

This Week's Citation Classic

Unger R H, Aguilar-Parada E, Müller W A & Eisentraut A M. Studies of pancreatic alpha cell function in normal and diabetic subjects. *J. Clin. Invest.* **49**:837-48, 1970.
[Dept. Int. Med., Univ. Texas, Southwestern Med. Sch., Dallas; and VA Hospital, Dallas, TX]

A-cell function was characterized in non-diabetics and juvenile-type and adult-type diabetics. In normals glucagon rose during arginine infusion and declined during hyperglycemia. In diabetics glucagon was high relative to glucose and overresponded to arginine. Diabetic A-cell dysfunction may contribute pathogenetically to the metabolic abnormalities of diabetes. [The SC® indicates that this paper has been cited over 390 times since 1970.]

Roger H. Unger
Department of Internal Medicine
University of Texas Health Science Center
at Dallas
Southwestern Medical School
Dallas, TX 75235

October 22, 1979

"This paper is widely cited because it is the first valid study of human A-cell function. It provided the first evidence that glucagon was a hormone in man, characterized normal human A-cell function, and showed that A-cell function was abnormal in diabetics. For Anna M. Eisentraut and me, it marked the end of a nine year effort to develop an immunoassay for glucagon in human plasma. In 1959, helped by advice from Berson and Yalow, we had developed a glucagon radioimmunoassay.¹ But valid measurements of glucagon in human plasma were impeded by inadequate sensitivity of our antisera against glucagon, nonspecificity of most of these antisera, and damage to the labeled glucagon when incubated in human plasma. For these reasons, between 1959 and 1968 we confined our work to dogs, in which the foregoing problems could be circumvented; incubation damage of the glucagon tracer in canine plasma was relatively slight, and by selective catheterization of the pancreatic and mesenteric veins and the inferior vena cava, the need for a highly sensitive assay was

reduced and discrimination between immunoreactivity of pancreatic and intestinal origin made possible.

"Although the dog work strongly suggested that glucagon was a true hormone, at least in that species, efforts to establish this in man were largely frustrated until 1968 when two fortunate unrelated events occurred. First, Anne Eisentraut, Nancy Whissen, and I observed that aprotinin (Trasylo) prevented incubation damage. Second, Anne Eisentraut discovered that the antiserum from one of 259 rabbits then undergoing immunization, rabbit G58, was remarkably different from that of the others. Not only was it highly sensitive, but it did not react appreciably with extrapancreatic sources of glucagon-like immunoreactivity, i.e., it was almost 'specific' for pancreatic glucagon. A valid assay for human glucagon was quickly developed and used for explorations of A-cell function reported in this and subsequent papers.

"Briefly, we found that in normal subjects glucagon was suppressed by hyperglycemia and stimulated by starvation, hypoglycemia, protein meals, and arginine infusion, suggesting that pancreatic glucagon behaved as a true hormone of 'glucose need' in normal man. This ended a controversy that had begun with the discovery of glucagon by Kimball and Merlin in 1923.² We also found that in diabetics the fasting levels of glucagon were high relative to the ambient blood glucose level, could not be suppressed by hyperglycemia, and were hyper-responsive to arginine infusion. This demonstration of abnormal A-cell function in diabetics has led to the 'bihormonal abnormality' concept of diabetes. This holds that certain of its metabolic abnormalities are the consequence, not of the insulin lack alone, but of insulin lack *plus* excessive glucagon secretion.³ Glucagon suppression can reduce both the marked endogenous hyperglycemia and hyperketonemia of diabetes, a fact which may have therapeutic implications for this disease."

1. **Unger R H, Eisentraut A M, McCall M S, Keller S, Lanz H C & Madison L L.** Glucagon antibodies and their use for immunoassay for glucagon. *Proc. Soc. Exp. Biol. Med.* **102**:621-3, 1959.
2. **Unger R H.** Diabetes and the alpha cell (Banting Memorial Lecture). *Diabetes* **25**:136-51, 1976.
3. **Raskin P & Unger R H.** Hyperglucagonemia and its suppression: importance in the metabolic control of diabetes. *N. Engl. J. Med.* **299**:433-6, 1978.