

This Week's Citation Classic

Müller W A, Faloona G R, Aguilar-Parada E & Unger R H. Abnormal alpha-cell function in diabetes. Response to carbohydrate and protein ingestion. *N. Engl. J. Med.* **283**:109-15, 1970. [Dept. Internal Medicine, Univ. Texas Southwestern Med. Sch., and Veterans Admin. Hosp., Dallas, TX]

Carbohydrate ingestion reduced glucagon secretion in nondiabetics, but not in diabetics. Protein meals doubled plasma glucagon in both. Induced hyperglycemia abolished the glucagon response to protein ingestion in nondiabetics, but had no effect in diabetics. This inappropriate hyperglucagonemia appears to be a hallmark of diabetes mellitus and worsens its metabolic state. [The SC® indicates that this paper has been cited in over 260 publications since 1970.]

Walter A. Müller
rue du Musée 9
2000 Neuchâtel
Switzerland
and

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

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"In 1960, Rosalyn S. Yalow and Solomon A. Berson reported on the first radioimmunoassay used to measure insulin.¹ During the same time period, Roger H. Unger and Anne M. Eisentraut in Dallas started to produce antisera against glucagon with the goal of measuring it in plasma by a similar assay. In contrast to the rapidly working insulin immunoassay, the glucagon immunoassay required another decade to become of equal quality. The common efforts of Unger and his coworkers Eisentraut and Virginia Harris made this possible.

"Müller was fortunate to join the team at the Veterans Administration Research Center in Dallas in 1969, shortly after the first antiserum, generously produced by the rabbit G-58, was capable of measuring true glucagon in peripheral blood from animals and humans. Eugenio Aguilar-Parada introduced Müller to

the human studies, teaching him how to perform arginine infusions and feeding strange meals to the laboratory staff and the diabetic US veterans.

"The first two papers appeared in 1969 and in April 1970^{2,3} describing in humans the inhibition of glucagon secretion by glucose and its stimulation by arginine infusions. Diabetics exhibited higher plasma glucagon concentrations. We then tested physiologic situations of feeding carbohydrate and protein. Patients and controls were asked to rapidly eat dry steaks kept warm in the oven used otherwise for drying glassware. Despite the even more unpalatable carbohydrate meals consisting of bread, spaghetti, rice, potatoes, and corn, our patients did not reject the food.

"It appears to us that there are two reasons why this paper has been cited so often. First, it was the first publication reporting reliable measurements of plasma glucagon in a physiological situation, namely, in response to ingested food, an important facet of human physiology and nutrition. Second, it revealed a new aspect of the pathophysiology of diabetes mellitus: diabetics exhibit higher glucagon concentrations and abnormal alpha-cell function, a possible pathogenetic feature of this disease. Indeed, we found it in all forms of diabetes that we studied.⁴

"The results were presented to the Southern Society for Clinical Investigation in New Orleans and to the American Society for Clinical Investigation in Atlantic City in 1970. With minor revisions, the manuscript was accepted for publication by the *New England Journal of Medicine*. We were proud that Unger was subsequently honored by receiving the Banting and Claude Bernard Medals. Unger has since made numerous contributions to the understanding of islet cell physiology and pathophysiology, particularly with respect to the interaction of the different islet cell hormones,⁵ whereas Müller was lately involved in studying the role of glucagon in protein metabolism.⁶

1. **Yalow R S & Berson S A.** Immunoassay of endogenous plasma insulin in man. *J. Clin. Invest.* **39**:1157-75, 1960. [Citation Classic. *Current Contents* (14):9. 4 April 1977.]
2. **Aguilar-Parada E, Eisentraut A M & Unger R H.** Pancreatic glucagon secretion in normal and diabetic subjects. *Amer. J. Med. Sci.* **257**:415-19, 1969.
3. **Unger R H, Aguilar-Parada E, Mailer W A & Eisentraut A M.** Studies of pancreatic alpha cell function in normal and diabetic subjects. *J. Clin. Invest.* **49**:837-48, 1970. [Citation Classic. *Current Contents/Clinical Practice* 8(2): 10. 14 January 1980.]
4. **Müller W A, Faloona G R & Unger R H.** The effect of experimental insulin deficiency on glucagon secretion. *J. Clin. Invest.* **50**:1992-9, 1971.
5. **Unger R H & Orci L.** Glucagon and the A cell. Physiology and pathophysiology. *N. Engl. J. Med.* **304**:1518-24: 1575-80, 1981.
6. **Müller W A, Cüppers H J, Zimmermann-Telschow H, Micheli H, Wyss T, Renold A E & Berger M.** Amino acids and lipoproteins in plasma of duodenopancreatectomized patients: effects of glucagon in physiological amounts *Fur. J. Clin. Invest.* **13**:141-9, 1983.