# This Week's Citation Classic®

**Swanson L W & Hartman B K.** The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-β-hydroxylase as a marker. *J. Comp. Neurol.* 163:467-506, 1975.

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The organizational principles of neural pathways that use noradrenaline as a neurotransmitter were described in this paper. The analysis was based on recently developed immunohistochemical methods and confirmed and extended results obtained by Swedish workers using histofluorescence. [The *SCI*® indicates that this paper has been cited in over 635 publications.]

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This work grew out of a happy series of coincidences at Washington University in the early 1970s. I had just finished a two-year postdoctoral fellowship with Max Cowan in the Department of Anatomy and had moved to the Department of Biology, where I began to examine possible central effects of nerve growth factor (NGF) with Rita Levi-Montalcini. She had just demonstrated that central injections of NGF led to the aberrant ingrowth of sympathetic fibers towards the injection site, and the question naturally arose as to whether the protein might influence the growth of central catecholaminergic fibers as well. The general distribution of central aminergic systems had been elegantly described several years earlier by A. Dahlström and K. Fuxe,[1,2] using the revolutionary histofluorescence method of their mentors, A. Carlsson, B. Falck, and N.-Å. Hillarp.[3] However, this approach had several limitations: it was difficult to distinguish unambiguously dopaminergic and noradrenergic fibers in some instances, and the procedure itself was somewhat difficult and required blocking the brain into many small pieces.

Fortunately, a new approach emerged. In 1970 B.K. Hartman and S. Udenfriend[4] reported the first successful application of the Coons indirect immunohistochemical method for the cellular localization of an antigen in brain tissue. Furthermore, the antigen they localized was the enzyme dopamine-β-hydroxylase (DβH), which converts dopamine to noradrenaline. The use of antisera to DβH therefore provided a simple way to distinguish between dopaminergic and noradrenergic neurons without resorting to pharmacological manipulations. Furthermore, the mapping process was considerably more convenient because complete sections through the brain could be examined. Nevertheless, in its earliest stages of development, the method developed by Hartman was technically demanding. Unfixed frozen tissue was cut on a cryostat and the sections were then fixed in chloroform-methanol; on humid days in St. Louis the staining was often a dismal failure.

Hartman was in the Department of Psychiatry at Washington University, and we decided to map in detail the distribution of DβH-immunoreactive neurons, fiber tracts, and terminal fields in the rat brain, which I viewed at the time as a necessary baseline for measuring central effects of NGF. As is so often the case in science, I was unable to find the hoped-for effects on the central noradrenergic system, but the resulting map of the system itself proved both interesting and useful.

In retrospect, there are several reasons this paper has been cited often. First, there continued to be a great deal of interest in the neurobiology of the central adrenergic system.[5] Second, the mapping was detailed, and it was presented in the classical neuroanatomical tradition. Third, an independent method (enzyme location) was used to confirm the histofluorescence (transmitter) results. And fourth, several important distinctions between catecholaminergic systems were made for the first time.

1. **Dahlström A & Fuxe K.** Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. *Acta Physiol. Scand.* 62(Supp.232):1-55, 1964. (Cited 1,810 times.)
2. **Fuxe K.** Evidence for the existence of monoamine-containing neurons in the central nervous system. IV. The distribution of monoamine terminals in the central nervous system. *Acta Physiol. Scand.* 64(Supp.247):37-85, 1965. (Cited 800 times.)
3. **Carlsson A, Falck B & Hillarp N-Å.** Cellular localization of brain monoamines. *Acta Physiol. Scand.* 56(Supp.196):1-27, 1962. (Cited 300 times.)
4. **Hartman B K & Udenfriend S.** Immunofluorescent localization of dopamine-β-hydroxylase in tissues. *Mol. Pharmacol.* 6:85-94, 1970. (Cited 80 times.)
5. **Björklund A & Lindvall O.** Catecholaminergic brain stem regulatory systems. (Mountcastle V B, Bloom F E & Geiger S R, eds.) *Handbook of physiology, section 1: the nervous system, vol. IV.* Bethesda, MD: American Physiological Society, 1986. p. 155-236.