L-Dopa in the Treatment of Parkinsonism
A Preliminary Appraisal*

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The treatment of parkinsonism from the time of its first clear description by Parkinson to the modern era has been less than satisfactory. Neurosurgical procedures directed at the pyramidal tracts ranged from the premotor cortex through the cerebral peduncles and into the spinal cord. The goal was to relieve unilaterally a single troublesome symptom, namely, tremor, leaving the problems of bradykinesia, gait, balance, posture, voice, speech, swallowing, and others untouched. Some success was obtained, usually at the price of significant weakness in the limbs involved. When the weakness diminished, as it often did following surgery, the tremor tended to recur.

Neurosurgical procedures directed at the basal ganglia ushered in a whole new phase of treatment, chiefly because relief of tremor, rigidity, and poor alternating movements could be obtained without producing any weakness whatsoever. This divorced the tremor and rigidity from what had previously been thought to be their intrinsic dependence upon the great voluntary motor pathway, the pyramidal tract. Reports from neurosurgical centers throughout the world concurred on this point.

Our own experiences have been extensively reported and show that alleviation of tremor and rigidity can be obtained in 85% to 90% of properly selected patients with cryosurgical lesions directed at the ventrolateral and posteroverventrolateral nuclei of the contralateral thalamus. Acceptable mortality and morbidity figures were also reported from our clinic in a series of nearly 3000 cases. The mortality in that series of consecutive operations done for parkinsonism was 1.4% while the morbidity was 4.6%, except for disturbances in speech, balance and gait, and mental problems. Here, the range was estimated from an earlier publication at 8% to 13%. However, the symptoms mentioned above in connection with pyramidal tract surgery have similarly remained recalcitrant to basal ganglia attack, and again, the inexorable downhill course for many patients continued unaltered. For such individuals, the long-term functional results were in no way comparable to those obtainable in persons simply with disabling tremor, rigidity, and poor movements, especially when these symptoms were largely unilateral.

Medical and drug treatment had always been disappointing, serving to give some relief to only 25% to 30% of patients. These results accrued with both natural and synthetic anticholinergic drugs, such as atropine and its derivatives, or trihexyphenidyl and related substances, antihistamines, and stimulants of the amphetamine type. None of these medications halted or even slowed the progressive course of the disease, and disabling symptoms continually appeared or advanced until the patient was unable to help himself in any way. Advanced cases showed premature aging, neurogenic bladder with overflow incontinence, difficulty with swallowing, inability to walk, and progressive mental deterioration of organic type. Drooling of saliva, and problems, of voice, speech, and even language became manifest in the late stages. Physical therapy and rehabilitation including speech therapy have likewise proven futile in these advanced cases, although some benefit has been obtained in earlier less-involved patients.

Background of Therapy with L-Dopa

The chief basis on which a rationale for treatment of parkinsonism with L-dopa rests is the finding by Hornykiewicz and

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and these form the basis for this preliminary report. The others have been excluded because the lapsed time is too short to permit reasonable evaluation. Eight patients have been treated for more than 4 months, 24 for more than 3 months, 29 more than 2 months, and 30 for over 1 month. Males and females are approximately equally represented, and the age range is similar to that of the population previously reported for our surgical series.

However, there is an increasing proportion of persons in the 8th decade while at the same time a greater number of markedly advanced and almost totally disabled persons are included. This, of course, is because patients and families as well as referring physicians will consider medical treatment where they would otherwise reject even a consideration of surgery. Thus, only one patient was less than 40 years of age, 14 were between 40 and 50, 21 between 50 and 60, 33 between 60 and 70, and 22 between 70 and 80 years of age. Only 20 had been ill for less than 5 years, 43 from 5 to 10 years, 20 from 10 to 15 years, and 8 had been afflicted for more than 15 years.

The drug was administered orally in the form of a 500 mg. tablet for most patients, with some, however, receiving a 250 mg capsule where tolerance was low. The dosage was built up slowly, as a rule from 500 mg per day to a level of 3 to 5 gm each day, usually in four divided doses spaced throughout the waking portion of the day. It was often given with meals or a small amount of milk to reduce the frequent nausea and vomiting encountered. A dosage of 3 gm per day was usually reached within a week, provided the patient was able to tolerate the drug. Most patients noted no effect, beneficial or toxic, from that dosage, but some were more sensitive and reacted strongly to 1 or 2 gm a day. Some required a larger amount, up to 8.5 gm per day in one case. About half the patients noted significant effects, both beneficial and toxic, at 4 to 5 gm per day. All but one of the patients were treated at first in the hospital as regular inpatients and were carefully monitored clinically and by laboratory study. Once the dosage was stabilized, the patient was discharged to continue treatment on an outpatient basis provided there were no toxic ef-