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Rush Limbaugh
The Rush Limbaugh Show
1270 Avenue of the Americas
New York, NY 10020

Dear Mr. Limbaugh,

I heard your accusations about Michael J. Fox and his appearance in a campaign advertisement for a candidate in favor of stem cell research. As the co-founder of the Congressional Working Group on Parkinson's Disease, I took offense to your comments, and I sincerely hope that such uninformed statements about people suffering from Parkinson's will not be repeated on your show.

I hope you will take this as an opportunity to learn more about Parkinson's Disease, its debilitating effects and the research being conducted to find a cure. To that end, I have enclosed a primer by the National Institutes of Health's National Institute of Neurological Disorders and Stroke entitled *Parkinson's Disease: Challenges, Progress, and Promise*. It is highly informative, and I hope you will take the time to read it.

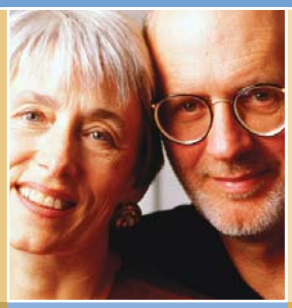
As you deliberate the stem cell research issue in the future, I hope you will consider that it represents serious hope for those afflicted by Parkinson's, as well as a number of other life-changing diseases. Michael J. Fox's message was an important one, and it deserves serious attention, not ridicule.

I thank you for your attention to the enclosed report, and I would be happy to answer any further questions you may have.

Sincerely,

Carolyn B. Maloney

CAROLYN B. MALONEY
Member of Congress



Parkinson's Disease:

Challenges, Progress, and Promise

NOVEMBER 2004

National Institute of
Neurological Disorders
and Stroke

National Institutes of Health

Contents

Margaret,

a woman in her thirties,...

...began to experience tremors and stiffness of her left arm while she walked. When these symptoms continued, she saw several neurologists to determine what was going on. Because she was young, the doctors initially thought she might have a brain tumor or multiple sclerosis. However, after a brain scan and neurological examinations, she was diagnosed with Parkinson's disease.

Margaret did not take any medications for the disease until several years after her diagnosis. She then began medication that reduced her symptoms but did not stop the disease from getting worse. She eventually developed involuntary movements called dyskinesias, which are a common side effect of levodopa, the most common Parkinson's drug. Because of this, she decided to undergo a new therapy called deep brain stimulation (DBS), which provides electrical stimulation to the brain through surgically implanted wires. The DBS immediately reduced the amount of levodopa Margaret needed to take, which stopped the dyskinesias. The stimulation has since been adjusted externally many times in order to improve control of her symptoms. While Margaret still takes medication, she needs fewer pills than before the DBS.

Now, almost 25 years after her diagnosis, Margaret is able to function very well in the morning and early afternoon. Late in the day, however, problems with balance, speech, and fatigue return. She manages by planning her activities carefully, avoiding many commitments during the late afternoon and evening, and increasing her medication when necessary.

Joel,

a retired university professor,...

...went for regular walks with his wife. Ten years ago, his wife began to notice that he was shuffling his feet and was not swinging his arms as most people do while walking. She also noticed some changes in his posture and unusual movements of his left arm. Joel's primary doctor referred him to a neurologist, who told him he had Parkinson's disease and prescribed a combination of drugs to treat the symptoms. He later saw a movement disorder specialist as well.

Joel's symptoms have gradually grown worse with time. He now has tremors and rigidity of movements on both sides of his body, and balance problems when his medication wears off. The disease also makes it difficult to project his voice. He takes a combination of drugs that help him to walk and to perform daily tasks. However, he can no longer work in the woodworking shop he had developed as a retirement hobby. His loss of mobility and speech impairment limit his social interactions. He and his wife also have had to give up many of their retirement travel plans.

Joel and Margaret are two of the many people in the United States who are living with Parkinson's disease (PD), a complex disorder of the central nervous system. PD is the second most common neurodegenerative disease in the United States, after Alzheimer's disease. The defining characteristics of PD include tremor, slowness of movement (bradykinesia), rigidity, and impaired balance and coordination. As these symptoms become more pronounced, patients may have difficulty walking, talking, or completing simple tasks. They also may experience depression, difficulty sleeping, and other problems.

Introduction

Ever since PD was first described in 1817, scientists have pursued the causes and treatment of the disease. In the early 1960s, scientists identified the primary problem underlying the disease: the loss of brain cells that produce a chemical called dopamine, which helps to coordinate and control muscle activity. This discovery led to the first successful treatment for PD and suggested ways of devising new and even more effective therapies. Parkinson's research continues to be a very active field, with new and intriguing findings reported every day.

Research suggests that PD affects at least 500,000 people in the United States, and some estimates are much higher. Society pays an enormous price for PD. The total cost to the nation is estimated to exceed $6 billion annually. The financial and public health impact of this disease is expected to increase as the population ages.

In recent years, Parkinson's research has advanced to the point that halting the progression of PD, restoring lost function, and even preventing the disease are all considered realistic goals. However, we cannot yet cure any major neurodegenerative disorder, and defeating PD remains a significant challenge.

The National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), has a long history of support for PD research. In 1997, recognizing the need to accelerate the pace of PD research, Congress signed the Morris K. Udall Parkinson's Disease Research Act into law. The Udall Act directed the NIH to expand and coordinate Parkinson's research with the purpose of finding a cure or treatment for this disease, and to award Core Center Grants — designated as Morris K. Udall Centers of Excellence for Parkinson's Disease (PD) Research — to encourage complementary research and to provide training for scientists undertaking PD research.

The Udall Centers of Excellence have embarked on diverse research avenues, but they all share a common goal: scientific research to improve the diagnosis and treatment of patients with PD and related neurodegenerative disorders and to gain a better understanding of the fundamental cause(s) of the disease. These centers, along with many other labs funded by the NIH, have made substantial progress in understanding PD. Some highlights of this research include the discovery and characterization of several genes linked to familial PD; the expansion of research on potential environmental factors that may underlie PD; and studies of potential new therapies, including growth factor administration, drug therapy, and deep brain stimulation.

As part of its mission to reduce the burden of neurological disease, NINDS is committed to expanding translational research – studies that translate or develop promising findings in basic research into effective treatments in the clinic. PD research is considered prime territory for translation because exciting new discoveries in basic science have accelerated our understanding of the disease over the past few years. The Institute is supporting three coordinated programs to encourage translational research projects that focus on PD and other neurological disorders. These programs provide tools and resources for therapy development, support work necessary to begin clinical testing, and offer career development and training experience for investigators interested in translational research.

The NIH conducts a vigorous and expanding program of research focused on PD. In 2000, the agency convened a workshop to create an agenda for PD research. The attendees included intramural, extramural, and industry scientists; representatives from several Parkinson's advocacy groups; and ethicists. They developed an agenda that comprises four major areas: understanding PD, developing new treatments, creating new research capabilities, and enhancing the research process.

The PD research agenda is also relevant for other diseases. PD research can lead the way in the fight against all forms of neurodegeneration, and research on other types of neuro-degeneration also can provide vital clues about how PD may be cured.

As part of the implementation process for the PD research agenda, NIH convened a summit with several outstanding scientists in July 2002 to gain a better sense of where the field of PD research stands internationally and to collect information on "roadblocks" that impede progress. This meeting led to a set of recommendations that were compiled into a matrix (see p. 4) of short-to-long range and low-to-high risk action items in order to address some of these roadblocks. The matrix identifies goals that can help to advance PD research and places them within a general time frame of when progress might reasonably be expected. This matrix helps to guide research planning at NIH, but is also designed as a tool for the entire PD community. It includes important responsibilities for voluntary and private funding organizations, and will lead to opportunities for collaboration with other government agencies and the international community as well. This matrix is intended to be a living document that can be revised and expanded as current goals are achieved and new goals are identified.

Twelve different NIH Institutes and Centers fund research on PD, including the National Institute of Neurological Disorders and Stroke, National Institute on Aging, National Institute of Mental Health, National Institute of Environmental Health Sciences, National Human Genome

Research Institute, National Institute on Deafness and Other Communication Disorders, National Institute of Nursing Research, National Institute on Drug Abuse, National Institute of Biomedical Imaging and Bioengineering, National Institute of Child Health and Human Development, National Center for Complementary and Alternative Medicine, and National Center for Research Resources. Representatives from each of these Institutes, as well as from the Department of Defense and the Department of Veterans Affairs, meet twice a year under the leadership of NINDS to discuss research and initiatives for PD, to plan meetings and workshops, and to coordinate research efforts across federal agencies. This committee is called the Parkinson's Disease Coordinating Committee (PDCC). Parkinson's is a multifaceted disease, and each of these Institutes brings a valuable perspective to confronting the biological complexities of the disorder, to pursuing the diverse therapeutic strategies showing promise, and to providing the resources necessary to carry out a research agenda of this breadth.

The NINDS also tracks PD research conducted in other countries. This worldwide tracking activity helps researchers identify potential areas for international collaboration and reduces the chance of duplicated activities.

This report serves to highlight and update the substantial progress made in PD research during the past 5 years. While the report highlights the work of the Udall Centers, many contributions have been made by other NINDS grantees and researchers around the world.

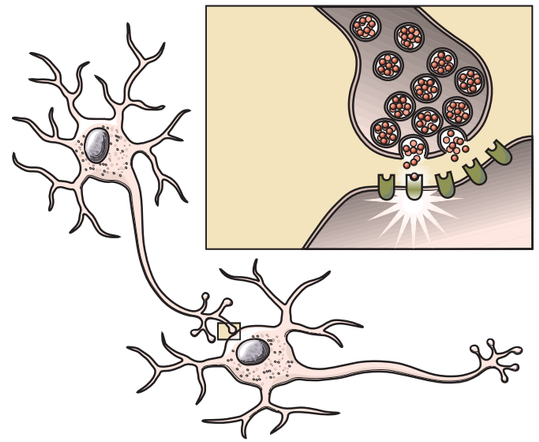
Parkinson's Disease Research Community Goals Matrix

	Short Term (0-3 years)	Medium Term (4-6 years)	Long Term (7-10 years)
High Risk	• Understanding Gene/Environment Interactions • Biomarker Development	• General Roadblocks to Advancing PD Research	• Translational Research/ Therapeutics Development
Medium Risk	• Core Facilities and Resources • Integration of PD Research Centers • Public-Private Partnerships • Gene Discovery • Translational Research/Therapeutics Development		
Low Risk	• Core Facilities and Resources • General Resources – Gene Therapy Resources – Animal Models – Brain Banks • Integration of PD Research Centers • Public-Private Partnerships • Basic Cell Biology Research • General Roadblocks to Advancing PD Research • Understanding Gene/Environment Interactions	• Core Facilities and Resources • Brain Banks • Clinical Trials of Non-motor Symptoms	

1. Brain and Movement: The Basics

When a person initiates a movement, information from the senses, from parts of the brain that control planning, and from other brain regions travels to a region called the striatum. The striatum then interacts with other areas of the brain — the substantia nigra, globus pallidus, and thalamus — to send out signals that control balance and coordination. These signals travel to the cerebellum, which controls muscle coordination, and then finally down the spinal cord to peripheral nerves in the limbs, head, and torso, where they control the muscles.

The molecules that carry information through the brain and spinal cord are called neurotransmitters. Neurotransmitters are special chemicals produced by neurons that accumulate in tiny sacs at the end of nerve fibers. When stimulated, these sacs release neurotransmitters into the gap between neurons, called a synapse. The neurotransmitters cross the synapse and attach to proteins called receptors on the neighboring cell. These signals change the properties of the receiving cell. If the receiving cell is also a neuron, it will carry the signal on to the next cell. If the receiving cell is a muscle fiber, it will react to the stimulation by contracting, which creates movement.



Neurons transmit signals across tiny spaces called synapses. Signaling chemicals called neurotransmitters are gathered into sacs called synaptic vesicles. When the nerve receives a signal, these sacs release their neurotransmitters into the synapse. Proteins called receptors, found on the receiving neuron, bind to the neurotransmitters and trigger a new nerve impulse.

2. What Goes Wrong In Parkinson's Disease?

The primary area of the brain that is affected by PD is the substantia nigra. It contains a specialized set of neurons that send signals in the form of a neurotransmitter called dopamine. The signals travel to the striatum via long fibers called axons. The activity of this pathway controls normal movements of the body.

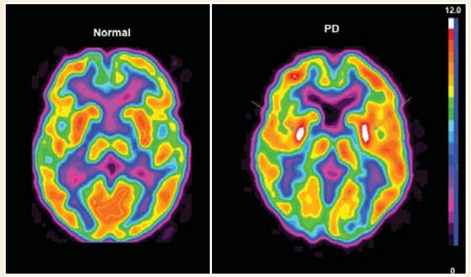
When neurons in the substantia nigra degenerate, the resulting loss of dopamine causes the nerve cells of the striatum to fire excessively. This makes it impossible for people to control their movements, leading to the primary motor symptoms of PD. Many Parkinson's patients eventually lose 80 percent or more of their dopamine-producing cells.

While the neurons' underlying cause of death remains uncertain, researchers have identified several cellular characteristics that are common in this disease and which appear to play a role in the neuronal degeneration. Chief among these characteristics is the presence of Lewy bodies in neurons of the substantia nigra, the brainstem, and other parts of the brain. Lewy bodies are dense clumps, or aggregates, of proteins.

Another cellular characteristic of PD is the presence of Lewy neurites – swollen nerve fibers containing alpha-synuclein and other proteins. The accumulation of alpha-synuclein in these nerve fibers may interfere with transmission of nerve signals or other important neuronal functions.

PD is a devastating and complex disease that interferes with movement more and more as time goes on. It also produces a wide range of other problems for patients. Symptoms of the disease vary somewhat, but they may include problems with swallowing and chewing, speech impairments, urinary problems or constipation, excessive sweating and other skin problems, depression and other emotional changes, and difficulties with sleep. No one can predict which of these symptoms will affect a particular patient, and the intensity of the symptoms varies from person to person. None of these secondary symptoms is fatal, although swallowing problems can cause choking.

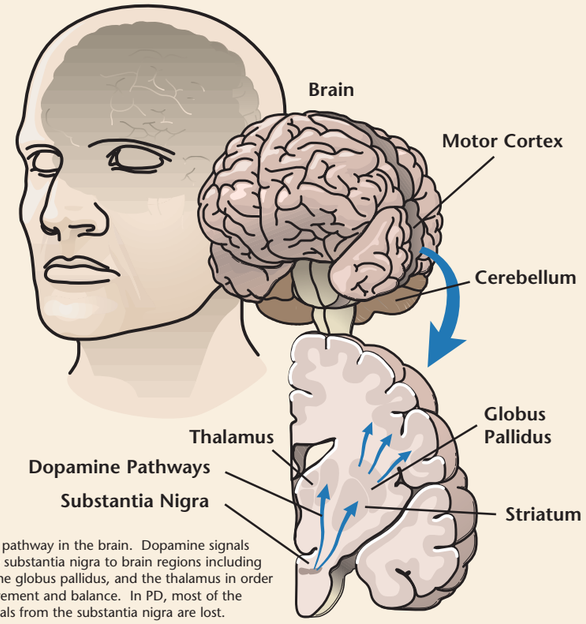
The progression of symptoms in PD may take 20 years or more. In some people, however, the disease progresses much more quickly. To the right is one commonly used system for describing how the symptoms of PD progress.



PET images from a normal volunteer (left) and a PD patient (right). The increased uptake of glucose in the striatum (arrows) of the PD subject, compared to the normal subject, is evident. Cortical glucose uptake is otherwise similar in the two subjects. The color scale on the right shows the cerebral glucose metabolic rate, which reflects the amount of brain activity. [Credit: David Eidelberg, M.D., The Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY]

Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS). This much more complicated scale has multiple ratings that measure mental functioning, behavior, and mood; activities of daily living; and motor function. Both the Hoehn and Yahr scale and the UPDRS are used to measure how individuals are faring and how much treatments are helping them.

Diagnosing PD is dependent on clinical observations. There are currently no blood or laboratory tests that have been proven to help in diagnosing this disease.



The dopamine pathway in the brain. Dopamine signals travel from the substantia nigra to brain regions including the striatum, the globus pallidus, and the thalamus in order to control movement and balance. In PD, most of the dopamine signals from the substantia nigra are lost.

Hoehn and Yahr Staging of Parkinson's Disease

Stage one	• Signs and symptoms on one side only • Symptoms mild • Symptoms inconvenient but not disabling	• Usually presents with tremor of one limb • Friends have noticed changes in posture, locomotion and facial expression
Stage two	• Symptoms are bilateral • Minimal disability • Posture and gait affected	
Stage three	• Significant slowing of body movements • Early impairment of equilibrium on walking or standing	• Generalized dysfunction that is moderately severe
Stage four	• Severe symptoms • Can still walk to a limited extent • Rigidity and bradykinesia	• No longer able to live alone • Tremor may be less than earlier stages
Stage five	• Cachectic stage • Invalidism complete • Cannot stand or walk	• Requires constant nursing care

3. How Can We Treat Parkinson's Disease?

There are currently two main types of treatment for PD: drug treatments and surgery.

Drug Treatments

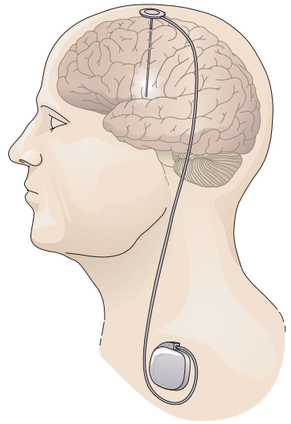
Medications for PD fall into three categories. The first category includes drugs that work directly or indirectly to increase the level of dopamine in the brain. People cannot simply take dopamine pills because dopamine does not easily pass through blood vessels into the brain. The most common drugs for PD are dopamine precursors – substances such as levodopa that cross the blood-brain barrier and are then changed into dopamine. Other drugs mimic dopamine, prevent or slow its breakdown, or increase the amount of it that is released.

The second category of PD drugs affects other neurotransmitters in the body in order to ease some of the symptoms of the disease. For example, anticholinergic drugs decrease the activity of the neurotransmitter acetylcholine. These drugs help to reduce tremors and muscle stiffness, which can result from having more acetylcholine than dopamine.

The third category of drugs prescribed for PD includes medications that help control the non-motor symptoms of the disease. For example, people with PD-related depression may be prescribed antidepressants.

Surgical Treatments

At present, there are two commonly used surgical treatments for PD: pallidotomy and deep brain stimulation. Because these procedures are invasive, they are usually reserved for severely afflicted Parkinson's patients who do not get adequate relief from medications.



One surgical treatment for PD is called deep brain stimulation (DBS). DBS can be performed on either one side (unilateral) or both sides of the body (bilateral). In bilateral DBS, electrodes are implanted in the subthalamic nucleus or the globus pallidus of the brain. Insulated wires are then passed under the skin of the head, neck, and shoulder to connect the electrodes to battery-operated neurostimulators that are implanted under the skin, usually near the collarbones. Impulses from the neurostimulators interfere with and block the brain signals that cause PD symptoms.

Brain surgery was one of the first treatments for PD. Surgeons discovered that, by removing or destroying parts of the brain that were "misfiring," some of the symptoms of PD could be alleviated. The most common early brain operations for PD were pallidotomy, which destroyed part of the globus pallidus, and thalamotomy, which destroyed part of the thalamus. These procedures were irreversible and often led to complications. Clinicians have improved these techniques a great deal, but while they are much safer now, they are still irreversible.

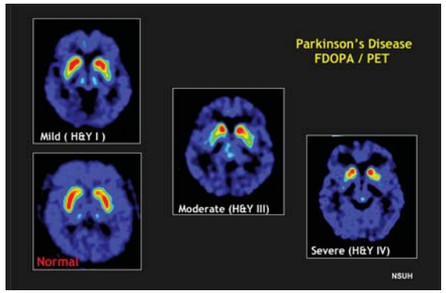
In recent years, scientists have found that they can mimic the effects of pallidotomy and thalamotomy by deep brain stimulation (DBS). With DBS, an electrode is implanted in the brain in a way that calms the abnormal neuronal firing. This procedure is much safer than pallidotomy or thalamotomy because the electrodes can be turned off if the patient

Deep Brain Stimulation

For many years, the only surgical treatments for PD were pallidotomy and thalamotomy – procedures in which surgeons selectively destroy small portions of the brain in order to relieve tremor and rigidity. The tissue destruction is irreversible. Because these procedures often led to troubling side effects, surgery was largely replaced with drug therapy once levodopa became available for PD in the 1960s.

In the 1980s, researchers in France discovered that chronic stimulation (now termed deep brain stimulation or DBS) of a brain region called the thalamus could block tremors in patients with essential tremor. Studies in a monkey model for PD also revealed the brain circuits that are altered in this disease and pointed to a brain region called the subthalamic nucleus as a key target. This discovery opened the door to a new era of surgical treatments. Investigators then examined the effects of stimulating the subthalamic nucleus in patients with PD and found that the stimulation had profound effects on patients' tremor, slowness, and stiffness. In DBS, electrodes are implanted into the brain and connected to a small electrical device called a pulse generator that can be externally programmed. DBS reduces the need for levodopa and related drugs, which in turn decreases the involuntary movements called dyskinesias that are a common side effect of levodopa. It also helps to alleviate fluctuations of symptoms and to reduce tremors, slowness of movements, and gait problems. Unlike pallidotomy and thalamotomy, DBS is reversible. However, it requires careful programming of the stimulator device in order to work correctly.

DBS has now been approved by the U.S. Food and Drug Administration, and it is widely used as a treatment for PD. It also is used to treat dystonia and essential tremor, and it is being tested for disorders such as Tourette syndrome, epilepsy, and depression. Researchers are continuing to study DBS and to develop ways of improving it. They are conducting clinical studies to determine the best part of the brain to receive stimulation and to determine the long-term effects of this therapy. They also are working to improve the technology available for DBS.



PET brain scan images from a normal control subject and three patients at different stages of PD. The images exhibit a progressive decline of dopamine uptake in the brain's striatum with increasing disease severity. H&Y is the Hoehn and Yahr scale reflecting the clinical severity of the disease. [Credit: David Eidelberg, M.D., The Institute for Medical Research, North Shore-Long Island Jewish Health System, Manhasset, NY]

experiences problems. The stimulation also can be adjusted to match the patient's needs. Because of this, DBS is now the primary surgical intervention for PD. In 1997, the U.S. Food and Drug Administration (FDA) approved DBS for the treatment of essential tremor using a single implanted electrode on one side of the brain. In January 2002, the FDA approved DBS for PD using two implanted electrodes — one on each side of the brain. Recently, the FDA also approved a technologically advanced electrode apparatus that can be controlled by the patient through use of a remote control device.

Complementary and Supportive Therapies

A wide variety of complementary and supportive therapies may be used for PD. Among these therapies are standard rehabilitation techniques, which can help with problems such as gait and voice disorders, tremors and rigidity, and cognitive decline. Exercise may help people improve their mobility. Physical therapy or muscle-strengthening exercises may tone muscles and put underused and rigid muscles through a full range of motion. Exercise cannot stop disease progression, but it may improve body strength so that the person can better cope with his or her disability. Researchers are studying whether exercise also may improve the response to levodopa and/or increase levels of beneficial compounds called neurotrophic factors in the brain. Targeted exercises also may improve balance, help people overcome gait problems, and strengthen certain muscles so that people can speak and swallow better. Although structured exercise programs help many patients, more general physical activity, such as walking, gardening, swimming, and using exercise machines, is also beneficial.

Some early reports suggested that dietary supplements may be protective in PD. In addition, a phase II clinical trial of a supplement called coenzyme Q10 suggested that large doses of this substance can slow disease progression in patients with early-stage PD. The NINDS and the National Center for Complementary and Alternative Medicine (NCCAM) are funding research to determine if folate, coffee, dietary antioxidants, fat, alcohol, and/or dairy products are beneficial. While there is currently no evidence that any specific dietary factor is beneficial in PD, a normal, healthy diet can promote overall well-being for PD patients just as it would for anyone else.

Other complementary therapies that are used by some individuals with PD include massage therapy, yoga, tai chi, acupuncture, ginkgo biloba (for concentration problems), and the Alexander technique, which optimizes posture and muscle activity. There have been limited studies suggesting mild benefits with many of these therapies, but they do not slow PD and there is no convincing evidence that they are beneficial.

4. Research Findings and New Directions

During the past five years, researchers have made substantial advances in our understanding of the biological factors involved in PD. They are beginning to decipher the roles of individual genes and environmental factors in PD and to learn how the interplay of these factors can lead to the disease. Each abnormal gene or environmental factor that is identified provides another clue to help solve the mystery of PD.

Genetics

Until the last decade, many researchers believed that PD was caused solely by environmental factors. However, the discovery of gene mutations in familial, or inherited, forms of PD has led to an explosion of research on PD genes and the function of the proteins that are encoded by these genes.

Although most people do not inherit PD, studying the genes responsible for the inherited cases can help researchers understand both inherited and sporadic (non-hereditary) cases of the disease. The same genes and proteins that are altered or missing in inherited cases may also be altered in sporadic cases by environmental toxins or other factors.

Identifying gene defects can also help researchers understand how PD occurs, develop animal models that accurately mimic the neuronal death in human PD, identify new drug targets, and improve diagnosis. The genetic approach has been very successful, with new discoveries occurring at an unprecedented pace. The following summary highlights current knowledge about the genes known to be involved in PD, and the functions of the proteins these genes produce.

alpha-synuclein

The first PD-related gene to be identified was alpha-synuclein. Researchers at NIH and other institutions studied the genetic profiles of a large Italian family and three Greek families with familial PD and found that their disease was related to a mutation in this gene.

They found a second alpha-synuclein mutation in a German family with PD. These findings prompted studies of the role of alpha-synuclein in PD, which led to the discovery that Lewy bodies from people with the sporadic form of PD contained clumps of alpha-synuclein proteins. This discovery revealed a potential link between hereditary and sporadic forms of the disease and sparked investigations into the normal function of alpha-synuclein as well as the possible effects of alpha-synuclein mutations on normal cellular activity.

One theory about how alpha-synuclein is associated with PD holds that the mutated protein interferes with cell membranes. Within the cell body, individual molecules of alpha-synuclein join together to form tiny protein threads called fibrils; this process is called fibrillization. Investigators at the Brigham and Women's Hospital Udall Center and elsewhere have shown that mutations in the alpha-synuclein gene disrupt the fibrillization process and lead to the accumulation of protofibrils, an intermediate step in alpha-synuclein fibrillization. They found that alpha-synuclein protofibrils have protein structures which resemble bacterial and insect toxins that make membranes leaky. This could trigger cell death and may explain the toxicity of Lewy body proteins. This idea is supported by studies from the Massachusetts General Hospital and Massachusetts Institute of Technology Udall Center showing that alpha-synuclein is located near cell membranes in postmortem brain tissue from people with diffuse Lewy body disease.

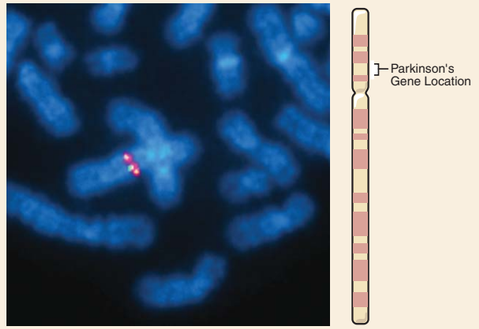
Another study suggests that a buildup of normal alpha-synuclein may clog up the cell's

protein disposal system and cause neurons to die. A group of researchers at NIH and other institutions investigated a rare familial form of early-onset PD and discovered that a multiplication of the normal alpha-synuclein gene, and a corresponding increase in alpha-synuclein protein, can cause the disease. The researchers analyzed blood samples from a family, the "Iowa kindred," in which many relatives developed PD or related neurological diseases. In the relatives with PD, the researchers found four copies of the alpha-synuclein gene — an abnormal triplication of three alpha-synuclein genes on one copy of chromosome 4 and one gene on the other chromosome 4 — instead of the usual two copies of the alpha-synuclein gene. This multiplication resulted in an abnormally large amount of alpha-synuclein in the cells.

A third theory proposes that mutant alpha-synuclein interferes with the normal housekeeping functions of cells and lets proteins build up to toxic levels. Researchers at the Columbia University Udall Center, along with colleagues at Brigham and Women's Hospital and the Albert Einstein College of Medicine, have found that normal alpha-synuclein is broken down by lysosomes, which act as the cell's garbage disposal system. Mutant alpha-synuclein, however, blocks the pathway into the lysosomes. This inhibits the breakdown of alpha-synuclein as well as other proteins. This may trigger a toxic buildup of protein "garbage" inside the cell.

Researchers are continuing to study the alpha-synuclein gene to clarify how it affects PD. For example, Mayo Clinic Udall Center researchers are assessing the alpha-synuclein gene in a large group of people with PD, and in a control group of healthy people who match the PD patients in age, gender, and demographics, in order to look for variations in the gene that may affect susceptibility to the disease. Investigators at the Johns Hopkins University Udall Center have developed mice with alpha-synuclein gene mutations and found that the mice accumulate alpha-synuclein in the midbrain, cerebellum, brainstem, and spinal cord and develop an adult-onset neurodegenerative disease with symptoms resembling human PD, including motor dysfunction, bradykinesia, and dystonia.

The discovery of alpha-synuclein has paved the way for other genetic linkage studies in families with PD (see Gene Discoveries, p. 15). Within the past 5 years, many regions of the genome have been linked to PD and four additional PD genes have been identified, including parkin, DJ-1, PINK1, and DRDN.



Researchers studying a family with a hereditary form of PD discovered that members of this family had a triplication of the normal alpha-synuclein gene on one chromosome. This image shows the three alpha-synuclein genes (pink) on one copy of chromosome 4.

Parkin

Genetic studies on a rare, juvenile-onset form of PD led to the discovery of the parkin gene. Originally, this form of PD was not linked to Lewy bodies. However, Mayo Clinic Udall Center scientists have found parkin mutations that are accompanied by Lewy body pathology. Further studies have shown that parkin is a part of the so-called ubiquitin-proteasome system, which breaks down proteins in the cell. This suggests that parkin mutations may lead to accumulation of toxic proteins within neurons. Researchers also have shown that parkin interacts with synphilin-1 and alpha-synuclein and mediates an important step in protein handling. When alpha-synuclein, another protein called synphilin-1, and parkin are injected together into cells in culture, they form inclusions in the cell that are similar to Lewy bodies. This suggests that parkin may be important in both inherited and sporadic forms of the disease. Several studies have suggested that normal parkin protects neurons from diverse threats, including alpha-synuclein toxicity, proteasomal dysfunction, and excitotoxicity. Other evidence indicates that

parkin degrades alpha-synuclein and that it accumulates on Lewy bodies in neurons within the substantia nigra, brainstem, and cortex of people with PD.

Findings from a different group of studies suggest that parkin may help to regulate the release of dopamine from substantia nigra neurons. In a mouse model for PD that is genetically engineered to lack the parkin gene, researchers found higher-than-normal levels of dopamine in the striatum. However, the neurons normally activated by dopamine required more stimulation to produce a response. The mice without parkin also had impairments in tests that require muscle coordination. These studies indicate that parkin may help to regulate the release of dopamine from nigral neurons.

Researchers at the Duke University Udall Center have shown that people with a parkin mutation in just one copy of the gene have a higher risk of getting PD as they get older than people without these mutations. Understanding why this happens could lead to strategies for preventing PD in people who are genetically predisposed to the disease.

DJ-1

The DJ-1 (PARK7) gene has been linked to another early-onset form of PD. This protein is involved in regulating gene activity and in protecting cells from a damaging process called oxidative stress. Mayo Clinic Udall Center researchers are screening patient samples for mutations in DJ-1, as well as other genes, to find out if these mutations are common among people with PD or restricted to just a few families. They also have evaluated DJ-1 in early-onset PD cases and identified a DJ-1 gene variation called R98Q.

Scientists at the Johns Hopkins University School of Medicine Udall Center have examined mutant DJ-1 genes in cultured human cells and found that the mutation reduces stability of the DJ-1 protein. These mutant proteins are degraded by proteasomes more quickly than usual and cannot form chains as the normal proteins do. Thus, the abnormal form of DJ-1 may not be able to perform its normal functions within the cell.

PINK1

Mutations in a gene called PTEN-induced kinase 1 (PINK1), also known as PARK6, have been identified in several families with PD. Kinases help to regulate protein function in both normal and disease states. The PINK1 gene codes for a protein active in mitochondria, which convert food into energy inside the cell. Cell culture studies suggest that PINK1 may help to protect the cell and that mutations in this gene may increase susceptibility to cellular stress. The discovery of this gene provides a direct molecular link between mitochondrial dysfunction and the development of PD.

Scientists at the Duke University Udall Center have shown that specific genetic variations in mitochondrial DNA, known as genetic polymorphisms, increase the risk of PD.

DRDN

Researchers at NIH and colleagues from several European institutions recently identified mutations in a gene called DRDN that appear to cause a late-onset form of PD. This gene, found in several English and Basque families, is located in a chromosomal region formerly called PARK8. DRDN codes for a protein called dardarin – a name derived from the Basque word for tremor. The function of this protein is still unknown.

Other Genes That May Play a Role in Parkinson's Disease

UCH-L1 – Scientists at NIH and elsewhere have identified a mutation in the Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1) gene in a German family with PD. In addition, researchers at the Mayo Clinic Udall Center have identified a variation of the gene, also called PARK5, that is associated with an increased risk of PD in some families. UCH-L1 is an important member of the ubiquitin-proteasome system that performs "ubiquitination," a process that tags proteins for breakdown. Ubiquitination is critical for the proper handling of misfolded proteins.

synphilin-1 – Researchers at the Johns Hopkins University School of Medicine Udall Center have found that a protein called synphilin-1 interacts with alpha-synuclein and promotes the formation of cellular inclusions resembling Lewy bodies. Studies are now underway to define the normal location and function of synphilin-1.

Gene Discoveries

One of the most dramatic changes in PD research in the past decade has been the emergence of genetics as a major tool for understanding the disease. Until the mid-1990s, most researchers believed that PD was caused solely by environmental factors. However, researchers at the UMDNJ-Robert Wood Johnson Medical School in New Jersey had identified an Italian family with what appeared to be an inherited form of PD. In 1995, they began to collaborate with researchers at the National Human Genome Research Institute (NHGRI), who analyzed DNA from these patients. Within a few years, the NHGRI researchers had traced the disease in this family to a mutation in the alpha-synuclein gene. Investigators soon identified alpha-synuclein mutations in several other families as well.

These findings touched off an explosion of work on the function of alpha-synuclein as well as intensive searches for other PD genes. Researchers soon discovered that alpha-synuclein is a major component of Lewy bodies, suggesting that it might play a role in sporadic forms of the disease as well as inherited ones. They also located four more PD genes – parkin, DJ-1, DRDN, and PINK1 – and several other genes that appear to influence the disease, although their role is not yet clear. In 2003, investigators at the National Institutes of Health and elsewhere discovered that, in one large family, a triplication of the normal alpha-synuclein gene caused the disease. The extra genes cause overproduction of alpha-synuclein, which can accumulate inside brain cells.

Together, these studies have dramatically changed researchers' understanding of how PD develops. Hundreds of investigators are now looking for additional PD genes and studying how the proteins produced by these genes affect cells. Others are examining how genes and environmental factors may interact to produce the disease. These studies may lead to vastly improved treatments for the disease, or possibly even ways of preventing it.

PACRG – This gene, called parkin co-regulated gene, was identified by researchers at the Mayo Clinic Udall Center. PACRG appears to interact with parkin and to be part of the protein degradation system. This protein also appears to be a component of Lewy bodies.

GSTO-1 and -2 – A gene called glutathione S-transferase omega-1 (GSTO-1) appears to affect the age of onset for PD and Alzheimer's disease. GSTO-1 is one of a family of genes that break down and recycle many compounds in cells, including drugs, carcinogens, and the products of oxidative stress. Studies suggest that GSTO-1 may modify an inflammatory compound called interleukin-1 beta and protect against the inflammation commonly found in brains from people with PD. Scientists also have identified a related gene, glutathione S-transferase omega-2 (GSTO-2).

tau – The tau protein is an important component of microtubules, which are part of the cell's structural support system and help to deliver substances throughout the cell. Recent studies have linked an abnormal tau protein to a parkinsonian disorder, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). Additional studies have suggested that aberrations in the tau protein contribute to the pathology of sporadic PD. Mayo Clinic Udall Center researchers are sequencing the tau gene in samples from their patients with familial parkinsonism to determine if it plays a role in these forms of PD.

fibroblast growth factor 2 – This growth factor helps to maintain neurons. Studies by Duke University researchers suggest that mutations in the FGF2 gene may be a risk factor for PD.

apolipoprotein E – Duke University researchers conducting a genomic screen to identify genes influencing age of onset for PD and Alzheimer's disease have found that normal genetic variations in the apolipoprotein E protein affect the age of onset for PD, just as they do for Alzheimer's.

PARK3, PARK9, PARK10, and PARK11 – These are chromosomal regions that have been implicated in families with PD. The chromosomal regions have not been narrowed down to specific genes, but researchers are working to identify the genes and to determine their function. People with PARK3 have a relatively late age of onset, much like sporadic PD. PARK9 has been identified in one Jordanian family. PARK10 is linked to age of onset of PD in Icelandic families. PARK11 was identified in pairs of siblings and appears to affect susceptibility to the disease.

The search for additional PD-related genes continues on many fronts. University of Virginia Udall Center researchers are working to define mitochondrial DNA (mtDNA) mutations that may be linked to PD. They have finished intensive sequencing of seven mitochondrial genes in frontal cortex samples from a small group of people with the disease and an equal number of controls. They found potentially important mutations in genes called ND2, ND4L, and ND5. These findings counter the hypothesis that PD is caused simply by an increase in age-related mtDNA mutations. The University of Virginia researchers also have developed methods to remove and replace the human mitochondrial genome. These technologies may lead to mitochondrial gene replacement as a method of treating PD and other sporadic neurodegenerative diseases. They could also be used to show whether these mitochondrial gene mutations cause PD and related diseases.

Duke University researchers also are investigating the role of the mitochondrial genome in PD. They have discovered that specific DNA regions and variations are associated with an increased risk of PD. This work has led to a collaborative study with the University of Virginia investigators to look more closely at how these mitochondrial DNA variations affect cellular functions.

Researchers are developing a variety of new approaches to speed research on genes and on the functions of the proteins they produce. For example, scientists at the Duke University Udall Center have developed a new approach called "genomic convergence" to study PD and other common diseases. This approach identifies and prioritizes candidate susceptibility genes for PD by taking data from gene expression studies and merging it with data from studies that detect chromosomal regions linked to PD (linkage analysis). Genes identified by the genomic convergence technique are relatively likely to play a role in PD. This combination of two powerful techniques saves investigators time and effort compared to studying the results of gene expression or linkage analysis alone. This approach has been used successfully to identify the GSTO-1 gene.

Researchers at the Duke University Udall Center have performed the first large expression studies to identify genes that are abnormally active or inactive in areas of the brain affected most by PD. They also have compared gene activity in PD with that in similar diseases such as progressive supranuclear palsy and FTDP-17. In addition, they have helped develop new gene analysis techniques that can determine if specific genetic variants make an individual more susceptible to PD. These tests, called the Pedigree Disequilibrium Test (PDT) and Geno-PDT, have improved on previously available techniques.

Mayo Clinic Udall Center researchers have gathered information and DNA samples from more than 200 PD families. They also are collaborating with investigators from other countries. They have worked with researchers at the University of British Columbia to study affected and unaffected PD family members with positron emission tomography (PET) scans. In addition, they have screened familial PD cases for DNA expansion mutations and identified 12 families who have mutations for spinocerebellar ataxia type 2. They also have worked with the European Consortium on Parkinson's Disease to complete a preliminary genetic analysis of 350 pairs of siblings. This effort has identified five regions of the genome that appear especially significant and are being studied for potential PD genes.

Several additional large-scale efforts to identify genes that play a role in PD are underway. NINDS is helping to sponsor PROGENI (Parkinson's Research: the Organized Genetics Initiative), which is looking at genes and other potential PD risk factors in 900 pairs of siblings in North America. Among other discoveries, this study has shown that mutations in the parkin gene may be a risk factor for late-onset PD as well as the juvenile-onset disease.

NINDS also is sponsoring a DNA and cell line repository to enhance gene discovery by supplying DNA samples, cell lines, and clinical and pedigree data to the neuroscience community.

Research on the genetics of PD also receives funding from other NIH institutes. The National Human Genome Research Institute is sponsoring a clinical study to identify people with inherited PD and to look for gene mutations in these individuals, and the National Institute of Environmental Health Sciences is sponsoring a study to look at nine candidate genes in a sample of 800 people with PD and their siblings to clarify what role these genes might play in the development of this disease.

Environmental Factors

Although the importance of genetics in PD is increasingly recognized, many researchers still believe that environmental exposures also increase a person's risk of developing the disease. Even when genes are a factor in the disease, as with many familial cases, exposure to toxins or other environmental factors may influence when symptoms of the disease appear and/or how the disease progresses.

One of the primary pieces of evidence that environmental factors play a role in the development of PD is that the relative risk of the disease is higher in industrialized countries than in less industrialized ones. In addition, studies have found that farmers and other agricultural workers have an increased risk of developing PD. Taken together, these studies suggest that toxic chemicals or exposure to other environmental factors present in industrial and agricultural areas might increase the risk of PD.

A cycad plant and cycad seed. Researchers suspect that a disorder with a unique combination of parkinsonian symptoms, dementia, and motor neuron disease, found in some people from the island of Guam, results from consumption of animals that eat neurotoxic cycad seeds found on that island.

Another piece of evidence comes from observations of people who have been accidentally poisoned with the toxin MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), which sometimes contaminates street drugs. MPTP is structurally similar to some pesticides. A breakdown product of MPTP, called MPP+, is toxic to substantia nigra neurons — the neurons that are affected in PD. MPTP produces a severe, permanent parkinsonian syndrome in affected people, and is now used to create animal models of PD. This discovery demonstrated that a toxic substance can damage the brain and produce parkinsonian symptoms.

A study of people in the World War II Veteran Twins Registry has suggested that genetic factors do not play a major role in causing sporadic PD that begins after age 50. However, genetic factors do appear to play a role when the disease begins at or before age 50. A number of other twin studies have found similar results. The chance that two siblings will both have PD is similar for fraternal and identical twins, suggesting that environmental exposures are more important than genetics in determining who will get the disease. Other studies have found that fraternal and identical twins of people with PD often have significant loss of dopamine neurons even when they don't experience any symptoms.

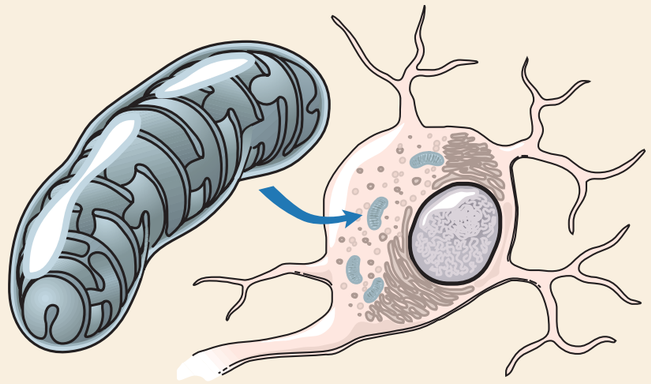
In another line of research, investigators are studying a disorder with a unique combination of parkinsonian symptoms, dementia, and motor neuron disease found in some people from the island of Guam to see if it might be due to an environmental factor or factors. A similar syndrome has been identified in people from the Kii peninsula in Japan. Researchers have long speculated that the disorder on Guam might be related to the consumption of animals that eat toxic cycad seeds found on that island. A 2002 study found neurotoxins in flour from cycad plants and showed that mice fed the cycad flour developed behavioral changes and neuron loss much like those seen in PD.

Viruses are another possible environmental trigger for PD. People who developed encephalopathy after a 1918 influenza epidemic were later stricken with severe, progressive Parkinson's-like symptoms. A group of Taiwanese women developed similar symptoms after herpesvirus infections. In the latter case, the symptoms were linked to a temporary inflammation of the substantia nigra, and later

disappeared. However, these cases showed that viruses can sometimes affect the region of the brain damaged in PD. Other studies have found evidence of activated immune cells and the accumulation of inflammation-associated proteins in PD. These changes might be triggered by viruses in some cases.

Scientists are continuing to study environmental toxins such as pesticides and herbicides that can cause PD symptoms in animals. Researchers supported by the NINDS and the National Institute on Aging have shown that exposing rodents to the pesticide rotenone can cause cellular and behavioral changes that mimic those seen in PD. Work supported by the National Institute of Environmental Health Sciences has shown that other agricultural compounds also can produce abnormalities in cells that are similar to those seen in PD. This research is supported through a program called the Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) Consortium. This program sponsors a variety of projects to examine how occupational exposure to toxins and use of caffeine and other substances may affect risk, and whether inherited genetic mutations may predispose certain people to developing PD after exposure to certain chemicals.

Researchers at Rush-Presbyterian-St. Luke's Medical Center have examined whether prenatal exposure to toxins may increase the risk of PD. They found that exposure to a bacterial toxin called lipopolysaccharide during development in rats leads to the birth of animals with fewer than the normal number of dopamine neurons. This dopamine neuron loss persists into the animals' adulthood and increases with age, which mimics the course of human PD.



Problems with mitochondria, the structures that produce energy for all cells, have been linked to the development of PD.

Along with genetic studies, these environmental studies lay the groundwork for a comprehensive understanding of how PD develops and how it might be prevented.

Pathways to Parkinson's Disease

Many researchers are working to understand the complex cellular activities and protein interactions that may lead to PD. Cellular factors that have been implicated in PD include mitochondrial interactions, oxidative stress, programmed cell death (a biochemical chain of events by which cells self-destruct), excitotoxicity, protein aggregation, immune factors, and the ubiquitin-proteasome protein degradation system. While these factors represent many different lines of research, scientists are beginning to understand how they may fit together to form a full picture of how PD develops.

Mitochondria, Oxidative Stress, and Programmed Cell Death

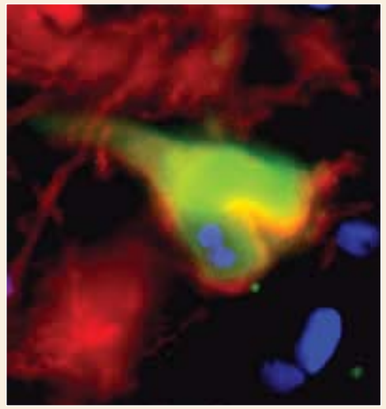
For years, mitochondria, the "energy plants" of the cell, have been implicated in the development of PD. Mitochondria are unique parts of the cell that have their own DNA (mtDNA). This DNA is separate from the genes found in the nucleus of every cell. Most research on the role of mitochondria in PD points to abnormalities in the largest component of the mitochondrial energy processing machinery — a group of proteins known as complex I.

Several lines of research suggest a mitochondrial role in protein aggregation, Lewy body formation, and neuronal death. Mitochondria are major sources of free radicals — highly unstable molecules that damage components of the cell, such as membranes, proteins, and DNA. This process is often referred to as oxidative stress. Oxidative stress-related changes, including free radical damage to DNA, proteins, and fats, have been detected in brains of PD patients.

Research has shown that an array of toxins, including MPTP and a pesticide and herbicide called rotenone, can affect mitochondrial complex I and increase the number of free radicals it produces. Researchers at the Columbia University Udall Center have found that these free radicals can modify alpha-synuclein in a way that causes it to aggregate or clump together into minute fibers, called fibrils.

Investigators at Emory University have modeled the process by which mitochondrial defects produce oxidative stress by using rotenone. In rats, chronic rotenone exposure causes oxidative protein and DNA damage and increases susceptibility to free radical-induced cell death. It also leads to the same pathological, biochemical, and behavioral features seen in PD. Despite the fact that it inhibits complex I throughout the brain, rotenone causes degeneration only in dopamine neurons. Studies suggest that these neurons are selectively vulnerable to complex I impairment.

Scientists at the Duke University Udall Center have found evidence that specific genetic variations in mtDNA, known as genetic polymorphisms, can increase the risk of getting PD, while other mtDNA variations are



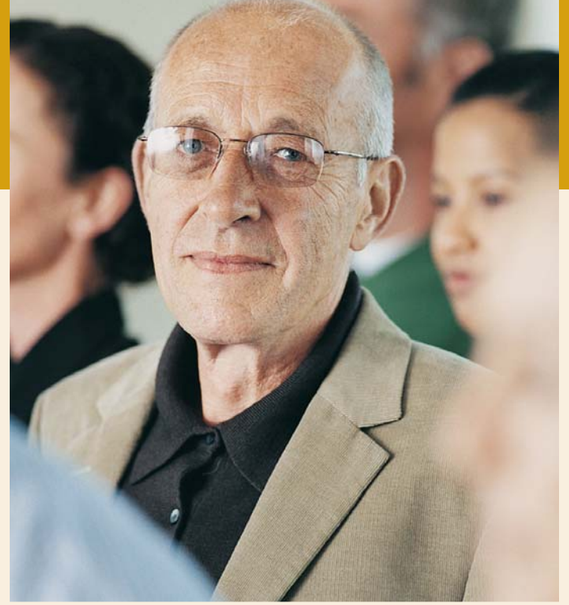
A dopamine-producing neuron that is undergoing programmed cell death after exposure to the toxin 6-hydroxydopamine. The red staining demonstrates that this is a dopamine neuron. The green shows cleavage of a cellular protein called actin due to activity of cell death proteins called caspases. The blue shows clumping of the neuron's nuclear DNA, due to programmed cell death. [Credit: Robert E. Burke, M.D., Columbia University, New York, NY. Reprinted from *Experimental Neurology*, 2002, vol. 175, with permission from Elsevier.]

associated with a lowered risk of the disorder. They also have found that PD patients have more mtDNA variations than patients with other movement disorders or Alzheimer's disease. Researchers still need to define how these mtDNA variations may lead to PD.

Mitochondria also are thought to initiate a process called programmed cell death. Programmed cell death, or apoptosis, is necessary for normal embryonic development. Scientists believe programmed cell death allows cells to die without disturbing their surrounding environment. However, programmed cell death also has been implicated in many neurodegenerative diseases and conditions, including PD. Several molecules are known to participate in the programmed cell death pathway; some promote cell survival while others promote cell death. An important topic in neuroscience research is the relationship between these pro-death and pro-survival molecules.

Mitochondria trigger programmed cell death by releasing a substance called cytochrome c that activates proteins called caspases and other cell death factors. Researchers believe this may occur in response to oxidative stress and mitochondrial toxins.

The idea that programmed cell death plays a role in PD has been strengthened by studies performed at the Udall Centers. For example, Columbia University scientists have discovered that, in an MPTP mouse model for PD, a pro-cell death molecule known as Bax is abundant in dopamine-producing neurons of the substantia nigra. They also showed that mice lacking the Bax gene were protected from brain damage caused by MPTP. These results



suggest that programmed cell death plays a role in animal models for PD and that it also may be involved in the human disease.

Scientists at the University of Virginia Udall Center have found that treatment with MPP+, a toxic derivative of MPTP that inhibits mitochondrial complex I, influences several molecules known to play a role in programmed cell death. Interestingly, some of these changes required activation of nitric oxide, a free radical that is often expressed in injured or damaged cells. The role of nitric oxide in programmed cell death was confirmed in an experiment in which cells were treated with nitric oxide instead of MPP+. This treatment produced the same programmed cell death-related changes as MPP+. Other experiments have shown that mice lacking Bax and nitric oxide are protected against MPTP toxicity.

Investigators at the University of Virginia Udall Center also have developed hybrid cells, called cybrids, in which mitochondrial DNA from PD patients is placed in neuroblastoma (cancer) cells. These cybrids develop Lewy bodies just like those in the dopamine neurons of PD patients. The cybrid cell lines with the lowest complex I activity make the most Lewy bodies. These findings show that PD mitochondrial gene expression in a cybrid model is sufficient to spontaneously cause development of Lewy bodies, providing strong support for the idea that mitochondrial defects are key to the development of sporadic PD.

Collectively, these results demonstrate that mitochondrial-induced programmed cell death contributes to the neuronal loss in PD. This suggests that a possible treatment strategy for PD is to inhibit the cascade of events associated with programmed cell death. Accordingly, scientists have discovered that inhibiting the release of cytochrome c and caspases from mitochondria with the drugs minocycline, pramipexole, and bongkreckic acid can protect cells from degeneration. These drugs may be clinically useful as neuroprotectants to prevent PD.

Protein Degradation (Ubiquitin-Proteasome System)

Another major area of PD research involves the cell's protein disposal system, called the ubiquitin-proteasome system. Researchers believe that if this disposal system fails to work correctly, toxins and other substances may build up to harmful levels, leading to cell death.

In the ubiquitin-proteasome system, a chemical called ubiquitin acts as a "tag" that marks certain proteins in the cell for degradation by the proteasomes. The ubiquitin-proteasome system involves interactions between several proteins, including parkin and UCH-L1. This suggests that disruption of the ubiquitin-proteasome pathway is part of the mechanism by which mutations in these genes cause PD.

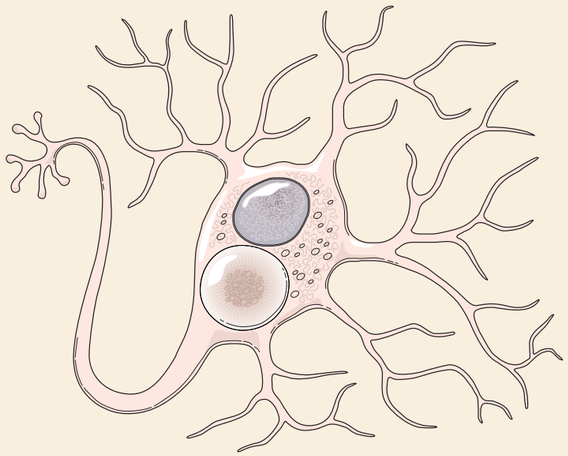
Studies have suggested that UCH-L1 is involved in the production of ubiquitin. Mutations in the parkin gene also interfere with normal proteasomal function. Scientists at the Johns Hopkins University Udall Center have shown that treatment with a toxin that inhibits the ubiquitin-proteasome system causes cells with mutant alpha-synuclein to be susceptible to programmed cell death. This cell death is accompanied by activation of caspases and by injury to the mitochondria. These changes could be blocked by cyclosporin A, which prevents the release of factors that activate caspases.

Proteasome inhibition results in accumulation of molecules normally degraded by the ubiquitin-proteasome pathway, such as p53, NFKB, and Bax. These molecules help to promote programmed cell death.

Protein Aggregation

PD is characterized by fibrillar inclusions inside the cell called Lewy bodies. Lewy bodies include clumps (aggregates) of alpha-synuclein fibrils and other proteins. There is strong evidence that this protein aggregation initiates a cascade of events that culminates in neurodegeneration. If so, then inhibiting aggregation may be a way of treating PD.

Many researchers are trying to learn the function of Lewy bodies. Some studies argue that Lewy bodies are a byproduct of degenerative processes within neurons, while others suggest that Lewy bodies are a protective mechanism by which neurons lock away abnormal molecules that might otherwise be harmful. In addition, some research suggests that protofibrils – an intermediate step in the development of alpha-synuclein fibrils – may be damaging to the cell.



This drawing shows a Lewy body, a hallmark of PD, inside the cell body of a neuron. Lewy bodies are clumps of alpha-synuclein and other proteins.

Researchers at the Brigham and Women's Hospital Udall Center have found that free radicals induce formation of alpha-synuclein-dopamine compounds that stabilize protofibrils. They also showed that the alpha-synuclein in protofibrils binds to vesicles inside the cell, which could trigger cell death and may explain the toxicity of alpha-synuclein and other fibril-forming proteins. They are now studying purified proteins under carefully controlled conditions in culture to determine what factors make the proteins clump together and what structure the aggregated proteins form. They are collaborating with other researchers to develop agents that can help to image protein aggregates using single photon emission computed tomography (SPECT), and they are investigating whether PD may result from a loss of normal alpha-synuclein function, rather than from the accumulation of aggregates.

Researchers at the Massachusetts General Hospital and Massachusetts Institute of Technology Udall Center have found that alpha-synuclein aggregates lead to altered gene expression. By studying brain tumor cells, they have found that overexpression of several chaperone proteins – proteins that help other proteins fold correctly – suppresses aggregation of alpha-synuclein. However, a mutant form of one of these proteins does not decrease alpha-synuclein aggregation. Taken together, these data suggest that molecular chaperones aid the handling of misfolded or aggregated alpha-synuclein.

Aberrations in the tau protein also may contribute to the protein aggregation seen in PD. Mayo Clinic Udall Center researchers have studied a line of mice, called hTau mice, that overexpress the tau protein. These mice have neurofibrillary tangles containing both synuclein and tau, and they exhibit premature cell death early in life. Experiments show that synuclein and tau may interact to promote the fibrillization of both proteins.

Excitotoxicity

Another common topic of PD research is excitotoxicity – overstimulation of nerve cells that leads to cell damage or death. In excitotoxicity, the brain becomes oversensitized to the neurotransmitter glutamate, which increases activity in the brain.

The dopamine deficiency in PD causes overactivity of neurons in the subthalamic nucleus, which may lead to excitotoxic damage there and in other parts of the brain. In addition, researchers have found that

> There is strong evidence that protein aggregation initiates a cascade of events that culminates in neurodegeneration. If so, then inhibiting aggregation may be a way of treating PD.

dysfunction of mitochondrial complex I, due to gene mutations or exposure to toxins, causes a decrease in the cell's energy supply. This can make dopamine-producing neurons vulnerable to glutamate and to an increased production of nitric oxide and other free radicals. These changes cause oxidative stress, cell death, and alpha-synuclein aggregation.

Other evidence that excitotoxicity plays a role in PD comes from a unique disease found in people from Guam. This disease features a combination of motor neuron disease, parkinsonian symptoms, and dementia, and researchers believe it results from a toxin that comes from cycad seeds and acts on glutamate receptors. This suggests that excitotoxicity is central to the development of the parkinsonian disorder in Guam.

Studies at Columbia University have shown that the normal form of parkin may play a role in preventing excitotoxicity in PD. Scientists found that parkin tags a protein called cyclin E, which accumulates in neurons that are dying from excitotoxicity, and causes its degradation. However, mutated parkin cannot trigger degradation of cyclin E. When the researchers increased the amount of parkin in dopamine neurons that were overstimulated with a drug called kainate, they found that the parkin reduced cyclin E and prevented the cells from dying. Reducing parkin in these neurons increased the amount of cell death due to overstimulation. Interestingly, the researchers found excess cyclin E in the dopamine neurons of some patients with sporadic PD as well as in patients with the inherited form of the disease that is linked to parkin.

Inflammation

Another interesting line of research on cell death in PD is focusing on the role of inflammation. Inflammatory responses occur in the brain during disease and after many types of injury. Studies in the last decade have shown that inflammation is common to a variety of neurodegenerative diseases, including PD, Alzheimer's disease, HIV-1 associated dementia, and amyotrophic lateral sclerosis. The inflammation in these diseases involves activation of microglia — specialized support cells in the brain that produce immune system signaling chemicals called cytokines. Several studies by Columbia University scientists have implicated pro-inflammatory molecules in cell death following MPTP treatment. Inhibiting the inflammatory response with drugs or by genetic engineering prevented some of the neuronal degeneration that normally occurs with MPTP treatment.

Although inflammation can be damaging, studies have shown that activating immune cells in specific ways also can protect nerve cells in animal models of spinal cord and brain injury. Recently, researchers at the University of Nebraska Medical Center and at the Columbia University Udall Center in New York successfully reduced the amount of neurodegeneration in a mouse model for PD by using an experimental vaccine to modify the behavior of microglia in the brain.

Research at the Columbia University Udall Center has shown that dopamine neurons in brains from patients with PD have higher levels of an inflammatory enzyme called COX-2 than those of people without PD. COX-2 triggers inflammation in damaged tissues. The scientists also found elevated levels of COX-2 in a mouse model for PD. When they gave these mice a drug called rofecoxib that inhibits COX-2, it doubled the number of neurons that survived. Surprisingly, however, the researchers did not find reduced inflammation with this drug. Instead, they found that the COX-2 inhibitor may protect neurons by preventing oxidative stress.

Other studies suggest that the protein GSTO-1, which has been linked to the age of onset of PD, may modify the inflammatory cytokine interleukin-1 beta and therefore may reduce the inflammation found in brains from people with PD. It also may protect against programmed cell death.

Models for Parkinson's Disease

Much of the research that is leading to advances in understanding and treating PD would not be possible without research models – cell lines and animals with features that mimic those of human PD. Scientists use these models to investigate questions such as what goes wrong in PD, how does cellular damage lead to behavioral symptoms, and how might potential new treatments affect the disease process. For example, levodopa, the drug most commonly used to treat PD, was shown to counteract PD symptoms in an animal model before it was tested in humans.

Researchers at the Udall Centers and other institutions are continually refining existing research models and developing new ones. Current models range from specialized, hybrid cells in culture dishes to rats and other animals with the same genetic defects identified in humans with PD. These models fall into three categories: toxin-induced models that show how environmental factors trigger parkinsonian symptoms, genetic models that show how gene defects can affect the brain, and spontaneously occurring models that mimic some of the features of PD. The cellular and behavioral changes in toxin-induced models often overlap with those that have gene defects, providing further evidence that PD results from both environmental and genetic factors.

Toxin-Induced Models

The two best-known and widely used animal models in PD research are the MPTP model and the 6-hydroxydopamine model. MPTP is a toxin that kills neurons in the substantia nigra, causing symptoms that closely resemble PD. Investigators discovered this reaction in the 1980s when heroin addicts in California who had taken a street drug contaminated with MPTP developed severe parkinsonism. This discovery allowed researchers to simulate PD in animals for the first time.

Research at the Columbia University Udall Center

has shown that dopamine neurons in brains from patients with PD have higher levels of an inflammatory enzyme called COX-2 than those of people without PD.

6-Hydroxydopamine is another toxin that kills dopamine neurons, producing neuron death and parkinsonian symptoms in rats and mice. The 6-hydroxydopamine model has been used to evaluate potential PD therapies such as cell transplantation and neurotrophic factors.

In the late 1990s, researchers at the Emory University Udall Center developed a new model using a pesticide and herbicide called rotenone. Rotenone interferes with the activity of mitochondrial complex I. The rotenone model is the first one that produces selective neuron degeneration, Lewy bodies, and behavioral changes similar to those seen in humans with PD. Rats exposed to rotenone develop large inclusions in substantia nigra neurons that resemble Lewy bodies and contain alpha-synuclein and ubiquitin. Rotenone-treated animals also develop bradykinesia, rigidity, and gait problems.

A common theme among the toxin-induced Parkinson models is that the toxins interfere with activities of mitochondria. This knowledge has helped researchers develop additional models using different agents that act on mitochondria. For example, scientists have developed new rodent models by administering the pesticides paraquat and maneb, and by using a combination of MPTP and the drug probenecid.

Genetic Models

The discoveries of genetic mutations in some hereditary cases of PD have prompted the development of mouse models genetically engineered to have mutations or deletions of PD genes. These so-called transgenic mice have become excellent models to study how PD develops. Genetic engineering has also

Neuroprotection

A major goal of PD research is the development of new therapies. Currently available treatments for PD can effectively control motor symptoms of the disease in the early stages, but they don't slow or halt the relentless progression of the disease. An explosion of discoveries during the past decade is now providing renewed hope of a therapy that will prevent the underlying nerve damage in this disease – a strategy known as neuroprotection.

The idea of neuroprotection for PD is not new. A number of clinical studies have tested different compounds to see if they might stop the disease progression. Some studies initially showed small positive effects, but most of these studies included a limited number of patients and did not examine the effects of these therapies over a long period of time. In addition, researchers have no good way of measuring whether these or other compounds truly prevent neuronal damage. Consequently, researchers cannot be sure that the positive effects seen in these studies are due to neuroprotection or if they represent short-term effects on symptoms.

Recently, a wealth of new information about how neurons may be damaged in PD has allowed investigators to identify many potential new ways of treating this disease, including nerve growth factors, anti-inflammatory drugs, and antioxidants. To overcome some of the problems that have plagued previous studies, in 2002 an NINDS-sponsored committee conducted a systematic review of data on 59 potential neuroprotective agents for PD. This committee ultimately selected four of the most promising drugs for study in a series of clinical trials known as Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD). These drugs — coenzyme Q10, GPI-1485, creatine, and minocycline — are now being tested at more than 40 centers in the United States and Canada. Researchers hope that this new approach to selecting and testing compounds will lead to the first proven neuroprotective therapy or therapies for PD and revolutionize treatment of this disease.

been used to develop cell lines that model some of the processes that go awry in PD.

One example of a genetic model — human neuronal cells that contain mutant alpha-synuclein — was developed by researchers at the Mayo Clinic Udall Center. These cells develop levels of alpha-synuclein 25- to 50-fold higher than in controls. When these cells are exposed to rotenone, unusual forms of synuclein begin to appear.

Researchers at the University of Virginia Udall Center have developed hybrid cells, called cybrids, that have mitochondrial DNA from PD patients inserted into tumor cells. These cybrids develop Lewy bodies just like those in the dopamine neurons of PD patients. Before this model was developed, researchers needed brain samples from PD patients in order to study Lewy bodies.

Researchers also have developed strains of mice with mutations in the alpha-synuclein and parkin genes. Mice with alpha-synuclein mutations develop an adult-onset neurodegenerative disease characterized by movement dysfunction and pathological aggregation of alpha-synuclein. Mice without the parkin gene show abnormal regulation of dopamine in the striatum and impairments in behavioral tests that require muscle coordination. Researchers are now working to develop animal models without normal DJ-1 function.

Spontaneously Occurring Models

Scientists have identified two spontaneously occurring strains of mice that may be useful as models for PD. The first strain is known as reeler mice. These mice have reduced dopamine activity in the striatum and several other brain areas, which results in an impaired gait. The second spontaneous mouse model for PD is called the quaking mouse because it develops tremors soon after birth. Due to a chromosomal deletion, these mice lack both the parkin gene and the PACRG gene. Unlike humans with parkin deletions, this mouse does not have a loss of dopamine-producing neurons or a buildup of alpha-synuclein. However, it may help investigators understand the function of the parkin protein.

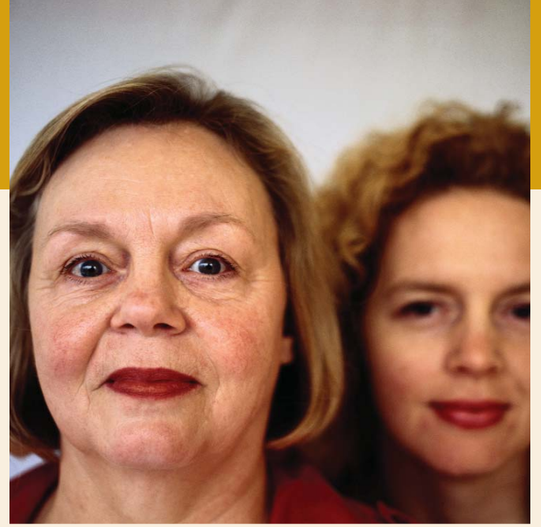
Therapeutic Approaches

While levodopa and other drugs can provide initial relief from parkinsonian symptoms, none of these treatments halts the loss of dopamine neurons and nerve fibers. Thus, new treatments that slow the underlying disease are desperately needed. As knowledge about this disorder grows, potential new ways of preventing and treating the disease are being revealed. Promising treatments in development include new drug therapies (including neurotrophins, neuroprotectants, and immunotherapy), surgical therapies, cell transplantation, gene therapy, and transcranial magnetic stimulation.

Drug Therapy

Current treatment for PD relies primarily on drugs to control the symptoms. While these drugs work well early in PD, they progressively fail as more nerve cells die. Drug-induced dyskinesias and fluctuations of motor symptoms also limit drug benefits in many cases.

Neurotrophic factors – molecules that support survival, growth, and development of brain cells – are one focus of new drug research. These chemicals are being studied as potential



therapies for many neurological diseases. Researchers are investigating whether neurotrophic factors can halt dopamine cell degeneration and help to repair brain cells in PD. One such drug, glial cell line-derived neurotrophic factor (GDNF), has been shown to protect dopamine neurons and to promote their survival in models of PD. Researchers at the University of Kentucky Udall Center have helped to develop a technique for delivering these molecules directly into the brain. When GDNF was given for a period of 3 to 6 months, it prompted repair of dopamine neurons and improvement in their function. It also seemed to protect damaged dopamine cells from further degeneration. The researchers are now conducting an FDA-approved Phase I

In recent years, Parkinson's research has advanced to the point that halting the progression of PD, restoring lost function, and even preventing the disease are all considered realistic goals.

dose-escalation trial of chronic GDNF administration in ten patients with advanced PD at the University of Kentucky Medical Center. The investigators also are studying the mechanisms by which neurotrophic factors affect the function of dopamine neurons and the long-term effects of these proteins on brain systems. Another clinical trial in the United Kingdom used tiny pumps implanted under the skin to deliver GDNF and has shown promising initial results.

GDNF is one of a family of compounds called neurotrophins or nerve growth factors. Many of these neurotrophins are potential therapies for PD. Examples include neurotrophin-4 (NT-4), brain-derived neurotrophic factor (BDNF), and fibroblast growth factor 2 (FGF-2). One study has shown that GDNF and NT-4 can protect dopamine neurons in culture from oxidative stress. Studies in mice have shown that BDNF can increase the number of dopamine receptors produced by brain cells. This may increase the brain's responsiveness to dopamine. Other studies have shown that BDNF protects dopamine neurons from damage in the 6-hydroxydopamine rat model for PD. FGF-2 is essential for the long-term survival of dopamine neurons, and impaired FGF-2 function may be a common underlying cause of the neuronal degeneration in PD. FGF-2 also stimulates the survival of dopamine neurons when they are transplanted into the brain.

Another developing area of PD drug research is neuroprotection – finding ways to prevent the ongoing degeneration of dopamine neurons that is a hallmark of PD. In 2002, a multicenter clinical trial suggested that a compound called coenzyme Q10 (also known as ubiquinone), which is believed to improve mitochondrial function, can slow the rate of deterioration in PD. Another early clinical trial tested a compound called GPI-1485, which acts as a neurotrophin, and found that it was well-tolerated and appeared to slow the loss of dopamine nerve terminals. A third drug, creatine, which affects mitochondrial function and acts as an antioxidant, prevents MPTP-induced neuronal damage in rats.

While levodopa and other current drugs can provide initial relief from parkinsonian symptoms, none of these treatments halts the loss of dopamine neurons and nerve fiber. Thus, new treatments that slow the underlying disease are desperately needed.

Investigators at the Harvard University Medical School and McLean Hospital Udall Center, along with other researchers, have identified genes that are neuroprotective in a variety of systems, from cell culture to primate models of PD. Increasing the expression of these genes, or mimicking their function with drugs, may be a new way to prevent brain damage in PD.

Therapies that change how the immune system reacts also may protect nerve cells in PD. For example, animal studies of the antibiotic minocycline, which has been used in humans for decades, have shown that it has anti-inflammatory effects in the brain and that it may prevent programmed cell death. In another study, researchers at the University of Nebraska Medical Center and the Columbia University Udall Center in New York have shown that an experimental vaccine using a drug called copolymer-1 can modify the behavior of supporting (glial) cells in the brain so that their responses are beneficial to the nervous system rather than harmful. The vaccine reduced the amount of neurodegeneration in a mouse model for PD. Another study by neurologists at the Columbia University Udall Center has shown that a drug called rofecoxib, which inhibits an inflammatory enzyme called COX-2, prevents about half of the dopamine neuron death in a mouse model for PD.

NINDS is now supporting a series of pilot clinical trials to test the effects of four of these potential neuroprotectants — coenzyme Q10, GPI-1485, creatine, and minocycline — in people with early, untreated PD (see Neuroprotection, p. 28). This series of clinical trials is called Neuroprotection Exploratory Trials in Parkinson's Disease (NET-PD). NINDS is also supporting a network of Parkinson's Disease Neuroprotection Clinical Centers to study these and other potential neuroprotectant drugs.

A variety of other compounds have been tested as potential therapies for PD. Some studies have found that proteins called alpha-2 adrenergic receptors play a role in the dyskinesias that commonly develop in PD patients treated with levodopa. Blocking these receptors has been successful in reducing dyskinesia in animal models of PD. An alpha-2 adrenergic receptor blocker called JP-1730 is now being studied in an NINDS-sponsored clinical trial to determine if it is safe and effective against dyskinesia and/or other PD symptoms. Another drug, levetiracetam, is also being tested in a controlled clinical trial to see if it can reduce dyskinesias in Parkinson's patients without interfering with other PD drugs. Levetiracetam, which is approved by the FDA to treat epilepsy, is not an alpha-2 adrenergic receptor blocker. Instead, researchers believe it may work by interfering with the neurotransmitter GABA (gamma-amino butyric acid).

Another clinical trial is studying GM1 ganglioside, a chemical which contributes to cell growth, development, and repair, to determine if this drug can improve symptoms, delay disease progression, and/or partially restore damaged brain cells in PD patients. Preliminary studies have shown beneficial effects of this drug on the dopamine system in animal models.

Several chemicals are being tested as potential treatments for the mood disorders that sometimes occur in people with PD. One clinical trial is investigating whether a drug called quetiapine can help to reduce psychosis and/or agitation in PD patients with

dementia, and in dementia patients with parkinsonian symptoms. Another clinical study is examining whether s-adenosyl-methionine (SAM-e), a food supplement that improves dopamine transmission, can help to alleviate depression in patients with PD.

A number of clinical studies have suggested that cholinesterase inhibitors, which are commonly used for Alzheimer's disease, can also have a positive effect on cognition, psychiatric symptoms, and global function in patients with PD plus dementia. Additional clinical studies are now underway.

Surgical Therapies

Surgical treatments for PD, especially pallidotomy and deep brain stimulation (DBS), are important options for improving the lives of people affected by this disease. Investigators are continuing to evaluate these procedures in patients.

NINDS is supporting a great deal of research about DBS, including studies that aim to improve the technology for DBS and a large-scale clinical trial done in collaboration with the Department of Veterans Affairs that compares DBS to the best medical management with drugs. Investigators are studying normal brain circuits in order to find the best placement for the electrodes in the brain and the best stimulation patterns for DBS. In addition, they are working to develop a screening tool to identify PD patients who will get the most benefit from DBS.

Cell Transplants

Cell replacement through transplantation is an emerging approach for repairing the damage PD causes in the brain. Many

Investigators at the Harvard University Medical School and McLean Hospital Udall Center, along with other researchers, have identified genes that are neuroprotective in a variety of systems, from cell culture to primate models of PD.

researchers are working to develop cell transplantation therapies. In addition to embryonic stem cells, which have the potential to become any kind of cell in the body, researchers are experimenting with adult neural stem cells, neural precursor cells, and fetal-derived dopamine-producing neurons. Even cells derived from non-neuronal tissue are being considered for PD research.

However, very little is known about these different types of cells, and researchers need to better understand the fundamental biology of stem cells and neural precursor cells before such technologies can be used to treat PD in a safe, effective, and predictable manner.

In several early clinical studies, grafting of fetal-derived dopamine tissue led to an increase in dopamine production in the brains of people with advanced PD. Unfortunately, these studies showed few long-term benefits and led to unanticipated side effects such as dyskinesias. These problems preclude widespread use of this particular approach.

Investigators at the Harvard University Medical School and McLean Hospital Udall Center have injected mouse embryonic stem cells directly into the rat brain and found that these cells can develop into dopamine neurons. They also have shown that they can generate dopamine neurons from rodent embryonic stem cells. They are now testing primate and human embryonic stem cells in animal models of PD with a goal of moving this therapy into human clinical trials.

Some researchers have found that muscle progenitor cells isolated from the muscle of adult rats can be induced to form cells with neuron-like properties. Although it is unclear whether these cells can actually function like neurons, this finding raises the possibility that muscle tissue may be a source of progenitor cells to treat diseases of the nervous system. In another study, researchers transplanted dopamine-producing brain cells from pigs into the brains of PD patients and found some evidence of clinical improvements. The immune systems of these patients had to be suppressed so that the grafted pig cells would not be rejected..

Yet another transplantation approach employs retinal pigment epithelial cells, which produce dopamine and can be cultivated in large numbers. These cells are attached to microscopic gelatin beads and implanted into the brains of PD patients as part of a clinical trial to determine if they can enhance brain levels of dopamine and thus reduce the symptoms of PD.

One of the key problems with stem cell transplantation is to control and manage how the cells become dopamine-producing neurons. Recently, investigators found that genetically engineering mouse embryonic

stem cells to produce a protein called Nurr1 led to a four- to five-fold increase in the number of dopamine neurons produced in culture. Nurr1 also enhanced the neurons' ability to produce and release dopamine. The identification of this important factor in dopamine neuron development paves the way for new therapies that require management of stem cell differentiation.

Other studies have shown that embryonic stem cells also form dopamine cells if they are transplanted directly into the brain and that these cells can reduce motor dysfunction and normalize dopamine production in an animal model of PD. A low cell concentration of embryonic stem cells increases the influence of the host brain, increasing the number of dopamine cells produced and reducing the likelihood that the stem cells will develop into tumors.

Researchers at NINDS are studying signals that control the proliferation and differentiation of stem cells. Along with other researchers, they have shown that stem cells can generate nerve cells that are capable of establishing connections (synapses) with other neurons. They also have shown that mouse embryonic stem cells can be manipulated to generate central nervous system stem cells.

The NIH has established an NIH Stem Cell Unit to help characterize stem cells for future clinical use and to learn how to control differentiation in federally approved stem cell lines.

Gene Therapy

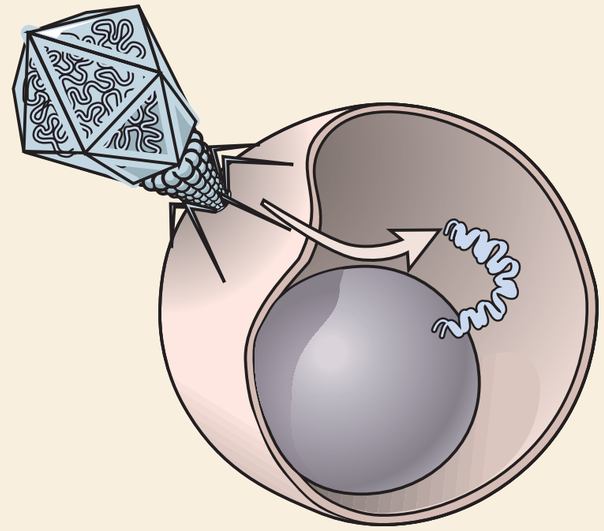
Gene therapy offers great potential for PD and many other brain disorders. With this type of therapy, viruses are engineered to deliver genes that increase the supply of dopamine, prevent cell death, or promote regeneration of neurons. Although this approach is promising, researchers need to develop efficient and safe means to deliver genes to brain cells in order for gene therapy to be used in humans. Many researchers are working to develop better viral vectors – viruses that can carry genes into the targeted cells – and to find ways of improving the transfer of these vectors to the brain. As researchers accumulate more information about the safety and efficacy of different delivery systems, research on gene therapy for PD can move forward.

Cell replacement through transplantation is an emerging approach for repairing the damage PD causes in the brain. Many researchers are working to develop cell transplantation therapies.

The NINDS is supporting a consortium called the Parkinson's Disease Gene Therapy Study Group, which is investigating dopaminergic enzyme gene therapy and neurotrophic gene therapy in animal models of PD. This consortium includes many Parkinson's experts from research centers across the country. The investigators are comparing different genes and testing different gene delivery approaches. As part of this project, researchers at Northwestern University in Illinois have developed a viral gene vector with a special modification that allows the introduced gene to be temporarily "turned off" when the patient is given a small dose of a specific antibiotic. The development of this vector should permit researchers to better control the delivery of genes once the vector is in the host. The researchers are now conducting safety and toxicity studies of this new vector with the hope that it will prove safe enough for testing in humans.

NINDS-funded investigators have found that using a genetically modified virus to deliver specific growth factors to primates with a parkinsonian condition leads to dramatic improvements in symptoms. Another group of researchers has shown that engineering a virus to deliver enzymes important for the production of levodopa can have beneficial effects in a rat model of PD.

Investigators also are experimenting with the gene for 1-amino acid decarboxylase (AADC), an enzyme that converts levodopa into dopamine. Research in animal models has shown that neurons in the striatum can be given the AADC gene using a viral vector,



The most common gene therapy strategy uses viruses to carry beneficial genes into targeted cells. Here a virus is shown attaching to a host cell. The viral DNA, which is contained in the capsule at the top of the virus, will be injected into the cell. Under normal circumstances, the viral DNA will then "hijack" the cell and force it to produce more viruses. In gene therapy, however, the virus' disease-causing genes are replaced with the beneficial gene, and the virus injects that gene into the cell.

causing them to convert levodopa to dopamine. This essentially mimics the function of the dopamine neurons that are lost in PD and may reduce the need for drugs that increase the level of dopamine in the brain.

Researchers also are experimenting with gene therapy to deliver the GDNF gene to the brain. In a monkey model, GDNF prevented dopamine neurons from dying, and the monkeys regained some of their lost motor skills.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a technique that uses an insulated wire coil placed on the scalp to create a magnetic pulse that stimulates the brain. Investigators at NINDS are conducting clinical studies of TMS and a related technique called transcranial electrical polarization to learn if they might have beneficial effects for people with PD. Studies have suggested that these techniques might be able to alter brain circuits in beneficial ways. Some studies of TMS have shown small effects on bradykinesia. TMS also may be able to produce beneficial effects on gait and freezing.

Other Clinical Research

While many clinical studies are investigating potential new treatments, clinical research also can help to reveal better ways of diagnosing and tracking PD.

In a series of studies, intramural researchers at NINDS have found evidence that PD causes widespread damage to the sympathetic nervous system, in addition to the substantia nigra. The sympathetic nervous system controls functions such as blood pressure and heart rate. Individuals with PD often experience symptoms such as orthostatic hypotension, or a drop in blood pressure upon standing, and the loss of sympathetic nerves observed in this study may help to explain why this occurs.

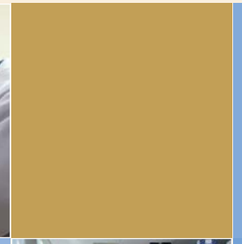
In another study, researchers at the Columbia University Udall Center have developed a method to track the progression of PD in patients at early stages of the disease using PET imaging techniques. These techniques allow the researchers to examine dopamine transporter binding, a measure of dopamine levels, in the brains of people with PD and in healthy individuals. They have found that the onset of motor symptoms in people with PD is accompanied by a 70 percent loss of dopamine in the brain. They also studied how DBS changes activity in the brain. PET imaging of PD patients shows hyperactivity in some brain regions prior to treatment, probably resulting from the loss of dopamine. DBS suppresses this hyperactivity. The stimulation also was accompanied by improvement in motor function. This study helped to reveal how DBS may improve symptoms in PD.

Researchers at the
Columbia University Udall Center
have developed a method to track the progression of PD
in patients at early stages of the disease using PET imaging techniques.

Some investigators are using neuroimaging of dopamine and other chemicals in the brain to assess how the brain functions during cognition, sleep, and activity, and how DBS changes these functions. Another NINDS-sponsored clinical study is using single photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) to examine the brain's nicotine receptors, which respond to the neurotransmitter acetylcholine. Previous studies have shown changes in the acetylcholine system in PD patients. These changes tend to be more pronounced in patients with dementia. The current study should clarify how acetylcholine interacts with other neurotransmitters in people with PD, and may lead to new ways of diagnosing or treating the disease.

Other researchers are assessing quality of life in patients with PD and other neurological conditions and working to develop a global statistical test for diagnosing PD.

Another important area of research aims to improve rehabilitation and assistive technology for people with PD. This research includes studies of ways to improve posture and movement in people after they have been treated with DBS, studies on the effects of exercise, studies of voice training, and development of an assistive device for people with vocal impairment. Other studies are focusing on treatments for cognitive impairment, memory problems, urinary tract dysfunction, sleep disorders, and micrographia (abnormally small handwriting due to difficulty with fine motor control).



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Conclusion

While Parkinson's is a complex disease, research has progressed a great deal in recent years. Halting the progression of PD, restoring lost function, and even preventing the disease are now considered realistic goals. Much of the recent progress has been funded by the NINDS through the Udall Parkinson's Disease Research Centers of Excellence and many other grants. Researchers have identified many susceptibility genes and potential environmental risk factors for PD, and these studies are contributing to a much-improved understanding of how PD develops. A number of promising therapies have been developed as a result of this understanding and are now being tested in humans and in animal models. Continuing studies to improve understanding of the underlying biology of the disease will lead to better ways of relieving the symptoms of Parkinson's patients and ultimately preventing or halting the disease.

Morris K. Udall Centers of Excellence for PD Research

Overview

As part of its efforts to defeat PD, the NINDS supports a number of Centers of Excellence for Parkinson's Disease Research throughout the country. The Centers' multidisciplinary research environment allows scientists to take advantage of new discoveries in the basic and technological sciences that can lead to clinical advances, and, in addition, allows for collaborations across centers which can expedite the pace of research. Most of the Centers also provide state-of-the-art training for young scientists who are preparing for research careers investigating PD and related neurological disorders. Some of the topics that the Centers address include:

- Neuronal and mitochondrial genetic studies to elucidate key proteins involved in neurodegeneration and to determine genetic differences between familial and sporadic PD
- Studies of the structure and function of proteins involved in cell death and degeneration
- Studies of the anatomical structures and brain chemicals involved in PD
- Studies to improve animal models of PD
- Imaging studies involving PET
- Studies of PD risk factors in people of different gender and ethnicity
- Animal studies testing possible PD treatments, such as neuroprotective therapies, implantation of genetically engineered cells, DBS, and levodopa drug therapy.

These Centers have contributed greatly to the PD research field. Their many significant achievements include discovery of the UCH-L1, PACRG, and GSTO-1 genes, development of the rotenone rat model for PD, the discovery that PD mitochondrial gene expression is sufficient to spontaneously cause development of Lewy bodies in cells, and the first United States clinical trial of chronic GDNF administration in patients with advanced PD.

Recently, the NINDS has funded a Parkinson's Disease Data Organizing Center (PD-DOC) to collect information from all PD centers, thus allowing for standardized data, resources, and reagents to be shared widely within the PD community. The NINDS hopes that research at these Centers of Excellence will lead to clinical trials of new treatments in patients with PD.

History

On November 13, 1997, the President of the United States signed into law The Morris K. Udall Parkinson's Disease Research Act (P.L. 105-78). Prior to the passage of this Act, the NINDS had already recognized the need to establish Centers of Excellence in PD research, and as a result, released an initial Request for Applications (RFA) to solicit these centers. Of the applications that were received in response to this RFA, NINDS selected three centers for funding. Following the passage of the Udall Act, NINDS issued a second RFA for PD Centers of Excellence and funded eight additional grants. All of the Udall Centers focus on scientific research designed to improve the diagnosis and treatment of patients with PD and related neurodegenerative disorders and on research to gain a better understanding of the fundamental cause(s) of the disease. The Centers have lived up to their expectation to foster an environment that enhances the research effectiveness of investigators in a multidisciplinary setting, utilizing specialized methods relevant to the study of these disorders.

The Centers of Excellence for Parkinson's Disease Research program was developed in honor of former Congressman Morris K. Udall, who died in 1998 after a long battle with PD. Mr. Udall was elected to the U.S. House of Representatives in 1961 in a special election to replace his brother Stewart who left the position to become President John F. Kennedy's Secretary of the Interior. Udall was diagnosed with PD in 1979, but he remained active as a Member of Congress until May 1991.

Future

NINDS is committed to continuing and enhancing the tradition of scientific excellence that has been fostered by the Udall Centers over the past 5 years. To this end, NINDS and the National Institute of Environmental Health Sciences released a Program Announcement in October 2002 to renew the Institute's commitment to the program and to aid current and prospective Udall Center investigators in developing competitive applications for funding. NINDS has also announced an increase in funds that may be allotted to the Centers to fund the types of clinical research needed to capitalize on the increasing number of findings in the basic sciences. In addition, NINDS staff members are working with the research community to develop a standard, minimum amount of clinical information to be collected about each PD patient, allowing information from different studies to be compared and combined. NINDS believes that all of these efforts will help to strengthen the Udall program in the coming years.

NINDS is committed to continuing and enhancing the tradition of scientific excellence that has been fostered by the Udall Centers over the past 5 years.

Udall Centers Across the Country

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Boston, Massachusetts
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New York City, New York
Director: Robert Burke, M.D.

Duke University
Durham, North Carolina
Director: Jeffery M. Vance, M.D.

Harvard University Medical School and McLean Hospital
Belmont, Massachusetts
Director: Ole Isacson, M.D.

Johns Hopkins University School of Medicine
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Director: Ted M. Dawson, M.D., Ph.D.

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Boston, Massachusetts
Director: Anne Young, M.D., Ph.D.

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University of Pittsburgh
Pittsburgh, Pennsylvania
Director: Michael J. Zigmond, Ph.D.

University of Virginia
Charlottesville, Virginia
Director: G. Fred Wooten, M.D.

Coordinating data and resources from all these centers:
Parkinson's Disease Organizing Center
University of Rochester
Rochester, New York
Director: Roger Kurlan, M.D.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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