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 posteroverentralateral 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

Received for publication May 22, 1969.
* Supported by the Allen P. and Josephine B. Green Foundation, and the Teagle Foundation, Inc. This paper was presented in part at the Cleveland Meeting of the American Association of Neurological Surgeons, April 14, 1969.
associates as early as 1960 that dopamine is virtually absent from the corpus striatum and substantia nigra in parkinsonian brains obtained at autopsy. They and others have also found abnormalities of other catecholemines and their metabolites in brain, blood, and urine. Much evidence, too, points to a nigro-striatal dopaminergic pathway. The importance of brain dopamine is further emphasized by the well-known fact that reserpine, which induces parkinsonian signs, depletes the brain of dopamine. Beneficial effects in parkinsonian patients from treatment with L-dopa were reported early, with reference especially to bradykinesia and rigidity. Some investigators disagreed. More definitively favorable results were obtained in a series of 28 cases, some followed for 2 years by Cotzias and associates, who noted also that toxic effects were more frequent when they used the racemic mixture of both D and L-dopa. Other clinicians have followed suit with their own series of cases. There is general agreement that the beneficial effects of L-dopa surpass those of any drugs used hitherto, and the improvement is especially noticeable for symptoms such as bradykinesia, balance, posture, gait, facial expression, and general well-being, not ordinarily susceptible to surgical treatment. However, improvement has likewise been reported for rigidity and tremor, although less dramatically. Toxic side-effects, including nausea, vomiting, and anorexia, fall in blood pressure with cardiac dysrhythmia and fainting, abnormal choreiform movements, and mental changes, have often limited the benefits obtainable.

**Objectives of This Study**

Our purpose was twofold: 1) to determine whether L-dopa provides a significant new treatment for Parkinson’s disease without producing harmful toxic effects; and 2) to determine the optimal therapeutic relationship between L-dopa and crysurgical thalamectomy.

**Materials and Methods**

We began our program of L-dopa treatment for parkinsonism in November, 1968, and currently have under treatment approximately 120 patients. Ninety-one have been receiving the drug for more than a month 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-
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Effects. Frequent visits were made to the clinic for regular evaluations and regulation of dosage. All patients were studied before treatment from the neurological and medical standpoints, with medical consultants likewise evaluating most of them before the commencement of treatment. Frequent neurological reexaminations were made in all cases, plus briefer evaluation during twice-daily ward rounds. Laboratory studies included blood count, urinalysis, blood chemistries (blood urea nitrogen, glucose, sodium, potassium, chlorides, cholesterol, bilirubin, cephalin flocculation, thymol turbidity, alkaline phosphatase, serum glutamic oxalacetic transaminase), and prothrombin time. These were rechecked about once a week. Electrocardiograms and chest x-ray films were also obtained.

The original plan to perform single or double blind studies in at least some of the patients has not yet been done, largely because the beneficial effects of the drug were so obvious in some patients that it was considered unnecessary in the initial stages of the project. Under the circumstances it might even be thought unfair to the patient to withhold the drug for longer or shorter periods. Instead, the patient’s previous state and our own large past experience were deemed adequate to form a basis for preliminary judgment. The same reasoning made us continue the patient’s previous medications in 35 cases, although 31 were thought suitable for a trial on L-dopa alone and 20 were able to use a lower dosage of their previous drugs.

Results

For some patients, the over-all results of treatment with L-dopa were encouraging. Many individuals were benefited in some way. Some were remarkably improved; a few appeared virtually normal after treatment. Approximately 25% were estimated to be in the markedly improved group, showing relief of many specific symptoms, improved function in daily activities, and a significant increase in activation level. Several had returned to work or had improved their work levels. Some 50% were sufficiently improved to make continued administration of L-dopa distinctly worthwhile.

About 25% received little or no beneficial result. The most far-advanced, elderly, most disabled patients, especially those with some degree of dementia, fared least well. This might be due to the short duration of follow-up in the present series, and it is possible that a longer period of therapy will increase the percentage of patients in the improved categories. It is to be expected, too, that the same will apply to the incidence of toxic effects.

Table 1 shows the effect of L-dopa on various symptoms of parkinsonism, not all of which were present simultaneously in all 91 individuals. As shown in this table,

<table>
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<th>TABLE 1</th>
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<td>Effect of L-dopa on 91 parkinsonian patients</td>
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<tr>
<td>Symptom</td>
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<td>Tremor</td>
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<tr>
<td>Rigidity</td>
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<td>Impaired alternating movements</td>
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<td>Bradykinesia</td>
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<td>Facial masking</td>
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<td>Impaired balance</td>
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<td>Impaired gait</td>
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<td>Impaired posture</td>
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<td>Impaired arm swing</td>
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<td>Voice problems</td>
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<td>Speech problems</td>
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* Indicates complete relief of symptom.
tremor was one of the symptoms least often relieved, but of greater importance was the fact that it did improve or disappear in some cases. So far, this has been true for the mild but not the severe tremors. A longer period of treatment with higher doses may well improve the results. Rigidity was significantly reduced, and alternating movements became more facile in a somewhat greater percentage.

The effect of L-dopa on bradykinesia and facial masking was clearly better; some 90% of patients showed a lessening of bradykinesia, one of the most disabling of parkinsonian signs and, when generalized, one of those not favorably affected by surgery.

L-dopa provided significant relief for difficulties with balance, gait, posture, and arm swing, markedly in some 20% to 25% and moderately in 46% to 70%; these incapacitating symptoms have not hitherto been reached by drugs or surgery and actually not much improved by intensive physiotherapy, either. The effect on voice and speech (exclusive of language) was less dramatic, yet a significant percentage of patients showed improvement, particularly in voice. Handwriting, both the actual performance and the end result, was better in virtually all patients.

The net result for patients who experienced reduction in severity of several major symptoms was better performance in activities of daily living and a lifting of emotional depression.

**Toxic Side Effects**

Undesirable side effects of L-dopa have played a distinct role in the management of patients with Parkinson’s disease. Most can be classified as not serious and reversible, but it should be noted that two of our patients have died while the drug was being administered. One of these deaths occurred in a 66-year-old patient after he had been discharged from the hospital and thereafter not seen clinically by any member of the staff; autopsy was not done. The second patient, a 71-year-old man, died in the hospital 9 days following a transurethral resection for benign prostatic hypertrophy; there was no post-mortem examination. The clinical diagnosis was pulmonary embolism presumably from pelvic veins secondary to his prostatic surgery. He had been receiving L-dopa for approximately 16 days and had reached a dosage level of 4 gm per day. He had been fully ambulatory since a day following prostatectomy and had tolerated the operation quite well. The L-dopa had not been discontinued for the operation. No valid judgment can be made in these two patients regarding the possible relationship between L-dopa and their deaths.

Table 2 summarizes the problems of toxicity caused by L-dopa. All responded to withdrawal of the drug or reduction in dosage. Mental abnormalities, usually of paranoid type, appeared early and at low daily doses of 1 to 2 gm in three patients. We have the impression that mental changes occur more often and more severely in elderly patients who already have some degree of organic mental syndrome. These are the patients, also, who are usually susceptible to small doses. Most abnormal movements did not appear unless dosage levels about 3 to 4 gm per day were employed. These were generally choreiform in nature, involving face, head, neck, shoulders, and occasionally the more distal limb musculature. They were usually mild but did require reduction in dosage. They sometimes persisted for several days to a week or more even after cessation of L-dopa. It is worth noting that the abnormal movements, which occurred in patients who had been previously operated upon, always developed on the previously unoperated side. If this turns out to be a regular observation, it would have great physiological significance.

Nausea and vomiting interfered with drug administration in two-thirds of patients, and

<table>
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<tr>
<th>Side-Effect</th>
<th>% of Cases</th>
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<tr>
<td>Nausea and vomiting</td>
<td>66%</td>
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<tr>
<td>Anorexia</td>
<td>31%</td>
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<tr>
<td>Involuntary movements (oral-facial dyskinesia and/or choreiform limb movements)</td>
<td>21%</td>
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<tr>
<td>Paranoid ideation with agitation and confusion</td>
<td>11%</td>
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<tr>
<td>Symptomatic hypotension with dizziness or syncope</td>
<td>2%</td>
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the incidence became higher if the drug was pushed too rapidly. Food or milk taken with the drug reduced the incidence of these symptoms. Most patients, even when hypertensive, experienced an initial lowering of the blood pressure; the blood pressure then returned to its previous level in some cases. For the most part, low normal readings are found in patients on L-dopa.

No dysrhythmias were observed in this series, although they have been reported by others. Electrocardiograms have remained normal or been unchanged. Other laboratory data showed no special evidence indicating that our patients had had any toxic action in their blood, liver, or kidneys.

At this time, the indications and contraindications for L-dopa treatment of parkinsonism are difficult to define. We are presently not recommending treatment for patients in a very early stage where symptoms are little or not at all disabling. Instead, such individuals are being followed carefully so that L-dopa therapy can be started if progression of the disease begins to be a threatening factor. In these patients, the small benefits that are possible are outweighed by the risk of toxic symptoms. Most of the contraindications are so far largely related to mental deterioration or anemia. Treatment was deferred in one patient with a hemoglobin of 7.5 gm, whereupon further study revealed carcinoma of the stomach with intra-abdominal metastases, to which the patient quickly succumbed.

Our data are as yet too few to make profitable an analysis of the relationships of L-dopa to the indications for surgery. It can be said with some degree of confidence, however, that L-dopa affects parkinsonian patients without regard to whether they have previously undergone basal ganglia surgery. Although 27 of our patients had not previously been operated on, 39 had undergone unilateral and 25 bilateral surgery.

A preliminary analysis comparing the results of treatment with L-dopa for relief of tremor, rigidity, and bradykinesia revealed too fine a breakdown into groups to justify any valid statistical conclusions. Larger numbers of patients in these three categories and longer follow-up will be necessary before a more minute analysis can be worthwhile. More time is needed, also, before one can say that patients not yet responding adequately to L-dopa require surgery. More study still will be needed before any reasonable judgment can be made of the patient's tolerance to such surgery.

Other questions for the future are these: What combination, if any, of medicine and surgery will give the greatest benefit with the least risk? What is the effect of L-dopa on the natural history of parkinsonism? Can specific symptoms such as dementia, disturbance of balance, dysarthria, loss of voice, excessive sweating and salivation, for example, be prevented from appearing? Will unilateral parkinsonian signs treated early enough with L-dopa be permanently prevented from spreading to the other side or to the midline?

As in all clinical studies, problems of rating and evaluating drug effects are difficult and frustrating, except where benefits or their lack are obvious, e.g., lysis of fever by appropriate antibiotics in acute infections. In so complicated an illness as parkinsonism, the already formidable difficulties are further compounded by the simultaneous use of other medications and even more so by the placebo effect of any new treatment. For L-dopa, the situation has been made worse by the large amount of publicity in the lay press. The need, therefore, for independent ratings of results by more than one observer using a single or double blind technique is particularly acute for the middle 50% of patients who seem to derive partial benefit. Some of these individuals, too, are soon disappointed by a failure to maintain their initial good results or a need to reduce their dosage to sub-optimal levels because of the late development of toxic effects.

There is hope now that the problem of toxicity may also be alleviated by the use of compound Ro-4-4602, which inhibits decarboxylation of L-dopa in extra-cerebral tissues.12 Because of all of these factors, we plan in the future to utilize all techniques necessary for excluding bias, especially when we approach the difficult problems relating L-dopa therapy to surgical treatment.

Summary

The discovery that striatal and nigral dopamine is depleted in parkinsonism has indicated that dopamine is probably a true
neuro-transmitter along a nigro-striatal pathway. Previous clinical investigations have shown that L-dopa, a precursor of dopamine, can alleviate many parkinsonian symptoms. L-dopa does not traverse the blood-brain barrier while dopamine does.

In our study of 91 patients treated with L-dopa, 75% showed marked or partial improvement. Patients who had previously undergone cryothalamectomy did not do so well. Far-advanced, badly disabled patients did least well. Tremor was lessened in a small number, especially when it was mild. Rigidity, bradykinesia, facial masking, voice, gait, and handwriting disturbances were often greatly diminished.

Toxic effects of L-dopa occurred in a high percentage of patients, especially anorexia, nausea, and vomiting, and sometimes in patients on low dosage. In many, the gastrointestinal symptoms gradually subsided. Dyskinesias, paranoid ideation, and hypotension were also noted, but all side effects were reversible especially if dosage was reduced.

The effect of L-dopa on the need for surgery has yet to be clarified, but it may obviate the necessity for operation in many. On the contrary, it may make surgery possible or safer for others. Numerous questions still remain unanswered and pose problems for future research.

References