Classic diseases revisited

Parkinson’s disease

JR Playfer

Summary

Parkinson’s disease is a common disabling disease of old age. The diagnosis of idiopathic Parkinson’s disease is based on clinical signs and has poor sensitivity, with about 25% of patients confidently diagnosed as having the disease actually having other conditions such as multi-system atrophy and other parkinsonism-plus syndromes. Benign essential tremor and arteriosclerotic pseudo-parkinsonism can easily be confused with Parkinson’s disease. The cause of Parkinson’s disease remains unknown. Speculative research highlights the role of oxidative stress and free radical mediated damage to dopaminergic cells. Parkinson’s disease is the one neurodegenerative disorder in which drugs have been demonstrated to be of value. There is now a wide variety of drugs and formulations available, including anticholinergics, amantidine, L-dopa, dopamine agonists including apomorphine, selegiline and soon to be available catechol-O-methyltransferase inhibitors. Disabling side-effects of treatment, fluctuations, dyskinesias and psychiatric problems require strategic use of the drugs available. There is an increasing potential for neurosurgical intervention.

Keywords: Parkinson’s disease, ageing

Cardinal features of parkinsonism

- bradykinesia
- rigidity
- tremor
- postural change

Box 1

In 1817 James Parkinson wrote his Essay on the shaking palsy; it remains in print today. The clinical syndrome of parkinsonism, characterised by slowly progressive bradykinesia, muscular rigidity and tremor, remains recognisable on simple observation and is diagnosed without recourse to the laboratory. The disease predominantly presents late in life. It is chronic and disabling yet, unlike other neurodegenerative diseases, a variety of drug treatments can reduce mortality and disability. More than 170 years after its original description our knowledge of the condition is changing more rapidly than ever.

Diagnosis

Parkinsonism is very common, the cumulative life-time risk of an individual developing the disease is 1 in 40. The cardinal clinical features are listed in box 1 but need some elucidation. The presence of two or more of these features enable the diagnosis of parkinsonism to be made. In patients with idiopathic Parkinson’s disease these features correlate with characteristic pathological changes in the pars compartment of the substantia nigra (box 2). In a recent prospective clinicopathological study by Hughes et al using material from the Parkinson Disease Society Brain Bank, 20% of patients confidently diagnosed by specialists having idiopathic Parkinson’s disease were found to have an alternative pathology at post mortem. It is likely in general clinical practice that only about two-thirds of patients with parkinsonism have true Lewy body idiopathic Parkinson’s disease.

Akinetia is the central disabling feature of parkinsonism causing a complex of symptoms which need to be distinguished from confusing variables. Slowness of movement occurs frequently in many conditions other than Parkinson’s disease and may be caused by extreme age alone. Bradykinesia has to be present for the diagnosis of Parkinson’s disease to be made and should affect the upper half of the body. Poverty of movement, especially affecting the complex facial musculature (facial aminia), difficulty in initiating movement, decremental amplitude of repetitive movements, reduced spontaneous movements, ie, arm swing, and fatigue are all typical of parkinsonism but need to be associated with at least one other major feature to be sure of the diagnosis. The physical signs usually present asymmetrical, becoming symmetrical as the disease progresses.

The increased muscle tone gives rise to pathognomic cogwheel rigidity if tremor is present. Rigidity contributes to the postural changes with a slight excess of axial flexor tone resulting in ‘simian posture’. Postural instability is usually a late feature of the disease. Over two thirds of patients with Parkinson’s disease present with a rest tremor. Classically, it is a pill-rolling tremor of 4–6 Hz seen at rest or while walking and abolished during purposeful activity such as drinking a cup of tea. To confuse matters, tremor can be absent or atypical, sometimes including an intentional element. Spectral analysis of tremor can clarify the diagnosis but is not used routinely.

The differential diagnosis of idiopathic Parkinson’s disease (box 3) can be divided into those cases which fail to meet the strict criteria for the diagnosis of parkinsonism and those which display the features of parkinsonism together with additional features and distinct pathologies. Two very important causes of diagnostic confusion belong to the former category of pseudo-parkinsonism. Benign essential tremor is an extremely common condition in old age. It is a more rapid, coarse tremor which often affects the head (titubation) or legs. The amplitude of the tremor increases towards the end of purposeful movement (hence cups of tea are often spilt). This type of tremor can be exacerbated by L-dopa but sometimes responds with alcohol, beta-blockers or primidone. Slowness of movement and rigidity are absent in this condition. The condition is usually familial and clear autosomal dominant pedigrees can be established in some families. It is unusual that phenotype finds expression so late in life. The second condition, pseudo-arteriosclerotic Parkinson’s disease, was brilliantly described by Critchley in 1929; unusually, he was able to reassess his original
Pathological features of Parkinson's disease

- loss of dopaminergic neurons
- Lewy bodies
- hyaline (colloid) inclusions
- loss of melanin
- loss of dopamine

Box 2

Drug-induced Parkinson's disease

- dopamine depletion (reserpine, tetrabenazine)
- dopamine receptor blockade
- neuroleptics: phenothiazines (chlorpromazine), butyrophenones (haloperidol), thioxanthenes (flupenthixol), substituted benzamides (sulpride)
- miscellaneous: prochlorperazine, metoclopramide, cinnarizine

Box 3

Classification of parkinsonism

Primary (idiopathic)
- Parkinson's disease
- juvenile parkinsonism

Secondary (acquired symptomatic)
- exogenous toxins: drugs, MPTP, manganese, carbon monoxide, 6-hydroxydopa
- post-infective: post-encephalitic
- trauma: pugilistic encephalopathy
- miscellaneous: space-occupying lesions, hydrocephalus
- hereditary: Huntington's disease, Wilson's disease, Hallervorden-Spatz disease, familial parkinsonism, familial basal calcification
- idiopathic: progressive supranuclear palsy, Shy-Drager, Guam complex, cortico-basal degeneration, Alzheimer's disease

Box 4

work over 50 years later in 1981. Before the realisation of the importance of dopamine deletion in the 1960s there had been a widespread belief that Parkinson's disease was due to arteriosclerosis. Critchley had deduced on purely clinical grounds that small infarcts in the basal ganglia could explain the symptomatology of some cases. Magnetic resonance imaging (MRI) has confirmed that lacunal infarcts and white matter changes can occur in cases fitting Critchley's description. Arteriosclerotic pseudo-parkinsonism occurs in elderly hypertensive patients and predominantly affects the lower half of the body. Gait apraxia is common and patients typically demonstrate 'marche a petit pas', postural instability, hesitation, and freezing. Dementia is the rule. This distinctive syndrome usually does not respond to L-dopa which, if tried, often exacerbates pre-existing neuropsychological problems.

Drugs may interfere with the action of dopamine in the brain either by causing depletion or blockage of the dopamine receptor (box 3). The importance of drug-induced parkinsonism is often underestimated. Dopamine-blocking drugs are widely used; drugs such as metelit and maxolon are often given for inappropriately long periods in the elderly. The parkinsonian features only reverse in about 50% of patients when the offending drug is withdrawn and reversal of effects can take many months in those who recover. Williamson speculated that patients who were pre-symptomatic with the pathology of idiopathic Parkinson's disease were more likely to develop this side-effect.

Knowledge of the 'Parkinson plus' and multisystem atrophy syndromes has expanded remarkably over the last few years. The distinction from idiopathic Parkinson's disease is important as it has implications for both treatment and prognosis. The pathology of multiple system atrophy is less specific and discrete than Parkinson's disease with cell loss and gliosis in structures additional to the basal ganglia. Variable distribution of pathology gives rise to differing clinical pictures – striato nigral degeneration giving predominantly Parkinsonian signs, Shy – Drager where autonomic abnormalities such as postural hypotension are prominent and olivopontine cerebellar atrophy where cerebellar signs predominate. Lewy bodies are absent but a cytological marker (oligodendrogirical cytoplasmic inclusion) has been described. The prognosis is poor, with respiratory, speech and swallowing complications being common. Dementia is rare. There is usually a poor or absent response to L-dopa.

Steele – Richardson – Olszewski disease results in the syndrome of progressive supranuclear palsy. These patients have cell loss and neurofibrillary tangles in the globus pallidus and subthalamic and dentate nuclei. Disability is high and these patients are often first recognised when in long-term care. Life expectancy is much reduced and response to L-dopa is usually poor. Patients can present with falls, they have marked axial rigidity, frontal lobe symptoms, speech disorders and the characteristic impairment of downward gaze which gives rise to an odd staring appearance.

Some of the new causes of Parkinsonism are given in box 4. They are more important for the clues they give to the aetiology of Parkinson’s disease than for their frequency in clinical practice.

Aetiology

The cause of Parkinson's disease is still unknown. The last few years has seen increasing speculation about possible mechanisms which bring about the loss of over 70% of the dopaminergic neurons in the substantia nigra leading to the loss of over 80% of striatal dopamine, the threshold for developing symptoms of Parkinson's disease. The incidence of Parkinson’s disease increases with advancing age but it is not due to ageing alone. Although it is normal to lose dopaminergic cells with increasing age, the rate of loss of cells would not give rise to parkinsonian symptoms until well after any normal expectation of life. The anatomical distribution of cells lost by ageing is different from that in Parkinson’s disease. Modern techniques such as positron emission tomography (PET) has shown that striatal dopamine does not significantly decrease as a consequence of normal ageing.

A consensus is emerging that Parkinson’s disease is probably due to environmental factors which are selectively toxic to the neuromelanin-containing cells in the pars compacta of the substantia nigra which produce dopamine. The impetus for such a view arises from two lines of research first developed in the 1980s. It has long been known that neuromelanin-containing cells can be sensitive to a variety of toxins, such as carbon monoxide, manganese, or 6-hydroxydopamine. Langston and his colleagues showed that methylphenyl-tetrahydropyridine (MPTP) a relatively simple organic molecule accidentally synthesised as a pethidine analogue for use as a drug of abuse, produced
selective destruction of dopaminergic cells. Drug abusers developed symptoms indistinguishable from Parkinson's disease after exposure to small amounts of this substance. The condition responded initially to anti-parkinsonian medication and higher primes exposed to the drug developed a close animal model of Parkinson's disease. It was discovered that MPTP was metabolised by an oxidation step catalysed by the enzyme monoamine-oxidase type B to give rise to the free radical MPP+. This is generated in glial cells but is then taken up by the dopamine uptake mechanism of neuromelanin-containing neurons. The biochemical damage induced is very specific to the mitochondrial respiratory enzymes, causing a reduction in activity of NADH-dependent mitochondrial complex 1. This abnormality has been found to mimic closely mitochondrial abnormalities in idiopathic Parkinson's disease which suggests that factors inducing pathological changes found in idiopathic Parkinson's disease have a similar mechanism to the MPTP model.

At the same time as the elucidation of MPTP, great interest was being shown in genetic factors in the development of Parkinson's disease. It had long been felt that genetic factors were important, as 10% of affected patients have a first degree relative with Parkinson's disease. Nevertheless, in the early 1980s, a series of twin studies, most notably by Ward and colleagues, showed that the concordance rate for developing Parkinson's disease between monozygotic and dizygotic twins showed no significant difference and, in fact, from these studies the calculated heritability was one of the lowest known for any disease. Recently one of the co-authors of this study, Duvoisin, has revisited the data and has suggested that variability of the time of expression of parkinsonism could be a factor leading to the underestimate of the genetic component of the disease. He has once again put forward the theory that autosomal dominant inheritance of a specific penetrance is a tenable model. This theory receives some support from kindred studies in Italy. There is presently intense interest in mitochondrial inheritance. Mitochondrial DNA is inherited entirely from the mother. The theory that a specific mitochondrial genetic defect may render patients more susceptible to toxic damage to mitochondria is being actively pursued experimentally but as yet results are conflicting.

Cahn and colleagues have suggested that idiopathic Parkinson's disease, as well as other degenerative diseases that arise in old age, ie, Alzheimer's disease and motor neuron disease, could arise from an environmental insult to the nervous system which remains subclinical for several decades and becomes expressed clinically as a consequence of age-related loss of neurons.

The MPTP model of Parkinson's disease suggests that its pathogenesis could be mediated by free radical damage to neurons. There is increasing circumstantial evidence that this is the case. Dopaminergic neurons could be particularly liable to oxidative stress because dopamine itself can undergo either enzymatic or auto-oxidation to give rise to hydroxyl radical formation. Under normal physiological conditions protective mechanisms involving glutathione and superoxide dismutase can protect the cell. In Parkinson's disease, with the decreasing number of functional cells, there is an increase in dopamine turnover in the surviving cells and hence an increased possibility of the protective mechanisms being overwhelmed. A number of recent observations strongly support the mechanism of oxidative stress (box 5).

It seems likely that Parkinson's disease results from a combination of aetiological factors. Unknown exogenous or endogenous toxic factors trigger free radical mediated damage to cells containing a susceptible genotype. Present research gives tantalising clues to the types of toxin that may be responsible but we do not yet have sufficient knowledge to eliminate risk factors and reduce the incidence of the disease.

Management

Parkinson's disease is a complex disorder. The range of disabilities caused by dopamine deletion require a multidisciplinary approach. Accurate assessment of the patients' problems and planning future management can all too easily be replaced by merely proffering the latest drug therapy.

The differing levels of intervention are illustrated in figure 1. Prevention remains a hope based on increased understanding of pathogenic processes. Reduction of handicap is the bottom line that can be achieved by multiple intervention, emphatically including physiotherapy, occupational therapy, speech therapy, social work and clinical psychology. Accurate assessment of patients with Parkinson's disease is essential in order to monitor the effectiveness of clinical interventions. There is no one accepted instrument for measuring disability in Parkinson's disease although the Hoehn and Yahr

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**Mechanisms of oxidative stress**

- impaired defence mechanisms to free radicals in substantia nigra: reduced glutathione, increased iron, decreased ferritin and superoxide dismutase
- evidence of free radical damage: lipid peroxidation, reduction of NADH-dependent mitochondrial complex 1 activity
- increased dopamine turnover

**Box 5**
scales and United Parkinson Disease Rating Scales (UPDRS) are most frequently used in clinical trials (boxes 6 and 7). Assessments are difficult because of the diversity of symptoms and signs with which patients present and the rapid variations that can occur over short periods of time. It has recently been suggested that physiotherapy slows progression of the disease. Benefits of speech and occupational therapies are clearly demonstrated by good scientific studies. This article will concentrate on the medically led interventions of drug treatment and, to a lesser extent, surgery.

There is great inter-individual variation in Parkinson’s disease; some of these differences are due to the age at onset of the disease. Patients developing the disease at less than 55 years are unlikely to have cognitive impairment. For those developing it later on this is a common finding. The response to drugs can be good in both groups, early-onset patients have a greater tendency to develop fluctuations of response and abnormal involuntary movements. These symptoms develop early in the course of the disease and although they may arise in late-onset patients, they are usually attenuated. Standardised mortality ratios in Parkinson’s disease show that there is only a slight reduction in life expectancy, although this is greater for younger onset patients. Anticholinergic drugs and complex drugs regimes are less well tolerated in older patients.

Parkinson’s original description said that ‘the senses and intellect are uninjured’ in Parkinson’s disease: with an increasing elderly population this is now seen to be far from true although there is great variability in the many experimental studies that have looked at this problem. It is likely that parkinsonian patients have between 15 and 20% increased risk of developing dementia. Even in patients without dementia, specific changes in cognitive function have been described in a large number of studies.

It has been suggested that there is slowing of thought bradyphrenia, analogous to the slowness of movement, and that patients with Parkinson’s disease demonstrate a reduced attention span/alertness, some slowing of the central processing of information and difficulty in switching sets. In addition to cognitive changes, psychiatric disease becomes more common in parkinsonian patients and depression is common. Toxic confusional psychoses resulting from drug treatment are characterised by visual hallucinations. Most drugs used to control these symptoms also worsen the motor side-effects as neuroleptic drugs block dopamine receptors. The use of atypical neuroleptics such as sulpiride and risperidone can be helpful.

**DRUG THERAPY**

Drug therapy is directed at correcting the deficiency of striatal dopamine. Dopamine does not cross the blood–brain barrier but striatal dopamine can be increased by the administration of its metabolic precursor, L-dopa which can both be absorbed from the gut and transferred across the blood–brain barrier by means of the large neutral amino acid transport mechanism. L-Dopa needs to be combined with a decarboxylase inhibitor, either benserazide (Madopar) or carbidopa (Sinemet), to prevent severe peripheral side-effects including nausea and vomiting and postural hypertension. L-Dopa combined with a decarboxylase inhibitor is by far the most effective symptomatic treatment for Parkinson’s disease. It is particularly effective in reducing the akinesia and rigidity but unfortunately is much less effective in the complex disabilities which arise either in long-standing disease or late-onset disease, problems such as balance, falling, cognitive impairment, speech and gait abnormalities. Because of the great inter-individual variation, all therapy has to be individualised to patients’ needs and the physician has to balance the benefits of reducing disability and handicap against the need to minimise long-term side-effects of drug treatment, in particular, the on/off phenomena, wearing off, and dyskinesias. It is estimated that 50% of patients will experience such side-effects within the first five years of starting L-dopa. Increasing age is associated with a significantly increased risk of developing impaired cognitive function, toxic psychosis, and postural hypotension may be exacerbated by treatment; lower doses are required with increasingly elderly patients (box 8).

There is now a wide range of dosage and formulations available for L-dopa. L-Dopa is never used without a decarboxylase inhibitor. Controlled studies have shown no difference between the efficacy of Madopar and Sinemet. The doses of the commonly used anti-parkinsonian drugs are summarised in the table. The regimes used in the individual patient vary widely and attempts to construct simple algorithms are bound to end in failure. Nevertheless, several principles do govern the strategy of use. Drugs are increasingly only introduced when patients have significant symptoms. In younger patients (<60 years) there is initial increasing use if the dopamine agonist pergolide is introduced before L-
Parkinson's disease

Box 7

Hoehn and Yahr scale

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>unilateral disease only</td>
</tr>
<tr>
<td>II</td>
<td>bilateral mild disease</td>
</tr>
<tr>
<td>III</td>
<td>bilateral disease with early impairment of postural stability</td>
</tr>
<tr>
<td>IV</td>
<td>severe disease requiring considerable assistance</td>
</tr>
<tr>
<td>V</td>
<td>confinement to bed or wheelchair unless aided</td>
</tr>
</tbody>
</table>

Box 8

Important factors in the management of elderly patients with parkinsonism

- age
- duration of the disease
- underlying pathology
- length of treatment with L-dopa
- treatment with other anti-parkinsonian agents
- other illnesses
- other medication
- intellectual impairment
- inter-individual variation

Box 9

Classification of drugs used in Parkinson's disease

- MAOB inhibitors: selegiline
- L-dopa: combined with extra cerebral decarboxylase inhibitors such as Madopar, Sinemet
- dopamine agonists: oral (bromocriptine); ergolines (lisuride, pergolide); subcutaneous apomorphine
- antimuscarinics: benzhexol, orphenadrine
- COMT inhibitors: tolcapone, entacapone
- miscellaneous: amantidine

Table: Doses of commonly used L-dopa preparations. The maximum dose is 600–800 mg L-dopa/day

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Initial</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-careldopa (L-dopa/carbidopa)</td>
<td>50/12.5*</td>
<td>1 dose bid or tid (older patients)</td>
<td>–</td>
</tr>
<tr>
<td>Sinemet LS</td>
<td>100/25*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sinemet CR 100</td>
<td>100/10</td>
<td>1 qid</td>
<td>–</td>
</tr>
<tr>
<td>Sinemet CR 125</td>
<td>100/25</td>
<td>1 dose tid (younger patients)</td>
<td>–</td>
</tr>
<tr>
<td>Sinemet CR 250</td>
<td>200/50*</td>
<td>1 tid</td>
<td>–</td>
</tr>
<tr>
<td>Sinemet 275</td>
<td>250/25</td>
<td>–</td>
<td>1 tid</td>
</tr>
<tr>
<td>Co-beneldopa (L-dopa/benserazide)</td>
<td>12.5/50</td>
<td>1 dose bid or tid (old)</td>
<td>–</td>
</tr>
<tr>
<td>Madopar 62.5</td>
<td>12.5/50</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Madopar 125</td>
<td>25/100*</td>
<td>1 dose tid (young)</td>
<td>–</td>
</tr>
<tr>
<td>Madopar CR</td>
<td>25/100*</td>
<td>1 tid</td>
<td>–</td>
</tr>
<tr>
<td>Madopar 250</td>
<td>50/200</td>
<td>1 tid</td>
<td>–</td>
</tr>
</tbody>
</table>

*Lower bioavailability of L-dopa approximately 70% of standard form

dopa. In older patients either Sinemet or Madopar are used early but in low doses with slow upward titration of dosage.

Controlled-release formulations of L-dopa help overcome some of the difficulties arising from its short half-life which may be responsible for some of the 'wearing off' and dystonic and dyskinetic effects. There is an increasing trend to use these controlled-release formulations early in the disease.27

There is also no clear consensus on the best strategy for combining L-dopa with the other classes of anti-parkinsonian agents available (box 9). Because L-dopa is effective at symptomatic relief there is a strong temptation to start the drug at diagnosis. Nevertheless, arguments have been put forward for delaying its use on the theoretical grounds that it might accelerate nigral cell death by increasing oxidative stress. The uses of high doses of L-dopa early in the disease is associated with accelerated development of receptor super-sensitivity and the early emergence of phenomena such as dyskinesia and on/off episodes. There is evidence that the introduction of the drug selegiline, a selective monoamine oxidase type B inhibitor can effectively delay the need to introduce L-dopa and may have neuroprotective effects in Parkinson's disease. The age of onset in patients is important in this decision; patients developing the disease over the age of 70 years are much less likely to develop fluctuations and abnormal involuntary movements so can be safely started on L-dopa early.

The arguments against starting L-dopa early in younger patients are theoretical and have not been strongly supported by clinical studies so far. Markham's study in the US showed no difference in the emergence of late complications between groups of patients started on early or late L-dopa therapy.28 Nevertheless, there is some caution in introducing L-dopa in younger patients when the symptoms are mild. Many patients benefit from the introduction of selegiline (L-deprenyl). Selegiline was shown in the Datatop study to delay the need for introduction of L-dopa therapy by an average of nine months.29 Although claims have been made for it being a neuroprotective agent, the drug does give mild symptomatic benefit to most patients (which makes it difficult to sustain the neuroprotective claim). It conserves dopamine by slowing down its breakdown. It is metabolised to metamphetamine which gives rise to beneficial stimulant and antidepressant effects, although this can also cause insomnia. When used as an adjunct to L-dopa, selegiline helps smooth out the early wearing-off effects but it can increase the dopaminergic stimulus, making dyskinesia and psychiatric side-effects more likely.

The value of selegiline in the treatment of Parkinson’s disease is currently subjected to a major reappraisal as a result of the interim findings of a prospective study comparing the effectiveness of L-dopa with L-dopa plus selegiline conducted by the Parkinson Disease Research Group in the UK. Following patients for five or six years after initial treatment, the group found a 60% increase in mortality in the combined treatment groups. They also found that the combined therapy appeared to have little therapeutic benefit. Such findings are bound to bring into question the value of selegiline, although further study is required to explain the findings.30

Claims have been made that, if dopamine agonists are introduced at an early stage, this reduces the risk of fluctuations later; this claim remains controversial. The use of de novo treatment with dopamine agonists alone is rarely sustained and most patients require the introduction of L-dopa within the first two years of treatment. Dopamine agonists are more likely to cause neuropsychiatric symptoms and therefore have to be used with more caution in older patients.
The Parkinson's Disease Research Group recently compared strategies of early treatment in an interim report. This showed little benefit from combined treatments and confirmed that in two-thirds of patients started on dopamine agonists alone the drug had to be withdrawn. Those remaining on dopamine agonists did, however, do well. Longer term follow-up of these patients is eagerly awaited.

Two other groups of drugs may be used in the early stage of the disease. Anticholinergic drugs such as benzzhexol and orphenadrine have mild antiparkinsonian effects said to be more effective on tremor than akinnesia and rigidity, while anticholinergic drugs are best avoided where they are old, as neuropsychiatric side-effects are common; around 70% of patients taking the drugs develop side-effects. Anticholinergics lower the threshold for development of visual hallucinations and dyskinetic movements; in addition, the anticholinergic effects can affect vision, give rise to difficulty in swallowing due to dry mouth, and precipitate the retention of urine in men with prostatic enlargement. These drugs should now be consigned to history in all but the mildly symptomatic young Parkinson patient in whom they may be useful in the very early stages. Amantadine was originally developed as an antiviral agent and its mild-parkinsonian effects were discovered by accident. Its actions are complex but they include the facilitation of the release of stored dopamine. It therefore can be useful as a temporary boost to anti-parkinsonian therapy given in a dose of 100 mg bid. The anti-parkinsonian effect soon wears off in chronic use and there is a high risk of side-effects such as vivido reticularis, persistent ankle oedema and neuropsychiatric effects. The drug can be usefully used where a patient has to meet unusual demands, for instance, an old patient attending her granddaughter's wedding where a temporary boost to medication can be of some benefit.

It is too early to say whether controlled release formulations started early in the disease, delay or reduce the effects of complications such as dyskinesia and fluctuations. The trial work at present being undertaken should resolve this problem. There are strong pharmacological arguments that continuous rather than intermittent dopamine receptor stimulation may be of benefit.

### MANAGEMENT OF LATER DISEASE

Although L-dopa is the best available treatment for Parkinson's disease, many problems are encountered in long-term usage (box 10). The appearance of fluctuations in motor function and sudden deteriorations during off periods affect all aspects of a patient's life, causing problems in speech, swallowing, respiration, and anxiety. Dyskinesias are highly variable, initially presenting at peak dose, with progression they become biphasic, occurring at the beginning and end of each dose period. Finally they become capricious and unpredictable, occupying long periods of the patient's day, while fixed, painful, dystonia can occur in the off periods. The pharmacokinetics of L-dopa are highly complex and individual problems cannot always be related to plasma levels of the drug. Pharmacodynamic variations cause the effects of L-dopa to be unpredictable. Because of these difficulties there is increasing interest in the use of dopamine agonists.

Three oral agonists are currently available in the UK, bromocriptine, lysuride and pergolide. In addition, apomorphine is available for parenteral use. Dopamine agonists are largely used as adjunct therapy with L-dopa. In the later stages of the disease they may partially substitute for L-dopa, allowing for the dose of L-dopa to be reduced, hopefully with the benefit of reducing side-effects such as abnormal involuntary movements or fluctuations. Agonists are contraindicated in patients with cognitive impairment or with severe postural hypotension. At the start of therapy domperidone 20 mg tid may be used to block the peripheral effects such as nausea and vomiting. It is essential that dopamine agonists are introduced by slow titration and in elderly patients often only very low doses are tolerated.

There is likely to be better appreciation of dopamine agonists as our understanding of dopamine receptors increases with the application of the techniques of molecular biology. In the early 1980s dopamine receptors were classified into types D1 and D2 on the basis of their pharmacological and biochemical categorisation, the D1 receptor being linked to adenylcyclase and the D2 receptors not. The D1 receptors were inhibited by a benzazepine, the D2 receptors were blocked by drugs such as spiperone. More receptors are now recognised by their ability to clone the genes responsible for the receptor proteins. Subsequent sequencing of the DNA has enabled the amino acid sequence of different receptors to be derived. The application of these techniques led to reclassification of dopamine receptors, although it is true to say that two families still exist, D1-like and D2-like.
structures for the receptors have been constructed which have common features, in particular the amino acid sequence for all receptors shows seven stretches of hydrophobic amino acids and these are likely to form membrane-spanning alpha helices (figure 2). The extra membranous loops form specific sites for binding dopamine agonists and antagonists, causing structural deformation of the protein which allows it to couple with GTP-binding proteins, leading to effector mechanisms with a second messenger. The nomenclature regarding dopamine receptors is constantly changing, the first five proteins to be characterised have been numbered D1 to D5 in order of their discovery. D1 and D5 are D1-type receptors while the others are D2 type receptors. The distribution of the specific receptors varies in different parts of the brain; D1 and D2 receptors are highly represented in the caudate and putamen but other receptors are better represented in the limbic and cortical regions. This raises the possibility of designing drugs for specific receptors to give selective effects and also will enable us to understand the action of present drugs in more detail (figure 3).35

Apomorphine is a D1 and D2 dopamine receptor agonist, with anti-parkinsonian properties equivalent to those of L-dopa. It causes severe vomiting when used on its own and this limited its therapeutic potential until the advent of the peripheral dopamine receptor antagonist drug domperidone. Over the last few years apomorphine has proved to be a major advance in the treatment of refractory on/off oscillations in Parkinson’s disease. It has been found that when patients are in the off-period the dopamine receptors remain responsive to apomorphine. The drug is administered either by Penject36 subcutaneous injection or by continuous intravenous drip infusion with other dopamine agonists which are derived from ergot derivatives, apomorphine gives fewer psychiatric side-effects when given by single subcutaneous injection. The drug begins to relieve symptoms within five or 10 minutes; it is therefore an ideal drug to be used to rescue people from off-periods. The establishment of the use of apomorphine requires considerable expertise and the support of a specialised Parkinson nurse. Side-effects include skin reactions, infection, drowsiness and yawning.36

**Future Developments in Drug Therapy**

It is likely that further dopamine agonists will be developed which, either by improved delivery systems or more specific targeting of sub-types of dopamine receptors, will have improved side-effect profiles. Ropinirole, pramipexole and carbidopamine are agonists in the later stages of development. Ropinirole is a non-ergoline agonist and may have less psychotoxicity than current agonists.37

Catechol-O-methyltransferase (COMT) inhibitors add an entirely new class of anti-parkinsonian drug. Used as an adjunct to L-dopa they prevent its O-methylation, which is an important synthetic pathway reducing the amount of dopamine reaching the brain. Two such drugs are soon to be available: tolcapone, which acts both peripherally and centrally, and entacapone, which acts peripherally. These drugs should modify the pharmacokinetics of L-dopa to enable a more prolonged and smoother response.36,39 Further drugs in development include reversible monoamine oxidase type B inhibitors and N-methyl-D-aspartate antagonists, of which full assessment is awaited.

**Surgery in Parkinson’s Disease**

Before the introduction of L-dopa in 1969, stereotactic surgery offered one of the few really effective treatments of Parkinson’s disease. With the realisation of the long-term limitations of L-dopa therapy, there is a resurgence of interest in surgical management. Techniques developed in animal experiments to study how the central nervous system regenerates have led to the development of neural transplantation as a treatment of Parkinson’s disease. Bjorklund and his colleagues showed that foetal ventral mesencephalon can survive implantation to a denervated striatum in rodent models. In 1982, two patients with Parkinson’s disease received autographs of adrenal medulla placed in the head of the right caudate nucleus with claims that this relieved parkinsonian symptoms. In the longer term, this was found not to be effective. A Swedish group based in Lund have continued with experiments using tissue dissected from the mesencephalon of human foetuses derived from therapeutic abortions between six and seven weeks. The material is implanted using stereotactic techniques. Their meticulous scientific work has shown that some grafts survive and produce dopamine and the technique does hold out the possibility of long-term improvement. Nevertheless much basic scientific work has to be done before this can be considered anything other than a highly experimental technique.40
There is renewed interest in stereotactic surgery in the management of Parkinson’s disease. Prior to the introduction of L-dopa, unilateral thalamotomy was the most effective method of controlling contralateral tremor and rigidity. The technique has a small but acceptable risk of hemiparesis. Bilateral thalamotomy carried increased risks including speech and swallowing disorders. The main disadvantage of this technique is the lack of benefit with regard to akinesia, speech and gait. Swedish studies pioneered the technique of posteroventral pallidotomy and several studies have now established this technique as more generally beneficial. The improvement of techniques such as computed tomography and magnetic resonance imaging (MRI) allows precise placement of high-frequency stimulating electrodes in the ventral intermediolateral nucleus. Stimulation of this area suppresses abnormal movements including drug-induced dyskinesia. The technique is safer than destructive lesions and can be used bilaterally and is being assessed by many centres around the world.41

The rapid advances in neuro-imaging using techniques such as PET, single photon emission CT (SPECT) and MRI have not only increased diagnostic precision but allowed more accurate assessment of the effects of surgical and pharmacological intervention in Parkinson’s disease.

Conclusion

Parkinson’s disease is probably the best understood of the neurodegenerative diseases and certainly the one in which we have most therapeutic options. Advances in our knowledge over the last few years have been spectacular and hold out the promise of further innovation in our management of this condition.

I gratefully acknowledge the permission of Professor PG Strange for the reproduction of figures 1 and 2.

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J. R. Playfer

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