Section of Neurology

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Involuntary Movements other than Parkinsonism

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Drug Treatment of Diseases Characterized by Abnormal Movements

As a result of recent pharmacological and clinical developments our concepts of abnormal movement disorders have been redrafted, and in this short paper the current state of drug treatment of abnormal movement disorders (excluding Parkinson's disease and Wilson's disease) is reviewed.

Tremor and myoclonus will be dismissed briefly, mainly because medical treatment of both is unsatisfactory. With regard to tremor it is important to note that essential (familial) tremor is usually no more than socially disabling, as indicated by the prefix 'benign'. On the whole, drugs are not very effective and will need to be taken for a lifetime. If disability warrants drug therapy, diazepam seems as useful as anything, particularly if given in the largest dose the patient can tolerate without drowsiness. One wonders if its effects are merely due to the relief of anxiety, which itself increases all tremors and abnormal movements. This consideration has led to the trial of β-adrenotrophic antagonists in tremor in view of the observation that it can be enhanced by intravenous adrenaline due to stimulation of peripheral β-adrenotrophic receptors (Marsden *et al.* 1967). Propranolol has been shown to produce a significant reduction of benign essential tremor when compared to placebo (Gilligan *et al.* 1972, Dupont *et al.* 1973), but it is a powerful drug with many pharmacological actions and for this reason it is probably only warranted in patients with disabling tremor. Although one hesitates deliberately to suggest reliance on alcohol, there is no doubt but that it is a most effective and dramatic palliative for essential tremor and many patients treat themselves by or to a tot in preparation for a social event. Why alcohol works is unknown (but must be explored, for it is a clue to the cause of a disease with no identified pathology).

Parkinsonian tremor responds as well as akinesia and rigidity to levodopa, given time, and again is rarely the cause of much functional deficit. It is cerebellar intention tremor that is devastating to the patient, particularly in the young person with disseminated sclerosis, and unfortunately it does not respond to drugs.

The medical treatment of myoclonus is also unsatisfactory. Anticonvulsants are given to those patients in whom myoclonus is accompanied by seizures, but although fits may be controlled, the myoclonus frequently persists unchanged or is only slightly improved. Myoclonus on action is particularly disabling, for it leads to frequent drop attacks on walking and to difficulty in using the arms. I know of no drug to help it. Tics may respond to drug treatment: childhood tics and the syndrome of Gilles de la Tourette have both been shown to be controlled by haloperidol in a double blind study (Connell *et al.* 1967).

Chorea (including hemiballism and orofacial dyskinesia) and generalized torsion dystonia may be considered together, for the abnormal movements of both can be reduced by the same groups of drugs, although neither can be cured. Reserpine, tetrabenazine (a short-acting reserpine analogue with less peripheral sympatholytic side-effects), phenothiazines (such as chlorpromazine, prochlorperazine, thiopropazate dihydrochloride, or trifluoperazine) and butyrophenones (such as haloperidol) all produce some improvement in most patients, provided they are given a large enough dose. The effect of these drugs has been widely studied in Huntington's chorea, where

reserpine (Kempinsky *et al.* 1960), tetrabenazine (Pakkenberg 1968) and phenothiazines (Riser *et al.* 1959) are effective. The choice between them really depends on the side-effects they produce, for all probably have a common mode of action. Tetrabenazine has enjoyed a recent vogue because of its relative lack of immediate toxicity. It is effective in reducing chorea and hemiballism and sometimes also orofacial dyskinesia and generalized torsion dystonia (Dalby 1969, Godwin-Austen & Clark 1971, Swash *et al.* 1972). However, in my experience, it frequently produces depression such that many patients later stop taking the drug. Tetrabenazine, reserpine, phenothiazine and butyrophenones all produce parkinsonism when given in high enough dosage and their beneficial actions on abnormal movements are related to the degree of parkinsonism produced, which is dose-dependent. The higher the dose given the better the effect on abnormal movements but the greater the akinesia and rigidity. A dose reduction leads to improvement in the drug-induced parkinsonism but the abnormal movements recur and it becomes necessary to settle for the best compromise between the two. (The addition of anticholinergics or amantadine to the regime of such patients does not adequately control the drug-induced parkinsonism, nor does levodopa reverse it.) The sleepiness produced by high dosage of phenothiazines or butyrophenones can be partially overcome by the use of dexamphetamine. Other drugs of limited value in these conditions are diazepam and anticholinergics, such as benzhexol. Despite early claims that levodopa improves patients with torsion dystonia, the general experience is that it is without effect (Barrett *et al.* 1970), or actually makes it worse (Cooper 1972). Levodopa is said to make chorea worse (*see* Klawans 1970).

Spasmodic torticollis must also be mentioned briefly, for it is a common problem. No drug cures spasmodic torticollis (or writer's cramp for that matter) and it is rare to obtain more than a modicum of benefit from drugs such as levodopa, tetrabenazine, phenothiazines, haloperidol, benzhexol, amantadine, diazepam and antidepressants (Shaw *et al.* 1972). It is usual to try a series of such drugs and rarely one of them, quite unpredictably, gives some symptomatic improvement.

Abnormal movements produced by phenothiazines and butyrophenones are common in general medical and psychiatric practice. Acute drug-induced torsion dystonia occurs at the onset of treatment, often within a few hours of the first dose. The dramatic dystonic posturings of neck, trunk and limbs respond quickly to intravenous anticholinergics such as benztropine and biperiden, or to intravenous diphenhydramine. Akathisia and delayed-onset tardive orofacial dyskinesia often persist or get worse when the offending drug is stopped. If the psychiatric condition permits, an attempt to stop the responsible phenothiazine or butyrophenone should be made, or the patient should be switched to the less toxic piperidine phenothiazine derivative thioridazine or to reserpine or tetrabenazine which do not themselves cause these tardive dyskinesias. If the psychiatric indications are over-riding, the abnormal movements may be controlled by doubling the dose of the offending drug. Anticholinergic drugs are ineffective.

Although the treatment of most abnormal movement disorders by drugs is unsatisfactory, the pharmacological actions of those that do have some beneficial effect are of great interest, for they give some clue as to the disordered pharmacology underlying the diseases in question. Those drugs that do control chorea, hemiballism, orofacial dyskinesia and torsion dystonia all interfere with cerebral dopamine. All such drugs (i.e. reserpine, tetrabenazine, phenothiazines and butyrophenones) cause drug-induced parkinsonism, due, it is believed, to their ability to block the effective action of dopamine in the corpus striatum. Thus reserpine and tetrabenazine deplete the brain of dopamine (*see* Carlsson 1966) while phenothiazines and butyrophenones may block dopamine receptors in the brain (*see* Van Rossum 1966). Naturally-occurring Parkinson's disease is associated with degeneration of the nigrostriatal pathway containing dopamine and dopamine deficiency in the corpus striatum (*see* Hornykiewicz 1966). Thus drug-induced parkinsonism and Parkinson's disease are associated with failure of dopamine action in the basal ganglia.

Abnormal movement disorders such as chorea and torsion dystonia can be controlled to some extent by those drugs that cause parkinsonism, and similar movement disorders can be produced by levodopa in patients with Parkinson's disease. The abnormal movements induced by levodopa treatment may be the result of excessive dopamine formation in the brain. They occur with equal frequency if peripheral dopa decarboxylation is inhibited, indicating that they are due to a central action of levodopa or its metabolites. They are dose-dependent in that they occur with high doses of levodopa, get worse if the dose of levodopa is increased and disappear if the dose of levodopa is suitably reduced, all of which suggest that they are due to the excessive production of some levodopa metabolite, most likely dopamine. They appear to be aggravated by concurrent administration of apomorphine (Cotzias *et al.* 1970) or another drug, ET-495, that is said to stimulate selectively central dopamine receptors in the abnormal parkinsonian brain (Vakil *et al.* 1973).

The fact that phenothiazines and butyrophenones which block central dopamine receptors also cause similar abnormal movements may be explained by the finding that such drugs cause a compensatory increase in dopamine synthesis, perhaps as a result of transynaptic biochemical negative feedback (Nybäck *et al.* 1967). Thus, the dyskinesias induced by phenothiazines and butyrophenones may be due to excessive dopamine synthesis, as may the similar movements induced by levodopa in patients with Parkinson's disease. Why phenothiazines and butyrophenones both cause and relieve certain abnormal movements remains a tantalizing enigma. Perhaps this paradox may be explained by the presence of different populations of dopamine-sensitive neurones in the corpus striatum, some of which are inhibited by application of dopamine, while others are excited (York 1970). Excessive dopamine synthesis due to neuroleptic drugs may lead to over-stimulation of one population of striatal neurones even while the other is blocked (*see* Klawans 1973). Such a hypothesis is attractive, but levodopa and neuroleptic drugs have many actions other than those on brain dopamine. Future biochemical and clinical pharmacological discovery may clarify the contribution of disordered pharmacology to abnormal movements and may lead to effective and rational drug therapy.

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Involuntary Movements other than Parkinsonism: Biochemical Aspects

Biochemical investigations on movement disorder in general have been strongly influenced by the approaches found so fruitful in the study of Parkinson's disease. Here, advances occurred in a rational sequence. Dopamine was found at high concentration in the normal basal ganglia, then at low concentration in the basal ganglia of patients, and only subsequently were low concentrations of its metabolite homovanillic acid found in the CSF during life (Hornykiewicz 1966). This striking success led to the analogy that other movement disorders might also be associated with disturbances of dopamine or of other central transmitter amines. As animal experiments provide evidence that CSF amine metabolite concentrations give some measure of the turnover of their parent amines in the brain (Guldberg 1969), these metabolites have been determined in lumbar CSF of patients with movement disorders. By determining homovanillic acid (HVA) we roughly measure brain dopamine turnover; by measuring 5-hydroxyindoleacetic acid (5HIAA) we roughly measure brain 5-hydroxytryptamine (5HT) turnover (though in the latter case spinal neurones also contribute).

It is important to realize what can be deduced about brain amines from metabolite concentrations in the lumbar sac. A CSF abnormality may reflect either abnormal metabolism within brain amine synthesizing neurones or an abnormal number of those neurones. Also the concentration in CSF of substances originating in brain is presumably influenced by the CSF volume/brain volume ratio. Transport of the amine metabolites from CSF to blood and from ventricles to lumbar sac will also affect concentrations.

Most of these factors influence both HVA and 5HIAA concentrations. Therefore similar abnormalities of concentration of both substances in the lumbar sac could be due either to abnormal brain turnover of both of their precursors or to nonspecific variables unrelated to turnover. A strikingly abnormal ratio of HVA to 5HIAA is more indicative of abnormal brain metabolism though it does not prove it.

Results

Table 1 summarizes determinations in my laboratory of HVA and 5HIAA in lumbar CSF of subjects with various movement disorders. Subjects were not on drugs known to influence amine metabolism. Material was obtained from