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.

Jacques de Champlain
Department of Physiology
Faculty of Medicine
Université de Montréal
Montréal, Québec H3C 3T8
Canada

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My enthusiasm to study the sympathetic nervous system came from a most stimulating post-doctoral 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 [DOCA-salt] in the rat). 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. 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 3H-adenosylmethionine. 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 on the purification of COMT in which they reported that CaCl2 was a potent inhibitor of COMT. After chelating calcium from the plasma with ethylene glycol tetracetic 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 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 cardiovascular functions and by a better therapeutic response to beta-blockers.

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.