

NEUROLOGICAL MANAGEMENT

Parkinson's disease

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Parkinsonism is a clinical syndrome dominated by a disorder of movement consisting of tremor, rigidity, elements of bradykinesia (slowness of movement), hypokinesia (reduced movement) and akinesia (loss of movement), and postural abnormalities. Parkinson's disease consists of the clinical syndrome of parkinsonism associated with a distinctive pathology consisting of degeneration of pigmented brain stem nuclei, including the dopaminergic substantia nigra pars compacta, with the presence of Lewy bodies in remaining nerve cells.

Parkinson's disease is a common and disabling illness affecting some 1 in 1000 of the population. Symptoms usually appear after the age of 50 years, but the young are not exempt. Prevalence in those over the age of 50 rises exponentially. A community-based survey in Aberdeen¹ revealed age-specific prevalence rates per 100 000 of the population of 47 between the ages of 40-49 years, 78 between 50-59, 254 between 60-69, and 832 between 70-79. Men and women are affected, and the disease occurs worldwide, although perhaps less frequently in China and Africa than in Western countries.

The Office of Health Economics² calculated that there were probably between 60 000-80 000 people suffering from Parkinson's disease in the United Kingdom. Harris³ estimated that there were 22 000 people disabled by Parkinson's disease living in the community, 22% of which were severely handicapped, 48.3% were appreciably handicapped, and 29.7% of which had a minor handicap. The Office of Health Economics² estimated that there were 15 000 patients with Parkinson's disease in hospital or residential care, 22 000 handicapped in the community and more than 30 000 in the community but not handicapped.

The Association of British Neurologists⁴ estimated that within a population of 250 000 people there would be 400 patients with Parkinson's disease, of whom 342 would have significant disability (see Wade and Langton-Hewer, 1987).⁵

The cause of Parkinson's disease is unknown. There may be a genetic predisposition rendering individuals more vulnerable to toxic substances. Some surveys have hinted that exposure to a rural environment including well water or pesticides may be of signifi-

cance, but no common environmental toxin has been identified.

The practical management of Parkinson's disease follows a series of steps in the individual's life history of their illness. For the purpose of this review, I will follow the patient from the time of their initial symptoms, through diagnosis and early management, into the complications of long term treatment and the problems of increasing disability.

Early symptoms

The characteristic tremor of Parkinson's disease affects about 70% of patients. Many present with much vaguer symptoms. Sensations of numbness or pain without demonstrable sensory loss often are described. Muscles may be referred to as painful and tender and limbs may be said to be weak or stiff. Difficulty with handwriting, or inability to undertake repetitive sequential tasks such as cleaning the teeth, winding a watch, doing up buttons or manipulating spoons may be the sole complaint for many months. Fatigue is a common complaint, as is depression and a vague sensation that the patient has slowed down and life has become weary. Unexplained weight loss may be prominent.

Against this background, a number of alternative diagnoses are often entertained to begin with. Everything may be attributed to a depressive illness. Aches and pains may be interpreted as due to rheumatism. Fatigue and weight loss may suggest a more sinister cause. The initial tendency for the symptoms to begin on one side of the body may be misinterpreted as a hemiparesis.

Diagnosis

Eventually, the characteristic features of parkinsonism are recognised, and the question then becomes whether this is due to Parkinson's disease or some other condition. The diagnosis is clinical for there is no test specific for Parkinson's disease. Even the most experienced neurologist may have difficulty in making the diagnosis at this stage of the illness.

In two recent series of patients diagnosed as having Parkinson's disease in life who came to autopsy,^{6,7} the pathological diagnosis was of some other condition in approximately

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a quarter of cases. The commonest alternative diagnoses were Steele-Richardson-Olszewski disease (progressive supranuclear palsy) and multiple system atrophy (Shy-Drager syndrome with autonomic failure, striatonigral degeneration, and olivopontocerebellar degeneration in various combinations). In the early stages of these conditions the eye movement disorder characteristic of progressive supranuclear palsy may not be apparent, and the symptoms and signs of autonomic failure and cerebellar deficit typical of multiple system atrophy may not be evident. PET imaging using ^{18}F -dopa and other ligands can discriminate typical Parkinson's disease from other parkinsonian syndromes in about 80% of cases, but is not specific or widely available.⁸

Hughes *et al.*,⁷ on the basis of the autopsy findings in 100 cases diagnosed as having Parkinson's disease in life, recommended the following clinical criteria to improve the success rate for diagnosing Parkinson's disease. There needs to be bradykinesia plus one of the following: a classic rest tremor, unilateral onset, progressive persistent asymmetry, an excellent response to levodopa (>70%), levodopa induced dyskinesias, and continued response to levodopa for at least five years. Parkinson's disease would be excluded if there were no response to levodopa, more than one affected relative, early dementia, early postural imbalance and falls, early autonomic findings, a significant abnormality of eye movement, and cerebellar or pyramidal signs.

A further series of 100 cases of pathologically proven Parkinson's disease⁹ found that tremor was present at the onset in 69%, and in the course of the disease in 75% of cases. Only 77% of patients had a "good" or "excellent" initial levodopa response. Accordingly, failure to respond to an apomorphine or levodopa challenge test (using single injections of apomorphine or a single dose of Sinemet or Madopar) does not exclude the diagnosis of Parkinson's disease; nor does it completely exclude a subsequent positive response to longer term oral levodopa therapy. Conversely, some patients with Steele-Richardson-Olszewski disease or multiple system atrophy may show a response to levodopa initially.

Initial treatment

Having made the diagnosis of Parkinson's disease, important decisions have to be made about subsequent management. These depend upon an open and frank discussion of prognosis, options for treatment and management, and the personal philosophy of the patient and their carer. These initial discussions will set the framework for a lifetime of living with Parkinson's disease.

Many patients seek as much information as they can find about their illness. The Parkinson's Disease Society provides a large range of excellent educational information. Patients need to know that Parkinson's dis-

ease cannot be cured, but that it can be effectively relieved by symptomatic treatment. Life expectancy is now near to normal, and the main issue is the maintenance of the best quality of life. Patients will also be reassured to know that there is only a small risk of passing the illness to their children. They need advice on diet, the need for exercise and sensible home exercise programmes,¹⁰ and they will seek reassurance on the effect of lifestyle on their illness and their illness on lifestyle. Moderate alcohol intake does not affect Parkinson's disease adversely, and there are no major bars to recreational activities. Discussion of the effect of the illness on sexual activity may be reassuring and specific problems associated with hygiene, childbirth, and hormone replacement therapy require discussion with women patients. The issue of driving should be raised and appropriate assessment undertaken. Most patients will not have major problems with speech, hand function, and walking at this stage, but those who do will benefit from contact with speech therapists, physiotherapists, and occupational therapists. Contact with Social Services may be required to sort out problems of housing, adaptation of the home, and financial difficulties.

As far as drug treatment is concerned, it should be pointed out that there are two categories of drug treatment to be considered: (a) treatment designed to slow the rate of progression of the disease (neuroprotection); and (b) symptomatic treatment.

NEUROPROTECTION

Nothing is known to halt Parkinson's disease, but in recent years there have been suggestions that the administration of selegiline (Deprenyl), an irreversible monoamine oxidase B inhibitor, may have an effect on the natural history of the illness. The rationale for the use of selegiline in early Parkinson's disease was that inhibition of monoamine oxidase B might prevent damage caused by dopamine metabolism resulting in oxidative stress, and also that selegiline had been found to prevent the capacity for 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to cause experimental parkinsonism in subhuman primates. These concepts lay behind the major DATATOP study in North America which investigated the effects of selegiline and vitamin E treatment in de novo patients with Parkinson's disease.^{11 12}

The major result of this study was that early selegiline treatment delayed the need for levodopa significantly (but vitamin E had no effect, either alone or in combination with selegiline). Selegiline itself was found to have a modest symptomatic antiparkinsonian action, so it proved impossible to decide definitely whether its effect in delaying the need for levodopa treatment was due to this symptomatic action or whether there was an additional true neuroprotective action.

Whether one should use selegiline at the time of diagnosis or not depends upon one's philosophy of levodopa treatment for

Parkinson's disease. Levodopa and other antiparkinsonian drugs offer only symptomatic relief, so it is crucial here to distinguish between the *impairments* typical of Parkinson's disease (tremor, rigidity, akinesia, and postural deficits), the *disabilities* they cause and the *handicaps* that result. Levodopa and other symptomatic antiparkinsonian drugs are employed to relieve disability and handicap.

If the strategy in an individual is to delay levodopa treatment for as long as possible (see below), then the early administration of selegiline at the time of diagnosis is a rational policy.

SYMPTOMATIC TREATMENT

There has been controversy over which drugs to use and when to use them! Much of this debate has turned on the issue of whether levodopa should be given early or late in Parkinson's disease. In fact, although the published work on this topic may seem polarised, in practice there is much less discord.

Levodopa is the most reliable and effective symptomatic treatment for Parkinson's disease. Most patients with true idiopathic Lewy body Parkinson's disease will respond to levodopa treatment. Indeed, failure to respond suggests (but does not prove) an alternative diagnosis.⁷ In contrast, directly acting dopamine agonists such as bromocriptine and pergolide only benefit about a third to a half of patients when given alone.¹³ The problem with levodopa is that a large portion of patients will develop complications of treatment after some years.¹⁴ These complications represent a complex interaction between the long term effects of the drug and the progression of the disease itself. Fluctuations and dyskinesias are a major problem in those with disease of younger onset, while the emergence of cognitive and psychiatric problems along with imbalance and speech difficulty tend to occur in the more elderly patient. The objective of symptomatic drug treatment in Parkinson's disease is to keep the patient functioning independently for as long as possible. Life expectancy in Parkinson's disease is now near to normal.¹⁵⁻¹⁷

Taking all these facts together, the critical issue in the management of Parkinson's disease becomes the need to individualise treatment. Decisions will be based upon firstly, the patient's age. The younger patient with Parkinson's disease, facing a long life with the illness, may opt to delay levodopa treatment until it is absolutely necessary. The elderly patient, with a limited life span, may opt for early levodopa treatment to get its benefits as soon as possible. Secondly, the patient's disability and handicap must be considered. In the early stages of Parkinson's disease, although impairment is evident, there may be little disability or handicap. At this stage, symptomatic treatment may not be required at all. Thirdly, the patient's expectations in the light of their social and occupational demands will affect decisions. An elderly,

retired individual may tolerate a level of impairment that would be insufferable to a young, active patient.

All these factors have to be taken into account in a final decision as to the use of symptomatic drug treatment at various stages of Parkinson's disease. The patient requires counselling on the options available, and the short and long term outlook faced. In the end analysis, patients will decide on the basis of their own individual philosophy, responsibilities and requirements.

Symptomatic treatment when disability and handicap occur

There comes a time when Parkinson's disease progresses to the point that symptomatic treatment needs to be initiated. The most common problems that patients and clinicians consider important for the decision to begin symptomatic agents are threat to employment; threat to ability to handle domestic, financial, or social affairs; threat to the ability to handle activities of daily living; and worsening gait and balance.

At this stage, disability and handicaps still may be mild and some might opt to use an anticholinergic drug or amantadine to provide initial symptomatic relief. Both drugs can improve function by about 20%, which is much less than the benefit obtained with levodopa or a dopamine agonist. This may be sufficient, however, to maintain independence initially. Anticholinergics and amantadine tend to produce unacceptable adverse effects, particularly in the elderly, where they may contribute to forgetfulness, memory difficulties, hallucinations, and even psychoses. Nevertheless, anticholinergics and amantadine may give valuable relief early in the illness, thereby avoiding the need for dopaminergic drugs. Anticholinergic drugs also may be helpful to suppress tremor resistant to other medications.

Eventually the time comes when stronger symptomatic treatment is required. The question then is whether to begin with levodopa or a directly acting dopamine agonist such as bromocriptine or pergolide. The aims now are to provide adequate symptomatic relief of disability and handicap, and to adopt a strategy least likely to lead to long term complications.

STRATEGIES TO DELAY OR PREVENT LONG TERM COMPLICATIONS

The dilemma in the choice between levodopa versus a dopamine agonist is due to the facts that (a) levodopa is more or less guaranteed to work, but has a high incidence of long term complications. (b) Bromocriptine and pergolide are less likely to be effective when given alone but, in those who can obtain adequate benefit, there is a lesser risk of the long term development of fluctuations and dyskinesias.

Using dopamine agonists as monotherapy will provide adequate symptomatic relief in only a minority of patients (ranging from

30%¹⁸ to around 50%^{13 19 20}). In the study by the Parkinson's Disease Research Group in the United Kingdom,²¹ of 263 patients entered into treatment with bromocriptine alone (mean dose 36 mg/day; range 7.5–120 mg/day) 181 withdrew, mainly due to lack of response (41 cases), deterioration despite treatment (30 cases), or adverse reactions (69 cases). The early use of dopamine agonist monotherapy, however, reduces the likelihood of developing complications such as fluctuations and dyskinesias in those who gain adequate relief.^{19 20 22} Furthermore, delaying the initiation of levodopa delays the time when such complications occur.^{23–26}

Again, the decision whether to use a dopamine agonist or levodopa often is decided according to individual circumstances. The patient in whom disability and handicap has reached a stage which urgently threatens independence or employment may opt for immediate levodopa treatment as the best guarantee of relief. Those in whom the pressure is less may opt for a dopamine agonist first as the best insurance against long term problems. The younger patient may wish to delay levodopa for as long as possible. The elderly patient may opt for early levodopa treatment because long term side effects are of less concern, and the neuropsychiatric side effects of directly acting dopamine agonists are more of a hazard.

If the decision is for levodopa, the next problem is whether to use standard Sinemet or Madopar, or the delayed release forms of Sinemet CR or Madopar CR. There are theoretical reasons in favour of Sinemet CR or Madopar CR.^{27 28} The large swings in levodopa plasma levels produced by standard Sinemet or Madopar may be deleterious and contribute to long term complications. Starting treatment with more stable blood levels produced by Sinemet CR or Madopar CR may decrease long term complications, and this theory is under clinical trial at the present time.

A few experience nausea and vomiting when levodopa is introduced, even when taking the drug after food. Usually this can be prevented by prefacing each dose with domperidone 10–20 mg an hour beforehand.

One strategy that has been advocated as a compromise is to employ a low dose of levodopa combined with a dopamine agonist. Rinne and colleagues^{19 29 30} have advocated this as a means of reducing to some extent the long term complications of fluctuations and dyskinesias. Although an attractive option, the evidence that combined treatment does indeed reduce long term side effects has come under recent criticism.^{31 32}

Strategies for treating complications of long term levodopa treatment

With long term treatment with levodopa (defined as greater than five years) only about 25% of patients continue to have a good, smooth response.^{14 33} Most patients develop either troublesome fluctuations, troublesome

dyskinesias, toxicity at therapeutic or sub-therapeutic dosages, or total or substantial loss of efficacy. There are three common patterns of late failure of chronic levodopa treatment: (a) the emergence of increasingly severe fluctuations and dyskinesias, which are particularly prevalent in younger patients; (b) the appearance of increasingly severe cognitive impairment and psychosis; often with (c) postural instability and falls, gait difficulties, and speech problems, which are particularly prevalent in the more elderly.

FLUCTUATIONS

The initial benefits of levodopa treatment are sustained. Most patients experience general improvement throughout the day with little response to each individual dose. With the passage of time, however, an increasing proportion of patients begin to experience fluctuations of their response.^{34–36} Most patients will develop fluctuations within about five years after starting levodopa therapy. Initially these take the form of the “wearing-off effect” or “end-of-dose deterioration”, which is defined as fluctuations in motor disability related to the timing of levodopa intake. With the passage of time and modification of treatment, such motor fluctuations become increasingly abrupt and random, culminating in the “on-off effect”, which is defined as sudden unpredictable fluctuations in motor disability unrelated to the timing of levodopa intake.

The main risk factors for fluctuations appear to be the duration of treatment^{25 26} and dosage.³⁷ As indicated above, using low doses of levodopa seems to delay the onset of this problem,³⁷ as does delaying the introduction of levodopa.²³ Fluctuations appear to be more common and occur sooner in patients who develop Parkinson's disease at a younger age.^{38 39}

Fluctuations in motor disability are often accompanied by a variety of other disabling, variable symptoms.⁴⁰ The associated dyskinesias are discussed below. During off periods, many patients complain bitterly of pain and other sensory complaints,^{41 42} akathisia,⁴³ respiratory distress,⁴⁴ depressive mood swings,^{45–47} sweating and other autonomic symptoms,⁴⁸ hallucinations,⁴⁵ anxiety and panic attacks,^{45 49} sometimes with screaming,⁵⁰ and slowing and impairment of thought processes.^{51 52}

In the fully developed “on-off” state, the swings in motor function and other symptoms may become highly unpredictable and rapid (“sudden offs”). Some doses of levodopa may fail to have any effect at all (“dose failures”), or there may be a considerable delay before the patient switches on (“delayed-on”). Furthermore, many patients describe diurnal variation in their responsiveness to levodopa, getting most benefit in the morning particularly after the first dose of the day, but less and less response as the day goes on with bad periods in the afternoon and evening.

Many mechanisms contribute to the emergence of fluctuations during long term lev-

odopa therapy.⁵³⁻⁵⁵ There appears to be no significant change in the peripheral pharmacokinetic handling of levodopa during long term treatment.⁵⁶ There is, however, a shortening of therapeutic benefit after each dose.⁵⁵ In addition, the character of the pharmacodynamic response to levodopa changes during long term treatment. When treatment is commenced, the degree of improvement bears a more or less linear relationship to dose and plasma levodopa level. In those who develop the "wearing-off" and particularly the "on-off" effect, however, this classic dose-response relationship changes into a sigmoid curve. Patients switch "on" at a critical level of plasma levodopa, below which they are "off" and above which they are more or less fully "on".⁵⁷ Increasing the dose of levodopa now does not improve the quality of the "on" period, but prolongs its duration. The absolute threshold for turning a patient with Parkinson's disease "on" with levodopa does not change during chronic treatment, but this critical threshold appears.

The emergence of a critical threshold has important implications for management. The natural response to the appearance of the "wearing off" effect is to reduce individual levodopa doses and increase their frequency. This strategy, however, although initially effective, often fails quite quickly. The smaller doses may produce peak plasma levels below threshold, so that the patient does not turn fully "on", or remains just at threshold so that they oscillate between "on" and "off". In addition, the smaller dose and lower plasma levels mean a reduced duration of response, even if threshold is reached.

Now, with plasma (and brain) levodopa levels hovering around threshold, peripheral pharmacokinetic factors assume greater importance. Delayed gastric emptying,⁵⁸ or large protein meals competing for absorption or brain entry of levodopa,⁵³ may drop brain levodopa levels to or below threshold, and reduce the duration of response even if it occurs.

In patients who have developed the "wearing-off" effect, and to a less predictable extent in those with the true "on-off" effect, maintaining a continuous supply of dopamine or a dopamine agonist to the brain, such as by intravenous^{53 59 60} or intestinal^{61 62} infusion of levodopa can overcome such fluctuations. The same can be achieved by a constant subcutaneous infusion of the dopamine agonist apomorphine.⁶³

Against this background, the following strategies are employed to try and overcome the emergence of fluctuations during chronic levodopa therapy.

Selegiline can be mildly effective in treating "wearing-off" problems.^{64 65} The addition of slow-release Sinemet CR or Madopar CR, to maintain more constant blood levels of levodopa, also may help particularly in the early stages of the emergence of this problem.⁶⁶⁻⁷² Many patients will also require supplemental standard Sinemet or Madopar as well as Sinemet CR or Madopar CR to obtain an

adequate response. It often takes over an hour for the delayed release medications to become effective, and patients frequently find that these formulations do not give a sufficient "kick-start" to switch them "on", especially with the first dose of the day. The addition of directly acting dopamine agonists, such as bromocriptine or pergolide,^{73 74} which have a longer biological half-life than levodopa, can also be used in combination with standard Sinemet or Madopar, and Sinemet CR or Madopar CR. There is some evidence that pergolide is more effective and better tolerated than bromocriptine.⁷⁵

Attention to gastric and dietary factors also becomes important. Dissolving levodopa in liquid before ingestion may help,⁷⁶ as may the use of the dispersible Madopar preparations, which act more quickly. Occasional patients may benefit from drugs enhancing gastric emptying or antacids.^{77 78} Taking levodopa before rather than after meals also may produce a more reliable and rapid effect.⁵⁸ Reduction in dietary protein also may be of benefit.⁷⁹

Despite these strategies, many patients evolve into the situation of sudden and unpredictable "off" periods. In these circumstances, subcutaneous apomorphine injections may be used to rescue patients from "off" periods, or apomorphine may be employed as a continuous subcutaneous infusion.^{63 80}

DYSKINESIAS

As motor fluctuations begin to develop during chronic levodopa therapy, a variety of dyskinesias appear.^{81 82} These are conventionally divided according to the time of their appearance after individual doses into: (a) those occurring at the peak of benefit—"peak dose dyskinesias"; (b) those occurring as mobility improves and/or as it wanes—"diphasic dyskinesias"; (c) those occurring in "off periods" or in the early morning—"off period dyskinesias". Peak dose dyskinesias are commonly choreic, ballistic, or stereotyped; less commonly they are dystonic; they tend to be more unsightly than disabling. Diphasic dyskinesias are similar in type to peak dose of dyskinesias, although dystonia is often more prominent and tends to be more severe and disabling. "Off period" dyskinesias tend to be dystonic, painful, and distressing. The pattern of dyskinesias, both in their character and timing, varies considerably from patient to patient, but is fairly consistent in each individual.

The mechanisms responsible for the appearance of dyskinesias are complex and not fully understood.^{83 84} Whereas the threshold for motor benefit from levodopa does not appear to change during chronic therapy, that for the production of dyskinesias decreases dramatically. Indeed, in those who have developed the typical "wearing-off" and "on-off" effect, the threshold for dyskinesias is similar to that required for motor benefit.⁸³ Diphasic dyskinesias⁸⁵ appear when the plasma level of levodopa is rising or falling

but not during the peak. Thus, patients describe a flurry of dyskinesias as the initial evidence of a levodopa effect; such dyskinesias may settle during the period of maximum mobility, only to reappear as the patient turns "off". Off period dyskinesias, especially the painful cramps and dystonias, may be evident first thing in the morning as well as during "off" periods during the day. Although they occur when mobility is at its worst, they disappear if levodopa is entirely withdrawn for a period of time.

Management of dyskinesias is difficult. Often reducing the dose of levodopa may improve the dyskinesias, but at the expense of intolerable worsening of mobility. When peak dose dyskinesias are causing disability, however, reducing each individual dose may resolve the problem. Alternatively, substituting an increasing dose of a dopamine agonist such as bromocriptine or pergolide while lowering the dose of levodopa can help.

Diphasic dyskinesias are even more difficult to manage. As they occur with intermediate plasma levels of levodopa, it would seem rational to increase levodopa intake.⁸⁶ Usually this eventually produces much more severe dyskinesias and other adverse effects. Lowering the dose is equally unsatisfactory because increasing parkinsonism ensues. The best strategy probably is to add increasing doses of an agonist such as pergolide while reducing levodopa intake.

"Off period" painful dystonia can be very disabling. The best way of preventing such dyskinesias is to try and overcome "off" periods by the strategies described above. Sometimes the addition of baclofen, an anticholinergic, or lithium is of benefit.

FREEZING, POSTURAL IMBALANCE, GAIT PROBLEMS AND SPEECH DIFFICULTIES

While chronic levodopa treatment continues to help some problems of Parkinson's disease, albeit for shorter and shorter periods of time and increasingly unreliably, other disabilities begin to emerge which are less responsive.

As "wearing-off" emerges, freezing episodes often appear during "off" periods. These particularly affect gait. Patients begin to experience start hesitation, and freezing on the turn or when passing through enclosed spaces.⁸⁷ Accompanying such freezing episodes is increasing instability of gait. Postural reflexes become impaired. Patients become increasingly unsteady, and no longer correct when imbalanced. Not only do they fail to take appropriate action to prevent a fall, but they also lose rescue reactions and so cannot protect themselves if they fall. A common problem arises from sudden unexpected freezing when walking. The feet get glued to the ground, momentum carries the patient forward, they cannot correct this imbalance but fall and injure themselves. Unexpected falls with injury thus become a major problem, particularly in "off" periods.⁸⁸

Speech also may be compromised, with increasing hypophonic dysfluency, hesitations, and even freezing during speech.^{89, 90} Swallowing too may be disturbed.⁹¹

Levodopa and dopamine agonists, during long term treatment, seem less capable of relieving these impairments of posture, gait, and speech.^{88, 92, 93} Reasons for the emergence of these difficulties during long term levodopa treatment may relate to progressive pathology²³ and the effects of ageing.⁹³ In particular, degeneration of neurons in those nuclei in brainstem centres controlling posture, locomotion, and speech may be involved.

Unfortunately, there is no effective way of managing these problems with medication, other than by attempting to control them with optimum levodopa and dopamine agonist replacement therapy. Once locomotor and speech problems begin to intrude, however, considerable help can be obtained from the physiotherapist, the speech therapist, and the occupational therapist.

Physiotherapy designed to improve gait patterns, and to educate the patient to minimise risks of falls is of benefit. Teaching strategies to ease getting out of the bed or a chair, to initiate walking and to manage turns is helpful. Walking aids are a problem to patients with Parkinson's disease. They tend to carry, rather than use a stick or frame; a wheeled rollator is often of more benefit. Other valuable aids include elevating chairs, house lifts, automatic controlled beds, bed-hoists, strategically placed rails, toilet aids, bath seats and showers, and feeding utensils. Unfortunately, about a half of patients and their carers need aids and equipment to assist daily living.⁹⁴ Close and regular contact with the occupational therapist and physiotherapist is essential to assess the need for appropriate assistance, which often requires a visit to the patient's home, and to select the most useful aids for the individual patient.⁹⁵ Liaison between the occupational therapist, physiotherapist, and social services is crucial to ensure the provision of such assistance, and the designated social worker can provide invaluable advice and practical help in financial matters. The Parkinson's Disease Society also provides considerable help in all these areas. It is the responsibility of the specialist and general practitioner, in liaison, to ensure that patients are referred early rather than late, and repeatedly, to the appropriate professionals.

Speech and feeding problems also may be a major cause of disability and handicap at this stage,^{91, 94} and the advice of the speech therapist now may be invaluable.⁹⁶⁻⁹⁸ Assessment of speech deficits, formal speech therapy and education, and the provision of appropriate communication aids may be required. Advice on dietary and swallowing strategies may be necessary and helpful.⁹⁹ Drooling of saliva, due to failure to swallow, is sometimes a major problem. An anticholinergic drug may help to dry the mouth.

It is also appropriate to consider the problems of the bladder and the bowels at this point, for at this stage of the illness these often cause considerable disability and distress.

Urinary frequency (especially at night) and

urgency due to detrusor instability are a common part of Parkinson's disease,¹⁰⁰ and can be improved with levodopa treatment. In elderly men there is the common added problem of the enlarged prostate. Frequently, it is difficult to know whether the prostate or the Parkinson's disease is responsible for urinary problems in men with Parkinson's disease. Referral to an expert urologist may be essential, and careful investigation is often required to distinguish outflow obstruction from the bladder dysfunction inherent to Parkinson's disease. Careful selection of those suitable for prostatic resection is essential if incontinence is to be avoided. An anticholinergic may help urgency and frequency, but can precipitate urinary retention (and glaucoma), and can make constipation worse.

Constipation is a very common problem in Parkinson's disease,^{99 101} caused by many factors including reduced mobility, anticholinergic drugs, dietary imbalance, and autonomic dysfunction. A high fibre diet with fruit, drinking more water, and bulk laxatives are useful.

Postural hypotension and syncope sometimes may be a problem in true Parkinson's disease, due partly to pathology in the autonomic nervous system and also to the effects of drug treatment. Head-up tilt of the bed at night, elastic stockings, and fludrocortisone may be required.

COGNITIVE AND NEUROPSYCHIATRIC PROBLEMS

Most patients with Parkinson's disease, early in their illness, have subtle changes on neuropsychological testing suggestive of frontal lobe dysfunction.^{52 102 103} In the early stages, however, these usually do not appear to cause obvious cognitive disability. With the passage of time, however, they may develop into a more disabling syndrome of abulia. Abulia refers to apathy, slowness of thought (bradyphrenia),¹⁰⁴ and blunting of drive and response to external stimuli. Such a syndrome may progress further with increasing impairments of memory to form a focal dementia of frontal lobe type. Around 20–30% of patients may go on to develop a more multifocal, pervasive dementia affecting many or all areas of cognitive function.¹⁰⁵ A particular characteristic of this syndrome, which predominantly affects the elderly patient with Parkinson's disease, is a fluctuating, confusional state often with visual, and even auditory, hallucinations.¹⁰⁶ Such patients may have good days where cognitive function appears relatively preserved interspersed with periods of mental confusion, impairment of attention, and hallucinations.

There are many reasons for cognitive impairment in Parkinson's disease.⁵¹ Drug treatment may be responsible, particularly anticholinergic agents in the elderly.¹⁰⁷ Undoubtedly some may develop the coincidental pathology of Alzheimer's disease which is common in the elderly. Some of the features of frontal lobe dysfunction may be attributed to increasing dopaminergic inactivation of frontocaudate cognitive systems. As

the disease advances, not only is there greater involvement of nigrocaudate dopaminergic pathways, but also it is likely that dopaminergic innervation of the frontal cortex itself is impaired. Another factor which has emerged in recent years is the realisation that Lewy body pathology in the cerebral cortex is much more widespread than was hitherto envisaged. The advent of ubiquitin immunostaining for Lewy bodies has shown that these inclusions are present in cortical neurons to some extent in virtually every patient with Parkinson's disease. In many of those with severe cognitive impairment there is widespread cortical Lewy body pathology. Diffuse Lewy body disease previously was thought to be a rare condition, but it is now suggested that it may be a common cause of the confused dementia in the elderly patient with Parkinson's disease.^{106 108–110}

Along with cognitive impairment, a number of neuropsychiatric problems also may emerge associated with chronic disease. Isolated visual pseudo-hallucinations are not infrequent. Patients may see human or animal "familiaris", which may or may not be threatening. Such hallucinations, which again are more common in the elderly patient, and particularly at night, may be due in part to drug intake. Reducing dopaminergic drugs often leads to their disappearance. Some patients, however, go on to develop a frank confusional state and may even become psychotic.

The appearance of disabling cognitive impairment or of a confusional state in a patient with Parkinson's disease should prompt a search for some intercurrent illness, including chest and urinary infections and metabolic disturbances. In many cases drug treatment is likely to be the cause. All anticholinergic drugs should be withdrawn, including amantadine. If the confusion does not clear, the dose of dopaminergic drugs needs to be reduced. Unfortunately, however, while the confusional state may clear as drugs are withdrawn, mobility may deteriorate. Often, as drugs are manipulated, a state is reached in which the patient is either mobile but confused and hallucinating, or mentally clear but immobile. The balance between the extremes may be brittle and it is very difficult to achieve a satisfactory compromise. In this situation, a limited drug holiday, withdrawing dopaminergic drugs for one day each week, sometimes helps to dispel the psychotoxicity, allowing a reasonable dose of drugs to maintain mobility on other days. Prolonged drug holidays have been abandoned, for the patient may deteriorate to a severe state of immobility, with risks of pneumonia or deep vein thrombosis. Indeed, dopaminergic drug withdrawal may precipitate a state of intense rigidity, mental confusion, and unexplained pyrexia akin to the neuroleptic malignant syndrome.

If drug manipulation fails, it may be necessary to use the atypical neuroleptic clozapine to control the neuropsychiatric complications. Clozapine, which acts predominantly through D-4 dopamine receptors, has much less

propensity to cause extrapyramidal side effects and to worsen mobility in Parkinson's disease. It is not devoid of this risk, but sometimes it can be employed successfully to control neuropsychiatric complications while maintaining an adequate dose of dopamine replacement therapy to maintain mobility.¹¹¹⁻¹¹³ There are, however, practical difficulties to the use of clozapine because of its tendency to produce agranulocytosis in a significant proportion of patients (perhaps 1-2%). This requires frequent and regular monitoring of blood counts and withdrawal of clozapine at the slightest hint of toxicity. An alternative strategy is to employ a small dose of a conventional neuroleptic, such as thioridazine at night.

Finally, mood changes are a major component of Parkinson's disease. Around two thirds of patients are significantly depressed.¹¹⁴⁻¹¹⁵ In part this is a natural reaction to the disabilities imposed by their illness but that may not be the only reason for depression in Parkinson's disease. It has been argued that pathology in serotonergic systems, and perhaps also in noradrenergic systems, known to occur in Parkinson's disease, may also contribute to depression. A nocturnal dose of tricyclic antidepressant such as imipramine or amitriptyline may be required. A sedative antidepressant with anticholinergic properties may also aid sleep and reduce nocturnal urinary frequency. Although a popular antidepressant drug, fluoxetine may increase parkinsonian disability.¹¹⁶ Occasionally, electroconvulsive therapy (ECT) may be required to treat severe depression in Parkinson's disease. Not only does ECT relieve the depression, but the parkinsonism also can improve temporarily.

Anxiety and panic attacks also can be a disabling feature of Parkinson's disease, especially during "off" periods. A benzodiazepine such as diazepam or a beta-blocker such as propranolol may help such patients.

Role of neurosurgery in Parkinson's disease

Before the introduction of levodopa treatment around 1970, stereotaxic surgery was widely employed to treat Parkinson's disease.¹¹⁷ The preferred target in most centres was the ventrolateral nucleus of the thalamus, in particular, the nucleus ventralis intermedius. A unilateral thalamotomy could successfully reduce or abolish contralateral tremor and rigidity in most patients, with an acceptably small (5-10%) risk of hemiparesis or hemiplegia. Bilateral thalamotomy, however, carried a higher (20% or so) risk of severe speech disturbance and other complications. Thalamotomy did not usually improve the various manifestations of akinesia, which often progressed to cause increasing disability.

Levodopa, for the first time, relieved akinesia, so the use of thalamotomy rapidly declined. It was reserved for the occasional patient with mainly unilateral drug resistant disabling tremor.¹¹⁸⁻¹¹⁹

As the long term complications of levodopa treatment emerged, and persisted in many

despite every attempt at drug manipulation, stereotaxic surgery has begun to undergo a renaissance, in three forms.¹²⁰

Laitinen and colleagues¹²¹ had continued Leksell's practice of posteroventral pallidotomy, and recently published evidence that this operation not only could improve tremor and rigidity, but also akinesia, gait, and speech. Furthermore, this lesion could reduce or abolish some disabling levodopa induced dyskinesias. The role of posteroventral pallidotomy is being re-evaluated in many centres.

Benabid *et al.*¹²² following the observation that suppression of tremor by electrical stimulation was a useful method of localising the target site for traditional thalamotomy, harnessed the technology of continuous electrical thalamic stimulation for suppression of tremor. The advantages of this method include a lower incidence of complications, and the opportunity for safe bilateral implantation. Furthermore, continuous thalamic stimulation also may suppress some levodopa induced dyskinesias. Again, this technique is under clinical trial worldwide.

Finally, much has been written about brain grafting for Parkinson's disease. Initial enthusiastic reports on the use of adrenal autografts into the striatum have been subsequently tempered by the realisation that the method was not very successful and carried high risks.¹²³ Adrenal grafting, in its original form, has been discarded. The use of fetal substantia nigra grafts into striatum, using stereotaxic methods, however, holds greater promise. Such grafts have been shown by PET to survive and to exert some beneficial effects for years.¹²⁴⁻¹²⁷ The method remains experimental at this stage, until the many practical problems surrounding it have been resolved.¹²⁸

Standards of care and audit

Despite the large number of patients with Parkinson's disease in the community, the complications of its treatment, and the disability it produces, there has been little formal investigation of audit in this condition.

The Association of British Neurologists¹²⁹ noted that Parkinson's disease was the 12th commonest condition referred to neurologists in the United Kingdom. They recommended that all such patients should be referred to a neurologist (unless geriatric referral was most appropriate), and that they should have CT of the brain (although many would not consider CT or MRI of the brain to be necessary, unless there is another positive indication).

A Working Group of the Royal College of Physicians¹³⁰ provided a series of recommendations for the management of a variety of neurological conditions, including Parkinson's disease. These could provide the standards against which quality of care may be audited. The working party of the Association of British Neurologists⁴ document on neurological rehabilitation in the United Kingdom also provides a set of general standards of care for those with neurological disability, which also can form the basis of audit of management of disability in those with Parkinson's disease.

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