CATECHOLAMINES AND AFFECTIVE ILLNESS: STUDIES WITH
L-DOPA AND ALPHA-METHYL-PARA-TYROSINE

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In this paper we will review previous data and present new data on the clinical effects of L-dihydroxyphenylalanine (L-DOPA) and alpha-methyl-para-tyrosine (a-MPT) in the affective disorders and on the biochemical pharmacology of these agents in man and in the laboratory animal. These studies were prompted by the catecholamine hypothesis, which remains of central importance in current research in the affective disorders (Bunney and Davis 1965; Schi1dkraut 1965). This hypothesis proposes that some, if not all, depressions are associated with a deficiency of catecholamines at functionally important adrenergic sites in brain, and that mania may be associated with an excess of these amines (Schi1dkraut 1965). Pharmacologic agents that cause an increase in active catecholamines released by appropriate neurons should be associated with alleviation of depression or production of mania, and pharmacologic agents that cause a decrease in the amount of catecholamines available to the receptor should be associated with worsening of depression or improvement of mania.

The amount of actually functioning norepinephrine in brain (as distinguished from total brain norepinephrine) cannot now be determined, however, and the sites that may be important in the affective disorders have not been identified. In the absence of this knowledge,

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one strategy of research has been to study the effects of psychopharmacologic agents on the biochemistry of catecholamines in whole brain or in regions of brain, and to correlate this knowledge with the clinical effects of the drug in affective disorder. Administration of precursors of biogenic amines and inhibitors of synthesis of these amines offers an opportunity to manipulate amines in brain in man in a relatively direct and specific way, and it may enable some derivatives of the catecholamine hypothesis to be tested clinically. Such drugs have multiple biochemical effects, however, which must be considered in order to interpret the results of clinical trials of precursors or inhibitors of synthesis.

L-DOPA is the precursor of dopamine (DA) and norepinephrine (NE), bypassing tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (Udenfriend 1966). In the rat, 50 mg/kg is the minimal dose required to produce catecholamine fluorescence in brain parenchyma (Bertler et al. 1966). Higher doses or combined use of L-DOPA with inhibitors of decarboxylation by oral administration are used in man (Goodwin et al. 1970a). At these higher doses in the rat, L-DOPA causes an increase in brain dopamine, but brain norepinephrine has been reported to show no change or only a slight and transient increase (Butcher and Engel 1969; Everett and Borcherding 1970; Gershon, Goodwin, and Gold 1970; Chalmers et al. to be published). Serotonin (5-HT) content of brain is decreased (Butcher and Engel 1969; Everett and Borcherding 1970). The effects of L-DOPA on turnover of central amines have been investigated by us, and our findings are presented below.

Prior to the introduction of high dosages of L-DOPA in the treatment for Parkinsonism, several studies of L-DOPA in depression were reported. In non-blind studies, in which up to 150 mg/day of DOPA was given, some improvement in depression and increased motor activity and speech were reported (Pare and Sandler 1959; Turner and Merlis 1964; Ingvarsson 1965). In a double-blind study using up to 1 gm/day of DL-DOPA with a monoamine oxidase inhibitor, Klerman et al. (1963) found no improvement in depression (Matussek, Pohlmeier, and Ruther 1966). In Parkinsonian patients treated with higher doses of L-DOPA, the reported behavioral changes included depression, hyperactivity, and hypomania (Calne et al. 1969; Goodwin-Austin et al. 1969; Yahr et al. 1969; Goodwin et al. 1970b; McDowell et al. 1970; O'Brien et al. 1971).

α-MPT is an inhibitor of the rate-limiting enzyme, tyrosine hydroxylase, and it causes marked depletion of brain norepinephrine and dopamine, but no change in 5-HT (Spector, Sjoerdsma, and Udenfriend 1965). Synthesis of norepinephrine in vivo from $^{14}$C-tyrosine in guinea pig brain is markedly diminished by α-MPT and this decreased synthesis correlates in time with the norepinephrine depletion. Synthesis of norepinephrine from $^{3}$H-DOPA, which occurs at a later point in the pathway of synthesis, is unaffected by α-MPT (Udenfriend et