection from the two types of human papillomavirus (HPV) that cause the majority of cervical cancers worldwide.

### **First Totally Implanted Permanent Artificial Heart Approved**

NIH's nearly half-century commitment to exploring innovative mechanical approaches for treating damaged hearts ultimately led to development of the first totally implanted artificial heart, approved by the U.S. Food and Drug Administration in September 2006. FDA approval is considered a significant milestone, because few options exist for patients with severe heart failure. The new device is intended for patients who are not eligible for a heart transplant and whose life expectancy without the device is only a month.

### **Diuretics Better at Preventing Heart Failure**

Diuretics are more effective than newer blood pressure-reducing medications in preventing heart failure, at least in the short term, according to an NIH-funded clinical study. Called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the study evaluated more than 42,000 people with high blood pressure, or hypertension, the leading risk factor for heart failure. The investigators observed that, during the first year of treatment, patients who received the newer, more expensive medications—calcium channel blockers or angiotensin converting enzyme (ACE) inhibitors—were twice as likely to be hospitalized or die from heart failure than those taking the less expensive diuretics. In later years, however, differences between the treatment groups declined.

### **Dietary Supplements May Not Help Knee Pain**

The popular dietary supplements glucosamine and chondroitin sulfate are commonly used to treat osteoarthritis, an often-painful condition caused by the wear and tear of cartilage in joints. But a four-year national trial sponsored by NIH found that these substances—naturally found in and around cartilage—are usually no more effective than a placebo in relieving osteoarthritis knee pain. A close examination of the 1,600 study participants showed that a small subgroup who had moderate-to-severe pain achieved relief through combined therapy that included both supplements. However, because of the small number of people in the subgroup, the finding needs to be confirmed in a study designed for this purpose. Ongoing research will also examine whether the supplements might slow progression of osteoarthritis.

### **Study Questions Artery-Opening Surgery After Heart Attack**

Opening up a blocked coronary artery can be life-saving in the first 12 hours after a heart attack, physicians agree. But a large NIH-funded clinical trial challenges the long-held belief that the same artery-opening procedure—known as balloon angioplasty—is also beneficial three or more days after a heart attack. In an international study involving more than 2,100 patients, researchers found that medically stable patients who received drug therapy and angioplasty 3-28 days after a heart attack did no better than those who received drug therapy alone, even after up to 5 years.

### **Herb Treatment Ineffective for Menopause Symptoms**

The widely used herbal supplement black cohosh is no more effective than a placebo in relieving the hot flashes and night sweats associated with menopause, according to a yearlong clinical study funded by NIH. The 351 study participants—all experiencing daily menopausal symptoms as the study began—were randomly assigned to receive either herbal regimens that included black cohosh; menopausal hormone therapy (estrogen with or without progesterone); or a placebo. Only the hormonal therapy successfully reduced symptoms.

### **Inexpensive Drug Can Prevent Postpartum Hemorrhage**

Researchers found that the drug misoprostol provides a safe, convenient, and inexpensive way to prevent postpartum hemorrhage, a major killer of women in developing countries, according to NIH scientists and their collaborators. Deaths from postpartum hemorrhage, excessive bleeding by the mother after giving birth, are rare in countries where hospitals and emergency care are readily available, but the condition can be life-threatening in regions where most births occur at home and medical care is harder to come by. In a clinical study conducted in rural villages in India, women who received the drug after birth were less likely to have serious postpartum bleeding, and had significantly reduced average blood loss, than women who received placebo.

### **Molecules in Blood Signal Problem Pregnancy**

A simple blood test may offer an early warning sign of pre-eclampsia, a life-threatening complication of pregnancy and the world's leading cause of premature birth. NIH-supported scientists found that blood levels of two proteins rise markedly up to three months before the appearance of pre-eclampsia symptoms, including high blood pressure and protein in the urine. Detecting high levels of these proteins may help not only to predict pre-eclampsia but also to distinguish it from other conditions with similar symptoms, including chronic high blood pressure and kidney disease.

### **Enhancing Diagnosis of Blood-Cell Cancers**

A multinational research team, including several NIH scientists, developed an experimental test that appears more effective than current techniques in distinguishing between two white-blood-cell cancers. Correct diagnosis is critical because the two cancers—Burkitt's lymphoma and diffuse large B-cell lymphoma—require very different treatments. The new diagnostic technique, known as gene expression profiling, simultaneously analyzes more than 2,500 genes to determine which are active in samples of cancerous cells. The two types of lymphoma were found to have distinctive gene expression patterns, allowing the researchers to accurately classify cancers from 71 patients. Further development, however, is needed before the test is ready for clinical use.

### **Experimental Medication Kicks Depression in Hours**

Current antidepressants usually take four to eight weeks to exert their effects. In a preliminary new study, NIH scientists found that a single intravenous dose of ketamine—a medication usually used in higher doses as an anesthetic—brought symptom relief to people with treatment-resistant depression in as little as two hours. Despite its effectiveness, ketamine is unlikely to be widely used for treating depression because of its potential side effects, including hallucinations and euphoria, at higher doses. Nevertheless, the findings may offer insights toward development of a new class of faster- and longer-acting antidepressant medications.

### **Experimental Ragweed Allergy Therapy Uses Fewer Shots**

An experimental treatment for ragweed allergies requires fewer injections than standard immunotherapy and leads to a marked reduction in symptoms that lasts for at least a year after therapy has stopped, according to a small clinical trial supported in part by NIH. As many as 40 million Americans suffer from seasonal allergies caused by airborne pollens like ragweed, one of the most common pollens in the United States. The new therapy, which combines a major ragweed molecule with a small DNA strand that stimulates the immune system, requires only six weekly injections. Current ragweed immunotherapy usually involves regular injections administered over several years.

### **Blood Test Predicts Complication of Sickle Cell Disease**

A hormone detected in a simple blood test can identify patients with sickle cell disease who have developed a life-threatening complication called pulmonary hypertension, according to a clinical study conducted by NIH scientists. The hormone is also a clear predictor of death in adults with sickle cell disease. This experimental test may one day help doctors identify patients for earlier treatment.

### **No Apparent Benefit to Monitoring Fetal Oxygen**

Electronic fetal monitoring is widely used to track the fetus's heart rate during labor and determine when an emergency Cesarean delivery might be needed. More recently, a technology called fetal oxygen saturation monitoring was developed to measure oxygen levels in fetal blood, in hope that additional health information might prevent problematic births and C-sections. However, an NIH-funded clinical trial involving more than 5,000 women showed that the new technology offers no apparent benefits, and in some cases even caused complications. The oxygen monitoring did not significantly reduce Cesarean delivery rates or improve the condition of infants at birth.

### **Smoking Affects Allergy in Infants**

Infants as young as 6 months old can become allergic to airborne substances, causing a stuffy nose, sneezing and other symptoms. In a study of the environmental factors that might trigger these allergies, NIH-funded researchers found that exposure to more than 20 cigarettes a day nearly tripled an infant's risk for developing allergies to airborne compounds by age 1. Mold, another suspected culprit, did not increase the allergy risk but did boost susceptibility to for upper respiratory infections. Other factors—like race, gender, pet ownership and breastfeeding practices—did not appear to affect allergy or respiratory infection risk.

### **Low-Calorie Diet Affects Aging-Related Factors**

Scientists have long known that sustained adherence to low-calorie diets substantially increases the lifespan of several laboratory animals. However, the effects of low-calorie diets on human aging have been unclear. An NIH-funded pilot study now shows that overweight people who cut their calories by 25% for six months have reduced fasting insulin levels and core body temperature, two markers that have been associated with increased longevity in humans. A longer-term clinical trial—conducted at three U.S. locations—will now evaluate the effects of reduced-calorie diets over a longer time period.

### **New Imaging Technique May Spot Early Indicators of Alzheimer's Disease**

A molecule that binds to abnormal proteins in the brain shows promise for enabling early and reliable diagnosis of Alzheimer's disease, a condition that today can be definitively diagnosed only at autopsy. The molecule, known as FDDNP, was developed and clinically evaluated by researchers supported in part by NIH. After intravenously administering FDDNP, the researchers obtained brain scans that could distinguish among individuals who were healthy, those who had Alzheimer's disease and those who had mild cognitive impairment, which sometimes progresses to Alzheimer's disease. Beyond aiding clinical detection, this new technique may also allow scientists to assess how well potential new Alzheimer's therapies slow or halt the disease's progress.

### **Better Detection of Blood Clots in the Lung**

Pulmonary embolism, a sudden and potentially deadly blockage in a lung artery, often arises when a blood clot breaks free from the deep veins of the leg and travels to the lung. Early detection and treatment is key, because pulmonary embolism leads to death in nearly a third of untreated cases. An NIH-funded study has shown that doctors can more accurately diagnose pulmonary embolism by combining a commonly used imaging test of the chest with a scan of the leg, where the blood clots typically originate. Pulmonary embolism affects an estimated 600,000 Americans each year, making it the fourth most common cardiovascular problem in the United States.

### **Low-Fat Diet's Benefits Unclear in Older Women**

Eating a low-fat diet high in fruits, vegetables and grains did not significantly lessen the risk of breast cancer, colorectal cancer or heart disease in healthy older women, according to results from the NIH Women's Health Initiative. Yet examination of the nearly 50,000 postmenopausal women who participated in the study provided some evidence that healthful eating can have certain benefits. For instance, breast cancer risk was 9% lower among women on the low-fat diet, although scientists say this modest difference may have been due to chance.

### **Circumcision Reduces Risk of AIDS Virus Infection**

Medically performed circumcision significantly reduces a man's risk of acquiring HIV through heterosexual intercourse, according to two NIH-funded clinical trials. The two studies involved a total of nearly 8,000 HIV-negative heterosexual men who were randomly assigned to be circumcised either soon after enrollment or two years later. The trials were halted early, because interim assessment of data clearly indicated that circumcision could reduce the likelihood of HIV acquisition by about 50%.

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## **GENOMICS AND GENETICS**

### **Gene Ups Diabetes Risk, Healthy Lifestyle Lessens Impact**

NIH-funded researchers confirmed that a variant gene discovered in early 2006 boosts susceptibility to type 2 diabetes. By examining data from a clinical study involving more than 3,500 individuals, the scientists also found that even people with the highest genetic risk—those who inherited two copies of the variant gene—could make positive lifestyle changes, including exercise and weight loss, that reduce their diabetes risk.

### **Researchers Assemble Monkey Genome**

A multicenter research team, funded in part by NIH, completed the draft genome sequence of the rhesus macaque monkey and deposited the information into free public databases. The rhesus macaque is the second non-human primate, after the chimpanzee, to have its genome sequenced. Overall, the macaque shares about 92-95% of its genome sequence with humans. Because of this similarity, the rhesus macaque is the principal non-human primate used for the study of human disease and plays an important role in drug and vaccine development.

### **MGene Discovered for Brittle Bone Disease**

NIH researchers reported that a previously unexplained fatal form of osteogenesis imperfecta (OI)—a rare bone-weakening disorder that can cause frequent fractures—results from a genetic defect in a protein involved in collagen production. This particular form of OI arises when a child inherits two defective copies of the gene. Although there is no treatment for OI, the finding may allow physicians to test for the recessive gene in families who have lost a child to OI. Discovery of the new gene may also lead to insights into the formation of bone and other tissues.

### **Pigment Gene Affects Melanoma Risk**

NIH scientists have uncovered a complex interaction between two genes that dramatically affects the likelihood of developing melanoma, an aggressive skin cancer. In a study involving nearly 200 Caucasians who had few signs of chronic sun damage, the researchers found that specific variations in a pigment-related gene enhances the risk of developing melanomas that have mutations in a cancer-causing gene known as BRAF. Potential melanoma drugs that target BRAF are now in clinical trials.

### Gene Affects Pain Sensitivity

NIH-funded researchers identified a human gene that affects sensitivity to short-term pain and the risk of developing chronic pain after surgery. The gene produces an enzyme that aids production of neurotransmitters, which deliver signals between nerve cells. The investigators found that chronic pain could be prevented in animals, following nerve injury or inflammation, by blocking increased activity of this gene. The findings point to potential new avenues for treating or preventing chronic pain, which affects as many as 50 million people in the United States.

### Mutant Gene More Than Doubles Susceptibility to Autism

In a family-based study involving more than 1,200 individuals with autism, NIH-funded scientists identified a mutant gene that more than doubles a child's risk of developing an autism spectrum disorder. The normal version of the gene is known to contribute not only to brain development but also to immune and gastrointestinal functions, which are sometimes impaired in children with autism. The implicated mutation creates a tiny variation in the part of the gene that turns it on and off. The mutation cuts the gene's expression by half, presumably impairing brain development.

### Researchers Identify Risk Gene for Obsessive-Compulsive Disorder

NIH scientists have identified a previously unknown gene variant that nearly doubles an individual's risk for obsessive-compulsive disorder (OCD), the fourth most prevalent mental health disorder in the United States. The implicated gene produces a cell-surface molecule that is targeted by popular antidepressant medications known as selective serotonin reuptake inhibitors (SSRIs), which are also used to treat OCD and other anxiety disorders. Improved knowledge of the gene's role in OCD may ultimately aid screening and treatment for the disorder.

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## NEW RESEARCH DIRECTIONS

### New Clues About the 1918 Flu Virus

The first comprehensive analysis of an animal's reaction to the 1918 influenza virus provides new insights into this deadly flu, which disproportionately killed young people in the prime of their lives. NIH-funded researchers found that the 1918 virus triggers a hyperactive immune response that may be the key to its lethal effects. The findings also suggest that all eight of the genes found in the 1918 virus help to make it so deadly. A deeper understanding of the 1918 virus will likely aid efforts to develop improved therapies against related viral threats, including the H5N1 avian influenza virus.

### Insight into Ear Infections

Chronic infection or inflammation of the middle ear, the area just behind the eardrum, is a common, often-recurring problem for children. A new study by NIH-funded scientists shows why the problem can be so persistent: bacteria can form a "biofilm" on the middle ear that helps them resist the body's immune system and antibacterial treatments. Because biofilms also play a role in other types of persistent infections, researchers are now investigating how bacterial biofilms form and how they elude antibiotics and other defenses.

### Watching Nicotine at Work in the Brain

A brain imaging study supported in part by NIH shows how the nicotine in just a few puffs of a cigarette can drive someone to continue smoking. The amount of nicotine in just one puff of a cigarette occupied about 30% of the brain's most common type of nicotine receptors, while three puffs of a cigarette occupied about 70%. Only when nearly all of the receptors were occupied, after smoking at least two and a half cigarettes, did the smokers become satiated, or satisfied, for a time. By better understanding how nicotine affects the brain, scientists hope to develop improved therapies for smokers who would like to quit.

### Restoring Function to Paralyzed Rats

Researchers used a novel technique involving embryonic stem cells to partially restore muscle function to paralyzed animals. With funding from NIH and other sources, the scientists cultured mouse embryonic stem cells with chemicals that triggered transformation into muscle-stimulating nerve cells, which were then transplanted into the spinal cords of rats. The transplants ultimately produced numerous connections between nerve and muscle cells, which improved muscle function in the paralyzed animals. Although the results are promising, much work remains before a similar strategy could be tried in humans.

### Elusive Sour Taste Cells Revealed

NIH scientists and their colleagues identified specialized taste cells on the tongue that detect sour flavors and may help to warn people and animals of acidic, spoiled and unripe food. The researchers had previously pinpointed the distinctive cell sensors that can detect sweet, bitter and umami (the taste of monosodium glutamate). Now only one mammalian taste-sensing cell is yet to be discovered—that for salty taste.

### Hints of Language Origin in Rhesus Monkey

Fossil records can't tell us where the building blocks of language appeared on the evolutionary timeline, but brain imaging might. Studies by an international research team, including NIH-funded scientists, revealed that, when contemplating the coos and screams of a fellow member of its species, the rhesus monkey (or macaque) uses brain regions that correspond to the two principal language centers in the human brain. The results suggest that a shared ancestor to humans and the macaque may have had the neural mechanisms upon which language was built.

### Unique Technique Improves Vision of Blind Mice

NIH-funded researchers are developing an inventive approach to restore vision to eyes that have lost their ability to detect light. The scientists studied mice that had been genetically bred to lose rods and cones, the light-sensitive cells in the retina of the eye. As rods and cones die, the mice go progressively blind, similar to the human blinding disease retinitis pigmentosa. Using gene transfer, the researchers restored some vision to the mice by inserting a light-absorbing protein into retina cells that normally do not detect light. The study raises the possibility of improving visual function, even after rods and cones have died, by making other cells in the retina sensitive to light.

### Bullied Mice Shed Light on Social Stress

By studying fearful mice that have been repeatedly bullied by bigger mice, NIH-funded scientists identified a brain molecule and circuitry that contribute to long-lasting social aversion. The researchers also showed that blocking the production or activity of this molecule, known as brain-derived neurotrophic factor, can counteract the social aversion caused by aggressive encounters. The findings offer new insights into the molecular pathways that affect social motivation and may aid development of new antidepressants.

### Botulism Toxin's Fatal Grip

Botulism toxins, produced by bacteria, are among the most potent and lethal known poisons. The toxins cause botulism, a sometimes-fatal muscle-paralyzing disease, and are potential bioterror agents. To better understand how the botulism toxin operates, two NIH-supported research teams used advanced technologies to see unprecedented details of the poisonous molecule latching onto nerve cell proteins. The studies revealed new information about how the toxin specifically grasps onto muscle-activating nerve cells and ultimately blocks communication at the junction where nerve and muscle cells meet. The new findings may aid in the development of more effective therapies or even a vaccine to prevent the neurotoxin's harmful effects.

### **A Promising Strategy for Artificial Bone**

NIH-supported scientists harnessed the unique physics of sea water as it freezes to guide the production of what could be a new generation of biocompatible materials for artificial bone. The researchers used a novel freezing technique to produce a thin-layered structure that closely mimics the natural scaffolding of bone. The scientists said their prototype scaffolds are ultra-lightweight and up to four times stronger than current porous ceramic implant materials.

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2005

## **DISEASE PREVENTION, DIAGNOSIS, AND TREATMENT**

**Study Shows Diuretics Work Better than Newer Medicines for High Blood Pressure** — The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a long-term, multi-center trial of antihypertensive therapies funded by NIH, found that diuretics work better than newer therapies in treating high blood pressure and reducing the risk of heart disease in both black and non-black patients. The large study, with 33,357 participants, concluded that diuretics should be the first therapy for most patients with high blood pressure.

**Tight Glucose Control Cuts Heart Disease by Half in People with Type 1 Diabetes** — People with type 1 diabetes can lower their risk of heart disease and stroke by about 50% by tightly controlling their blood glucose levels, according to a study supported by NIH. The findings were based on a follow-up study of patients who took part more than a decade ago in the Diabetes Control and Complications Trial, a major clinical study funded by NIH along with Genentech, Inc. Continuing studies will reveal whether the same applies to those with type 2 diabetes, the more prevalent form of the disease.

**Computer Models Guide Avian Flu Outbreak Planning** — Computer models developed by the NIH-funded Models of Infectious Disease Agent Study (MIDAS) research network found that a carefully chosen combination of public health measures, if implemented early, could stop the spread of an avian flu outbreak at its source. The researchers found that antiviral treatment is a critical component of a multi-pronged approach.

**Cognitive Therapy Reduces Repeat Suicide Attempts by 50 Percent** — People who had recently attempted suicide were 50% less likely to try to kill themselves again within 18 months when they were treated with cognitive therapy, according to researchers supported by NIH and the Center for Disease Control and Prevention.

**First Phase II Trial of HIV/AIDS Vaccine** — An HIV/AIDS vaccine developed by scientists at NIH's Dale and Betty Bumpers Vaccine Research Center moved into its second phase of clinical testing in October. This vaccine contains synthetic genes representing HIV subtypes found in Europe, North America, Africa and Asia that account about 85% of HIV infections worldwide.

**Study Finds Vitamin E Does not Protect Women from Heart Attack, Stroke or Cancer** — The Women's Health Study, a long-term clinical trial funded by NIH, found that vitamin E supplements don't protect healthy women against heart attacks and stroke. They also had no effect on the most common cancers in women or on total cancers.

**Older Children Can Benefit From Treatment For Childhood's Most Common Eye Disorder** — Surprising results from a nationwide clinical trial supported by NIH showed that many children age seven through 17 with amblyopia (lazy eye) may benefit from treatments that are more commonly used on younger children. Treatment improved the vision of many of the 507 older children with amblyopia studied at 49 eye centers. Previously, many eye care professionals thought that treating amblyopia in older children would be of little benefit.

**NIH Researchers Confirm Effectiveness of Immunotherapy Approach to Melanoma** — A team of NIH researchers found that patients with advanced melanoma who hadn't responded to standard therapies had a significant reduction in the size of their cancers as a result of receiving a new immunotherapy. This immunotherapy consisted of a combination of chemotherapy and reintroduction of the patients' own white blood cells. The white blood cells were removed from the patients, "re-educated" to attack the tumor, and then reintroduced into the patient. The promise of this therapy is that a patient's own immune system can be used to effectively treat existing tumors.

**Possible Treatment Changes for Asthma** — Some people with mild persistent asthma may be able to control their asthma by taking corticosteroids only when needed, according to a new study supported by NIH. Official guidelines for this type of asthma recommend daily long-term control medication to prevent symptoms, along with quick-relief medication as needed to treat acute symptoms. In this study, those who took corticosteroids based on their symptoms had about the same number of asthma flare-ups as those taking daily, long-term control medications. The finding needs to be confirmed in a larger study, but it raises the possibility that some patients may be able to safely avoid the expense and inconvenience of daily medication.

**Substance in Urine Predicts Development of Preeclampsia** — A substance found in the urine of pregnant women can be measured to predict the later development of preeclampsia, according to research supported by NIH. A pregnant woman with preeclampsia develops dangerously high blood pressure and begins excreting protein in her urine. In some cases, the condition may progress to eclampsia, a series of potentially fatal seizures. Researchers found that women were highly likely to develop preeclampsia if they had low levels of a substance known as placental growth factor in their urine. They plan to try to refine the finding into an accurate clinical test.

**Study Links Obesity and Dementia** — In a 27-year study of over 10,000 people supported by NIH, researchers found that middle-aged people who were obese (those with a body mass index of 30 or above) had a 74% increased risk of dementia later in life compared to people of normal weight (body mass index 18.6-24.9), while overweight people (body mass index 25.-29.9) had a 35% greater risk. It's not clear why heavier people developed dementia more often, but eating a low-fat diet and exercising regularly may help reduce the risk of developing the memory loss, concentration problems and other symptoms of dementia later in life.

**Rapid New Test Developed for Inherited Immune Deficiency** — NIH researchers developed a new laboratory method that rapidly identifies babies born with inherited forms of Severe Combined Immunodeficiency (SCID), an illness in which the infant fails to develop a normal immune system. SCID babies can be infected by a wide range of viruses, bacteria and fungi that are normally controlled by a healthy baby's immune system. If undetected and untreated, SCID typically leads to death before the baby's first birthday. The new genetic test, which still must be validated before widespread use, could someday be added to the panel of tests that already screen newborns for a variety of disorders.

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## **GENOMICS AND GENETICS**

**Dog Genome Sequence Published** — An international team supported by NIH published the genome sequence of the dog. Because of selective breeding over the past few centuries, modern dog breeds are a model of genetic diversity, from 6-pound Chihuahuas to 120-pound Great Danes, from high-energy Jack Russell Terriers to mild-mannered basset hounds, and from the herding instincts of Shetland sheepdogs to pointers pointing. However, selective breeding has also caused many dog breeds to be predisposed to genetic disorders including heart disease, cancer and blindness. In combination with the human genome, the dog genome sequence will help researchers identify genetic contributors to several diseases.

**Genome Comparison Finds Chimps, Humans Very Similar at the DNA Level** — The Chimpanzee Sequencing and Analysis Consortium, which is supported in part by NIH, described its landmark analysis comparing the genome of the chimp ( *Pan troglodytes* ) with that of humans ( *Homo sapiens* ). The chimp sequence draft represents the first non-human primate genome. Our closest living relatives share 96% of our DNA sequence.

**Three Deadly Parasite Genomes Sequenced** — An international group of researchers working in more than 20 laboratories around the globe and funded in part by NIH sequenced the genomes of three parasites that cause deadly insect-borne diseases: African sleeping sickness, leishmaniasis and Chagas disease. Knowing the full genetic make-up of the three parasites might lead to better ways to treat or prevent the diseases they cause.

**Map of Human Genetic Variation Completed** — The International HapMap Consortium, a public-private effort to chart patterns of genetic variation in the world's population, published the human haplotype map, or HapMap. With more than 1 million markers of genetic variation, the HapMap is a comprehensive catalog of human genetic variation showing "neighborhoods" of correlated genetic variation, or haplotypes, across the entire human genome. Researchers will be able to identify genetic contributions to common diseases far more efficiently using HapMap data than with traditional approaches.

**Multi-Species Genome Comparison Sheds New Light on Evolution and Cancer** — Researchers reconstructed the genomes of long-extinct mammals and determined the rates of mammalian chromosome evolution by aligning the human, mouse, rat, cow, pig, dog, cat and horse genomes. The study, funded in part by NIH, found that evolution rates dramatically accelerated around 65 million years ago, a period that marked the end of the age of reptiles and the arrival of the age of mammals. The researchers also found that, contrary to what scientists had long thought, mammalian chromosomes seem to have breakpoint "hotspots." These tend to have a high gene density and also seem to be associated with cancer-associated chromosome abnormalities. As more genomes become available, these relationships will become clearer.

**Gene Found to Increase Risk of the Most Common Cause of Blindness** — Three independent research teams supported by NIH found a gene, called complement factor H (CFH), that affects a person's risk of developing age-related macular degeneration (AMD), the leading cause of blindness in people over age 60. One team, which included NIH's own researchers, found that people with this variant of the CFH gene are more than seven times more likely to develop the disease. The discovery suggests new avenues for researchers to pursue in developing ways to diagnose and treat AMD.

**Gene Found to Increase Risk of the Most Common Cause of Blindness** — Three independent research teams supported by NIH found a gene, called complement factor H (CFH), that affects a person's risk of developing age-related macular degeneration (AMD), the leading cause of blindness in people over age 60. One team, which included NIH's own researchers, found that people with this variant of the CFH gene are more than seven times more likely to develop the disease. The discovery suggests new avenues for researchers to pursue in developing ways to diagnose and treat AMD.

**Scientists Detect Probable Genetic Cause of Some Parkinson's Disease Cases** — Two new studies strongly suggest that a mutation in a recently discovered gene is the most common genetic cause of Parkinson's disease identified to date. The finding could lead to the development of a genetic test to detect the mutation in individuals at risk. Parkinson's disease, which affects at least 500,000 Americans, is a progressive neurological disorder that is caused by the degeneration of nerve cells in the portion of the brain that controls movement. Scientists have long suspected genetics play a role in the onset of the disease. In these studies, the investigators, which included investigators at NIH, found that a mutation in the gene LRRK2 appears to occur in at least one of every 60 people who have the disease.

**Scientists Analyze Human Chromosomes 2 and 4** — A detailed analysis of chromosomes 2 and 4 by researchers supported by NIH detected the largest "gene desert," a region without of any protein-coding genes, known in the human genome and uncovered more evidence that human chromosome 2 arose from the fusion of two ancestral ape chromosomes. Chromosome 4 has long been of interest to the medical community because it holds the gene for Huntington's disease, polycystic kidney disease, a form of muscular dystrophy and a variety of other inherited disorders. Chromosome 2 is noteworthy for being the second largest human chromosome, trailing only chromosome 1 in size, and home to the gene with the longest known protein-coding sequence — for a muscle protein called titin.

**Research Sheds New Light on Role of Sex Chromosomes in Health and Disease** — Two studies provided a detailed analysis of the X chromosome's DNA sequence and a survey of its gene activity. This first comprehensive analysis of the sequence of the human X chromosome, supported by NIH as well as by the Department of Energy, provides new insights into the evolution of sex chromosomes and the biological differences between males and females. Even though it contains only 4% of all human genes, the X chromosome accounts for almost 10% of inherited diseases caused by a single gene, including red-green color blindness, hemophilia, some forms of mental retardation and Duchenne muscular dystrophy. More than 300 diseases have already been linked to it.

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## NEW RESEARCH DIRECTIONS

**Protein Structure Initiative Advances to Rapid Production Phase** — The Protein Structure Initiative (PSI) completed its first 5-year phase and moved into its second. The PSI, which is funded largely by NIH, aims to figure out the three-dimensional shapes of proteins, with the long-term goal of being able to predict most protein structures from their DNA sequences. More than 1,100 protein structures were solved in the PSI's first phase, which was dedicated to figuring out how to process proteins and determine their three-dimensional structures more efficiently. Phase 2 is the production phase, in which thousands more protein structures will be solved and put into the Protein Data Bank (<http://www.rcsb.org/pdb/>), a public repository with powerful tools for processing protein structure information.

**Scientists Discover How Ebola Virus Infects Cells** — Researchers supported in part by NIH identified two cellular enzymes that the Ebola virus must have to reproduce. Ebola virus reproduction in laboratory-grown cells was severely hampered by chemicals that inhibited these enzymes. These chemicals will now be further studied as possible treatments for Ebola virus infections in humans.

**Combination Therapy Leads to Partial Recovery from Spinal Cord Injury in Rats** — A new method using both stem cells and gene therapy promoted the growth of myelin, the "insulation" around nerve fibers, in the damaged spinal cords of rats. It improved the animals' motor function and electrical conduction from the brain to the leg muscles. The finding, which was funded in part by NIH, may lead to new ways of treating spinal cord injury in humans.

**Gene Knockout Creates Fearless Mouse** — Knocking out a gene in the brain's fear hub created mice unperturbed by situations that would normally trigger fear responses, researchers funded in part by NIH discovered. The gene codes for a protein called stathmin, which appears to be critical for the amygdala, where the brain's fear circuitry is centered, to rearrange connections and form fear memories. This finding may eventually lead to improved treatments for anxiety disorders.

**Brain Chemical Plays Key Role in Both Food and Drug-Seeking Behavior** — Orexin, a brain chemical involved in feeding behavior, arousal and sleep, also plays a role in reward function and drug-seeking behavior, according to NIH-funded research in rats. Activation of orexin-secreting brain cells in the hypothalamus, a brain region that controls many vital functions such as eating, body temperature and fat metabolism, is strongly correlated with food- and drug-seeking behaviors. This finding helps to better identify the neural pathways involved in drug abuse, craving and relapse, and may ultimately help scientists find more effective therapies.

**Researchers Pinpoint Chemical that Links Taste Buds to the Nervous System** — Researchers funded by NIH pinpointed the chemical responsible for transmitting signals from the taste buds — small sensory bumps on the tongue, throat and roof of the mouth—to the taste nerves leading to the brain. Adenosine 5'-triphosphate (ATP), a high-energy molecule crucial for helping cells in the body to function, turns out also to be the key neurotransmitter linking taste buds to the nervous system. This finding provides scientists with a more complete picture of the complicated process, helping advance the study of taste and taste disorders.

**Exercise Slows Development of Alzheimer's-Like Brain Changes in Mice** — Physical activity appears to inhibit Alzheimer's-like brain changes in mice, according to a new study supported by NIH. Long-term physical activity enhanced the learning ability of mice and decreased the level of plaque-forming beta-amyloid protein fragments — a hallmark characteristic of Alzheimer's disease — in their brains. Further research will help reveal if the same holds true in people.

**Possible Mechanism for Link between Sleep Disturbances and Metabolic Syndrome** — A new mouse study supported by NIH suggests that a brain system that controls the sleep/wake cycle might also play a role in regulating appetite and metabolism. Mice with a mutation in a gene called "Clock," which helps drive circadian rhythm, ate significantly more and gained more weight. This finding could help explain why disrupted sleep patterns — particularly when combined with a high-fat diet — are sometimes associated with excessive weight gain and the onset of metabolic syndrome, a cluster of conditions shown to increase a person's risk of heart disease and stroke. At least 40 million Americans have chronic sleep problems, and an additional 20 million experience occasional sleeping problems. As many as 47 million Americans have metabolic syndrome.

**Microbicides Protect Monkeys Against HIV-Like Virus** — Experiments in female monkeys showed for the first time that vaginal gels known as microbicides can protect against an HIV-like virus. The research, funded largely by NIH, suggests that microbicides could potentially provide a safe, effective and practical way to prevent HIV transmission to women.

**Artificial Light at Night Stimulates Breast Cancer Growth in Laboratory Mice** — Results from a study in laboratory mice showed that nighttime exposure to artificial light stimulated the growth of human breast tumors by suppressing levels of the hormone melatonin. The study, which was supported by NIH, also showed that extended periods of nighttime darkness greatly slowed the growth of these tumors. These results might explain why female night shift workers have a higher rate of breast cancer. They also offer a potential explanation for the epidemic rise in breast cancer incidence in industrialized countries like the U.S.

**Substance Protects Resilient Staph Bacteria** — NIH researchers identified a promising new target in their fight against a dangerous bacterium that sickens people in hospitals, especially people who receive medical implants such as catheters, artificial joints and heart valves. A substance found on the surface of *Staphylococcus epidermidis* was, for the first time, shown to protect the harmful pathogen from natural human defense mechanisms that would otherwise kill the bacteria. *S. epidermidis* is one of several hard-to-treat infectious agents that can be transmitted to patients in hospitals via contaminated medical implants.

**Novel Therapy Tested in Mice Could Chase Away Cat Allergies** — A molecule designed to block cat allergies successfully prevented allergic reactions in laboratory mice as well as in human cells in a test tube, NIH-funded researchers reported. The injectable treatment puts a brake on the release of a key chemical from cells involved in cat allergy reactions. That chemical, histamine, brings on allergy symptoms such as sneezing, wheezing, itching, watery eyes, and sometimes asthma. When a cat-allergic person touches or inhales a protein found in cat saliva or dander (small flakes from its skin or hair), key immune system cells respond by spewing out histamine. Allergy experts estimate that 14 percent of children 6 to 19 years old are allergic to cats. In the future, the investigators say, these promising results could lead to a new therapy not only for human cat allergies, but also possibly for severe food allergies such as those to peanuts.

**Gene Therapy Restores Hair Cells and Improves Hearing in Deaf Guinea Pigs** — Researchers supported by NIH successfully used gene therapy to grow new hair cells and restore some hearing in deaf guinea pigs. The scientists used a harmless virus to insert a gene called *Atoh1*, a key regulator of hair cell development, into cells in the inner ears of deaf adult guinea pigs. Eight weeks after treatment, new hair cells had grown in the ears treated with *Atoh1*, and their hearing had improved. This is the first time that researchers have restored auditory hair cells in live adult mammals. The researchers caution that it will be several years before *Atoh1* gene therapy will be ready to test in humans. Nevertheless, this study is an important advance in hearing research. Scientists are now one step further in the search for new ways to treat hearing loss, a condition affecting about 28 million Americans.

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2004

## DISEASE PREVENTION, DIAGNOSIS AND TREATMENT

**New Treatment Improves Outlook for Breast Cancer Survivors** — An international clinical trial supported in part by NIH concluded that women should consider taking letrozole after five years of tamoxifen treatment to continue to reduce the risk of breast cancer recurrence. This very important advance in breast cancer treatment will improve the outlook for many thousands of women.

**Gene Mutation Linked to Drug Effectiveness in Lung Cancer** — Mutation of a gene involved in non-small cell lung cancer determines whether the drug gefitinib (Iressa™) will cause the tumors to shrink. Gefitinib is one of a new generation of cancer chemotherapy drugs designed to target specific molecular defects that cause cancer. Previously, gefitinib had been shown to cause tumor regression in certain patients but not others, and researchers hadn't been able to predict which ones would respond. The mutation, discovered by a team that included NIH researchers, is in a gene that codes for the epidermal growth factor (EGF) receptor — the enzyme through which EGF sparks cell growth. Inhibition of this type of enzyme has recently been a focus for cancer researchers, but gefitinib had not been as effective as some had expected based on earlier clinical trials conducted in Japan. With this new discovery,

doctors will be able to select those lung cancer patients who could benefit from gefitinib.

**Molecular Test Can Predict Risk of Breast Cancer Recurrence** — A new test can predict the risk of breast cancer recurrence and may help identify women who will benefit most from chemotherapy, according to research supported by NIH. The researchers used tissue samples and medical records from women enrolled in clinical trials of the cancer drug tamoxifen, which blocks the effect of estrogen on breast cancer cells. These women had a kind of breast cancer called estrogen receptor-positive, lymph node-negative (which means it needs estrogen to grow but has not spread to the lymph nodes). Using samples from 447 patients and a collection of 250 genes, the researchers created a formula that can measure the risk that a given cancer will recur. Their results suggest that almost half of the 43,000 US women that are diagnosed with estrogen-dependent, lymph-node negative breast cancer every year may not need to go through the discomfort and side effects of chemotherapy.

**Estrogen and Heart Disease** — NIH instructed participants in the estrogen-alone study of the Women's Health Initiative (WHI), a large multi-center trial, to stop taking their study pills and to begin the follow-up phase of the study. After careful consideration of the data, NIH concluded that with an average of nearly 7 years of follow-up completed, estrogen alone does not appear to affect (either increase or decrease) heart disease, a key question of the study. At the same time, estrogen alone appears to increase the risk of stroke and decrease the risk of hip fracture. It has not increased the risk of breast cancer during the time period of the study. The increased risk of stroke in the estrogen-alone study is similar to what was found in the WHI study of estrogen plus progestin when that trial was stopped in July 2002. The NIH believes that an increased risk of stroke is not acceptable in healthy women in a research study.

**Rotavirus Vaccine Created by NIH Scientists Licensed for Commercialization** — An effective oral rotavirus vaccine created by NIH scientists in the 1980s and developed further through a cooperative research and development agreement with an industry partner has now been licensed by the NIH Office of Technology Transfer to BIOVIRx, Inc. This vaccine can help prevent the hundreds of thousands of deaths annually from rotavirus diarrhea in children living in developing countries.

**Effectiveness of Safer Smallpox Vaccine Demonstrated Against Monkeypox** — A mild, experimental smallpox vaccine known as modified vaccinia Ankara (MVA) is nearly as effective as the standard smallpox vaccine in protecting monkeys against monkeypox, a study by NIH researchers found. Monkeypox is used to test the effectiveness of a smallpox vaccine because of its similarity to the smallpox virus. These findings are important in the search for a replacement vaccine for people with health conditions that would prevent them from using the current smallpox vaccine.

**Mutant Gene Linked to Treatment-Resistant Depression** — A mutant gene that starves the brain of serotonin, a mood-regulating chemical messenger, has been discovered and found to be ten times more prevalent in depressed patients, researchers funded by NIH have found. The gene codes for the brain enzyme tryptophan hydroxylase-2, which makes serotonin. The mutant version results in 80 percent less of the neurotransmitter. It was carried by nine of 87 depressed patients, three of 219 healthy controls and none of 60 bipolar disorder patients. Patients with the mutation failed to respond well to the most commonly prescribed class of antidepressant medications, which work via serotonin, suggesting that the mutation may underlie a treatment-resistant version of the illness.

**Combination Treatment Most Effective in Adolescents with Depression** — A clinical trial of 439 adolescents with major depression found a combination of medication and psychotherapy to be the most effective treatment. Funded by the NIH, the study compared cognitive-behavioral therapy (CBT) with fluoxetine, currently the only antidepressant approved by the Food and Drug Administration for use in children and adolescents. Seventy-one percent of participants responded to the combination of fluoxetine and CBT.

**Researchers Report Early Success Using Saliva to Detect Oral Cancer** — Scientists funded by NIH took a major step forward in using saliva to detect oral cancer. The scientists found that they could measure for elevated levels of four distinct cancer-associated molecules in saliva and distinguish with 91 percent accuracy between healthy people and those diagnosed with oral squamous cell carcinoma. This so-called "proof-of-principle" study marks the first report in the scientific literature that distinct patterns of "messenger RNA" not only are measurable in saliva but can indicate a developing tumor. Messenger RNA (mRNA) is the molecular intermediate between gene and protein, using the information in a gene to guide how a protein is made. With further refinement of this test, the researchers hope to attain the necessary 99 to 100 percent accuracy of commercial diagnostic tests. Oral squamous cell carcinoma is the sixth most common cancer in the US. Currently, no biochemical or genetic diagnostic tests are commercially available for oral cancer.

**Crohn's Disease Treatment Shows Promise in Clinical Trial** — In a small, initial clinical trial led by NIH researchers, doctors found that up to 75 percent of people with Crohn's disease responded to an experimental new treatment and up to 50 percent had long-term remission of symptoms. Crohn's, which affects an estimated 500,000 Americans, is an autoimmune disease that attacks the bowels, causing abdominal pain, cramping, diarrhea and rectal bleeding. In severe cases, damaged bowel sections have to be surgically removed. The new treatment is an antibody designed to disable interleukin-12 (IL-12), an immune system protein involved in inflammation. People with Crohn's produce excess IL-12.

**Substances Found in Blood May Predict Development of Preeclampsia** — Abnormal levels of two molecules found in the blood appear to predict the development of preeclampsia, a life-threatening complication of pregnancy, according to a study by a team that included NIH researchers. Pregnant women with preeclampsia can develop dangerously high blood pressure and begin excreting protein in the urine. In some cases, the condition may progress to eclampsia, a series of potentially fatal seizures. Being able to predict the development of preeclampsia may enable doctors to treat the condition before it becomes a serious problem.

**"Care Managers" Help Depressed Elderly Reduce Suicidal Thoughts** — An intervention that includes staffing doctors' offices with depression care managers helps depressed elderly patients reduce suicidal thoughts, a study funded by NIH found. Older Americans comprise 13 percent of the population but account for 18 percent of all suicides. The major risk factor for suicide in late life is major depression. Since most older Americans who kill themselves have seen their doctor within the previous month, treating depression in primary care can be an effective way to save lives.

**Methamphetamine Withdrawal and Brain Changes** — NIH researchers were part of a team that used PET (positron emission tomography) scans to find that people who have recently stopped abusing the powerfully addictive drug methamphetamine may have brain abnormalities similar to those seen in people with mood disorders. The findings suggest that health workers might improve success rates for methamphetamine users receiving addiction treatment by also providing therapy for depression and anxiety.

**Emotion-Regulating Protein Lacking in Panic Disorder** — Three brain areas of panic disorder patients are lacking in a key component of a chemical messenger system that regulates emotion, researchers at NIH discovered. The scientists used PET (positron emission tomography) scans to visualize a type of serotonin receptor called the serotonin 5-HT1A receptor, and compared the brains of people who suffered from panic disorder to those who did not. A new radioactive tracer developed by NIH Clinical Center PET scan scientists binds to the receptors, revealing their locations and a numerical count by brain region. In the panic disorder patients, the receptor is reduced by nearly a third in three structures straddling the center of the brain. This finding is the first in living humans to show that 5-HT1A, which is pivotal to the action of widely prescribed anti-anxiety medications, may be abnormal in panic disorder patients.

## GENOMICS AND GENETICS

**Sequencing Consortium Reports Finished Human Genome Sequence** — The International Human Genome Sequencing Consortium, led in the United States by NIH's National Human Genome Research Institute (NHGRI) and the Department of Energy (DOE), published its scientific description of the finished human genome sequence, reducing the estimated number of human protein-coding genes from 35,000 to only 20,000-25,000, a surprisingly low number for our species.

**Scientists Compare Rat Genome With Human, Mouse** — An international research team supported by NIH completed a high-quality draft sequence of the genome of the laboratory rat, and used that data to explore how the rat's genetic blueprint stacks up against those of mice and humans. The rat sequence draft represents the third mammalian genome to be sequenced to high quality and described in a major scientific publication. Comparing the human genome with those of other organisms is helping researchers to better understand the complex genomic components involved in human health and disease.

**Researchers Compare Chicken and Human Genomes** — An international research consortium supported by NIH has found that chickens and humans share more than half of their genes, but that their DNA sequences diverge in ways that may explain some of the important differences between birds and mammals. The International Chicken Genome Sequencing Consortium analyzed the sequence of the Red Jungle Fowl (*Gallus gallus*), which is the progenitor of domestic chickens. The chicken is the first bird, as well as the first agricultural animal, to have its genome sequenced and analyzed. Recent outbreaks of avian flu have highlighted the importance of learning more about the chicken genome.

**Gene Variants May Increase Susceptibility to Type 2 Diabetes** — International research teams that included several NIH researchers found variants in a gene called hepatocyte nuclear factor 4 alpha (HNF4A) that may predispose people to type 2 diabetes, the most common form of the disease. For years, scientists have known that single-gene mutations contribute to rare forms of diabetes that account for about 2 to 3 percent of all diabetes cases, but type 2 diabetes, which accounts for 90 to 95 percent of all diabetes cases in the U.S., is caused by more than a problem with one gene. Type 2 diabetes usually begins after age 40 in overweight, inactive people and is more common in those with a family history of diabetes. In the United States, type 2 diabetes disproportionately affects African Americans, Hispanic/Latino Americans, and American Indians. Finding a gene that may increase susceptibility to type 2 diabetes is a major breakthrough, but translating this discovery into a treatment that benefits people with diabetes or those at risk is still years away. Scientists need to learn much more about this gene.

**Genome Sequence Reveals Leaner, Meaner Intestinal Parasite** — Researchers supported by NIH completed the genome sequence of *Cryptosporidium parvum*, an insidious, one-celled, waterborne parasite that lodges in the intestines of infected people and animals, and for which there is currently no effective treatment. *Cryptosporidium* is an extremely hardy parasite found in water supplies throughout the world, including the United States. For people with weakened immune systems such as those with HIV/AIDS, the parasite can lead to serious or life-threatening illness. *Cryptosporidium* has been difficult to study up until now because it has been virtually impossible to grow in the laboratory. With a better understanding of this parasite's biology, researchers will be better positioned to find treatments that zero in on unique biological processes essential for the organism's survival.

**Gene Involved in Juvenile Rheumatoid Arthritis** — A genetic variation within the interleukin-6 (IL-6) gene increases susceptibility to systemic juvenile rheumatoid arthritis (JRA), according to researchers funded by NIH and the Arthritis Research Campaign. Juvenile rheumatoid arthritis, which has three main forms, affects each child differently. Some experience swollen, painful or stiff joints. Other common symptoms include skin rashes, weak muscles, fevers and swollen glands. Systemic juvenile rheumatoid arthritis, the most severe type, can also affect internal organs such as the heart, liver, spleen and lymph nodes. Twenty percent of children with JRA have the systemic form. Scientists suspect that JRA is caused by a combination of environmental and genetic factors.

**Genes That Determine How Pollution Affects Allergies** — Researchers funded by NIH identified a set of genes that influences how pollution affects allergies. People with certain versions of the genes were more likely to have an allergic reaction to ragweed when it was mixed with diesel exhaust particles. These genes code for antioxidant proteins in the lungs that the scientists believe detoxify chemicals found in diesel exhaust particles. This discovery may help scientists identify people whose asthma and hay fever are more affected by pollution. It might also help accelerate the development of drugs to treat and prevent these disorders.

**Honey Bee Genome Assembled** — The first draft version of the honey bee genome sequence has been deposited into free public databases. The sequence of the honey bee, *Apis mellifera*, was funded largely by NIH, along with the U.S. Department of Agriculture. The honey bee is valued by farmers for its ability to produce honey and pollinate crops. Biologists also are interested in the honey bee's social instincts and behavioral traits.

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## NEW RESEARCH DIRECTIONS

**Sperm Provides Target for New Contraceptive Approach** — A team of researchers funded by NIH found an enzyme in sperm that is necessary for sperm movement. Mice bred to lack this enzyme produce sperm that cannot swim toward egg cells to fertilize them. The enzyme, known as GAPDS, is essentially the same as an enzyme produced in human sperm. It is found in the sperm's flagellum, the snake-like tail which whips back and forth to propel the sperm forward. Researchers believe that designing a drug to disable this enzyme might provide the basis for an effective new form of male contraception. An understanding of the enzyme and related chemical reactions might also lead to insights into treatment for some forms of male infertility.

**Researchers Identify Brain Protein that Halts Progression of Alzheimer's** — Researchers funded by NIH have identified a protein in the brain that halts the progression of Alzheimer's disease in human brain tissue. The protein, known as transthyretin, protects brain cells from gradual deterioration by blocking another toxic protein that contributes to the disease. Scientists are hopeful that this research will inspire a new approach to the treatment of Alzheimer's, one focused on preventing the loss of the brain cells instead of treating the resulting symptoms. More studies are needed to understand how transthyretin might be used in treating Alzheimer's patients.

**Scientists Take 'Snapshot' of Molecular Tether for Anthrax and Staph Bacteria** — Scientists funded by NIH have snapped a picture of the molecular tether that anthrax- and staph-causing bacteria use to hook onto human red blood cells. The tether, an enzyme called sortase B, allows the bacteria to rob the cells of iron, which they need to survive. Anthrax infection can be life-threatening, while staph is responsible for a range of health problems, including skin infections and food poisoning. The scientists hope to use their knowledge of this enzyme's structure to rationally design new antibiotics that would nip dangerous bacteria in the bud, before they have a chance to cause infections.

**Researchers Find Protein That Makes Long-Term Memory Possible** — From language to literature, from music to mathematics, a single protein, known as mBDNF, appears central to the formation of the long-term memories needed to learn these and all other disciplines. This discovery brings the possibility of studying this protein system in people with learning and memory disorders and perhaps designing new medications to help compensate for these problems.

**Brain Signal Predicts Working Memory Prowess** — A person's capacity for visual working memory can be predicted by his or her brain waves, researchers funded by NIH discovered. Some people are better than others at remembering what they have just seen — holding mental pictures in mind from moment to moment. The researchers found that a key brain electrical signal leveled off when the number of objects held in a person's mind exceeded their capacity to accurately remember them, while it continued to soar in those with higher capacity.

**New Technique Helps Scientists Solve 3-D Protein Structures** — A new technique for engineering protein crystals is helping scientists figure out the three-dimensional structures of some important biological molecules, including a key plague protein whose structure has previously eluded researchers. The "crystal engineering" technique, developed with support from NIH, promises to help pharmaceutical companies develop more effective drugs to treat various diseases by tailor-making molecules to "fit" a protein's shape.

**New Eggs Continue to Develop in Adult Mice** — Contrary to long-held scientific views that the number of oocytes (eggs) in the ovaries of most mammals is fixed at birth, scientists supported by NIH reported that new oocyte-containing follicles continue to develop in the ovaries of adult mice. The research suggests that these new oocytes come from stem cells located in the ovary. Scientists have long believed that no new oocytes were made after the ovary of any mammal, including a woman, was formed, but this study provides evidence challenging this belief.

**HIV-Blocking Protein in Monkeys** — Scientists funded by NIH identified a protein that blocks HIV replication in monkey cells. Humans have a similar protein, although it is not as effective at stopping HIV. The protein, called TRIM5-alpha, blocks a key early stage of HIV infection: the removal, or uncoating, of the protective shell surrounding HIV's genetic material. This coat, called the capsid, must be removed before HIV can insert its genetic material into the host cell's DNA and begin to make copies of itself. The identification of a specific protein that powerfully inhibits viral uncoating provides a scientific springboard for future HIV/AIDS therapies.

**Monkey Talk, Human Speech Share Left-Brain Processing** — NIH researchers were part of a team that used PET (positron emission tomography) to pinpoint circuits in the monkey brain that could be precursors of those in humans for speech and language. As in humans, an area specialized for processing species-specific vocalizations is on the left side of the brain. An area near the left temple responded significantly more than the same area on the right to monkey calls, but not to other animal calls, human voices or various other sounds.

**Transgenic Animals Produced Using Cultured Sperm** — NIH researchers, in collaboration with Japanese colleagues, successfully created transgenic zebrafish — ones to which novel genes have been added — using sperm cells grown under laboratory, or in vitro, conditions. This is the first time that sperm cells have been cultured entirely in vitro and used to produce a transgenic animal. This achievement has implications for a wide range of research from developmental biology to gene therapy. The new technique has the potential to speed the production of many different types of transgenic animals that can shed new light on human development and disease.

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## 2003

**Human Genome Project Completed** — The International Human Genome Sequencing Consortium, led in the United States by NIH, completed the Human Genome Project more than 2 years ahead of schedule and for a cost substantially less than the original estimates. The international effort to sequence the 3 billion DNA letters is considered by many to be one of the most ambitious scientific undertakings of all time. The first draft of the human sequence was completed in June 2000. Since then, researchers have worked to convert the "draft" sequence into a "finished" sequence, which covers about 99 percent of the human genome's gene-containing regions, and has been sequenced to an accuracy of 99.99 percent. All of the sequence data have been deposited into public databases and made freely available to scientists around the world, with no restrictions on their use or redistribution.

**Anthrax Genome Completed** — The complete genetic blueprint of *Bacillus anthracis* — the microbe that gained notoriety during the 2001 anthrax mail attacks — has been completed by NIH-funded researchers. This bacterium, which can cause potentially fatal inhalational anthrax, differs very little from a common soil bacterium related to it. Scientists hope that the genetic differences between these two may reveal valuable clues to its vulnerabilities.

**New "Prehypertension" Category** — NIH published new clinical practice guidelines for the prevention, detection, and treatment of high blood pressure — a major risk factor for heart disease and the chief risk factor for stroke and heart failure. The guidelines define a new blood pressure category called "prehypertension" that includes about 22 percent of American adults, or about 45 million people. Americans' lifetime risk of developing hypertension is greater than previously thought, according to the new guidelines. Medications and lifestyle changes are both crucial parts of treatment.

**SARS Cause Identified** — NIH-supported investigators studied 50 Hong Kong patients with severe acute respiratory syndrome (SARS) and identified the virus that was causing the disease. It was revealed to be a new strain of coronavirus, a type of virus formerly associated in humans only with the common cold. Over 8,000 people worldwide became sick with SARS during the outbreak of 2003, according to the World Health Organization; of these, 774 died. The virus's isolation set the stage for the rapid sequencing of its genome as well as investigations into diagnostic tests and therapeutics to combat it.

**Heart Stem Cells Identified** — A new study funded by NIH shows that the adult heart may contain stem cells that have the potential to regenerate tissue when the heart is damaged, such as during a heart attack. The heart had long been considered an organ that wasn't able to renew itself. Scientists now hope to harness these cells to develop new therapies to repair damaged hearts.

**Ebola Vaccine Progress** — A single shot of a fast-acting, experimental Ebola vaccine successfully protected monkeys from the deadly virus after only one month. Scientists at NIH's Dale and Betty Bumpers Vaccine Research Center (VRC) and the United States Army Medical Research Institute of Infectious Diseases at Fort Detrick, MD designed the vaccine. If this vaccine proves similarly effective in humans, it may one day allow scientists to quickly contain Ebola outbreaks with the same strategy successfully used in the past against smallpox. In November, VRC scientists opened the first human trial of a vaccine designed to prevent Ebola infection, administering the vaccine to a volunteer at the NIH Clinical Center in Bethesda.

**Structure of HIV-Neutralizing Antibody Solved** — A team of scientists whose leaders are funded by NIH solved the three-dimensional structure of an antibody that is able to neutralize HIV, the virus that causes AIDS. The antibody, called 2G12, was isolated about a decade ago from one of the rare HIV-positive people whose body is able to successfully combat the virus. The structure of the 2G12 antibody provides scientists with a template in their attempts to design innovative vaccines to trigger the body's production of HIV-neutralizing antibodies.

**New Treatment For Breast Cancer Survivors** — An international clinical trial found that post-menopausal survivors of early-stage breast cancer who took the drug letrozole after completing an initial 5 years of tamoxifen therapy had a significantly reduced risk of cancer recurrence compared to women taking a placebo. The women taking letrozole had a reduction in the number of recurrences of cancer in their previously affected breast, a reduction in the number of new cancers in their opposite breast, and a reduction in the spread of the cancer outside their breast. Deaths from breast cancer were also reduced. While tamoxifen is widely used to prevent breast cancer recurrence in post-menopausal women, it stops being effective after about 5 years because, researchers believe, tumors become resistant to it. NIH participated in and partly supported this Canadian-led study. Novartis, which manufactures letrozole (also known as Femara®), provided the drug for the trial.

**Gene Linked to Depression** — Researchers supported by NIH found a gene, the serotonin transporter gene (5-HTT), that influences whether people become depressed when faced with major life stresses such as relationship problems, financial difficulties and illness. The gene by itself does not cause depression, but it does affect how likely people are to get depressed when faced with major life stresses. Those who carried one version of the gene had more symptoms of depression, more diagnoses of depression, and more thoughts of or attempts at suicide after stressful life events than those who didn't carry it. Significantly, among those who hadn't experienced major life stresses during the study, the gene played no detectable role in their risk of depression or suicide.

**Gene Affects College Drinking Habits** — Researchers identified a gene, the serotonin transporter gene (5-HTT), that may predispose young people to harmful drinking habits. A team of scientists interviewed college students about their alcohol consumption and then analyzed their genetic profiles, or genotypes. They found that students who shared a particular variant of 5-HTT consumed more alcohol per occasion, more often drank expressly to become inebriated, and were more likely to engage in binge drinking than students without the variant.

**Gene Signaling Puberty** — NIH-funded researchers, using tools from the NIH-sponsored Human Genome Project, identified a gene that appears to be a crucial signal for the beginning of puberty in human beings as well as in mice. Without a functioning copy of the gene, both humans and mice appear to be unable to enter puberty normally.

**Stem Cells from Baby Teeth** — A team led by NIH researchers discovered that "baby" teeth, the temporary teeth that children begin losing around their sixth birthday, contain a rich supply of stem cells in their dental pulp. The cells, named SHED, remain alive inside the tooth for a short time after it falls out of a child's mouth. This easily accessible source of stem cells could be readily harvested for research. Scientists hope they can learn to manipulate them to repair damaged teeth, induce the regeneration of bone, and treat neural injury or disease.

**Women's Heart Attack Signs Differ From Men's** — A new study — one of the first to look at symptoms before and during heart attacks in women — found that fewer than 30% of women reported chest pain and discomfort prior to a heart attack, and 43% didn't experience chest pain during one. Most doctors consider chest pain the most important heart attack symptom for both men and women, but the women's most frequently reported early warning symptoms were unusual fatigue (70.7%), sleep disturbance (47.8%), and shortness of breath (42.1%). This finding may help women and their doctors more accurately identify the early warning symptoms of a heart attack so that they can better forestall or prevent the attacks.

**Moderate Physical Activity Promotes Weight Loss** — Women trying to lose weight can benefit as much from moderate physical activity as from an intense workout, according to a new study supported by NIH. With a diet reduced in calories and fat, physical activity of moderate intensity is enough to help overweight people lose weight. The key is not how intense your workouts are, the study suggests, but how much total energy you burn in the end.

**Insight into Parkinson's Disease** — NIH researchers were part of a team that discovered that too much of a normal form of the -synuclein gene may cause Parkinson's disease. Mutations in the -synuclein gene were previously linked to the disease in some families. These researchers were investigating a rare form of early-onset Parkinson's disease in one family for many years, and were puzzled because a genetic analysis of some family members failed to reveal an -synuclein mutation. The scientists thought perhaps an entirely different genetic mutation might account for this family's Parkinson's disease. But they found that, instead of the usual two copies of the -synuclein gene, the people in this family had four copies. This multiplication of the -synuclein gene resulted in them having too much synuclein. Buildup of the protein is believed to cause their Parkinson's disease symptoms. Parkinson's disease is the second most common neurodegenerative disease in the U.S., after Alzheimer's disease, currently affecting at least 500,000 Americans.

**Potential Screening Tool for Alzheimer's Disease** — NIH scientists found that levels of two key proteins could be used to distinguish clinically diagnosed Alzheimer's patients from controls. The proteins, beta-amyloid and tau, are located in the cerebrospinal fluid, which bathes the brain. Scientists hope that "markers" such as these could eventually be used as predictive and diagnostic tools to help identify people at risk for developing Alzheimer's disease who may not yet show any symptoms. Longer term studies are now under way to further test these markers.

**Very Low Lead Levels Linked with IQ Deficits** — A study funded by NIH suggested that lead may be harmful to young children even at very low blood concentrations. The five-year study found that children who have blood lead concentration lower than 10 micrograms per deciliter suffer intellectual impairment from the exposure. Previous research has focused primarily on lead's effects in the 10 to 30 micrograms per deciliter range. Ten micrograms per deciliter is the threshold currently used by the Centers for Disease Control and Prevention to define an elevated lead level.

**Diagnosis and Treatment of Liver Cancer** — A pattern of gene activity unique to hepatocellular carcinoma (HCC), a type of liver cancer, was identified by NIH researchers in collaboration with surgeons in Shanghai, China. The pattern, akin to a molecular signature, can be used to classify metastatic HCC patients and identify genes related to patient survival. Researchers identified one particular gene called osteopontin as a potential therapeutic target. HCC is one of the most common and aggressive malignant tumors worldwide. These findings pave the way for development of a diagnostic test that may help predict whether a cancer will spread, and might help physicians decide on the best treatment for a patient.

**Protein Tied to Preeclampsia** — Researchers supported by NIH linked excess levels of a protein called sFlt1 to the condition preeclampsia, a leading cause of fetal complications including low birth weight, premature birth, and stillbirth. Preeclampsia affects up to 5 percent of pregnancies. It is characterized by increased blood pressure and protein in the mother's urine. Preeclampsia can cause seizures and lead to eclampsia, the second leading cause of maternal death in the U.S. This discovery is an important step in the effort to design better treatments for the condition.

**How the Embryo Attaches to the Uterus** — Researchers supported by NIH have discovered how an embryo attaches to the wall of the uterus in what may be one of the earliest steps needed to establish a successful pregnancy. After an egg is fertilized, a specialized protein called L-selectin on the embryo surface binds to carbohydrates on the uterine wall. Scientists think that this interaction slows the embryo down to a complete stop so it can then attach to the wall of the uterus. The finding may lead to insights into infertility and early pregnancy loss.

**Filtering Water with Cloth Reduces Cholera** — An international research team funded by NIH found that filters made from old cotton saris cut the number of cholera cases in rural Bangladesh villages almost in half. Other inexpensive cloth should work just as well in other parts of the world where cholera is endemic. Cholera is a waterborne disease that causes severe diarrhea and vomiting, killing thousands of people around the world every year. This simple preventive measure has the potential to make a significant impact on a global health problem.

**Single Protein Key to Both Bacterial and Viral Infections** — A single protein acts as a key switch point in frontline immune system reactions to both bacterial and viral infections, according to a team of scientists supported by NIH. This may explain why certain symptoms, such as fever, occur regardless of the cause of infection.

**Understanding Anthrax** — A study of anthrax in mice by NIH scientists showed that the toxins released by the bacteria don't kill as scientists had previously believed. Anthrax was thought to kill like many other bacteria, through the body's release of chemicals called cytokines. But this study found no link between cytokines and anthrax's toxic effects. Researchers still don't know exactly how the anthrax toxins lead to death, but this result suggests that current efforts to design cytokine-suppressing drugs to treat anthrax may be misguided. This information is crucial for the design of future therapies.

**New Insights Into Antidepressants** — Blocking the formation of neurons in the hippocampus area of the brain blocks the behavioral effects of antidepressants in mice, according to researchers funded by NIH. Their finding lends new credence to the idea that antidepressants lift mood, at least in part, by causing new neurons to grow in the brain. This idea also may explain why antidepressants typically take a few weeks to work.

**New Drug to Suppress the Immune System** — A new immunosuppressant drug, CP-690,550, developed by Pfizer Global Research and Development with help from NIH researchers, has been successfully tested in mice and monkeys, and may eventually prove to be a major help for those needing organ transplants or with autoimmune diseases. Immunosuppressant drugs are designed to inhibit the body's immune system so that the body doesn't reject transplanted organs, and to treat autoimmune diseases such as lupus, rheumatoid arthritis, eczema and psoriasis — conditions in which the body's own immune system attacks healthy, normal tissue as if it were an invading microbe. The new drug suppresses the immune system with fewer side effects than other drugs. Further animal studies are now being done to determine if it could be tested safely in humans.

**Progress Shown in Death Rates From Four Leading Cancers** — Death rates from the four most common cancers — lung, breast, prostate, and colorectal — continued to decline in the late 1990s according to new data from the "Annual Report to the Nation on the Status of Cancer, 1975-2000." For all cancers combined, the death rate began to stabilize in the late 1990s, showing neither an increase nor a decrease, while the incidence rate (newly diagnosed cases) began to stabilize in the middle of the decade.

**Cigarette Smoke Affects More Than the Lungs** — Research supported by NIH shows that cigarette smoke not only directly and often fatally damages the lungs; it also decreases levels of a critical enzyme called monoamine oxidase B (MAO B) in the kidneys, heart, lungs, and spleen. The researchers compared PET scans showing MAO B activity in both smokers and nonsmokers. They observed that MAO B activity in the peripheral organs was reduced by one-third to almost one-half in the smokers. While the medical consequences of this finding aren't yet clear, it highlights the fact that many organs throughout the body are affected by the chemical compounds in tobacco smoke.

**Subversive Strep Bug Strategy Revealed** — NIH researchers have discovered how *Streptococcus pyogenes* (*S. pyogenes*), the bacterium responsible for strep throat and "flesh-eating" infections, gains a foothold in the body by subverting a key immune system cell. Using microarray technology, which allows researchers to determine which genes are active within cells, the researchers created a "snapshot" of how all the genes in neutrophils — a type of white blood cell and central player in the body's innate immune system — react following exposure to a variety of bacteria. *S. pyogenes* stimulated almost 400 neutrophil genes that were not activated by the other kinds of bacteria, and also caused the neutrophils to self-destruct in an uncontrolled fashion. Knowing how this common bug bacterium evades our immune defenses opens exciting new avenues for research into ways to hamper it.

**Promising West Nile Virus Vaccine Protects Monkeys** — NIH scientists have created a promising vaccine against West Nile virus by replacing parts of a distantly related virus with proteins from the West Nile virus. This hybrid vaccine protects monkeys from West Nile infection. West Nile virus is spread to people by mosquitoes. It usually produces mild, flu-like symptoms but can cause a deadly encephalitis, or inflammation of the brain. The disease is most severe among the elderly, and has sickened over 8,500 and claimed around 200 lives in the United States in 2003.

**Estrogen and Progestin Therapy Increases Risk of Dementia** — Healthy postmenopausal women taking combination hormone therapy had twice the rate of dementia as those taking a placebo. The findings are part of the Women's Health Initiative, a large multi-center research study funded by NIH. The women had stopped taking the therapy in July 2002 when participants were found to have an increased risk of breast cancer, heart disease, stroke, and blood clots. These findings further support the conclusion that the risks of taking estrogen plus progestin outweigh the benefits.

**Gene for premature aging disorder identified** — A team led by NIH scientists found that mutations in a gene called lamin A (LMNA) are responsible for Hutchinson-Gilford progeria syndrome (HGPS), a disorder that causes a dramatic form of premature aging, with death coming on average at age 13. LMNA is a key protein component of the membrane surrounding the cell's nucleus. This discovery may shed light on the general phenomenon of human aging as well as HGPS.

**Key to Hepatitis C Virus Persistence Found** — NIH-funded scientists discovered how hepatitis C virus (HCV) thwarts the immune system's efforts to eliminate it. Persistent HCV infection is a major cause of liver disease worldwide and is the leading reason for liver transplants in this country. Using cells grown in the laboratory, researchers found that a type of enzyme manufactured by HCV called a protease inhibits an immune system molecule called interferon regulatory factor-3 (IRF-3), which is a key player in fighting viruses. Researchers showed that interfering with the protease restored IRF-3 function. They hope this finding could eventually lead to more effective treatments for liver disease caused by HCV.

**Warfarin Prevents Recurrence of Blood Clots** — Long-term, low-dose warfarin treatment prevents the recurrence of the blood-clotting disorders deep vein thrombosis (DVT) and pulmonary embolism. A large NIH-funded trial showed so much benefit to the patients taking warfarin that the study was stopped early. These findings show that recurrent blood clots can be avoided using an inexpensive and safe therapy.

**Tamoxifen Reduces Breast Cancer Risk** — More than two million women who have a high risk of developing breast cancer would be likely to benefit from taking the breast cancer prevention drug tamoxifen, according to an analysis by NIH researchers. Tamoxifen was approved five years ago as the first drug to prevent breast cancer. It can halve the incidence of breast cancer in women who are most likely to develop the disease. The decision to take tamoxifen will depend on factors such as a woman's age, breast cancer risk factors, and family history.

**Protein From Algae Inhibits Ebola** — A bacterial protein known to reduce the ability of the human immunodeficiency virus (HIV) to infect cells was also found to inhibit the Ebola virus. The protein, cyanovirin-N, is found in blue-green algae. An NIH-led team found that the protein inhibits Ebola infection by interfering with the virus's ability to enter cells, and can extend the survival of Ebola-infected mice. This study provides important insights that may help in the development of medicines to combat Ebola infection, which causes severe hemorrhagic fever and has a high mortality rate.

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## 2002

**Mouse Genome Sequenced** - The international Mouse Genome Sequencing Consortium, jointly funded by several NIH Institutes along with the Wellcome Trust, published a high quality draft sequence of the mouse genome - the genetic blueprint of a mouse - together with a comparative analysis of the mouse and human genomes. This is the first time scientists have compared the human genome with another mammal's. Because the mouse carries a very similar set of genes, this information will allow scientists to learn more about human genes and the proteins they encode, leading to a better understanding of human disease and improved treatments and cures. The sequence is posted on the Internet, where it is freely available.

**Estrogen Plus Progestin Increases Breast Cancer Risk** - NIH stopped a major clinical trial of the risks and benefits of combined estrogen and progestin in healthy menopausal women due to an increased risk of invasive breast cancer. The large multi center trial also found increases in coronary heart disease, stroke, and pulmonary embolism in study participants on estrogen plus progestin compared to women taking placebo pills. There were noteworthy benefits of estrogen plus progestin, including fewer cases of hip fractures and colon cancer, but on balance the harm was greater than the benefit.

**Smallpox Vaccine Dilution Trial** - An NIH-supported clinical trial demonstrated that the existing U.S. supply of smallpox vaccine - 15.4 million doses - could successfully be diluted up to five times and retain its potency, greatly expanding the number of people it could protect from the contagious disease.

**Anthrax Genomes Sequenced** - Researchers reported the genetic comparison of two important strains of the anthrax bacterium, an isolate from the 2001 Florida anthrax attack and the well known Ames strain. NIH teamed with the Office of Naval Research, the National Science Foundation, and other agencies to fund the research. Whole genome sequencing and computational methods allowed the researchers to identify differences between the strains for further study. In the future, these techniques can be used to trace the origin of anthrax strains, determine if those strains have been genetically modified, and assess differences in their ability to cause disease or resist antibiotics.

**Structure of Last Toxic Anthrax Protein Solved** - Researchers supported by NIH solved the three dimensional structure of edema factor (EF), one of the three toxic proteins responsible for the deadly effect of the anthrax bacterium, *Bacillus anthracis*. EF was the last of the three to have its three-dimensional structure solved, an important step in designing antidotes.

**Small RNA, Big Potential** - Two separate teams of researchers supported by NIH developed new technology using "small RNAs" to interfere with the activity of specific genes in mammalian cells. The technique holds great potential for studying genes, and is being tested therapeutically to see if it could interfere with viruses like HIV. Small RNAs have recently emerged as a powerful tool to "silence" genes in a process called RNA interference, or RNAi, so that cells cannot make the protein encoded by a specific gene. This was the first time scientists had been able to successfully perform RNAi in mammalian cells. Science magazine named small RNAs its top breakthrough of 2002.

**Improved Heart Failure Survival** - Survival after a heart failure diagnosis has greatly improved over the past 50 years, according to a study which analyzed data from NIH's landmark Framingham Heart Study (FHS). The risk of dying after being diagnosed with heart failure has dropped by about a third in both men and women. New cases of heart failure dropped by about a third for women during the same period. However, the number of new cases for men remained unchanged. Better prevention and treatments have contributed to overall progress in these rates, but heart failure remains deadly; more than 50 percent of those given a diagnosis of heart failure in the 1990s died within five years.

**Detecting Ovarian Cancer** - By uniting proteomics and an artificial intelligence program, scientists from NIH and the Food and Drug Administration reported that patterns of proteins found in patients' blood serum may reflect the presence of ovarian cancer, even at early stages. The test can be completed in 30 minutes and uses blood obtained from a finger prick. The emerging concept that an entire pattern of proteins can contain important diagnostic information is potentially applicable to any type of disease.

**Predicting Chemotherapy Response** - Patterns of genes that are active in tumor cells can predict whether patients with diffuse large B cell lymphoma (DLBCL) are likely to be cured by chemotherapy, NIH-sponsored scientists reported. The researchers used DNA microarray technology, which allows researchers to determine which genes are active within cells, to analyze thousands of genes in lymphoma biopsy samples and found that the activity of as few as 17 genes could be used to predict patients' response to treatment. DLBCL is the most common type of non Hodgkin's lymphoma in adults, and standard chemotherapy for the disease is effective in only 40 percent of patients. Profiling gene expression in patients' tumors may help clinicians decide which patients are suitable candidates for standard therapy and which should consider other options for treatment.

**Malaria Parasite and Mosquito Genomes Completed** - The genome sequences of *Plasmodium falciparum*, the most lethal malaria causing parasite, and *Anopheles gambiae*, a mosquito that transmits the parasite to humans, were completed by two international research teams partly supported by NIH. These sequences will help scientists gain a deeper understanding of the disease and its transmission.

**Malaria Drug Resistance Gene** - The malaria causing parasite *Plasmodium falciparum* became resistant to the anti malarial drug chloroquine through mutations in a single parasite gene named *pfcr*, NIH-supported scientists reported. This finding has potentially important implications for malaria treatment and control. Scientists hope to develop methods for diagnosing different variants of *P. falciparum* infection in patients, so that health officials might then be able to match the most effective drugs for each infection.

**Improved Diet and Exercise Delays Type 2 Diabetes** - A major clinical trial sponsored by NIH found that people at high risk for type 2 diabetes can delay and possibly prevent the disease by improving their diet and exercising. Diet and exercise leading to weight loss of 5 to 7 percent reduced diabetes incidence by 58 percent in people at high risk. The study found that the oral diabetes drug metformin (Glucophage) also reduces type 2 diabetes risk, although not as effectively as lifestyle changes.

**Traditional Diuretics Better Than Newer Medicines for Treating Hypertension** - Less costly diuretics ("water pills") work better than newer drugs to treat hypertension (high blood pressure) and prevent some forms of heart disease, according to a large clinical trial supported by NIH. The study compared a diuretic with a calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor, and an alpha adrenergic blocker. About 24 million Americans currently take drugs to lower their blood pressure, at an estimated annual cost of about \$15.5 billion.

**How Light Resets Your Internal Clock** - A light sensitive protein in the eye called melanopsin plays a key role in synchronizing daily rhythms to the day /night cycle, according to research supported by NIH. A "clock" within the brain normally governs daily rhythms like sleeping and waking, body temperature and eating. Each day, this internal clock is reset by light, which is somehow detected by the eyes even when the rods and cones, the photoreceptors for vision, are removed. Researchers found that mice lacking a gene for melanopsin did not reset their circadian rhythms normally when exposed to light.

**Scientists Glimpse Enzymes at Work Inside Living Cells** - Using advanced imaging technology and computational simulations, NIH scientists led a team that glimpsed the action of an enzyme at work within living cells for the first time. RNA polymerase I, which is made up of more than ten protein subunits, "reads" genes from DNA. By analyzing the time it took for the enzyme's many subunits to arrive at a gene and assemble into a functioning complex, researchers discovered that RNA polymerase I is constantly assembling and disassembling itself from a large pool of subunits within the cell. Subunits come together and form a complex each time a gene is read, on average every 1.4 seconds. Once a complete enzyme finishes reading a gene, the subunits quickly disassemble and scatter throughout the cell. Researchers think that the dynamic nature of these cellular machines allows them to assemble as needed so that they can respond quickly to changing conditions in the cell.

**Hypertension and Kidney Disease in African Americans** - The largest clinical trial ever conducted in African Americans with kidney disease has concluded that an angiotensin converting enzyme (ACE) inhibitor is superior to drugs in two other classes (calcium channel blocker (amlodipine, Norvasc®) and a beta blocker (metoprolol, Toprol XL®)) for slowing kidney disease due to hypertension. The NIH-funded study also found that very low blood pressure provides no additional benefit for the kidneys than the established standard. Hypertension accounts for 25 percent (87,000) of the nearly 379,000 Americans treated for kidney failure in 2000. Black Americans are six times more likely than whites to develop kidney failure from hypertension, and account for 32 percent (122,000) of all treated patients.

**More Surgical Patients Die When Nurse Caseloads Increase** - A study of 168 hospitals in Pennsylvania by NIH-funded researchers found that for each additional patient over four in a registered nurse's workload, the risk of death increases by 7% for surgical patients. In hospitals with eight patients per nurse, patients have a 31% greater risk of dying than in hospitals with four patients per nurse. On a national scale, staffing differences like this could result in as many as 20,000 unnecessary deaths each year.

**Drug Successfully Delivered to Primate Brainstem** - NIH researchers used a technique called convection enhanced delivery (CED), which was developed at NIH, to deliver a tracer molecule to the primate brainstem. They then used magnetic resonance imaging (MRI) to track the tracer's movement throughout the brain. Current drug treatments of brainstem tumors are largely unsuccessful because the drugs often fail to bypass the blood brain barrier, the lining protecting the brainstem. This study showed that researchers can effectively deliver drugs to the primate brainstem and monitor how the drugs spread inside the brain, providing hope for improving treatment of brainstem tumors and other brain diseases.

**Key Gene Identified in Cleft Lip and Palate** - Scientists supported by NIH discovered the gene that causes Van der Woude syndrome, which causes cleft lip and palate along with other birth defects. The gene, called IRF6, seems to play a key role in the normal formation of the lips, palate, skin, and genitalia. Further study of the gene should provide molecular clues into normal human development and might suggest strategies to prevent birth defects such as cleft lip and palate.

**Genetic Defect Responsible for Devastating Brain Disorder** - An international team led by NIH researchers used the technique of haplotype mapping - finding blocks of genes that are passed on together through generations - to discover the genetic cause for a rare form of microcephaly, a fatal brain disorder that has stricken infants among the Older Order Amish community in Lancaster County, PA for nine generations. The defect, in a gene called DeoxyNucleotide Carrier (DNC) causes developing cells to lose their ability to transport the building blocks of DNA into the mitochondria, the tiny structures that function as the cells' metabolic power houses. Researchers believe that without this carrying ability, called mitochondrial deoxynucleotide transport, the cell's mitochondria cannot make DNA properly, thus causing the brain of the unborn child to develop abnormally.

**New Approach Shrinks Tumors in Patients with Melanoma** - NIH researchers demonstrated a new approach to cancer treatment that replaces a patient's immune system with cancer fighting cells. Thirteen patients with metastatic melanoma (a deadly form of skin cancer) who had not responded to standard treatments were treated with immune cells produced in the laboratory specifically to destroy their tumors. The treatment resulted in at least 50 percent tumor shrinkage in six of the patients, with no growth or appearance of new tumors. Four additional patients had some cancer growths disappear. With further research, scientists hope that this experimental technique, known as adoptive transfer, might be applied to other types of cancer as well as infectious diseases such as AIDS.

**Multiple Pets May Decrease Children's Allergy Risk** - Children raised in a house with two or more dogs or cats during the first year of life may be less likely to develop allergic diseases than children raised without pets, according to a study supported by NIH.

**Complicated Relationship Between Cats and Asthma Risk** - A study supported by NIH confirmed previous reports that exposure to cats during infancy can actually protect children against developing asthma, but with one important caveat. When the child's mother has asthma, then a cat in the home actually triples the risk that a child will develop persistent wheezing - an initial indication of asthma - by age five.

**Premature Menopause Linked to Adrenal Condition** - NIH researchers found that women with spontaneous premature ovarian failure (POF) are at higher risk for developing a serious condition called primary auto immune adrenal insufficiency, or Addison's disease, in which the body attacks the adrenal glands. A test called the adrenal antibody test proved effective in detecting the adrenal condition in women with POF. This early detection is critical, as Addison's disease can be easily treated with medication that replaces the hormones the adrenal glands are not making. By age 40, an estimated one percent of American women develop POF, in which the ovaries stop producing eggs and reproductive hormones well in advance of natural menopause.

**Arrhythmia in African Americans Tied to Gene** - Scientists supported by NIH identified a gene variant of the cardiac sodium channel gene SCN5A that is associated with arrhythmia - abnormal heart rhythm - in African Americans. The gene variant, which is present in an estimated 4.6 million African Americans, may one day be used to assess the risk of arrhythmia and help prevent it.

**Lipid Abnormalities Linked To Lou Gehrig's Disease** - Abnormally high levels of two common lipids (the building blocks of fat) in motor nerve cells may be responsible for the development of amyotrophic lateral sclerosis (ALS), according to NIH investigators. Also called Lou Gehrig's disease, ALS is a progressive, neurological disease affecting as many as 20,000 Americans. ALS leads to paralysis, and is often fatal within five years of diagnosis. This new insight might help scientists develop treatments to slow or arrest the disease's progression.

**Clues to Extended Life** - A study by NIH investigators found that men who had lower body temperatures, lower blood insulin levels or higher blood levels of a steroid called DHEAS as they aged tended to live longer. These are three well established characteristics of calorie restriction in animals, but the men were not stringently dieting, to the researchers' knowledge. The relationship between these three characteristics and longer life is being further explored.

**Excess Body Weight Associated with Increased Risk of Heart Failure** - Excess body weight is strongly associated with an increased risk of heart failure, according to a study supported by NIH. Extreme obesity had previously been associated with heart failure, but this new study found that the risk increases continuously with increasing body weight; it is 34 percent higher for people who are overweight and 104 percent higher for those who are obese.

**Gene Affects Response to Scary Faces** - NIH scientists, using Functional Magnetic Resonance Imaging (fMRI) scans, revealed that people who have one particular version of the human serotonin transporter gene had more activity in the brain structure known as the hub of fear, the amygdala, when they saw pictures of scary faces. This gene's effect on the amygdala may help shape a person's natural temperament.

**Ovarian Cancer Linked to Estrogen Replacement Therapy** - NIH researchers found that women who used estrogen replacement therapy after menopause were at increased risk for ovarian cancer. No increased risk for ovarian cancer was found in women using estrogen progestin therapy.

**Gene Implicated in Mental Retardation** - Researchers supported by NIH discovered a gene on the X chromosome called AGTR2 that, when abnormal, appears to result in male mental retardation. Clues in its structure led the scientists to suggest that AGTR2 may be involved in blood vessel function or development during brain development.

**No Association Found Between Oral Contraceptive Use and Breast Cancer** - Women who took oral contraceptives at some point in their lives are no more likely to develop breast cancer between the ages of 35 and 64 than other women the same age, according to a study supported by NIH.

**Vasectomies and Prostate Cancer** - Contrary to some earlier studies, a new study partly funded by NIH found that men who undergo vasectomies are no more likely to develop prostate cancer than men who don't. Prostate cancer is a leading form of cancer among men in the United States, second only to skin cancer.

**Eye Drops to Treat Glaucoma** - Scientists supported by NIH found that eye drops to reduce pressure inside the eye delayed the onset of primary open angle glaucoma, the most common form of glaucoma and one of the nation's leading causes of vision loss, by more than 50 percent after five years. Between three and six million people in the U.S. have elevated eye pressure and are at increased risk for developing open angle glaucoma.

**Molecularly Targeted Drug Slows Metastatic Kidney Cancer** - NIH researchers reported that the molecularly targeted drug bevacizumab slowed tumor growth in patients with metastatic renal cell carcinoma, the most common form of kidney cancer in adults.

**HIV Infects Cells Sent to Fight It** - Scientists at NIH were among a group demonstrating that HIV disables the immune system's response against the virus by disproportionately infecting the very cells designed to fight it. HIV undermines the body's ability to protect against disease by depleting helper T cells, which help direct the immune system's response to microbial invaders. The researchers found that the helper T cells programmed to fight HIV are two to five times more likely to be infected with HIV than helper T cells programmed to take on other pathogens.

**Delaying Teen Drinking** - A study funded by NIH showed that two brief family intervention programs are a cost-effective way to delay teen drinking. Between the critical ages of 13 and 16, fewer teens in the two treatment groups started to use alcohol than in the control group.

**Single Gene Change Caused Plague** - A single gene change played a key role in the evolution of bubonic plague, according to researchers at the Rocky Mountain Laboratories, an NIH research outpost. The new gene allowed a relatively benign bacterium that causes a mild human stomach illness acquired through contaminated food or water to change into the flea borne agent of the "Black Death," which killed one fourth of Europe's population in the 14th century.

**Gene for Inherited Gum Condition** - An international team of scientists partly supported by NIH identified the first gene that, when altered, triggers hereditary gingival fibromatosis, or HGF, the most common of the rare inherited gum conditions in which gums grow abnormally over the teeth.

**Obese Youth and Type 2 Diabetes** - Many obese children and adolescents have impaired glucose tolerance, according to research funded by NIH. Impaired glucose tolerance is a known risk factor for type 2 diabetes. The incidence of type 2 diabetes has been rising steadily in children, especially minority adolescents. Glucose tolerance testing may be a practical way to identify obese children at high risk for type 2 diabetes and target them for intensive weight loss treatment.

**Eye Drops Treat Lazy Eye** - Scientists supported by NIH found that atropine eye drops given once a day to treat moderate amblyopia, or lazy eye, work as well as the standard treatment of patching one eye. Amblyopia is the most common vision problem in children, affecting two or three of every 100 children. This finding could lead to more success in correcting amblyopia by helping children avoid the social stigma of wearing an eye patch and making it easier for parents to help their kids stick to the treatment.

**West Nile Virus Vaccine Protects Mice** - A research team from NIH and Walter Reed Army Institute of Research have developed a vaccine that protects mice from West Nile virus infection. Researchers hope this accomplishment will help them develop a successful vaccine for humans.

**New Gene for Deafness Found** - Mutations in a gene recently identified by NIH researchers called TMC1 can cause nonsyndromic hearing loss. Nonsyndromic hearing loss, which is not accompanied by other inherited problems like changes in skin or hair pigmentation, accounts for approximately two thirds of all hereditary hearing loss. Scientists think the protein encoded by TMC1 plays a role in allowing ear hair cells to respond to sound vibrations, which the cells ultimately convert into electrical signals that travel to the brain.

**Hypertension Risk High** - Middle aged Americans face a 90 percent chance of developing high blood pressure at some time during the rest of their lives, according to a new study supported by NIH. However, the study also had some good news for Americans: The risk of developing severe high blood pressure has decreased in the past 25 years, due partly to improved treatment.

**Leptin Reverses Symptoms of a Rare Form of Diabetes** - Scientists at NIH and the University of Texas Southwestern Medical Center have successfully used the hormone leptin to treat patients suffering from lipodystrophy, a rare and difficult to treat disorder that shares some of the characteristics of typical type 2 diabetes.

**High Homocysteine Levels Linked to Alzheimer's** - People with elevated levels of the amino acid homocysteine in their blood had nearly double the risk of developing Alzheimer's disease (AD), according to a new report from NIH-supported scientists. Blood levels of homocysteine can be reduced by increasing intake of folic acid (or folate) and vitamins B6 and B12, and the therapeutic use of these compounds is now being explored.

**First Vaccine Against Deadly Staph Bacteria** - NIH scientists and the company Nabi have developed the first successful vaccine against *Staphylococcus aureus*, a major cause of infection and death among hospital patients. This bacterium causes illnesses ranging from minor skin infections to life threatening diseases such as severe pneumonia, meningitis, and infections of the heart and bloodstream. Recently, researchers have discovered strains of the bacteria that are resistant to the antibiotics used to treat them, making a preventive vaccine critical.

**Mentally Stimulating Activities May Reduce Alzheimer's Risk** - Scientists supported by NIH found that more frequent participation in mentally stimulating activities like doing crossword puzzles or playing cards is associated with a reduced risk of Alzheimer's disease (AD).

**First Genetically Engineered "Knockout" Pigs** - NIH-supported scientists created the world's first "knockout" pigs, which are lacking one of a pair of genes that triggers immune rejection of pig organ transplants in humans. This is an important step for developing genetically engineered pigs that can be used as sources of organs for human transplantation.

**Glaucoma Gene Identified** - NIH-supported researchers identified a gene associated with primary open angle glaucoma (POAG) which they named optineurin, or OPTN. POAG affects 33 million individuals worldwide and is a leading cause of blindness. Researchers hope to use this finding to develop a way to diagnosis POAG before symptoms appear.

**Leading Cause of Gastroenteritis Identified** - Investigators led by a researcher on the NIH campus successfully identified a group of Norwalk like viruses as the leading cause of gastroenteritis in Maryland nursing homes. Gastroenteritis is an intestinal illness that can cause vomiting, diarrhea, abdominal cramps, fever, chills and headaches, and can lead to serious complications in the elderly, many of whom are already struggling with other illnesses.

**Help for Urinary Incontinence** - Researchers supported by NIH showed that rural older women with urinary incontinence (UI) who received a behavioral management intervention in their homes reduced UI severity by 61% compared to the control group, whose UI severity increased by 184%. The intervention consisted of behavioral changes, bladder training, and pelvic muscle exercises with biofeedback. UI is a leading reason for people in rural areas to move to a nursing home; controlling it would lead to a better quality of life and allow people to remain longer in their homes.

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## 2001

**DASH (Dietary Approaches to Stop Hypertension) Diet Lowered Blood Pressure** - found that the DASH (Dietary Approaches to Stop Hypertension) diet combined with reduced intake of sodium lowered blood pressure for all groups of people, not just those with high blood pressure. The diet is rich in fruits, vegetables and low-fat dairy foods but low in fats, cholesterol and sweets. Middle-aged Americans face a 90 percent chance of developing high blood pressure at some time during the rest of their lives, according to NIH's National Heart, Lung and Blood Institute (NHLBI). The condition can lead to stroke, heart disease and kidney failure. (Intramural and Extramural)

**New, "Hidden" Influenza Virus Protein** - an international team including NIH scientists found a new, "hidden" influenza virus protein scientists hadn't previously known about that proved toxic to human cells. This new protein may be key to the mystery of what makes some influenza strains so deadly. (Intramural)

**How HIV Travels into and out of Cells** - discovered that HIV, the virus that causes AIDS, must attach to cholesterol-rich regions of a cell's membrane in order to enter and infect the cell. The finding provides a more detailed picture of how HIV travels into and out of cells and points to possible ways to block that travel. (Intramural)

**Antibody Designed to Deliver a Toxin to Cancer Cells** - designed an antibody to recognize and directly deliver a toxin to cancer cells using recombinant DNA technology. This "immunotoxin" induced complete remission in 11 of 13 patients with hairy-cell leukemia that was resistant to previous chemotherapy. The compound, BL22, has been licensed to AlbaPharm, Inc., of Rockville, Md. The company, in collaboration with NCI scientists, will conduct a larger clinical trial that will involve patients with this cancer of the immune system from throughout the country. (Intramural)

**Strains of the Bacterium Chlamydia Trachomatis Cause Blindness** - found a gene encoding a cell-destroying toxin that enables certain strains of the bacterium *Chlamydia trachomatis* to cause blindness and debilitating genital tract infections. (Intramural)

**Treating Depression Can Significantly Reduce Hospital Stay** - found that a program to train health care providers to diagnose and treat depression can significantly reduce the time that patients spend clinically depressed for a cost of less than \$500 per depressed patient. Over a two-year period, the program reduced the length of patients' depression by well over a month and increased the time they spent employed by about four work weeks. (Extramural)

**Shape of Sperm Determines Fertility** - found that the shape of a man's sperm appears to be the best way to know if he is fertile. Sperm concentration and motility (how well they move) are also important. However, none of these measures can completely predict fertility. (Intramural and Extramural)

**Genetic Basis of Two Rare Disorders Identified** - identified the genetic basis of two rare disorders, familial cold autoinflammatory syndrome (FCAS), in which affected people develop rashes and other symptoms when exposed to cold air, and Muckle-Wells syndrome (MWS), which causes deafness as well as periodic fevers. Symptoms of both syndromes are caused by an altered immune system protein named cryopyrin. The scientists believe that cryopyrin is part of the innate immune system — an evolutionarily ancient defense system that is present in plants and other lower organisms. The identification of the gene underlying FCAS and MWS will help researchers understand the origin of these rare conditions and may point them in new directions for treatments. (Extramural)

**Nutrient Combination Lowers Risk of Age-related Macular Degeneration** - showed that people at high risk of developing advanced stages of age-related macular degeneration (AMD) significantly lowered that risk by taking a high-dose combination of zinc and the antioxidants vitamin C, vitamin E and beta-carotene. These nutrients are the first effective treatment to slow the progression of AMD, a leading cause of visual impairment and blindness in Americans 65 years of age and older. (Intramural and Extramural)

**Surgical Risks in Emphysema Patients** - established scientifically-based selection criteria for identifying emphysema patients that would receive little benefit from a new treatment called lung volume reduction surgery (LVRS) and are at high risk of death from the procedure. Emphysema is a disabling condition in which the fine architecture of the lung is destroyed, leading to large holes in the lung, obstruction of the airways, trapping of air, and difficulty exchanging oxygen. Typically caused by cigarettes, the disease affects approximately 2 million Americans and kills more than 17,000 people in the U.S. each year. This research will let doctors identify which patients would do better receiving medical treatments such as medications, exercise rehabilitation, and nutritional supplementation rather than LVRS. (Extramural)

**Cell Receptor Discovered** - discovered the receptor on the outside of cells that protective antigen (PA), one of the three toxic proteins produced by anthrax bacteria, uses to get inside. Part of the receptor was used by the scientists to overwhelm the toxins and protect cells in a culture from being killed by anthrax toxins. This approach might eventually lead to a similar therapy in people. The receptor can also now be used as a tool to find potential medicines that block anthrax toxin from binding to it. (Extramural)

**Proteins Crystal Structure Solved** - solved the crystal structure of one of the three toxic proteins produced by anthrax bacteria, lethal factor (LF), and discovered how it interacts with the specific proteins it destroys inside the cell. LF kills macrophages, a key cell of the human immune system. This structural information can now be used to look for therapeutic agents to block LF's deadly activity. (Intramural and Extramural)

**Anthrax Toxin Inhibitor** - designed an inhibitor of anthrax toxin by looking for random peptides (portions of proteins) that blocked the three anthrax toxic proteins from binding to each other. The scientists tested the inhibitor in rats that are highly sensitive to anthrax toxin and found that an injection could completely protect the rats from anthrax toxin without any noticeable side effects. This, or another inhibitor developed with a similar approach, might now be developed as a medicine to combat anthrax toxin when antibiotic treatment is too late. (Extramural)

**Streptococcus pneumoniae Sequenced** - sequenced the genome of a virulent strain of *Streptococcus pneumoniae*. *S. pneumoniae* kills millions of people, especially the elderly, worldwide each year with pneumonia, blood stream infections and meningitis, and many strains have become resistant to common antibiotics. The examination of this sequence and comparison with other strains should provide targets for the development of new drugs and vaccines. (Extramural)

**Key to Strain's Virulence** - found that a small change in the genetic sequence of one of influenza virus's 10 genes (known as PB2) was key to one strain's virulence, a significant advance toward understanding the molecular basis of why some strains kill so many people while others are relatively benign. The influenza virus constantly changes, and new strains emerge each year, thus requiring new vaccines each year. In order to prepare effective vaccines or design more effective antiviral drugs, it is critical to understand what makes some strains of the virus so deadly. (Extramural)

**Porphyromonas gingivalis Sequenced** - sequenced the genome of *Porphyromonas gingivalis*, a bacterium thought to play a major role in gum disease. It is the first oral disease-causing microbe to be completely sequenced. This data should help researchers develop better ways to prevent or eradicate gum disease. (Extramural)

**COMT Increases Risk of Schizophrenia** - deciphered how a variant form of a gene called COMT affects the prefrontal cortex of the brain to slightly increase the risk for schizophrenia. This is one of the first studies to show how a specific gene contributes to a mental illness. (Intramural and Extramural)

**Artificial Neural Network** - developed a method that, by combining microarray (or gene chip) technology with a form of artificial intelligence called an artificial neural network (ANN), can tell the difference between four childhood cancers that often look alike. Using traditional diagnostic technologies, the tumors caused by these four unique types of cancer — neuroblastoma, rhabdomyosarcoma, non-Hodgkin's lymphoma (Burkitt's lymphoma) and Ewing's sarcoma — are difficult to tell apart. Gene chip technology was used to analyze the pattern of activity of thousands of genes at once while an ANN "learned" how to recognize the genetic patterns produced by each type of cancer. As a result of this work, the different cancers can now be classified with much greater accuracy. An accurate diagnosis can be critical for a child's survival, as the treatments for these tumors are quite different. This study should also help lead to the discovery of genes that are altered in these tumors, and ultimately to the development of effective new treatments. (Intramural)

**Anti-cancer Drug Targets Chronic Myelogenous Leukemia** - funded the lion's share of the basic research that eventually led to the discovery and development by the drug company Novartis of a new drug known as Gleevec. It is the first anti-cancer drug specifically developed to target a molecular problem that causes a particular type of cancer, in this case, chronic myelogenous leukemia (CML). In this disease, too many white blood cells are made in the bone marrow. In a clinical trial, Gleevec restored normal blood counts in 53 out of 54 patients with CML. Side effects thus far seem very mild. NCI and Novartis are conducting clinical trials to determine the long-term effectiveness of this drug. (Intramural and Extramural)

**Mouse Embryonic Stem Cells Produce Insulin** - turned mouse embryonic stem cells into cells that produced insulin and showed other characteristics of pancreatic islet cells. Diabetes, which affects 16 million people in the US, results from abnormal function of pancreatic islets. This research may be an important step toward a diabetes treatment, as stem cells may enable doctors to overcome the problems of availability and tissue rejection seen in transplants. (Intramural and Extramural)

**Streptococcus pyogenes Sequenced** - completed sequencing the 1.8 million DNA base pairs of *Streptococcus pyogenes*, a bacterium that causes a wide variety of human diseases including strep throat, scarlet fever, the skin infection impetigo, pneumonia, acute kidney inflammation, toxic shock syndrome, blood "poisoning," acute rheumatic fever, rheumatic heart disease, and the flesh-eating disease known as necrotizing fasciitis. Having this bacterium's genome will help in the development of new prevention and treatment attempts such as creating vaccines. (Extramural)

**Develop Genetic Test for Breast Cancer** - developed a new genetic test that can distinguish between two types of hereditary breast cancer — caused by BRCA1 and BRCA2 mutations — and sporadic breast cancer. The new approach, using microarray technology to analyze the activity of over 5300 genes at once, was developed by a team of international researchers that included NIH scientists. This advance should ultimately help physicians quickly and accurately diagnose the cause of a woman's breast cancer and guide decisions about the most effective treatment. (Intramural)

**Discovery of Gene for Sweet Taste Receptors** - discovered the gene that codes for sweet taste receptors in the mouth. NIDCD scientists were among three separate research groups reporting the discovery of this gene. Taste receptor cells contain molecular receptors that respond to chemicals in food and drink to create the sensation of taste. The discovery of this receptor may help in the development of better artificial sweeteners, and in learning why some people seem to have more of a sweet tooth than others. Taste defects are also associated with many health problems such as obesity, diabetes, hypertension and malnutrition. (Intramural and Extramural)

**Vaccine for Typhoid Fever** - developed and tested the first vaccine capable of protecting children ages 2 to 5 against typhoid fever. Seemingly the most effective typhoid vaccine ever developed, it is also virtually free of side effects. Spread by fecal contamination of drinking water or food, or by person to person contact, typhoid fever is common in developing countries without adequate sewage and sanitation. Symptoms include fever, stomach pains, weight loss, loss of appetite, delirium, severe diarrhea (in children), and constipation (in adults). About 16 million people worldwide develop typhoid each year, and 600,000 die from it. (Intramural and Extramural)

**Cocaine Addiction is Chronic** - found, using rats, that craving for cocaine seems to increase, rather than decrease, in the days and months after drug use has stopped. This phenomenon helps explain why cocaine addiction is a chronic, relapsing disease. (Intramural)

**Losing Weight Lowers Risk of Diabetes**

– found that people at high risk for type 2 diabetes can sharply lower their chances of getting the disease by losing weight (5 percent to 7 percent of their body weight) and by getting 30 minutes of walking or other moderate exercise every day. (Extramural)  
– found evidence that human heart muscle cells do regenerate to some degree after a heart attack. Scientists previously assumed that when the heart is damaged — such as after a heart attack — heart muscle cells do not regenerate and the damage is permanent. This finding opens up the possibility of repairing the heart after a heart attack. (Extramural)

**Adult Stem Cells Become Heart Cells** – demonstrated that adult stem cells isolated from mouse bone marrow could become functioning heart muscle cells when injected into a damaged mouse heart. The new cells at least partially restore the heart's ability to pump blood. (Intramural and Extramural)

**Genome of Deadly E. coli O157:H7 Sequenced** – completed sequencing the genome of the deadly E. coli O157:H7, a bacterium which is becoming a worldwide public health threat through contaminated ground beef, milk, fruits and vegetables. Comparing the sequence of this strain with that of harmless strains of the bacterium will help scientists understand why some forms cause disease, and help in finding ways to detect and prevent harmful strains from spreading and causing disease. (Extramural)

**Rhesus Monkey Genetically Modified** – successfully introduced a new gene into rhesus monkeys. This is the first time that a primate, the group of mammals that includes human beings, has been genetically modified. The accomplishment could lead to the development of new, more relevant animal models that provide insights into a variety of human disorders, including cancer, cystic fibrosis and Alzheimer's disease. (Extramural)

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## 2000

**Working Draft of the Human Genome** – assembled a working draft of the sequence of the entire human genome, the genetic blueprint for a human being. This draft contains overlapping fragments of DNA sequence—the order of the four chemical bases that make up DNA—covering approximately 90 percent of the genome, with some gaps and ambiguities. Sequence information from this public project has been continuously, immediately and freely available with no restrictions on its use or redistribution. Already, many tens of thousands of genes have been identified and dozens of disease genes pinpointed by access to the working draft. The international Human Genome Sequencing consortium responsible for this working draft includes scientists at 16 institutions in the United States, France, Germany, Japan, China, and Great Britain. The project is funded by grants from government agencies and public charities in these various countries. (Intramural and Extramural)

**Stem Cell Transplants Reverse Kidney Cancer** – reversed advanced kidney cancer in some patients using blood stem cell transplants from a healthy sibling. Advanced kidney cancer is often resistant to therapy and is usually fatal in less than a year. Of 19 patients who did not respond to prior therapy, three had total regression of the disease after the stem cell transplantation and seven had partial regression. Although this was a small study with a relatively short follow-up, the high response rate is very encouraging. (Intramural)

**Identified a Gene Associated with Primary Pulmonary Hypertension** – identified a gene, BMPR2, associated with primary pulmonary hypertension (PPH), a rare but devastating lung disease that causes an uncontrolled build-up of cells in blood vessels in the lungs. The resulting blockages in the blood vessels force the heart to pump harder and increase blood pressure. With current treatments, life expectancy for people with PPH is on average less than three years. Now that a gene has been identified, scientists can focus on learning how it works so that they can better devise treatments. (Extramural)

**Identified Ebola Virus Protein** – identified the protein in Ebola virus which causes the massive internal bleeding that kills people with the disease. The protein destroys endothelial cells—the cells that line blood vessel walls. Ebola virus, depending on the strain, can kill up to 90 percent of the people it infects. Now that scientists have found the responsible protein and gained insight into how it works, they can focus on new drugs or vaccines to combat its deadly effects. (Intramural and Extramural)

**Oxidative Stress and Aging** – found that treating the worm *C. elegans* with antioxidants increased the worms' life spans by approximately 44%. Although these worms are far from human, these experiments further a growing body of evidence supporting the theory that oxidative stress plays a major role in aging. (Extramural)

**Found Blood Vessels of Colon Cancers and Normal Colon Tissue are Different** – found differences in the expression of nearly 80 different genes between the blood vessels of human colon cancers and normal colon tissue. This accomplishment gives scientists a host of new targets in their attempts to shut off the growth of the blood vessels that growing tumors in the colon need to survive. (Extramural)

**Identified a Gene that Makes Malaria Resistant to Chloroquine** – identified a gene that makes the malaria parasite resistant to chloroquine, the former mainstay, low-cost anti-malarial drug. Malaria strikes 300 to 500 million people each year, and kills 1 million. Chloroquine has been losing its effectiveness against the parasite, and no alternative approaching its affordability and effectiveness has yet emerged. This gene discovery will help scientists explore ways to overcome the parasite's resistance to chloroquine, and also help them detect chloroquine-resistant parasites in people living in areas where malaria is endemic. (Intramural and Extramural)

**Discovered Pore-like Holes in the Membranes of Malaria Infected Red Blood Cells** – discovered pore-like holes in the membranes of red blood cells infected by the malaria parasite. Made by the parasites, these channels allow them to get extra nutrients from outside the cells to support their explosive growth and multiplication within. Searching for drugs that block this channel may lead to new ways to combat this parasite. (Intramural)

**Sequenced Genome of the Bacteria that Causes Cholera** – determined the complete genomic sequence of the bacteria that causes cholera. Cholera causes severe diarrhea, killing nearly 8,500 people worldwide last year and striking another 223,000. This accomplishment should speed the development of vaccines and drugs to fight the disease. (Extramural)

**Found That the Patterns of Genes Expressed Could Predict Melanomas Progression** – identified several genes that can be used to predict particularly aggressive malignant melanomas. Scientists used gene chips to look at the activity of thousands of genes in 31 different melanomas and seven normal tissue samples. They found that the patterns of genes expressed could predict the melanomas' progression. This discovery will help doctors separate tumors that look the same under the microscope into clinically significant groups. It will also help scientists focus in on new targets for drugs to combat the disease. (Intramural and Extramural)

**Identified the Protein RhoC** – identified a protein called RhoC that can cause metastasis in melanoma cells. Metastasis, the spread of cancer cells to other parts of the body, is perhaps the biggest threat to survival in patients with solid tumors. (Extramural)

**Identified Possible New Targets for TB Treatment** – identified several genes in a bacterium that allow it to persist as a chronic tuberculosis (TB)-like infection in leopard frogs. These bacteria are related to that causing TB in humans, and follow the same pattern of infection as TB when they infect frogs. Two of the genes with very similar counterparts in TB bacteria were found to be necessary for the bacterial infection to persist. They may, therefore, be good targets for new drugs against TB, which kills an estimated 2 million people each year and persists in approximately one-third of the world's population. (Extramural)

**Completed Sequencing the Genome *Drosophila melanogaster*** – completed sequencing the genome of the fruitfly *Drosophila melanogaster*, one of the most intensely studied creatures in biology. Fruitflies are used to study a host of basic biological questions related to aging, development, learning, memory and more. This milestone, which proved the speed and value of a new technique called whole-genome shotgun sequencing, was accomplished through the combined effort of public and private laboratories. (Extramural)

**Demonstrated Two Subtypes of Diffuse Large B-cell Lymphoma** – used microarray technology to show that there are actually two subtypes of diffuse large B-cell lymphoma (DLBCL). Until this work, which used the new technology to look at approximately 1.8 million measurements of gene expression from 96 different samples, scientists had been unable to account for the fact that 40% of DLBCL patients respond well to therapy, yet the remainder succumb to the disease. Microarray technology allows scientists to look at how thousands of genes are expressed at once, a scale previously unimaginable. This is just the first demonstration of a technique that promises to revolutionize cancer diagnosis as well as many other areas of scientific research. (Intramural and Extramural)

**Genetically Modified Hot Pepper Tolerant Mice** – found that mice genetically engineered to remove the receptor that responds to hot peppers developed an amazing tolerance for hot sauce, and surprisingly also showed less sensitivity to other types of pain. The mice tolerated heat better, and their cells weren't as affected by an acidic solution designed to mimic internal inflammation. This hot pepper receptor is an important new potential target molecule for developing drugs for pain relief. (Extramural)

**Showed that the Human Brain is Constantly Growing and Changing Well into Puberty** – created the most detailed maps yet of the developing human brain, using high-resolution three-dimensional magnetic resonance imaging to show that the human brain is constantly growing and changing well into puberty. By repeatedly scanning the brains of children three to 15 years old over a four year period, scientists were able to see huge growth between the ages of three and six in the area of the brain that helps sustain attention and regulates the organization and planning of new actions. Between six and 13, the highest growth rates were in the region specialized for language. Somewhere between 11 and 15, growth in this region slows down, reflecting the difficulty most people have in learning new languages after the age of 12. (Intramural and Extramural)

**Discovered a Mutation that Causes Hypertension** – discovered a mutation that causes one form of early-onset hypertension, a condition that is particularly dangerous during pregnancy. Hypertension during pregnancy raises the risk of pre-eclampsia, which can be fatal for mother and fetus. Identifying women at risk for the condition can help doctors intervene early to prevent it. (Extramural)

**Identified a Protein that Predicts the Risk of a Woman Having a Heart Attack** – identified a protein, C-reactive protein, that predicts the risk of a woman having a heart attack better than cholesterol. It can be detected with a simple, inexpensive blood test. People who know they are at risk for heart attacks can take aggressive steps to try to prevent them. (Extramural)

**Oxygen Can Cut the Rate of Wound Infections in Half** – demonstrated that a simple and inexpensive change in basic surgical procedures—giving patients more oxygen during and immediately after surgery—can cut the rate of wound infections in half, thus saving millions of dollars in hospital costs by helping to prevent post-surgical wound infection, nausea and vomiting. (Extramural)

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## 1995-1999

**Completed Sequence of Human Chromosome 22** – completed first sequence of a human chromosome, chromosome 22. Genes on chromosome 22 have been implicated in immune system function, congenital heart disease, schizophrenia, mental retardation, birth defects, and several cancers, including leukemia. The 33.4 million nucleotides that make up chromosome 22 comprise the longest continuous stretch of DNA ever deciphered. (Extramural)

**Strategy for Preventing Mother to Infant HIV Virus Transmission** – demonstrated an affordable and practical strategy for preventing transmission of the HIV virus from mother to infant. A single oral dose of the antiretroviral drug nevirapine given to an HIV-infected woman in labor and another to her baby within three days of birth reduced the transmission of virus by half compared with a similar short course of AZT. If used in developing countries, this treatment might prevent some 300,000 to 400,000 newborns per year from becoming infected and eventually developing AIDS. (Extramural)

**Cesarean Sections Reduce Risk of HIV Transmission** – the risk of pregnant women infected with HIV transmitting the virus to their infants was reduced by about 50 percent if they delivered by cesarean section before they went into labor and before their membranes ruptured. (Intramural and Extramural)

**Salmonella "Master" Gene** – found "master" gene that makes Salmonella a deadly bacteria. Without the gene for an enzyme called Dam, Salmonella bacteria not only did not kill the mice they were injected into, but also served as a vaccine against future infection by deadly Salmonella. Because Dam is found in many other dangerous bacteria, this discovery opens possibilities for a whole new generation of antibiotics and vaccines against virulent bacteria. (Extramural)

**Sleep Deprivation and the Body** – first demonstration that sleep deprivation may have a harmful effect on the body, not just the mind. The bodies of men whose sleep was severely restricted for one week had characteristics that mimicked some of the hallmarks of aging, including lowered glucose tolerance, which is a risk factor for diabetes, obesity and hypertension; and raised cortisol levels, a condition thought to be involved in insulin resistance and memory problems. The negative effects of sleep deprivation could be corrected by normal sleep. (Extramural)

**Gene Map of Major Histocompatibility Complex** – completed the sequence and gene map of a region essential to the immune system, the human major histocompatibility complex (MHC). The MHC is associated with more diseases than any other region of the human genome. One group of proteins encoded by the genes of the MHC are the markers of self that appear on almost all body cells and thus play a critical role in rejection of organ transplants as well as in autoimmune diseases like rheumatoid arthritis. A second group of proteins which the MHC codes for helps fight foreign invaders like viruses and bacteria. (Extramural)

**Genetic Map of Malaria Parasite** – completed the first high-resolution genetic map of *Plasmodium falciparum*, the deadliest malaria parasite. This accomplishment will help scientists find new targets for improved diagnostic tools, therapies and vaccines. Each year *P. falciparum* malaria affects up to 500 million people worldwide and kills more than 2 million, primarily young children in sub-Saharan Africa. (Intramural and Extramural)

**Women with Preeclampsia** – women with preeclampsia, a potentially fatal complication of pregnancy, were found to have an imbalance of two key chemical compounds that control blood pressure, prostacyclin and thromboxane, months before the symptoms of preeclampsia appeared. The discovery suggests strategies for designing new treatments for the condition. There is currently no cure for preeclampsia. Characterized by high blood pressure, excessive weight gain, headaches and other symptoms, preeclampsia may progress to convulsions and bring about a variety of other birth complications. About 5 percent of first-time mothers develop preeclampsia. (Intramural)

**Link Between Mothers with Hypothyroidism and Lower IQs of Children** – children born to mothers with untreated hypothyroidism during pregnancy were found to score lower on IQ tests than children of healthy mothers, suggesting that early detection and treatment of hypothyroidism in pregnant women may be a critical part of prenatal care. Hypothyroidism is a condition in which the thyroid gland does not produce enough hormone, leading to fatigue and a lack of energy; coarse, brittle hair; thick, coarse skin; and a lowering of the metabolic rate. About 3% of women of childbearing age develop the condition, but hypothyroidism often goes undetected because the women do not yet have obvious physical signs or symptoms. (Extramural)

**Transgenic Mice with Enhanced Memory** – created transgenic mice that showed enhanced performance in six different memory tests. Scientists achieved the result by getting adult mice to express a juvenile form of one brain receptor. This research is a major advance in understanding memory and learning. (Extramural)

**A Single Gene Affects Mice Sociability** – a single gene was found to make laboratory mice more friendly and affectionate toward their cage mates. Receptors for the hormone vasopressin were taken from the sociable prairie vole and put into laboratory mice. When the mice were injected with vasopressin, they became more affectionate. This study is the first to show that even complex social behavior can be radically affected by a single gene. (Extramural)

**Back to Sleep Campaign Reduces Rate of Sudden Infant Death Syndrome** – between 1992 and 1996, the rate of Sudden Infant Death Syndrome (SIDS) dropped by 38 percent. Much of that drop was likely due to a 66 percent decrease during the same period in the number of U.S. infants being placed to sleep on their stomachs. The Back to Sleep Campaign, a national campaign that encourages infants to be placed to sleep on their backs, was launched by NICHD in partnership with several other organizations in 1994. (Intramural and Extramural)

**New Strategy for Treating Cancer** – developed promising new strategy for treating cancer in a mouse model. Rather than directly attacking cancerous cells, which can develop resistance to chemotherapeutic drugs, researchers starved them by targeting drugs to the new blood vessels that nourish the tumors. This method spares other tissues in the body, and proved to be effective in mice. Human trials are currently underway. (Extramural)

**Resetting the Body's Biological Rhythm** – demonstrated that the human circadian clock can be reset by applying light to the back of the knees. Scientists had previously assumed that the body's internal timekeeping clock was set exclusively by light reaching the eyes. This discovery was a surprising step in understanding how the body's biological rhythm is set. (Extramural)

**Nicotine Addiction Molecule Identified** – identified a particular molecule involved in nicotine addiction, a subunit of a known nicotine receptor. Mice lacking this molecule don't self-administer nicotine like normal mice. This discovery uncovers a potential target for developing medications to treat nicotine addiction. (Extramural)

**Lifestyle Modifications Can Control High Blood Pressure** – losing weight and cutting down on salt were found to lessen and sometimes eliminate the need for blood pressure-lowering medications in elderly people with high blood pressure. The study showed that lifestyle modifications can be used to control high blood pressure. About 50 million Americans have high blood pressure, and it is one of the most important risk factors for cardiovascular disease. (Extramural)

**Vitamin E Supplements Reduce Prostate Cancer Incidence** – vitamin E supplements were found to substantially reduce the incidence of prostate cancer and death in male smokers. Men of 50-69 years old who took a moderate dose of vitamin E daily for five to eight years had 32 percent fewer diagnoses of prostate cancer and 41 percent fewer prostate cancer deaths compared to men who did not receive the vitamin. (Extramural)

**Safe Screening for Down Syndrome** – developed a safe and effective method of screening for Down syndrome in the first trimester of pregnancy. Previous methods of screening for fetuses with Down syndrome during the first trimester carried significant risks of miscarriage. (Extramural)

**Edible Vaccine Found Effective** – showed for the first time that an edible vaccine can safely trigger significant immune responses in people. Volunteers developed the responses after eating bite-sized pieces of raw potato that had been genetically engineered to produce part of the toxin secreted by the *Escherichia coli* bacterium, which can cause diarrhea. This accomplishment is a significant milestone on the road to developing inexpensive vaccination programs, and is of particular importance to developing countries. (Extramural)

**Mutations in the Gene MYO15 Can Cause Deafness** – identified mutations in a newly discovered gene, MYO15, that can cause one of the most common forms of inherited deafness, nonsyndromic recessive deafness. Research on a similar protein in mice leads scientists to speculate that MYO15 plays an important role in the functioning of the inner ear hair cells. (Intramural and Extramural)

**Bacterium that Causes Syphilis Sequenced** – sequenced the complete genome of *Treponema pallidum*, the bacterium that causes syphilis. This accomplishment will help advance the development of vaccines and diagnostic tests. Syphilis is a sexually transmitted disease that can cause serious heart abnormalities, mental disorders, blindness, other neurologic problems, and death. (Extramural)

**HIV Surface Protein Resolved** – resolved the three-dimensional structure of gp120, the surface protein that the HIV virus uses to attach itself to immune system cells. The discovery allows scientists to identify important target sites for developing new drugs and vaccines. (Extramural)

**Tamoxifen Lowers Risk of Breast Cancer** – showed that women at high risk of developing breast cancer who took tamoxifen had 49% fewer cases of breast cancer than those who didn't. Tamoxifen was hailed as the first drug to prevent breast cancer in women at high-risk for the disease. Because of the incidence of side effects from the drug, it may be most beneficial for women at high risk for breast cancer. (Extramural)

**New Insights into Chlamydial Infections** – completed the sequence of the *Chlamydia trachomatis* genome, providing new insights into chlamydial infections and ways to combat them. Chlamydia is the most prevalent bacterial sexually transmitted disease in the United States, leading to infertility, tubal pregnancy and chronic pelvic pain. The same bacterium can also infect the eye, causing trachoma, the leading cause of preventable blindness in the developing world. (Extramural)

**Sequenced the Genome of *Caenorhabditis elegans*** – sequenced the complete genome of the tiny roundworm *Caenorhabditis elegans* in 1998, representing the first time that scientists have spelled out the genetic instructions for a complete animal that, like humans, has a nervous system, digests food, and has a sexual reproductive system. (Extramural)

**Three-Dimensional Structure of Tubulin Solved** – three-dimensional structure of the tubulin molecule solved by electron crystallography. Tubulin, a major part of every cell's skeleton, is the target of taxol, a potent anti-cancer drug. Knowing the three-dimensional structure of tubulin will aid attempts to find and design new anti-cancer drugs. (Extramural)

**Identified a Gene that Causes Parkinson's** – identified a defective gene that causes some inherited cases of Parkinson's disease. The discovery provides clues to how nerve cells are killed in the disease and suggests possible new therapeutic strategies. Parkinson's disease, characterized by trembling and a loss of muscular control, afflicts about 500,000 people in the United States. (Intramural and Extramural)

**Identified Gene Which Controls Circadian Rhythms** – identified the Clock gene, which controls circadian rhythm in mammals. Biological clocks are disturbed in problems ranging from jet lag to manic depressive illness. (Extramural)

**Basic Aspects of Brain Organization Can Change** – discovered that people blind from birth actually rewire their brains to use the primary "visual" areas of the cerebral cortex to read Braille. This discovery shows that even basic aspects of brain organization can change, at least in the very young. (Intramural and Extramural)

**Applied Functional Magnetic Resonance Imaging** – pinpointed the area of the brain involved in seeing and storing working, short-term memories of a face or a series of letters. A time course of brain activity was observed for the first time with high resolution using an advanced technology called functional magnetic resonance imaging (fMRI). (Extramural)

**Laser Capture Microdissection (LCM) Technique** – developed the laser capture microdissection (LCM) technique, which allows scientists for the first time to pinpoint and remove targets as small as one cell from a sample without damaging either the target or the surrounding tissue. Earlier extraction methods either fragmented the sampled cells or destroyed the surrounding tissues. The precision of LCM is invaluable in analyzing cells from patients with diseases such as cancer. (Intramural)

**New Target for Anti-Malarial Therapies** – identified the protein that causes red blood cells to clump together and block blood flow during an infection by the malaria parasite. This discovery provides a new target for anti-malarial therapies. Malaria is one of the most serious and complex health problems facing humanity in the 20th century. Worldwide, between 300 and 500 million people are infected and between 1.5 and 2.7 million die of malaria each year. (Intramural and Extramural)

**Discovered a Gene Involved in Age-Related Macular Degeneration** – discovered a gene, STGD1, involved in age-related macular degeneration, the leading cause of blindness in older Americans. The scientists found mutations in this gene in 16 percent of the 167 cases of age-related macular degeneration they studied. (Intramural and Extramural)

**Glaucoma Genes Identified** – genes for two different forms of glaucoma, juvenile angle glaucoma and primary congenital glaucoma, identified. These discoveries advance the understanding of the causes of glaucoma and may lead to early detection and improved treatments. Glaucoma, a condition where pressure builds up in the eye and damages the optic nerve, blinds almost 12,000 people in the United States each year, and accounts for 15% of blindness worldwide. (Extramural)–complete sequence of *Escherichia coli* genome published. *E. coli* is a laboratory workhorse with a long and rich history, and was the largest and most complex bacterial genome to be completely sequenced at the time (1997). This accomplishment gives researchers a powerful new tool for understanding fundamental questions of biological evolution and function. (Extramural)

**Low Fat Diet Reduces Blood Pressure** – nationwide "Dietary Approaches to Stop Hypertension" (DASH) trial showed that a diet low in fat and high in vegetable, fruit, and low fat dairy foods significantly and quickly lowered blood pressure. A DASH diet could reduce some people's need for medication to control their hypertension. High blood pressure affects about one in four Americans, and can lead to coronary heart disease and strokes. (Extramural)

**Werner's Syndrome Gene Identified** – identified the gene which causes Werner's syndrome, a rare and ultimately fatal genetic disease with symptoms resembling premature aging. People with Werner's syndrome get gray hair, lose elasticity in their skin, and develop cataracts while in their twenties, and most die before age 50. They can also develop several age-related diseases at a young age, including atherosclerosis, cancer, diabetes, and osteoporosis. Scientists think that the genetic defect causing Werner's syndrome allows DNA damage to accumulate, thus leading to the premature development of age-related diseases. This discovery is important not only for understanding the biological processes involved in aging, but also in understanding the array of rare tumors and other age-related diseases associated with Werner's syndrome. (Extramural)

**New Strategies for Combating AIDS** – identified two key molecules on the surface of immune cells that the HIV-1 virus needs in order to enter immune cells and begin its attack. People with two mutant copies of one of these molecules were found to resist HIV infection. These findings suggest new strategies for combating AIDS. (Intramural and Extramural)

**Mutated Gene Predisposes Men to Prostate Cancer** – identified a gene, HPC1, that when mutated predisposes men to prostate cancer. The researchers estimate that 1 in 500 men have an altered version of this gene, and that it is responsible for at least a third of familial prostate cancer. (Extramural)

**Biological Link Between Cigarette Smoking and Lung Cancer Found** – found the first direct biological link between cigarette smoking and lung cancer. DNA mutations caused by the cigarette smoke byproduct benzo[a]pyrene in the tumor suppressor gene p53 were found to be the same as those found in lung cancer cells. Scientists have long associated cigarette smoking with lung cancer, but this discovery uncovers the molecular basis for how smoking leads to lung cancer. (Extramural)

**Inherited Epilepsy Gene** – identified mutations in a gene that lead to an inherited form of epilepsy. While inherited epilepsy is rare, understanding how the defects in this gene lead to epilepsy may give scientists insight into how epilepsy develops in other people. Epilepsy is estimated to affect more than 2.5 million Americans, about 1 percent of the population. (Extramural)

**Completed DNA Sequence of Brewer's Yeast** – DNA sequence completed of the brewer's yeast *Saccharomyces cerevisiae*, a simple model system for understanding complex problems in cell biology. This was the largest genome to be completely sequenced at the time (1996), and will aid greatly in the analysis of yeast genes and their products. (Extramural)

**Cerebellum and Sensory Input** – discovered that the cerebellum is involved in perceiving sensory input, challenging the prevailing view that it serves only in controlling muscles. (Extramural)

**Protease Inhibitors Prolong Lives of AIDS Patients** – a new class of anti-HIV drugs called protease inhibitors shown to help significantly prolong the lives of AIDS patients. NIH-supported basic research paved the way for the development of this new class of drugs, from discovering the HIV protease enzyme to determining its three-dimensional structure in order to design drugs to block its action, to conducting drug-screening efforts and clinical trials. (Extramural)

**Drug t-PA1 Approved After a 5-Year Clinical Trial Funded by NINDS** – a 5-year clinical trial funded by NINDS led to a rapid decision by the Food and Drug Administration (FDA) to approve the clot-dissolving drug t-PA1 for the emergency treatment of stroke. Those treated with t-PA1 within 3 hours of their initial stroke symptoms were at least 30 percent more likely than untreated patients to recover from their stroke with little or no disability. (Extramural)

**Progestin Counteract Estrogen's Deleterious Effects** – "PEPI" trial changed the course of hormone replacement therapy (HRT) for postmenopausal women. The study found that including progestin in HRT substantially reduced the increased risk of cancer of the endometrium (lining of the uterus) associated with taking estrogen alone. HRT is used to counteract the symptoms many women experience as their body adjusts to the fall in their body's estrogen levels during menopause: hot flashes and flushes, sweats, sleep disturbances and an increased rate of bone loss that may result in osteoporosis and bone fractures. Progestin seems to counteract estrogen's deleterious effect on the uterus by preventing overgrowth of the endometrial lining. (Intramural and Extramural)

**Cancer Mortality Rate Falls** – the cancer mortality rate fell nearly 3 percent between 1991 and 1995, the first sustained decline since national record keeping started in the 1930's.

**Robust Telomerase Activity Detected in Human Tumors** – an "immortality" enzyme, telomerase, was found to be active in many types of cancers, but is not generally detectable in cells that age and die normally. Telomerase is thought to reverse the cell's aging process. Bestowing immortality on the cell, however, leads to the uncontrolled growth that characterizes tumors. This robust telomerase activity has been detected in 80-90% of human tumors, providing important insight into the events that lead to cancer. (Extramural)

**Zidovudine (AZT) Found to Reduce the Risk of HIV Transmission From Mother to Infant** – treating HIV-infected pregnant women and their newborns with zidovudine (AZT) was found to reduce the risk of HIV transmission from mother to infant by approximately two thirds. Maternal-infant transmission is the primary means by which young children become infected with HIV. This finding opened the door to a major preventive effort. (Extramural)

**"Obese" Gene Discovered** – discovered the obese gene, which causes gross obesity in mice when not produced properly, along with its human counterpart. The protein for which obese codes, leptin, is now the subject of clinical trials attempting to combat human obesity. (Extramural)

**Gene Involved in Usher Syndrome Discovered** – first discovery of a gene involved in Usher syndrome (US), the most common cause of combined hearing and vision problems in the United States. More than half of the estimated 16,000 people in this country who are deaf and blind are believed to have US. People with this form of Usher Syndrome, Type 1B, are profoundly deaf from birth and have severe balance problems. They often begin to develop vision problems by the time they are ten, and tend to progress rapidly until they are completely blind. This discovery is a major step forward in understanding the causes of Usher Syndrome and pinpointing potential targets for therapy. (Extramural)

**Gene Responsible for Ataxia Telangiectasia (A-T) Discovered** – discovery of the gene and mutations responsible for ataxia telangiectasia (A-T), a complex inherited childhood disorder characterized by weakened muscle control, a sensitivity to x rays, an unusually high risk of diabetes, lung infections, dilated blood vessels in the eyes and other parts of the face, and a predisposition to many different types of cancer. People with A-T usually die of respiratory failure or cancer by their early twenties. Researchers are particularly interested in A-T because it affects so many different systems in the body. The A-T protein was found to communicate with the tumor suppressor gene p53, which normally helps to halt cell growth and allow DNA damage to be repaired. Scientists believe it also communicates with other important proteins in the cell. (Intramural and Extramural)

**Overwhelming Success in Treatment for Sickle Cell Anemia** – a clinical trial of treatment for sickle cell anemia was halted early due to its overwhelming success. Daily administration of the drug hydroxyurea reduced the frequency of painful episodes and related hospital visits by about 50%; reduced the frequency of acute chest syndrome, a life-threatening complication of sickle cell anemia characterized by chest pain, fever, prostration, and an abnormal chest X-ray; and reduced the number of blood transfusions for patients in the study. Sickle cell anemia is an often fatal disease that affects millions throughout the world. Approximately 2 million Americans carry the sickle cell trait, and about 72,000 are affected by the disease. (Intramural and Extramural)

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## 1990-1994

**Two Breast Cancer Susceptibility Genes Identified** – identified two breast cancer susceptibility genes, BRCA1 and BRCA2, that together account for up to 70% of all hereditary breast cancers (between 5% and 10% of all breast cancer is hereditary). Mutations in BRCA1 and BRCA2 have also been implicated in ovarian cancers, and BRCA2 mutations have now been associated with increased risks of cancers of the prostate, pancreas, gallbladder, bile duct, and stomach as well as malignant melanoma. (Extramural and Intramural)

**Genes Involved in Colon Cancers Identified** – identified four genes that may be involved in over 13% of colon cancers. These genes code for proteins engaged in DNA "mismatch repair", a form of genetic spell-checking. Once scientists linked one mismatch repair protein to human colon cancer, previous research using bacteria pointed them to the other three human genes. (Extramural and Intramural)

**Primary Gene Responsible for Kidney Cancer Identified** – identified the gene responsible for the most common type of kidney cancer, sporadic (nonfamilial) clear cell carcinoma, which accounts for about 85 % of all kidney cancers. This gene had been previously identified as the cause of the inherited cancer syndrome von Hippel-Lindau (VHL) disease, which leads to tumors in the adrenal glands, the kidneys, the pancreas, and parts of the nervous system including the brain, eye and spinal cord. (Intramural)

**Mutations in p53 Lead to Tumor Formation** – discovered the most frequently mutated gene in human cancer, which codes for the p53 protein. This protein acts like an emergency brake in the cell cycle. Mutations in p53 lead to uncontrolled cell growth and tumor formation. (Extramural)

**The First Trial of Gene Therapy in Humans** – first trial of gene therapy in humans, in which infusions of genetically altered cells were used to treat adenosine deaminase deficiency, a rare genetic disease that cripples the immune system. (Intramural)

**Discovered the Gene Involved in Fragile X Syndrome** – discovered the gene involved in fragile X syndrome, the most common inherited form of mental retardation in males. In 1980s, discovered the fragile X syndrome. (Extramural)

**Effective Treatment for Rheumatoid Arthritis** – proved the safety and effectiveness of methotrexate for treating rheumatoid arthritis and juvenile rheumatoid arthritis. (Extramural)

**Osteoarthritis Gene** – found for the first time a gene that causes a form of osteoarthritis. (Extramural)

**Effective Treatment for Lupus** – determined an effective treatment for lupus kidney disease. This work has been going on since the 1970s. (Intramural)

**Estrogen and Bone Loss** – determined mechanisms by which estrogen is effective against bone loss. (Extramural)

**Three-Dimensional Structure of Myosin** – determined the three-dimensional structure of myosin, a protein critical to generating force and motion in nearly all living things. (Extramural)

**New Methods for Growing Skin** – developed new methods for growing sheets of skin to treat people with burns and blistering diseases. (Extramural)

**Determined the Gene Responsible for Ichthyosis** – determined the gene and structural defect in the skin responsible for a form of ichthyosis. (Intramural and extramural)

**Control of Glucose Levels and Diabetes** – showed that tight control of blood glucose levels effectively delays the onset and slows the progression of long-term diabetes complications including diabetic retinopathy, nephropathy, and neuropathy in patients with insulin-dependent diabetes. (Extramural)

**Cholesterol Reduction and Heart Disease** – showed that people who already have some form of heart disease can benefit from cholesterol reduction. (Extramural and National Cholesterol Education Program; work also done during the 1980s but became clear in the 1990s)

**Familial Hypercholesterolemia** – discovered and characterized the genetic abnormality of a second form of familial hypercholesterolemia. (Extramural)

**First Effective Treatment for Spinal Cord Injury** – demonstrated the first effective treatment for spinal cord injury. Patients treated with methylprednisolone within the first 8 hours of a spinal cord injury recovered more motor and sensory function than patients who did not receive this drug. (Extramural)

**Drug Treatment for Parkinson's Disease** – found a new drug that, when added to the standard levodopa/carbidopa treatment, prolongs by more than 60 percent the relief of symptoms in patients with Parkinson's disease. (Intramural)

**Valium Reduces Risk of Seizures in Infants** – found that valium, given at times of fever, safely reduces the risk of febrile seizure recurrences in infants and children. (Extramural)

**New Drug for Epilepsy** – helped to develop a major new drug for epilepsy, felbamate, that is safe at high doses and does not have side effects commonly associated with other antiepileptic drugs. (Intramural)

**Alzheimer's Risks** – showed that the gene dose of apolipoprotein E type 4 is a major risk factor for late-onset Alzheimer's disease. (Extramural)

**Bone Mass in Children and Calcium** – discovered that a calcium intake by children that is higher than the recommended daily allowance significantly increased their gain in bone mass. (Extramural)

**Drug Treatment for Stroke Prevention** – found that drug treatment can help prevent strokes in older people with isolated systolic hypertension. (Extramural)

**Treatment with Aspirin Lowers Risk of Heart Attack** – showed that treatment with aspirin or warfarin dramatically lowers the risk of stroke in patients with atrial fibrillation. Widespread application of this finding could result in prevention of 20,000 to 30,000 strokes per year in the United States. (Extramural)

**Taxol** – developed taxol as a therapy for ovarian and breast cancer. (Extramural; also during the late 1980s)

**Advances in Cancer Treatment** – supported the development of limb-sparing surgery for cancer patients and lumpectomy plus radiation rather than mastectomy for breast cancer. (Extramural; this work has been done since the 1970s.)

**Developed Methods of Hypertension Control** – developed and disseminated methods of hypertension control. In 1972, based on scientific evidence of the importance of detecting and treating hypertension, NHLBI established the National High Blood Pressure Education Program. During the term of the program, deaths due to stroke declined by more than 57 percent and deaths due to heart attacks declined by about 50 percent. The association of these dramatic declines with the NHLBI program suggests that the hypertension research and education efforts of NHLBI have contributed substantially to a major advance in the nation's health. (This effort has been under way since 1970s.)

**CMV Retinitis Treatment** – improved treatment for CMV retinitis, a potentially blinding retinal disease that affects about one of every four people with AIDS. (Intramural and extramural)

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## 1980s

**Gene Transfer in Humans** – first transfer of a foreign gene into humans. (Intramural)

**Cystic Fibrosis Gene Identified** – identified the cystic fibrosis gene, thus allowing for improved diagnosis and early treatment. This discovery also laid the groundwork for attempts to cure the disease through gene therapy. (Extramural)

**Drug Treatment for HIV** – identification of the first drug to show any efficacy against HIV in laboratory tests and the first administration of the drug to a patient with AIDS. (Intramural)

**Treatment for Wegener's Disease** – development of successful treatments for several formerly fatal diseases – such as Wegener's granulomatosis – that are characterized by inflammation of the walls of blood vessels. (Intramural; work started in 1970s)

**Provided Evidence for Other Forms of Hepatitis** – provided indisputable evidence that 90% of post-transfusion hepatitis still being seen after development of the screening test for hepatitis B was due to one or more previously unrecognized human hepatitis viruses. Showed that the first of these, the hepatitis C virus, was a transmissible agent. (Intramural)

**Antibody Receptor Structure Determined** – determined the complete structure of the IgE receptor that is involved in triggering allergic reactions. (Intramural)

**Demonstrated Acyclovir Safe for Herpes Treatment**–demonstrated that continual use of the antiviral drug acyclovir was safe and effective in preventing recurrences of oral and genital herpes infections. (Intramural)

**Estrogen and Bone Loss** – proved the effectiveness of estrogen replacement for stopping the bone loss of osteoporosis. (Extramural)

**Verified DES Exposure Related to Reproductive Abnormalities** – developed a mouse model that verified the relationship between prenatal exposure to diethylstilbestrol (DES) and reproductive tract abnormalities in male and female children of mothers who were prescribed the drug during pregnancy. (Intramural)

**New Treatment for Diabetic Complications** – determined the sequence of reactions triggered by the enzyme aldose reductase (AR) that underlie the development of diabetic complications such as sugar cataracts and nerve damage. This finding resulted in studies of AR inhibitors as a new treatment for these problems. (Intramural)

**Developed New Oral Contraceptives** – developed a long-acting androgen contraceptive, as well as safer and more effective short- and long-acting estrogens and progestogens for oral contraceptives. (Extramural; the estrogen work was done in late 1980s and early 1990s)

**EPO to Correct Anemia** – used recombinant erythropoietin to correct anemia in patients with end-stage renal disease. (Extramural)

**Cholesterol's Role in Heart Disease** – discovered cholesterol's role in heart disease and the effects of lowering cholesterol. Discovery of the LDL receptor and the regulation of cholesterol metabolism. (Extramural; Nobel prize in 1985)

**Proved That Lowering Cholesterol Reduces the Risk of Heart Disease** – provided the first definitive proof in humans that lowering blood cholesterol reduces the risk of coronary heart disease. The study showed that dietary restriction of cholesterol and fat along with a cholesterol-lowering drug reduced cholesterol levels and caused a 19 percent reduction in definite coronary heart disease death or nonfatal heart attacks. Moreover, the degree of reduction in coronary heart disease risk was found to be related to the degree of cholesterol lowering, with a 2-percent reduction in risk observed for every 1-percent reduction in serum cholesterol. (Extramural)

**Guidelines on Cholesterol Screening** – provided the guidelines for physicians on cholesterol screening and, in the 1990s, for the public on how to lower their cholesterol levels.

**Pioneered the Angiographic Studies** – pioneered the angiographic studies that showed that decreasing one's cholesterol levels does slow the progression of fatty deposits and can shrink them in the coronary arteries. (Extramural)

**Revised Current Understandings of Coronary Lesions** – revised the understanding of which coronary lesions are really important in angiography by showing that lipid-rich plaques can be more dangerous than advanced lesions and that these dangerous lesions can be treated through cholesterol reduction methods. (Extramural; also during the 1990s)

**Studies on Estrogen and Heart Attacks** – conducted observational studies that showed that women who took estrogen supplementation had a markedly reduced death rate from heart attacks. (Extramural)

**Surfactant** – developed a surfactant to prevent or treat respiratory distress syndrome. (Extramural)

**Developed New Technology for Making Vaccines** – developed the new conjugate technology for making vaccines and developed one for *H. influenzae* type b that is effective in infants. (Intramural)

**Chemotherapy and Leukemia** – developed supportive treatments for patients with leukemia who are prone to infections after chemotherapy. (Extramural and Intramural; also during the 1970s)

**New Therapies for Sickle Cell Disease** – conducted studies of sickle cell disease leading to the development of clinically useful therapies to elevate fetal hemoglobin as a treatment for sickle cell and thalassemia syndromes. (Intramural; work done since the 1960s)

**Retinal Cell Transplantation** – helped to establish the scientific basis for retinal cell transplantation that could have huge treatment ramifications for blinding diseases such as macular degeneration and retinitis pigmentosa. (Extramural)

**Therapy for Protecting the Vision of Premature Infants** – showed that briefly freezing the outer part of the retina with a probe can protect the vision of many premature infants with retinopathy of prematurity. This research could save the Federal government as much as \$20 million annually. (Extramural)

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## 1970s

**Genetic Origin of Cancer** – discovered that oncogenes have normal cellular functions, thus laying the cornerstone for understanding the genetic origin of cancer and widening the insight into the complicated signal systems that govern the normal growth of cells. (Extramural; Nobel prize in 1989)

**First Successful Cure for Childhood Leukemia** – development of the first successful cure for a childhood cancer (leukemia). This played a major role in establishing chemotherapy as a standard cancer treatment. (Intramural; work was done during the 1950s and 1960s)

**Discovered Lyme Disease** – discovered Lyme disease and developed treatment for it. (Extramural and intramural)

**Treatment for Psoriasis** – developed a treatment (PUVA) for the skin disorder psoriasis. (Extramural)

**Identified Agents of Various Infectious Diseases** – identified or isolated the agents responsible for a number of infectious diseases including hepatitis A and intestinal infections, particularly infant diarrhea. (Intramural)

**Normal Aging Versus Disease** – established the importance of distinguishing between the normal processes of aging and the changes produced by diseases in later life. Also, developed the ability to make such distinctions. (Intramural; this work continues through today.)

**Described Hormone Interactions During Menstruation** – provided the first comprehensive description of the sequence of hormonal interactions during the menstrual cycle. This laid the foundation for modern reproductive endocrinology and new approaches to contraception and infertility. (Intramural)

**Home Pregnancy Tests** – developed the assay for human chorionic gonadotropin that evolved into the home pregnancy tests. (Intramural)

**Developed a Microassay for Thyroid Hormone** – developed a microassay for thyroid hormone that made simultaneous screening of newborns for both congenital hypothyroidism and PKU possible. Studies showed the effectiveness of this screening and thyroid hormone replacement in preventing mental retardation; screening for both disorders is now mandatory in all 50 states. (Extramural; also during early 1980s)

**Demonstrated Efficacy of Amniocentesis** – demonstrated the safety and accuracy of prenatal diagnosis of congenital disorders associated with mental retardation by means of amniocentesis. (Extramural)

**Role of Asbestos in Cancer** – elucidated the role of asbestos in cancer especially when smoking is a risk factor. (Intramural and extramural)

**Identified Carcinogens in Tobacco Smoke** – identified the specific carcinogens in tobacco smoke and their mechanisms of action, as well as the hazards of smokeless tobacco. (Intramural and extramural)

**Testicular Cancer Cure** – discovery of cisplatin as a cure for testicular cancer. (Extramural)

**Laser Surgery an Effective Treatment for Diabetic Retinopathy** – established laser surgery as a safe and effective treatment for diabetic retinopathy. It is estimated that laser surgery for this disease will save the Federal government up to \$2.8 million over the next 20 years. (Extramural)

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## 1960s

**Demonstrated Laboratory Protein Synthesis** – demonstrated that the information required to fold the polypeptide chain of ribonuclease into the specific three-dimensional form of the active enzyme resides in the sequence of amino acids. Thus it became clear that this protein could be synthesized in the laboratory by joining the proper amino acids in the correct order and allowing the chain of amino acids to spontaneously fold. (Intramural; Nobel prize in 1972)

**Discovered of a New Mechanism for Infectious Diseases** – recognized the first human slow virus disease, kuru, which is a degenerative, fatal infection of the central nervous system. This discovery of a new mechanism for infectious diseases revolutionized thinking in microbiology and neurology. (Intramural; Nobel prize in 1976)

**Cracked the Genetic Code** – cracked the genetic code, deciphering how nature uses the order of DNA bases to produce proteins that determine the nature and characteristics of all living things. (Nobel prize in 1968) This has led to major advances in our understanding of genes and their roles in health and disease as well as to revolutionary new ways to treat or prevent diseases through the use of recombinant DNA technology (the development of which was supported by NIH) and gene therapy (which was first done by NIH intramural scientists).

**Advanced the Understanding of Brain Chemistry** – defined the mechanisms that regulate noradrenaline, one of the most important neurotransmitters in the brain. This discovery provided a clearer understanding of the chemistry of the brain and its effect on human behavior, which, in turn, has led to the development of better drugs for treating mental disorders. (Intramural; Nobel prize in 1970)

**Discovered Surface Antigen of the Hepatitis B Virus** – discovered the Australian antigen, later identified as the surface antigen of the hepatitis B virus and principal diagnostic indicator of serum hepatitis. This led to a test to screen donated blood for the presence of hepatitis B, greatly reducing the risk of transfusion hepatitis. (Intramural and extramural; Nobel prize in 1976)

**Developed Rubella Vaccine** – developed the first licensed rubella vaccine and the first test for rubella antibodies that was practical for large scale testing (rubella hemagglutination inhibition test). (Intramural)

**Hodgkin's Lymphoma** – discovered an effective combination drug therapy for Hodgkin's lymphoma. (Intramural)

**Tooth Decay is Caused by Bacteria** – discovered that tooth decay is caused by bacteria. (Intramural)

**Effectiveness of Using Lights for Jaundice in Newborns** – clarified the safety and effectiveness of using lights rather than exchange transfusion for jaundice in newborn infants. (Extramural)

**Effectiveness of Neonatal Screening for PKU** – documented the effectiveness of neonatal screening and dietary restriction in preventing mental retardation due to phenylketonuria. (Extramural)

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## 1950s

– first complete removal and successful replacement of a patient's diseased mitral valve with an artificial one, which was developed at NIH. (Intramural)

– identified or isolated a number of agents responsible for respiratory infections ranging from croup to pneumonia. (Intramural)

– discovered the cure for choriocarcinoma. (Intramural)

– created a system of mouse plasma cell tumors that made possible the development in 1975 of hybridomas, cells that produce monoclonal antibodies. These antibodies have revolutionized biomedical research. (Intramural)

– discovered that low levels of fluoride in drinking water could prevent tooth decay. This work began in the 1930s, continued through the 1940s and culminated in the 1950s. (Intramural)

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## 1887-1950

The list of NIH research advances, 1887-1950, was compiled by Victoria A. Harden and Harriet Greenwald. Selected portions were published as "Timeline of NIH Discoveries, 1887-1929," in NIH Alumni Association newsletter, *Update 2* (Winter 1990): 8-11; and "Timeline of NIH Discoveries, 1930-1940," in *ibid.* 4 (Winter 1992): 9-11. For further information email: [history@nih.gov](mailto:history@nih.gov)

**1950** Earl Stadtman of NHI discovered phosphotransacetylase, elucidating the role of acetyl CoA in fatty acid metabolism.

**1950** Roger M. Cole and Byron J. Olson in collaboration with Veterans Administration physicians conducted epidemiologic studies of army veterans, reaffirmed the preponderance of sarcoidosis in blacks in the U.S. and implicated a rural southern birthplace of both black and white patients as a predominant association with this disease--the etiology of which is still unclear.

**1950** Bernard (Steve) Brodie of NHI published a paper on procaine that was illustrative of the "new pharmacology"--a rational introduction of biochemistry and organic chemistry in the analysis of drug metabolism and disposition.

**1950** Dorland J. Davis and Margaret Pittman identified the causative organism (Koch-Weeks bacillus) of epidemic bacterial conjunctivitis. Known as *Hemophilus aegyptius*, it occurs in warm climates only during the breeding seasons of the gnat (or the "eye" fly). They found that zinc sulfate and streptomycin were curative.

**1950** Robert W. Berliner of NHI conducted work on renal physiology that led to a new theory concerning the mechanism of urinary excretion and concentration.

**1950's** Seymour S. Kety at NIMH conducted pioneer cerebral blood flow experiments that revealed metabolic activity of the brain.

**1949-50** NIH started the Heart Disease Epidemiology study at Framingham, Massachusetts, which became a population laboratory for research on life style factors in the development of cardiovascular diseases. This ongoing study has provided a basis for heart disease prevention programs. It gave the world the term "risk factors" to describe behaviors or conditions that increase the chance of disease.

**1940-57** Ben D. Chinn, Leon Jacobs, Lucy V. Reardon, Charles W. Rees, and Bruce Phillips in the Laboratory of Tropical Diseases developed techniques for cultivating *Entamoeba histolytica*, in standardized culture media.

**late 1940's- early 1950's** In the microsomes of rabbits' livers, Julius Axelrod discovered a new class of enzymes, cytochrome-P450 monooxygenases, which exerted a profound influence in many areas of research, including studies of the metabolism of normally occurring compounds and investigations of carcinogenesis.

**Late 1940's- early 1950's** Extensive research on enzymes was carried out by Arthur Kornberg, Leon Heppel, Herbert Tabor, Jesse Greenstein, Alton Meister, Herbert Sober and their colleagues. The work of Arthur Kornberg laid the groundwork for his later important discoveries on the synthesis of DNA, for which he was awarded the Nobel Prize in 1959.

**1940's-50's** Bernard Horecker and colleagues elucidated the reactions of the pentose phosphate pathway.

**1940's-50's** Chester Emmons first pointed out reservoirs of histoplasmosis in soil and bats (1948), of coccidioidomycosis in soil (1942), and of cryptococcosi in soil and pigeon droppings (1951). These findings were crucial to understanding the sources of infection by these pathogenic fungi so that patients could be tested and treated.

**1940's** The nutrition group, including W. Henry Sebrell, Floyd Daft, James Hundley, Harris Isbell, Arthur Kornberg, and others published reports identifying a blood abnormality due to folic acid deficiency, the adrenal degeneration resulting from pantothenic acid deficiency, and the differentiation between liver necrosis and liver cirrhosis.

**1949** Louis Olivier performed controlled studies on the role of hypersensitivity in schistosome dermatitis, demonstrating that lesions increase with repeated exposure to larvae of avian schistosomes.

**1947-48** Henry Kaplan showed the origin of lymphoid tumors in irradiated mice.

**1947** Jesse P. Greenstein of NCI summed up 20 years of research in his book, *Biochemistry of Cancer*. The work analyzed and synthesized what was known at the time about oncologic biochemistry.

**1946** The Research Grants Office was created at NIH in January to administer the Office of Scientific Research and Development projects transferred to the Public Health Service at the end of World War II and to operate a program of extramural research grants and fellowship awards.

**1946** Margaret Pittman revised the formula medium for the sterility testing of biologic products. It is now used worldwide.

**1946** In a period of 8 months, Robert J. Huebner, William L. Jellison, and their colleagues elucidated a new disease, rickettsialpox, in cooperation with New York State health authorities. They described the disease, its etiological agent, its reservoir in mice, and its vector, a rodent mite.

**1946** Lloyd Law of NCI introduced the L1210 murine leukemia cell line tumor used in the cancer drug screening program.

**1945-1950's** Everette May and colleagues working with Lyndon Small's medicinal chemistry group, synthesized phenazocine, a non-addicting substitute for morphine.

**1945** W. Ray Bryan, Michael B. Shimkin, Howard B. Andervont, Herbert Kahler and Thelma B. Dunn published the first NCI monograph, Mammary Tumors in Mice, which showed that the mouse breast cancer "agent" was a filterable virus.

**1945** Ralph Wyckoff and Robley William introduced the shadowing of electron microscope specimens with heavy metal specimens to accentuate their contrast.

**1945** Karl Habel cultivated mumps virus in embryonated eggs and devised serological tests for its presence.

**1945** Frederick J. Brady and colleagues pioneered the use of radioisotopes in pharmacology, especially to identify the sites of activity of drugs in animals infected with filariid parasites.

**1943** Harold W. Chalkley devised a method that now bears his name for the quantitative morphologic analysis of tissues.

**1943** Margaret Pittman began work on the intracerebral challenge potency assay for pertussis vaccine. The standardization effected within 5 years a tenfold drop in pertussis infant mortality in the U.S.

**1943** Glenn H. Algire, using the transparent-chamber technique, demonstrated a method for making microscopic studies in vivo to view tumor growth in the mouse.

**1943** Wilton R. Earle of NCI, who had in the 1930's pioneered the process of growing cells in culture, published a classic paper describing the production of malignancy in vitro. Katherine K. Sanford of Earle's group developed the first clone from an isolated cancer cell. Virginia J. Evans also devised a medium that supported growth of cells from many tissues of different animals.

**1943** Sanford M. Rosenthal, Herbert Tabor, R. Carl Millican, and Kehl Markley demonstrated that shock in burn patients can be treated by a salt and soda solution administered orally.

**1942** A classic manual describing and illustrating the stages of the malaria parasites was prepared by Aimee Wilcox and Inez Demonet.

**1942** Chester Emmons first pointed out reservoirs of coccidiomycosis in bats.

**1942** Francis Arnold introduced the Syrian hamster as a suitable animal model for the study of dental caries research.

**1942** "Louisiana pneumonitis," a human disease possibly related to psittacosis, was discovered and studied in great detail by Bryan J. Olson, Carl Larson, Waldo L. Treuting and George Fite.

**1942** Karl Habel succeeded in passaging a rubella virus isolate through chick embryos and monkeys, providing an animal model to study the growth of the virus and the disease it caused.

**1942** Lloyd Felton, utilizing pneumococcal polysaccharides, demonstrated a phenomenon known as "immunological paralysis" or immune tolerance.

**1942** Willard H. Wright, Eloise Cram, Walter L. Newton, and colleagues launched research that helped eliminate parasitic eggs and cysts from public water supplies.

**1941-45** During World War II, research at NIH included the development of an oxygen-supply apparatus to prevent pilot death when airplanes climbed too rapidly. This work was done collaboratively with the U.S. Navy in NIH laboratories.

Studies were conducted at NIH on the effects of radiation related to the development of the atom bomb. Studies were also conducted on the nature of wound healing.

NIH tested clothes for the military. Willard H. Wright impregnated DDT into clothing as a protection against lice.

Roderick Murray and J. T. Tripp supervised the first program on blood and blood products to establish standards for an uncontaminated blood supply. John Oliphant and Alexander Hollaender later designed an apparatus in which serum or plasma could be irradiated to destroy hepatitis virus so that it could be safely used.

**1941** Floyd C. Turner published data showing the induction in rats of sarcomas by subcutaneously implanted bakelite disks.

**1941** Harold L. Stewart and Egon Lorenz demonstrated by chemical carcinogenesis the induction of adenocarcinoma of the glandular stomach of mice, which was the first demonstration of cancer induction by chemicals in any species of laboratory animal.

**1941** Dean Cowie and Leonard Scheele's survey of procedures used in handling and storing radium loaned to hospitals led to recommendations that exposure doses should be lower.

**1941** Jonathan L. Hartwell published a Survey of Compounds Which Have Been Tested For Carcinogenic Activity, the first of a series of surveys and indices for investigators concerned with chemical carcinogens.

**1938-41** G. Robert Coatney and Martin D. Young described the differing characteristics of infections caused by strains of malaria parasites obtained from different places around the world. Different strains of the malarial parasite can cause infections with different pathology.

**1941** Ida A. Bengtson and Norman Topping developed a complement fixation test for diagnosis of rickettsial diseases.

**1940-42** Walter E. Heston demonstrated the genetic susceptibility of mice to spontaneous pulmonary tumors. This led to his findings via transplantation of the site of gene action being in the tissue itself.

**1940** Karl Habel produced an improved, killed rabies vaccine that eliminated foreign brain tissue that had caused paralysis in some patients.

**1939-40** Hugh G. Grady and Harold L. Stewart first identified the type II cell of the pulmonary alveolus as the cell of origin of the common alveogenic tumours of the lungs of mice.

**1930's** Jerald G. Wooley and W. Henry Sebrell developed the first satisfactory diets for experimental rabbits and investigated the connection between nutrition and infection by studying the pneumococcus-infected mice that were deficient in thiamine and riboflavin.

**1930's** Howard B. Andervont's research at NCI increased understanding of genetic factors in mammary, hepatic and pulmonary tumors in mice.

**1939** Margaret Pittman showed that sulfapyradine was effective against nontype-specific *Haemophilus influenzae*.

**1930's** Margaret Pittman extended investigations on potency requirements for *Haemophilus influenzae* antiserum and diagnosis requirements of the six capsular types.

**1930's** Sanford M. Rosenthal developed a treatment for mercury poisoning used widely before the advent of dimercaptoethanol.

**1930's-40's** Two of Claude Hudson's many contributions to carbohydrate chemistry: 1) he showed that mutarotation of natural glucose in water was subject to general acid-base catalysis; 2) he developed a "lactone rule," noting that the optical rotatory sign of an aldonic acid lactone was controlled by the configuration of the carbon bearing the hydroxyl group involved in the ring closure.

**1938-40** Charles W. Rees developed a micromanipulator that permitted microscopic handling of amoebic cysts as well as other organisms.

**1939** Louis Schwartz and H. R. Foerster described industrial dermatitis and melanosis due to photosensitization.

**1939** Charles Armstrong adapted the Lansing strain of poliomyelitis to cotton rats and then to laboratory mice, thus providing investigators with an inexpensive experimental animal for polio studies.

**1938-50** John Bozicevich developed immunological methods for the diagnosis of helminth parasitic infections.

**1938-40** Murray J. Shear of NCI reported that a basic fraction of creosote oil enhanced the production of mouse tumors. He termed this fraction to be a source of a "cocarcinogen."

**1938** W. Henry Sebrell and Roy F. Butler published the first clinical description of ariboflavinosis, a human riboflavin deficiency.

**1938** Gordon E. Davis and Herald R. Cox identified a new rickettsial disease, which they called Nine Mile Fever. Rolla E. Dyer first showed the relationship of the organism to that of Australian Q Fever, and its identity was subsequently confirmed by the complement-fixation and vaccine studies of Ida E. Bengtson.

**1938** Herald R. Cox discovered that rickettsiae could be cultivated successfully in the yolk-sacs of chick embryos. During World War II, all rickettsial vaccines were produced by this method.

**1937-41** Harold L. Stewart and Howard B. Andervont first described the pathology and proper histological classification of the adenomatous lesion of the glandular stomach of strain I mice, which was important to the understanding of carcinogenesis.

**1937-38** Henry Klein, Carroll E. Palmer, John W. Knutson devised a DMF (Decayed Missing Filled) Index guide that became the standard epidemiological tool for studies and surveys of children's dental status.

**1938** Margaret Pittman showed that the precipitin reaction around meningococcus colonies on immune serum agar plates was directly correlated with the mouse potency assay of each lot of antiserum.

**1937** Margaret Pittman, Sara E. Branham, and E. M. Sockrider showed the type specificity of meningococcus by use of the Petrie's precipitin test.

**1937** Maurice C. Hall developed a technique, known as the "NIH swab," to diagnose enterobiasis; it is still the accepted technique.

**1937** Maurice C. Hall, Willard H. Wright and colleagues launched a series of studies that demonstrated the extent of human trichinosis in the United States and contributed to methods for its control.

**1937** Sanford M. Rosenthal, Hugo Bauer and Sara E. Branham began pioneering work on the sulfonamides and their application to humans in the treatment of bacterial infections.

**1936-40** Maurice I. Smith, Ralph D. Lillie, and Benton B. Westfall reported on the toxicology, pathology and metabolism of selenium.

**1935** Lawrence Kolb reported a series of studies on innovative treatment for drug addicts who were patients in the PHS Hospital in Lexington, Kentucky.

**1934** Ida A. Bengtson began standardization of antitoxin for six species of *Clostridium* which cause gas gangrene.

**1934** Charles Armstrong and Ralph D. Lillie identified the lymphocytic choriomeningitis virus that caused a disease, commonly termed "Armstrong's disease," in house mice and in humans exposed to infected mice.

**1933** Louis Schwartz, F.C. Makepeace, and H. Trendley Dean published findings showing the hazardous effects of radium dial painting.

**1932** A section on heart disease supervised by Arthur M. Stimson began to study the causes of rheumatic fever. It signaled the first involvement of NIH with heart disease.

**1931** H. Trendley Dean and Elias Elvove started work on the mystery of "mottled enamel" -- later called fluorosis. During the next 10 years, aided by Frank McClure and Francis Arnold, they laid the basis for the controlled use of fluoride to prevent cavities.

**1931** Rolla E. Dyer, Lucius F. Badger, and Adolph S. Rumreich demonstrated that Rocky Mountain spotted fever existed on the eastern seaboard of the United States and that endemic (murine) typhus was transmitted by rat fleas.

**1930** Maurice I. Smith, Elias Elvove and their collaborators discovered the cause of "Jamaican Ginger" paralysis.

**1930** Sara E. Branham identified a new organism, *Neisseria flavescens*, as a rare cause of meningitis and septicemia in humans, but one requiring careful differentiation from meningococcus. In 1970 she was honored posthumously by the name of a new genus, *Branhamella*.

**1930** Maurice I. Smith developed a quantitative colorimetric reaction for the ergot alkaloids.

**1930** Ralph Lillie demonstrated that the cause of psittacosis was a rickettsia-like organism (later placed in the genus *Chlamydia*) instead of a virus. The research of his colleague Charles Armstrong on the disease resulted in governmental regulation of the importation of psittacine birds.

**1920s** Ida A. Bengtson and Charles Armstrong worked on the problems of food poisoning and botulism as a result of improperly canned foods. Their work contributed to better and safer methods of canning.

**1920s** Lawrence Kolb conducted early studies on narcotic addiction and its relationship to crime and personality. In association with Albert C. Dumez, he was able to produce morphine and heroin dependence in monkeys.

**1920s** Lewis R. Thompson worked on problems of industrial health and contributed a series of well-known monographs on the health of workers subject to lung diseases from workplace dust.

**1920s** Carl Voegtlin, who was in charge of cancer research at the Hygienic Laboratory, conducted early studies on the biochemistry of cancerous and normal tissue. He also investigated the effects of nutrients--protein, riboflavin and biotin--on liver tumors in rats. These studies were among the earliest on the relationship between nutritional factors and cancer.

**1928** William Mansfield Clark published a summary of his classic work during the decade on oxidation-reduction systems.

**1926** James P. Leake wrote the authoritative study on the multiple pressure method of vaccination for smallpox.

**1926** Kenneth F. Maxcy identified an "endemic" form of typhus fever in the southeastern United States and suggested that some parasite of the rat might be its vector.

**1925** Carl Voegtlin described much of the pharmacology of arsphenamine and related arsenicals.

**1925** Rolla E. Dyer defined the unit for scarlet fever streptococcus antitoxin.

**1925** Charles Armstrong showed that 25% of commercial bunion pads commonly used to cover smallpox vaccinations were contaminated with tetanus spores. His recommendations that such dressings be abandoned saved lives and stimulated the development of the multiple pressure method of vaccination.

**1925** Joseph W. Schereschewsky, head of a PHS Special Cancer Investigations Laboratory established in 1922 in Cambridge, Massachusetts (in cooperation with Harvard University Medical School), published a statistical review of cancer death figures in the United States, 1900-1920, which increased interest in cancer research.

**1924** Roscoe R. Spencer and Ralph R. Parker produced a vaccine against Rocky Mountain spotted fever, the first human vaccine prepared from the bodies of arthropod vectors.

**1923** Atherton Seidell developed a physiological test for the activity of vitamin preparations.

**1923** William Mansfield Clark alerted the public to the dangers of tetraethyl lead in gasoline, and further field studies, conducted by James P. Leake, set the standards for the safe level of lead in gasoline.

**1922** Ida A. Bengtson discovered a new variety of *Clostridium botulinum*. This strain was designated as type "C."

**1919** Edward Francis extended the earlier observations on tularemia. His other studies, continued into the 1920s, clarified the nature of the agent, its distribution in animals, the role of ticks and deer flies as vectors and the routes of infection in man. The bacterium was later named *Francisella tularensis* in his honor.

**1918** Alice C. Evans described the organism that caused undulant fever. Her work hastened the pasteurization of milk in the United States. She also initiated the collection and study of streptococci and their bacteriophages.

**1917** Mather H. Neill discovered that scrotal reactions of guinea pigs with "Mexican" typhus (later known as murine typhus) could be used as a differential test with "European," or epidemic, typhus. It was first known as the Neill phenomenon (later called the Neill-Mooser phenomenon after Neill and Herman Mooser, a Swiss pathologist working in Mexico).

**1916-1918** During World War I, work by Hygienic Laboratory investigators changed the way smallpox vaccinations were administered to soldiers. They also found that shaving brushes were a source of anthrax and tetanus infections, and production methods were changed.

**1915** Edward Francis improved the method for embalming, which was of great importance for intrastate shipping of bodies.

**1914** Walter L. Treadway conducted first Hygienic Laboratory survey on mental health studying the role of public and private agencies in ministering to social needs. He continued over the next fifteen years to do surveys on mental health and other problems.

**1914** Joseph Goldberger identified pellagra as a nutritional deficiency disease.

**1913-1919** Earle B. Phelps in the Division of Chemistry conducted a series of studies on water pollution and the biochemistry of sewage and industrial wastes which had far reaching importance for pure water.

**1911-1914** George W. McCoy, Charles W. Chapin, William B. Wherry, and B. H. Lamb elucidated a new disease, tularemia.

**1911** John F. Anderson and Joseph Goldberger first transmitted measles (rubeola) to monkeys by contact.

**1911** John F. Anderson and Wade H. Frost provided the first laboratory evidence of polio infection in persons with non-paralytic disease. This paper was followed by other studies and field investigation in the Hygienic Laboratory on poliomyelitis.

**1910** Joseph H. Kastle described the oxidases and other oxygen-catalysts concerned in biological oxidations.

**1910** John F. Anderson and Wade H. Frost extended earlier studies on hypersensitivity and used for the first time the word "allergen" in reference to allergic antibodies.

**1910** William H. Schultz described the contraction of the isolated strip of sensitized guinea pig ileum when suspended in a bath of physiological solution and challenged by specific corresponding antigen. This reaction became known as the Schultz-Dale phenomenon (the "Dale" from the similar work of English physiologist and pharmacologist Sir Henry H. Dale).

**1909** George W. McCoy published a report on 99 neoplasms found in 100,000 rats examined in the plaque control investigation in California. This was the first involvement of the Hygienic Laboratory in cancer research.

**1909** John F. Anderson and Joseph Goldberger confirmed Charles Nicolle's finding that the body louse was the vector of epidemic typhus fever. They were the first to transmit typhus by direct inoculation of the organisms into experimental animals.

**1908-1911** John F. Anderson, Leslie L. Lumsen and Wade H. Frost expanded scope of earlier typhoid studies and results of their investigations into stream pollution, milk standards, and water purity became classic examples of epidemiological methods and training.

**1908** George W. McCoy first demonstrated that rodents were a reservoir of bubonic plague.

**1908** Arthur M. Stimson developed a better method for rabies vaccine preparation so it could be sent more safely and thus be more widely distributed.

**1908** Milton J. Rosenau and John F. Anderson established the standard unit for tetanus antitoxin.

**1907** Joseph H. Kastle and other workers in the Division of Chemistry designed a "hemoglobinometer" to measure hemoglobin in blood. An advance over techniques then in use, it became the standard method for several decades.

**1907** Reid Hunt described the toxic effects of methyl and ethyl alcohols.

**1907** Joseph H. Kastle developed a reagent for the recognition and estimation of free hydrochloric acid in gastric contents. The reagent he identified became known as "Kastle's reagent."

**1906** Milton J. Rosenau, Leslie L. Lumsen, Joseph H. Kastle and other Hygienic Laboratory workers conducted an epochal investigation on the origin and prevalence of typhoid fever in the District of Columbia which became the catalyst for later, broader epidemiological studies.

**1906** Reid Hunt discovered the hypotensive effects of acetylcholine.

**1906** Milton J. Rosenau and John F. Anderson published a pioneering study on anaphylaxis.

**1906** Walter W. King showed the transmission of Rocky Mountain spotted fever by infected ticks to guinea pigs.

**1905** Milton J. Rosenau established the standard for diphtheria antitoxin.

**1905** Reid Hunt demonstrated the presence of thyroid hormone in the blood and introduced the acetonitril test for thyroid.

**1902-03** Julius O. Cobb and John F. Anderson initiated first Hygienic Laboratory studies on Rocky Mountain spotted fever (RMSF). Their works launched forty-five years of research on RMSF.

**1902** Charles Wardell Stiles identified the hookworm as the cause of anemia in the southern U.S. Although this discovery was made a few months before he joined the Hygienic Laboratory, his subsequent work on hookworm over the next two decades helped to eliminate it as a problem in the South.

**1890s** Joseph J. Kinyoun designed the Kinyoun-Francis Sterilizer, a shipboard disinfectant apparatus used effectively for quarantine procedures.

**1895** Joseph J. Kinyoun launched production of diphtheria antitoxin at the Hygienic Laboratory, one of the first places it was produced in the United States.

**1887** Laboratory of Hygiene founded. Director Joseph J. Kinyoun made the first laboratory diagnosis of cholera in the western hemisphere.

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