

## This Week's Citation Classic

Maickel R P, Cox R H, Jr., Saillant J & Miller F P. A method for the determination of serotonin and norepinephrine in discrete areas of rat brain. *Int. J. Neuropharmacol.* 7:275-82, 1968.  
[Lab. Psychopharmacology, Depts. Pharmacology and Psychology. Indiana Univ., Bloomington, IN]

**A method is described for the quantitative measurement of levels of serotonin and norepinephrine in geographically specific portions of the rat brain by utilization of a selective solvent extraction procedure and specific spectrophotofluorometric techniques. [The SC<sup>®</sup> indicates that this paper has been cited over 505 times since 1968.]**

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May 27, 1981

"The fact that this paper has been labeled a *Citation Classic* is proof that the phrase 'build a better mousetrap and the world will beat a path to your door' holds true even in scientific research! But, after all, what is a new analytical procedure other than a 'better mousetrap'—an improved means for doing a necessary job? The aura attached to a major scientific breakthrough often hides the fact that much of the work involved is not glorious and spectacular. So it was with the development of this method, now labeled as a much-referenced citation.

"My undergraduate training as a chemist was followed by graduate and postdoctoral research in chemical pharmacology in the laboratory of B.B. Brodie at the National Institutes of Health during the period 1955-1965. This was an exciting era, especially since that laboratory was one of the world centers in brain biogenic amine research. Such research demanded new, more sensitive analytical methods; the technology we now

know as spectrophotofluorometry was born there. Methods emanated in a virtually unending stream: 5HT, 5HIAA, norepinephrine, epinephrine, tryptamine, histamine. The procedures were similar: homogenization, extraction, back-extraction, and conversion to a fluorophore.

"In 1963, I was intrigued by the fact that o-phthalaldehyde (OPT) reacted with amino acids to form colored derivatives, but produced a powerful fluorophore with histamine. More than two years later (interrupted by a move to Indiana University) the research effort culminated; a number of 3,5-disubstituted indoles reacted with OPT under rigorous conditions (10 N HCl, 100°) to yield highly fluorescent products. By combining this procedure with an iodine oxidation of norepinephrine to a trihydroxyindole, homogenizing the brain tissue directly in acidified n-butanol, extracting into dilute acid, and scaling down volumes, the 'mousetrap' was designed. Two additional years of repetitive testing and retesting, modifying and discarding modifications, culminated in this publication. The procedure was convenient, sensitive, specific, and cost-effective, and was thoroughly use tested before publication, thus accounting for the article's frequent citation.

"I would be remiss if I did not acknowledge Raymond H. Cox, Jr., and Francis P. Miller (then graduate students in my laboratory); without their tireless efforts and long hours, the trial and error process would have been significantly more lengthy and considerably less effective. In addition, Jean Saillant served as our technical help, performing many repetitive tasks with skill and precision. One final comment must be made. Although the 'mousetrap' was completed in 1967, at least two dozen modifications and improvements have been reported in the intervening 13 years, most recently in the *Journal of Chromatography and in Pharmacology, Biochemistry, and Behavior*.<sup>1,2</sup> Obviously, science, as time, marches on."

1. Ogasahara S, Mandai T, Yamatodani A, Watanabe T, Wada H & Seki T. Simple method for the simultaneous determination of noradrenaline, dopamine and serotonin by stepwise elution from a short column of weak cation-exchange resin. *J. Chromatography* 180:119-26, 1979.
2. Jacobowitz D M & Richardson J S. Method for the rapid determination of norepinephrine, dopamine, and serotonin in the same brain region. *Pharmacol. Biochem. Behav.* 8:515-19, 1978.