Review Articles

Medical Progress

PARKINSON'S DISEASE

First of Two Parts

ANTHONY E. LANG, M.D., AND ANDRES M. LOZANO, M.D.

MORE than 180 years ago, James Parkinson first described the disorder that bears his name, and 30 years ago levodopa, still the most effective therapy, was introduced. Parkinson's disease is a neurodegenerative disorder of unknown cause that affects over 1 million people in North America. Age is the single most consistent risk factor, and with the increasing age of the general population, the prevalence of Parkinson's disease will rise steadily in the future. The impact of the disease is indicated by the fact that mortality is two to five times as high among affected persons as among age-matched controls,[1-3] resulting in a marked reduction in life expectancy.[2] In fact, neurodegenerative diseases (Parkinson's disease, motor neuron disease, and dementia) are projected to surpass cancer as the second most common cause of death among the elderly by the year 2040.[4] Thus, Parkinson's disease greatly shortens life as well as causing debility during life.

DIAGNOSIS AND CLINICAL FEATURES

The classic triad of major signs of Parkinson's disease is made up of tremor, rigidity, and akinesia. The diagnosis of Parkinson's disease is made on the basis of clinical criteria. Underdiagnosis is common; in recent door-to-door studies, up to 24 percent of cases were newly detected at the time of the survey.[5] Misdiagnosis is also an important problem, because the syndrome of parkinsonism may have a number of different causes, such as drugs, Wilson's disease, and other neurodegenerative diseases. The gold standard for the diagnosis of Parkinson's disease remains the neuropathological examination. There is still no biologic marker that unequivocally confirms the diagnosis. In autopsy studies, a final diagnosis of Parkinson's disease before death has been incorrect in about 24 percent of cases.[6,7] This figure will probably improve with the application of more rigorous diagnostic criteria. Table 1 summarizes features that may be helpful in distinguishing parkinsonism due to other common causes from Parkinson's disease.

The combination of asymmetry of symptoms and signs, the presence of a resting tremor, and a good response to levodopa best differentiates Parkinson's disease from parkinsonism due to other causes. Although asymmetric onset is typical of Parkinson's disease, it may also be seen in other disorders, particularly cortical–basal ganglionic degeneration (CBGD)[10] and hemiparkinsonism–hemiatrophy.[11] The infrequent occurrence of the classic 4-to-6-Hz tremor at rest in other parkinsonian disorders makes this a useful differentiating feature, but it is also absent in up to one quarter of cases of Parkinson's disease.[7] Well over 90 percent of patients with Parkinson's disease have a good initial response to levodopa. Thus, the absence of such a response is an important clue to an alternative diagnosis. However, other parkinsonian disorders, especially multiple-system atrophy,[8] may initially respond well to levodopa.

Routine imaging of the brain is rarely helpful in distinguishing parkinsonism due to other causes from Parkinson's disease. Magnetic resonance imaging (MRI) may show mixed low and high signal intensity and atrophy in the putamen in patients with striatonigral degeneration (one subtype of multiple-system atrophy),[12] pontine and cerebellar changes in olivopontocerebellar atrophy (another subtype of multiple-system atrophy), midbrain atrophy in progressive supranuclear palsy, asymmetric cortical atrophy in CBGD, and a mixture of striatal infarcts and subcortical and periventricular white-matter changes in cases of vascular parkinsonism. Other, rarer causes of parkinsonism, such as Wilson's disease, calcification of the basal ganglia, hydrocephalus, and brain tumors, are also associated with changes on anatomical imaging studies. Functional imaging techniques have been used extensively in an attempt to distinguish Parkinson's disease from other disorders. Table 2 provides a summary of these studies. Distinguishing Parkinson's disease from other diseases is important in establishing the diagnosis and the prognosis; this is particularly true in clinical investigations of Parkinson's disease, including studies of potential causal factors, and trials of new therapies such as neuroprotective agents and surgical procedures.

From the Division of Neurology, Department of Medicine (A.E.L.), and the Division of Neurosurgery, Department of Surgery (A.M.L.), University of Toronto and the Toronto Hospital; and the Morton and Gloria Shulman Movement Disorders Center, the Toronto Hospital (A.E.L.) — all in Toronto. Address reprint requests to Dr. Lang at Toronto Hospital, 399 Bathurst St., MP 11, Toronto, ON M5T 2S8, Canada.

TABLE 1. FEATURES THAT HELP TO DISTINGUISH PARKINSONISM DUE TO OTHER COMMON CAUSES FROM PARKINSON'S DISEASE.

DIAGNOSIS	IMPORTANT CLINICAL DISTINGUISHING FEATURES	RESPONSE TO LEVODOPA
Multiple-system atrophy (includes striatonigral degeneration, sporadic olivopontocerebellar atrophy, and Shy–Drager syndrome)	Early dysautonomia (including orthostatic hypotension and sexual impotence) and bladder dysfunction (with autonomic and nonautonomic components) Cerebellar dysfunction Pyramidal tract signs Stimulus-sensitive myoclonus of hands and face Extreme forward neck flexion Mottled, cold hands Inspiratory stridor Prominent dysarthria	Good response initially evident in 20 percent and sustained response in 13 percent[8] Dyskinesias or motor fluctuations possible; cranial dystonia may be prominent Patients wheelchair-bound despite response to levodopa (early loss of postural reflexes, with or without ataxia)
Progressive supranuclear palsy	Supranuclear vertical ophthalmoplegia Other oculomotor and eyelid disturbances Axial rigidity greater than limb rigidity Early falls, speech and swallowing disturbances Nuchal extension Cognitive or behavioral changes Higher incidence of hypertension than in Parkinson's disease and other neurodegenerative causes of parkinsonism[9]	Good response rarely evident; benefit only to classic parkinsonian features such as limb rigidity, bradykinesia, and rare examples of tremor at rest
Cortical–basal ganglionic (corticobasal) degeneration	Apraxia, cortical sensory changes, alien-limb phenomenon Pronounced asymmetric rigidity Limb dystonia Stimulus-sensitive myoclonus	Usually negligible
Vascular parkinsonism	"Lower-half" parkinsonism with gait disturbances predominating, often with minimal upper-body involvement Additional neurologic deficits (e.g., pyramidal tract signs, pseudobulbar palsy)	Usually poor
Dementia with Lewy bodies	Early dementia Rigidity usually more prominent than bradykinesia or tremor Spontaneous hallucinations, fluctuating cognitive status, falls Pronounced sensitivity to extrapyramidal side effects of neuroleptic drugs	Motor features may respond well; psychiatric side effects

Dementia is increasingly recognized as an important feature of Parkinson's disease in the elderly. A new diagnosis of dementia occurs 6.6 times as frequently in elderly patients with Parkinson's disease as in elderly controls.[27] In a large population-based survey in Norway, 28 percent of patients with Parkinson's disease had dementia,[28] and in another study, 65 percent of surviving members of a cohort of patients over the age of 85 had dementia.[27] The presence of dementia further shortens survival in patients with Parkinson's disease.[3]

PATHOLOGICAL FINDINGS

Parkinson's disease is characterized by the progressive death of selected but heterogeneous populations of neurons (Fig. 1), including the neuromelanin-laden dopaminergic neurons of the pars compacta of the substantia nigra, selected aminergic brain-stem nuclei (both catecholaminergic and serotoninergic), the cholinergic nucleus basalis of Meynert, hypothalamic neurons, and small cortical neurons (particularly in the cingulate gyrus and entorhinal cortex), as well as the olfactory bulb, sympathetic ganglia, and parasympathetic neurons in the gut. Not all dopaminergic projection areas are equally susceptible. Within the substantia nigra pars compacta, neuronal loss tends to be greatest in the ventrolateral tier (loss is estimated to be 60 to 70 percent at the onset of symptoms), followed by the medial ventral tier and dorsal tier.[29] This pattern of cell loss is relatively specific to Parkinson's disease; it is the opposite of that seen in normal aging and differs from patterns found in striatonigral degeneration and progressive supranuclear palsy. It results in a regional loss of striatal dopamine, most prominently in the dorsal and intermediate subdivisions of the putamen,[30] a process that is believed to account for akinesia and rigidity. This pattern of cell loss also correlates with the degree of expression of messenger RNA for the dopamine transporter.[31] Another important pathological feature is the presence of degenerating ubiquitin-positive neuronal processes or neurites (Lewy neurites),

TABLE 2. FUNCTIONAL IMAGING IN THE DIAGNOSIS OF PARKINSONISM.*

AREA OF INTEREST	TECHNIQUE	FINDINGS IN PARKINSON'S DISEASE	FINDINGS IN OTHER PARKINSONIAN DISORDERS
Status of nigral dopaminergic neurons	PET with F-dopa, others SPECT with [^{123}I]β–CIT,[13,14] others	Putamen uptake reduced much more than caudate nucleus uptake	In multiple-system atrophy: putamen uptake reduced more than caudate nucleus uptake In PSP or CBGD: reduction in caudate nucleus uptake equivalent to that in putamen[15] Normal uptake in manganese toxicity,[16] dopa-responsive dystonia[17]
Striatal dopamine receptors (most current ligands bind dopamine D2 receptors)	PET with [^{11}C]raclopride, [^{11}C]methylspiperone SPECT with [^{123}I]iodobenzamide,[18] others	Uptake increased in putamen in untreated Parkinson's disease; normalized by treatment and may be reduced late in disease[19]	Reduced uptake in striatum in diseases in which neurodegeneration or damage affects dopamine-receptor–bearing striatal neurons (e.g., multiple-system atrophy)
Striatal opiate receptors	PET with [^{11}C]diprenorphine	Uptake normal; reduced uptake in patients with dyskinesias[20]	Uptake reduced in multiple-system atrophy and PSP[21]
Cerebral metabolism	PET with [^{18}F]fluorodeoxyglucose	Regional metabolism normal; "scaled subprofile model" demonstrates distinctive topographic contrast profile characterized by covarying metabolic asymmetries of basal ganglia and thalamus[22]	Regional metabolism reduced in areas of degeneration; relative metabolic patterns differ from those in Parkinson's disease
Neuronal integrity and metabolism	^{1}H-labeled magnetic resonance spectroscopy for neuronal marker NAA (also NAA:creatine ratio)	Levels normal in striatum[23,24] (one study found reduced levels in patients with untreated Parkinson's disease but normal levels in treated patients[25])	Reduced levels in striatum and variably in other areas in PSP,[24] multiple-system atrophy,[23] CBGD,[24] and parkinsonism due to boxing[26]

*PET denotes positron-emission tomography, SPECT single-photon-emission computed tomography, [^{123}I]β–CIT iodine 123-2β-carbomethoxy-3β-(4-iodophenyl)tropane, PSP progressive supranuclear palsy, CBGD cortical–basal ganglionic degeneration, and NAA *N*-acetyl aspartate.

which are found in all affected brain-stem regions, especially the dorsal motor nucleus of the vagus.[32]

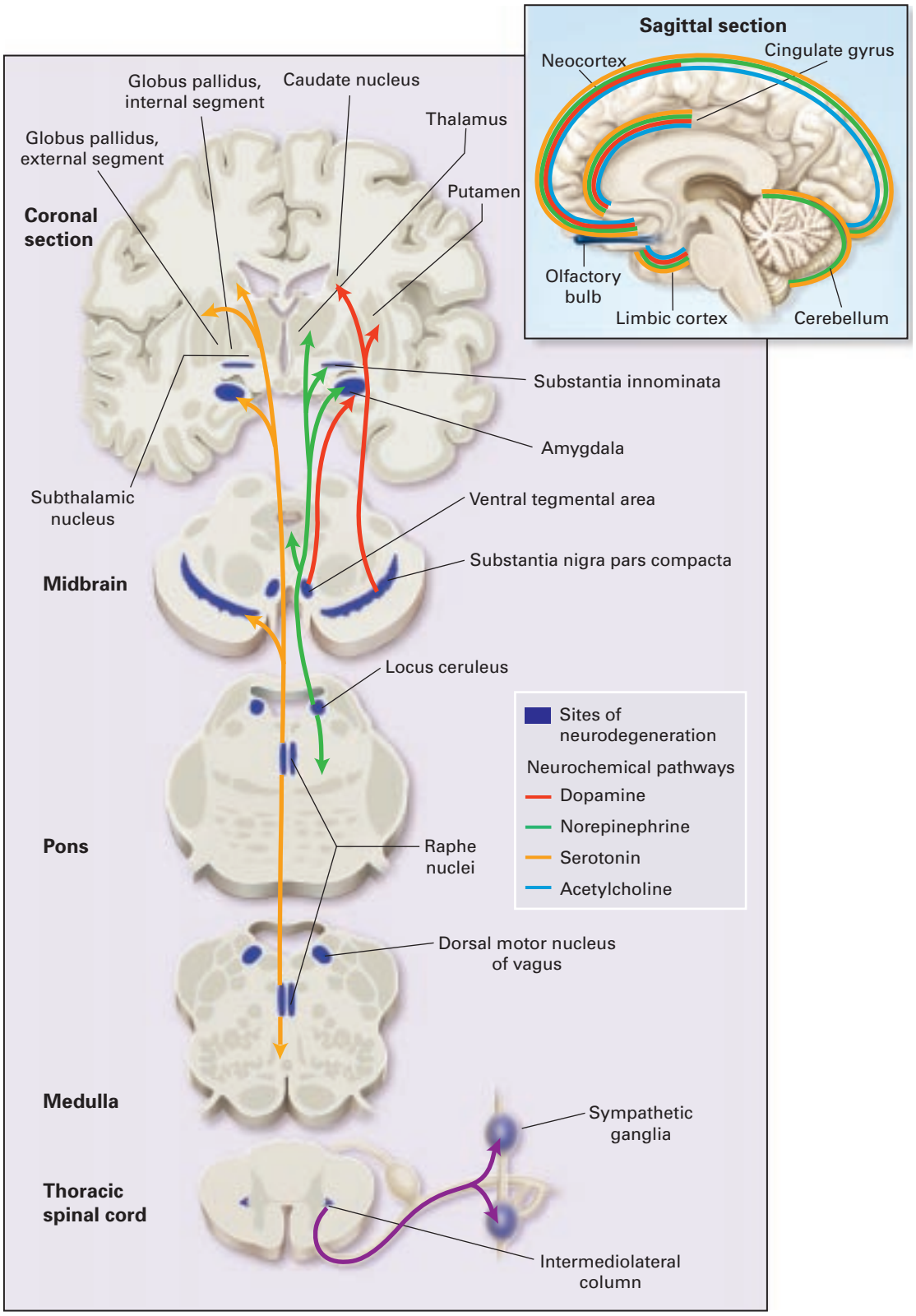
It has been suggested that a greater degree of medial nigral cell loss, with enhanced involvement of projections to the caudate nucleus, could result in more cognitive dysfunction.[33] Other potential factors in the varied cognitive changes in Parkinson's disease[34] include the involvement of other subcortical structures, such as the nucleus basalis of Meynert and locus caeruleus, and cerebral cortical areas, especially the entorhinal cortex. In the autopsy series described by Hughes et al.,[7] 44 percent of patients found to have Parkinson's disease had dementia in life; of these, 29 percent had coexisting Alzheimer's disease, 10 percent had numerous cortical Lewy bodies (dementia with Lewy bodies is now recognized as the second most common cause of neurodegenerative dementia[35]), and 6 percent had a possible vascular cause, leaving 55 percent with no definite pathological explanation for the dementia other than Parkinson's disease. Recently, the degree of cognitive impairment in this last group of patients was shown to be correlated with the density of Lewy neurites in the CA2 field of the hippocampus.[36] Other possible clinical–pathological correlations include neurodegenerative changes in the olfactory bulb causing anosmia; degeneration in the intermediolateral columns of the spinal cord, sympathetic and

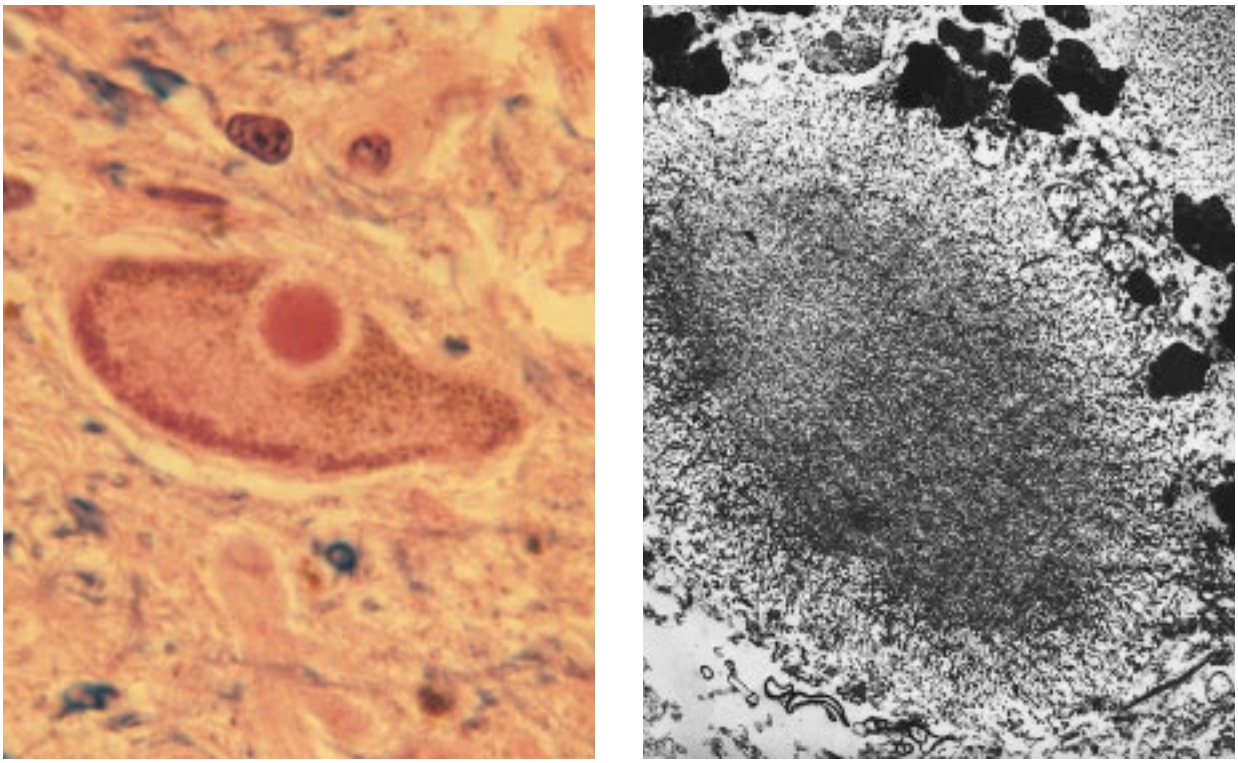
Figure 1. The Sites of Neurodegeneration and Neurochemical Pathways Involved in Parkinson's Disease.

The sites characterized by pathological changes in Parkinson's disease are dark blue (see the text for details). The neurochemical pathways that are affected by this disease are indicated by the colored arrows. The destinations of these pathways are indicated on the axial "sections" by the points of the arrows and on the sagittal section of the brain by colored outlining (red indicates dopamine; green, norepinephrine; orange, serotonin; and turquoise, acetylcholine).

The most important site of changes is the substantia nigra pars compacta, the origin of the dopaminergic nigrostriatal tract (to the caudate nucleus and putamen). The ventral tegmental area projects dopaminergic pathways to the entorhinal cortex, olfactory tubercle, cingulate gyrus, and frontal cortex. The locus ceruleus projects widespread noradrenergic connections to the spinal cord (descending arrow), cerebellum, central gray matter of the midbrain, amygdala, substantia innominata, thalamus, limbic cortex, and neocortex. The raphe nuclei project widespread serotonergic fibers to the spinal cord (descending arrow), cerebellum, substantia nigra, amygdala, striatum, and cortex. The substantia innominata contains the nucleus basalis of Meynert, the source of widespread cerebral cholinergic input. Finally, the intermediolateral column is the source of preganglionic sympathetic fibers (purple).

Dopamine deficiency in the nigrostriatal pathway accounts for most of the classic clinical motor features of Parkinson's disease. The exact roles of the well-established disturbances in the other neurochemical pathways in the genesis of various motor and nonmotor features of Parkinson's disease remain uncertain.


Sagittal section
Neocortex
Cingulate gyrus
Olfactory bulb
Limbic cortex
Cerebellum
Coronal section
Globus pallidus, internal segment
Caudate nucleus
Thalamus
Globus pallidus, external segment
Putamen
Substantia innominata
Amygdala
Subthalamic nucleus
Ventral tegmental area
Substantia nigra pars compacta
Midbrain
Locus ceruleus
Sites of neurodegeneration
Neurochemical pathways
Dopamine
Norepinephrine
Serotonin
Acetylcholine
Pons
Raphe nuclei
Dorsal motor nucleus of vagus
Medulla
Sympathetic ganglia
Thoracic spinal cord
Intermediolateral column



A B

Figure 2. A Typical Lewy Body.

Panel A shows the Lewy body in the cytoplasm of a pigmented dopaminergic neuron in the substantia nigra (hematoxylin–eosin and Luxol fast blue, ×100). Ultrastructural examination (Panel B) shows an accumulation of filaments and granular material with a dense core and loose radiating peripheral filaments (×21,560). Courtesy of Dr. Catherine Bergeron.

parasympathetic ganglia, and possibly the central amygdaloid nucleus[37] causing autonomic dysfunction; and degeneration in the brain-stem serotoninergic and noradrenergic nuclei and possibly the amygdaloid nucleus causing behavioral dysfunction, including depression, which occurs in approximately one quarter of patients.[38]

The Lewy body is an eosinophilic hyaline inclusion consistently observed in selectively vulnerable neuronal populations. Lewy bodies in the brain stem and basal forebrain are usually more than 15 μm in diameter, with a spherical, dense hyaline core, a clear halo, and often a targetoid appearance (Fig. 2). Cortical Lewy bodies, which are more readily seen with anti-ubiquitin staining, are smaller and lack a distinct core. The accumulation of neurofilaments in Lewy bodies appears to be chiefly the result of post-translational changes that occur after their normal synthesis and assembly, rather than the result of altered neurofilament expression.[39] The Lewy body contains a variety of other constituents, and its antigenic determinants can be divided into four groups[40]: structural elements of Lewy-body filaments, proteins that represent a cellular response to Lewy-body formation, enzymes such as phosphatases and kinases, and other cytosolic proteins that probably become trapped in Lewy bodies during their formation. The mechanism of Lewy-body formation, the importance of the Lewy body to the pathogenesis of Parkinson's disease, and its role in the neurodegenerative process remain unknown.

The Lewy body may be a nonspecific feature, unrelated to the pathogenesis of the disorder. In favor of this argument is the fact that Lewy bodies are not specific to Parkinson's disease and are found in small numbers in other neurodegenerative disorders. Their presence might also indicate neurons that have sequestered toxic proteins and have thus provided a successful defense against the neurodegenerative process. However, an alternative view is that the formation of Lewy bodies from neurofilament subunits could alter the critical structural functions of neurofilaments in axons, possibly leading to a dying back of the axonal connections from the pars compacta of the substantia nigra to the striatum.[41] Gibb and Lees[42] found that the age-specific prevalence of Lewy bodies in the brains of persons without clinically evident Parkinson's disease increased from 3.8

percent to 12.8 percent between the sixth and ninth decades of life. Associated pathological changes suggested that such incidental Lewy-body disease is actually a presymptomatic stage of Parkinson's disease. The prevalence of incidental Lewy-body disease is 5 to 20 times that of overt Parkinson's disease. If in fact it does represent preclinical Parkinson's disease, the magnitude of the problem is staggering, since the prevalence of Parkinson's disease in the population over the age of 80 years is 1 in 10.

The duration of the preclinical phase, between the onset of the pathological changes in the nigra and the loss of sufficient striatal dopamine to cause symptoms of Parkinson's disease, has been controversial and has implications for a number of issues. Studies of potential causal factors (e.g., possible exposure to an exogenous toxin), the evaluation of preclinical diagnostic testing (e.g., positron-emission tomography), and the use of protective therapies, when these become available, in populations at risk would all be strongly influenced by knowledge of the duration of this preclinical period. Some studies have suggested a very long preclinical or prodromal period (up to several decades)[43]; however, postmortem data[29,44] and studies using positron-emission tomography[45] support a latency period of less than five years.

PATHOGENESIS AND MECHANISMS OF CELL DEATH

In humans the pars compacta of the substantia nigra contains approximately 450,000 dopaminergic neurons. As estimated on the basis of positron-emission tomography with [^{18}F]fluoro-L-dopa (F-dopa) and postmortem studies, the rate of nigral neuronal loss is faster initially and then tends to approach the normal age-related decline.[29,46] 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a meperidine analogue occasionally used accidentally by heroin addicts, is a potent neurotoxin with selective effects on nigral dopaminergic neurons. Severe parkinsonism has developed in some subjects exposed to MPTP, whereas others have had subtle neurologic deficits or none. Follow-up studies with positron-emission tomography in the latter cases[47] also showed a slow, progressive decline in F-dopa activity. This apparently progressive neurodegeneration after a brief exposure to a neurotoxin earlier in life, combined with other evidence such as the well-known occurrence earlier in this century of delayed-onset, progressive parkinsonism after encephalitis lethargica, suggests that Parkinson's disease may arise as a consequence of a single event rather than an ongoing process.[48] The propensity for such events to lead to parkinsonism is also believed to be related to predetermined genetic susceptibility (as discussed below).

The mechanisms responsible for cell death in Parkinson's disease are largely unknown. Increasing evidence suggests that neuronal death in the pars compacta of the substantia nigra may be apoptotic,[49] but this notion is not universally accepted.[50] Among the factors that have been implicated in neuronal degeneration in Parkinson's disease are mitochondrial dysfunction, oxidative stress, the actions of excitotoxins, deficient neurotrophic support, and immune mechanisms. A critical question is why specific neurons are selectively vulnerable in Parkinson's disease. One possible answer may lie in their ability to take up both endogenous and extrinsic toxic compounds through selective carrier mechanisms, such as the dopamine transporter. Other possible explanations include increased metabolic stress, high physiologic rates of protein oxidation, selective generation of potential toxins or failure to detoxify or dispose of them (possibly because of the presence of neuromelanin), and specific requirements for neurotrophic support.

Mitochondrial Dysfunction and Oxidative Metabolism

Mitochondrial dysfunction and oxidative metabolism are critical components of most current theories of nigral degeneration in Parkinson's disease. MPTP toxicity is due to the inhibition of complex I (NADH–ubiquinone oxidoreductase) of the mitochondrial electron-transport chain, leading to energy failure and cell death. In Parkinson's disease, there is a 30 to 40 percent decrease in complex I activity in the substantia nigra pars compacta,[51] as well as a lesser defect in other tissues.[52,53] This defect could contribute to energy failure of the cell, predisposing it to other toxic or genetic insults or increasing its susceptibility to apoptosis.

Under normal circumstances there is a tight regulation of the production and disposal of several powerful oxidants that are produced in the course of neural metabolism. These include hydrogen peroxide, as well as radicals (any species that contain one or more unpaired electrons) such as superoxide, peroxyl radicals, nitric oxide, and hydroxyl radicals. These molecules react with nucleic acids, proteins, lipids, and other molecules, altering their structure and causing cellular damage. Several lines of evidence suggest that in Parkinson's disease, there is an excess of reactive oxygen species and increased oxidative stress. Elevation of iron levels detected in the pars compacta of the substantia nigra in patients with Parkinson's disease is believed to be an important factor in causing oxidative stress.[54] Interestingly, increased iron and reduced complex I activity are not found in the brains of patients with incidental Lewy body disease, suggesting that these may be later or secondary changes. However, a reduction in the level of reduced glutathione is evident even at this early stage.[55]

The metabolism of endogenous dopamine may also produce a number of toxic byproducts that could contribute to the heightened state of oxidative stress in Parkinson's disease.[56] This possibility has

prompted the concern that treatment with levodopa, through its conversion to dopamine, may further accelerate the death of neurons in the pars compacta of the substantia nigra. Indeed, this was one of the arguments for delaying the use of levodopa in Parkinson's disease[57] although, as we will discuss in the second part of this review, experimental evidence of the toxic effects of levodopa is conflicting, and clinical observations in humans without Parkinson's disease who are given levodopa do not confirm its toxicity.[58]

Excitotoxins

The concept of excitotoxicity has been applied to a number of neurodegenerative diseases, including Parkinson's disease.[59] Persistent activation of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor increases intracellular levels of calcium ions, potentially leading to the activation of proteases, endonucleases, phospholipases, and nitric oxide synthase, with the resulting generation of reactive nitric oxide free radicals. This process, furthermore, releases iron from ferritin, induces lipid peroxidation, and impairs mitochondrial function. The role of increased intracellular calcium ions in the events leading to cell death is supported by the observation that dopaminergic neurons expressing the calcium-binding protein calbindin may be selectively preserved in Parkinson's disease.[60] As we will discuss in the second part of this review, the subthalamic nucleus is overactive in Parkinson's disease. The resulting excessive glutamatergic drive could be a source of excitotoxicity in the nigra.

Neurotrophic Factors

Neurotrophic factors have an important role in neuronal survival and differentiation during development and after injury. Inadequate levels of neurotrophic support lead to apoptotic neuronal death in several systems. Glial-derived neurotrophic factor (GDNF)[61] and brain-derived neurotrophic factor (BDNF) have potent protective and regenerative effects on dopaminergic neurons.[62,63] The discovery of the benefits of BDNF and GDNF in animal models of parkinsonism raises the possibility that the supply of these or other neurotrophic substances may be limited or that their downstream signaling paths may be dysfunctional in Parkinson's disease, leading to degeneration of dopaminergic cells.

Immune Factors

Finally, immune factors may contribute, at least secondarily, to progressive nigral cell loss. This possibility is supported by the finding of HLA-DR–positive reactive microglia,[64] as well as increased levels of cytokines such as interleukin-1 and tumor necrosis factor α in the pars compacta of the substantia nigra even in the late stages of the illness.

EPIDEMIOLOGY AND GENETICS

Parkinson's disease occurs throughout the world, in all ethnic groups, and affects both sexes roughly equally or with only a slight predominance among males.[65] The prevalence increases exponentially with age between 65 and 90 years; approximately 0.3 percent of the general population and 3 percent of people over the age of 65 have Parkinson's disease.[66] Five to 10 percent of patients have symptoms before the age of 40 (this variety of the disorder is classified as "young-onset Parkinson's disease"). The lowest reported incidence is among Asians and African blacks, whereas the highest is among whites. African blacks have a much lower incidence than American blacks; however, the prevalence of Lewy bodies in the brains of Nigerians is similar to that in Western populations.[67] This pattern suggests that the propensity for the development of Parkinson's disease is universal but that local environmental factors may have a role in causing the disorder; however, underascertainment rather than fundamental environmental differences could also explain these findings.

Although the disease was first formally described at the time of the Industrial Revolution — a fact that suggests that exogenous toxins may have an important causative role — descriptions of what could well have been Parkinson's disease (*kampavata,* which consisted of tremor and akinesia) are found in ancient ayurvedic literature in India (from 4500 to 1000 B.C.).[68] The discovery of the selective ability of MPTP to induce nigral cell death spawned broad interest in potential environmental factors capable of causing Parkinson's disease. This concept is further supported by the ability of various toxins to cause symptomatic forms of parkinsonism.[69]

A rural environment has generally, although not always, been found to be associated with an elevated risk of Parkinson's disease. There is varying support for a relation with such factors as the use of herbicides or pesticides and exposure to well water. Even if one accepts the role of pesticide use, the proportion of patients with such exposure, and therefore the importance of this risk to the public health, is limited to approximately 10 percent (95 percent confidence interval, 2 to 25 percent) of the population with Parkinson's disease.[70]

One factor consistently associated with a reduced risk of Parkinson's disease is smoking.[71] One of the more recent large-scale evaluations demonstrating this negative association found that ever having smoked reduced the risk of Parkinson's disease by half (the odds ratio for ever having smoked among patients with Parkinson's disease, as compared with the general population, was 0.5 [95 percent confidence interval, 0.3 to 0.7]).[72] However, another recent study found that this reduction in risk was restricted to those with a relatively young age at the onset of disease.[73]

A number of studies have evaluated diet in patients with Parkinson's disease, in an attempt to assess the possible role of inadequate intake of antioxidants, which might have predisposed patients to insult from other exogenous or endogenous sources. In general, these studies have been inconclusive, although a recent large, community-based study in the Netherlands found that vitamin E intake was significantly lower among patients with Parkinson's disease than among controls.[74]

There is increasing evidence that genetic factors have an important role in Parkinson's disease. Several other causes of parkinsonism are hereditary.[75] Earlier studies of twins were originally believed to have excluded an important genetic contribution to Parkinson's disease, since they failed to show a higher concordance among monozygotic than among dizygotic twins.[76] However, several lines of evidence have suggested the need for a reconsideration of this issue. A recent large study, for example, found high rates of concordance among monozygotic twins when one twin had young-onset disease.[77] Epidemiologic studies have found that, apart from age, a family history of Parkinson's disease is the strongest predictor of an increased risk of the disease,[78] although the role of shared environmental exposure in some families must be considered. A small number of multigenerational families have been reported to have pathologically confirmed Parkinson's disease (including Lewy bodies).[79] However, in most of these families the disease has somewhat atypical features, such as an onset at a young age, a rapid course to death, and frequent dementia.

Most of the available evidence supports an autosomal dominant inheritance of Parkinson's disease, even in families with a small number of affected members. To date, evaluations of candidate genes involved in the dopamine system in these families and in patients with apparently sporadic Parkinson's disease have been generally unrewarding. A major breakthrough in this field has recently come with the identification of two distinct mutations in the α-synuclein gene (*SNCA*) located on chromosome 4q. One mutation (Ala53Thr) was reported in a single large Italian family with very high penetrance (roughly 90 percent) and three smaller Greek families that may be very distantly related,[80] and the other (Ala30Pro) was reported in a family of German origin.[81] α-Synuclein is a highly conserved, abundant 140-amino-acid protein of unknown function that is expressed mainly in presynaptic nerve terminals in the brain.[82] These observations promise to provide important insights into the pathogenesis of nigral degeneration and Lewy-body pathology.[83,84] However, several studies have failed to detect mutations in *SNCA* in a large number of other families[81,85,86] and in sporadic cases,[81] suggesting that Parkinson's disease is only rarely caused by such mutations. In contrast to the somewhat atypical clinical features of the disease in the families with mutations in the gene coding for α-synuclein (especially the young age at onset and the rapid course), linkage to chromosome 2p13 has been found in six families with parkinsonism that more closely resembles sporadic Parkinson's disease (mean age at onset, 54 to 63 years).[87] In this instance penetrance was 40 percent or less, suggesting that this and other low-penetrance susceptibility alleles may underlie the disease process, whereas other factors, both genetic and nongenetic, could determine the severity of the disease.

Most patients do not have a clear family history of autosomal dominant disease, probably because either the causative genes have low penetrance or the cause of the disorder is multifactorial (a combination of genetic predisposition and environmental exposure). Numerous studies have searched for genetic factors that predispose people to injury from various exogenous toxins. Of all the detoxifying enzymes, debrisoquine 4-hydroxylase (CYP2D6) has received the most attention, and it has been suggested that people who metabolize debrisoquine poorly could be predisposed to the toxic effects of certain substrates of the CYP2D6 enzyme system. Despite initially positive research findings, there is increasing evidence against this association, however.[88] On the other hand, a recent study, which also failed to confirm the role of CYP2D6, found that the slow-acetylator genotype for *N*-acetyltransferase 2 was present significantly more often in patients with familial Parkinson's disease (prevalence, 69 percent) than in controls (37 percent), whereas the frequency in patients with sporadic Parkinson's disease was intermediate between the two.[89]

A critical question is whether the changes defined in mitochondrial complex I function are inherited or acquired.[90] Although only rare families have been thought to show the matrilineal inheritance typical of mitochondrial disorders,[91] Swerdlow et al.[92] have provided convincing evidence of widespread and genetically based mitochondrial dysfunction in Parkinson's disease in studies with engineered cells, known as "cybrids," in which the mitochondrial DNA came from patients with Parkinson's disease but the chromosomal DNA did not. These cybrids have a 20 percent reduction in complex I activity, increased production of oxygen radicals, and increased susceptibility to MPP^+ (1-methyl-4-phenylpyridinium ion). These findings are compatible with either an inherited defect of mitochondrial DNA or an acquired disorder resulting from direct damage (e.g., damage caused by a toxin) to the mitochondrial genome of the parkinsonian donor platelets.

The general goal of current genetic studies in the area of Parkinson's disease is to find putative susceptibility genes. It is believed that a robust method of achieving this goal is the use of the sibling-pair tech-

nique, which requires large-scale collaboration. Several of these studies are under way. Finally, mention must be made of an autosomal recessive form of neuronal degeneration involving the pars compacta of the substantia nigra and locus caeruleus without Lewy-body formation, which causes young-onset (often juvenile-onset) levodopa-responsive parkinsonism. Very recently, mutations of a newly defined gene on the long arm of chromosome 6 have been identified in patients with this disorder.[93] The protein product, named parkin, is homologous with the ubiquitin family of proteins involved in the pathogenesis of several neurodegenerative diseases. Although this disorder was originally believed to be rare and to occur almost exclusively in the Japanese, there is mounting evidence that it is found in other populations and may account for a substantial minority of patients previously considered to have young-onset Parkinson's disease.

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