"MODERN TREATMENT OF PARKINSON'S DISEASE"

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Many clinical trials extending over periods of up to 12 months and concerned with several thousands of patients have clearly established that l-dopa is the most effective drug at present available for the treatment of Parkinson's disease (Brogden, Speight and Avery, 1971). This report is concerned with the long-term effect of l-dopa and attempts to ascertain if the early therapeutic success is maintained, lost or enhanced, and if treatment with l-dopa can arrest or retard the natural progression of the disease.

A previous study of 51 patients suffering from idiopathic paralysis agitans, who had taken l-dopa for 12 to 20 months, showed that a progressive improvement of most disabilities occurred during the first 12 months of l-dopa therapy (Selby, 1973). Not only did the number of patients who responded to the drug increase after four to six months of continuous treatment, but there was an even greater shift from a slight to a moderate or marked degree of improvement. This trend was most obvious for relief from akinesia and rigidity, where the proportion of patients showing marked improvement more than doubled as treatment continued beyond four to six months, but marked alleviation of tremor also rose from 21% of patients at the six months stage to 37% after 12 months treatment.

Improvement in gait, on the other hand, occured mainly during the first six months of treatment, although some of the most severely affected patients learned to walk independently only after this period of time.

The progressive recovery from specific disabilities is reflected again in the restoration of independence for daily activities and in the assessment of the patients' overall improvement. The proportion of greatly improved patients rose from 27% at the four to six months stage to 40% at the final assessment.

It is interesting to speculate on the mechanisms for such a continuing and progressive recovery in a significant proportion of patients. As a working hypothesis some "disuse atrophy" of the cell body or axon, or more probably of the synaptic vesicles which contain the transmitter substance could be considered. Is it conceivable that dopamine derived from therapeutic administration of l-dopa could result in a gradual restoration of such functioning vesicles? Such a hypothesis can be reconciled with the common appearance of l-dopa induced involuntary choreiform movements which may be due either to a relative excess of dopaminergic transmission or to the accumulation of a metabolite of dopamine which has an effect on synaptic transmission. It is relevant to this argument that these involuntary movements develop earlier and are more severe in patients who show a spectacular response after only a few weeks treatment with l-dopa.

There was also a significant shift towards lower doses of Larodopa after the first six months of treatment; whereas only 18% of patients took less than 3,000 mg, per day during the first six months, these relatively low doses were used by 34% of patients after 12 to 20 months. Dosage requirements in excess of 4,000 mg. per day fell from 45% of our cases at six months to 28% after 12 months. In many, but not all cases this reduction in the dose of l-dopa was demanded by the appearance of drug-induced dyskinetic movements. In some instances these dyskinesias subsided only at sub-optimal dosage levels with a consequent recurrence of some Parkinsonian symptoms. Some of these patients were then helped by the addition of Amantadine to the smaller dose of l-dopa.

The series of 51 cases reviewed above is included in a larger group of 80 cases of idiopathic paralysis agitans who have now taken l-dopa for two to three years. Detailed and regular observations on these patients have shown that their long-term response to l-dopa therapy follows one of four distinctive patterns.

Group I. These patients were severely disabled, and many gave a history of rapidly progressive Parkinson's disease before treatment with l-dopa was begun. Improvement was slow to appear, tended to increase during the first six to twelve months of treatment, and was then maintained at a moderate, but satisfactory level. After 18 months to two years some signs of a slight progression of the disease were noted, mainly a decline in voice volume and speech, a slight deterioration of gait and postural equilibrium, and a mild progression of rigidity. An

increase in the dose of l-dopa is of limited benefit only and normal levels of dopa in the serum and of its metabolites in the urine show that there is no disorder of metabolism of the drug (Liberman et al., 1972). The majority of these patients never develop drug-induced abnormal movements, and this may be an indication that they have a poorly responsive dopaminergic system. The severity of their Parkinson's disease before l-dopa therapy implies more advanced structural changes, perhaps with fewer available synaptic vesicles, or alternately some abnormalities at the uptake sites. The late recurrence of some Parkinsonian symptoms appears to be due to the natural progression of the disease and not to the development of drug resistance.

Group II consists of patients who were only moderately disabled when treatment was begun. Although they may have had Parkinson's disease for several years, progression of thier illness was slow and most were able to care for themselves. Their response to l-dopa was clearly evident during the first six months, though moderately slow to appear, and progressive improvement occurred over 12 months and was then maintained with little or no decline after two to three years. They showed either minimal or no drug-induced abnormal movements and were easily maintained on a stable dosage without adverse side-reactions. These patients evidently have much less structural damage of the nigro-striatal dopaminergic pathways and a sufficient number of intact synapses. The relatively benign nature of their Parkinson's disease before they were treated with l-dopa has been maintained and it may be predicted that future progression will be very slow.

Group III is also concerned with patients with only a mild to moderate disability, which did not progress rapidly at any stage of their Parkinson's disease. Tremor was usually a prominent symptom. The characteristic feature of this group is a rapid and spectacular improvement during the first two to three months of treatment with l-dopa at relatively low dosage levels. During early review examinations virtually no signs of an extrapyramidal disorder can be detected. Soon afterwards involuntary movements appear, often a twisting of the limbs and painful dystonic postures of the feet and toes. These drug induced dyskinesias may be quite violent and usually demand a reduction in the dose of l-dopa to sub-optimal levels. These patients are extremely sensitive to the smallest changes in dose, which has to be regularly and carefully adjusted. They fare best on frequent small doses of l-dopa, of the order of 100 to 250 mg. every one to two hours.

These clinical events can hardly be explained on the basis of structural lesions in the extrapyramidal system alone. Some anomaly in either the uptake or breakdown of dopamine must be an important causal factor. Peripheral decarboxylase inhibitors administered together with l-dopa have no influence on the incidence and severity of these dyskinesias. They may be related to O-methylated derivatives of dopamine, as Ericsson (1971) reported that treatment with a catechol-O-methyl transferase (COMT) inhibitor, N-butyl gallate, not only reduced the abnormal movements, but also enhanced the desired therapeutic effect of l-dopa.

Group IV. A small number of patients experienced marked diurnal fluctuations (oscillations) in performance, which may be quite dramatic and include periods of hypotonia and "akinesia paradoxica" (Barbeau, 1971). They appear only rarely during the first few months of treatment, but tend to develop after 18 months to two years. Patients are quick to recognize a decline in their voice, mobility and gait which may occur regularly at a specific time of day and can persist for up to three hours.

In our series of patients no relationship between the occurrence of these "oscillations" and the severity or rate of progression of Parkinson's disease could be established. There is, however, a definite and direct relationship to the appearance of drug induced abnormal movements. The administration of peripheral decarboxylase inhibitors in addition to l-dopa may reduce the degree of these fluctuations and alter their timing, but does not abolish them. They can usually be minimised by a slow and cautious reduction in the dose of l-dopa and by the administration of smaller doses at more frequent intervals.

Anomalies in the absorption of l-dopa or in the rate of metabolic turnover of dopamine appear to be the most likely cause of these striking oscillations in the patient's well-being and physical capabilities. Muenter and Tyce (1971) distinguish

two types of response to treatment with l-dopa:

(a) long duration response of three to five days.

(b) short duration response of one to five hours.

They found that the short duration effect was not apparent in mild cases, but became progressively more obvious in some of the more severely disabled patients. Absorption of l-dopa from the gastro-intestinal tract tends to become more rapid during the first few months of treatment.

Stroka et al. (1972) have recently reported a careful metabolic study of a patient with marked diurnal fluctuations in performance. The plasma levels of dopa during "good periods" were 1850 μg/1., compared with 20 μg/1. during "bad periods", and the average three-hour urinary excretion of dopa and its metabolites was five to ten times greater during "good periods" than during "bad periods". Decarboxylase inhibitors altered these ratios only to a minor degree, although the patient subjectively felt a little better. These observations suggest that the rate of absorption of l-dopa from the gastro-intestinal tract must be a major factor in the causation of fluctuations in the patient's clinical state.

Side Effects:

The incidence of gastro-intestinal side effects, such as anorexia, nausea and vomiting declined after the first few months of treatment. These symptoms recurred in a few patients after a missed meal, during an intercurrent illness, or when drug-induced abnormal movements or oscillations in performance demanded frequent administration of l-dopa independent of meals. Postural hypotension did not appear for the first time after 12 months or more of l-dopa therapy, nor did it become more severe in thoe patientss where it was recorded from the beginning of the trial. In a few of the very elderly patients some defects of memory and concentration were reported, but the more striking changes in critical function, including a decreased attention span, constructional apraxia and frontal lobe-like disturbances described by Barbeau (1971) have as yet not become obvious in our patients.

No late changes in the peripheral blood, liver and renal function, serum calcium and uric acid were found, nor were there any adverse effects on electrocardiograms.

CONCLUSIONS

In less than one half of our patients who have taken l-dopa continuously for two to three years a slight deterioration of speech, gait, postural equilibrium and manual dexterity occurs, whereas recurrence of tremor is unusual. In a few cases of unilateral Parkinsonism, mild rigidity, tremor and akinesia appeared in the limbs which were not affected when treatment with l-dopa was begun.

A comparison of the rate of progression of paralysis agitans treated with anticholinergic drugs alone before the discovery of l-dopa with the fate of the patients reported in this study justifies the conclusion that treatment with l-dopa retards the natural progression of Parkinson's disease to a very significant degree.

Dopamine deficiency is clearly not the primary cause of Parkinsonism, but is merely a result of a pathological process which, beyond the invariable loss of pigmented cells in the compact zone of the substantia nigra, is still an enigma. Treatment with l-dopa cannot arrest this pathological process, but can diminish its effects by restoring dopamine also to the newly involved synapses; in this manner the natural progression of the disease is greatly retarded.

In a proportion of patient anomalies in the absorption of l-dopa from the gastro-intestinal tract, or in the metabolic breakdown of dopamine in the brain produce striking clinical manifestations, which do not appear to be due to specific structural changes in the "extrapyramidal" pathways, and do not influence the course of the disease.

BIBLIOGRAPHY

1. BARBEAU, A.; "Long-term Side-effects of Levodopa." Letters to the Editor, *Lancet,* i: 395: 1971.
2. BRODGEN, R.N.; SPEIGHT, T.M. and AVERY, G.S.; "Levo-dopa: A Review of its Pharmacological Properties and Therapeutic Uses with Particular Reference to Parkinsonism." *Drugs,* 2: 262-400, 1971.
3. ERICSSON, A.D.; "Potentiation of the L-Dopa Effect in Man by the Use of Catechol-O-Methyl transferase Inhibitors." *J. Neurol. Sci.,* 14:193–97, 1971.
4. LIEBERMAN, A.N.; GOODGOLD, A.L. and GOLDSTEIN, M.; "Treatment Failures with Levodopa in Parkinsonism." *Neurology (Minneap.)* 22: 1205–10 1972.
5. MUENTER, M.D. and TYCE, G.M.; "L-Dopa Therapy of Parkinson's Disease: Plasma L-Dopa Concentration, Therapeutic Response, and Side-Effects," *Mayo Clin. Proc.,* 46: 231–39, 1971.
6. SELBY, G.; "Long-term Treatment with Laevo-dopa." *Proceedings of Third Asian and Oceanian Congress of Neurology,* Bombay, 1971, (in press).
7. SROKA, H.; EICHHORN, F.; RUTENBERG, A.; RADWAN, H. and BORNSTEIN, B.; "A clinico-biochemical Correlation in a Parkinsonian Patient Treated with Levodopa and Decarboxylase Inhibitor (Ro4–4602). A Model Study" *J. Neurol. Sci.,* 17: 61–68, 1972.

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Since introduction of l-dopa, the general trend of treatment of Parkinson's Disease has changed and progressed a great deal. However, it remains still as a symptomatic treatment, and is not a causative one. Any treatment at present cannot prevent or stop the start or the progress of the disease, which is now being confirmed by the neuropathological study of the patient's brain who had been under long-term l-dopa treatment.

As well recognized, l-dopa has the most remarkable effect on akinesia and on rigidity and much less on tremor. If we show this in the statistical data of 133 cases of idopathic parkinsonism in two and half years from early 1969 to July, 1971, rigidity is improved very markedly and moderately in about 81.4%, though tremor was influenced in about 55%. At present, the number of cases in our series of l-dopa treatment is over 500, but these statistical ratio of effect do not differ much in the larger experiences. Of course these values may be changeable, depending on different groups of patients at different clinical stages, clinical presentations and at different stages of general physical and mental incapacitation.

Rigidity and akinesia are considered to be caused by dopamine deficiency due to a pathological lesion of the nigrostriatal tract. Experimental lesion within this tract produces parkinson-like muscle stiffness and slowness of movements in animals. The injection of harmaline (3, 4-dihydroharmine), which is the blocker of monoaminoxidase, produces rigidity of muscles in animals with shivering-like shaking. An intravenous injection of l-dopa reverses these effects.

Rigidity is tentatively interpreted as the result of the release of the activity from inhibitory control by the nigrostriatal system, though the final explanation is still not available. These pallidal hyper-activity producing rigidity may be conducted to the thalamic ventrolateral nucleus (VL), for which the stereotaxic surgical lesion has a definite effect either by pallidotomy, ansotomy or by VL-thalamotomy. Anticholinergic synthetic drugs such as trihexyphenidyl is also well known to be effective in influencing this symptom.

Akinesia had been really the most difficult and untreatable symptom in Parkinsonism by both pharmacological and surgical methods, until the l-dopa therapy became available. The most important progress of introduction of l-dopa therapy exists in its clear and definite effect on akinesia, usually being accompanied by the remarkable improvement of ADL of the severely incapacited patients. The cause of idiopathic or primary severe akinesia accompanied by slight rigidity in the disease, such as slowness of movement, inability of initiation of movements, frozen gait or difficulty of speech or of handwriting, is now clarified as due to the result of dopamine deficiency in the striatam. Effect on such akinesia, idiopathic and secondary, was observed, dramatically in 55.6% and markedly 25.8%.

The secondary akinesia due to high-grade muscular rigidity can also be well alleviated by routine l-dopa therapy, paralleling a diminution of rigidity.

Tremor, however, responded in only about half of the cases. These well-improved cases were usually the cases with moderate tremor coexisting with marked rigidity. The cases of tremor only, or of violent tremor with much slighter rigidity has less possibility of being alleviated by l-dopa. For this condition, trihexyphenidyl therapy or the stereotactic-neurosurgery is indicated.

Deteriorating psychic symptoms such as paranoid, hallucinatory experiences or a general lowering of mental capacity including mild disturbance of consciousness may occur with l-dopa therapy and therefore this form of therapy is contraindicated.

Depressive moods of psychoneurotic states observed in the Parkinsonian patients are sometimes reduced by this therapy. Autonomic symptoms may also improve.

Side-effects of l-dopa therapy are also important from both clinical and theoretical points of view. The gastrointestinal side-effects (about 52% of the above series of cases), insomnia or slight lowering of blood pressure can be easily controlled or avoided by the use of other drugs, such as anti-emetics or cardio-vascular stimulants. But about 30—40% of such side-effects should inhibit the further use of l-dopa. The most troubling and sometimes disturbing side-effects are psychic (13.6%) and choreo-dystonic movement, especially in the peroral and neck area (7.5%). For the purpose of minimizing the dosage of l-dopa, the use of peripheral inhibitor of

dopa-decarboxylase is now seriously being examined.

Considering the whole clinical picture of each individual patient, the varied combination of different therapeutic devices as referred above, should seriously be considered and evaluated. However, despite of these side-effects l-dopa is of significant importance in therapy. The value of anticholinergic medication and stereotaxic-neurosurgery has not taken second importance if the patient's total clinical picture is very carefully analysed and considered.

In the author's clinic, hemi-parkinsonism with moderate tremor and rigidity was treated more effectively by stereotaxic-neurosurgery and the bilateral cases by pharmacological means using l-dopa with concomittant anticholinergic medication.

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Parkinson's disease belongs to a group of extra pyramidal disorders embraced by the term Parkinsonism, which covers a clinical syndrome of hypokinetic and hyperkinetic symptomatology. The cardinal features of Parkinsonism are Tremor, rigidity and bradykinesea, which are present in varying degrees in a particular patient associated with, at times, with such features as speech and swollowing difficulties, hyperhidrosis, hypersalivation, occulogyric crisis and psychological disturbances. The clinical details will not be discussed here and my remarks will be directed towards the treatment.

Until such time as the aetiology and pathogenesis of the Parkinson's disease are defined clearly, the treatment remains as supportive, symptomatic and palliative. It is only in patients with symptomatic parkinsonism resulting from the use of such drugs as phenothiazine derivatives or occurring in association with specific disease process that the treatment of the causative agents may result in the improvement of the symptoms otherwise Parkinsonism is a progressive syndrome.

As you all are well aware that the treatment of Parkinsonism is mainly medical, that is, drug treatment associated with psychotherapy and physiotherapy. In the last 3 decades, the neurosurgical treatment has also become established in the management of patients with Parkinsonism and my remarks are mainly directed towards this aspect of the treatment.

As far as the surgical treatment is concerned, until 1940, the attention of the neurosurgeon, dealing with the involuntary movements, was focussed on the mortor cortex and pyramidal tract. Bucy and his co-workers had stated that the surgical alleviation of the involuntary movements was dependent upon the production of paralysis on damage to pyramidal tract or to corticospinal pathways. They held this view in spite of the work of Russel Meyer in 1940, who had shown that open surgery on pallidofugal pathways was capable of reducing tremor without producing paralysis, but the open operation carried mortality rate of 15.7%, but his work was the herald of the basal ganglion surgery in the management of the Parkinsonism. His report was followed by work of Fenlon (1953), Guiot and Barion (1952), who showed that lesion produced in the globus pallidus alleviated the tremor. Cooper (1953) observed that unilateral resting tremor and rigidity was abolished in a patient following ligation of anterior choroidal vessel. Subsequently by his observations on fifty-five patients following this procedure, he concluded that ligation of this vessel resulted in the lesion of bentro lateral region of thalmus, globus pallidus, pallidofugal and cerebellofugal pathways and thereby controlled the tremor and rigidity. In 1955, Hassler pointed out the importance of the ventro lateral neucleus of thalmus in management of Parkinsonism. Subsequently Speigal et al (1963), Fager (1968) and others suggested lesions in the subthalamic region, believing that relatively small lesions in this site where the fibres are most concentrated, would prove more effacadious and less prone to complications.

While the anatomical sites for surgical lesions were being defined, sophisticated and safe methods for making such lesions were being developed. In 1947 Speigal and Wycis, developed technique of

stereotactic surgery for use in man and in 1954, they reported their experience with stereotactic methods for producing lesions in the ansa lenticularis in cases of Parkinsonism. Since then many types of stereotoxic instruments have been devised and at the first international congress of the neurological science in Brussells in 1957, Parkinson's disease and its stereotactic treatment were discussed in detail. In the course of years, the technique has been modified and perfected, and has now become generally accepted in the management of Parkinsonism and other extra pyramidal disorders, intractable pain and epilepsy.

The technical details and various methods of producing lesions are not described here. The basic principle of the surgical management is the production of precise, well controlled, discrete and predictable lesions in the pallido thalamic complex without the production of sensory or motor defecit. As of the cardinal features of Parkinsonism, tremor and rigidity are most amenable to the surgical procedures whilst disturbance of gait and posture, if not due to tremor and rigidity, usually do not show improvement. Similarly other akinetic symptom are not alleviated by the surgery. Furthermore, in some despite total abolition of tremor and rigidity that patient may become increasing bradykinetic, during the ensuing years.

To ensure possible benefits to the patient of stereotactic surgery, especially now when there have been advances in the drug therapy, long term results of the operation have to be considered. Various long term follow-ups (Cooper 1969, Van Manen 1970 and others) have shown that there is a significant relationship between pre-operative status of the patient and results of the surgery. Gillingham et al (1960) have shown, in consecutive series of 131 patients, that results in the first 60 unselected cases were less successful than the subsequent 71 selected cases. Various reports have shown that the results of surgery are dependent on age, severity of neurological symptoms, disability, presence of hypertension and diabetes. The published reports suggest that with satisfactory criteria for selection of patients and standardization of the technique, the tremor and rigidity can be controlled in 90 per cent of good risk patients. Furthermore when the tremor and rigidity has been abolished for more than one (Cooper 1969) to three months (Van Manen (1970) the results are expected to be permanent. No one denies the benefits of surgery in the management of Parkinsonism, but there is a risk of morbidity and mortality, though less than 1% in skilled hands, even in good risk patients. Although it is possible to classify the patients for surgery on a clinical basis, there are great many individual factors which will influence the decision whether a patient should or should not undergo surgery. An ideal candidate for surgery is a young person with unilateral tremor and rigidity with minimal or no hypokinetic symptoms, who is still actively employed or can go back to work following surgery, but on the other hand should one recommend surgery in view of the possible morbidity and mortality. Should one wait till progression of disease makes him totally dependent on others in spite of the drug therapy. I think one has to consider these philosophical questions in the light of continuing advances in drug therapy specially the use of L-Dopa and Amantadine. But not all patients respond to this therapy and therefore neurosurgery still has an important role to play in management of the patients with Parkinson's disease.

BIBLIOGRAPHY

1. BUCY, R.C., CASE, J.T. (1939) Arch. Neurol. *41* 721.
2. COOPER, I.S. (1969) Involuntary Movement Disorders. Publish. Harper and Row.
3. FAGER, C.S. (1968) J. Neurosurg. *28* 145.
4. FEULON, F. (1955) quoted by Cooper I.S. (1969).
5. GILLINGHAM, F.J., WATSON, W.S., DONALDSON, A.A., and NAUGHTON, J.A.L. (1960) Brit. Med. J. 1395.
6. GUIOT, G. and BRION, S. (1952). Quoted by COOPER I.S. (1969).
7. HASSLER, R., (1955) Proceedings of Second International Congress of Neuropathology Pt. 1 pp. 29–40. Pt. IV pp. 637–642. Amsterdam Excerpta Media.
8. MEYER, R., (1942) Assn. Res. Nerv. Ment. Dis. Proc. *21* 602–665.
9. SPEIGAL, E.A., and WYCIS, H.T. (1954) Arch. Neurol. Psychiat. *71* 598.
10. SPEIGAL, E.A., and WYCIS, H.T. SZELKELEY, E.G., ADAMS, J.F., FLANAGAN, M. and BAIRD, H.W. (1963) J. Neurosurgery *20* 871.
11. VAN MANEN (1970) Psychiat. Neurol., Neurochurgia *73* 365.

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Recent Progress in Medical Treatment and its Pharmacological Basis.

Parkinsonism or Parkinson's Syndrome or the shaking palsy is commonly regarded as a degenerative disease of later life, manifesting primarily with akinesia or bradykinesia, rigidity and tremor. The common pathological findings, as described by Lewy in 1921, include atrophy and destruction of nerve cells in the zona compacta of the substantia nigra which, on naked eye examination, appear smaller and less uniformly pigmented than normal. The other pigmented nuclei in the locus caeruleus, the dorsal nucleus of the vagus and the substantia innominata of Reichert and the globus pallidus habitually show lesions. Lesions in the corpus striatum and the cerebral cortex are minimal.

Anatomical and Neurophysiological Basis of Parkinsonion Symptoms and Signs.

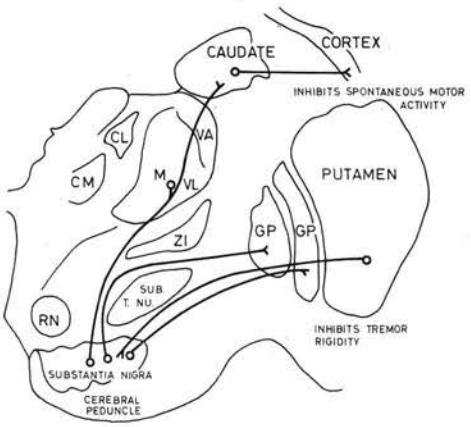
The extrapyramidal nuclei include:—

1) the corpus striatum, by which is meant the caudate nucleus and putamen,
2) the globus pallidus,
3) the substantia nigra and
4) the subthahlmic nucleus of Luysi.

These nuclei are interconnected to each other by afferent and efferent tracts and have, in turn closed circuit connections with the cerebral cortex, thalmus, brain stem and spinal centres.

Experimentally and surgically, it has been shown that lesions of the globus pallidus or its thalmic connections via the Forel's fields reduce rigidity and, to a lesser extent, tremor. Therefore, it is possible that rigidity and tremor are secondary to pallidal overactivity and this, in turn, is inhibited by nigro-pallidal connections directly and nigro-striatal connections indirectly. In Parkinsonism, with loss of neurons in the zona compacta, this nigral inhibition of the globus pallidus is lost and thus the development of rigidity and tremor. Further, the loss of nigro-reticulospinal pathway leads to a decrease of inhibitory influence on the gamma loop, leading to rigidity and akinesia.

Fig. I TRANSVERSE SECTION OF BASAL GANGLIA



CL Central lateral intralaminar nucleus
CM Nucleus centrum medianum
RN Red nucleus
SUB. T. NU. Subthalamic nucleus
M Ventral lateral nucleus —medical part
ZI Zona Incerta
VL Ventral lateral nucleus
VA Ventral anterior nucleus
GP Globus pallidus

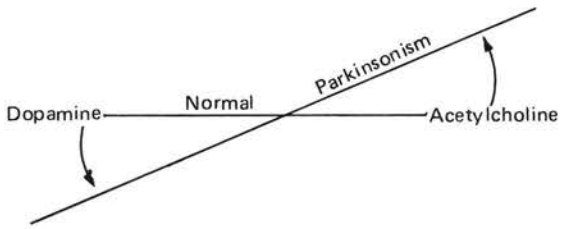
It has further been shown that the striatum normally has a depressant effect on spontaneous motor activity of the cerebral cortex. (This is possibly the explanation for the chorea and hyperactivity seen in Huntington's chorea, in which disorder, the primary pathology is striatal degeneration). The substantia nigra, in turn, has an inhibitory effect on the striatum. Thus, the loss of nigral inhibitory influence in Parkinsonism leads to increase of striatal inhibitory effect on the motor cortex, resulting in akinesia or bradykinesia.

The above anatomical and neurophysiological considerations help to explain a possible hypothesia for the cardinal signs and symptoms of Parkinsonism, namely, akinesia, rigidity and tremor.

Pharmacological Basis of Parkinsonism

The pharmacology of Parkinsonism is based on two basic principles. The first is that acety-

choline and dopamine have antagonistic effects on the neurons of the striatum and that normal striatal function depends upon a delicate balance between these two neurotransmitters. The second is that a shift of this balance in favour of acetycholine or disfavour of dopamine tends to produce the symptoms of Parkinsonism.



Belladonna alkaloids have been used in the treatment of Parkinsonism for over 75 years. Feldberg, in 1945, suggested that the usefulness of atropine and the atropine-like drugs in the treatment of Parkinsonism was based upon the central anticholinergic effects of these drugs. It has also been shown that cholinergic drugs like Prostigmine (or Physostigmine) will aggravate the symptoms in a Parkinsonian patient.

Carlsson, in 1959, showed by histochemical fluorescent technique that the striatum is rich in dopamine. He further showed that the dopamine is not within the cell bodies of the striatal neurons but is located within a dense meshwork of nerve terminals, the cell bodies of which are the neurons of the substantia nigra.

Poirier and Sourkes, in 1965, showed that the destruction of the substantia nigra results in loss of dopamine in the ipsilateral striatum. This nigro-striatal pathway has its cells of origin in the substantia nigra and its termination in the striatum. These neurons contain dopamine which they release upon the receptor neurons of the striatum.

Hornykiewicz, in 1966, showed that the physiologically important lesion in Parkinsonism is destruction of the nigro-striatal dopaminergic neuronal system, whereas the striatal neurons themselves are relatively well preserved. Subsequently other workers showed that the cerebrospinal fluid and the urine of Parkinsonian patients contain lesser concentration of HVA (Homovanillic Acid) and DOPAC (3-4-Dihydroxyphenylacetic Acid), which are the metabolic and products of dopamine metabolism.

Using intravenuous L-Dopa, Birkmayer and Hornykiewicz, in 1962, demonstrated a decrease in akinesia in 20 Parkinsonian patients. In the same year, Barbeau, using oral L-Dopa, described short lasting but definite improvements in both tremor and rigidity. Subsequently, Cotzias in 1967, Melvin Yahr in 1968 and McDowell in 1970, well substantiated the use of L-Dopa in Parkinsonism. Thus, the pharmacological basis of treating Parkinsonism is based on either restoring dopaminergic activity by replacement therapy or inhibition of its breakdown, or preventing excess chlonergic activity. Incidentally, some authors, including McGeer and Barbeau, believe that the tremmor of Parkinsonism is due to an imbalance of the serotogenic-histamine system.

Drugs Elevating Concentration of Dopamine:

1. L-Dopa
2. Amantadine (Symmetril)
3. Apomorphine
4. Alpha-Methyl Dopa Hydergine
5. MAO Inhibitors (Iproniazid, Imipramine, Desipramine)
6. 5-04 Tryptophan.

Drugs Decreasing Effective Concentration of Dopamine:

1. Reserpine – leads to depletion of brain dopamine + serotinin.
2. Phenothiazines – interferes with action of dopamine on receptor sites.
3. Pyridoxal Phosphate – potentiates peripheral decarboxylase activity and decreases central dopamine concentration.

Anti-Cholinergic Drugs:

1. Artane
2. Cogentin
3. Pagitane
4. Kemadrin
5. Akineton

Anti-Histamines:

1. Benadryl
2. Disipal
3. Phenoxene

Drug Therapy of Parkinson's Syndrome:

I. *Atropine-like Drugs*

This group of drugs, which include Artane, Cogentin, Pagitane, Kemadrine and Akineton, is one of the most commonly used anti-Parkinsonian drug groups. Essentially, they act by inhibiting cholinergic activity on striatal neurons. I am not going to elaborate on these drugs except to say

that they should not be used on patients with glaucoma and enlarged prostate. The side effects of these atropine-like drugs include headache, giddiness, blurred vision, mydriasis, dry mouth, epigastric distress and nausea, and confusion, agitation and psychosis. Atropine-like drugs can be used with dopaminergic drugs.

II. *Anti-Histamine Drugs*

This group which includes Benadryl, Disipal and Phenoxene is used empirically and is known to be more effective on tremmor than rigidity or akinesia. The side effects, other than their sedative properties, is less significant. The anti-histamines also work by producing cholinergic block.

III. *Amantadine Hydrochloride (Symmetril)*

Amantadine Hydrochloride (AH) is a 10 carbon cage amine. It first came into clinical use as a prophylactic agent against A2 influenza. Schwab et. in 1967, first used AH in Parkinson's Syndrome after one of his patients reported remission of her symptoms while taking the drug to prevent influenza. According to Schwab's report, 66 percent of the patients, out of163, showed subjective or objective improvement of akinesia, rigidity and tremmor. Patients usually noted improvement within 3 days of starting AH. Improvement was especially reported in hand-writing, dexterity, walking, balance and general mobility. They also had a sense of well-being. Results or improvement did not correlate well with age, sex or aetiology of Parkinson's Syndrome or previous Stereotaxic Surgery. Abrupt withdrawal of the drug seemed to aggravate the symptoms in several patients. Side effects are mild and include drowsiness, constipation and slurring of speech. AH is usually given in a dose of 100 mgm, twice a day. Further increasing the dosage has not been shown to improve the symptoms. In about 20 percent of patients, the drug's effect may undergo a partial decrease after 2–8 weeks of medication. This is believed to be due to exhaustion of the presynaptic dopaminergic pool. AH acts by mobilising existing stores of dopamine and inhibiting presynaptic re-uptake of dopamine. It thus increases available dopamine to the dopaminergic striatal neurons. Because of Amantadine's dependence on the dopaminergic system, patients who do well on Amantadine do well on L-Dopa and vice versa. Both drugs can be given simultaneously to the same patient. Unlike L-Dopa, AH is effective in drug induced Parkinson's Syndrome.

IV. *Larodopa (L-Dopa)*

The first report on L-Dopa treatment in Parkinsonism was published in 1961 By Birkmayer and Hornykiewicz who observed improvement of akinesia by slowly injecting 25–150 mgm. of L-Dopa intravenously. Subsequent reports of L-Dopa were not encouraging because the authors gave too low a dosage. In 1967, Cotzias did an extensive study and found striking improvement of Parkinsonian manifestations in 50 percent of 16 patients administered 3–16 Grm. of L-Dopa daily. He and his associates were the first to recognize the necessity of giving large doses. However, they subsequently recognized transient granulocytpoenia in some of the patients. They also found that the L-Dopa was more effective with less side effects than the D-isomer.

The rationale for the treatment with L-Dopa has been discussed earlier under pharmacology of Parkinsonism. L-Dopa ameliorates the symptoms of Parkinsonism by reinstitution of dopaminergic inhibition of the striatal neurons. The dosage of L-Dopa varies from patient to patient, and in the same patient at various times. Essentially, patients should be started on the lowest possible divided dosage, i.e. 125 mgm. qid., and this should be gradually and intermittently increased every 3rd to 5th day to the maximum dose that ameliorates symptoms or produces toxic effects. In my experience, most patients seem to do well on 3–4 Grm. of L-Dopa in divided doses.

The time of response and the degree of response seem to vary from patient to patient. As a rule, patients show some response within 2–3 weeks of starting on L-Dopa and akinesia is the first symptom to respond, followed by rigidity and finally by tremmor. Shuffling, associated movements, posture, festination, articulation, facial expression, dysphagia, lacrimation and salivation, all show progressive regression. Compelling evidence now exists that a large fraction of patients with Parkinson's Syndrome show striking and sustained improvement when treated with L-Dopa. L-Dopa can be administered with standard anticholinergic drugs or Symmetril. Failure to respond to L-Dopa is related to degeneration of striatal dopaminergic receptors. Patients who fail to respond to large and prolonged doses of L-Dopa are not likely to respond to Amantadine because both these drugs require functional dopaminergic receptor neurons.

The side effects of L-Dopa include:–

1. Nausea and vomiting
   – transient
2. Anorexia
   – transient
3. Postural hypotension
   – may be alarming.
4. Cardiac dysrhythmia
   –
5. Psychic manifestations
   – restlessness
   – heightened nervous tension
   – nocturnal hallucination
   – insomnia
   – toxic delirium
6. Transient effects
   – sense of body warmth
   – hyperhydrosis
   – excessive nasal discharge
   – pupillary dilation and widening of palpebral fissure.
7. Dyskinesias
   – grotesque facial grimacing
   – exagerated chewing
   – twisting and torsion of tongue
   – rhythmic closing and opening of eyes
   – head bobbing
8. Laboratory
   – positive coomb's test
   – leucopaenia
   – raised SGOT and BUN.

Of all the side effects, postural hypotension, Cardiac dysrhythmias and dyskinesias are the most troublesome. The dyskinesias are probably due to denervation hypersensitivity of striatal neurons, i.e. in unilateral Parkinsonism on L-Dopa, the uninvolved side does not show any dyskinesia. Treatment of the side effects, essentially consists of lowering of L-Dopa and reinstituting therapy in graduated doses.

Pyridoxal Phosphate (Vitamin B6) should not be given to patients on L-Dopa because it potentiates peripheral dopa-decarboxylase activity and, therefore, there is increased dopamine peripherally with its attendant side effects with decreased dopamine centrally. In severe cerebral toxicity due to L-Dopa, large doses of Vitamin B6 can act as an antidote.

L-Dopa has been shown to be effective in the treatment of chronic manganese poisoning, in which disorder the predominant symptoms are dystonias or Parkinsonian symptoms. Although the pathological lesion in chronic manganese poisoning is unknown, it is believed to be a dopaminergic deficiency disorder.

It appears that the introduction of L-Dopa in the past decade has opened a whole vista of neurochemical approach in the treatment of hitherto untreatable neurological disorders.

CONCLUSION

The date and observations reviewed above are in agreement with a comprehensive theory of the neuropharmacology of Parkinson's Syndrome. The most consistent lesion is degeneration of the cell bodies of the zona compacta of the substantia nigra. The result is a loss of dopaminergic input into the ipsilateral striatum. This loss of dopaminergic influence on the striatum is now felt tc be the principal factor in the production of Parkinsonian symptoms. Dopamine and acetycholine have antagonistic effects on the striatal neurons and the loss of dopamine in Parkinsonism leaves the acetycholine unantagonised. This is the rationale for the therapeutic use of anticholinergic drugs. L-Dopa ameliorates the symptoms of Parkinsonism by reinstituting dopamine inhibition of striatal neurons. Amantadine acts by blocking pre-synaptic re-uptake of dopamine and thereby prolonging its effects on striatal neurons.

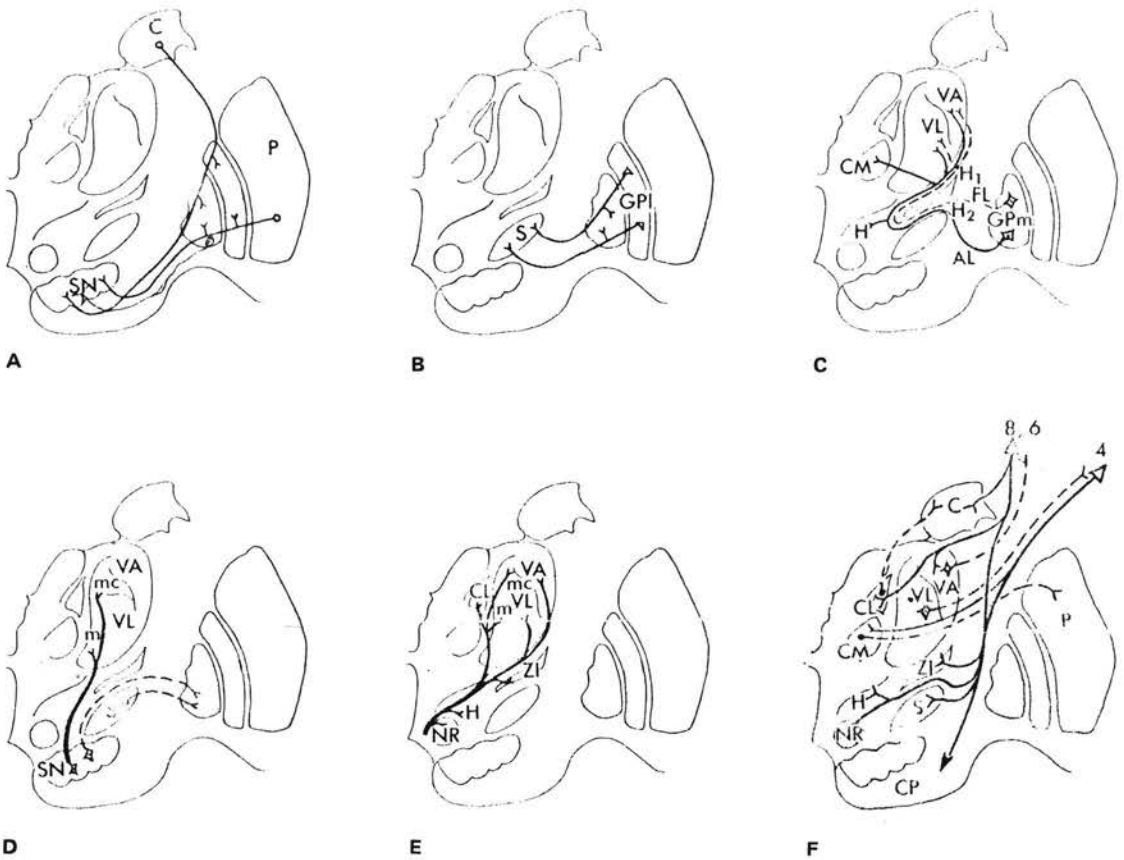
BIBLIOGRAPHY

1. McDOWELL, F.; LEE, J.E.; SWIFT, T.; SWEET, R.D.; OGSBURY, J.S. and KESSLER, J.T.; "Treatment of Parkinson's Syndrome with L-Dihydroxyphenylalanine (Levodopa)." *Annals of Internal Medicine,* 72:29–35, 1970.
2. COTZIAS, G.C.; PAPAVASILIOU, P.S. and GALLEN, R.; "Modification of Parkinsonism – Chronic Treatment with L-Dopa." *The New England Journal of Medicine,* 280:337–345, 1969.
3. WURTZMAN, R.J.; "Catecholamines and Neurological Diseases." *The New England Journal of Medicine,* 282:45–46, 1970.
4. COTZIAS, G.C.; "Metabolic Modifications of Some Neurological Disorders." *Journal of the American Medical Association,* 10:1255–62, 1969.
5. DALLOS, V.; HEATHFIELD, K.; STONE, P. and ALLEN, F.; "The Comparative Value of Amantadine and Levodopa. *Post Graduate Medical Journal,* 48:354–58, 1972.
6. TYCE, G.M.; MUENTER, M.D. and OWEN, C.A.; "DOPA in Plasma during DOPA Treatment of Patients with Parkinson's Disease." *Mayo Clinic Proceedings;* 45:438–43, 1970.
7. "Symposium on Lavodopa in Parkinson's Disease." *Neurology:* 22.No. 5, 1972.
8. O'REILLY, S.; "Dopamine and Basal Ganglia

Disorders." *Neurology* 15:280–85, 1965.

9. KLAWANS, H.L.; "The Pharmacology of Parkinsonism." *Diseases of the Nervous System,* 29:806–815, 1968.
10. SCHWAB, R.S.; "Amantadine in the Treatment of Parkinson's Disease." *Journal of the American Medical Association,* 208:1168–70, 1969.
11. MENA, I.; COURT, J.; FUENZALIDA, S.; PAPAVASILIOU, P.S. and COTZIAS, G.C.; "Modification of Chronic Manganese Poisoning." *The New England Journal of Medicine,* 282:5–13, 1970.
12. BRODY, J.A.; CHASE, T.N.; and GORDON, E.R.; "Depressed Monoamine Catabolite Levels in Cerebrospinal Fluid of Patients with Parkinsonism Dementia of Guam." *The New England Journal of Medicine,* 282:947–49, 1970.

Figure II



A to F, Transverse sections depicting: A, striatonigral connections; B, connections of the lateral pallidum; C, connections of the medial pallidum; D, nigrothalamic and pallidal connections; E, brachium conjunctivum–diencephalic connections; F, thalamocortical, thalamostriatal, and corticodiencephalic connections.

KEY FOR ABBREVIATION USED

AL – ansa lenticularis
C – caudate nucleus
CL – central lateral intralaminar nucleus
FL – fasciculus lenticularis
CM – nucleus centrum medianum
CP – basis pedunculi
GPL – globus pallidus, lateral segment
GPM – globus pallidus, medial segment
H, H1, H2 – H-fields of Forel
IC – internal capsule
NR – red nucleus
P – putamen
RF – reticular formation
S – subthalamic nucleus
SN – substantia nigra
VA – ventral anterior nucleus
(mc – magnocellar part)
VL – ventral lateral nucleus
(m – medial part)
ZI – zona incerta