

# L-Dopa and Mental Illness

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L-dopa (3,4-L-Dihydroxyphenylalanine), a precursor of dopamine, is a metabolic step in the formation of catecholamines. The actual interest of levodopa lies in its therapeutic action on true Parkinsonism, where it controls the rigidity and, to a lesser extent, the tremor.

In July, 1968, we first studied the action of levodopa in schizophrenic patients with drug-induced Parkinsonism. Our results indicated an aggravation of neurological and psychiatric symptoms<sup>1</sup>. On our second project with Parkinson patients without mental illness, it was observed that the onset of psychotic symptoms, such as hallucinations, persecutory delusions, severe depression, insomnia, agitation, and increased libido<sup>2</sup>, began with the addition of levodopa treatment. Our third study with schizophrenic patients, without true or drug-induced Parkin-

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sonism, showed an exacerbation of their mental symptoms<sup>3</sup> with L-dopa administration. While we carried out these experiments, we warned the medical profession that L-dopa could aggravate, precipitate, or cause mental illness<sup>2</sup>. At the same time, medical reports began to indicate the presence of psychiatric symptoms in Parkinson patients treated with L-dopa in 2.5 to 55.5 percent of the cases treated<sup>4</sup>.

At this point, it might be of interest to briefly describe some of the basic properties of L-dopa that are related to the behavioral field. Most of L-dopa is concentrated in the periphery, heart and chromaffin tissue of the adrenal glands. After crossing the blood-brain-barrier, it is localized in subcortical areas, mainly the caudate nucleus, lentiform nucleus, hypothalamus, and hippocampus, as dopamine<sup>5</sup>.

It has been suggested that L-dopa might have its own carrier system<sup>6</sup>, where

magnesium and calcium play an important role in the transport and storage of amines. Storage and release of these substances are to be considered, because they are closely related to numerous physiological mechanisms. For instance, an increased release of amines can be obtained by insulin hypoglycemia after reserpine injection<sup>7</sup>. L-dopa appears to have no direct pharmacological action<sup>8</sup>, thus it will show its effects by way of either dopamine, noradrenalin, or adrenalin activity.

Among the main metabolic and pharmacological action, we have: (1) a hypoglycemic reaction caused by a depletion of free fatty acids (F.F.A.)<sup>9</sup>; (2) a Pyridoxine (vitamin B6) deficiency<sup>10</sup>; (3) increased oxygen consumption<sup>11</sup>; (4) vasodilating and vasoconstricting properties<sup>12</sup>; (5) formation of severe gastric ulcers and death in rats under stress<sup>13</sup>; (6) anorexia and loss of weight<sup>14</sup>.

As far as behavior is concerned, the interest of this compound in animal and human research dates back to 1959. In mice, behavioral changes included alertness, responsiveness, irritability, and aggressiveness<sup>15</sup>. For other investigators, the administration of L-dopa in mice caused depressed searching activity<sup>16</sup> and psychotic symptoms such as stupor, catatonia, and rage<sup>17</sup>. In cats pretreated with the MAOI, phenylazine, shrieking, defensiveness, attempts to escape, and hallucinations were observed<sup>18</sup>.

The psychoactive properties of levodopa have been investigated since 1959, after it was postulated that depression was associated with a depletion of serotonin or norepinephrine<sup>19</sup>. Following this hypothesis, many investigators have used levodopa with contradictory results<sup>20 21 22 23</sup>. The present thought seems to show levodopa having a depressant activity. Our findings indicated an alerting effect with small doses and a depressant effect with higher doses. Levodopa, like many other substances which act upon brain structures, may have a biphasic action.

Levodopa is a compound that, given to anyone,

will always produce a side effect. This would indicate a multiplicity of physiological activities and the importance of this metabolite. Neurological side effects that should be considered are: (a) involuntary movements, (b) dyskinesias, such as grimacing, yawning, gnawing, nodding of the head, and opisthotonus. Psychotic symptoms comprise the whole scope, but, basically, the main ones are perceptual disturbances (mostly auditory and visual hallucinations), and paranoid delusions. Affect is also altered, with tendencies toward depression, at times severe, with suicidal attempts. Anxiety, agitation, and irritability accompanied by insomnia are not uncommon findings. Penile erections have also been observed with and without sexual fantasies, and, in addition, an increased libido. It has been reported that, in patients suffering from impotence, the administration of levodopa improves the condition without causing psychoses<sup>24</sup>. This last report leads us to believe that it is necessary to have a pathological substratum in order to produce psychiatric symptoms after levodopa administration.

At this point the first step to clarify would be if levodopa's psychiatric symptoms are toxic effects caused by drug administration. In this regard, we have found no hypnagogic symptoms or confusional states proper of a toxic delirium. The fact that levodopa is synthesized in our bodies would also speak against drug toxicity, favoring a precursor or a pathological metabolite in some individuals. Besides, at the same dose level not every Parkinson patient manifests psychiatric disturbances, while to the contrary many psychotic patients become aggravated. It has been noticed that L-dopa resembles mescaline and its derivatives. It has been observed that phenylethylamine derivatives with a 2,4,5, substitution pattern, such as 6-hydroxydopamine, have high hallucinatory activity in man<sup>25</sup>. The intraventricular administration of the latter into rat brains caused a marked and long-lasting deficit in brain

stimulation and other rewarding behaviors in the rat<sup>26</sup>. The same report adds that depletion of brain norepinephrine induced by 6-hydro-xydopamine was prevented by prior treatment with chlorpromazine. The controversial issue of 3,4-dimethoxy-phenylethy-lamine should also be considered to be part of an aberrant pathway of an endogenous psychotogen.

In regard to Parkinson's disease, it is not uncommon to see these patients suffering from some form of mental illness, such as depression, dementia, or chronic organic brain syndrome. In these cases, and in postencephalitic Parkinson, levodopa is not indicated, for it might cause acute psychoses. Therefore, it seems that levodopa has a psychotomimetic activity in two medical entities, schizophrenia and Parkinsonism. In retrospect, it has been suggested in 1955 that there is a relationship between the caudate nucleus and schizophrenia<sup>27</sup>. Numerous publications have reported gross behavioral changes produced by direct stimulation or inhibition of the caudate nucleus in animal<sup>28</sup>, and man<sup>29</sup>.

Anatomical destruction of basal ganglia, in chronic manganese poisoning and carbon monoxide intoxication, might provoke not only Parkinsonism but psychosis. Furthermore, drugs which have an antiparkinsonian effect, belladone, its derivatives, and synthetic compounds, all have psychotomimetic properties. It is interesting to observe that amantadine, a flu vaccine, can be used as an anti-Parkinsonian agent and might provoke psychotic episodes. On the other hand, neuroleptic drugs which have antipsychotic activity are characterized by inducing Parkinsonism. For some psychopharmacologists, these drugs must cause Parkinsonism in order to improve the psychosis. Among these drugs, chlorpromazine and haloperidol in schizophrenic patients with drug-induced Parkinsonism increase the urinary excretion of dopamine and homovanillic acid, both catabolites of dopa.<sup>30,31</sup> It was interesting to observe in

Parkinson patients treated with levodopa that psychiatric symptoms were preceded by an improvement of their Parkinsonism.

Is there a relationship among schizophrenia, Parkinson's disease, phenothiazines, and anti-Parkinson agents? So far, they seem to have a common denominator: the basal ganglia. Does the basal ganglia integrate part of a higher nervous center? It should be considered the possibility of histochemical complex where, according to various molecular concentrations and tissue integrity, it could lead to various neuropsychiatric disorders, with or without neurological or psychiatric predominance. This would help to explain the irreversibility of chronic schizophrenias. No doubt what we consider schizophrenia today probably includes more than one disease. Similar symptoms do not always mean the same illness.

Mental illness may manifest itself not only through psychiatric symptoms but by the presence of physical symptoms commonly seen in internal medicine. The incidence of thyroid dysfunctions, functional hypoglycemia, electrolyte imbalance, vascular changes, etc., in so-called schizophrenia appears to be more than coincidental. Furthermore, the therapeutic corrections of these disorders help to improve the psychiatric illness. It has been said that biological tests in schizophrenia had always proved to be negative and poorly illustrative. This statement was correct for the epoch during which it was made. These days, the impressive advance in technology invites the researchers to try again.

In summary, the catecholamine theory of schizophrenia and its relationship to the basal ganglia offers some good steps to unify part of the scattered research material of mental illness. The possibility of modifying some of these factors by means of psychopharmacological agents brings an inductive method that, within its simplicity, might help to build more complex deductions.

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