COMMENTARY

Parkinson's: What Do We Know About the Disease and What Can Be Done About It?

Alain L. Fymat

International Institute of Medicine and Science, California, U.S.A.

ABSTRACT

In this article, I aim to answer important questions regarding Parkinson's disease and the associated dementia. While the disease was identified and described over a century ago, we still have not as yet been able to ferret out its root cause, notwithstanding the tremendous progress made in recent years. Like for many other diseases, it is believed to involve three main causal components (inherited genetics, environmental influences, and, to a much lesser extent, lifestyle choices), which collectively determine if someone will develop the disease. I will survey its signs, symptoms (motor and non-motor), risks, and stages, distinguishing between the disease's early- and late-onset. While discriminating between the disease and its associated dementia, I will localize the latter within the broad spectrum of dementias. I will also describe what happens to the brain as the disease takes hold and evolves. A number of medical conditions called Parkinsonisms may have one or more of their signs and symptoms mimicking Parkinson's. I will discuss them in some detail, including their five proposed mechanisms (protein aggregation in Lewy bodies, disruption of autophagy, mitophagy, neuroinflammation, and breakdown of the blood–brain barrier). I will further describe the approach to diagnosis, prediction, prevention, and prognosis. While there is no cure and treatment for each affected person, motor symptoms are managed with several medications (Levodopa always combined with a dopa decarboxylase inhibitor and sometimes also with a catechol-O-methyltransferase [COMT] inhibitor, dopamine agonists, and monoamine oxidase-B [MAOB]-inhibitors) and eventually surgical therapy. Numerous pharmaceutical agents are also available for individual non-motor symptoms (L-Dopa emulsions, non-ergot dopamine agonists, cholinesterase inhibitors for dementia, modafinil for daytime sleepiness, and quetiapine for psychosis). Fortunately, we can track the drug effectiveness with exosomes. Keeping in mind patients and their caregivers/partners, I will outline available complementary therapies, palliative care, and rehabilitation, measures they can take beyond seeking standard treatments, and supporting and advocating organizations at their disposal. Finally, I will survey promising new research vistas in the field.

Key words: Dementia, environmental, genetics, lifestyle influences, motor and non-motor symptoms, Parkinsonism, Parkinson's disease

WHAT IS PARKINSON'S DISEASE (PD)?

Described in 1817 by the British surgeon, Dr. James Parkinson, in his classical Essay on the Shaking Palsy, it is a long-term, slowly progressing neurodegenerative disorder that mainly affects the central nervous system.[1-3] It belongs to a group of conditions called motor system (or movement) disorders. It is a common, disabling, and currently incurable condition. The disease affects over 2% of people over the age of 75. It usually begins around age 60 (so-called "late onset"), but it can start earlier ("young [or early] onset"). Early-onset forms are often, but not always, inherited and some forms have been linked to specific gene mutations. However, although some cases of Parkinson's appear to be hereditary, and a few can be traced to specific genetic mutations, in most cases, the disease occurs randomly

Address for correspondence: Alain L. Fymat, International Institute of Medicine and Science California, U.S.A.

and does not seem to run in families. Nonetheless, while it has not been proven to be hereditary, it has been noted that those with a family member affected are more likely to get the disease themselves.[4-6] Some studies have proposed that it is more common in men than women (about 50% more), but others failed to detect any differences between the two sexes.

WHAT CAUSES PARKINSON'S?

The motor symptoms of the disease result from the death of nerve cells (neurons) in the substantia nigra, a region of the midbrain that controls movement. Normally, these neurons produce an important brain chemical known as dopamine. When the neurons die or become impaired, they produce less dopamine, which causes the movement problems of Parkinson's.[7] The disease results from either the insufficient production of dopamine or/and the loss of dopamine-producing ("dopaminergic") brain cells. The reason for this cell death is poorly understood but involves the build-up of proteins into so-called Lewy bodies (aggregations of proteins) within the neurons.[8] Scientists still do not know what causes cells that produce dopamine to die.[8-10]

People with Parkinson's also lose the nerve endings that produce norepinephrine, the main chemical messenger of the sympathetic nervous system, which controls many automatic functions of the body, such as heart rate and blood pressure.[11] The loss of norepinephrine might help explain some of the non-movement features of Parkinson's, such as fatigue, irregular blood pressure, decreased movement of food through the digestive tract, and sudden drop in blood pressure when a person stands up from a sitting or a lying-down position.

Unfortunately, however, notwithstanding the tremendous progress made in recent years in better understanding the disease and its possible causes, the fact that the disease was identified and described over a century ago, and despite the expenditures of large sums of monies and the conduct of hundreds of clinical trials, we have not as yet been able to ferret out the root cause of the disease. Like for many other diseases, it is believed to involve what I call the guity triad: Genetic, environmental, and lifestyle (acronym "GEL") factors. These three main causal components vary in importance from person to person and also vary over time even for the same person. For example, there is an increased risk of getting Parkinson's for those with a family member affected as they are more likely to get the disease themselves (genetic risk). Likewise, there is an increased risk in people exposed to certain pesticides (environmental risk). There is a further increased risk among those who have had prior head injuries (lifestyle risk). Surprisingly, there appears to be a reduced risk in tobacco smokers and those who drink coffee or tea.

WHAT ARE THE SIGNS, SYMPTOMS, AND STAGES OF THE DISEASE?

There is a long list of recognized motor and non-motor symptoms and early and late symptoms. They are extensively discussed in my book (see in the list of references). I shall not elaborate further on them here. However, Parkinson's impacts people in different ways and not everyone will experience all the symptoms of the disease; if they do, they will not necessarily experience them in quite the same order or with the same intensity. However, symptoms may not always tell the whole story!

In the early stages, the face may show little or no expression, the arms may not swing when walking, and the speech may become soft or slurred. Early symptoms are subtle, starting gradually, sometimes on one side of the body with a barely noticeable tremor in just one hand, later on, both sides. These symptoms generally develop slowly over the years, the progression being often a bit different from one person to another due to the diversity of the disease. As the symptoms become more pronounced, patients may have trouble walking, talking, or completing other simple tasks. They may also have problems such as depression and other emotional changes; sleep disruptions; trouble chewing, swallowing, or speaking; urinary problems or constipation; and skin problems. Progression tends to be slow and variable and the symptoms may begin to interfere with daily activities. However, these symptoms appear in other diseases as well so that not everyone with one or more of these symptoms has the disease. In some people, the disease evolves more quickly than in others and it is not possible to predict what course the disease will take.

As neurons in parts of the brain become impaired or die, people may experience four primary symptoms: (1) Tremor, or trembling in the hands, arms, legs, jaw, and face; (2) rigidity, or stiffness of the limbs or trunk of the body; (3) bradykinesia, or slowness of movement; and (4) gait and postural instability, or impaired balance and coordination. This condition may be remembered by the acronym "TRBG."

There are typical patterns of progression that have been defined in 5 stages. Various rating scales may be used not only by the clinician but also by the patient to help understand and gauge the progression of the disease over the years. Like for other neurodegenerative diseases, particularly Alzheimer's disease, they focus either on functional or/and cognitive abilities.[12] They include the original and the "modified Hoehn and Yahr rating scale," the "Unified PD rating scale," the "Schwab and England Activities of Daily Living scale," the "Movement Disorders Society-Unified PD rating scale," and others for specific symptoms.[13,14] These several scales

are used to describe how individuals are faring and help assess treatment response.

ASIDE FROM THE AGE OF OCCURRENCE, HOW DO EARLY-ONSET AND LATE-ONSET DIFFER?

Young-onset Parkinson's occurs in people younger than 50 years of age. It affects about 2%-10% of the one million Parkinson's people in the United States. The younger the patient is, the more likely the disease is genetic. Motor and non-motor symptoms for young- and late-onset Parkinson's are similar except for certain differences. Young-onset individuals have a more frequent family history of Parkinson's and a longer survival (due to their younger age). They also may experience slower progression of symptoms, more side effects from dopaminergic medications, and more frequent dystonias (cramping and abnormal postures such as arching of the foot). Thankfully, younger brains have a higher neuroplasticity potential, which allows them to handle and respond to disease and therapy differently. Socially, people who are affected by Parkinson's at a younger age experience the disease differently – they may be at a different stage of their career and often have less time to engage in their care. They may also have children or are planning to have children and have questions regarding passing on Parkinson's genes.

In late-onset, the symptoms generally come in slowly over time. Early in the disease, the most obvious symptoms are shaking, rigidity, slowness of movement, and difficulty walking. Thinking and behavioral problems may also occur. In the advanced stages, dementia (a general mental deterioration due to organic or psychological factors) becomes common. Depression and anxiety are also common, occurring in more than a third of late-onset individuals. Other symptoms include sensory, sleep, and emotional problems.

IS PD THE SAME AS PD DEMENTIA?

PD is a risk factor (a precursor) for the later-occurring PD dementia; it speeds up the decline in cognition leading to dementia. Up to 78% of people with Parkinson's have dementia. To be clear, not all Parkinson's individuals will necessarily develop dementia.[8]

HOW IS PD DIFFERENT FROM DEMENTIA WITH LEWY BODIES?

PD dementia is but one component of what is known as Lewy body dementias, which are characterized by abnormal deposits of Lewy bodies (alpha-synuclein protein) in the brain, which were discovered by Frederic Lewy in 1912. The other component is dementia with Lewy bodies. (Note the important distinction between Lewy body dementias and dementia with Lewy bodies). A "diffuse" Lewy body disease was also described by Kenji Kosaka more than half a century later, in 1976.[8]

PD dementia starts as a movement disorder but progresses to include dementia and changes in mood and behavior. Its signs, symptoms, and cognitive profile are similar to those of dementia with Lewy bodies. After dementia has taken place, PD dementia and dementia with Lewy bodies are clinically similar. There are a few distinctions, however. Thus, delusions in PD dementia are less common than in dementia with Lewy bodies. Furthermore, persons with PD dementia are typically less caught up in their visual hallucinations than those with dementia with Lewy bodies. Further, there is a higher incidence of tremor at rest in the former than in the latter individuals, and signs of Parkinsonism are likewise less symmetrical.

In general, accepted diagnostic criteria are the same for the two types of dementia, except that PD dementia is distinguished from dementia with Lewy bodies by the time frame in which dementia symptoms appear relative to Parkinsonian symptoms. Thus, dementia with Lewy bodies is diagnosed when cognitive symptoms begin before or at the same time as Parkinsonism. On the other hand, PD dementia is the diagnosis when PD is well established before dementia occurs, that is, the onset of dementia is more than a year after the onset of Parkinsonian symptoms.

WHAT HAPPENS TO THE BRAIN IN PD?

In a healthy human brain, the neurons are specialized cells that process and transmit information through electrical and chemical signals. They send messages between different parts of the brain and from the brain to the muscles and organs of the body. Parkinson's disrupts this communication among neurons, resulting in loss of function and cell death. It also disrupts the function and survival of neurons as well as their several key biological processes. When the communication between neurons breaks down, metabolism is impaired, and the ability of neurons to maintain and repair themselves, remodel their synaptic connections or regenerate new neurons (which are all important processes for locomotion, learning, memory, and possibly brain repair) also deteriorate. These changes may have started perhaps decades earlier or more, beginning gradually and getting worse over time. As the disease progresses, motor symptoms develop in the substantia nigra region of the brain and worsen as the condition progresses over time, more quickly in some persons than in others. During the disease, additional non-motor symptoms progressively manifest themselves. However,

these symptoms are not necessarily indicative of Parkinson's as they may also appear in other diseases as well.

Modern imaging technologies (particularly DaTscan with Iodine-123 Ioflupane) show the Parkinson-diseased brain to be a profound modification of a healthy brain with shrinkage and even near-disappearance of the substantia nigra. The deterioration from a normal brain is striking and may be used to gauge the degree of severity of Parkinson's.[10]

WHAT IS PARKINSONISM?

Medical conditions other than Parkinson's may have one or more of the signs and symptoms mimicking Parkinson's. "Parkinsonism" is a general term used to describe them. PD is the most common form of Parkinsonism. It is sometimes called "idiopathic Parkinsonism," meaning Parkinsonism with no identifiable cause.[15,16]

Parkinsonism is a clinical syndrome characterized by tremor, rigidity (stiffness), bradykinesia (slowness of movement), and gait and postural instability (imbalance) – again the acronym TRBG. It is found in idiopathic PD due to nigrostriatal degeneration, after which it was named, dementia with Lewy bodies, and many other conditions. "Parkinsonism" is a general term used to describe them all. Several neurodegenerative disorders may also present with Parkinsonism; they are sometimes referred to as "atypical Parkinsonism" or "Parkinson + plus syndromes," that is, Parkinsonism plus some other distinguishing features. They include multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration syndrome, dementia with Lewy bodies, and synucleinopathy. Additional Parkinsonisms are: Drug-induced Parkinsonism, vascular Parkinsonism, psychogenic Parkinsonism, essential tremor, post-encephalitic Parkinsonism, toxin-induced Parkinsonism, and Parkinson-dementia complex of Guam. Furthermore, there are several instances where Parkinsonism results from neurological disorders, including arteriosclerotic Parkinsonism, post-traumatic Parkinsonism, and normal pressure hydrocephalus. Parkinsonian symptoms further appear in individuals with other distinct neurological disorders such as Wilson's disease, Huntington's disease, Alzheimer's disease, spinocerebellar ataxia, and Creutzfeldt-Jakob disease. In addition, there are three important conditions related to Parkinson's, specifically melanoma, neurogenic orthostatic hypotension, and pseudobulbar affect. Each of these disorders has specific features that help to distinguish it from Parkinson's. All these various types of Parkinsonism are discussed and categorized in my book.

The clinical diagnosis of Parkinsonism is often straightforward, which obviates additional tests in many cases. However, for incomplete syndromes, or overlap between multiple concurrent conditions, particularly early on, an improvement in diagnostic accuracy may be possible using the DaTscan visualization modality I mentioned earlier. However, I must emphasize that DaTscan was not designed to distinguish between these different conditions.

IS PARKINSON'S A GENETIC DISEASE?

A large international study suggested that the more variants a person has, the greater the risk, up to 3 times higher, for developing the disorder in some cases. The researchers confirmed that 24 variants represent genetic risk factors for Parkinson's, including six variants that had not been previously identified. Some of the newly identified genetic risk factors are thought to be involved with Gaucher's disease, regulating inflammation and the nerve cell chemical messenger dopamine as well as alpha-synuclein – a protein that has been shown to accumulate in the brains of Parkinson's individuals. Notwithstanding the above extensive and interesting results, further research is needed to determine the roles of the variants identified.[17,18]

Of individuals having Parkinson's, around 15% have a first-degree relative who has the disease and 5–10% are known to have forms of the disease that occur because of a mutation in one of several specific genes. However, harboring one of these gene mutations may not necessarily lead to the disease. Susceptibility factors put the individual at an increased risk, often in combination with other risk factors, which also affect the age of onset, severity, and progression. Even when someone has a gene mutation associated with Parkinson's, the likelihood of developing the disease is low. The reason is that whereas, on the one hand, certain genes cause Parkinson's, on the other hand, other genes may protect some people from developing it. Right now, we believe that inherited genetics, environmental influences, and, to a much lesser extent, lifestyle choices (the perennial triad) collectively determine if someone will develop the disease.

WHAT IF I CARRY THE GENE?

Parkinson's is rarely hereditary. Thus, if a person tests positive for a certain associated gene mutation their risk may increase, but they may still never develop the disease. Again, we are speaking of risk (not causal) factors. It is possible for someone who tests positive for a Parkinson's mutation to inherit other genes, be exposed to environmental factors or have lifestyle choices that do not lead to developing Parkinson's. Genetic research has made great strides to help scientists better understand the biology of Parkinson's and guide the development of palliative treatments. Soon, knowing a person's genetic background may help predict the most effective treatments.

Genetic tests are not generally available, nor are they recommended for most people with Parkinson's because mutations in these genes occur so rarely. Furthermore, there is no difference in the treatment provided whether the disease has or does not have a known genetic cause. Nonetheless, there are ongoing clinical trials testing therapies to treat Parkinson's people who carry certain gene mutations. It can be important to know which gene mutation you carry. I suggest, therefore, that concerned individuals consult with their doctor when considering a genetic test to determine if they are eligible to participate in gene-based clinical trials. One study, the "Parkinson's Foundation Genetics Initiative," is the first national Parkinson's study to offer free genetic testing plus counseling for Parkinson's-related genes through medical professionals. It is hoped that this program will uncover more details about how genetic factors play a role in Parkinson's, helping us better understand this complex disease.

WHAT ARE THE POSTULATED THEORIES OF PARKINSON'S?

As I indicated earlier, for most people with Parkinson's, the disease is caused by a combination of underlying genetic predisposition, environmental exposures, and, to a much lesser extent, lifestyle choices. Theoretically, genes may play a larger role in young-onset rather than late-onset, while environmental factors may play more of a role in sporadic Parkinson's.[19] However, to date, researchers have found this hard to prove, as we are still improving our understanding of the biological mechanisms of the disease. Recently, scientists have discovered genes that can cause or increase the risk of developing Parkinson's at a younger age. Nonetheless, the root cause remains unknown as we do not yet fully understand the deep neurobiology of the disease. However, the disease mechanisms which express it are somewhat understood from the pathophysiology of the disease, that is, the death of dopaminergic neurons as a result of changes in biological activity in the brain that result in the near disappearance of the substantia nigra.

There are several proposed mechanisms for neuronal death, not all of which being well understood. The five major mechanisms (which can best be remembered by the acronym PAMNB) are: Protein aggregation in Lewy bodies (this is the bundling called "oligomerization" of the alpha-synuclein protein forming Lewy bodies in neurons); disruption of autophagy (this is a mechanism by which inner components of the cell are broken down and recycled for use, helping to clear aggregated proteins and regulating cellular function); changes in cell metabolism or mitochondrial function (or "mitophagy" wherein mitochondrial function is disrupted, inhibiting energy production and resulting in cell death); neuroinflammation (it is better understood for microglia are recognized as the innate immune cell of the central nervous system); and breakdown of the blood-brain barrier (here, protein aggregates or cytokines from neuroinflammation may interfere with cell receptors and alter their function; also known as vascular leakiness, it can eventually cause neurons to alter their function and shift toward apoptotic behavior or cell death).

Exposure to certain toxins has caused Parkinsonian symptoms in rare circumstances (such as exposure to MPTP, an illicit drug, or in miners exposed to the metal manganese). Other still-unidentified environmental factors may also cause Parkinson's in genetically susceptible individuals. Main environmentally-caused Parkinsonisms are postencephalitic Parkinsonism; drug-induced Parkinsonism; toxin-induced Parkinsonism; and Parkinsonism-dementia complex of Guam.

HOW DOES PARKINSON'S PROGRESS?

The current theory is a part of the so-called Braak's hypothesis wherein the earliest signs of the disease occur in the enteric nervous system, the medulla, and the olfactory bulb. They progress to the substantia nigra and cortex over time. This theory is increasingly borne out by evidence that non-motor symptoms, such as a loss of sense of smell (hyposomia), sleep disorders, and constipation, may precede the motor features of the disease by several years. For this reason, researchers are increasingly focused on these non-motor symptoms for early detection and to look for ways to stop its progression.

WHAT ARE THE CURRENT APPROACHES TO DIAGNOSING PARKINSON'S?

Making an accurate diagnosis of Parkinson's, particularly in its early stages, is difficult, but a skilled practitioner can come to a reasoned conclusion.[20] It is first made by an internist or family physician. Many people seek an additional opinion from a neurologist with experience and specific training in the assessment and treatment of Parkinson's. Such a specialist who has had extra training (usually a 1- or 2-year fellowship) in Parkinson's and other movement disorders is referred to as a movement disorders specialist.[21] I recommend that a person with symptoms resembling those of Parkinson's consider making an appointment with such a specialist. Brain scans or laboratory tests can be helpful to rule out other disorders. However, there is no "one way" to diagnose the disease!

Many disorders can cause symptoms similar to those of Parkinson's. People with Parkinson's-like symptoms that result

from other causes are sometimes said to have Parkinsonism, as I discussed at length earlier. While these disorders initially may be misdiagnosed as Parkinson's, certain medical tests, as well as responses to drug treatments, may help to distinguish them from Parkinson's. Since many other diseases have similar features but require different treatments, it is important to make an exact diagnosis as soon as possible. Unfortunately, there are currently no blood or laboratory tests to diagnose non-genetic cases. Diagnosis is, therefore, based on a person's medical history and a neurological examination. Improvement after initiating medication is another important hallmark of the diagnosis.

It is important to remember that two of the four main symptoms (tremor, rigidity, bradykinesia, gait, and postural instability – my earlier mnemonic TRBG) must be present over a while for a neurologist to consider a Parkinson's diagnosis. Other possible causes of these symptoms need to be ruled out. Finally, three or more of the following supportive features are required during onset or evolution: unilateral onset, tremor at rest, progression in time, asymmetry of motor symptoms, response to Levodopa for at least 5 years, clinical course of at least 10 years, and appearance of dyskinesia induced by the intake of excessive Levodopa.

CAN PARKINSON'S BE PREDICTED AND PREVENTED?

In rare cases, where people have an inherited form of Parkinson's, they can be tested for known gene mutations. However, this genetic testing can have far-reaching implications and people should carefully consider whether they want to know the results of such tests. In most cases, however, there is no way to predict or prevent sporadic Parkinson's. Researchers are still looking for a biomarker – a biological abnormality that all people with the disease might share – that could be detected by screening techniques or by a simple chemical test given to people who do not yet have any Parkinsonian symptoms. This could help doctors identify people at risk of the disease. It might also allow them to find treatments that will stop the disease process in the early stages.

Studies have demonstrated that synuclein builds up in nerve cells years before symptoms occur. Loss of a sense of smell, constipation, restless legs, and rapid-eye-movement sleep disorder[22] are potentially caused by these early changes. One important area of research in this domain involves imaging techniques, such as special magnetic resonance or nuclear imaging techniques.

As for prevention, exercise in middle age may reduce the risk of Parkinson's later in life. Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee. People who smoke cigarettes or use smokeless tobacco are less likely than non-smokers to develop the disease, and the more they have used tobacco, the less likely they are to develop Parkinson's disease PD. It is not known what underlies this effect. Antioxidants such as vitamins C and E have been proposed to protect against the disease, but the results of studies have been contradictory and no positive effect has been proven. The results regarding fat and fatty acids have been contradictory, with various studies reporting protective effects, risk-increasing effects, or no effects. There have been preliminary indications that the use of anti-inflammatory drugs and calcium channel blockers may be protective. Non-steroidal anti-inflammatory drugs, apart from aspirin, have been associated with a reduction in incidence in the development of Parkinson's (at least 15% higher in long-term and regular users). Unfortunately, lifestyle factors and many medications seem to offer extremely little, if any, potential benefit in the prevention of Parkinson's.

IF I HAVE PARKINSON'S, WHAT WOULD BE MY PROGNOSIS?

As stated earlier, Parkinson's is both chronic (meaning it persists over a long period of time) and invariably progressive (meaning its symptoms grow worse over time). Although some people become severely disabled, others experience only minor motor disruptions. Tremor is the major symptom for some individuals while, for others, tremor is only a minor complaint, with other symptoms being more troublesome. It is currently not possible to predict which symptoms will affect an individual, and the intensity of the symptoms also varies from person to person.

Untreated, individuals are expected to lose independent ambulation after an average of 8 years and be bedridden after 10 years. However, it is uncommon to find untreated people nowadays. Medication (Levodopa) has improved the prognosis of motor symptoms, while at the same time, it is a new source of disability because of its undesired effects after years of use. In people taking Levodopa, the progression time of symptoms to a stage of high dependency from caregivers may be over 15 years. However, it is hard to predict what course the disease will take for a given individual. Age is the best predictor of disease progression. The rate of motor decline is greater in those with less impairment at the time of diagnosis, while cognitive impairment is more frequent in those who are over 70 years of age at the onset of symptoms.

Since current therapies improve motor symptoms, disability at present is mainly related to non-motor features of the disease. Nevertheless, the relationship between disease progression and disability is not linear. Disability is initially related to motor symptoms. As the disease advances, disability is more

related to motor symptoms that do not respond adequately to medication, such as swallowing/speech difficulties and gait/balance problems; and also to Levodopa-induced complications, which appear in up to 50% of individuals after 5 years of Levodopa usage. Finally, after 10 years, most people with the disease have autonomic disturbances, sleep problems, mood alterations, and cognitive decline. All of these symptoms, especially cognitive decline, greatly increase disability.

The life expectancy of people with Parkinson's is reduced. Mortality ratios are around twice those of unaffected people. Cognitive decline and dementia, old age at onset, a more advanced disease state and the presence of swallowing problems are all mortality risk factors. On the other hand, a disease pattern mainly characterized by tremors, as opposed to rigidity, predicts an improved survival. Death from aspiration pneumonia is twice as common in individuals with Parkinson's as in the healthy population.

HOW IS PD TREATED?

There is no cure and treatment for each affected person is only directed at improving the associated symptoms. Treatments consist of medication and eventually surgical therapy. There are many medications available, although none yet that stop, reverse, or arrest the progress of the disease. It is common for people with Parkinson's to take a variety of these medications – all at different doses and at different times of day – to manage symptoms. While keeping track of medications can be a challenging task, understanding medications and sticking to a schedule will provide the greatest benefit from the drugs and avoid unpleasant "off" periods due to missed doses.

Initial treatment is typically with the anti-Parkinson medication Levodopa (also called L-dopa) with dopamine agonists being used once Levodopa becomes less effective. As the disease progresses and neurons continue to be lost, these medications become less effective while at the same time, they produce a complication marked by involuntary writhing movements. Diet and some forms of rehabilitation have shown some effectiveness in improving symptoms. Surgery to place microelectrodes for deep brain stimulation has been used to reduce motor symptoms in severe cases where drugs are ineffective. In contrast to these two situations, treatments for non-movement-related symptoms such as sleep disturbances and emotional problems are less effective. Other treatments include lifestyle modifications, such as getting more rest and exercise.

HOW IS THE DISEASE MANAGED?

The main families of drugs useful for treating motor symptoms are Levodopa, always combined with a dopa decarboxylase inhibitor and sometimes also with a COMT inhibitor, dopamine agonists, and MAO-B inhibitors. Nerve cells use Levodopa to make dopamine to replenish the brain's dwindling supply. The stage of the disease and the age at disease onset usually determine which group of medications is most useful.

Four stages are usually distinguished: (1) In the initial stage, treatment aims for an optimal trade-off between symptom control and treatment side-effects. The start of Levodopa treatment may be postponed by initially using instead other medications such as MAO-B inhibitors and dopamine agonists, in the hope of delaying the onset of complications due to Levodopa use. Nonetheless, Levodopa is still the most effective treatment for motor symptoms and should not be delayed in those whose quality of life is impaired by those symptoms. Levodopa-related dyskinesias correlate more strongly with the duration and severity of the disease than the duration of the Levodopa treatment, so delaying this therapy may not provide much longer dyskinesia-free time than early use; (2) the second stage is associated with the development of complications related to Levodopa usage. The aim here is to reduce symptoms while controlling fluctuations in the effect of the medication. Sudden withdrawals from medication or overuse have to be managed. When oral medications are not enough to control symptoms, surgery (deep brain stimulation), subcutaneous waking-day apomorphine infusion, and enteral dopa pumps can be of use; (3) the third stage applies when symptoms unrelated to dopamine deficiency or Levodopa treatment may predominate. It presents many challenging problems requiring a variety of treatments for psychiatric symptoms, orthostatic hypotension, bladder dysfunction, etc.; and (4) in the final stages of the disease, palliative care is provided to improve the quality of life.

WHAT ARE THE CHALLENGES OF TREATING MOTOR AND NEUROPSYCHIATRIC SYMPTOMS?

Neurologists can choose from a large number of compounds to treat the motor symptoms effectively for several years, if not decades. Furthermore, owing to advances in internal medicine, anesthesia, and surgery, Parkinson's patients live longer but within the optimal therapeutic balance between motor- and non-motor symptoms with a minimum of adverse effects.

With advancing age and duration of the disease, gait problems (which do not respond to dopamimetic therapy) combined with the increased risk of falls and fractures develop, including autonomic dysfunctions such as urinary incontinence and severe obstipation, sleep impairment, pain syndromes, and neuropsychiatric symptoms such as depression, impulse control disorders, punding, hallucinations, overt psychosis

in part induced by dopamimetic therapy, and cognitive impairment progressing to dementia. Still further, the extent of comorbidity increases with orthopedic syndromes, diabetes mellitus, metabolic syndrome, heart failure, and stroke.

Thus, the weight of therapeutic need has shifted from "just" making or keeping the patient mobile to the challenge of fine-tuning a therapeutic combination of drugs for (1) the treatment of motor and non-motor symptoms, (2) motor and non-motor complications and, in accordance with other medical treatments and care, and (3) treatment that is acceptable to the patient and the caring partner(s).

WHAT IS THE PHARMACOLOGICAL THERAPY FOR MOTOR SYMPTOMS?

Medications for Parkinson's fall under six categories, the cornerstone remaining Levodopa: (1) Drugs that increase brain levels of dopamine (Levodopa, Carbidopa); (2) drugs that mimic dopamine (dopamine agonists: Apomorphine, pramipexole, ropinirole, rotigotine); (3) drugs that inhibit dopamine breakdown (MAO-B inhibitors: Rasagiline, selegiline); (4) other drugs that inhibit dopamine breakdown (COMT inhibitors: Entacapone, tolcapone); (5) drugs that decrease the action of acetylcholine (anticholinergics: Benztropine, ethopropazine, trihexyphenidyl); and (6) drugs with an unknown mechanism of action (amantadine).

Difficulties may be encountered in the course of the disease such as more pronounced symptoms before the first dose of medication in the morning and between doses as the period of effectiveness after each dose begins to shorten accompanied by sudden, unpredictable "off periods" where the medications do not seem to be working (this is the so-called wearing-off effect).

One approach to alleviating these side effects is to take Levodopa more often and in smaller amounts. People with PD should never stop taking Levodopa without their physician's input because rapidly withdrawing the drug can have potentially serious side effects. When recommending a course of treatment, a doctor will assess how much the symptoms disrupt the person's life and then tailor therapy to the person's particular condition. Since no two people will react the same way to a given drug, it may take time and patience to get the dose just right. Even then, symptoms may not be completely alleviated.

To delay or ameliorate the motor complications associated with L-Dopa therapy, several other classes of drugs are available to be prescribed before the use of, or in combination with, L-Dopa. The L-Dopa effect can be enhanced and prolonged in either of the following two ways: (1) Combination with peripheral inhibitors of degrading enzymes (benserazide or carbidopa – a standard combination; COMT) and (2) centrally active inhibitors of the degrading enzyme MAO-B (rasagiline, selegiline).

AND, HOW ABOUT THE PHARMACOLOGY FOR NON-MOTOR SYMPTOMS?

There are numerous pharmacotherapies available for individual non-motor symptoms though mostly by employing a given compound approved to treat one or more of those symptoms. For example, people with Parkinson's-related depression may be prescribed antidepressants.

There are certain advanced pharmacological therapeutic options that currently include: (1) L-Dopa emulsion that can be applied by an external pump through a percutaneous tubing into the jejunal cavity to provide a nearly constant continuous supply of L-Dopa to the blood and thus to the central nervous system and (2) non-ergot dopamine agonists (apomorphine, piribedil – that is only registered in Europe, pramipexole, ropinirole, and rotigotine).

Other drugs include cholinesterase inhibitors (for dementia); modafinil (for daytime sleepiness); and quetiapine (for psychosis).

CAN THE DRUG EFFECTIVENESS BE TRACKED?

Yes, with the use of exosomes.[23] These nanoscale particles are produced by all types of cells and circulate in the bloodstream. Exosomes originating from neurons carry an information-rich cellular cargo and can cross the blood-brain barrier. Several previous studies have demonstrated that it is possible to track key disease-related proteins within this exosome cargo and that this technique can successfully differentiate between healthy control samples and those from patients with Parkinson's (and also Alzheimer's). In clinical trials, exosomes are an additional analytical tool to show target engagement and to help speed up the validation of potential new drugs.

WHAT ABOUT SURGERY TREATMENTS?

Therapy resistance, fluctuations, and dyskinesias may develop over time. To provide treatment to these chronically and severely affected patients, surgical approaches have been developed since the 1950s and 1960s. Treating motor symptoms with surgery was once a common practice but, since the discovery of Levodopa, the number of operations had

declined. However, studies in the past few decades have led to great improvements in surgical techniques, so that surgery is again being used in people with advanced Parkinson's for whom drug therapy is no longer sufficient.[24,25]

Surgery for Parkinson's can be divided into three main groups: (1) Radiofrequency lesioning (in the 1960s, it was performed in the subthalamus; newer technologies have since replaced it); (2) deep, high-frequency brain stimulation (for those who do not respond well to medications). Deep brain stimulation increased the therapeutic options for it is effective not only in very advanced cases but also for patients who have just started to develop motor complications.[26,27] It also allows one to decrease the amount of pharmacotherapy (Levodopa and related drugs), resulting in fewer motor or neuropsychiatric adverse effects, or both. It is not generally an option for people with memory problems, hallucinations, severe depression, poor health, or a poor response to Levodopa. It has not been demonstrated to be of benefit for "atypical" Parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, or post-traumatic Parkinsonism, which also do not improve with Parkinson's medications. Further, as with any brain surgery, it has potential complications, including stroke or brain hemorrhage, which are, however, rare. There is also a risk of infection, which may require antibiotics or even replacement of parts of the system; and (3) magnetic resonance-guided high-intensity focused ultrasound for the treatment of Parkinson's, neuropathic pain, and essential tremor.

HOW DOES ONE COPE WITH BALANCE PROBLEMS?

Although not strictly Parkinson's problems, balance problems and disorders are nonetheless important because they are germane to movement disorders. Balance problems are among the most common reasons that older adults seek help from a doctor. They are often caused by disturbances in the inner ear, vertigo being a common symptom. Having good balance means being able to control and maintain one's body's position, whether moving or remaining still. Good balance helps to walk without staggering, get up from a chair without falling, climb stairs without tripping, and bending over without falling. Good balance is important to help get around, stay independent, and carry out daily activities.

People are more likely to have problems with their balance as they get older. However, age is not the only reason these problems occur. Some balance disorders are caused by problems in the inner ear, particularly the vestibular system also known as the labyrinth. A condition called labyrinthitis occurs when the labyrinth becomes infected or swollen. It is typically accompanied by vertigo and imbalance. Upper respiratory infections, other viral infections, and, less commonly, bacterial infections can also lead to labyrinthitis. Some medications can also cause a balance problem. Some people with a balance disorder may not be able to fully relieve their dizziness and will need to find ways to cope with it. A vestibular rehabilitation therapist can help to develop an individualized treatment plan.

Some diseases of the circulatory system, such as stroke, can cause dizziness and other balance problems. Low blood pressure can also cause dizziness. Head injury and many medicines may also lead to balance problems. Many people with advanced Parkinson's suffer from gait (walking) dysfunction, freezing of gait, and postural instability. These symptoms can cause falling, resulting in a multitude of injuries, a loss of personal freedom, caregiver stress, and a reduction in the quality of life. Medications, such as Levodopa, rarely help with these specific motor symptoms, while deep brain stimulation results are limited and unpredictable for these particular symptoms. The fact is, current Parkinson's medications, therapies or surgical procedures do not effectively address this debilitating unmet need. This lack of options might be changing due to an intervention called spinal cord stimulation, a device that alters nerve activity by sending a low-voltage electrical current to select areas of the spinal cord.

For more information about balance problems and disorders, falls and prevention, contact the Parkinson's Foundation; the National Institute on Deafness and Other Communication Disorders; the Mayo Clinic; and MedlinePlus.gov (National Library of Medicine); and other organizations.

ARE THERE COMPLEMENTARY THERAPIES?

While many Parkinson's patients choose conventional medications and treatments, complementary and supportive therapies may provide additional symptom relief. These include: (1) Therapeutic approach (for speech and swallowing evaluation and therapy); (2) standard physical, occupational, and speech therapy techniques (for such problems as gait and voice disorders, tremors and rigidity, and cognitive decline); (3) diet and vitamin supplements (at this time, there are no specific vitamins, minerals, or other nutrients that have any proven therapeutic value); (4) exercise (to improve mobility and flexibility, tone and strengthen muscles, improve body strength and balance, and minimize gait problems); and (5) others (massage therapy to relieve tension and stress, meditation, yoga, hypnosis, acupressure, acupuncture, physiotherapy, dance interventions, and logopedic training of dysphagia).

WHAT ABOUT PALLIATIVE CARE AND REHABILITATION?

Palliative care is specialized medical care for providing relief from the symptoms, pain, and stress of illnesses and

improving the quality of life for both the suffering person and their family and carers. As Parkinson's is not yet a curable disease, all treatments are focused on slowing decline and improving the quality of life and are therefore palliative in nature. Palliative care should be sought earlier, rather than later in the disease course, serving an important role in addressing goals of care.

Regarding rehabilitation, exercise programs are recommended. There is some evidence that speech or mobility problems can improve with rehabilitation, although studies are scarce and of low quality. Regular physical exercise with or without physical therapy can be beneficial to maintain and improve mobility, flexibility, strength, gait speed, and quality of life.

HOW DOES ONE COPE WITH PARKINSON'S?

While Parkinson's usually progresses slowly, eventually, daily routines may be affected – from socializing with friends to earning a living and taking care of a home. These changes can be difficult to accept. Support groups can help people cope with the disease's emotional impact. They can also provide valuable information, advice, and experience to deal with a wide range of issues, including locating doctors familiar with the disease and coping with physical limitations.

Individual or family counseling may also help people find ways to cope. People with Parkinson's may also benefit from being proactive and finding out as much as possible about the disease to alleviate fear of the unknown and to take a positive role in maintaining their health. Many people with Parkinson's continue to work either full- or part-time, although they may need to adjust their schedule and working environment to accommodate their symptoms.

For more information about palliative care contact: CaringInfo; the Center to Advance Palliative Care; Visiting Nurse Associations of America; and other similar organizations.

WHAT CAN ONE DO BEYOND SEEKING STANDARD TREATMENTS?

Because symptom deterioration is often significantly slower in those who take a positive and proactive stance toward their condition than in those who do not, I suggest as many of the following 12 steps as possible: (1) Become well informed about the disease: This is one important long-term strategy. Furthermore, programs that teach families about the various stages of Parkinson's and about ways to deal with difficult behaviors and other caregiving challenges can help. For more information about Parkinson's brain changes, contact: The National Institute of Neurological Disorders and Stroke; the National Institute on Aging; the Parkinson's Foundation; the Michael J. Fox Foundation for Parkinson's Research; Eldercare Locator; MedlinePlus.gov; the National Human Genome Research Institute; and the National Center for Biotechnology Information; (2) ask questions of your doctors and be an active advocate for yourself; and (3) begin treatment early in the disease process to help preserve daily functioning for some time. An early diagnosis also helps families plan for the future. They can take care of financial and legal matters, address potential safety issues, learn about living arrangements, and develop support networks; (3) look for new treatments as Parkinson's research has developed to a point where scientists are starting to look beyond treating symptoms and thinking about addressing underlying disease processes; (4) enroll in ongoing clinical trials that develop and test several possible interventions, including drug therapy, cognitive training, and physical activity, and treatments used for cardiovascular disease and diabetes; (5) exercise; (6) maintain mental function to help engaging in mentally-stimulating activities as well as with one or more of the appropriate medications that have been FDA-approved. Even though they only treat symptoms of Parkinson's and do not change the underlying process, these medications can help in the young- and late-onset cases. However, they can be effective for some but not all people and may help only for a limited time; (6) manage behavior to make people with Parkinson's more comfortable and ease things for caregivers; (7) beware of balance problems and disorders to help walk without staggering, get up from a chair without falling, climb stairs without tripping, and bend over without falling, get around, stay independent, and carry out daily activities; (8) improve speech and communication; (9) keep talking; (10) practice good "voice hygiene;" (11) participate in creative arts therapies (painting, drama, dance, and music) to help improve the quality of life; and (12) reduce stress, a must as stress worsens every symptom.

IS SUPPORT FOR FAMILIES AND CAREGIVERS AVAILABLE?

Caring for a person with Parkinson's can have high physical, emotional, and financial costs. The demands of day-to-day care, changes in family roles, and decisions about placement in a care facility can be difficult. Several evidence-based approaches and programs can help. Researchers are continuing to look for new and better ways to support caregivers.

Good coping skills, a strong support network, and respite care are other ways that help caregivers handle the stress of caring for a loved one with Parkinson's. For example, staying physically active provides physical and emotional benefits.

Some caregivers have found that joining a support group is a critical lifeline. These support groups allow caregivers to find respite, express concerns, share experiences, get tips, and receive emotional comfort. Many organizations sponsor in-person and online support groups, including groups for people with early-stage Parkinson's and their families.

WHAT ARE THE ADVOCATING AND SUPPORTING ORGANIZATIONS?

Nineteen main U.S. organizations support PD patients and their families: (1) The American Academy of Neurology; (2) The American PD Association; (3) The Bechmann-Strauss Dystonia and Parkinson Foundation; (4) Caring.com; (5) CurePSP (Foundation for Progressive Supranuclear Palsy/ Corticobasal Syndrome and Related Brain Diseases); (6) The International Parkinson's and Movement Disorders Society; (7) The Michael J. Fox Foundation for Parkinson Research; (8) The National Institute of Neurological Disorders and Stroke; (9) The National Parkinson's Foundation; (10) The Parkinson Action Network; (11) The Parkinson Study Group; (12) The PD Foundation; (13) Partners in Parkinson's; (14) The Society of Nuclear Medicine and Molecular Imaging; (15) The Davis Phinney Foundation; (16) The National Parkinson Foundation; (17) The Parkinson Alliance; (18) The Tremor Action Network; and (19) The (U.S.) Department of Veterans' Affairs – PD Research.

There are many other supporting organizations across the world, including, in particular, the European PD Association.

ANY NEW RESEARCH VISTAS IN THE FIELD?

Yes! Beginning in 1997, the world of PD research began changing dramatically with contemporaneous advances in immunotherapy, genetics, neuroprotective treatment, and nanomedicine.

The immunotherapeutic strategy relies on the critical assumptions that alpha-synuclein is accessible in the extracellular space (trans-synaptic spreading), antibodies against alpha-synuclein reach the brain in sufficient quantity, and they trap alpha-synuclein aggregates when these are released ("spread") into the extracellular synaptic space. However, one important limitation of active and passive immunotherapy is the low amount of antibodies that can pass the blood-brain barrier; this may be overcome by coupling antibodies to the peptide penetratin. To traverse this barrier, my book includes a whole chapter in which I propose and discuss the use of nanobiotechnology methods and procedures.[28-35]

Gene therapy may play an important role in the search for PD-modifying therapy.[36] It typically involves the use of a non-infectious virus (i.e., a viral vector such as the associated adenovirus) to shuttle genetic material into a part of the brain. The gene used leads to the production of an enzyme that helps to manage Parkinson's symptoms or protect the brain from further damage. In 2010, there were four clinical trials using gene therapy. So far, no important adverse effects in these trials have been reported, although the clinical usefulness of gene therapy has not yet been established.

Investigations on neuroprotection are at the forefront of Parkinson's research: (1) Several molecules have been proposed as potential treatments. However, none of them have been conclusively demonstrated to reduce degeneration. Agents currently under investigation include: Anti-apoptotic (Omigapil, CEP-1347); antiglutamatergic; MAO inhibitors (Selegiline, Rasagiline); promitochondrials (coenzyme Q10, creatine); calcium channel blockers (Isradipine); growth factors; and vaccines (PD01A to prime the immune system has entered clinical trials in humans); (2) neural transplantation (cell transplants in which dissociated cells are injected into the substantia nigra in the hope that they will incorporate themselves into the brain in a way that replaces the dopamine-producing cells that have been lost.[37] No long-term benefit has been shown so far. An additional significant problem was the excess release of dopamine by the transplanted tissue, leading to dystonia; (3) stem cell transplants (performed into the brains of rodents and monkeys, they have been found to survive and reduce behavioral abnormalities); (4) spinal cord stimulation;[38] (5) focused ultrasound;[39,40] (6) transcranial magnetic stimulation temporarily improves Levodopa-induced dyskinesias. Its usefulness in Parkinson's is an open research topic; and (7) nutrients (caffeine, inosine, isradipine, and nicotine) have shown some benefits but not so for vitamins or food additives.

Being able to traverse or bypass the blood-brain barrier while delivering therapeutic compounds at the right locations in the right dosage amounts would herald a new approach I proposed for the treatment of PD. This is what nanomedicine and nanobiotechnology promise to do. However, while the technology is now well known, its application to Parkinson's has not yet been undertaken.

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