Patient Handouts

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Parkinson Disease

What is Parkinson's disease?

Parkinson's disease belongs to a group of conditions called movement disorders. The four main symptoms are tremor, or trembling in hands, arms, legs, jaw, or head; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance. These symptoms usually begin gradually and worsen with time. As they become more pronounced, patients may have difficulty walking, talking, or completing other simple tasks. Not everyone with one or more of these symptoms has PD, as the symptoms sometimes appear in other diseases as well.

PD is both chronic, meaning it persists over a long period of time, and progressive, meaning its symptoms grow worse over time. It is not contagious. Although some PD cases appear to be hereditary, and a few can be traced to specific genetic mutations, most cases are sporadic — that is, the disease does not seem to run in families. Many researchers now believe that PD results from a combination of genetic susceptibility and exposure to one or more environmental factors that trigger the disease.

PD is the most common form of parkinsonism, the name for a group of disorders with similar features and symptoms. PD is also called primary parkinsonism or idiopathic PD. The term idiopathic means a disorder for which no cause has yet been found. While most forms of parkinsonism are idiopathic, there are some cases where the cause is known or suspected or where the symptoms result from another disorder. For example, parkinsonism may result from changes in the brain's blood vessels.

What causes the disease?

Parkinson's disease occurs when nerve cells, or neurons, in an area of the brain known as the substantia nigra die or become impaired. Normally, these neurons produce an important brain chemical known as dopamine. Dopamine is a chemical messenger responsible for transmitting signals between the substantia nigra and the next "relay station" of the brain, the corpus striatum, to produce smooth, purposeful movement. Loss of dopamine results in abnormal nerve firing patterns within the brain that cause impaired movement. Studies have shown that most Parkinson's patients have lost 60 to 80 percent or more of the dopamine-producing cells in the substantia nigra by the time symptoms appear. Recent studies have shown that people with PD also have loss of the nerve endings that produce the neurotransmitter norepinephrine. Norepinephrine, which is closely related to dopamine, is the main chemical messenger of the sympathetic nervous system, the part of the nervous system that controls many automatic functions of the body, such as pulse and blood pressure. The loss of norepinephrine might help explain several of the non-motor features seen in PD, including fatigue and abnormalities of blood pressure regulation.

Many brain cells of people with PD contain Lewy bodies – unusual deposits or clumps of the protein alpha-synuclein, along with other proteins. Researchers do not yet know why Lewy bodies form or what role they play in development of the disease. The clumps may prevent the cell from functioning normally, or they may actually be helpful, perhaps by keeping harmful proteins "locked up" so that the cells can function.

Scientists have identified several genetic mutations associated with PD, and many more genes have been tentatively linked to the disorder. Studying the genes responsible for inherited cases of PD can help researchers understand both inherited and sporadic cases. The same genes and proteins that are altered in inherited cases may also be altered in sporadic cases by environmental toxins or other factors. Researchers also hope that discovering genes will help identify new ways of treating PD.

Although the importance of genetics in PD is increasingly recognized, most researchers believe environmental exposures increase a person's risk of developing the disease. Even in familial cases, exposure

to toxins or other environmental factors may influence when symptoms of the disease appear or how the disease progresses. There are a number of toxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, or MPTP (found in some kinds of synthetic heroin), that can cause parkinsonian symptoms in humans. Other, still-unidentified environmental factors also may cause PD in genetically susceptible individuals.

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 contracting herpes virus infections. In these women, the symptoms, which later disappeared, were linked to a temporary inflammation of the substantia nigra.

Several lines of research suggest that mitochondria may play a role in the development of PD. Mitochondria are the energy-producing components of the cell and are major sources of free radicals — molecules that damage membranes, proteins, DNA, and other parts of the cell. This damage 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.

Other research suggests that the cell's protein disposal system may fail in people with PD, causing proteins to build up to harmful levels and trigger cell death. Additional studies have found evidence that clumps of protein that develop inside brain cells of people with PD may contribute to the death of neurons, and that inflammation or overstimulation of cells (because of toxins or other factors) may play a role in the disease. However, the precise role of the protein deposits remains unknown. Some researchers even speculate that the protein buildup is part of an unsuccessful attempt to protect the cell. While mitochondrial dysfunction, oxidative stress, inflammation, and many other cellular processes may contribute to PD, the actual cause of the dopamine cell death is still undetermined.

Who gets Parkinson's disease?

About 50,000 Americans are diagnosed with PD each year, but getting an accurate count of the number of cases may be impossible because many people in the early stages of the disease assume their symptoms are the result of normal aging and do not seek help from a physician. Also, diagnosis is sometimes difficult and uncertain because other conditions may produce symptoms of PD and there is no definitive test for the disease. People with PD may sometimes be told by their doctors that they have other disorders, and people with PD-like diseases may be incorrectly diagnosed as having PD.

PD strikes about 50 percent more men than women, but the reasons for this discrepancy are unclear. While it occurs in people throughout the world, a number of studies have found a higher incidence in developed countries, possibly because of increased exposure to pesticides or other toxins in those countries. Other studies have found an increased risk in people who live in rural areas and in those who work in certain professions, although the studies to date are not conclusive and the reasons for the apparent risks are not clear.

One clear risk factor for PD is age. The average age of onset is 60 years, and the incidence rises significantly with increasing age. However, about 5 to 10 percent of people with PD have "early-onset" disease that begins before the age of 50. Early-onset forms of the disease are often inherited, though not always, and some have been linked to specific gene mutations. People with one or more close relatives who have PD have an increased risk of developing the disease themselves, but the total risk is still just 2 to 5 percent unless the family has a known gene mutation for the disease. An estimated 15 to 25 percent of people with PD have a known relative with the disease.

In very rare cases, parkinsonian symptoms may appear in people before the age of 20. This condition is called juvenile parkinsonism. It is most commonly seen in Japan but has been found in other countries as well. It usually begins with dystonia and bradykinesia, and the symptoms often improve with levodopa medication. Juvenile parkinsonism often runs in families and is sometimes linked to a mutated parkin gene.

What are the symptoms of the disease?

Early symptoms of Parkinson's disease are subtle and occur gradually. Patients may be tired or notice a general malaise. Some may feel a little shaky or have difficulty getting out of a chair. They may notice that they speak too softly or that their handwriting looks cramped and spidery. They may lose track of a word or thought, or they may feel irritable or depressed for no apparent reason. This very early period may last a long time before the more classic and obvious symptoms appear.

Friends or family members may be the first to notice changes. They may see that the person's face lacks expression and animation (known as "masked face") or that the person remains in a certain position for a long time or does not move an arm or leg normally. Perhaps they see that the person seems stiff, unsteady, and unusually slow.

As the disease progresses, the shaking, or tremor, that affects the majority of Parkinson's patients may begin to interfere with daily activities. Patients may not be able to hold utensils steady or may find that the shaking makes reading a newspaper difficult. Parkinson's tremor may become worse when the patient is relaxed. A few seconds after the hands are rested on a table, for instance, the shaking is most pronounced. For most patients, tremor is usually the symptom that causes them to seek medical help.

People with PD often develop a so-called parkinsonian gait that includes a tendency to lean forward, small quick steps as if hurrying forward (called festination), and reduced swinging of the arms. They also may have trouble initiating movement (start hesitation), and they may stop suddenly as they walk (freezing).

PD does not affect everyone the same way, and the rate of progression differs among patients. Tremor is the major symptom for some patients, while for others, tremor is nonexistent or very minor.

PD symptoms often begin on one side of the body. However, as it progresses, the disease eventually affects both sides. Even after the disease involves both sides of the body, the symptoms are often less severe on one side than on the other. The four primary symptoms of PD are:

• **Tremor**. The tremor associated with Parkinson's disease has a characteristic appearance. Typically, the tremor takes the form of a rhythmic back-and-forth motion of the thumb and forefinger at three beats per second. This is sometimes called "pill rolling." Tremor usually begins in a hand, although sometimes a foot or the jaw is affected first. It is most obvious when the hand is at rest or when a person is under stress. In three out of four patients, the tremor may affect only one part or side of the body, especially during the early stages of the disease. Later it may become more general. Tremor is rarely disabling and it usually disappears during sleep or improves with intentional movement.

• **Rigidity**. Rigidity, or a resistance to movement, affects most parkinsonian patients. A major principle of body movement is that all muscles have an opposing muscle. Movement is possible not just because one muscle becomes more active, but because the opposing muscle relaxes. In Parkinson's disease, rigidity comes about when, in response to signals from the brain, the delicate balance of opposing muscles is disturbed. The muscles remain constantly tensed and contracted so that the person aches or feels stiff or weak. The rigidity becomes obvious when another person tries to move the patient's arm, which will move only in ratchet-like or short, jerky movements known as "cogwheel" rigidity.

• **Bradykinesia**. Bradykinesia, or the slowing down and loss of spontaneous and automatic movement, is particularly frustrating because it is unpredictable. One moment the patient can move easily. The next moment he or she may need help. This may well be the most disabling and distressing symptom of the disease because the patient cannot rapidly perform routine movements. Activities once performed quickly and easily — such as washing or dressing — may take several hours.

• **Postural instability**. Postural instability, or impaired balance and coordination, causes patients to develop a forward or backward lean and to fall easily. When bumped from the front or when starting to walk, patients with a backward lean have a tendency to step backwards, which is known as *retropulsion*. Postural instability can cause patients to have a stooped posture in which the head is bowed and the shoulders are

drooped.

A number of other symptoms may accompany PD. Some are minor; others are not. Many can be treated with medication or physical therapy. No one can predict which symptoms will affect an individual patient, and the intensity of the symptoms varies from person to person.

• **Depression**. This is a common problem and may appear early in the course of the disease, even before other symptoms are noticed. Depression may not be severe, but it may be intensified by the drugs used to treat other symptoms of Parkinson's disease. Fortunately, depression can be successfully treated with antidepressant medications.

• **Emotional changes**. Some people with Parkinson's disease become fearful and insecure. Perhaps they fear they cannot cope with new situations. They may not want to travel, go to parties, or socialize with friends. Some lose their motivation and become dependent on family members. Others may become irritable or uncharacteristically pessimistic.

• **Difficulty in swallowing and chewing**. Muscles used in swallowing may work less efficiently in later stages of the disease. In these cases, food and saliva may collect in the mouth and back of the throat, which can result in choking or drooling. Medications can often alleviate these problems.

• **Speech changes**. About half of all parkinsonian patients have problems with speech. They may speak too softly or in a monotone, hesitate before speaking, slur or repeat their words, or speak too fast. A speech therapist may be able to help patients reduce some of these problems.

• **Urinary problems or constipation**. In some patients bladder and bowel problems can occur due to the improper functioning of the autonomic nervous system, which is responsible for regulating smooth muscle activity. Some people may become incontinent while others have trouble urinating. In others, constipation may occur because the intestinal tract operates more slowly. Constipation can also be caused by inactivity, eating a poor diet, or drinking too little fluid. The medications used to treat PD also can contribute to constipation. It can be a persistent problem and, in rare cases, can be serious enough to require hospitalization.

• **Skin problems**. In Parkinson's disease, it is common for the skin on the face to become very oily, particularly on the forehead and at the sides of the nose. The scalp may become oily too, resulting in dandruff. In other cases, the skin can become very dry. These problems are also the result of an improperly functioning autonomic nervous system. Standard treatments for skin problems help. Excessive sweating, another common symptom, is usually controllable with medications used for Parkinson's disease.

• **Sleep problems**. Sleep problems common in PD include difficulty staying asleep at night, restless sleep, nightmares and emotional dreams, and drowsiness or sudden sleep onset during the day. Patients with PD should never take over-the-counter sleep aids without consulting their physicians.

• **Dementia or other cognitive problems**. Some, but not all, people with PD may develop memory problems and slow thinking. In some of these cases, cognitive problems become more severe, leading to a condition called Parkinson's dementia late in the course of the disease. This dementia may affect memory, social judgment, language, reasoning, or other mental skills. There is currently no way to halt PD dementia, but studies have shown that a drug called rivastigmine may slightly reduce the symptoms. The drug donepezil also can reduce behavioral symptoms in some people with PD-related dementia.

• **Orthostatic hypotension**. Orthostatic hypotension is a sudden drop in blood pressure when a person stands up from a lying-down position. This may cause dizziness, lightheadedness, and, in extreme cases, loss of balance or fainting. Studies have suggested that, in PD, this problem results from a loss of nerve endings in the sympathetic nervous system that controls heart rate, blood pressure, and other automatic functions in the body. The medications used to treat PD also may contribute to this symptom.

• **Muscle cramps and dystonia**. The rigidity and lack of normal movement associated with PD often causes muscle cramps, especially in the legs and toes. Massage, stretching, and applying heat may help with these cramps. PD also can be associated with dystonia — sustained muscle contractions that cause forced or twisted positions. Dystonia in PD is often caused by fluctuations in the body's level of dopamine. It can usually be relieved or reduced by adjusting the person's medications.

• **Pain**. Many people with PD develop aching muscles and joints because of the rigidity and abnormal postures often associated with the disease. Treatment with levodopa and other dopaminergic drugs often alleviates these pains to some extent. Certain exercises also may help. People with PD also may develop pain due to compression of nerve roots or dystonia-related muscle spasms. In rare cases, people with PD may develop unexplained burning, stabbing sensations. This type of pain, called "central pain," originates in the brain. Dopaminergic drugs, opiates, antidepressants, and other types of drugs may all be used to treat this type of pain.

• **Fatigue and loss of energy**. The unusual demands of living with PD often lead to problems with fatigue, especially late in the day. Fatigue may be associated with depression or sleep disorders, but it also may result from muscle stress or from overdoing activity when the person feels well. Fatigue also may result from akinesia – trouble initiating or carrying out movement. Exercise, good sleep habits, staying mentally active, and not forcing too many activities in a short time may help to alleviate fatigue.

• **Sexual dysfunction**. PD often causes erectile dysfunction because of its effects on nerve signals from the brain or because of poor blood circulation. PD-related depression or use of antidepressant medication also may cause decreased sex drive and other problems. These problems are often treatable.

What other diseases resemble Parkinson disease?

A number of disorders can cause symptoms similar to those of PD. People with symptoms that resemble PD but that result from other causes are sometimes said to have parkinsonism. Some of these disorders are listed below.

• **Postencephalitic parkinsonism**. Just after the first World War, a viral disease, encephalitis lethargica, attacked almost 5 million people throughout the world, and then suddenly disappeared in the 1920s. Known as sleeping sickness in the United States, this disease killed one third of its victims and in many others led to post-encephalitic parkinsonism, a particularly severe form of movement disorder in which some patients developed, often years after the acute phase of the illness, disabling neurological disorders, including various forms of catatonia. (In 1973, neurologist Oliver Sacks published Awakenings, an account of his work in the late 1960's with surviving post-encephalitic patients in a New York hospital. Using the then-experimental drug levodopa, Dr. Sacks was able to temporarily "awaken" these patients from their statue-like state. A film by the same name was released in 1990.) In rare cases, other viral infections, including western equine encephalomyelitis, eastern equine encephalomyelitis, and Japanese B encephalitis, can leave patients with parkinsonian symptoms.

• **Drug-induced parkinsonism**. A reversible form of parkinsonism sometimes results from use of certain drugs, such as chlorpromazine and haloperidol, which are prescribed for patients with psychiatric disorders. Some drugs used for stomach disorders (metoclopramide), high blood pressure (reserpine), and epilepsy (valproate) may also produce parkinsonian symptoms. Stopping the medication or lowering the dosage of these medications usually causes the symptoms to go away.

• **Toxin-induced parkinsonism**. Some toxins — such as manganese dust, carbon disulfide, and carbon monoxide — can cause parkinsonism. The chemical MPTP also causes a permanent form of parkinsonism that closely resembles PD. Investigators discovered this reaction in the 1980s when heroin addicts in California who had taken an illicit street drug contaminated with MPTP began to develop severe parkinsonism. This discovery, which showed that a toxic substance could damage the brain and produce parkinsonian symptoms, caused a dramatic breakthrough in Parkinson's research: for the first time, scientists were able to simulate PD in animals and conduct studies to increase understanding of the disease.

• **Arteriosclerotic parkinsonism**. Sometimes known as pseudoparkinsonism, vascular parkinsonism, or atherosclerotic parkinsonism, arteriosclerotic parkinsonism involves damage to the brain due to multiple small strokes. Tremor is rare in this type of parkinsonism, while dementia — the loss of mental skills and abilities — is common. Antiparkinsonian drugs are of little help to patients with this form of parkinsonism.

• **Parkinsonism-dementia complex of Guam**. This disease occurs among the Chamorro populations of Guam and the Mariana Islands and may be accompanied by a motor neuron disease resembling amyotrophic lateral sclerosis (Lou Gehrig's disease). The course of the disease is rapid, with death typically occurring within 5 years.

• **Post-traumatic parkinsonism**. Also known as post-traumatic encephalopathy or "punch-drunk syndrome," parkinsonian symptoms can sometimes develop after a severe head injury or frequent head trauma that results from boxing or other activities. This type of trauma also can cause a form of dementia called dementia pugilistica.

• **Essential tremor**. Essential tremor, sometimes called benign essential tremor or familial tremor, is a common condition that tends to run in families and progresses slowly over time. The tremor is usually equal in both hands and increases when the hands are moving. The tremor may involve the head but usually spares the legs. Patients with essential tremor have no other parkinsonian features. Essential tremor is not the same as PD, and usually does not lead to it, although in some cases the two conditions may overlap in one person. Essential tremor does not respond to levodopa or most other PD drugs, but it can be treated with other medications.

• **Normal pressure hydrocephalus**. Normal pressure hydrocephalus (NPH) is an abnormal increase of cerebrospinal fluid (CSF) in the brain's ventricles, or cavities. It occurs if the normal flow of CSF throughout the brain and spinal cord is blocked in some way. This causes the ventricles to enlarge, putting pressure on the brain. Symptoms include problems with walking, impaired bladder control leading to urinary frequency or incontinence, and progressive mental impairment and dementia. The person also may have a general slowing of movements or may complain that his or her feet feel "stuck." These symptoms may sometimes be mistaken for PD. Brain scans, intracranial pressure monitoring, and other tests can help to distinguish NPH from PD and other disorders. NPH can sometimes be treated by surgically implanting a CSF shunt that drains excess cerebrospinal fluid into the abdomen, where it is absorbed.

• **Progressive supranuclear palsy**. Progressive supranuclear palsy (PSP), sometimes called Steele-Richardson-Olszewski syndrome, is a rare, progressive brain disorder that causes problems with control of gait and balance. People often tend to fall early in the course of PSP. One of the most obvious signs of the disease is an inability to move the eyes properly. Some patients describe this effect as a blurring. PSP patients often show alterations of mood and behavior, including depression and apathy as well as mild dementia. The symptoms of PSP are caused by a gradual deterioration of brain cells in the brainstem. It is often misdiagnosed because some of its symptoms are very much like those of PD, Alzheimer's disease, and other brain disorders. PSP symptoms usually do not respond to medication.

• **Corticobasal degeneration**. Corticobasal degeneration results from atrophy of multiple areas of the brain, including the cerebral cortex and the basal ganglia. Initial symptoms may first appear on one side of the body, but eventually affect both sides. Symptoms are similar to those found in PD, including rigidity, impaired balance and coordination, and dystonia. Other symptoms may include cognitive and visual-spatial impairments, apraxia (loss of the ability to make familiar, purposeful movements), hesitant and halting speech, myoclonus (muscular jerks), and dysphagia (difficulty swallowing). Unlike PD, corticobasal degeneration usually does not respond to medication.

• **Multiple system atrophy**. Multiple system atrophy (MSA) refers to a set of slowly progressive disorders that affect the central and autonomic nervous systems. MSA may have symptoms that resemble PD. It also may take a form that primarily produces poor coordination and slurred speech, or it may have a mixture of these symptoms. Other symptoms may include breathing and swallowing difficulties, male impotence,

constipation, and urinary difficulties. The disorder previously called Shy-Drager syndrome refers to MSA with prominent orthostatic hypotension — a fall in blood pressure every time the person stands up. MSA with parkinsonian symptoms is sometimes referred to as striatonigral degeneration, while MSA with poor coordination and slurred speech is sometimes called olivopontocerebellar atrophy.

• **Dementia with Lewy bodies**. Dementia with Lewy bodies is a neurodegenerative disorder associated with abnormal protein deposits (Lewy bodies) found in certain areas of the brain. Symptoms can range from traditional parkinsonian symptoms, such as bradykinesia, rigidity, tremor, and shuffling gait, to symptoms similar to those of Alzheimer's disease. These symptoms may fluctuate, or wax and wane dramatically. Visual hallucinations may be one of the first symptoms, and patients may suffer from other psychiatric disturbances such as delusions and depression. Cognitive problems also occur early in the course of the disease. Levodopa and other antiparkinsonian medications can help with the motor symptoms of dementia with Lewy bodies, but they may make hallucinations and delusions worse.

• **Parkinsonism accompanying other conditions**. Parkinsonian symptoms may also appear in patients with other, clearly distinct neurological disorders such as Shy-Drager syndrome (sometimes called multiple system atrophy), progressive supranuclear palsy, Wilson's disease, Huntington's disease, Hallervorden-Spatz syndrome, Alzheimer's disease, and Creutzfeldt-Jakob disease. Each of these disorders has specific features that help to distinguish them from PD.

MSA, corticobasal degeneration, and progressive supranuclear palsy are sometimes referred to as "Parkinson's-plus" diseases because they have the symptoms of PD plus additional features.

How is Parkinson disease diagnosed?

There are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. Therefore the diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal. Since many other diseases have similar features but require different treatments, making a precise diagnosis as soon as possible is essential so that patients can receive the proper treatment.

How is the disease treated?

At present, there is no cure for Parkinson's disease. But a variety of medications provide dramatic relief from the symptoms.

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. 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 or prevent or slow its breakdown.

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 interfere with production or uptake 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, that is, the symptoms that don't affect movement. For example, people with PD-related depression may be prescribed antidepressants.

• **Levodopa**. The cornerstone of therapy for PD is the drug levodopa (also called L-dopa). Levodopa (from the full name L-3,4-dihydroxyphenylalanine) is a simple chemical found naturally in plants and animals.

Levodopa is the generic name used for this chemical when it is formulated for drug use in patients. Nerve cells can use levodopa to make dopamine and replenish the brain's dwindling supply. People cannot simply take dopamine pills because dopamine does not easily pass through the blood-brain barrier, a lining of cells inside blood vessels that regulates the transport of oxygen, glucose, and other substances into the brain. Usually, patients are given levodopa combined with another substance called carbidopa. When added to levodopa, carbidopa delays the conversion of levodopa into dopamine until it reaches the brain, preventing or diminishing some of the side effects that often accompany levodopa therapy. Carbidopa also reduces the amount of levodopa needed.

Levodopa is very successful at reducing the tremors and other symptoms of PD during the early stages of the disease. It allows the majority of people with PD to extend the period of time in which they can lead relatively normal, productive lives.

Although levodopa helps most people with PD, not all symptoms respond equally to the drug. Levodopa usually helps most with bradykinesia and rigidity. Problems with balance and other non-motor symptoms may not be alleviated at all.

People who have taken other medications before starting levodopa therapy may have to cut back or eliminate these drugs in order to feel the full benefit of levodopa. People often see dramatic improvement in their symptoms after starting levodopa therapy. However, they may need to increase the dose gradually for maximum benefit. A high-protein diet can interfere with the absorption of levodopa, so some physicians recommend that patients taking the drug restrict their protein consumption during the early parts of the day or avoid taking their medications with protein-rich meals.

Levodopa is often so effective that some people may temporarily forget they have PD during the early stages of the disease. But levodopa is not a cure. Although it can reduce the symptoms of PD, it does not replace lost nerve cells and it does not stop the progression of the disease.

Levodopa can have a variety of side effects. The most common initial side effects include nausea, vomiting, low blood pressure, and restlessness. The drug also can cause drowsiness or sudden sleep onset, which can make driving and other activities dangerous. Long-term use of levodopa sometimes causes hallucinations and psychosis. The nausea and vomiting caused by levodopa are greatly reduced by combining levodopa and carbidopa, which enhances the effectiveness of a lower dose.

Dyskinesias, or involuntary movements such as twitching, twisting, and writhing, commonly develop in people who take large doses of levodopa over an extended period. These movements may be either mild or severe and either very rapid or very slow. The dose of levodopa is often reduced in order to lessen these drug-induced movements. However, the PD symptoms often reappear even with lower doses of medication. Doctors and patients must work together closely to find a tolerable balance between the drug's benefits and side effects. If dyskinesias are severe, surgical treatment may be considered. Because dyskinesias tend to occur with long-term use of levodopa, doctors often start younger PD patients on other dopamine-increasing drugs and switch to levodopa only when those drugs become ineffective.

Other troubling and distressing problems may occur with long-term levodopa use. Patients may begin to notice more pronounced symptoms before their first dose of medication in the morning, and they may develop muscle spasms or other problems when each dose begins to wear off. The period of effectiveness after each dose may begin to shorten, called the wearing-off effect. Another potential problem is referred to as the on-off effect — sudden, unpredictable changes in movement, from normal to parkinsonian movement and back again. These effects probably indicate that the patient's response to the drug is changing or that the disease is progressing.

One approach to alleviating these side effects is to take levodopa more often and in smaller amounts. People with PD should never stop taking levodopa without their physician's knowledge or consent because rapidly withdrawing the drug can have potentially serious side effects, such as immobility or difficulty breathing.

Fortunately, physicians have other treatment choices for some symptoms and stages of PD. These therapies include the following:

• **Dopamine agonists**. These drugs, which include bromocriptine, pergolide, apomorphine, pramipexole, and ropinirole, mimic the role of dopamine in the brain. They can be given alone or in conjunction with levodopa. They may be used in the early stages of the disease, or later on in order to lengthen the duration of response to levodopa in patients who experience wearing off or on-off effects. They are generally less effective than levodopa in controlling rigidity and bradykinesia. Many of the potential side effects are similar to those associated with the use of levodopa, including drowsiness, sudden sleep onset, hallucinations, confusion, dyskinesias, edema (swelling due to excess fluid in body tissues), nightmares, and vomiting. In rare cases, they can cause compulsive behavior, such as an uncontrollable desire to gamble, hypersexuality, or compulsive shopping. Bromocriptine and pergolide sometimes also cause fibrosis, or a buildup of fibrous tissue, in the heart valves or the chest cavity. Fibrosis usually goes away once the drugs are stopped.

• **MAO-B inhibitors**. These drugs inhibit the enzyme monoamine oxidase B, or MAO-B, which breaks down dopamine in the brain. MAO-B inhibitors cause dopamine to accumulate in surviving nerve cells and reduce the symptoms of PD. Selegiline, also called deprenyl, is an MAO-B inhibitor that is commonly used to treat PD. Studies supported by the NINDS have shown that selegiline can delay the need for levodopa therapy by up to a year or more. When selegiline is given with levodopa, it appears to enhance and prolong the response to levodopa and thus may reduce wearing-off fluctuations. Selegiline is usually well-tolerated, although side effects may include nausea, orthostatic hypotension, or insomnia. It should not be taken with the antidepressant fluoxetine or the sedative mepiridine, because combining seligiline with these drugs can be harmful. An NINDS-sponsored study of seligiline in the late 1980s suggested that it might help to slow the loss of nerve cells in PD. However, follow-up studies cast doubt on this finding. Another MAO-B inhibitor, rasagiline, was approved by the FDA in May 2006 for use in treating PD.

• **COMT inhibitors**. COMT stands for catechol-O-methyltransferase, another enzyme that helps to break down dopamine. Two COMT inhibitors are approved to treat PD in the United States: entacapone and tolcapone. These drugs prolong the effects of levodopa by preventing the breakdown of dopamine. COMT inhibitors can decrease the duration of "off" periods, and they usually make it possible to reduce the person's dose of levodopa. The most common side effect is diarrhea. The drugs may also cause nausea, sleep disturbances, dizziness, urine discoloration, abdominal pain, low blood pressure, or hallucinations. In a few rare cases, tolcapone has caused severe liver disease. Because of this, patients taking tolcapone need regular monitoring of their liver function.

• **Amantadine**. An antiviral drug, amantadine, can help reduce symptoms of PD and levodopa-induced dyskinesia. It is often used alone in the early stages of the disease. It also may be used with an anticholinergic drug or levodopa. After several months, amantadine's effectiveness wears off in up to half of the patients taking it. Amantadine's side effects may include insomnia, mottled skin, edema, agitation, or hallucinations. Researchers are not certain how amantadine works in PD, but it may increase the effects of dopamine.

• **Anticholinergics**. These drugs, which include trihexyphenidyl, benztropine, and ethopropazine, decrease the activity of the neurotransmitter acetylcholine and help to reduce tremors and muscle rigidity. Only about half the patients who receive anticholinergics are helped by it, usually for a brief period and with only a 30 percent improvement. Side effects may include dry mouth, constipation, urinary retention, hallucinations, memory loss, blurred vision, and confusion.

When recommending a course of treatment, a doctor will assess how much the symptoms disrupt the patient's life and then tailor therapy to the person's particular condition. Since no two patients will react the same way to a given drug, it may take time and patience to get the dose just right. Even then, symptoms may not be completely alleviated.

Medications to treat the motor symptoms of Parkinson disease

Drugs that increase brain levels of dopamine
• Levodopa
Drugs that mimic dopamine (dopamine agonists)
• Apomorphine
• Bromocriptine
• Pramipexole
• Ropinirole
Drugs that inhibit dopamine breakdown (MAO-B inhibitors)
• Selegiline (deprenyl)
Drugs that inhibit dopamine breakdown (COMT inhibitors)
• Entacapone
• Tolcapone
Drugs that decrease the action of acetylcholine anticholinergics)
• Trihexyphenidyl
• Benztropine
• Ethopropazine
Drugs with an unknown mechanism of action for PD
• Amantadine

Medications for non-motor symptoms. Doctors may prescribe a variety of medications to treat the non-motor symptoms of PD, such as depression and anxiety. For example, depression can be treated with standard anti-depressant drugs such as amytriptyline or fluoxetine (however, as stated earlier, fluoxetine should not be combined with MAO-B inhibitors). Anxiety can sometimes be treated with drugs called benzodiazepines. Orthostatic hypotension may be helped by increasing salt intake, reducing antihypertension drugs, or prescribing medications such as fludrocortisone.

Hallucinations, delusions, and other psychotic symptoms are often caused by the drugs prescribed for PD. Therefore reducing or stopping PD medications may alleviate psychosis. If such measures are not effective, doctors sometimes prescribe drugs called atypical antipsychotics, which include clozapine and quetiapine. Clozapine also may help to control dyskinesias. However, clozapine also can cause a serious blood disorder called agranulocytosis, so people who take it must have their blood monitored frequently.

Surgery

Treating PD with surgery was once a common practice. But after the discovery of levodopa, surgery was restricted to only a few cases. Studies in the past few decades have led to great improvements in surgical techniques, and surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient.

Pallidotomy and thalamotomy. The earliest types of surgery for PD involved selectively destroying specific parts of the brain that contribute to the symptoms of the disease. Investigators have now greatly refined the use of these procedures. The most common of these procedures is called pallidotomy. In this procedure, a surgeon selectively destroys a portion of the brain called the globus pallidus. Pallidotomy can improve symptoms of tremor, rigidity, and bradykinesia, possibly by interrupting the connections between the globus pallidus and the striatum or thalamus. Some studies have also found that pallidotomy can improve gait and balance and reduce the amount of levodopa patients require, thus reducing drug-induced dyskinesias and dystonia. A related procedure, called thalamotomy, involves surgically destroying part of the brain's thalamus. Thalamotomy is useful primarily to reduce tremor.

Because these procedures cause permanent destruction of brain tissue, they have largely been replaced by deep brain stimulation for treatment of PD.

Deep brain stimulation. Deep brain stimulation, or DBS, uses an electrode surgically implanted into part of the brain. The electrodes are connected by a wire under the skin to a small electrical device called a pulse

generator that is implanted in the chest beneath the collarbone. The pulse generator and electrodes painlessly stimulate the brain in a way that helps to stop many of the symptoms of PD. DBS has now been approved by the U.S. Food and Drug Administration, and it is widely used as a treatment for PD.

DBS can be used on one or both sides of the brain. If it is used on just one side, it will affect symptoms on the opposite side of the body. DBS is primarily used to stimulate one of three brain regions: the subthalamic nucleus, the globus pallidus, or the thalamus. However, the subthalamic nucleus, a tiny area located beneath the thalamus, is the most common target. Stimulation of either the globus pallidus or the subthalamic nucleus can reduce tremor, bradykinesia, and rigidity. Stimulation of the thalamus is useful primarily for reducing tremor.

DBS usually reduces the need for levodopa and related drugs, which in turn decreases dyskinesias. It also helps to relieve on-off fluctuation of symptoms. People who initially responded well to treatment with levodopa tend to respond well to DBS. While the benefits of DBS can be substantial, it usually does not help with speech problems, "freezing," posture, balance, anxiety, depression, or dementia.

One advantage of DBS compared to pallidotomy and thalamotomy is that the electrical current can be turned off using a handheld device. The pulse generator also can be externally programmed.

Patients must return to the medical center frequently for several months after DBS surgery in order to have the stimulation adjusted by trained doctors or other medical professionals. The pulse generator must be programmed very carefully to give the best results. Doctors also must supervise reductions in patients' medications. After a few months, the number of medical visits usually decreases significantly, though patients may occasionally need to return to the center to have their stimulator checked. Also, the battery for the pulse generator must be surgically replaced every three to five years, though externally rechargeable batteries may eventually become available. Long-term results of DBS are still being determined. DBS does not stop PD from progressing, and some problems may gradually return. However, studies up to several years after surgery have shown that many people's symptoms remain significantly better than they were before DBS.

DBS is not a good solution for everyone. It is generally used only in people with advanced, levodopa-responsive PD who have developed dyskinesias or other disabling "off" symptoms despite drug therapy. It is not normally used in people with memory problems, hallucinations, a poor response to levodopa, severe depression, or poor health. DBS generally does not help people with "atypical" parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, or post-traumatic parkinsonism. Younger people generally do better than older people after DBS, but healthy older people can undergo DBS and they may benefit a great deal.

As with any brain surgery, DBS has potential complications, including stroke or brain hemorrhage. These complications are rare, however. There is also a risk of infection, which may require antibiotics or even replacement of parts of the DBS system. The stimulator may sometimes cause speech problems, balance problems, or even dyskinesias. However, those problems are often reversible if the stimulation is modified.

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 used in DBS.

Complementary and supportive therapies

A wide variety of complementary and supportive therapies may be used for PD. Among these therapies are standard physical, occupational, and speech therapy techniques, which can help with such problems as gait and voice disorders, tremors and rigidity, and cognitive decline. Other types of supportive therapies include the following:

Diet. At this time there are no specific vitamins, minerals, or other nutrients that have any proven therapeutic value in PD. Some early reports have suggested that dietary supplements might be protective in PD. In

addition, a phase II clinical trial of a supplement called coenzyme Q10 suggested that large doses of this substance might slow disease progression in patients with early-stage PD. The NINDS and other components of the National Institutes of Health are funding research to determine if caffeine, antioxidants, and other dietary factors may be beneficial for preventing or treating PD. While there is currently no proof that any specific dietary factor is beneficial, a normal, healthy diet can promote overall well-being for PD patients just as it would for anyone else. Eating a fiber-rich diet and drinking plenty of fluids also can help alleviate constipation. A high protein diet, however, may limit levodopa's effectiveness.

Exercise. Exercise can help people with PD improve their mobility and flexibility. Some doctors prescribe physical therapy or muscle-strengthening exercises to tone muscles and to put underused and rigid muscles through a full range of motion. Exercises will not stop disease progression, but they may improve body strength so that the person is less disabled. Exercises also improve balance, helping people minimize gait problems, and can strengthen certain muscles so that people can speak and swallow better. Exercise can also improve the emotional well-being of people with PD, and it may improve the brain's dopamine synthesis or increase levels of beneficial compounds called neurotrophic factors in the brain. Although structured exercise programs help many patients, more general physical activity, such as walking, gardening, swimming, calisthenics, and using exercise machines, also is beneficial. People with PD should always check with their doctors before beginning a new exercise program.

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

How can people cope with Parkinson disease?

While PD usually progresses slowly, eventually the most basic daily routines may be affected — from socializing with friends and enjoying normal relationships with family members to earning a living and taking care of a home. These changes can be difficult to accept. Support groups can help people cope with the disease emotionally. These groups can also provide valuable information, advice, and experience to help people with PD, their families, and their caregivers deal with a wide range of issues, including locating doctors familiar with the disease and coping with physical limitations. A list of national organizations that can help patients locate support groups in their communities appears at the end of this brochure. Individual or family counseling also may help people find ways to cope with PD.

People with PD also can benefit from being proactive and finding out as much as possible about the disease in order to alleviate fear of the unknown and to take a positive role in maintaining their health. Many people with PD continue to work either full- or part-time, although eventually they may need to adjust their schedule and working environment to cope with the disease.

Can scientists predict or prevent Parkinson disease?

In most cases, there is no way to predict or prevent sporadic PD. However, researchers are looking for a biomarker — a biochemical abnormality that all patients with PD might share — that could be picked up by screening techniques or by a simple chemical test given to people who do not have any parkinsonian symptoms. This could help doctors identify people at risk of the disease. It also might allow them to find treatments that will stop the disease process in the early stages.

Positron emission tomography (PET) scanning may lead to important advances in our knowledge about PD. PET scans of the brain produce pictures of chemical changes as they occur. Using PET, research scientists can study the brain's dopamine receptors (the sites on nerve cells that bind with dopamine) to determine if the loss of dopamine activity follows or precedes degeneration of the neurons that make this chemical. This information could help scientists better understand the disease process and may potentially lead to improved treatments.

In rare cases, where people have a clearly inherited form of PD, researchers can test for known gene

mutations as a way of determining an individual's risk of the disease. However, this genetic testing can have far-reaching implications and people should carefully consider whether they want to know the results of such tests. Genetic testing is currently available only as a part of research studies.

What research is being done?

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. While the ultimate goal of preventing PD may take years to achieve, researchers are making great progress in understanding and treating PD.

One of the most exciting areas of PD research is genetics. Studying the genes responsible for inherited cases can help researchers understand both inherited and sporadic cases of the disease. 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.

As discussed in the “What Genes are Linked to Parkinson's Disease?" section, several genes have been definitively linked to PD in some people. Researchers also have identified a number of other genes that may play a role and are working to confirm these findings. In addition, several chromosomal regions have been linked to PD in some families. Researchers hope to identify the genes located in these chromosomal regions and to determine which of them may play roles in PD.

Researchers funded by NINDS are gathering information and DNA samples from hundreds of families with PD and are conducting large-scale gene expression studies to identify genes that are abnormally active or inactive in PD. They also are comparing gene activity in PD with gene activity in similar diseases such as progressive supranuclear palsy.

Some scientists have found evidence that specific variations in the DNA of mitochondria – structures in cells that provide the energy for cellular activity — can increase the risk of getting PD, while other variations are associated with a lowered risk of the disorder. They also have found that PD patients have more mitochondrial DNA (mtDNA) variations than patients with other movement disorders or Alzheimer's disease. Researchers are working to define how these mtDNA variations may lead to PD.

In addition to identifying new genes for PD, researchers are trying to learn how known PD genes function and how the gene mutations cause disease. For example, a 2005 study found that the normal alpha-synuclein protein may help other proteins that are important for nerve transmission to fold correctly. Other studies have suggested that the normal parkin protein protects neurons from a variety of threats, including alpha-synuclein toxicity and excitotoxicity.

Scientists continue to study environmental toxins such as pesticides and herbicides that can cause PD symptoms in animals. They have found that exposing rodents to the pesticide rotenone and several other agricultural chemicals can cause cellular and behavioral changes that mimic those seen in PD. Other studies have suggested that prenatal exposure to certain toxins can increase susceptibility to PD in adulthood. An NIH-sponsored program called the Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) focuses on how occupational exposure to toxins and use of caffeine and other substances may affect the risk of PD.

Another major area of PD research involves the cell's protein disposal system, called the ubiquitin-proteasome system. If this disposal system fails to work correctly, toxins and other substances may build up to harmful levels, leading to cell death. The ubiquitin-proteasome system requires interactions between several proteins, including parkin and UCH-L1. Therefore, disruption of the ubiquitin-proteasome system may partially explain how mutations in these genes cause PD.

Other studies focus on how Lewy bodies form and what role they play in PD. Some studies suggest that Lewy bodies are a byproduct of degenerative processes within neurons, while others indicate that Lewy bodies are a protective mechanism by which neurons lock away abnormal molecules that might otherwise be

harmful. Additional studies have found that alpha-synuclein clumps alter gene expression and bind to vesicles within the cell in ways that could be harmful.

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. Researchers also have found that dysfunction of the cells' mitochondria can make dopamine-producing neurons vulnerable to glutamate.

Other researchers are focusing on how inflammation may affect PD. Inflammation is common to a variety of neurodegenerative diseases, including PD, Alzheimer's disease, HIV-1-associated dementia, and amyotrophic lateral sclerosis. Several studies have shown that inflammation-promoting molecules increase cell death after treatment with the toxin MPTP. Inhibiting the inflammation with drugs or by genetic engineering prevented some of the neuronal degeneration in these studies. Other research 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. Inhibiting COX-2 doubled the number of neurons that survived in a mouse model for PD.

Since the discovery that MPTP causes parkinsonian symptoms in humans, scientists have found that by injecting MPTP and certain other toxins into laboratory animals, they can reproduce the brain lesions that cause these symptoms. This allows them to study the mechanisms of the disease and helps in the development of new treatments. They also have developed animal models with alterations of the alpha-synuclein and parkin genes. Other researchers have used genetic engineering to develop mice with disrupted mitochondrial function in dopamine neurons. These animals have many of the characteristics associated with PD.

Biomarkers for PD – measurable characteristics that can reveal whether the disease is developing or progressing – are another focus of research. Such biomarkers could help doctors detect the disease before symptoms appear and improve diagnosis of the disease. They also would show if medications and other types of therapy have a positive or negative effect on the course of the disease. Some of the most promising biomarkers for PD are brain imaging techniques. For example, some researchers are using positron emission tomography (PET) brain scans to try to identify metabolic changes in the brains of people with PD and to determine how these changes relate to disease symptoms. Other potential biomarkers for PD include alterations in gene expression.

Researchers also are conducting many studies of new or improved therapies for PD. While deep brain stimulation (DBS) is now FDA-approved and has been used in thousands of people with PD, researchers continue to try to improve the technology and surgical techniques in this therapy. For example, some studies are comparing DBS to the best medical therapy and trying to determine which part of the brain is the best location for stimulation. Another clinical trial is studying how DBS affects depression and quality of life.

Other clinical studies are testing whether transcranial electrical polarization (TEP) or transcranial magnetic stimulation (TMS) can reduce the symptoms of PD. In TEP, electrodes placed on the scalp are used to generate an electrical current that modifies signals in the brain's cortex. In TMS, an insulated coil of wire on the scalp is used to generate a brief electrical current.

One of the enduring questions in PD research has been how treatment with levodopa and other dopaminergic drugs affects progression of the disease. Researchers are continuing to try to clarify these effects. One study has suggested that PD patients with a low-activity variant of the gene for COMT (which breaks down dopamine) perform worse than others on tests of cognition, and that dopaminergic drugs may worsen cognition in these people, perhaps because the reduced COMT activity causes dopamine to build up to harmful levels in some parts of the brain. In the future, it may become possible to test for such individual gene differences in order to improve treatment of PD.

A variety of new drug treatments are in clinical trials for PD. These include a drug called GM1 ganglioside that increases dopamine levels in the brain. Researchers are testing whether this drug can reduce symptoms, delay disease progression, or partially restore damaged brain cells in PD patients. Other studies are testing whether a drug called istradefylline can improve motor function in PD, and whether a drug called ACP-103 that blocks receptors for the neurotransmitter serotonin will lessen the severity of parkinsonian symptoms and levodopa-associated complications in PD patients. Other topics of research include controlled-release formulas of PD drugs and implantable pumps that give a continuous supply of levodopa.

Some researchers are testing potential neuroprotective drugs to see if they can slow the progression of PD. One study, called NET-PD (Neuroexploratory Trials in Parkinson's Disease), is evaluating minocycline, creatine, coenzyme Q10, and GPI-1485 to determine if any of these agents should be considered for further testing. The NET-PD study may evaluate other possible neuroprotective agents in the future. Drugs found to be successful in the pilot phases may move to large phase III trials involving hundreds of patients. A separate group of researchers is investigating the effects of either 1200 or 2400 milligrams of coenzyme Q10 in 600 patients. Several MAO-B inhibitors, including selegiline, lazabemide, and rasagiline, also are in clinical trials to determine if they have neuroprotective effects in people with PD.

Nerve growth factors, or neurotrophic factors, which support survival, growth, and development of brain cells, are another type of potential therapy for PD. One such drug, glial cell line-derived neurotrophic factor (GDNF), has been shown to protect dopamine neurons and to promote their survival in animal models of PD. This drug has been tested in several clinical trials for people with PD, and the drug appeared to cause regrowth of dopamine nerve fibers in one person who received the drug. However, a phase II clinical study of GDNF was halted in 2004 because the treatment did not show any clinical benefit after 6 months, and some data suggested that it might even be harmful. Other neurotrophins that may be useful for treating PD include neurotrophin-4 (NT-4), brain-derived neurotrophic factor (BDNF), and fibroblast growth factor 2 (FGF-2).

While there is currently no proof that any dietary supplements can slow PD, several clinical studies are testing whether supplementation with vitamin B12 and other substances may be helpful. A 2005 study found that dietary restriction — reducing the number of calories normally consumed – helped to increase abnormally low levels of the neurotransmitter glutamate in a mouse model for early PD. The study also suggested that dietary restriction affected dopamine activity in the brain. Another study showed that dietary restriction before the onset of PD in a mouse model helped to protect dopamine-producing neurons.

Other studies are looking at treatments that might improve some of the secondary symptoms of PD, such as depression and swallowing disorders. One clinical trial is investigating whether a drug called quetiapine can reduce psychosis or agitation in PD patients with dementia and in dementia patients with parkinsonian symptoms. Some studies also are examining whether transcranial magnetic stimulation or a food supplement called s-adenosyl-methionine (SAM-e) can alleviate depression in people with PD, and whether levetiracetam, a drug approved to treat epilepsy, can reduce dyskinesias in Parkinson's patients without interfering with other PD drugs.

Another approach to treating PD is to implant cells to replace those lost in the disease. Researchers are conducting clinical trials of a cell therapy in which human retinal epithelial cells attached to microscopic gelatin beads are implanted into the brains of people with advanced PD. The retinal epithelial cells produce levodopa. The investigators hope that this therapy will enhance brain levels of dopamine.

Starting in the 1990s, researchers conducted a controlled clinical trial of fetal tissue implants in people with PD. They attempted to replace lost dopamine-producing neurons with healthy ones from fetal tissue in order to improve movement and the response to medications. While many of the implanted cells survived in the brain and produced dopamine, this therapy was associated with only modest functional improvements, mostly in patients under the age of 60. Unfortunately, some of the people who received the transplants developed disabling dyskinesias that could not be relieved by reducing antiparkinsonian medications.

Another type of cell therapy involves stem cells. Stem cells derived from embryos can develop into any kind

of cell in the body, while others, called progenitor cells, are more restricted. One study transplanted neural progenitor cells derived from human embryonic stem cells into a rat model of PD. The cells appeared to trigger improvement on several behavioral tests, although relatively few of the transplanted cells became dopamine-producing neurons. Other researchers are developing methods to improve the number of dopamine-producing cells that can be grown from embryonic stem cells in culture.

Researchers also are exploring whether stem cells from adult brains might be useful in treating PD. They have shown that the brain's white matter contains multipotent progenitor cells that can multiply and form all the major cell types of the brain, including neurons.

Gene therapy is yet another approach to treating PD. A study of gene therapy in non-human primate models of PD is testing different genes and gene-delivery techniques in an effort to refine this kind of treatment. An early-phase clinical study is also testing whether using the adeno-associated virus type 2 (AAV2) to deliver the gene for a nerve growth factor called neurturin is safe for use in people with PD. Another study is testing the safety of gene therapy using AAV to deliver a gene for human aromatic L-amino acid decarboxylase, an enzyme that helps convert levodopa to dopamine in the brain. Other investigators are testing whether gene therapy to increase the amount of glutamic acid decarboxylase, which helps produce an inhibitory neurotransmitter called GABA, might reduce the overactivity of neurons in the brain that results from lack of dopamine.

Another potential approach to treating PD is to use a vaccine to modify the immune system in a way that can protect dopamine-producing neurons. One vaccine study in mice used a drug called copolymer-1 that increases the number of immune T cells that secrete anti-inflammatory cytokines and growth factors. The researchers injected copolymer-1-treated immune cells into a mouse model for PD. The vaccine modified the behavior of supporting (glial) cells in the brain so that their responses were beneficial rather than harmful. It also reduced the amount of neurodegeneration in the mice, reduced inflammation, and increased production of nerve growth factors. Another study delivered a vaccine containing alpha-synuclein in a mouse model of PD and showed that the mice developed antibodies that reduced the accumulation of abnormal alpha-synuclein. While these studies are preliminary, investigators hope that similar approaches might one day be tested in humans.

What can I do to help?

The NINDS and the National Institute of Mental Health jointly support two national brain specimen banks. These banks supply research scientists around the world with nervous system tissue from patients with neurological and psychiatric disorders. They need tissue from patients with PD so that scientists can study and understand the disorder. Those who may be interested in donating should contact:

Rashed M. Nagra, Ph.D., Director
Human Brain and Spinal Fluid Resource Center
Neurology Research (127A) W. Los Angeles Healthcare Center
11301 Wilshire Boulevard, Building 212
Los Angeles, CA 90073
310-268-3536
Page: 310-636-5199
http://brainbank.ucla.edu/

Francine M. Benes, M.D., Ph.D., Director
Harvard Brain Tissue Resource Center
McLean Hospital
115 Mill Street
Belmont, MA 02478
617-855-2400
800-BRAIN BANK (272-4622)
www.brainbank.mclean.org

Two other organizations also provide research scientists with nervous system tissue from patients with neurological disorders. Interested donors should write or call:

National Disease Research Interchange
1628 JFK Boulevard
8 Penn Center, 8th floor
Philadelphia, PA 19103
215-557-7361
800-222-NDRI (6374)
www.ndriresource.org

UM/NPF Brain Endowment Bank
University of Miami Dept. of Neurology
1501 N.W. 9th Avenue, Room 4013 (D 4-5)
Miami, FL 33136
305-243-6219
800-UM-BRAIN (862-7246)

The Mohammed Ali Parkinson Center at the Barrow Neurological Institute in Phoenix, Arizona, has developed a national registry of people with PD in order to help in the development of new therapies and to allow researchers to quickly identify and notify people about research studies for which they are eligible. Anyone diagnosed with PD is eligible to take part in this registry. For more information, contact:

Parkinson's Disease Registry
500 W. Thomas Rd., Suite 720
Phoenix, Arizona 85013
info@maprc.com
602-406-6315
877-287-7122 (toll free)
www.maprc.com/home/info/registry.aspx

Some states, including California and Nebraska, also have registries of people with PD.

People with PD who wish to help with research on this disorder may be able to do so by participating in clinical studies designed to learn more about the disease or to test potential new therapies. Information about many such studies is available free of charge from the Federal government's database of clinical trials, clinicaltrials.gov.

A good source for finding clinical trials specifically on PD is the www.PDtrials.org web site, which lists studies sponsored by the National Institutes of Health and other federal agencies, as well as private industry and institutions at locations across the United States.

For clinical trials taking place at the National Institutes of Health, additional information is available from the following office:

Patient Recruitment and Public Liaison Office
Clinical Center
National Institutes of Health
Building 61, 10 Cloister Court
Bethesda, Maryland 20892-4754
800-411-1222
TTY: 301-594-9774 (local), 866-411-1010 (toll free)
http://www.cc.nih.gov/recruit/index.html

Information resources

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

American Parkinson Disease Association
135 Parkinson Avenue
Staten Island, NY 10305-1425
http://www.apdaparkinson.org
718-981-8001, 800-223-2732 Calif: 800-908-2732

Michael J. Fox Foundation for Parkinson's Research
Church Street Station
P.O. Box 780
New York, NY 10008
http://www.michaeljfox.org
212-509-0995

National Parkinson Foundation
1501 N.W. 9th Avenue
Bob Hope Road
Miami, FL 33136-1494
http://www.parkinson.org/
305-243-6666, 800-327-4545

Parkinson Alliance
P.O. Box 308
Kingston, NJ 08528-0308
http://www.parkinsonalliance.org
609-688-0870, 800-579-8440

Parkinson's Action Network (PAN)
1025 Vermont Ave. N.W., Suite 1120
Washington, DC 20005
http://www.parkinsonsaction.org
800-850-4726, 202-638-4101

Parkinson's Disease Foundation (PDF)
1359 Broadway, Suite 1509
New York, NY 10018
http://www.pdf.org/
212-923-4700, 800-457-6676

Parkinson's Institute
675 Almanor Avenue
Sunnyvale, CA 94085
http://www.thepi.org
408-734-2800, 800-655-2273

Parkinson's Resource Organization
74-478 Highway 111, No 102
Palm Desert, CA 92260-4135
http://www.parkinsonsresource.org
760-773-5628, 310-476-7030, 877-775-4111

WE MOVE (Worldwide Education & Awareness for Movement Disorders)
5731 Mosholu Avenue
Bronx, NY 10024
http://www.wemove.org
347-843-6132

Bachmann-Strauss Dystonia & Parkinson Foundation
Fred French Building 551 Fifthe Aveneue, at 45th Street
Suite 520
New York, NY 10176
http://www.dystonia-parkinsons.org
212-241-5614

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