Description of Parkinson's Disease as a Clinical Syndrome

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ABSTRACT: Parkinsonism is a clinical syndrome comprising combinations of motor problems—namely, bradykinesia, resting tremor, rigidity, flexed posture, "freezing," and loss of postural reflexes. Parkinson's disease (PD) is the major cause of parkinsonism. PD is a slowly progressive parkinsonian syndrome that begins insidiously and usually affects one side of the body before spreading to involve the other side. Pathology shows loss of neuromelanin-containing monoamine neurons, particularly dopamine (DA) neurons in the substantia nigra pars compacta. A pathologic hallmark is the presence of cytoplasmic eosinophilic inclusions (Lewy bodies) in monoamine neurons. The loss of DA content in the nigrostriatal neurons accounts for many of the motor symptoms, which can be ameliorated by DA replacement therapy—that is, levodopa. Most cases are sporadic, of unknown etiology; but rare cases of monogenic mutations (10 genes at present count) show that there are multiple causes for the neuronal degeneration. The pathogenesis of PD remains unknown. Clinical fluctuations and dyskinesias are frequent complications of levodopa therapy; these, as well as some motor features of PD, improve by resetting the abnormal brain physiology towards normal by surgical therapy. Nonmotor symptoms (depression, lack of motivation, passivity, and dementia) are common. As the disease progresses, even motor symptoms become intractable to therapy. No proven means of slowing progression have yet been found.

KEYWORDS: Parkinson's disease; parkinsonism; Lewy body; dopamine; levodopa

HISTORICAL INTRODUCTION

Clinical Description

By amazing coincidence, James Parkinson published a monograph describing the entity subsequently bearing his name in the same year, 1817, that the New York Academy of Sciences was founded.[1] He described six individuals with the clinical features. One was followed in detail over a long period of time; the other five consisted of brief descriptions, including two whom he had met walking in the street and another whom he had observed at a distance. Such distant observations without a medical examination demonstrates how readily distinguishable the condition is

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merely from the patients' appearance of flexed posture, resting tremor, and shuffling gait. Parkinson's opening description has the key essentials: "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured." Despite the small number of patients examined, Parkinson provided a detailed description of the symptoms and also discussed the progressive worsening of the disorder, which he called the *shaking palsy* and by the Latin term *paralysis agitans*.

In his monograph, Parkinson reviewed the different kinds of tremors previously reported and specifically cited the tremor in his "An Essay on the Shaking Palsy" as occurring when the body part is at rest and not during an active voluntary movement. Seventy years later Charcot emphasized that tremor need not be present in the disorder and argued against the term *paralysis agitans*; he suggested, instead, that the name of the disorder be *Parkinson's disease* (see Goetz, 1987[2] for English translation).

The terms *paralysis* and *palsy* in *paralysis agitans* and *shaking palsy* are also inappropriate. There is no true paralysis. Today, the "lessened muscular power" mentioned by Parkinson is recognized to be a slowness of movement that is called *akinesia*, *hypokinesia*, or *bradykinesia*, all three terms often being used interchangeably. These terms represent a paucity of movement in the absence of weakness or paralysis.

Recognition and development of the term *akinesia* came about slowly. Charcot, in his Tuesday Lessons of 1888, related slowness to rigidity and specifically excluded weakness as a cause (see Ref. 2). Gowers in 1893[3] described Parkinson's disease as consisting of tremor, weakness, rigidity, flexed posture, and short steps, with slowness due in part to rigidity. Oppenheim in 1911[4] mentioned that impairment and retardation of active movements might occur in the absence of rigidity. He did not relate it to weakness. Wechsler in the 1932 edition of his textbook[5] commented on the special difficulty of initiation of movement as a feature of slowness. Wilson in his large neurology opus of 1940[6] used the terms *akinesia*, *akinesis*, and *hypokinesia*. Under these terms, he related the masked facies, the unblinking eyes, the poverty of movement, and the patient sitting immobile. Schwab, England, and Peterson devoted an entire paper in 1959[7] to the subject of akinesia, which by this time was firmly established as the "lessened muscular power" mentioned by Parkinson. Within the definition of *akinesia*, these authors mentioned fatigue, decrementing amplitude of movements, difficulty shifting to other contraction patterns, apathy, inability to complete actions, difficulty initiating an act, and the ability to reach normal movement briefly under sudden motivation. Furthermore, they described the difficulty for a patient with Parkinson's disease to execute two motor events simultaneously, all under the rubric of *akinesia*.

Pathology of Parkinson's Disease

It was many years after Parkinson's original description before the basal ganglia were recognized by Meynert in 1871[8] as being involved in disorders of abnormal movements. And it was not until 1895 that the substantia nigra was suggested to be affected in Parkinson's disease. Brissaud (1895)[9] suggested this on the basis of a report by Blocq and Marinesco (1893)[10] of a tuberculoma in that site that was associ-

ated with hemiparkinsonian tremor. These authors were careful to point out that the pyramidal tract and the brachium conjuctivum above and below the level of the lesion contained no degenerating fibers. The importance of the substantia nigra was emphasized by Tretiakoff in 1919,[11] who studied the substantia nigra in nine cases of Parkinson's disease, one case of hemiparkinsonism, and three cases of postencephalitic parkinsonism, finding lesions in this nucleus in all cases. With the hemiparkinsonian case Tretiakoff found a lesion in the nigra on the opposite side, concluding that the nucleus served the motor activity on the contralateral side of the body. The substantia nigra, so named because of its normal content of neuromelanin pigment, was noted to show depigmentation, loss of nerve cells, and gliosis. These findings remain the histopathologic features of the disease. In his study, Tretiakoff also confirmed the earlier observation of Lewy (1914),[12] who had discovered the presence of cytoplasmic inclusions in Parkinson's disease, now widely recognized as the major pathologic hallmark of the disorder and referred to as *Lewy bodies*.

Foix and Nicolesco made a detailed study of the pathology of Parkinson's disease in 1925[13] and found that the most constant and severe lesions are in the substantia nigra. Since then many workers, including Hassler (1938)[14] and Greenfield and Bosanquet (1953),[15] have confirmed these findings and added other observations, including involvement of other brain stem nuclei such as the locus ceruleus.

Biochemistry of Parkinson's Disease

Prior to 1957, the parkinsonian syndrome in animals and humans induced by reserpine was thought to be due to a depletion of brain serotonin. But in that year Carlsson and colleagues[16] discovered that L-dopa reversed the reserpine-induced parkinsonian state in rabbits; while the precursor of serotonin, L-5-hydroxytryptophan, did not. L-dopa is the precursor to dopamine and norepinephrine, and at that time it was thought that dopamine did not have an independent function but served solely as a precursor of norepinephrine. In 1958, after he developed a method for its chemical assay, Carlsson determined that dopamine was present in brain.[17] By the following year the regional distribution of dopamine was mapped out in brain in both animals[18] and humans.[19] In 1959, at the International Catecholamine Symposium, Carlsson suggested that Parkinson's disease was related to brain dopamine.[20] In 1960, Ehringer and Hornykiewicz, using Carlsson's methodology, measured dopamine and norepinephrine in humans with basal ganglia disorders and discovered a neostriatal dopamine deficiency in parkinsonism.[21] Thus began the modern era of understanding parkinsonism and the role of dopamine in brain. Carlsson's contributions eventually led to his being awarded the Nobel Prize in Physiology and Medicine in 2000.

DISTINGUISHING BETWEEN PARKINSON'S DISEASE AND PARKINSONISM

The syndrome of parkinsonism must be understood before understanding what is Parkinson's disease. Today, the term *parkinsonism* is defined by any combination of six specific motoric features: tremor at rest, bradykinesia, rigidity, loss of postural reflexes, flexed posture (FIG. 1), and the freezing phenomenon (where the feet are

FIGURE 1. Drawing of a patient with Parkinson disease demonstrating the flexed posture typically seen in this disorder. (Modified from Gowers, 1893, p. 639.[3])

transiently "glued to the ground")[22] (TABLE 1). Not all six of these cardinal features need be present, but at least two should be before the diagnosis of parkinsonism is made, with at least one of them being tremor at rest or bradykinesia. Parkinsonism is classified into four categories (TABLE 2). PD or primary parkinsonism will be the principal focus of this volume. It is the category that is most commonly encountered by the general clinician; it is also the category on which much research has been carried out and the one we know the most about. The great majority of cases of primary parkinsonism are sporadic, but in the last few years several gene mutations have been discovered to cause PD (TABLE 3). Whether primary parkinsonism is genetic or idiopathic in etiology, the common denominator is that it is not caused by known insults to the brain (the main feature of secondary parkinsonism) and is not associated with other motoric neurologic features (the main feature of Parkinson-plus syndromes). The uncovering of genetic causes of primary parkinsonism has shed light on probable pathogenetic mechanisms that may be a factor in even the more common idiopathic cases of PD. It may even turn out that many of the idiopathic cases will be linked to gene mutations, this discovery is yet to be made. Although the term *idiopathic PD* has been applied to primary parkinsonism, the fact that there are now known genetic causes encourages us to adopt instead the term *primary parkinsonism*, for the former term implies that the etiology is unknown.

Three of the most helpful clues that one is likely to be dealing with PD rather than another category of parkinsonism are: (1) an asymmetrical onset of symptoms (PD often begins on one side of the body); (2) the presence of rest tremor (although rest tremor may be absent in patients with PD, it is almost always absent in Parkinson-

TABLE 1. Six cardinal clinical features of parkinsonism

Tremor at rest	Flexed posture of neck, trunk, and limbs
Rigidity	Loss of postural reflexes
Bradykinesia/hypokinesia/akinesia	Freezing phenomenon

TABLE 2. Classification of the parkinsonian states

Primary parkinsonism (Parkinson's disease)
Sporadic
Known genetic etiology (see Table 3)
Secondary parkinsonism (environmental etiology
Drugs
Dopamine receptor blockers (most commonly antipsychotic medications)
Dopamine storage depletors (reserpine, tetrabenazine)
Postencephalitic
Toxins: Mn,CO, MPTP, cyanide
Vascular
Brain tumors
Head trauma
Normal-pressure hydrocephalus
Parkinsonism-plus syndromes
Progressive supranuclear palsy
Multiple system atrophy
Cortical-basal ganglionic degeneration
Parkinson-dementia-ALS complex of Guam
Progressive pallidal atrophy
Diffuse Lewy body disease (DLBD)
Heredodegenerative disorders
Alzheimer's disease
Wilson's disease
Huntington's disease
Frontotemporal dementia (tau mutation on chromosome 17q21)
X-linked dystonia-parkinsonism (in Filipino men; known as lubag)

plus syndromes); and (3) substantial clinical response to adequate levodopa therapy (usually, Parkinson-plus syndromes do not respond to levodopa therapy). In this chapter, we will concentrate on PD and not the other categories of parkinsonism. One common misdiagnosis as PD is the presence of tremor due to the entity known as *essential tremor*, which can even be unilateral, although it more commonly is bilateral. Helpful in the diagnosis is that the tremor due to PD is a rest tremor (tremor appears with the affected body part is at rest), whereas the tremor due to essential tremor is not present at rest, but appears with holding the arms in front of the body and increases in amplitude with activity of the arm, such as with handwriting or performing the finger-to-nose maneuver.

TABLE 3. Genetic forms of primary parkinsonism

Name of gene	Protein	Chromosome
	Autosomal dominant transmission	
PARK1	α-synculein	4q21-q22
PARK3	?	2p13
PARK4	Iowa pedigree: PD/ET	4p15
PARK5	ubiquitin C terminal hydrolase-L1 (UCH-L1)	4p14
PARK8	?	12p11.2-q13.1
Dopa-responsive dystonia	GTP cyclohydrolase 1	14q22.1-q22.2
	Autosomal recessive transmission	
PARK2	parkin (ubiquitin ligase)	6q25.2-q27
PARK6	?	1p35-p36
PARK7	DJ-1	1p36
PARK9	?	1p36
PARK10	?	1p32
Tyrosine hydroxylase deficiencey		11p11.5

CLINICAL FEATURES AND EPIDEMIOLOGY OF PARKINSON'S DISEASE

The symptoms of PD begin insidiously and gradually worsen. Rest tremor, because it is so obvious, is often the first symptom recognized by the patient. But the illness sometimes begins with bradykinesia; and in some patients, tremor may never develop. Bradykinesia manifests as slowness, such as slower and smaller handwriting, decreased arm swing and leg stride when walking, decreased facial expression, and decreased amplitude of voice. Rest tremor can be intermittent at the beginning, being present only in stressful situations; eventually it tends to be present most of the time and worsens in amplitude with stress or excitement. There is a steady worsening of symptoms over time; if untreated, the symptoms lead to disability with severe immobility and falling. The early symptoms and signs of PD—rest tremor, bradykinesia, and rigidity—are related to progressive loss of nigrostriatal dopamine. These signs and symptoms result from striatal dopamine deficiency and are usually correctable by levodopa and dopamine agonists. As PD progresses over time, symptoms that do not respond to levodopa develop, such as flexed posture, the freezing phenomenon, and loss of postural reflexes; these are often referred to as non-dopamine-related features of PD. Moreover, bradykinesia that responded to levodopa in the early stage of PD increases as the disease worsens and no longer fully responds to levodopa. It is particularly these intractable motoric symptoms that lead to the disabilities of increasing immobility and balance difficulties (FIG. 2).

While the motor symptoms of PD dominate the clinical picture—and even define the parkinsonian syndrome—many patients with PD have other complaints that have been classified as *nonmotor* (see TABLE 4). These include fatigue, depression, anxiety, sleep disturbances, constipation, bladder and other autonomic disturbances (sexual, gastrointestinal), and sensory complaints. Sensory symptoms include pain,

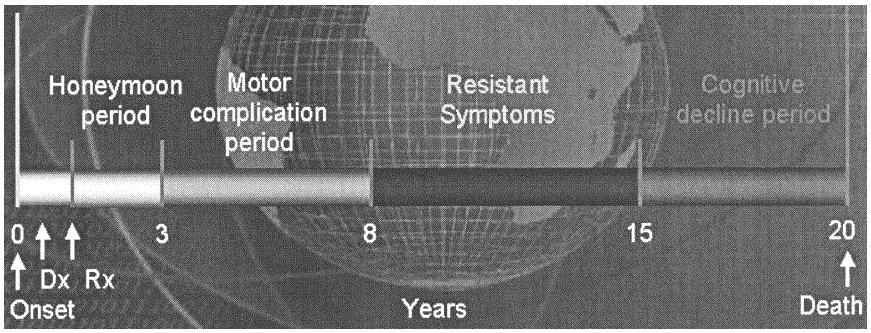

FIGURE 2. Diagram of a typical clinical course of Parkinson's disease despite therapy.

TABLE 4. Nonmotor features of Parkinson's disease

Personality and behavior	***Autonomic***
depression‘	hypotension
fear	bladder problems
anxiety	constipation
passivity	sexual dysfunction
dependence	seborrhea
loss of motivation, apathy	sweating
Cognition and mental	***Sleep problems***
bradyphrenia	sleep fragmentation
"tip of the tongue" phenomenon	REM sleep behavior disorder
dementia	excessive daytime sleepiness
Sensory	altered sleep-wake cycle
pain	***Fatigue***
paresthesiae	
numbness	
burning	
akathisia	
restless legs syndrome	

numbness, tingling, and burning in the affected limbs; these occur in about 40% of patients. Behavioral and mental alterations are common and include changes in mood, decreased motivation and apathy, slowness in thinking (bradyphrenia), and a declining cognition that can progress to dementia. Dementia is most common in those with an older age at onset of PD and can occur in about 40% of such patients; this becomes more disabling than the motoric features of PD (FIG. 2).

The development of dementia in a patient with parkinsonism remains a difficult differential diagnosis. If the patient's parkinsonian features did not respond to levodopa, the diagnosis is likely to be Alzheimer disease, which can occasionally present with features of parkinsonism. If the presenting parkinsonism responded to levodopa and the patient developed dementia over time, the diagnosis could be either

PD or diffuse Lewy body disease (DLBD) (also called dementia with Lewy bodies). If hallucinations occur with or without levodopa therapy, DLBD is the most likely diagnosis. DLBD is a condition where Lewy bodies are present in the cerebral cortex as well as in the brain stem nuclei. The heredodegenerative disease known as *frontotemporal dementia* is an autosomal dominant disorder due to mutations in the tau gene on chromosome 17; the full syndrome presents with dementia, loss of inhibition, parkinsonism, and sometimes muscle wasting.

Although PD can develop at any age, it begins most commonly in older adults, with a peak age at onset at around 60 years. The likelihood of developing PD increases with age, with a lifetime risk of about 2%.[23] A positive family history doubles the risk of developing PD to about 4%. Twin studies indicate that PD with an onset under the age of 50 years is more likely to have a genetic relationship than PD with a later age at onset.[24] Males have higher prevalence and incidence rates than females. Patients with PD can live 20 or more years, depending on the age at onset. The mortality rate is about 1.6 times that of normal individuals of the same age.[25] Death in PD is usually due to some concurrent unrelated illness or due to the effects of decreased mobility, aspiration, or increased falling with subsequent physical injury. At the present time, approximately 850,000 individuals in the U.S. have PD, with the number expected to grow as the population ages.

There are no practical diagnostic laboratory tests for PD, and the diagnosis rests on the clinical features and on excluding other causes of parkinsonism. The research tool of fluorodopa (FDOPA) positron emission tomography (PET) measures levodopa uptake into dopamine nerve terminals, and this shows a decline of about 8% per year of the striatal uptake. A similar result is seen using ligands for the dopamine transporter, either by PET or by single-photon emission computed tomography (SPECT); these ligands also label the dopamine nerve terminals. All these neuroimaging techniques reveal decreased dopaminergic nerve terminals in the striatum in both PD and the Parkinson-plus syndromes and do not distinguish between them. A substantial response to levodopa is most helpful in the differential diagnosis, indicating presynaptic dopamine deficiency with intact postsynaptic dopamine receptors, features typical of PD.

Some adults may develop a more benign form of PD, in which the symptoms respond to very-low-dosage levodopa, and the disease does not worsen severely with time. This form is usually due to the autosomal dominant disorder known as dopa-responsive dystonia, which typically begins in childhood as a dystonia. But when it starts in adult life, it can present with parkinsonism. There is no neuronal degeneration. The pathogenesis is due to a biochemical deficiency involving dopamine synthesis. The gene defect is for an enzyme (GTP cyclohydrolase I) required to synthesize the cofactor for tyrosine hydroxylase activity, the crucial rate-limiting first step in the synthesis of dopamine and norepinephrine. Infantile parkinsonism is due to the autosomal recessive deficiency of tyrosine hydroxylase, another cause of a biochemical dopamine deficiency disorder.

PATHOLOGY, BIOCHEMISTRY AND PHYSIOLOGY OF PARKINSON'S DISEASE

PD and the Parkinson-plus syndromes have in common a degeneration of substantia nigra pars compacta dopaminergic neurons, with a resulting deficiency of striatal

TABLE 5. Dopamine concentration in striatum is associated with severity of bradykinesia

Severety of bradykinesia	Caudate nucleus	Putamen
Mild	0.58 (13)	0.44 (12)
Marked	0.44 (9)	0.05 (9)
Normal controls	2.65 (28)	3.44 (28)

NOTE: Date from Bernheimer *et al*.[26] Results are means in μg/g fresh tissue. Numbers in parentheses are the number of cases studied.

dopamine due to loss of the nigrostriatal neurons. Accompanying this neuronal loss is an increase in glial cells in the nigra and a loss of the neuromelanin normally contained in the dopaminergic neurons. In PD, intracytoplasmic eosinophilic inclusions, called Lewy bodies, are usually present in many of the surviving neurons. It is recognized today that not all patients with PD have Lewy bodies; those with the homozygous mutation in the PARK2 gene—mainly young-onset PD patients—have nigral neuronal degeneration without Lewy bodies. Lewy bodies contain many proteins, including the fibrillar form of α-synuclein, discovered because PARK1's mutations involve the gene for this protein. There are no Lewy bodies in the Parkinson-plus syndromes.

With the progressive loss of the nigrostriatal dopaminergic neurons, there is a corresponding decrease of dopamine content in both the nigra and the striatum, which, as mentioned above, accounts particularly for the bradykinesia and rigidity in PD. There are compensatory changes, such as supersensitivity of dopamine receptors, so that symptoms of PD are first encountered only when there is about an 80% reduction of dopamine concentration in the putamen (or a loss of 60% of nigral dopaminergic neurons).[26] With further loss of dopamine concentration, parkinsonian bradykinesia becomes more severe (TABLE 5). The progressive loss of the dopaminergic nigrostriatal pathway can be detected *in vivo* using PET and SPECT scanning; these show a continuing reduction of FDOPA and dopamine transporter ligand binding in the striatum.[27–31]

The consequence of nigrostriatal loss is an altered physiology downstream from the striatum. The striatum contains D1 and D2 receptors. The current thinking is that dopamine is excitatory at the D1 receptor and inhibitory at the D2 receptor. Deficiency of dopamine at these receptors results in alteration at the downstream nuclei: excessive activity of the subthalamic nucleus and globus pallidus interna, and increased inhibition in the thalamus and cerebral cortex.[32–34] These altered physiological patterns are restored towards normal with treatment by levodopa.

CAUSES AND PATHOGENESIS OF PD AND PARKINSON-PLUS SYNDROMES

Other than known genetic causes of PD (TABLE 3), the etiology of these disorders remains unknown. Three (PARK1, PARK2, and PARK5) of the four identified mutated genes causing PD—involving the proteins α-synuclein, parkin, and ubiquitin C terminal hydrolase-L1—point to an impairment of protein degradation with a buildup of toxic proteins that cannot be degraded via the ubiquitin-proteasomal path-

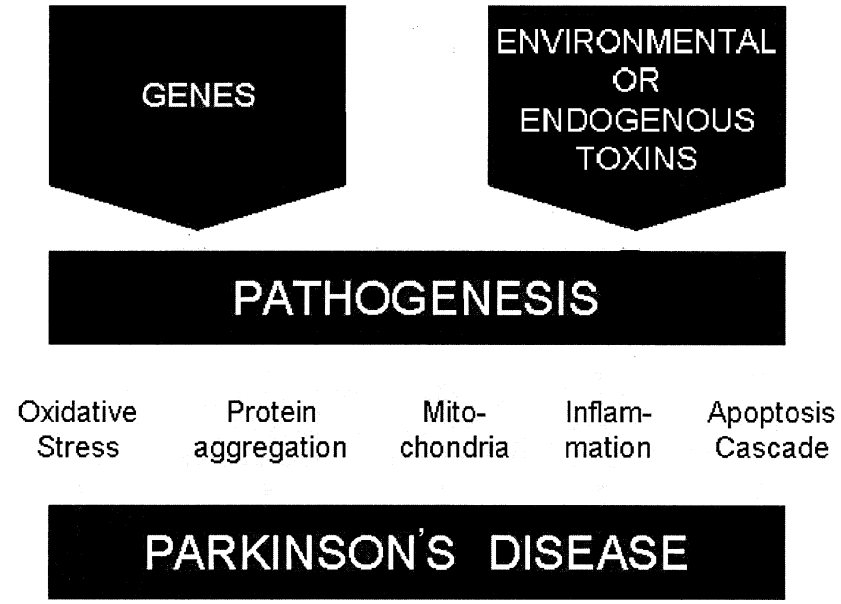

FIGURE 3. Diagram of the concept of the etiology and pathogenesis of Parkinson's disease.

way. The fourth, PARK7—involving a nuclear protein of unknown function—appears also to play a role in protein degradation. These findings have led to the concept that perhaps most, if not all, cases of sporadic PD have an impairment of protein degradation. A current hypothesis is that oxidative stress with the formation of oxyradicals, such as dopamine quinone, can lead to reactions with α-synuclein to form oligomers of α-synuclein (so-called protofibrils), which accumulate because they cannot be degraded by the ubiquitin-proteasomal pathway, leading finally to cell death.[35] Other pathogenetic mechanisms being considered are (1) other effects from oxidative stress, such as the reaction of oxyradicals with nitric oxide to form the highly reactive peroxynitrite radical; (2) impaired mitochondria leading to both reduced ATP production and accumulation of electrons that aggravate oxidative stress, with the final outcome being apoptosis and cell death; and (3) inflammatory changes in the nigra, producing cytokines that augment apoptosis (FIG. 3). These actions lead to an apoptotic cascade that leads to cell death. These concepts on pathogenesis are leading researchers to test agents that affect these potential mechanisms in an attempt to reduce the rate of neurodegeneration in PD.

THERAPY OF PARKINSON'S DISEASE

Neuroprotective Therapy

So far no drug or surgical approach has been shown unequivocally to slow the rate of progression of PD, but if any drug should be proved to delay the progression of the disease process, it should be incorporated in treatment early in the course of the dis-

ease. There are some controlled clinical trials that were sufficiently positive to have raised the possibility that the propargylamine agents selegiline and rasagiline and the mitochondrial enhancing agent coenzyme Q_{10} could have some neuroprotective qualities.[36–38] Larger clinical trials with neuroimaging of striatal dopamine nerve terminals would be necessary to provide adequate documentation of neuroprotection.

Symptomatic Therapy

Dopamine replacement therapy is the major medical approach to treating PD, and a variety of dopaminergic agents are available (TABLE 6). The most powerful drug is levodopa. It is usually administered with a peripheral decarboxylase inhibitor to prevent formation of dopamine in the peripheral tissues. In addition to being metabolized by aromatic amino acid decarboxylase, levodopa is also metabolized by catechol-O-methyltransferase (COMT) to form 3-O-methyldopa. The use of a COMT inhibitor with levodopa can extend the plasma half-life of levodopa without increasing its peak plasma concentration and can thereby prolong the duration of action of each dose of levodopa. Although levodopa is the most effective drug to treat the symptoms of PD, about 60% of patients develop troublesome complications of disabling response fluctuations (the "wearing-off" effect) and dyskinesias after five years of levodopa therapy; younger patients (less than 60 years of age) are particularly prone to developing these problems even sooner.

The next most powerful drugs in treating PD symptoms are the dopamine agonists. Several of these are available. Apomorphine may be the most powerful, but it needs to be injected or taken sublingually. The others agonists are effective orally. Pergolide, pramipexole, and ropinirole appear to be equally effective; and all are more powerful than bromocriptine. Cabergoline and lisuride are not available in the U.S. Cabergoline has the longest half-life and therefore may prove ultimately to be most useful. Compared to levodopa, dopamine agonists are more likely to cause hallucinations, confusion, and psychosis, especially in the elderly. Thus, it is safer to use levodopa in patients over the age of 70 years. They are also more likely to cause drowsiness and, after several years of use, can cause leg edema. On the other hand, controlled clinical trials have revealed that dopamine agonist therapy is less likely to produce dyskinesias and the wearing-off phenomenon than levodopa.[39,40] But these trials also showed that levodopa provides greater symptomatic benefit than do dopamine agonists. The neuroimaging component of these studies reveals that striatal dopamine nerve terminals disappear at a faster rate with levodopa treatment than with the agonists. There is uncertainty about how to apply the information gleaned from these studies to the patient; a frank discussion between physician and patient should lead to the appropriate treatment for that individual.

TABLE 6. Dopaminergic agents used in the treatment of Parkinson's disease

Dopamine precursor: levodopa	Dopamine agonists: bromocriptine, pergolide, pramipexole, ropinirole, apomorphine, and cabergoline
Peripheral decarboxylase inhibitors: carbidopa, benserazide	Dopamine releaser: amantadine
Catechol-O-methyltransferase inhibitors: tolcapone, entacapone	MAO type B inhibitor: selegiline, rasagiline

Amantadine has several actions: it has antimuscarinic effects, but more importantly it can activate release of dopamine from nerve terminals, block dopamine uptake into the nerve terminals, and block glutamate receptors. Its dopaminergic actions make it a useful drug to relieve symptoms in about two-thirds of patients, but it can induce livedo reticularis, ankle edema, visual hallucinations, and confusion. Its antiglutamatergic action is useful in reducing the severity of levodopa-induced dyskinesias. The elderly do not tolerate amantadine well because of the adverse mental effects. Monoamine oxidase type B (MAO-B) inhibitors (e.g., selegiline) offer mildly effective symptomatic benefit and are without the hypertensive "cheese effect" seen with MAO-A inhibitors; therefore, they can be used in the presence of levodopa therapy. Although there has been considerable debate about the possible protective benefit of selegiline, recent studies evaluating its long-term use indicate that selegiline is associated with less freezing of gait and with a slower rate of clinical worsening compared to placebo-treated subjects. These benefits appear to be separate from its mild symptomatic effects because all subjects were receiving the symptomatic benefit from concurrent levodopa therapy.[36] Nondopaminergic agents are also useful to treat many PD symptoms, both motoric and nonmotoric; they are beyond the scope of this review.

Surgical Therapy

Surgery for PD is becoming increasingly available as new techniques of electrical stimulation have been developed and a better understanding of basal ganglia physiology has been attained. Stereotaxic deep brain stimulation (DBS) is fast becoming the treatment of choice because ablative lesioning involves greater risk of inducing neurological deficits. With stimulating electrodes, the stimulation can be adjusted, and the electrodes can be removed if necessary. However, DBS is more costly than creating a lesion in the target, and frequent adjustments of the stimulator are usually needed. The location of the stereotaxic target is the other major factor that needs to be individualized for each patient. The thalamus, particularly the ventral intermediate nucleus, appears to be the most successful target for controlling tremor, but this target does not eliminate bradykinesia; so stereotaxic thalamotomy or thalamic DBS is not a preferred choice today. The globus pallidus interna is a more satisfactory target for controlling choreic and dystonic dyskinesias due to levodopa therapy. But the subthalamic nucleus appears to be the best target for controlling bradykinesia. DBS of the subthalamic nucleus, by reducing bradykinesia, allows for a reduction of levodopa dosage, thus reducing the severity of dyskinesias as well. This surgical approach seems the most promising. Surgical procedures for patients with PD are best performed at specialty centers by an experienced team consisting of a neurosurgeon, a neurophysiologist to monitor the target during the operative procedure, and a neurologist to program the stimulators. The patient needs close follow-up to adjust the stimulator settings to their optimum.

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