

This Week's Citation Classic

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Alberti K G M M, Christensen N J, Christensen S E, Prange Hansen Aa, Iversen J, Lundbaek K, Seyer-Hansen K & Ørskov H. Inhibition of insulin secretion by somatostatin. *Lancet* 2:1299-301, 1973.
[Second University Clinic of Internal Medicine, Kommunehospitalet, Aarhus, Denmark]

Somatostatin was isolated from the hypothalamus and synthesized in 1973. Intravenous glucose tolerance tests in normal subjects demonstrated that somatostatin reduced insulin responses and decreased the glucose-disappearance rate. The effect was direct on the pancreatic B-cell as demonstrated in perfused pancreas. This was the first demonstration of an extrapituitary effect of somatostatin. [The *SCI*[®] indicates that this paper has been cited in over 395 publications since 1973.]

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"This study was a by-product of our hypothesis¹ that growth hormone is a causal factor in diabetic angiopathy. Prange Hansen had demonstrated that diabetics in ordinary clinical metabolic control had a two to three times elevated diurnal plasma growth hormone and this hyperproduction was metabolically dependent.² This fact, combined with the demonstration in the first randomized controlled clinical trial³ that hypophysectomy delays the development of diabetic retinopathy, launched the hypothesis.

"A logical consequence was to find pharmacology able to suppress growth hormone secretion. After having administered about 100 different drugs during several more growth hormone stimulation (exercise) tests, the hypothalamic growth hormone inhibitor somatostatin was isolated by Guillemin and co-workers in 1973.⁴

"Norman Grant of Wyeth Laboratories, Philadelphia, heard of our efforts and favoured us with some synthetic somatostatin at a very early and very appropriate point in time. With this we succeeded by a hairbreadth to be the first to demonstrate in man the inhibitory effect on growth hor-

mone secretion (active in diabetics as well as controls).⁵ Somatostatin was destined not to be the ideal growth hormone suppressor taken daily by most diabetics and this is partly due to its other than growth hormone inhibitory effects—of which the world was totally unaware in autumn 1973.

"Although the experimental design had been less than ideal for the purpose, we noted that with overnight fast and exercise, suppressed plasma insulin seemed even lower in those receiving somatostatin infusion. We quickly examined our insulin responses to glucose with and without preceding injection of somatostatin and established with our last smidgen that this new insulin inhibition had direct action on the B-cell. This we published in December 1973; later followed a series of reports on somatostatin's inhibitory effects on glucagon and a lot of other hormones—and somatostatin became invaluable in studies of metabolic effects of hormones.

"I note with some regret that we concluded: 'These effects of somatostatin are definitely not physiological.... It is highly improbable that somatostatin ever reaches concentrations in the systemic circulation that would have any effect on insulin secretion.' But how were we to know that loads of readily releasable somatostatin was present in the pancreatic D-cell adjacent to the B-cell—and that the insulin inhibitory action would take on a new dimension and detonate a prolific series of studies of possible paracrine effects in the pancreas and elsewhere?

"So, our explanation that this paper reached the *Citation Classics*' hit list is that we happened to have some somatostatin very early; that we stumbled on its very first discovered extrapituitary action (when we urgently were looking for another effect); that the somatostatin field of research exploded thereafter; and that we ranked the order of coauthors alphabetically so it glared at observers from the top of reference lists."

1. Lundbaek K, Christensen N J, Jensen V A, Johansen K, Steen Olsen T, Prange Hansen A, Ørskov H & Østerby R. Diabetes, diabetic angiopathy, and growth hormone. (Hypothesis.) *Lancet* 2:131-3, 1970.
2. Prange Hansen Aa. Normalization of growth hormone hyperresponse to exercise in juvenile diabetics after 'normalization' of blood sugar. *J. Clin. Invest.* 50:1806-11, 1971.
3. Lundbaek K, Malmros R, Andersen H C, Rasmussen J H, Bruntse E, Madsen P H & Jensen V A. Hypophysectomy for diabetic angiopathy. A controlled clinical trial. (Östman J, ed.) *Diabetes: proceedings of the Sixth Congress of the International Diabetes Federation, Stockholm, Sweden, 30 July-4 August 1967*. Amsterdam: Excerpta Medica, 1969. p. 127-39.
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5. Prange Hansen Aa, Ørskov H, Seyer-Hansen K & Lundbaek K. Some actions of growth hormone release inhibiting factor. *Brit. Med. J.* 3:523-4, 1973.