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1

A short history of neuroendocrine tumours and their peptide hormones

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The discovery of neuroendocrine tumours of the gastrointestinal tract and pancreas started in 1870, when Rudolf Heidenhain discovered the neuroendocrine cells, which can lead to the development of these tumours. Siegfried Oberndorfer was the first to introduce the term carcinoid in 1907. The pancreatic islet cells were first described in 1869 by Paul Langerhans. In 1924, Seale Harris was the first to describe endogenous hyperinsulinism/insulinoma. In 1942 William Becker and colleagues were the first to describe the glucagonoma syndrome. The first description of gastrinoma by Robert Zollinger and Edwin Ellison dates from 1955. The first description of the VIPoma syndrome by John Verner and Ashton Morrison dates from 1958. In 1977, the groups of Lars-Inge Larsson and Jens Rehfeld, and of Om Ganda reported the first cases of somatostatinoma. But only in 2013, Jens Rehfeld and colleagues described the CCK-oma syndrome. The most recently updated WHO classification for gastrointestinal neuroendocrine tumours dates from 2010.

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Neuroendocrine cells and neuroendocrine tumours in the gastrointestinal tract

In 1870, the German physiologist Rudolf P.H. Heidenhain (1834–1897) (Fig. 1) was the first to recognize the existence of a group of gastrointestinal cells that were separate from oxyntic, chief and enteric cells and noted their "yellow" chromate staining properties [1]. This observation was amplified in 1897 by the Russian anatomist and histologist (later he was also minister of education in the Russian empire) Nikolai K. Kultschitzky (1856–1925) (Fig. 1) [2]. Subsequently Carmèlo Ciaccio (1877–1956) introduced the term "enterochromaffin" in 1907 [3]. The Estonian pathologist Harry Kull (1886–1933) noted in 1925 that the gastrointestinal tract contained cells with a morphology similar to that of chromaffin cells [4]. In 1914, the French surgeon Antonin Gosset (1872–1944) and the French-Canadian pathologist Pierre Masson (1880–1959) used silver impregnation techniques and demonstrated the argentaffin-staining properties of carcinoid tumours [5,6]. They suggested that neuroendocrine (NE) tumours (NETs) might arise from the enterochromaffin (EC) cells (Kultschitzky's cells) of the intestinal mucosa [2,5,6]. In 1938, the Austrian pathologist Friedrich Feyrter (1895–1973) (Fig. 3) proposed that NETs were derived from the diffuse endocrine system, based on his observation of "clear cells" (Helle Zellen) throughout the gut and pancreas, which displayed characteristic light microscopic and histochemical features in their reactions with silver salts (e.g. argentaffinity and argyrophilia) [7] (see Fig. 2).

The German pathologist Siegfried Oberndorfer (1876–1944) (Fig. 4) was the first to introduce the term carcinoid for these NETs of the gastrointestinal tract [8]. In 1907, he presented first his observations on carcinoid tumours at the convention of the German Pathological Society (Deutsche Gesellschaft für Pathologie) in Dresden and he subsequently published his seminal paper "Karzinoide Tumoren des Dünndarms" [8]. He described a 48-year-old woman who had presumably died of tuberculosis. At autopsy, four pea-sized tumours were found in the ileum. Each tumour was found in the submucosa, with the surrounding intestinal mucosa and neighbouring serosa showing no reactive inflammation. By using the diminutive noun "Karzinoide Tumoren", Oberndorfer sought to distinguish these seemingly benign tumours from malignant adenocarcinomatous lesions [8,9]. In retrospect it is evident that the German pathologist Theodor Langhans (1839–1915) in 1867 [10], the German pathologist Otto Lubarsch (1860–1933) in 1888 [11] and the British physician/physiologist William Bramwell Ransom (1861–1909) in 1890 [12] had previously observed similar lesions, but they had not been clearly recognized as a distinct entity. Langhans described a carcinoid-like tumour at autopsy in a

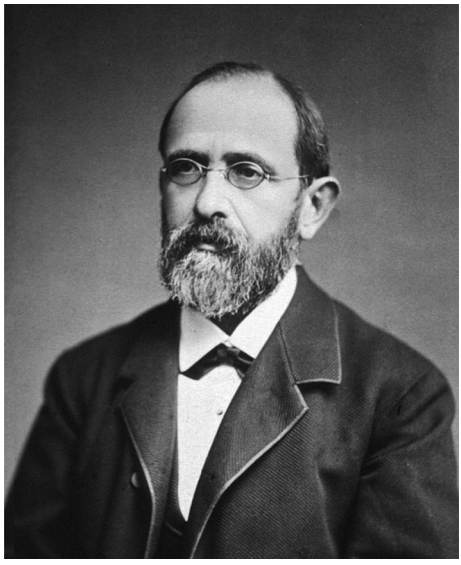

Fig. 1. Rudolf P.H. Heidenhain (1834–1897).