# Clinical Algorithm

## Parkinson's disease

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Idiopathic Parkinson's disease is a degenerative neurological disorder classically presenting in old or late middle age. The brain shows characteristic cell loss and depigmentation in pigmented brain stem nuclei. The presence of rounded eosinophilic intracytoplasmic inclusions, known as Lewy bodies, in some of the affected neurons is a sine qua non for definitive pathological diagnosis. In life, however, the diagnosis of idiopathic Parkinson's disease rests entirely on clinical features and is primarily one of exclusion.

### Parkinsonism

The first prerequisite is the recognition of parkinsonism, which comprises two or more of the following signs: tremor, rigidity, akinesia, and postural abnormality (either flexed posture or impaired postural reflexes). From then onwards unusual clinical features, with or without the results of ancillary investigations, may point to alternative causes of the syndrome. Many of these atypical features may be evident only with time, so that a clinical diagnosis of idiopathic Parkinson's disease must be continually re-evaluated. Progress down the algorithm therefore resembles an upside down version of snakes and ladders: the appearance of an unusual feature at any time in the course of the disease may call for the whole case of differential diagnosis to be reopened. Here we briefly consider the important features of the different diagnostic possibilities in the boxes across the middle of the algorithm in a more conventional manner. This background information provides the rationale underlying the algorithm.

*Benign essential tremor*—This monosymptomatic disorder, dominantly inherited but with variable penetrance, is commoner than Parkinson's disease and shows a similar rising prevalence with increasing age. It is often temporarily relieved by alcohol, improved by β blockers, and exacerbated by β agonist drugs. It is probably the most frequent cause of misdiagnosis. Although cogwheeling of affected limbs due to the tremor is allowable, classical rigidity, akinesia, and other parkinsonian features are lacking. Some patients with idiopathic Parkinson's disease may display a fast postural tremor as well as, or sometimes instead of, a classic slow resting tremor. Also, many patients with akinetic-rigid parkinsonism may never develop tremor.

*Postencephalitic Parkinson's disease*—Enecephalitis lethargica is the only frequently accepted encephalitic cause of persisting Parkinson's disease.[1] Cases are extremely rare. Although the typical patient gives a history of encephalitis and oculogyric crises followed by the development of parkinsonism at a relatively young age, diagnosis is confounded on the one hand by the fact that patients without a preceding history of oculogyric crises or encephalitis have been described (one of the latter showing at necropsy the classical sequelae of encephalitis lethargica[2]) and on the other by the fact that several patients with the changes of idiopathic Parkinson's disease may give a history of some unrelated encephalitic illness. Persisting signs of pupillary or oculomotor disturbance or of associated dystonia and extremely slow progression of the disease may be useful clinical clues. The diagnostic importance of oculogyric crises occurring in a patient with Parkinson's disease receiving dopaminergic treatment is unknown.

*Huntington's disease*—Most patients with akinetic-rigid Huntington's disease are young (onset before age 20), 90% inheriting their "Westphal variant" from an affected father. Additional dystonic features are common and mental changes profound. Older subjects with Huntington's disease rarely present with an akinetic-rigid syndrome, but in many adult patients parkinsonian features develop as the disease progresses, even without neuroleptic treatment.[3] The family history and the mental changes point towards the diagnosis. A paucity of α rhythm on the electroencephalogram and caudate atrophy on computed tomography may provide additional clues. A gene specific test on DNA harvested from whole blood may become available.

*Wilson's disease*—Young subjects with parkinsonism (onset before age 40) should have blood and urine tests of copper metabolism and slit lamp examination for Kayser-Fleischer rings. Traditional teaching holds that neurological Wilson's disease never begins after the age of 40, is never diagnosed after the age of 50, and is always associated with Kayser-Fleischer rings. Despite two recently reported, and hotly debated, possible exceptions to these rules,[4,5] for practical purposes Kayser-Fleischer rings are always found in neurological Wilson's disease (but not hepatic Wilson's disease) so long as slit lamp examination is performed by an experienced ophthalmologist. Other family members may be affected, and a history of parental consanguinity may be elicited.

*Drug induced parkinsonism* is common and, like idiopathic Parkinson's disease, the incidence increases with age. It can result from treatment with any neuroleptic (dopamine receptor blocking) drug of the phenothiazine, butyrophenone, thioxanthene, or benzamide class and also from treatment with dopamine depleting agents such as reserpine and tetrabenazine. Causative drugs commonly overlooked are metoclopramide (Maxolon), prochlorperazine (Stemetil), and various antidepressant-anxiolytic-neuroleptic combinations, such as Motival. It is also surprising how often a history of depot injections is not picked up. If the condition is due to drugs alone such patients usually recover after six months without medication, although 18 months to two years may occasionally be necessary. When parkinsonism persists after this period the patient may have been destined to develop idiopathic Parkinson's disease anyway. Several patients whose first parkinsonian symptom is a vague complaint of unsteadiness or "dizziness" may in fact be given prochlorperazine, thus hastening the appearance of other features of the disease. The reason some patients treated with antidopaminergic drugs develop parkinsonism whereas others of the same age treated with the same doses do not is unknown but may well be related to the extent of their basal gangliar "dopamine reserve" (in idiopathic Parkinson's disease 80% of dopamine reserve is lost before clinical signs appear). Those with drug induced parkinsonism may be at increased risk of developing idiopathic Parkinson's disease later, but epidemiological evidence for this is lacking.

*Arteriosclerotic pseudoparkinsonism*—Until recently many papers referred to arteriosclerotic Parkinson's disease as an aetiological subgroup. Now, however, cerebrovascular disease is recognised to play no part in Parkinson's disease and the condition is now dubbed arteriosclerotic pseudoparkinsonism. Most patients display neither classical rest tremor nor true akinesia and usually walk with an erect "military," albeit shuffling, gait (the term "marche à petit pas" was originally coined for these subjects). Those affected are most often elderly and hypertensive and may have other vascular risk factors, suffer additional dementia, and show lacunar infarcts in basal ganglia, larger multiple infarcts elsewhere, or extensive symmetrical white matter lucency ("Binswanger change") on computed tomography. Matters are complicated by the fact that the infarcts may be too small to be demonstrable on computed tomography and also that idiopathic Parkinson's disease and lacunar infarction are often associated since both conditions are common among the elderly. Only in the minority with coincidental

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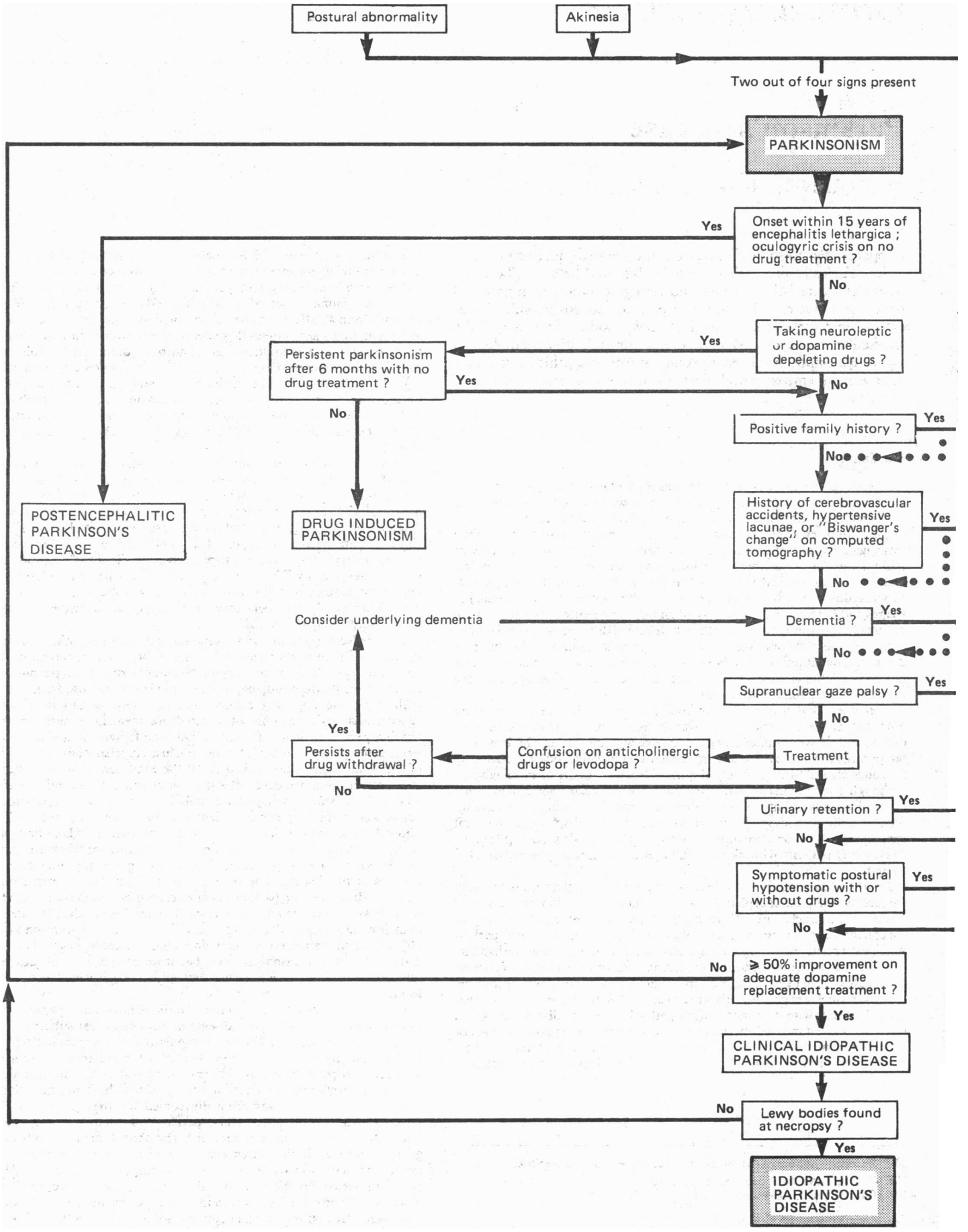
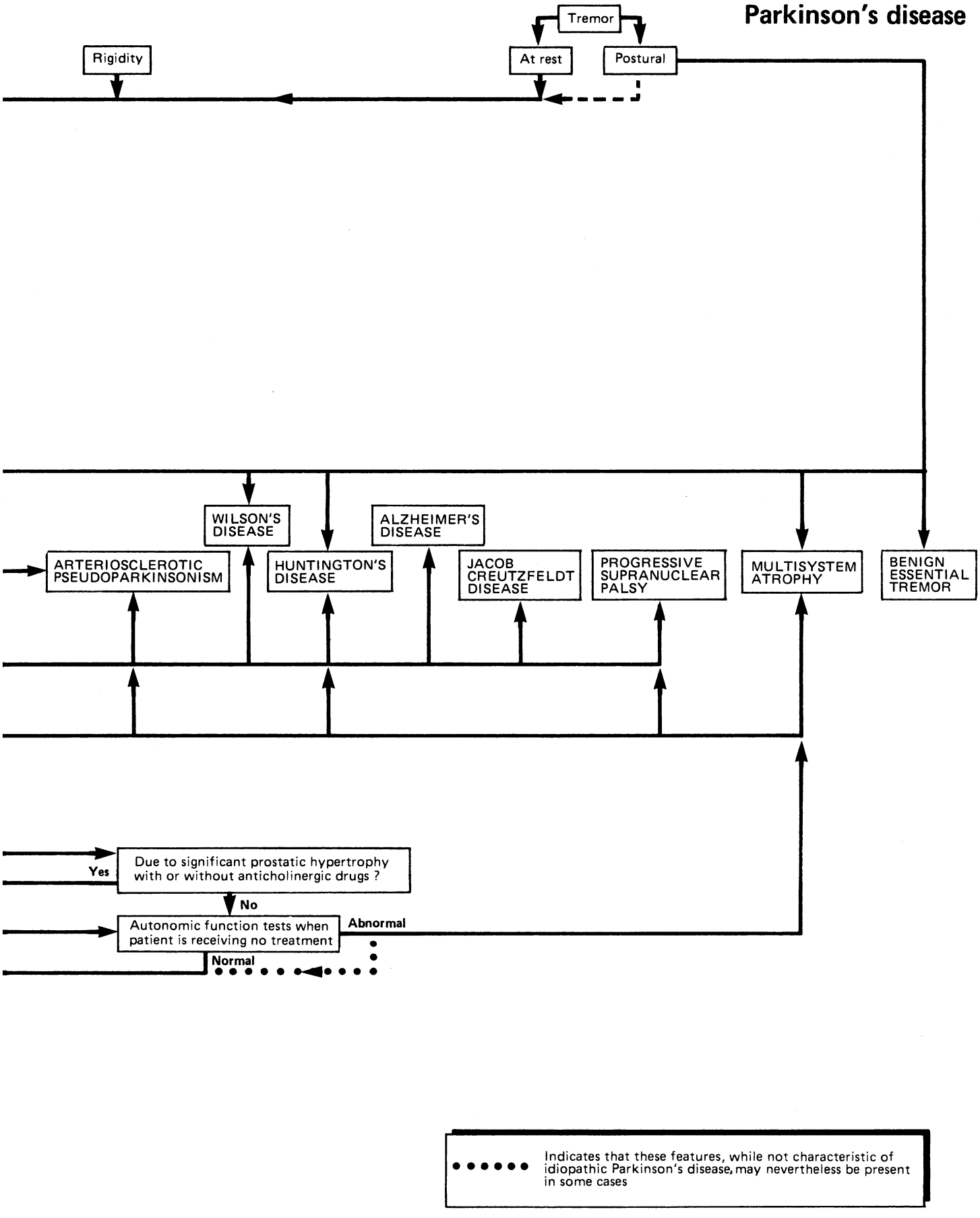

Postural abnormality
Akinesia
Two out of four signs present
PARKINSONISM
Onset within 15 years of encephalitis lethargica ; oculogyric crisis on no drug treatment ?
Yes
No
Taking neuroleptic or dopamine depeleting drugs ?
Yes
Persistent parkinsonism after 6 months with no drug treatment ?
Yes
No
No
Positive family history ?
Yes
No
POSTENCEPHALITIC PARKINSON'S DISEASE
DRUG INDUCED PARKINSONISM
History of cerebrovascular accidents, hypertensive lacunae, or "Biswanger's change" on computed tomography ?
Yes
No
Consider underlying dementia
Dementia ?
Yes
No
Supranuclear gaze palsy ?
Yes
No
Yes
Persists after drug withdrawal ?
Confusion on anticholinergic drugs or levodopa ?
Treatment
No
Urinary retention ?
Yes
No
Symptomatic postural hypotension with or without drugs ?
Yes
No
No
≥ 50% improvement on adequate dopamine replacement treatment ?
Yes
CLINICAL IDIOPATHIC PARKINSON'S DISEASE
No
Lewy bodies found at necropsy ?
Yes
IDIOPATHIC PARKINSON'S DISEASE


Parkinson's disease
Tremor
Rigidity
At rest
Postural
WILSON'S DISEASE
ALZHEIMER'S DISEASE
ARTERIOSCLEROTIC PSEUDOPARKINSONISM
HUNTINGTON'S DISEASE
JACOB CREUTZFELDT DISEASE
PROGRESSIVE SUPRANUCLEAR PALSY
MULTISYSTEM ATROPHY
BENIGN ESSENTIAL TREMOR
Yes
Due to significant prostatic hypertrophy with or without anticholinergic drugs ?
No
Autonomic function tests when patient is receiving no treatment
Abnormal
Normal
Indicates that these features, while not characteristic of idiopathic Parkinson's disease, may nevertheless be present in some cases

idiopathic Parkinson's disease will antiparkinsonian treatment sometimes be helpful, and even then possible benefits must be weighed against an increased risk of drug induced confusion.

*Multiple system atrophy*—Some patients with multiple system atrophy may display clear cerebellar or pyramidal features incompatible with a diagnosis of idiopathic Parkinson's disease. Others, however, present a picture of akinetic-rigid parkinsonism, usually (but not always) with lack of, or poor response to, dopamine replacement treatment. There are often additional signs and symptoms of autonomic failure which may antedate the parkinsonian features. These are often brought to doctors' attention when severe postural hypotension develops on treatment with dopaminergic drugs or urinary retention develops on treatment with anticholinergic drugs. In the absence of evidence of lesions affecting neurological systems other than the extrapyramidal and autonomic it is impossible to distinguish definitely during life between cases of multiple system atrophy with autonomic failure (the disease described by Shy and Drager)[6] and cases of idiopathic Parkinson's disease with autonomic failure.[7] The presence of disproportionate brain stem and cerebellar atrophy on computed tomography, younger mean age of onset, and possibly poor or absent response of the extrapyramidal syndrome to dopamine replacement may be pointers to multiple system atrophy, but diagnostic certainty can be obtained only after death. A supranuclear gaze palsy may be seen in this condition[8] as well as in progressive supranuclear palsy.

*Progressive supranuclear palsy (Steele-Richardson-Olszewski disease)*—The supranuclear gaze paresis of this condition[9] may present at any stage of the illness, so that repeated review of eye movements in any patient with "Parkinson's disease" is important. The paresis always affects downwards gaze and more severely than other directions. In very late cases a nuclear ophthalmoplegia may also be present. These signs may also appear in multisystem atrophy, the multi-infarct state,[10] and very advanced cases of Huntington's disease. Axial rigidity and neck extension may be present, as may severe speech and swallowing difficulties. In contrast to multisystem atrophy, autonomic failure is not a feature.

*Alzheimer's disease*—Many patients with Alzheimer's disease have mild extrapyramidal signs, usually in the form of an akinetic-rigid syndrome.[11] Both Alzheimer's disease and idiopathic Parkinson's disease are common, and hippocampal neurofibrillary tangles or brain stem Lewy bodies are 10 times more common in elderly brains than the prevalence of clinical Alzheimer's disease or idiopathic Parkinson's disease respectively. By chance, there will be considerable overlap between the two conditions.[12] Only about 20% of patients with Parkinson's disease suffer dementia[13] and then usually at an advanced age. Most of these patients with Lewy bodies and dementia probably have some additional and coincidental Alzheimer type change or cerebral infarction, or both.

*Jacob-Creutzfeldt disease*—This very rare condition usually presents with a short history of a rapidly progressive dementia, often with an additional akinetic-rigid syndrome. Myoclonus is often prominent, although a mild degree of myoclonus is also not uncommon in Alzheimer's disease. The disease is usually fatal within months. In only a few cases, where the illness may last several years, can the condition be misdiagnosed as a malignant form of Parkinson's disease.

## Recognising the typical case

This list of 10 differential diagnoses of parkinsonism is not exhaustive but covers the conditions that most often cause diagnostic difficulty. Other rare examples of conditions causing secondary parkinsonism include space occupying brain lesions, hydrocephalus, hemiatrophy, anoxia, carbon monoxide intoxication, Fahr's syndrome, manganese intoxication, pallidopyramidal degeneration, Hallervorden-Spatz disease, and congophilic angiopathy. Of considerable theoretical interest is the recently described pure (and levodopa responsive) parkinsonian syndrome resulting from deliberate self administration of, or occupational exposure to, the meperidine analogue 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[14]

Recognition of alternative causes of parkinsonism rests on the detection of atypical features, and this in turn depends on familiarity with typical cases. The vast majority of patients with parkinsonism will present little difficulty. They have no history of encephalitis, severe head injury, cardiovascular or autonomic disease, and have not been taking antidopaminergic or illicit drugs. There will usually be no family history of tremor, parkinsonism, or dementia. Examination will show only features of parkinsonism, with intact intellect and normal autonomic, pyramidal, and cerebellar function. Pupillary reactions and eye movements will be esssentially normal (although defective convergence and hypometric saccades and saccadic pursuit, and limited upgaze in elderly subjects, are allowable). Computed tomography, electroencephalography, and tests of intellectual function should be normal for the patient's age. The evolution of the condition should be appropriate to idiopathic Parkinson's disease, so that prominent early instability with falls and a rapid downhill course to severe disability over five years or so should be viewed with suspicion. Finally, perhaps the most useful single distinguishing feature is the degree of clinical improvement after adequate dopamine replacement treatment. Patients with the characteristics listed above can be given a confident clinical diagnosis of idiopathic Parkinson's disease, but in even the most experienced hands postmortem examination of the brain may disclose an unsuspected alternative diagnosis.

Some patients with parkinsonian symptoms, however, do not fulfil all these criteria. In practical terms, they fall into two groups: those in whom examination and investigations point with reasonable certainty to an alternative diagnosis, and those with ambiguous findings, who pose difficult diagnostic problems. Thus, patients may have evidence of dementia or autonomic failure due to idiopathic Parkinson's disease alone and may give a positive family history of benign essential tremor, Parkinson's disease, or dementia (all three conditions being common). For the same reason patients with idiopathic Parkinson's disease may also have coincidental cerebrovascular disease or changes characteristic of Alzheimer's disease, making the development of dementia more likely.

## Conclusion

Accurate diagnosis of Parkinson's disease has important implications, firstly, for prognosis, drug treatment, and general management of the individual patient and, secondly, for research. Usually there is no problem in diagnosing the typical case. However, the more exposure one has to patients with parkinsonian symptoms, and the more one is alert to atypical features, the more one recognises patients in whom one has reservations about diagnosing idiopathic Parkinson's disease. One is then faced with an increasing number of patients who may not have idiopathic Parkinson's disease, or who may have idiopathic Parkinson's disease but with other disease as well. Only careful clinicopathological correlation will ultimately increase our awareness and understanding of this problem. With this in mind, the Parkinson's Disease Society has set up a brain bank. Further details can be obtained from the PDS Brain Bank, Department of Neurology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

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