Drug Treatment of Disease

DRUG TREATMENT OF PARKINSONISM

BY

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The drug treatment of Parkinsonism is merely palliative and not curative. Nevertheless, by steadily continued medication wisely prescribed and controlled, some of the more distressing symptoms may certainly be alleviated. As might be expected, cessation of drug treatment is followed by a relapse or exacerbation. Some of the symptoms of Parkinsonism prove to be more obstinate than others: for example, tremor is particularly difficult to check; whereas rigidity, and feelings of weakness or heaviness of the limbs, usually respond moderately well to medication.

The recent introduction of surgical methods of alleviation will probably not influence the scope of drug treatment in this malady. Parkinsonism, be it remembered, is a progressive affection, and surgery is scarcely likely to stem its advance. Even a fairly successful surgical intervention does not render the patient altogether free of symptoms; drugs will still be needed, even though the dosage may be smaller.

As in the case of many other chronic disorders, patients vary in their reaction to the disease. They differ in their standards of personal discomfort. They also differ in the rate of advance of the disease, and in respect of the individual sensitivity towards a particular drug. A preparation which suits one patient—or even the majority—may upset another. Some patients seem to be intolerant of almost every medicament that the practitioner can devise; fortunately, however, such troublesome cases are comparatively uncommon.

Since the end of the second world war the type of drug therapy used in cases of Parkinson's disease has notably changed. Up to about 1947 reliance was placed chiefly upon preparations of the Solanaceae—hyoscyne, hyoscyamine, atropine, belladonna, stramonium. Since that date these drugs have been virtually superseded by a number of synthetic preparations. These are claimed to be more effective—as indeed they generally are—and also to be complicated by fewer unpleasant side-effects. These comparatively new preparations fall into two main classes—namely, antispasmodics and antihistaminics. Some practitioners prefer to give these two classes of drug together.

Antispasmodics

Physicians with a wide experience of the drug treatment of Parkinsonism not unnaturally differ somewhat in their choice of these remedies. It would probably not be an exaggeration, however, to state that one preparation stands out as the drug of choice in the experience of most practitioners. This is *benzhexol* ("artane," "pipanol"), usually known in America as trihexyphenidyl. It is benzhexol which appears to suit best the greatest number of patients with Parkinsonism. As with almost every form of medication, the patient should start with small doses and then gradually increase them as his tolerance increases. Benzhexol is marketed in tablets of two strengths—namely, 2 mg. and 5 mg. Ordinarily the best policy is to start with one tablet of 2 mg. twice daily. The dosage may be increased at the end of a week to thrice daily. Thereafter it can slowly be augmented. Some doctors prefer to rely exclusively upon

the 2-mg. tablets rather than the 5-mg., and to prescribe if need be two or three such tablets, twice, thrice, or even four times a day. Quite high dosage is at times possible, though rarely so.

Side-effects of benzhexol sometimes appear in sensitive subjects even with small doses, but fortunately not often. With larger doses, nausea may occur and even vomiting. Even more common is a complaint of vague cephalic sensations, sometimes described as muzziness, heavy-headedness, or a tightness within the head. This particular symptom is often relieved by tablets of amphetamine combined with acetylsalicylic acid.

After benzhexol the second place among the most favoured drugs is less easy to identify. Perhaps the next most useful drug—though not as well known as benzhexol—is *benztropine methanesulphonate* ("cogentin"). This is a comparative newcomer, but it is already proving useful. Perhaps it influences tremor better than any other available preparations. This drug is dispensed in tablets of 2 mg. One may start treatment with half a tablet (i.e., 1 mg.) once a day, and thereafter cautiously the dosage may be increased. The drug acts slowly, and, being long-acting and cumulative, a single morning dose may prove adequate. Side-effects include some dryness of the mouth, nausea, and occasionally skin rashes.

Another deservedly popular drug, almost as valuable as benzhexol, is *procyclidine* ("kemadrin"). The clinical action is very similar to that of benzhexol. It is put up in 5-mg. tablets and treatment may be started with half a tablet twice a day until such time as one is sure that the drug is proving serviceable. Among the rare side-effects are dryness of the mouth, blurred vision from pupillary dilatation, and dizziness.

Some neurologists, however, are inclined to look upon *ethopropazine* ("lysivane") as the most useful drug. Some patients with Parkinsonism prefer this to benzhexol, just as some others (larger probably in number) would vote contrariwise. Ethopropazine is chemically related to an older preparation—namely, diethazine—but it is more active and yet less toxic.

After the foregoing drugs there is a considerable gap in the utility of the other pharmacological agents. Here one can include caramiphen or phenylcyclopentane carboxylic acid ("parpanit")—actually the first of the "newer" drugs which appeared after the war. A preparation which seems to be gaining favour is β -dimethylaminoethyl-2-methylbenzhydryl ether hydrochloride ("disipal"). This drug is dispensed in tablets of 50 mg., and the ordinary dose is four such tablets a day, cautiously increased to eight. It is said to act somewhat as a euphoriant, and to possess only the usual side-effects, which are readily overcome. The combination of this drug with ethopropazine has recently been advocated as an efficient remedy.

Antihistaminics

In addition to the foregoing spasmolytic drugs, there are various antihistaminics which are often given in cases of Parkinson's disease. Though at times administered alone, more often they are prescribed in association with one of the spasmolytics—e.g., benzhexol—and the combination is indeed often a useful one. Most popular of this class of drugs in the treatment of Parkinsonism is diphenhydramine ("benadryl"), put up in capsules containing 50 mg. The ordinary dose is one capsule one or four times daily. The commonest side-effect is drowsiness, and indeed this fact

may be utilized with advantage; the patient with Parkinsonism who has difficulty in getting off to sleep may well take 50–150 mg. (i.e., 1–3 capsules) on retiring. Another popular preparation is phenindamine ("thephorin") given in doses of 100 to 200 mg. either alone or preferably combined with benzhexol (8–10 mg. daily) or procyclidine (5–15 mg. daily). Thenindamine is marketed in 25-mg. tablets.

Psychiatric Symptoms

Although the phenomenon is quite rare, some patients unfortunately develop flamboyant psychiatric symptoms when taking these post-war remedies. In such cases it seems as though switching from one preparation to another does not meet the situation, and these types of drug simply have to be withheld altogether.

These unusual symptoms comprise in the first place a gradually mounting degree of confusion—of which the patient, incidentally, is fully aware. Then develop ideas of reference, at first regarded by the patient as foolish, but gradually increasing in plausibility. Next come vivid fantasies both in the sleeping and the waking states. Lastly an actual hallucinosis supervenes, with visions of imaginary animals and people, usually of a bizarre and even horrific nature. Tactile and auditory hallucinations are less common. Nothing short of complete abstinence from drug therapy is effective, and the patient regains intellectual normality only at the cost of enhanced physical disability.

Solanaceous Drugs

Finally, it is worth bearing in mind the older, that is pre-war, remedies which used to help patients with Parkinsonism. They still deserve a place within our armamentarium not only for those cases in which the newer drugs are badly tolerated, but also as an adjuvant. In other words, combinations of the antispasmodics with the solanaceous drugs may prove to be quite useful. Of the latter drugs, hyoscine hydrobromide was the one most often used. It was generally prescribed in initial doses of 1/150 gr. (0.4 mg.) thrice daily, often in a mixture to which potassium bromide 5–10 gr. (0.3–0.65 g.) and tincture of nux vomica 10 minims (0.6 ml.) were added. Sometimes it was prescribed in the form of a tabella which was allowed to dissolve under the tongue.

Atropine or belladonna were also given. Patients with the post-encephalitic types of Parkinsonism seemed to respond better than cases of paralysis agitans—but that, of course, is the common experience and applies to all forms of drug therapy. Those patients who are particularly incommode by excessive salivation are often helped most by atropine or belladonna. Large doses are needed, and it is difficult to avoid such complicating symptoms as blurred vision, palpitations, and nausea. When employing belladonna it is worth remembering that, while young patients tolerate this drug well, some are naturally sensitive to it. In these cases the side-effects may be so distressing as to preclude the drug, and the major complications include psychiatric states of confusion and mild delirium.

Formerly some attention was paid to what was called the Kleeman treatment. At times it was beneficial and it may still have a small place in the modern therapy of Parkinsonism. The object here was to give the patient rapidly increasing amounts of atropine so as to condition the patient to comparatively high doses. Kleeman would begin with 0.5 mg. of atropine daily in the form of a ½% solution of atropine sulphate given in two doses (one drop containing 0.25 mg.). This is increased by 0.5 mg. daily, spread over three doses, so long as any clinical improvement is produced. Thereafter the dose is gradually reduced in order to determine the optimal amount. Kleeman found this to be as a rule 3 to 7 mg. of atropine daily (though some other physicians used even higher doses).

There were several useful and "elegant" preparations on the market which were often of great service in the treatment of Parkinsonism. They were relatively mild in effect.

and, being largely devoid of complications, could be prescribed with considerable latitude. Some of these preparations combined in pillule or tablet form small amounts of hyoscine, atropine, and hyoscyamine.

Lastly, stramonium was a most useful palliative treatment, especially in the post-encephalitic varieties of the disease. By shrewd prescribing, it was possible gradually to increase the dosage and to attain comparatively high and clinically effectual amounts. Though the tincture of stramonium was often prescribed—doses starting at 10 minims (0.6 ml.)—experience showed that the dried extract of the drug (ext. stramonii sicc., U.S.P.) was the most effective. Here the initial dosage was ordinarily 0.25 g. three times a day. The side-effects of stramonium resemble those of atropine, but they were less common and milder.

A. F. Hurst, who never shrank from prescribing drugs in high dosages, used to advocate the giving of large amounts of stramonium, by dint of gradual augmentation coupled with the administration of pilocarpine. Treatment would begin by the patient taking 10 minims (0.6 ml.) of tinct. stramonii in ½ fl. oz. (14 ml.) of water on waking, after lunch, and after tea. If stiffness interfered with sleep, a fourth dose was given to the patient as he retired. On alternate days 1 drachm (3.5 ml.) would be added to each dose, so that in eight days the dose would be doubled. This gradual increase would go on until the patient complained of blurred vision or undue dryness of the mouth. Pilocarpine nitrate, 1/10 gr. (6.5 mg.), would then be added to the latest dose of stramonium, and once more the increase of 1 drachm (3.5 ml.) on alternate days would go on, until slight toxic symptoms developed.

EARLY DISTURBANCE OF BEHAVIOUR IN RELATION TO MENTAL DEFECT*

BY

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In the majority of cases of mental defect there are no specific or qualitatively distinct forms of behaviour which could be the basis for early recognition of abnormality. In most instances there exist merely quantitative changes; the behaviour of the child has not reached the level of development which might be expected in view of the chronological age.

Value of Early Assessment

I would like first to ask what is the purpose of the medical adviser in attempting to make an early diagnosis of mental defect and, indeed, to question whether such attempts are always wholly praiseworthy. For practical purposes it is possible to distinguish between two levels of mental defect, high grade and low grade. The former term covers the feeble-minded; the legal validity of this term as at present used has been called into question, and there is some danger that it may be replaced by the even more elastic word "psychopath." The low-grade patients include the idiots and imbeciles, and for those who prefer some attempt at numerical estimation an intelligence quotient of 50 is usually taken as marking the borderline between the high- and low-grade groups.

In regard to adult mental defectives, more than half the population of institutions is made up of high-grade cases (O'Connor and Tizard, 1956). In the case of children, however, the position is quite different, since the Education Act of 1944 removed the necessity to

*Based on lecture to Assistant County Medical Officers, Essex, 1957.