

Ministry of Defence

Synopsis of Causation

Parkinson's Disease

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

- 1.1 Parkinson's disease is a slowly progressive degenerative condition of the central nervous system that affects body movement by altering the overall tone and control of skeletal muscle action. It was first described as the 'shaking palsy' by the physician James Parkinson in 1817.^{1,2}
- 1.2 It results from a deficiency of dopamine, a chemical neurotransmitter in the brain. This substance is produced by cells of the [substantia nigra](#), whose [axons](#) project into the [basal ganglia](#), an area of the brain that influences motor control by way of the [extra-pyramidal pathways](#).
- 1.3 The pathophysiology of the condition is characterised by a loss of pigmented neurones in the substantia nigra of the basal cell ganglions of the brain stem. The presence of Lewy bodies (concentric cellular inclusions in the pigmented neurones of the substantia nigra) was thought to be pathognomonic but these have since been found in other brain disorders and are not specific to Parkinson's disease. Approximately 60-80% of dopaminergic neurones are lost before clinical symptoms appear.¹
- 1.4 A parkinsonian syndrome may result from a primary deficiency of dopamine production by the neurones of the substantia nigra but may also arise secondary to other neurological diseases and from toxicity. Nomenclature is often used inconsistently. For the purposes of this review the term "Parkinson's disease" will be used to describe the primary condition and "parkinsonism" or "secondary parkinsonism" to refer to the syndrome resulting from other causes.
- 1.5 Synonyms: Parkinson's disease has been known by a variety of names including the original 'paralysis agitans' (Shaking palsy), 'idiopathic parkinsonism', and idiopathic Parkinson's disease.

2. Clinical Features

2.1 Parkinson's disease is the fourth most common of the degenerative neurological disorders of the elderly. Prevalence in UK, Canada and USA is between 200 and 300 per 100,000.^{1,3} Prevalence rises with age and affects 0.4% of those over 40 yrs old and 1% of those over 65 yrs old. The mean age of onset is 57 yrs. It can occur in childhood or adolescence (juvenile parkinsonism). It is 1.5 times more common in men than women.^{1,2}

2.2 The essential clinical features are:

- Tremor
- Rigidity
- [Bradykinesia](#)
- Impaired postural reflexes

In later stages there may be a decline in cognitive function.⁴

The disease begins insidiously and effects may be noticed first by relatives and friends. There is thought to be a 'pre-clinical phase' that may last several years when dopamine production may be falling. Progression tends to be slower when presenting in younger patients and may run a course over 35 yrs. The first symptoms may be non-specific such as fatigue or depression.

2.3 Early signs of movement loss that may first be noticed by others are:

- Infrequent blinking
- Lack of facial expression
- Decreased spontaneous movement and gestures
- Effects on speech – [dysphonia](#) and [dysarthria](#)

2.4 Tremor may be the first symptom noticed by the patient. When present it is a typical, low frequency, unconscious 'pill rolling' movement of the fingers, starting usually in one hand. Typically the tremor is maximal at rest, absent during sleep, and lessens with intentional movement such as reaching or grasping. It may be more noticeable with emotional stress or tiredness. Hands, arms and legs may be first affected by tremor and as the condition progresses, the jaw, tongue and eyelids become involved.

2.5 In some patients tremor is absent and only rigidity occurs. The effects of bradykinesia and rigidity are generally more disabling than tremor. Tremor can be embarrassing but the effects of rigidity impede manual dexterity, balance and walking. As the condition progresses, movement becomes slower and more laborious ([bradykinesia](#)), with loss of spontaneous gestures. The face develops a mask-like expressionless character which may be mistaken for depression. Posture becomes stooped and it becomes difficult to initiate walking, with short shuffling steps which may break into a short-stepped run to maintain balance. This is described as the typical '[festinating gait](#)'. Impaired control of the small muscles of the hand often results in changes in the handwriting with decreasing size of the script ([micrographia](#)) and use of fewer words. The combination of these factors leads to significant impairment of activities of daily living such as dressing, bathing and using cutlery.

- 2.6 In addition to the signs referred to above that will have been evident on observation, clinical examination reveals features of rigidity. Attempts to move a limb joint passively are met with increased resistance which is either smooth (lead-pipe rigidity) or intermittent and oscillatory (cog-wheel rigidity).
- 2.7 Impairment of [postural reflexes](#) with instability is an important stage in development as it responds poorly to treatment and leads to significant disability.
- 2.8 Dementia is a late manifestation of the condition and affects around 30% of sufferers. Short-term memory is affected but [aphasia](#) is rare.
- 2.9 Depression occurs in between 15 -20% of patients at some stage of the illness.
- 2.10 There is no specific test for the diagnosis of Parkinson's disease. Diagnosis is largely based on clinical presentation, examination, progress of symptoms and response to treatment with [dopaminergic medication](#). Magnetic resonance imaging (MRI) and computerised axial tomography (CT) are unremarkable. In atypical presentations of parkinsonism, MRI or CT may identify an underlying condition. Positron emission tomography (PET) and single photon emission CT (SPECT) are useful diagnostic imaging studies but they are not widely available and are not indicated in cases that have a typical clinical presentation.

3. Aetiology

- 3.1 There is no known cause for Parkinson's disease and it is likely that it is due to a complex association of genetic and environmental factors. Problems with case definition, study design, size and methodology compound the difficulties of interpretation of study results. In addition, reliance on self reporting and difficulties in obtaining objective data on environmental exposure, make it difficult to evaluate the many claimed causative associations. Secondary parkinsonism can arise from a variety of causes such as the toxic effects of drugs and chemicals and Parkinson-like movement disorders may be encountered as a component of other neurological diseases.
- 3.2 The motor effects of Parkinson's disease are due to reduced production of dopamine from the [substantia nigra](#) of the [basal ganglia](#), resulting in inhibition of impulses in the direct motor pathways of the [thalamus](#). These impulses normally affect fine control of voluntary muscle movement.
- 3.3 It is helpful to consider causes under the following headings:
- Parkinson's disease
 - Secondary parkinsonism
 - Parkinson-like movement disorders secondary to other neurological disease
- 3.4 **Parkinson's disease.** In Parkinson's disease there is a progressive failure in production of dopamine. The reasons for this are not known but various factors may play a part. Genetic and environmental factors are possibly at play.
- 3.4.1 **Genetic factors.** A direct genetic cause of Parkinson's disease has not been established. One study compared concordance rates of Parkinson's disease in [monozygotic](#) and [dizygotic](#) male twins where one twin was suspected of having Parkinson's disease. This study concluded that there was no evidence that genetic factors play a significant role in typical Parkinson's disease that begins after age 50. However, genetic factors may play a part in cases where the condition presents below age 50.⁵
- 3.4.2 **Environmental factors.** The fact that many toxins can cause symptoms indistinguishable from Parkinson's disease suggests that long-term exposure to low dose environmental toxins may possibly result in 'idiopathic' Parkinson's disease.⁶
- 3.4.3 Factors that have been postulated as being associated with the development of Parkinson's disease include the use of pesticides, living in a rural environment, consumption of well water, exposure to herbicides, and proximity to industrial plants or quarries. Several studies have found an association between rural living, drinking well water and an increased incidence of Parkinson's disease. It is not clear whether this may be due to contamination of supplies by herbicides or pesticides, or to naturally occurring high levels of potentially toxic metals such as manganese in drinking water. Both factors could be present in rural communities.⁷

- 3.4.4 Although there is evidence of a link between Parkinson's disease and sources of drinking water in rural living there is nothing to indicate that short-term exposure to a contaminated water supply is a factor in causation.^{7,8}
- 3.5 **Secondary parkinsonism.** Symptoms of Parkinson's disease are commonly known to be caused specifically by certain drugs and toxins.
- 3.5.1 **Psychotropic drugs.** [Psychotropic](#) or [neuroleptic](#) drugs, particularly the phenothiazine and butyrophenone groups, are used for treatment of schizophrenia or in short-term use for severe anxiety. They act by interfering with dopaminergic transmission in the brain by blocking dopamine receptors. They produce side effects of typical Parkinson-type symptoms which progress slowly with continued treatment. In around 90% of patients the symptoms remit if the drug is withdrawn. The side effects can be reduced by giving concomitant drugs to counter the effects.^{1,2}
- 3.5.2 **Metoclopramide.** This drug is used to treat gastro-intestinal disturbances and nausea. The drug is generally prescribed for short courses to treat acute symptoms but long term use can result in parkinsonism.
- 3.5.3 **1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).** MPTP is an unwanted by-product of illicit attempts to synthesise [meperidine](#) for drug abusers and results in severe parkinsonism after injection.⁹ The [neurotoxic](#) effects are limited to damage of the [substantia nigra](#) and consistently cause a parkinsonian state.
- 3.5.4 **Neurotoxins.** Apart from the toxic effects of inhibition of dopamine due to drugs, a variety of neurotoxins can have a similar effect. Substances that have been implicated include:^{10,11,12}
- Manganese
 - Copper
 - Lead
 - Mercury
 - Iron
 - Herbicides e.g. paraquat and rotenone
- 3.5.5 These can be encountered occupationally and can be absorbed by inhalation or ingestion. Manganese neurotoxicity is well accepted as a cause of parkinsonism and is prescribed under the UK Industrial Injuries Scheme. Others may form part of a multifactorial cause. Inhalation of manganese fumes can cause acute poisoning, with Parkinson-type presentation. Doses of manganese as low as 2mg/m³ can be toxic in susceptible individuals and three months or more exposure can lead to chronic poisoning.¹³
- 3.5.6 **Exposure to [cycad](#) neurotoxins.** It has been postulated that servicemen who were imprisoned in Japanese prison camps during the Second World War (Far East Prisoners of War – FEPOWs) are at an increased risk of Parkinson's disease. This theory was based on the work of an American neuro-epidemiologist who contended that it was due to ingestion of cycad neurotoxins during captivity. This has not been confirmed by other researchers. An

epidemiological study by the UK Medical Research Council compared the mortality rate between 1952 and 1997 of 11,134 ex-FEPOWs with that expected from national rates for the male population of England and Wales.¹⁴ This study found that the death rate from Parkinson's disease among FEPOWs was lower than the national average. Although there is a hypothetical link between consumption of cycad-based flour and late development of degenerative neurological disease this statistically valid study based on sound methodology provided no evidence to indicate that Parkinson's disease in FEPOWs is greater than in the population generally. Since this study was published in 1999 there has been no further published work progressing the cycad or any other delayed neurotoxin theory of neurodegenerative disease.

3.5.7 **Smoking.** Parkinson's disease appears less common in smokers than non-smokers and despite some findings to the contrary there is a large body of evidence that indicates that smoking tobacco protects against the condition, possibly by inhibiting the effect of [monoamine oxidase](#), an enzyme which breaks down dopamine in the body.^{15,16,17}

3.6 **Trauma.** Dementia pugilistica experienced by boxers is a well-documented syndrome with features of parkinsonism, ataxia and intellectual loss. It results from repeated head trauma over a period of years. The effects of single or infrequently repeated head injury are less clear.

- Results of studies into causative links with head injury have been inconsistent, with design limitations such as small numbers of cases and controls and reliance on retrospective self reporting rather than documented incidents and injuries^{18,19}
- One study from the Mayo Clinic looked at the effects of non-repetitive head injury using a case-control study of subjects with Parkinson's disease and showed an increased risk from head injury with an odds ratio of 4.3 with an associated 95% confidence interval of 1.2 to 15.2.²⁰ The study was population based with 196 cases and the same number of age- and sex-matched controls. Episodes of head trauma were taken from case notes and there were only 13 cases of head trauma with varying degrees of severity. The results showed that the frequency of head trauma was significantly higher in cases than in controls but the association only related to more severe head trauma and late onset disease. The numbers were small and other factors such as personality type or the effects of motor dysfunction increasing the incidence of head trauma could have influenced the outcome. Although the results suggested an association between late-onset Parkinson's disease and head trauma, the overall population attributable risk was low as head trauma of this degree is a relatively rare event
- Review of other literature suggests that, although a potential factor in Parkinson's disease, the link is tenuous and the effect of head trauma remains but one of the many factors considered over the years but not proven to be implicated in causation²¹

3.7 **Disorders secondary to other neurological disease.** The basal ganglia and the motor control systems of the brain stem can be affected by other degenerative neurological diseases including:

- Cerebro-vascular disease and stroke
- Cortical degeneration
- Multiple system atrophy
- Progressive supranuclear palsy (Steele–Richardson syndrome)
- [Prion disease](#)

In these cases the features of the presenting condition usually appear first, with movement disorder appearing subsequently. However with multiple system atrophy and progressive supranuclear palsy, the presenting signs can be similar to parkinsonism and the full diagnosis may take some time to become evident as more specific features appear. Cerebrovascular degeneration is more likely to compound the effects of parkinsonism than to be a precipitating factor.

- 3.8 **Benign essential tremor.** This is sometimes confused with parkinsonism but the tremor is postural and worse on movement. It can continue for many years and except in long-standing and very severe forms of the condition it is characteristically absent at rest.

4. Prognosis

- 4.1 Parkinson's disease is progressive and there is no effective treatment to reverse its progress. Treatment is aimed at reducing and controlling symptoms, reducing disability and prolonging the period before disability becomes severe. Parkinson's disease is uncommon before age 40 but in cases that present early, the course may run over 35 years. There appears to be no significant reduction in life expectancy but obviously cases starting in later life run a shorter course. Although progression tends to become slower with time, the patient is likely to have a markedly reduced quality of life. In the late stages the illness can produce severe disability and dependence. Side effects from medication such as depression and dementia can compound the disability, and [dysphagia](#) can lead to distressing drooling and reduced nutrition.¹ Impairment in respiratory muscle function combined with poor nutrition and posture can lead to postural pneumonia and death.
- 4.2 [Dopaminergic drugs](#) are the mainstay for reducing the main symptomatic effects of Parkinson's disease, but treatment does not reverse the progress of the condition. Although this treatment is effective in reducing symptoms for several years, with time the response becomes less effective. Drug treatment is continually developing with newer substances helping to prolong the beneficial effect and delay the onset of disability. Neurosurgical procedures are also showing promise.
- 4.3 Parkinson-type side effects of anti-psychotic drugs which inhibit the action of dopamine are usually reversible on cessation of treatment. However as the need to continue treatment for the underlying condition may be essential, the side-effects may have to be tolerated.

5. Summary

- 5.1 Parkinson's disease is one of the more common of the degenerative diseases of the nervous system, affecting one in five hundred people, mainly beyond the age of 50 years.
- 5.2 It has typical clinical features of increased muscle tone, resting tremor and slowness of movement.
- 5.3 Other conditions affecting the central nervous system can produce a syndrome indistinguishable from Parkinson's disease.
- 5.4 The causes of Parkinson's disease are unknown and it is possible that multiple factors, both genetic and environmental, contribute. Although epidemiological studies have identified a number of environmental exposures associated with an increased risk of Parkinson's disease, none has been proven as causative.
- 5.5 Parkinson's disease is slowly progressive and irreversible but where a parkinsonian syndrome is the result of adverse effects of psychotropic drug treatment, it may improve when the drug is withdrawn.
- 5.6 Treatment is aimed at reducing the severity of symptoms and delaying the onset of disability.

6. Related synopses

Stroke

Motor Neurone Disease

7. Glossary

aphasia	Loss of speech due to a brain disorder.
axon	A cylindrical projection from a nerve cell which forms the essential part of a nerve fibre for carrying nerve impulses.
basal ganglia	Several large clusters of nerve cells, deep within the cerebral hemispheres of the brain.
bradykinesia	Slowness of movement, paucity of spontaneous movement, or reduced amplitude of movement.
cycads	Plants of the genus cycadales, found in tropical areas, which are used in some communities as a source of starch to supplement diet. They contain a neurotoxic substance that can produce a variety of neurological symptoms.
cytoplasm	The complex substance of chemical compounds and structures within an animal cell, excluding the nucleus.
dementia	Irreversible deterioration of mental faculties.
dizygotic twins	Twins developed from two separate eggs – non-identical twins.
dopaminergic medication or drugs	Drugs that mimic the effect of dopamine in the brain.
dysarthria	A problem with speech due to difficulty with articulation resulting from a disorder of muscle control or structural damage to the organs of speech.
dysphagia	Difficulty in swallowing.
dysphonia	Hoarseness or speech difficulty caused by impaired function of the vocal cords.
extra-pyramidal pathway	System consisting of nerve cells, nerve tracts and pathways that connects the brain to spinal nerves and is concerned with regulating movements such as balance and walking.
festinating gait	Involuntary hastening of the gait to prevent falling forward.
hypokinesia	Reduced movement.

meperidine	US name for pethidine. An opiate-based narcotic pain killer.
micrographia	A change in the handwriting with the script becoming smaller and more cramped.
monoamine oxidase inhibitor	A substance that counters the effect of a body enzyme that breaks down monoamines such as dopamine in the body.
monozygotic twins	Twins developed from a single egg – identical twins.
neuroleptic	A substance that affects the nervous system.
neurotoxins	Poisons that destroy nerve tissue.
postural reflexes	Involuntary reflex muscle control that maintains position, posture and balance.
prion disease	A disease caused by an infectious protein particle. Prion diseases include Creutzfeldt-Jacob disease (CJD) and its variants in humans, bovine spongiform encephalopathy (BSE) or ‘mad cow disease’ in cattle, and ‘scrapie’ in sheep.
psychotropic drug	A substance that exerts its effects on the mind.
substantia nigra	Grey matter cells of a typical appearance, found in the basal ganglia of the brain. They are associated with production of dopamine.
thalamus	Collection of grey matter at the base of the brain through which impulses pass to and from the brain.

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