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Oberndorfer and His Successors: From Carcinoid to Neuroendocrine Carcinoma

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Abstract The year 2007 the centenary of Siegfried Oberndorfer's seminal description of special tumors of the small intestine which he called "Karzinoide Tumoren" (carcinoids). Their endocrine nature was suggested by Pierre Masson in 1914. The work of Friedrich Feyrter and later Anthony Pearse established the concept of a diffuse endocrine cell system. They suggested that there is a family of endocrine cells whose members originate at different sites in the organism and give rise to similar tumors, the carcinoids. Subsequent studies revealed that the individual members of the endocrine cell system are distinguished from each other by the expression of specific polypeptides (i.e., hormones). Common to all of these cells is the expression of general markers such as synaptophysin and chromogranin A. This led to the term neuroendocrine cell system and consequently neuroendocrine tumor. Although many tumors are similar in histological appearance, biologically they show heterogeneity, which has important implications for treatment. Therefore, efforts have been made to define the neuroendocrine neoplasms on the basis of features that discriminate the tumors with almost no risk/low risk of malignancy from low-grade and high-grade malignant tumors. For the gastroenteropancreatic neuroendocrine tumors, this resulted in a new World Health Organization classification that was recently followed by a tumor–nodes–metastasis classification.

Keywords Oberndorfer · carcinoid · neuroendocrine tumor

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Siegfried Oberndorfer (Fig. 1) was born in 1876 in Munich, Germany, and died of a thymoma in 1944 in Istanbul, Turkey. In 1907, while working in the Department of Pathology of the Hospital "rechts der Isar" in Munich, Oberndorfer reported on little tumors ("Geschwülstchen") of the small intestine [1]. He described six cases, two of which he had collected in Geneva where he worked in 1900–1901 [2], and emphasized the benign nature of these lesions. In retrospect, it is clear that similar tumors had been reported before 1907 [3]. In 1838, Merling reported a tumor of the appendix that could have been a carcinoid [4]. In 1867, Langhans [5] saw a polypous tumor in the ileum, and in 1882, Beger [6] described an adenocarcinoma of the appendix. In 1888, Lubarsch [7] gave a classical description of multiple carcinoids in the ileum in two patients and he called these tumors little carcinomata. An ileal tumor metastasizing into the liver and, judging from the illustrations, a typical carcinoid of insular type was reported by Ransom [8] in 1890.

When Oberndorfer demonstrated his results on the carcinoids before the German Pathology Society in Dresden, his suggestion that the lesions represented a special cancer was heavily debated [9]. A number of renowned pathologists considered them either malformations, adenomyomas, or a tumorous change of a heterotopic pancreas anlage [10]. However, as more and more such small tumors were detected and described in the intestine, the neoplastic nature of the lesion was generally accepted. It was further recognized that carcinoids not only occur in the ileum or the appendix (Fig. 2), but may also arise at other sites of the gastrointestinal tract and even outside the gut (see Table 1).

In 1910, Hübschmann [11] compared the tumor cells with the cells that had been described by Kultchitzky in the crypts of Lieberkühn. These cells corresponded to those that had already been found and described by Heidenhain

Fig. 1 Siegfried Oberndorfer and his daughter Helene ("Leni") in Munich in 1911, the time when the nature of the carcinoids was heavily debated among the leading pathologists in Germany and when Oberndorfer was appointed Professor at the Medical Faculty of the University of Munich at the age of 35

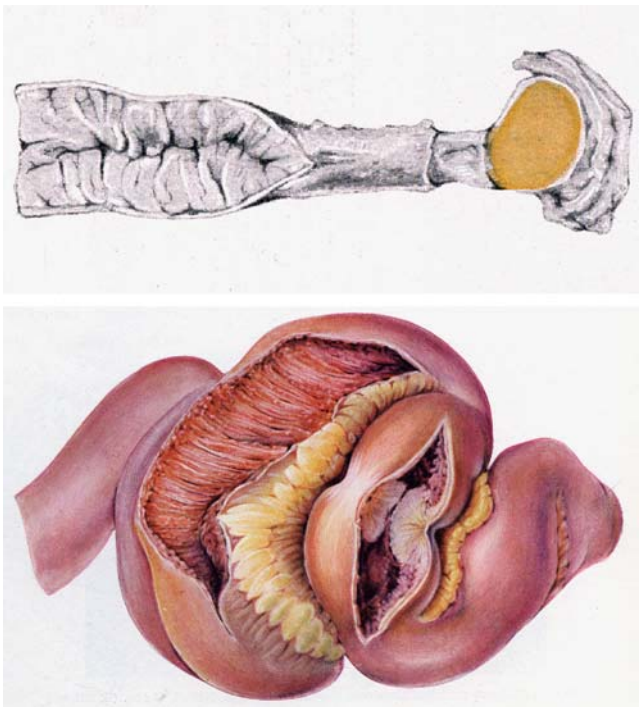

Fig. 2 Illustrations of carcinoids of the appendix (*top*) and the ileum (*bottom*), presented in Oberndorfer's textbook article of 1929 [33]

Table 1 First Descriptions of well Differentiated Neuroendocrine Tumors, i.e. Carcinoids, apart from Ileal or Appendiceal Tumors (see [41])

Site	Date	Author
Rectum	1912	Saltykow
Colon	1912	Saltykow
Stomach	1923	Askanazy
Meckel's diverticulum	1926	Stewart and Taylor
Duodenum	1929	Wolfer
Gallbladder	1929	Jöel
Ovary	1939	Stewart
Pancreas	1959	Pataky
Common bile duct	1968	Little
Esophagus	1969	Brenner

[12] in the stomach in 1870 and by Schmidt and Ciaccio [13] in the gastrointestinal tract of humans and animal species. Ciaccio coined the termed enterochromaffin cells. Soon after Hübschmann, Masson [14] developed his

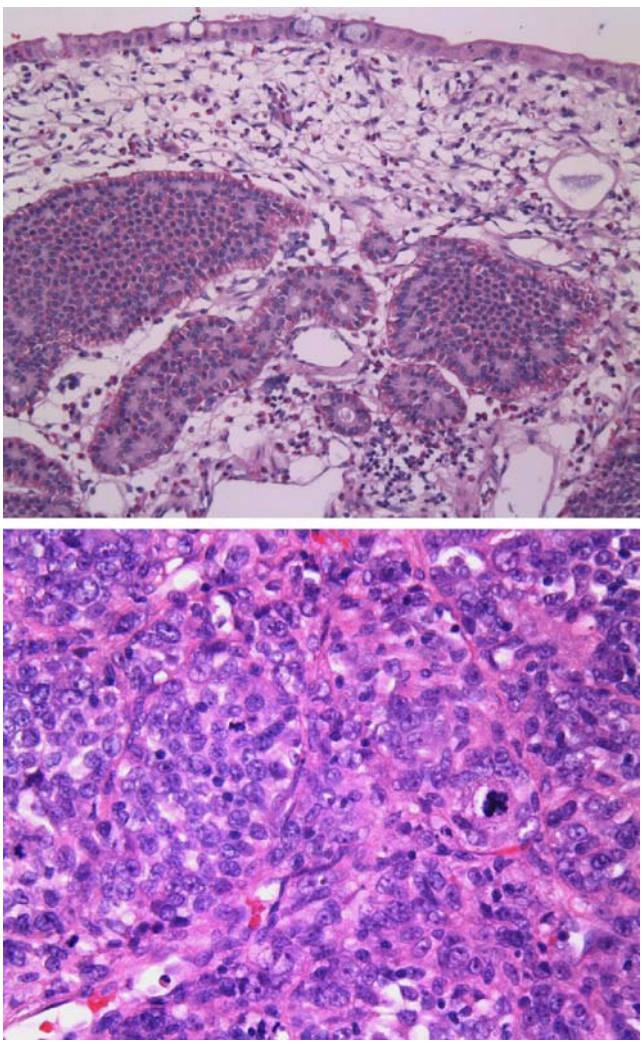

Fig. 3 The histological spectrum of neuroendocrine tumors (NET): well differentiated NET (*top*) and poorly differentiated NET (*bottom*)

argentaffinity reaction and demonstrated that the granules in the Kultchitzky cells and the cells of the carcinoids both stained with his silver technique. Consequently, Masson termed the intestinal carcinoids argentaffinoma [15]. He also suggested that the Kultchitzky cells and the tumor cells have an endocrine function and concluded that carcinoids are endocrine tumors. Although many other histogenetic pathways were discussed over the years, the origin from the so-called enterochromaffin cells of the intestinal mucosa was finally accepted [16].

The endocrine cell system that gives rise to carcinoids was further expanded by the work of Friedrich Feyrter on the diffuse endocrine system that was composed of argentaffin-positive and argyrophilic clear cells [17, 18]. A further step forward in characterizing these endocrine cells was made by Anthony Pearse in 1969 [19]. Applying histochemical methods, he discovered that certain endocrine cells, among them the endocrine cells of the gastrointestinal tract and pancreas, are capable of "amine precursor uptake and decarboxylation" (APUD). Consequently, he called these cells APUD cells. In a second step, he postulated that they derived from the neural crest. However, the neural crest origin of the diffuse neuroendocrine system proved to be wrong and has currently been replaced by the concept of the entodermal origin of the neuroendocrine cells of the gastrointestinal tract [20–22]. However, Pearse's and already Feyrter's concept suggested that there is a family of endocrine cells, whose members originate at different sites in the organism, but because of their common features give rise to similar tumors.

Slowly, it was also recognized that carcinoids and the similar-looking islet cell tumors may cause hormonal syndromes. The first hormonal syndrome ascribed to an endocrine tumor was a hypoglycemic syndrome associated with an islet cell tumor [23]. Descriptions of patients suffering from diarrhea, cyanosis, cough, and flushing started in 1931 [24, 25]. The first report of a carcinoid syndrome, however, was probably by Ransom [8], who described a 50-year-old woman with severe diarrhea and a metastasizing tumor originating from small nodules in the ileum. It was not until 1953 that the carcinoid syndrome was fully recognized and then related to the hypersecretion of serotonin from the carcinoid tumor [26–28]. Other syndromes were discovered in the following years [29–32].

Originally, Oberndorfer considered carcinoids to be benign, although Ransom's case had clearly metastasized [8] and one of Lubarsch's cases probably too [7]. As more and more carcinoids with lymph node and liver metastases were observed, he admitted that some carcinoids may also be malignant. In his contribution to Henke and Lubarsch's textbook on pathological anatomy and histology in 1929, he therefore distinguished carcinoids with benign behavior from "malignant carcinoids" [33]. The discussion on the benign and/or malignant nature of carcinoids continued for a long time until it was generally accepted that all carcinoids have a malignant potential [34, 35], although varying from low grade to high grade [36]. As the histological features of "high grade" or "atypical" carcinoids only barely resembled or had no resemblance to the carcinoid described by Oberndorfer, the term neuroendocrine tumor/carcinoma was introduced, first in the lung [37] and later also elsewhere [36].

In recent years, it has become clear that the morphological and biological features of neuroendocrine tumors (NETs), especially those arising from the gastroenteropancreatic system, are heterogeneous, not only biologically because of their different hormone content but also morphologically. Although similar in appearance, subtle differences were detected in NETs. They were ascribed to tumors at specific sites and with a specific hormone content. Moreover, the broad use of general neuroendocrine markers, such as neuron specific enolase, chromogranin A, or synaptophysin, surprisingly revealed that also epithelial neoplasms, whose histological features were not suggestive of an endocrine tumor, may be of neuroendocrine nature [36] (Fig. 3). Finally, it was shown that NETs may distinctly differ in their natural course and ability to metastasize. In the last two decades, efforts have therefore been made to define NET features that discriminate tumors with almost no risk/low risk from low-grade, malignant, well-differentiated neuroendocrine carcinomas and high-grade, malignant, poorly differentiated carcinomas in the different parts of the digestive system and elsewhere. This resulted in a new World Health Organization classification of the gastroenteropancreatic NETs [38]. Further efforts are still necessary, however, to improve the prognostic assessment of an individual NET [39, 40].

In summary, with his publication in 1907 Oberndorfer opened up the realm of neuroendocrine neoplasms. Of course, he was not aware that he had discovered a new territory and only towards the end of his life he realized that his early observations on the carcinoids were his most important work [42].

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