A REVIEW OF DRUG THERAPY IN PARKINSONISM*

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THE ideal treatment would correct or eliminate the cause or causes of parkinsonism and would not only relieve its symptoms but would prevent the progression of the underlying disease process and, hopefully, would completely reverse the disease once established. Until such time as an etiologic therapy will be possible, however, we must continue to rely on a supportive, palliative, and symptomatic therapy. As symptomatic treatment, our present armamentarium, consisting of a small number of centrally active anticholinergic drugs, leaves much to be desired, for we can provide only incomplete relief of some of the symptoms and we cannot alter the progress of the disease. At best, we may expect a modest improvement in mobility and general motor performance, subjective well-being—perhaps due to a euphoriant effect—and a slight decrease of tremor and rigidity.

Most clinicians agree that the beneficial effect on rigidity is greater than that on tremor. Precise measurements using accelerometers and force-displacement transducers have confirmed this impression.[1, 2] Rigidity, however, has generally been used in a broad sense to reflect mobility and general motor performance, thereby encompassing the meaning of the term akinesia. Although a decrease in tremor and rigidity defined as increased resistance to passive movement can be shown by strain-gauge measurements, it is doubtful just how these changes relate to the over-all increase in spontaneity of movement and general mobility that may be observed on medication.

Primarily akinetic patients having little or no tremor or rigidity and patients in whom these positive manifestations have been effectively reduced by stereotactic surgical procedures may derive as much benefit as the more typical or unoperated patients. Careful observation

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suggests that the benefits derived from anti-Parkinson drug therapy depend not only on a reduction of tremor and rigidity but reflect a more general effect, including an amelioration of akinesia and gait disturbances.

Recently, greater emphasis has been placed on the bradykinesia, the gait disturbance and the loss of postural and righting reflexes in parkinsonism[3] and there has been a corresponding tendency to relate the effects of new drugs to these negative phenomena. In contrast, 19th-century authors devoted more attention to tremor and described treatment chiefly in terms of its calming effect. Our notions of the effects of newer medication do not necessarily reflect differences in drug action but rather changes in our clinical concepts.

Although it has often been implied that certain drugs are especially beneficial for particular aspects of the Parkinson syndrome, there is little evidence that there really are significant differences in the way each drug influences the parkinsonian patient. When specific comparisons have been made, no significant differences have been observed. Attempts to study in detail the effects of drugs on specific manifestations of the Parkinson syndrome have not thus far shed light on their mode of action, and one may wonder whether such an approach is likely to be fruitful. In the light of these circumstances—changing concepts of the action of the standard drugs, uncertainty as to the basic nature of their effects, and difficulty in distinguishing one drug from another—it seems preferable at this time simply to consider anti-Parkinson activity in a broad sense.

Certain important aspects of drug therapy, although familiar to clinicians experienced in treating parkinsonism, have received little mention in the literature and have not received sufficient attention in the evaluation of new drugs. For example, few investigators have taken into account the relationship between the severity of the disease and the degree of benefit that drug treatment may provide.[4] We have been impressed by the observation that very early cases who present only tremor and little akinesia or gait disturbance frequently derive so little benefit that they are unwilling to accept the usual atropinic side effects while the more advanced cases with gait disturbance and difficulty in performing routine daily living activities seem to derive the most benefit. Indeed, in such cases, cessation of drug therapy frequently produces a marked aggravation of parkinsonism. An ambulatory patient, largely

independent in his daily living activities, suddenly is confined to bed and chair unable to arise, dress, or feed without assistance.[5] Usually the "withdrawal response" reaches its peak in two or three days and may be promptly terminated by reinstitution of drug treatment. Parenteral administration in such cases may result in noticeable improvement in 20 to 30 minutes, although the full therapeutic response may not be achieved for several days. Thus patients in a moderately severe stage of the disease often display a striking improvement on medication as compared to their status on placebo. Such cases of dramatic response to therapy are encountered in almost any drug trial and have often been presented as evidence of clinical efficacy. The failure to consider the severity of the patient's disease may account at least in part for conflicting and sensational reports of drug effects. Far-advanced patients in the cachectic stage of Parkinson's disease are not benefited by drug therapy. Their rigidity and tremor may be reduced and their mobility may be slightly increased, but the response is usually not sufficient to represent a significant change in function.

As progression of the disease carries the patient though stages of increasing severity and disability, response to therapy may be observed to change from little or no benefit to a definite effect and then, in later stages, it may appear that the drugs are losing their efficacy. Many clinicians have spoken of the development of tolerance to the beneficial effects of the drugs and have advocated changing periodically to others, thereby justifying the promotion of a number of similar—indeed clinically indistinguishable—drugs for the treatment of parkinsonism. Is it tolerance or progression of the disease? The observation of a withdrawal response in such circumstances often serves to settle the question.

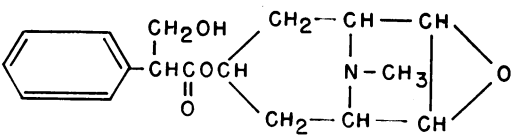
It is another familiar but poorly documented observation that the relationship of therapeutic response to dosage is not fully linear. On progressively increasing the daily dosage of a standard drug, one soon reaches a level beyond which further increase does not yield additional benefit. In fact, the patients may be made worse and atropinism is likely to result. The optimal dosage varies considerably from one patient to another and may be much smaller than that usually recommended. There is also considerable individual variation in tolerance of side effects so that the toxic dosage range may be very close to or overlap the optimal anti-Parkinson dose. A superior anti-Parkinson effect at a dosage level producing unacceptable toxic effects is frequently observed

but has only occasionally been recorded.

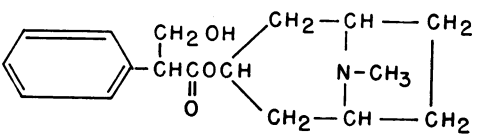
The marked day-to-day and diurnal variability in the manifestations of parkinsonism reflecting psychic and other factors most dramatically exemplified in the well-known paradoxical kinesia are greater than the best drug response. The remarkable effect of motivational factors in particular complicate assessment of treatment and would seem to compromise seriously the value of any observation confined to a brief period of time. Thus attempts to obtain objective measurements because they are necessarily brief and periodic are not reliably representative of the patient's status during a meaningful period of time such as a day or an entire week.

The multiplicity of the pharmacologic actions of our anticholinergic drugs is reflected in their troublesome side effects and toxicity. The least discussed but most frequent of the toxic effects includes the psychic changes that in the fully developed syndrome are readily recognized as the classical atropine psychosis. The most common psychic effect, and it occurs in many if not all individuals taking these drugs, is an impairment of recall and recent memory. Recent experiences with atropine coma used as a somatic therapy in psychiatry[6] and studies of the psychic effects of atropine and related drugs in normal subjects[7] indicate that these drugs may properly be considered psychotomimetic agents. Indeed, deliberate use of the amnesic effects has long been recognized in anesthesia, and abuse of the belladonna alkaloids as hallucinogenic agents has been recorded.[8] More gross psychotoxicity such as mental confusion, restlessness, disorientation, and hallucinations—chiefly visual—occur in at least one fourth to one third of Parkinson patients on routine dosages.[9] Larger doses may produce vertigo, slurred speech, ataxia, hyperreflexia, and extensor plantar responses. It is sometimes difficult to know whether such effects reflect the disease or the toxic effects of the drugs; frequently they are erroneously ascribed to the disease.

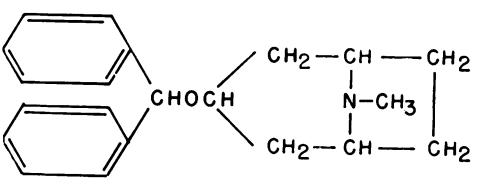
It is not necessary to review here the usual peripheral atropinic side effects such as mydriasis, paresis of accommodation, reduced salivation, etc. Several toxic effects, however, deserving particular mention include the aggravation of coexisting glaucoma, increasing the constipation, which is itself a common feature of paralysis agitans, urinary retention in men with prostatism, parotitis, and hyperthermia. The suppression of peripheral heat-loss mechanisms predisposes to fever in warm weather and may have serious consequences. Indeed, in Forrer's atropine coma



SCOPOLAMINE



ATROPINE



BENZTROPINE
(Cogentin)

Fig. 1

therapy,[6] hyperthermia has seemed to be the chief danger and was responsible for the only death encountered in an extensive experience with massive dosages.

The Drugs

It is probably safe to say that every medicinal alkaloidal preparation known to man has been employed in the treatment of parkinsonism at some time in the past century. Surely it is significant that only those containing atropine or scopolamine have consistenly maintained a reputation for clinical value. Although they are perhaps somewhat less troublesome with respect to peripheral anticholinergic side effects, none of the synthetic drugs presently available possesses a greater degree of anti-Parkinson activity.

The first synthetics tried in parkinsonism were the quartenary derivatives of atropine and scopolamine. Their failure indicates that it is the central actions of atropine that are the basis of its anti-Parkinson

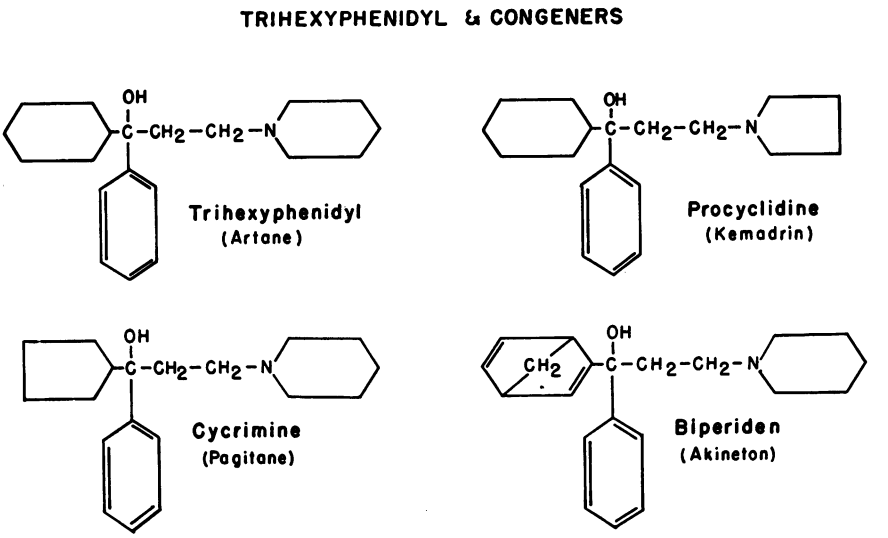


Fig. 2

activity. Numerous atropinelike derivatives have been obtained by modifying the acidic moiety of atropine. One of these, Cogentin, is simply the diphenyl ether of tropanol and closely resembles atropine (Figure 1). It is the most potent of the synthetic anti-Parkinson drugs, being effective in doses of ½ to 1 mg. orally, but does not really differ from atropine in any clinically significant way.

Other synthetic drugs comparable to atropine in anti-Parkinson activity fall into one of two groups: trihexyphenidyl and its congeners, and the aminoethyl derivatives of phenothiazine.

Trihexyphenidyl was one of a series of piperidine compounds developed by Denton and his co-workers[10] and investigated in the 1940's by Cunningham[11] for antispasmodic activity. Additional analogues of this series of compounds were subsequently developed and a number have received trial in the treatment of parkinsonism; three are commercially available in the United States (Figure 2). It is not surprising from a glance at their molecular structure that these drugs are equipotent and clinically indistinguishable.

The first group of phenothiazine derivatives introduced into clinical medicine (Figure 3), Fenethazine, Phenergan, Diparcol, and Parsidol, were found to have some anti-Parkinson activity. Like atropine, they

AMINOETHYL DERIVATIVES OF PHENOTHIAZINE

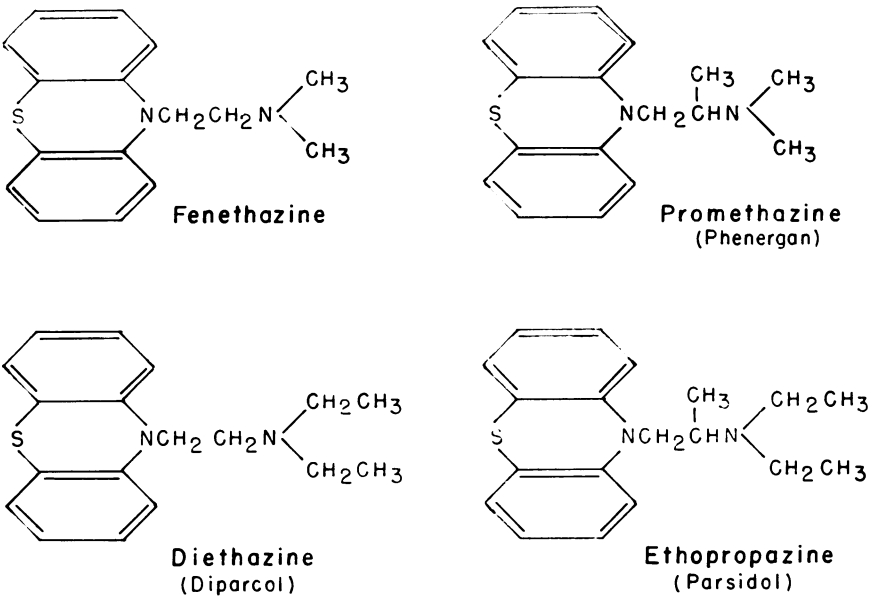


Fig. 3

possess significant anticholinergic, antihistaminic, sedative, and local anesthetic properties. Diparcol was withdrawn from clinical use in the United States about 10 years ago because of reports of agranulocytic reactions, but it is still used in other countries. Such accidents have also occurred with Parsidol as with other phenothiazine derivatives.

Three antihistamines – diphenhydramine (Benadryl), orphenadrine hydrochloride (Disipal), and chlorphenoxene (Phenoxene)—are currently promoted as secondary drugs for the treatment of parkinsonism. The latter two are closely related derivatives of Benadryl and their structural similarity is evident at a glance (Figure 4). Individuals vary in their tolerance to the side effects of these drugs—drowsiness is the most troublesome—but otherwise no reason has yet been shown for preferring one of these agents to another. Many other antihistamines seem to be equally effective, and some are employed as anti-Parkinson agents in other countries. Orphenadrine citrate has been marketed as Norflex for use as a muscle relaxer in a tablet containing a larger amount of

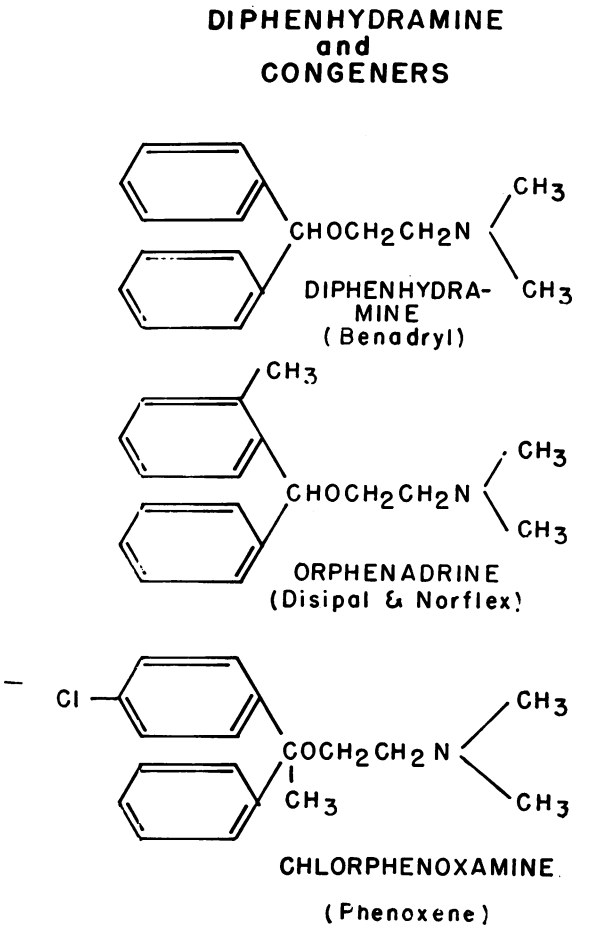


Fig. 4

orphenadrine. In some patients it may be a more satisfactory dosage form than Disipal.

Newer Therapeutic Approaches

The mounting tide of interest in the biogenic amines in recent years has led to the suggestion that a defect in catecholamine metabolism may play a significant role in the Parkinson syndrome. The original Brodie hypothesis relating the clinical effects of reserpine to the marked depletion of norepinephrine and serotonin that this agent caused in the central nervous system as in other organs naturally suggested that a similar

abnormality might be involved in parkinsonism. Although reports of various abnormalities detectable in the urine have not been confirmed, O. Hornykiewicz's finding that the concentrations of dopamine, norepinephrine, and serotonin in the brain as measured in postmortem material are greatly decreased in parkinsonians[12] has lent some substance to this hypothesis. The fact that these deficits were found in postencephalitic as in idiopathic cases, however, suggests that these chemical abnormalities are secondary to the basic disease process and raises some doubts regarding their relationship to the symptoms. Recent reports of a similar decrease in biogenic amines following experimental lesions at various sites in the brain in animals raise many interesting questions and indicate the need of caution in interpreting the chemical data available at this time.

Whatever merit the catecholamine theory of parkinsonism may ultimately prove to possess, a number of therapeutic experiments have been based on this new rationale. DOPA has been administered orally and parenterally in the hope of correcting the deficiency of catecholamines in the basal ganglia. The akinesia of parkinsonism is said to be reversed for periods of time varying from 4 to 24 hours. Initial enthusiastic reports have been followed by indications that pretreatment with MAO inhibitors is necessary to obtain an appreciable "DOPA effect." Subsequently a number of investigators, repeating a pattern that is all too familiar in the history of the treatment of parkinsonism, have studied the use of DOPA but have either been unable to confirm the described response to DOPA or have noted only an occasional and transient effect. Despite enthusiastic claims of therapeutic benefit, no evidence has been presented that the DOPA effect is in any way specific or that it differs from the effect of other sympathomimetic amines. Similar responses have been noted before with the use of amphetamine and other analeptics. In any case, the cardiovascular pressor response to DOPA and the need of parenteral administration render this mode of treatment clinically impractical.

Monoamine oxidase inhibitors have been advocated with a view to retarding the catabolism of the biogenic amines and thereby increasing their cerebral concentration. Bernheimer *et al.* have recently reported that MAO inhibitors alone restore the cerebral catecholamine levels to normal in parkinsonians.[13] However, despite several favorable reports, extensive clinical trials of MAO inhibitors have not established their

value in parkinsonism, not even in drug-induced pseudoparkinsonism, and their alleged efficacy remains unproved. In view of recent experiences with MAO inhibitors and catechol-containing foods, the combined use of these agents with DOPA as advocated by Hornykiewicz cannot be recommended as a routine procedure, even if it did produce a significant remission of parkinsonism. It is interesting, incidentally, to note that the alkaloid harmaline now known to be a very potent MAO inhibitor was extensively used in parkinsonism in the 1930's, ultimately with negative results.[14]

The fact that pyridoxine is essential to the enzymatic decarboxylation of DOPA to dopamine has suggested the use of this vitamin with a view to influencing catecholamine metabolism favorably. There has been some recent comment citing a favorable response that seems difficult to accept in view of the careful evaluation of this agent conducted by Barker and others circa 1940 with negative results.[15]

In view of the catecholamine hypothesis of parkinsonism, the effect of alpha-methyl dopa should be of great interest. Unfortunately, clinical data available at this time are confusing. Although it has been reported to benefit parkinsonism, this drug has also been reported to aggravate or even induce parkinsonism. In a clinical trial using both oral and parenteral administration in doses producing sedation and subjective symptoms of hypotension we did not find an appreciable effect in a single case of parkinsonism. In some instances, there appeared to be an increase in tremor—an effect noted since by others.

Another recent therapeutic approach suggested by the analogy of akinesia with the psychomotor retardation of depression is the use of the so-called "psychic energizers." Imipramine in particular has been advocated with the implication of a certain specificity for akinesia, and a number of reports seem to confirm a definite if limited therapeutic effect. In our own experience, both imipramine and amitriptyline can be used with slight benefit in most parkinsonians but do not seem to be in any way specific for akinesia. In a double-blind comparison of imipramine versus desmethylimipramine and placebo, we found a slight but definite anti-Parkinson effect but could not distinguish the secondary analogue from the placebo. Since desmethylimipramine retains the psychotropic effects of imipramine, it seems doubtful that the anti-Parkinson efficacy of the latter drug can be ascribed to its "energizing" effect.

Neuropharmacology

Although we do not really know how the anti-Parkinson drugs produce their therapeutic effect, it seems likely that it relates in some way to their central anticholinergic activity. A perusal of the molecular configuration of effective drugs in comparison with ineffective analogues indicates readily that the structural correlates of anti-Parkinson activity are those generally recognized as the correlates of central anticholinergic activity. All are tertiary amines with the nitrogen atom preferably inclosed in a ring structure and situated at the optimal distance from the acidic moiety of the drug molecule for anticholinergic activity. All anti-Parkinson drugs share with atropine the property of blocking electrocortical arousal, whether induced by photic stimulation or by direct electrical stimulation of the mesencephalic reticulum. Their clinical efficacy correlates well with their ability to block in animals the effects of the centrally active cholinergic tremorine but not with other tremorigenic agents such as nicotine, harmine, strychnine, and numerous aliphatic alcohols, each of which seems to have its own set of antagonists. The mechanism of action of tremorine has been related by some to changes in the biogenic amines but it must be noted that it also produces a marked increase of acetylcholine in the brain that correlates well with the time of appearance and the duration of tremor.[16]

Present pharmacological and physiological data suggest that the site of action of the anti-Parkinson drugs lies in the brain stem. In support for this view we may note that they suppress tremor produced by stimulating the mesencephalic reticular substance or by lesions placed in the mid-brain tegmentum. Moreover, many neurons in the reticular system appear to be cholinergic and cholinoceptive. Acetylcholinesterase is present in the reticular system as well as in the substantia nigra and cranial n. motor nuclei. Iontophoretic stimulation with microelectrodes of reticular neurons in the brain stem of cats indicate that many are cholinoceptive, some adrenoceptive, while a third group seems to possess both properties. It may be suggested that anti-Parkinson drugs act by inhibiting cholinoceptive neurons in the brain stem and perhaps the thalamus.

The synthetic drugs that have been used in parkinsonism were by-products of the search for a peripheral anticholinergic drug that would

not have the central effects of atropine. However, if anti-Parkinson activity is in fact due to inhibition of cholinoceptive neurons in the brain stem, then we should be looking for the opposite, that is, a centrally active anticholinergic with little or no peripheral effect.

Evidence is available that suggests that this is entirely feasible. Various modifications of atropine congeners are known that can greatly reduce peripheral antiacetylcholine activity without losing the ability to block tremorine-induced tremor.[17] There is also reason to believe that undesirable central effects may be reduced by appropriate modifications.

Studies of structure-activity relationships among psychotomimetic drugs suggest the possibility of finding an agent lacking the toxic psychic effects that so often complicate our present therapy of parkinsonism. Psychotomimetic activity can apparently be dissociated from anticholinergic activity.[18] The fact that Brom-LSD lacks the hallucinogenic properties of LSD although it produces other central effects suggests the possible value of investigating the effect of similar substitutions on one of our standard anti-Parkinson agents. These brief speculations are presented merely to suggest that with the knowledge and methods now available we may very well be able to develop more satisfactory anti-Parkinson drugs than we now possess.

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