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Trendelenburg U. Supersensitivity and subsensitivity to sympathomimetic amines. *Pharmacol. Rev.* 15:225-76, 1963.
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Denervation supersensitivity turned out to involve two entirely different mechanisms: on the one hand, a 'site of loss' (neuronal uptake) is lost; on the other hand, effector cells adapt to the loss of sympathetic tone. [The *SCI*® indicates that this paper has been cited in over 580 publications since 1963.]

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"Four weeks after removal of the superior cervical ganglion, the cat's nictitating membrane responds to 1/1,000 of the dose of noradrenaline that was needed to elicit a similar response in the innervated side.[1] Why? I fell in love with this fascinating problem during my training in Oxford (J.H. Burn), and a systematic study was carried out at the department of pharmacology, Harvard Medical School (O. Krayer). Help came from experienced colleagues, N. Weiner and J.R. Crout, who provided the sadly missing biochemical know-how, and also from an international mix of young trainees, J.S. Gravenstein, W.W. Fleming, B. Gomez Alfonso de la Sierra, and A.J. Muskus.

"Virtually all earlier explanations of denervation supersensitivity attempted to find *one* explanation.[2] The realization that there are two entirely different types of supersensitivity did not come as a sudden flash of inspiration—it grew slowly.

"One type of supersensitivity (later termed 'prejunctional'[3] or 'deviation' supersensitivity[4]) involved the loss (denervation) or the inhibition (cocaine) of a site of loss (neuronal uptake). This leads to an increased concentration of the agonist at the receptors. The other type of supersensitivity[4] (later termed 'postjunctional'[3] or 'nondeviation' supersensitivity[4]) reflects the ability of the effector cells to (slowly) adapt to any interruption of the flow of tonic impulses; the responsiveness of the cells to a given agonist concentration increases. Once we realized that we were dealing with two entirely different types of supersensitivity, the experimental facts of several decades fell into a meaningful pattern—and this is what the review was about.

"It was Fleming who inherited the nondeviation supersensitivity which continues to pose the intriguing question whether charges in receptor populations provide the *full* explanation.[5] My own interest was captivated by a second 'deviation supersensitivity' to catecholamines, namely, that induced by inhibition of extraneuronal uptake or catechol-O-methyl transferase.[6] This type proves that we need *both* nomenclatures, since it turned out to be 'postjunctional deviation supersensitivity.'"

1. **Langer S Z, Draskoczy P R & Trendelenburg U.** Time course of the development of supersensitivity to various amines in the nictitating membrane of the pithed cat after denervation or decentralization. *J. Pharmacol. Exp. Ther.* 157:255-73, 1967. (Cited 105 times.)
2. **Cannon W B & Rosenblueth A.** *The supersensitivity of denervated structures.* New York: Macmillan, 1949. 245 p. (Cited 295 times.)
3. **Trendelenburg U.** Mechanisms of supersensitivity and subsensitivity to sympathomimetic amines. *Pharmacol. Rev.* 18:629-40, 1966. (Cited 390 times.)
4. **Fleming W W.** Supersensitivity in smooth muscle. Introduction and historical perspective. *Fed. Proc.* 34:1960-70, 1975.
5. **Fleming W W, McPhillips J J & Westfall D P.** Postjunctional supersensitivity and subsensitivity of excitable tissues to drugs. *Rev. Physiol. Biochem. Exp. Pharmacol.* 68:55-119, 1973.
6. **Trendelenburg U.** A kinetic analysis of the extraneuronal uptake and metabolism of catecholamines. *Rev. Physiol. Biochem. Pharmacol.* 87:33-115, 1980.