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# This Week's Citation Classic

**Schildkraut J J.** The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Amer. J. Psychiat.* 122:609-22, 1965. [Sect. Psychiatry, Lab. Clinical Science, National Institute of Mental Health, Bethesda, MD]

Pharmacological findings suggesting that the clinical effects of various mood altering drugs might be related to their neuropharmacological effects on catecholamine metabolism led to the formulation of a hypothesis concerning the biochemical pathophysiology of the affective disorders. [The ***SCI***® indicates that this paper has been cited over 735 times since 1965.]

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"This review was written in 1965, while I was a clinical associate in Seymour Kety's laboratory at the National Institute of Mental Health. At that time, basic neuropharmacological studies of the newly introduced clinically effective antidepressants and other mood altering drugs were beginning to suggest that the clinical effects of these drugs might be related to their effects on catecholamine metabolism. This, in turn, led to the formulation of the catecholamine hypothesis of affective disorders, which proposed that 'some, if not all, depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at functionally important adrenergic receptor sites in the brain,' whereas manias might be associated with an excess of catechol-amines.

"By focusing on the evidence supporting this hypothesis, I hoped that my review would stimulate this field of research at a critical point in its early development.

"While the catecholamine hypothesis of affective disorders remains to beverified, the expanding body of research on catecholamine metabolism in patients with affective disorders provides evidence of its heuristic value. Moreover, during the past decade, many studies[1] have explored the role of catecholaminergic neuronal systems in various aspects of animal behavior, and these studies have suggested that catecholaminergic neurons may be of importance in the mediation of many of the psychological functions that are altered in affective disorders, including arousal, motor activation, reinforcement, and reward. These factors may explain why this paper has been highly cited.

"However, even in 1965, it was clearly recognized that abnormalities in catecholamine metabolism alone could not conceivably account for all of the diverse clinical and biological phenomena in all types of affective disorders. Thus, in my review, I stressed that this hypothesis was 'at best a reductionistic oversimplification of a very complex biological state' that undoubtedly involved many other biochemical abnormalities (including alterations in the metabolism of indole-amines and other neurotransmitters, ionic changes, and endocrine disturbances), as well as physiological and psychological factors.

"The clinical and biological heterogeneity of the depressive disorders also was discussed in this review, since it seemed likely that the clinical heterogeneity of depressions might be related, in part, to differences in catecholamine metabolism, and that biochemical measures related to catecholamine metabolism might help to differentiate among subtypes of depressive disorders. While further investigation is still needed, many studies[1] already have provided evidence supporting this possibility, and we are now beginning to see the first practical clinical applications emerging from this line of research."

1. **Schildkraut J J. The current status of the catecholamine hypothesis of affective disorders.(Lipton M A, DiMascio A & Killam K** F, **eds.)** *Psychopharmacology: a generation of progress.* **New York: Raven Press,** 1978. p. 1223-34.