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Parkinson's Disease

Parkinson's disease (also known as **Parkinson disease** or **PD**) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions.[1]

Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and a loss of physical movement (akinesia) in extreme cases. The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

PD is the most common cause of chronic progressive parkinsonism, a term which refers to the syndrome of tremor, rigidity, bradykinesia and postural instability. PD is also called "primary parkinsonism" or "idiopathic PD" (classically meaning having no known cause although this term is not strictly true in light of the plethora of newly discovered genetic mutations). While many forms of parkinsonism are "idiopathic", "secondary" cases may result from toxicity most notably of drugs, head trauma, or other medical disorders. The disease is named after English apothecary James Parkinson, who made a detailed description of the disease in his essay: "An Essay on the Shaking Palsy" (1817).

Classification

The term Parkinsonism is used for symptoms of tremor, stiffness, and slowing of movement caused by loss of dopamine. "Parkinson's disease" is the synonym of "primary parkinsonism", *i.e.*, isolated parkinsonism due to a neurodegenerative process without any secondary systemic cause. In some cases, it would be inaccurate to say that the cause is "unknown", because a small proportion is caused by genetic mutations. It is possible for a patient to be initially diagnosed with Parkinson's disease but then to develop additional features, requiring revision of the diagnosis.[2]

There are other disorders that are called *Parkinson-plus diseases*. These include: multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Some include dementia with Lewy bodies (DLB) — while idiopathic Parkinson's disease patients also have Lewy bodies in their brain tissue, the distribution is denser and more widespread in DLB. Even so, the relationship between Parkinson disease, Parkinson disease with dementia (PDD), and dementia with Lewy bodies (DLB) might be most accurately conceptualized as a spectrum, with a discrete area of overlap between each of the three disorders. The cholinesterase inhibiting medications have shown preliminary efficacy in treating the cognitive, psychiatric, and behavioral aspects of the disease of both PD and DLB. The natural history and role of Lewy bodies is little understood.

These Parkinson-plus diseases may progress more quickly than typical idiopathic Parkinson disease. If cognitive dysfunction occurs before or very early in the course of the movement disorder, then DLBD may be suspected. Early postural instability with minimal tremor, especially in the context of ophthalmoparesis, should suggest PSP. Early autonomic dysfunction, including erectile dysfunction and syncope, may suggest MSA. The presence of extreme asymmetry with patchy cortical cognitive defects such as dysphasia and apraxias (especially with "alien limb" phenomena) should suggest CBD.

The usual anti-Parkinson's medications are typically either less effective or completely ineffective in controlling symptoms; patients may be exquisitely sensitive to neuroleptic medications like haloperidol, so correct differential diagnosis is important.

Essential tremor may be mistaken for Parkinson's disease, but lacks all other features besides tremor, and has particular characteristics distinguishing it from Parkinson's disease, such as improvement with beta blockers and alcoholic beverages.[1]

Wilson's disease (hereditary copper accumulation) may present with parkinsonian features; young patients presenting with parkinsonism or any other movement disorder are frequently screened for this rare condition, because it may respond to medical treatment. Typical tests are liver function, slit lamp examination for Kayser-Fleischer rings, and serum ceruloplasmin levels.

Signs and symptoms

Main article: Signs and symptoms of Parkinson's disease

Parkinson's disease affects movement, producing motor symptoms.[1] Non-motor symptoms, which include autonomic dysfunction, cognitive and neurobehavioral problems, and sensory and sleep difficulties, are also common but are under-appreciated.[1]

Motor

Four motor symptoms are considered cardinal in PD: tremor, rigidity, bradykinesia and postural instability.[1] Tremor is the most apparent and well-known symptom.[1] It is most commonly a rest tremor: maximal when the limb is at rest and disappearing with voluntary movement and sleep.[1] It affects to a greater extent the most distal part of the extremity and is typically unilateral at onset.[1] Though around 30% of PD sufferers do not have tremor at disease onset most of them would develop it along the course of the disease.[1] Rigidity is due to joint stiffness and increased muscle tone, which combined with a resting tremor produce a ratchety, "cogwheel rigidity" when the limb is passively moved.[1] Rigidity may be associated with joint pain, such pain being a frequent initial manifestation of the disease.[1] Bradykinesia (slowness of movement) is the most characteristic clinical feature of PD and it produces difficulties not only with the execution of a movement but also with its planning and initiation.[1] The performance of sequential and simultaneous movements is also hindered.[1] In the late stages of the disease postural instability is typical, which leads to impaired balance and falls.[1]

PD motor symptomatology is not limited to these four symptoms. Gait and posture disturbances such as decreased arm swing, a forward-flexed posture and the use of small steps when walking; speech and swallowing disturbances; and other symptoms such as a mask-like face expression or a small handwriting are only examples of the ample range of common motor problems that can appear with the disease.[1]

Neuropsychiatric

Parkinson's disease causes neuropsychiatric disturbances, which include mainly cognition, mood and behavior problems and can be as disabling as motor symptoms.[1]

Cognitive disturbances occur even in the initial stages of the disease in some cases.[4] A very high proportion of sufferers will have mild cognitive impairment as the disease advances.[1] Most common cognitive deficits in non-demented patients are executive dysfunction, which translates into impaired set shifting, poor problem solving, and fluctuations in attention among other difficulties; Slowed cognitive speed, memory problems; specifically in recalling learned information, with an important improvement with cues; and visuospatial skills difficulties, which are seen when the person with PD is for example asked to perform tests of facial recognition and perception of line orientation.[4]

Deficits tend to aggravate with time, developing in many cases into dementia. A person with PD has a sixfold increased risk of suffering it,[1] and the overall rate in people with the disease is around 30%.[4] Moreover, prevalence of dementia increases in relation to disease duration, going up to 80%.[4] Dementia has been associated with a reduced quality of life in disease sufferers and caregivers, increased mortality and a higher probability of attending a nursing home.[4]

Cognitive problems and dementia are usually accompanied by behavior and mood alterations, although these kind of changes are also more common in those patients without cognitive impairment than in the general population. Most frequent mood difficulties include depression, apathy and anxiety.[1] Obsessive–compulsive behaviors such as craving, binge eating, hypersexuality, pathological gambling, or other, can also appear in PD, and have been related to a dopamine dysregulation syndrome associated with the medications for the disease.[1]

Other

In addition to cognitive and motor symptoms PD can impair other body functions. Sleep problems can be worsened by medications for PD, but they are a core feature of the disease.[1] They can manifest as excessive daytime somnolence, disturbances in REM sleep or insomnia.[1] The autonomic system is altered which can lead for example to orthostatic hypotension, oily skin and seborrheic dermatitis, excessive sweating, urinary incontinence and altered sexual function.[1] Constipation and gastric dysmotility can be severe enough to endanger comfort and health.[5] PD is also related to different ophthalmological abnormalities such as decreased blink rate and alteration in the tear film, leading to irritation of the eye surface, abnormalities in ocular pursuit and saccadic movements and limitations in the upward gaze.[1] Changes in perception include reduced sense of smell and sensation of pain and paresthesias.[1]

Causes

Most people with Parkinson's disease are described as having idiopathic Parkinson's disease (having no specific known cause). There are far less common causes of Parkinson's disease including genetic, toxins, head trauma, cerebral anoxia, and drug-induced Parkinson's disease.

Genetic

Someone who has Parkinson's disease is more likely to have relatives that also have Parkinson's disease. However, the inheritance of Parkinson's disease is usually complex and not due to a single gene defect.

A number of specific genetic mutations causing Parkinson's disease have been discovered. Genes identified as of 2008 are Alpha-synuclein (SNCA), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin) , PINK 1 and DJ-1.[6] With the exception of LRRK2 they account for a small minority of cases of PD.[6]

The most common known genetic risk factor for Parkinson's is a mutated glucocerebrosidase gene, which is involved in Gaucher's disease; carriers of these mutations have a fivefold risk of developing Parkinson's.[7] There is also recent evidence that a common gene defect contributes susceptibility to both Parkinson's Disease and Alzheimer's disease.[8]

Toxins

One theory holds that many or even most cases of the disease may result from the combination of a genetically determined vulnerability to environmental toxins along with exposure to those toxins.[9] This hypothesis is consistent with the fact that Parkinson's disease is not distributed homogeneously throughout the population; its incidence varies geographically. However, it is not consistent with the fact that the first appearance of the syndrome predates the first synthesis of the compounds often attributed to causing Parkinson's disease. The toxins most strongly suspected at present are certain pesticides and transition-series metals such as manganese or iron, especially those that generate reactive oxygen species,[10][11] and/or bind to neuromelanin, as originally suggested by G.C. Cotzias.[12][13]

In a longitudinal investigation, individuals who were exposed to pesticides had a 70% higher incidence of PD than individuals who were not exposed.[14] Studies have found an increase in PD in individuals who consume rural well water; researchers theorize that water consumption is a proxy measure of pesticide exposure. In agreement with this hypothesis are studies which have found a dose-dependent increase in PD in persons exposed to agricultural chemicals.

Signs of mercury poisoning share different symptoms with PD such as tremor, psychosis, memory deficits, disturbances in muscle control and coordination,anosmia and failure of autonomic nervous system.[15] Mercury has been suggested to have a role in the etiology of PD.[16] PD-like mercury poisoning can be treated with chelating agents such as penicillamine.[17]

Head trauma

Head trauma is considered a risk factor for PD since past episodes are reported more frequently by individuals with Parkinson's disease than by others in the population.[18] Nevertheless recent primary studies have suggested that head trauma may actually be a result of early symptoms of clumsiness associated with PD,[19] or that there is no true relationship between severe head injury and the disease.[20]

Pathophysiology

The symptoms of Parkinson's disease result from the greatly reduced activity of pigmented dopamine-secreting (dopaminergic) cells in the pars compacta region of the substantia nigra (literally "black substance"). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway.

The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.

There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteasome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins

between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.[21]

Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanin in the affected neurons of the substantia nigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species.[10] Iron also induces aggregation of synuclein by oxidative mechanisms.[22] Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known. The aggregates may be merely a normal reaction by the cells as part of their effort to correct a different, as-yet unknown, insult. Based on this mechanistic hypothesis, a transgenic mouse model of Parkinson's has been generated by introduction of human wild-type alpha-synuclein into the mouse genome under control of the platelet-derived-growth factor-β promoter.[23]

A recent view of Parkinson's disease implicates specialized calcium channels that allow substantia nigra neurons, but not most neurons, to repetitively fire in a "pacemaker" like pattern. The consequent flooding of calcium into these neurons may aggravate damage to mitochondria and may cause cell death. One study has found that, in experimental animals, treatment with a calcium channel blocker isradapine had a substantial protective effect against the development of Parkinson's disease.[24]

Diagnosis

Typically, the diagnosis is based on medical history and neurological examination conducted by interviewing and observing the patient in person using the Unified Parkinson's Disease Rating Scale. A radiotracer for SPECT scanning machines called DaTSCAN and made by General Electric is specialized for diagnosing Parkinson's Disease, but it is only marketed in Europe. Due to this, the disease can be difficult to diagnose accurately, especially in its early stages. Due to symptom overlap with other diseases, only 75% of clinical diagnoses of PD are confirmed to be idiopathic PD at autopsy.[25] Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Usually doctors look for shuffling of feet and lack of swing in the arms. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal.

Clinical practice guidelines introduced in the UK in 2006 state that the diagnosis and follow-up of Parkinson's disease should be done by a specialist in the disease, usually a neurologist or geriatrician with an interest in movement disorders.[2]

Treatment

Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, physiotherapy, exercise, and nutrition.[2] One could consult an occupational therapist on a broad range of methods, therapy, and assistive equipment to make Parkinson's more manageable in the areas of personal care, productivity and leisure. At present, there is no cure for PD, but medications or surgery can provide relief from the symptoms.

Levodopa

The most widely used form of treatment is L-dopa in various forms. L-dopa is transformed into dopamine in the dopaminergic neurons by L-aromatic amino acid decarboxylase (often known by its former name dopa-decarboxylase). However, only 1-5% of L-DOPA enters the dopaminergic neurons. The remaining L-DOPA is often metabolised to dopamine elsewhere, causing a wide variety of side

effects. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa, and so eventually becomes counterproductive.

Carbidopa and benserazide are dopa decarboxylase inhibitors. They help to prevent the metabolism of L-dopa before it reaches the dopaminergic neurons and are generally given as combination preparations of carbidopa/levodopa (co-careldopa) (e.g. Sinemet, Parcopa) and benserazide/levodopa (co-beneldopa) (e.g. Madopar). There are also controlled release versions of Sinemet and Madopar that spread out the effect of the L-dopa. Duodopa is a combination of levodopa and carbidopa, dispersed as a viscous gel. Using a patient-operated portable pump, the drug is continuously delivered via a tube directly into the upper small intestine, where it is rapidly absorbed. Another drug, Stalevo (carbidopa, levodopa and entacapone), is also available for treatment.

Tolcapone inhibits the COMT enzyme, thereby prolonging the effects of L-dopa, and so has been used to complement L-dopa. However, due to its possible side effects such as liver failure, it's limited in its availability. A similar drug, entacapone has not been shown to cause significant alterations of liver function and maintains adequate inhibition of COMT over time.[26]

Dopamine agonists

The dopamine agonists bromocriptine, pergolide, pramipexole, ropinirole , piribedil, cabergoline, apomorphine, and lisuride are moderately effective. These have their own side effects including those listed above in addition to somnolence, hallucinations and/or insomnia. Several forms of dopamine agonism have been linked with a markedly increased risk of problem gambling. Dopaminergic treatment for depression in patients with Parkinson disease may be associated with impulse control disorders.[27] Dopamine agonists initially act by stimulating some of the dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms.

Dopamine agonists can be useful for patients experiencing on-off fluctuations and dyskinesias as a result of high doses of L-dopa. Apomorphine can be administered via subcutaneous injection using a small pump which is carried by the patient. A low dose is automatically administered throughout the day, reducing the fluctuations of motor symptoms by providing a steady dose of dopaminergic stimulation. After an initial "apomorphine challenge" in hospital to test its effectiveness and brief patient and primary caregiver (often a spouse or partner), the latter of whom takes over maintenance of the pump. The injection site must be changed daily and rotated around the body to avoid the formation of nodules. Apomorphine is also available in a more acute dose as an autoinjector pen for emergency doses such as after a fall or first thing in the morning. Nausea and vomiting are common, and may require domperidone (an antiemetic).

Pramipexole was proposed in late 2009 as an early-stage treatment alternative to Levodopa.[28]

Recently there has been a consensus that younger patients first be treated with dopamine agonists while older patients be given Levodopa[29]

MAO-B inhibitors

Selegiline and rasagiline reduce the symptoms by inhibiting monoamine oxidase-B (MAO-B). MAO-B breaks down dopamine secreted by the dopaminergic neurons, so inhibiting it will result in inhibition of the breakdown of dopamine. Metabolites of selegiline include L-amphetamine and L-methamphetamine (not to be confused with the more notorious and potent dextrorotary isomers). This might result in side effects such as insomnia. Use of L-dopa in conjunction with selegiline has increased mortality rates that have not been effectively explained. Another side effect of the combination can be stomatitis. One report raised concern about increased

mortality when MAO-B inhibitors were combined with L-dopa;[30] however subsequent studies have not confirmed this finding.[31]

Unlike other non selective monoamine oxidase inhibitors, tyramine-containing foods do not cause a hypertensive crisis.

Surgery and deep brain stimulation

Treating Parkinson's disease with surgery was once a common practice, but after the discovery of levodopa, surgery was restricted to only a few cases. Studies in the past few decades have led to great improvements in surgical techniques, and surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient.

Deep brain stimulation is presently the most used surgical means of treatment, but other surgical therapies that have shown promise include surgical lesion of the subthalamic nucleus[32] and of the internal segment of the globus pallidus, a procedure known as pallidotomy.[33]

Neurorehabilitation

There is partial evidence that speech or mobility problems can improve with rehabilitation although studies are still scarce and of low quality.[34][35][36][37] Regular physical exercise and/or therapy can be beneficial to the patient for maintaining and improving mobility, flexibility, strength, gait speed, and quality of life;[36] and speech therapy may improve voice and speech function.[37] One of the most widely practiced treatment for the speech disorders associated with Parkinson's disease is the Lee Silverman Voice Treatment (LSVT). LSVT focuses on increasing vocal loudness.[38]

Prognosis

PD is not considered to be a fatal disease by itself, but it progresses with time. The average life expectancy of a PD patient is generally lower than for people who do not have the disease.[39] In the late stages of the disease, PD may cause complications such as choking, pneumonia, and falls that can lead to death.

The progression of symptoms in PD may take 20 years or more. In some people, however, the disease progresses more quickly. There is no way to predict what course the disease will take for an individual person. With appropriate treatment, most people with PD can live productive lives for many years after diagnosis. There are some indications that PD acquires resistance to drug treatment by evolving into a Parkinson-plus disorder, usually Lewy body dementia, although transitions to progressive supranuclear palsy or multiple system atrophy are not unknown.[40][41]

One commonly used system for describing how the symptoms of PD progress is called the Hoehn and Yahr scale. Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS). This much more complicated scale has multiple ratings that measure motor function, and also mental functioning, behavior, mood, and activities of daily living. Both the Hoehn and Yahr scale and the UPDRS are used to measure how individuals are faring and how much treatments are helping them. It should be noted that neither scale is specific to Parkinson's disease; that patients with other illnesses can score in the Parkinson's range.

Epidemiology

According to some sources, Parkinson's disease is marginally less prevalent in those of African ancestry.[42] The average crude prevalence is estimated at being from 120-180 out of 100,000 among the caucasian (white) community.[43] For the Parsi community in Mumbai, India the rate is approximately double.[43][44]

History

Symptoms of Parkinson's disease have been known and treated since medieval times, most notably by Averroes.[45] However, it was not formally recognized and its symptoms were not documented until 1817 in *An Essay on the Shaking Palsy*[46] by the British physician James Parkinson. Parkinson's disease was then known as *paralysis agitans*, the term "Parkinson's disease" being coined later by Jean-Martin Charcot.[47]

The underlying biochemical changes in the brain were identified in the 1950s due largely to the work of Swedish scientist Arvid Carlsson, who later won a Nobel Prize. L-dopa entered clinical practice in 1967,[48] and the first large study reporting improvements in patients with Parkinson's disease resulting from treatment with L-dopa was published in 1968.[49]

Research directions

Animal models

The tragedy of a group of drug addicts in California in the early 1980s who consumed a contaminated and illicitly produced batch of the synthetic opiate MPPP brought to light MPTP as a cause of Parkinson symptoms. This made it possible to develop the first animal model for Parkinson's. MPTP's toxicity likely comes from the generation of reactive oxygen species through tyrosine hydroxylation.[50] The book *The Case of the Frozen Addicts* by William Langston documents this tragedy and describes the first attempts at fetal brain tissue transplants to treat PD.

Other toxin-based models employ PCBs,[51] paraquat[52] (a herbicide) in combination with maneb (a fungicide),[53] rotenone[54] (an insecticide), and specific organochlorine pesticides including dieldrin[55] and lindane.[56]

Gene therapy

Currently under investigation is gene therapy.[57] This involves using a non-infectious virus to shuttle a gene into a part of the brain called the subthalamic nucleus (STN). The gene used leads to the production of an enzyme called glutamic acid decarboxylase (GAD), which catalyses the production of a neurotransmitter called GABA.[58] GABA acts as a direct inhibitor on the overactive cells in the STN.

GDNF infusion involves the infusion of GDNF (glial-derived neurotrophic factor) into the basal ganglia using surgically implanted catheters. Via a series of biochemical reactions, GDNF stimulates the formation of L-dopa. GDNF therapy is still in development.

Neuroprotective treatments

Neuroprotective treatments are at the forefront of PD research, but are still under clinical scrutiny.[59] These agents could protect neurons from cell death induced by disease presence resulting in a slower progression of disease. Agents currently under investigation as neuroprotective agents include anti-apoptotic drugs (CEP 1347 and CTCT346), lazaroids, bioenergetics, antiglutamatergic agents and dopamine receptors.[60] Clinically evaluated neuroprotective agents are the monoamine oxidase inhibitors selegiline[61] and rasagiline, dopamine agonists, and the complex I mitochondrial fortifier coenzyme Q10.

Neural transplantation

The first prospective randomised double-blind sham-placebo controlled trial of dopamine-producing cell transplants failed to show an improvement in quality of life although some significant clinical improvements were seen in patients below the age of 60.[62] A significant problem was the excess release of dopamine by the transplanted tissue, leading to dystonias.[63] Research in African green monkeys suggests that the use of stem cells might in future provide a similar benefit without inducing dystonias.[64]

Alternative Treatments

Nutrients have been used in clinical studies and are used by people with PD in order to partially treat PD or slow down its deterioration. The L-dopa precursor L-tyrosine was shown to relieve an average of 70% of symptoms.[65] Ferrous iron, the essential cofactor for L-dopa biosynthesis was shown to relieve between 10% and 60% of symptoms in 110 out of 110 patients.[66][67]

More limited efficacy has been obtained with the use of THFA, NADH, and pyridoxine—coenzymes and coenzyme precursors involved in dopamine biosynthesis.[68] Vitamin C and vitamin E in large doses are commonly used by patients in order to theoretically lessen the cell damage that occurs in PD. This is because the enzymes superoxide dismutase and catalase require these vitamins in order to nullify the superoxide anion, a toxin commonly produced in damaged cells. However, in the randomized controlled trial, DATATOP of patients with early PD, no beneficial effect for vitamin E compared to placebo was seen.[61] Coenzyme Q10 has more recently been used for similar reasons. MitoQ is a newly developed synthetic substance that is similar in structure and function to coenzyme Q10. Most of these therapies are covered in Dr. Laurie Mischley's *Natural Therapies for Parkinson's Disease*.[69]

Studies looking at qigong in PD have not reached consensus on its efficacy.[70][71]

Mucuna pruriens, is a natural source of therapeutic quantities of L-dopa, and has been under some investigation.[72]

Society and culture

Research and Support Organizations

In 1957, William Black, President of Chock full o'Nuts coffee company, founded the Parkinson's Disease Foundation (PDF) after one of his company's employees was diagnosed with Parkinson's. Black launched the organization with a $250,000 grant to support Parkinson's Research.[73] While at first a regional organization, PDF expanded the scope of its activities throughout the U.S., and merged with the United Parkinson Foundation in 1999. Today, PDF focuses on funding research to learn the causes of and find a cure for Parkinson's, as well as providing education and support for people with Parkinson's in the U.S. Since it was founded in 1957, PDF has provided more than $80 million to research.[74]

The European Parkinson's Disease Association is an organization based in Europe that supports Parkinson's disease research.

Actor Michael J. Fox, whose book, *Lucky Man* (2000), focused on his experiences with the disease and his career and family travails in the midst of it, established *The Michael J. Fox Foundation for Parkinson's Research* to develop a cure for Parkinson's disease. Another foundation that supports Parkinson's research was established by professional cyclist Davis Phinney. The Davis Phinney Foundation strives to improve the lives of those living with Parkinson's disease.

Notable sufferers

In addition to Michael J. Fox and Davis Phinney, famous sufferers include Pope John Paul II, baseball manager Sparky Anderson, playwright Eugene O'Neill, political commentator Michael Kinsley, artist Salvador Dalí, hockey player Brent Peterson, boxer Muhammad Ali, basketball player Brian Grant, evangelist Billy Graham and former US Attorney General Janet Reno. Political figures suffering from it have included Adolf Hitler (not confirmed), Francisco Franco, Deng Xiaoping and Mao Zedong, and former Prime Minister of Canada Pierre Trudeau. Numerous actors have also been afflicted with Parkinson's such as: Terry-Thomas, Deborah Kerr, Kenneth More, Vincent Price, Jim Backus and Michael Redgrave. Helen Beardsley (of *Yours, Mine and Ours* fame) also suffered from this disease toward the end of her life. James Doohan also suffered from Parkinson's disease, and later, Alzheimer's. Director George Roy Hill (The Sting, Butch Cassidy and the Sundance Kid) also suffered from Parkinson's disease.

The film *Awakenings* (starring Robin Williams and Robert De Niro and based on genuine cases reported by Oliver Sacks) deals sensitively and largely accurately with a similar disease, postencephalitic parkinsonism.

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Parkinson's Disease: Hope Through Research (National Institute of Neurological Disorders and Stroke)

World Parkinson Disease Association

GeneReview/NIH/UW entry on LRRK2-Related Parkinson Disease