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## Parkinsons disease and related movement disorders

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**Author:**

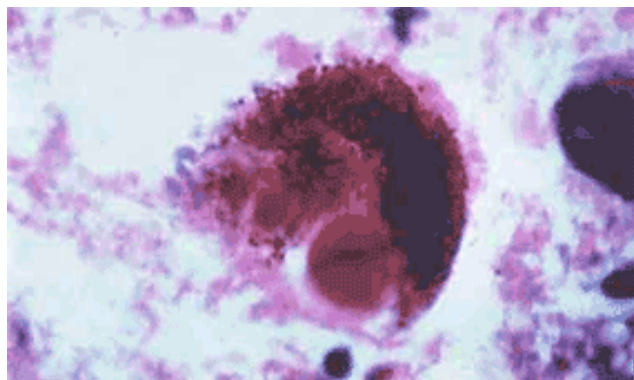
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*“In this article I review the history, pathology, aetiology, classification, clinical diagnosis and treatment of Parkinson’s disease and its imitators.”*

Over 180 years ago, James Parkinson described a neurodegenerative disease that bears his name. Now 30 years after the introduction of levodopa, the most effective therapy for the disease, we still do not understand the cause or have a cure.

However, basic neurobiological research of the last few years has given us many fundamental insights into the disease. It is a common disorder, largely of ageing people, probably with genetic and environmental causes.

There is no useful, validated biochemical diagnostic marker for the disease, so the question ‘what is Parkinson’s disease?’ is difficult. The gold standard for diagnosis is neuropathological examination of the brain. Loss of selected but heterogenous neurons and eosinophilic hyaline neuronal inclusions (see picture below) in selected vulnerable neuronal populations are the hallmarks of the disease, but this information is not available during the patient’s life.



For practical purposes we define the disease by the clinical syndrome of Parkinsonism (2). Difficulties may

arise because although idiopathic Parkinson’s disease (IPD) is the commonest cause of Parkinsonism the practitioner will encounter, a variety of related disorders (‘atypical’ Parkinsonian conditions) may be similar clinically. Routine cerebral imaging (MRI and CT) is normal in IPD and only sometimes distinguishes it from other atypical Parkinsonian conditions. Several functional imaging techniques have been investigated as diagnostic tools, but these are not always easily available and there are difficulties with sensitivity and specificity.

Thus two autopsy studies (1, 2) have shown the diagnosis of IPD in life is inaccurate in approximately 25% of cases. The resulting diagnostic imprecision affects not just individual patients, but also questions concerning the epidemiology and cause of the disease and the evaluation of clinical therapeutic trials.

Parkinsonism is a syndrome manifested by any combination of the following cardinal features:

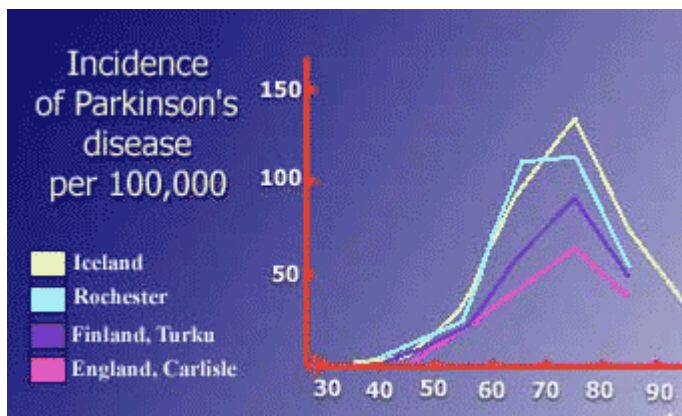
1. Rest tremor
2. Rigidity
3. Bradykinesia (slowness of movement)
4. Loss of postural reflexes
5. Freezing (or “motor blocks” - transient inability to perform voluntary movements)

**Categories of Parkinsonism:**

CATEGORY	ITEMS/FEATURES
Definite Parkinsonism: at least 2 of these features (right) including at least one of (1) or (2)	1. Rest tremor 2. Rigidity 3. Bradykinesia (slowness of movement) 4. Loss of postural reflexes
Probable Parkinsonism: if items (1) or (2) alone are present	5. Freezing
Possible Parkinsonism: if items (3), (4), or (5) are present alone or in combination	

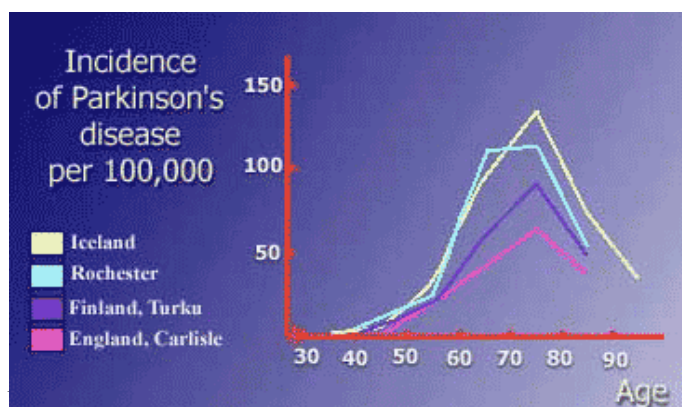
**3. How common is Idiopathic Parkinson’s disease?**

IPD is found throughout the world in all races. It affects males and females about equally or with a slight male predominance (3).



The prevalence rises exponentially with age, after the age of 65. Approximately 0.3% of the general population and 3% of people over the age of 65 have IPD diagnosed clinically (4). About 10% of patients have an onset of disease before the age of 40 - “young-onset” Parkinson’s disease.

**DEMOGRAPHICS - Age distribution**



Asians and African blacks have the lowest reported incidence of the disease. To what extent this reflects environmental or genetic differences or differences in ascertainment is not clear, but the prevalence of Lewy bodies in the brains of Nigerians is similar to that of Western populations (5).

Smoking is consistently associated with a lowered risk for the development of IPD (6). The odds ratio of ever having smoked among Parkinson’s disease patients compared with the general population was 0.5 (95% CI 0.3-0.7) in one study (7). The implications of this association are not clear.

**Rural living**

Living in a rural environment has often been associated with an increased risk of IPD, possible relating to the influence of pesticide chemicals or consumption of well water. However, the magnitude of this risk in the population of affected individuals is only 10% (8).

Diet has been evaluated in many studies to determine if antioxidants present in food protect predisposed patients from the disease. Most of these studies are small or inconclusive.

**Genes**

A recent large study found high concordance among monozygotic twins when one twin has early-onset disease (9). Several multigenerational families have been described, with pathologically confirmed Parkinson’s disease although in these there are usually atypical features such as rapid rate of progression or a high frequency of dementia (10). Mutations in 1 exon of the alpha-synuclein gene were recently discovered in a large Italian and 3 smaller Greek families that may have been related (11) and in another exon of the same gene in a German family (12). However, the disease is rapidly progressive and has a young age onset in these families. Moreover, mutations in this gene have not been found in other families and sporadic IPD. In young-onset Parkinson’s disease, the frequency of mutations in the PARKIN gene is high when a first degree family member is also affected (13). Mutations in this gene were originally described in autosomal recessive Japanese pedigrees with prominent sleep benefit, sensitivity to extrapyramidal side effects of L-DOPA and absence of nigral Lewy bodies in pathologically studied cases. A susceptibility locus on chromosome 2 in familial PD with features more closely resembling sporadic IPD has been described in 6 families with autosomal dominant inheritance with low penetrance (14).

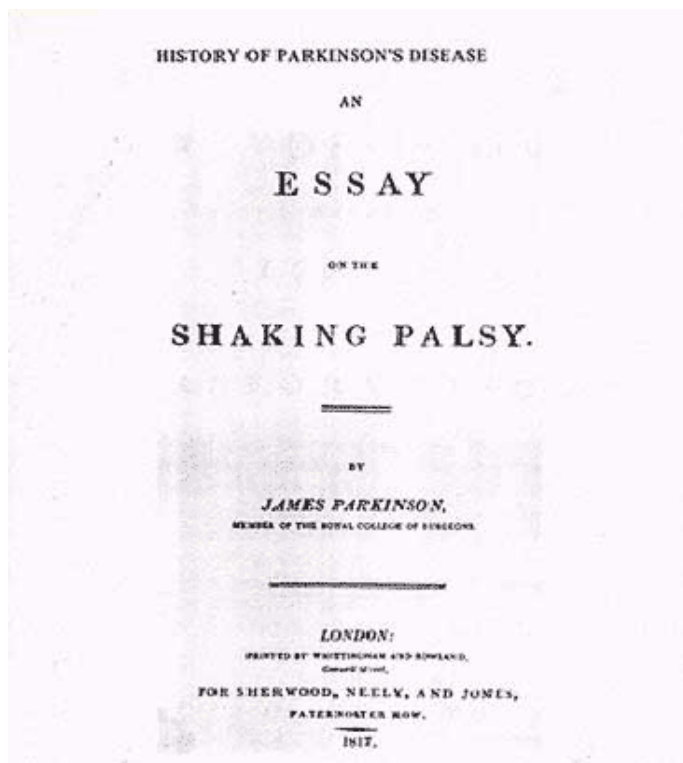
**History of the disease**

4500-1000 BC

Early descriptions include tremor and akinesia in ancient Indian Ayurvedic literature from 4500-1000 BC. It was called Kampavata in the ancient Indian medical text Basavarajiyam. Several natural products were used in the treatment. The powdered seeds of the *Mucuna Pruriens* (Atma gupta in Sanskrit) contain levodopa and, in Ayurvedic medicine, the powder is used in various neurological and reproductive diseases.

1817

An eclectic London surgeon and apothecary, James Parkinson (1755-1828), formally described the disease in 1817 in a classic monograph "Essay on the Shaking Palsy".



In his day he was well known as a social reformer, a member of several secret political societies and avid pamphleteer under the pseudonym of "Old Hubert", denouncing, amongst other evils "the intolerable grievance of paying numerous burthensome and unnecessary taxes", a foremost and early palaeontologist and geologist.

He described six patients, all with tremor, but apparently did not physically examine them, failing to recognize rigidity, bradykinesia, freezing and postural instability. Parkinson's definition of the shaking palsy was succinct.

Robert Bentley Todd commented extensively on the "Essay on the shaking palsy" in 1834 and 1854.

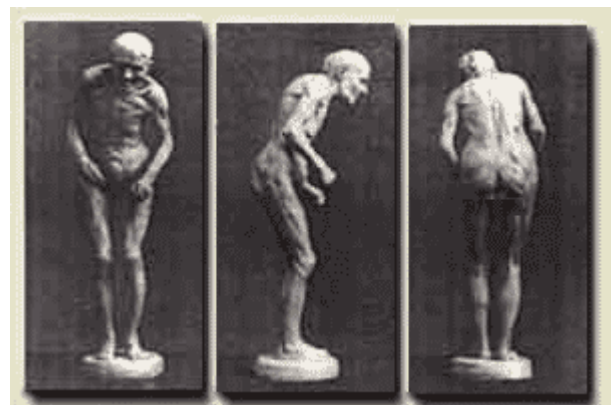
"The disease approaches gradually and almost imperceptibly, generally commencing with a sense of

weakness and slight tremor of the hands and arms, and occasionally of the head. After a lengthened period, perhaps a year, the patient loses his balance in walking and bends forward. The feet are powerless and tremble. The tremor becomes a permanent, overpowering, and does not even cease when the parts are firmly supported. Head, hands, and feet, are in constant tremulous movement. When the patient attempts to walk he throws himself upon the toes and front of the foot, walks hastily and insecurely, in constant danger of falling on his face. The tremor now continues during sleep, and becomes so violent that the bedstead shakes and the patient wakes up. He is unable to read or write, and being unable to eat by himself, requires to be fed. Mastication is difficult, the saliva flows from the mouth. There is constant constipation, the trunk is bent forwards, the chin rest on the sternum. At last, there is entire loss of speech and deglutition, involuntary evacuations, stupor and death.

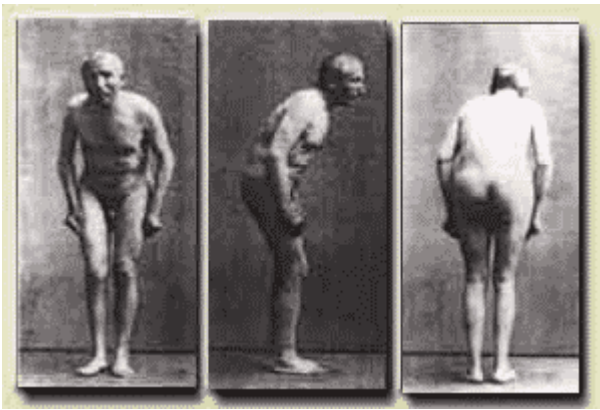
After a time the patient finds that he cannot perform small actions with the diseased arm; he cannot button his clothes, nor pick up a pin...then he notices that he cannot write so well as formerly; his handwriting becomes tremulous...the leg goes through the same series of symptoms...he speaks slowly and hesitantly, but yet his mental faculties do not seem to suffer much...these cases are exceedingly chronic.... The patient begins to stoop; he finds he cannot hold himself erect; and in some instances his gait is apt to pass into that which is known as symptomatic of the disease termed "paralysis agitans". (1854)

1888

In 1888 Jean-Marie Charcot elaborated on the clinical signs, describing muscular rigidity, postural deformity and characteristic facial expression. This was later depicted in drawing and sculpture by Paul Richer, an intern of Charcot and later Chief of the Laboratory at La Salpetriere and Professor of Creative Anatomy at the National School of Fine Arts. Charcot suggested the disorder be called Parkinson's disease.



Statuette by Paul Richer of a 58-year-old woman with paralysis agitans.



This photograph of a patient with paralysis agitans was often used in demonstrations, showing typical posture and facial features.

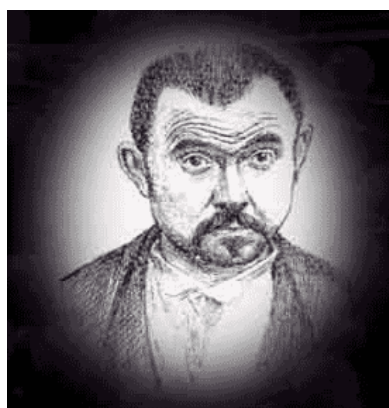
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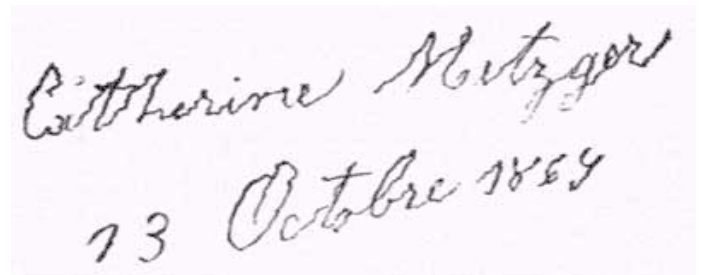
The picture shows deformity of the fingers in a patient with paralysis agitans.



Facial features of a patient with paralysis agitans, as drawn by Paul Richer in 1888

1888

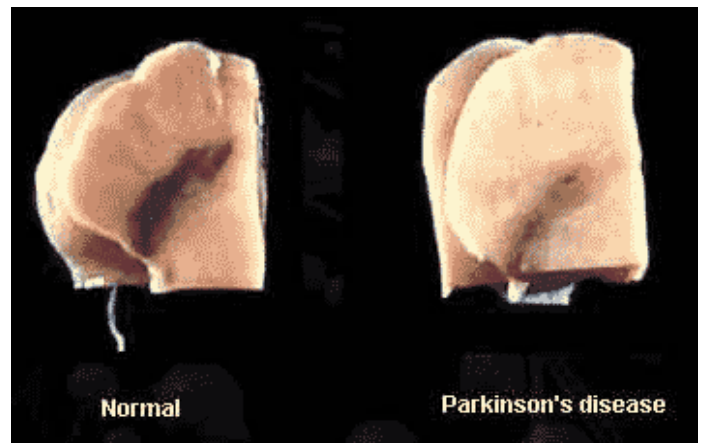
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**Writing is affected in Parkinson's disease as seen in the above specimen of a patient (1872) of Professor Charcot at the Hospital St Louis. The letters are very tremulous, mainly noted in the up-strokes.**

1919

In 1919, Tretiakoff, a neuropathologist first described the degeneration of the substantia nigra and the loss of the melanin containing cells.



1959

In 1959, Arvid Carlsson suggested the degenerating cells produce dopamine.

1969

In 1969 George Cotzias showed large doses of L-dopa, the dopamine precursor, produced dramatic improvement in patients with the disease.

**Clinical features of Idiopathic Parkinson's disease**

**Tremor**

Classic parkinsonian tremor is a rest tremor of 4-5 Hz affecting the limbs, asymmetric or unilateral in the

early stages of the disease. The combination of postural deformity and tremor can produce the unique tremor which Charcot described as follows: “The patient closes the fingers on the thumb as though in the act of spinning wool” or “crumbing bread”.

In the limbs it is distal. Arms are affected more commonly than legs. Less commonly it is present in lips, chin and tongue.

Rest tremor is prominent when the part is supported and is reduced on action. It may be intermittent, particularly in the early stages of the disease. The video shows the tremor typical of early IPD.

50% of patients with IPD also have action tremor. A minority (10%) have only action tremor. The frequency of the action tremor may be the same as the rest tremor (Type I tremor) or faster at 6-12 Hz (Type II tremor).

Up to 25% of patients with IPD may never have rest tremor (15). Tremor is abolished during sleep.

### **Rigidity**

Rigidity is of the extrapyramidal “plastic” or “lead-pipe” type, i.e. not dependent on the velocity of passive muscle stretch.

Many patients, particularly those with tremor have cog-wheeling but anyone with tremor (e.g. a patient with severe essential tremor) may have cog-wheeling.

### **Bradykinesia (slowed movement)**

Bradykinesia, hypokinesia (reduced movement), and akinesia (loss of movement) may be seen in a progressive decrement in the speed and amplitude of rapid succession movements e.g. finger tapping or fist opening and closing.

These are the most common and disabling features of Parkinsonism. It also manifests in other ways:· Reduced swallowing leading to drooling. Drooling is common in IPD and is not due to excessive production of saliva.· Reduction of arm swing during walking.· And micrographia are other examples

### **Loss of postural reflexes**

Loss of postural reflexes occurs usually after the disease has been present for some years: early loss of postural reflexes suggests a parkinsonian syndrome other than IPD.

The postural righting reflex is first reduced and then lost. It may be seen in the *retropulsion* (i.e. taking several steps backwards) that occurs in the “pull test” in which the patient is pulled sharply backwards by the shoulders. Loss of postural reflexes coupled with a flexed posture

may lead to *festination*, where the patient takes faster and faster steps attempting to move the feet below the centre of gravity.

### **Freezing**

Freezing is a special transient form of alkinesia. It can affect the legs on walking or turning.

Freezing commonly occurs at gait initiation (“gait ignition failure”), when the patient attempts to negotiate narrow spaces (e.g. going through a doorway) or when the patient approaches a destination (e.g. a meter or so from a chair). The feet seem temporarily “glued to the floor”.

Many patients discover methods of breaking freezing (e.g. marching on the spot, counting in their heads, or using visual cues like stepping over a crack in the floor, etc.)

Freezing may affect speech causing palilalia and eye opening called “apraxia of lid opening” or levator inhibition.

The combination of freezing and loss of postural reflexes can be extremely dangerous, exposing the patient to falls.

### **Other motor phenomena**

Postural deformity in IPD, a dystonic phenomenon is characteristic and progresses as the disease advances. Typically, the patient is flexed axially and in the limbs. Later in the disease, the patient may develop a lateral trunk tilt.

Ulnar deviation of the hands, extension of the interphalangeal joints and flexion of the metacarpophalangeal joints may stimulate the changes of rheumatoid arthritis.

Transient painful flexion spasms of the feet can occur as part of the disease and also as part of the treatment. Facial expression is characteristically reduced even in the early phases of the illness.

There may be discordance between volitional facial movements and facial expression with emotion.

The voice may become softer and hoarser.

### **Non-motor**

Dementia may occur in IPD, but usually later in the course of the illness and more commonly in the older patient. Dementia early in the course of the illness, particularly in younger patients suggests another cause for the Parkinsonism, commonly Alzheimer’s disease or diffuse Lewy body disease. A new diagnosis of

dementia in elderly patients with IPD occurs 6.6 times more frequently than in elderly controls (16). In a large population-based survey in Norway (17), 28% of patients with IPD had dementia and in another study (16), 65% of surviving members of a cohort of patients over the age of 85 had dementia.

Other common changes in personality and thinking include rigidity and inflexibility, loss of motivation and energy and difficulty in attending to more than one mental task at a time.

- The “tip-of-the-tongue” phenomenon and mild memory dysfunction is common even in the non-demented patient.

- Mild autonomic disturbances (e.g. orthostatic hypotension, constipation) are common in IPD but when profound suggest another parkinsonian disorder.

- Skin changes in the form of seborrhoeic dermatitis are common.

- Depression occurs in 50% of patients at some stage of the disease. It may be associated with anxiety.

- Loss of smell occurs early in the disease and sometimes precedes the motor manifestations by years. Interestingly, smell is preserved in progressive supranuclear palsy and MPTP induced Parkinsonism (58).

- Sensory symptoms occur commonly, often even in the early stages of the disease. Patients may complain of an aching pain or tingling and parasthesiae in the limbs.

- Weight loss may occur even early in the course of the illness independently of swallowing difficulties.

Mortality is 2-5 times as high in patients compared with age-matched controls (6, 18), resulting in reduced life expectancy (6).

Debility has a complex relationship to clinical features. Axial rigidity is more disabling than limb rigidity. Rest tremor unless severe is often not disabling. Bradykinesia, rigidity and loss of postural reflexes are more disabling than tremor or rigidity.

Non-motor manifestations such as loss of motivation, depression, constipation and sensory symptoms contribute greatly to disability.

Parkinsonism has many causes (**Table 2**). The task of the practitioner is to determine if the patient is likely to have the most common cause of IPD or one of the diseases simulating it.

The diagnosis is clinical.

Certain clinical features suggest the cause of the Parkinsonism is IPD and others point to an alternative diagnosis.

**Table 2.** Aetiological classification of Parkinsonism

### Primary Idiopathic Parkinson’s disease

1. Parkinson’s disease
2. Juvenile Parkinsonism

### Multiple systems Degeneration (Parkinson’s plus)

1. Progressive Supranuclear Palsy (PSP)
2. Multiple System Atrophy (MSA)
  - a) Strionigral degeneration (SND)
  - b) Olivopontocerebellar atrophy (OPCA)
  - c) Shy-Drager syndrome (SDS)
3. Parkinson’s-ALS-Dementia complex
4. Cortico-basal-ganglionic degeneration (CBGD)
5. Progressive Pallidal Atrophy
6. Parkinson dementia syndromes
  - a) Autosomal dominant Lewy body disease (alpha-synuclein mutations)
  - b) Diffuse cortical Lewy body disease (DLBD)
  - c) Pick’s disease and other fronto-temporal dementias

### Other Heredo-degenerative Disease

- Huntington’s disease (HD)
  - Wilson’s disease (WD)
  - Hallevorden-Spatz (now called Martha-Alma disease)
  - Autosomal dominant spinocerebellar degenerations
  - X-linked dystonia Parkinsonism
  - Neuroacanthocytosis
  - Mitochondrial cytopathy
  - Familial basal ganglia calcification (Fahr’s syndrome)
- hemiparkinson-hemiatrophy syndrome etc.

### Secondary

1. Infectious
  - a) Postencephalitic
  - b) AIDS
  - c) Subacute sclerosing panencephalitis (SSPE)
  - d) Creutzfeld-Jacob disease (CJD)

2. Drugs and Toxins

*Dopamine blocking drugs, Dopamine depleting drugs (e.g. reserpine, tetrabenazine), alpha methyl DOPA, Lithium, MPTP, Carbon Monoxide, Manganese, Mercury, Carbon disulphide, cyanide, methanol, ethanol, etc.*

3. Vascular

4. Trauma

5. Other

Parathyroid disease hypothyroidism, Non-Wilsonian hepato-cerebral degeneration, brain tumour, paraneoplastic disease, normal pressure hydrocephalus (NPH) etc.

**Differential diagnosis of parkinsonism**

**Table 3**

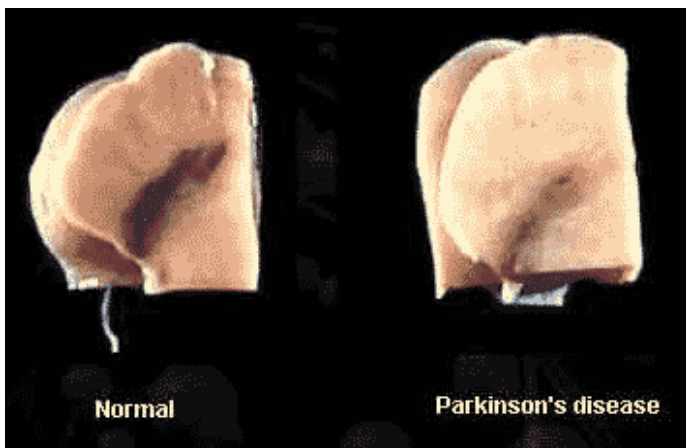
Clinical Feature	Answer
Good, sustained response to I-DOPA	IDIOPATHIC PARKINSON'S DISEASE (IPD)
Marked asymmetry in sign	IDIOPATHIC PARKINSON'S DISEASE (IPD); Cortico-basal-ganglionic degeneration (CBGD); Hemiatrophy-hemiparkinsonism
Rest tremor	IDIOPATHIC PARKINSON'S DISEASE (IPD); SECONDARY PARKINSONISM
History of drugs/toxins/encephalitis	Postinfectious/toxin induced
Severe unilateral rigidity	Cortico-basal-ganglionic degeneration (CBGD)
Cortical sensory signs, alien limb, unilateral cortical myoclonus or apraxia	Cortico-basal-ganglionic degeneration (CBGD)
Early dementia	Diffuse cortical Lewy body disease (DLBD); Alzheimer's disease (AD); Fronto-temporal dementia
Early spontaneous hallucinations, marked fluctuation in cognitive status, syncopal spells, marked aggravation of parkinsonism with small neuroleptics	Diffuse cortical Lewy body disease (DLBD)
Psychosis with small doses of L-DOPA	Diffuse cortical Lewy body disease (DLBD); Alzheimer's disease (AD)

Clinical Feature	Answer
Early loss of postural reflexes, impaired voluntary eye movements, deep nasolabial folds, nuchal dystonia, abducted arms on walking, pure freezing	Progressive Supranuclear Palsy (PSP)
Laryngeal stridor, cerebellar dysarthria, symptomatic orthostatic hypotension, incontinence, mottled and cold hands	Multiple System Atrophy (MSA)
Lower motor neuron signs	Multiple System Atrophy (MSA); Fronto-temporal dementia
Upper motor neuron signs pseudobulbar palsy	Multiple System Atrophy (MSA); Vascular Parkinsonism
"Lower-half" parkinsonism, i.e. gait disturbance predominating with minimal upper body involvement	Vascular Parkinsonism
Kayser Fleischer ring	Wilson's disease

**Cause and pathophysiology of Idiopathic Parkinson's disease**

The aetiology of IPD is unknown. At birth, the nigra contain about 400,000 dopaminergic cells, falling to 250,000 by the age of 60 (19). There is a parallel loss of dopamine in the striatum (20). When the cell population or the dopamine content reaches 20% of the youthful levels, signs of parkinsonism appear (21). This age-related loss of cells can be linked with the development of IPD in 3 ways:

1. Increased rate of dopamine containing neurons in IPD
2. Fewer dopamine-containing neurons at birth
3. Environmental factors (e.g. trauma, infection or toxin) that exacerbates the loss of dopaminergic neurons



### Depigmentation in basal ganglia

Increasing evidence suggests constitutional and environmental factors are important. In the 1980's, 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), a contaminant of street drugs and selectively toxic to nigral dopaminergic neurons, was found to produce a severe parkinsonian syndrome in some, but not all, exposed individuals. Follow-up studies with PET (positron emission tomography) scans showed slow progressive decline in fluorodopa uptake, suggesting a 'one-hit' hypothesis in a genetically susceptible individual. Analogous events are postulated in IPD. The two major biochemical abnormalities in the substantia nigra at the time of death are depleted reduced glutathione and mitochondrial Complex I activity. The factors implicated in neuronal degeneration in IPD include:

**Oxidative stress:** In normal circumstances, cellular defences protect against damaging reactive oxygen species- hydrogen peroxide and free radicals such as superoxide, peroxy, nitric oxide and hydroxyl radicals. These compounds react with lipids, proteins and DNA, altering structure and function. This oxidative stress is increased in IPD. Increasing iron in pars compacta of the substantia nigra and depleted reduced glutathione (one of 2 major free radical scavengers in the brain, the other being glutathione peroxidase) are believed to be factors contributing to increased oxidative stress in IPD. Dopamine turnover can also produce oxidant stress as dopamine oxidation leads to the formation of hydrogen peroxide (22). This is one of the reasons that levodopa (which is converted to dopamine) has been regarded by many as potentially harmful to the remaining nigral dopaminergic cells (23) although it is debated whether this is important in practice (24).

**Mitochondrial dysfunction:** Several investigators have repeatedly shown a modest (30-40%) decline in mitochondrial Complex I activity in platelets, muscle and discrete brain regions of patients with IPD (25). Oxidative stress, by damaging mitochondria, may

reduce Complex I activity. The mitochondrial respiratory chain, particularly when impaired, is a potent source of free radicals. Reduced Complex I activity may also generate oxidative stress and deplete reduced glutathione. Two independent studies have suggested the origin of the Complex I deficiency in IPD is the mitochondrial DNA (26, 27), except in rare exceptions (28) specific mitochondrial DNA mutations have not been found in parkinsonian conditions.

**Excitotoxicity:** This concept has been applied to IPD and other neurodegenerative diseases (29). The central hypothesis is that activation of NMDA receptors is followed by accumulation of intracellular calcium ions, which promote the formation of free radicals. Failure of cellular energy metabolism is postulated to cause neuronal depolarisation and the activation of NMDA receptors, tying this hypothesis in with the mitochondrial dysfunction. Oxidative stress would further compromise cellular energy metabolism by inhibition of the mitochondrial respiratory chain.

**Neurotrophic factors:** Neuronal differentiation, and survival in development and after injury depends on adequate levels of neurotrophic factors. Glial derived neurotrophic factor (GDNF) and brain-derived growth factor (BDNF) have a role in dopaminergic neuronal protection and regeneration and have therapeutic benefit in animal models of parkinsonism (30). Thus it has been hypothesized that a growth factor deficiency may be a factor in the dopaminergic cell loss in IPD.

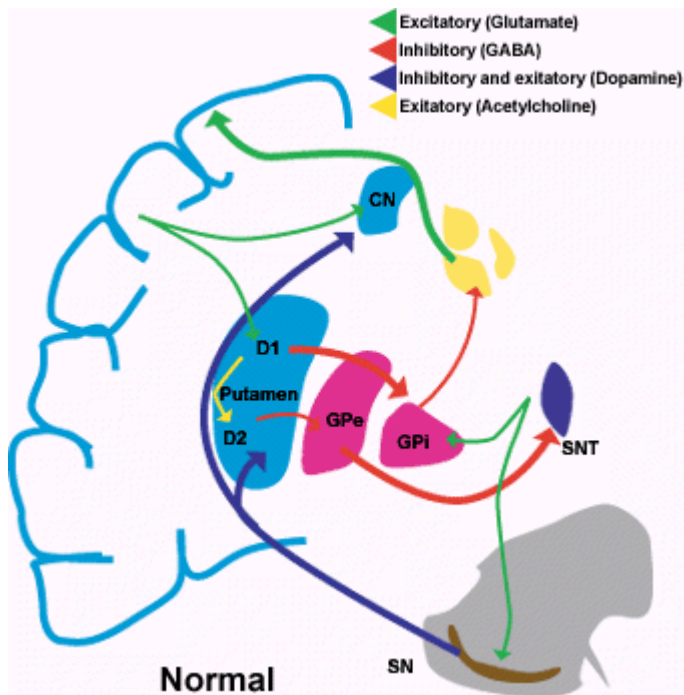
**Immune factors:** The finding of HLA-DR-positive reactive microglia, increased levels of cytokines in the pars compacta, even in late stages of the illness have suggested a role for the immune system in nigral degeneration (31).

### Cause and pathophysiology of Idiopathic Parkinson's disease?

Primate models of MPTP parkinsonism have shown the dopamine deficiency state is accompanied by an increased activity of GABA (inhibitory) output nuclei in the internal segment of the globus pallidus. A model of basal ganglia circuitry has been proposed to explain these changes (see next screen). Although this model has been invoked to explain changes occurring in the disease and with treatment, it is incomplete as it ignores other projections to the external segment of the globus pallidus and fails to predict the effect of surgical interventions in IPD. For example, the model predicts thalamotomy should reduce activation of the cortex and worsen IPD and pallidotomy at the internal segment of the globus pallidus should produce hemi-ballism. Neither is the case: thalamotomy is very effective for Parkinsonian tremor

and pallidotomy reduces hyperkinesias (dyskinesias) in IPD.

A model of basal ganglia circuitry.



### Principles of treatment

1. Keep the patient functioning as long as possible
2. If drugs/implants etc. are found to be neuro-protective, give them precedence
3. Individualise therapy

### Treatment can be categorised as:

1. Non-drug therapy
2. Drug therapy
  - a) Protective or preventive drugs
  - b) Symptomatic treatment
3. Restorative or regenerative therapy

### NON-DRUG THERAPY

Physical activity to promote and maintain flexibility. Stretching exercises are particularly useful. Loss of motivation and social isolation are common and difficult problems in IPD and a good exercise regimen would integrate as much social interaction as possible. Gait training can be effective particularly in the latter stages of the disease to teach patients to overcome freezing. A good physiotherapist understands the cognitive changes in patients, which often result in a change away from “multi-tasking”.

### An appropriate diet

Constipation is a common problem and vegetable content in the diet should be encouraged for this reason alone. Studies evaluating the effect of diet in slowing progression of the disease have been inconclusive but it has been hypothesized that inadequate intake of dietary

antioxidants might predispose patients to endogenous and exogenous aetiologic factors in the disease. A recent community-based study in the Netherlands found a high intake of dietary vitamin E might protect against the development of IPD (32).

### Measures to help sleep

Many patients experience an improvement of symptoms after sleep (33), while others are worse in the mornings before they take the first dose of medicine. Sleep disturbance is very common in IPD and is multifactorial - due to medication or the disease. Apart from adjustment to medications, simple practical measures like using silk sheets or pyjamas can help the patient to roll over in bed.

Speech therapists and physiotherapists can be very helpful in the management of symptoms that do not respond well to pharmacotherapy. (Parkinson’s disease support groups are particularly useful in addressing issues centering on lifestyle and there is a number of excellent books written for the patient).

## DRUG THERAPY

### 1. Protective therapy

Early ideas that the selective monoamine oxidase (MAO-B) inhibitor, selegiline, delayed the progression of the disease were not sustained in a large prospective trial in the late 1980’s (34). The observed effects with this agent were probably due to a mild symptomatic effect of the drug.

A recent prospective study in Britain (35) raised a question mark over this drug when it found excess mortality in patients taking it together with levodopa, but the study has not been replicated. The mortality occurred relatively abruptly quite some time after the initiation of therapy, making the finding dubious from a biological perspective and other studies in patients using selegiline, with or without levodopa have not shown any increase in mortality associated with the use of the drug (36).

There is currently no proven therapy for slowing the progression of the disease, despite investigation of a number of potential drugs like high doses of vitamin E.

### 2. Symptomatic therapy

#### a) Early medical treatment

There has been considerable controversy regarding the early use of levodopa in IPD. It appears the later motor complications of dyskinesias appear in subjects who have been “primed” with levodopa. The risk of these complications is thought to be related to the duration of illness (degree of striatal dopaminergic denervation) and the pulsatile nature of dopaminergic stimulation during

therapy. Thus most clinicians treating Parkinson's disease prefer to be cautious about using levodopa in high doses early in the disease (37, 38). On the other hand, despite theoretical concerns, evidence that levodopa accelerates the progression of the disease in patients is lacking. Much of the gains in life expectancy in IPD have occurred since the introduction of levodopa and delaying the introduction of levodopa till disability is considerable, may shorten survival (39). Therefore, treatment is individualized with the goal of providing maximal comfort and improved quality of life while limiting reversible long-term effects of levodopa therapy. The latter may be achieved by the judicious use of dopamine agonists, amantadine or anticholinergics. Dopamine agonists, perhaps because of longer half-life and fewer fluctuations of striatal dopaminergic stimulation infrequency result in motor fluctuations and dyskinesias. Amantadine is mild indirect dopaminergic acting by augmenting dopamine release from storage sites and possibly by blocking dopamine into presynaptic nerve terminals. It also has some anticholinergic properties. It is effective in about two thirds (2/3) of patients with early IPD.

### b) Problems in later IPD and their management

The usual response to levodopa in IPD is a good smooth response. However, by five years, only 25% of patients continue to have a good smooth response to levodopa therapy. The complications of levodopa therapy are listed below:

**Wearing off** is the common and is also known as 'end-of-dose' deterioration. There is a gradual erosion of benefit of the drug usually 1-3 hours after the dose. The clinical response can be maintained experimentally if a continuous supply of dopamine or dopamine agonist is provided to the striatum by intravenous or intestinal infusions of levodopa or by subcutaneous infusions of a dopamine agonist. In practice, the problem is managed by:

- giving smaller, more frequent doses of standard levodopa or dissolved levodopa
- the use of controlled release levodopa preparations
- the use of a drug to extend the plasma half-life of levodopa by interfering with metabolism (e.g. the MAO-B antagonist selegiline and the new catechol-O-methyl (COMT) inhibitors tolcapone and entacapone)
- the addition of a dopamine agonist or use of subcutaneous apomorphine

**“Sudden-off”**. Unlike the gradual loss of benefit in the “wearing-off” phenomenon the “sudden-off” reaches a peak within several seconds. This phenomenon is probably caused by changes in receptor sensitivity (a pharmacodynamic rather than pharmacokinetic change).

Dopamine agonists, amantadine and selegiline are ineffective and the problem remains difficult to treat.

**Episodic failure** to respond is a related problem but probably reflects variations in gastric absorption. It may be overcome by giving dissolved levodopa.

**Delayed On.** Some patients have a delayed in the onset of action of the first dose in the morning. It is not clear if this is pharmacokinetic or pharmacodynamic in origin. In some, dissolved levodopa or the use of agents that promote gastric motility (e.g. cisapride) may help.

**Peak dose dyskinesias:** most commonly the appearance of chorea and dystonia when the plasma levels of levodopa are high after a dose. Management involves lowering the dose of levodopa with or without adding a dopamine agonist. Amantadine, possibly by its NMDA receptor antagonism, has been reported to reduce dyskinesias by up to 60% (41). The atypical neuroleptic clozapine, may also be effective (42), but this is usually an impractical solution because of idiosyncratic neutropenia and the need for regular haematologic monitoring.

**Diphasic dyskinesia** takes the form of dyskinesia (dystonia or chorea) followed by improvement and then dyskinesia again around the time of the dose. The dyskinesia does not occur at peak dose, but as the plasma levels of dopamine are rising or falling. The mechanism is unclear, but pharmacodynamic factors are probably important. The addition of a dopamine agonist may help.

**“Yo-yo-ing”** refers to the swings between peak dose dyskinesia and off states. Pharmacodynamic and pharmacokinetic factors are probably important. Again, the addition of dopamine agonists with lowered levodopa doses may be effective.

**Simultaneous parkinsonism and dyskinesia:** in some patients, parkinsonism and dyskinesias occur together, reflecting the topographical distribution of dopamine receptors and the pattern of disease involvement. The upper body may be dyskinetic and the legs Parkinsonism - 'somatotopic differentiation'. It can be difficult to manage.

**Off dystonia.** Dystonia is not always related to high plasma levels. In fact, early morning dystonic foot cramps can be a feature of untreated IPD. This dystonia can be painful and disabling 'off' phenomenon. Preventing 'off' periods is the best way to prevent or manage 'off' dystonia.

**Mental complications** can occur at any time in the disease, but happen more frequently with higher doses of

medication, in the older patient and the patient with pre-existing cognitive dysfunction.

- Neuropsychiatric effects include sedation, vivid dreams (often the harbinger of hallucinosis) and hallucinations. Hallucinations are the strongest predictor of nursing home placement (43) and associated with increased mortality (44).
- In severe cases not responding to medication adjustment, the use of an atypical neuroleptic is indicated. Low dose clozapine has shown to be very useful in this regard (45).
- The role of newer agents such as quetiapine is not yet resolved, but olanzapine and reserpine may worsen parkinsonism (46, 47).

**Dementia.** Although the newer cholinergic agents in use in Alzheimer's disease (e.g. donepezil and rivastigmine) have not been fully evaluated in IPD as in Alzheimer's disease, they are effective in dementia with Lewy bodies (48). Theoretically these agents may worsen parkinsonism by increasing striatal dopaminergic activity.

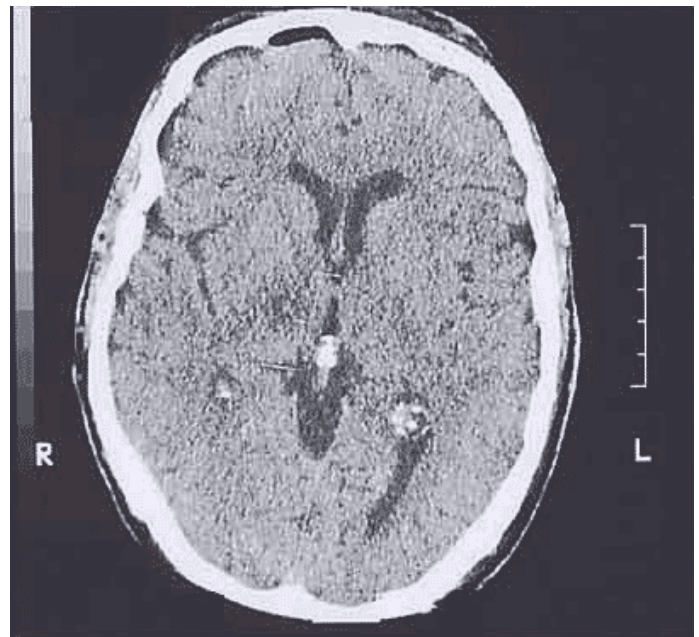
## SURGICAL AND RESTORATIVE THERAPY

### 1. Surgical therapy

Magnetic resonance imaging and improved stereotactic procedures coupled with an interest in the pathophysiology of parkinsonism in MPTP treated primate models has led to a resurgence of interest in surgery for IPD. The functional model of the basal ganglia predicts that reduction of the excessive inhibitory output from the internal segment of the globus pallidus or the excessive drive of the subthalamic drive to both segments of the globus pallidus should increase activation of the pre-motor cortices and result in a restored state. To some extent this occurs with pallidotomy and deep-brain stimulation of the internal segment of the globus pallidus although all predictions based on the model are not sustained, such as the effectiveness of thalamotomy for tremor.

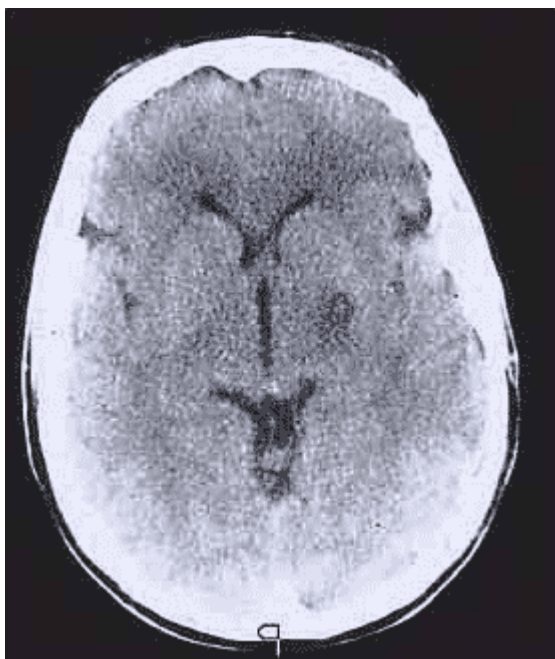
Surgery is currently reserved for disabling, medically refractory disease.

- The ventro intermediate thalamic nucleus is the surgical target for tremor and can result in an 80% reduction of tremor (49). Akinesia is not helped greatly and gait disturbance may increase.



### Lesion from a right thalamotomy performed for tremor predominant disease

- Medial pallidotomy (see scan - right) can improve contralateral drug-induced dyskinesias by more than 80% and produce a 30% improvement in total motor scores (50). However, with the exception of improvement in dyskinesias, the effects may be short-lived, lasting only 3-6 months. Bilateral pallidotomy is associated with a greater risk of cognitive side effects and bulbar dysfunction. It has been suggested (51) medial pallidotomy be considered under the following conditions:
  - (a) At centres with a team of physicians with substantial expertise and experience in the field
  - (b) In patients with disabling idiopathic Parkinson disease, without dementia, and who have exhausted medical therapy
  - (c) Patients should be examined by means of standardized rating scales preoperatively and postoperatively to ensure quality of care at each centre
  - (d) For symptoms that respond best viz. medication-induced dyskinesias, rigidity, and tremor. Balance, gait disorders, and hypophonia are generally less responsive to surgery
  - (e) The institution's complication rate should be discussed with the patient before surgery



**Lesion from a left pallidotomy**

Chronic bilateral high frequency electrical stimulation of the internal segment of the globus pallidus (52) (see scan - right) and sub-thalamic nucleus (53) has been explored as a safer alternative to bilateral pallidotomy. It is an increasingly attractive form of therapy with main disadvantages being cost, access and labour intensiveness.



**CT scan showing artefact from left pallidal stimulator**

## 2. Restorative therapy

Autologous adrenal medullary transplantation has been abandoned because of lack of efficacy. Recent findings using positron emission tomography indicate allogenic human embryonic mesencephalic dopaminergic neurons may be functionally integrated in the patient's brain and release dopamine into the striatum. Grafted patients have shown clinically useful, partial recovery of motor function bilaterally but predominantly contralateral to

the graft. Gait, speed, balance and dyskinesias do not consistently improve (54). Adverse events are no greater than for other general intracranial procedures (55).

Limitations are:

1. Large amounts of human embryonic mesencephalic tissue are needed for therapeutic effects. Xenotransplantation from porcine sources is being actively studied around the world.
2. Symptomatic relief is incomplete and varies between patients.
3. Patient selection and grafting procedure have not been optimised

- Success with intraventricular GDNF in primate models (30) has led to the investigation of this approach in human IPD. The success of this approach will depend on demonstration of safety and the development of efficient delivery methods into the brain (56). Approaches being investigated include the use of encapsulated cells and viral vectors.

- Gene therapy approaches are also the subject of current investigation. For example, implanted cells may be first genetically modified *ex vivo* or therapy may be based on the administration of antisense oligonucleotides affecting expression of genes in the dopamine pathway, neurotrophic factors etc.

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