

# This Week's Citation Classic™

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Porte D, Jr., Graber A L, Kuzuya T & Williams R H. The effect of epinephrine on immunoreactive insulin levels in man. *J. Clin. Invest.* 45:228-36, 1966.  
[Department of Medicine, University of Washington, Seattle, WA]

The paper describes the effects of an epinephrine infusion to inhibit plasma insulin responses to glucose, glucagon, and tolbutamide in man. [The SCI® indicates that this paper has been cited in over 615 publications since 1966.]

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"In 1963, I arrived at the laboratory of R.H. Williams as a postdoctoral fellow. Having studied with Richard Havel in San Francisco, I was interested in the role of the sympathetic nervous system in the regulation of free fatty acid (FFA) mobilization from adipose tissue.<sup>1</sup> To evaluate this system, Alan Graber and I gave prolonged infusions of epinephrine to a male subject. We found that FFA levels rose and then returned to basal despite continued administration of the amine. Since hyperglycemia and tachycardia persisted, we concluded that reesterification of FFA in adipose tissue or inhibition of lipolysis by insulin might be involved. Therefore, we asked Kuzuya (now at Jichi Medical School, Japan), another postdoctoral fellow, to apply the newly developed radioimmunoassay for insulin to samples from our catecholamine infusions to determine which mechanism was most likely. To our surprise, insulin levels did not change during the epinephrine infusions but rose dramatically upon their termination.

"Since the concept of the autonomic nervous system regulating the peripheral endocrine system was not considered likely at that time, we performed a number of control studies with glucose and tested other insulin secretagogues; all were inhibited. This finding had important implications

for metabolic regulation and suggested that many older studies in which insulin secretion had been assumed to parallel glucose levels would need to be reexamined. Before submission of the work, I had the opportunity to present it at a major national meeting. Afterward, I received a letter and reprint<sup>2</sup> from Colwell pointing out that he had predicted such a finding 30 years earlier when he observed inhibition of glucose metabolism during an epinephrine infusion. So much for the originality of my scientific finding!

"Nevertheless, the concept was new to most scientists and opened up enough new questions that I have spent the next 20 years studying its implications. What has developed is the idea that the peripheral nervous system regulates many hormones, not just those of the endocrine pancreas, and that the central nervous system in turn is regulated by peptide hormones secreted by peripheral endocrine cells.<sup>3</sup> A critical role for the neural control of islet function in the development of stress hyperglycemia has also been delineated.<sup>4</sup>

"The newness of the idea and its applicability to many other endocrine glands, plus the large number of diabetes-related investigators, are the most likely explanations for the large number of citations.

"In 1970, I was fortunate to be selected by the American Diabetes Association to receive the Eli Lilly Award for scientific achievement; and, in 1984, I received the David Rumbaugh Award of the Juvenile Diabetes Foundation. Both of these honors I relate in part to this early study and its findings.

"It is always pleasing to look back on research studies such as this one that had such a positive influence on a field as well as on one's own career. The finding added an entirely new area to my research and began my interest in neural-endocrine interactions and the regulation of carbohydrate metabolism. Since the finding did not represent conventional wisdom at the time, I am grateful that my mentor, Williams, and the scientific system allowed me considerable freedom to pursue these studies. I hope our system of scientific evaluation retains such flexibility in the future."

1. Havel R J & Goldfien A. The role of the sympathetic nervous system in the metabolism of free fatty acids. *J. Lipid Res.* 1:102-8, 1959. (Cited 345 times since 1959.)
2. Colwell A R & Bright E M. The use of constant glucose injections for the study of induced variations in carbohydrate metabolism. IV. Suppression of glucose combustion by continuous prolonged epinephrine administration. *Amer. J. Physiol.* 92:555-67, 1930. (Cited 10 times since 1955.)
3. Woods S C, Smith P H & Porte D, Jr. The role of the nervous system in metabolic regulation and its effects on diabetes and obesity. (Brownlee M, ed.) *Handbook of diabetes mellitus: intermediary metabolism and its regulation, volume III.* New York: Garland Publishing Co., 1981. p. 209-71.
4. Porte D, Jr. & Woods S C. Neural regulation of islet hormones and its role in energy balance and stress hyperglycemia. (Ellenberg M & Rifkin H, eds.) *Diabetes mellitus: theory and practice.* New York: Medical Examination Publishing Co., 1983. p. 267-94.