1 On Parkinson's Disease

This book presents a theory concerning certain symptoms associated with the major neuropsychiatric disorders of Parkinson's disease (PD). We will, therefore, need to present the basics of PD for readers not familiar with the condition.

PD is a progressive neurodegenerative disorder that most commonly strikes people over 60 years of age. The mean duration of the disease is approximately 13 years, and the mean age at death is approximately 73. Its cardinal clinical manifestations are four major motor deficits: resting tremor, rigidity, bradykinesia, and gait dysfunction. I will discuss these fundamental motor problems more thoroughly later. PD, however, is also associated with many nonmotor deficits, including autonomic dysfunction, pain, mood disorders, sleep problems, and cognitive impairment. Both the motor and the nonmotor deficits of PD are due, in part, to degeneration of pigmented dopaminergic neurons in the substantia nigra pars compacta (SNc) coupled with intracytoplasmic proteinaceous inclusions known as Lewy bodies. There is degeneration in all of the other major neurotransmitter nuclei (e.g., the noradrenergic locus caeruleus, the serotonergic raphe nucleus, etc.) as well, but given that the motor deficits and some of the nonmotor deficits of PD can be partially reversed or alleviated by dopamine replacement therapy, it is reasonable to assume that loss of midbrain dopamine contributes significantly (but not solely) to these motor and some of the nonmotor (neuropsychiatric/cognitive) deficits of PD.

This book is concerned primarily with the neuropsychiatric and cognitive deficits of PD, though I believe the nonmotor features of PD are significantly influenced by the motor dysfunction of the disease. Both the motor and nonmotor features of the disease are partially due to and shaped by reduction in the magnitude of phasic bursting in dopaminergic terminals that carry predicted error signals vis-à-vis motor outputs and behavioral actions. I will be arguing that the cognitive, mood, and personality changes of PD are essentially due to inability to activate fully agentic

aspects of the self that (as I will show in a later chapter) are themselves rooted in motor and cognitive control system dynamics that depend on phasic bursting in nigrostriatal, basal ganglia, and mesocortical dopamine systems.

What Is Parkinson's Disease?

Parkinson's disease is the second most common neurodegenerative disorder (after Alzheimer's disease) with an estimated 5 million affected people throughout the world. These numbers should rise as populations age and environmental toxins proliferate (age and toxins are two major risk factors for PD).

Men are twice as likely as women to develop PD. Estrogens may offer some protection against PD, as when women develop PD, they develop it at an older age on average than do men. If men have the disease, they manifest motor symptoms of PD at about age 60, but if women have PD, they typically manifest the motor symptoms at age 62 or 63. In the first few years of the disease, women, on average, also exhibit less severe motor deficits but more severe treatment-related dyskinesias. Dyskinesias are uncontrollable and sometimes painful jerky and jumpy movements and motor tics.

A notable recent study (Gao, Simon, Han, Schwarzschild, & Ascherio, 2009) suggested that people with red hair had an approximately twofold higher risk for PD relative to those with black hair. People who carried a gene mutation that influences both skin and hair color (MC1R Arg151Cys variant allele) had a significantly increased risk for PD. This gene presumably influences levels of melanin and neuromelanin in the person's body. Independent studies of the cell loss in PD have demonstrated that severity of PD is associated with loss of pigment-containing cells of the substantia nigra—the cells that produce dopamine. If people with red hair have lower baseline levels of these pigmented cells in the substantia nigra, then they would be more vulnerable to PD if and when it strikes. There is also an older body of literature (reviewed in Geschwind & Galaburda, 1985a–c, 1987) that suggests that hypopigmented individuals (like people with red or blond hair) also tend to be less strongly right-handed than other people. Non-right-handedness, in turn, sometimes indexes less lateralization in brain organization. For example, people with various neuropsychiatric disorders exhibit less strongly lateralized ear preferences and hand preferences. If that is indeed the case, then hypopigmented people with PD may be at greater risk for certain types of neuropsychiatric disorder compared with that of non-hypopigmented people with PD because of the reduced asymmetry that characterizes the brains of hypopigmented individuals. But all of

this is as yet speculation. We will see below that there are other less "colorful" reasons (besides reduced asymmetry) to expect neuropsychiatric disorders in PD.

History of Study of PD

Although PD was likely known to the ancients, it was not seriously studied until the medieval period (apparently by the Islamic philosopher Averroes). PD was not well recognized in the ancient world probably because not many people lived into their sixties or seventies in that time, so PD must have been more rare in the ancient world than it is today. The scientific study of PD did not commence until James Parkinson published his "Essay on the shaking palsy" in 1817 when he was 62. Parkinson based his analyses on clinical observations of six patients, three of them "from a distance." Apparently, he observed and talked with these three only on the street and not in his clinic. Despite this paucity of material, he managed to identify the major motor deficits and postural abnormalities of the disease. Whereas he recognized delirium as one possible outcome of the progression of the disease, he did not seem to think that intellectual or cognitive deficits were part of the intrinsic nature of the disease. As physicians became more aware of Parkinson's monograph, "paralysis agitans" began to be recognized as a clinical syndrome in its own right.

Jean-Martin Charcot (1825–1893) was a celebrated French neurologist working at the Salpêtrière Hospital in Paris. He knew about Parkinson's monograph but had trouble getting a copy of it. He had been making systematic observations of patients with paralysis agitans (though Charcot did not like that name for the disease) for years. Once he got a copy of Parkinson's essay, Charcot added new symptoms that characterized the disease in terms similar to those described by Parkinson. He suggested that the disease be named after Parkinson, and from that point on, the signs and symptoms of PD were recognized as a syndrome, or collection of symptoms, that likely had a common cause. Charcot did not stop at clinical observation of the disease. He also devised all kinds of therapies to treat the disease including an innovative vibration therapy. He had noticed that some PD patients felt better after they had undergone bone-jarring carriage or train rides. He developed an automated vibratory chair (fauteuil trépidant; Goetz, 2009) and had patients sit in it for 30-minute sessions and then observed improvement in symptoms. Oddly enough, this innovative therapeutic strategy was never followed up after Georges Gilles de la Tourette developed a helmet that vibrated the head on the premise that the brain was the crucial site of action for the disease. Whereas Gilles de la Tourette was correct in that assumption,

he was incorrect in assuming that vibrating the head would necessarily yield greater therapeutic benefit. When the vibratory helmet seemed unimpressive in its effects, new therapeutic innovation to treat PD slowed considerably.

In the early decades of the twentieth century, a flu epidemic swept the world. Some victims of this epidemic developed signs of PD and their cases were studied intensively, thus advancing knowledge of the parkinsonian symptoms. Neuropathologic studies of the brainstems of some of these patients yielded clues as to brain lesions that might cause PD symptoms. In the 1950s, the most crucial discovery in PD science was made when the substantia nigra, a site associated with the production of dopamine, was identified as a site of damage in parkinsonian syndromes. In 1960, dopamine was found to be decreased in the brains of people with PD. In 1961–1962, the first successful trials of levodopa occurred. Levodopa is an amino acid precursor to the biochemical synthesis pathway that manufactures dopamine. By increasing dopamine's precursor, the chances that more dopamine would be manufactured in the brain itself increased. By 1968, patients were being treated with levodopa and with spectacular success.

Levodopa (L-dopa; LD) therapy worked so well for some patients that it seemed that they could live relatively normal lives. This was the dramatic breakthrough everyone had been hoping for. Could people be cured simply by taking a supplement? It was soon discovered, however, that LD had unpleasant side effects (nausea and dyskinesias) and could not prevent progression of the disease. Attention turned to finding ways to ameliorate the unpleasant side effects of LD. The nausea was soon brought under control by the addition of a peripheral dopamine blocker. LD increased both central and peripheral dopamine, and when it did so in the periphery, it created severe nausea. However, a drug called carbidopa could block the synthesis of dopamine in the periphery, and when added to LD, the new drug combination worked pretty well. Nevertheless, no solution has yet been found for the dyskinesias that plague many patients on LD, nor has it been possible to slow progression of the disease.

In an effort to augment LD or to ameliorate some of its dyskinetic side effects, new catecholaminergic drugs like bromocriptine and the monoamine oxidase (MAO)-B inhibitor deprenyl were developed in the 1970s. Pergolide, selegiline, and antioxidant therapies were developed in the 1980s. Meanwhile, deep brain stimulation therapies were introduced in the late 1980s, and neurosurgical techniques were refined in the 1980s and 1990s. In 1997, the U.S. Food and Drug Administration (FDA) approved use of deep brain stimulation (DBS) of the subthalamic nucleus for treatment of tremor. By stimulating the subthalamic nucleus, one could release

from inhibition targets downstream from the nucleus that controlled motor output and thus improve some motor functions in PD. Throughout the 1990s, many of the genetic defects that have been implicated in PD were discovered. Identification of these genetic abnormalities and their associated metabolic effects would lead to new therapies that targeted those metabolic defects in the 2000s. A gene therapy (that did not work so well) for PD was introduced in 2005. Gene therapies, neuroprotective therapies, antiapoptotic therapies, complementary and alternative medicine (CAM) therapies, and all kinds of other therapies as well have been developed in the first decade of the twenty-first century. None of these therapies, however, have yet proved able to prevent progression of the disease or the dyskinesias, though DBS seems to help some people sometimes with dyskinesias and other PD symptoms.

In a recent study (Weaver et al., 2009) of more than 200 advanced-stage PD patients, researchers found that DBS was more effective than standard forms of therapy in improving drug "on time" (when good motor response to LD was achieved). Patients in the DBS group gained as much as 4½ hours of on time compared with that of the control therapy group. In DBS, electrodes are implanted in the brain and connected to a small electrical device called a pulse generator that can be controlled by the patient and/or the doctor. DBS is used to stimulate those brain regions that have been damaged by the disease. The study involved patients with bilateral implantation of stimulators, meaning that devices were implanted on both sides of the brain. Unilateral forms of implantation carry fewer risks, but of course DBS of any kind requires surgery, and surgery always carries significant risks when compared to less invasive therapies.

The Gold Standard Therapy for PD and Its Vicissitudes

The gold standard treatment for PD is LD. In the first couple of years of the disease, LD practically normalizes the motor deficits of PD for most, but not all, patients with PD. Unfortunately, it does this for only a certain amount of time and over only a certain number of years. The side effects of LD such as nausea, dyskinesia, and low blood pressure have been minimized by the creation of Sinemet, which is a combination of carbidopa and LD. Carbidopa is a dopa decarboxylase inhibitor that potentiates the effect of LD by modifying the body's metabolism of the substance so that it is not converted to dopamine until it reaches the brain. In most countries, carbidopa/LD dose levels are designated as a fraction. For example, a 25/100 prescription indicates that the pill is composed of 25 mg carbidopa and 100 mg LD.

To augment use of dopamine in the brain and potentially reduce the side effects of LD (like dyskinesias), other dopaminergic agents besides LD have been developed. The agonists act directly on dopamine receptors, whereas the catechol-*O*-methyltransferase (COMT) and MAO inhibitors act to inhibit breakdown of existing depots of dopamine in the system. There are several types of dopamine agonists: bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), ropinirole (Requip), lisuride, and cabergoline. All of these agonists are important in the story of impulsivity syndromes in PD, so we will have occasion to speak of them again in that chapter. These agonists stimulate dopaminergic activity in the reward centers of the brain by stimulating D_2 receptors. Pramipexole and ropinirole in addition stimulate D_3 receptors. Because the D_3 receptor is involved in mood, personality, and emotion, pramipexole and ropinirole may affect mood as well as motor symptoms. All of these agonist drugs also affect cognitive functions, usually working memory functions, as well. The COMT inhibitors, such as tolcapone (Tasmar) and entacapone (Comtan), act to use existing dopamine levels (by inhibiting the breakdown of dopamine by COMT in the synaptic cleft). The MAO-B inhibitors, such as selegiline (Eldepryl) and rasagiline (Azilect), act to inhibit enzymatic MAO-B activity, which normally breaks down dopamine. Amantadine appears to enhance the activity of both catecholamines (dopamine and norepinephrine). Anticholinergic drugs are sometimes used to decrease cholinergic effects in the motor system that appear to potentiate dyskinesias and other motor problems. See table 1.1 for a list of drugs used to treat PD.

The positive effects of dopaminergic therapy for PD are undeniable. People with PD are able to lead largely normal lives for several years after they are diagnosed with the disease. LD therapy also appears to increase life expectancy and may even slow the progression of the disease, though this latter claim is hotly disputed. PD patients treated with LD spend 3 to 5 years more in each Hoehn–Yahr stage compared with patients in the pre-LD era, but it is not yet entirely clear if

Table 1.1
Primary drugs used to relieve the motor symptoms of PD

LD
LD plus peripheral dopa decarboxylase inhibitors (DDIs)
Dopamine receptor agonists
LD plus COMT inhibitors
MAO inhibitors
Anticholinergics
Amantadine

this is due to LD per se or just to better medical treatment more generally. Sporadic neuroimaging findings also suggest that LD may be somewhat toxic to cells that normally manufacture dopamine. However, the jury is still out on this important issue.

Regardless of the outcome of the issue of the effect of LD on dopamine cells, it is clear that LD is associated with the eventual production of disabling motor problems called dyskinesias and motor fluctuations. Duration of exposure to LD, LD dose, PD severity, and age of patient are all strong predictors of dyskinesias and motor fluctuations. Between 50% and 100% of all PD patients taking LD for more than 6 years will develop disabling peak-dose dyskinesias. Various solutions have been offered to handle the problem of dyskinesias and motor fluctuations in PD. These include early use of agonists instead of LD, controlled instead of bolus release of LD, and DBS therapies. All of these techniques have helped but not yet solved the problem of severe motor side effects of LD.

The above are the basic facts of the clinical presentation of PD treatment that the reader will need to know to appreciate the discussion that follows in other chapters on the neuropsychiatric disorders of PD. I will next provide a more in-depth discussion of the natural history of PD symptoms focusing on when and what kind of neuropsychiatric disorders appear at which stage of the disease. Before summarizing the natural history of the disease and its fundamental causes, however, I think it will be valuable to present a few case studies of patients with PD so that the reader can get a feel for the human effects of this disease. I will focus on what the disease does to the self of the patient, but note that each case of PD is unique. There are no hard and fast rules for the effects of PD on the self. Some patients succumb to depression, whereas others wear themselves out with rage against the disease. Most find some balance of acceptance of the limitations that the disease imposes on the self while not allowing the disease to define who they are and what they can do. It is ultimately impossible to capture PD's protean effects on mind and body in any book or summary. Nor is it possible, finally, to capture the courage, good humor, and extraordinary grace that people with PD display when they are confronted with such a devastating disease.

Case Studies

First, I wish to make some general observations on the persistent claim, idea, or "story" that one hears in neurology clinics around the world that a disproportionate number of persons with PD are exceptionally intelligent, ambitious, persistent,

meticulous, and dedicated to "their" work (Horowski, Horowski, Calne, & Balne, 2000; Jones, 2004). I personally agree with this story, though I have no data to support it. Nevertheless, my impression is that the kinds of people who develop PD tend to be unusually intelligent and very interested in accomplishment. They tend to be the kind of people who are driven by a desire to achieve something significant, or so the claim goes. Take, for example, the case of Thomas Hobbes (1588–1679), who is best known for his political philosophy, although during his day he was more widely known as a scientist, mathematician, a translator of the Greek classics (such as Thucydides' *Histories*), and as a fierce and passionate writer on religious questions. He developed the "shaking palsy" sometime in the mid-1640s when he was around age 50. He would dictate his works to his secretaries because he could no longer write himself. He wrote the *De Cive* [*On the Citizen*] (1642) right before the onset of his PD, and he wrote his most famous book, *Leviathan*, in 1650–1651, right after onset of the disease. PD, apparently, does not prevent creative work of a very high intellectual caliber, and in some mysterious way (given the timing of Hobbes' greatest works), it may actually promote great creative works—at least in those capable of such great works.

My own subjective impression of the many hundreds of patients with PD that I have worked with over the years agrees with this story concerning people with PD. I will say more about the so-called premorbid personality type of PD in another chapter, but suffice it to say here that among the many unresolved issues concerning those two great disorders that affect midbrain dopaminergic systems, PD and schizophrenia, is the issue of their association with exceptional talent and intelligence in either the patients themselves or their first-degree relatives. The data to support these associations are strong with respect to schizophrenia and still only impressionistic in the case of PD, but I believe those data will eventually support the association of PD and exceptional talent. Nevertheless, I as of yet know of no studies that have compared the percentages of eminent individuals with PD (and their first-degree relatives) with the percentages of eminent persons with a similar long-term neurologic illness like multiple sclerosis or Huntington's disease or even schizophrenia. See box 1.1 for names of some famous people who are known or suspected to have had PD.

I now turn to some recent cases of PD. It may be instructive to begin with two cases of prominent people with PD and then turn to two cases of nonfamous but arguably equally intelligent and accomplished people with PD.

Pope John Paul II had been something of an athlete in his youth. He particularly loved to hike in the mountains and to ski. After becoming a priest, he rose rapidly

Box 1.1
Famous People Suspected of Having PD

Here are some famous politicians, good and bad, who either are known to have had PD or are strongly suspected to have had PD:

Senator Claiborne Pell of Rhode Island (1918–2009)
Governor George Wallace of Alabama (1919–1998)
Mayor John Lindsay of New York (1921–2000)
Prime Minister Enoch Powell of Britain (1912–1998)
Prime Minister Pierre Trudeau of Canada (1919–2000)
Chairman Mao Zedong of China (1893–1976)
Deng Xio Ping of China (successor to Mao) (1904–1997)
Francisco Franco of Spain (1892–1975)

in the ranks of the Roman Catholic hierarchy, very ably representing his Polish flock as bishop during the years of communist rule in Poland. After becoming pope, he faced one crisis after another with aplomb and intelligence. He served as pope for 12 years after receiving the diagnosis at age 72. As with most other persons with PD, the disease itself probably began some years before the diagnosis. If so, that would indicate that for the majority of his pontificate (that lasted some 25 years), he had suffered from some degree of PD. He is credited by most historians with playing a crucial role in the peaceful overthrow of the Polish communist dictatorship during the late 1980s. He wrote thousands of pages of religious texts as well as plays and philosophical treatises. His papal encyclicals were considered masterpieces by many. He even had a few bestsellers on the spirituals lists! He had survived an assassination attempt in 1981, and throughout his pontificate, he kept up a physical pace that made the young people around him breathless. He traveled virtually every year, ultimately visiting some 129 countries outside of Italy itself. After he developed PD, he regularly called attention to the disease during his papal audiences and met several times with representatives of PD service organizations, hoping to boost their efforts at serving the PD community. Taken together, this man's accomplishments, despite the PD, have to be reckoned impressive and even extraordinary. Perhaps the Vatican obscured any neuropsychiatric disorders that the pope grappled with due to his PD, but if so, it would constitute a miracle of media management tactics as the man was constantly in the public

eye right up to his death. Did he grapple with depression, apathy, anxiety, or even sleep problems (all common disorders associated with PD)? We do not know. He clearly evidenced speech and language problems in the last years of his life. We will cover speech and language disorders of PD in another chapter, but that is about all we know of the pope's PD, besides the crucial fact that the man flourished despite the PD.

The actor Michael J. Fox was diagnosed with PD at the very young age of 29. Thus, he has lived with the disease for well nigh 20 years. Instead of retiring from the world after he received the diagnosis, he created a charitable foundation that has raised an enormous amount of money to fund PD research, especially research that focuses on the creation of immediate ameliorative therapies for patients and their families. The Michael J. Fox Foundation has taken a leadership role in the PD advocacy community and thus has immeasurably enriched the lives of all PD patients and their families. Like Pope John Paul II, Michael J. Fox travels the world doing dozens of interviews, meeting with politicians of every stripe and variety, conducting nonstop fundraisers, asking for money from the rich and powerful, and, unlike the former pope, doing all this while raising a family of four kids! Although PD must have slowed him down in some crucial respects, it is hard to see how. In his memoirs, Fox displays a healthy sense of humor about his PD symptoms, describing scene after scene of his dyskinesias intruding into meetings with the rich and famous. Fox says that he has never struggled with depression, but he also understands that he has been unusually lucky in this regard. Years ago, he struggled with drinking problems, but that seems not to have reemerged during his PD.

Thomas Graboys, once a star cardiologist in Boston, is now retired from his work as a cardiologist because of the onset of PD. He lost his first wife (Caroline) to cancer just a few years before he was diagnosed with PD. In addition, Graboys' form of PD involves a severe form of Lewy body disease, and thus he is also dealing with progressively worsening dementia. Graboys (and we along with him) rages against his PD, his dementia, and all of his other losses. His memoirs (Graboys & Zheutlin, 2008) give us detailed accounts of his efforts to resist depression and, with the help of a psychotherapist, to funnel his rage and grief away from his loved ones and his caretakers and onto God or the fates. Over and over in his memoirs, Graboys broods over the effects of the disease on his primary relationships, especially with his wife. Among the many neuropsychiatric problems PD patients have to contend with, one of the most searing is their anxiety. Notably, the anxiety is most often about becom-

ing a burden on their families. Graboys lays out all of the dilemmas, frustrations, hopes, and fears he has for every relationship in his life—from those with his former patients to those with his grandchildren, and especially for that with his wife, Vicki. Graboys displays a fierce determination to prevent the disease from defining him, and thus he shows us that PD cannot be considered apart from the person it afflicts. Each case of PD is unique.

In 1987, Morton Kondracke's wife, Milly, noticed that she could not write a normal letter "K" and that her handwriting was becoming cramped. This handwriting difficulty is a very common complaint of patients with PD. It sometimes takes the form of a micrographia (i.e., very small and cramped script). Thomas Hobbes, the political philosopher mentioned above, displayed signs of micrographia until he had to turn over all his major writing tasks to his assistants after his PD progressed. At the age of 47, Milly found herself grappling with similar handwriting problems and then was eventually diagnosed with PD. Kondracke was a prominent TV political commentator and journalist. When his wife developed PD, he unfailingly gave himself to her service and then later wrote a beautiful set of memoirs (Kondracke, 2001) about her illness. Like most people with PD, she battled severe depression throughout the illness. The two of them searched desperately for a cure, going from doctor to doctor, each time having to wearily tell the story of her symptoms. Like many other patients with PD, Milly was eventually put on a huge assortment of pills that in combination were potentially lethal and, in any case, clearly affected her neuropsychiatric status. After the danger of polypharmacy was eliminated, Milly decided to undergo a 2-day-long brain surgery, including a pallidotomy, and then an implantation of a device to support DBS. Neither surgery worked for her. Throughout her battle with PD, Milly experienced multiple falls and often had to be rushed to the emergency room for stitches. As the PD progressed, she could no longer swallow properly or speak properly. They had to sell their house (at a huge loss) to move to a safer environment for Milly. Using paper letters, Milly often spelled out the words "I don't want to live like this!" and "I want to die." Milly died in 2004. Those are the bare facts of Milly's story. When I discuss the neuropsychiatric syndromes of PD in this book, it must be remembered that those syndromes happen to real people like Milly. Sometimes these people find themselves in desperate straits, trying to find some relief from a chronic illness and often undergoing new medical treatments that raise hope for a while but usually end up helping only a small minority of PD patients. The spectacular success associated with LD is, unfortunately, an all too rare medical story.

Although Pope John Paul II and Michael J. Fox have demonstrated that one can live fully with PD, the bitter reality lies somewhere between the Pope's and Fox's experiences and that of Dr. Graboys' and Milly Kondracke's experiences. There is continual loss, continual strain on family relationships, continual crises, constant temptations to depression, and constant frustration with the health care system. Despite all these challenges people with PD typically find a way to live well and even flourish. This is the context within which we will be examining the neuropsychiatric disorders of PD. We must constantly remember that we are dealing with human beings who are confronting tremendous suffering and loss on an almost daily basis. But they are also people who find ways to hold onto joys and produce new ones in their lives. They do not stop living just because of the disease. It is a remarkable fact that despite the ravages of the disease, each patient with PD never allows himself or herself to be defined by the disease. I will be arguing throughout this book that the main effect of PD with respect to its neuropsychiatric effects is an assault on the agentic aspects of the self. The agentic self is the acting self, the doing self, the self that plans, moves, searches for valued things, and attains its goals. There is an abundance of evidence for my position on the agentic self in PD, yet it must not be forgotten there is this other aspect of the self, the self that refuses to be defined by the disease, that seems not to be affected or even impaired by the disease.

I now turn to a detailed description of the clinical course of the disease.

Neuropsychiatric Disorders of PD

The neuropsychiatric symptoms of PD such as depression, apathy, anxiety, hallucinations, and psychosis characteristically appear or emerge at different stages of the disease, and they all exhibit complex relationships with the classical motor (tremor, bradykinesia, rigidity, and postural instability) deficits of the disease. For example, although depression is common even before onset of the motor symptoms, it becomes severe in the mid and late stages of the disease. Apathy is more common in later stages, whereas anxiety disorders are more common in early- and mid-stage patients. Speech act deficits appear in the early and mid stages of the diseases as well. In addition to differing as a function of stage of disease, symptoms are also influenced by side of onset of the disease. Keeping in mind the dependence of neuropsychiatric and cognitive deficits of PD on stage and side of onset of PD, I will review the natural clinical history of PD in what follows. I will conclude this chapter with a discussion of the proposed causes of PD.

Diagnostic Criteria for PD

Most scientific papers on PD use the diagnostic criteria for PD that were developed by the UK Parkinson's Disease Society Brain Bank (see table 1.2; Hughes, Daniel, Kilford, & Lees, 1992). The criteria require that the patient display slowed movement (bradykinesia) and at least one of the other three cardinal signs of PD (tremor, postural instability, and rigidity). Once these hurdles are cleared, the criteria require that other potential causes of these motor deficits be ruled out. Other potential causes include brain injury of various kinds, related disorders such as progressive supranuclear palsy, and various forms of dementing illnesses. If the motor deficits ever remitted for a sustained period of time, PD is not the likely diagnosis. Exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)—a drug that becomes toxic to dopamine cells when broken down in the brain and that was found in some recreational drugs back in the 1980s—can cause parkinsonism as well. Step 3 in the diagnosis involves the collection of supportive data such as unilateral signs (tremor on one side of the body, etc.) and a good response to LD therapy.

Hoehn and Yahr Rating Scale

Once a diagnosis of PD has been made, the patient can expect the disorder to get progressively worse over the duration of several years. Most patients will pass through well-known stages of the disease, termed Hoehn–Yahr stages (Hoehn & Yahr, 1967), as the disorder moves from being a largely asymmetric tremor with very few other symptoms to whole-body shakiness, postural instabilities, and significant mood and mental problems. Sometimes the patient progresses into a full-blown dementia that mimics Alzheimer's dementia, but thankfully not every patient faces this prospect.

The most widely used rating scale for stage identification is the Hoehn–Yahr scale (see table 1.3). This scale was based on clinical observations of the natural history of the disease as it occurred in hundreds of patients before the discovery of LD. It describes five general stages in PD, ranging from stage 1 (unilateral disease, limited to one side of the body) to stage 5 (wheelchair bound or bedridden unless aided).

For more detailed observations of the motor symptomatology of any given patient, neurologists use the Unified Parkinson Disease Rating Scale (Fahn, Elton, and Members of the UPDRS Development Committee, 1987; Goetz et al., 2008). This set of scales is also very often used in research on PD.

Table 1.2
UK Parkinson's Disease Society brain bank clinical diagnostic criteria

Step 1: Diagnosis of parkinsonian syndrome • Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) • And at least one of the following: Muscular rigidity 4–6 Hz rest tremor Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.
Step 2: Exclusion criteria for PD • History of repeated strokes with stepwise progression of parkinsonian features • History of repeated head injury • History of definite encephalitis • Oculogyric crises • Neuroleptic treatment at onset of symptoms • More than one affected relative • Sustained remission • Strictly unilateral features after 3 years • Supranuclear gaze palsy • Cerebellar signs • Early severe autonomic involvement • Early severe dementia with disturbances of memory, language, and praxis • Babinski sign • Presence of cerebral tumor or communicating hydrocephalus on CT scan • Negative response to large doses of LD (if malabsorption excluded) • MPTP exposure
Step 3: Supportive prospective positive criteria for PD (three or more required for diagnosis of definite PD) • Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry affecting side of onset most • Excellent response (70% to 100%) to LD • Severe LD-induced chorea • LD response for 5 years or more • Clinical course of 10 years or more

Source: From Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery, and Neuropsychiatry, 55*, 181–184. Reprinted with permission.

Table 1.3
Hoehn–Yahr (HY) Parkinson's Disease Rating Scale

Stage 1 • Signs and symptoms appear only on one side of the body. • Symptoms are mild. • Symptoms may be inconvenient, but they are not disabling. • Usually a tremor is present in only one limb. • Friends and other loved ones have noticed changes in posture, movement, and in facial expression.
Stage 2 • Symptoms appear on both sides of the body. • Symptoms cause minimal disability. • Posture and gait are affected.
Stage 3 • Body movements are slowed significantly. • Symptoms cause moderately severe problems with normal functioning.
Stage 4 • Symptoms are severe. • The individual can still walk, but only to a limited extent. • There is rigidity and slowness of movement. • One is no longer able to live alone.
Stage 5 • Wheelchair bound.

The Unified Parkinson's Disease Rating Scale

The Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987; Goetz et al., 2008) is a composite set of scales consisting of six sections. Each item within each section asks a trained physician or scientist to rate the patient's abilities/performance on a scale of 0 to 4 (normal to severely affected). The UPDRS takes approximately 20 to 30 minutes to administer. Part I of the UPDRS consists of four items assessing cognitive symptoms, mood, motivation, and the presence or absence of a thought disorder. Part II consists of 13 items describing difficulties on performance of a number of activities of daily living such as bathing, dressing, using utensils, and so forth. Part III is a 14-item section on tremor, assessment of facial and generalized bradykinesia, disease severity, finger tapping against the thumb, clenching and unclenching a fist, rising from a chair, and other tasks. Part IV assesses duration, severity, and timing of dyskinesias and motor fluctuations and the presence or absence of anorexia, sleep disturbance, or orthostatic hypotension. Part V is a modified version of the Hoehn–Yahr staging system,

and Part VI is a disability scale estimating the degree of dependency in daily activities.

In general, controlled studies have found that when different trained physicians and technicians individually administer the UPDRS to the same patients, they generally get the same results. Interrater reliability correlations have been as high as 0.80 on most items (speech being the exception). The test–retest reliability of the UPDRS is also relatively high. Intraclass coefficients in the studies with the largest number of participants were over 0.90 for overall UPDRS score and around 0.80 for subscales. The UPDRS has been criticized for years for not adequately assessing nonmotor symptoms of PD such as sleep disturbances, cognitive deficits, anxiety, fatigue, depression, and autonomic symptoms such as impotence, orthostatic hypotension, and bladder and bowel dysfunction. A task force was convened by the Movement Disorder Society (MDS) in the early 2000s to add new items to the UPDRS to assess nonmotor deficits (Goetz et al., 2008). The task force completed its work in 2009, and the new version of the scales, the MDS-UPDRS, is available on the MDS Web site (www.movementdisorders.org). This new scale is an important positive development for people interested in the study of neuropsychiatric disorders of PD as it will allow us to more easily examine quantitative relationships between severity of motor and nonmotor (e.g., mood) symptoms of PD.

Clinical Symptoms and Course of PD

The average age of PD onset is approximately 50 to 60 years, but there are forms of PD where age of onset is below 40. Approximately 5% of patients present symptoms before the age of 40. An asymmetric resting tremor is the most common initial symptom to lead to the diagnosis, accounting for as many as 70% of cases. When patients think back as to early signs of their PD, they may point to pain in the shoulder, muscle rigidity, problems with fine motor skills like handwriting, buttoning up a shirt, sleep problems, and a general lack of energy. Controlled, large population studies where health status was followed in thousands of people over decades suggested that constipation, loss of smell (anosmia), and signs of rapid eye movement (REM) sleep behavior disorder (RBD; where people act out violent dreams in their sleep) very strongly predicted the onset of PD years later (Abbott et al., 2007). We will see later in the discussion of pathologic causes of PD that these early signs of PD may be due to cellular degeneration associated with Lewy body inclusions in the brain stems and homeostatic centers of the brains of people at risk for developing PD. Basically, the pathology that causes PD starts in the brain stem and then

ascends up through the neuraxis until it reaches the cortex. Thus, the first signs of PD should be related to functions handled by the brain stem and then to functions handled by the autonomic regulatory centers of the brain.

The classic triad of symptoms of PD is tremor, rigidity, and bradykinesia, and each of these change with stage of disease (Fahn et al., 1987; Global Parkinson's Disease Survey Steering Committee, 2002; Goetz et al., 2008; Hoehn & Yahr, 1967). Many experts add a fourth symptom, gait/postural instability, to the classical triad.

Bradykinesia

Bradykinesia, or slowed movement, manifests itself in various forms such as slowed walking, reduced eye blink rates, and fewer overall movements than that of the average person. The slowed movements begin in the early stages and then in later stages the individual manifests an overall paucity of movements.. All of this points to a diminution in the power of the agentic self to initiate and implement actions. Sometimes the patient will also demonstrate reduced power in his voice so that it becomes difficult to hear. Facial expressions appear immobile or "masked." To underline the fact that the bradykinesia encompasses more than basic motor acts, the patient often exhibits problems with planning, initiating, and executing coordinated and sequential actions. Notably, bradykinesia of PD is linked with something known as *kinesia paradoxica*. Patients with severe poverty of movement can sometimes demonstrate that their capacity for movement is quite intact as when someone yells fire or when someone is about to fall. In these cases, the patient can run out of the building or catch the falling person and so forth. The problem is that the agentic self does not have enough strength to initiate and control actions. Motor programs are intact and available, but the patient has difficulty activating them and controlling them once activated. Activation and control, as we will see in another chapter, requires an intact agentic self.

What causes bradykinesia? Degree of bradykinesia is correlated with degree of cell loss in the dopaminergic striatum. The reduction in the dopaminergic signal to the basal ganglia leads to reduced activation levels in the putamen and globus pallidus (cell groups in the basal ganglia that control implementation of motor actions), thus resulting in a reduction in the muscle force produced at the initiation of movement.

Tremor

The tremor seen in PD is a rhythmic, resting tremor that occurs intermittently in one limb for a few minutes and then appears a few minutes later in another limb.

Like bradykinesia, it, too, is affected by mental phenomena: it increases when the patient is concentrating or feeling anxious. An estimated 30% of patients with PD do not have resting tremor. For patients with tremor, it usually begins in one hand and then, in later stages of the disease, it appears in both limbs. Tremor in the hand usually occurs at a frequency between 4 and 6 Hz and almost always has a "pill-rolling" phenomenology that spreads from one hand to the other. Characteristically, rest tremor disappears with action and during sleep.

Rigidity

Because the muscles in PD are constantly contracted, they eventually stretch and shorten all the muscles in the body leading to painful contractures in the hands and feet as well as in the back. These pulled muscles draw the head and neck downward, thus producing a stooped posture, poor balance, propulsion (a tendency to run forward), and falling. Rigidity is experienced by patients as muscle stiffness, soreness, or cramping. When physicians test for rigidity, they look for resistance to passive movement of a limb. The resistance to movement takes on a "cogwheel" form. All of these forms of rigidity get worse with progression of the disease.

Postural Instability and Freezing

Postural instability is the bane of PD patients and their families as it leads to falls and injuries and compromises independence. It usually occurs in later stages of the disease, and it, along with freezing of gait, is the most common cause of falls in PD. Freezing is a form of akinesia (a loss of movement) and is one of the most disabling symptoms of PD. About half of all patients with PD report freezing phenomena. It typically manifests as a sudden inability to continue walking or to initiate a movement or to close one's eyelids and so forth. This is, of course, extremely dangerous when one is crossing a busy street facing oncoming traffic. Notably, patients often develop tricks to overcome freezing attacks such as imagining a line on the floor and using that to move forward or marching to an internal musical beat, and so forth. The basic idea is to use some external salient stimulus to help control movement because the internal control of movement is lost.

Nonmotor Features of PD

Nonmotor deficits of PD include autonomic dysfunction, pain and sensory abnormalities, cognitive/neurobehavioral disorders, and sleep abnormalities. Because the rest of this book is about the neurobehavioral abnormalities of PD, I will mention

the autonomic abnormalities only here. In addition to the primary motor problems of PD, patients are afflicted with a host of other symptoms that are due to loss of normal autonomic nervous system (ANS) function, which in turn may be due to loss of dopamine innervation to ANS regulatory control centers. Some of these problems include constipation, sluggish bladder, decreased sexual libido, anosmia, hot flashes or chills, edema, seborrhea, excessive sweating, conjunctivitis, swallowing difficulties, and many other symptoms besides. These various afflictions need to be kept in mind when one considers the ability of PD patients to cope with the neuropsychiatric disorders of PD.

Pain in PD

Although it is clear that a majority of patients with PD report significant pain at all stages of the disease (Drake, Harkins, & Qutubuddin, 2005; Goetz, Tanner, Levy, Wilson, & Garron, 1986), it is unclear to what extent pain disturbances are due to or shaped by mood disturbances or to more central pain processing abnormalities (Djaldetti et al., 2004; Snider, Fahn, Isgreen, & Cote, 1976). In a recent study (McNamara, Stavitsky, Harris, Szent-Imrey, & Durso, 2010), we found significantly greater pain intensity ratings in PD than in control participants. All of the McGill Pain Questionnaire (Melzack, 1975) subscale scores in a left-onset PD (LPD) group were significantly related to overall mood dysfunction, but this was not the case for the right-onset PD (RPD) group. The associations between mood and pain in the LPD group were quite striking, reaching an almost perfect correlation. In addition, we found some evidence for differing expression of other pain symptoms among PD patients as a function of side of motor symptom onset. Patients with left-onset disease and greater right hemispheric pathology reported greater amounts of present pain intensity than that of control participants. Thus, we have clear evidence that one of the most disabling nonmotor symptoms of PD is related to higher control centers in the central nervous system (CNS). There is some evidence in the literature suggesting that impairment in right forebrain systems may lead to enhanced pain perception. The prefrontal cortex is known to be involved in descending pain inhibitory systems (Borckardt et al., 2007), and dopaminergic dysfunction in right forebrain neural networks may impair prefrontal inhibitory functions as well, thus resulting in increased pain perception. Notably, 15 minutes of left prefrontal repetitive transcranial magnetic stimulation decreases pain perception in healthy adults (Borckardt et al., 2007).

Having briefly reviewed the clinical course of PD, I turn now to a consideration of the causes of PD.

Causes of PD

Oxidative Stress

One of the normal consequences of biochemical processes in our bodies is the production of free radicals. These are reactive oxygen species that can damage cells in myriad ways. Mitochondria produce these and also handle them. However, mitochondria may be one of the sites of pathology in PD, and thus free radicals build up over time in persons at risk for PD. They tend to accumulate in sites that engage in a lot of metabolic work like the pigmented cells of the substantia nigra; thus, the pigmented cells of the substantia nigra are particularly vulnerable to oxidative stress and cell damage.

Environmental Toxins

A large number of epidemiologic studies have indicated that rates of PD are higher in areas where exposure to environmental toxins is a risk. Exposure to pesticides, carbon monoxide, heavy metals, or toxins in the food supply may cause damage to vulnerable CNS sites like the substantia nigra. A recent study (Costello, Cockburn, Bronstein, Zhang, & Ritz, 2009) investigated the effects of exposure to the pesticide maneb and the herbicide paraquat. The researchers found that persons who lived within 500 meters of fields sprayed with either of these two agents between 1974 and 1999 had a 75% increased risk for developing PD.

Whether the proximate cause of PD is exposure to toxins or oxidative stress, it is now understood that certain genes increase vulnerability to the disease as well.

Genetics of PD

Approximately 5% to 10% of patients with PD have a familial pattern of inheritance, and to date, linkage has been reported with 11 different genes (see table 1.4). Familial PD has been described in association with mutations in *alpha-synuclein*, ubiquitin carboxy-terminal hydrolase L1 (*UCH-L1*), *parkin*, *DJ-1*, PTEN-induced kinase 1 (*PINK1*), *LRRK2* (leucine-rich repeat kinase 2), and, more recently, in the genes encoding for Omi/HtrA2 and ATP13A2. Even patients with sporadic PD who have typical clinical and pathologic features with no family history are often found to have LRRK2 mutations. Many of these genes impact, in one way or another, the metabolic processing of protein manufacture and degradation. For example, alpha-synuclein clumps, or aggregates, called protofibrils, cause cell membrane (including mitochondrial membrane) destruction and eventual cell

Table 1.4
Genes linked to PD

Locus	Gene/Protein	Inheritance Pattern	Clinical Phenotype
PARK1	SNCA/α-synuclein	Autosomal dominant	Mid-age onset (45–60 years with typical PD ± dementia)
PARK2	PARK2/parkin	Autosomal recessive	Juvenile (<20 years) onset with atypical features
PARK3	Unknown	Autosomal dominant	Typical PD
PARK5	UCH-L1	Autosomal dominant	Mid-age onset with typical PD
PARK6	PINK1	Autosomal recessive	Early onset (20–45 years) PD with slow progression
PARK7	PARK7/DJ-1	Autosomal recessive	Early onset PD with slow progression
PARK8	LRRK2/dardarin	Autosomal dominant	Mid-age onset with typical PD ± dementia and amyotrophy
PARK10	Unknown	Genetic susceptibility	Typical PD
PARK11	Unknown	Genetic susceptibility	Typical PD
FTDP-17	MAPT/tau	Autosomal dominant	Parkinson's associated with frontotemporal dementia
SCA2	ATXN2/ataxin-2	Autosomal dominant	Typical PD
SCA3	ATXN2/ataxin-3	Autosomal dominant	Typical PD
Nurr1	NR4A2/NURR1	Likely autosomal dominant	Typical PD
Synphilin-1	SNCAIP/synphilin-1	Likely autosomal dominant	Typical PD
Mitochondria	NADH complex 1	Mitochondrial inheritance (maternal line)	Typical PD

Source: Modified from Butler and McNamara (2011, in press).

death. These alpha-synclein-related proteinaceous inclusions may be a major source of Lewy body deposition in cells in the CNS. Lewy bodies are one of the hallmark pathognomic features of PD (see below). Alpha-synuclein production is enhanced in tandem with high levels of oxidative stress as well. All of this points to the idea that cell death in the substantia nigra in PD is due, ultimately, to genetic defects that lead to failure to dispose of protein aggregates and breakdown in degradation of these aggregates through the ubiquitin/proteasome pathway. These biochemical failures that lead to protein clumps result, ultimately, in Lewy body inclusions in various cell groups in the CNS, including the striatal dopamine groups. The Lewy body inclusions disrupt cellular functions and then the cells die off.

Neuropathology and Progression of PD

Braak and colleagues (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004) proposed that the varying degrees of synuclein pathology follow a definite sequence

Table 1.5
Pathologic stages of PD proposed by Braak and colleagues

Stage 1: Medulla oblongata and olfactory bulb lesions in dorsal nucleus of cranial nerves IX and X. Intermediate reticular formation, olfactory bulb, and anterior olfactory nuclei.
Stage 2: Pontine tegmentum pathology of stage 1 plus lesions in caudal raphe in n. gigantocellular reticular nucleus and coeruleus-subcoeruleus complex.
Stage 3: Midbrain pathology of stage 2 plus lesions in pars compacta of substantia nigra.
Stage 4: Basal prosencephalon and mesocortex pathology of stage 3 plus prosencephalic lesions, anteromedial temporal mesocortex and allocortex (CA-2 plexus).
Stage 5: Neocortex pathology of stage 4 plus lesions in prefrontal cortex and sensory association neocortical areas.
Stage 6: Neocortex pathology of stage 5 plus lesions in first-order sensory association cortex, premotor cortex, and primary sensory and motor cortex.

Source: Modified from Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research*, *318*(1), 121–134.

of stages (see table 1.5). In their proposed schema, PD pathology progresses through six stages, spreading from the medulla (stage 1) to the pons and upper brain stem (stages 2 to 3), to the anterior temporal mesocortex (stage 4), and then to the neocortex (stages 5 to 6). In short, when the synuclein pathology reaches stage 3 or 4, pathology involves the substantia nigra and other midbrain structures.

Neuropathologic studies of PD suggest that clinical signs of PD begin to emerge when the ventrolateral region of the substantia nigra has lost greater than 60% of its neurons due to synuclein pathology. Clinical, pathology, and neuroimaging studies all suggest that the neuropathologic process begins approximately 5 years before the clinical onset of symptoms.

The progression of PD, however, may be nonlinear, with a more rapid rate of decline in early disease and slower progression later, or vice versa, with rapid decline later and steady decline initially. Only empirical work will resolve this issue. The Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP, 1996) study enrolled 800 subjects with early (Hoehn–Yahr stage 1 and 2) untreated PD patients. Three hundred fifty-three of these patients were treated with placebo or placebo plus tocopherol, which was found to be ineffective. Overall, the total UPDRS score in these individuals worsened by 14% per year (approximately 4 points), and the motor portion of the UPDRS score worsened by 9% per year (approximately 2.5 points).

And finally, there is one last clinical factor that we need to discuss to understand the neuropsychiatric disorders of PD: asymmetric side of onset.

Asymmetry in PD

The motor symptoms of PD initially present predominately on one side of the body, and though poorly understood, this asymmetric disease profile may significantly influence survival rates of PD patients (Elbaz et al., 2003), response profiles to LD (Dethy et al., 1998), and risk for development of neuropsychiatric syndromes and dementia (Amick, Grace, & Chou, 2006; Direnfeld et al., 1984; Djaldetti, Ziv, & Melamed, 2006; Kaaisenen et al., 2001; Starkstein, Mayberry, Leiguarda, Preziosi, & Robinson, 1992; Tomer & Aharon-Peretz, 2004; Tomer, Levin, & Weiner, 1993). The prognostic utility of asymmetric disease profiles (e.g., the presence and magnitude of asymmetric disease presentation), in short, may be considerable. Yet, very little work has been done on the prognostic utility or clinical correlates of asymmetric disease in PD. Animal models have shown asymmetric behavior to be associated with an imbalance of neostriatal dopamine content. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies in humans, furthermore, have consistently demonstrated correlations between reduced striatal and prefrontal dopaminergic activity contralateral to the clinically more affected side and the motor, mood, and cognitive functions associated with that side of the brain (reviewed in Djaldetti et al., 2006).

Recent epidemiologic and prevalence studies, using rigorous measurement criteria to define asymmetry, have demonstrated that between 50% and 60% of cases of PD evidence marked asymmetry of at least three motor symptoms throughout the course of the disorder. Uitti, Baba, Whaley, Wszolek, and Putzke (2005) reported that disease duration, age at onset, and left-handedness were significantly associated with asymmetric disease. That is, shorter symptomatic disease duration was associated with a greater degree of asymmetric disease, an earlier age at disease onset was associated with a greater degree of overall asymmetry, and left-handed individuals tended to have more severe disease on the left side of the body. Whereas the first two correlates (shorter duration and early age at onset) could be explained by supposing that as PD progresses symptoms become more bilaterally distributed, the link with left-handedness is more difficult to explain. Notably, Biary and Koller (1985) reported a higher incidence of left-handedness in patients with essential tremor relative to that of age-matched controls. Uitti et al. (2005) suggested that the reserve of dopamine levels in the right hemisphere (controlling the left hand) of left-handed individuals is not as high as the reserve of right-hemisphere dopamine in right-handed individuals. But, this theory would predict more severe disease on the left side of the body for both left- and right-handed individuals. Thus, the handedness correlate remains a mystery.