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This Week's Citation Classic

Price H L, Linde H W, Jones R E, Black G W & Price M L. Sympatho-adrenal responses to general anesthesia in man and their relation to hemodynamics. *Anesthesiology* **20:**563-78, 1959
[Dept. Anesthesiology, University of Pennsylvania School of Medicine, Philadelphia, PA]

The development of a sensitive, highly specific method for detecting catecholamines permitted us to determine, for the first time, whether or not certain general anesthetics caused sympathetic nervous excitation in man. We found that diethyl ether and cyclopropane did so, thus explaining the great safety of these anesthetic agents, since their directly depressant actions on myocardium are partially antagonized by sympathetic stimulation. [The *SCI*® indicates that this paper has been cited over 215 times since 1961.]

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"Shortly after the end of the Second World War, a new class of general anesthetics was introduced into clinical practice. These agents had in common extreme potency, halogen substitutions for hydrogen on the parent molecule, lack of explosion hazard, and severe circulatory depression in the recipient. It occurred to us that, since some of the older and safer anesthetics had been suspected of inducing sympathetic nervous activation (which could have counteracted the directly depressant actions of the anesthetics), the newer agents might simply fail to do so.

"Unfortunately, there was at this time no acceptable way of estimating the level of sympathetic nervous discharge in man. Attempts were soon to be made to measure concentrations of epinephrine and norepinephrine in plasma, but these were of limited specificity, since they involved condensation with ethylenediamine and therefore did not distinguish between simple catechol nuclei and the catecholamines which possessed biological activity. It was at this point that the trihydroxyindole method, developed in Scandinavia by Lund,[1] came to our attention. This method, while specific for catechol compounds possessing a BOH grouping characteristic of the naturally occurring biologically active sympathetic amines, was of limited sensitivity and not suitable for analyzing the low levels of epinephrine and norepinephrine which ordinarily occur in plasma.

"The principal impetus which made the cited study possible was the use of a two wave-length activation of the fluorescent trihydroxyindole compound produced, suggested by a colleague A. deT. Valk, and to further refinements by my wife, ML. Price, without whose efforts this work would never have come to fruition.

"The basic finding was that the older, safer anesthetics are sympathetic excitants, while most halogenated agents and the barbiturates are either depressants or have no effect. This action appears to explain the relative safety of the older anesthetics such as cyclopropane and diethyl ether, which are both capable of increasing plasma levels of norepinephrine in man. Of course, it was recognized at the time that there would be difficulties in interpretation, and the bulk of the paper dealt with various considerations needed to put the data into perspective. Viewed in retrospect, the interpretations offered appear prescient and they seem to have withstood the test of time."

1. Lund A. Fluorimetric determination of adrenaline in blood; chemical constitution of adrenolutine (the fluorescent oxidation product of adrenaline). *Acta Pharmacol. Toxicol.* **5:**121-8, 1949.