Parkinsonism
(Parkinson's Disease)

Parkinson's disease is a neurodegenerative disease of the substantia nigra (an area in the basal ganglia). The disease was first discovered and its symptoms documented in 1817 (Essay on the Shaking Palsy) by the British physician Dr. James Parkinson; the associated biochemical changes in the brain of patients were identified in the 1960s.

The disease is a progressive movement disorder of the extrapyramidal system, which controls and adjusts communication between neurons in the brain and muscles in the human body.

In the United States, the prevalence of Parkinson's Disease is 160 per 100 000 people, though this increases with age, as indicated by the mean onset of 55 years of age. Symptoms usually begin in the upper extremity, and are usually unilateral at onset.

Causes

The cause of Parkinson's disease is not known. Geneticists have since 1997 found nine different specific genetic defects, each of which causes the disease in one or a few families with extraordinarily high incidences of the disease, but such families are rare. While a strong inheritance pattern occurs in only a very small percentage of cases, an affected individual is three to four times more likely than an unaffected individual to have a close relative with Parkinson's. Having a parent with Parkinson's raises one's lifetime risk of developing the disorder threefold, from the general population's figure of 2% to about 6%. Genes that have been identified include alpha-synuclein, ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin, and DJ-1.

A popular theory holds that the disease might result in most cases from the combination of a subtle genetically determined vulnerability to environmental toxins along with mild exposure to those toxins. The toxins most strongly suspected at present are certain pesticides and industrial metals. MPTP is used as a model for Parkinson's as it can rapidly induce parkinsonian symptoms in patients/animals of any age. Other toxin-based models employ paraquat (an herbicide) or rotenone (an insecticide).

Minor past episodes of head trauma are also more commonly reported by sufferers than by others in the population. While emotional or a psychological trauma can precipitate the initial symptoms or aggravate existing symptoms, this is not the actual cause of the disorder.

The symptoms of Parkinson's disease result from the loss of dopamine-secreting (dopaminergic) cells in the pars compacta region of the substantia nigra. These neurons project to the striatum and their loss leads to inhibition of the direct pathway of movement and activation of the indirect pathway of movement. Since the direct pathway facilitates movement and the indirect pathway inhibits movement, the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in an excessive inhibition of the thalamus, leading to hyperkinesia.

Brain cells producing other brain chemicals such as GABA, norepinephrine, serotonin and acetylcholine exhibit minor damage in Parkinson's disease, accounting for some of the wide array of symptoms.

The mechanism by which the brain cells in Parkinson's are lost appears to center on an abnormal accumulation of the protein alpha-synuclein in the damaged cells. This protein forms proteinaceous cytoplasmic inclusions called Lewy bodies. The precise mechanism whereby 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. It does appear that alpha-synuclein aggregation is enhanced by the presence of dopamine and the byproducts of dopamine production.

Symptoms

Symptoms may vary among patients, and additionally may vary greatly over time in a single patient. However, the cardinal symptoms are:

- tremor (while this is the best known symptom, it is not displayed by an estimated 30% of patients),
- rigidity (increased tone or stiffness in the muscles),
- akinesia (lack of spontaneous movement) and bradykinesia (slowness of movement),
- failing balance,
- walking problems.

The mnemonic TRAP (Tremor; Rigidity; Akinesia/bradykinesia; Postural instability) can be used to remember these symptoms.

Additionally, the following signs and symptoms are commonly associated with Parkinson's Disease:

Psychological

- depression (occurs in 50% of cases)
- anxiety or panic attacks

- dementia, in approximately 20% of all patients, typically starting with slowing of thought and progressing to difficulty organizing thoughts
- altered sexual function
- sleep disturbances
- dizziness

Physical

- speech problems (hypophonia; vocal cords can also be affected, causing monotonous, soft speech qualities),
- stooped or flexed posture,
- constipation,
- fatigue (up to 50% of cases),
- loss of sense of smell,
- oily skin,
- difficulty in swallowing,
- masked facies,
- drooling,
- micrographia (small handwriting)
- decreased arm swing
- difficulty rolling in bed
- slowness of gait
- pain

Symptoms usually only begin to appear after about 80% of the dopamine in the brain has been lost. More recent data based on PET scans suggests that symptoms may occur when 50-60% of dopaminergic neurons are lost. The level of dopamine will continue to fall slowly over time, with an attendant worsening of symptoms.

It is an incapacitating disease, disturbing some important human functions and in some cases resulting in a substantial reduction in quality of life. As in many neurologic diseases, psychological complications are often extremely serious and require the patient's family members and relatives to pay keen attention to the emotional fragility that usually follows the emergence of the disease; indeed, the depression which often results is seen by many as one of the worst aspects of the disease. In some cases drugs are employed, especially in the fight against depression (given that Parkinson's-related depression is mainly induced by a complex of chemical-physical factors). Also, some common side effects of therapy can put the patient in a condition of humble self-consideration. External help is required to control the administration of the prescribed therapy: since patients are often confused or depressed, there is a risk of their improperly implementing the therapeutic regimen if left to their own devices, leading to symptoms not being adequately controlled.

Parkinson's disease is very widespread, with about 150-200 cases per 100,000 population at any given time. About 2% of the population develops the disease some time during life. Cases are reported at all ages, though it is quite rare in people younger than 30 and

the average age at which symptoms begin is 58-60; the risk of developing it substantially increases with age. It occurs in all parts of the world, but appears to be more common in people of European ancestry than in those of African ancestry. Those of East Asian ancestry have an intermediate risk. It is more common in rural than urban areas and men are affected slightly more often than women.

Diagnosis

The differential diagnosis for a patient presenting with Parkinsonian symptoms is:

- Idiopathic Parkinson's Disease
- Essential tremor
- Parkinson plus syndromes
- Secondary parkinsonism due to drugs, toxins, stroke, head trauma, or hydrocephalus

Parkinson's tremors differ from essential tremors in that the latter are posture or action tremors, have bilateral tremors involving the hands, head and voice, and are alcohol responsive. In contrast, Parkinson's tremors are rest tremors, and usually start unilaterally.

Treatment

The treatment of Parkinson's disease mainly relies on replacing dopamine with levodopa (L-DOPA) or mimicking its action with dopamine agonists such as pramipexole, ropinirole, pergolide or bromocriptine. Discovered as a Parkinson's treatment by Arvid Carlsson, levodopa is a dopamine precursor that is transfomed into dopamine by the brain. Levadopa is almost always supplemented with carbidopa, a drug which prevents levodopa from being metabolized in the gut, liver and other tissues, thus allowing more levodopa to reach the brain and allowing for a reduced dosage, thus reducing some of the side effects. The most frequent side effects of these dopaminergic drugs are nausea, sleepiness, dizziness, involuntary writhing movements and visual hallucinations. Often times, the treatment of the Parkinson's patient with these two drugs can result in them very much "coming back to life" in the eyes of their family and doctors, to the point of them appearing to not have any disease at all. However, the drugs are not effective forever. Sometimes a point is reached where the drugs only work for a few hours, or become completely ineffective.

As in many other diseases, the therapy requires a continuing regimen of medicines, the dosage of which has to be specifically calculated for each single case and might vary during the evolution of the disease. The treatment is complex and usually consists of a mixture of drugs (basically focused on levodopa), some of which compensate for the side effects of others. Amantadine hydrochloride, anticholinergics and COMT inhibitors tolcapone or entacapone are sometimes prescribed. Tolcapone should be used with extreme caution because of the possibility of liver failure. However entacapone has not been shown to cause significant alterations of liver funtion. Foods rich in proteins can reduce the uptake of levodopa, because the same uptake system is used both by certain amino acids and levodopa. However, this can usually be dealt with by redistributing meal times: in many cases it is advisable to move the consumption of proteins towards the

evening, so to have symptoms appearing when the patient has less need of mobility. While these therapies are a good attempt at treating the symptoms, they are not a cure--they do not attack the underlying cause of the disease which is a loss of dopamine producing neurons.

Regular physical exercise and/or therapy are beneficial to the patient and essential for maintaining and improving mobility, flexibility, balance and a range of motion, and for a better resistance against many of the secondary symptoms and side effects.

Surgical interventions are currently being researched, and deep brain stimulation is presently the most popular and effective such treatment. In the future, implantation of cells genetically engineered to produce dopamine or stem cells that transform into dopamine-producing cells may become available.

Even these, however, will not constitute cures because they do not address the widespread loss of several different types of cells in the brain and even for the dopamine-producing cells, do not re-establish all of the original connections with neighboring brain cells. A true cure will have to detect the earliest signs of the disorder before they cause important symptoms and will intervene in the process that damages the brain cells in the first place.

In the early stages Parkinson's disease does not necessarily affect intellectual integrity, apart from the emotional effects of eventual psychological complications, and in those cases where the patient is still compos mentis, their role in the treatment is fundamental. The patient's cooperation is required in order to provide the physicians with all the details that might help in the making a correct diagnosis and consequent determination the best appropriated therapy. Conversely, it is crucial for doctors to explain the precise extent of the disease's progress, and provide as much information as possible about the prescribed therapy, how the symptoms and side effects can be reduced. Working together in this manner, the patient and doctor can ensure the maximum quality of life for the sufferer.

Parkinson-Plus diseases

There are other disorders that are called Parkinson-Plus diseases. These include:

- Multiple System Atrophy (MSA)
- Shy-Drager Syndrome (SDS)
- Striatonagral degeneration (SND)
- Olivopontocerebellar Atrophy (OPCA)
- Progressive Supranuclear Palsy (PSP)

Patients often begin with typical Parkinson's disease symptoms and these Parkinson-Plus diseases can only be diagnosed when other symptoms become apparent after some years. These Parkinson-Plus diseases usually progress more quickly than the typical main illness, and the usual anti-Parkinson's medications do not work as well at controlling symptoms.

Secondary Parkinsonism

Secondary parkinsonism (or briefly Parkinsonism) is a term used for a symptom constellation that is similar to that of Parkinson's disease but is caused by other disorders or medications. Major reasons for secondary parkinsonism are stroke, encephalitis, narcotics, toxins and carbon monoxide poisoning, and normal pressure hydrocephalus.

There are other idiopathic (of unknown cause) conditions as Parkinson's disease that may cause parkinsonism. In these conditions the problem is not the deficient production of dopamine but the inefficient binding of dopamine to its receptors located on the globus pallidus.

Notable Parkinson's sufferers

One famous sufferer of young-onset Parkinson's is **Michael J. Fox**, who has written a book about his experience of the 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; the state of the art in treatment remains roughly the same as it was at the time of the events depicted, the 1960s, although patients with postencephalitic parkinsonism lose benefit from their medication far faster than do patients with Parkinson's disease.

Other famous people with Parkinson's include:

- Muhammad Ali (suffers from Pugilistic Parkinson's syndrome)
- Pope John Paul II
- Janet Reno
- Margaret Bourke-White
- Farnsworth Wright
- Adolf Hitler
- Salvador Dali
- Barry Ethridge
- Brockman Adams
- Ozzy Osbourne