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The GI Effects of GLP-1 – The Genesis of Longstanding Progress

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Behind every major discovery is a backstory of scientific advances that created the technology and knowledge that provided the substrate on which creativity, innovation, and persistence generated a paradigm shift that radically changes the approach to a disease entity. Such is the case for the discovery of the glucagon-like peptides (GLP), whose stable analogs have immeasurably contributed to the therapy of metabolic diseases and intestinal failure [1–3].

In this issue of *Digestive Diseases and Sciences* [4], Professor Jens J. Holst comments on his 1993 publication in this journal [5] that has been cited over 550 times as of this writing. This publication, as Prof. Holst describes, focuses on the important but often underappreciated gastrointestinal effects of GLP-1 that are key to understanding its mechanism of action. Professor Holst is a notable and highly-cited Danish physiologist who has been interested in the effect of gut hormones on pancreatic endocrine function since his initial experience in the laboratory of Prof. Jens F. Rehfeld in Copenhagen in the early 1970s, where he published his first major paper describing the effects of "gut glucagon" on hypoglycemia. [6] He then published the first detailed description of the insulinotropic effect of GLP-1 in 1987 (Fig. 1). [7] He has spent the rest of his career studying the insulinotropic and gastrointestinal effects of gut hormones, in particular proglucagon-derived peptides and specifically GLP-1.

Several recent reviews have covered the history of gut hormones that affect pancreatic endocrine function, including one by Jens Rehfeld. [8] The finding that substances derived from the gut mucosa affect pancreatic endocrine function dates to the early twentieth century from some of the classical experiments of Bayliss and Starling [9] to those of the Belgian physiologist Jean La Barre, who is credited with coining the term "incrétine", a contraction of intestine and secretin, [10] now used to describe a gut-derived peptide hormone released by oral glucose that affects the release of pancreatic endocrine hormones, as differentiated from the "excretins" such as secretin and cholecystokinin, that release fluid, bicarbonate, and enzymes from the exocrine pancreas.

What hampered all of these early studies was the inability to unambiguously identify the substance contained in duodenal mucosal extracts and the hormone released from the pancreas, since all of the early studies were mostly reliant on measuring the effect of mucosal extracts on glycemic control. The major breakthroughs that enabled the discovery of the structure and effects of the incretins included the development of the radioimmunoassay (RIA) by Rosalind Yalow and Solomon Berson in 1960 [11] working at the Bronx Veterans Affairs Medical Center that was recognized by the awarding of the 1977 Nobel Prize in Physiology and Medicine, the second such prize awarded to a woman. The ability of the RIA to accurately measure substances in body fluids in picomolar concentrations revolutionized endocrinology and related fields. The other major advance was the ability to sequence peptide hormones, described by the Swedish chemist Pehr Edman in 1949, [12, 13] in his novel method of attaching an adduct to the peptide N-terminal, hydrolyzing, and repeating, that enabled scientists to sequence peptides with the technique eventually termed the "Edman degradation", which remains to this day an important method for peptide sequencing. At about the same time, Frederick Sanger of the University of Cambridge was determining the peptide sequence of insulin through a related technique [14, 15]. Dr. Sanger was awarded the Nobel Prize in Chemistry in 1958 for this work, underscoring its impact on science, since sequencing enabled scientists to identify the structure of peptides with great accuracy and relative ease. Inexplicably, Prof. Edman did not receive any major international prizes for his work, although his name became synonymous with the sequential method for peptide sequencing that was used as a primary method well into the 1990s.

Jens Holst, along with Dan Drucker and Joel Habener, was awarded the 2021 Canadian Gairdner Award for their discovery and contributions to the understanding of the mechanism of action and effects of GLP-1 and GLP-2. I would like to thank Jens for his most welcome contributions to Digestive Disease and Sciences and hope that by reading his article you will further understand not only the

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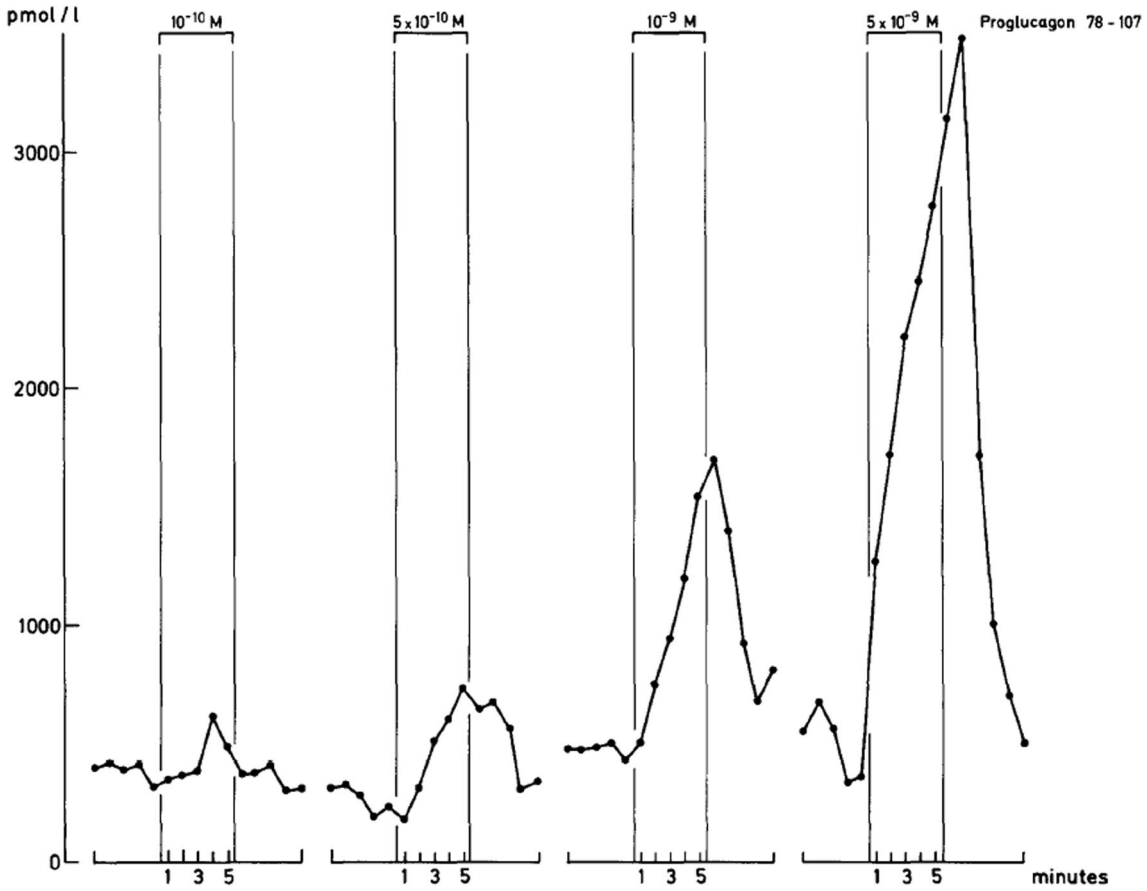

Fig. 1 Initial direct demonstration of the insulinotropic effect of truncated GLP-1 on the isolated porcine pancreas. The abscissa depicts the concentration of insulin released into the effluent whereas the concentration of perfused truncated GLP-1 is depicted at the top of each column. Reproduced from [7] with permission from the publisher John Wiley and Sons

importance of his discovery, but also the 'thrill of the chase' that accompanies the pursuit of the unknown.

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