Parkinson's Disease

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What Is Parkinson's Disease?

Parkinson's disease is a slowly progressive disorder that affects movement, muscle control, and balance. It occurs when the following process occurs:

- Parkinson's develops as cells are destroyed in certain parts of the brain stem, particularly the crescent-shaped cell mass known as the *substantia nigra*.
- Nerve cells in the substantia nigra send out fibers to the *corpus stratia*, gray and white bands of tissue located in both sides of the brain.
- There the cells release *dopamine*, an essential neurotransmitter (a chemical messenger in the brain). *Loss of dopamine in the corpus stratia is the primary defect in Parkinson's disease.*
- Dopamine is one of three major neurotransmitters known as *catecholamines*, which help the body respond to stress and prepare it for the fight-or-flight response. Loss of dopamine negatively affects the nerves and muscles controlling movement and coordination, resulting in the major symptoms characteristic of Parkinson's disease.

According to research published in 2000, the disease process also impairs nerve endings in the heart that regulate the release of norepinephrine, a hormone that regulates blood pressure, pulse rate, perspiration, and other automatic responses to stress. Such effects could be responsible for the abrupt drops in blood pressure when standing that some patients experience. Further research is underway to determine if the loss of nerve terminals is confined to the heart or if it affects other organs as well.

What Causes Parkinson's Disease?

Parkinson's disease is referred to as *idiopathic*, which means that the cause is unknown. This term distinguishes the primary disease from *parkinsonism*, which are the symptoms occurring from a known cause.

Although it is clear that dopamine deficiency is the primary defect in Parkinson's disease, researchers now must discover how this dopamine is lost. Studies indicate that the culprit is not a single cause, but is a combination of genetic susceptibility, biologic factors, and environmental assaults. Even with some understanding of the abnormal biological mechanisms in the brain that cause Parkinson's disease, no one knows at this time how long it takes before nerve damage and dopamine loss trigger symptoms. At this time, the best guess is about five years.

Biologic Factors

Abnormal Apoptosis (Programmed Cell Death). In everyone, cells in the body are programmed to naturally die through a genetically regulated process called apoptosis. In Parkinson's disease, there is some evidence that this process goes awry in nerve cells. Research has detected abnormal levels of enzymes, such as caspases and cyclin-dependent kinases, which may play a critical role in apoptosis.

Lewy Bodies. Fibrous deposits known as *Lewy bodies* are the hallmark signs of Parkinson's disease. They are found in the substantia nigra, the place in the brain where dopamine is first released. It is not clear whether Lewy bodies are the major killers of the nerve cells or whether they are simply a byproduct of the degenerative process. Some experts believe that the formation of Lewy bodies occurs in very early stages of Parkinson's and may be a harbinger of the full-blown disease. They are found not only in the brains of patients with Parkinson's disease, but, in rare cases, may show up in cells in other parts of the body (the heart, intestine), causing severe disabling symptoms. These substances are also present in other diseases that cause dementia and can occur in people without neurologic symptoms.

Complex I and Oxygen-Free Radicals. Some research has observed that certain Parkinson's patients have a 30% to 40% reduction in an enzyme called complex I. Some theories suggest the following path for its role in Parkinson's:

- Complex I is found in mitochondria, sausage-like structures in cells that generate energy, and low amounts of it lead to energy loss in the cell.
- This makes the cell vulnerable to the assault of *oxygen free radicals*, which are unstable molecules produced by the natural chemical processes in the body. Because free radicals are missing an electron, they tend to bind with other molecules in the body.
- This can set off a chemical chain reaction that damages any cell, including nerve cells in the brain, and even interferes with their DNA.
- People who have insufficient amounts of complex I, either from genetic abnormalities or other factors, then may be more susceptible to nerve injury developing Parkinson's disease.

NMDA Receptors. Also of interest are processes that occur in an area of the brain called the subthalamic nucleus. Here, receptors known as glutamatergic N-methyl-D-aspartate (NMDA) become persistently overexcited and produce high levels of calcium ions within brain cells. This in turn leads to a cascade of events that trigger oxygen-free radicals. Agents inhibiting the NMDA receptors now show promise in treating Parkinson's.

Immune Factors. An overresponsive immune system may also play a role in perpetuating Parkinson's disease by producing certain factors called cytokines (eg, interleukin-1, tumor necrosis factor) in response to the initial damage, which can further injure cells in the brain.

Genetic Factors

Genetic factors are important in causing Parkinson's disease. The strongest genetic evidence is for early-onset Parkinson's. The role of genes in late-onset, the much more common form of the disorders, is not yet clear. The cases of genetic early-onset Parkinson's disease have been detected in specific family groups. They are uncommon and generally unrelated to the disease process in the great majority of Parkinson's cases. Nevertheless, they are proving to be useful in understanding the nature of degenerative nerve diseases in general. The following are the main known examples of these genetic diseases.

Defective Alpha Synuclein. Genetic abnormalities in a protein called alpha synuclein has been detected in some early-onset Parkinson's patients of European descent. A genetic defect causes the alpha synuclein proteins to collect and clump together, most likely forming Lewy bodies.

Parkin Gene. The parkin gene was first recognized as being responsible for a rare form of Parkinson's disease that occurs in children and adolescents. Parkin is a protein that is similar to one known as ubiquitin, which is found in Parkinson's disease and other neurologic diseases. Research now suggests that the parkin gene may also be the cause of many cases of early-onset Parkinson's in young adults. (Parkinson's cases associated with this mutation tend to progress slowly and respond well to treatment, even after years of symptoms. Dementia is also rare with this form.)

Environmental Assaults and Oxygen-Free Radicals

Environmental toxins, infections, and other triggers can provoke excessive production in the body of oxygen free-radicals, damaging particles that can injure cells and even affect genetic material. Such oxidative stress may play a major role in the deterioration of nerve cells that lead to Parkinson's.

Infectious Agents. Recent biochemical advances have identified immune factors that suggest a viral presence in the Lewy bodies and swollen nerve pathways of Parkinson's brains. Influenza and other potent viruses have long been known to be a cause of parkinsonism. In one well-known example, a major flu epidemic causing encephalitis in the early twentieth century left many of its victims with parkinsonism.

Environmental and Industrial Chemicals. Intense exposure to certain environmental and industrial chemicals is also being studied.

- *Pesticides and Herbicides.* Mounting evidence implicates pesticides and herbicides as important factors in many cases of Parkinson's disease. A higher incidence of parkinsonism has long been noted in people who live in rural areas, particularly those who drink private well water or are agricultural workers. A large 2000 study found a strong link between high exposure to insecticides and herbicides at home and a 50% to 70% increase in risk of Parkinson's. An important 2000 animal study implicated rotenone, a common organic chemical in pesticides. It resembles chemicals that inhibit enzymes important for energizing cells. This effect could unleash oxygen-free radicals, which are unstable particles that can injure brain cells. Further research is needed to determine whether it causes Parkinson's in people who work with it or ingest its residue in food.
- *Other Chemicals.* Intense exposure to other industrial chemicals and metals (manganese, copper, lead, iron, mercury, zinc, aluminum, and others) has also been linked with parkinsonism, which is often reversible. The role of long-term exposure in the development of Parkinson's disease is unclear.

Aging Process

Most, but not all, Parkinson's victims are elderly. Some studies indicate that the *very* elderly are not susceptible to the disease, indicating that the aging process itself is not the major player in the disease. Aging *does* appear to reduce the concentration of dopamine in structures called dopamine transporters, which carry the neurotransmitter back and forth between nerve cells. Some researchers posit that any excessive stress on these transporters might trigger Parkinson's disease in the aging, and more vulnerable, brain.

What Are the Symptoms of Parkinson's Disease?

Tremors

Symptoms often start with tremor, which may occur in the following way.

- Tremor may first be only occasional, starting in one finger and spreading over time to involve the whole arm. The tremor is often rhythmic, 4 to 5 cycles per second, and frequently causes an action of the thumb and fingers known as *pill-rolling*.
- Tremor can occur when the limb is at rest or when it is held up in a stiff unsupported position. They usually disappear briefly during movement and do not occur during sleep.
- Tremors can also eventually occur in the head, lips, tongue, and feet. Symptoms can occur on one or both sides of the body. In one study, 44% of patients reported experiencing *internal* tremors lasting less than half an hour, but occurring several times a week.

Motion and Motor Impairment

A number of symptoms involve motor impairment:

- Slowness of motion (*bradykinesia*) is one of the classic symptoms of Parkinson's disease. After a number of years, muscles may freeze up or stall, usually when a patient is making a turn or passing through narrow spaces, such as a doorway.
- Patients may eventually develop a stooped posture and a slow, shuffling walk. The gait can be erratic and unsteady.
- Intestinal motility, eg, swallowing, digestion, and elimination, may also slow down, causing eating problems and constipation.

- Muscles may become rigid (*akinesia*), which often begins in the legs and neck. Muscle rigidity in the face can produce a mask-like, staring appearance.
- Limiting abnormalities in the hand may develop in late stages. Handwriting, for instance, often becomes diminutive.
- Normally spontaneous muscle movements, such as blinking, may need to be done consciously.

Other Symptoms of Parkinson's Disease

Other symptoms include the following:

- Depression. Depression caused by chemical changes in the brain may be an early symptom of Parkinson's. Depression is a common problem in older people, however, and it is likely not to be recognized as a symptom.
- Orthostatic hypotension. Some patients experience a sudden drop in blood pressure when they stand. This can cause dizziness and fainting.
- Changes in sensations of temperature, hot flashes, and excessive sweating.
- Leg disorders. Cramps and burning sensations in the legs are common. Restless legs syndrome affects some patients. This is an irresistible urge to move the calves, which often occurs at night, disturbing sleep. [*See* the Well-Connected Report *Leg Disorders*.]
- Changes in Migraine Symptoms. In people with a history of migraine, the onset of Parkinson's is associated with change in migraine symptoms (most often improvement).

Who Gets Parkinson's Disease?

Parkinson's disease affects about 3% of Americans over 65 years old. Experts estimate that this percentage could double in the next 30 to 40 years. The symptoms of parkinsonism (tremor, gait disturbance, bradykinesia, and rigidity) occur in even more people, estimated to be 8 million over 65. In a study that included very mild symptoms, parkinsonism occurred in about 15% of people 65 to 74 years of age, about 30% in those 75 to 84, and over half of people older than 85.

Age

The average age of onset of Parkinson's disease is 55. About 10% of Parkinson's cases are in people younger than 40 years old. Older adults are at higher risk for both parkinsonism and Parkinson's disease. There is some evidence, however, that the risk declines significantly after 75 and that the very elderly are at *low* risk.

Gender

Some research indicates that men may face up to twice the risk as women. Estrogen may offer some protection for women up until menopause. One study suggested that the disease also progresses more rapidly in men than women, but these results may only indicate that men are less responsive to the treatments for Parkinson's. Older women seem to be more at risk for gait disturbance and men for rigidity and tremor.

Relatives

People with siblings or parents who developed Parkinson's at a younger age are at higher risk for Parkinson's disease, but relatives of those who were elderly when they had the disease appear to have an average risk.

Ethnicity

African- and Asian-Americans have a lower risk than European-Americans.

The Effect of Cigarettes and Coffee on Parkinson's Disease

Smoking. Cigarette smokers appear to have a *lower* risk for Parkinson's disease, indicating some protection by nicotine. This finding, of course, is no excuse to smoke, but such protection may help researchers develop new therapies.

C*offee Consumption.* In a 30-year 2000 study of Japanese-American men, coffee consumption was associated with a lower risk for Parkinson's disease and the more coffee they drank, the lower their risk became. Caffeine, which is a known central nervous system stimulant, appears to be the protective factor. The study did not prove that coffee actually protects against Parkinson's, however, and further research is needed.

How Serious Is Parkinson's Disease?

General Outlook

Parkinson's disease is not fatal, but it reduces longevity. Parkinson's disease can seriously impair the quality of life, however, and may sometimes lead to severe incapacity within 10 to 20 years. The physical and emotional impact on the family should not be underestimated as the patient becomes increasingly dependent on their support.

Treatments are increasingly effective in alleviating symptoms and even slowing progression of the disease. Taking the medications over time, however, can produce significant side effects. Newer agents may help reduce these occurrences.

Motor Impairment

The negative effect of overall motor and muscle impairment on daily life can be considerable in Parkinson's patients. Specific symptoms may also indicate a more or less severe condition:

- *Tremor predominant.* In younger patients tremor is usually predominant and progression of the disease is slow.
- *Postural instability and gait disturbed (PIGD).* Elderly people are more apt to have disturbed gait and unstable posture. Some studies have suggested that if these symptoms appear early, they predict a faster decline than having tremor predominant. Gait disturbance is a particularly serious sign in the elderly. For one, it increases the risk for falls and injury.

Speech Impairment

More than 70% of Parkinson's patients, by some estimates, develop some speech difficulty caused by rigidity of the facial muscles, loss of motor control, and impaired breath control. Tone can become monotonous, words may be repeated over and over, or the rate of speech may even be very fast.

Impact on Emotions

Depression is extremely common, affecting up to 40% of Parkinson's patients. Depression can be caused in Parkinson's patients from many factors related to the disease.

- The disease itself causes changes in chemicals in the brain that effect mood and well being.
- The emotional impact of the symptoms on daily life can be devastating without help and support.
- All drug treatments used for Parkinson's disease have side effects that cause neurologic and psychiatric disturbances.
- Sexuality is also reduced. This is an area not often studied but which is important for many patients' well-being. A 2000 study reported that not only did sexual dysfunction occur, but affectionate touching and expression of feelings were reduced, even though both partners maintained a desire for intimacy.

Effects on Thinking and Mental Status

Impaired Thinking (Cognitive Impairment). Defects in thinking, memory, language, and problem solving skills may occur early on in untreated patients or late in the course of the disease. Mental decline is a major reason for decisions to enter nursing homes. Researchers reporting on a syndrome of impaired mental performance, insomnia, and depression in Parkinson's patients suggested that treating depression and insomnia may also improve mental functions.

Dementia. Dementia is about six times more common in the elderly Parkinson patient than in the average older adult. It is most likely to occur in older patients who have had major depression. Unlike in Alzheimer's, language is not usually affected in Parkinson's related dementia.

Sleep Disorders. Parkinson's patients are at higher risk for sleep disorders as well. In general, they have a higher risk for disturbed sleep. Cramps and restless legs can also keep them awake. And, some of the medications cause vivid dreams as well as waking hallucinations.

Other Problems that Impair Daily Life

A number of other problems associated with Parkinson's disease affect daily life. They include the following:

- Constipation is a major problem for Parkinson patients and occurs both as a result of the disease and a side effect of its treatment. Laxatives, stool softeners, and other medications may be prescribed. The drug cisapride (Propulsid) appears to help some people with constipation and a poor response to levodopa [*see* Diet, *in this report*].
- Bladder control and urinary incontinence are also important symptoms. [*See* the Well-Connected Report *Incontinence.*]
- The sense of smell is impaired in about 70% of patients.
- Vision is also affected, including color perception.

What Will Confirm the Diagnosis of Parkinson's Disease?

It is difficult to diagnose Parkinson's in early stages. Studies indicate that even general neurologists make an incorrect initial diagnosis of Parkinson's disease in between 25% and 35% of cases. Researchers are hopeful that objective and simple blood or imaging tests will be available in the near future to identify the disease early in its development. At this time, however, the disease is diagnosed almost primarily by its symptoms.

Medical and Personal History

A medical and personal history should include any relevant symptoms as well as any medications being taken, and exposure to environmental toxins is very important.

Diagnosing by Symptoms

Early Symptoms. Early treatment may help slow progression, so an early diagnosis of Parkinson's is highly desirable. Early symptoms are often mild however, so Parkinson's disease can be missed, particularly in young adults. Repeated assessment of symptoms over time is important to improving the accuracy of diagnosis. Too often, for example, a younger person with Parkinson's may be diagnosed with mental illness, because even the physician may suspect the disease only in older people.

Parkinson's may be suspected in patients with the following symptoms:

- Slowness and difficulty of movement. These are usually the first symptoms, so the patient will be asked to walk and probably to get out of a chair, preferably a deep one. (Early gait *disturbance*, however, often indicates a disease *other* than Parkinson's disease.)
- A tremor when their limb is relaxed. (About 25% of Parkinson's patients will not have a tremor, however.)
- Symptoms on one side of the body.
- A powerful early response to the drug levodopa (the primary treatment for Parkinson's). It should be noted that some patients with a very similar condition called multiple system atrophy will have a good initial response to levodopa, but it is not usually sustained.

Later Symptoms. In later stages of Parkinson's disease, the symptoms are usually unmistakable, and the problem can often be diagnosed using simple physical tests and a medical and personal history.

Imaging Techniques

Although imaging techniques, such as computerized tomography (CT), magnetic resonance imaging (MRI), or positron-emission tomographic (PET), are not usually necessary when physical symptoms of Parkinson's disease are obvious, they are occasionally used to rule out other medical problems.

Research is ongoing to determine if imaging tests can detect early and late stages of Parkinson's and allow physicians to gauge disease progression and effectiveness of treatment. Single photon emission computed tomography (SPECT) is an advanced imaging technique showing great promise.

Ruling out Causes of Parkinsonism and Diseases that Mimic Parkinson's Disease

When symptoms resemble Parkinson's disease but have an identifiable cause, the syndrome is known as *parkinsonism*. People who have parkinsonism, but not Parkinson's disease, often have additional neurologic symptoms. A number of conditions can also have similar or some of these symptoms.

Drugs. Certain drugs or medications account for about 4% of all cases of parkinsonism. According to some studies, patients who experience drug-induced parkinsonism may actually be at an increased risk of developing Parkinson's disease later in life. A number of drugs can cause these symptoms:

- Neuroleptics, drugs used to treat schizophrenia and other psychoses. They include haloperidol (Haldol), thioridazine (Mellaril), and chlorpromazine (Thorazine). (New drugs, called atypical antipsychotics do not pose as high a risk.)
- Valproate (Depakote), used for epilepsy.
- Metoclopramide (Octamide, Maxolon, Reglan), used for stomach disorders, is an important cause of these symptoms in the elderly; the symptoms persist sometimes for months after the drug has been withdrawn.
- Studies have also found a link between meperidine (Demerol) and Parkinson's.

Other Neurologic Conditions. Many medical conditions may cause symptoms of Parkinson's disease:

- Hardening of the arteries (arteriosclerosis) in the brain can cause multiple small strokes, which can produce loss of motor control.
- Coexisting Alzheimer's disease may confuse the diagnosis. In one study 23% of people with Alzheimer's also met the criteria for Parkinson's disease.
- A disease known as dementia with Lewy bodies has similar symptoms, but is marked by early dementia.
- Encephalitis caused by influenza has been known to cause parkinsonism.
- Some people have a condition called essential tremor, which unlike the tremor of Parkinson's disease, often occurs in the head and voice and is usually worse during motion, as opposed to rest.
- Progressive supranuclear palsy has similar symptoms, but involves less tremor and earlier rigidity, and it tends to affect both sides of the body symmetrically.
- Multiple system atrophy (previously called Shy-Drager syndrome) is a degenerative nerve disease that also affects movement and blood pressure and has many of the symptoms of Parkinson's disease.
- There have been reports of parkinsonian symptoms developing or worsening as a result of subdural hematomas (a collection or clot of blood on the surface of the brain). Such patients recover after removal of the hematomas.
- Other problems that may mimic Parkinson's disease include Wilson's disease, thyroid abnormalities, hydrocephalus, tumors, and a number of degenerative neurologic diseases.

Gluten. One study found that an immune response to a protein found in gluten, a substance in wheat, rye, and barley, can cause muscle weakness and neurologic problems similar to parkinsonism.

What Are General Guidelines for Treating the Stages of Parkinson's?

Overall Goals

The goals of treatment for Parkinson's disease are to relieve disabilities and to balance the problems of the disease with the side effects of the medications. Treatment is *very* individualized for this complicated problem, and patients must work closely with physicians and therapists throughout the course of the disease to customize a program suitable for their particular and changing needs. Patients should never change their medications without consulting their physicians, and they should never stop taking their medications abruptly.

There is no standard method for treating the earliest symptoms. Before symptoms become disabling, some patients prefer trying lifestyle changes first, including exercise and diet. When the patient and physician determine that medication is necessary, the patient will start out with as low a dose as possible of any drug used.

Treatments by Stage of Parkinson's Disease	
Onset of Mild Symptoms	Life-Style Changes (Exercise, Diet) Drugs: · Amantadine · Selegiline · Anticholinergic (for tremor)
Onset of Moderate Symptoms	· Levodopa (L-dopa) · Dopamine Agonists supplemented with L-dopa as necessary · Catechol-O-Methyl Transferase Inhibitor
Long-Term Maintenance Therapy	Levodopa in combination with: · Selegiline · Dopamine Agonists · Catechol-O-Methyl Transferase Inhibitors · Amantadine
Advanced Disease	Experimental Drugs Surgical Procedures: · Pallidotomy · Thalamotomy · Radiosurgery · Neurostimulation

Treatments for Onset of Parkinson's Disease

Levodopa, or L-dopa, is converted to dopamine in the brain and so acts as a replacement drug. L-dopa has been used for years and is the gold standard for treating Parkinson's disease. It is used in nearly all phases of the disease. The standard preparation combines levodopa with an anti-nausea agent carbidopa (Sinemet, Atamet).

The timing for adding appropriate treatments, including starting L-dopa, may be as follows:

· Early mild symptoms may be treated with physical therapy and certain drugs (amantadine, anticholinergic drugs, selegiline).

· L-dopa is almost always initiated as a first treatment in people over 70 with significant symptoms.

· For younger adults who develop moderate symptoms and who will require treatment for decades, physicians now often use drugs that preserve any residual natural dopamine, called dopamine agonists. When symptoms become pronounced or other drugs are no longer effective, then L-dopa is given to the patient. [For more details, *see* What Is Levadopa (L-Dopa)? *and* What Are the Other Drugs Used for Parkinson's Disease?, *below*.]

There is major debate, however, about delaying L-dopa treatment and using the newer dopamine agonists first in younger adults other than those with early-onset disease. [*See Box* Debate Concerning Delay of L-Dopa.]

Debate Concerning Delay of L-Dopa

According to a 2001 survey, 79% of American neurologists now use dopamine agonists as the first treatment for most patients. At an international meeting on Parkinson's disease, however, most of the physicians attending a seminar on this issue signified that they chose L-dopa first.

Arguments for Early Use of Agonists. The basic arguments for early use of dopamine agonists before starting L-dopa in most adults are as follows

- The primary reason is to delay the following complications of L-dopa that occur after five to fifteen years of treatment:

  Levodopa becomes less effective and the patient experiences symptoms of the return of the disease, called the wearing-off effect.

  By increasing the dosage of L-dopa to compensate for this loss of effectiveness, patients may then experience dyskinesia (the inability to control muscles) and extreme motor fluctuations as they cycle through these toxins followed by symptoms of the disease, called the on-off effect. [See Reducing Long-Term Complications of Levodopa Use Once They Occur, below.]

- Some 2000 studies reported that newer agents (pergolide, pramipexole, ropinirole) delayed the time for these complications by about a year. In fact, patients taking ropinirole experienced significantly less frequent and severe dyskinesia than those taking L-dopa.
- There is also some belief that L-dopa may harm nerve cells and become toxic over time.

Arguments for Early Use of L-Dopa. Experts who believe that L-dopa should be used early on in most adults are supported by the following arguments and studies:

- Careful reviews of studies indicate that taking L-dopa for a long time does not harm remaining dopamine nerve cells, and in fact, may even promote recovery of those that are damaged.
- There is some evidence that taking levodopa early in the course of the illness can prolong life.
- It is true that certain symptoms may become less responsive to L-dopa, but most patients, if not all, derive substantial benefit from the drug throughout their lives.
- The newer drugs still have not been proven to be better than L-dopa. Comparison studies in 2000 did indeed report that two of these agents (pergolide, pramipexole) delayed motor complications during the first one or two years. A third comparison agent, ropinirole, achieved lower rates of dyskinesia, but patients reported equal ability to cope with daily life with L-dopa and ropinirole. Compared to all three, L-dopa produced greater improvement in motor function, and by year three there appears to be no difference in disease progression among these agents.
- The first five years of the disease is generally marked by mild side effects. And, although dopamine agonists delay L-dopa complications, they actually have more severe side effects (such as nausea and hallucinations). Younger adults, then, who take L-dopa might have a better quality of life during those early years when they are most active.
- The wearing off effect may occur in fewer patients taking L-dopa than indicated by early studies. In a well-known 1977 study, for example, only a third of patients retained the initial benefits after five years. In a 1999 controlled study, however, the drug was still effective in 80% of patients after first five years of therapy.

Long-Term Maintenance Therapy

To reduce the effects of complications of L-dopa (fluctuation and the wearing-off effect) during maintenance therapy, it is important to maintain as consistent a level of dopamine as possible. In general, physicians are increasingly using combinations of levodopa and other drugs to reduce adverse effects. Such drugs include the following:

- *Monoamine oxidase inhibitors.* Selegiline agent is most commonly used and may delay the wearing-off effect for six months to a year, although some people have experienced a delay as long as two years. Selegiline does not have much impact on the on-off phenomenon itself.
- *Dopamine agonists.* (Newer ones: pramipexole and ropinirole. Older one: pergolide). These are useful for both early wearing off and for on-off motor fluctuations, particularly when dyskinesia is present.
- *Catechol-o-methyl transferase (COMT) inhibitors.* Tolcapone and entacapone are useful for wearing-off and motor fluctuations if dyskinesia is not a factor.
- Amantadine. This drug is helpful as an additional drug for patients with dyskinesia.

Some experts strongly recommend starting out with low doses of several drugs rather than high doses of a single one. In one 2000 comparative study of COMT inhibitors and dopamine agonists, pergolide, pramipexole, and entacapone achieved the best reductions in "off" times (during which immobility occurs). Pramipexole and entacapone achieved the lowest doses of L-Dopa and had the fewest side effects. Although patients reported the most side effects from tolcapone and pergolide, fewest patients withdrew from pergolide. There are many options, however, and there is no one optimal approach for all patients.

Treating Advanced Disease

Eventually, symptoms such as stooped posture, freezing, and speech difficulties may not respond to drug treatment. (Total unresponsiveness is unlikely, however, even after 20 years of treatment.) The following approaches may be tried:

- Simply increasing the dose of levodopa or its frequency raises an unacceptable risk of the distressing side effects. Some physicians have tried hospitalizing patients, totally withdrawing the levodopa, and then readministering it, but benefits were seen for only a few months, and there were some dangerous risks to the process of withdrawal, including pneumonia and blood clots in the lungs.
- Surgical treatments, including pallidotomy, neurostimulation, and transplantation may help some patients. [*See* What Are Surgical Procedures for Parkinson's Disease?, *below*.]
- Research is ongoing to develop drugs and procedures that will manage advanced disease and possibly even reverse the process. [*See* What Are Other Drugs Used for Parkinson's Disease?, *below*.]

What Is Levadopa (L-Dopa)?

Levodopa, or L-dopa, which is converted to dopamine in the brain, remains the gold standard for treating Parkinson's disease. The standard preparations (Sinemet, Atamet) combine levodopa with carbidopa, which improves the action of levodopa and reduces some of its side effects, particularly nausea. Levodopa can also be combined with benserazide (Madopar) with similar results, but Sinemet is almost always used in America. Dosages vary, although the preparation is usually taken in three or four divided doses per day.

Indications of Early Treatment Success or Failures

In general L-Dopa has the following effects on Parkinson's disease:

- It is most effective against rigidity and slowness.
- It produces less benefit for tremor, balance, and gait.

In half of Parkinson's patients, levodopa significantly improves the quality of life for many years. In some cases symptoms do not improve after two or three months.

There may be different reasons for failure:

- Other neurologic problems may be causing the symptoms.
- Some Parkinson's patients have abnormalities in other brain sites that do not respond to L-dopa.
- Sometimes patients are so depressed they cannot tell if the drug is beneficial or not, and only a series of physical examinations by the doctor will indicate that the drug is actually helping.
- One study indicated that men may be less responsive to L-dopa than women, although this finding needs to be confirmed in further trials. The observation could also simply indicate that the disease progresses more swiftly in men.

Toxic Effects

The toxic effects of levodopa with or without carbidopa are considerable.

Physical Side Effects. The physical side effects are as follows:

- *Circulation and the heart*. Low blood pressure is a common problem during the first few weeks, particularly if the initial dose is too high. The addition of extra supplements of carbidopa reduces this effect to some degree. The patient should drink lots of fluids and possibly increase salt intake to maintain normal blood pressure. In some cases the drug may cause heart rhythm disturbances.
- *Gastrointestinal side effects.* Stomach and intestinal side effects are common even with carbidopa. Taking the drug with food can alleviate the nausea. It should be noted, however, that proteins interfere with intestinal absorption of levodopa, and some physicians recommend not eating any protein until nighttime in order to avoid this interference. The drug can also cause gastrointestinal bleeding.

Psychiatric Side Effects. The major adverse effects of the drug are psychiatric. Patients taking levodopa, especially in combination with other drugs, can experience the following:

- Confusion.
- Extreme emotional states, particularly anxiety.
- Vivid dreams.
- Visual and possibly auditory hallucinations.
- The drug may even unmask dementia that had not been previously noticed.

It should be noted that levodopa provokes fewer psychiatric side effects than other drugs used for Parkinson's disease, including anticholinergics, selegiline, amantadine, and dopamine agonists [*see below*].

Because psychiatric side effects often occur at night, if they are severe some physicians recommend reducing or stopping the evening dose.

The Wearing-Off Effect and Dyskinesia

Within four to six years of treatment with levodopa, the effects of the drug in many patients begin to last for shorter periods of time (called the *wearing-off effect*). [See Box Wearing-Off Effect.] After a few years of L-dopa, patients may experience the following pattern of complications:

- Patients often first notice slowness (bradykinesia) or tremor in the morning before the next dose is due.
- Less commonly, some experience painful *dystonia,* muscle spasms that can cause sustained contortions of various parts of the body, particularly the neck, jaw, trunk, and eyes and possibly the feet.
- Patients must increase the frequency of levodopa doses. This puts them at risk for *dyskinesia* (the inability to control muscles) which usually occurs when the drug level peaks. Dyskinesia can take many forms, most often uncontrolled flailing of the arms and legs or *chorea*, rapid and repetitive motions that can affect the limbs, face, tongue, mouth, and neck. Dyskinesia is not painful, but it is very distressing.

- In some people, eventually duration of effectiveness may last only one to two hours and most patients start to experience motor fluctuations.
- In about 15% to 20% of patients the fluctuations become extreme, a phenomenon known as the *on-off effect*, which consists of unpredictable, alternating periods, sometimes within minutes or seconds, of dyskinesia and immobility. (The transition may follow such symptoms as intense anxiety, sweating, and rapid heartbeats.)

Reasons for the Wearing-Off Effect. Debate is ongoing about the cause of the wearing-off effect and dyskinesia, Some theories suggested for these effects are the following:

- The disease progresses beyond the ability of levodopa to control it.
- Some patients become tolerant to prolonged exposure to dopamine and, at the same time, the disease is progressing.
- The brain's own dopamine neurons become incapable of storing dopamine and when the levodopa wears off, little or no natural dopamine remains.
- Levodopa itself accelerates the disease by producing oxygen free radicals, unstable particles that increase injuries to the brain and dopamine degradation.

Preventing the Wearing-Off Effect. To reduce the effects of fluctuation and the wearing-off effect, it is important to maintain as consistent a level of dopamine as possible. Unfortunately, levodopa is poorly absorbed and may remain in the stomach a long time. A number of strategies are being developed to take care of these problems:

- Some patients take multiple small doses on an empty stomach, crushing the pills and mixing them with a lot of liquid.
- A liquid form of Sinemet may produce fewer fluctuations and a prolonged "on" time compared with the tablet.
- A prolonged release version of levodopa and carbidopa (Sinemet CR) is also available to control fluctuations for some people. (Some evidence suggests that there is no actual difference in symptom control between the sustained and immediate release forms, but patients on Sinemet CR tend to experience a better quality of life.)

What Are Other Drugs Used for Parkinson's Disease?

Selegiline and Other Monoamine Oxidase Inhibitors

Benefits. Selegiline (Eldepryl, Movergan), also known as deprenyl, is an antioxidant drug that blocks monoamine oxidase B, an enzyme that degrades dopamine. Until recently, selegiline (Eldepryl, Movergan), or deprenyl, was the drug most commonly used in early-onset disease and in combination with levodopa for maintenance.

Debate over Mortality Rates. Of great concern was a long-term study and its 1998 update that suggested an increased risk of death after people had taken Sinemet combined with selegiline (particularly in the third and fourth years) compared to those taking Sinemet alone. Shedding some light on these negative results was another study that reported a high incidence of orthostatic hypotension (a severe drop in blood pressure) in some people taking Sinemet plus selegiline. (It should be noted that other Parkinson's drugs can also cause orthostatic hypotension. This indicates a more serious condition, regardless of the drug taken.) On the encouraging side, an analysis of five long-term studies found no increased mortality rate using the combination. And, a 2000 study in Scotland also found that patients taking selegiline in combination with L-dopa were no more likely to die than people without Parkinson's. In fact, in this study, those taking the combination had the same mortality rate as people without Parkinson's, while those taking levodopa alone had the highest death rate.

Other Adverse Effects. Selegiline has other side effects that are important:

- It has adverse interactions with nearly every antidepressant, some very serious. Patients suffering from depression should discuss all treatment options with their physician.
- People taking any monoamine oxidase inhibitor are at risk for high blood pressure if they consume tyramine-containing foods or beverages, including aged cheeses, most red wines, vermouth, dried meats and fish, canned figs, fava beans, and concentrated yeast products.

Dopamine Agonists

Dopamine agonists stimulate dopamine receptors in the substantia nigra, the part of the brain in which Parkinson's is thought to originate.

Newer Dopamine Agents. Pramipexole (Mirapex) and ropinirole (Requip) are proving to be safe and effective for both initial sole therapy and in combination with L-dopa. Pramipexole appears to be more effective and have fewer side effects than ropinirole. Each may delay the wearing-off complications compared to L-dopa. Studies in 2000 reported, however, that neither controls the disease any better over time, and L-dopa still appears to achieve better motor control. After three years, there is no difference in disease progression among patients taking any of these drugs.

Ropinirole has shown the following recent results:

- A five-year comparison study with levodopa found that ropinirole was more than twice as effective in controlling dyskinesias. In fact, patients taking ropinirole alone experienced no progression of dyskinesia. There were no significant differences in the number and severity of complications. Overall, however, the effectiveness of the two drugs was comparable in terms of daily living, probably because L-dopa still controlled motor symptoms better.

Pramipexole has shown the following recent results:

- A large, US-Canadian 2000 study found that 72% of patients who took pramipexole as their first therapy remained free of dyskinesia for two years, compared to 49% of those taking levodopa. Pramipexole therapy, however, resulted in fewer benefits in symptoms overall, and a greater incidence of sleepiness, fluid build-up, and hallucinations.

Side effects of pramipexole and ropinirole vary but can be severe and include the following:

- Gastrointestinal side effects (nausea and constipation). (Nausea can be controlled by drugs, such as domperidone.)
- Headache.
- Orthostatic Hypotension. (Sudden drop in blood pressure upon standing up.)
- Nasal congestion.
- Nightmares, hallucinations, and even psychosis. (More severe than with L-dopa for both agents.)
- Sudden sleep attacks. These can be very serious, particularly if patients are driving.

Pergolide. Pergolide (Permax) is an older agent and the most powerful of all dopamine agonists. In a 2000 study comparing it to L-dopa, patients taking pergolide had fewer complications than those taking L-dopa. After three years, however, there was no difference in complications or disease progression. And, those taking L-dopa achieved better improvement in motor function. Pergolide is not as selective as the newer agonists and therefore may have more widespread side effects. No direct comparative studies have been conducted at this time, however, to demonstrate whether the new agonists are any better or more tolerable.

Side effects include nausea, dizziness, insomnia, and weight loss. Uncommon, but serious side effects have been reported, including scarring on the outside of the lungs or other organs and skin abnormalities. Experts recommend periodic monitoring for these side effects for patients taking any ergot-derived dopamine agonist.

Other Dopamine Agonists. Other dopamine agonists, include bromocriptine (Parlodel), lisuride, and cabergoline (a long-acting agent not yet available in the US).

Apomorphine is a dopamine agonist used as a single daily injection. It is particularly effective when administered as a "rescue" drug in people experiencing on-off effects severe enough to require going off L-dopa for a few days. It causes vomiting, however, and needs to be used with domperidone, an anti-nausea drug. Other side effects are excitability and aggression. Patches, nasal sprays, and other forms of apomorphine are showing promise as alternatives to injections. Apomorphine may also be particularly helpful in alleviating nighttime symptoms, including pain and restless legs syndrome.

Catechol-O-Methyl Transferase Inhibitors

The catechol-O-methyl transferase (COMT) inhibitors, entacapone (Comtan) and tolcapone (Tasmar), increase concentrations of existing dopamine in the brain. Both drugs improve motor fluctuations related to the wearing-off effect and have shown impressive results in improving "on" time and reducing the requirements for L-dopa. Entacapone appears to be more effective with fewer side effects than tolcapone.

Side Effects. Side effects include the following:

- Involuntary muscle movements.
- Mental confusion and hallucinations.
- Nausea and vomiting.
- Cramps.
- Headache.
- Urine discoloration. (This is a harmless side effect but should be reported.)
- Explosive diarrhea (with tolcapone).
- Less commonly, constipation, susceptibility to respiratory infection, sweating, dry mouth.
- Of major concern are reports of a few deaths from liver damage in patients taking tolcapone and the drug has been taken off the market in many countries. In the US it is now recommended only for patients who do not have severe movement abnormalities and who cannot take other treatments. Entacapone does not appear to have the same effects on the liver and does not need monitoring as tolcapone does. Patients should watch out for symptoms of liver damage, including jaundice (yellowish skin), fatigue, and loss of appetite.

If the patient does not respond to the drug within three weeks, it should be withdrawn. No one should withdraw abruptly from these drugs.

Anticholinergic Drugs

Anticholinergics are generally used only against tremor in the early stages. They are not as effective against bradykinesia and posture problems and may increase the risk for dementia in late stages. Among the many anticholinergics are trihexyphenidyl (Artane, Trihexy), benztropine (Congentin), biperiden (Akineton), procyclidine (Kemadrin), and ethopropazine (Parisdol). Orphanadrine (Norflex) is a drug with anticholinergic properties but is also a muscle relaxant and does not cause urinary retention.

Other drugs with anticholinergic properties may be used in combination therapies or for elderly people who cannot tolerate the more powerful drugs. They include the antihistamine diphenhydramine (Benadryl) and tricyclic antidepressants, such as amitriptyline (Elavil, Endep) and doxepin (Adapin, Sinequan). These drugs have some side effects that are different from the anticholinergic agents, which should be discussed with the doctor.

Side effects or Anticholinergics. Anticholinergics commonly cause dryness of the mouth (which can actually be an advantage in some people who experience drooling). Other side effects are nausea, urinary retention, blurred vision, and constipation. These drugs can also increase heart rate, worsen constipation, and cause urine retention in men with enlarged prostate. Anticholinergics can sometimes cause significant mental problems, including memory loss, confusion, and even hallucinations, which can be particularly problematic for elderly people with signs of existing dementia and people taking tricyclic antidepressants. People with glaucoma should use these drugs cautiously.

Amantadine

Amantadine (Symadine, Symmetrel) stimulates the release of dopamine and may be used for patients with early mild symptoms. Unlike the anticholinergics, also used for mild symptoms, it has some benefit against muscle rigidity and slowness. According to some studies, it can also benefit patients in advanced stages who are unresponsive to other drugs. Possibly accounting for such benefits, researchers in 1999 found that amantadine increases certain factors in the immune system (interferon-gamma and interleukins 2 and 10) that may play a role in the disease process. It is less powerful than levodopa and may lose its effectiveness after about half a year. It may also reduce motor fluctuations brought on by levadopa, however, and these benefits appear to persist for at least a year.

Side Effects. Side effects are similar to those of anticholinergic drugs and also may include swollen ankles and mottled skin. Visual hallucinations are known effects. Overdose can cause serious and even life-threatening toxicity. Patients with Parkinson's should not withdraw from this drug abruptly: in rare instances it can cause acute delirium or a life-threatening condition called neuroleptic malignant syndrome. Pregnant or nursing women should not use this drug.

Experimental Agents

Nicotine Replacement. Investigators have been studying nicotine administration because of the observation that smokers appear to have a lower risk for Parkinson's disease. Studies on nicotine patches have been conflicting, however; although some suggest benefit, one 1999 study reported *worsening* motor control in patients who wore 35 mg patches.

Mirtazapine. Of particular interest was the incidental discovery in 1999 that the unique antidepressant mirtazapine reduced tremors and dyskinesia in a small group of patients. This finding certainly warrants more study.

Glutamate Blockers. A number of experimental drugs, including remacemide and riluzole, are being investigated for Parkinson's disease because they block the actions of glutamate, an amino acid that is a particularly potent nerve cell killer. Some of these drugs block a receptor group to glutamate called N-methyl-D-aspartate (NMDA). NMDA antagonists are showing some promise for reducing symptoms of Parkinson's disease, particularly tremor. They include memantine and budipine.

Genetic Therapy. Another area of research is therapy that administers genes that code proteins responsible for producing dopamine or protect or even heal nerve cells damaged by Parkinson's disease.

Miscellaneous Treatments for Some other Disorders Associated with Parkinson's or its Treatments

Conditions associated with motor impairment and other symptoms of Parkinson's disease may require a variety of treatments. The following is a brief sample of some of them.

- Antidepressants. Physicians have been concerned that common antidepressants known as selective serotonin-reuptake inhibitors (SSRIs), which include fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil), may cause Parkinson-like symptoms. A 2000 study of Paxil was encouraging; the SSRI reduced depression and did not increase motor fluctuations (although one patient experienced severe tremors).
- *Antipsychotic Medications.* Some studies indicate that the drug clozapine (Clozaril) and quetiapine Seroquel, normally used in schizophrenia, may help offset the psychiatric side effects. In one study quetiapine also improved memory and concentration. These drugs have some serious side effects and need to be used with caution. (Similar drugs, such as risperidone or olanzapine, that are alternative agents used schizophrenia, can actually worsen Parkinson's symptoms.)
- *Botulism Toxin for Drooling.* In search of a simple solution to the problem of drooling, scientists have reported that injections of very small amounts of botulinum toxin A effectively reduce saliva production and drooling. In such small amounts the toxin is safe.
- *Collagen Injections to Treat Voice Loss.* A relatively simple procedure of injecting collagen appears to be a safe and effective method of improving the voice and speech disorders caused by Parkinson's disease. The procedure augments the collagen in the vocal fold, and was found in a preliminary 1999 study to significantly help 75% of those who had the injections.
- *Hormone Replacement Therapy*. Studies indicate that taking hormone replacement therapy after menopause reduces the risk of developing Parkinson's. Other studies show that it may also reduce the severity of early-onset Parkinson's as well as dementia related to the disorder.

What Are Surgical Procedures for Parkinson's Disease?

Pallidotomy

The Procedure. Pallidotomy is a surgical procedure that may be appropriate for some patients when drug therapy no longer works. In some patients, it restores normal brain activity related to voluntary movement. It does not cure the disease, however, and its primary benefit is to allow people to continue on Sinemet without incurring its side effects. The procedure is irreversible and generally works as follows:

- The patient's head is immobilized using a stereotactic frame and imaging techniques are used to visualize the injured areas.
- The neurosurgeon drills a small hole into the skull and inserts an electrode.
- The electrode generates a current and heat to destroy small amounts of tissue in the *globus pallidus*, a part of the brain responsible for many Parkinson's symptoms, particularly those that develop after long-term use of levodopa.
- The patient is awake during the operation, which takes about six hours.
- The hospital stay averages two days.

To date, the standard procedure involves one side of the brain (unilateral pallidotomy). A 1999 review of 10 studies reported that unilateral pallidotomy is relatively safe and effective but more experience is needed to determine the full benefits and long-term effects.

Bilateral pallidotomy (surgery on both sides of the brain) is currently being researched. While some patients have reported good improvement with the procedure, it can cause a range of cognitive, behavioral, and emotional dysfunctions.

Candidates. In general, appropriate candidates for unilateral pallidotomy are patients with advanced disease who no longer benefit from drug treatments.

Unfortunately, only about 5% to 10% of Parkinson's patients are candidates. The procedure is generally *not* recommended for the following:

- Patients who do not respond to levodopa.
- The very elderly.
- Patients who's primary symptom is tremor.
- Patients who's predominant symptoms are freezing and falling (especially during on-periods).
- Patients who have serious medical or mental disorders.
- Patients with parkinsonism (as opposed to idiopathic Parkinson's disease).

Benefits. The best results occur in patients with the following symptoms:

- Dyskinesias.
- Rigidity.
- Tremor.

Significant improvements in dyskinesia, tremor, slow movements, and rigidity have been reported on the side of the body opposite to where the surgery occurred and such benefits persist in many patients for at least five years (the longest study so far). To a lesser degree, these symptoms initially improved on the same side of the body as the surgery but were not sustained over time. In one study, half of the patients went from being dependent to independent, particularly in being able to feed and dress themselves, and remained that way for the next two years. The improvement in daily functioning, however, appears to diminish over time.

Surgery has less effect on the following symptoms:

- Balance, gait disorders, and freezing. (In one study, however, about half of patients who could stand independently before the procedure reported better stability and fewer falls. The procedure does not restore the ability to stand independently in patients who could not do so before surgery.)
- Voice volume. (Some studies have reported, however, that voice volume improved considerably after surgery in some patients with mild problems, especially when it was performed on the patient's right side.)

Complications. Surgical experience is improving outcomes, but even in centers with high track records, serious and permanent complications occur in 0.41% to 23% of cases. Serious complications include stroke, paralysis, numbness, and impaired peripheral vision, perhaps even blindness. Studies show that neuropsychologic problems such as a decline in memory capacity and verbal fluency (particularly after left-side operations), and apathy may also occur. The procedure can even be fatal. Patients should have the surgery performed only in centers that have experience with the procedure.

Stereotactic Thalamotomy

Thalamotomy uses the same techniques as in pallidotomy, but it is performed on the thalamus, which is a major brain center for relaying messages. Thalamotomy has been reported to significantly reduce or completely stop tremor in 80% to 90% of patients. It does not appear to have much effect on other symptoms. Because tremor is not as significant a disability as other Parkinson's symptoms, the value of this procedure is limited. Complications are similar to pallidotomy, except there is no danger of vision loss.

Neurostimulation (Deep Brain Stimulation)

Procedures called neurostimulation, also called deep brain stimulation, use electric pulse generators to control symptoms. They are proving to be safe and effective alternatives to surgery. Appropriate candidates are similar to those for surgery. (Patients being given neurostimulation, however, should not have pacemakers.) Like pallidotomy and thalamotomy, neurostimulation is not a cure; on the other hand, it does not remove brain tissue and is reversible. Complications occur in 2% to 4% of operations. The most serious is bleeding, which can cause stroke. Of some concern, however, is a possible risk for hemorrhage during implantation, and some experts are not convinced of the safety of implanting a polyurethane device in the brain.

Neurostimulation of the Thalamus. Neurostimulation of thalamus helps patients with tremor and is proving to be as effective and safer than thalamotomy. One procedure (Activa Tremor Control System) involves the following:

- The surgeon implants a tiny pulse generator near the collar bone, which is connected to four electrodes that have been implanted in the thalamus of the brain.
- The generator delivers programmed pulses to the thalamus, which the patient can turn on and off using a magnet held over the skin.
- When the pulses are turned on, the tremor is suppressed.

Studies are reporting improvement in tremor in up to 85% of patients, although only on one side of the body. Long-term effects are still unknown, although studies are indicating that it is safe and effective. The generator must be replaced every three to five years, and the procedure is very expensive. Such unilateral procedures have little effect on daily living activities or motor function.

Neurostimulation of the Subthalamic Nucleus or Globus Pallidus. Double (bilateral) implants are being studied, which include implants in either the subthalamic nucleus or globus pallidus. These areas control symptoms of rigidity and involuntary motion. Subthalamus stimulation appears to be the preferred approach. Some studies have reported improved gait, walking ability, and less upper limb rigidity. One 2000 study found an overall reduction of levodopa by 80% with subthalamus stimulation. The subthalamic approach also appears to require less battery power than globus pallidus stimulation, so batteries need to be replaced less often. This approach may also correct failure of globus pallidal stimulation in some cases. Of concern was a small study suggesting that the procedure may actually accelerate mental decline in some patients, particularly those over 69 years old.

Tissue Implantation

Fetal Cell Implantation. Experimental surgery was showing promise using fetal brain cells rich in dopamine implanted in the substantia nigra. Of great concern, however, are studies in 2000 and 2001 reporting the development of severe dyskinesias (in the absence of levodopa) in implant patients. In some cases it was severe enough to make walking impossible or require pallidotomy. There was no benefit at all in older patients and minimal benefits in those under 60. This is a major setback for this approach.

Alternative Implant Sources. The use of fetal tissue is extremely controversial, however, and research is ongoing for alternatives, including the use of cells from other mammals or human placentas and the use of synthetic microspheres to deliver dopamine directly to the brain. Some researchers hope to use cloning techniques on animal fetuses as a source for dopamine-producing nerve cells. Animal and laboratory studies are also using gene therapies and other advanced treatments for transplanting dopamine-producing cells or nerve-protecting cells into the brain.

Radiosurgery

Radiosurgery is a non-invasive surgical technique typically used for brain cancer that is now being investigated for both thalamotomy and pallidotomy in patients who are not candidates for standard surgery. It employs a so-called gamma knife, which is not a knife at all, but 300 intersecting radiation beams that are directed through holes in a helmet to target precisely affected sites in the brain. Early studies are showing that it improves symptoms after about six to eight weeks. The only side effect reported so far has been swelling in the brain in a few patients, which appears to resolve over time.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) employs high frequency magnetic pulses that target affected areas of the brain. It is noninvasive and is being investigated for Parkinson's disease, and one 1999 study reported symptom improvement in patients treated twice a day. Unfortunately, a 2001 study reported that symptoms actually worsened with this approach.

What Lifestyle Changes Can Help Parkinson's Disease?

Dietary Factors

No special diets or natural foods have been shown to slow down the progression of Parkinson's disease, but there are some dietary recommendations.

Protein. High levels of proteins compete with levodopa for transport to the brain and reduce its effectiveness. Avoiding protein altogether is not the solution, since malnutrition can result. Some experts advise the following. Most experts now recommend trying to maintain a carbohydrate-to-protein ratio of 7:1 throughout the day. This may be difficult to calculate and some physicians recommend simply keeping proteins to 12% of total daily calories.

As an aid in calculation, it may be helpful to note that food labels indicate proteins in grams and that one gram of protein equals four calories. Good control of protein intake may help minimize fluctuations and wearing-off and may allow some patients to reduce their daily levodopa dosage.

Restricting Calories. Animal studies indicate that reducing calorie intake may help reduce toxic effects on nerve degeneration.

Fruits and Vegetables and Increasing Fiber. Eating whole grains and fresh fruits and vegetables is the best approach for any healthy life. A diet rich in fruits and vegetables may help protect nerve cell function. Many of these foods are also often rich in fiber, which is particularly important for helping to prevent constipation. People whose diets have been low in fiber should increase it gradually. It is best to obtain dietary fiber, soluble or insoluble, in the natural form of whole grains, nuts, legumes, fruits and vegetables; if it proves difficult to do so, psyllium, a grain naturally found in India, is an excellent soluble fiber supplement (Metamucil, Fiberall, Perdiem Fiber). Non-caffeinated beverages are particularly important in preventing constipation. Coffee and tea can actually reduce fluids by increasing urination.

Fish Oil. Omega-3 fatty acids, which are found in oily fish, are proving to have powerful anti-inflammatory effects and may also be nerve protective.

Vitamins. No evidence exists that vitamins improve the outlook of Parkinson's disease. However, some people believe that vitamin B6 (pyridoxine) is beneficial because it is necessary in the production and metabolism of dopamine. Most B vitamins play important roles in the brain and central nervous system. Although the major food sources of B vitamins are meats and dairy products, which are high in protein, these vitamins are also found in whole grains and are added as supplements to commercial cereals. Co-enzyme Q10, a vitamin-like antioxidant substance may have protective benefits for Parkinson's patients and is available in natural product stores. Some people think certain antioxidant vitamins, such as C and E, may be helpful. High doses (2000 IU per day) of vitamin E have shown no benefit in Parkinson's disease, however, and research is now suggesting that some antioxidant vitamins may even become harmful in high doses.

Rehabilitation, Exercise, and Other Helpful Therapies

Physical therapy is extremely important for the Parkinson's patient and usually follows an approach that uses active and passive exercise, gait training, practice in normal activities, and if needed, hot or cold treatments, water therapy, and electrical stimulation. Exercise is also essential for well-being; it is a common denominator in patients who are able to maintain productive years.

Exercise Programs. Exercise programs are used defined as passive or active.

- Passive exercise, mostly stretching and manipulation of muscles by a physical therapist, is aimed at preventing muscles from shortening. An active exercise program that begins with slow and gentle exercises and becomes progressively more intense may improve mobility in patients with early and mid-stage Parkinson's disease.
- Active exercises are used to help range-of-motion, coordination, and speed. Patients should continually make efforts to practice movement, even simple ones, such as marching in place, making circular arm movements, and raising the legs up and down while sitting. Patients who enjoy sports or the use of exercise equipment should continue with these activities even if their skills diminish, assuming there are no other medical conditions that would prevent them.

Gait Training. Practicing new methods for standing, walking, and turning are important for retaining balance. The following tips may be helpful:

- Take large steps when walking forward, raising the toes at the forward step, and hitting the ground with the heel.
- Small steps should be taken while turning.
- When walking or turning, the legs should be 12 to 15 inches apart to provide a wide base.
- Patients should not wear rubber or crepe-soled shoes because they grip the floor and may cause the patient to fall forward.
- The use of rhythmic stimulation, such as the use of a metronome (a simple device used by musicians to keep time), may be even more effective than music in enabling some patients to walk faster and take longer steps. One study found that setting a metronome rhythm to about 10% faster than the patient's fastest gait offers significant improvement over walking to no rhythm at all or to a rhythm that matches the gait.

Reducing Muscle Freezing. The patient should practice regular daily activities that simplify actions and reduce the incidence of muscle freezing. Most often, freezing occurs when a patient begins to move or is presented with an obstacle. The following may be helpful.

- Simply being touched by another person can sometimes release the patient (although a Parkinson's patient should never be pulled or pushed).
- If the legs feel frozen, simply lifting the toes may free spasm.
- Rocking from side to side is useful.
- Humming a marching tune helps. In fact, music has been shown to help people move and to get out of bed in the morning. Some report that wearing a Walkman and turning music on in situations associated with freezing, such as crossing a street, is helpful.
- Because trying to coordinate a number of physical operations at the same time can cause freezing, the patient might find it helpful to divide actions into separate events. For instance, when going through a doorway, a patient should approach the door, stop, open the door, stop, and then walk through the doorway.

Sleep Deprivation Therapy. Sleep deprivation therapy may have a role in treating some cases of depression and some studies are finding some benefits on the depression, tremor, and rigidity experienced by Parkinson's patients. Scientists believe that sleep deprivation produces certain anticholinergic effects, which may ameliorate both depression and Parkinson's symptoms.

Mental Therapies. Some studies indicate that being mentally fit may be as important for Parkinson's patients as being physically fit. Mental training may actually increase dopamine in the brain. Some experts recommend the following:

- Selecting or learning new hobbies that require finger and hand mobility, such as sewing, carpentry, fishing, or playing cards may be helpful.
- Deep breathing and relaxation exercises may help maintain proper speech control, control tremor, and reduce anxiety.
- Psychologic therapy and support is important for the depression and loss of motivation that often accompany this difficult condition. One study suggests that marital stress can even produce loss of mobility. Although psychological and behavioral therapies can be expensive, a number of support programs and groups that can be invaluable for the patient and the family are available at little or no cost.

Speech Therapy. Speech therapy may be required for those who develop a monotone voice and lose volume. A technique called the Lee Silverman Voice Treatment may be particularly effective. It has five major components:

1. Focus on the voice ("think loud / think shout").
2. High effort (pushes patients to overcome limitations).
3. Intensive treatment (16 sessions in one month).
4. Calibration (learning to know and accept the amount of effort needed to produce normal sound so it becomes automatic).
5. Quantification (continuous feedback to objectively document success).

Equipment and Devices. A number of devices can be helpful. The following are some examples:

- Rails can be installed where the patient needs support in getting up or down, such as along the bed and in the bathroom.
- Walkers with locking wheels are helpful.
- Chairs should have straight backs, with firm seats and arm rests.
- Firm mattresses and satin sheets or less expensive sheets with high thread counts are useful for helping patients slide out of bed.

Where Else Can Help Be Obtained for Parkinson's Disease?

National Parkinson Foundation, 1501 NW 9th Ave., Bob Hope Road, Miami, FL 33136-1494. Call (800-327-4545) or on the Internet (http://www.parkinson.org/)
This is a primary resource of information for PD. The staff is very responsive and sends out an extremely useful package of materials. They also have a quarterly newsletter, *Parkinson Report*, which describes recent research, provides information on new clinical trials, and offers excellent articles on personal and professional aspects of PD.

American Parkinson's Disease Association, 1250 Hylan Blvd., Suite 4B, Staten Island, NY 10305. Call (800-223-2732) or on the Internet (http://www.apdaparkinson.com)

National Institute of Neurological Disorders and Stroke, Office of Communications and Public Liasons, PO Box 5801, Bethesda, MD 20824. Call (800-352-9424) or on the Internet (http://www.ninds.nih.gov)
The NINDS gives information on participation in major clinical trials.
(http://www.ninds.nih.gov/HEALINFO/disorder/parkinso/pdhtr.htm) Is the specific address for an excellent overview on Parkinson's.

Parkinson's Disease Foundation, 710 West 168th St., New York, NY 10032-9982, Call (800-457-6676) or (212-923-4700), or on the Internet (http://www.parkinsons-foundation.org/ or www.pdf.org)
Offers good basic information, including an excellent booklet, *Exercise for the Parkinson Patient with Hints for Daily Living,* and provides a quarterly newsletter.

American Association of Neurologic Surgeons, 550 Meadowbrook Drive, Rolling Meadows, Illinois 60008-3845. Call (847-378-0500) or (888-566-AANS (2267) or (http://www.neurosurgery.org/)

Parkinson's Institute, 1170 Morse Ave., Sunnyvale, CA 94089-1605, Call (408-734-2800).

Parkinson's Support Groups of America, 11376 Cherry Hill Road, No. 204, Beltsville, MD 20705. Call (301-937-1545)

Sammons Preston and Enrichments, PO Box 5050, Bolingbrook, IL 60440. Call (800-323-5547) or on the Internet (www.sammonspreston.com)
Offers a catalogue and provides many items that improve the quality of life for a Parkinson's patient, including aids for eating, exercising, turning handles and knobs, and accessories for wheelchairs.

American Speech-Hearing-Language Association (ASHA), 10801 Rockville Pike, Rockville, MD 20852 (Call-800-498-2071) or TDD (301-897-5700) or on the Internet (http://www.professional.asha.org.

Other Good Sites
Harvard Medical School site for Parkinson's (http://pdweb.mgh.harvard.edu/)
Awakenings. This s~~S~~ite connects to European Parkinson's Disease Association and has other support information (http://www.parkinsonsdisease.com/).
Excellent physican-run site (http://www.wemove.org/

FIND A NEUROLOGIST

http://www.aan.com/rostersearch_f.html

FIND A NEUROSURGEON

http://www.neurosurgery.org/health/findaneurosurgeon.html (also includes neurosurgeons worldwide)

Recent Literature
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