

This Week's Citation Classic

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Polak J M, Pearse A G E, Grimelius L, Bloom S R & Arimura A. Growth-hormone release-inhibiting hormone in gastrointestinal and pancreatic D cells.

Lancet 1:1220-2, 1975.

[Depts. Histochem. and Med., Royal Postgrad. Med. Sch., London, England and Vet. Admin. Hosp., and Tulane Univ. Sch. Med., New Orleans, LA]

This paper provided morphological evidence for the production of an active peptide, somatostatin (or growth-hormone release-inhibiting hormone), by an endocrine cell type of the pancreatic islets which had been described 44 years before as separate and distinct from the A and B cells.¹ The peptide product of this 'third' type was then unknown. [The SC¹® indicates that this paper has been cited in over 380 publications since 1975.]

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"In 1931 a 'third' type of endocrine cell (the D cell of the pancreas) was recognised in human pancreatic islets.¹ D cells were later found to be present in the islets of many other species.

"In spite of its distinctive morphology, the function and putative product of the third cell type remained mysterious. Many peptides were proposed as possible products of the D cell of the pancreatic islets. Among them, gastrin was the favourite candidate, in view of the repeated finding of pancreatic gastrinomas (responsible for the classical features of the Zollinger-Ellison syndrome) and the need to find their cell of origin, this type of tumour being one of the most common islet cell tumours. All efforts proved fruitless. In fact, many workers argued about the real identity of the D cell of the pancreas and suggested that this distinct cell type might merely be a modified A cell; some even proposed the term A₃ cell because of its alleged close morphological resemblance to the glucagon producing A₁ cell of the pancreas.

"In 1974, Lars Grimelius came to the department of histochemistry for a two-year sabbatical. He came from Uppsala with a

Royal Society scholarship to work on the growing points of immunocytochemistry. Grimelius joined the department shortly after the revolutionary discovery of the potent hypothalamic inhibitor for the release of growth hormone (or somatotrophin) named growth-hormone release-inhibiting factor,² later renamed somatostatin. Among its inhibitory actions, its powerful effect as an inhibitor of the release of pancreatic hormones was soon realised. The potent inhibitory actions of extracts of pancreatic D (A₃) cells on the secretion of insulin had been reported as early as 1969.³

"In view of this, it seemed appropriate to investigate whether this newly discovered peptide originated from the D cells of the human pancreas. We were indeed in possession of the most appropriate technology. Grimelius, the inventor of the famous Grimelius silver impregnation technique for staining the A, glucagon, cells of the pancreas, was able to use not only his own technique but also that proposed by Hellman and Hellerstrom for the visualisation of D (A₃) cells of the pancreatic islets.⁴ I myself was involved in the development of refined and specific immunocytochemical methods for the localisation of peptide hormones in endocrine cells, and Akira Arimura was generous enough to allow us to use his excellent antibodies to somatostatin. The winds of fortune were blowing in our direction, and in 1975 we were able to demonstrate confidently the presence of somatostatin-like immunoreactivity in the 'third' endocrine cell type of the pancreas, the D cells, and thus the long sought peptide product for the D cells was at last recognised. The finding of somatostatin-like immunoreactivity in the D cells of the pancreas has been repeatedly reported by many workers throughout the world.

"Since its discovery, somatostatin has generated an overwhelming interest from most scientific disciplines and it is clear that the knowledge of its precise cellular origin must have set up the ground basis for the understanding of its mode of action and putative role in human pathology; without doubt this is the reason why the paper is so popularly quoted."

1. Bloom W. A new type of granular cell in the islets of Langerhans of man. *Anat. Rec.* 49:365-84, 1931.
2. Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J & Guillemin R. Hypothalamic polypeptide that inhibits the secretion of immunoreactive growth hormone. *Science* 179:77-9, 1973.
3. Hellman B & Lernmark A. Inhibition of the *in vitro* secretion of insulin by an extract of pancreatic α_1 cells. *Endocrinology* 84:1484-8, 1969.
4. Hellman B & Hellerstrom C. The specificity of the argyrophil reaction in the islets of Langerhans in man. *Acta Endocrinol.* 36:22-30, 1961.