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This Week's Citation Classic®

de Champlain J, Farley L, Cousineau D & van Ameringen M-R. Circulating catecholamine levels in human and experimental hypertension. *Circ. Res.* 38:109-14, 1976.
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This paper describes the successful adaptation of a sensitive radioenzymatic technique for the measurement of plasma catecholamines and reports that those levels are increased in about 50 percent of hypertensive patients, suggesting a participation of the sympathetic nervous system in the maintenance of hypertension in that subgroup. [The SCI® indicates that this paper has been cited in over 295 publications.]

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My enthusiasm to study the sympathetic nervous system came from a most stimulating postdoctoral traineeship at NIH with Julius Axelrod. During those years, in collaboration with Lawrence Krakoff, we were the first to demonstrate the major participation of the sympathetic nervous system in the development of hypertension in one experimental model (deoxycorticosterone acetate-salt [DOCA-salt]) in the rat.[1]

Because of my clinical training, I was stimulated in later years to test that hypothesis in human hypertension, but no reliable means for studying sympathetic activity in humans were available until 1970. Then, the development of highly sensitive radioenzymatic techniques for the measurement of catecholamines (CA) provided the possibility of using circulating CA as an index of sympathetic activity in humans. Original techniques were time-consuming and costly, so that they were never popularized. The first simple radioenzymatic technique was published by Coyle and Henry in 1973.[2] This technique was based on the conversion of CA into radioactive methylated metabolites by incubation of the sample with catechol-*O*-methyl transferase (COMT) in the presence of ^{3}H-S-adenosyl methionine. This technique worked beautifully in tissues, but unfortunately it was useless in plasma because COMT activity was totally inhibited by the presence of an unknown inhibitor.

I suspected that calcium could be that inhibitor after reading a paper by Axelrod and Tomchick[3] on the purification of COMT in which they reported that $CaCl_2$ was a potent inhibitor of COMT. After chelating calcium from the plasma with ethylene glycol tetraacetic acid (EGTA), we had the satisfaction of eliminating 50 percent of the inhibition. Thereafter, we could eliminate almost all of the inhibition by adding an excess of magnesium, which is an activator of COMT but was removed by EGTA.

Adapting that technique for use in plasma was very satisfying and exciting, but I did not feel, at the time, that it deserved a publication by itself. In fact, we did publish data on plasma CA in the dog using that technique[4] before publishing the procedures that led to the modification of the technique. The decision to publish those procedures was taken after we had received several requests from various laboratories to tell them about our modified technique. However, other more specific techniques for the differential measurement of epinephrine (E) and norepinephrine (NE) quickly became available so that I doubt that our paper was often cited only for that purpose.

Although our technique did not differentiate between NE and E, it allowed us to observe that total plasma CA levels were increased in DOCA-salt hypertensive rats and that 40 to 50 percent of hypertensive patients had elevated CA levels. On that basis, we proposed to subdivide the population of hypertensives into two subgroups: the normoadrenergic (normal CA) and hyperadrenergic (elevated CA) patients. Through further studies we were able to demonstrate that hyperadrenergic patients are also characterized by hyperkinetic cardiac functions and by a better therapeutic response to beta-blockers.[5]

I therefore believe that our paper was often quoted mainly because it introduced the concept that the sympathetic tone and reactivity were increased in an important, distinct subgroup of hypertensive patients.

1. de Champlain J, Krakoff L R & Axelrod J. Catecholamine metabolism in experimental hypertension in the rat. *Circ. Res.* 20:136-45, 1967. (Cited 135 times.)
2. Coyle J T & Henry D. Catecholamines in fetal and newborn rat brain. *J. Neurochemistry* 21:61-7, 1973. [See also: Coyle J T. Citation Classic. *Current Contents/Life Sciences* 27(51):18, 17 December 1984.]
3. Axelrod J & Tomchick R. Enzymatic O-methylation of epinephrine and other catecholamines. *J. Biol. Chem.* 233:702-5, 1958. (Cited 900 times.)
4. Yamaguchi N, de Champlain J & Nadeau R. Correlation between the response of the heart to sympathetic stimulation and the release of endogenous catecholamines into the coronary sinus in the dog. *Circ. Res.* 36:662-8, 1975. (Cited 105 times.)
5. de Champlain J, Cousineau D & Lapointe L. Evidences supporting an increased sympathetic tone and reactivity in a subgroup of patients with essential hypertension. *Clin. Exp. Hypertens.* 2:359-77, 1980. (Cited 20 times.)

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