Parkinson's Disease HANDBOOK

A Guide for Patients and Their Families

APDA
TO EASE THE BURDEN
TO FIND THE CURE
American Parkinson Disease Association

American Parkinson Disease Association, Inc.

AMERICAN PARKINSON DISEASE ASSOCIATION, INC.

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PARKINSON'S DISEASE HANDBOOK

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This handbook is a guide for Parkinson's disease patients and their families and is not intended as a substitute for medical diagnosis and treatment.

A Message From The APDA's President

You have heard the diagnosis, "You have Parkinson's disease ," and have turned to the American Parkinson Disease Association (APDA) for information. Our "Parkinson Disease Handbook" has been written for you, your family members, health care providers and the general population wanting to know about this disease that affects more than 1.5 million Americans.

The authors are three distinguished physicians with many years of experience in Parkinson's disease (PD) research and treatment. Here you will learn important information about PD, its symptoms, and the latest available medical and surgical treatments. As you read through this handbook, keep in mind that each person's experience with PD is unique – not all the information may be pertinent to you.

We hope that you will consider APDA your partner as you seek additional information and support. Our mission is to "Ease the Burden – Find the Cure," which we meet through a national network of Chapters, Information & Referral (I&R) Centers and support groups, and annual multi-million dollar funding of promising new medical and scientific research toward understanding and eradicating the disease.

APDA's "Parkinson Disease Handbook" is just one of a number of free publications about all aspects of living with PD. You may download many of them directly from our Web site, www.apdaparkinson.org, or phone APDA national headquarters at 800-223-2732. When you call, ask for the flyer "Basic Information about Parkinson's Disease" and our quarterly newsletter. These contain a complete listing of our booklets and supplements. Also sign up for our free monthly e-newsletter with timely information about PD and coping tips.

I also encourage you to contact your nearest APDA I&R Center listed at the back of this booklet and on our Web site. These Centers are a valuable resource for physician and services referrals, education materials and programs, local support group meetings, and general assistance.

My very best wishes.

Joel A. Miele Sr., P.E.
President

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I. INTRODUCTION

Parkinson's disease (PD) was first described by Dr. James Parkinson in a little book entitled *An Essay on the Shaking Palsy*, published in 1817. For the next century, the condition was known popularly as the shaking palsy and in the medical community by its Latin equivalent, *paralysis agitans*. These terms are misleading, however, implying that people are paralyzed with this disorder, which is not the case. It is sometimes called *idiopathic parkinsonism* (the term idiopathic means that the cause is unknown), but more commonly today it is simply called Parkinson's disease, to honor the physician who first described it.

What is PD? PD is a disorder of the central nervous system, involving primarily a degeneration of certain nerve cells in deep parts of the brain called the *basal ganglia*, and in particular a loss of nerve cells (or neurons) in a part of the brainstem called the *substantia nigra*. These cells make the neurochemical messenger dopamine, which is partly responsible for starting a circuit of messages that coordinate normal movement. In the absence (or with substantial reduction, more than 80% of the normal level) of dopamine, the neurons in the receiving area (called *dopamine receptors*) in the next part of the basal ganglia circuit called the *striatum* are not adequately stimulated, and the result is impairment of movement with tremor, slowness, stiffness, or balance problems, among other symptoms, which will be discussed in the next section. Under the microscope, the damaged and dying neurons in the substantia nigra show a round inclusion called a *Lewy body*, which is considered to be specific to PD. Because of this, the disorder is sometimes called *Lewy body PD, Lewy body parkinsonism*, or simply *Lewy body disease*.

PD occurs in roughly the same proportions in men and women (although there may be a slight preponderance of affected men) throughout the world. Initial symptoms may appear at any age, although under 40 is uncommon and under 20 is very rare (but it happens!). Most commonly, the first symptoms are noted in the 60's or 70's. The average age of onset of PD is about 59.

Why do these neurons degenerate? The exact reason is not yet known; this topic is a target of significant research, and is discussed further in the section on the cause of PD (Chapter IV).

PD is just one type of *parkinsonian syndrome*, or *parkinsonism*. Parkinsonism can be thought of as a general term, encompassing PD and related syndromes. We will discuss these other conditions in the section on the other syndromes related to PD (Chapter III).

PD is a chronic, usually slowly progressive illness, but the rate of progression will vary from person to person. Although there are many features of PD that most patients will share, exactly how it affects any given patient is very individual, and precisely what happens to one patient in the course of the

illness may not necessarily follow suit in another. Symptoms in some people will remain very mild and will not restrict the day-to-day activities for many years, whereas symptoms in others will progress to disability much faster.

Diagnosis is based almost exclusively on the history of the person's illness and the physician's clinical examination. There are no really adequate nor specific blood or radiologic tests in common usage to make an absolute diagnosis of PD. Although there is at present no cure for PD (one can only cure a disease when one knows the cause), there is a large and growing number of treatments (Chapter V) for the disorder that can improve or even normalize the quality of life for a very long time.

II. SIGNS AND SYMPTOMS

A large number of signs (what the doctor sees) and symptoms (what the patient experiences) define PD. The classic trio, tremor, muscle rigidity, and bradykinesia (slowness), are joined by other primary symptoms (balance, posture, and walking problems) and an excess of secondary or associated difficulties. Italicized words indicate the medical terms to describe some of the symptoms.

A. Initial Symptoms

The first symptoms of PD may vary from patient to patient, but commonly a feeling of "weakness" or fatigue may occur, although it should be noted that, if tested, all individual muscles would be strong. The "weakness" is more a vague problem with getting started, initiating movement, and carrying out the movement at the previous level of speed and accuracy. Initial symptoms generally begin on one side of the body and remain on one side (*unilateral*) for some time. Shaking or trembling, usually of the hands, and usually on one side (right and left are affected equally, and do not depend on which hand is dominant), may also occur very early in the condition. The shaking is generally at rest, when the hand is just lying in the lap, or upon walking. Dragging of one leg (if there is a tremor, it is usually on the same side) is also a common complaint early on. Changes in handwriting (getting smaller), voice (softer, sometimes a bit hoarse), facial expression (the so-called Parkinsonian mask), and trouble with initiating movement (getting out of a chair, a car, or a bathtub, for instance) or walking may also be present. Also seen in the early stages are drooling, particularly at night, and mild depression or anxiety.

When early symptoms begin to interfere with work or activities of daily living, initiation of antiparkinson therapy is indicated. Another important point to remember is that the symptoms of PD, most prominently tremor, may be uncovered or aggravated temporarily by stress or stressful situations. Stress, however, does not cause PD.

A bit later on in typical, "garden-variety" PD, one may encounter problems with posture (becoming stooped; patients are frequently told by family members to stand up straight) and maintaining balance, which may be quite disabling. When these occur very early in the disease, especially in the absence of tremor, we must consider other atypical forms of parkinsonism (see next section).

B. Primary Symptoms

Tremor at rest is the characteristic feature of PD that earned it the earlier name of the shaking palsy. Rest tremor occurs rarely in any other condition. The tremor is slow and rhythmic. It usually begins in one hand and only later spreads to involve the other side. Occasionally, the feet or legs may also exhibit a tremor, again usually greater on the side of initial involvement. The lips and jaw may also shake. Less commonly, the head and neck may shake as well.

The rest tremor is the predominant type seen in PD, and the tremor usually reduces or disappears upon performing a purposeful movement. In some patients, however, the tremor may be present when holding up the outstretched arms (*postural or sustention tremor*) or when performing various movements (*action tremor*). Rest tremor, especially when mild, is rarely functionally limiting, although many people feel self-conscious about the shaking, whereas action tremor may interfere with certain functions, such as eating soup or drinking from a full cup.

Another type of tremor experienced by some people with PD is internal tremor; this can usually only be felt by the patient and not seen by the examiner. It may be very disturbing to the patient.

Rigidity is a term meaning a tightness or increase in muscle tone at rest or throughout the entire range of motion of a limb. It may be felt as a stiffness in the limbs, the neck, and even the trunk. This stiffness is often mistaken for arthritis (a common condition, and one that may also be present). Improvement in rigidity, however, occurs with antiparkinson medications. Arthritis medications (such as anti-inflammatories) do not help the parkinsonian symptoms.

Bradykinsia is Greek meaning "slow movement," and the feature which characterizes all forms of parkinsonism. It manifests in a variety of ways, including the mask-like expression (*hypomimia*) with decreased eye blinks, slowness in arising or initiating movement, and decrease in fine motor coordination (manifested by the inability to button a shirt, cut meat, etc.). Difficulty with turning over in bed is a mark of bradykinesia, as are problems with handwriting becoming slow and small (*micrographia*). Many of the manifestations of bradykinesia may be very disabling as they progress, although they respond well to treatment.

Gait (walking) may be very slightly impaired early on, but usually is not disabling. Decrease in the natural arm swing is seen first, and only later do problems with slow, small steps and shuffling (*festination*) occur. Patients may begin to propel themselves forward as they accelerate with rapid, short steps (*propulsion*). In advanced PD (and sometimes as a side-effect of treatment), there may be episodes of *freezing* in which the feet appear to be glued to the floor. This phenomenon usually happens at doorways, curbs, elevators, etc. It may sometimes be overcome by visualizing an obstruction to step over, marching to verbal commands, or actually stepping over lines placed on the floor, among other tricks.

Balance problems and impairment of posture usually occur late in the course of typical PD, and are unquestionably the most disabling of all the symptoms. Patients occasionally complain of "dizziness" when they mean that their balance or equilibrium is off. Inability to maintain a steady, upright posture

or to take a corrective action to prevent a fall often results in just that—falling. Patients tend to go backwards as well (*retropulsion*), and a light shove may cause the patient to continue taking many steps backwards or to fall. The use of balance aids (canes or walkers) becomes necessary, and patients may eventually require a wheelchair.

C. Symptoms Related to Treatment

End-of-dose failure and the on-off phenomenon: When symptomatic antiparkinson therapy is instituted (especially with the mainstay of treatment, levodopa), patients usually have a smooth response for a long time. After years of treatment, however, there may be a *wearing-off* of the beneficial effect of a medication before the next dose is taken; that is, the patient may respond and feel good ("*on*") for a period of time and then the effect of the medication wears off, causing the parkinsonian symptoms to return ("*off*"). This is a common situation in the PD patient, and *end-of-dose failure* may be corrected by shortening the interval between doses, or by adding additional medications. As these *motor fluctuations* progress, however, the interval between doses may be very short. In severe, advanced patients, there occasionally arises a complication of long-term therapy where the response to medication is unpredictable; this is termed the *on-off* phenomenon, in which the patient may cycle from on to off or back again during one dosage interval, or the medication may never kick in at all. The on-off phenomenon is very difficult to treat.

Dyskinesias: Usually seen as a *peak-dose* phenomenon (when a dose of levodopa is at its highest point in its dosing interval, also called *high-dopa dyskinesias*), abnormal involuntary movements (*dyskinesias*) with irregular, flowing, dance-like or jerky motions may occur in any or all parts of the body; these are called *choreic or choreiform movements* or simply *chorea* (from the Greek word for "dance"). Less commonly, dyskinesias may occur as the dose is wearing off (which we call *wearing-off or low-dopa dyskinesias*). Dyskinesias may be *choreic* or *dystonic* in nature. Dystonia may also occur as *high-dopa* (usually above the neck) or *low-dopa* (usually in the lower part of the body) phenomena.

D. Secondary Symptoms

Speech: Speech problems are not uncommon in PD. Initially, the voice may merely become softer, but may also start off strong and fade away. There may be a loss of the normal variation in volume and emotion in the voice, and the patient may talk in a monotone, like a computer. Speaking rapidly, with the words crowded together, similar to the short, shuffling, propelling steps when walking, is also characteristic of parkinsonian speech. Sometimes hoarseness is a problem, and occasionally the patient may slur words. In more advanced disease, a type of stuttering (*palilalia*), likened to the freezing phenomenon, can occur.

Swallowing: Problems with swallowing (*dysphagia*), when they occur in PD, happen late in the course of the disease. Swallowing is an automatic but complex act, and the inability of the tongue and throat muscles in PD to coordinate the movement of food to the back of the mouth and down the upper part of the esophagus may result in pooling of food in the throat. The patient may feel as if food is getting stuck. Both solids and liquids are a problem, while soft or puréed food goes down more easily.

Drooling: Drooling (*sialorrhea*) is similar to the problems experienced with swallowing, in that saliva pools in the back of the throat. When enough is accumulated in the mouth, it may spill out and the patient may drool. Drooling is probably related to a decrease in the swallowing of saliva, not excess production of saliva.

Seborrheic dermatitis: A common skin disorder in many people, excessive oily secretions, particularly on the forehead and scalp, may be a problem in PD. It may cause the skin to be greasy, and the skin becomes red, itchy, and flaky. On the scalp, it results in dandruff.

Ankle Swelling: Another common problem in the general population as people age, swelling (*edema*) of the feet and ankles may occur frequently in PD, and occasionally is a side effect of some antiparkinson medications. It probably is a result of pooling of fluid in the lowest part of the body when there is reduced muscle movement to squeeze the veins and propel fluid back to the heart.

Visual problems: Many people have problems with their eyes. Nearsightedness, farsightedness, and cataracts are not related to PD. Sometimes, however, people may complain of some mild double vision or problems with the eyes "bouncing" around, that is, they may have difficulty reading (especially small print) because they lose the line. These situations may be related to PD.

Weight loss: Loss of weight, sometimes considerable, is a common occurrence in PD, and should trigger an evaluation for some other serious medical problem. In the absence of other disorders, severe weight loss may easily be attributed to PD, and although it may be of concern, the weight loss usually levels off. It may result from a generally decreased appetite in PD, swallowing difficulties, other gastrointestinal disturbances, or excessive movement (either severe tremor or, in the advanced, treated patient, severe abnormal involuntary movements).

Constipation and other gastrointestinal (GI) problems: Constipation is a very common problem, and may occur more in older people and in a generation taught from an early age that one ***must*** move one's bowels daily. This is not necessarily true. PD, however, may slow the bowels down (just as the rest of the body is slowed down), and the side effects of antiparkinson treatment may also contribute to this problem.

Abdominal distention or bloating may also occur in PD, and occasionally may cause significant discomfort. Nausea and vomiting may occur in untreated PD, but are more common as an adverse effect of medications used to treat PD, especially in the early stages.

Urinary problems: Urinary *frequency* (urinating very often because the bladder does not empty fully each time) and *urgency* (the feeling that one must void right away, even if the bladder is not full) are not uncommon in PD. The normal reflex mechanisms controlling the bladder may be impaired in PD, and is a problem mostly at night. There may also be difficulties with hesitancy in beginning to void, slowness in voiding, and overfill of the bladder; the latter may result in accidents if the patient cannot make it to the toilet in time. It should be remembered that other conditions can cause or worsen these situations, particularly urinary tract infections, prostate problems in men and, in women (especially those who have given birth), a "dropped" bladder or uterus.

Sexual dysfunction: Sexual desire (*libido*) may be reduced in PD; in some cases, there may be complex psychological issues (combining sexual desire and performance with a medical condition), and in others it may be a direct, neurochemical effect of the disorder. Treatment of PD with antiparkinson drugs frequently improves libido, and occasionally exaggerates it (which may likewise also create problems). Physical problems, particularly in men with inability to achieve erections (*impotence*), inability to maintain erections, or incomplete erections may be part of the PD, or may result from other causes.

Dizziness and lightheadedness: "Dizziness" is a very vague term to the physician. It could mean imbalance, lightheadedness (probably the most common description), or actual spinning (*vertigo*). Vertigo is probably a result of other conditions and should be addressed accordingly. Lightheadedness, however, may be related to PD, and, when it is severe, may result in actual black-outs or fainting. This usually results from a drop in blood pressure upon change of position (from lying to sitting or sitting to standing) (*orthostatic or postural hypotension*). Again, sometimes another medical condition is present (such as dehydration), but it may be part of the PD or a complication of the medical treatment of PD.

Aches, pains, and dystonia: Nonspecific discomfort may be a part of PD. Numbness and tingling (paresthesias) may occur in limbs; occasionally, they may result from other medical conditions, such as pinched nerves from arthritis in the neck or low back, but in the absence of these problems, they may be attributed to PD. Tightness and cramping in muscles (*dystonia or dystonic cramps*), particularly in the feet and legs, may be common occurrences, and may occur early in the disease, even before treatment is instituted. The pain in the legs may be so severe as to cause patients to have back surgery for presumed sciatica! Dystonia may also involve twisting or torsioning of muscles.

Any muscle may be affected by dystonia or dystonic cramping, including the neck (*cervical dystonia*), eyelids (*blepharospasm*), jaw, arms, legs and feet. Blepharospasm, where the eyes are forced closed or are unable to be opened normally, occurs more often from too much antiparkinson medication, whereas toe or calf dystonia more commonly happens in the untreated or undertreated state. Rarely, dystonia can affect the chest wall muscles and other muscles involved in breathing (*respiratory dystonia*), and shortness of breath may result. This can be very frightening. If lung and heart disease are ruled out, however, it should be remembered that respiratory dystonia, although disturbing, is not dangerous.

Sweating: As with problems of bowel and bladder, impotence, and blood pressure, sweating in PD may result from disturbances in the part of the nervous system (*autonomic nervous system*) that control these automatic functions. Disorders of the autonomic nervous system are called *dysautonomia*. When dysautonomia is acute, we may be dealing with one of the atypical parkinsonisms called Shy-Drager syndrome (see next chapter). Still, dysautonomia is compatible with a diagnosis of PD, and abnormalities of sweating, particularly excessive sweating, are not uncommon in PD. It frequently involves the upper part of the body more than the lower, and may be a sign of untreated or undertreated parkinsonism. Profuse, drenching sweats may occur infrequently but may be very bothersome, and may be associated with the wearing-off of medication in the advanced patient.

E. Symptoms Related to Mentation, Behavior, or Mood

Depression, anxiety, and panic attacks: Depression and anxiety occur in as many as 50% of PD patients. Sometimes, they may be among the first symptoms of PD, and in a small number of patients, the initial symptom may be frank *panic attacks*, with full-blown palpitations, hyperventilation, sweating, pallor, and a feeling of impending doom. Depression may lead to loss of motivation, and the patient may not want to do anything all day. These disorders of mood may be in small part a reaction to the disease itself, but more often result from biochemical deficiencies in the brain of neurochemicals related to dopamine (called *norepinephrine* and *serotonin*) which are responsible for mood regulation and are reduced (like dopamine, although not as drastically) in PD. Rarely, the depression may be so severe as to require significant psychiatric intervention. More commonly, anxiety and depression are mild; they sometimes improve with antiparkinson therapy, but frequently require additional medications (see Chapter V, “Treatment”).

Disturbances of sleep: All humans must go through a normal sleep cycle in the regular rhythm of the day, but the sleep cycle is frequently abnormal in those with PD (*insomnia*). Inability to fall asleep (*primary insomnia*) is less common in PD than the inability to stay asleep (*secondary insomnia*); that is, patients fall asleep with no problem, but wake up frequently throughout the

night. More problematic is the individual who catnaps throughout the day and cannot sleep at night, reversing the normal sleep cycle. Some people have very vivid dreams (usually from too much antiparkinson medication) and may talk or thrash in their sleep; this condition is common in PD and called *REM sleep behavior disorder* (RBD). It rarely bothers the patient, but may have a strong effect on the patient's bed partner. Kicking and jerking of the limbs (*nocturnal myoclonus*) during sleep may also occur. If one wakes up, instead of getting up and wandering through the house, it is important to try to go back to sleep to get a good night's rest, if possible.

Dementia, memory loss, and confusion: Problems with thinking, word-finding, judgment, and other features of *cognitive* function (*dementia*) may occur in up to 40-50% of PD patients, especially late in the disease and in older patients. These problems are often milder than the dysfunction seen in Alzheimer's disease (AD) and are part of the pathology of PD. Problems with memory, for instance, are very prominent in AD but less common in PD. When these problems occur early in the course, along with hallucinations and other symptoms, there may be more extensive involvement of the brain with degenerating neurons demonstrating Lewy bodies (see Introduction), and this related disorder, demonstrating Lewy bodies throughout the brain, has been termed *dementia with Lewy bodies* (DLB) (see next section). PD patients who develop similar symptoms late in the course are said to have *PD-dementia* (PDD). Pathologically, a similar picture is seen throughout the brain in both DLB and PDD, labeled *diffuse Lewy body disease*. Although occasionally AD may occur together with PD, it is important to realize that mental dysfunction may be attributed to the PD (or DLB) alone, without AD. Confusion may become a problem; it is frequently worsened by antiparkinson medications.

Hallucinations and psychosis: One complication of antiparkinson medication may be disturbances of perception, with *hallucinations* (seeing people or things that aren't really there. They are usually visual, rarely *auditory* [hearing]). *Delusions* (a fixed but erroneous idea or notion) or *paranoia* (feeling that people are out to get them, for example) may also occur. These symptoms constitute *drug-induced psychosis*, although sometimes, especially in DLB, they may occur without any antiparkinson medications at all. Frequently, psychotic symptoms, especially when severe, may indicate an underlying complication of dementia.

III. OTHER PARKINSONISMS

PD is ***not*** related to other neurological conditions such as Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), polio, or muscular dystrophy, and the signs and symptoms of PD are entirely different from this collection of nervous system diseases. There are, however, a large number of related *parkinsonian syndromes* or *atypical parkinsonisms*, also called *Parkinson-plus syndromes*, which look like PD but have other clinical features and other pathology. In general, PD is much more treatable than most of its atypical cousins; many of the latter have a shorter, more disabling course. Some are inherited and some are not; some occur in children and some rarely if ever arise before late middle age. Differentiating PD from these other disorders is important for issues of treatment and long-term planning. The list is quite long, so we will only discuss the major parkinsonian syndromes, along with related disorders commonly misdiagnosed as PD.

Dementia with Lewy Bodies: As mentioned in the previous section, *dementia with Lewy bodies* (DLB) is closely related to PD as the pathology consists of the pathologic hallmark of PD, the Lewy body, seen extensively throughout the brain. It differs in that the cognitive problems occur before the parkinsonism or within one year of the the motor symptoms. In addition, patients with DLB also have visual hallucinations (usually without medication) and "fluctuations" in level of consciousness, which are also described as "*zone-out periods*." During these periods (which may last minutes or hours, rarely up to a couple of days), the patients are essentially unresponsive. All tests (neurological, cardiac, general medical, blood tests) are negative and they come out of them spontaneously. While the actual reason for these periods is unknown, they appear to be benign and do not cause the patient any harm. The parkinsonism may improve with medications used in PD, and the cognitive and psychiatric symptoms respond to medications directed at those features.

Progressive Supranuclear Palsy: The most common of the atypical parkinsonisms is a disorder called *progressive supranuclear palsy* (PSP), also known in England as Steele-Richardson-Olszewski syndrome for the doctors who first described it. PSP may appear initially like typical PD, or patients may complain more of gait disorder and frequent falls, visual abnormalities, or speech or swallowing problems. Tremor is usually absent. Falling, imbalance, and problems with walking occur much earlier than in PD, and the disease course is shorter. The neck may be very rigid, with hyperextension. Patients assume a "wide-eyed, astonished, staring" expression. The hallmark of the disease is the inability to look down voluntarily (supranuclear gaze palsy); later, other eye movement abnormalities may occur. No medications have been found to be consistently useful for more advanced cases of PSP.

Multiple Systems Atrophy: *Multiple system atrophy* (MSA) is a "lumper's" term for the three main disorders called *olivopontocerebellar atrophy* (OPCA), *Shy-Drager syndrome* (or primary or progressive autonomic failure with MSA)

(SDS), and *striatonigral degeneration* (SND). All of them may be characterized by parkinsonism, although rest tremor is slight or absent. Again, the course is more rapid than PD and treatment is not as effective, because more areas of the brain are affected than in PD. Distinguishing features of these disorders include:

OPCA: an unsteadiness or imbalance called *ataxia*, where the impairments of balance, stability, and coordinated movements are out of proportion to other signs and symptoms.

SDS: parkinsonism with *dysautonomia* (see Signs and Symptoms), where the dysautonomia precedes or dwarfs the parkinsonism. These patients often have severe orthostatic hypotension (a decrease in blood pressure upon standing up).

SND: may appear clinically identical to PD, although tremor tends to be less prominent, and gait and balance problems may occur earlier. Diagnosis is usually considered in patients with parkinsonism in whom there is no response at all to levodopa or other antiparkinson drugs, and in fact some patients get a paradoxical worsening on levodopa and many will have dyskinesias even though they have no effective improvement from the medication.

Cortical-Basal Ganglionic Degeneration: The least common of the four main Parkinson-plus syndromes, *corticobasal degeneration* (CBD) is characterized by very asymmetric involvement of one arm (before eventually involving the other side) with extreme rigidity, a foreign feeling or involuntary positioning of the limb (*alien limb phenomenon*), a loss of knowing what to do with the hand (for example, forgetting how to brush one's teeth, snap one's fingers, or show the "V" for victory sign) (*apraxia*), and loss of some sensations on that side. There is infrequent rest tremor and, again, early problems with gait and balance. Dementia may occur early. CBD, like PSP, almost never occurs before age 50 and the course is relatively short. No treatments have been found to be effective.

Vascular Diseases: Strokes due to hardening of the arteries or small blood vessels (*arteriosclerosis*) usually come on suddenly, causing paralysis of one side of the body. Rarely, multiple little strokes in deep parts of the brain, each too small to be noticed or causing only brief weakness, may eventually result in cumulative damage to the circuit that causes the symptoms of parkinsonism. *Vascular* parkinsonism is generally considered to be a "lower-body" parkinsonism, causing problems with gait and balance, but rare tremor. Sometimes, impairment of mental function may be seen. Patients tend to be older with a history of high blood pressure (*hypertension*), diabetes, or heart conditions. Treatment should be aimed at correcting the heart problems, blood pressure, cholesterol, and/or blood sugar.

Drugs and Toxins: A variety of drugs and toxins have been found to be responsible for the development of parkinsonian syndromes. Most cause only

temporary problems, but one *toxin* has resulted in permanent parkinsonism. This toxin is *MPTP*, a "designer drug" similar to heroin. In humans and laboratory animals, it has caused an irreversible, very rapidly developing parkinsonism, clinically indistinguishable from PD except for the speed of development following exposure (drug addicts and organic chemists have been the highest risk groups). Severity appears to relate to degree of exposure, and so far MPTP parkinsonism has not appeared to be a progressive disorder. Patients respond well to antiparkinson medications. It has proved valuable in providing animal models of PD for research. Also, poisoning with manganese has been reported to cause parkinsonism.

Reversible cases of *drug-induced* parkinsonism have been associated with a number of drugs: *antipsychotic medications*, used largely to treat schizophrenics, such as haloperidol (Haldol®), fluphenazine (Prolixin®), and chlorpromazine (Thorazine®); certain *anti-nausea* drugs that are chemically related to the antipsychotic drugs, such as prochlorperazine (Compazine®); metoclopramide (Reglan®), a highly prescribed medication for improving stomach and bowel movement; and alpha-methyl dopa (Aldomet®), a formerly popular antihypertensive, although now used rarely. Any patient showing signs of parkinsonism should be asked about medication history, and all patients should be aware of the medications that they take or previously took.

Post-Encephalitic Parkinsonism: A consequence of *Von Economo's* or *epidemic encephalitis* or *encephalitis lethargica* (not the post-World War I influenza epidemic) that occurred worldwide in the second and third decades of the 20th century, *post-encephalitic parkinsonism* (PEP) accounted for about 12% of parkinsonism seen at major centers in the first half of the century; there are now very few patients left with this disorder. The cause was almost certainly a virus, but it has never been identified. Of people affected with encephalitis lethargica, not all developed parkinsonism; development of this condition ranged from weeks or months to years following the encephalitis exposure. The parkinsonism is quite typical, with tremor being as prominent as in PD. Other features, however, distinguish PEP from PD, the most dramatic being a dystonic deviation of the eyes (*oculogyric crisis*). Other features include young onset, bizarre personality and other behavioral changes, paralysis, and extreme fatigue or sleepiness. When levodopa was introduced, a population of PEP patients was started on this drug, but few could tolerate the briskly developing side effects. A fascinating and poetic description of this condition is to be found in the popular book, and later movie, *Awakenings* by Dr. Oliver Sacks.

Normal Pressure Hydrocephalus: *Normal pressure hydrocephalus* (NPH) is uncommon but potentially reversible and rarely may appear to have a parkinsonian syndrome; it may be distinguished by its classic trio of gait disorder, urinary incontinence, and dementia. It is caused by enlargement of the fluid cavities of the brain called the ventricles, and there is compression of the centers that control walking, voiding, and thinking. It may sometimes be

improved by removing the fluid from the brain, most effectively done by insertion of a tube called a *shunt* from the brain to another part of the body (often the abdomen) to drain the fluid away. A not infrequent side effect of shunting, however, particularly in elderly people, is the development of subdural hematomas, a collection of blood and fluid between the brain and the hard lining of the brain under the skull; these can cause more problems and need further neurosurgical intervention.

Essential Tremor: Because the tremor is the hallmark of this (often inherited) condition, *essential tremor* (ET) is commonly mistaken for PD. It has also been called benign or familial ET. The tremor, however, is different: it is primarily a tremor that is at its worst on action, less severe on posture-holding, and rare at rest. The hands are most often affected, and there may be a tremor of the head and neck, usually a head nod ("yes-yes" tremor) or shake ("no-no" tremor). The voice has a tremulous quality (and, when mild, may sound like a vibrato in singing) which is not seen in PD. The legs are rarely affected, and there is no slowness, stiffness, or other features of PD. Some patients with *presumed* ET may eventually develop PD, however.

Dystonia: *Primary, or idiopathic, dystonia* may occur in individuals of any age. In childhood, it tends to start in the foot and gradually involve the entire body. Adult-onset dystonia tends to be in one body location (*focal dystonia*) and remain there. Most frequent areas of involvement are the neck (*cervical dystonia*), eyelids (*blepharospasm*), lower face (*Meige syndrome*), or hand (*writer's cramp dystonia*). As previously mentioned, dystonia as a *secondary* feature may occur as part of PD. Occasionally, a patient with what appears to be primary focal dystonia may later develop PD.

Dopa-Responsive Dystonia: *Dopa-responsive dystonia* (DRD) is a disorder that usually begins in childhood, is more common in girls than in boys, is characterized by mild parkinsonism with more pronounced dystonia, worsening as the day wears on, and dramatic, prolonged response to low-dose levodopa. It may be confused with juvenile-onset PD.

Alzheimer's disease: Occasionally, some patients with *Alzheimer's disease* (AD) may demonstrate features of parkinsonism. Also occasionally, the pathology of PD and AD may occur in the same person. As previously discussed, PD-D and DLB are characterized by parkinsonism and mental dysfunction and may be mistaken for AD. Nevertheless, PD is ***not*** AD, and does not lead to AD. Since there are currently no tests to determine what the exact diagnosis is (or diagnoses are), only post-mortem examination of the brain is the "gold-standard" for precise diagnosis.

IV. THE CAUSE OF PARKINSON'S DISEASE

The cause of any disease is two separate issues. One, the *etiology*, concerns how the individual acquired the illness and the *pathogenesis* concerns the abnormal processes in the body that produce the signs and symptoms of the disease. For example, the etiology of acne is skin oil and bacteria, while its pathogenesis is blockage of pores with resulting infection and inflammation. For PD, our understanding of the etiology is poor to fair and our knowledge of the pathogenesis is fair to good.

A. Etiology (How PD is Acquired)

Genetics Versus Environment: Most experts believe that the *etiology* of PD is an exposure to an as-yet unidentified chemical in the food, air or water in a person with a genetic (inherited) vulnerability to that chemical. The experts disagree on whether the exposure (*environment*) or the vulnerability (*genetics*) is more important. Those in the *environmental* camp say that most people in the population have the inherited susceptibility just by virtue of being human and that the factor critical to the development of PD is the degree of exposure to the environmental factor. Those in the *genetic* camp say that most people have the environmental exposure just by virtue of living in the world and the critical factor is an inherited susceptibility. Time will tell who is right and just what the genetic and environmental factors are. Most experts think this will be worked out in the coming decades.

The Environmental Hypothesis: The idea that PD is mostly the result of exposure to a poisonous chemical became popular in the early 1980's. At that time, there appeared a report of several young intravenous drug users in California who developed a severe and sudden illness that looked just like PD. A team of researchers led by Dr. J. William Langston discovered, by a remarkable piece of medical detective work, that the drug users had all injected themselves with a homemade chemical that they thought was a legal form of heroin, a "designer drug." The basement chemist who sold them the drug had attempted a shortcut in the recipe, producing an unintended byproduct, *methyl-phenyl-tetrahydropyridine* (MPTP). Dr. Langston and others eventually found, through animal experiments, that the most important action of MPTP is to damage the *substantia nigra*, which is the part of the brain affected in PD.

MPTP is a simple chemical similar to naturally-occurring components of many plants. Its chemical structure is similar to that of some commonly-used weed killers, such as paraquat. Furthermore, it poisons the chemical systems of brain cells in the same way as does rotenone, a popular garden and farm insecticide found in your local hardware store. These insights have prompted speculation that the etiology of PD may be a long-term, low-level exposure to MPTP or some similar chemical in our food, water, air or other aspect of our environment.

Support for the *environmental hypothesis* has also come from surveys of PD patients and controls (that is, people without PD but with the same sex, age, socioeconomic group and area of residence as the patients). These surveys have

shown that early in life, PD patients are more likely than controls to have lived in rural areas, to have worked at farming, to have consumed well water, and to have been exposed to pesticides and herbicides. More recent surveys have found that the last factor—pesticides and herbicides—is the only strong "independent" risk factor among these. In other words, the two survey groups (PD patients and controls) differed with regard to rural living, farming and well water use only because those factors tended to occur in the same people who had been exposed to pesticides and herbicides.

The failing of the environmental hypothesis is that no one has been able to connect any specific pesticide or herbicide to PD. People participating in surveys of early-life exposures are usually unable to recall names of specific chemicals, if they ever knew them at all. There are no "clusters" of PD cases among workers in factories manufacturing specific pesticides/herbicides or among workers who apply the chemicals to crops. Furthermore, no one has succeeded in producing PD in animals by exposing them to commonly-used pesticides or herbicides. These problems do not disprove the environmental hypothesis. They just suggest that the answer is more complicated.

The Genetic Hypothesis: The environmental hypothesis must contend with another obstacle: If PD is caused by a chemical in the food, air or water, why does the disease occur in only 2% of the population some time during life? This dilemma of the "pure" environmental hypothesis has convinced most experts that there is some factor inborn to the individual, probably genetic in origin, that makes some people, but not most, susceptible to the toxic effect of the suspected environmental factor(s). After all, most human diseases, including cancer, arteriosclerosis, and infections are caused by some combination of exposure plus inborn susceptibility.

Most genetic brain disorders occur during infancy or childhood, but some do not. A prime example among the movement disorders is *Huntington's disease*, a degenerative disorder far less common than PD, usually starting in the 30's, 40's or 50's and producing dementia and violent, involuntary movements. Huntington's runs in families in an *autosomal dominant* hereditary pattern. That means that each child of an affected individual has a 50% (one chance out of two) risk of developing the disease and that the disease occurs with equal frequency in the two sexes.

Evidence for a Genetic Etiology: In a survey at Robert Wood Johnson Medical School, 53% of PD patients who had full information about all of their grandparents, aunts, uncles and parents reported at least one such relative with the disease. Furthermore, surveys of patients and controls have shown that parents and siblings (brothers and sisters) of the patients are anywhere from two to ten times as likely to have PD as parents and siblings of controls. This does not prove a genetic cause, however—relatives usually share environmental exposures, too!

Stronger evidence for a genetic contribution to the cause of PD comes in several forms. One is that when a PD patient reports having two relatives with PD in previous generations, it is very rare for one of the affected relatives to be on the

patient's mother's side and one to be on the father's side, as would often occur in an environmentally caused disease.

Another line of evidence is that some families have an especially strong and obvious autosomal dominant pattern causing PD in many members and other families living in the same places have no PD. The largest such family known, the *Contursi kindred*, originated in a town by that name in southern Italy. It includes 60 members with PD over five generations. Its inheritance pattern, and that of many smaller such families, is autosomal dominant with an approximately 50% risk to offspring of affected individuals, as in Huntington's disease. The variation in the disease within the Contursi kindred, ranging in age of symptom onset from 20 to 85, with some members having tremor and others not, is similar to that of PD in general. This suggests that differing intensities of environmental exposures need not be invoked to explain the wide symptom range of PD in general.

Families like the Contursi kindred are extremely rare, however. One reason is that PD tends to occur later in life, when its symptoms may be mistaken for those of arthritis, strokes, normal aging, and many other conditions. Or affected individuals may have died before the symptoms or signs of PD appeared at all. In any case, by the time someone participating in a present-day research survey acquires PD, his/her parents, not to mention grandparents, are likely to be long-deceased, their medical conditions a dim memory. Yet another problem is that PD may display only a single symptom, such as forgetfulness, muscle stiffness, poor balance, or shuffling gait. Such isolated symptoms may not suggest a diagnosis of PD. A family history of a late-life-onset, difficult-to-diagnose condition like PD may, for all these reasons, be obscured.

The Nature of the PD Gene: The gene causing Huntington's disease has been found. Genes causing some cases of other *neurodegenerative diseases* (that is, conditions that involve progressive loss of brain cells, such as Alzheimer's disease and Lou Gehrig's disease) have also been found. It seems likely that a gene or genes accounting for some or most cases of PD will also be found. It may be a gene necessary to rid the body of a toxic environmental chemical, as suggested by the environmental hypothesis, or, as is the case for Huntington's disease and the Contursi kindred, it may be a gene apparently unrelated to environmental factors. The greatest likelihood is that PD will be found to be a mixture of diseases, some mostly genetic, some mostly environmental, but all producing a similar set of changes in the brain.

B. Pathogensis (Abnormal Processes in the Body that Produce PD)

Even if we never find the etiology of PD, we could stop or even reverse the damage of the disease through an understanding of the abnormal sequence of steps that take place inside the brain that lead to cell loss.

Loss of Dopamine-Producing Brain Cells: We do not yet know whether PD is caused by a genetic or an environmental factor, but we do know that the symptoms are caused by loss of certain clusters of brain cells. The most important of these are clusters that make a chemical called *dopamine*. The cells transport the dopamine through long, thin tubes called axons from the cell body, where most of the cell's vital machinery is located, to the terminals, which contact other brain cells. The terminals send messages to neighboring brain cells in the form of minute droplets of dopamine that float across the narrow gap (*synapse*) between the terminals of one brain cell to the *receptors* of an adjacent cell. Each brain cell uses only one kind of chemical messenger, or *neurotransmitter*. In PD, those cells that make dopamine gradually die off.

But the situation is more complicated. In PD, not all of the dopamine-producing brain cell clusters die off. In addition, a few brain cell clusters that use other neurotransmitters such as *acetylcholine, serotonin* and *norepinephrine* also die off. No one is sure just what all of these cells have in common that makes only them—and not most other areas of the brain—vulnerable to whatever causes PD.

PD even affects nerve cells outside the brain. Loss of nerve cells in oil glands in the skin produces an oily complexion and often, a red, blotchy rash as a result. Loss of nerve cells in other organs can cause, in some patients, heartburn, constipation, poor urinary bladder control, and impotence.

As the brain cells (and dopamine-producing nerve cells in the intestines and elsewhere) in PD sicken, they develop unusual spherical blobs, called Lewy bodies (pronounced in English, "Louie") after the German pathologist who discovered them. There is something unique to PD that produces Lewy bodies, as they are rare or absent in other neurodegenerative diseases, even in those affecting the dopamine-producing brain cells.

The Substantia Nigra: The dopamine-producing brain cell cluster that dies off first in PD and accounts for most of its symptoms is the *substantia nigra*, meaning “dark substance." What makes it dark is grains of a dark pigment, *melanin*, in some of the cells. A slightly different type of melanin colors skin and hair. Dark people and fair people, however, have the same amounts of melanin in their substantia nigras. The substantia nigra is located in the *midbrain*, the uppermost third of the *brainstem*, which is the roughly cylindrical portion that connects the brain to the spinal cord. The brainstem is jam-packed with many cell clusters with functions as vital as that of the substantia nigra. The dopamine-producing cells of the substantia nigra send their projections (axons) upward into the bottom portion of the brain (cerebrum), connecting with *dopamine receptors* in the next part of the circuit, the *striatum*.

The Connections of the Dopamine-Producing Cells: The cerebrum, the large, wrinkled part of the brain, is where thought processes occur. The part of the cerebrum, however, that receives the dopamine-encoded messages from the substantia nigra is not directly involved in mental functions, but in control of movement. Located near the base of the cerebrum, this part is called the basal

ganglia and it does not degenerate in PD. ("Ganglia" are large clusters of brain cells.) The various parts of the basal ganglia are interconnected in a complicated way that has been partially worked out only recently. When the substantia nigra fails to provide adequate input to the striatum because of the damage from PD, the function of the various parts of the circuit is not balanced.

The net effect is that the last two stations in the complicated circuitry of the basal ganglia, the *subthalmic nucleus* and the *internal globus pallidus*, become overactive. This overstimulates another part of the cerebrum called the *thalamus*. When this situation is partly corrected by surgical procedures called *subthalamotomy* or *pallidotomy* which destroy parts of the subthalamic nucleus and the internal globus pallidus, or by electrical stimulation of those structures to interrupt signals, some PD symptoms improve. This will be discussed further in the chapter on treatment of PD.

The 80% Threshold: Patients with PD often wonder what activities or exposures in the few weeks before their first symptoms appeared could have caused the disease. If there was such an etiologic event, it would have occurred years or even decades, not weeks, before. The first symptoms of PD do not appear until 80% of the dopamine at the terminals of the substantia nigra neurons, in the *striatum*, is lost. (This occurs when about half of the neurons themselves are lost.) Apparently, the brain can compensate for lesser degrees of dopamine loss, but eventually the passage of time is “the straw that breaks the camel's back" and symptoms appear.

That last straw is sometimes a stressful emotional event or a non-neurological medical event such as a limb injury, a heart attack or major surgery. How these stresses knock out the way the brain compensates is not understood. We do know that these events are not the "cause" of PD, but it is clear that they can reveal the disease a few months or years sooner than it would have revealed itself.

The Parkinson Iceberg: If you have to lose 80% of your dopamine before showing signs of PD, and if this process occurs gradually over many years, there must be many people who are on their way to developing PD but have not reached the 80% threshold. In fact, more than 10% of elderly people who die of non-neurological illnesses do not have signs of PD but do have Lewy bodies in their brains as determined at autopsy. These brains also show loss of substantia nigra neurons in the same pattern (although in fewer numbers) as occurs in full-blown PD. Had these people lived longer, they presumably would have started to show signs of PD. It has been calculated that among the living population, such *pre-symptomatic* PD is 10 to 20 times as common as *symptomatic* PD. The latter, therefore, represents the small, exposed portion of a very large iceberg. If there are about half a million patients with PD in the US, there must be another 5 to 10 million with presymptomatic PD. As we make in-roads against killers like cancer and heart disease, more and more of the presymptomatic group will live to show signs of PD.

Are the Mitochondria Involved?: Brain cells are rich in mitochondria, the structures inside cells that use oxygen to turn food into energy for the cell's use. For this task, mitochondria have their own set of chemical tools (*enzymes*) and even have their own genes carrying the genetic code for some of these enzymes. If there is damage to mitochondria, to any of their enzymes, or to any of the genes that encode the instructions for making those enzymes, the whole cell will malfunction and possibly die. In PD, a certain group of mitochondrial enzymes called *Complex I* is not working properly.

One possible cause of this malfunction in Complex I may be a poison from the environment. We know that MPTP damages dopamine-producing brain cells by impairing the function of their Complex I. Furthermore, the popular garden insecticide *rotenone* acts in the same way.

Another possibility is that one or more of the genes directing the cell's manufacture of Complex I are malfunctioning. But no such genetic defect has been found for sure in patients.

Are Free Radicals Involved?: *Free radicals* are chemicals produced as by-products of many normal chemical reactions in the body, especially the manufacture of dopamine. *Radicals* are fragments of molecules that are usually found only as parts of larger molecules, where they are harmless. But sometimes, these fragments are produced in an unattached state. They then try to attach themselves to any molecules that happen to be nearby. In so doing, they cause *oxidation*, which damages normal proteins and other chemicals in cells. Healthy cells have enzymes that act as *free-radical scavengers*, mopping up free radicals before they can do much oxidative damage. (Nevertheless, free radicals are suspected as causes of many illnesses, including arthritis, cancer and hardening of the arteries.)

In brain cells of people with PD, there are more free radicals than normal and there is clear evidence of excessive oxidation. One popular theory is that this oxidation causes the damage to the dopamine brain cells. An alternative theory states the opposite: that the brain cell damage (whatever its cause) causes the increase in free radicals by depriving the cells of their normal free radical-scavenging enzymes. Despite our ignorance on this point, Vitamin E, which mops up free radicals, has been tested as a prevention and treatment for PD. Unfortunately, it was ineffective, and there is no evidence that other antioxidants such as Vitamin C or coenzyme Q10 help PD either, but other drugs that combat the action of free radicals in different ways may yet work (see “Treatment,” Chapter V).

Some New Ideas, Some Old Ideas: In the near future, you may begin to hear about other theories of the etiology and pathogenesis of PD. One involves *growth factors*, which are proteins produced by brain cells that maintain their normal structure and repair damage. Another involves *nitric oxide*, a very simple molecule (one nitrogen atom and one oxygen atom) that is starting to be implicated in many types of normal body functions and in some disease processes.

You may also hear about the epidemic of encephalitis (inflammation of the brain caused by a virus) in the years after World War I, or even of the worldwide flu epidemic that preceded it as the cause of PD. These notions have been discredited.

Similarly, there is no evidence that PD is caused by *prions*, the infectious particles thought to cause "mad cow disease" and a few types of degenerative human brain disease.

Repeated *minor head trauma* such as that suffered by boxers has long been known to cause a PD-like condition in some cases, but Lewy bodies and other features of PD are absent. Nevertheless, several careful surveys have found that patients with PD are more likely to have had minor head injuries in the years before their PD began than did controls. We do not know whether this result was biased by a greater tendency of PD patients to recall such details or whether a little trauma can actually accelerate the degenerative process of PD somehow.

A similar problem faces us in interpreting the finding that patients with PD are less likely to have been cigarette smokers (during the years before the symptoms began) than controls. Most researchers think that people who have a mild (pre-symptomatic) deficiency of dopamine fail to experience the satisfaction provided by a potentially addictive habit, thereby avoiding becoming addicted. A few researchers think that something in cigarette smoke may actually reduce one's risk of developing PD. No one, however, recommends smoking to avoid PD.

Those with PD now should be encouraged by the speed with which we are coming to understand the etiology and pathogenesis of the condition. There is every reason to believe that these efforts will produce a way of arresting the progress of the disease well within the lifetime of a patient diagnosed in the early part of the new millennium.

V. TREATMENT

There is as yet no cure for PD and no medication that slows or stops the progression. Treatment is, therefore, aimed at suppressing or reducing the symptoms of disease with the least amount of adverse effects from the drugs. All of the strategies outlined in this chapter are intended to inform patients and their families about some of the options available to them. This information is meant to be discussed with the treating physician. Patients should not attempt any of these suggestions without consulting their physician since these strategies may not be applicable in every case and there may be more appropriate advice for any given individual situation.

A. Initial Treatment of Early Disease

Since, as noted above, there is no medication to cure or slow down the disease process, a major question that faces patients and physicians is when to start treatment and with what drug in a patient newly-diagnosed with PD. Most PD experts agree that treatment should not be started until a patient is experiencing some "functional disability" from the disease. The key concept here is the definition of the word "functional" because functional disability may be different for different people. In general, it means that the patient is having difficulty or is unable to do something that is important to his or her well-being or interests. For example, a surgeon with a little bit of difficulty manipulating objects with his dominant hand may be functionally disabled by this problem. A retired accountant may not be functionally disabled by the very same symptoms. Whether or not a patient is functionally disabled is a decision that should be made by both patient and physician together and appropriate treatment begun at that time. Functional disability, however, should not be measured only in relation to work. Hobbies or sports activities can be very important to people and should enter into the consideration of whether or not a patient is functionally impaired. Many patients' symptoms begin with tremor. As a rule, resting tremor is rarely disabling for most patients.

B. Medications for Parkinson's Disease

Levodopa: The most important and most effective drug to treat the symptoms of PD is *levodopa* and almost every patient will eventually be taking this medication. Levodopa is an *amino acid* similar to those derived from the protein in food and crosses from the intestinal tract to the blood and eventually from the blood to the brain. Once in the brain, it is converted to *dopamine*, the neurochemical that is reduced in patients with PD. Taking levodopa restores the amount of dopamine in the *substantia nigra* and *striatum* to near normal levels and thereby reduces the symptoms and signs of the disease. Levodopa helps all the major signs and symptoms in the majority of patients. In fact, if a patient is not helped by levodopa, this is often evidence that the patient may be suffering from one of the other forms of parkinsonism described earlier. Nausea is the most common side-effect experienced by patients who take levodopa. With persistence, most patients can overcome this problem. Because approximately 50% of patients taking levodopa eventually develop motor

fluctuations and dyskinesias, and because dopamine metabolism results in free radical production, the idea that levodopa is toxic to dopamine producing neurons has persisted despite multiple human studies to the contrary. To date, there is no solid evidence from studies in PD patients that levodopa administration increases the rate of disease progression.

Levodopa/carbidopa (*Sinemet*®): Because of the nausea many patients experience when taking levodopa alone, it is invariably taken in combination with carbidopa (trade name: *Sinemet*®). This nausea is caused by the conversion of levodopa to dopamine in the intestine and blood before levodopa reaches the brain, and by direct stimulation by levodopa of the vomiting center in the brain. Carbidopa blocks the conversion of levodopa to dopamine only in the intestine and blood (not in the brain) and thereby markedly reduces the incidence of nausea and vomiting. It also ensures that more levodopa goes into the brain and is not wasted by conversion to dopamine in the blood or intestine. Patients taking the combination, therefore, require less levodopa per dose than if they were to take levodopa alone. For these reasons it is the most common form in which patients take levodopa. Levodopa/carbidopa comes in two forms, *standard* or *immediate-release* and *controlled-release* (CR). The standard form is absorbed quickly while the CR form is absorbed over several hours. Many patients who develop end-of-dose wearing-off symptoms are helped by switching from the regular to the CR form of levodopa.

Monamine oxidase inhibitors: selegiline (Deprenyl®, Eldepryl®, Zelapar®) and rasagiline (Azilect®): By interfering with one of the enzymes that break down dopamine (*monoamine oxidase*, or *MAO-B*), selegiline or rasagiline can enhance and prolong the effect of each dopamine molecule. It was once hoped that selegiline might slow the progression of PD but few physicians still believe this to be the case. Whether or not rasagiline slows the progression of disease is still under investigation: a recent study suggests that it may, but this is not proven. Both drugs may be used as a first drug for the treatment of early PD and seem to be of moderate help to about 60% of such patients. This benefit is sufficient to satisfy most patients for approximately one year, after which they may elect to start levodopa treatment, either by adding levodopa to selegiline or rasagiline or by switching to a levodopa preparation. Some patients encounter difficulty sleeping when they take selegiline. Therefore, it is usually given at breakfast and lunch but not bedtime. In patients with more advanced disease, adding selegiline or rasagiline to levodopa may help patients who are experiencing end-of-dose failure using levodopa alone. In these patients, adding selegiline or rasagiline may worsen or bring on high dopa or peak-dose dyskinesias. As of this writing, the FDA still requires that patients taking rasagiline be aware that they should adhere to a low *tyramine* diet because of the theoretical possibility that MAO inhibition and elevated tyramine intake may cause uncontrolled increases in blood pressure that may lead to stroke. Foods that should be avoided included aged cheeses, beer, red wine, liver, pickled products, salami, sausage, sauerkraut and all aged and fermented products. This list is not comprehensive and patients taking

rasagiline should refer to a more complete list before starting the drug. The FDA also recommends that patients starting rasagiline should not be on SSRI antidepressants.

Dopamine agonists: There are currently two approved *dopamine agonists* in use today: pramipexole (Mirapex®) and ropinirole (Requip®). These are synthetic compounds that mimic the action of dopamine at the *dopamine receptor* (the message receiver) in the striatum. These agents are not as powerful as levodopa and are usually used in addition to levodopa for patients who experience end-of-dose failure using levodopa alone. They can also be used early in the disease to delay the use of levodopa. Major side-effects of all agonists include nausea, nightmares, and hallucinations. More problematic is more recent recognition of sleepiness and sleep attacks as well as obsessive-compulsive behaviors; these are seen with all the agonists. Recent evidence suggests that dopamine agonist-induced obsessions and compulsive behaviors are not rare. Major reported compulsions include gambling, sexual obsessions, excessive spending, hobbies out of control, and eating disorders, among others. All patients on dopamine agonists should be asked about any change in behaviors at each doctor visit.

Another agonist used for many years, pergolide (Permax®), was withdrawn from the market because of concerns about heart valve abnormalities. Another older agonist, bromocriptine (Parlodel®), has not been withdrawn, but is in the same family as pergolide and should be avoided. Patients who have recently been on these drugs should continue to have an echocardiogram regularly to examine their heart valves.

A newer agonist, rotigotine (Neupro®), was briefly available in patch form but was withdrawn from the market because of problems with effective delivery of drug through the skin. It is currently not available.

In addition, there is an injectable form of a dopamine agonist called apomorphine (Apokyn®). This may be useful as a “rescue” for patients who have “on-off” phenomena.

Anticholinergics: *Anticholinergic* drugs were among the earliest used to treat PD even before the era of levodopa. Members of this class of drugs include trihexyphenidyl (Artane®), benztropine (Cogentin®), and biperiden (Akineton®). Another one, ethopropazine (Parsidol® or Parsitan® in Canada) is no longer available in the US, but still available in Canada. Anticholinergics do not act directly on the dopamine system but act to block the effect of another neurotransmitter, *acetylcholine*. Acetylcholine interacts with dopamine receptors in the striatum. Blocking acetylcholine serves to reduce the inequality that results from the loss of dopamine. These drugs are really only effective against tremor and are often used in younger patients whose tremor does not respond to levodopa. They should be used with great care in older patients. Major side-effects from these drugs include dry mouth, decreased memory, confusion, blurred vision, difficulty with urination, and worsening constipation. The risk:benefit ratio of these drugs make them less commonly used today to treat PD.

Amantadine (*Symmetrel*®): *Amantadine* may have a number of chemical actions in the brain. It has anticholinergic activity, may help release dopamine, and may even have an effect on *excitatory neurotransmitters* in the basal ganglia. All three of these actions help relieve the symptoms of PD. It is sometimes used early in the course of the illness even before institution of levodopa therapy. It may be added to levodopa, particularly in patients with tremor that is not entirely relieved by levodopa. More recently, amantadine has been recognized to reduce dyskinesias in patients with motor fluctuations. The main side-effect of amantadine includes a benign skin discoloration, usually in the lower legs, called *livedo reticularis*. Ankle swelling is also seen. Some patients may have increasing confusion or hallucinations.

Beta-blocking agents: Beta-blockers such as propranolol (Inderal®) are infrequently used in PD patients. Although the most characteristic tremor associated with PD is a resting tremor, many patients have tremors that worsen with posture or action. Beta-blockers may help these tremors somewhat. Major side-effects include low blood pressure, slow heart rate, and depression.

COMT Inhibitors: Two drugs, tolcapone (Tasmar®) and entacapone (Comtan®), are *catechol-O-methyltransferase (COMT) inhibitors*. Stalevo® is a combination of carbidopa/levodopa and entacapone. COMT inhibitors work in conjunction with levodopa preparations (Sinemet®) to prevent the breakdown of levodopa in the intestine. By blocking the COMT enzyme, COMT inhibitors help more levodopa reach the brain, where it is converted into dopamine, improving control of PD symptoms. While both agents are COMT inhibitors, they are not the same. Entacapone is a mild adjunctive drug, whereas tolcapone is longer-acting and works well in more advanced fluctuators. Because of the rare risk of liver injury associated with use of tolcapone, the FDA advises all patients taking tolcapone to have liver function tests performed every two to four weeks during the first six months after starting the drug.

C. Surgery

All the major surgical procedures performed to relieve symptoms of PD are done *stereotactically*. This means that the target cells in the brain, which have been selected either for destruction or stimulation, are reached with the aid of a computerized guidance system through a small hole in the skull. A needle is guided to the appropriately-chosen target and the cells in the targeted *nucleus* (group of cells) are then either destroyed or stimulated electrically. Virtually all procedures done at the present time are stimulations, more commonly known as *deep brain stimulation*, rather than ablation or destruction of cells. Stimulation parameters can be adjusted for maximum benefit after surgery while the destructive procedure, once done, cannot be changed afterwards to enhance benefit. Furthermore, if complications occur, the stimulator can be turned off or the wire can be removed. An ablative procedure cannot be reversed. It is also safer to reach deep targets like the *subthalamic nucleus* (STN) with the stimulation procedure. The three chief targets of both destructive

and stimulation therapies are the *thalamus*, the *internal globus pallidus*, and the *subthalamic nucleus*.

Thalamotomy destroys a small group of cells in the *thalamus*, a major area that receives information from the basal ganglia. **Thalamic stimulation** affects the same group of cells. These procedures are used only to abolish *tremor* on the side of the body opposite to the surgery.

Pallidotomy destroys a group of cells in the *internal globus pallidus*, the major area from which information leaves the basal ganglia. **Pallidal stimulation** affects the same group of cells. These procedures are most effective in relieving dyskinesias and tremor but also helps some of the other symptoms of advanced PD.

Subthalamic stimulation differs from the previous two targets in that destroying the target is almost never done. The cells are stimulated electrically and thereby stop functioning. The advantage of stimulation, especially in this nucleus, is that it is not permanent and can be more safely done on both sides of the brain if necessary. This is the current preferred target and procedure for the surgical treatment of PD.

Much more needs to be learned about the effectiveness of all these procedures and also about the relative effectiveness of one procedure over another. At present, they should be reserved for patients with advanced disease that is not adequately or smoothly responding to medications or with very complicated treatment regimens and severe dyskinesias or *motor fluctuations* (severe cycling from "on" to "off"). Patients need to understand that they cannot expect symptoms not responsive to levodopa to be helped by deep brain stimulation. For example, gait disturbances such as falling related to postural instability or freezing during the "on" state will not improve with deep brain stimulation. Major symptoms that may be helped by surgery are stiffness, slowness, fine motor coordination, tremor, and dyskinesias. Dyskinesias benefit because stimulation allows patients to reduce their levodopa and other PD medication intake. The bottom line is that surgery for PD is not a cure, and it does not allow the elimination of all medication. In the right hands, it is a very effective additional treatment for appropriate patients with advanced PD.

D. Treatment of Motor Complications: End-of-dose "Wearing-Off," Dyskinesias, and Freezing

As PD progresses, patients begin to notice that the beneficial effect from each dose of levodopa begins to wear off several hours after a dose. There are many different approaches to alleviate these problems and we will only mention a few of them. Patients on standard levodopa preparations can often be switched to a *controlled-release* formulation with improvement. On the other hand, shortening the interval between doses of levodopa may help some patients. Another useful strategy is to add a *dopamine agonist, a COMT*

inhibitor, or *MAO-B inhibitor* to levodopa. Patients who have difficulties with the levodopa dose "kicking in" in the morning can take a standard levodopa dose somewhat earlier than usual. Other patients with "kick in" problems can crush their standard levodopa pills or dissolve them and take the medication in liquid form (*liquid levodopa*).

With disease progression, dyskinesias (usually *peak-dose* or *high-dopa chorea*) develop in many patients. Most patients do not mind mild *choreiform* movements and consider it a small price to pay for good mobility. If the dyskinesias become troublesome, however, strategies to cope with this problem usually are aimed at reducing the amount of levodopa at each dose. If patients are already on an MAO-B inhibitor, this drug can be reduced or discontinued. Reducing levodopa may worsen some of the symptoms of PD. Dopamine receptor agonists can then be added to the lower doses of levodopa since they have less of a tendency to worsen dyskinesias than does levodopa itself.

Freezing of gait is one of the most frustrating problems a PD patient can encounter, and one of the most difficult to treat. Tricks such as marching in place, swaying from side to side, or stepping over an object or series of parallel lines may help get patients going. One should remember to stop and "regroup" if freezing prevents proceeding on in a smooth fashion. Sometimes reducing the dose of levodopa helps to decrease freezing.

E. Treatment of Secondary Symptoms or of Symptoms Related to Treatment with Antiparkinson Drugs

Speech: *Speech therapy* may help patients articulate more clearly and with more force. Most patients can learn the basics in one or two sessions. Prolonged traditional speech therapy is rarely of value. A special program, called the Lee Silverman Voice Therapy (LSVT), is often effective for many patients. Sometimes increasing antiparkinson drugs can help soft speech although many times the price paid in additional side effects is not worth the benefit.

Swallowing: Difficulty in swallowing (dysphagia) should be attended to immediately because it can cause food to go into the lungs (*aspiration*), which can cause pneumonia. A formal dysphagia evaluation by a speech therapist is important. Soft or puréed foods are more easily swallowed than chunks or liquids. Slowing down, chewing food well, and taking smaller bites are all useful strategies. Patients should eat only when they are "on" (when the levodopa is working) since the likelihood of food getting into the lungs is much greater if a patient attempts to eat at times when the levodopa dose is not fully effective. Some patients may benefit from an increase in the antiparkinson medications.

Drooling: Antiparkinson medications frequently dry the mouth and reduce drooling. This is especially true of the anticholinergic drugs, although side-effects from these agents may preclude their use in many patients, especially the elderly. Carrying a handkerchief, sucking on candies or chewing gum are helpful.

Seborrheic dermatitis: Antiparkinson medications, skin lotions and dandruff shampoos help this problem. Tar-based shampoos are most effective when used twice weekly but should not be overused.

Ankle Swelling: Ankle swelling should be evaluated by the patient's primary care doctor for an indication of problems with the heart, blood vessels or kidneys. If there are no medical problems causing ankle swelling and it is thought due to the relative immobility caused by PD, exercising the feet and sitting with the legs elevated may help. Ankle swelling can also be caused by anti-parkinson medications, particularly amantadine and dopamine agonists. Compressive stockings and reducing salt intake are often of benefit. Some patients may need mild *diuretics* (water pills).

Visual problems: Patients need to consult an eye doctor to ascertain if there is any correctable problem intrinsic to the eye. If the eye problems are related to PD, properly fitted prism glasses may help for double vision. Alternatively, one can use a magnifying lens and a straight edge under each line, following it down as one reads, for the problem of losing lines with small type.

Weight loss: Many PD patients have some degree of weight loss, but it should still be evaluated by a primary care physician to exclude causes other than PD. Adding dietary supplements high in calories, fat and carbohydrates can help stem the loss of weight. These additional calories should be taken after meals so as not to decrease the appetite at mealtime for a normal, balanced diet. Ice cream, commercial supplements, or anything the patient particularly favors provide a good source of additional calories.

Constipation and other gastrointestinal problems: Almost every patient with PD suffers from constipation. Anticholinergic medications worsen this symptom; sometimes, these drugs can be reduced or discontinued with resultant benefit. Increasing exercise and fluid intake are very helpful. Intake of high fiber food such as vegetables, high fiber cereal, and fruits should be increased. Bananas, however, must be avoided as they increase constipation. Intake of low fiber foods such as cakes and bread should be reduced. *Stool softeners*, when prescribed by the physician, must be taken regularly, but they *only* soften stool but do not reduce constipation. Finally, *laxatives* can be used judiciously but regularly with the consultation of a physician.

Nausea is frequently related to antiparkinson medications (levodopa or the dopamine agonists). When increasing the dosage of these drugs, going very slowly and gently may eliminate nausea over time; reduction in medications may also help the nausea, but may result in the patient being more "off." Adding extra carbidopa (Lodosyn®) to the Sinemet® (carbidopa-levodopa) is often helpful. Severe abdominal or bowel pain, blood in the stool, or severe difficulty moving the bowels warrants a medical evaluation.

Urinary problems: Once it is determined that urinary problems are not due to a medical condition or a bladder or a prostate problem, there are several

approaches to alleviate *urinary frequency*, the most common urinary problem in PD patients. Urgency and frequency at night can be decreased by reducing fluid intake after dinner. Anticholinergic medications can be prescribed in some patients. There are a number of specific medications in this and other categories that are useful for this condition in PD patients. The use of all these drugs needs to be discussed with a physician since they have side effects. In case of severe problems, evaluation by an experienced urologist is in order.

Sexual dysfunction: Sexual dysfunction may be the result of problems other than PD and a medical/urologic work-up should be done. Physical problems related to PD are often best handled by open communication between partners and health care professionals. A urologist experienced in treating impotence or difficulties with erection can offer remedies that help many patients including medications that enhance erectile function in men. Depression can often be the cause of sexual problems and should be treated when present.

Dizziness and lightheadedness: Lightheadedness due to a sharp drop in blood pressure when assuming the erect posture (*orthostatic hypotension*) may indicate that *antihypertensive* (blood pressure) medications should be reduced or discontinued, if patients are taking them. Patients should learn to rise slowly from the lying or sitting position and "regroup" when first standing to give the body a chance to adjust to the changes in blood pressure. Compressive stockings may help, as may additional fluid and salt intake. Finally, specific medications to reduce the drop in blood pressure can be prescribed by a physician.

Aches, pains and dystonia: Nonspecific aches and pains often respond to mild over- the-counter pain medications (aspirin, acetaminophen (Tylenol®), or *anti-inflammatories* like ibuprofen). Dystonia (severe cramping) may need the addition or readjustment of antiparkinson medications. Some patients with severe cramps can get injection of botulinum toxin (Botox®) to the affected muscles with excellent but temporary relief.

Sweating: Profuse sweating that drenches the body and clothes may respond to an adjustment of antiparkinson medications. With time, it sometimes disappears on its own.

F. Treatment of Symptoms Related to Mentation, Behavior and Mood

Depression, anxiety, and panic attacks: These symptoms, when severe, are related to biochemical changes in the brain and are not simply a "psychological" reaction to having PD. They should be diagnosed carefully by the treating physician and treated with appropriate medications. There are many different medications available to treat depression, anxiety, and panic attacks. Both the older *antidepressants: tricyclics*; examples are amitriptyline (Elavil®), nortriptyline (Pamelor®), or imipramine (Tofranil®) and the newer ones:

serotonin reuptake inhibitors, like escitalopram (Lexapro®), sertraline (Zoloft®), or paroxetine (Paxil®), may be effective for depression. Some newer drugs have anti-anxiety effects. A newly published study examining the treatment of depression in people with PD showed that nortriptyline was more helpful than paroxetine. *Anti-anxiety agents: benzodiazepines*; examples are diazepam (Valium®), lorazepam (Ativan®), or alprazolam (Xanax®) may also be considered for anxiety and panic. They need to be chosen carefully and tailored to the individual complaints with due respect for their potential side-effects and benefits.

Disturbances of sleep: If sleeplessness is due to vivid dreams, nightmares, or thrashing around in bed, reduction or elimination of nighttime antiparkinson medications can help. If patients have trouble falling asleep or if they awaken early in the morning, there is likely a biochemical disturbance of the sleep-wake cycle. Specific medications to help this condition include some of the same drugs used to treat depression. They should be used under the careful supervision of a physician experienced with these agents. Excessive daytime sleepiness is often caused by poor sleep during the night and may be corrected by improving nighttime sleep. A specific sleep disturbance called REM sleep behavior disorder is characterized by the patient thrashing (running, fighting) in his sleep, often with talking or yelling; the patient is dreaming but is unaware of the activity. The condition responds very well to low doses of clonazepam at bedtime.

Dementia, cognitive dysfunction, confusion: There are no specific treatments for these symptoms often associated with PD. Since these problems may be worsened by antiparkinson medications, slow reduction and elimination of the worst offenders should be instituted even at the cost of increasing some of the PD symptoms. Drugs most likely to worsen memory loss and confusion include anticholinergics, amantadine, selegiline, and the dopamine agonists, but even levodopa can play a role. One of the medications used to treat Alzheimer's disease, rivastigmine (Exelon®) has been approved by the FDA for dementia associated with PD, and is now available in patch form.

Hallucinations and psychosis: This very debilitating problem should be addressed as soon as it arises since severe hallucinations and psychosis often lead to the need for nursing home placement. The drugs most likely to aggravate this condition are the same as those that worsen cognition and confusion listed above and should be reduced and eventually eliminated. Hallucinations usually consist of seeing people or animals but all types of hallucinations have been reported. Paranoia, particularly about monetary and sexual subjects, are frequent. If drug reduction is ineffective or inappropriate, the newer dopamine-blocking agents can be used to treat hallucinations and psychosis. Quetiapine (Seroquel®) is often the treatment of first choice. The dose needs to be increased slowly until benefit is achieved. Clozapine (Clozaril®) is another drug that can be used to block hallucinations and

psychosis in PD patients. Because a small number of patients lose their white blood cells on this medication, using clozapine requires a weekly blood test. To many patients and families, this risk and bother is worth the great benefit of keeping a patient functioning at home and avoiding nursing home placement.

G. Treatments of No Value or of Unproven Value

There are theoretical reasons that have been put forth over the years suggesting that dozens of different medicines may help PD patients. A large National Institutes of Health (NIH)-sponsored study of Vitamin E in PD did not show that it was of any value. Other medications of unproven value include Vitamin C, NADH, glutathione, melatonin, and coenzyme Q10, just to name a few of the most popular or commercially-driven candidates. Megavitamins also have no role. Some of these drugs are quite expensive and are no substitute for a healthy, well-balanced diet and medications of proven value.

H. Treatments to Avoid

PD patients must avoid medications that block the *dopamine receptors* since this action will worsen the symptoms of PD. Such drugs include the typical *antipsychotic drugs* (also called major tranquilizers) like haloperidol (Haldol®) and chlorpromazine (Thorazine®), drugs to stop nausea such as prochlorperazine (Compazine®), and drugs for gastrointestinal complaints such as metoclopramide (Reglan®). Vitamin B_6 (pyridoxine) in extremely large doses should be avoided by patients taking levodopa. The reason is that this vitamin increases the conversion of levodopa to dopamine before it gets to the brain and, therefore, interferes with the antiparkinson effect of levodopa; the amounts found in regular multivitamins, however, are not a problem. Patients on selegiline or rasagiline should not get meperidine (Demerol®), (a powerful narcotic pain killer), since adverse interactions between these two drugs have been reported. Ephedrine-like drugs found in some cold remedies also should be avoided; when in doubt, ask your pharmacist or physician. Every physician that one sees should be aware of ***all*** the medications, even over-the-counter drugs that a patient takes, to avoid any serious drug interactions.

I. Diet

All patients should eat a balanced diet to maintain good physical and mental health. In some patients, protein ingestion interferes with levodopa absorption and thereby prevents some doses of levodopa from “kicking in” properly. This is never a problem if a patient is not on levodopa or early in the treatment of PD, but may affect more advanced patients with end-of-dose failure or “on-off” difficulties. Rearranging the protein-containing meals to nighttime may help, as can reduction of total protein. Patients not experiencing these problems with levodopa should not worry about their protein intake.

J. Exercise

A number of studies has shown that patients with PD who exercise regularly do better than those who do not. A recent study in rats showed that exercised animals produced more dopamine in their brains than the non-exercised control rats, suggesting that exercise in general may help to keep the brain producing more dopamine in everyone, even people with PD. In humans, all sorts of exercise have been looked at, and most patients recognize the benefit of staying active, regardless of their physical limitations. Even patients confined to wheelchairs can maintain some degree of exercise. Tai chi, Qi gong, yoga and other related methods can help with balance and well-being. Strength training and aerobic exercise should also be included in an exercise regimen. Above all, it has been demonstrated that the beneficial effects of exercise are only maintained with ongoing activity. Patients should be encouraged to be active and participate in various exercise regimens regularly.

VI. SOCIAL ISSUES AND PATIENT SUPPORT

When patients are first diagnosed with PD, the issue may arise about when to tell others and whom to tell about the diagnosis. Many patients are reluctant to tell friends or even family members. This concealment often causes anxiety in social situations which may worsen symptoms like tremor. Other patients are afraid to tell their boss or co-workers for fear of being fired. This can lead to a situation where co-workers suspect that something is wrong and may jump to the erroneous conclusion that the patient has been drinking or is on drugs. All situations such as those outlined above need to be considered on an individual basis. Most times, the employer and co-workers are very helpful and non-discriminatory once the diagnosis is known. Occasionally the opposite is the case. Discussing these issues with a physician is important since sometimes issues of job safety may be involved. The same goes for driving a car, although most PD patients have no problem driving and continue to work as efficiently as before the disease was diagnosed, until the disease is quite advanced. Decisions about what and how much a patient can do should be made as a team by the patient, the family, and the physician.

It is important to remember that PD affects both patients and families, particularly the spouse. The spouse is the major support for the patient, both physically and psychologically. Spouses need to have time to relax and need a good night's sleep. They need to take time to have hobbies and interests of their own. Providing support for the patient should not be a full-time job. If the spouse gets sick or becomes emotionally and physically worn down, it does no one any good, least of all the patient.

Most areas of the country have *support groups* to help patients and their families. These groups can provide help with day-to-day issues, provide a forum for gathering information about PD, and serve as a place to make new friends who share similar problems. There are even separate support groups for young or newly-diagnosed patients and for caretakers. Many support groups are affiliated with the American Parkinson Disease Association, Inc. (APDA). The APDA funds a number of Information and Referral Centers (see back cover for names and addresses) which can assist patients with referrals to physicians and other local resources, including support groups, and provide literature on PD. The APDA also provides funds for research grants and awards George C. Cotzias research fellowships to promising young researchers in PD. The APDA is a resource for every patient with PD.

The APDA offers several valuable educational booklets and educational supplements for PD patients and their caregivers. Single copies of each of these publications are available without charge from both the APDA national office at 1-800-223-2732 and from the Information and Referral Centers (see inside back cover).

VII. GLOSSARY

Italicized words are cross-referenced in the Glossary.

acetylcholine - a *neurotransmitter.*

amantadine - an antiparkinson medication; it may be used early in the disease or added to *levodopa*.

anticholinergics - a class of antiparkinson medications that are mostly useful for *tremor*.

apomorphine - a dopamine agonist administered by injection.

atypical parkinsonisms - disorders related to PD in that they are characterized by *bradykinesia* and sometimes *rigidity*, and balance problems, but have other clinical features and other *pathology*. *Tremor* is less common in these disorders.

autonomic nervous system - a part of the nervous system responsible for control of bodily functions that are not consciously directed; for example, heart rate, blood pressure, sweating, intestinal movements, temperature control.

basal ganglia - The interconnected cluster of nerve cells that coordinate normal movement, made up in part by the *substantia nigra, striatum, subthalamic nucleus*, and *globus pallidus*.

blepharospasm - forced closure of the eyelids.

bradykinesia - literally, “slow movement”; one of the main symptoms of PD.

bromocriptine - a *dopamine agonist*.

carbidopa - a drug, used with *levodopa*, to block the breakdown of *levodopa* to *dopamine* in the intestinal tract and in the blood.

catechol-*O*-methyltransferase (COMT) - an enzyme that breaks down *dopamine* at the *dopamine receptor* in the brain and that breaks down *levodopa* in the intestinal tract.

catechol-*O*-methyltransferase (COMT) inhibitors - a class of antiparkinson drugs that blocks the enzyme *COMT* preventing the breakdown of *levodopa* in the intestinal tract by blocking intestinal *COMT*, thus allowing more *levodopa* to cross into the blood and then into the brain.

cervical dystonia - torsioning or twisting of the neck.

chorea - jerky, random, dance-like, involuntary movements, usually seen in PD from too much medication.

cognitive function - the ability to think, to remember, to plan, and to organize information.

COMT - see *catechol-O-methyltransferase*

deep brain stimulation - electrical stimulation of certain parts of the brain (the current preferred target is the *subthalamic nucleus*) to treat PD.

delusions - erroneous beliefs that cannot be altered by rational argument.

dementia - a progressive decline in mental functions.

diffuse Lewy body disease - PD pathology that has spread to include many parts of the brain and usually is characterized by both *parkinsonism* and *dementia*.

dopamine - the primary chemical messenger of the *basal ganglia*; it is reduced in PD.

dopamine agonists - synthetic compounds that mimic the action of dopamine at the dopamine receptor in the striatum; examples are *pergolide, pramipexole, and ropinirole*.

dopamine receptor - the area of the nerve cell in the *striatum* that receives the *dopamine* message from the *substantia nigra*.

dysautonomia - abnormalities of the *autonomic nervous system*, which include such automatic functions as sweating, temperature regulation, blood pressure, urination, bowel movements, and penile erection.

dyskinesias - abnormal involuntary movements associated with use of antiparkinson medication.

dysphagia - difficulty with or abnormality of swallowing.

dystonia - in PD, tightness, spasm, or cramping of muscles; may also involve twisting or posturing of muscles.

end-of-dose failure - a loss of benefit from a dose of *levodopa*, typically at the end of a few hours.

entacapone - a *COMT inhibitor*.

enzyme - a protein or chemical tool that speeds up the rate of a biological reaction; *MAO-B* and *COMT* are enzymes that break down *dopamine*.

etiology - the cause of a disease, or how it is acquired.

festination - slow, small, shuffling steps.

freezing - inability to move or getting “stuck”, as with the feet appearing to be glued to the floor.

gait - the manner in which a person walks.

globus pallidus - a part of the basal ganglia; the ***internal*** part of the globus pallidus is what is targeted by *pallidotomy* to treat PD.

hallucinations - false perception of something that is not really there. In PD, they are usually things or people patients see (*visual hallucinations*), but occasionally things they may hear (*auditory hallucinations*) or feel (*tactile hallucinations*).

high-dopa dyskinesias - abnormal movements that occur when the *levodopa* in the blood is at its highest level.

hypomima - the mask-like expression typical of PD.

levodopa - the chemical precursor of *dopamine* and the most effective treatment for PD.

Lewy body - the spherical inclusion seen in the *dopamine*-producing nerve cells of the *substantia nigra* indicating a damaged and dying cell; the pathologic hallmark of PD.

low-dopa dyskinesias - abnormal movements that occur when doses of *levodopa* are wearing off, or when the *levodopa* in the blood is at a low or falling level.

MAO-B - see *monoamine oxidase-B*

mentation - mental or *cognitive function*.

micrographia - the very small handwriting seen in PD.

monoamine oxidase-B (MAO-B) - an enzyme that breaks down *dopamine* in the area of the *dopamine receptor*.

monoamine oxidase-B (MAO-B) inhibitors - a class of antiparkinson drugs (for example, *selegiline* and *rasagiline*) that blocks the enzyme *MAO-B*, preventing the breakdown of *dopamine* in the area of the *dopamine receptor*.

motor fluctuations - the complications of the treatment of PD affecting ability to move; examples are *wearing-off of dose, on-off phenomenon*, and *dyskinesias*.

neuroprotective - a strategy (for example, a drug) that protects the nerve cells from further degeneration or dying; an agent that may slow the progression of disease.

neurotransmitter - a chemical messenger; *dopamine* is a neurotransmitter.

norepinephrine - a *neurotransmitter*.

off - the state of re-emergence of parkinsonian signs and symptoms when the medication's effect has waned.

on - improvement in parkinsonian signs and symptoms when the medication is working optimally.

on-off phenomenon - unpredictable, usually abrupt oscillations in motor state.

orthostatic hypotension - a significant drop in blood pressure on changing position (going from lying to sitting to standing), often accompanied by lightheadedness or passing out.

pallalia - stuttering or stammering speech in PD.

pallidal stimulation - electrical stimulation rather than destruction of cells in the the *internal globus pallidus* to treat the symptoms of PD.

pallidotomy - surgical destruction of a small group of cells in the *internal globus pallidus*, the major area from which information leaves the *basal ganglia*, most effective in relieving dyskinesias and other symptoms of advanced PD.

paranoia - an irrational belief that others are "out to get" an individual, making the patient suspicious and untrusting.

parkinsonian syndromes - disorders related to PD in that they are characterized by *bradykinesia* and sometimes *rigidity*, and balance problems, but have other clinical features and other *pathology*. Tremor is less common in these disorders.

parkinsonism - the motor picture that makes up PD: *bradykinesia, rigidity, tremor*, balance and *gait* problems.

pathogensis - the abnormal processes in the body that produce the signs and symptoms of a disease.

pathology - the study of a disease process, including what is affected and what it looks like under a microscope.

peak-dose dyskinesias - abnormal movements that occur when the *levodopa* in the blood is at its highest level.

pergolide - a *dopamine agonist*.

pramipexole - a *dopamine agonist*.

propulsion - propelling forward as the patient accelerates with rapid, short steps.

psychosis - a mental syndrome in which the patient loses contact with reality; psychotic manifestations include *delusions, hallucinations*, and *paranoia*.

rasagiline - an antiparkinson medication, it inhibits one of the enzymes (*monoamine oxidase*, or *MAO-B*) that breaks down *dopamine*; it may be used alone as a first-line treatment or in addition to *levodopa*.

retropulsion - stumbling or falling backwards.

rigidity - a tightness or increase in muscle tone at rest or throughout the entire range of motion of a limb; it may be felt as a stiffness by the patient.

ropinirole - a *dopamine agonist*.

seborrhea - excessive oily secretions of the skin, particularly on the forehead and scalp, causing a flaky, red, itchy condition.

selegiline (deprenyl) - an antiparkinson medication, it inhibits one of the enzymes (*monoamine oxidase*, or *MAO-B*) that breaks down *dopamine*; it may be used alone as a first-line treatment or in addition to *levodopa*.

serotonin - a *neurotransmitter*.

sialorrhea - drooling.

striatum - part of the *basal ganglia* circuit; it receives connections from the *substantia nigra* and contains the *dopamine receptors*.

substantia nigra - meaning “dark substance,” the part of the *brainstem* that produces *dopamine* and that degenerates in PD.

subthalamic nucleusea - a part of the *basal ganglia*; the primary target of *deep brain stimulation* to treat PD.

subthalamic stimulation - electrical stimulation rather than destruction of cells in the *subthalamic nucleus* to treat the symptoms of PD.

thalamic stimulation - electrical stimulation rather than destruction of cells in the *thalamus* to treat tremor.

thalamotomy - surgical destruction of a small group of cells in the *thalamus*, a major area of the brain that receives information from the basal ganglia, to abolish *tremor* on the side of the body opposite the surgery.

thalamus - a part of the brain that receives information from the basal ganglia.

tolcapone - a *COMT inhibitor*.

tremor - rhythmic shaking, usually of the hand (but also may affect the leg, lips, or jaw), that occurs at rest in PD. In PD, It may occur less commonly on holding up the hands (postural or sustention tremor) or when moving a limb (action tremor).

wearing off - a loss of benefit from a dose of *levodopa*, typically at the end of a few hours.

wearing-off dyskinesias - abnormal movements that occur when doses of *levodopa* are wearing off, or when the *levodopa* in the blood is at a low or falling level.

APDA Information and Referral (I & R) Centers

Alabama, Birmingham
University of Alabama at Birmingham
205-934-9100

Arizona, Phoenix
Banner Good Samaritan Medical Center
602-839-3542

Arizona, Tucson
University of Arizona
520-626-5055
866-897-1261

Arkansas, Hot Springs
St. Joseph's Regional Health Center
800-345-6621
501-622-3990

California, Fountain Valley
Orange Coast Memorial Medical Center
714-378-5022
877-610-2732

California, Laguna Hills
Saddleback Memorial Medical Center
877-610-2732
714-378-5022

California, Long Beach
Long Beach Memorial Medical Center
877-610-2732
714-378-5022

California, Los Angeles
Cedars-Sinai Health System
310-423-7933
877-223-3277

California, Los Angeles (UCLA)
Reed Neurological Research Center
310-206-9799

California, Northridge
Center for Aging Research
818-885-8623
866-499-2732

California, Pasadena
Huntington Hospital
626-397-2684

California, San Diego
Information & Referral Center
858-273-6763

California, Stanford
Stanford University Medical Center
650-724-6090
866-250-2414

Connecticut, New Haven
Hospital of Saint Raphael
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Florida, Jacksonville
Mayo Clinic, Jacksonville
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Florida, Deerfield Beach
North Broward Medical Center
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954-786-2305

Florida, St. Petersburg
Edward White Hospital
727-328-6246

Georgia, Atlanta
Emory University School of Medicine
404-728-6552

Illinois, Chicago
Central DuPage Hospital
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630-933-4383

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Iowa Health - DesMoines
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877-872-6386

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University of Kentucky
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866-554-2732

Louisiana, New Orleans
Ochsner Clinic Foundation
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Louisiana, Shreveport
Louisiana State University
318-675-6142

Maine, Falmouth
Maine Medical Center
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800-832-4116

Maryland, Baltimore
University of Maryland
800-862-5457

Massachusetts, Boston
Boston University School of Medicine
617-638-7737
800-651-8466

Minnesota, Minneapolis
Abbott Northwestern Hospital
Minneapolis Neuroscience Inst.
612-863-5850
888-302-7762

Mississippi, Gulfport
Gulfport Memorial Hospital
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601-618-2772

Missouri, St. Louis
Washington University Medical Center
314-362-3299

Montana, Great Falls
Benefis Health Care
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800-233-9040

Nebraska, Omaha
Creighton University
402-449-4535
866-626-7347

Nevada, Las Vegas
702-464-3132

Nevada, Reno
V.A. Medical Center
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New Hampshire, Lebanon
Dartmouth-Hitchcock Medical Center
603-650-5280

New Jersey, New Brunswick
Robert Wood Johnson University Hospital
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New Mexico, Albuquerque
University of New Mexico
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New York, Albany
The Albany Medical College
518-262-6402

New York, Far Rockaway
Peninsula Hospital
718-734-2876

New York, Manhattan
New York University
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New York, Old Westbury
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St. Catherine's of Siena Hospital
631-862-3560

New York, Staten Island
Staten Island University Hospital
718-226-1856

New York, Westfield
Westfield Memorial Hospital
716-793-2112

Ohio, Kettering
Kettering Medical Center
937-903-0699

Oklahoma, Tulsa
Hillcrest Medical Center System
918-747-3747

Pennsylvania, Erie
Health South Rehabilitation Hospital
814-456-4210

Pennsylvania, Philadelphia
Crozer-Chester Medical Center
610-447-2911

Pennsylvania, Pittsburgh
Allegheny General Hospital
412-441-4100

Rhode Island, Warwick
Kent Hospital
401-736-1046

Tennessee, Memphis
Methodist Hospital
901-516-0677

Tennessee, Nashville
Centennial Medical Center
615-342-4635
800-493-2842

Texas, Dallas
Baylor University Medical Center
214-820-3800

Texas, Lubbock
Convenant Hospital
806-785-2732
800-687-5498

Texas, San Antonio
The University of Texas HSC
210-450-0551

Texas, Tyler
East Texas Medical Center
903-596-3648
866-491-2732

Utah, Salt Lake City
University of Utah
801-585-2354

Vermont, Burlington
University of Vermont
802-847-3366
888-763-3366

Virginia, Charlottesville
University of Virginia Medical Center
434-982-4482

Washington, Seattle
University of Washington
206-277-5516
800-329-8387

Wisconsin, Madison
St. Mary's Hospital
608-229-7628

DEDICATED CENTERS

Armed Forces Veterans
Reno, NV
775-328-1715

Young Onset Center
Central DuPage Hospital
Winfield, IL

Please contact the nearest I & R Center for information regarding Support Groups and Chapters or call the National Office at 1-800-223-2732.

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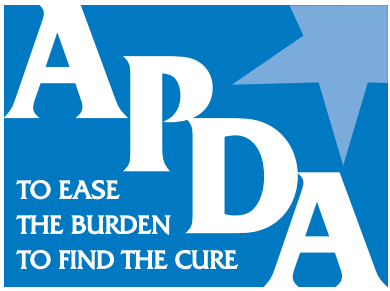

American Parkinson Disease Association, Inc.
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135 Parkinson Ave.
Staten Island, NY 10305-1946
1-800-223-2732
www.apdaparkinson.org
apda@apdaparkinson.org

APDA Young Onset Center
Central DuPage Hospital
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Winfield, IL 60190
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www.youngparkinsons.org
apda@youngparkinsons.org

APDA West Coast Office
10850 Wilshire Boulevard, Suite 730
Los Angeles, CA 90024
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APDA National Resource Center for Rehabilitation
Boston University College of Health & Rehabilitation Sciences - Sargent College
635 Commonwealth Avenue
Boston. MA 02215
1-888-606-1688
www.bu.edu/sargent
rehab@bu.edu

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