CHAPTER 71

PARKINSON'S DISEASE

Anthony H. V. Schapira

Parkinson's disease (PD) is a neurodegenerative disease with initial clinical features that are predominantly the result of loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) of the midbrain. As the disease progresses, the involvement of additional brain areas in the degenerative process produces mainly nondopaminergic, nonmotor features. The discovery of dopamine deficiency in PD and the introduction of levodopa have provided patients with a significant improvement in both quality of life and life expectancy, but the treatment of nonmotor features and slowing of disease progression remain important unmet needs for patients.

HISTORICAL PERSPECTIVE

James Parkinson is credited with providing the first and definitive clinical description of a disease, *paralysis agitans,* that was subsequently to bear his name. Parkinson was born in 1755 in what was then the village of Hoxton near London. His *Essay on the Shaking Palsy* was published in 1817 and was based on six patients, three of whom were only observed and not examined by Parkinson. His description remains one of the most-published detailed analyses of the clinical effects of PD and also makes comment on the etiology and pathogenesis of the disease. His observations on pathology were naturally limited; he did suggest that the disease had its origins in the medulla, "although that part contained within the cervical vertebrae" (sic). Suggestions for the relief of symptoms included the letting of blood from the upper cervical area and the production of a purulent discharge with the use of the Sabine Liniment.

Several physicians published case reports based on Parkinson's description. However, it was Charcot who made significant advances in the clinical classification and differential diagnosis of PD and was the first to propose its eponymous label. The motor and nonmotor features of PD are well described in these early works. The pathological definition of PD evolved rather slowly, perhaps reflecting the complex nature of the type and distribution of degenerative changes. Lewy described the intracytoplasmic inclusions that are a hallmark of the disease in 1912, and Trétiakoff is attributed with locating the cell degeneration in the substantia nigra. Various descriptions of pathological changes followed, including the presence of tangles and the distribution of degeneration, although many cases may not have been "idiopathic" PD.

In 1960, Ehringer and Hornykiewicz identified the dopamine deficiency in PD striatum.[1] Studies on the replacement of dopamine with DL-dopa produced equivocal results until used in sufficient quantity.[2] This began the era of symptomatic treatment for PD, which has remained focused on the dopaminergic system for almost 40 years.

EPIDEMIOLOGY

Defining the epidemiology of PD is confounded by several variables that include the difficulty in diagnosis and the age dependence of the disease. Several studies have sought to define incidence. In the United States, the age-adjusted figure is 13.5 to 13.9 per 100,000 person-years.[3,4] The age-adjusted prevalence is approximately 115 per 100,000 and is estimated as 1.3 per 100,000 under age 45 years and 1192.9 per 100,000 in those aged 75 to 85 years.[3] A prevalence study in Holland found 3100 cases per 100,000 aged 75 to 85 years and 4300 per 100,000 for those over age 85 years.[6] The geographical distribution of the disease appears similar across the United States and Japan, but failure to adjust population figures for age can lead to widely discrepant results, such as the prevalence of 10 per 100,000 in Nigeria.[7]

PATHOLOGY

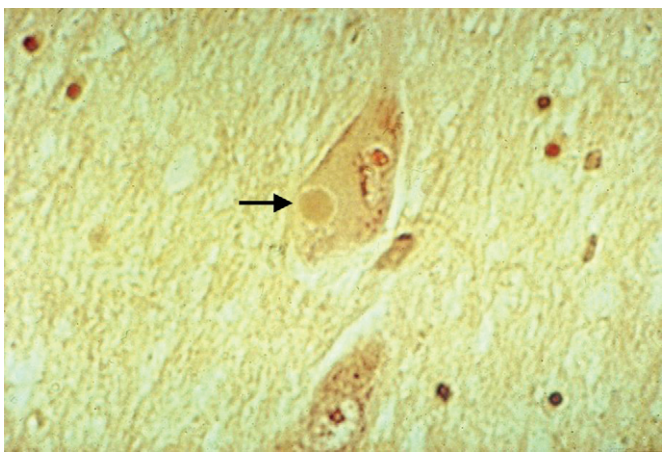
Macroscopic examination of the sectioned PD brain shows depigmentation of the substantia nigra and locus ceruleus. The characteristic pathological change of PD is the loss of pigmented dopaminergic neurons, particularly in the ventral tier of the SNc with intracytoplasmic eosinophilic inclusions (Lewy bodies) in a proportion of the surviving neurons (Fig. 71–1). The SNc also contains activated microglia and extracellular neuromelanin. There is also cell loss in the locus ceruleus; the nucleus basalis of Meynert; the dorsal motor nucleus of the vagus; the Edinger-Westphal, raphe, and pedunculopontine nuclei; and the pons, midbrain, spinal cord, and peripheral sympathetic ganglia. Lewy bodies may be found in these areas and in the cortex. Thus, in addition to the dopaminergic system, the cholinergic, serotonergic, γ-amino butyric acid, and adrenergic transmitter systems are involved in PD.

Lewy bodies have attracted considerable attention over the years, as they may hold important clues to pathogenesis of the disease. They are 5 to 30 μm in diameter with a hyaline

eosinophilic core, which may be dense and composed of concentric lamellae; a pale halo may be seen around the core. Electron microscopy demonstrates 7- to 20-nm intermediate filaments. The Lewy body is composed of a number of different proteins, staining for ubiquitin, α-synuclein, and proteasomal components. It is not known whether these inclusions represent a protective response to aggregate abnormal or toxic proteins, or whether their formation is part of a toxic process that damages the cell.

Studies suggest that the earliest pathological changes are seen in the dorsal motor nucleus and in the olfactory bulbs and nucleus—Braak stages 1 and 2[8] (Fig. 71–2). In this context, it is noteworthy that loss of olfactory function can occur at a time prior to the onset of dopaminergic symptoms or signs and may serve to define an "at-risk" population.[9] Lewy bodies then develop in the locus ceruleus and progress in the medulla and pons.[10] The appearance of inclusions in the SNc defines the onset of Braak stage 3 with progression to stage 4. At this stage there is also degeneration in the pedunculopontine nucleus, the dorsal raphe nuclei, and the hypothalamus. Stages 5 and 6 involve progressive involvement of the cerebral cortex and neurodegeneration in those regions already affected.

However, it is important to note that Braak's staging was based on Lewy body formation and distribution and not on neuronal degeneration. In this context, the SNc remains the first location of degeneration in PD.



■ **Figure 71–1.** A Lewy body (*arrow*).

ETIOLOGY

The etiology of PD is believed to involve both genetic and environmental factors. Several gene mutations have been described in monogenic forms of familial PD, and some of these are also found in apparently sporadic late-onset PD. Nevertheless, these account for only a small proportion of PD patients. Epidemiological studies have discovered certain lifestyle associations with PD, and some specific toxins have been identified that can induce a parkinson-like state in humans or animals.

Genetic Factors

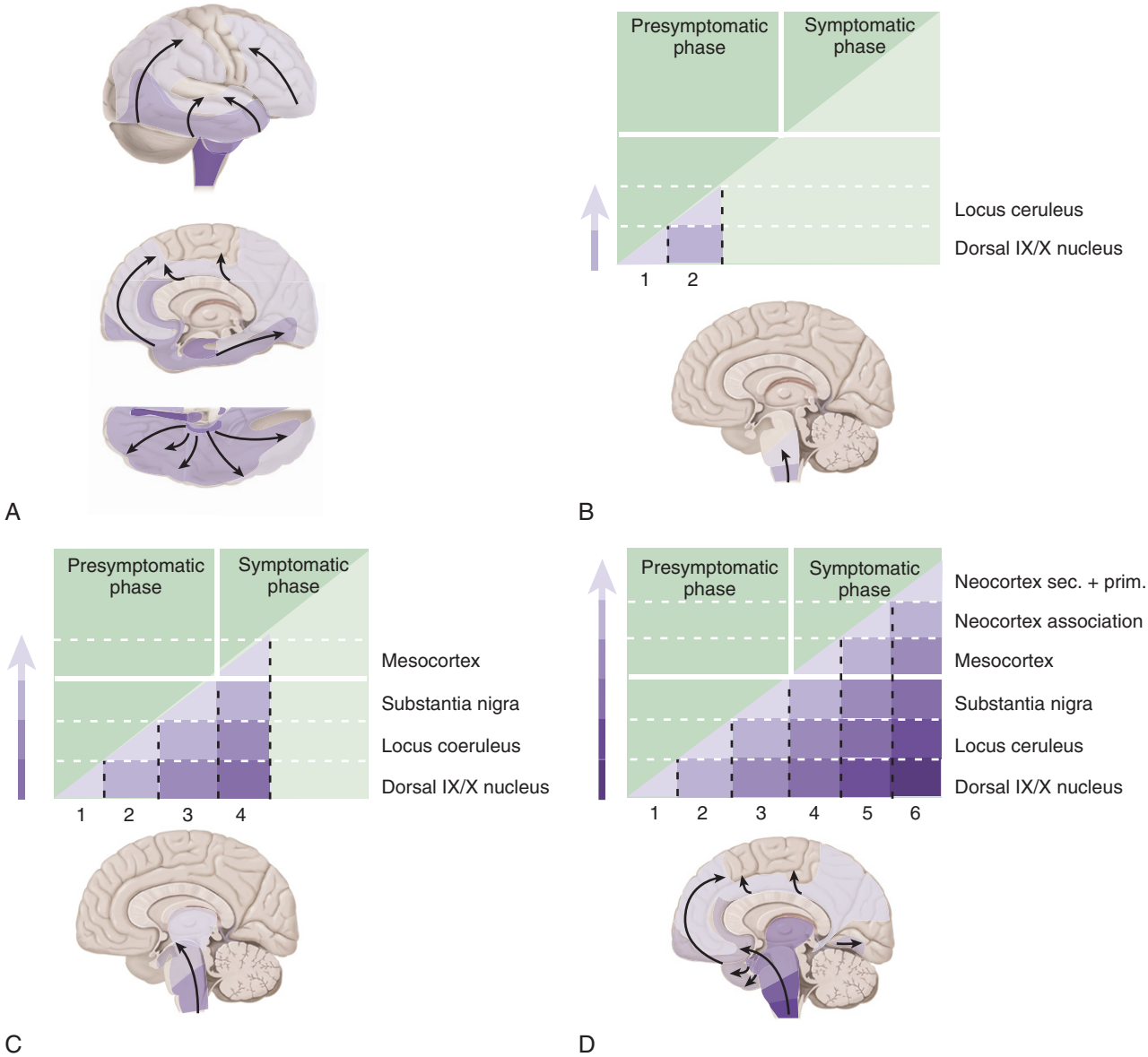
Sir William Gowers recognized that there was an increased prevalence of PD among the relatives of sufferers and proposed a genetic cause.[11] Epidemiological studies evaluating the genetic contribution of PD are complicated by ensuring an accurate clinical diagnosis, inability to identify presymptomatic cases and the need for an appropriate control population. Case-control studies have confirmed Gowers' observation that PD is more common in relatives of PD cases compared with matched controls.[12-16] The relative risk of developing PD in family members has varied widely between different studies, but in many, incomplete family information was obtained and only one study has been population based.[16] Overall, the relative risk in first-degree relatives of PD cases is increased approximately two- to threefold.[17]

A large PD twin study showed no significant concordance for PD among monozygotic twins, suggesting that there was no significant genetic contribution to PD.[18] However, there was significant concordance for those with onset before age 50 years, implying that young-onset PD is more likely genetically determined. Another smaller twin study using fluorodopa positron emission tomography (PET) to image dopaminergic function in both affected and unaffected monozygotic and dizygotic twin pairs demonstrated an increased concordance for PD among identical twins.[19] At follow-up, the combined concordance levels for subclinical dopaminergic dysfunction and clinical PD were 75% in the 12 monozygotic twins and 22% in the 9 dizygotic twins evaluated twice.

Table 71–1 shows the current list of genes known to cause PD. *PARK1* through *PARK9* have been discovered using large single or combined pedigrees, whereas *PARK10* and *PARK11* have been identified using association techniques.

TABLE 71–1. *Park* Genes

	Inheritance	Locus	Onset (y)	Lewy Bodies	Gene
Park 1	Autosomal dominant	4q21	40s	+	*α-synuclein*
Park 2	Autosomal recessive	6q25	20s	–	*parkin*
Park 3	Autosomal dominant	2p13	60s	+	?
Park 4	Autosomal dominant	4q21	30s	+	*α-synuclein*
Park 5	Autosomal dominant	4p15	50s	+	*UCH-L1*
Park 6	Autosomal recessive	1p35	30s	?	*Pink-1*
Park 7	Autosomal recessive	1p36	30s	?	*DJ1*
Park 8	Autosomal dominant	12p	—	±	*LRRK2*
Park 9	Autosomal recessive	—	—	?	?
Park 10	Autosomal recessive	1p32	—	?	?
Park 11	?	2q36-37		?	?



■ **Figure 71–2.** Braak staging of Parkinson's disease. *(From Del Tredici K, Rub U, De Vos RA, et al: Where does Parkinson's disease pathology begin in the brain? J Neuropathol Exp Neurol 2002; 61:413-426; and Braak H, Del Tredici K, Rub U, et al: Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24:197-211.)*

α-Synuclein (PARK1)

PARK1 involves mutations in the *α-synuclein* gene.[20,21] The first families with an *α-synuclein* mutation originated from southern Italy and Greece, and with the description of several additional families with the same A53T mutation, it is believed that they have a common founder. Age at onset was young (mean, 46 years) with a low frequency of tremor and relatively rapid disease progression, although symptoms were levodopa responsive.[22] Pathological analysis of the few brains available revealed the presence of Lewy bodies in the substantia nigra and locus ceruleus.[23] Linkage to markers on chromosome 4q21-q23 was demonstrated and the locus designated *PARK1*.[24] Further analyses identified a mutation in exon 4 of the gene encoding α-synuclein resulting in an alanine-to-threonine substitution at codon 53 (A53T), which was also found in affected members of three Greek families with early-onset autosomal dominant PD.[20] A second mutation (A30P) was later found in a small German family with PD,[21] but extensive study in large groups of PD families and sporadic cases has not identified other patients or families with this mutation.[25-28]

α-Synuclein is a protein of 140 amino acids that is predominantly expressed in neurons and is one of the most common brain proteins. Its normal function remains unclear, although it plays a role in synaptic plasticity based on song-learning studies in the zebra finch[29] and vesicular regulation of dopamine release from knockout mice.[30] A key observation linking α-synuclein to PD was the demonstration that it is one of the principal components of Lewy bodies.[31] Lewy bodies are intracytoplasmic aggregates comprising several proteins, including ubiquitin and α-synuclein, and have supported the notion that abnormal protein handling might be important in

PD pathogenesis. Furthermore, mutant isoforms of α-synuclein more readily oligomerize and it has been suggested that its tendency to aggregate into misfolded structures may confer toxic properties to the protein. Indeed, overexpression of wild-type or mutant protein in transgenic mice or *Drosophila* reproduces many of the behavioral and pathological features of PD.[32,33]

Multiplications of the wild-type *α-synuclein* gene have been described in PD families. A triplication of the gene was identified in a large autosomal dominant kindred with PD and tremor,[34] and duplication of the gene was found in one of 42 familial probands of early onset PD.[35] A third α-synuclein point mutation (E46K) has been reported in an autosomal dominant family with parkinsonism and Lewy body dementia.[36]

Several models of abnormal α-synuclein expression have been developed. Knockout of the gene in mice resulted in no detectable abnormality other than an alteration of dopamine release in response to rapid stimulation, although this has no clear functional correlate.[30] Overexpression of wild-type human α-synuclein in mice resulted in loss of dopaminergic terminals, intranuclear and cytoplasmic ubiquitin-rich nonfibrillar α-synuclein inclusions in the substantia nigra, hippocampus, cortex, and a rotor-rod motor deficit at 1 year.[32] Overexpression of human wild-type and mutant α-synuclein in flies caused a loss of dopaminergic neurons, Lewy body–like inclusions with fibrillar α-synuclein, and a motor deficit with no significant difference between wild-type and mutant α-synuclein.[33] Additional mouse models of α-synuclein expression have demonstrated inclusion formation and spinal cord pathology but no dopaminergic cell loss, and motor deficit at late stage.[37] Virus-mediated overexpression of α-synuclein induces nigral degeneration in rodents.[38]

The *α-synuclein* mutations result in the protofibrillar form, which is considered the more toxic form of the protein. The A53T and A30P *α-synuclein* mutations promote protofibril formation and A30P inhibits conversion to fibrils.[39] Catecholamines, including dopamine and levodopa, inhibit fibril formation in vitro, and this is reversed by antioxidants; that is, catechol oxidation promotes protofibril formation.[40] This observation would support a protective role for Lewy bodies in PD. An important observation revealing a potential toxic mechanism for α-synuclein is that the mutant A30P form increases toxicity to dopamine, increasing cell death and free radical–mediated damage.[41] The authors proposed that the mutation impaired vesicular uptake of dopamine, resulting in higher cytoplasmic or extravesicular synaptic concentrations of dopamine that would in turn cause free radical–mediated damage. Phosphorylation at the Ser129 residue is required to mediate the toxicity of α-synuclein and increased the formation of inclusions in SHSY-5Y cells.[42] This phosphorylated form of α-synuclein is present in Lewy bodies.[43] Prevention of this phosphorylation by substitution of an alanine residue reduced inclusion formation in the SHSY-5Y model, and in the *Drosophila* model this same mutation at 129 that prevents phosphorylation protected against dopaminergic neuronal loss.[44]

Parkin (PARK2)

PARK2 gene mutations were first identified in autosomal recessive juvenile-onset parkinsonism (ARJPD).[45] ARJPD has been most commonly seen in the Japanese population and is characterized by onset before age 40 years, symptomatic improvement following sleep, mild dystonia, and a good response to levodopa.[46] Resting tremor is seen less frequently than in idiopathic PD, and patients may have brisk tendon reflexes but no other pyramidal, cerebellar, or autonomic features. The disease is often symmetrical and dyskinesias develop early but progression is usually slow. Pathologically, there is dopaminergic cell loss in the SNc and locus ceruleus but no Lewy bodies are seen.[47] The gene responsible for ARJPD was mapped to 6q25.2-q27,[48] and in 1998 the gene was discovered and named *parkin*.[45] Affected patients carry deletions or point mutations in various parts of the *parkin* gene.[49,50] The absence of Lewy bodies in ARJPD may simply reflect the limited time over which the pathology has evolved. However, the relationship of *parkin* mutations to idiopathic PD has been highlighted by the identification of *parkin* mutations in apparently sporadic cases of PD and by the description of Lewy bodies in *parkin* positive patients with later-onset disease than ARJPD.[51,52] *Parkin* mutations are a common cause of PD under age 25 years but rare over age 40 years.[53,54] *Parkin*-related PD has been reported in multiple generations in families without consanguinity, suggesting a pseudo-autosomal dominant mode of inheritance for some mutations.[55,56] Fluorodopa positron emission tomography (PET) in *parkin* patients demonstrates reduced uptake in the striatum, although there is some discordance regarding the symmetry and pattern of this reduction[57,58] However, the rate of loss of fluorodopa PET signal was slower in the *parkin* patients than in sporadic PD.[59] Asymptomatic heterozygous *parkin* mutation carriers had intermediate levels of striatal fluorodopa PET uptake compared with normal controls and homozygous symptomatic patients.[58] This suggests an intermediate stage of nigrostriatal dysfunction that may interact with other genetic or environmental factors to induce PD. The frequency of heterozygous *parkin* mutation carriers is not known.

PARK2 encodes parkin, which functions as an E3 ligase, ubiquinating proteins for destruction by the proteosome.[60,61] Several substrates for parkin have been identified, including a 22-kDa glycosylated form of α-synuclein, parkin-associated endothelin receptor-like receptor (Pael-R), and CDCrel-1. Overexpression of Pael-R causes it to become ubiquinated, insoluble, and unfolded and leads to endoplasmic reticulum stress and cell death.[62] It has been demonstrated to accumulate in its insoluble form in the brains of patients with *parkin* mutations, suggesting a possible toxic mechanism. CDCrel-1 is a protein involved in cytokinesis and may influence synaptic vesicle function.[61] Overexpression of *parkin* protected against dopaminergic loss in rodents coexpressing α-synuclein, suggesting a protective role for parkin.[63]

A *parkin* knockout mouse model has been described.[64] This showed an increase in striatal extracellular dopamine, a reduction in synaptic excitability, and a mild nonprogressive motor deficit at 2 to 4 months. There was no loss of dopaminergic neurons and no inclusion formation. Dopamine receptor binding affinities and *parkin* E3 ligase substrate levels were normal. Interestingly, these mice had decreased striatal mitochondrial respiratory chain function and reductions in specific respiratory chain and antioxidant proteins.[65] *Parkin* knockout flies developed muscle pathology, mitochondrial abnormalities and apoptotic cell death.[66] Overexpression of *parkin* in PC12 cells indicated that it is associated with the mitochondrial outer membrane.[67] *Parkin*-positive patients have decreased lymphocyte

complex I activity.[68] The ability of parkin to ubiquinate proteins may be impaired by *S*-nitrosylation, which in turn may be a consequence of excitotoxicity-mediated damage.[69]

UCH-L1 (PARK5)

A further mutation in the gene encoding ubiquitin carboxyhydrolase (UCH)-L1 again supported the relevance of the ubiquitin-proteosomal system (UPS) in PD pathogenesis.[70] UCH-LI is an enzyme that hydrolyzes the C-terminus of ubiquitin to generate ubiquitin monomers that can be recycled to clear other proteins. A missense mutation was identified in two siblings with typical PD in a German family demonstrating apparent autosomal dominant inheritance.[70] Age at onset was 49 years in one and 51 years in the other. The mutant form of UCH-L1 was shown to have reduced enzyme activity resulting in impaired protein clearance through the ubiquitin-proteasome pathway. However, no other mutations in this gene have been identified in other families, suggesting it is a rare cause of PD.[71,72] Given that no further cases of PD have been described with mutations in this gene, some doubt has been cast on the relevance of UCH-L1 to PD.

PINK1 (PARK6)

The *PARK6* locus (chromosome 1p36[73]) was first identified in a large consanguineous Italian family and subsequently in an additional three Italian families and others from Europe and elsewhere, including Asia.[74-78] The mean age at onset ranges from 21 to 57 years. Progression is usually slow and patients exhibit a good response to levodopa. *PARK6* mutations appear to be a rare cause of PD.

The *PINK1* (PTEN-induced kinase 1) gene is ubiquitously transcribed and is believed to encode a mitochondrial kinase.[74,79] It is believed that *PINK1* may play a role in protecting cells against stress conditions that affect mitochondrial membrane potential, but the downstream targets through which *PINK1* mediates its protection have not been identified. As 11 of the 14 reported mutations fall into the kinase domain of *PINK1*,[74,76,77] altered phosphorylation of target proteins probably represents a key pathogenic mechanism, leading to abnormal stress response and neurodegeneration. The reversible phosphorylation of proteins is an important method of regulating cellular activities.[80] Up to 30% of eukaryotic proteins are phosphorylated,[81] and there are more than 500 human genes encoding protein kinases.[82] The phosphorylation of mitochondrial proteins is considered pivotal to the regulation of respiratory activity in the cell and to signaling pathways leading to apoptosis, as well as for other vital mitochondrial processes. For instance the phosphorylation of α-synuclein is an important step in mediating its toxicity (see earlier), and Lewy bodies do contain the phosphorylated form of this protein.

DJ-1 (PARK7)

The *PARK7* locus on chromosome 1p36, only about 25 cM from the *PARK6* locus, was first identified in a small group of young-onset PD patients in a remote region of Holland.[83] Average age at onset is 32 years, with a currently reported range of 25 to 40 years. Onset is asymmetrical, progress is slow, and there is a good response to levodopa. Tremor is infrequent, and psychiatric disturbances have been described in some. Fluorodopa PET scans demonstrate a symmetrical reduction in uptake. No pathological studies of *PARK7* patients have been undertaken at the time of writing.

PARK7 encodes *DJ-1*; mutations are autosomal recessive and comprise both deletions and point mutations that result in a loss or inactivation of the protein. Its function is unknown, but it is widely distributed and conserved. It can protect against toxicity mediated by free radicals and transfers to the outer mitochondrial membrane under conditions of oxidative stress.[84,85] Wild-type *DJ-1* is also located in the mitochondrial matrix and intermembraneous space, and this distribution is not altered by mutations in the protein.[86]

LRRK2 (PARK8)

Mutations in the *LRRK2* gene are the most common cause of either familial or "sporadic" PD identified to date. The *LRRK2* G2019S mutation alone has been reported in 2.8% to 6.6% of autosomal dominant PD families[87-89] and in 2% to 8% of sporadic cases.[90-92] The G2019S mutation has variable penetrance, with 17% at 50 years and 85% at 70 years, a profile that mimics idiopathic, sporadic PD. Although other *LRRK2* mutations are described, the G2019S mutation remains the most common cause of either sporadic or familial PD. This mutation has not been seen in Alzheimer's disease or in parkinsonian syndromes other than idiopathic PD.[93,94]

Many of the reported cases of *LRRK2* mutations have typical features of PD with asymmetrical onset of tremor, bradykinesia, and rigidity. As noted, the age at onset is variable with occasional very late onset cases[89] and a report of one carrier male reaching 89 years with only subtle neurological changes.[95] Patients have a good response to levodopa but develop motor complications including dyskinesias. Fluorodopa PET and imaging using ligands for the dopamine transporter with single-photon emission computed tomography (SPECT) demonstrate changes typical of those seen in idiopathic PD.[96] Although all *LRRK2* mutant brains examined to date demonstrate loss of dopaminergic neurons in the SNc, one of the morphological hallmarks of idiopathic PD, additional pathology may also be seen. Pure nigral neuronal degeneration was found in the first family linked to this locus[97]; neurofibrillary tangles, abnormal tau deposits, and widespread Lewy body synucleinopathy have been described in others, including one family with anterior horn cell loss.[98,99] Three brains of "sporadic" PD with G2019S *LRRK2* mutations have had pathological examination and all have demonstrated nigral neuronal loss and Lewy body formation typical of PD.[90] All of these subjects had PD based on clinical criteria.

The *LRRK2* gene encodes a 286-kDa cytoplasmic protein that is widely expressed in the brain.[100] *LRRK2* is a member of the ROCO protein family and appears to have multiple functions, at least by virtue of its predicted structure. These include a Ras/GTPase domain involved in cytoskeletal responses to external stimuli, vesicular trafficking and the stimulation of stress-activated kinase.[101] The leucine-rich motif may have numerous functions, including protein-protein interactions and substrate binding for ubiquitination. The *LRRK2* kinase domain belongs to the MAPKKK family of kinases with catalytic activity for both serine/threonine and tyrosine residues.

The G2019S mutation changes a highly conserved glycine at the start of the kinase activation segment, and it has been postulated that this has an activating effect causing a "gain of

function" compatible with its autosomal dominant inheritance pattern.[89] *LRRK2* also has a WD40 domain, which again may be involved in cytoskeletal assembly and signal transduction.

PARK9, PARK10, and *PARK11*

The *PARK9* locus on chromosome 1p36 was described in an autosomal recessive, juvenile-onset parkinsonian disorder with pyramidal features, ophthalmoplegia, and dementia.[102,103] *PARK10* on chromosome 1p32 was identified in the families of Icelandic PD patients with late-onset disease.[104] *PARK11* was obtained by association studies, and little information is available on phenotype.

Genetic Associations

Only a minority of cases of PD are part of a clear familial pedigree. Some of the single-gene mutations described above may account for a proportion of the remaining patients. However, our current understanding is that such single-gene causes of PD will remain in the minority. Thus, the large proportion of PD patients may develop their disease as a result of environmental factors, polygenic influences, or a combination of the two. There have been several genetic association studies attempting to determine significant polymorphisms that may increase or decrease the risk for PD. Further evidence for the role of genes in PD comes from genome-wide screens.[105,106] The first found 174 families with a minimum of two clinically affected individuals with PD per family and identified a marker from the intronic region of *parkin* in an early-onset group and a region on 9q in a dopa-resistant group. In the total sample, areas of interest were found on chromosomes 5q, 8p, and 17q. Data from the second genome-wide linkage study used a sample of 113 affected sibling pairs with PD and identified suggestive linkage on chromosomes 1, 9, 10, and 16, with no evidence implicating the regions containing *parkin, α-synuclein,* or *tau* genes. However, additional studies have shown that *α-synuclein* promoter region variants can influence the risk for PD.[107,108] Those alleles that increase α-synuclein expression lead to an increased risk for developing PD, an observation in line with the multiplications of the gene causing familial PD (see earlier). Similarly, variants that influence *parkin* expression can also modulate the risk for PD: in this case, those alleles that lower *parkin* expression enhance the risk for PD.[109] Mutations in the gene for glucocerebrosidase have been associated with an increased risk for PD among Ashkenazi Jews.[110] Glucocerebrosidase deficiency causes type 1 Gaucher's disease. Thirty-one of 99 Ashkenazi PD patients had one or two mutant alleles of the glucocerebrosidase gene (GBA), and 95 of 1543 controls (Ashkenazi) were carriers. Those with GBA mutations had onset of their PD around age 60 years and clinical features typical of idiopathic disease.

Genetic Causes of Parkinsonism

Several disorders that include parkinsonism in their phenotype have been characterized at the genetic level (Table 71–2). The frontotemporal dementias are discussed in detail in Chapter 73, the dystonias in Chapter 35, Huntington's disease in Chapter 67, Wilson's disease in Chapter 108 and the inherited ataxias in Chapter 68, so these will be discussed only briefly here.

TABLE 71–2. Secondary Familial Parkinsonism

- PSP, CBD—tau H1 haplotype
- FTDP-17 complex—tau mutation
- X-linked parkinsonism-dystonia (Lubag)
- Spinocerebellar ataxia (SCA 2) in Chinese—ataxin 2
- SCA 3/MJD—ataxin 3
- Fragile X mental retardation—CGG repeat in FMR-1 gene NB premutations
- Wilson's disease—P-type ATPase
- Hallevorden-Spatz syndrome—PANK2
- Dopa responsive dystonia—GTP cyclohydrolase 1
- Dystonia-parkinsonism—Na-K pump mutation

The frontotemporal dementias and parkinsonism linked to chromosome 17 (FTDP-17) usually have onset in the fifth decade, although the age range is wide (25 to 75 years). Symptoms are of gradual onset and include motor dysfunction in the forms of parkinsonism, behavioral, and personality disorders and cognitive decline.[111] Patients may exhibit apathy, depression, aggression, disinhibition, obsessive-compulsive disorder, executive dysfunction, and nonfluent aphasia. Patients and families tend to fall into either the predominantly parkinsonian or dementia types. Pathological examination shows severe frontotemporal atrophy and degeneration that includes the substantia nigra and the basal ganglia. There are tau accumulations in the remaining neurons and glia. FTDP-17 is autosomal dominant and is due to mutations in the *tau* gene. Although the genotype-phenotype relationship is relatively loose, those with the parkinsonism predominant form more commonly have exon 10′ or 5′ mutations.

Certain of the spinocerebellar ataxias (SCAs) are associated with parkinsonism and indeed may even manifest with this feature. SCA2 dopa-responsive parkinsonism is most often observed in the Chinese Asian population.[112,113] Patients may have asymmetrical disease; a resting tremor and the presence of ataxia and abnormal eye movements may make differentiation from other parkinsonian disorders difficult if genetic testing is not performed. Imaging with fluorodopa PET has produced variable results from changes typical of those seen in PD[114] to severe involvement of the caudate.[115] The demonstration of an abnormally expanded CAG repeat in the *ataxin-2* gene confirms *SCA2*. *SCA3* (Machado-Joseph disease) mutations in conjunction with parkinsonism have been found most often in Caribbean populations.

Fragile X mental retardation complex is a common cause of mental retardation. It is an X-linked disease caused by an abnormal CGG expansion in the *FMRI* gene, which results in reduced gene expression. Intermediate length repeats can be a cause of tremor-ataxia parkinsonism in men. About 60% of these patients have a postural tremor, ataxia, autonomic dysfunction, impaired cognition, and symmetrical parkinsonism.[116,117]

Patients with very large expansions of CAG repeats in the *huntingtin* gene can present with juvenile-onset Huntington's disease, known as the Westphal variant. The predominant features are those of bradykinesia and rigidity with little, if any, response to levodopa.

Dystonia in association with parkinsonism is seen in a number of genetic diseases. X-linked dystonia parkinsonism was first reported in men from an island in the Philippines who

had early onset of action tremor, dystonia, blepharospasm, and parkinsonism in 40% (Lubag) with poor response to levodopa. This disease is referred to as DYT3.[118] Rapid-onset dystonia parkinsonism (DYT12) is an autosomal dominant disorder associated with bulbar features including dysarthria and dysphagia, dystonia, postural instability, and bradykinesia. Symptoms progress rapidly over hours and may be precipitated by physical or emotional stress. There is usually a poor response to levodopa. Mutations in the *ATP1A3* gene that encodes a subunit of the sodium-potassium channel have been described in this disorder.[119]

Mitochondria have their own DNA, and the mitochondrial genome encodes 13 proteins of the oxidative phosphorylation system in addition to 2 ribosomal and 22 transfer RNAs. The discovery of complex I deficiency in PD substantia nigra (see later) raised the possibility that the mutation of genes (nuclear or mitochondrial) encoding complex I subunits might be involved in determining the enzyme's defective activity. As mitochondrial DNA (mtDNA) is inherited in a strictly maternal pattern, if there were full penetrance of such a mtDNA gene defect, mitochondrial inheritance should be identifiable in pedigrees with parkinsonism. Such maternal inheritance has been described in PD[120] but appears rare. However, it is known that 40% of patients with proven mitochondrial diseases and mtDNA mutations present as sporadic cases. Thus maternal inheritance is not a sine qua non of mtDNA gene defects. However, molecular genetic investigations of mtDNA have so far been unable to identify any specific mutation that clearly co-segregates with PD.

Studies using age-matched controls found no increase in the 5-kilobase mitochondrial deletion mutation in PD substantia nigra.[121] Several studies have sequenced mtDNA in PD, but these have all used unselected patients in terms of their complex I activity.[122,123] Although some reports have suggested an increased frequency of certain mtDNA polymorphisms in PD, this has not been replicated in all studies.[124-128] Two studies have demonstrated a relationship between mtDNA haplotypes and the risk for developing PD. The first showed a reduced risk for PD in individuals with haplotypes J and K,[129] and the second, a 22% decrease in PD in those with the UKJT haplotype cluster.[130] In contrast, a smaller study reported an increased risk for PD with haplotypes J and T.[131]

Mutations in the gene for mtDNA polymerase gamma (*POLG)* have been demonstrated in patients with progressive external ophthalmoplegia and parkinsonism. Autosomal dominant or recessive inheritance of progressive external ophthalmoplegia with age at onset ranging from 10 to 54 years was followed some years later (range, 6 to 40 years) by the development of an asymmetrical, levodopa-responsive bradykinetic rigid syndrome together with resting tremor in some patients. Additional features included variable limb, pharyngeal or facial weakness, cataracts, ataxia, peripheral neuropathy, and premature ovarian failure.[132] Muscle biopsy demonstrated ragged red, cytochrome oxidase–negative fibers in all patients with multiple mtDNA deletions on Southern blotting. Symmetrically reduced striatal 18-fluorodopa PET was seen in two patients. Brain histology was available on an additional two patients; both showed severe loss of substantia nigral dopaminergic neurons but without the development of Lewy bodies or other synuclein aggregates. Four families had the same A2864G mutation inherited in autosomal fashion in three and with a founder effect in the fourth. Mutations in the exonuclease or polymerase portions of the gene were identified in the autosomal recessive families. Another patient with autosomal dominant progressive external ophthalmoplegia parkinsonism and an A2492G mutation has been reported.[133]

Environmental Factors

Several studies have sought to define the environmental contributions to the etiology of PD. A rural residency appears to increase the risk of the development of PD and, in particular, young-onset PD.[134-136] However, this finding has not been confirmed in all studies.[137] Rural living is associated with farming and pesticide use, and an association with the agricultural industry has been found with increased incidence in PD patients.[138-140] In addition, another lifestyle study showed increased herbicide exposure in patients with PD.[141] Organochloride pesticides were identified as risk factors in a German case-control study[142] with the offending agent being identified as the organochloride dieldrin, which was found in 6 of 20 PD brains and none of 14 control brains.[143] Another study identified dithiocarbamates as a risk factor for PD,[137] a compound that has also been shown to enhance 1-methyl 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity.[144] Some studies have found that the significant association of PD with farming as an occupation cannot be accounted for by pesticide exposure alone.[139] Another rural factor that has been linked to PD is the consumption of well water,[145] although this may simply be further evidence in support of herbicides or pesticides as etiological factors for PD.

Carbon monoxide is a common environmental pollutant that may also play an important role in cell signaling. Acute carbon monoxide poisoning results in the complexing of carbon monoxide with the ferrous iron, protophorphyrin IX, and this prevents the carriage of oxygen. In addition, carbon monoxide is a potent inhibitor of cytochrome oxidase (complex IV) of the mitochondrial respiratory chain. Survivors of carbon monoxide poisoning have developed parkinsonism within a few days or weeks of exposure.[146] The affected patients show necrosis of the globus pallidus on computed tomography scanning and magnetic resonance scanning.

Pyrethroid pesticides, when administered parenterally to rodents, cause a reduction in tyrosine hydroxylase–positive dopaminergic neurons in the nigrostriatum and an increase in dopamine transporter and brain-derived neurotrophic factor expression.[147-150] These results indicate that commonly used pesticides can cross the blood-brain barrier and induce damage to the basal ganglia. Rotenone, a pesticide commonly used in the United States, when infused into rodents, can result in degeneration of nigrostriatal neurons and the formation of α-synuclein–rich Lewy-like inclusions.[151] Paraquat, a widely used herbicide, has been shown to increase α-synuclein fibril formation in vitro in a dose-dependent fashion and to increase α-synuclein protein expression in mice with the reversible development of aggregates in substantia nigra dopaminergic neurons.[152] Anonnacin, a component of sour-sop in the Caribbean, has been shown to produce a PD-like phenotype in humans and nigrostriatal loss in animals.[153] MPTP, a meperidine analog designer drug, is known to produce parkinsonism in humans, other primates, and rodents through uptake and conversion mechanisms that target the nigrostriatal pathway,[154] It is noteworthy that these agents result in inhibition of

mitochondrial NADH CoQ reductase (complex 1) and are free radical generators, features of direct relevance to idiopathic PD.

Manganese is a constituent of several pesticides and herbicides as well as being an anti-knock additive to lead-free petrol. Manganese is neurotoxic to the basal ganglia and produces a parkinsonian syndrome with damage predominantly to the globus pallidum. There have been numerous reports of manganism developing among individuals exposed to manganese dioxide ore, usually by inhalation of manganese dust. Exposure is typically chronic over 6 months to 16 years, and the onset of manganism is slow, beginning with apathy, muscle weakness and cramps, and general irritability. Progression occurs and is characterized by dysarthria and psychosis followed by severe rigidity, anarthria, and dystonia.[155] Manganese predominantly appears to affect the globus pallidus with sparing of the substantia nigra.[156] There has been interest in the potential for manganese containing steel to induce parkinsonian features in welders,[157] although this association is controversial. At present, it is not known if manganese-containing pesticides can induce PD.

Between 1917 and 1919, there was an epidemic of an influenza-like illness starting in Austria and France and spreading throughout Europe and North America. The illness was characterized by fever, headache, lethargy, and paralysis, particularly of the extraocular muscles. Following this, stupor, coma, sleep disturbance, and seizures could occur. Ocular gyric crises were seen in a high proportion of patients. Mortality was 30% to 40%, and parkinsonism developed in the majority of survivors over the next 10 years.[158,159] The specific agent causing encephalitis lethargica was never identified. Although there has been no outbreak of encephalitis lethargica since the 1920s, infection as a cause for PD has still attracted some attention. There are numerous anecdotal reports of infections, particularly encephalitis, being associated with parkinsonism. These include a wide variety of viruses, bacteria (including *Borrelia burgdorferii* [Lyme disease]), and even fungi, such as *Cryptococcus* or *Aspergillus*. However, there is no evidence to suggest that any of these are relevant to the vast majority of patients with idiopathic PD. For instance, patients who develop PD before the age of 40 have no greater history of central nervous system infection than do patients who develop the disease over the age of 60. Intrauterine exposure to, for instance, the influenza viruses pandemic from 1890 to 1930 has not been supported by any association with year of birth.[160] Searches for viral particles of antigens within the brains of patients with PD have not proved rewarding.[161]

Two environmental factors are recognized to lower the risk for PD: cigarette smoking[162] and coffee drinking.[163] The mechanisms through which they can reduce risk are not known. Coffee drinking appears more protective for men, so it is possible that there is an interaction with endocrine factors. There is evidence of active inflammatory change in the substantia nigra at the time of death in PD, with microglial activation, and expression of proinflammatory cytokines.[164-166] The role of this inflammatory change is unknown but has been believed to be relevant to pathogenesis and neuronal damage. Similar changes have been seen in AD brain and prompted retrospective analyses that subsequently demonstrated the potential for anti-inflammatory agents to reduce the risk for AD, although this effect remains controversial.[167,168] A similar study in PD has also shown that use of a nonsteroidal anti-inflammatory drug two or more times per week can produce a 45% lower risk for PD.[169]

PATHOGENESIS

Several biochemical abnormalities have now been identified in PD substantia nigra. These include abnormal iron accumulation, alteration in the concentration of iron binding proteins, evidence for increased oxidative stress and oxidative damage, and mitochondrial complex I deficiency. There is also evidence of increased nitric oxide formation and the generation of nitrotyrosine residues within PD substantia nigra. Each of these factors may form part of the pathogenesis of nigral cell death as well as potentially being etiological factors in themselves. Several of these mechanisms have already been discussed in the section on genetic causes of PD above, given that the monogenic forms of PD appear to involve identical pathogenetic pathways that are seen in idiopathic PD.

Iron

High iron concentrations are found in control substantia nigra, globus pallidus and striatum. In PD, there is a 35% increase in substantia nigra iron levels.[170,171] Other degenerative diseases involving cell loss in the basal ganglia also showed increased iron in these areas, such as progressive supranuclear palsy and multiple system atrophy. These studies suggested that increased iron concentrations were a reflection of neuronal cell loss rather than any specific pathogenetic factor. High concentrations of iron were also found in macrophages, astrocytes, and reactive microglia in the PD substantia nigra.[172] One study, however, using x-ray microanalysis, found increased levels of iron in neuromelanin. In this respect, neuromelanin could again act as a toxic sink.[173] In contrast, another study found no difference in iron concentrations between melanized and nonmelanized cells in controls but a significant increase in the cytoplasm of dopaminergic neurons.[174] However, there was no apparent correlation between the high concentrations of iron and morphological alterations in the neurons that might suggest degeneration.

Iron is capable of catalyzing oxidative reactions that may generate hydrogen peroxide and the hydroxyl ion.

$$O_2 + Fe^{2+} \leftrightarrow O_2^{\bullet -} + Fe^{3+}$$

$$H_2O_2 + Fe^{2+} \leftrightarrow OH^{\bullet} + OH^{-} + Fe^{3+}$$

Thus, if iron is available in a free and reactive form, it has the potential for exacerbating oxidative stress and damage. Iron is normally bound to ferritin, which exists in two forms, H and L. Most brain ferritin is in the H form. Three studies have now been undertaken on ferritin concentrations in PD brain. One used a polyclonal antibody predominantly against L-ferritin and found a significant decrease in the concentration of this protein in PD substantia nigra and other areas.[175] This decrease was not seen in other parkinsonian syndromes such as progressive supranuclear palsy or multiple system atrophy. Another study,[176] again using an antibody against mainly L-ferritin, found an increase in the number of ferritin-positive microglia in substantia nigra. This latter work used immunohistochemistry and therefore is not directly quantifiable. In addition, this study incorporated parkinsonian syndromes as well as idiopathic PD into the disease group (M. Youdim, personal

TABLE 71–3. Oxidative Damage in Parkinson's Disease

- Decreased PUFA
- Increased malondialdehyde
- Increased superoxide dismutase
- Increased lipid hydroperoxide
- Decreased reduced glutathione
- Increased OH^8dG levels
- Increased free iron
- Increased protein carbonyls
- Increased nitrotyrosine

communication). A third and more comprehensive study involved monoclonal antibodies against both L and H ferritin together with a double capture technique incorporated into an enzyme-linked immunosorbent assay study together with Western blotting studies of PD substantia nigra protein.[177] The results did not identify any significant difference in ferritin levels between control and PD substantia nigra. Thus, there are no hard data that ferritin levels are abnormal in PD. Indeed, ferritin has such a high iron binding capacity that the increase of iron noticed in PD brain may not require any increased buffering capacity from ferritin.

Oxidative Stress and Damage

There are several lines of evidence that suggest increased oxidative stress and oxidative damage to biomolecules in PD substantia nigra (Table 71–3).

1. Glutathione (GSH) in its reduced form is an important compound in antioxidant defense and in the repair of oxidized proteins. It is oxidized to its disulfide, GSSG. High GSH/GSSG ratios are maintained by glutathione (GSSG) reductase, which converts GSSG to GSH. There is evidence that GSH levels are decreased in PD substantia nigra.[178,179] Total GSH levels appear to be slightly lower in PD substantia nigra. This combination suggests enhanced free radical generation in the PD nigra.
2. Superoxide dismutase (SOD) exists in cytosolic (copper/zinc [Cu/Zn]) SOD and mitochondrial manganese (Mn) SOD forms and is important in dismutating superoxide ions. Thus, levels of this enzyme are indicative of superoxide generation. Both copper/zinc and manganese SOD appear to be increased in PD substantia nigra.[180,181] High levels of copper/zinc SOD are expressed at the mRNA level in control and PD nigral pigmented neurons.[182,183] Taken together, these observations suggest that PD nigral neurons in particular are exposed to increased superoxide generation.
3. Levels of polyunsaturated fatty acids,[184] malondialdehyde, and hydroperoxides are increased in PD substantia nigra. These are the products of free radical damage to lipid membranes and imply oxidative damage in PD. Free radical damage to DNA produces intracellular 8-hydroxydeoxyguanosine. Elevated concentrations of this product are seen in PD in the nuclear DNA and particularly in the mtDNA fractions from patients with PD.[185] Levels of these products are also particularly high in control brains in the substantia nigra and striatum, confirming that, even in controls, this area of the brain is a site of high oxidative stress.

The free radical gas nitric oxide ($NO^{\bullet}$) is present in many tissues, including the central nervous system. $NO^{\bullet}$ is generated by the conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). At least three NOS isoforms are recognized and are all expressed within the brain. $NO^{\bullet}$ acts as an atypical molecular messenger but at higher concentrations may have a toxic role and be implicated in the neurodegeneration that occurs in PD. As a free radical, $NO^{\bullet}$ could potentially contribute to dopaminergic neuronal death by mechanisms such as increased lipid peroxidation, release of iron(II), and damage to DNA. It can also inhibit a number of enzymes such as cytochrome *c* oxidase and superoxide dismutase and affects mitochondrial function by inhibiting complexes II, III, and IV. Animal studies have implicated $NO^{\bullet}$ in nigrostriatal neuronal loss. In addition to its possible neuroprotective effect with regard to 1-methyl-4 phenylpyridinium (MPP^+) toxicity, 7-nitroindazole (7-NI) also protects in the methamphetamine animal model of PD.[186] NOS activity is at its highest in the nigrostriatal system in nonhuman primates and humans. Attempts to demonstrate altered levels of $NO^{\bullet}$ in the brains of PD patients have been inconclusive with both decreased and increased levels of cerebrospinal fluid nitrate, a marker of NOS activity, being seen.[187-189]

Mitochondrial Dysfunction

The first link between mitochondria and PD was made in 1989 when a defect in the activity of respiratory chain protein complex I was identified in substantia nigra from patients with PD.[190,191] This study has been expanded over the years, and results to date show that there is a specific defect of approximately 35% complex I deficiency in PD nigra.[177] This defect in complex I activity in PD brain does not affect any other part of the respiratory chain. In addition, no defect in mitochondrial activity has been identifiable in any other part of PD brain, including the caudate putamen, globus pallidus, tegmentum, cortex, cerebellum, and substantia innominata.[192]

Following the report of complex I deficiency in PD substantia nigra, respiratory chain abnormalities were described in skeletal muscle mitochondria from PD patients. This particular area has proved very contentious, with several groups either describing similar defects or no abnormality whatsoever (see Schapira[193] for review). Two magnetic resonance spectroscopy studies on skeletal muscle mitochondrial function in PD have shown conflicting results.[194,195] Finally, mitochondrial complex I deficiency was also identified in platelet mitochondria of PD patients.[196-198] In contrast to skeletal muscle, there is a consensus among several laboratories that complex I deficiency does exist in PD platelet mitochondria. The majority of studies, however, suggest that this deficiency, as least based on a group-to-group analysis, is modest (about 20% to 25%) (see Schapira[193] for review). The complex I deficiency in PD lacks the sensitivity to allow its use as a biomarker of PD.

The discovery of complex I deficiency in PD and the role of mitochondria in PD has been enhanced by the subsequent identification of mutations in genes encoding mitochondrial proteins, such as *PINK1* and *DJ1*, as causes of autosomal recessive PD, and by the mitochondrial abnormalities associated with *α-synuclein* and *parkin* expression (see earlier). Furthermore, the environmental toxins causing parkinsonism identified so far are all mitochondrial inhibitors of complex I, such as MPTP, rotenone, and annonacin.

CLINICAL FEATURES

Presymptomatic

Epidemiological studies have been able to identify a number of clinical features that may predate the clinical diagnosis of PD by several years. In some part, these represent "risk" factors, but they also reflect known pathological changes that are believed to represent early PD.

Olfactory dysfunction is common in PD and eventually affects up to 90% of patients.[199] It has been suggested that hyposmia may be a preclinical marker for PD,[200,201] and olfactory deficits have been reported in asymptomatic relatives of patients with PD, some of whom subsequently developed PD.[202,203] A prospective study involving 361 asymptomatic relatives of PD patients identified 40 with hyposmia.[9] Within 2 years of follow-up, 10% of this subgroup had developed PD and another 12% had detectable presynaptic abnormalities on their dopamine transporter SPECT scan. No relative with normal smell had an abnormal SPECT scan or developed PD. It is tempting to relate these findings to Braak's findings of Lewy body distribution in the olfactory nucleus in stage 1. Olfactory dysfunction has also been reported in diffuse Lewy body disease and multiple system atrophy. Vascular parkinsonism, cortocobasal degeneration, progressive supranuclear palsy, and *parkin*-associated PD usually have intact olfactory function.[204-206]

Rapid eye movement (REM) behavior disorder (RBD) is a common sleep disorder in PD. It is characterized by loss of the normal skeletal muscle atonia during REM sleep, thus enabling patients to physically enact their dreams, which are often vivid or unpleasant.[207-210] Vocalizations (talking, shouting, vocal threats) and abnormal movements (arm/leg jerks, falling out of bed, violent assaults) are commonly reported by bed partners. In PD, up to one third of patients meet the diagnostic criteria of RBD.[207,208] RBD appears to frequently precede the development of motor signs of PD and longitudinal data that suggest that RBD heralds the onset of motor symptoms in up to 40% of PD patients.[211,212] In patients with isolated RBD, imaging studies have indicated a small but significant reduction in striatal dopaminergic uptake that may suggest preclinical PD.[213,214] The anatomical basis of RBD is believed to involve the pontomedullary area resulting from degeneration of lower brainstem nuclei like the pedunculopontine and subceruleal nucleus; this area is consistent with Braak stages 1 and 2.

Constipation often precedes the diagnosis of PD.[215-218] A prospective study of 7000 men for 24 years assessed *inter alia* for bowel habits found that those with constipation (less than one bowel movement per day) had a threefold risk of subsequently developing PD.[219] The mean interval between the administration of the bowel questionnaire and the development of PD was 10 years. Colonic dopaminergic neurons degenerate with Lewy body formation in PD, although constipation does not respond well to dopaminergic treatment.[220-222]

Motor Features

The typical early motor features of PD are bradykinesia, rigidity, and tremor. Postural instability, along with several additional motor and nonmotor symptoms, generally develop later in the disease.

Bradykinesia manifests in many ways, including a difficulty or delay in initiating voluntary movement, multitasking, or undertaking rapid motor tasks in sequence. A poverty of movement becomes evident, especially to family and friends. This may be represented by a reduction in spontaneous gestures, decreased facial movement, and blinking. Involvement of the limbs may be seen with impaired fine movements of a hand and in the dominant hand leads to progressive micrographia. There are problems with fastening buttons or a brassiere, tying laces, or using a screwdriver. The patient's gait becomes slow, small stepped, and shuffling, with the patient sometimes "chasing his own center of gravity." The arm on the affected side does not swing as much as the contralateral arm. The patient may complain of difficulty turning over in bed or rising from a chair. Freezing usually occurs later in the course of PD, but some patients experience "gait ignition failure," especially when approaching a doorway. Observation of the patient's gait can reveal important features that raise the clinician's suspicion of a diagnosis of PD. Physical examination for bradykinesia will evaluate rapid alternating movements and, in idiopathic PD, show asymmetry of speed, amplitude, and rhythm in the early stages. Examples of helpful maneuvers include finger or heel tapping, pronation-supination of the outstretched arms, and rapid flexion-extension of the extended fingers at the metacarpophalangeal joints.

Rigidity represents an increase in tone that is present throughout the range of movement and is independent of the speed at which the limb is moved. The tremor of PD may superimpose on rigidity to produce cog-wheeling, and this phenomenon may be absent if there is no tremor. Examination of the wrist with gentle flexion-extension movements is the best means to elicit cog-wheeling, and this can be repeated at the elbow. Rigidity affects the patient's posture, producing a flexion at most joints including the spine, and this produces the simian posture typical of PD. An extreme form of this is known as camptocormia.[223] Postural abnormalities also affect the distal limbs with extension of the fingers and flexion of the metacarpophalangeal joints or dorsiflexion of the great toe (striatal hand or toe).

The development of an asymmetrical intermittent resting tremor at 4 to 6 Hz is estimated to be a manifesting feature in 70% of PD patients. In addition, there is often a higher frequency (about 12 Hz) small-amplitude postural tremor.[224] The resting hand tremor is referred to as "pill-rolling" in the style of the pharmacists of the nineteenth century, who would prepare their tablets by hand. A tremor may affect other parts including the foot or leg (in which it may first manifest), lips, jaw, and tongue.[225] A head tremor, titubation, is more suggestive of essential tremor. The resting tremor is exacerbated by physical or emotional stress and can in the early stages be voluntarily inhibited for short periods. The tremor usually becomes bilateral after about 5 to 6 years, although the first affected side most often remains the more severe.[226]

Nonmotor Features

The widespread and progressive neurodegeneration in the PD brain leads to the emergence of a variety of features that are collectively grouped under the title of nonmotor symptoms. These are predominantly, but not exclusively, the consequence of loss of nondopaminergic pathways (Table 71–4). The

nonmotor symptoms of PD range from cognitive problems such as apathy, depression, anxiety disorders, and hallucinations to fatigue, gait and balance disturbances, hypophonia, sleep disorders, sexual dysfunction, bowel problems, drenching sweats, sialorrhea, and pain. These symptoms are often the most troubling for patients and contribute significantly to morbidity and impaired quality of life.[227] Diplopia is a frequent symptom even in early PD, although the neurological basis is not known.

Abnormalities of sleep are common in PD and are the result of a combination of the natural consequences of aging, the underlying disease pathology,[228] motor and nonmotor complications,[229,230] and drugs.[231] Disordered sleep often results in excessive daytime sleepiness, and this in turn may be compounded by the sedative effect of dopaminergic drugs.[232] Excessive daytime sleepiness and involuntary dozing affects up to 50% of PD patients and may be preclinical markers.[233] In some, excessive daytime sleepiness has been linked to the development of sudden onset of sleep and a pattern reminiscent of narcolepsy with abnormal sleep latency period (<5 minutes) in 30% of PD patients. Polysomnographic studies have showed transition from wakefulness to sleep stage 2 within seconds without the sudden onset of REM sleep.[234,235] Following reports of road traffic accidents caused by "sudden irresistible attacks of sleep" in eight PD patients, a large body of research focused on the possible effects of dopaminergic drugs and disease progression and the occurrence of sudden onset of sleep.[232,236-238] The issue remains unclear, although is now regarded as part of the nonmotor complex of the disease progression in PD.[239]

Sexual and bladder dysfunction is common and occurs in both sexes. The dopaminergic treatment of PD may lead to increased sex drive, but the effects of the disease often result in impaired sexual performance.[240] Bladder abnormalities particularly cause problems at night with nocturia, which when associated with bradykinesia during nocturnal "off" causes considerable discomfort.

Pain is a frequent symptom in PD, and some patients present especially with shoulder pain. Pain, anxiety, akathisia, respiratory distress, depressive mood swings, and slowed and impaired thought are symptoms that may be experienced during "off" periods and that will respond, at least in part, to dopaminergic therapy.[241-243]

DIFFERENTIAL DIAGNOSIS

The diagnosis of PD is best predicted by the presence of an asymmetrical bradykinetic rigid syndrome with a resting tremor and a good response to levodopa.[244] The diagnostic specificity of these criteria is estimated at 98.6%, and sensitivity, at 91.1%.[245] However, many patients still present a diagnostic challenge, especially those who have no tremor or those with marked asymmetrical tremor but limited bradykinesia or rigidity[246] (Tables 71–5 and 71–6). Imaging studies on early PD patients recruited into neuroprotection trials indicate that approximately 10% have normal PET or SPECT scans.[247,248] The Parkinson-plus disorders, dementia with Lewy bodies, Wilson's disease, and tremor are covered in Chapters 72, 70, 108, and 33, respectively, and some of the additional diseases that may mimic PD have been discussed earlier. The clinical features of the main disorders that require differentiation from PD are covered only briefly in the context of diagnosis (see Table 71–4).

TABLE 71–4. Symptoms Less Responsive to Dopaminergic Therapy

Motor	Postural instability
	Gait disorders
	Speech problems
Mental changes	Dementia
	Depression
	Anxiety
	Apathy
Autonomic nervous system dysfunction	Orthostatic hypotension
	Constipation
	Sexual dysfunction
	Urinary problems
	Sweating
Sensory phenomenon	Pain
	Dysesthesias
Sleep disturbances	Sleep fragmentation
	Sleep apnea
	REM behavioral disorder

TABLE 71–5. Differential Diagnosis of Parkinson's Disease

- Drug-induced parkinsonism
- Essential tremor
- Multiple system atrophy
- Progressive supranuclear
- Corticobasal degeneration
- Vascular parkinsonism
- Diffuse Lewy body dementia
- Post-encephalitic parkinsonism
- Wilson's disease
- Toxins, such as carbon monoxide, manganese

TABLE 71–6. Clinical Features of Parkinsonian Disorders

Multiple System Atrophy	Corticobasal Degeneration	Progressive Supranuclear Palsy
Cerebellar, pyramidal signs	Asymmetrical onset	Down gaze palsy
Anterocollis	Apraxia	Staring appearance
Early falls	Aphasia	Pseudobulbar features
Autonomic failure	Cortical sensory loss	Axial rigidity
Bulbar features	Alien limb	Early falls
Myoclonus	Dystonia	
	Focal myoclonus	

Drug-Induced Parkinsonism

Any dopamine receptor blocker has the potential to induce parkinsonism. In practice, the most common causes are the major neuroleptics, but drugs such as metoclopramide can also induce symptoms that may be confused with PD. A drug history is essential when considering PD. Clinical clues for drug-induced parkinsonism include symmetry and the absence of a resting tremor, although their presence does not exclude a drug cause. The presence of akathisia and orofacial dyskinesias supports a drug cause.[249] Withdrawal of the drug may result in remission, although this can take months or years, and in some patients, the parkinsonism and related movement disorders are permanent.

Essential Tremor

Typical essential tremor comprises a bilateral usually symmetrical, visible, and persistent upper limb postural or kinetic tremor.[250] Bradykinesia, rigidity, and postural abnormalities are not present. The tremor of essential tremor is present at rest in only 10% of cases[251] but, when present or when asymmetrical, can cause difficulty with a distinction from PD, although such patients usually evolve to PD.[252] The presence of a head or voice tremor, a strong and usually autosomal dominant family history, and improvement with alcohol all favor a diagnosis of essential tremor. In contrast, clear asymmetry, the presence of bradykinesia or rigidity, and leg tremor support a diagnosis of PD.

Multiple System Atrophy

Multiple system atrophy is a multicentric neurodegenerative disease that includes degeneration of the SNc and hence clinical features that can mimic PD. However, multiple system atrophy patients exhibit additional symptoms that may be predominantly cerebellar or parkinsonian with autonomic failure.[253] Onset is similar in age to PD. The diagnosis of multiple system atrophy is supported by the presence of early cerebellar signs, autonomic failure such as bladder dysfunction or postural hypotension, early falls, pyramidal signs, myoclonus, bulbar features, pronounced anterocollis, and a rapid course. The response to levodopa is usually limited in degree and time,[254] although some patients can develop dyskinesias, particularly of the orofacial and cervical musculature; they are rare.[255]

Progressive Supranuclear Palsy

Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) typically manifests with gaze palsy, particularly of the vertical downward plane, a staring appearance, symmetrical parkinsonism, and pseudobulbar palsy.[256] Axial greater than limb rigidity and falls within the first year are suggestive of progressive supranuclear palsy.[257] Response to dopaminergic therapy is poor.

Corticobasal Degeneration

Corticobasal degeneration usually manifests as an asymmetrical disorder that may include abnormal limb posturing (alien limb), dystonic upper limb posturing with irregular jerks, cortical sensory deficits, primary progressive aphasia, apraxia, and parkinsonism. Tremor is uncommon; cognitive disturbance, particularly involving frontal lobe function, is often seen and frequently is the manifesting sign.[258] The disease is rapidly progressive, and there is no or only a very poor response to levodopa.

Vascular Parkinsonism

This is a diagnosis that can only be made with confidence in the clinic when there is evidence of widespread vascular disease and usually a history of stepwise progression. The clinical features are usually bilateral if not symmetrical; tremor is rare and gait abnormality is common. The latter manifests as a type of apraxia with a wide-based small stepping gait and freezing, so-called lower body parkinsonism.[259] There may be a mild to moderate response to levodopa.

Dementia With Lewy Bodies

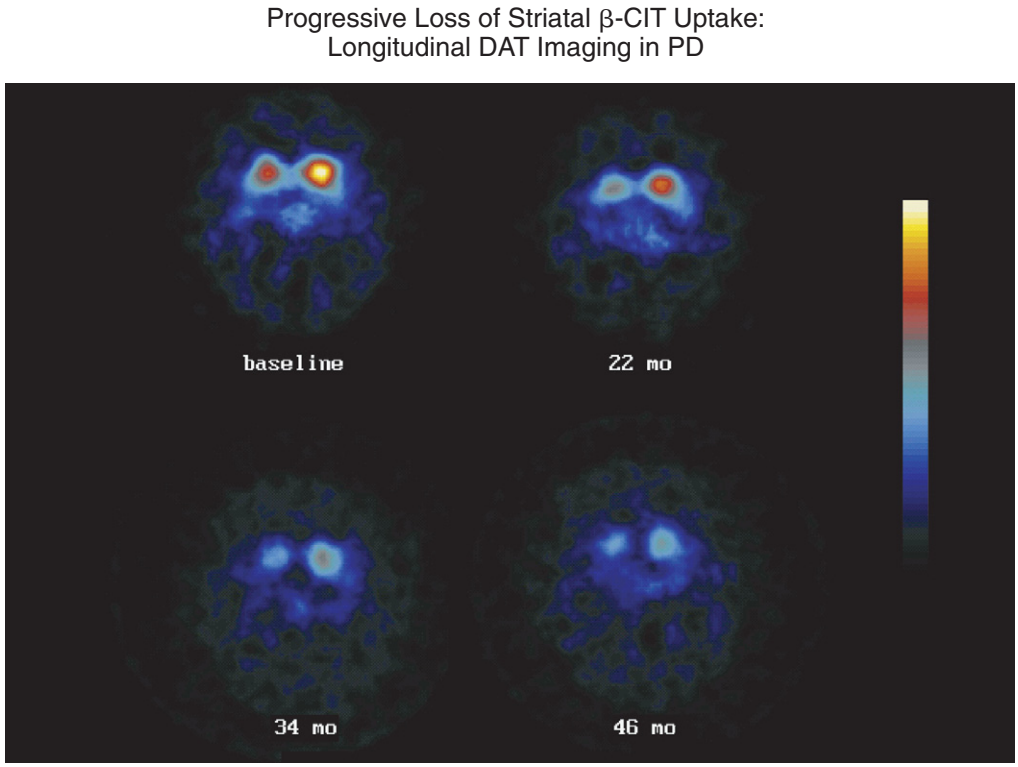
Dementia will develop in approximately 30% to 40% of PD patients, although it occurs at least 12 months (and usually longer) after the appearance of the motor features.[260,161] The clinical diagnosis of dementia with Lewy bodies will be based on the presence of a progressive dementia with fluctuating attentional and visuospatial components, hallucinations, and parkinsonism that usually develops within 1 year of the dementia.

INVESTIGATION

The diagnosis of PD remains essentially a clinical one with investigations mainly being used to exclude other diagnoses.

Imaging by computed tomography is normal in idiopathic PD. There may be superimposed changes of atrophy or cerebrovascular disease, although in the case of the latter this should not be so severe as to raise the diagnosis of vascular PD. CT is helpful in excluding normal pressure hydrocephalus or the rare case of tumor (usually benign) causing parkinsonian features. Magnetic resonance imaging in routine clinical practice has greater definition than CT but does not reveal any specific features for PD. However, magnetic resonance imaging may be useful in helping to differentiate PD from other parkinsonian syndromes. Patients with multiple system atrophy may demonstrate brainstem, cerebellar, and dentate atrophy with hyperintensity of the middle cerebellar peduncle, cerebellum, inferior olives, and pontine fibers producing the "hot cross bun" sign.[262,263] There may be putaminal atrophy or lateral putaminal hyperintensity (slit sign). Magnetic resonance volumetry is the most sensitive in distinguishing PD, multiple system atrophy, and progressive supranuclear palsy but is not widely available.[264]

Imaging with SPECT for the dopamine transporter has become increasingly available and can be used to differentiate PD from essential tremors or drug-induced PD, even in early disease. The signal in PD shows an asymmetrical reduction in transporter binding, particularly affecting the putamen (Fig. 71–3). It cannot distinguish PD from multiple system atrophy or progressive supranuclear palsy unless performed using voxel-based statistical parametric mapping.[265] SPECT can be



■ **Figure 71–3.** Sequential β-CIT uptake in Parkinson's disease. *(From the Parkinson Study Group: Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287:1653-1661. Copyright © 2002 American Medical Association. All rights reserved.)*

used to follow progression in PD, and it has been calculated that there is an annual loss of 8% to 11% of transporter signal in the early stages of PD.[266,267] However, as mentioned, approximately 10% of patients believed by neurologists to have PD have normal imaging on PET or SPECT. It remains unclear whether these patients could have been distinguished by more accurate clinical assessment. SPECT can also be used to image sympathetic cardiac innervation in PD with iodine-123–labeled metaiodobenzylguanidine. This shows postganglionic sympathetic denervation in PD patients, in contrast to retained innervation in multiple system atrophy or progressive supranuclear palsy, with 90% specificity and sensitivity, although the metaiodobenzylguanidine scan may be normal in early PD.[268,269]

PET scanning has provided valuable insights into the etiology and progression of PD and may emerge as an imaging marker for the latter together with SPECT. However, PET remains relatively limited in its availability and is unlikely to become used in routine practice in the near future. PET in PD has mainly used fluorodopa to demonstrate the integrity of the nigrostriatal system and, like SPECT for the dopamine transporter, shows asymmetrical loss affecting predominantly the putamen and less so the caudate.

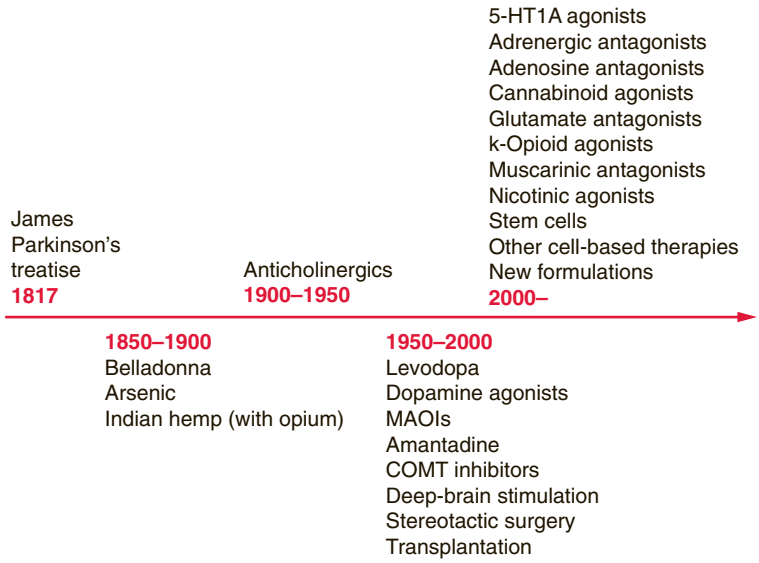
Transcranial ultrasound has attracted increasing attention.[270] This technique may demonstrate hyperechogenicity of the substantia nigra in over 90% of PD patients.[271] Additional studies are required to assess its reproducibility in other centers and its application to diagnosis and the differentiation of PD from other parkinsonian diseases.

Routine neurophysiological studies are not helpful in the evaluation of PD patients. Autonomic function testing is useful in identifying patients with multiple system atrophy. For instance, 50% of multiple system atrophy patients have a 30 mm Hg systolic or greater than 15 mm Hg diastolic fall in blood pressure with head-up tilt compared with 20% of PD patients.[246] Such drops in blood pressure occur earlier in the course of multiple system atrophy than in PD. The presence of sphincter denervation early in the course of disease favors multiple system atrophy, but none of the autonomic function studies accurately distinguishes PD from the parkinsonian syndromes, except progressive supranuclear palsy, in which autonomic function usually remains intact.[272]

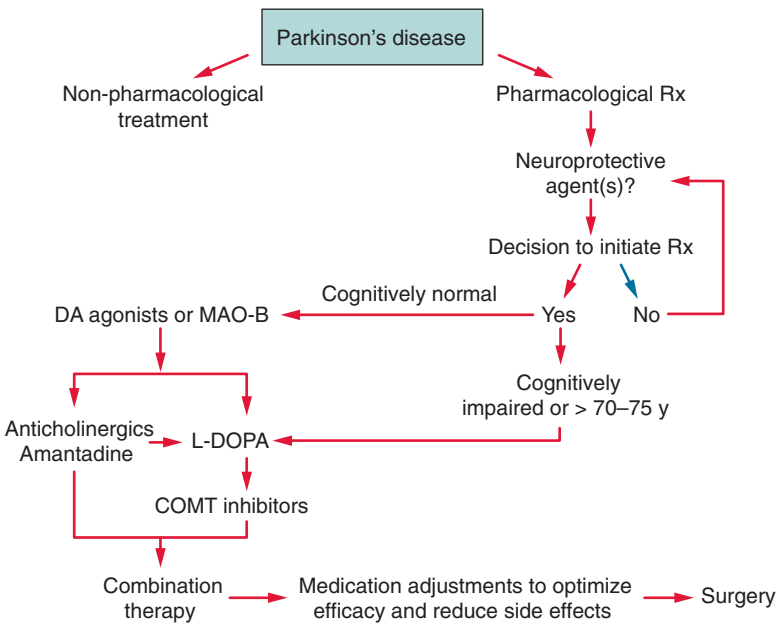
A good response to dopaminergic therapy is considered an integral part of the confirmation of the diagnosis of PD. It has been suggested that a challenge with levodopa or apomorphine might be a useful aid when there is uncertainty regarding diagnosis.[273,274] However, there are problems with interpretation, with 20% of parkinsonian multiple system atrophy patients having a positive response and positive responses may also be seen in progressive supranuclear palsy or vascular parkinsonism.[275] In assessing a patient's potential clinical response to levodopa, it is best to build up gradually to a dose of not less than 1000 mg for a duration of at least 2 months before an accurate view of responsiveness is obtained in the parkinsonian syndromes.

TREATMENT

The treatment of PD comprises several stages determined by the natural progression of the disease and by the complications that can develop as a consequence of drug use. Dopaminergic agents are the drugs that are most effective in



■ **Figure 71–4.** Evolution of the treatment of Parkinson's disease.



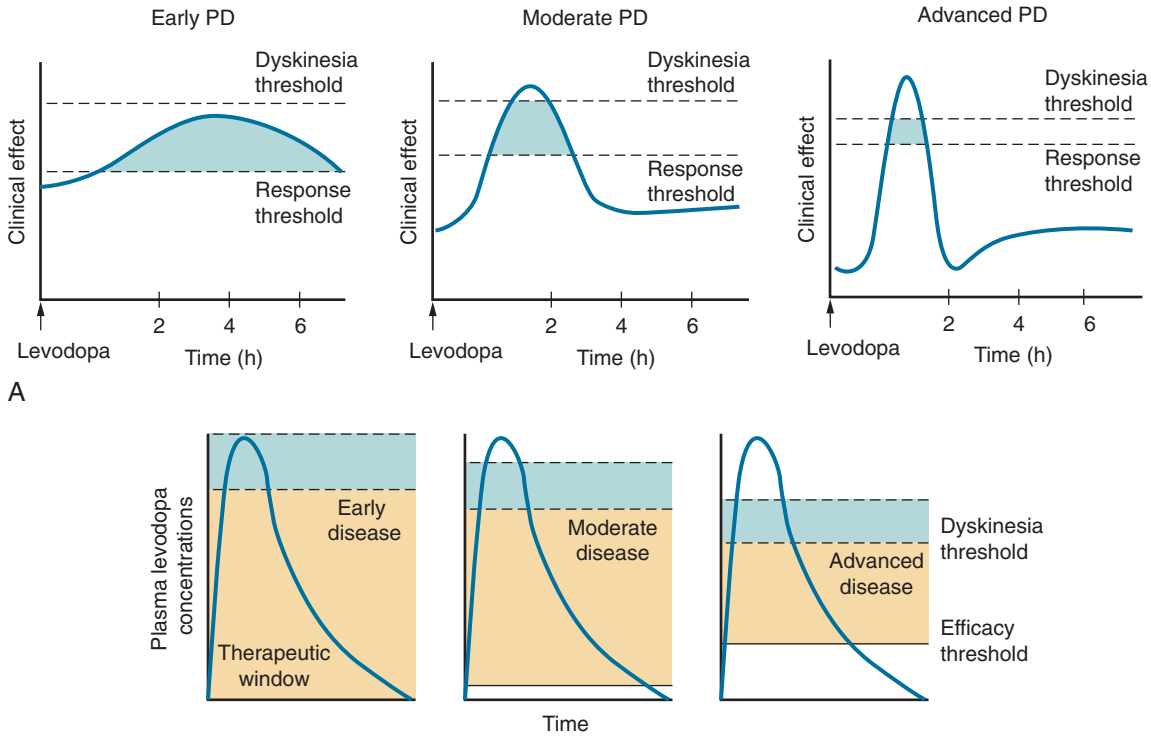
■ **Figure 71–5.** An algorithm for the treatment of Parkinson's disease.

improving the motor deficits of PD and include levodopa, dopamine agonists, and the monoamine oxidase B (MAO-B) inhibitors. Several new drugs will shortly be released and reflect the rapid increase in treatment options for PD (Fig. 71–4). An algorithm for the use of drugs in PD is suggested in Figure 71–5.

Levodopa

Levodopa was the first drug to be used to replace the dopamine deficiency of PD and remains the "gold standard" against which the efficacy of others are judged. Only 1% of an oral dose of levodopa is absorbed into the blood because of extensive metabolism in the gut and so it is routinely combined with a dopa-decarboxylase inhibitor to reduce peripheral metabolism that in turn both increases absorption to 10% and decreases side effects. Levodopa and other dopaminergic agents improve both the quality of life and life expectancy of PD patients.[276-278] It provides rapid and effective relief of bradykinesia, rigidity, and associated pain and improves tremor in many patients. Levodopa improves symptoms in early PD patients by 12 or 13 Unified Parkinson's Disease Rating Scale (UPDRS) points after 3 months.

Side effects are mainly gastrointestinal and consist of nausea, vomiting, and anorexia. These usually disappear over 2 to 3 weeks but may persist in some patients. They can be prevented or treated with domperidone 10 to 20 mg t.i.d., taken usually for a period of 2 to 4 weeks. Constipation, orthostatic hypotension, akathisia, hallucinosis, and daytime sleepiness are less common and are seen more often in the elderly population. Constipation, which can also be a consequence of PD itself, usually responds to standard treatments, including increased fluid, bowel training, timing of evacuation to the patient being "on," and increased fiber intake. Symptomatic orthostatic hypotension may respond to simple advice regard-



■ **Figure 71–6.** Treatment complications with levodopa. Early use of levodopa produces a long-duration response. With disease progression this shortens, and in clinical terms, patients begin to oscillate between being "on" with dyskinesias and being "off" (*A*). The pharmacokinetics of levodopa do not change with disease progression (*B*), but the progress of the disease and the changes induced by levodopa produce downstream changes that are believed to induce the dyskinesias.

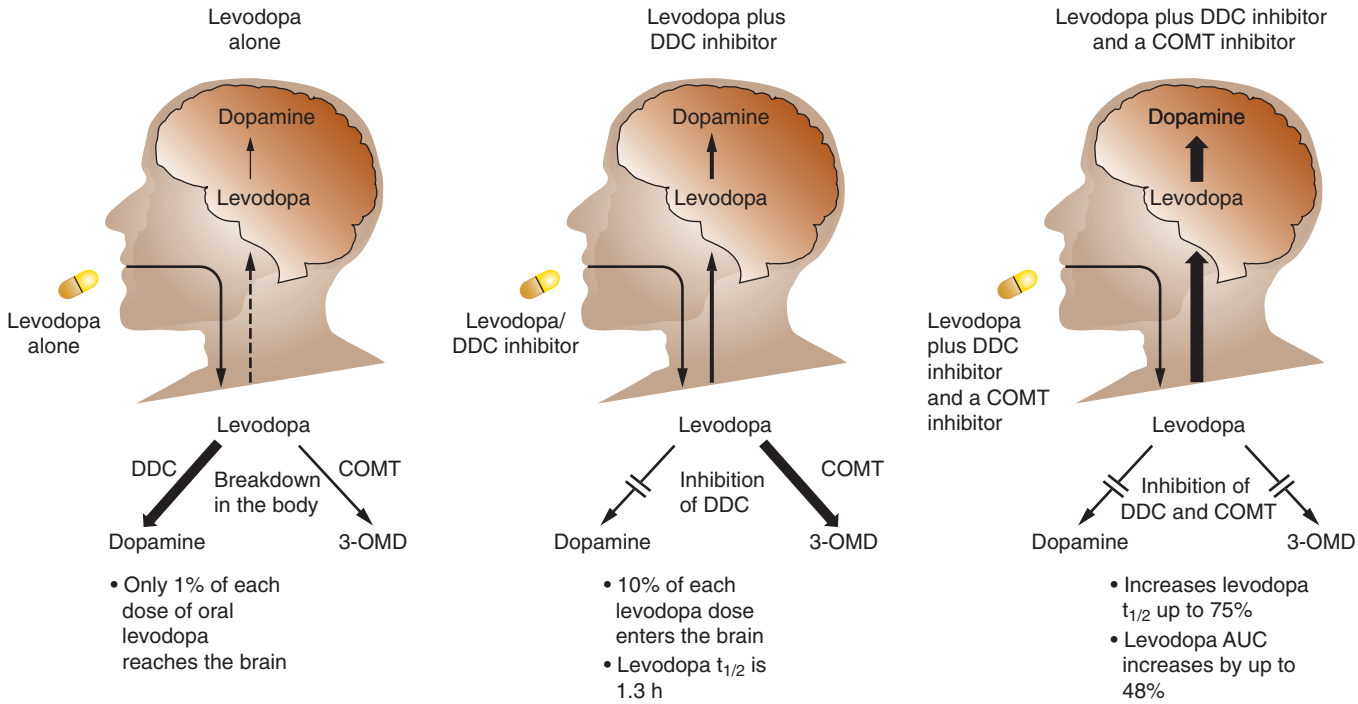
ing postural change, maintaining hydration, the use of pressure stockings, antidiuretic hormone, midodrine, or fludrocortisone. Akathisia, hallucinosis, and daytime sleepiness can all occur as a consequence of PD itself and dopaminergic treatments in general. If due to the latter, they may respond to a reduction in dose. Hallucinations in particular are recognized as a consequence of PD pathology that develop in the mid to advanced stages of the disease.[279] Some patients experience additional psychiatric effects from dopaminergic therapy, including obsessive traits, punding, and pathological gambling.[280-282] These problems usually respond to a reduction in dopaminergic therapy but sometimes require the use of antipsychotic medication of the type less likely to exacerbate PD.

Levodopa has a long-duration response in early disease that enables adequate symptomatic control with dosage schedules of three times daily (Fig. 71–6). Disease progression, however, erodes the usefulness of levodopa as 70% of patients develop motor complications within 6 years of initiation of the drug.[283,284] Wearing off effects frequently require modification of dosage and/or dose frequency or the introduction of additional or alternative therapies. Interestingly, so long as the plasma levodopa concentration is maintained, the clinical response will persist[285,287] and "wearing off" does not occur if the drug is given by continuous infusion.[288,289] A significant long-term complication of levodopa use is the development of dyskinesias. Dyskinesias develop at a rate of approximately 10% per annum, although this rate is much greater in young onset PD patients, of whom 70% will have dyskinesias within 3 years of levodopa initiation.[290] The mechanisms by which these motor complications develop are not completely understood, but pulsatile stimulation of dopamine receptors by short-acting agents, including levodopa, and the degree of striatal denervation have been implicated.[291] Dyskinesias may occur at the time of maximal clinical benefit and peak concentration of levodopa (peak dose dyskinesias) or appear at the onset and wearing off of the levodopa effect (diphasic dyskinesias). Motor complications can be an important source of disability for some patients who cycle between "on" periods, which are complicated by dyskinesias, and "off" periods, in which they suffer severe parkinsonism.

Thus, levodopa offers a rapidly effective means to treat the motor symptoms of PD with a tolerable early side effect profile but more serious long-term complications.

Catechol-*O*-methyl Transferase Inhibitors

The routine combination of levodopa with a dopa decarboxylase (DDC) inhibitor improves absorption but the majority of levodopa is still metabolized in the gut by catechol-*O*-methyl transferase (COMT), which produces 3-*O*-methyldopa. COMT inhibition therefore offers a strategy to increase levodopa absorption and improve kinetics (Fig. 71–7). Two selective COMT inhibitors are available for clinical use for the treatment of PD. These drugs exert profound influences on levodopa kinetics by increasing its bioavailability and elimination half-



■ **Figure 71–7.** The strategy of COMT inhibition.

life. This allows more stable levodopa plasma levels to be obtained via the oral route and, conceivably, more sustained brain dopaminergic stimulation to be attained.

Entacapone is a selective, reversible inhibitor of COMT. It does not cross the blood-brain barrier and acts primarily in the gut. Entacapone essentially increases both the peripheral and central availability of levodopa. The plasma elimination of a 200-mg oral dose of entacapone is 1 to 2 hours. The pharmacokinetics of entacapone, particularly its elimination characteristics, are similar to those of levodopa, allowing coadministration of these agents. The recommended dose of entacapone is a 200-mg tablet administered with each dose of levodopa/carbidopa, up to a maximum of 10 times daily (in Europe) and 8 times daily (in the United States). It should be noted that only the dose of levodopa should be titrated; the dose of entacapone administered with each dose of levodopa should remain the same (200 mg). Entacapone is effective in patients with wearing-off–type motor fluctuations and can produce an increase in "on" time and a reduction in "off" time by an average of 60 minutes per day.[292] The most common adverse effect seen with entacapone is dyskinesia, which reflects increased central dopaminergic activity. Reducing the daily levodopa dosage by about 25% may be necessary to minimize possible dopaminergic adverse effects. This reduction may be made at the time of entacapone introduction in those patients on more than 800 mg of levodopa daily or in those already with dyskinesias, but generally it is better to delay changing the levodopa dose until the patient's response can be evaluated. Physicians should be aware that dopaminergic adverse events generally occur within 24 hours of initiating entacapone and may require an immediate adjustment of the levodopa dosage. Entacapone may be combined with both standard and controlled-release formulations of levodopa/carbidopa and may be administered with or without food.

The introduction in 2003 of Stalevo, a combination of levodopa, dopadecarboxylase inhibitor, and entacapone, offered an opportunity to simplify the dosage regimen for patients on entacapone. Patients stable on levodopa and entacapone given separately can be converted straight over to the equivalent dose of Stalevo. Stalevo tablets should not be cut or crushed; only one should be taken at each dose time, and they must not be combined with additional entacapone.

Tolcapone (unlike entacapone) can cross the blood-brain barrier[293] and may produce some central COMT inhibition, although its clinical effect is likely to be minimal. A study in newly diagnosed, levodopa-naïve patients with PD failed to show any clinical efficacy with the introduction of tolcapone either alone or with selegiline.[294] Tolcapone has a similar half-life to entacapone; however, due to a greater bioavailability and smaller volume of distribution, tolcapone produces a greater inhibition of COMT and is required only on a three-times-daily regimen.[295] Although tolcapone is available now in both Europe and North America, its use is restricted by its potential to cause severe hepatic toxicity.[296] It should not be given to patients with impaired liver function, and those PD patients taking tolcapone require regular monitoring of hepatic enzymes. This effect on liver function is not seen with entacapone and probably reflects their differing potency in inducing mitochondrial permeabilization.[297] The use of tolcapone is generally limited to those patients who have failed to derive significant benefit from entacapone. Both entacapone and tolcapone can induce diarrhea, which is more common and may be severe and explosive with the latter drug.[298]

Dopamine Agonists

Several dopamine agonists are available for use in PD and fall broadly into two groups: ergot and non-ergot. Ergot agonists

include bromocriptine, cabergoline, lisuride, and pergolide, and non-ergot agonists include apomorphine, piribedil, ropinirole, and pramipexole. Bromocriptine, cabergoline, pergolide, pramipexole, and ropinirole have all been studied for monotherapy use in early PD,[299-308] as well as for adjunctive treatment in more advanced PD.[309-316] They have all demonstrated a significant beneficial effect on motor function and activities of daily living. Their side effect profile is similar to that of levodopa in terms of inducing dopaminergic related symptoms such as nausea, vomiting, and postural hypotension but are associated with a higher rate of peripheral edema, somnolence, and hallucinosis, particularly in the elderly. Somnolence with dopamine agonists is mainly seen during the early dose escalation phase, and patients should be warned of this and the rare but important side effect of sudden onset of sleep.[317] In patients with early PD (mean age, 61 years), hallucinosis also occurred more frequently during dose escalation but, like sedation, settled to a rate no higher than levodopa during maintenance.

The use of dopamine agonists is rarely associated with the development of pleural, pericardial, or peritoneal fibrosis.[318] A report has linked pergolide with fibrotic cardiac valvular disease[319] in a pattern similar to that seen with other agents that also stimulate the 5-hydroxytryptamine$_2$ receptor, including methysergide and fenfluramine. There are insufficient data at present to know whether this complication is associated with ergot agonists alone, all dopamine agonists, or all dopaminergic drugs and whether the effect is dose or time related or both. Until such time as additional information becomes available, vigilance is recommended and, when necessary, appropriate investigations (echocardiogram, chest radiography, and erythrocyte sedimentation rate) and referral to a cardiologist.

Dopamine agonist monotherapy can effectively control dopaminergic symptoms for a period of time. Long-term follow-up indicates that approximately 85%, 68%, 55%, 43%, and 34% of PD patients initiated on pramipexole or ropinirole are still controlled on monotherapy at 1, 2, 3, 4, and 5 years, respectively.[317,320,321] However, this is dependent on the agonist being used at an appropriate dose. Nevertheless, patients will require levodopa supplementation at some point during their disease. If used correctly, agonists can produce symptom control comparable with levodopa. Although the two monotherapy studies quoted earlier showed superiority for levodopa in UPDRS scores by up to 5 points, patients in the agonist arms had comparable quality of life scores and could have taken supplemental levodopa if the physician or patient believed it was required. The explanation for this discrepancy might be because the UPDRS score does not capture all the benefit that a patient might derive from a dopamine agonist, including possible nonmotor effects such as an antidepressive action.

Several trials have now confirmed that bromocriptine, cabergoline, pergolide, pramipexole, and ropinirole are associated with a significantly reduced risk for the development of motor complications in comparison with levodopa[303,307,320-322] (Fig. 71–8). In the pramipexole study, quality of life scores were also equivalent for the 4-year period.[317] This implies that the patients were equally well controlled on agonist (with levodopa supplementation when required) or levodopa alone. Of course the levodopa group had more dyskinesias, but at 4 years these did not intrude significantly into patient quality of life or start to limit treatment options for motor control.

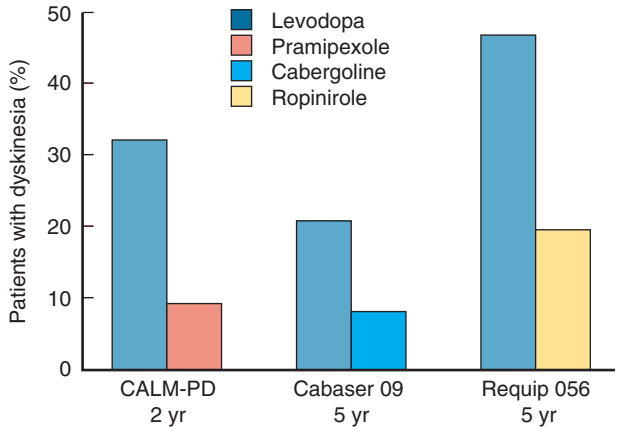


Figure 71–8. Dopamine agonists delay the development of dyskinesias. *(Results are from Rinne UK, Bracco F, Chouza C, et al: Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009. Study Group. Drugs 1998; 55[Suppl 1]:23-30; Rascol O, Brooks DJ, Korczyn AD, et al: A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000; 342:1484-1491; and Parkinson Study Group: Pramipexole vs levodopa as initial treatment for Parkinson disease. A randomized controlled trial. JAMA 2000; 284:1931-1938.)*

In conclusion, dopamine agonists provide effective control of PD-related motor symptoms, delay the onset of motor complications, delay the introduction of levodopa, enable a lower dose of levodopa to be used, and, in the case of pramipexole and ropinirole in particular, offer the possibility for some disease-modifying effect.

Monoamine Oxidase-B inhibitors

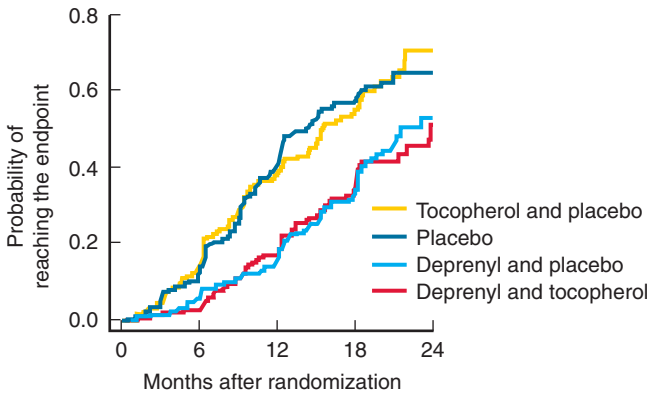
Two compounds of the propargylamine group, selegiline (deprenyl) and rasagiline, both of which are irreversible MAO-B inhibitors, have demonstrated symptomatic effect in PD patients and neuroprotective efficacy in the laboratory.

Selegiline has been available for several years and showed benefit as adjunctive treatment for PD. The DATATOP study was a prospective double-blind, placebo-controlled trial that investigated the effect of selegiline 5 mg twice daily or 2000 IU vitamin E, or both, as putative neuroprotective therapies.[324] The time until PD patients required levodopa was used as the primary endpoint. No beneficial effect of vitamin E was detected at the dose given. In contrast, selegiline significantly delayed the need for levodopa compared with placebo, an effect consistent with slowing of disease progression (Fig. 71–9). However, selegiline was also found to exert a mild symptomatic effect that confounded interpretation of the study. In an attempt to avoid this confound, selegiline was compared with placebo using as the primary endpoint, the change in motor score between an untreated baseline visit and an untreated final visit performed after 12 months of treatment and 2 months of study drug withdrawal.[325] In this study, PD patients treated with selegiline had less deterioration from baseline than those receiving placebo, again suggesting that selegiline might be neuroprotective. In a long-term follow-up study of the DATATOP cohort, levodopa

patients who had been taking selegiline for 7 years, compared with those who were changed to placebo after 5 years, had a significantly slower decline and less wearing off, on-off, and freezing but more dyskinesias than in those on deprenyl.[326] Although one study did suggest that selegiline use might be associated with excess mortality, a large meta-analysis indicates that no such effect is evident and confirms the clinical efficacy of this drug in PD with the total UPDRS score being improved by 2.7 points at 3 months.[327] There is no evidence at present that MAO-B inhibition itself delays the development of motor fluctuations other than through the delay in introduction of levodopa and an ability to use a lower dose.

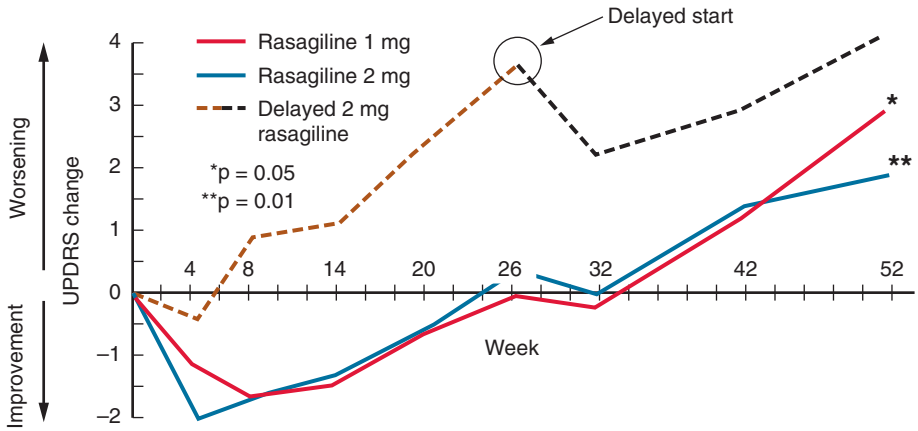
Rasagiline (*N*-propargyl-1-*R*-aminoindan) is a relatively selective irreversible MAO-B inhibitor. This selectivity is important in avoiding the "cheese effect" of MAO-A inhibitors. However, higher doses (greater than 2 mg/day) of rasagiline will begin to inhibit MAO-A and so should be avoided. Rasagiline is a propargylamine and so is structurally related to selegiline but is approximately 10 to 15 times more potent. It has good central nervous system penetration and a long half-life that allows a once-daily dosage schedule. Rasagiline is metabolized to aminoindan in contrast to selegiline, which is metabolized to metamphetamine. This difference may have clinical relevance in terms of side effect profile and the potential for disease modification (see later).

Rasagiline has been studied in patients with early PD[328] (Fig. 71–10). Patients with early PD were randomized to placebo or rasagiline (1 or 2 mg/day). In the placebo and rasagiline 1-mg and 2-mg groups, 81%, 83%, and 80%, respectively, were still on "monotherapy" at 6 months, and there were no statistical differences in the rates for either levodopa supplementation or patient withdrawal. At the end of the 6-month period, the 1-mg rasagiline group had an improved UPDRS score compared with a placebo of 4.2 units, and this was 3.56 for the 2-mg group. The degree of motor improvement over the 6-month period was comparable with that seen for selegiline in the DATATOP study[324] but not as great as that seen for dopamine agonists. There were no significant differences in the adverse event profile between the treatment arms and placebo. At 6 months, the two treatment arms were almost back to their respective baseline UPDRS scores. The initial 6-month period was extended by an additional 6 months.[328] Patients were continued on their original dose of rasagiline or, if on placebo, were given rasagiline 2 mg/day. Patients requiring additional dopaminergic therapy were prescribed either levodopa or a dopamine agonist. For the entire 12-month period, deterioration from baseline scores was 3.01, 1.97, and 4.17 UPDRS units for the 1-mg, 2-mg, and delayed 2-mg cohorts, respectively. Those given rasagiline 1 mg/day for 12 months compared with those on the 2-mg dose for only the last 6 months maintained a total UPDRS improvement of 1.82 UPDRS units. The 12-month rasagiline 2-mg group had a 2.29-unit improvement over the 2-mg 6-month group. There was no significant excess of adverse events in the rasagiline arms compared with the placebo arm.



■ **Figure 71–9.** The results of the DATATOP study. *(From the Parkinson Study Group: Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993; 328:176-183. Copyright 1993 Massachusetts Medical Society. All rights reserved.)*

Two studies have been published on the efficacy of rasagiline in PD patients already taking levodopa. The PRESTO trial investigated PD patients on stable levodopa with at least 2.5 hours of "off" (i.e., poor motor state).[329] Placebo decreased "off" time by 0.9 hour (15% of "off" time) and rasagiline 1 mg/day by 1.9 hours, equating to a 29% reduction in "off" time. Benefits were seen within 6 weeks of randomization and maintained throughout the 26-week study period. The improvement in "off" time was accompanied by a corresponding increase in "on" time, but 32% of the extra "on" time in the 1-mg group was troublesome with dyskinesia although this did not lead to any early terminations. The 1-mg rasagiline dose also resulted in significant improvements in the UPDRS score. The LARGO study investigated the effect of 1 mg/day rasagiline compared with entacapone or placebo in PD patients on stable levodopa but with at least 1 hour of motor fluctuations per day.[330] Placebo reduced "off" time by 0.4 hour, both rasagiline and entacapone decreased "off" time by 1.2 hours. There was a comparable and



■ **Figure 71–10.** Results of the TEMPO study. *(From the Parkinson Study Group: A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 2004; 61:561-566. Copyright © 2004 American Medical Association. All rights reserved.)*

significant increase in "on" time without dyskinesias of 0.8 hour with both drugs. These two studies demonstrate that once-a-day rasagiline (1 mg) significantly improves PD control in patients optimized on levodopa with or without additional therapy. Its efficacy is comparable with entacapone but probably less than that of dopamine agonists, which induce a 1- to 2-hour improvement in PD control.[314,315]

Other Drugs

Anticholinergics were used to treat the symptoms of PD prior to the introduction of levodopa. Relatively little data are available on their potency and tolerance. Clinical trials have shown a modest benefit for anticholinergics in improving bradykinesia and rigidity,[331-333] but this was at the expense of impaired cognitive function. Benztropine was equivalent to clozapine in producing a mild improvement in tremor.[334]

Amantadine produces mild and transitory improvements in PD symptoms, with benefits usually lasting 6 to 9 months.[335] Although some have suggested that in pure PD patients the effects are more long lasting.[336] It is generally considered unsuitable for monotherapy in PD and is mostly used as an adjunct. Improvements in bradykinesia and rigidity are generally of the same order of magnitude as anticholinergics, but their combination is additive.[337,338] Amantadine use is also limited by its potential to induce cognitive defects.

Initiation of Treatment

Treatment for PD is always tailored to the specific needs and circumstances of the patient. Traditionally, drug treatment has been initiated only when the patient's symptoms interfered significantly with their employment or social activities. The rationale for this was very reasonable: the treatments available were considered symptomatic only and incapable of modifying the course of the disease. Advances in our understanding of the pathophysiology and pharmacology of PD and the availability of new treatments for the disease have required reevaluation of this strategy.[340]

The clinical onset of PD motor features is directly associated with a series of functional changes in basal ganglia circuits and their target projections.[341] Basal ganglia output becomes abnormal and clinical features appear, when dopamine levels fall to less than 7% in MPTP-treated nonhuman primates.[342,343] The corresponding figure in humans is not known but may be around 20% to 30%. The estimated asymptomatic latent period of approximately 6 years[344] in idiopathic PD (and longer in familial PD) indicates the remarkable capacity for the basal ganglia to cope with progressively lower levels of dopamine, the compensatory mechanisms maintaining apparently normal motor function over the intervening years to diagnosis. These compensatory mechanisms include increased striatal dopamine turnover and receptor sensitivity, upregulation of striatopallidal enkephalin levels, increased subthalamic excitation of the globus pallidum pars externa, and maintenance of cortical motor area activation.[345,346] These observations, although neither completely defined nor understood, support the notion that declining dopamine levels during the early phase of PD put the basal ganglia level under stress. The onset of clinical symptoms denotes the point of failure to deal adequately with dopamine depletion. It might be that early correction of the basal ganglia functional abnormalities caused by dopaminergic

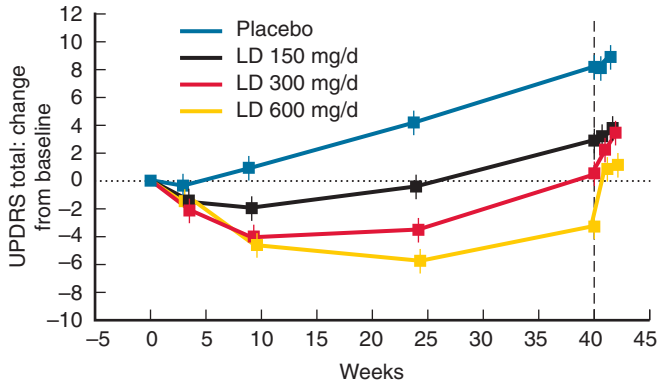


Figure 71–11. Results of the ELLDOPA study. *(From Fahn S, Oakes D, Shoulson I, et al: Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351:2498-2508. Copyright 2004 Massachusetts Medical Society. All rights reserved.)*

cell loss and dopamine deficiency is a means to support the intrinsic physiological compensatory mechanisms and both limit and delay the circuitry changes that evolve as PD progresses. Review of the outcomes of the DATATOP, ELLDOPA (Fig. 71–11), and TEMPO studies may support such a proposition.[340] In these studies, those patients who received effective symptomatic treatment earlier in the course of their PD fared significantly better clinically than those initiated on placebo even when, as in the case of TEMPO, they were switched to the active drug after only 6 months.

Given this, consideration of treatment initiation at the diagnosis of PD appears to be an increasingly viable and indeed attractive option for patients. Early restoration of basal ganglia physiology will support the compensatory events and delay the irreversible modification of circuitry that characterizes the clinical progression of PD. Such an effect may lead to lasting clinical benefit for the patient. However, dopaminergic treatment can be associated with unwanted side effects that may include gastrointestinal disturbances, cognitive problems, and sedation (see earlier). These need to be weighed against the symptomatic improvement that the patient will experience and the hypothetical long-term benefit outlined here.

Once an agreement has been reached between the physician and patient on the introduction of drug therapy, consideration needs to be given to the choice of drug to start. As emphasized earlier, this needs to be individualized to the patient. The following therefore represents a general view of initiation options. Those aged 70 to 75 years or younger, with no cognitive impairment and no significant comorbidity, should be considered for introduction of a dopamine agonist or a MAO-B inhibitor. The agonist will improve motor dysfunction more than an MAO-B inhibitor, but the latter is probably better tolerated and the choice between these will depend on the patient's degree of symptomatic dysfunction. For those patients over age 70 to 75 years, or alternatively, those with cognitive dysfunction or significant comorbidity, levodopa would be the drug of choice for the initiation of therapy.

Maintenance of Treatment

Most PD patients respond well to the initiation of dopaminergic therapy in small doses. However, some require regular uptitration of their dose before an adequate control of motor function is reached. This is particularly true of the dopamine

agonists that may need to be increased to, for example, 3 mg of pramipexole or 12 to 15 mg of ropinirole before there is a good response. Some patients will need these doses to be increased as their disease progresses. As indicated earlier, regardless of what drug is first used, PD patients will eventually require levodopa. This is most often introduced as a three-times-daily regimen, although the short half-life of the drug means that this falls well short of providing continuous dopaminergic stimulation. A higher frequency of administration would provide better symptom control and possibly less risk of the development of motor complications but needs to be balanced against a likely lower rate of compliance.

Motor Complications

The majority of PD patients will develop wearing off or dyskinesias at some point in the course of their disease. Although the use of dopamine agonists will delay the onset, once levodopa is introduced the risk for their appearance increases. It is possible that the initiation of levodopa with a COMT inhibitor might delay the onset of motor complications, but evidence for this is lacking at present. The development of dyskinesias is probably related to dose of levodopa[347,348] as well as duration,[349,350] so the continuation of the dopamine agonist or MAO-B inhibitor to limit the levodopa dose is beneficial.

Wearing off equates to the loss of effectiveness of a given dose of dopaminergic therapy and the emergence of the primary motor features of PD (i.e., bradykinesia and rigidity) that remain responsive to dopaminergic treatment. Patients recognize this as a return of symptoms prior to their next dose ("end-of-dose failure"), although some mistakenly associate it with the administration of the next dose given the medication's latency of effect. As noted, wearing off is eliminated by continuous administration of either levodopa or a dopamine agonist.[288,289,351] Although these methods are effective, they are not practical for the majority of patients. The simplest strategy is to increase the frequency of administration of levodopa, although this too may become difficult as dosage regimens increase to six or more times per day. Controlled-release formulations have proved disappointing with often little improvement in duration of response and problems with unpredictability of absorption and motor response. One open-label study demonstrated that the addition of cabergoline, a long-acting ergot dopamine agonist, to patients taking pramipexole or ropinirole, both non-ergots, resulted in improved motor control.[352]

The addition of a COMT or MAO-B inhibitor to levodopa significantly improves "off" time (see earlier) and is an easy and effective strategy for managing wearing off.[329,330,353]

Dyskinesias are typically choreiform, occasionally dystonic involuntary movements induced predominantly by exposure to levodopa or other short-acting dopaminergic drugs. At first, patients may be unaware of the movements, but they may be noticed by relatives or friends who are frequently more troubled by them than the patient. However, they progress with time and not only cause difficulty and embarrassment but also begin to restrict options for improving motor control. The impact of dyskinesias on quality of life is limited in the beginning. However, this changes as dyskinesias become more severe and options for motor control become limited.

The practical management of dyskinesias depends on the severity of the involuntary movements and their relationship to medication dosage schedule. They may be peak dose, biphasic, or random. Peak dose dyskinesias are related to high plasma concentrations of levodopa and can be managed by fractionating levodopa doses to avoid such peaks. This may or may not require an increase in the total daily dose. Alternative strategies include the introduction of a dopamine agonist if the patient is not already taking such an agent and if he or she remains a suitable candidate. Long-acting agonists are particularly useful in the management of dyskinesias, presumably due to their ability to provide more continuous dopaminergic stimulation while avoiding rapid fluctuations in receptor stimulation.[298] Biphasic dyskinesias occur when plasma levodopa concentration is rising or falling and are associated with generally lower plasma levodopa concentrations. They tend to be more stereotypical and repetitive and to involve the lower extremities. They are more troublesome to manage but may respond to higher levodopa doses designed to keep the plasma concentrations above a critical level.[354]

Amantadine has demonstrated efficacy in improving peak dose dyskinesias.[355-357] The effective dose is 200 to 400 mg/day in two divided doses. The severity of dyskinesias may be reduced by 24% to 56% and the effect sustained at 1 year.

The potential for the continuous parenteral administration of dopamine agonists or levodopa to improve or abolish motor fluctuations including dyskinesias has been discussed. Apomorphine infusions or duodenal infusion of levodopa offer significant benefits for select patients and can be considered an option prior to surgery.

Management of Nonmotor Complications

Depression and, to some extent, apathy (anhedonia) may respond to tricyclics such as amitriptyline or to selective serotonin reuptake inhibitors. Pramipexole may be useful as an antidepressant, separate from its action to improve the motor features of PD.[358-360] Anxiety and panic attacks can be prominent in PD, and these may sometimes relate to "wearing off" and so respond to strategies outlined for this complication. However, additional anxiolytic therapy may be needed in some patients.

Hallucinations, if due to drugs, usually respond to a reduction in dose. However, in some patients, this is difficult due to re-emergence of motor features, and they may respond to clozapine or quetiapine.[361-363] Hallucinations are, of course, an important symptom of diffuse Lewy body disease, and their emergence early in the course of PD is a risk factor for dementia. PD patients who demonstrated dementia after the 2 years diagnosis of PD showed a modest but significant improvement in cognitive function with rivastigmine, to a degree similar to that seen with this drug in Alzheimer's disease.[364]

Several strategies are available to improve both nighttime sleep and daytime alertness in PD and include improving sleep hygiene, treating nocturnal motor problems, better managing nocturia, modifying medication,[317] and using modafinil in patients with refractory daytime drowsiness.[365]

Viagra or apomorphine can, in select cases, usefully manage the sexual dysfunction associated with PD.[366,367] Bladder abnormalities particularly cause problems at night but can be improved by a range of options that include nonpharmacological and pharmacological strategies. The latter include the use

of oxybutinin, detrusitol, or amitriptyline in patients with concomitant depression. Sialorrhea and drooling are often the result of reduced frequency of swallowing and may be helped by simple things such as chewing gum or sucking sweets. Anticholinergic drugs may help but often cause unwanted side effects. Botulinum toxin can be used for refractory cases.[368] Constipation may respond to dopaminergic drugs and bowel training. Aperients often need to be added.

Surgery

Surgical approaches to the management of PD have been practiced since the mid-twentieth century. The discovery of dopamine depletion and the subsequent introduction of oral levodopa made surgery less attractive. The recognition of motor complications and the development of severe dyskinesias in some patients led to a resurgence of interest in lesioning the brain to control these features. Advances in surgical technique in neurophysiology and in molecular cell biology have provided the stimulus for the generation of a wide range of nonmedical options for PD (Table 71–7).

Destructive Lesions

Thalamotomy may produce a reduction in tremor and bradykinesia; the best results have been achieved with lesion in the ventrointermediate nucleus.[369] However, thalamotomy is not particularly helpful for bradykinesia or rigidity, and the procedure can be associated with significant morbidity related to the placement of the lesion.[370] Thalamotomy has largely been replaced by medical therapies or deep brain stimulation. Posteroventral *pallidotomy* can provide long-lasting improvement in contralateral dyskinesia and some improvement in bradykinesia and rigidity in PD patients.[371-374] Like thalamotomy, pallidotomy has become less common as deep brain stimulation has become more available. However, both destructive lesions may still be offered when symptoms significantly affect one side (bilateral destructive lesions cause increased complications including bulbar dysfunction) and when the opportunity for regular and expensive follow-up is limited.

Subthalamotomy has been shown to improve parkinsonian motor abnormalities including dyskinesias in animal models[375-377] and in PD patients.[378-380] However, dyskinesia and hemiballismus have also been reported, following subthalamotomy, which in a few cases have been permanent.[381,382]

TABLE 71–7. Surgical Treatments for Parkinson's Disease

Ablative procedures
Thalamotomy
Pallidotomy
Subthalamotomy
Deep brain stimulation
VIM nucleus of thalamus
Globus pallidus pars interna
Subthalamic nucleus
Restorative procedures
Cell-based therapies
Fetal human nigral cells
Fetal porcine nigral cells
Retinal pigmented epithelial cells
Stem cells
Trophic factors
Gene therapies

Stimulation

Deep brain stimulation was first proposed as a treatment in PD by Benabid based on his experience with high-frequency stimulation as a means of confirming the target site for an ablative lesion.[383] Deep brain stimulation can be used for bilateral procedures with relative safety. Also, the stimulator can be adjusted to maximize benefits and reduce side effects. Deep brain stimulation simulates the effect of a lesion but avoids the need to create a destructive brain lesion. The precise mechanism of action is unknown, but possibilities include depolarization blockade, release of inhibitory neurotransmitters, backfiring, and inhibition of aberrant neuronal signals.[384]

Deep brain stimulation of the ventral intermediate nucleus significantly improves contralateral tremor and is comparable in effect with destructive lesions but is superior in terms of side effects.[385-387] Benefits are long-lasting and have been shown to persist for more than 10 years. However, only tremor is improved and there is no effect on bradykinesia, rigidity, or dyskinesias. Thus deep brain stimulation of the ventral intermediate nucleus is not as attractive as deep brain stimulation of other targets. Deep brain stimulation of the subthalamic nucleus[388,389] or globus pallidum interna[390-394] improves all of the cardinal features of PD as well as dyskinesias. Patients who could not be further improved with medical therapies (typically because of motor complications) experienced a substantial reduction in disability following deep brain stimulation of the subthalamic nucleus or globus pallidum interna. Long-term studies demonstrate that benefits of deep brain stimulation persist over more than 5 years of follow-up, although disability still progresses from year to year, reflecting degeneration in nondopaminergic sites.[395]

Adverse events with deep brain stimulation can be related to the intracranial procedure, the electrode system, and stimulation. The surgical procedure can be associated with hemorrhage, tissue damage, and infection. In a multicenter study, 7 of 143 patients experienced hemorrhage and neurological deficits persisted in 4.[394] Problems can also occur in relation to the device including lead breaks, lead migration, infection, and skin erosion.[397] These occur in about 2% to 3% of cases and occasionally require replacement of the electrode. Severe depression and suicidal ideations or riotous laughing have been observed with stimulation of the subthalamic nucleus,[398] suggesting that basal ganglia circuits are involved with higher cortical and/or limbic as well as motor functions. The use of diathermy during surgical procedures should be avoided in patients with deep brain stimulation as excess heat might be conducted to the brain by the electrode wire and cause necrosis.

Deep brain stimulation, particularly of the subthalamic nucleus or globus pallidum interna, offers a significant benefit to those patients who have severe dyskinesias not controlled by standard means. Parkinsonian features are also improved but no more than can be achieved by dopaminergic medication. Deep brain stimulation is relatively safe if performed by an experienced surgeon but still carries some small risk of permanent neurological deficit (often quoted as less than 1%).

Patients should be carefully selected; those with cognitive impairment are excluded because of the risk of exacerbating this with surgery. Continuous follow-up is required, and the procedure is expensive.

Fetal nigral transplantation has been evaluated in two double-blind, placebo-controlled trials. The first randomized 40 patients to receive a transplantation or placebo procedure and followed them for 1 year.[399] Modest benefits of transplantation were observed in UPDRS scores of activities of daily living and motor function in patients younger than 60 years. There was a significant increase in striatal fluorodopa uptake on PET, and there was modest survival of implanted cells at postmortem. The procedure was well tolerated, but approximately 15% of transplanted patients developed dyskinesias that persisted for days or weeks after levodopa was discontinued and this was a source of major disability in some patients.[400] Quality of life, the primary endpoint, was not improved. The second trial was a 2-year double-blind placebo-controlled study that used a slightly different implantation protocol.[401] Transplanted patients were not significantly improved in comparison with placebo patients, despite having significant increases in striatal fluorodopa uptake on PET and survival of implanted dopaminergic neurons at postmortem. Over one half (56%) of the transplanted patients in this study developed dyskinesia during the practically defined off state when they had been held off levodopa for more than 12 hours ("off-medication dyskinesia"). This phenomenon was not observed in nontransplanted patients. The precise mechanism responsible for off-medication dyskinesia remains unknown.

Glial-derived neurotrophic factor has attracted attention as a potential treatment for PD because of its capacity to protect or rescue dopaminergic neurons in tissue culture[402] and in MPTP-treated monkeys.[403] Intraventricular administration of GDNF to PD patients did not produce benefit.[404] One open-label study used an infusion pump to directly administer glial-derived neurotrophic factor into the striatum in five PD patients.[405] There was an improvement in UPDRS motor scores during practically defined off as well as a small increase in striatal fluorodopa uptake around the catheter tip. However, a double-blind trial comparing glial-derived neurotrophic factor with placebo was negative.[406]

Gene and stem cell therapies are the subject of intense research effort but have yet to lead to clinically applicable treatments superior to those currently available.

NEUROPROTECTION

The limitations of symptomatic dopaminergic treatment have led to the search for agents to slow the progression of neurodegeneration in PD and thereby help prevent or slow clinical progression or even reverse deficits by restoring normal function to defective neurons. It is accepted that such a strategy will be successful only if degeneration is ameliorated in multiple neurotransmitter systems, preventing the progression of both motor and nonmotor features. The drugs that have received most attention in relation to neuroprotection include the MAO-B inhibitors and dopamine agonists, although others, including coenzyme Q_{10}, growth factors, antiapoptotic agents, and glutamate inhibitors, have also been the subjects of clinical trials in PD.

MAO-B Inhibitors

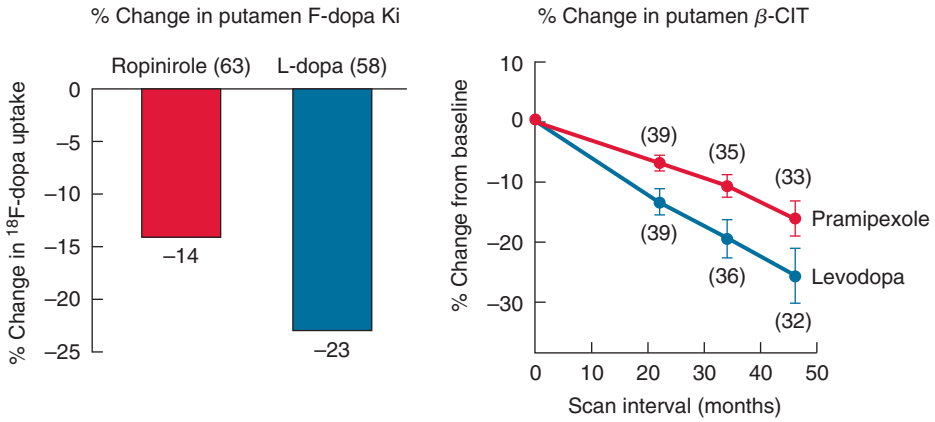
Selegiline can protect cultured dopaminergic neurons against the toxicity of MPP^+ and, in animal models, can reduce dopaminergic cell loss in response to MPTP.[407-410] Selegiline also protects against apoptotic cell death induced by serum and growth factor withdrawal,[411,412] possibly via an increased production of Bcl2. Selegiline, by virtue of its MAO-B activity, will reduce the turnover of dopamine and so reduce free radical generation. The production of reactive oxygen species and free radical–mediated damage to lipids and proteins have been implicated in PD pathogenesis. Thus, this property, together with the ability for selegiline to protect against MPTP toxicity, led to the evaluation of this drug in the first clinical trial for neuroprotection in PD.

The results of the DATATOP and other studies using selegiline and the TEMPO study investigating rasagiline were discussed earlier. There appeared to be some benefit for selegiline, but interpretation is difficult in view of trial design and the compound's inherent symptomatic action. The results of the delayed start design for TEMPO rasagiline were positive and support a neuroprotective action of the drug, but additional confirmatory trials are required before this drug can be accepted as neuroprotective.

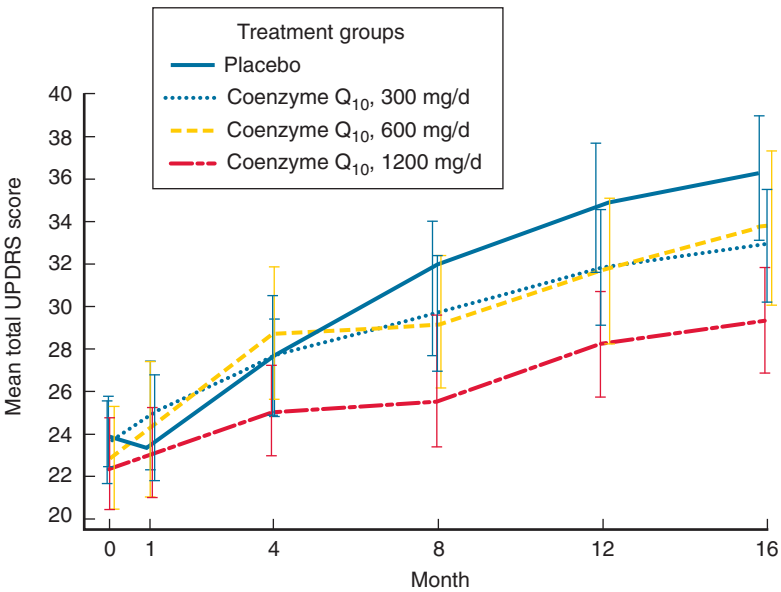
Dopamine Agonists

Dopamine agonists have antioxidant activity as a result of their hydroxylated benzyl ring structure, and numerous laboratory studies have demonstrated neuronal protection against free radical–generating systems. These include attenuation of the effects of MPP^+, dopamine, 6-hydroxydopamine, and nitric oxide and upregulation of protective scavenging enzymes such as catalase and superoxide dismutase.[413-421] However, these benefits are predominantly seen at relatively high concentrations, which may not be relevant in clinical practice. Dopamine agonists have demonstrated antiapoptotic activity in laboratory studies. For instance, pramipexole reduces cell death, prevents the release of cytochrome *c* and caspase activation in dopaminergic cells treated with MPP^+ or rotenone, and prevents a fall in mitochondrial membrane potential.[422,423] Importantly, this dopamine agonist has also shown protective effects in the MPTP primate model of PD.[424] Several studies suggest that dopamine agonists exert their protective effects not through stimulation of either D_2 or D_3 receptors, but rather via some alternative mechanism. The potential for dopamine agonists to protect nondopaminergic cells, if translated to the clinic, would have profound implications for disease modification and in particular for preventing the development of nonmotor features in PD.

Two studies have sought to determine whether the neuroprotective benefits of dopamine agonists seen in the laboratory can be transferred to patients to modify the course of PD (Fig. 71–12). The CALM-PD study used 2β-carboxymethoxy-3β(4-iodophenyl)tropane (β-CIT) SPECT to follow the rate of loss of dopamine transporter as a marker of dopaminergic nigrostriatal cell density.[247] Patients with early PD were randomized to pramipexole or levodopa and followed for a total of 4 years; levodopa supplementation was allowed in both arms. At 2, 3, and 4 years, there was a significant reduction in the rate of transporter loss in the pramipexole group, averaging at approximately 40%, consistent with the drug having a relatively



■ **Figure 71–12.** Results of SPECT and PET data from dopamine agonist neuroprotection studies. *(From the Parkinson Study Group: Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287:1653-1661; and Whone AL, Watts RL, Stoessl AJ, et al: Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 2003; 54:93-101. Copyright © 2002 American Medical Association. All rights reserved.)*



■ **Figure 71–13.** Results of the coenzyme Q_{10} study. *(From Shults CW, Oakes D, Kieburtz K, et al: Effects of coenzyme Q_{10} in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002; 59:1541-1550. Copyright © 2002 American Medical Association. All rights reserved.)*

protective effect in comparison with levodopa. A similar result was seen in the REAL-PET ropinirole study that used a similar trial design but used PET to follow loss of nigrostriatal cell density with fluorodopa.[248] This demonstrated an approximately 34% reduction over 2 years in the ropinirole group compared with those on levodopa. These studies have generated considerable interest and debate.[425,426] Both studies demonstrate that dopamine agonists are associated with a significant delay in the rate of decline of a surrogate imaging marker of nigrostriatal function.

One interpretation of these findings is that these two dopamine agonists slow the rate of cell loss in the substantia nigra of PD patients, and this is consistent with the laboratory findings outlined above. However, neither showed a corresponding clinical benefit, but it can be argued that the time course of the trials was too short to permit such an effect to be detected in the context of viable compensatory mechanisms and powerful symptomatic effects, and this will only become apparent with longer follow-up.

Another interpretation of these studies is that levodopa is toxic to nigral neurons. There is concern that levodopa might be toxic as it undergoes oxidative metabolism and has the potential to generate cytotoxic free radicals.[427] Levodopa has been shown to be toxic to cultured dopamine neurons, but there is no convincing evidence that levodopa is toxic in in vivo models or in PD patients.[428] The ELLDOPA trial investigated the possibility that levodopa may be toxic in PD patients but produced conflicting results. In this study, untreated PD patients were randomized to a total daily dose of 150, 300, or 600 mg of levodopa or placebo. β-CIT SPECT was used as an endpoint for integrity of the nigrostriatal system. Levodopa was associated with a significant increase in the rate of decline of imaging marker over 9 months compared with placebo, consistent with a toxic effect.[429] Clinical evaluation, however, showed that those patients on levodopa had better UPDRS scores compared with placebo after 2 weeks of washout (see Fig. 71–9). This would, in contrast, be indicative of a protective effect of levodopa. However, intellectual parsimony would dictate that the simplest explanation for this clinical effect was that the washout period was too brief to eliminate the symptomatic benefits of levodopa.

Finally, it has been proposed that the differences between the effects of levodopa and dopamine agonists seen in the CALM-PD and REAL-PET studies are not related to any direct effect of the drugs on dopamine neuron survival or degeneration but rather to a pharmacologic difference in the capacity of

these drugs to regulate the dopamine transporter or fluorodopa metabolism.[426,430,431] However, a review of studies testing the effects of levodopa and dopamine agonists on transporter and fluorodopa metabolism reveals that the data are conflicting and that at present there is insufficient information for or against such an effect.[425]

In conclusion, the results of the two clinical trials of dopamine agonists using imaging endpoints support, but do not prove, a disease-modifying effect in patients.

Coenzyme Q_{10}

Coenzyme Q_{10} has been evaluated in a pilot study of early PD patients to determine whether it might have disease-modifying capabilities.[432] The rationale for the use of coenzyme Q_{10} in PD was based on the observation that mitochondrial complex I activity is decreased in the PD substantia nigra, PD patients have reduced levels of coenzyme Q_{10}, and this compound protects against MPTP toxicity. Coenzyme Q_{10} is both an antioxidant and an integral component of oxidative phosphorylation that has been shown to enhance electron transport. It is presumed not to have any symptomatic effect. Patients were randomized to either a placebo arm or one of three doses of coenzyme Q_{10} (300, 600, or 1200 mg) and followed for 16 months. There was a significant benefit for coenzyme Q_{10} 1200 mg in terms of change from baseline in total UPDRS compared with placebo at 16 months and a nonsignificant trend to benefit for lower doses (Fig. 71–13). This interesting and important result is sufficient to support further study of coenzyme Q_{10} but insufficient at present to advocate that PD patients should use this compound.

KEY POINTS

- PD is an etiologically heterogeneous disorder.
- Several genetic causes have been characterized and appear to result in downstream effects that include abnormal free radical metabolism, defective mitochondrial function, and dysfunction of the ubiquitin proteasomal system.
- The diagnosis of PD is clinical but can be helped in certain circumstances by imaging with SPECT.
- The differential diagnosis includes a range of bradykinetic diseases such as multiple system atrophy and a number of genetic parkinsonian disorders.
- Treatments are available for the dopaminergic related motor features of PD but the nonmotor symptoms dominate the advanced disease state and require specific attention.
- Treatment options for PD should be discussed early with the newly diagnosed patient, although initiation may be delayed.
- The drug used to begin treatment depends on the patient's characteristics, but consideration should be given to the balance between effective control and long-term complications of drug therapy.
- Surgery is an important option, although it is usually reserved for the more advanced patient. Most surgery for PD is undertaken to control dyskinesias.

Suggested Reading

Ebadi M, Pfeiffer RF, eds: Parkinson's Disease. Boca Raton: CRC Press, 2005.

Nutt JG, Wooten GF: Clinical practice. Diagnosis and initial management of Parkinson's disease. N Engl J Med 2005; 353:1021-1027.

Olanow CW, Schapira AHV, Agid Y: Neurodegeneration and prospects for neuroprotection and rescue in Parkinson's disease. Ann Neurol 2003; 53(Suppl 3):S1-S170.

Samii A, Nutt JG, Ransom BR: Parkinson's disease. Lancet 2004; 363:1783-1793.

Schapira AHV, Olanow CW, eds: Principles of Treatment in Parkinson's Disease. Philadelphia: Butterworth Heinemann, 2005.

References

1. Ehringer H, Hornykiewicz O: Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Klin Wochenschr 1960; 38:1236-1239.
2. Cotzias GC, Van Woert MH, Schiffer LM: Aromatic amino acids and modification of parkinsonism. N Engl J Med 1967; 276:374-379.
3. Mayeux R, Marder K, Cote LJ, et al: The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. Am J Epidemiol 1995; 142:820-827.
4. Bower JH, Maraganore DM, McDonnell SK, et al: Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976-1990. Neurology 1999; 52:1214-1220.
5. Van Den Eeden SK, Tanner CM, Bernstein AL, et al: Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol 2003; 157:1015-1022.
6. de Rijk MC, Breteler MM, Graveland GA, et al: Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995; 45:2143-2146.
7. Zhang ZX, Roman GC: Worldwide occurrence of Parkinson's disease: an updated review. Neuroepidemiology 1993; 12:195-208.
8. Del Tredici K, Rub U, De Vos RA, et al: Where does parkinson disease pathology begin in the brain? J Neuropathol Exp Neurol 2002; 61:413-426.
9. Ponsen MM, Stoffers D, Booij J, et al: Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 2004; 56:173-181.
10. Braak H, Del Tredici K, Rub U, et al: Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24:197-211.
11. Gowers WR: A Manual of Diseases of the Nervous System. London: Churchill, 1888, p 996.
12. Payami H, Larsen K, Bernard S, et al: Increased risk of Parkinson's disease in parents and siblings of patients. Ann Neurol 1994; 36:659-661.
13. Bonifati V, Fabrizio E, Vanacore N, et al: Familial Parkinson's disease: a clinical genetic analysis. Can J Neurol Sci 1995; 22:272-279.
14. Vieregge P, Heberlein I: Increased risk of Parkinson's disease in relatives of patients. Ann Neurol 1995; 37:685.
15. De Michele G, Filla A, Volpe G, et al: Environmental and genetic risk factors in Parkinson's disease: a case-control study in southern Italy. Mov Disord 1996; 11:17-23.
16. Marder K, Tang MX, Mejia H, et al: Risk of Parkinson's disease among first-degree relatives: A community-based study. Neurology 1996; 47:155-160.
17. Gasser T: Genetics of Parkinson's disease. Ann Neurol 1998; 44(3 Suppl 1):S53-S57.

18. Tanner CM, Ottman R, Goldman SM, et al: Parkinson disease in twins: an etiologic study. JAMA 1999; 281:341-346.
19. Piccini P, Burn DJ, Ceravolo R, et al: The role of inheritance in sporadic Parkinson's disease: evidence from a longitudinal study of dopaminergic function in twins. Ann Neurol 1999; 45:577-582.
20. Polymeropoulos MH, Lavedan C, Leroy E, et al: Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 1997; 276:2045-2047.
21. Kruger R, Kuhn W, Muller T, et al: Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet 1998; 18:106-108.
22. Golbe LI, Di Iorio G, Sanges G, et al: Clinical genetic analysis of Parkinson's disease in the Contursi kindred. Ann Neurol 1996; 40:767-775.
23. Golbe LI, Di Iorio G, Bonavita V, et al: A large kindred with autosomal dominant Parkinson's disease. Ann Neurol 1990; 27:276-282.
24. Polymeropoulos MH, Higgins JJ, Golbe LI, et al: Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. Science 1996; 274:1197-1199.
25. Chan P, Tanner CM, Jiang X, et al: Failure to find the alpha-synuclein gene missense mutation (G209A) in 100 patients with younger onset Parkinson's disease. Neurology 1998; 50:513-514.
26. Vaughan JR, Farrer MJ, Wszolek ZK, et al: Sequencing of the alpha-synuclein gene in a large series of cases of familial Parkinson's disease fails to reveal any further mutations. The European Consortium on Genetic Susceptibility in Parkinson's Disease (GSPD). Hum Mol Genet 1998; 7:751-753.
27. Warner TT, Schapira AH: The role of the alpha-synuclein gene mutation in patients with sporadic Parkinson's disease in the United Kingdom. J Neurol Neurosurg Psychiatry 1998; 65:378-379.
28. Parsian A, Racette B, Zhang ZH, et al: Mutation, sequence analysis, and association studies of alpha-synuclein in Parkinson's disease. Neurology 1998; 51:1757-1759.
29. George JM, Jin H, Woods WS, et al: Characterization of a novel protein regulated during the critical period for song learning in the zebra finch. Neuron 1995; 15:361-372.
30. Abeliovich A, Schmitz Y, Farinas I, et al: Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. Neuron 2000; 25:239-252.
31. Spillantini MG, Schmidt ML, Lee VM, et al: Alpha-synuclein in Lewy bodies. Nature 1997; 388:839-840.
32. Masliah E, Rockenstein E, Veinbergs I, et al: Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. Science 2000; 287:1265-1269.
33. Feany MB, Bender WW: A Drosophila model of Parkinson's disease. Nature 2000; 404:394-398.
34. Singleton AB, Farrer M, Johnson J, et al: Alpha-synuclein locus triplication causes Parkinson's disease. Science 2003; 302:841.
35. Farrer M, Kachergus J, Forno L, et al: Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol 2004; 55:174-179.
36. Zarranz JJ, Alegre J, Gomez-Esteban JC, et al: The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Ann Neurol 2004; 55:164-173.
37. Giasson BI, Duda JE, Quinn SM, et al: Neuronal alpha-synucleinopathy with severe movement disorder in mice expressing A53T human alpha-synuclein. Neuron 2002; 34:521-533.
38. Kirik D, Rosenblad C, Burger C, et al: Parkinson-like neurodegeneration induced by targeted overexpression of alpha-synuclein in the nigrostriatal system. J Neurosci 2002; 22:2780-2791.
39. Conway KA, Lee SJ, Rochet JC, et al: Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. Proc Natl Acad Sci U S A 2000; 97:571-576.
40. Conway KA, Rochet JC, Bieganski RM, et al: Kinetic stabilization of the alpha-synuclein protofibril by a dopamine-alpha-synuclein adduct. Science 2001; 294:1346-1349.
41. Tabrizi SJ, Orth M, Wilkinson JM, et al: Expression of mutant alpha-synuclein causes increased susceptibility to dopamine toxicity. Hum Mol Genet 2000; 9:2683-2689.
42. Smith WW, Margolis RL, Li X, et al: Alpha-synuclein phosphorylation enhances eosinophilic cytoplasmic inclusion formation in SH-SY5Y cells. J Neurosci 2005; 25:5544-5552.
43. Hasegawa M, Fujiwara H, Nonaka T, et al: Phosphorylated alpha-synuclein is ubiquitinated in alpha-synucleinopathy lesions. J Biol Chem 2002; 277:49071-49076.
44. Chen L, Feany MB: Alpha-synuclein phosphorylation controls neurotoxicity and inclusion formation in a Drosophila model of Parkinson disease. Nat Neurosci 2005; 8:657-663.
45. Kitada T, Asakawa S, Hattori N, et al: Mutations in the *parkin* gene cause autosomal recessive juvenile parkinsonism. Nature 1998; 392:605-608.
46. Yamamura Y, Sobue I, Ando K, et al: Paralysis agitans of early onset with marked diurnal fluctuation of symptoms. Neurology 1973; 23:239-244.
47. Takahashi H, Ohama E, Suzuki S, et al: Familial juvenile parkinsonism: clinical and pathologic study in a family. Neurology 1994; 44(3 Pt 1):437-441.
48. Matsumine H, Saito M, Shimoda-Matsubayashi S, et al: Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. Am J Hum Genet 1997; 60:588-596.
49. Hattori N, Kitada T, Matsumine H, et al: Molecular genetic analysis of a novel *parkin* gene in Japanese families with autosomal recessive juvenile parkinsonism: evidence for variable homozygous deletions in the *parkin* gene in affected individuals. Ann Neurol 1998; 44:935-941.
50. Abbas N, Lucking CB, Ricard S, et al: A wide variety of mutations in the *parkin* gene are responsible for autosomal recessive parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. Hum Mol Genet 1999; 8:567-574.
51. Farrer M, Chan P, Chen R, et al: Lewy bodies and parkinsonism in families with *parkin* mutations. Ann Neurol 2001; 50:293-300.
52. West A, Periquet M, Lincoln S, et al: Complex relationship between *parkin* mutations and Parkinson disease. Am J Med Genet 2002; 114:584-591.
53. Lucking CB, Durr A, Bonifati V, et al: Association between early-onset Parkinson's disease and mutations in the *parkin* gene. French Parkinson's Disease Genetics Study Group. N Engl J Med 2000; 342:1560-1567.
54. Kann M, Jacobs H, Mohrmann K, et al: Role of *parkin* mutations in 111 community-based patients with early-onset parkinsonism. Ann Neurol 2002; 51:621-625.
55. Klein C, Pramstaller PP, Kis B, et al: Parkin deletions in a family with adult-onset, tremor-dominant parkinsonism: expanding the phenotype. Ann Neurol 2000; 48:65-71.
56. Lucking CB, Bonifati V, Periquet M, et al: Pseudo-dominant inheritance and exon 2 triplication in a family with *parkin* gene mutations. Neurology 2001; 57:924-927.
57. Thobois S, Ribeiro MJ, Lohmann E, et al: Young-onset Parkinson disease with and without *parkin* gene mutations: a fluorodopa F 18 positron emission tomography study. Arch Neurol 2003; 60:713-718.

58. Hilker R, Klein C, Ghaemi M, et al: Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the *parkin* gene. Ann Neurol 2001; 49:367-376.
59. Khan NL, Brooks DJ, Pavese N, et al: Progression of nigrostriatal dysfunction in a *parkin* kindred: an [18F]dopa PET and clinical study. Brain 2002; 125:2248-2256.
60. Shimura H, Hattori N, Kubo S, et al: Familial Parkinson disease gene product, *parkin*, is a ubiquitin-protein ligase. Nat Genet 2000; 25:302-305.
61. Zhang Y, Gao J, Chung KK, et al: Parkin functions as an E2-dependent ubiquitin-protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. Proc Natl Acad Sci U S A 2000; 97:13354-13359.
62. Imai Y, Soda M, Inoue H, et al: An unfolded putative transmembrane polypeptide, which can lead to endoplasmic reticulum stress, is a substrate of *parkin*. Cell 2001; 105:891-902.
63. Lo BC, Schneider BL, Bauer M, et al: Lentiviral vector delivery of *parkin* prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. Proc Natl Acad Sci U S A 2004; 101:17510-17515.
64. Goldberg MS, Fleming SM, Palacino JJ, et al: Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. J Biol Chem 2003; 278:43628-43635.
65. Palacino JJ, Sagi D, Goldberg MS, et al: Mitochondrial dysfunction and oxidative damage in *parkin*-deficient mice. J Biol Chem 2004; 279:18614-18622.
66. Greene JC, Whitworth AJ, Kuo I, et al: Mitochondrial pathology and apoptotic muscle degeneration in Drosophila *parkin* mutants. Proc Natl Acad Sci U S A 2003; 100:4078-4083.
67. Darios F, Corti O, Lucking CB, et al: Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. Hum Mol Genet 2003; 12:517-526.
68. Muftuoglu M, Elibol B, Dalmizrak O, et al: Mitochondrial complex I and IV activities in leukocytes from patients with *parkin* mutations. Mov Disord 2004; 19:544-548.
69. Chung KK, Thomas B, Li X, et al: S-nitrosylation of *parkin* regulates ubiquitination and compromises *parkin*'s protective function. Science 2004; 304:1328-1331.
70. Leroy E, Boyer R, Auburger G, et al: The ubiquitin pathway in Parkinson's disease. Nature 1998; 395:451-452.
71. Harhangi BS, Farrer MJ, Lincoln S, et al: The Ile93Met mutation in the ubiquitin carboxy-terminal-hydrolase-L1 gene is not observed in European cases with familial Parkinson's disease. Neurosci Lett 1999; 270:1-4.
72. Lincoln S, Vaughan J, Wood N, et al: Low frequency of pathogenic mutations in the ubiquitin carboxy-terminal hydrolase gene in familial Parkinson's disease. Neuroreport 1999; 10:427-429.
73. Valente EM, Bentivoglio AR, Dixon PH, et al: Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. Am J Hum Genet 2001; 68:895-900.
74. Valente EM, Abou-Sleiman PM, Caputo V, et al: Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 2004; 304:1158-1160.
75. Bentivoglio AR, Cortelli P, Valente EM, et al: Phenotypic characterisation of autosomal recessive PARK6-linked parkinsonism in three unrelated Italian families. Mov Disord 2001; 16:999-1006.
76. Rohe CF, Montagna P, Breedveld G, et al: Homozygous PINK1 C-terminus mutation causing early-onset parkinsonism. Ann Neurol 2004; 56:427-431.
77. Hatano Y, Li Y, Sato K, et al: Novel PINK1 mutations in early-onset parkinsonism. Ann Neurol 2004; 56:424-427.
78. Valente EM, Salvi S, Ialongo T, et al: PINK1 mutations are associated with sporadic early-onset parkinsonism. Ann Neurol 2004; 56:336-341.
79. Unoki M, Nakamura Y: Growth-suppressive effects of BPOZ and EGR2, two genes involved in the PTEN signaling pathway. Oncogene 2001; 20:4457-4465.
80. Hunter T: Signaling: 2000 and beyond. Cell 2000; 100:113-127.
81. Cohen P: The origins of protein phosphorylation. Nat Cell Biol 2002; 4:E127-E130.
82. Manning G, Whyte DB, Martinez R, et al: The protein kinase complement of the human genome. Science 2002; 298:1912-1934.
83. van Duijn CM, Dekker MC, Bonifati V, et al: Park7: a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am J Hum Genet 2001; 69:629-634.
84. Bonifati V, Rizzu P, van Baren MJ, et al: Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 2003; 299:256-259.
85. Canet-Aviles RM, Wilson MA, Miller DW, et al: The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. Proc Natl Acad Sci U S A 2004; 101:9103-9108.
86. Zhang L, Shimoji M, Thomas B, et al: Mitochondrial localization of the Parkinson's disease related protein DJ-1: implications for pathogenesis. Hum Mol Genet 2005; 14: 2063-2073.
87. Di Fonzo A, Rohe CF, Ferreira J, et al: A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson's disease. Lancet 2005; 365:412-415.
88. Nichols WC, Pankratz N, Hernandez D, et al: Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. Lancet 2005; 365:410-412.
89. Kachergus J, Mata IF, Hulihan M, et al: Identification of a novel LRRK2 mutation linked to autosomal dominant parkinsonism: evidence of a common founder across European populations. Am J Hum Genet 2005; 76:672-680.
90. Gilks WP, Abou-Sleiman PM, Gandhi S, et al: A common LRRK2 mutation in idiopathic Parkinson's disease. Lancet 2005; 365:415-416.
91. Deng H, Le W, Guo Y, et al: Genetic and clinical identification of Parkinson's disease patients with LRRK2 G2019S mutation. Ann Neurol 2005; 57:933-934.
92. Zabetian CP, Samii A, Mosley AD, et al: A clinic-based study of the LRRK2 gene in Parkinson disease yields new mutations. Neurology 2005; 65:741-744.
93. Hernandez D, Paisan RC, Crawley A, et al: The dardarin G 2019 S mutation is a common cause of Parkinson's disease but not other neurodegenerative diseases. Neurosci Lett 2005; 389:137-139.
94. Toft M, Sando SB, Melquist S, et al: LRRK2 mutations are not common in Alzheimer's disease. Mech Ageing Dev 2005; 126:1201-1205.
95. Kay DM, Kramer P, Higgins D, et al: Escaping Parkinson's disease: a neurologically healthy octogenarian with the LRRK2 G2019S mutation. Mov Disord 2005; 20:1077-1078.
96. Adams JR, van Netten H, Schulzer M, et al: PET in LRRK2 mutations: comparison to sporadic Parkinson's disease and evidence for presymptomatic compensation. Brain 2005; 128: 2777-2785.
97. Funayama M, Hasegawa K, Kowa H, et al: A new locus for Parkinson's disease (PARK8) maps to chromosome 12p11.2-q13.1. Ann Neurol 2002; 51:296-301.
98. Wszolek ZK, Pfeiffer RF, Tsuboi Y, et al: Autosomal dominant parkinsonism associated with variable synuclein and tau pathology. Neurology 2004; 62:1619-1622.
99. Zimprich A, Biskup S, Leitner P, et al: Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004; 44:601-607.

100. Ross OA, Farrer MJ: Pathophysiology, pleiotrophy and paradigm shifts: genetic lessons from Parkinson's disease. Biochem Soc Trans 2005; 33:586-590.
101. Ridley AJ: Rho family proteins: coordinating cell responses. Trends Cell Biol 2001; 11:471-477.
102. Hampshire DJ, Roberts E, Crow Y, et al: Kufor-Rakeb syndrome, pallido-pyramidal degeneration with supranuclear upgaze paresis and dementia, maps to 1p36. J Med Genet 2001; 38:680-682.
103. Najim al-Din AS, Wriekat A, Mubaidin A, et al: Pallido-pyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol Scand 1994; 89:347-352.
104. Hicks AA, Petursson H, Jonsson T, et al: A susceptibility gene for late-onset idiopathic Parkinson's disease. Ann Neurol 2002; 52:549-555.
105. Scott WK, Nance MA, Watts RL, et al: Complete genomic screen in Parkinson disease: evidence for multiple genes. JAMA 2001; 286:2239-2244.
106. DeStefano AL, Golbe LI, Mark MH, et al: Genome-wide scan for Parkinson's disease: the GenePD Study. Neurology 2001; 57:1124-1126.
107. Farrer M, Maraganore DM, Lockhart P, et al: alpha-Synuclein gene haplotypes are associated with Parkinson's disease. Hum Mol Genet 2001; 10:1847-1851.
108. Tan EK, Tan C, Shen H, et al: Alpha synuclein promoter and risk of Parkinson's disease: microsatellite and allelic size variability. Neurosci Lett 2003; 336:70-72.
109. West AB, Maraganore D, Crook J, et al: Functional association of the *parkin* gene promoter with idiopathic Parkinson's disease. Hum Mol Genet 2002; 11:2787-2792.
110. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R: Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med 2004; 351:1972-1977.
111. Foster NL, Wilhelmsen K, Sima AA, et al: Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. Conference Participants. Ann Neurol 1997; 41:706-715.
112. Hulette CM, Pericak-Vance MA, Roses AD, et al: Neuropathological features of frontotemporal dementia and parkinsonism linked to chromosome 17q21-22 (FTDP-17): Duke Family 1684. J Neuropathol Exp Neurol 1999; 58:859-866.
113. Gwinn-Hardy K, Chen JY, Liu HC, et al: Spinocerebellar ataxia type 2 with parkinsonism in ethnic Chinese. Neurology 2000; 55:800-805.
114. Lu CS, Wu Chou YH, Yen TC, et al: Dopa-responsive parkinsonism phenotype of spinocerebellar ataxia type 2. Mov Disord 2002; 17:1046-1051.
115. Shan DE, Soong BW, Sun CM, et al: Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism. Ann Neurol 2001; 50:812-815.
116. Hagerman RJ, Leehey M, Heinrichs W, et al: Intention tremor, parkinsonism, and generalized brain atrophy in male carriers of fragile X: Neurology 2001; 57:127-130.
117. Jacquemont S, Hagerman RJ, Leehey M, et al: Fragile X premutation tremor/ataxia syndrome: molecular, clinical, and neuroimaging correlates. Am J Hum Genet 2003; 72:869-878.
118. Haberhausen G, Schmitt I, Kohler A, et al: Assignment of the dystonia-parkinsonism syndrome locus, DYT3, to a small region within a 1.8-Mb YAC contig of Xq13.1. Am J Hum Genet 1995; 57:644-650.
119. de Carvalho AP, Sweadner KJ, Penniston JT, et al: Mutations in the Na^+/K^+-ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron 2004; 43:169-175.
120. Wooten GF, Currie LJ, Bennett JP, et al: Maternal inheritance in Parkinson's disease. Ann Neurol 1997; 41:265-268.
121. Schapira AH, Holt IJ, Sweeney M, et al: Mitochondrial DNA analysis in Parkinson's disease. Mov Disord 1990; 5:294-297.
122. Ozawa T, Tanaka M, Ino H, et al: Distinct clustering of point mutations in mitochondrial DNA among patients with mitochondrial encephalomyopathies and with Parkinson's disease. Biochem Biophys Res Commun 1991; 176:938-946.
123. Ikebe S, Tanaka M, Ozawa T: Point mutations of mitochondrial genome in Parkinson's disease. Brain Res Mol Brain Res 1995; 28:281-295.
124. Shoffner JM, Brown MD, Torroni A, et al: Mitochondrial DNA variants observed in Alzheimer disease and Parkinson disease patients. Genomics 1993; 17:171-184.
125. Lucking CB, Kosel S, Mehraein P, et al: Absence of the mitochondrial A7237T mutation in Parkinson's disease. Biochem Biophys Res Commun 1995; 211:700-704.
126. Kosel S, Grasbon-Frodl EM, Hagenah JM, et al: Parkinson disease: analysis of mitochondrial DNA in monozygotic twins. Neurogenetics 2000; 2:227-230.
127. Richter G, Sonnenschein A, Grunewald T, et al: Novel mitochondrial DNA mutations in Parkinson's disease. J Neural Transm 2002; 109:721-729.
128. Vives-Bauza C, Andreu AL, Manfredi G, et al: Sequence analysis of the entire mitochondrial genome in Parkinson's disease. Biochem Biophys Res Commun 2002; 290:1593-1601.
129. van der Walt JM, Nicodemus KK, Martin ER, et al: Mitochondrial polymorphisms significantly reduce the risk of Parkinson disease. Am J Hum Genet 2003; 72:804-811.
130. Pyle A, Foltynie T, Tiangyou W, et al: Mitochondrial DNA haplogroup cluster UKJT reduces the risk of PD. Ann Neurol 2005; 57:564-567.
131. Ross OA, McCormack R, Maxwell LD, et al: mt4216C variant in linkage with the mtDNA TJ cluster may confer a susceptibility to mitochondrial dysfunction resulting in an increased risk of Parkinson's disease in the Irish. Exp Gerontol 2003; 38:397-405.
132. Luoma P, Melberg A, Rinne JO, et al: Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. Lancet 2004; 364:875-882.
133. Mancuso M, Filosto M, Oh SJ, et al: A novel polymerase gamma mutation in a family with ophthalmoplegia, neuropathy, and parkinsonism. Arch Neurol 2004; 61:1777-1779.
134. Rajput AH, Uitti RJ, Stern W, et al: Early onset Parkinson's disease in Saskatchewan-environmental considerations for etiology. Can J Neurol Sci 1986; 13:312-316.
135. Rajput AH, Uitti RJ, Rajput AH: Neurological disorders and services in Saskatchewan: a report based on provincial health care records. Neuroepidemiology 1988; 7:145-151.
136. Behari M, Srivastava AK, Das RR, et al: Risk factors of Parkinson's disease in Indian patients. J Neurol Sci 2001; 190:49-55.
137. Semchuk KM, Love EJ, Lee RG: Parkinson's disease and exposure to rural environmental factors: a population based case-control study. Can J Neurol Sci 1991; 18:279-286.
138. Barbeau A, Roy M, Bernier G, et al: Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. Can J Neurol Sci 1987; 14:36-41.
139. Gorrell JM, DiMonte D, Graham D: The role of the environment in Parkinson's disease. Environ Health Perspect 1996; 104:652-654.
140. Fall PA, Fredrikson M, Axelson O, et al: Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord 1999; 14:28-37.
141. Semchuk KM, Love EJ, Lee RG: Parkinson's disease and exposure to agricultural work and pesticide chemicals. Neurology 1992; 42:1328-1335.

142. Seidler A, Hellenbrand W, Robra BP, et al: Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology 1996; 46:1275-1284.
143. Fleming L, Mann JB, Bean J, et al: Parkinson's disease and brain levels of organochlorine pesticides. Ann Neurol 1994; 36:100-103.
144. Corsini GU, Pintus S, Chiueh CC, et al: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity in mice is enhanced by pretreatment with diethyldithiocarbamate. Eur J Pharmacol 1985; 119:127-128.
145. Tanner CM, Goldman SM: Epidemiology of Parkinson's disease. Neurol Clin 1996; 14:317-335.
146. Klawans HL, Stein RW, Tanner CM, et al: A pure parkinsonian syndrome following acute carbon monoxide intoxication. Arch Neurol 1982; 39:302-304.
147. Elwan MA, Richardson JR, Guillot TS, et al: Pyrethroid pesticide-induced alterations in dopamine transporter function. Toxicol Appl Pharmacol 2005.
148. Pittman JT, Dodd CA, Klein BG: Immunohistochemical changes in the mouse striatum induced by the pyrethroid insecticide permethrin. Int J Toxicol 2003; 22:359-370.
149. Bloomquist JR, Barlow RL, Gillette JS, et al: Selective effects of insecticides on nigrostriatal dopaminergic nerve pathways. Neurotoxicology 2002; 23(4-5):537-544.
150. Imamura L, Yasuda M, Kuramitsu K, et al: Deltamethrin, a pyrethroid insecticide, is a potent inducer for the activity-dependent gene expression of brain-derived neurotrophic factor in neurons. J Pharmacol Exp Ther 2006; 316:136-143.
151. Betarbet R, Sherer TB, MacKenzie G, et al: Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nat Neurosci 2000; 3:1301-1306.
152. Manning-Bog AB, McCormack AL, Li J, et al: The herbicide paraquat causes up-regulation and aggregation of alpha-synuclein in mice: paraquat and alpha-synuclein. J Biol Chem 2002; 277:1641-1644.
153. Champy P, Hoglinger GU, Feger J, et al: Annonacin, a lipophilic inhibitor of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats: possible relevance for atypical parkinsonism in Guadeloupe. J Neurochem 2004; 88:63-69.
154. Tipton KF, Singer TP: Advances in our understanding of the mechanisms of the neurotoxicity of MPTP and related compounds. J Neurochem 1993; 61:1191-1206.
155. Hochberg F, Lilienfeld D, Olanow W, et al: Progression after chronic manganese exposure. Neurology 1993; 43:1479-1483.
156. Mena I: Manganese poisoning. In: Vinken PJ, Bruyn GW, editors. Handbook of Clinical Neurology. Amsterdam: North Holland Publishing Company, 1979, pp 217-237.
157. Jankovic J: Searching for a relationship between manganese and welding and Parkinson's disease. Neurology 2005; 64: 2021-2028.
158. Ziegler L: Follow-up studies in persons who have had epidemic encephalitis. JAMA 1928; 21:138-141.
159. Von Economo C: The Sequelae of Encephalitis Lethargica. New York: Oxford University Press, 1931, pp 105-106.
160. Ebmeier KP, Mutch WJ, Calder SA, et al: Does idiopathic parkinsonism in Aberdeen follow intrauterine influenza? J Neurol Neurosurg Psychiatry 1989; 52:911-913.
161. Schwartz J, Elizan TS: Search for viral particles and virus-specific products in idiopathic Parkinson disease brain material. Ann Neurol 1979; 6:261-263.
162. Baron JA: Cigarette smoking and Parkinson's disease. Neurology 1986; 36:1490-1496.
163. Ascherio A, Zhang SM, Hernan MA, et al: Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol 2001; 50:56-63.
164. McGeer PL, Itagaki S, Boyes BE, et al: Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology 1988; 38:1285-1291.
165. Boka G, Anglade P, Wallach D, et al: Immunocytochemical analysis of tumor necrosis factor and its receptors in Parkinson's disease. Neurosci Lett 1994; 172:151-154.
166. Hunot S, Dugas N, Faucheux B, et al: FcepsilonRII/CD23 is expressed in Parkinson's disease and induces, in vitro, production of nitric oxide and tumor necrosis factor-alpha in glial cells. J Neurosci 1999; 19:3440-3447.
167. McGeer PL, Schulzer M, McGeer EG: Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. Neurology 1996; 47:425-432.
168. In t' Veld BA, Ruitenberg A, Hofman A, et al: Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 2001; 345:1515-1521.
169. Chen H, Zhang SM, Hernan MA, et al: Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003; 60:1059-1064.
170. Dexter DT, Wells FR, Agid F, et al: Increased nigral iron content in postmortem parkinsonian brain. Lancet 1987; 2:1219-1220.
171. Sofic E, Paulus W, Jellinger K, et al: Selective increase of iron in substantia nigra zona compacta of parkinsonian brains. J Neurochem 1991; 56:978-982.
172. Jellinger K, Paulus W, Grundke-Iqbal I, et al: Brain iron and ferritin in Parkinson's and Alzheimer's diseases. J Neural Transm Park Dis Dement Sect 1990; 2:327-340.
173. Jellinger K, Kienzl E, Rumpelmair G, et al: Iron-melanin complex in substantia nigra of parkinsonian brains: an x-ray microanalysis. J Neurochem 1992; 59:1168-1171.
174. Hirsch EC, Brandel JP, Galle P, et al: Iron and aluminum increase in the substantia nigra of patients with Parkinson's disease: an X-ray microanalysis. J Neurochem 1991; 56:446-451.
175. Dexter DT, Carayon A, Vidailhet M, et al: Decreased ferritin levels in brain in Parkinson's disease. J Neurochem 1990; 55:16-20.
176. Riederer P, Sofic E, Rausch WD, et al: Transition metals, ferritin, glutathione, and ascorbic acid in parkinsonian brains. J Neurochem 1989; 52:515-520.
177. Mann VM, Cooper JM, Daniel SE, et al: Complex I, iron, and ferritin in Parkinson's disease substantia nigra. Ann Neurol. 1994. Dec;36:876-81.
178. Perry TL, Godin DV, Hansen S: Parkinson's disease: a disorder due to nigral glutathione deficiency? Neurosci Lett 1982; 33:305-310.
179. Sian J, Dexter DT, Lees AJ, et al: Alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. Ann Neurol 1994; 36:348-355.
180. Marttila RJ, Lorentz H, Rinne UK: Oxygen toxicity protecting enzymes in Parkinson's disease. Increase of superoxide dismutase-like activity in the substantia nigra and basal nucleus. J Neurol Sci 1988; 86:321-331.
181. Saggu H, Cooksey J, Dexter D, et al: A selective increase in particulate superoxide dismutase activity in parkinsonian substantia nigra. J Neurochem 1989; 53:692-697.
182. Hirsch EC, Graybiel AM, Agid Y: Selective vulnerability of pigmented dopaminergic neurons in Parkinson's disease. Acta Neurol Scand Suppl 1989; 126:19-22.
183. Ceballos I, Lafon M, Javoy-Agid F, et al: Superoxide dismutase and Parkinson's disease. Lancet 1990; 335:1035-1036.
184. Dexter D, Carter C, Agid F, et al: Lipid peroxidation as cause of nigral cell death in Parkinson's disease. Lancet 1986; 2:639-640.

185. Sanchez-Ramos J, Ocervik E, Ames BN: A marker of oxyradical-mediated DNA damage (8-hydroxy-2′-deoxyguanosine) is increased in nigro-striatum of Parkinson's disease brain. Neurodegeneration 3. 1994;197-204.
186. Itzhak Y, Ali SF: The neuronal nitric oxide synthase inhibitor, 7-nitroindazole, protects against methamphetamine-induced neurotoxicity in vivo. J Neurochem 1996; 67:1770-1773.
187. Kuiper MA, Visser JJ, Bergmans PL, et al: Decreased cerebrospinal fluid nitrate levels in Parkinson's disease, Alzheimer's disease and multiple system atrophy patients. J Neurol Sci 1994; 121:46-49.
188. Molina JA, Jimenez-Jimenez FJ, Navarro JA, et al: Cerebrospinal fluid nitrate levels in patients with Parkinson's disease. Acta Neurol Scand 1996; 93(2-3):123-126.
189. Qureshi GA, Baig S, Bednar I, et al: Increased cerebrospinal fluid concentration of nitrite in Parkinson's disease. Neuroreport 1995; 6:1642-1644.
190. Schapira AH, Cooper JM, Dexter D: Mitochondrial complex 1 deficienty in Parkinson's disease. Annals of neurology 1989; 26:122-123.
191. Schapira AH, Cooper JM, Dexter D, et al: Mitochondrial complex I deficiency in Parkinson's disease. Lancet 1989; 1:1269.
192. Schapira AH, Mann VM, Cooper JM, et al: Anatomic and disease specificity of NADH CoQ1 reductase (complex I) deficiency in Parkinson's disease. J Neurochem 1990; 55:2142-2145.
193. Schapira AH: Evidence for mitochondrial dysfunction in Parkinson's disease—a critical appraisal. Mov Disord 1994; 9:125-138.
194. Taylor DJ, Krige D, Barnes PR, et al: A 31P magnetic resonance spectroscopy study of mitochondrial function in skeletal muscle of patients with Parkinson's disease. J Neurol Sci 1994; 125:77-81.
195. Penn AM, Roberts T, Hodder J, et al: Generalized mitochondrial dysfunction in Parkinson's disease detected by magnetic resonance spectroscopy of muscle. Neurology 1995; 45:2097-2099.
196. Parker WD Jr, Boyson SJ, Parks JK: Abnormalities of the electron transport chain in idiopathic Parkinson's disease. Ann Neurol 1989; 26:719-723.
197. Krige D, Carroll MT, Cooper JM, et al: Platelet mitochondrial function in Parkinson's disease. The Royal Kings and Queens Parkinson Disease Research Group. Ann Neurol 1992; 32:782-788.
198. Haas RH, Nasirian F, Nakano K, et al: Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease. Ann Neurol 1995; 37:714-722.
199. Ansari KA, Johnson A; Olfactory function in patients with Parkinson's disease. J Chronic Dis 1975; 28:493-497.
200. Doty RL, Deems DA, Stellar S: Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 1988; 38:1237-1244.
201. Doty RL, Stern MB, Pfeiffer C, et al: Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1992; 55:138-142.
202. Montgomery EB Jr, Baker KB, Lyons K, et al: Abnormal performance on the PD test battery by asymptomatic first-degree relatives. Neurology 1999; 52:757-762.
203. Markopoulou K, Larsen KW, Wszolek EK, et al: Olfactory dysfunction in familial parkinsonism. Neurology 1997; 49:1262-1267.
204. Hawkes C: Olfaction in neurodegenerative disorder. Mov Disord 2003; 18:364-372.
205. Boeve BF, Silber MH, Ferman TJ, et al: Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001; 16:622-630.
206. Khan NL, Katzenschlager R, Watt H, et al: Olfaction differentiates *parkin* disease from early-onset parkinsonism and Parkinson disease. Neurology 2004; 62:1224-1226.
207. Gagnon JF, Bedard MA, Fantini ML, et al: REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 2002; 59:585-589.
208. Comella CL, Tanner CM, Ristanovic RK: Polysomnographic sleep measures in Parkinson's disease patients with treatment-induced hallucinations. Ann Neurol 1993; 34:710-714.
209. Ohayon MM, Caulet M, Priest RG: Violent behavior during sleep. J Clin Psychiatry 1997; 58:369-376.
210. Fantini ML, Ferini-Strambi L, Montplaisir J: Idiopathic REM sleep behavior disorder: toward a better nosologic definition. Neurology 2005; 64:780-786.
211. Schenck CH, Bundlie SR, Mahowald MW: Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 1996; 46:388-393.
212. Olson EJ, Boeve BF, Silber MH: Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000; 123:331-339.
213. Albin RL, Koeppe RA, Chervin RD, et al: Decreased striatal dopaminergic innervation in REM sleep behavior disorder. Neurology 2000; 55:1410-1412.
214. Eisensehr I, Linke R, Noachtar S, et al: Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder. Comparison with Parkinson's disease and controls. Brain 2000; 123:1155-1160.
215. Byrne KG, Pfeiffer R, Quigley EM: Gastrointestinal dysfunction in Parkinson's disease. A report of clinical experience at a single center. J Clin Gastroenterol 1994; 19:11-16.
216. Korczyn AD: Autonomic nervous system screening in patients with early Parkinson's disease. In Przuntek H, Riederer P, eds: Early Diagnosis and Preventive Therapy in Parkinson's Disease. Vienna: Springer-Velag, 1989, pp 41-48.
217. Ashraf W, Pfeiffer RF, Park F, et al: Constipation in Parkinson's disease: objective assessment and response to psyllium. Mov Disord 1997; 12:946-951.
218. Astarloa R, Mena MA, Sanchez V, et al: Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease. Clin Neuropharmacol 1992; 15:375-380.
219. Abbott RD, Petrovitch H, White LR, et al: Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 2001; 57:456-462.
220. Singaram C, Ashraf W, Gaumnitz EA, et al: Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 1995; 346:861-864.
221. Mathers SE, Kempster PA, Swash M, et al: Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? J Neurol Neurosurg Psychiatry 1988; 51:1503-1507.
222. Edwards LL, Quigley EM, Harned RK, et al: Defecatory function in Parkinson's disease: response to apomorphine. Ann Neurol 1993; 33:490-493.
223. Djaldetti R, Mosberg-Galili R, Sroka H, et al: Camptocormia (bent spine) in patients with Parkinson's disease—characterization and possible pathogenesis of an unusual phenomenon. Mov Disord 1999; 14:443-447.
224. Hoehn MM, Yahr MD: Parkinsonism: onset, progression and mortality. Neurology 1967; 17:427-442.
225. Hunker CJ, Abbs JH: Uniform frequency of parkinsonian resting tremor in the lips, jaw, tongue, and index finger. Mov Disord 1990; 5:71-77.

226. Scott RM, Brody JA, Schwab RS, et al: Progression of unilateral tremor and rigidity in Parkinson's disease. Neurology 1970; 20:710-714.
227. Hely MA, Morris JG, Reid WG, et al: Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2004; 20:190-199.
228. Jellinger KA: Pathology of Parkinson's disease. Changes other than the nigrostriatal pathway. Mol Chem Neuropathol 1991; 14:153-197.
229. Lees AJ, Blackburn NA, Campbell VL: The nighttime problems of Parkinson's disease. Clin Neuropharmacol 1988; 11:512-519.
230. van Hilten B, Hoff JI, Middelkoop HA, et al: Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. Arch Neurol 1994; 51:922-928.
231. Paus S, Brecht HM, Koster J, et al: Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord 2003; 18:659-667.
232. Hobson DE, Lang AE, Martin WR, et al: Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. JAMA 2002; 287:455-463.
233. Garcia-Borreguero D, Larosa O, Bravo M: Parkinson's disease and sleep. Sleep Med Rev 2003; 7:115-129.
234. Tracik F, Ebersbach G: Sudden daytime sleep onset in Parkinson's disease: polysomnographic recordings. Mov Disord 2001; 16:500-506.
235. Ulivelli M, Rossi S, Lombardi C, et al: Polysomnographic characterization of pergolide-induced sleep attacks in idiopathic PD: Neurology 2002; 58:462-465.
236. Frucht S, Rogers JD, Greene PE, et al: Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52:1908-1910.
237. Schapira AH: Sleep attacks (sleep episodes) with pergolide. Lancet 2000; 355:1332-1333.
238. Olanow CW, Schapira AH, Roth T: Waking up to sleep episodes in Parkinson's disease. Mov Disord 2000; 15:212-215.
239. Rye DB, Bliwise DL, Dihenia B, et al: FAST TRACK: daytime sleepiness in Parkinson's disease. J Sleep Res 2000; 9:63-69.
240. Basson R: Sex and idiopathic Parkinson's disease. Adv Neurol 2001; 86:295-300.
241. Marsden CD: Problems with long-term levodopa therapy for Parkinson's disease. Clin Neuropharmacol 1994; 17(Suppl 2):S32-S44.
242. Hillen ME, Sage JI: Nonmotor fluctuations in patients with Parkinson's disease. Neurology 1996; 47:1180-1183.
243. Goetz CG, Tanner CM, Levy M, et al: Pain in Parkinson's disease. Mov Disord 1986; 1:45-49.
244. Hughes AJ, Daniel SE, Kilford L, et al: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55:181-184.
245. Hughes AJ, Daniel SE, Ben Shlomo Y, et al: The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002; 125(Pt 4):861-870.
246. Tolosa E, Wenning G, Poewe W: The diagnosis of Parkinson's disease. Lancet Neurol 2006; 5:75-86.
247. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287:1653-1661.
248. Whone AL, Watts RL, Stoessl AJ, et al: Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 2003; 54:93-101.
249. Hardie RJ, Lees AJ: Neuroleptic-induced Parkinson's syndrome: clinical features and results of treatment with levodopa. J Neurol Neurosurg Psychiatry 1988; 51:850-854.
250. Deuschl G, Bain P, Brin M: Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 1998; 13(Suppl) 3:2-23.
251. Cohen O, Pullman S, Jurewicz E, et al: Rest tremor in patients with essential tremor: prevalence, clinical correlates, and electrophysiologic characteristics. Arch Neurol 2003; 60:405-410.
252. Chaudhuri KR, Buxton-Thomas M, Dhawan V, et al: Long duration asymmetrical postural tremor is likely to predict development of Parkinson's disease and not essential tremor: clinical follow up study of 13 cases. J Neurol Neurosurg Psychiatry 2005; 76:115-117.
253. Wenning GK, Ben Shlomo Y, Magalhaes M, et al: Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 1994; 117:835-845.
254. Colosimo C, Albanese A, Hughes AJ, et al: Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from Parkinson's disease. Arch Neurol 1995; 52:294-298.
255. Hughes AJ, Colosimo C, Kleedorfer B, et al: The dopaminergic response in multiple system atrophy. J Neurol Neurosurg Psychiatry 1992; 55:1009-1013.
256. Litvan I, Agid Y, Calne D, et al: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47:1-9.
257. Collins SJ, Ahlskog JE, Parisi JE, et al: Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria. J Neurol Neurosurg Psychiatry 1995; 58:167-173.
258. Grimes DA, Lang AE, Bergeron CB: Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology 1999; 53:1969-1974.
259. Winikates J, Jankovic J: Clinical correlates of vascular parkinsonism. Arch Neurol 1999; 56:98-102.
260. Marder K, Tang MX, Cote L, et al: The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol 1995; 52:695-701.
261. McKeith I, Mintzer J, Aarsland D, et al: Dementia with Lewy bodies. Lancet Neurol 2004; 3:19-28.
262. Schrag A, Good CD, Miszkiel K, et al: Differentiation of atypical parkinsonian syndromes with routine MRI. Neurology 2000; 54:697-702.
263. Kraft E, Trenkwalder C, Auer DP: T2*-weighted MRI differentiates multiple system atrophy from Parkinson's disease. Neurology 2002; 59:1265-1267.
264. Schulz JB, Skalej M, Wedekind D, et al: Magnetic resonance imaging-based volumetry differentiates idiopathic Parkinson's syndrome from multiple system atrophy and progressive supranuclear palsy. Ann Neurol 1999; 45:65-74.
265. Scherfler C, Seppi K, Donnemiller E, et al: Voxel-wise analysis of [123I]beta-CIT SPECT differentiates the Parkinson variant of multiple system atrophy from idiopathic Parkinson's disease. Brain 2005; 128:1605-1612.
266. Marek KL, Seibyl JP, Zoghbi SS, et al: [123I] beta-CIT/SPECT imaging demonstrates bilateral loss of dopamine transporters in hemi-Parkinson's disease. Neurology 1996; 46:231-237.
267. Poewe W, Scherfler C: Role of dopamine transporter imaging in investigation of parkinsonian syndromes in routine clinical practice. Mov Disord 2003; 18(Suppl 7):S16-S21.
268. Braune S, Reinhardt M, Schnitzer R, et al: Cardiac uptake of [123I]MIBG separates Parkinson's disease from multiple system atrophy. Neurology 1999; 53:1020-1025.
269. Courbon F, Brefel-Courbon C, Thalamas C, et al: Cardiac MIBG scintigraphy is a sensitive tool for detecting cardiac sympathetic denervation in Parkinson's disease. Mov Disord 2003; 18:890-897.
270. Becker G, Seufert J, Bogdahn U, et al: Degeneration of substantia nigra in chronic Parkinson's disease visualized by

transcranial color-coded real-time sonography. Neurology 1995; 45:182-184.
271. Berg D, Siefker C, Becker G: Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. J Neurol 2001; 248:684-689.
272. Kimber J, Mathias CJ, Lees AJ, et al: Physiological, pharmacological and neurohormonal assessment of autonomic function in progressive supranuclear palsy. Brain 2000; 123:1422-1430.
273. Barker R, Duncan J, Lees A; Subcutaneous apomorphine as a diagnostic test for dopaminergic responsiveness in parkinsonian syndromes. Lancet 1989; 1:675.
274. Merello M, Nouzeilles MI, Arce GP, et al: Accuracy of acute levodopa challenge for clinical prediction of sustained long-term levodopa response as a major criterion for idiopathic Parkinson's disease diagnosis. Mov Disord 2002; 17:795-798.
275. Clarke CE, Davies P: Systematic review of acute levodopa and apomorphine challenge tests in the diagnosis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 2000; 69:590-594.
276. Rajput AH: Levodopa prolongs life expectancy and is nontoxic to substantia nigra. Parkinsonism Relat Disord 2001; 8:95-100.
277. Karlsen KH, Tandberg E, Arsland D, et al: Health related quality of life in Parkinson's disease: a prospective longitudinal study. J Neurol Neurosurg Psychiatry 2000; 69:584-589.
278. Clarke CE, Zobkiw RM, Gullaksen E: Quality of life and care in Parkinson's disease. Br J Clin Pract 1995; 49:288-293.
279. Williams DR, Lees AJ: Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. Lancet Neurol 2005; 4:605-610.
280. Evans AH, Katzenschlager R, Paviour D, et al: Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord 2004; 19:397-405.
281. Molina JA, Sainz-Artiga MJ, Fraile A, et al: Pathologic gambling in Parkinson's disease: a behavioral manifestation of pharmacologic treatment? Mov Disord 2000; 15:869-872.
282. Dodd ML, Klos KJ, Bower JH, et al: Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005; 62:1377-1381.
283. Fahn S: Adverse effects of levodopa. In Olanow CW, ed: The Scientific Basis for the Treatment of Parkinson's Disease. Carnforth: Parthenon Publishing Group, 1992, pp 89-112.
284. Contin M, Riva R, Martinelli P, et al: A levodopa kinetic-dynamic study of the rate of progression in Parkinson's disease. Neurology 1998; 51:1075-1080.
285. Shoulson I, Glaubiger GA, Chase TN: On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 1975; 25:1144-1148.
286. Hardie RJ, Lees AJ, Stern GM: On-off fluctuations in Parkinson's disease. A clinical and neuropharmacological study. Brain 1984; 107:487-506.
287. Mouradian MM, Heuser IJ, Baronti F, et al: Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. Ann Neurol 1990; 27:18-23.
288. Nutt JG: On-off phenomenon: relation to levodopa pharmacokinetics and pharmacodynamics. Ann Neurol 1987; 22:535-540.
289. Kurth MC, Tetrud JW, Tanner CM, et al: Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa/carbidopa in Parkinson's disease patients with "on-off" fluctuations. Neurology 1993; 43:1698-1703.
290. Kostic V, Przedborski S, Flaster E, et al: Early development of levodopa-induced dyskinesias and response fluctuations in young-onset Parkinson's disease. Neurology 1991; 41:202-205.
291. Obeso JA, Rodriguez-Oroz C, Chana P, et al: The evolution and origin of motor complications in Parkinson's disease. Neuroogy 2000; 55(Suppl 4):S13-S20.
292. Parkinson Study Group: Entacapone improves motor fluctuations in levodopa-treated Parkinson's disease patients. Ann Neurol 1997; 42:747-755.
293. Russ H, Muller T, Woitalla D, Rahbar A, Hahn J, Kuhn W: Detection of tolcapone in the cerebrospinal fluid of parkinsonian subjects. Naunyn Schmiedebergs Arch Pharmacol 1999; 360:719-720.
294. Hauser RA, Molho E, Shale H, et al: A pilot evaluation of the tolerability, safety, and efficacy of tolcapone alone and in combination with oral selegiline in untreated Parkinson's disease patients. Tolcapone De Novo Study Group. Mov Disord 1998; 13:643-647.
295. Jorga KM: COMT inhibitors: pharmacokinetic and pharmacodynamic comparisons. Clin Neuropharmacol 1998; 21:S9-S16.
296. Assal F, Spahr L, Hadengue A, et al: Tolcapone and fulminant hepatitis. Lancet 1998; 352:958.
297. Korlipara LV, Cooper JM, Schapira AH: Differences in toxicity of the catechol-O-methyl transferase inhibitors, tolcapone and entacapone to cultured human neuroblastoma cells. Neuropharmacology 2004; 46:562-569.
298. Marco AD, Appiah-Kubi LS, Chaudhuri KR: Use of the dopamine agonist cabergoline in the treatment of movement disorders. Exp Opin Pharmacother 2002; 3:1481-1487.
299. Olanow CW: Single blind double observer-controlled study of carbidopa/levodopa vs bromocriptine in untreated Parkinson patients. Arch Neurol 1988; 45:205.
300. Staal-Schreinemachers AL, Wesseling H, Kamphuis DJ, et al: Low-dose bromocriptine therapy in Parkinson's disease: double-blind, placebo-controlled study. Neurology 1986; 36:291-293.
301. Rinne UK, Bracco F, Chouza C, et al: Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 Collaborative Study Group. Neurology 1997; 48:363-368.
302. Rinne UK, Bracco F, Chouza C, et al: Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. Drugs 1998; 55. Suppl 1:23-30.
303. Barone P, Bravi D, Bermejo-Pareja F, et al: Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. Pergolide Monotherapy Study Group. Neurology 1999; 53:573-579.
304. Parkinson Study Group: Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. JAMA 1997; 278:125-130.
305. Shannon KM, Bennett JP Jr, Friedman JH: Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group. Neurology 1997; 49:724-728.
306. Korczyn AD, Brunt ER, Larsen JP, et al: A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. Neurology 1999; 53:364-370.
307. Adler CH, Sethi KD, Hauser RA, et al: Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group. Neurology 1997; 49:393-399.
308. Hoehn MM, Elton RL: Low dosages of bromocriptine added to levodopa in Parkinson's disease. Neurology 1985; 35:199-206.
309. Toyokura Y, Mizuno Y, Kase M, et al: Effects of bromocriptine on parkinsonism. A nation-wide collaborative double-blind study. Acta Neurol Scand 1985; 72:157-170.

310. Inzelberg R, Nisipeanu P, Rabey JM, et al: Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 1996; 47:785-788.
311. Olanow CW, Fahn S, Muenter M, et al: A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. Mov Disord 1994; 9:40-47.
312. Diamond SG, Markham CH, Treciokas LJ: Double-blind trial of pergolide for Parkinson's disease. Neurology 1985; 35:291-295.
313. Guttman M: Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology 1997; 49:1060-1065.
314. Lieberman A, Ranhosky A, Korts D: Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. Neurology 1997; 49:162-168.
315. Lieberman A, Olanow CW, Sethi K, et al: A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Ropinirole Study Group. Neurology 1998; 51:1057-1062.
316. Schapira AH: Excessive daytime sleepiness in Parkinson's disease. Neurology 2004; 63(Suppl 3):S24-S27.
317. Holloway RG, Shoulson I, Fahn S, et al: Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol 2004; 61:1044-1053.
318. Muller T, Fritze J: Fibrosis associated with dopamine agonist therapy in Parkinson's disease. Clin Neuropharmacol 2003; 26:109-111.
319. Van Camp G, Flamez A, Cosyns B, et al: Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004; 363:1179-1183.
320. Rascol O, Brooks DJ, Korczyn AD, et al: A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000; 342:1484-1491.
321. Parkinson Study Group: Pramipexole vs levodopa as initial treatment for Parkinson disease: A randomized controlled trial. JAMA 2000; 284:1931-1938.
322. Oertel WH: Pergolide versus levodopa (PELMOPET). Mov Disord 2000; 15(Suppl 3):4.
323. Schapira AH: Disease modification in Parkinson's disease. Lancet Neurol 2004; 3:362-368.
324. Parkinson Study Group: Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993; 328:176-183.
325. Olanow CW, Hauser RA, Gauger L, et al: The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol 1995; 38:771-777.
326. Shoulson I, Oakes D, Fahn S, et al: Impact of sustained deprenyl (selegiline) in levodopa-treated Parkinson's disease: a randomized placebo-controlled extension of the deprenyl and tocopherol antioxidative therapy of parkinsonism trial. Ann Neurol 2002; 51:604-612.
327. Ives NJ, Stowe RL, Marro J, et al: Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525. patients. BMJ 2004; 11:329.
328. Parkinson Study Group: A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 2004; 61:561-566.
329. Parkinson Study Group: A randomized placebo-controlled trial of rasagiline in levodopa-treated patients with Parkinson disease and motor fluctuations: the PRESTO study. Arch Neurol 2005; 62:241-248.
330. Rascol O, Brooks DJ, Melamed E, et al: Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 2005; 365:947-954.
331. Cantello R, Riccio A, Gilli M, et al: Bornaprine vs placebo in Parkinson disease: double-blind controlled cross-over trial in 30. patients. Ital J Neurol Sci 1986; 7:139-143.
332. Martin WE, Loewenson RB, Resch JA, et al: A controlled study comparing trihexyphenidyl hydrochloride plus levodopa with placebo plus levodopa in patients with Parkinson's disease. Neurology 1974; 24:912-919.
333. Cooper JA, Sagar HJ, Doherty SM, et al: Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. Brain 1992; 115:1701-1725.
334. Friedman JH, Koller WC, Lannon MC, et al: Benztropine versus clozapine for the treatment of tremor in Parkinson's disease. Neurology 1997; 48:1077-1081.
335. Schwab RS, England AC Jr, Poskanzer DC, Young RR: Amantadine in the treatment of Parkinson's disease. JAMA 1969; 208:1168-1170.
336. Factor SA, Molho ES: Transient benefit of amantadine in Parkinson's disease: the facts about the myth. Mov Disord 1999; 14:515-517.
337. Parkes JD, Baxter RC, Marsden CD, Rees JE: Comparative trial of benzhexol, amantadine, and levodopa in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1974; 37:422-426.
338. Walker JE, Albers JW, Tourtellotte WW, et al: A qualitative and quantitative evaluation of amantadine in the treatment of Parkinson's disease. J Chronic Dis 1972; 25:149-182.
339. Shulman LM, Minagar A, Rabinstein A, et al: The use of dopamine agonists in very elderly patients with Parkinson's disease. Mov Disord 2000; 15:664-668.
340. Schapira AH, Obeso JA; Timing of treatment initiation in Parkinson's disease: a need for re-appraisal? Ann Neurol 2006; 59:559-562.
341. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, et al: Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 2000; 23(Suppl):S8-S19.
342. Pifl C, Schingnitz G, Hornykiewicz O: Striatal and nonstriatal neurotransmitter changes in MPTP-parkinsonism in rhesus monkey: the symptomatic versus the asymptomatic condition. Neurochem Int 1992; 20(Suppl):295S-297S.
343. Sossi V, Fuente-Fernandez R, Holden JE, et al: Changes of dopamine turnover in the progression of Parkinson's disease as measured by positron emission tomography: their relation to disease-compensatory mechanisms. J Cereb Blood Flow Metab 2004; 24:869-876.
344. Hilker R, Schweitzer K, Coburger S, et al: Nonlinear progression of Parkinson disease as determined by serial positron emission tomographic imaging of striatal fluorodopa F 18 activity. Arch Neurol 2005; 62:378-382.
345. Bezard E, Boraud T, Bioulac B, et al: Involvement of the subthalamic nucleus in glutamatergic compensatory mechanisms. Eur J Neurosci 1999; 11:2167-2170.
346. Bezard E, Dovero S, Prunier C, et al: Relationship between the appearance of symptoms and the level of nigrostriatal degeneration in a progressive 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned macaque model of Parkinson's disease. J Neurosci 2001; 21:6853-6861.
347. Fabbrini G, Mouradian MM, Juncos JL, et al: Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part I: Ann Neurol 1988; 24:366-371.
348. Horstink MW, Zijlmans JC, Pasman JW, et al: Which risk factors predict the levodopa response in fluctuating Parkinson's disease? Ann Neurol 1990; 27:537-543.
349. Roos RA, Vredevoogd CB, van der Velde EA: Response fluctuations in Parkinson's disease. Neurology 1990; 40:1344-1346.

350. Koller WC, Hutton JT, Tolosa E, et al: Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. Neurology 1999; 53:1012-1019.
351. Stocchi F, Ruggieri S, Vacca L, et al: Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 2002; 125(Pt 9):2058-2066.
352. Stocchi F, Vacca L, Berardelli A, et al: Dual dopamine agonist treatment in Parkinson's disease. J Neurol 2003; 250:822-826.
353. Rinne UK, Larsen JP, Siden A, et al: Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology 1998; 51:1309-1314.
354. Lhermitte F, Agid Y, Signoret JL: Onset and end-of-dose levodopa-induced dyskinesias. Possible treatment by increasing the daily doses of levodopa. Arch Neurol 1978; 35:261-263.
355. Verhagen ML, Del Dotto P, van den MP, et al: Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. Neurology 1998; 50:1323-1326.
356. Metman LV, Del Dotto P, LePoole K, et al: Amantadine for levodopa-induced dyskinesias: a 1-year follow-up study. Arch Neurol 1999; 56:1383-1386.
357. Snow BJ, Macdonald L, Mcauley D, et al: The effect of amantadine on levodopa-induced dyskinesias in Parkinson's disease: a double-blind, placebo-controlled study. Clin Neuropharmacol 2000; 23:82-85.
358. Corrigan MH, Denahan AQ, Wright CE, et al: Comparison of pramipexole, fluoxetine, and placebo in patients with major depression. Depress Anxiety 2000; 11:58-65.
359. Lemke MR, Brecht HM, Koester J, et al: Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. J Neuropsychiatry Clin Neurosci 2005; 17:214-220.
360. Rektorova I, Rektor I, Bares M, et al: Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol 2003; 10:399-406.
361. Pollak P, Tison F, Rascol O, et al: Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry 2004; 75:689-695.
362. Fernandez HH, Trieschmann ME, Burke MA, et al: Long-term outcome of quetiapine use for psychosis among Parkinsonian patients. Mov Disord 2003; 18:510-514.
363. Mancini F, Tassorelli C, Martignoni E, et al: Long-term evaluation of the effect of quetiapine on hallucinations, delusions and motor function in advanced Parkinson disease. Clin Neuropharmacol 2004; 27:33-37.
364. Emre M, Aarsland D, Albanese A, et al: Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351:2509-2518.
365. Happe S, Pirker W, Sauter C, et al: Successful treatment of excessive daytime sleepiness in Parkinson's disease with modafinil. J Neurol 2001; 248:632-634.
366. Raffaele R, Vecchio I, Giammusso B, et al: Efficacy and safety of fixed-dose oral sildenafil in the treatment of sexual dysfunction in depressed patients with idiopathic Parkinson's disease. Eur Urol 2002; 41:382-386.
367. O'Sullivan JD: Apomorphine as an alternative to sildenafil in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002; 72:681.
368. Mancini F, Zangaglia R, Cristina S, et al: Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. Mov Disord 2003; 18:685-688.
369. Narabayashi H: Stereotaxic Vim thalamotomy for treatment of tremor. Eur Neurol 1989; 29(Suppl 1):29-32.
370. Tasker RR: Thalamotomy. Neurosurg Clin N Am 1990; 1:841-864.
371. Dogali M, Fazzini E, Kolodny E, et al: Stereotactic ventral pallidotomy for Parkinson's disease. Neurology 1995; 45:753-761.
372. Baron MS, Vitek JL, Bakay RA, et al: Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann Neurol 1996; 40:355-366.
373. Lang AE, Lozano AM, Montgomery E, et al: Posteroventral medial pallidotomy in advanced Parkinson's disease. N Engl J Med 1997; 337:1036-1042.
374. Fine J, Duff J, Chen R, et al: Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease. N Engl J Med 2000; 342:1708-1714.
375. Bergman H, Wichmann T, DeLong MR: Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990; 249:1436-1438.
376. Aziz TZ, Peggs D, Sambrook MA, et al: Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 1991; 6:288-292.
377. Guridi J, Herrero MT, Luquin MR, et al: Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis. Brain 1996; 119:1717-1727.
378. Alvarez L, Macias R, Guridi J, et al: Dorsal subthalamotomy for Parkinson's disease. Mov Disord 2001; 16:72-78.
379. Su PC, Tseng HM, Liu HM, et al: Treatment of advanced Parkinson's disease by subthalamotomy: one-year results. Mov Disord 2003; 18:531-538.
380. Alvarez L, Macias R, Lopez G, et al: Bilateral subthalamotomy in Parkinson's disease: initial and long-term response. Brain 2005; 128:570-583.
381. Chen CC, Lee ST, Wu T, et al: Hemiballism after subthalamotomy in patients with Parkinson's disease: report of 2 cases. Mov Disord 2002; 17:1367-1371.
382. Tseng HM, Su PC, Liu HM: Persistent hemiballism after subthalamotomy: the size of the lesion matters more than the location. Mov Disord 2003; 18:1209-1211.
383. Benabid AL, Pollak P, Louveau A, et al: Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987; 50:344-346.
384. Benazzouz A, Hallett M: Mechanism of action of deep brain stimulation. Neurology 2000; 55(Suppl 6):S13-S16.
385. Blond S, Caparros-Lefebvre D, Parker F, et al: Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J Neurosurg 1992; 77:62-68.
386. Benabid AL, Pollak P, Gao D, et al: Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996; 84:203-214.
387. Koller W, Pahwa R, Busenbark K, et al: High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 1997; 42:292-299.
388. Limousin P, Pollak P, Benazzouz A, et al: Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995; 345:91-95.
389. Limousin P, Krack P, Pollak P, et al: Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998; 339:1105-1111.
390. Kumar R, Lozano AM, Kim YJ, et al: Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 1998; 51:850-855.
391. Bejjani B, Damier P, Arnulf I, et al: Pallidal stimulation for Parkinson's disease. Two targets? Neurology 1997; 49:1564-1569.

392. Pahwa R, Wilkinson S, Smith D, et al: High-frequency stimulation of the globus pallidus for the treatment of Parkinson's disease. Neurology 1997; 49:249-253.
393. Siegfried J, Lippitz B: Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. Neurosurgery 1994; 35:1126-1129.
394. Volkmann J, Sturm V, Weiss P, et al: Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. Ann Neurol 1998; 44:953-961.
395. Krack P, Batir A, Van Blercom N, et al: Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003; 349:1925-1934.
396. The Deep-Brain Stimulation for Parkinson's Disease Study Group: Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001; 345:956-963.
397. Oh MY, Abosch A, Kim SH, et al: Long-term hardware-related complications of deep brain stimulation. Neurosurgery 2002; 50:1268-1274
398. Krack P, Pollak P, Limousin P, et al: Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann Neurol 1998; 43:180-192.
399. Freed CR, Greene PE, Breeze RE, et al: Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Eng J Med 2001; 344:710-719.
400. Greene PE, Fahn S, Tsai WY, et al: Severe spontaneous dyskinesias: a disabling complication of embryonic dopaminergic tissue implants in a subset of transplanted patients with advanced parkinson's disease. Mov Disor 1999; 14:904.
401. Olanow CW, Goetz CG, Kordower JH, et al: A double blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003; 54:403-414.
402. Bjorklund LM, Sanchez-Pernaute R, Chung S, et al: Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci U S A 2002; 99:2344-2349.
403. Gash DM, Zhang Z, Cass WA, et al: Morphological and functional effects of intranigrally administered GDNF in normal rhesus monkeys. J Comp Neurol 1995; 363:345-358.
404. Nutt JG, Burchiel KJ, Comella CL, et al: Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. Neurology 2003; 60:69-73.
405. Gill SS, Patel NK, Hotton GR, et al: Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. Nat Med 2003; 9:589-595.
406. Lang AE, Gill S, Patel NK, et al: Randomized control trial of intraputaminal glial cell line-derived neurotrophic factor infusion in Parkinson's disease. Ann Neurol 2006; 59:459-466.
407. Mytilineou C, Cohen G: Deprenyl protects dopamine neurons from the neurotoxic effect of 1-methyl-4-phenylpyridinium ion. J Neurochem 1985; 45:1951-1953.
408. Tatton WG, Greenwood CE: Rescue of dying neurons: a new action for deprenyl in MPTP parkinsonism. J Neurosci Res 1991; 30:666-672.
409. Wu RM, Chiueh CC, Pert A, et al: Apparent antioxidant effect of l-deprenyl on hydroxyl radical formation and nigral injury elicited by MPP+ in vivo. Eur J Pharmacol 1993; 243:241-247.
410. Wu RM, Chen RC, Chiueh CC: Effect of MAO-B inhibitors on MPP+ toxicity in Vivo. Ann N Y Acad Sci 2000; 899:255-261.
411. Tatton WG, Ju WY, Holland DP, et al: (-)-Deprenyl reduces PC12 cell apoptosis by inducing new protein synthesis. J Neurochem 1994; 63:1572-1575.
412. Wadia JS, Chalmers-Redman RM, Ju WJ, et al: Mitochondrial membrane potential and nuclear changes in apoptosis caused by serum and nerve growth factor withdrawal: time course and modification by (-)-deprenyl. J Neurosci 1998; 18:932-947.
413. Ogawa N, Tanaka K, Asanuma M, et al: Bromocriptine protects mice against 6-hydroxydopamine and scavenges hydroxyl free radicals in vitro. Brain Res 1994; 657(1-2):207-213.
414. Muralikrishnan D, Mohanakumar KP: Neuroprotection by bromocriptine against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in mice. FASEB J 1998; 12:905-912.
415. Kondo T, Ito T, Sugita Y: Bromocriptine scavenges methamphetamine-induced hydroxyl radicals and attenuates dopamine depletion in mouse striatum. Ann N Y Acad Sci 1994; 738:222-229.
416. Finotti N, Castagna L, Moretti A, et al: Reduction of lipid peroxidation in different rat brain areas after cabergoline treatment. Pharmacol Res 2000; 42:287-291.
417. Yoshioka M, Tanaka K, Miyazaki I, et al: The dopamine agonist cabergoline provides neuroprotection by activation of the glutathione system and scavenging free radicals. Neurosci Res 2002; 43:259-267.
418. Nishibayashi S, Asanuma M, Kohno M, et al: Scavenging effects of dopamine agonists on nitric oxide radicals. J Neurochem 1996; 67:2208-2211.
419. Gomez-Vargas M, Nishibayashi-Asanuma S, Asanuma M, et al: Pergolide scavenges both hydroxyl and nitric oxide free radicals in vitro and inhibits lipid peroxidation in different regions of the rat brain. Brain Res 1998; 790:202-208.
420. Iida M, Miyazaki I, Tanaka K, et al: Dopamine D2. receptor-mediated antioxidant and neuroprotective effects of ropinirole, a dopamine agonist. Brain Res 1999; 838:51-59.
421. Clow A, Freestone C, Lewis E, et al: The effect of pergolide and MDL 72974 on rat brain CuZn superoxide dismutase. Neurosci Lett 1993; 164:41-43.
422. Kakimura J, Kitamura Y, Takata K, et al: Release and aggregation of cytochrome c and alpha-synuclein are inhibited by the antiparkinsonian drugs, talipexole and pramipexole. Eur J Pharmacol 2001; 417:59-67.
423. Gu M, Iravani MM, Cooper JM, King D, et al: Pramipexole protects against apoptotic cell death by nondopaminergic mechanisms. J Neurochem 2004; 91:1075-1081.
424. Iravani MM, Haddon CO, Cooper JM, et al: Pramipexole protects against MPTP toxicity in nonhuman primates. J Neurochem 2006; 96:1315-1321.
425. Schapira AH, Olanow CW: Neuroprotection in Parkinson disease: mysteries, myths, and misconceptions. JAMA 2004; 291:358-364.
426. Ahlskog JE: Slowing Parkinson's disease progression: recent dopamine agonist trials. Neurology 2003; 60:381-389.
427. Olanow CW: A radical hypothesis for neurodegeneration. Trends Neurosci 1993; 16:439-444.
428. Agid Y, Olanow CW, Mizuno Y: Levodopa: why the controversy? Lancet 2002; 360:575.
429. Fahn S, Oakes D, Shoulson I, et al: Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351:2498-2508.
430. Albin RL, Frey KA; Initial agonist treatment of Parkinson disease: a critique. Neurology 2003; 60:390-394.
431. Wooten GF: Agonists vs levodopa in PD: the thrilla of whitha. Neurology 2003; 60:360-362.
432. Shults CW, Oakes D, Kieburtz K, et al: Effects of coenzyme Q_{10} in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002; 59:1541-1550.