

This Week's Citation Classic

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Carlton P L. Cholinergic mechanisms in the control of behavior by the brain.

Psychol. Rev. 70:19-39, 1963.

[Squibb Institute for Medical Research, New Jersey]

A number of experimental results cohere in suggesting that brain-acetylcholine acts to inhibit nonrewarded behaviors. This activity thereby provides a kind of 'guidance system' by which irrelevant behaviors are eliminated from the animal's goal-directed repertoire of responses. [The *Science Citation Index*® (SCI®) and the *Social Sciences Citation Index*™ (SSCI™) indicate that this paper has been cited over 300 times since 1963.]

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"Shortly after I had received my Ph.D., about 20 years ago, I was employed at the Squibb Institute for Medical Research. The situation was an uncomfortable one because, although I knew something about behavior, I knew nothing about drugs. Fortunately, the Institute then supported a basic research program of which I was a part. Thus, I was able to set out on a course of remediation under the superb tutelage of the late B.N. Craver. That period at the Institute was, in effect, a post-doctoral experience that could not have been duplicated elsewhere.

"I soon came to realize that, of the many classes of drugs, the anticholinergics were among the best understood because the role of acetylcholine in the peripheral nervous system had been well worked out. It occurred to me that if it could be assumed that the peripheral rules about the anticholinergics applied to the brain, it might be possible to use these drugs

as tools to understand some of the normal brain mechanisms that control behavior. That is, if it were possible to attenuate the actions of brain-acetylcholine and observe the behavioral consequences, it might be possible to infer the role of acetylcholine when its function was not attenuated. The logic was the same as that in neurology where the effects of a lesion permit inferences about function when the lesion is absent. The fundamental difference was that I was thinking in terms of chemically defined, not anatomically defined, systems in the brain.

"About two years later I had learned a great deal about general pharmacology and had a vast collection of data on the anticholinergics that I did not understand. At that time I reread an article by E. Hearst¹ for what must have been the fourth or fifth time. Hearst had found that the normal decline in responding due to nonreward did not occur when anticholinergics were given. Thus, acetylcholine might be required for nonreward to have its impact on behavior. Furthermore, it dawned on me that this simple idea could account for the otherwise confusing array of data I had on hand. Those data and that idea were the basis of this paper.

"In retrospect, I am both gratified and disappointed by the attention the paper has ultimately received. On the positive side, the most important idea that drugs can be used as analytical tools for understanding behavior has apparently made its impact; the effects of the anticholinergics are certainly better understood; some anatomical bases for the chemically defined processes have been elucidated. On the negative side, a great deal of the research that the paper engendered has been directed at testing something called 'Carlton's theory' when there is, in fact, no theory to be tested at a purely behavioral level. The paper embodies a very circumstantial conjecture that can only be evaluated by direct measurement of acetylcholine activity, independently of the behavioral effects themselves. That process of evaluation has not been undertaken."

1. **Hearst E.** Effects of scopolamine on discriminated responding in the rat. *J. Pharmacol. Exp. Ther.* 126:349-58, 1959.