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This Week's Citation Classic®

Falck B, Hillarp N-Å, Thieme G & Torp A. Fluorescence of catechol amines and related compounds condensed with formaldehyde. *J. Histochem. Cytochem.* 10:348-54, 1962.
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When enclosed in a dry protein film, dopa and primary catecholamines react readily, and secondary catecholamines more slowly, with gaseous formaldehyde forming intensely fluorescent products in a two-step reaction. The first step is a ring closure for which the 3-OH group is essential. [The *SCI*® indicates that this paper has been cited in more than 2,435 publications.]

Shining Monoamines Illuminate Own Function

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To unveil, once in a lifetime, something profoundly exciting, and find the keys to a host of significant problems, is a fabulous experience that I wish for every colleague. Here is the tale of such an event.

In the 1950s, it was known that dopamine, norepinephrine, epinephrine, and serotonin were present in many invertebrate and vertebrate organs, but their function was not clear simply because the cells containing them had not yet been identified. This was the situation when Nils-Åke Hillarp and I set about to visualize the monoamines with the fluorescence microscope.

We had observed that the monoamines were easily dislocated from their cellular stores, which is disastrous for their localization, and we tried to prevent this by treating sections of freeze-dried tissue with gaseous reagents. Formaldehyde (FA) was found to be the reagent of choice. FA vapor generated from a saturated FA solution induced a norepinephrine fluorescence in adrenal medullary cells whose intensity was almost beyond belief compared to what was known then.[1] Our greatest dream was, however, still not fulfilled: to prove the transmitter function of monoamines by visualizing them in nerve cells. A first study of the reaction mechanism with FA was reported in the paper that is the topic of this *Citation Classic*. We found that the catecholamines reacted readily when enclosed in a dry protein film. In parallel studies of tissues, it became clear that the catecholamines and serotonin could form intensely fluorescent compounds in freeze-dried specimens exposed to dry formaldehyde gas—that is, under conditions of such dryness that any dislocation could be avoided.[2] The essential condition was found! It was a fantastic day when we saw the first neurons emitting a brilliant fluorescence due to their content of norepinephrine. We began to dream about all the fields that should—and did!—open up in neurobiology. The methodological details were soon developed[3] and Hillarp, at the Karolinska Institute, and I, at the University of Lund, found ourselves surrounded by productive young scientists with whose help the work progressed rapidly. The harvest was plentiful and the first reports on neuronal peripheral[2,3] and central[4] monoamine stores appeared in 1962.

The fluorescence method was accepted rapidly by many scientists outside Sweden[5] and initiated a vast number of projects, some of which branched out in unexpected directions. For example, I could not have imagined in 1961 when I, as the first, saw central dopamine neuron fluorescence that central nervous system neurons would have a pronounced ability to regenerate—a discovery[6] that would lead to cell grafting, a new approach for the treatment of Parkinson's disease.

Awards were not very usual in the early 1960s. The most prized was perhaps the initiative of the *Brain Research Bulletin*[5] to combine six issues into one volume filled with reports based on the fluorescence method, thus displaying the spectrum of research projects that profited from the fluorescence method.

1. **Falck B & Torp A.** A fluorescence method for histochemical demonstration of noradrenalin in the adrenal medulla. *Medna Exp.* 5:429-32, 1961.
2. ----------. New evidence for the localization of noradrenalin in the adrenergic nerve terminals. *Medna Exp.* 6:169-72, 1962.
3. **Falck B.** Observations on the possibilities of the cellular localization of monoamines by a fluorescence method. *Acta Physiol. Scand.* 56(Supp. 197):1-24, 1962. (Cited 1,565 times.)
4. **Carlsson A, Falck B & Hillarp N-Å.** Cellular localization of brain monoamines. *Acta Physiol. Scand.* 56(Supp. 196):1-26, 1962. (Cited 475 times.)
5. **Sladek R J & Björklund A,** eds. Monoamine transmitter histochemistry; a twenty-year commemoration. (Whole issue.) *Brain Res. Bull.* 9, 1982. 827 p. (Cited 600 times.)
6. **Katzman R, Björklund A, Owman Ch, Stenevi U & West K.** Evidence for regenerative axon sprouting of central catecholamine neurons in the rat mesencephalon following electrolytic lesions. *Brain Res.* 25:579-96, 1971. (Cited 175 times.)

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