

Weissman A, Koe B K & Tenen S S. Antiamphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmacol. Exp. Ther.* 151:339-52, 1966.

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This paper deals with the action of alpha-methyl-tyrosine (AMT) as a blocking agent on the behavioral effects of amphetamine. [The *SCI*® indicates that this paper has been cited in more than 470 publications.]

## Amphetamine: Juxtaposition of Behavioral and Biochemical Studies

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At age 24, I was among the wave of Skinnerian psychologists hired into the pharmaceutical industry during the late 1950s. The impetus for this influx derived from new drugs for psychiatric disorders—reserpine and chlorpromazine for schizophrenia, iproniazid for depression, meproamate for anxiety. Companies wanted trained, young scientists to conduct psychopharmacology research, and reports that chlorpromazine blocked conditioned avoidance behavior made operant conditioning all the rage.

Once hired by Pfizer, I tried to build confidence—Pfizer's and my own—by exposing well-trained rats to drugs that worked. No agent was more reliable than amphetamine, and my earliest behavioral pharmacology publications often included data on its stimulant and anorectic effects. Some of these studies turned out to be important. For example, my reports that the anorexia produced by p- or m-trifluoromethyl-amphetamine (synthesized at Pfizer by Gerald F. Holland) is not accompanied by stimulation<sup>1,2</sup> helped point a French company towards synthesizing and developing fenfluramine. But the publications with the greatest impact, the subject of this *Classic* and one appearing a year earlier,<sup>3</sup> reported that alpha-methyl-tyrosine (AMT) blocks the behavioral effects of amphetamine, showing that amphetamine depends on intact catecholamine biosynthesis to exert its central actions.

During early 1965, Barry Bloom, then director of medicinal chemistry and, for many later years, president of Pfizer's Central Research Division, attended a New York Academy of Sciences lecture at which Sidney Udenfriend first described AMT as an inhibitor of tyrosine hydroxylase, the rate-limiting step in the biosynthesis of dopamine and norepinephrine. Bloom knew that Max Hughes, then a Pfizer chemist, was coincidentally synthesizing analogs of alpha-methyl-thyroxine, and that one of Hughes's intermediates was an easy synthetic step away from AMT. When Hughes made AMT available at Bloom's request, I asked my laboratory assistant, Charles Scott, to check that AMT would *potentiate* the stimulant action of amphetamine in rats. After all, reserpine, like AMT, depletes catecholamine stores from rat brain, and reserpine had long been known to potentiate the stimulant effects of amphetamine. Scott conducted the test but returned dejected. Not only did the experiment fail, but amphetamine seemed to be *blocked* by AMT. We confirmed this unexpected finding. B. Ken Koe, an organic chemist who had joined my psychopharmacology group as a homegrown, capable biochemist, embarked on a series of in vitro and in vivo studies, and Stanley S. Tenen, an experimental psychologist who was the third member of our group, contributed anorectic data.

The AMT article in *JPET* was followed a few months later by another noteworthy paper<sup>4</sup> that also became a *Citation Classic*. These two *Classics*, published in the same journal and year, reported important discoveries, but also illustrated at an early juncture the benefit of juxtaposing results from behavioral and neurobiochemical studies.

Most of the researchers involved in these events of more than a quarter-century ago—Bloom, Holland, Hughes, Koe, Scott, and myself—have enjoyed long, stable scientific careers at Pfizer, covering a wide variety of projects and capacities. Scott retired in 1986 after 36 years as an active employee, but the rest of us remain, each with well over 30 years of productive and rewarding service.

1. Weissman A & Schneider J A. Some anorectic and behavioral properties of P-1727, the p-trifluoromethyl analogue of amphetamine. *Pharmacologist* 2:71, 1960.

2. Holland G F, Buck C J & Weissman A. Anorexigenic agents: aromatic substituted 1-phenyl-2-propylamines. *J. Med. Chem.* 6:519-24, 1963.

3. Weissman A & Koe B K. Behavioral effects of L-alpha-methyl-tyrosine, an inhibitor of tyrosine hydroxylase. *Life Sci.* 4:1037-48, 1965.

4. Koe B K & Weissman A. p-Chlorophenylalanine: a specific depletor of brain serotonin. *J. Pharmacol. Exp. Ther.* 154:499-516, 1966. (Cited 1,640 times.) [See also: Weissman A & Koe B K. *Citation Classic. Current Contents/Life Sciences* 33(41):21, 8 October 1990.]

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