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# The Neglected Side of Parkinson's Disease

*Shaking and slowness of movement may be the most obvious symptoms, but they are often not the most debilitating ones*

Ted L. Rothstein and C. Warren Olanow

Parkinson's disease may not be an epidemic, but it's more common than you might think. Approximately 1,000,000 Americans suffer from the illness, with 60,000 new cases appearing each year in the United States alone. This neurodegenerative disorder, which is both progressive and incurable, usually begins around age 60, so neurologists believe that its prevalence is likely to increase dramatically with the graying of the nation's population. But Parkinson's disease shouldn't be thought of only as an affliction of old age; it can also strike considerably earlier in life, a fact that has become well known through such prominent examples as Michael J. Fox (diagnosed at age 30) and Muhammad Ali (at age 42).

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For decades, researchers have understood that such classic symptoms of the disease as shaking, slowness of movement and problems with balance result from the loss of *dopaminergic* nerve cells (so named because they use the chemical dopamine as a neurotransmitter) in a part of the brain stem called the *substantia nigra pars compacta*. One of the greatest success stories of modern medicine came when neuroscientists recognized that there was a dopamine deficiency in the brains of patients with Parkinson's disease and used this knowledge to develop treatments designed to boost levels of this important brain chemical. This strategy has now benefited millions of people, enabling patients who once would have been crippled by the illness to live relatively normal lives.

There are, however, aspects of the disease that do not respond to this treatment. Unfortunately, many physicians are not particularly familiar with these nondopaminergic manifestations. Such features, which include sleep disorders, dementia and difficulty walking, are very important for the clinician to address, both because they are common and because they frequently represent the main source of disability for patients. They are also interesting to study because they may provide investigators with clues to why cells degenerate in Parkinson's disease, which in turn may help researchers to develop more effective therapies. What's more, there is mounting evidence that certain nondopaminergic symptoms may antedate the development of the classic motor features of the disorder and thus may permit early diagnosis.

By recognizing these early warning signs, physicians might even be able to treat patients preemptively. The hope is that doing so could delay or perhaps even arrest the disease before the more

typical problems emerge and the damage wrought by Parkinson's becomes irreversible. Before considering such promising opportunities for the future, it is worthwhile to review how the disease has been understood in the past.

## The Dopamine Revolution

One can find many references to the symptoms of Parkinson's disease throughout history. The Greeks, and in particular the noted physician Galen, wrote about them, and they are described in ancient Chinese medical writings.

The first detailed account of Parkinson's disease came in 1817, when the English physician James Parkinson published a monograph titled "An Essay on the Shaking Palsy." Parkinson provided a clear description of the major clinical features of this disorder, and his portrayal has withstood nearly 200 years of observation. Interestingly, Parkinson's monograph was based on his analysis of just six patients. In recognition of this seminal contribution, in the late 19th century the great French neurologist Jean Martin Charcot coined the term "Parkinson's disease."

Parkinson described various clinical findings: tremor or trembling movements, particularly while at rest; stiffness or rigidity of muscles; slowness of movement, which is also known as *bradykinesia*; and difficulty with walking and maintaining balance. Patients with Parkinson's disease also frequently demonstrate a masklike facial appearance, reduced blinking, small handwriting, loss of speech volume and melody, and a flexed posture with tilting of the body. These motor symptoms progress gradually over the years and were the main cause of disability in the era before effective drug treatment became available.



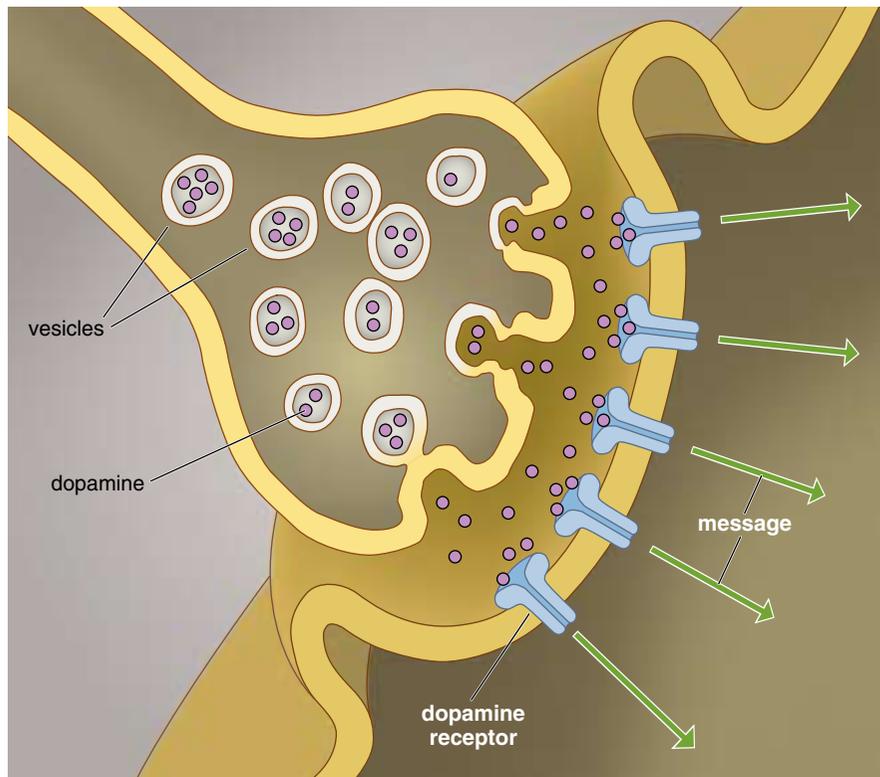
Bettman/Corbis

**Figure 1.** Although Parkinson's disease is normally an affliction of old age, it can strike considerably earlier in life. Three-time world heavyweight boxing champion Muhammad Ali (Cassius Clay, Jr.), for example, was diagnosed with Parkinson's disease at the age of 42, just three years after his final fight. He is shown here (*foreground*) in a 1965 match with Floyd Patterson.

Whereas James Parkinson defined in the early 19th century the classic motor features of the disease that bears his name, it was not until the beginning of the 20th century that sci-

entists began to get an idea of what was going on inside the nervous systems of people with this condition. At that time, autopsy studies showed that the disease is associated with a

loss of pigmented dopaminergic nerve cells in the substantia nigra pars compacta. (Substantia nigra means, literally, "black substance"; researchers now understand that these cells gain



**Figure 2.** Parkinson's disease is well known for its effect on neurons that use dopamine to pass signals. When this brain chemical is released from storage vesicles in one cell, it triggers changes in special receptors on the other cell, thereby conveying the neural message.

their dark coloration from the oxidation of dopamine to form the black pigment neuromelanin.) In addition, some of the remaining nigral nerve cells contain abnormal protein inclusions known as Lewy bodies, named in honor of Freidrich H. Lewy, who first described them in 1912.

The significance of Lewy bodies is still not known, and there is debate as to whether they are toxic and contribute to nerve-cell death or reflect a protective mechanism that arises in response to the accumulation of abnormal proteins. Lewy bodies turn up in postmortem studies of some individuals who did not evidence any neurological impairment during life. So it seems possible that these individuals had a preclinical form of Parkinson's disease.

The importance of dopamine in Parkinson's disease first became apparent in the 1950s when the Swedish scientist Arvid Carlsson found that *reserpine*, a drug that blocks dopamine uptake into storage vesicles within cells, caused rabbits to develop pronounced slowness and a syndrome resembling Parkinson's disease. Carlsson further showed that this effect could be reversed by the restoration of dopamine. For this seminal work, he was award-

ed the 2000 Nobel Prize in Physiology or Medicine.

In 1960, the biochemist Oleh Hornykiewicz at the University of Vienna discovered that the disease is accompanied by dramatically reduced levels (80 to 90 percent) of dopamine in the *striatum*, a part of the brain that is connected to nerve cells in the substantia nigra pars compacta by what is known as the *nigrostriatal tract*. The striatum and substantia nigra are part of a group of deep nuclei within the brain called the *basal ganglia*, which control and facilitate normal movement. Experimentally, damage to the substantia nigra pars compacta, which can be induced with certain neurotoxins, reproduces in animals the classic features of the illness.

Once clinicians figured out the importance of dopamine in the development and progression of Parkinson's disease, they sought ways to replace this crucial chemical. Dopamine itself is not effective as a drug because it does not cross the blood-brain barrier, an obstacle that prevents most chemicals from entering the brain. However, levodopa, a naturally occurring amino acid found in many foods (for example, fava beans), can be transported by

large carrier molecules into the brain where it can then be converted to dopamine by the decarboxylase enzyme.

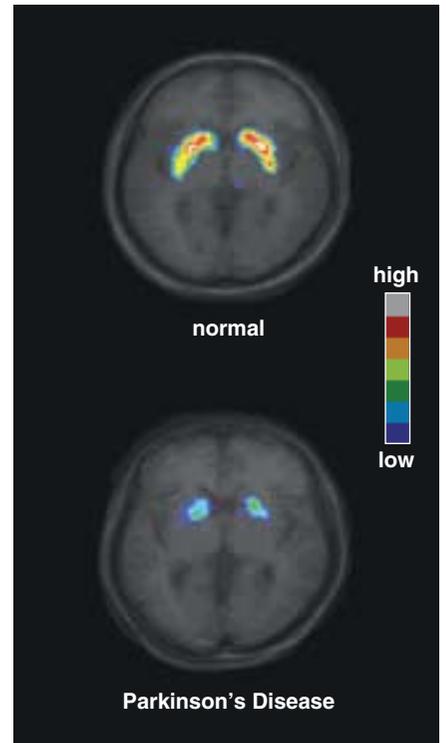
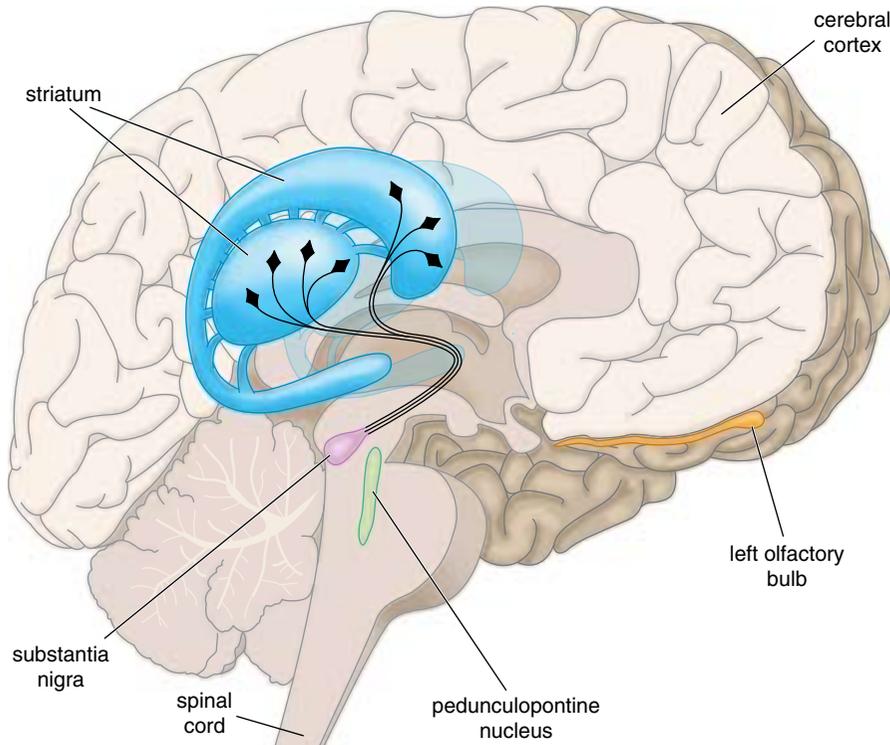
In 1961, Hornykiewicz and his colleague Walter Birkmayer reported dramatic benefits to a few patients with Parkinson's disease following small doses of levodopa, but it was not until 1967 that George C. Cotzias and colleagues at Brookhaven National Laboratory demonstrated that levodopa could consistently ameliorate the debilitating motor symptoms, thus revolutionizing the treatment of Parkinson's disease. Levodopa is typically administered in combination with a drug that prevents it from being metabolized to dopamine outside the brain—either carbidopa or benserazide hydrochloride. In the 40 years since its development, levodopa has helped millions of patients throughout the world. Indeed, it remains the most effective treatment for Parkinson's disease and is the "gold standard" against which new drugs must be compared.

### Outside the Realm of Dopamine

Unfortunately, levodopa therapy doesn't satisfactorily control many clinical aspects of Parkinson's disease, presumably because they result from degeneration of nondopaminergic parts of the nervous system.

Researchers are discovering that the pathology of the disease is far more extensive than their predecessors initially appreciated and is not restricted to dopaminergic nerve cells in the substantia nigra pars compacta. Indeed, they have identified signs of neurodegeneration with the development of Lewy bodies in nondopaminergic regions of the brain, the spinal cord and the peripheral nervous system, which use a variety of different neurotransmitters (such as serotonin, norepinephrine and acetylcholine). Strangely, some regions of the brain can suffer profound nerve-cell loss with Lewy-body formation, while neighboring areas are completely spared, indicating that some as-yet-unknown factors make only certain nerve cells vulnerable to degeneration in Parkinson's disease.

Although nondopaminergic symptoms are common, doctors may not think to ask about them and thus may not realize that they are causing problems for their patients. And both patients and doctors often do not appreciate that nondopaminergic parts of the disease frequently constitute a signifi-



**Figure 3.** The classic symptoms of Parkinson's disease arise from degeneration of dopaminergic cells in a region of the brain stem called the substantia nigra (purple) and in the striatum (blue), a structure found in both left and right sides of the brain that is directly connected with the substantia nigra. At right, Positron Emission Tomography (PET) reveals that dopaminergic neural activity in the striatum is much higher in normal subjects than in patients with Parkinson's disease. These PET scans are superimposed on a grayscale MRI image and are constructed to mimic looking down on a horizontal slice of the brain. (PET images courtesy of Alain Dagher, Montreal Neurological Institute, McGill University.)

cant source of disability. This phenomenon is illustrated by the Sydney multicenter study, which followed more than 100 Parkinson's disease patients for 15 years. One third of them survived; of those, four-fifths displayed gait impairment with falls (leading to leg fracture in one-fifth of the subjects evaluated), and about the same fraction demonstrated cognitive impairment (with half of those meeting standard criteria for dementia). Other nondopaminergic symptoms that the researchers described in this population were choking, difficulty with swal-

lowing, urinary problems and severe constipation. In virtually all instances, severe nondopaminergic difficulties (such as dementia), not the classic motor features of the disease, were ultimately responsible for placement of the patient in a nursing home.

#### Asking Patients

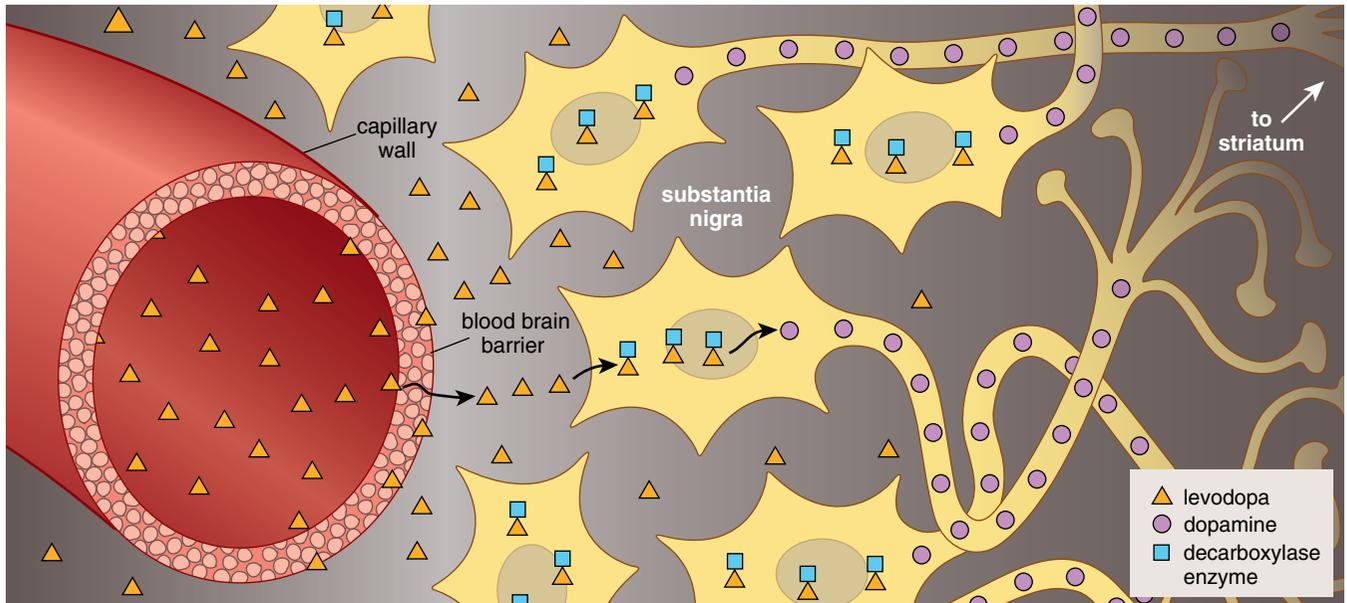
The frequency and importance of nondopaminergic problems in Parkinson's disease are also readily apparent in the results of a study that one of us (Olanow) recently conducted in collabora-

tion with several colleagues. We developed a questionnaire and rating scale focusing on these nondopaminergic symptoms and found that they occur in patients with Parkinson's disease far more often than they do in otherwise healthy people of similar age. This research also showed that the frequency and severity of these nondopaminergic manifestations increase along with the progression of the classic motor impairments of Parkinson's disease.

Sadly, people with this condition have to cope with even more than what



**Figure 4.** Tissues taken from the substantia nigra pars compacta normally show a high density of dark-colored nerve cells under microscopic inspection (left). But people with Parkinson's disease experience extensive loss of such pigmented neurons (middle). An enlarged view of one of the surviving neurons reveals a Lewy body (indicated by arrow at right), an inclusion within the cell containing dysfunctional protein masses. (Images courtesy of Martha Simmons.)



**Figure 5.** Standard therapy for Parkinson’s disease is to boost levels of dopamine within the brain. Because dopamine itself does not cross the blood-brain barrier, physicians administer the dopamine precursor levodopa, which is carried across capillary walls and then becomes available to neurons within the brain. In these cells, the decarboxylase enzyme converts levodopa to dopamine.

is on the list of common symptoms. With advancing disease, many also begin to have a stooped posture, shuffle as they walk, have difficulty making a turn and lose control of their balance so that they find themselves involuntarily running forward or backward to stay upright. In addition, patients may experience “freezing episodes” during which they have difficulty starting to walk, or they may suddenly stop for several seconds or even minutes in the middle of walking, particularly as they pass through a doorway or encounter a curb. As a result, patients are at increased risk of falling and breaking bones, and frequently they must rely on a walking aid or wheelchair to maintain

mobility. The precise site in the brain that is responsible for this gait impairment is not known, although a region in the upper brain stem known as the *pedunculopontine nucleus* has recently been implicated.

Dementia, a progressive decline in cognitive function sufficient to interfere with one’s usual daily activities, is another important feature of Parkinson’s disease that does not respond to, and may in fact be worsened by, dopamine-replacement therapy. Studies suggest that dementia eventually develops in 40 to 80 percent of patients with Parkinson’s disease—more than six times the rate expected in the general population. The dementia of Par-

kinson’s disease primarily affects what are known as executive functions, such as the ability to focus one’s attention, make coherent decisions, plan and organize, and visualize the spatial arrangement of objects. This mental handicap differs from the dementia of Alzheimer’s disease, which primarily affects higher cortical functions, such as memory, calculations and language. People with Parkinson’s dementia also commonly experience visual hallucinations, which can be the first indication of dementia. Autopsy studies of patients with dementia from Parkinson’s disease often reveal Lewy-body inclusions throughout the cerebral cortex, a region of the brain where thought processes take place. And these tissues also show Alzheimer pathology at an unusually high frequency.

Patients with Parkinson’s disease experience many other ailments that do not stem directly from depleted dopamine—depression, for example, is present in approximately half of these people. Researchers have debated whether depression is an inherent part of the disease, possibly related to alterations in the brain’s serotonin levels. Others contend that it develops as a consequence of patients having to live with the knowledge that they have a progressive neurodegenerative disorder.

Disturbed sleep is another aspect of Parkinson’s disease that does not respond to, and may even be aggravated by, dopamine therapies. As many as

features of Parkinson’s disease	
dopaminergic	nondopaminergic
tremor, particularly at rest	gait disorder (falling, freezing, postural instability)
rigidity	decreased sense of smell
general slowness of movement	choking, drooling
masklike facial expression	autonomic (sexual, gastrointestinal, urinary, blood pressure) dysfunction
reduced blinking	sleep disturbances
small handwriting	mood disorders, depression
low-volume speech	dementia

**Figure 6.** Many features of Parkinson’s disease, including those that are most widely recognized, result from the loss of dopaminergic neurons (left). But degeneration of nondopaminergic parts of the brain in Parkinson’s disease causes symptoms (right) that can be even more debilitating.

70 percent of patients with this disease have some sort of sleep disorder. The lack of restorative nighttime sleep causes them to experience excessive daytime drowsiness—some have even fallen asleep while driving. Another problem that is also frequently seen is Rapid Eye Movement (REM) behavior disorder, where the “sleep paralysis” that normally prevents us from acting out our dreams during REM sleep fails to occur. The resultant thrashing can cause serious injury to the patient or to his or her bed companion. People with Parkinson’s disease may also experience restless-leg syndrome, a condition in which there is an inexplicable urge to move one’s legs, particularly when lying down at night.

Other nondopaminergic difficulties can include a drop in blood pressure on standing, slowed gastrointestinal transit with resulting constipation, increased urinary frequency and incontinence, and erectile dysfunction. It also appears that the nerves serving the heart may be compromised in some patients with Parkinson’s disease, perhaps contributing to complaints of light-headedness and fatigue.

Although many of the symptoms of Parkinson’s disease can be readily classified as dopaminergic or non-dopaminergic, others don’t seem to fit this simple categorization. Recently, physicians have noticed that treatment with levodopa and other dopaminergic drugs renders some patients susceptible to impulse-control disorders, including pathologic gambling, hypersexuality, compulsive shopping and eating, and a tendency to perform useless tasks compulsively and repetitively, a behavior neurologists call *punding*. Because dopamine is a key part of the brain’s reward system, these disorders are thought to be related to a dopamine imbalance, which probably results from there being too much dopamine in some parts of the brain (from the medications) and too little in other parts (from the underlying disease). Investigators are focusing intense scrutiny on this issue, which may one day provide insight, not only into Parkinson’s disease, but also into the nature of addiction.

### A Sign of Things to Come

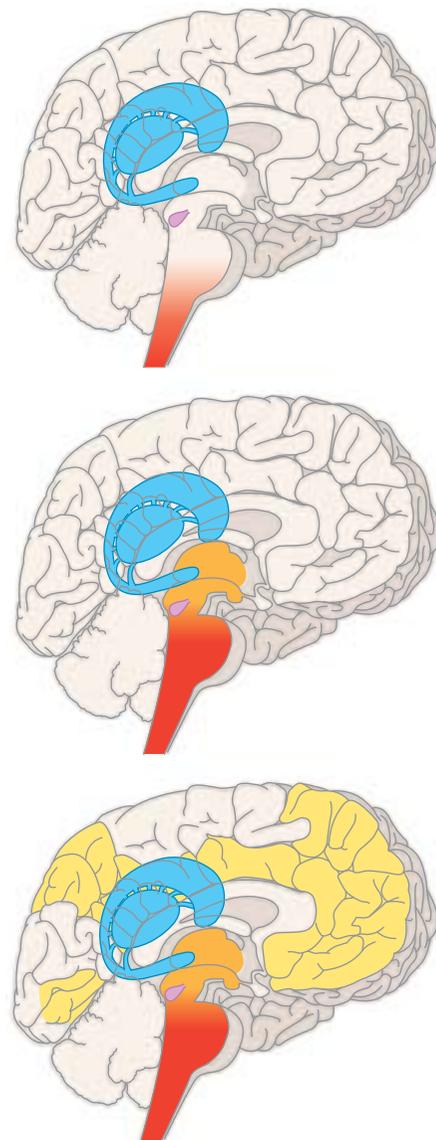
Considerable evidence now suggests that the earliest symptoms of Parkinson’s disease may be nondopaminergic ones. Support for this possibility comes

from the work of Heiko Braak at the Johann Wolfgang Goethe University in Frankfurt. In 2003 he and his colleagues carried out postmortem examinations of the brains of elderly people to determine the distribution of Lewy bodies and *Lewy neurites* (abnormal protein aggregates found in the slender extensions that radiate from the body of a nerve cell). Based on his results he believed that the pathological changes in brains of patients with Parkinson’s disease begin in the olfactory regions and the lower brain stem (two non-dopaminergic areas) and then spread to involve the more classic dopaminergic areas in the midbrain (for example, the substantia nigra pars compacta). In the final stage, pathologic changes are found diffusely throughout the cerebral cortex, likely accounting for the dementia that so frequently accompanies motor impairments. That is, he argued that nondopaminergic regions are affected before dopaminergic ones.

Unfortunately, Braak’s study did not include clinical assessments, so one can’t really be sure whether his staging scheme is completely correct. Nonetheless, his results raise the interesting possibility that the lower brain stem and olfactory regions may be the first sites of neural damage. If so, it makes sense that certain nondopaminergic symptoms might precede the development of the classic motor difficulties, an observation that may allow physicians to better predict the course of the disease.

Clinical findings seem to support this argument. One is the observation that a loss in the sense of smell is a common feature in Parkinson’s disease. This impairment may exist for many years before motor difficulties appear. Studies of asymptomatic relatives of patients with Parkinson’s disease show that those with a compromised sense of smell are more likely than ones with a normal sense of smell to have reduced dopaminergic activity (as evidenced by brain-imaging studies) and to go on to develop the hallmark motor deficits of Parkinson’s disease.

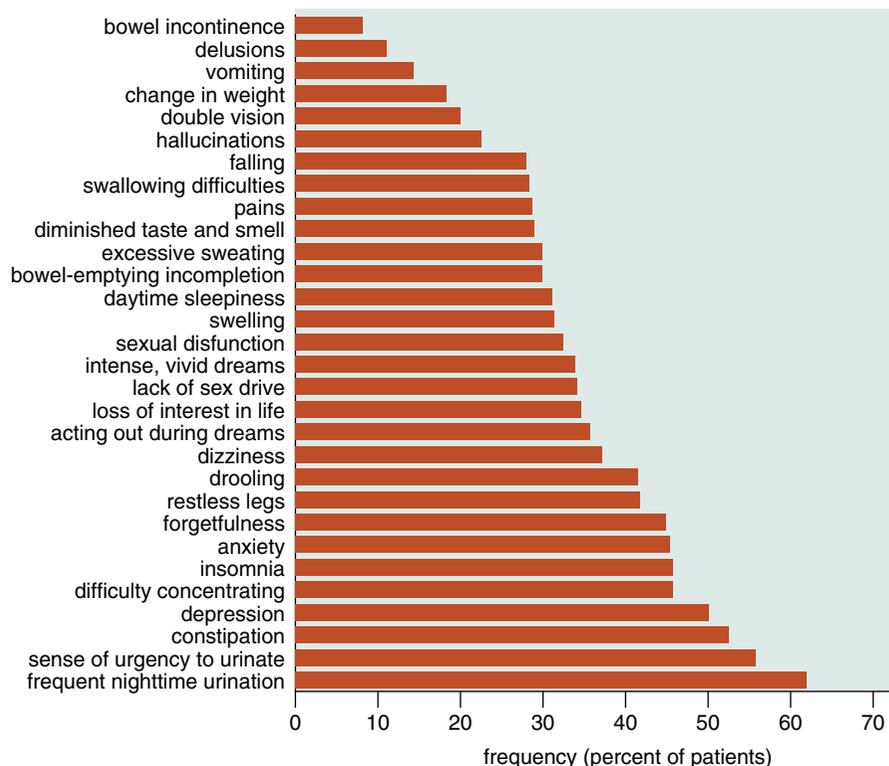
This tendency was demonstrated in a 2004 study. A group of researchers in Amsterdam led by Henk W. Berendse of the Vrije Universiteit Medical Center examined more than 300 asymptomatic relatives of patients with Parkinson’s disease and identified 40 with a diminished sense of smell. Over the course of the next two years, the classic motor



**Figure 7.** Postmortem studies suggest that neural degeneration progresses systematically in Parkinson’s disease. The first portion of the brain affected (*top*) appears to be in the brain stem (*red*). Later (*middle*), degeneration expands to include the substantia nigra (*purple*), the striatum (*blue*) and other portions of the mid-brain (*orange*). In its later stages (*bottom*), the disease begins also to compromise portions of the cerebral cortex (*yellow*).

symptoms developed in four of them, who were thus diagnosed as having Parkinson’s disease. Within those two years, Parkinson’s disease developed in half of those who had displayed both an abnormal sense of smell and reduced dopaminergic activity. Yet during this same period, none of the relatives with a normal sense of smell were diagnosed with the disease.

A weakened sense of smell is not the only possible manifestation of early Parkinson’s disease. People with REM



**Figure 8.** Although they are largely unappreciated by physicians, many nonmotor symptoms arise in patients with Parkinson's disease.

behavior disorder frequently have reduced dopaminergic activity in the striatum, and their brain tissues often show mild Parkinson's pathology in postmortem studies. What's more, about half of the people with REM behavior disorder and no other neurological symptoms will eventually go on to experience the classic motor impairments of Parkinson's disease.

Constipation may also be an early warning sign. Autopsy studies have revealed Lewy bodies in the networks of cells that innervate the colon in patients with Parkinson's disease as well as in individuals who hadn't displayed any neurological deficits before they died. This finding raises the possibility that the latter group may, in fact, have had early Parkinson's disease and, had they not died of other causes, may have gone on to develop the classic motor impairments.

Epidemiologic studies provide further support for this notion. During the course of the Honolulu Heart Study, which followed 8,000 men of Japanese ancestry for 31 years to assess risk factors for heart disease, 96 subjects developed Parkinson's disease. A look back at information collected years earlier revealed that Parkinson's disease was 2.7 to 4.5 times more likely to

develop in patients who had less than one bowel movement per day than in those who had one or two movements per day. And those with Parkinson's disease were more likely to have had chronic constipation at an earlier age, again suggesting that this seemingly minor problem could be an early harbinger of a devastating neurological condition.

### Unmet Needs

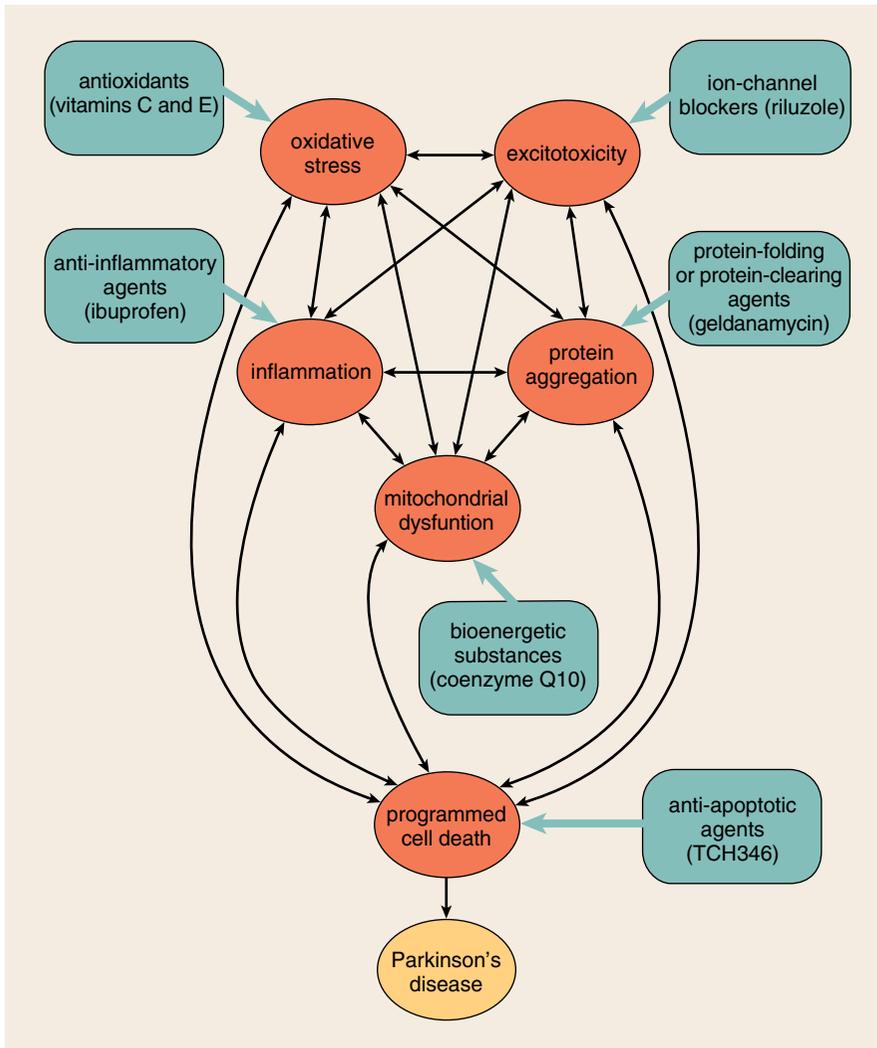
Clearly, Parkinson's disease is more than just a dopaminergic illness. Further study of the nondopaminergic features may help physicians to identify and develop new therapies—and new strategies are sorely needed. Although levodopa is able to correct some of the most debilitating symptoms, eventually disability develops that this drug cannot control. What these people really need is a treatment that addresses the underlying cause of the affliction. Such a neuroprotective therapy would slow or, ideally, stop the disease in its tracks.

Of course, researchers would have much better results designing therapies to delay progression of the disease if they understood what caused it in the first place. Cell death in Parkinson's disease has been linked to several dif-

ferent factors, including accumulation of free radicals (molecules with unpaired electrons that are consequently highly reactive and can damage neighboring molecules), malfunctioning mitochondria (the energy powerhouses for cells), excitotoxicity (a pathological process by which excess levels of the neurotransmitter glutamate cause an influx of calcium ions that then kill or damage the cells), inflammation, apoptosis (programmed cell death) and the deficiency of certain cell-growth factors. In addition, recent research has indicated that the death of these neurons may be connected to an impairment in the cell's capacity to clear abnormal and misfolded proteins. This concept may provide an explanation for the presence of Lewy bodies, which may be the vehicle by which a nerve cell tries to remove, or at least segregate, these unwanted proteins. It is not immediately obvious, however, how all these different processes interact and whether they are necessarily the same from person to person. So although researchers may design neuroprotective strategies to target specific problem areas, a given approach may work for only a subset of patients—if it works at all.

Thus far, investigators have tested a number of candidate agents, including antioxidants that clear free radicals, bioenergetics that enhance mitochondrial function and antiapoptotics that interfere with the proteins that signal the cell to commit suicide. However, to date no drug has demonstrated the ability to slow the degeneration of neurons.

One of the main challenges lies in the design of clinical trials that can accurately assess the effect of a given substance on the underlying disease. None of the end points that have been used thus far have proved to be good yardsticks for measuring the rate of disease progression. Even if considerable improvement is seen during testing, it remains difficult for physicians to determine whether the putative neuroprotective agent actually slowed the death of brain cells or merely ameliorated symptoms in a way that masks their ongoing loss. And one can't simply wait for the drug to wear off to make that judgment, because that might require weeks or months—far too long for patients to go without treatment. Until researchers are able to address these problems, efforts to develop neuroprotective drugs will likely remain unsuccessful.



**Figure 9.** More than one mechanism (red) may be responsible for killing nerve cells in Parkinson's disease. Indeed, the different forces at work may feed on one another. Physicians have tried to protect neurons from damage by giving patients certain nutritional supplements or drugs, although none of these attempted interventions (green) has yet proved effective.

The nondopaminergic features of Parkinson's disease may, however, provide a way out of this conundrum. These symptoms do not respond to current drug therapies and, indeed, progress despite them. So if a drug introduced early in a patient's treatment results in a delay in the emergence of the nondopaminergic problems, this result would be consistent with the agent being truly neuroprotective. And even if the drug's effect were only to alleviate symptoms, the discovery would still be momentous, because no drug is currently known to be able to help with the nondopaminergic aspects of the disease. For these reasons, the major trial sponsored by the National Institutes of Health (NIH Exploratory Trials in Parkinson's Disease, or "NET-PD") will use non-

dopaminergic features as primary endpoints.

Because some nondopaminergic features manifest themselves years before the classic motor symptoms of the disease first appear, physicians may be able to identify people who are in the earliest stages of the illness. These individuals could be ideal candidates for testing an experimental neuroprotective therapy. Indeed, it may be essential to introduce such agents at this stage, when the disease is not so far advanced, if the intervention is to slow the natural progression of the illness in a significant way. The hope is that such early treatment might entirely prevent the emergence of the motor impairments.

Ironically, the current interest in the nondopaminergic symptoms comes as a direct result of the wide-

spread success of levodopa therapy, without which physicians would have continued to focus on the more dramatic motor features of Parkinson's disease. Our current challenge is to develop new treatments that can ameliorate, or better yet prevent, the development of all aspects of this debilitating illness.

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