CLASSICAL PERSPECTIVES

Secretin and the exposition of hormonal control

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'I happened to be present at their discovery. In an anaesthetized dog, a loop of jejunum was tied at both ends and the nerves supplying it dissected out and divided so that it was connected with the rest of the body only by its blood vessels. On the introduction of some weak HCl into the duodenum, secretion from the pancreas occurred and continued for some minutes. After this had subsided a few cubic centimetres of acid were introduced into the enervated loop of jejunum. To our surprise a similarly marked secretion was produced. I remember Starling saying: "Then it must be a chemical reflex." Rapidly cutting off a further piece of jejunum he rubbed its mucous membrane with sand in weak HCl, filtered, and injected it into the jugular vein of the animal. After a few moments the pancreas responded by a much greater secretion then had occurred before. It was a great afternoon.' C. J. Martin's first hand account of 'The crucial experiment' in the discovery of secretin (Bayliss & Starling, 1902*b*), which was performed at University College London on 16th January 1902 and was recorded in his obituary of Ernest Henry Starling (Martin, 1927), provides fabulous insight into the excitement of the moment.

Bayliss and Starling first communicated their discovery to the Royal Society only one week after the experiment (Bayliss & Starling, 1902*a*) and published the full account of the experiments leading to the discovery of secretin in *The Journal of Physiology* later that same year (Bayliss & Starling, 1902*b*). These experiments were important not only for the understanding of the regulation of exocrine pancreatic secretion, but for the wider recognition of chemical control of physiological functions. Starling developed his ideas of chemical control and these were elaborated in his series of four Croonian Lectures to the Royal College of Physicians, London in 1905 (Starling, 1905*a*,*b*,*c*,*d*). He introduced the term hormone, derived from ὁρμάω (I arouse to activity) – this name suggested by Mr W. B. Hardy (Bayliss, 1924), to describe those chemical messengers which 'have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream' (Starling, 1905*a*). Starling drew heavily on his own studies on secretin in formulating his ideas about hormonal control. However, he also acknowledged the earlier studies of Oliver and Schäfer (who later took the name of Sharpey-Schafer, himself recognized as one of the pioneers of endocrinology) (1895) who, in demonstrating that the medulla of the suprarenals (adrenals) contained a substance that when injected caused a marked rise in blood pressure, had set the ground work for the discovery of adrenaline. Starling further recognized in his Croonian Lectures that hormones may be divided into those that increase the activity of an organ, such as secretin and adrenaline, and those that increase the growth of a tissue or organ (Starling, 1905*a*). Thus in the last of his lecture series, his discussion focused on the importance of hormones from the thyroid gland, testis and ovaries, together with the response of the mammary glands during pregnancy, as examples of hormonal control of growth (Starling, 1905*d*). Dual functionality of some hormones, activity and growth, is now widely recognized. While secretin does not have major growth functions, the hormone gastrin, first described by Edkins (1905, 1906), a colleague at University College, and highlighted as another example of hormonal control of activity by Starling (1905*c*), is recognized has having important functions in regulating secretion of gastric acid and, more recently, cell proliferation, migration and differentiation in the gastric mucosa (e.g. see Dockray, 1999).

The proposal of chemical (hormonal) control of pancreatic secretions very much conflicted with the contemporaneous views of the Pavlov school that only neural reflexes were involved in the response of the pancreas to duodenal acidification. Indeed, Bayliss & Starling were unable to repeat the work of Pavlov demonstrating vagal nerve enhancement of pancreatic secretion, leading them to suggest only hormonal control was important (Starling, 1905*b*). This failure was discovered to be due to pre-anaesthetic morphine treatment and Starling later recognized dual, hormonal and neural, control of pancreatic secretions (Gregory, 1962). The discovery of secretin also required Pavlov to revise his views about the singular importance of neural control mechanisms. Babkin was present in Pavlov's laboratory in St Petersburg when Bayliss and Starling's experiment was repeated. 'The effect of secretin was self-evident. Pavlov and the rest of us watched the experiment in silence. Then without a word, Pavlov disappeared into his study. He returned half an hour later and said, "Of course they are right. It is clear that we did not take out an exclusive patent for the discovery of the truth"' (Babkin, 1949). Pavlov turned his attention to the study of conditioned reflexes.

Our understanding of secretin and pancreatic secretions has developed. However, the salient findings of Bayliss and Starling concerning secretin have stood the test of time. Thus secretin is recognized as the key pathway mediating a now classical negative feedback reflex. Acidic chyme, emptying from the stomach, stimulates upper small intestinal mucosal S cells to release secretin. Secretin stimulates the flow of a bicarbonate-rich pancreatic secretion which empties into the duodenum, thus neutralizing the acid chime and removing the stimulus for secretin release. Of wider significance, the concept of hormonal regulation and the definition of a hormone basically remain to this day as originally outlined in Starling's Croonian Lectures.

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