CURRENT SURVEY

Current concepts of Parkinsonism

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THERE has been a striking renewal of interest in Parkinson's disease and related conditions in the last 10 years. Until this time, there was little treatment available which was really effective. As with many other chronic diseases of the nervous system, the condition was widely thought of as being progressive and incurable. The discovery of an abnormality in the dopamine content of the basal ganglia and the subsequent elucidation of levodopa and amantadine have revolutionized the treatment of the condition. Though the problems of Parkinson's disease are far from a complete solution, the importance of repeated clinical, pathological and histochemical investigation of hitherto obscure diseases of the nervous system is emphasized by the results obtained in this disease. A similar but earlier situation was seen in Wilson's disease where a fundamental biochemical anomaly was discovered, and a rational form of specific therapy was evolved.

Classification

The commonest type of Parkinsonism encountered is idiopathic paralysis agitans (see Table 1). Drug-induced Parkinsonism is still common in mental hospitals, but all other forms are relatively rare. A post-encephalitic aetiology is acceptable if (a) there is a definite history of encephalitis, usually before 1930, (b) the onset of symptoms occurs before the age of 40, and (c) if oculogyric crises, tics or bizarre dystonic features are evident. Arteriosclerotic Parkinsonism is unacceptable as a clinical diagnosis unless the patient has had several defined episodes of 'stroke', and is, usually, hypertensive. The occurrence of idiopathic Parkinsonism in patients with cerebrovascular disease is not uncommon, but there is rarely evidence of a causal relationship. Parkinsonian signs are fairly common in a wide variety of diffuse cerebral degenerations, and are also seen following severe closed head injuries and occasionally in cases of brain tumour (Wilson, 1940; Pearce, Aziz & Gallagher, 1968). Even more rarely Parkinsonism

may be associated with carbon monoxide (Garland & Pearce, 1967) or manganese poisoning, and in cases of neurosyphilis (Table 1).

TABLE 1. Classification of Parkinsonism

Common types	Rare causes
Idiopathic paralysis agitans	Cerebral atrophy Cerebral trauma (severe) Cerebral tumour
Post-encephalitic Parkinsonism	Cerebrovascular disease Carbon monoxide poisoning Manganese poisoning
Drug-induced Parkinsonism	Neurosyphilis

Pathogenesis

The most constant pathological finding in Parkinsonism is a loss of pigmented neurones of the pars compacta of the substantia nigra. Less constantly there is a depletion of small nerve cells in the globus pallidus. Lewy bodies are characteristically seen in these areas but are not specific for the syndrome. The dopamine content of the substantia nigra and the corpus striatum is constantly depleted, to about 10% of normal, and this is reflected indirectly by a tendency to low homovanillic acid (HVA) in the cerebrospinal fluid (CSF). The degree of cell loss in the substantia nigra is proportional to the loss of dopamine in the striatum (Hornykiewicz, 1970). The brains of Parkinsonian patients also show some degree of depletion of serotonin, and this substance is derived from tryptophan.

Since HVA is one of the main metabolic breakdown products of dopamine, it is not unexpected that the measurements of this substance in the CSF has disclosed abnormally low values in most Parkinsonian patients. In many subjects the level is considerably increased by treatment with levodopa, which suggests that exogenous levodopa is transformed to dopamine within the central nervous system.

There is some evidence that the response to dopa therapy can be predicted by the level of HVA in the cerebrospinal fluid. It has been suggested that this test can be improved by measuring the CSF HVA after probenecid.

Mechanisms of drug therapy

Normal central transmission of nerve impulses reflects a balanced state involving three different biochemical systems (Table 2). These involve the passage of the nerve impulses across the synaptic

cleft by (1) dopamine, (2) acetylcholine, and (3) serotonin-histamine systems. In Parkinson's disease dopaminergic transmission is defective due to depletion of dopamine in the granular stores within the nerve cell. Since the dopamine and acetylcholine systems are to some extent opposite in action, Parkinsonian features may be improved by (1) the use of anti-cholinergic drugs such as belladonna or Artane, (2) by drugs increasing dopaminergic transmission or (3) by drugs inhibiting histamine or serotonin (Fig. 1). Dopaminergic transmission is

TABLE 2. Possible mechanism of drug action in Parkinsonism

	Neurotransmitter		
	Histamine serotonin	Dopamine	Acetylcholine
Actions of neuro-transmitter	Increases tremor and ? dyskinesia	Relieves: Rigidity ++ Akinesia ++ Postural imbalance ++ Tremor + Excess → dyskinesias	Increases: Rigidity ++ Akinesia + Postural imbalance + Tremor 0
Effect of drugs	Inhibited by antihistamines and ? antiserotonin drugs	Increased by levodopa and dopa decarboxylase inhibitors	Inhibited by anticholinergics

FIG. 1

FIG. 2

enhanced by the use of levodopa which can cross the blood-brain barrier and can be converted by the enzyme dopadecarboxylase into dopamine, and a similar effect may be achieved by the use of decarboxylase inhibitors (see Figs. 1 and 2).

The main effect of acetylcholine would appear to be in maintaining rigidity of the skeletal muscles and this probably operates both at a central level and by the peripheral release of this substance from pre-ganglionic and post-ganglionic nerve endings. These effects are blocked by anti-cholinergic drugs. The role of the serotonin-histamine system is not yet clear, but there is some evidence that this form of central neuro-transmission is important in the maintenance of tremor. The sympatholytic and ganglion-blocking effects of anti-histamines may be responsible for the slight improvement found after the use of these drugs. The administration of prostigmine considerably aggravates the abnormal movements of Huntington's chorea, and there is some evidence that this substance also aggravates Parkinsonian tremor; attempts have been made to use this as a test for predicting the response to treatment (Weiner, Harrison & Klawans, 1969).

Tryptophan has been suggested for the treatment of the depression and dyskinesias which complicate levodopa treatment, since there is some evidence of serotonin depletion in these patients. Abnormalities of tryptophan metabolism have been found in spontaneous depression, and chorea seen in pellagra—a tryptophan-deficiency state. However, the results of such therapy in small numbers of cases

have been variable, and sometimes unsatisfactory (Chase, 1970; Lehmann, 1971).

The mechanisms of action of amantadine are not precisely known; there is some evidence that it increases central neuronal catecholamine release, and it may also increase the small non-granular stores of dopamine (Fig. 2).

The main effect of increasing dopamine stores (as reflected by increased CSF levels of HVA) is clinically apparent as improvement in akinesia, abnormal and unstable posture of the body and limbs, voice, speech and rigidity. Some improvement of lesser degree is found in cases with severe tremor.

Clinical features

The prevalence of Parkinsonism is approximately one in every 1700 (Garland, 1952) in this country, and the maximum age at onset is between the ages of 50 and 70 years. The classical features of Parkinsonism are:

- (1) akinesia;
- (2) rigidity;
- (3) tremor.

Akinesia is manifest very early in the disease, but may be difficult to detect unless the patient is subjected to meticulous examination. Masking of the face, poverty and slowness of movement at rest are characteristic. The voice is monotonous and lacks its normal variation of pitch and volume. The fingers and later the arms tend to become slightly flexed, and eventually result in a characteristic stooped posture involving the neck, trunk and limbs. The

length of step is reduced and when marked leads to the characteristic shuffling gait. Postural abnormalities are also evident in the characteristic sudden way in which the patient drops into a chair, and in the difficulty he experiences in turning over in bed, or in crawling. In attempting to walk the legs may appear frozen and glued to the ground, but with persistence this gives way to a freer gait with limited steps and a tendency to shuffle. In the early stages these features may be slight in degree and easily missed, but they are most obvious to the vigilant observer, as the patient enters the consulting room.

Rigidity is usually of cog-wheel type, but this is often compounded by a lead-pipe type of diffuse rigidity. It appears earliest in the posterior muscles of the neck, and tends to be most evident in the proximal muscles of the limbs. Part of the sensation of rigidity imparted to the examiner's hands may be due to superimposed tremor.

The *tremor* of Parkinson's disease is usually recognizable on sight as a rhythmic intermittent affair initially confined to the fingers and wrists, or of one or both upper limbs. As the disease advances the tremor may be coarser in amplitude and affect more proximal segments of the limbs including the legs. Present at rest, the tremor is inhibited by voluntary movement, and is sometimes accentuated when the patient attempts to walk. Ocular signs are present in almost every patient, and often at an early stage of the illness. Infrequent blinking, and blepharoclonus when the eyelids are gently closed, are present in most patients. Tapping over the glabella elicits continued blinking of the eyes at the same speed and rhythm as the tapping motion. This contrasts with the normal subject in whom the reflex blinking ceases after less than five taps. It is important to avoid visual threat when tapping this area, and if performed with care this sign is present in almost every subject with Parkinsonism at an early stage (Pearce *et al.*, 1968). Impaired upward gaze and ocular convergence are found in many patients, and these signs may be combined with pupillary abnormalities in post-encephalitic Parkinsonism. Tremor and rigidity are often most marked in the arms, but rarely the legs are most affected early in the disease. Marked asymmetry of tremor and bradykinesia are common and may mimic pyramidal tract lesions in 'hemi-Parkinsonism'. A frozen shoulder or writer's cramp may precede the more classical signs of the disease by some months or years, and may be the earliest warning of the affliction.

Management

Although it is logical to treat all early cases of Parkinsonism with drugs to increase the dopamine stores, there is yet no evidence that such therapy alters the natural history of the disease, as opposed

to altering its clinical manifestations. If it could be shown that early treatment with levodopa would arrest the progression of the disease, then it would be proper to treat every case as early as possible, for the patient's lifetime. However, in the absence of such information, many early cases in which disability is virtually non-existent can be properly managed without drug therapy, but kept under observation.

Anti-cholinergic drugs

The use of anti-cholinergic drugs alone is justified in a mild case with slight functional disability, and it matters little which drug is used. A dry mouth, toxi-confusional states and urinary retention are not uncommon side-effects, particularly in the elderly, and therefore the dose should be small initially and gradually increased. Artane (benzhexol) 2–5 mg t.d.s., Disipal (orphenadrine) 50–100 mg t.d.s., Cogentin (benztropine) 1–2 mg daily are the drugs most commonly used. These produce improvement in the rigidity and subjective stiffness in some patients, but the degree of objective improvement is of the order of 20%. Sudden withdrawal can have a strikingly deleterious effect (Hughes *et al.*, 1971) and should be avoided.

Amantadine

If anti-cholinergic drugs fail to satisfactorily reduce the patient's symptoms, a trial of amantadine is indicated (Parkes *et al.*, 1970; Hunter *et al.*, 1970). This drug is introduced in a dosage of 100 mg b.d. and produces a significant beneficial effect beyond that obtained with anti-cholinergic drugs in about 50% of the patients (Pearce & Rao, 1970). The objective degree of improvement is of the order of 20–50%. The speed of onset is rapid and marked improvement is seen within 2–7 days in most cases. If a beneficial effect is not apparent by the end of 2 weeks, the dose may be cautiously increased to 300 or 400 mg/day (Parkes *et al.*, 1970). If this fails to be effective the drug should be abandoned. Amantadine is most valuable in the relief of akinesia, postural instability and rigidity (Rao & Pearce, 1971). A beneficial effect on severe tremor is rare. Side-effects of clinical importance are virtually non-existent in the standard dose of 100 mg b.d., but confusional states and hallucinations can develop in doses above 300 mg daily, but such doses are rarely indicated. Livedo reticularis and mild oedema of the legs occur in about 60% of patients, but are of no clinical importance.

Levodopa

Levodopa is indicated in patients not responding adequately to amantadine and anti-cholinergic drugs. It is usual to start with a dose of 0.25 g b.d. This can

be increased at weekly intervals by 0.5 g increments. Most patients obtain an adequate response on a total daily dosage of the order of 2.5–5.0 g. The drug should be administered in divided doses, usually on a 6-hourly basis with food, but after prolonged administration it is sometimes necessary to reduce the time intervals to 4-hourly, depending upon the variation of the patient's symptoms.

A beneficial effect is apparent in over 75% of cases. In the Eaton collaborative study (Keenan, 1970), of 509 patients followed for a mean of 10 months, the results of objective measurements were deemed moderate to excellent in 67%; only 10% were failures. The degree of objective improvement is of the order of 25–75%, and tends to be greater than that obtained from amantadine (Pearce, 1971). Rigidity, akinesia, gait and postural instability are features most affected by levodopa; the tremor may also be improved in a few cases, after prolonged treatment. The improvement produced by levodopa may take 2–4 months to be apparent. The beneficial effects of levodopa are not infrequently unintentionally inhibited by co-existing medication with phenothiazines (for nausea), reserpine (for hypertension) and pyridoxine (latent in 'tonics'). These are to be avoided as are possible causes of adverse drug interaction—notably MAO inhibitor drugs. Early side-effects consist of nausea, vomiting and transient confusional or hallucinatory states; these are related to dose and are reversible. Postural hypotension can be demonstrated in many cases but only rarely does this produce symptoms or necessitate reduction of dosage. Involuntary movements of the lips, tongue, face and jaw reported in 25% of cases, are usually more troublesome to relatives than to the patients. Dyskinesias affecting the neck and limbs, simulating torticollis and athetosis tend to develop after treatment of over 1 year's duration in some patients (Barbeau, 1971). These, too, are rarely prohibitive, but in some instances the dose of levodopa must be reduced on account of such movements. It is doubtful whether combinations of amantadine and levodopa have an additive effect, but levodopa may produce an improvement in the amantadine-treated patient, but not vice-versa (Godwin-Austen *et al.*, 1970).

It is clear that the continued use of levodopa is associated with frequent and sometimes serious side-effects, but these can usually be satisfactorily controlled by modification of the dose and timing of administration of the drug. This has to be carefully tailored to the needs of each individual patient. Poor results are seen in some advanced cases, especially if there is co-existing hypertensive cerebrovascular disease, and also in drug-induced Parkinsonism and in those with gross dementia. It is possible that if used in combination with decarb-

oxylase inhibitors (RO-44602) that a reduced dose of levodopa will be sufficient to control the symptoms. Used alone, however, RO-44602 has prohibitive side-effects. The combination has the added theoretical benefit of reduced toxicity due to levodopa and particularly a reduction in the increased catecholamine effects of levodopa on the myocardium. It is likely that further modifications of this treatment will develop in the near future, with increased effectiveness and reduced toxicity. One such possibility is 3-O-methyldopa, a new precursor of dopamine (Bartholini, Kurama & Pletscher, 1971).

Stereotaxic surgery

The vogue for stereotaxic surgery has been considerably impeded by the advent of levodopa, and although some authorities have said that surgical treatment has no place in the management of Parkinsonism, this is probably an overstatement. Patients with intractable and predominantly unilateral tremor in whom akinesia and postural defects are minimal are still substantially benefited by stereotaxic operations, though it is clear that these only modify the tremor and that the central features of the disease progress and eventually become disabling.

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