PARKINSON'S DISEASE

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Introduction

The prospects for Parkinson's sufferers have improved immensely with the advent of new drug treatments. More recently the notion that transplantation could, either wholly or partially, alleviate the difficulties associated with Parkinson's disease raised further hopes. As Fahn (1988) says, 'We are living in an exciting time in the history of knowledge and treatment of Parkinson's disease.'

Parkinson's disease is a progressive, degenerative condition of the central nervous system which produces three main symptoms: tremor (shaking of the limbs or head); slowness of movement (bradykinesia), or inability to initiate it (akinesia); and muscular rigidity leading to bowed posture and immobile face. The symptoms may occur alone or in combination, and in most patients one symptom predominates. Tremor, whilst not universal, is the most common symptom. Parkinson's disease generally strikes in later life, with few cases among those under 40; usually it becomes clinically recognisable at around the age of 60.

Two major advances can be identified in the treatment of Parkinson's disease. Firstly, the introduction of levodopa in the late 1960s, which remains today the mainstay of treatment for Parkinson's. Secondly, the MPTP[1] experience of the late 1970s led to the emergence of selegiline therapy, which may slow the progression of the disease and extend the useful life of levodopa, in the early 80s. The 1980s also saw attempts to overcome the disabling effects of Parkinson's disease via transplantation. Several hundred such operations

BOX 1 **Manifestations of Parkinson's Disease**

Cardinal manifestations: Tremor, rigidity, bradykinesia (slowness of movement) and postural instability (chasing one's own centre of gravity).

Secondary manifestations: Incoordination, micrographia (writing difficulties), blurred vision, impaired upgaze, blepharospasm (spasm of the eyelids), dysarthia (slurring of speech), dysphagia reflex (difficulty in swallowing), sialorrhea (drooling), masked facies (expressionless face), monotone voice, hand and foot deformities, festinating gait (short, quick, tottering steps; appearing to constantly fall forwards), cogwheel rigidity (muscle relaxes and stiffens intermittently giving a jerky movement), dystonia (muscle spasm), edema (swelling of the extremities), kyphosis (curvature of the spine), pain and sensory symptoms, constipation, urinary urgency, hesitancy and frequency, loss of libido, impotence, freezing, dementia, depression.

Source: Adapted from Stern and Hurtig, (1988).

1 MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) is a commercially available chemical intermediate. It was inadvertently self-administered by young drug abusers who believed it to be 'synthetic heroin'. It caused a severe and permanent parkinsonian syndrome in the users.

have now been carried out. Whilst much research is continuing in this and other areas concerned with the treatment of Parkinson's disease, it remains for the present an incurable malady even if its progression may be slowed and disabling symptoms ameliorated. As Langston (1990) says, '... although we may still be far from being able to predict or prevent Parkinson's disease, for the first time virtually all the components of such a strategy are being actively investigated. While prevention of the disease is still not within our grasp, it may no longer be beyond our reach.' It is thus felt that the recent developments leading to a far greater understanding of the disease and its probable causes will enable a further landmark in the history of Parkinson's disease to be achieved in the near future.

The previous OHE booklet on Parkinson's disease was written in 1974. In the intervening years significant changes in the management of the disease have occurred, thus it is useful to reassess the means of treating this distressing affliction.

History of Parkinson's Disease

Parkinson's disease was not clinically recognised until the nineteenth century. There is evidence, however, to suggest that it existed prior to the Industrial Revolution and may have occurred throughout history. Leonardo Da Vinci's (1452-1519) anatomical manuscripts in the Windsor Castle collection, for example, describe how some subjects 'move their trembling limbs such as the head or the hands without permission of the soul; which soul in all its power cannot prevent these limbs from trembling.' An explanation for the lack of material regarding Parkinson's disease – or related syndromes – prior to the nineteenth century is possibly because the disease tends to occur at ages above the prevailing life expectancy of earlier periods; also the initial symptoms are often insufficient to distinguish sufferers from the general population, thus the condition may have had a very low perceived prevalence and gone largely unnoticed.

James Parkinson, a London GP, in his 1817 booklet 'An Essay on the Shaking Palsy' gave the disease he was describing a latin synonym 'paralysis agitans'. He defined the disease as being one with, 'involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from walking to a running pace: the senses and intellect being uninjured.' Parkinson went on to explain the progression of the disease with hands and legs failing to 'answer with exactness to the dictates of the will'. Writing becomes nearly impossible and eating a chore. Eventually speech becomes 'scarcely intelligible', saliva begins to drool from the mouth and 'urine and faeces are passed involuntarily'. Parkinson based his observations on six individuals – most of whom he had casually sighted and there is no evidence that he actually examined any of them. Robert Bentley Todd in his 1834 article 'paralysis' said, 'the disease approaches gradually and almost imperceptibly, generally commencing with a weakness and slight tremor of the hands and arms, and occasionally of the head.... The tremor becomes permanent, overpowering, and does not even cease when the parts are firmly supported... 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... At last, there is entire loss of speech and deglutition, involuntary evacuations, stupor and death.'

The French neurologist, Charcot, writing in the 1860s, criticised the term 'paralysis agitans' or 'shaking palsy' because he believed it was an inappropriate name for a disorder in which muscular power was often well maintained until the late stages. Also 'agitans' or 'shaking' was not wholly appropriate when the disease could manifest itself in severe forms without tremor. Charcot proposed the term 'Parkinson's disease'.

Trousseau (1859), also a French neurologist, had noted that intellectual impairment could occur: 'the intellect is at first unaffected, but gets weakened at last; the patient loses his memory, and his friends soon notice that his mind is not so clear as it was..' Sir William Gowers, in his 'Manual on Diseases of the Nervous System' (1888), examined evidence from over 80 cases of Parkinson's disease. He found a slight male predominance and an incidence highest among 50-60 year olds with some cases emerging in the 40-50 and 60-70 age bracket. The relatively few cases in the 60-70 age bracket was presumably because only a minority of the population at that time would have lived to such an age. Gower believed arsenic and cannabis, possibly combined with opium, to be the optimal treatment.

During World War 1 there was an outbreak of encephalitis lethargica, a viral infection of the brain which occurred in epidemics from about 1915 to 1925, resulting in a wave of Parkinsonism. It then became clear that Parkinson's disease could emanate from a number of sources, although post-encephalitic Parkinsonism differed from true Parkinson's disease in some respects. Charcot suggested that the name of the disorder be changed to 'Parkinson's syndrome', however, this term was unfortunately never adopted and today the majority of cases are labelled 'idiopathic Parkinson's disease'; meaning that it originates from an unknown cause. Parkinson's syndrome has been used to describe drug induced Parkinsonism and Parkinsonism in multiple system atrophies (eg. progressive supranuclear palsy, Pick's disease, Creutzfeld-Jacob disease).

The classic symptoms of Parkinson's disease, namely, tremor, muscular rigidity, and slowness of movement were shown, in 1915, by Tretiakoff in Paris, to reflect a dysfunction in the region of the brain called the substantia nigra – a deeply pigmented nerve-centre about the size of a large bean. In the 1950s in Sweden it was discovered that this collection of nerve cells produced and stored the chemical dopamine. Deficiency of dopamine caused by damage to the substantia nigra led to the symptoms of Parkinsonism. Again in Sweden, in 1957, Professor Carlsson suggested that a metabolic precursor of dopamine – levodopa – might be used in the treatment of the disease. Levodopa was formally accepted for therapeutic use in 1970.

Epidemiology

Parkinson's disease is estimated to affect about 100,000 people in the UK. Leaving aside dementia, Parkinson's disease is the most common neurological condition to affect the elderly British population after epilepsy and cerebrovascular disease; it is more common than

multiple sclerosis. It ranks equally with stroke in causing disability. Parkinson's disease affects approximately one in every 500 people (Royal College of Physicians, 1986). Schoenberg (1986) suggests that it has an incidence of approximately 20 new cases per 100,000 population per annum. Studies based in Rochester (Minnesota) over the period 1945 to 1979 showed the rate of new cases varying from 16 to 21 per 100,000 population per annum. The incidence of Parkinson's disease increases with age until around 75 when there is a decline in new cases, about ten per cent of cases emerge before the age of 40. In the UK approaching 10,000 people develop Parkinson's disease every year.

There are problems associated with using medical records to estimate the prevalence of Parkinson's disease because only those with signs or symptoms who are sufficiently motivated to seek medical attention will appear on such records. There also needs to be a uniform diagnostic criterion to establish a consistent diagnosis. Such difficulties were demonstrated in Baltimore where there appeared to be a greater prevalence of Parkinson's disease among whites than among blacks. In order to verify this finding a door-to-door survey was carried out in Mississippi which revealed virtually no difference in the rates between the two races. Interestingly 32 per cent of cases among whites and 58 per cent among blacks were newly diagnosed by the survey. However, Mutch (1988) working in Scotland still believes that Parkinson's disease is most common in white races, least common among blacks and intermediate in Mediterranean and yellow races. Mutch does accept that such differences may have been exaggerated by problems in method ascertainment, but points to well conducted recent studies in Japan, China and Nigeria which suggest that the true prevalence among these countries may be lower than in predominantly white areas.

The validity of epidemiological studies was reviewed by McKeigue and Marmot (1990) who say that the proportion of reported cases excluded after neurological review varies from 11 to 44 per cent, with most of the exclusions being rediagnosed as essential tremor[2], cerebrovascular disease, or drug-induced Parkinsonism. On the other hand, mild cases may escape diagnosis altogether. Schoenberg et al (1985) found that 42 per cent of cases were diagnosed for the first time by investigators carrying out a survey. In Aberdeen Mutch et al (1986) found that of 393 cases of Parkinson's disease 18.1 per cent were drug induced and 14.5 per cent did not have Parkinson's disease. The diagnosis of Parkinson's disease is

2 As Playfer (1991) says, '...all that shakes is not Parkinsonism. Indeed, the commonest cause of tremor in the elderly is benign essential tremor.' Essential tremor is a familial tremor that tends to increase with age but is not associated with any other nervous symptoms.

especially difficult because there is no biological marker or diagnostic scan generally available so the diagnosis relies upon clinical judgement. Non response to treatment, rapid disease progression, and early dementia development all question an initial diagnosis of Parkinson's disease. Positron emission tomography (PET) enables the loss of dopamine from the basal ganglia to be detected during life. However, the ordinary clinic or hospital does not presently have access to PET scanning so the diagnosis of Parkinson's disease has to be made clinically.

Population projections suggest that there is going to be a significant increase in the numbers of elderly in the forthcoming years. The US Bureau of the Census estimates that those at or over 65 in the USA are likely to increase from 25 million (1980) to 32 million (2000). UK population projections based on mid-1987 population statistics suggest that those aged 65-74 will increase from 5.0 million in 1988 to 6.8 million by 2031; with most of this growth towards the end of the period. For those over 75 the numbers are expected to increase from 3.9 million (1988) to 5.4 million (2031). Thus, there is likely to be a considerable increase in the numbers of those most at risk of developing Parkinson's disease.

Survival rates for the first 5 years after diagnosis of Parkinson's disease are close to that of the general population but subsequently fall to 75 per cent at 10 years and 67 per cent at 15 years (Nobrega et al, 1969). The proportion of Parkinson's sufferers having Parkinson's disease mentioned on their death certificate ranges from 30 to 60 per cent. In England and Wales about one in three sufferers have Parkinson's disease mentioned as the underlying cause of death. The official death rate from Parkinson's disease per million population in England and Wales for males is 74, and for females 66. For the world these figures are 43 and 21, respectively. Parkinson's disease was given as the cause of death for 3,992 people in England and Wales in 1988 (OPCS, 1990). The age and gender distribution of these deaths are shown in Table 1.

Table 1 **Recorded deaths mentioning Parkinson's disease on the death certificate; classified by age and gender**

	Total	*<40*	*40-49*	*50-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*	*90-94*	*>94*
Male	2093	0	3	8	38	156	345	526	576	329	99	73
Female	1899	0	0	10	27	81	185	425	561	410	171	29

Source: Adapted from OPCS, 1990.

Aetiological problems

In this section explanations of the cause of Parkinson's disease will be considered. Areas of attention will include genetic or hereditary theories, environmental explanations, lifestyle hypotheses and some combinations of these. Subsequently concern will be focused on how Parkinson's disease can be classified into various subgroups, followed by a discussion of Parkinsonian syndromes; syndromes quite distinct from, but all too often mistaken for, true idiopathic Parkinson's disease.

The tremors and lack of muscular control so characteristic of Parkinson's disease are the result of a progressive loss of nerve cells in an area of the midbrain known as the substantia nigra. The job of these cells is to produce the neurotransmitter dopamine. As a result of the loss of cells too little dopamine is produced. Clinical manifestation of Parkinson's disease occurs when neuronal loss can no longer be compensated for to produce normal functioning.

'Within a decade we have gone from having no idea of the cause of Parkinson's disease to being able to hypothesise explanations and speculate how one could reduce its incidence.' (Williams, 1991)

Genetic and hereditary theories

Whether or not Parkinson's disease is genetically acquired has long been debated. Many studies have produced a positive family history, but often these studies include aunts, uncles, grandparents, cousins, and even those related by marriage. In one study the average family consisted of 45 individuals. Many of the relatives mentioned as having Parkinson's disease actually had a different disease such as essential tremor. Even if a positive family history exists it may be that family members tend to share the same environment and are therefore susceptible to an agent in the environment which may be responsible for causing Parkinson's disease. Thus, hereditary factors in recent times have usually been given a minor role. This, however, does not rule out a nonhereditary, possibly congenital genetic defect.

Environmental explanations

The simplest hypothesis is that Parkinson's disease is due to an MPTP-like neurotoxin in the environment, however, no such substance has yet been identified. Marsden (1990) believes that the 1980s saw two important pieces of information giving insight into the extrinsic causes of Parkinson's disease. Firstly, the realisation that inheritance was not important in the aetiology of the disease – although this is not a universally held belief; and secondly, the discovery of MPTP, a human neurotoxin that could selectively destroy the substantia nigra, inducing neuropathological and neurochemical changes like those of Parkinson's disease, and cause illness similar to

Parkinson's disease. Alternatively there may have been toxic exposure early in life, even in utero, that caused subclinical nigral damage. The effects of normal ageing in addition to this exposure may lead to Parkinson's disease later in life.

During the 1980s the dominant hypothesis in the aetiology of Parkinson's disease has been the 'environmental theory'. Nevertheless Golbe (1990) still suggests that genetic factors may play a necessary and perhaps primary role in the cause of Parkinson's disease. The possibility that Parkinson's disease may be rarer among black and yellow races suggests that a racially related genetic factor might be significant. However, the MPTP experience provided circumstantial evidence in support of an environmental theory. MPTP is a commercially available chemical intermediate used in the synthesis of more complex chemical compounds. It was inadvertently self-administered by several young drug abusers as an alternative to heroin. The addicts then acquired a severe and permanent Parkinsonian syndrome which responded favourably to anti-Parkinsonism drugs. The first documented case of MPTP poisoning was in a 23 year-old chemistry graduate who, by accident, produced MPTP as a byproduct in the synthesis of MPPP (1-methyl-4-phenylpyridinium). The graduate had made MPPP for several months and used it with no ill effects. In November 1978 he took certain shortcuts in one preparation. After a few days of injecting the man presented with severe rigidity, weakness, muteness, tremor, flat facial expression, and seborrhoea (greasiness of the skin). Treatment with levodopa led to a marked improvement. When the treatment was discontinued Parkinsonian features returned and levodopa therapy was then restarted leading again to rapid improvement. The patient eventually died from a drug overdose of cocaine and codeine.

There were several reports from California where MPTP-contaminated MPPP was sold as 'synthetic heroin'. Users became symptomatic within one week and by two weeks were experiencing general bradykinesia, immobility, fixed stare, drooling, and facial seborrhoea. Because only one such patient has been examined post-mortem it is difficult to generalise concerning the precise changes which occur in the brain and whether these changes are identical or similar to those in Parkinson's disease, or indeed if the changes would be identical if the MPTP poisoning occurred gradually over a longer period of time, or among an older age group.

Guam, a small island in the western Pacific, showed a high prevalence of amyotrophic lateral sclerosis (ALS) among the Chamorro Indians who lived there. This syndrome is linked to Parkinsonism-dementia complex (PDC). It is common for Chamorro's to take jobs with the US military on leaving Guam in their teens or early twenties, often spending decades away from their native environment.

Some of these men developed signs of ALS-PDC while away from Guam, suggesting that if an environmental toxin is responsible a very long latent period may occur between exposure and expression of the symptoms. Williams (1990) states that, 'Parkinson's disease may be conceived as being an environmental toxin working upon a genetically susceptible individual. The relationship between the extrinsic and intrinsic factors might be complex and relate to metabolic abnormalities in the patient.' If an environmental toxin is important in the genesis of Parkinson's disease, then the appropriate metabolism to investigate might be in the liver with its important detoxification role rather than the brain which would merely show the result of damage caused by the toxin. It has been suggested that recent evidence indicating that pre-clinical Parkinson's disease exceeds clinically recognisable Parkinson's disease by a factor of 16 means that a Parkinsonian gene could be present and manifest itself as incidental Lewy body[3] disease or oligosymptomatic Parkinsonism – impossible to diagnose. The concept of a 'Parkinsonian iceberg' has been put forward with only the tip visible as an overt clinical disease.

About five per cent of nigral cells are lost each decade after the age of 50, but in the process of normal ageing cells are lost predominantly from the dorsal region of the substantia nigra rather than in the ventrolateral area; the main site of cell loss in Parkinson's disease. This suggests that the disease is not simply an accelerated process of normal ageing. The rate of cell death is fairly rapid and suggests that clinical signs will begin to develop within five or six years of the onset rather than the long incubation period which has often been suggested.

Lifestyle and personality factors

As always happens with a disease where the causes are still unknown there have been assertions made between certain factors or lifestyles and the development of the disease. These theories have been propounded with varying degrees of credibility. For instance, a dislike of green vegetables has been suggested as a common feature among Parkinson's sufferers along with a low proportion of smokers; although the latter may be explained by premorbid behaviour leading to an abstention from smoking. The notion of premorbid behaviour characteristics is based on the assumption that initially levels of dopamine are reduced sufficiently to produce a change in personality but not to produce any problems with movement. It has

3 Lewy bodies are characteristic neuronal inclusions, present in virtually all cases of classical Parkinson's disease. They are not uncommon in Alzheimers disease and in brains from people over 60 – however, such individuals may have had subclinical Parkinson's disease.

also been suggested that patients with Parkinson's disease are introverted, emotionally and attitudinally inflexible and predisposed to depressive illness. However, it is not known whether these are risk factors or secondary developments in the subclinical stage of the disease. Ogawa et al (1984) analysed smoking histories in relation to personality attributes to see whether a negative association with smoking due to a special premorbid personality of Parkinsonians existed. Both the male and female Parkinson's patients smoked significantly less than control groups. The females with Parkinson's disease were inclined to be 'taciturn, introvert, unsociable, gloomy, timid, and passive' at a premorbid stage, whereas male personality profiles were less clear cut. The risks appeared to decrease with strong-minded, optimistic, and self-confident categories. Ogawa and his colleagues concluded that smoking and personality are independent risk factors. However, Sagar (1991) believes that the personality types who are prone to Parkinson's disease are also the personality types who tend not to smoke, he adds that research evidence indicates that smoking 'definitely does not' protect against Parkinson's disease. The smoking and personality theory would explain the data from England and Wales which show that smokers have a relative risk of acquiring Parkinson's disease of 0.5 compared to non-smokers. Those smokers who do get Parkinson's disease tend to have an earlier age of onset than non-smokers. The relative risk of those who had given up smoking compared to those who had never smoked was 0.58.

Kondo (1986) suggests that most cases are due to the combined or cumulative effect of many relatively minor factors. He sees established risk factors as being advanced age, less smoking, a special premorbid personality, head injury and affliction of family members; however, it is unlikely that general consensus could be found concerning these 'established' risk factors. Kondo also produces a list of debatable risk factors including, low blood pressure, habitual constipation and reduced physical activity. Marttila and Rinne (1986) conclude that '... no high risk group can now be identified.'

Classifications of Parkinson's disease

Two types of Parkinson's disease have been suggested. Type One usually striking before the age of 60; Type Two after the age of 60. Common to both these subgroups of Parkinson's disease are tremor, rigidity and bradykinesia. At autopsy Lewy body inclusions are found in the substantia nigra of both groups. Godwin-Austin and Lowe found a slight male predominance among Type One patients with equal numbers of men and women among Type Two patients. Type One was more slowly progressive with nearly 14 years, on average, from diagnosis to dependency, against nearly six years for

Type Two sufferers. This disparity meant that dependency among both groups developed in their late 60s. There was a notable difference in treatment related disability with 'on-off' attacks more frequent and severe among Type One sufferers with 66 per cent experiencing such attacks against 11 per cent in Type Two patients. However, clinically significant dementia was only noted in 8.7 per cent of Type One cases against 46.6 per cent in the Type Two category. The clinical significance of the two types of Parkinson's disease is that Type One has a better prognosis, particularly with regard to dementia, and a better response to treatment. However, Type One cases are more likely to develop severe dyskinetic side-effects of levodopa therapy.[4]

Gerstenbrand and Werner have a different approach to classification believing that Parkinsonian syndromes can be broken down into three categories. Firstly, true idiopathic Parkinson's disease; secondly, secondary (symptomatic) Parkinsonism; thirdly, Parkinsonism in multiple system degenerations. Gerstenbrand and Werner suggest that true idiopathic Parkinson's disease can be subdivided into three clinically identifiable types. Type One and Type Two Parkinson's disease suggested earlier could possibly be further broken down into each of these three classifications; with most cases falling into the first category: firstly, classical Parkinson's disease with akinesia, rigidity and tremor (ART-type); secondly, akinetic-rigid type with little or no tremor (AR-type); thirdly, tremor-dominant type with mild akinesia and rigidity (T-type). The majority of patients with idiopathic Parkinson's disease can be assigned to the 'classical' variety or ART-type. A good levodopa response is usually obtained and fluctuations do not usually develop before 3-5 years. AR-type often has an earlier age of onset and appears to be the most frequent type of juvenile disease. It tends to be associated with rapid progression and poor levodopa response, with an earlier development of response fluctuations and abnormal involuntary movements after long-term levodopa therapy. Dementia is common among the AR-types. T-type Parkinson's disease has the best prognosis with slower progression and less likelihood of severe disability than the other two. T-type is also less commonly associated with dementia or depression.

Secondary Parkinsonism may occur after administration of neuroleptic agents eg. phenothiazines. Various toxic chemicals are able to cause Parkinsonism; manganese intoxication is probably

4 Rajput et al (1986) looking into early onset Parkinson's disease (EPD) – that is, onset before the age of 40 – found no sex, racial or occupational predisposition to EPD, however, all the subjects were raised in small communities which had no central water supply, thus, it is believed that the EPD cases under observation were caused by exposure to some agent predominantly found in rural areas and that childhood drinking water is a likely vehicle for such an agent.

responsible for more cases of Parkinsonism than any other toxin. Chronic exposure to a high level of manganese dust is required. The reasons underlying individual susceptibility are unknown and early withdrawal from the exposure may result in total recovery. Carbon monoxide, a colourless, odourless, nonirritating gas, can produce damage to the central nervous system. Toxicity from carbon monoxide can be caused by suicide attempts using exhaust fumes and the resulting Parkinsonism can remain static or improve. Carbon dilsulfide, cyanide and methanol have all been reported to cause Parkinsonism. MPTP, unlike other toxins, produces a pure form of Parkinson's disease. Parkinsonism following encephalitis lethargica is the most distinct type of secondary disease both clinically and pathologically, for which reason it has frequently been independently classified.

Thirdly, there is Parkinsonism in multiple system atrophies. These are frequently misdiagnosed as idiopathic Parkinson's disease, despite having distinctive clinical conditions including akinetic-rigid manifestations, poor or absent response to levodopa treatment and rapid progression. There are various multiple system atrophies or Parkinsonism-plus syndromes. Striatonigral degeneration is initially diagnosed as Parkinson's disease, however, tremor and dementia are uncommon. There is also a lack of responsiveness to levodopa. Diagnosis of striatonigral degeneration can be confirmed only at postmortem, when Lewy bodies are not usually found. Progressive supranuclear palsy (PSP) was identified by Steele in 1964. The average age at onset is 58 with death occurring 2-12 years later. Men are affected by PSP more often than women. Falling, postural instability, memory problems, speech difficulties and axial rigidity are predominant symptoms. The hallmark of PSP is a paralysis of vertical gaze and dementia is especially common in the late stages of the illness. PSP is usually initially diagnosed as Parkinson's disease but the response to antiparkinsonism medications is poor and inconsistent. No effective therapy exists for the treatment of PSP.

Olivopontocerebellar atrophies (OPCA) are a heterogenous group of disorders sharing some common clinical and pathological features. These disorders are frequently misdiagnosed as Parkinson's disease, however, the response to levodopa is usually limited and transient. Degenerative diseases which have Parkinsonian features include: Alzheimer's disease, Pick's disease, Shy-Drager syndrome, Creutzfeld-Jacob disease, 'atherosclerotic' or 'senile' Parkinsonism, idiopathic dystonia-Parkinsonism, primary pallidal atrophy, Parkinsonism ALS-dementia complex of Guam. Central nervous system disorders that may cause Parkinsonism include: stroke, tumour, trauma, and subdural haematoma. There are also hereditary disorders associated with Parkinsonism, which include Wilson's disease,

Huntington's disease and Hallervorden-Spatz disease. The most common condition misdiagnosed as Parkinson's disease is essential tremor, although on rare occasions the two may coexist.

It has been proposed that patients with dementia suffer from a disorder entirely distinct from classical Parkinson's disease, and that such patients represent a combination of Lewy body disease with Alzheimers disease. However, several studies have failed to find Alzheimer-like changes in demented patients.

'Although the cause of Parkinson's disease remains an enigma, the avenues for exploration are now more clearly defined.' (Burton and Calne, 1990) There are many similar syndromes to Parkinson's disease and this makes identification and classification of various symptoms into distinct disease categories a complex and difficult task. Many patients are thus misdiagnosed as Parkinson's disease sufferers, particularly at initial diagnosis when features characteristic of that condition may in fact indicate wider central nervous system pathology.

Treatment and therapy

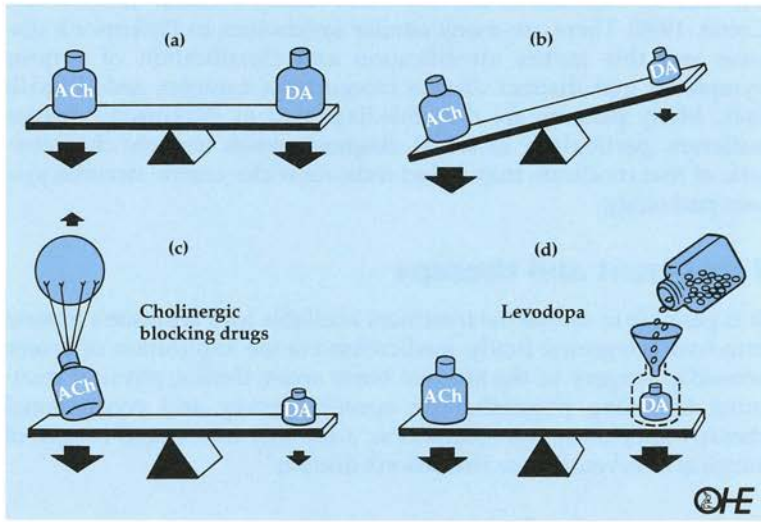
It is possible to divide the treatment available for Parkinson's disease into four categories: firstly, medication via the application of drugs; secondly, surgery to the affected brain areas; thirdly, physical treatment including physiotherapy, speech therapy and occupational therapy and, lastly, transplantation, a recently introduced branch of surgical intervention for Parkinson's disease.

Medicines used in Parkinson's disease

With regard to medication, all drugs presently in use are directed towards re-establishing normal neurotransmitter function to the affected brain region; their primary pharmacological effect either to increase dopaminergic or decrease cholinergic activity (see Figure 1). Treatment is palliative and symptomatic. The main approaches to the medical management of Parkinson's disease include dopamine substitution by levodopa, which is decarboxylated to dopamine when it penetrates the blood-brain barrier, inhibition of dopamine breakdown by monoamine oxidase inhibitors and stimulation of dopamine receptors by dopamine agonists.

There are two main groups of drugs taken for Parkinson's disease: anticholinergics and dopaminergics. Anticholinergic therapy is the oldest form of pharmacotherapy, being introduced by Charcot in 1867. Synthetic anticholinergics were first developed in 1946. Anticholinergics and levodopa work in quite different ways and so it is not unusual to take both simultaneously. Anticholinergics have a greater effect on rigidity and only a slight effect on tremor and slow-

Figure 1 **Diagrammatic representation of the balance between dopamine (DA) and acetycholine (ACh) acting as antagonistic neurotransmitters. (a) Normally there is a balance. (b) In Parkinsonism, dopaminergic function is reduced, so that the balance is disturbed in the direction of cholinergic dominance. (c) This disturbance may be corrected by reducing the effect of acetycholine with anticholinergic drugs such as procyclidine or benzhexol. (d) Alternatively, the balance may be restored by administering the immediate precursor of dopamine, levodopa.**



Source: Adapted from Eldepryl (Selegiline Hydrochloride): In the treatment of Parkinson's disease. Britannia Pharmaceuticals Ltd (1989).

ness of movement. Various anticholinergics are available and they all tend to exhibit similar side-effects such as dryness of the mouth, blurring of vision, nausea, palpitations, constipation and slowness or hesitancy in urinating. Some patients, especially the elderly, may become confused or forgetful on high doses or may complain of loss of balance or dizziness. Anticholinergics are said to have a modest effect on the reversal of Parkinsonian symptoms; this is partly due to the fact that they have to be used in restricted doses because of their disturbing side effects. However, Yahr (1990) claims that 'anticholinergic agents still have a most useful role in the treatment of Parkinson's disease.'

Parkinson's disease was the first example of a neurological disease consistently correlated with a deficiency in a specific neurotransmit-

BOX 2 **Medicines used in Parkinson's Disease**

Anticholinergics – block the action of one of the brain chemicals: acetylcholine. They are often used as a first-line therapy for mild cases; or in combination with levodopa. Such drugs include: benzhexol, benztropine and procyclidine. They may be especially useful in people who produce alot of saliva because of the effects of drying the mouth.

Amantadine – is used under similar circumstances to anticholinergics. It is used in patients with mild disease and sometimes those with predominant tremor. Effect of the drug used alone is relatively slight, but it can be a useful addition to levodopa therapy.

Levodopa – passes from the blood stream into the brain and once there is converted to dopamine; the missing neurotransmitter in Parkinsonians. Levodopa combined either with benserazide or carbidopa are the main drugs in use. In these preparations less levodopa is used so there are fewer side-effects experienced than with levodopa alone. Both preparations can be taken in the form of tablets or capsules. A dispersible version of levodopa and benserazide, which can be suspended in water, is particularly helpful to people who have difficulty in swallowing tablets or capsules. Also the medication reaches the bloodstream quicker than from ordinary tablets, so it is useful in providing a 'kick start' in the mornings or during 'off' periods. A controlled release version of the same combination yields a longer lasting effect and fewer fluctuations. Levodopa can abolish all signs of the disease (in the early stages at least). Virtually all patients will respond and indeed failure to respond is often seen as a possible clue to a misdiagnosis of Parkinson's disease. The major long-term problem is the on-off syndrome which is the primary cause of handicap in a number of people who have had Parkinson's for some years.

Bromocriptine – dopamine is produced by one cell and used to transmit messages to a second cell. One approach to treatment is to bypass the dopamine completely and pass the message to the second cell. Bromocriptine acts directly on the receptor. (Similar drugs are pergolide, lisuride and mesulergine). Bromocriptine is rarely used alone, but more often in combination with levodopa. The advantages of combining the two enables a reduction in the daily dosage of levodopa, with no loss of efficacy and fewer side-effects. It can also help counter on-off fluctuations because it has a longer duration of action and smoothes out on-off switches.

Selegiline – is a MAO-B inhibitor which prevents the breakdown of dopamine in the brain. It is taken in the form of a 5mg tablet once or twice daily. It is given in addition to levodopa. It may have a protective effect delaying the need for levodopa treatment.

Apomorphine – is never used except in the more advanced stages of the disease. It has to be given by injection because it cannot be taken in tablet form. Apomorphine can considerably help patients who have severe on/off swings.

Source: Sagar (1991)

ter, ie. dopamine. By studying the brains of Parkinsonian patients at postmortem it was found that they had low levels of monoamines, especially dopamine. This was the rationale behind the introduction of levodopa as a therapy for Parkinson's disease. Levodopa was

detected in 1913 by Guggenheim, however, it was not until 1961 that it was first introduced into clinical practice by Birkmayer to treat Parkinson's disease (after initially being suggested for this purpose by Carlsson in 1957). This marked the first attempt to cure a brain disease by exogenously administering a neurotransmitter precursor. 'There is no doubt that today the substitution of striatal dopamine deficiency with levodopa remains the most effective treatment for Parkinson's disease.' (Rinne, 1989)

Dopaminergic tablets have the greatest effect on slowness of movement and difficulty in initiating movement. Problems with walking and speech are also often helped and rigidity much relieved. Tremor is usually the last symptom to respond and it may take six months of dopaminergic treatment before the greatest benefit in any aspect is experienced. It is now normal practice to use tablets containing levodopa and a substance potentiating the beneficial effects of levodopa (a decarboxylase inhibitor). Orally administered with a decarboxylase inhibitor (carbidopa or benserazide) it has a high therapeutic index with effective control of Parkinsonian symptoms in 70-80 per cent of patients. Optimal therapeutic benefits are usually limited to the initial 3-5 years of its use after which diminution of benefit begins to develop. The majority of patients will experience a 30-50 per cent reduction in efficacy after five years of levodopa therapy. Adverse reactions including the 'on-off' phenomena may occur; a minority benefit from a drug holiday where treatment is discontinued for a period and then restarted. Taken orally the tablet proceeds through the stomach and gets absorbed into the blood stream and then passes into the brain. The barrier that prevents certain substances from reaching the brain, including dopamine, allows levodopa to enter. Once there levodopa is chemically converted into dopamine. Carbidopa is added to prevent an enzyme in the gut from destroying the levodopa before it reaches the blood stream. Levodopa treatment gives early side-effects of nausea or loss of appetite, dizziness and faintness. Other side-effects such as restless movement of the face or limbs develop later on in treatment. The emergence of late symptoms is probably more common if a high dosage is used. The lowest dose of levodopa sufficient to control the disabling symptoms is usually the recommended dose.

Birkmayer cites five historical stages in the clinical use of levodopa therapy. In stage one levodopa was used alone. The trigger for the clinical application of levodopa was the observation by Carlsson et al in 1957 that the inhibitory effect of reserpine on the motor activity in rabbits can be antagonized by dopamine. The notion of using levodopa gained more relevance when a decreased concentration of dopamine in the basal ganglia of Parkinson's patients was detected. When levodopa was applied to Parkinson disease patients for the

first time in 1961 it appeared to produce dramatic results; a few minutes after the injection akinetic patients were able to get up and walk around. Hoehn (1986) reported on the findings of a study which compared 204 Parkinson's disease sufferers who were not treated with levodopa (1950-1964) with 182 who were (1968-82). Levodopa therapy was started immediately, or at least within one year of diagnosis, in 84 cases. In 98 cases levodopa was delayed one to eight years after diagnosis. One hundred and sixty-eight were on levodopa combined with carbidopa and 14 were on levodopa alone. Treated patients were at each of stages one to five of the Hoehn-Yahr scale (see Box 4 for an explanation of this scale) for three to five years longer than untreated patients. The duration of the illness was longer and disability and death were significantly less when patients were treated with levodopa. With an onset of Parkinson's disease 1-5 years before the end of the study nine per cent of treated and 28 per cent of untreated patients were disabled or dead. At 6-10 years the figures were 29 per cent and 62 per cent respectively. At 11-15 years the figures were 55 per cent and 85 per cent respectively. A significantly larger proportion were disabled or dead if treatment was postponed from one to eight years.

Fluctuations in response ('on-off' phenomena) were said to be strongly correlated with youthful onset of the disease and were not related to dosage or initiation of levodopa. The mean age at death of untreated patients was 67 compared with 73 for treated patients. Death at 75 plus occurred in 59 per cent of levodopa patients against only 20 per cent in the pre-levodopa era. Hoehn claims that the beneficial effect is more noticeable the earlier the treatment is undertaken; observed/expected mortality was not significantly different from the unaffected population among those where levodopa treatment was initiated within one year of diagnosis. Levodopa is not thought to retard or prevent the underlying brain pathology of Parkinson's disease.

The second stage in the clinical use of levodopa involved adding a decarboxylase inhibitor. After a while it became clear that the effects of levodopa only lasted 15 to 30 minutes, however, Birkmayer discovered that by applying benserazide to Parkinson disease patients the clinical effect was better and longer lasting than using levodopa alone. The dopa decarboxylase is blocked by the benserazide leading to a higher proportion of levodopa in the brain giving a longer lasting effect. Benserazide itself cannot pass through the blood-brain barrier.

Stage three combined levodopa with a dopamine receptor agonist. One of the most challenging problems in the treatment of Parkinson's disease is the large number of patients who, after a favourable response to levodopa and a decarboxylase inhibitor, fail to maintain the benefit. This can take the form of 'wearing off' or 'on-off' phe-

nomena. The early combination of low dose levodopa and a dopamine agonist (bromocriptine, pergolide, or lisuride) appears to reduce Parkinsonian disability and inhibit the development of fluctuations in response. This approach seems to offer a better long-term treatment than high-dose levodopa, presumably by maintaining normal functioning of the striatal dopamine neurotransmission for a longer period than levodopa alone. Results with this method are unpredictable; some patients are greatly benefitted, others not at all. The side effects can be considerable so this method of treatment should be used carefully and the therapeutic regimen individualised. A recent 24 week multi-centre placebo-controlled trial of 189 Parkinson's patients, who were experiencing sub-optimal levodopa responses, found that 25 per cent of the pergolide-treated group had a 50 per cent improvement in disability compared with only five per cent of the placebo group. Also patients not responding to bromocriptine were switched to pergolide and some improvement was noted; whereas no improvement appeared when non-responders to pergolide where switched to bromocriptine. Pergolide, unlike bromocriptine, acts on both D1 and D2 dopamine receptors; it also appears to have a longer duration of action. Professor Olanow, of the University of South Florida, believes that treating patients with levodopa will provide short term relief of symptoms at the cost of adding to the long term dopamine burden – free radical attack[5]. With early application of a dopamine agonist the life of dopaminergic neurones may indirectly be prolonged. The agonist enables dopaminergic transmission to occur and thus relieve Parkinsonian symptoms; but it should not kill any more neurones because it does not, like dopamine itself, lead to free radical production. The response to dopamine agonists deteriorates after 6-12 months when levodopa will be required.

Levodopa plus a monoamine oxidase B (MAO-B) inhibitor developed as the fourth stage. MAO inhibitors inhibit the oxidation (burning up) of brain chemicals. In Parkinson's disease the dopamine deficit can be corrected by inhibition of dopamine degradation.

The fifth and final stage involves the use of levodopa and iron. Exogenous substitution of dopamine by levodopa stops endogenous production of the neurotransmitter. This implies that levodopa treatment will further reduce an already reduced endogenous production of dopamine. This appears to be the case in a number of instances where even after increasing the dosage the treatment became inef-

5 Free radicals are toxic agents which are released in the process of certain normal biological processes. Potent trapping agents of free radicals are depleted in the substantia nigra of Parkinsonian patients. Free radicals can cause cell damage and tissue injury.

fective. The number of such patients is increasing due to the extending life expectancy of Parkinson disease sufferers. Stimulation of endogenous biosynthesis may be a strategy to overcome this. Iron stimulates dopamine synthesis. Only one iron compound, oxyferriscorbone, proved to be useful in patients. With it, disability could be significantly reduced for all grades of severity, although it does not work for all sufferers. The addition of iron represents a new therapeutic principle working on the basis of stimulation rather than supplementation. In summary Birkmayer says, 'according to our experience of more than 25 years, the following conclusions can be drawn: levodopa is the essential drug for therapy of Parkinson's disease. The other compounds discussed in this review are additives that are more or less effective depending on their route of administration. The goal of an optimized therapy is to use the lowest effective dosage of levodopa in combination with various additives.'

A recent advance has been the use of selegiline hydrochloride. It was discovered in 1964 and its MAO-B blocking potential was recognised in 1972. In 1974 Kroll et al reported on selegiline claimed to be a specific MAO-B inhibitor. The clinical experience with it demonstrated an improvement of symptoms, prolongation of life, few side effects, and a reduction in fluctuations. In brief selegiline appears to offer the following benefits: it slows the progression of the disease, extends the useful life of levodopa, has a low cost and good safety record and allows a reduction in levodopa dosage. Studies undertaken in Vienna in 1975 first reported selegiline's efficacy. These findings were later confirmed by other studies. Just as carbidopa helped to stop levodopa from being destroyed outside the brain so selegiline conserves the dopamine once it has been synthesised in the brain. The DATATOP study from the USA, funded by a $10 million grant from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), found a 57 per cent reduction in those needing levodopa at one year after diagnosis in those treated with selegiline compared with a control group. Eight hundred people took part in the DATATOP study with the trial running from September 1987 until November 1988. The researchers concluded that selegiline may improve the symptoms and thereby bridle the progression of the disease, or it may exert a protective effect against some unknown environmental toxin which damages nigral cells, alternatively it may prevent the expected decline in the disease process. Other major advantages of selegiline therapy are that it does not have troublesome side effects and smooths out on/off swings, especially reducing off periods in patients with more advanced disease. They recommended treatment with selegiline for otherwise untreated patients in the early stages of Parkinson's disease. Tetrud and Langston produced similar results concluding that,

BOX 3 **Case studies**

A 63-year-old man was referred by his GP thought to have been suffering from arthritis. However, his GP suspected that Parkinson's disease may have been the cause of the man's problems. By the time a specialist saw him he had started using levodopa and benserazide and become completely symptom-free. On examination no evidence of Parkinson's disease was apparent, but when his medication intake was reduced by half at a later re-examination there were clear signs of Parkinson's and his symptoms had returned. Thus, treatment can entirely negate the symptoms of Parkinson's in the early stages of the disease.

A 74-year-old woman had had Parkinson's for over eight years. She began to notice that each dose of treatment was wearing off before the next one was due. She had been taking carbidopa and benserazide three times daily. Her GP initially altered the dose to seven times daily then nine and finally ten times daily. On the latter dose the lady became severely confused, believing that her daughter was trying to kill her, often phoning the police to complain about this. She also believed that 'wasps' and 'helicopters' were flying through her room without warning. After admission to hospital her dosage was reduced to eight tablets daily. All confusion and hallucinations ceased and satisfactory mobility was achieved. It is therefore important to treat patients on their own merits and adjust the medication accordingly.

Source: Sagar 1991

firstly, selegiline appears to be a remarkably safe drug in patients with untreated Parkinson's disease, producing no observed serious side effects. Secondly, early selegiline therapy delays the need for levodopa treatment. Finally, selegiline slows the rate of progression of Parkinson's disease. However, it is not known yet whether there are any long-term disadvantages of this treatment that might cause a less optimistic view of it to be taken in the future.

Regional variations in case management

If a world-wide perspective on treatment strategies is taken, it can be seen that there are considerable discrepancies between countries in the manner in which they treat Parkinson's disease. Italian neurologists tend to use dopamine agonists at the earliest opportunity, apparently convinced that levodopa accelerates neuronal death. In the USA physicians risk being sued if they do not prescribe selegiline at the first sign of tremor and may prefer to add a dopamine agonist before initiating levodopa. In Britain, and to a lesser extent France, there appears to be a wish to stick to levodopa as the first line of therapy; adding an agonist when efficacy starts to decline or side effects become unacceptable (Bryan, 1991).

Physical treatment

Physiotherapy is generally accepted to supplement the effects of drug treatment. Tremor is the least amenable symptom to physical

treatment. However, physiotherapy has a place in the treatment of tremor in helping to alleviate the effect of psychological tension which exacerbates tremor; physiotherapy combined with relaxation exercises can reduce tremor severity. With regard to rigidity physiotherapy can often achieve an improvement in movement and relief of pain. Patients may enjoy pain relief associated with rigidity after vibro-massage to the affected region. Akinesia is the cause of greatest disability among Parkinson's disease sufferers. Akinesia refers to abnormal slowness and a reduced range of voluntary movements and also to difficulty in initiating movement and the tendency for any voluntary movement to come to an involuntary halt. Self-correction of posture in front of a mirror is a useful technique which the subject can follow unsupervised. Physiotherapy has an important role to play in preventing or reversing fear of falling and giving reassurance concerning such fears. Short shuffling paces may be lengthened into a normal stride by the patient having to step over lines marked on the floor. There are also several techniques to overcome difficulty in initiating movement. Music therapy has been suggested as an aid to relaxation in the physical treatment of Parkinson's disease.

Occupational therapy can also be beneficial to the Parkinson sufferer. Furniture can be rearranged so that patients can easily negotiate rooms with their walking frames, uneven rugs should be removed and chairs placed on non-slippery surfaces. Many other aids are also available, such as, walking, bathing, feeding, toilet, bedroom, dressing, and kitchen aids. Voice amplifiers, book holders and other devices are also obtainable.

Speech therapy can help in correcting speech defects that cause patients to become increasingly isolated even within their own families. However, Dr. Hildrick Smith (1991) claims that whilst '42 per cent of people with Parkinson's disease have speech problems sufficient to make it difficult for them to communicate with other people or to use a telephone, only a very small number are referred to a speech therapist.'

Surgical treatment

Surgical treatment for Parkinson's disease has been undertaken since the 1940s. Stereotaxy[6], especially thalamotomy (creating a lesion in a region of the thalamus by stereotaxic devices), enjoyed popularity for about 15 years (1957-72). After levodopa became established, however, the number of such operations fell dramatically. Today only a few departments remain active with none treating more than

6 Use of a stainless steel frame screwed into the bony cranium to assess by stereo X-rays any exact point on the brain.

50 patients a year. The main criticisms of stereotaxic surgery were that it did not influence the progression of the disease and whilst relieving tremor and rigidity it may not affect akinesia. There are also certain hazards in undertaking surgery which might even endanger life. However, stereotaxic methods have continued to improve and the introduction of microelectrodes means that targeting and production of discrete lesions is more selective and accurate. Complications and side effects are now almost nil and a much higher percentage of good results can now be achieved.

The target symptoms for stereotaxic surgery are tremor and rigidity, akinesia has never been alleviated by surgery. When pure akinesia dominates over other symptoms surgery helps little. It is thus important to diagnose rigid-akinetic states accurately as to whether they are secondary to marked rigidity or a manifestation of primary akinesia. Since levodopa can alleviate akinesia 'long-lasting overall improvement of the classical symptoms, tremor, rigidity and akinesia, can usually be managed through judiciously selected combinations of medical and surgical treatment.' (Narabayashi, 1990) Narabayashi says that the longest amelioration of rigidity and tremor known to him is 21 years. He adds that the degree of tremor improvement is much greater than can be anticipated from well designed pharmacological treatments. Narabayashi argues that 'for severe disabling tremor in either Parkinsonian or non-Parkinsonian patients, stereotaxic micro-thalamotomy is the treatment of choice and should be carefully considered when medication has failed.' However, Sagar (1991) claims that 'only a very small minority of people with Parkinson's disease are now more likely to benefit from this sort of operation than from some adjustment of their drug treatment – it is always worth a very enthusiastic attempt to get the drug treatment right before embarking on this sort of surgery.'

Transplantation

The first and only neurologic disease to be investigated with transplantation techniques is Parkinson's disease. Transplantation as a treatment for Parkinson's disease emerged in the early 1980s. If successful it would mean that patients would not have to rely on drugs for the rest of their of lives. In 1981 in Sweden attempts were made to transplant a patient's own adrenal medulla[7] into the caudate nucleus (part of the basal ganglia). The team hoped to provide a supply of endogenous dopamine, and by opting for an autograft to avoid the immunological problems of transplantation. The benefits in four patients were slight and transitory. In 1985 Buckland et al reported

7 The adrenal medulla is the central part of the adrenal gland which sits just above the kidney and contains dopamine-producing cells.

the results of adrenal medullary tissue transplants in two severely disabled Parkinson's disease patients. Both patients showed a decrease in rigidity during the first week after the operation. One patient demonstrated an improvement in hand movement 6 months after surgery while on lower doses of levodopa and bromocriptine. However, such improvements proved to be only transient with the benefits lasting less than a year. Lindvall et al in 1987 reported on two more patients who had undergone transplantation. One of the patients showed an immediate decrease in rigidity and improvement in tests of the hand and arm. In the same year Madrazo, in Mexico, documented marked improvement in two patients (aged 35 and 39) following transplantation of adrenal medullary tissue. After 10 months one patient showed an improvement in facial expression, speech, ability to eat, reduction in rigidity, akinesia and tremor. The other transplantee demonstrated a marked decrease in tremor and rigidity. In 1989 Allen et al reported on initial clinical results in 18 recipients of adrenal medullary autotransplantation. Of the 18, 12 were under 50 and six were over 60. One year after surgery four of the 12 younger patients showed a distinct improvement as assessed by the Columbia Rating Scale (CRS). None of the older patients showed any marked improvement at six months. No permanent surgical morbidity or mortality was encountered. Stability showed the most improvement followed by dexterity, gait and speech, in fact, only rigidity did not show any significant improvement in any patient. Allen et al comment that, 'it is unclear why some patients improved and others did not. The reasons for the improvement are unknown.' Stern (1990) says that 'if anything truly beneficial has emerged so far from the transplantation era, it has been the realization that such procedures are experimental, unproven and need to be conducted with the greatest care and objectivity.' Perhaps researchers in this field should take the advice of Sladek and Shoulson (1988) who call for 'patience rather than patients.'

Attempts have been made to transplant using fetal substantia nigra. The fetal tissue must be obtained when the fetus is 8 to 12 weeks old. This method of operation, of course, raises ethical dilemmas. Moral qualms have been expressed concerning the use of aborted fetuses and it is feared that the women's welfare may be jeopardised if more risky abortion techniques were used in order to preserve the fetal brains for transplantation. Some people see abortion itself as morally unacceptable. However, given that abortions do take place, the question then becomes: is it justifiable to use the fetal tissue? It is important to realise that the question of abortion and the consideration of using fetal cells for transplantation are separate moral issues. Marsden (1990) feels that fetal cell transplants have a more impressive scientific background than medullary tissue autotransplants but more evidence is required in this area to comment further on its effectiveness.

Alternative medicine

Acupuncture can help to relieve pain, so some benefit may be gained by those patients where pain is a prominent feature of the disease. It is probably not likely to help other patients. Hypnosis and yoga can produce relaxation; thus helping stressful or highly strung patients. It is known that stress and mental agitation can cause the symptoms of Parkinson's disease to become worse. However, for the majority of sufferers the benefit from this type of treatment is probably limited. Although since Yoga is also a form of exercise it may produce some effects similar to physiotherapy. Homoeopathy has not been commonly used to treat Parkinsonism so little is known about its effectiveness. Certainly doctors would not recommend alternative medicine as a substitute for drug treatment, but it may be a useful complement to such therapy. It is advisable for anyone considering alternative medicine to discuss this option thoroughly with a knowledgable professional.

Discussion

One point to bear in mind when treating Parkinson's disease is that, as Yahr (1990) says, 'hard and fast rules regarding treatment, when applied indiscriminately to all patients, give less than optimal results. Indeed in Parkinson's disease treatment programmes are best individualized using as a guide not only the patient's symptomatology but also the degree of functional impairment and the expected benefits to risks obtainable from presently available pharmacological agents.' Thus, each patient should be given treatment appropriate to their own individual needs.

In the future it is likely that research will centre on improvements in neuroprotective treatment to slow down or prevent the progression of the disease, protect against free radical damage, and to diagnose the disease early. Detection of preclinical Lewy bodies, for example, with fluorodopa and positron emission tomography (PET) scanning, may be a possibility which would enable identification of dopamine deficiency insufficient to produce overt clinical signs. PET technology is, however, extremely expensive. Steventon et al (1990) suggest that MAO-B in patients with Parkinson's disease may be structurally different from the general population. Such structural differences may be a marker for preclinical disease. If so the implications are considerable since they postulate that earlier treatment with selegiline may be more effective and stop, rather than abate, disease progression since secondary mechanisms of cell destruction may occur in the late stages of the disease. Steventon et al suggest that this could have implications for the preventive treatment of other neurodegenerative diseases such as motor neuron disease or Alzheimers disease.

Birkmayer claims he is '... convinced that we are on the road to

BOX 4 **Some popular measurement and assessment scales used in Parkinson's disease**

Hoehn and Yahr scale (1967): 5 stages based on the level of disability.
Stage 1 – unilateral involvement only, usually with minimal or no functional impairment.
Stage 2 – bilateral or midline involvement, without impairment of balance.
Stage 3 – first sign of impaired righting reflexes. Evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending on the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.
Stage 4 – disease fully developed, severely disabling; the patient is still able to walk and stand unassisted but is markedly incapacitated.
Stage 5 – confinement to bed or wheelchair unless aided Patients are considered disabled if they are confined to bed or wheelchair (stage 5) or if they were unable to feed or clothe themselves or leave their homes unaided (stage 4).

The most recently introduced method is the Unified Parkinson's Disease Rating Scale (UPDRS, 1987). This is a multi-authored attempt to combine the best features of existing systems. Whilst comprehensive it is time consuming taking upto 30 minutes to complete. There are five basic sections to the scale. Part one is based on a 0-4 quantitative scale encompassing 31 items measuring symptoms and signs divided into three sections. Firstly, there is an assessment of mentation, behaviour and mood. Secondly, activities for daily living are evaluated. Finally, there is an examination of motor function. Part two has 11 items attempting to qualitatively and quantitatively assess the complications of dopaminergic therapy. Parts 3 and 4 are the established Hoehn and Yahr staging scale (see above) and the Schwab-England Aids to Daily Living (ADL) scale. The latter scale is based on a percentage system with 100 per cent representing a completely independent person, able to do chores without slowness, difficulty or impairment. The individual is essentially normal and unaware of any difficulty. There is a sliding scale in operation with 10 per cent intervals, such that, at 0 per cent vegetative functions such as swallowing, bladder and bowel operation are not functioning and the individual is bedridden. The UPDRS is completed with a recording of weight, sitting and standing blood pressure and pulse.

Sources: Hoehn, Yahr (1967); Koller W C (1987)

new therapeutic tools for the cure and prevention of this disease.' Fahn (1988) echoes these thoughts posing the question: 'Are we now on the threshold of another revolution – not only in therapy but also in prevention?'

The costs of Parkinsonism

The principal cost of Parkinson's disease occurs due to its social and personal effects. Nevertheless there are also substantial economic costs for the health service.

Economic costs

Parkinson's disease is responsible for considerable hospitalisation costs. The last available HIPE (Hospital In-patient Enquiry) data (1985) show that Parkinson's disease accounted for an average of 1816 NHS beds used daily in England with a mean duration of stay for each patient of 50.9 days. This implies that 2175[8] beds were used daily in the UK for Parkinson's patients in NHS hospitals. The Department of Health estimated that in 1990 there was a hospital cost of £878 per in-patient week (for acute beds). Table 2 shows that the cost to the NHS of Parkinson's disease per annum, solely for bed occupancy, is over £99 million. The average Parkinson's patient will thus cost approximately £6,400 for their 50.9 days stay in hospital.

Parkinson's sufferers accounted for an estimated 303,351 consultations with general practitioners in 1989 in the UK, according to morbidity estimates projected from 1981 statistics. At the average estimated cost per consultation of £6.72 (1988) this amounts to £2,038,518. It is probable that the actual costs would now be greater than this figure given that the consultation costs refer to 1988.

The total sales value for all drugs used in the treatment of Parkinson's disease approaches £25 million per annum; most of this expenditure emanating from retail pharmacy and dispensing GPs, although hospitals account for over £1.5 million. However, some of the drugs used in the treatment of Parkinson's disease are also prescribed for other disorders; but these tend to be drugs worth relatively little in terms of cash sales value. Current estimates are that approximately eight hundred and fifty thousand general practice prescriptions are written annually for Parkinson's sufferers. Hospital prescribing accounts for about eight per cent of drugs used in this area. Levodopa drugs, anticholinergics, selegiline and bromocriptine account for the vast majority of these prescriptions.

Table 2 **Bed costs incurred by Parkinson's patients**

Bed type	*Beds used daily (1985)*	*Cost per week (1990)*	*Annual cost at 1990 prices*
Acute	2175	£878	£99,301,800

Table 3 **The annual costs of Parkinson's disease to the NHS**

	Hospitalisation	*GPs*	*Medication*	*Total*
Costs	£99m	£2m	£25m	£126m

8 This figure was arrived at by taking the HIPE data to represent 83.5 per cent of the UK total, since Englands' population is 83.5 per cent of the total UK population.

Taking the hospital, general practice and medication costs together, Table 3 shows the estimated costs of the disease to the National Health Service in the UK to be £126 million per annum. This is likely to be a minimum estimate as some costs to the NHS of Parkinson's disease will be hidden, for example, those who fall as a result of their condition and require hospital attention will not be classified under Parkinsonism expenditure.

Looking at total costs to the national economy of the USA, it is suggested that these costs could be reduced by advances in therapy to arrest the development or progression of the disease. Kurlan et al (1988) estimated that if a hypothetical drug slowed the advance of Parkinson's disease by 10 per cent it would realise savings of approximately $327 million annually for the health care economy of the US. This figure was calculated by estimating the number of individuals with Parkinson's disease whose employment would be prolonged and then calculating the annual additional taxes being paid ($70.1 million) and the corresponding decrease in disability payments ($104.6 million), as well as delayed institutionalisation ($384.3 million). Against these savings were the additional costs of annual medication ($152.2 million) and home care ($79.9 million). The researchers conclude that protective experimental strategies for the treatment of Parkinson's disease can be justified on economic grounds as well as on the basis of clinical value and scientific merit. In practice it would appear that selegiline slows the progression of the disease rather more than 10 per cent; thus savings accrued by using this therapy are likely to be greater than the $327 million per annum for the US health care economy quoted by Kurlan et al.

Since Parkinson's disease is predominantly a disease of old age, indicators such as lost national income or working years lost may tend to underestimate the significance of the disease, because disability severe enough to prevent the possibility of employment is likely to most affect those who are approaching, or those already at, retirement age. Thus whilst the economic significance of Parkinson's disease, in terms of lost GDP, may appear fairly modest its effects on thousands of sufferers can be devastating.

Financial, personal and practical help for Parkinson's patients can emanate from a number of sources. The social services department may be contacted in relation to meals on wheels, occupational therapy, aids and adaptations in the home, sitters, minders and care attendants, day centre care, short-term respite care, and residential nursing homes (a list of private and local authority run homes). The local DSS Office can be of help when enquiring about income support, income maintenance, housing benefit, community charge benefit, paying for attendance care and residential care, mobility allowance, prescriptions, optical and dental treatment and fares to

hospital.

Financial problems and job-related anxiety can exacerbate physical symptoms. This concern may be more prominent in the younger patients who may still have dependents to provide for. Evidence from the USA indicates that medication costs can be a source of worry with expenditure which can vary from $25-700 per month (Vernon and Stern, 1988). This is unlikely to be so in the UK, but other financial costs to the patient, such as a reduced pension if early retirement is necessary or modification of the home to allow for disability, may be a financial burden borne by the patient.

Social and personal aspects

Falling

Falls are a major health problem among the elderly. Thirty per cent of those aged over 65 living in the community fall at least once each year; rising to 40 per cent among those over 80 years old. Falling accounts for the majority of deaths related to injury and is the sixth leading cause of death among the elderly. Even when there is no physical injury falls can lead to a fear of falling, restriction of activity, loss of confidence, mobility and independence. Often falls are associated with disease- and age-related declines in neurologic and muscoskeletal function. Nevitt et al (1989) carried out a study of 266 women and 59 men aged 60 plus reporting at least one fall in the previous 12 months. Parkinson's disease was diagnosed in 12 of the subjects.

Over half the falls caused soft-tissue injuries. About a quarter of the falls led to a limitation of normal activities, because of injury or fear of falling. In eight per cent of the falls the subject was unable to get up unaided and remained on the ground for at least five minutes. Parkinson's disease was the highest relative risk factor associated with two or more falls in the 12 month follow-up period. This is probably due to problems of postural control associated with the disease. Lying on the floor unable to get up may exacerbate feelings of helplessness and fear of falling. The researchers claim that 'extreme fear of falling may also lead to social isolation, immobility, and institutionalisation.' It is intimated that physical therapy which improves mobility, strength, and balance may reduce the risk of multiple falls. Modifying the home environment to remove potential hazards may reduce the risk of falling in the home. Nevertheless, it is clear that the risk of falling among Parkinson's patients is relatively high and a fear of falling could be partly responsible for restrictions in normal activity, social isolation, loss of confidence, mobility and independence.

Mobility and independence are often connected with the ability to drive. People with Parkinson's disease are required to notify the driving vehicle licensing centre (DVLC) at Swansea of their condition, however, whilst the disease is only mild, driving is no problem. Although, a licence limited to one, two, or three years may be issued after which the person's condition will be reassessed. Motor insurance companies should also be notified of the diagnosis of Parkinson's disease. The Parkinson's Disease Society can usually suggest some amenable companies to people experiencing difficulties with their own insurance firm.

Psychological and social factors

Psychologic and social factors may significantly increase disability and interfere with the acceptance and adjustment to the disease. There needs to be more emphasis on psychosocial factors because their neglect could disrupt even the best therapeutic programs. During the initial stages of the disease facial expression may be normal and posture erect, the most common initial symptom is involuntary tremor of one extremity. Patients are often unable to write properly, button shirts, or cut food. As the disease progresses a masked face may develop with decreased blinking and general slowness in daily activities. Depressive symptoms are common and estimates range from 30 to 90 per cent of the amount of patients so affected. It is not known whether depressive and other cognitive impairments are reactive or specific to the disease process. Levin and Weiner (1987) argue that in the early stages of Parkinson's disease the psychologic changes may be more devastating and disabling than the actual motor disability. At a time when other people are thinking of retiring and enjoying their freedom and independence, Parkinson's patients must face the prospect of being physically and economically dependent. Anger and guilt at becoming a burden may be expressed. A feeling of helplessness and a loss of control may arise because the cause of Parkinson's disease is unknown and the illness progressive and degenerative following an unpredictable course. It has been estimated that 80 per cent of Parkinson's sufferers become severely disabled or die within 10 years of diagnosis (Fry et al, 1986).

Intervention strategies and support groups

Levin and Weiner (1987) suggest that intervention strategies ought to be aimed at minimising helpless and dependent behaviour and should encourage the individual and family to confront the diagnosis and explore its meaning for the individual and family unit. The family should be directed towards openly expressing feelings and apprehensions associated with the disease, leaving the family in a better position to learn about Parkinsonism and establish a reality

from which the patient and family may begin to adjust. Group therapy or support groups are useful to form a social support structure in which patients can learn to adjust and share their experiences, it may also increase motivation to pursue self-care. Family members may assume too many responsibilities rendering the patient more dependent than the motor symptoms warrant. Such behaviour can be counterproductive to independent living and to the successful adjustment to a chronic disorder.

A different strategy may be needed for moderately disabled patients where difficulties with gait and balance may be developing and the side effects of dopaminergic medication may be experienced. The most disturbing of these is the 'on-off' side effect. During the 'on' phase the patient is quite mobile showing almost no symptoms, but in the 'off' phase becomes fully disabled; unable to walk, rise from a chair, or use their hands effectively. The 'off' phenomena can be potentially dangerous, for example, striking when a sufferer is crossing the road. Dyskinesia is another important drug-induced problem causing 'dance-like' limb movements, a chewing lower jaw, darting tongue, and to and fro movements of the head and neck. The patient thus appears to be fidgety, twitchy or restless. Such actions are symptoms of dopaminergic overactivity. Drug-induced behavioural problems include insomnia, vivid nightmares, hallucinations, delusions and paranoid confusional states.

By this stage Parkinson disease symptoms have reached a point of reducing the patient's capacity to maintain an independent lifestyle. The variability of the symptoms may lead to stress and tension in the patient's caregiver: one moment the patient can carry out a task ('on' phase) the next they cannot ('off' phase). Speech impairments, fatigue and loss of facial expression often make communication difficult. Depressive symptoms may compound this problem. Feelings of anger and resentment by carers are often expressed. Perhaps there are also economic considerations along with an anxiety and fear of changes.

At this stage of the disease Levin and Weiner argue that the long-term goals should include: a) an acceptance of the disability and physical limitations while promoting a healthy self-image; b) accept changing role relationships while maintaining feelings of independence and self-esteem; c) develop effective strategies for coping with emotionally stressful situations; d) express fears and concerns and correct myths and misconcepts. Levin and Weiner argue that for family members the long-term goals should include: a) an understanding of the patients disability and assisting nondisabled members to cope with these changes and with feelings of anger and distress; b) recognizing and alleviating feelings of guilt and helplessness; c) understanding that unaffected family members have important and

valid needs as well; d) learn how to set limits on the patient while still promoting independence and self-esteem.

In severely disabled patients 'on' time may become fairly infrequent leading to more time in a totally dependent state. As symptoms progress self-imposed social isolation and withdrawal may increase. In a survey by Longstreth et al (1984) patients ranked sexual activity and handwriting as the two most important losses experienced in advanced disease. There is relatively little in the form of intervention that can be carried out now, however, it may be worthwhile to help the family carry out difficult decisions.

Vernon and Stern (1988) say that, 'emotional flexibility, a sense of humour, and above all, a sense of irony can reduce stress and tension in the struggle to cope with the vagaries of Parkinson's disease, in which emotional state mirrors motor dysfunction. Fun and recreation are vital pursuits in day-to-day planning.' Support groups for Parkinson's disease sufferers and their families can offer a wide range of activities including health education, social mixing, companion hours, assistance with shopping, friendly visitors and phone calls to the house-bound. There are over 300 support groups in USA,

BOX 5 **Parkinsonian patient profile**

Parkinsonian patient profile	Special attention care provider
Parkinsonians may:	Precautions:
1. Choke on food a. be unable to feed themselves	1. Make sure food is in small pieces and has been swallowed.
2. Develop pneumonia easily.	2. Move patient every 2 hours.
3. Have difficulty in communicating; low voice, slow to start speaking, mumble words.	3. Take time to listen; check patient as often as possible.
4. Suffer from constipation.	4. Patients need bulk in diet. Special foods to watch: a. proteins (quantity) b. vitamin B-6 (avoid or limit) c. laxative
5. Suffer from stress, which aggravates symptoms and creates more problems.	5. Patience and TLC are as essential as the medication.
6. Be rigid or dyskinetic, and also be confused at times.	6. It is vital that medicine be administered at the proper time ALWAYS.
	Additional problems:
	There is a special need for some manner of exercise every day.

(The Parkinsonian Society of Greater Washington)

Source: Vernon and Stern (1988)

England, Canada and Japan. The Carers National Association Crossroads can provide access to mutual support groups. Box 5 replicates a Parkinsonian Patient Profile developed by the Parkinsonian Society of Greater Washington.

Communication issues

Pinder (1990), looking into the issue of doctor-patient communication with regard to Parkinson's disease, suggests that doctors see it as less distressing for patients to have the prospect of disability when they are old than when they are young. As one doctor put it, 'I've never made a diagnosis in someone under seventy. So I haven't seen it as an issue that involved a lot of doctor-patient interaction.' Older people were seen as less questioning patients with a greater respect for doctors. The doctors in the survey did admit that they could be guilty of 'ageism'. Doctors also appeared to have a different approach to their patients according to how they viewed the patients intellectual capabilities. An example of this is the following statement made by a doctor: 'I think she had a rather low IQ and I don't think she asked any questions about the illness. Of course I think its a different kettle of fish if someone's educated...' Another doctor spoke of his general strategy towards all patients saying, 'I don't think I'd ever be terribly enthusiastic about trying to tell Parkinson's patients what the future holds, which is really not very good...' However, a patient who had done some research into Parkinson's said, 'I understand it more so that I can cope with it. Cope with what comes along. You must know about it to cope with it.' But it came as a surprise to Pinder to find patients who preferred not to know about the disease. With some people the uncertainty of not knowing gave them hope. Knowledge was seen as a potential threat. As one patient said, 'I certainly wouldn't like someone to tell me all the things that could go wrong with this Parkinson's because I'd worry myself sick about it ... twelve years have gone by and I'm still mobile ... Live for today and worry about tomorrow tomorrow.' Pinder concluded that the right not to know was as important as the right to know, with even some highly educated, intelligent patients preferring not to know.

Pinder found that mood swings, induced by the medication, led to damaged marriages and relationships. She observed that 'spouses felt trapped in a relationship that resembled less a marriage and more a nurse-patient relationship. As most patients were retired, the loss of social contacts and strained marital relationships were correspondingly harder to bear.' She concluded that it is vital for GPs to have an in-depth understanding of what it is like to have a chronic illness. 'This, I believe, is the key to better communication.' (Pinder, 1990)

Dementia and Parkinson's disease

In the area of mental awareness, to begin with at least, the Parkinson patient has a normal mental state but is slow thinking (bradyphrenia); social isolation and depression may account for pseudodementia. Two factors were thought to be possibly responsible for the high prevalence of dementia among Parkinson's sufferers. Firstly, the introduction of dopaminergic agonists has increased the longevity of Parkinson disease sufferers. With an increased life-expectancy patients could develop senile dementia of an Alzheimer type. However, the dementia incidences are higher than would be expected for the general population; thus, the occurrence of dementia cannot be solely explained by an increase in life-expectancy. Secondly, the dementia experienced could be related to the drug therapy rather than the disease itself. This hypothesis is difficult to evaluate because levodopa is rarely used to treat any other condition.

The signs of Alzheimer's disease are rather frequent in the brains of Parkinsonian patients. This raises the question of whether the patient is suffering from Parkinson's disease with marked dementia or Alzheimers with marked Parkinsonism, or indeed a chance co-occurrence of the two. Korczyn et al (1986) reporting on a study of 137 patients with Parkinson's disease found that patients with dementia were older than the nondemented and Parkinson's disease was diagnosed at a more advanced age. The duration of the disease was slightly longer in the demented. A history of smoking was less common among the demented than the nondemented. Korczyn et al (1986) conclude that, 'it is our belief that dementia is one of the protean manifestations of Parkinson's disease, together with bradykinesia, rigidity, tremor, and loss of postural reflexes.' Table 4 demonstrates the uncertainty that surrounds the prevalence of

Table 4 **Dementia among Parkinson's patients**

Author	*Year published*	*Sample size*	*Location*	*Estimated prevalence per cent*
Pollack and Hornabrook	1966	131	New Zealand	20
Mindham	1970	89	England	35
Celesia and Wanamaker	1972	153	USA	40
Martin et al	1973	100	USA	81
Marttila and Rinne	1976	444	Finland	29
Lieberman et al	1979	520	USA	32
Stroka et al	1981	93	USA	28
Rajput et al	1984	138	USA	31
Lees	1985	48	England	15
Mutch et al	1986	252	Scotland	37

Source: Adapted from Wilcock GK (1987)

dementia in Parkinson's patients.

However, Brown and Marsden (1984) suggest that figures such as in Table 4 may be misleading and a more valid measurement is to ascertain the increased risk of developing dementia because one has Parkinson's disease. They claim that the increased risk, over similarly aged people in the general population, may only be 10-15 per cent.

Conclusion

Overall Parkinson's disease imposes economic costs on the health service and is also responsible for costs to the patient both financially and, possibly more disturbingly, in terms of relationships and social activity. Support groups and various forms of assistance and relief are available to alleviate some of the difficulties associated with Parkinson's disease.

The future

There seems to be general consensus that it is an exciting time to be involved in the battle against Parkinson's disease. Research laboratories are publishing encouraging new facts and discoveries which must be of comfort to patients and their relatives. Expectations are high; however, many feel that some recent assertions are rather too optimistic. Nevertheless, the chance of progress in the treatment of Parkinson's disease, in the near future, appears to be a real possibility. Early detection, preventative measures and even a cure are all prospects that may be accomplished.

For the time being Parkinson's disease remains an incurable ailment, but with careful individual therapeutic manipulation its symptoms can be largely controlled, in many cases, for the best part of a decade after a clinical diagnosis is made. This means that disability does not usually strike until a sufferer has had Parkinson's for several years. The treatment now available to patients gives vast improvements over that of the last decade or two. Levodopa therapy with various adjuvants has meant better control of 'on-off' fluctuations and a smoother response to treatment, thus improving the quality of life for Parkinson's patients. A cure or prevention strategies may be on the horizon; but whilst much is being discovered with regard to Parkinson's disease there is still much about it which remains enigmatic.

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