Current Management of Parkinsonism

JOHN R. TAYLOR, M.D.

Assistant Professor, Department of Neurology, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

James Parkinson, a London general practitioner and political activist,[1] delivered his essay on the shaking palsy in 1817 and encouraged others who "humanely employ anatomical examination" to study the cause and nature of "this malady." Even in his wildest fantasies I seriously doubt that he dreamed of the extent to which his advice would be followed. Today, in spite of a recognized incidence of only 20 cases per 100,000 persons per year,[2] articles concerning this disorder appear in nearly every issue of many neurology journals. The reason for this interest is explained by the significant work that took place in the 1960's. During that period a series of biochemical steps leading from tyrosine to biogenically active amines was elucidated,[3] and, further, the action of these amines at brain synapses was convincingly hypothesized.[4] Tyrosine is converted to levodopa and then to dopamine, a neurotransmitter. Since dopamine parenterally does not enter the brain, it was found that large doses of its precursor, levodopa, resulted in some levodopa entering the brain, driving the reaction in favor of more dopamine, and therefore enhancing neurotransmission. It is this concept that has excited neurologists out of all proportion to the frequency of Parkinson's disease in the general population. As is now known, the pathology of Parkinson's disease lies in the substantia nigra,[5] where neurons that ordinarily project to the striatum[6] and transmit via dopamine are degenerating; hence the rationale for the use of levodopa as a therapeutic tool. As attractive as this model is, I remain suspicious that the mechanisms are far more complex than as yet determined.

Correspondence and reprint requests to: Dr. John R. Taylor, Department of Neurology, Box 698, Medical College of Virginia, Richmond, Virginia 23298.

In the management of Parkinson's disease, one must be reasonably certain of the diagnosis. In spite of the foregoing sophisticated biochemistry, there is really no laboratory test for the disease, so it becomes an entity that must be recognized on purely clinical grounds. While the differential diagnosis can be quite extensive and includes such rare entities as manganese poisoning, as well as such usually apparent causes as phenothiazine intoxication or carbon monoxide sequelae, several disorders and etiologies account for most of our diagnostic problems. Although we think of Parkinsonism as a triad of rest tremor, rigidity, and akinesia, the onset may be with any one of these, and if it is with tremor, the distinction from essential tremor may be difficult. Essential tremor, sometimes inherited as an autosomal dominant, is occasionally seen and resembles Parkinson's disease. The tremor is a little faster[7] and while many authors state that it begins in an arm, as does Parkinsonism, the head often begins to titubate soon after the tremor begins in the hand. The onset of essential (or familial) tremor is usually earlier than in Parkinson's disease, and may even be in childhood. Its progression is slow, and it often stabilizes so that the physician may encounter a patient who recounts years of tremor, often misdiagnosed as nervousness or Parkinsonism. The rigidity and akinesia of the latter are never present in essential tremor. Patients with essential tremor usually display more tremor on intention than at rest, and often find that a moderate amount of alcohol relieves their tremor for a time. The combination of family history, long-standing symptoms, head titubation, and absence of either rigidity or akinesia will almost always establish the diagnosis of essential tremor. Levodopa is of no value.

Cerebellar tremor associated with cerebellar degeneration or other cerebellar diseases is an occa-

sional problem. Usually the absence of rest tremor, akinesia, and rigidity, plus other signs, for example, truncal ataxia, will allow an easy distinction.

A variety of degenerative diseases may present with poverty of motion and a degree of rigidity. Most of the presenile dementias can present in this fashion, but the predominance of the dementing element usually permits an easy differential diagnosis to be made. Certain rare entities have been a problem, however, one of which is progressive supranuclear palsy.[8] Patients with this disease display many Parkinsonian features, including, occasionally, involuntary movements; however, early loss of voluntary vertical gaze, especially down gaze (with spared reflex gaze mechanisms, for example, oculovestibular reflexes) associated with conspicuous rigidity, along with a fairly rapid course, are usually enough to permit most clinicians to arrive at the diagnosis. Levodopa is of limited, if any, benefit.

Shy-Drager syndrome (idiopathic orthostatic hypotension)[9] is another rare syndrome that has led to some diagnostic difficulty, though usually easily resolved. This disease reflects, to some extent, a continuum of Parkinsonism; however, the Shy-Drager syndrome evinces a much more profound involvement of autonomic nuclei, with consequent severe orthostatic hypotension, anhidrosis, and incontinence, to the degree that the usually present bradykinesia, rigidity, and occasional tremor are overshadowed. Nevertheless, since orthostatic hypotension is occasionally a feature of Parkinsonism, the distinction is sometimes a problem. Patients with Shy-Drager syndrome respond poorly to levodopa.

Apart from these syndromes, the differential diagnosis of Parkinson's disease revolves mainly around its etiology. Though some reputable investigators appear to feel that the encephalitis epidemic in the second and third decades of this century accounts for most of the Parkinsonism we see, I believe that there are multiple etiologies for the disease just as there are for hemiplegia, and that the duty of physicians encountering patients with Parkinsonism is to attempt to elucidate the etiology.

Another area of interest that should be mentioned is genetic Parkinson's disease.[10] There is abundant evidence that familial clustering occurs in Parkinsonism, and the finding that individuals predisposed to developing Parkinsonian symptoms, after treatment with phenothiazines, have a higher incidence of family members with spontaneous Parkinson's disease[11] adds further weight to the idea that some Parkinsonism is hereditary, perhaps an inherited tyrosine hydroxylase deficiency. Nevertheless, this is not sufficiently established to require genetic counseling, nor is hereditary Parkinsonism sufficiently different from other forms to necessitate differences in therapy. Furthermore, familial clustering alone is insufficient evidence to rule out an infectious etiology.

Therapeutic avenues open to the physician managing patients with Parkinson's disease can best be summarized by considering the past, present, and future. That the treatment of this complex disease should change over the years is not surprising; however, that the treatment should take such profound swings over a period of fifteen years is surprising.

The Past. Charcot is said to have noted the value of atropine over 100 years ago.[12] Since then, and until levodopa appeared on the scene, atropine and about seven or eight similar drugs were the medications of choice in Parkinson's disease. The differences in these drugs are not great,[13] and all share, to a variable degree, anticholinergic side effects. The peripheral side effects of these drugs are well known; however, centrally, drug intoxication may lead to ataxia, dysarthria, hyperthermia, and frank psychosis. The drugs must be introduced in low dosages and increased slowly until improvement occurs or side effects force a halt to further increment of dosage. A modest improvement in rigidity and tremor can be expected in 70% of patients; however, akinesia does not respond to this treatment.[14] These drugs remain valuable in the treatment of mild Parkinsonism and as adjuncts to levodopa. Diphenhydramine (Benadryl®), an antihistamine, also possesses an atropine-like action, inhibiting striatal dopamine uptake, and is only mildly less potent than benztropine (Cogentin®).

Amphetamines enjoyed some popularity in the past. These drugs are chemically similar to dopamine and seem to be beneficial. Their benefits, however, are not great enough to override their side effects, and they are no longer used to any extent. Surgery, involving destructive lesions in several areas of the brain, but mostly in the thalamus, enjoyed a brief popularity in the fifties and early sixties. Useful mainly for tremor and least valuable in akinesia, thalamotomy procedures were often impermanent in their benefits and had occasional failures as well as complications, such as hemiplegia. As a result, the

use of thalamotomy waned rapidly after the development of levodopa, and the operation is now rarely performed for Parkinson's disease.

The Present. Long in preparation, levodopa has been in widespread experimental use for over seven years, and in general use for over five years.[15] First evaluations, particularly with patients early in the course of their disease, indicated that 70% of patients experienced at least a 50% improvement in their symptoms, especially akinesia and rigidity. This is a remarkable improvement for most patients. To achieve this goal, the daily dosage must be slowly worked up to levels of 5 to 9 gm, initiated at levels of 125 to 250 mg daily, with food. Single doses should not exceed 1.5 to 2.0 gm[13]; hence the need for multiple doses. The frequency of side effects is extensive. In one series of 100 patients,[16] 49 developed abnormal involuntary movements, 45 had gastrointestinal problems, 30 had psychiatric manifestations, and 11 had symptomatic hypotension. Other side effects occurred less frequently. As a result of these side effects, especially nausea, many patients never reach maximum dose levels, and treatment is discontinued because they cannot tolerate useful levels of the drug. Part of this problem has been solved by combining levodopa with carbidopa which is a chemical "look-alike" of levodopa that inhibits dopa-decarboxylase extracerebrally. Thus, since 95% of levodopa is decarboxylated before it reaches the brain[17] (and is therefore therapeutically ineffective), a combination drug allows levodopa to reach the brain in greater amounts respective to the oral dose. The only combination currently available commercially is Sinemet 25/250® (Merck, Sharp, and Dohme). This product provides a carbidopa:levodopa ratio of 1:10, and since carbidopa blocks at least 75% to 80% of peripheral decarboxylation of levodopa, it follows that a Sinemet 25/250® is roughly equivalent to 1.0 gm of oral levodopa, and in practice this seems to be the case. In switching from levodopa to Sinemet 25/250®, stop levodopa for 8 hours, then resume Sinemet 25/250® at one-fourth the dose for levodopa. The only real advantage to the combination is the avoidance of nausea, though a reduction in cardiac arrhythmias and in hypotension has been reported.[17] According to an oral communication from B. A. Huffman, in February 1976, the price of this combination drug is 15% to 20% above levodopa alone and since its chief value is in preventing nausea, the increased expense is hardly justified for those who tolerate, one way or the other, this side effect. Nonetheless, this combination drug offers a considerable advantage to those patients who seem unable to overcome nausea at even low doses. In addition, and of minor importance with out-patients, one can advance the dosage faster with combination therapy since nausea is a minimal problem. Finally, carbidopa inhibits the action of pyridoxine in reversing levodopa action; hence ordinary multivitamins may be used when indicated.

Other side effects that deserve special mention are the involuntary movements and the psychologic problems. Both can take almost any form, both are quite common complications, and, as a rule, the development of either problem is best managed by a reduction in dose. Both are central effects of levodopa; hence they readily occur with either levodopa alone or in combination with carbidopa.

A final note on side effects relates to orthostatic hypotension. This is a well-recognized side effect, and patients on levodopa should have periodic *standing* blood pressure determinations. A reduction in levodopa dose is usually required if this side effect occurs.

Other drugs may also be used to advantage with levodopa or levodopa/carbidopa. Atropine-like agents have already been mentioned, and while they were never shown to provide more than a 20% improvement in symptoms, this margin may occasionally be useful along with levodopa. Amantadine, originally an antiviral drug, has more merit as an adjunct as well as acting alone. In one study[18] involving 48 patients, benefits of 21% to 39% occurred in major Parkinsonian disabilities. Side effects, consisting mainly of gastrointestinal disturbances, sleep disturbances, and hallucinations occurred with amantadine, but the frequency of these is low. The dose used in this study was amantadine 200 mg daily in divided doses. There is a tendency for benefits to decline after several months.

Propranolol, a beta adrenergic blocking agent, has also been used in a variety of states with tremor[19,20] and consequently we have tried it in combination with other drugs to relieve the tremor of Parkinson's disease. The results have not been measured, but on occasion this has seemed to be a useful drug. Other clinicians[21] have had similar experiences. A maximum dose of 180 to 200 mg/day must be approached cautiously.

One may wonder why several drugs other than levodopa have been mentioned. Several facets of the nature of levodopa therapy account for this. First, a

fairly large group of patients do not respond well to it. Second, certain patients are unable to achieve adequate levels due to side effects. And, finally, there appears to be developing a "resistance" to levodopa benefit.[15] This resistance takes several forms, but occurs in one way or another in the majority of patients. In Barbeau's series, the percentage of patients with excellent or good results initially was 79% and dropped to 29% at 6 years, and 25% had stopped levodopa. The predicted survival of severely akinetic patients is 9.7 years,[22] thus it is suggested that levodopa probably will not stop the progression of Parkinsonism. Some investigators feel that there may be a finite period of time in which levodopa is effective and therefore withold the drug until disability is beginning to become clearly evident.

The resistance to treatment takes many forms, but three mechanisms stand out:

1. End-of-dose akinesia. Parkinsonian symptoms recur progressively earlier following a dose. Levodopa levels are low, and more frequent spacing of the drug is beneficial.

2. On/Off phenomenon. Patients note periods in which there is a sudden return of Parkinsonian symptoms, the "Off" period. The "On" period, unfortunately, is nearly always complicated by dyskinesias, usually appendicular and fairly distressing. In one report,[23] 29 such patients were encountered in a population of 300 Parkinson patients. Nineteen had been on medication more than 24 months, suggesting that the duration of the disease or of levodopa therapy is of significance. The "Off" period is characterized by low levodopa levels. This phenomenon is poorly understood and its management a subject of debate. Nevertheless, two views are worth mentioning. The first[24] embraces the concept that a hypersensitivity of the receptor occurs and suggests gradual reduction in levodopa dose to levels of about one-fifth the previous maintenance dose. The second[25] involves a reduction in presumably competing amino acids in the diet by reducing protein intake from the normal 1.0 to 2.0 gm/kg to .5 gm/kg, along with the usual dosages of levodopa and an inhibitor. Both methods, as well as a variety of other drug manipulations, have some merit; however, this problem remains quite serious.

3. Akinesia paradoxica. Sudden "blocking" seems to occur, often triggered by a sudden change in afferent sensory input (as unexpected stress), and the patient "freezes," often falling. Blood levels of levodopa are usually high,[21] and the theory is that there is a sudden, unanswered demand on the noradrenalin "drive" mechanism, now depleted by involvement of the locus ceruleus.[21] Fortunately, this complication is quite uncommon, since its management and pathogenesis remain uncertain.

In numerous other ways, and in spite of many drugs, Parkinsonian patients seem to gradually lose the benefit of medication and deteriorate after a number of years.

Several other facets of the treatment of Parkinsonism deserve special mention. A certain number of patients develop a mild-to-moderate dementia.[26] This part of the picture does not seem to be wholly reversible with levodopa and thus becomes part of the overall management. Discussion of this is beyond the scope of this paper. Another important part of present management is physical therapy. The motivation and assistance provided by this modality is of inestimable value, and no experienced clinician doubts the value of maintaining mobility in the patient with Parkinsonism. Seriously affected patients are best cared for by facilities offering this form of treatment.

Evaluation of the physician's treatment is quite important, since the probability of eventual failure is high. With any given patient, the physician must establish methods of continuing patient evaluation that include such actions as rising from a chair, handwriting, drawing whorls, and activities of daily living.[17] Once clear regression occurs, efforts at combating this, while often futile, must be instituted, and a periodic semi-quantitative evaluation of the patient is useful.

The Future. A number of pharmacologic attempts to alter Parkinson's disease are in progress, but most show little potential. Two that show the greatest possibility of success presently are bromocriptine[27,28] and apomorphine.

Bromocriptine, an ergot alkaloid containing a lysergic-acid residue, activates dopaminergic receptors. The evidence cited is but a single study in which 19 patients received an optimum dose of 20 to 75 mg daily; the original study consisted of 28 patients, but 1 failed to follow directions and 8 had intolerable side effects. Side effects, usually dose dependent, were in every way similar to levodopa, except for four new reactions: erythema, edema, and tenderness of the ankles; burning discomfort of the eyes; diplopia; and frequent extrasystoles. Of the 19 who continued bromocriptine, all but 4 were able to omit their levodopa or levodopa/carbidopa. All noted improvement

of Parkinsonian symptoms while on bromocriptine as compared to a placebo, but the authors were unable to draw any conclusion comparing bromocriptine and levodopa. The drug appears to have some promise, particularly since it obviates the necessity of having endogenous dopa decarboxylase, which is also depleted in the striatum of Parkinsonian patients as the disease progresses.

A second drug offering some promise is N-propylnoraporphine, an analog of apomorphine having a nephrotoxic dose far in excess of its therapeutic dose.[29] In the series by Cotzias et al,[29] all 24 patients improved, and the "On-Off" phenomenon of 6 patients, still present on N-propylnoraporphine alone, was abolished by co-administration of alpha-methyl dopahydrazine. Side effects, including drug-related renal toxicity in two patients, were not uncommon, and further evaluation is necessary.

Summary. While an exhaustive review of available management has not been attempted, the frequently missed differential diagnoses and important therapeutic modalities have been discussed. No treatment seems to stay the inexorable progression of this disease, but several avenues offer the patient a better quality of life as the disease proceeds.

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