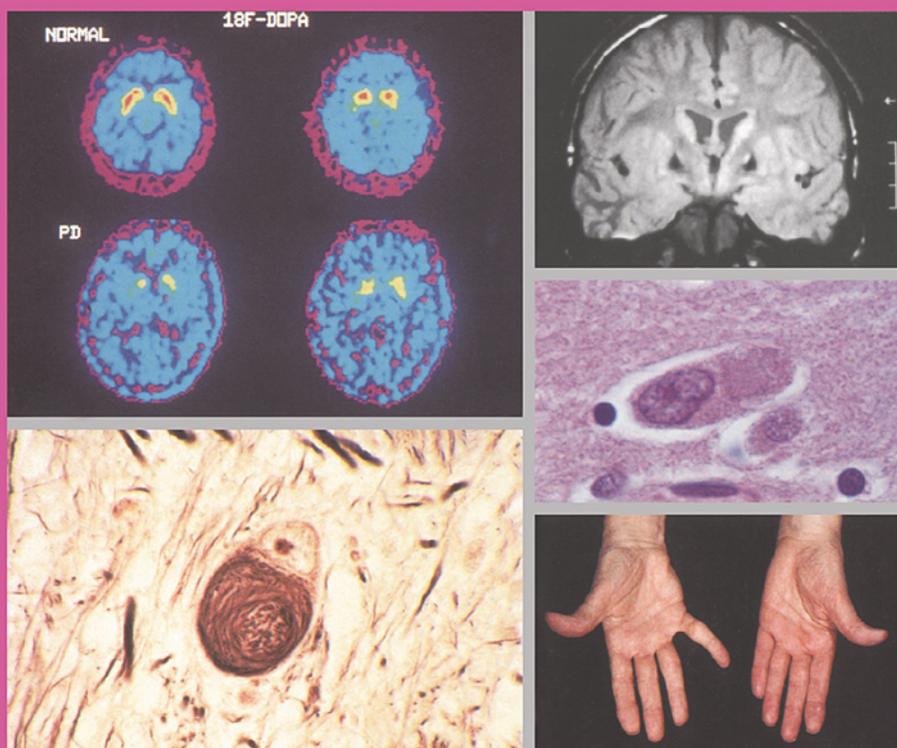An Illustrated Pocketbook of

PARKINSON'S DISEASE

AND RELATED DISORDERS

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An Illustrated Pocketbook of MRI. Disease and Related Disorders

An Illustrated Pocketbook of Parkinson's Disease and Related Disorders

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Contents

v

Anatomy

The neurons of the corpus striatum receive an excitatory input from the cerebral cortex and the thalamus. The major outputs project to the globus pallidus and the substantia nigra pars reticula (SNr), and use gamma-aminobutyric acid (GABA) as a transmitter. Major efferent pathways from the globus pallidus interna and the SNr project to the thalamus. Feedback to the striatum is through the dopaminergic striatonigral pathway originating in the substantia nigra pars compacta (SNc; Figure 1).

These separate pathways utilize different neuropeptides and dopamine receptors. The direct pathway from the striatum to the globus pallidus interna (GPi) and SNr expresses substance P and dynorphin, and uses D1 dopamine receptors. The neurons projecting from the striatum to the external segment of the globus pallidus (GPe) express enkephalin and use D2 receptors. (Some neurons express both receptors.)
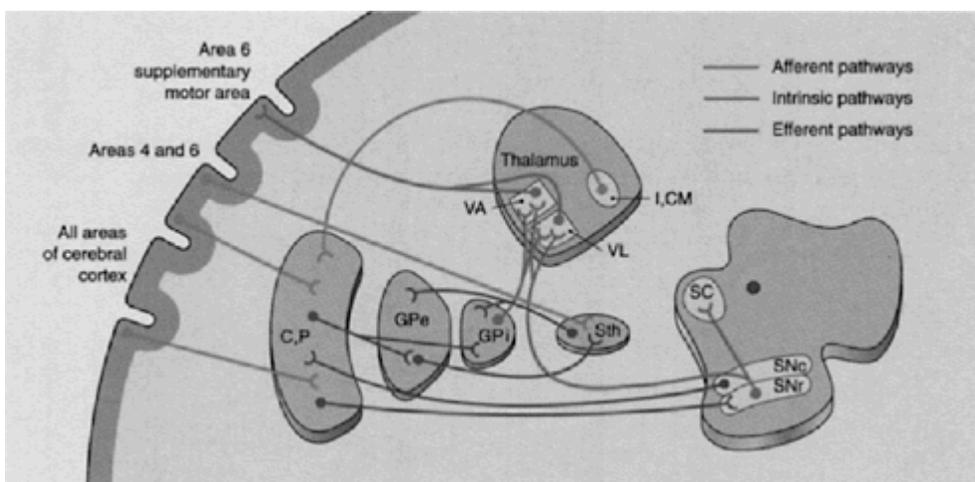
Figure 1 Major pathways of the basal ganglia. Modified from Riley DE, Lang AE. In Bradley WG, *et al., Neurology in Clinical Practice.* London: Butterworth Heinemann, 1996

Depletion of dopamine in the striatum results in increased activity of the striatopallidal pathway and decreased activity in the direct pathway. These effects (the former leading to disinhibition of the subthalamic nucleus) lead to increased activity of the GABAergic neurons of the output nuclei of the basal ganglia. Increased inhibitory output from these nuclei may be responsible for the bradykinesia seen in patients with Parkinson's disease (Figure 2).
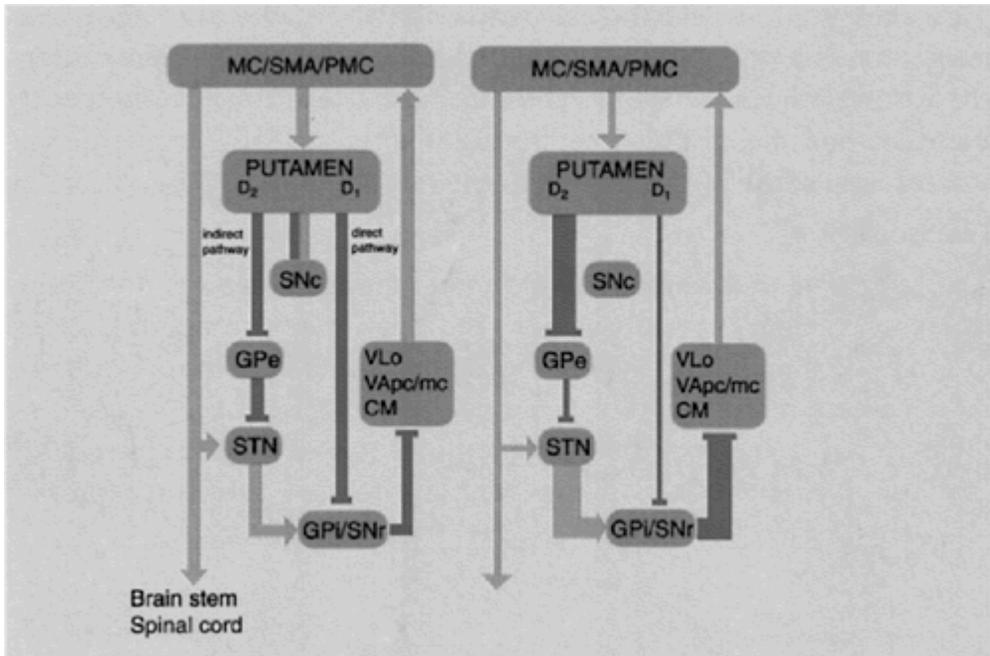
Figure 2 Connections of striatal output neurons. Modified from Goetz CG, De Long MR, Penn RD, Bakay RA. Neurosurgical horizons in Parkinson's disease. *Neurology* 1993;43:l–7

Parkinson's disease

Any discussion of the clinical characteristics of Parkinson's disease must take into account the inaccuracies of clinical diagnosis. In a successive series of 100 patients with a clinical diagnosis of Parkinson's disease, only 76 fulfilled the criteria for diagnosis at postmortem examination (Table 1). Attempts to tighten the diagnostic criteria lead to increased specificity but reduced sensitivity.

Neuropathology

Typically, there is loss of at least 50% of the melanin-containing nerve cells of the substantia nigra, the changes being concentrated in the central part of the zona compacta (Figure 3). Accompanying these changes is depletion of tyrosine hydroxylase, the rate-limiting enzyme in the biosynthetic pathway for catecholamines (Figures 4 and 5). A characteristic, indeed inevitable, finding is the presence of Lewy bodies in some of the remaining nerve cells (Figure 6).

Table 1 Pathological findings in 100 successive Parkinsonian patients

Idiopathic Parkinson's disease	76
Progressive supranuclear palsy	6
Multiple system atrophy	5
Alzheimer's disease	3
Alzheimer-type pathology with striatal involvement	3
Lacunar state	3
Nigral atrophy	2
Postencephalitic parkinsonism	1
Normal (?essential tremor)	1

Together with Lewy body formation, degenerative changes occur at other sites, including the locus ceruleus, the dorsal motor nucleus of the vagus, the hypothalamus, the nucleus basalis of Meynert and the sympathetic ganglia. Cortical Lewy bodies are probably present in all patients with idiopathic Parkinson's disease, although not with the frequency that would permit a diagnosis of cortical Lewy body disease *(vide infra)*.

In parkinsonian patients with cortical dementia, the pathological changes are either those of cortical Lewy body disease, or those associated with Alzheimer's disease, including senile plaques, neurofibrillary tangles, granulovacuolar degeneration, and nerve cell loss in the neocortex and hippocampus.
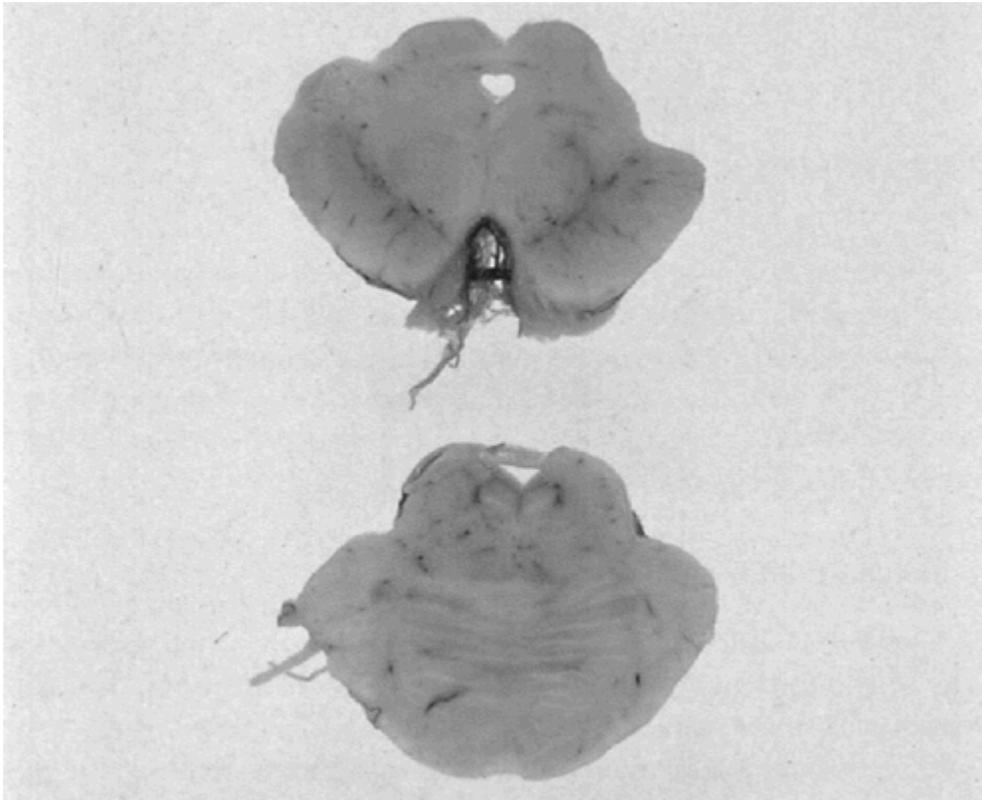
Figure 3 Parkinson's disease: horizontal sections of midbrain (upper) and pons (lower). Courtesy of S.E.Daniel, The Parkinson's Disease Society Brain Research Centre, Institute of Neurology, London, UK

Epidemiology

The prevalence of Parkinson's disease has been reported to lie between 30 and 300 per 100 000, producing approximately 60 to 80 000 cases in the United Kingdom. Prevalence increases with age and the disease is slightly more common in men (Figure 7). Cigarette smoking provides some protective effect, whereas the risk is possibly increased in those with a history of herbicide or metal exposure. A family history of Parkinson's disease is associated with an increased disease risk. Both autosomal-dominant and autosomal-recessive forms of the disease are recognized.

Clinical features

Typically, the condition produces bradykinesia, tremor, rigidity, and impairment of postural reflexes. An asymmetrical onset is characteristic.

Bradykinesia

Paucity of movement can affect any activity and is best measured by assessing aspects of daily living. The problem tends to involve one upper limb initially, leading to difficulty with fine tasks, such as manipulating
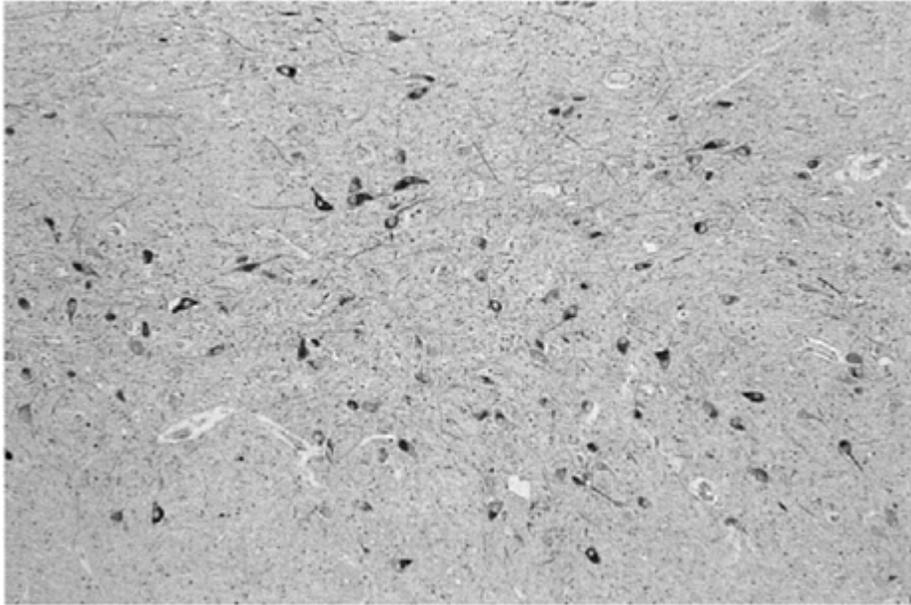
Figure 4 Parkinson's disease: control section of normal substantia nigra (immunostained for tyrosine hydroxylase). Courtesy of S.E.Daniel, The Parkinson's Disease Society Brain Research Centre, Institute of Neurology, London, UK

a knife or fork, dressing or shaving. The patient's handwriting typically becomes reduced in size if the dominant hand is affected (Figure 8). Associates are likely to comment on a reduction of arm swing when walking. Facial immobility is evident, with a lack of animation and immediate emotional response (Figure 9). The posture is stooped, and becomes more so as the condition progresses (Figures 10 and 11). Walking becomes slowed, with a tendency to reduce stride length and an increased number of steps being taken when turning. The problem can be assessed by asking the patient to repetitively tap with the hand or foot, or to mimic a polishing motion with the hand, or to rhythmically clench and unclench the fingers (Figure 12). Even if the amplitude of such movements is initially retained, it soon diminishes and may even cease.

Rigidity

The rigidity associated with Parkinson's disease is also often asymmetrical at onset. It tends to be diffusely distributed throughout the limb although, initially, it may be more confined. It persists throughout the range of motion of any affected joint. A characteristic judder (cogwheeling) occurs at a frequency similar to that of the postural tremor seen in Parkinson's disease rather than at the rate of the resting tremor. If the rigidity is equivocal, it can be activated by contracting the contralateral limb.

Tremor

The classical parkinsonian tremor occurs at rest, at a frequency of around 3–4 Hz (Figure 13). It is present in over 70% of cases at diagnosis. The tremor briefly inhibits during a skilled activity. A faster, postural tremor of around 6–8 Hz is sometimes evident, initially at a time when the rest tremor is absent. The rest
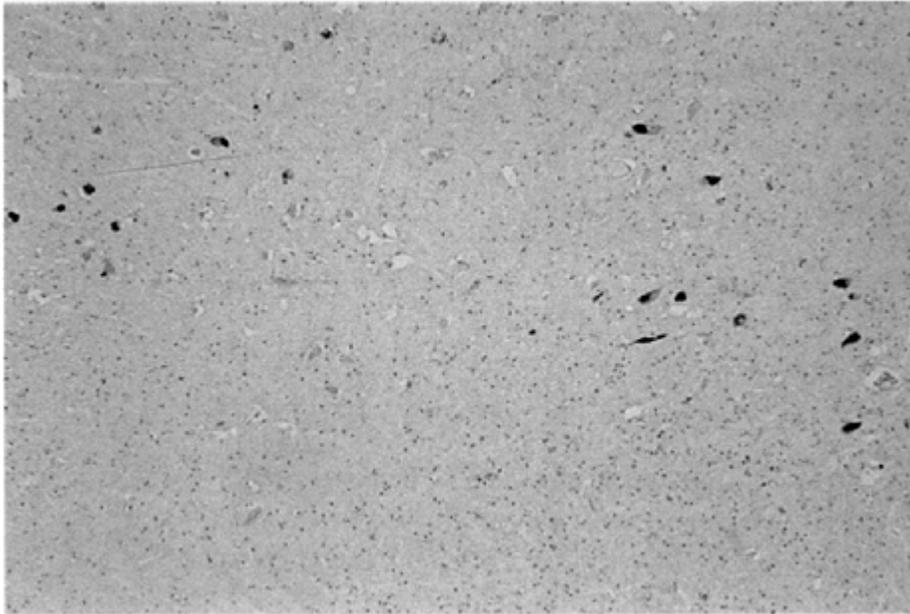
Figure 5 Parkinson's disease: substantia nigra showing depletion of tyrosine hydroxylase (immunostained for tyrosine hydroxylase). Courtesy of S.E.Daniel, The Parkinson's Disease Society Brain Research Centre, Institute of Neurology, London, UK

tremor most commonly involves the upper limb, producing either flexion/extension movements or pronation/supination, or a combination of these.

Postural reflexes

In addition to abnormalities of posture, the patient has difficulty maintaining posture when suddenly pushed forwards or backwards. Other features of Parkinson's disease include dementia (perhaps in around 15–20% of patients), autonomic dysfunction (principally in the form of urinary urgency and occasional incontinence) and a variety of eye signs, including broken pursuit movements, and some limitation of upward gaze and convergence. A positive glabellar tap (producing repetitive blinking during tapping over the glabella) occurs in the majority, but is also seen in Alzheimer's disease.

Imaging

Although imaging techniques, particularly positron emission tomography (PET) scanning, are not relevant to the diagnosis of most patients with Parkinson's disease, they do provide insight into the pathophysiology of the disease and can assume clinical relevance where clinical presentation is atypical. PET scans using 6–[18F]-fluorodopa show reduced uptake of the isotope, particularly in the putamen, and mainly contralateral to the clinically more affected side (Figure 14).
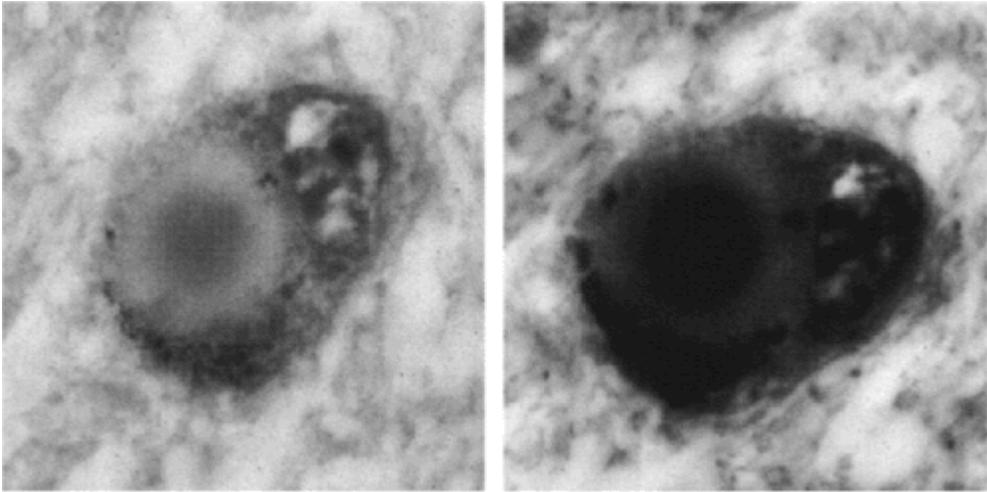
Figure 6 Parkinson's disease: microscopic views of a Lewy body stained by H & E (left) and by modified Bielschowsky stain (right). Courtesy of W.R.G.Gibb, Institute of Psychiatry, London, UK
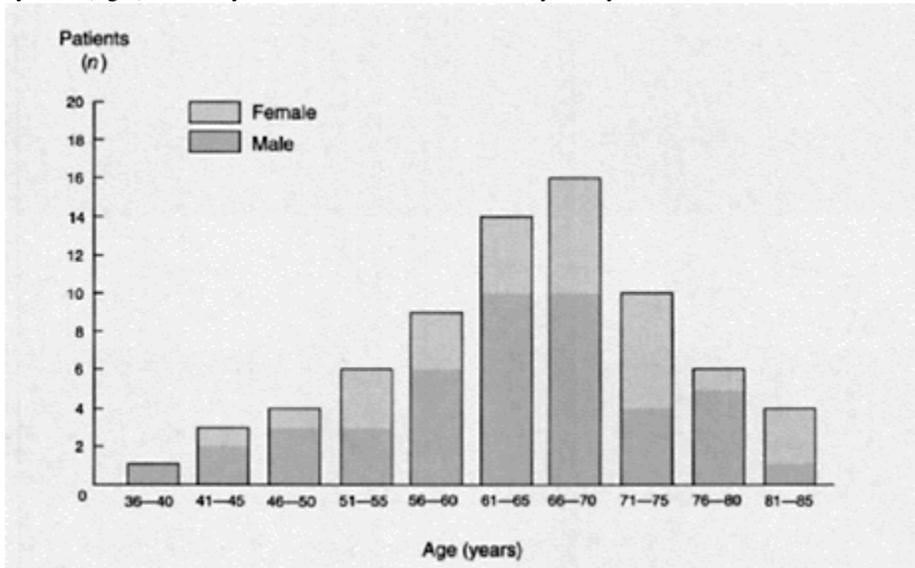

Figure 7 Parkinson's disease: graph showing age and gender distribution at the time of diagnosis

Drug intervention

There are potentially several stages during the synthesis, release and metabolism of dopamine within the central nervous system at which intervention, by enhancing dopamine levels, may influence the clinical manifestations of Parkinson's disease.

Dopa is converted to dopamine within the dopaminergic neuron by the action of L-aromatic amino acid decarboxylase (dopa decarboxylase). The dopamine is then transported into storage vesicles before being released, through depolarization and entry of calcium ions, to act on the postsynaptic dopamine receptor site.

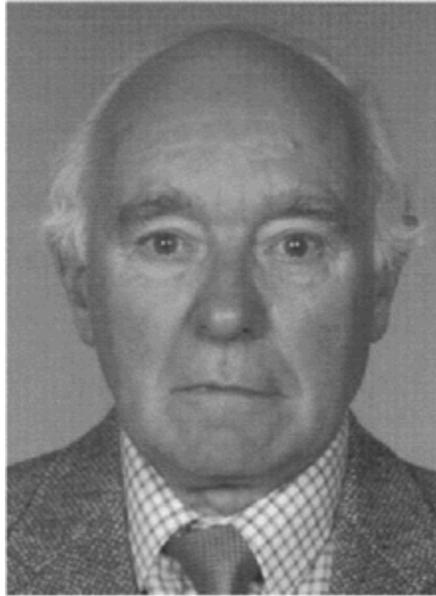**Figure 8** Parkinson's disease: micrographia

Figure 9 Parkinson's disease: facial appearance

Some of the dopamine is taken up again in the dopaminergic neuron, while another part is converted within glial cells to 3-methoxytyramine, by the action of catechol O-methyltransferase (COMT). The 3-methoxytyramine is then metabolized by monoamine oxidase-B to homovanillic acid (HVA). Some of the dopamine that is taken up again into the neuron is transported back into storage vesicles, whereas the remainder is metabolized by monoamine oxidase-B to 3,4-dihydrophenylacetic acid (DOPAC). Dopaminergic activity can therefore be enhanced by providing more precursor (dopa; Figure 15), stimulating dopamine release (amantadine), using an agonist to act on the dopamine receptor site (bromocriptine, pramipexole, lysuride, pergolide, ropinirole or cabergoline), or inhibiting dopamine breakdown through inhibition of either monoamine oxidase (selegiline) or of COMT (tolcapone, entacapone). Tolcapone is no longer licensed in the United Kingdom.

   Dopa, combined with dopa decarboxylase inhibitor, remains the cornerstone of treatment. The use of subcutaneous apomorphine as a diagnostic test for idiopathic Parkinson's disease has been advocated, but both false-positive and false-negative results occur. There is no consensus as to whether agonist therapy should be introduced earlier or later. After 5–10 years, major therapeutic problems arise, with loss of efficacy, fluctuations in response, and the emergence of increasingly uncontrollable dyskinesias or dystonic
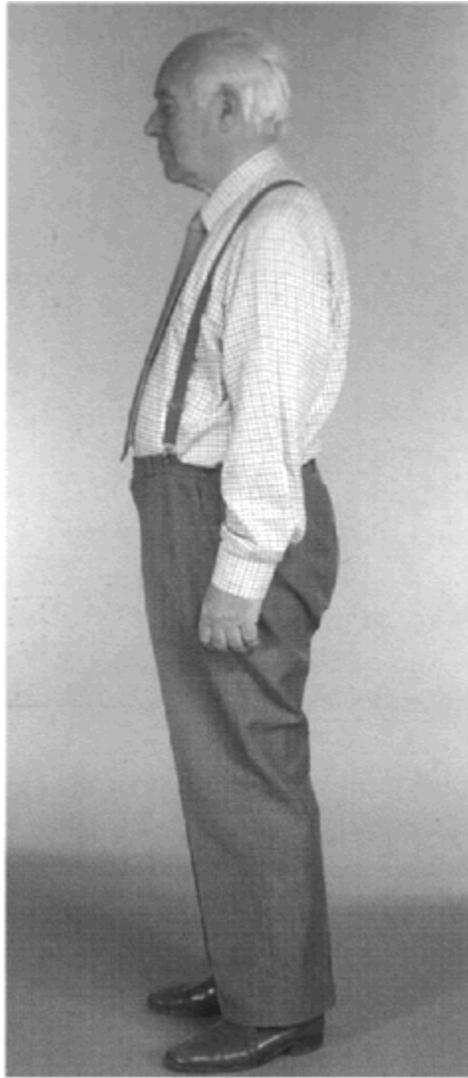
Figure 10 Posture in early Parkinson's disease

posturing (Figures 16 and 17). These problems have stimulated consideration of other therapeutic approaches, including thalamic and pallidal surgery, and transplantation of dopaminergic grafts. Such grafts, derived from human embryonic mesencephalic tissue, have been shown to have a functional effect for at least 3 years after transplantation, as substantiated by evidence of enhanced putaminal fluorodopa uptake over the same period (Figure 18).
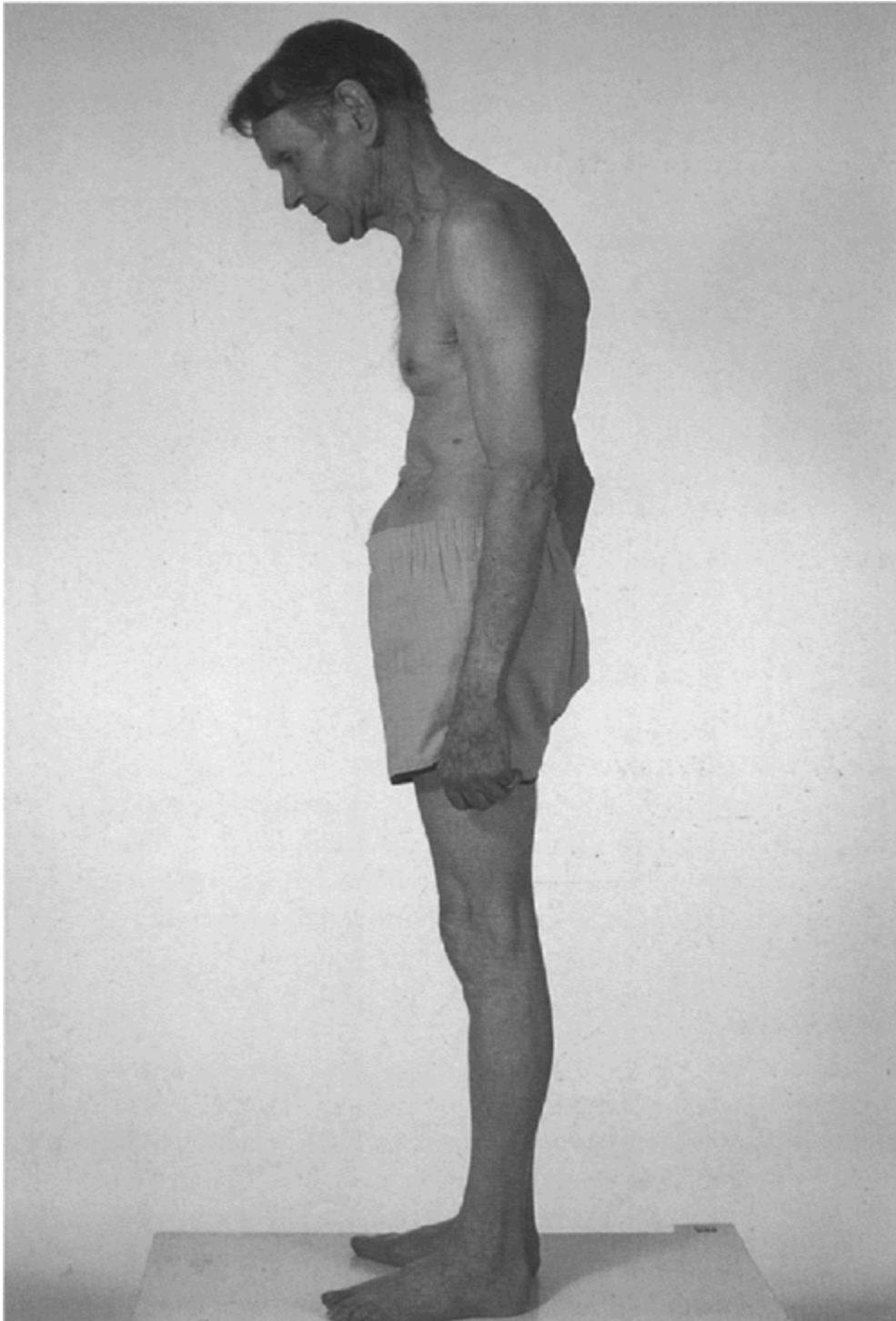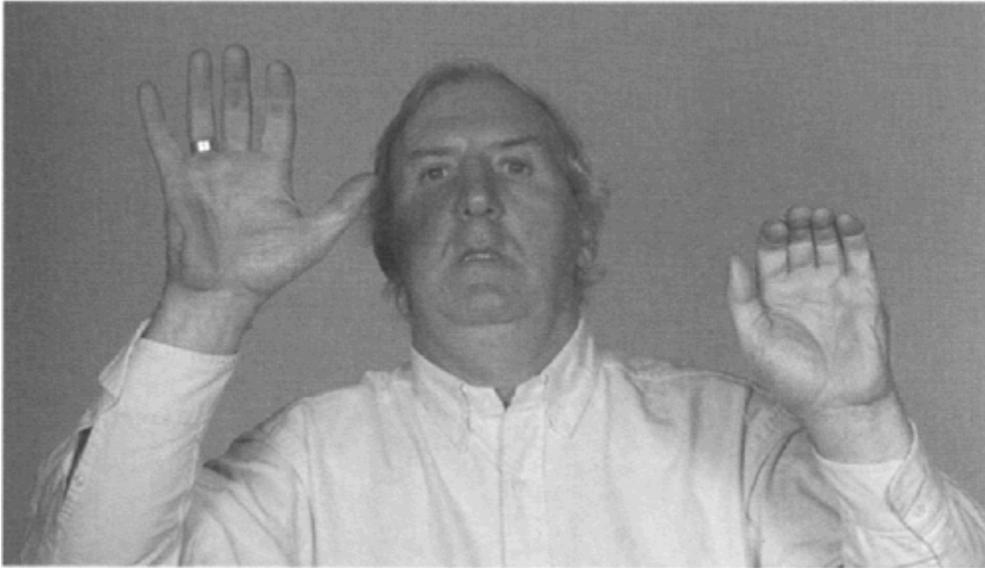
Figure 11 Posture in later-stage Parkinson's disease

Figure 12 Parkinson's disease: impaired fist clenching