Gastrin/ECL Cells in Gastric Cancer

Subjects: Oncology

Contributor: Helge Waldum

The enterochromaffin-like (ECL) cell has long been acknowledged to give rise to neuroendocrine tumours (NETs), but not to play any role in carcinogenesis of gastric adenocarcinomas. However, when examining human gastric adenocarcinomas with the best methods presently available (immunohistochemistry with increased sensitivity and in-situ hybridization), it became clear that many of these cancers expressed neuroendocrine markers, suggesting that some of these tumours were of neuroendocrine, and more specifically, ECL cell origin. Furthermore, the carcinogenic effect of Helicobacter pylori is also most probably mediated by gastrin. Thus, the ECL cell and its main regulator, gastrin, are central in human gastric carcinogenesis, which make new possibilities in prevention, prophylaxis, and treatment of this cancer.

Keywords: gastric cancer,ECL cell,gastrin

1. Introduction

Gastric cancer has, worldwide, shown a marked reduction in prevalence during the last decades [1]. Nevertheless, gastric cancer is still an important disease being responsible for one-third of cancer deaths [1]. Furthermore, in 1995, a break in the falling prevalence was registered in young Americans [2]. *Helicobacter pylori* is the dominating cause of gastric cancer [3], and the reduction in the prevalence of gastric cancer most probably is due to a decline in *H. pylori* infection. For decades, hypoacidity has been recognized as an important factor in gastric carcinogenesis [4][5], and since the 1950s, gastritis has been associated with gastric cancer [6]. With the description of tumours in the oxyntic mucosa in rodents after long-term dosing with the first proton pump inhibitor (PPI) omeprazole [7], and the insurmountable histamine-2 (H-2) antagonist loxtidine [8], there has been concern that long-term inhibition of gastric acid secretion could also promote cancer in humans. Gastrin was early recognized to be the cause of the oxyntic mucosal tumours of enterochromaffin-like (ECL) cell origin in the rodents [9] (Table 1).

Table 1. Conditions acknowledged, predisposing to gastric cancer at different points of time.

Condition	Time
Hypoacidity	Forties
Gastritis	Fifties
Helicobacter pylori	Early nineties
Gastrin	Two thousand

(Gastrin is the common factor for the first three conditions).

2. ECL Cell Properties

For one-hundred years, we have known the three principal gastric acid secretagogues: acetylcholine, gastrin, and histamine. The histamine producing ECL cell was identified by Håkanson and Owman [10] in the late 1960s, but some stuck to the mast cell as the relevant histamine producing cell until the 1980s [11]. Since then, the ECL cell has been acknowledged as the cell producing the histamine participating in the regulation of gastric acid secretion. Taking into consideration the central role of histamine in this regulation as shown by the efficient inhibition of acid secretion by H-2

antagonists [12], the control of the ECL cell function became important. Gastrin was early shown to stimulate the formation of histamine [13][14], and in isolated rat stomach [15], and isolated oxyntic mucosal cells [16][17] to augment histamine release. Thus, from a functional point of view, it was evident that the ECL cell had a gastrin receptor and by using the isolated rat stomach in combination with a fluorinated gastrin analogue in a concentration within the physiological range, we could show that the gastrin receptor was located to the ECL cell, but not to the parietal cell [18]. Quite recently, the localization of the gastrin receptor on the ECL cell and a progenitor was confirmed [19], and the closely related enterochromaffin (EC) cell was reported to serve as a reserve stem cell in the small intestine [20]. The acetylcholine analogue carbachol did not stimulate histamine release, but apparently had a direct effect on the parietal cell [21], whereas another neuro-agent, pituitary adenylate cyclase-activating polypeptide (PACAP) was a potent and efficient stimulator of histamine release [22]. In isolated ECL cells, PACAP was shown to efficiently stimulate ECL cell proliferation, even exceeding the effect of gastrin [23]. However, in vivo studies on the role of PACAP on ECL cell proliferation is missing. Somatostatin is an important physiological inhibitor of histamine release by interaction with a somatostatin-2 receptor on the ECL cell [24]. The ECL cell produces Reg protein [25], basic fibroblast growth factor (b-FGF) [26], as well as calbindin [27], and when exposed to elevated concentrations of gastrin, glycoprotein hormone α-subunit [28][29]. At least Reg protein and b-FGF can play a role during tumourigenesis. Finally, the vesicular amine transporter 2 is expressed in ECL cells [30] and may be used in the identification of this cell. The ECL cell is localized in the periphery at the base of oxyntic glands, which normally in man are found in the fundus and corpus of the stomach. However, it has become clear that oxyntic glands also occur in the antral mucosa [31], and although the ECL cell was not specifically described in oxyntic glands at this location, there is every reason to assume that these glands are complete with all cell types including the ECL cell.

3. Regulation of ECL Cell Proliferation

Generally, there is a close relationship between regulation of function and growth, which is also true for the ECL cell. Thus, gastrin is the most important regulator of ECL cell function, as well as proliferation. Hypergastrinemia induces ECL cell hyperplasia up to a certain level, at which a new equilibrium is reached [32]. Apparently, a substance from the ECL cell has a negative effect on its own proliferation. There is no threshold concentration for the trophic effect of gastrin on the ECL cell [33], and the maximal effect is reached at a concentration of a few hundred pmol/l [34][35]. There is an inverse relationship between gastric acidity and gastrin in blood [36], and the gastrin values hitherto accepted to be within the normal range are too high since, at the time of establishing gastrin immunoassays, a high proportion of asymptomatic individuals representing normal had *H. pylori*-induced gastritis, most of whom probably with reduced gastric acid secretion [37]. Every long-term hypergastrinemia, irrespective of cause, results in ECL cell hyperplasia [38][39]. Even in the normal situation, gastrin influences ECL cell growth since antrectomy resulting in gastrin reduction reduces ECL density [40]. PACAP released from the vagal nerves causes not only stimulation of ECL cell histamine release [22], but also probably mediates the trophic effect of the vagal nerves, shown in rats with unilateral vagotomy [41]. Being a neurotransmitter, PACAP´s role in gastric human physiology and pathology has not been as thoroughly investigated as gastrin. However, in mice, unilateral vagotomy was reported to suppress gastric tumourigenesis [42]. Somatostatin must, in the stomach, be regarded as a paracrine regulator influencing neighbour cells via elongations [43]. Treatment of ECL cell neuroendocrine tumours (NETs) with a somatostatin analogue may remove macroscopic tumours as well as reduce accompanying ECL cell hyperplasia [44] by interaction with a somatostatin receptor type 2 [45].

4. ECL Cell Hyperplasia

In any species, every condition with long-term hypergastrinemia results in ECL cell hyperplasia [39]. This is true for rats [7], mice [8], Japanese cotton rats [46], man with autoimmune oxyntic gastritis [47], with *H. pylori* infection affecting the oxyntic mucosa [48], with gastrinoma [49][50], and treatment with efficient inhibitors of acid secretion [38]. Even in dogs, dosing with inhibitors of acid secretion resulting in marked reduction in acid secretion, hypergastrinemia caused an increase in proliferation in the oxyntic mucosa [51]. After a variable time of hyperplasia and depending of the natural life span of the species, ECL cell derived neoplasia develops.

5. ECL Cell Neuroendocrine Tumours (NETs)

Gastrin immunoassays were developed around 1970 [52][53], and it was soon shown that patients with reduced gastric acidity had markedly elevated gastrin values [54]. Later, small tumours in the oxyntic mucosa of patients with atrophic gastritis and pernicious anaemia were described as gastric carcinoids (now called gastric NETs) [55]. The fundamental role of gastrin in the pathogenesis of gastric NETs was realized when similar tumours also occurred in patients with gastrinoma [56], causing Bordi to write a paper suggesting that these tumours were hormonally induced [57]. However, another Italian central in neuroendocrine pathology, Solcia, together with co-authors concluded that gastrin can "promote

the proliferation of ECL cells but is per se apparently unable to induce ECL cell transformation" [58]. This view was supported by a recent review from the group of Robert T. Jensen [59]. Thus, in contrast to gastric NETs, gastrin has been claimed not to play any role in the development of gastric cancer. Patients with autoimmune chronic atrophic gastritis often have very high gastrin values and they are prone to develop ECL cell NETs [34][55][60][61][62][63]. Moreover, in patients with *H. pylori* gastritis, ECL cell NETs occur [64][65], but not as prevalently as in patients with autoimmune gastritis. The discrepancy between gastrin values in atrophic gastritis whether due to autoimmunity or *H. pylori* infection is most probably due to concomitant antral atrophy in the latter condition [66]. In patients with gastric NETs the inflammation has been thought to be the cause leading to ECL cell transformation, whereas hypergastrinemia then must be responsible for the ECL proliferation and perhaps should make these cells more prone for tumour development.

However, in patients with gastrinoma, there is no inflammation in the oxyntic mucosa. The transformation of ECL cells into tumour cells has been explained by the genetic defect since they occur mainly in patients with gastrinoma as part of multiple endocrine neoplasia type I (MEN-I) [56][67]. These patients have an increased frequency of tumours originating from many different endocrine cells. Nevertheless, ECL cell NETs also occur, but more seldom, in gastrinoma patients without MEN-1 [68][69] indicating that hypergastrinemia is enough to induce such tumours. The ECL cells in sporadic gastrinoma patients also show expression of the alpha subunit of human chorionic gonadotropin [33]. Moreover, gastric NETs have been described in patients with elevated gastrin due to long-term treatment with inhibitors of gastric acid secretion, particularly proton pump inhibitors [70][71][72][73]. Therefore, it seems obvious that hypergastrinemia itself is enough to induce gastric NETs in man, as has been shown for rodents after long-term drug induced hypoacidity [7][8] or due to partial corpectomy [74]. Moreover, in man, surgery-induced hypergastrinemia leads to gastric NETs [75].

6. ECL Cell NETs and Gastric Carcinomas

It has long been accepted that the ECL cell may develop into neuroendocrine carcinomas defined as type 3, according to Rindi et al. [76]. These tumours occur in patients without hypergastrinemia but taking into consideration that the ECL cell has a growth-stimulating gastrin receptor, gastrin could nevertheless play a role in tumour development. However, such tumours probably develop by chance-mutation in a gene central in ECL cell growth. Gastric cancers are not seldom detected in patients with ECL cell NETs secondary to autoimmune gastritis [77][78]. Moreover, in a systematic literature search on the co-occurrence of NETs, and adenocarcinomas in the same segment of the gastrointestinal tract, a highly significant association was found [79]. By applying immunohistochemistry with improved sensitivity, we could show that nearly all (seven of eight) carcinomas removed from patients with marked hypergastrinemia expressed neuroendocrine markers [80], suggesting that they originated from neuroendocrine cells. Therefore, the gastric cancers in patients with pernicious anaemia, until now classified as adenocarcinomas, may be neuroendocrine carcinomas developed from ECL cells. In general, when using immunohistochemistry with increased sensitivity we demonstrated neuroendocrine differentiation in tumour cells in a significant proportion of gastric cancers [81]. By immunoelectron microscopy, we also demonstrated chromogranin A positive granules in gastric cancer cells [82]. We have previously focused on the classification of gastric carcinomas based on non-specific histochemical methods, not taking notice of much more specific and sensitive methods, such as immunohistochemistry and in-situ hybridization [83]. Thus, the unspecific periodic acid-Schiff (PAS) stain method has been accepted as a proof of mucin. PAS positive tumour cells were therefore regarded to be of exocrine cell origin enabling classification of tumours as adenocarcinomas, even without glandular growth pattern. However, we could not detect mucin expression, either by immunohistochemistry or in-situ hybridization, in contrast to neuroendocrine expression in many gastric PAS positive carcinomas of particularly the diffuse type, according to Lauren [84]. Neuroendocrine expression was especially marked in the signet ring cell subtype [85], a finding also reported by others [86][87][88]. It is therefore possible that the ECL cell gives rise to an important proportion of gastric carcinomas. We have also described a patient with pernicious anaemia who developed a gastric NET, which was removed endoscopically but re-occurred in lymph nodes, which were removed surgically. After some years, the patients died of a highly malignant neuroendocrine carcinoma demonstrating that gastric ECL cells have a malignant potential [89]. Furthermore, in a Spanish family with a missense mutation in one of the genes coding for the proton pump, not only gastric NETs, but also a carcinoma were described [90], although we later reclassified the latter tumour as a neuroendocrine carcinoma [91]. Reclassification of adenocarcinomas to neuroendocrine tumours was suggested more than 40 years ago [92], and an adenocarcinoma producing neuron-specific enolase [93], a neuroendocrine marker more specific than hitherto appreciated [94], has been reported.

The ECL cell may play an important role in gastric carcinogenesis also indirectly by the release of Reg protein, which has been shown to stimulate proliferation of gastric cells and differentiation along parietal and chief cell lineages [95], and thus mediate the general trophic effect of gastrin on oxyntic mucosa [25]. An increase in Reg protein release due to ECL cell hyperplasia would cause a chronic growth stimulation of the stem cell which in long-term would be expected to increase the risk of cancer development, presumably of the intestinal type, which also has been reported [96]. In this connection, we

will recall that hypergastrinemia presently is the most probable mechanism for the carcinogenic effect of *H. pylori* gastritis [97]. The carcinogenic effect of *H. pylori* gastritis seems not to be the infection directly, but indirectly by the secondary atrophy of the oxyntic mucosa [98], which necessarily will lead to hypergastrinemia and ECL cell hyperplasia. The hyperplastic ECL cell may develop further into tumour cells leading to ECL cell NETs or further to neuroendocrine carcinomas and carcinomas hitherto classified as adenocarcinomas, and then, mainly of diffuse type according to Lauren. Alternatively, by stimulation of the stem cell via Reg protein, the ECL will predispose to adenocarcinoma, mainly of intestinal type.

The normal ECL cell as well as ECL cell in NETs produce b-FGF [26]. The fibrosis, which is a central feature of diffuse gastric carcinomas as exemplified by linitis plastica, may be due to release of b-FGF from ECL cell derived tumour cells. In fact, overexpression of b-FGF mRNA was reported particularly in carcinomas of scirrhous type [99], which ordinarily are heavily fibrotic. Moreover, there is a case report of a patient with scirrhous type gastric cancer who had aggressive fibroses in the head and neck with scattered b-FGF positive gastric cancer cells [100]. This cancer could be an example of highly malignant tumour derived from the ECL cell.

7. Mixed Tumours with Neuroendocrine and Adenocarcinoma Components

There are many descriptions of reclassification of gastric carcinomas initially classified as adenocarcinomas and later reclassified as neuroendocrine carcinomas [101][102][103], demonstrating difficulties in the distinction between these two entities in man, such as in rodents [104].

8. The Carcinogenic Effect of Hypoacidity, Whether Caused by Oxyntic Gastritis, Due to “Autoimmunity" or H. pylori, as Well as Inhibitors of Gastric Acid Secretion, is Mediated by Gastrin

Hypoacidity was the first condition recognized to play a role in gastric carcinogenesis [5] followed by gastritis a few years later [6] when leading to oxyntic atrophy [98], hypoacidity, and, thus, hypergastrinemia. With the central role of gastrin in gastric carcinogenesis, it was therefore to be expected that long-term treatment with efficient inhibitors of gastric acid secretion necessarily would predispose to gastric neoplasia. The target cell of gastrin, the ECL cell, develops into neoplasia when exposed to long-term hypergastrinemia in all species examined adequately. When examining gastric carcinomas with the most sensitive and specific methods available, ECL cell differentiation is revealed in many of the tumours until now classified as adenocarcinomas [83]. Moreover, the practice of dismissing neuroendocrine differentiation in cancer cells when found only in a few of them [105][106][107], seems from a biological point of view very odd. Furthermore, there are many reports of gastric tumours composed of a NET, as well as an adenocarcinoma component [108][109][110], or neuroendocrine carcinoma and adenocarcinoma [111] showing the close connections between these entities. Gastrin receptors have also been described on gastric carcinoma cells [112][113]. Gastric cancer may also be due to infection with Epstein Barr virus [114]. Interestingly, the genetic changes in carcinomas due to Epstein Barr virus and *H. pylori* do not share similarities [115], suggesting different mechanisms in the carcinogenic process. There is one publication describing different genetic patterns between gastric carcinoma of diffuse and intestinal type [116], but this has not been confirmed. Finally, there are two known hereditary conditions predisposing to gastric cancer, mutation of the CDH 1 gene coding for E-cadherin predisposing to diffuse gastric cancer at young age [117] and mutation of the ATP4A gene coding for one of the genes of the proton pump leading to ECL cell derived tumours of variable malignancy [90][91] (Table 2).

Table 2. Causes of gastric cancer.

Causes of Gastric Cancer	Gastrin Driven	Probably not Gastrin Driven
Helicobacter pylori	x	
Autoimmune gastritis	x	
Drugs inhibiting gastric acid secretion	x	
Genetic; ATP4 mutation [90]	x	

Genetic: Hereditary diffuse gastric cancer, CDH 1 mutation [117]	x
Virus: Epstein Barr virus [114]	x

Chronic inflammation is believed to be an important factor in carcinogenesis, including gastric cancer secondary to gastritis [118][119]. However, *H. pylori* gastritis does not seem to have a direct carcinogenic effect, since the risk is eliminated when *H. pylori* is eradicated at an early phase before having caused oxyntic atrophy [120]. Those having developed oxyntic atrophy maintain risk of gastric cancer years after having lost the infection, due to lack of gastric acidity or *H. pylori* eradication [121][122]. In general, to our knowledge, a bacterium has hitherto not been shown to have a direct carcinogenic effect. On the other hand, the gastric lymphoma secondary to *H. pylori* infection is cured by *H. pylori* eradication [123].

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca: A Cancer J. Clin. 2018, 68, 394–424, doi:10.3322/caac.21492.
2. Bergquist, J.R.; Leiting, J.L.; Habermann, E.B.; Cleary, S.P.; Kendrick, M.L.; Smoot, R.L.; Nagorney, D.M.; Truty, M.J.; Grotz, T.E. Early-onset gastric cancer is a distinct disease with worrisome trends and oncogenic features. Surgery 2019, 166, 547–555, doi:10.1016/j.surg.2019.04.036.
3. Parsonnet, J.; Friedman, G.D.; Vandersteen, D.P.; Chang, Y.; Vogelman, J.H.; Orentreich, N.; Sibley, R.K. Helicobacter pylori infection and the risk of gastric carcinoma. New Engl. J. Med. 1991, 325, 1127–1131, doi:10.1056/nejm199110173251603.
4. Grossman, M.I.; Kirsner, J.B.; Gillespie, I.E. Basal and histalog-stimulated gastric secretion in control subjects and in patients with peptic ulcer or gastric cancer. Gastroenterology 1963, 45, 14–26.
5. Comfort, M.W.; Kelsey, M.P.; Berkson, J. Gastric acidity before and after the development of carcinoma of the stomach. Collect. Pap. Mayo Clin. Mayo Found 1946, 38, 24–30.
6. Morson, B.C. Intestinal metaplasia of the gastric mucosa. Br. J. Cancer 1955, 9, 365–376, doi:10.1038/bjc.1955.35.
7. Havu, N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 1986, 35, 42–55, doi:10.1159/000199381.
8. Poynter, D.; Selway, S.A.; Papworth, S.A.; Riches, S.R. Changes in the gastric mucosa of the mouse associated with long lasting unsurmountable histamine H2 blockade. Gut 1986, 27, 1338–1346, doi:10.1136/gut.27.11.1338.
9. Hakanson, R.; Sundler, F. Proposed mechanism of induction of gastric carcinoids: The gastrin hypothesis. Eur. J. Clin. Investig. 1990, 20, S65-71.
10. Hakanson, R.; Owman, C. Concomitant histochemical demonstration of histamine and catecholamines in enterochromaffin-like cells of gastric mucosa. Life Sci. 1967, 6, 759–766, doi:10.1016/0024-3205(67)90133-6.
11. Chuang, C.N.; Chen, M.C.; Soll, A.H. Regulation of histamine release from oxyntic mucosa. Yale J. Biol. Med. 1992, 65, 753–759
12. Black, J.W.; Duncan, W.A.; Durant, C.J.; Ganellin, C.R.; Parsons, E.M. Definition and antagonism of histamine H 2 -receptors. Nature 1972, 236, 385–390, doi:10.1038/236385a0.
13. Kahlson, G.; Rosengren, E.; Svahn, D.; Thunberg, R. Mobilization and formation of histamine in the gastric mucosa as related to acid secretion. J. Physiol. 1964, 174, 400–416.
14. Ding, X.Q.; Chen, D.; Håkanson, R. Cholecystokinin-B receptor ligands of the dipeptoid series act as agonists on rat stomach histidine decarboxylase. Gastroenterology 1995, 109, 1181–1187, doi:10.1016/0016-5085(95)90577-4.
15. Sandvik, A.K.; Waldum, H.L.; Kleveland, P.M.; Schulze Sognen, B. Gastrin produces an immediate and dose-dependent histamine release preceding acid secretion in the totally isolated, vascularly perfused rat stomach. Scand. J. Gastroenterol. 1987, 22, 803–808, doi:10.3109/00365528708991918.
16. Brenna, E.; Waldum, H.L. Studies of isolated parietal and enterochromaffin-like cells from the rat. Scand. J. Gastroenterol. 1991, 26, 1295–1306.

17. Prinz, C.; Kajimura, M.; Scott, D.R.; Mercier, F.; Helander, H.F.; Sachs, G. Histamine secretion from rat enterochromaffinlike cells. Gastroenterology 1993, 105, 449–461.

18. Bakke, I.; Qvigstad, G.; Sandvik, A.K.; Waldum, H.L. The CCK-2 receptor is located on the ECL cell, but not on the parietal cell. Scand. J. Gastroenterol. 2001, 36, 1128–1133.

19. Sheng, W.; Malagola, E.; Nienhüser, H.; Zhang, Z.; Kim, W.; Zamechek, L.; Sepulveda, A.; Hata, M.; Hayakawa, Y.; Zhao, C.M.; et al. Hypergastrinemia Expands Gastric ECL Cells Through CCK2R(+) Progenitor Cells via ERK Activation. Cell Mol. Gastroenterol. Hepatol. 2020, 10, e431 434–449, doi:10.1016/j.jcmgh.2020.04.008.

20. Sei, Y.; Feng, J.; Zhao, X.; Wank, S.A. Role of an active reserve stem cell subset of enteroendocrine cells in intestinal stem cell dynamics and the genesis of small intestinal neuroendocrine tumors. Am. J. Physiol. Gastrointest. Liver Physiol. 2020, 319, G494–g501, doi:10.1152/ajpgi.00278.2020.

21. Sandvik, A.K.; Mårvik, R.; Dimaline, R.; Waldum, H.L. Carbachol stimulation of gastric acid secretion and its effects on the parietal cell. Br. J. Pharm. 1998, 124, 69–74, doi:10.1038/sj.bjp.0701802.

22. Sandvik, A.K.; Cui, G.; Bakke, I.; Munkvold, B.; Waldum, H.L. PACAP stimulates gastric acid secretion in the rat by inducing histamine release. Am. J. Physiol. Gastrointest Liver Physiol. 2001, 281, G997–g1003, doi:10.1152/ajpgi.2001.281.4.G997.

23. Läuffer, J.M.; Modlin, I.M.; Hinoue, T.; Kidd, M.; Zhang, T.; Schmid, S.W.; Tang, L.H. Pituitary adenylate cyclase-activating polypeptide modulates gastric enterochromaffin-like cell proliferation in rats. Gastroenterology 1999, 116, 623–635, doi:10.1016/s0016-5085(99)70184-8.

24. Sandvik, A.K.; Waldum, H.L. The effect of somatostatin on baseline and stimulated acid secretion and vascular histamine release from the totally isolated vascularly perfused rat stomach. Regul. Pept. 1988, 20, 233–239.

25. Fukui, H.; Kinoshita, Y.; Maekawa, T.; Okada, A.; Waki, S.; Hassan, S.; Okamoto, H.; Chiba, T. Regenerating gene protein may mediate gastric mucosal proliferation induced by hypergastrinemia in rats. Gastroenterology 1998, 115, 1483–1493, doi:10.1016/s0016-5085(98)70027-7.

26. Bordi, C.; Falchetti, A.; Buffa, R.; Azzoni, C.; D'Adda, T.; Caruana, P.; Rindi, G.; Brandi, M.L. Production of basic fibroblast growth factor by gastric carcinoid tumors and their putative cells of origin. Hum. Pathol. 1994, 25, 175–180, doi:10.1016/0046-8177(94)90275-5.

27. Furness, J.B.; Padbury, R.T.; Baimbridge, K.G.; Skinner, J.M.; Lawson, D.E. Calbindin immunoreactivity is a characteristic of enterochromaffin-like cells (ECL cells) of the human stomach. Histochemistry 1989, 92, 449–451.

28. Bordi, C.; D'Adda, T.; Azzoni, C.; Pilato, F.P.; Caruana, P. Hypergastrinemia and gastric enterochromaffin-like cells. Am. J. Surg. Pathol. 1995, 19, S8–S19.

29. Bordi, C.; D'Adda, T.; Ceda, G.P.; Bertele, A.; Pilato, F.P.; Ceresini, G.; Baggi, M.T.; Missale, G. Glycoprotein hormone alpha subunit in endocrine cells of human oxyntic mucosa. Studies on its relation to neuroendocrine tumors. Hepato-Gastroenterology 1990, 37, 108–114.

30. De Giorgio, R.; Su, D.; Peter, D.; Edwards, R.H.; Brecha, N.C.; Sternini, C. Vesicular monoamine transporter 2 expression in enteric neurons and enterochromaffin-like cells of the rat. Neurosci. Lett. 1996, 217, 77–80.

31. Choi, E.; Roland, J.T.; Barlow, B.J.; O'Neal, R.; Rich, A.E.; Nam, K.T.; Shi, C.; Goldenring, J.R. Cell lineage distribution atlas of the human stomach reveals heterogeneous gland populations in the gastric antrum. Gut 2014, 63, 1711–1720, doi:10.1136/gutjnl-2013-305964.

32. Håkanson, R.; Tielemans, Y.; Chen, D.; Andersson, K.; Mattsson, H.; Sundler, F. Time-dependent changes in enterochromaffin-like cell kinetics in stomach of hypergastrinemic rats. Gastroenterology 1993, 105, 15–21, doi:10.1016/0016-5085(93)90005-w.

33. Peghini, P.L.; Annibale, B.; Azzoni, C.; Milione, M.; Corleto, V.D.; Gibril, F.; Venzon, D.J.; Delle Fave, G.; Bordi, C.; Jensen, R.T. Effect of chronic hypergastrinemia on human enterochromaffin-like cells: Insights from patients with sporadic gastrinomas. Gastroenterology 2002, 123, 68–85, doi:10.1053/gast.2002.34231.

34. Sjoblom, S.M.; Sipponen, P.; Karonen, S.L.; Jarvinen, H.J. Mucosal argyrophil endocrine cells in pernicious anaemia and upper gastrointestinal carcinoid tumours. J. Clin. Pathol. 1989, 42, 371–377.

35. Brenna, E.; Waldum, H.L. Trophic effect of gastrin on the enterochromaffin like cells of the rat stomach: Establishment of a dose response relationship. Gut 1992, 33, 1303–1306, doi:10.1136/gut.33.10.1303.

36. Gedde-Dahl, D. Fasting serum gastrin levels in humans with low pentagastrin-stimulated gastric acid secretion. Scand. J. Gastroenterol. 1974, 9, 597–599.

37. Waldum, H.L.; Rehfeld, J.F. Gastric cancer and gastrin: On the interaction of Helicobacter pylori gastritis and acid inhibitory induced hypergastrinemia. Scand. J. Gastroenterol. 2019, 54, 1118–1123,

doi:10.1080/00365521.2019.1663446.

38. Lamberts, R.; Creutzfeldt, W.; Stockmann, F.; Jacubaschke, U.; Maas, S.; Brunner, G. Long-term omeprazole treatment in man: Effects on gastric endocrine cell populations. Digestion 1988, 39, 126–135, doi:10.1159/000199615.
39. Waldum, H.L.; Brenna, E.; Sandvik, A.K. Relationship of ECL cells and gastric neoplasia. Yale J. Biol. Med. 1998, 71, 325–335.
40. Axelson, J.; Ekelund, M.; Håkanson, R.; Sundler, F. Gastrin and the vagus interact in the trophic control of the rat oxyntic mucosa. Regul. Pept. 1988, 22, 237–243, doi:10.1016/0167-0115(88)90036-5.
41. Hakanson, R.; Vallgren, S.; Ekelund, M.; Rehfeld, J.F.; Sundler, F. The vagus exerts trophic control of the stomach in the rat. Gastroenterology 1984, 86, 28–32.
42. Zhao, C.M.; Hayakawa, Y.; Kodama, Y.; Muthupalani, S.; Westphalen, C.B.; Andersen, G.T.; Flatberg, A.; Johannessen, H.; Friedman, R.A.; Renz, B.W.; et al. Denervation suppresses gastric tumorigenesis. Sci. Transl. Med. 2014, 6, 250ra115, doi:10.1126/scitranslmed.3009569.
43. Larsson, L.I.; Goltermann, N.; de Magistris, L.; Rehfeld, J.F.; Schwartz, T.W. Somatostatin cell processes as pathways for paracrine secretion. Science 1979, 205, 1393–1395, doi:10.1126/science.382360.
44. Fykse, V.; Sandvik, A.K.; Qvigstad, G.; Falkmer, S.E.; Syversen, U.; Waldum, H.L. Treatment of ECL cell carcinoids with octreotide LAR. Scand. J. Gastroenterol. 2004, 39, 621–628, doi:10.1080/00365520410005225.
45. Prinz, C.; Sachs, G.; Walsh, J.H.; Coy, D.H.; Wu, S.V. The somatostatin receptor subtype on rat enterochromaffinlike cells. Gastroenterology 1994, 107, 1067–1074, doi:10.1016/0016-5085(94)90231-3.
46. Waldum, H.L.; Rørvik, H.; Falkmer, S.; Kawase, S. Neuroendocrine (ECL cell) differentiation of spontaneous gastric carcinomas of cotton rats (Sigmodon hispidus). Lab Anim. Sci. 1999, 49, 241–247.
47. Villanacci, V.; Casella, G.; Lanzarotto, F.; Di Bella, C.; Sidoni, A.; Cadei, M.; Salviato, T.; Dore, M.P.; Bassotti, G. Autoimmune gastritis: Relationships with anemia and Helicobacter pylori status. Scand. J. Gastroenterol. 2017, 52, 674–677, doi:10.1080/00365521.2017.1288758.
48. Annibale, B.; Aprile, M.R.; D'Ambra, G.; Caruana, P.; Bordi, C.; Delle Fave, G. Cure of Helicobacter pylori infection in atrophic body gastritis patients does not improve mucosal atrophy but reduces hypergastrinemia and its related effects on body ECL-cell hyperplasia. Aliment. Pharmacol. Ther. 2000, 14, 625–634, doi:10.1046/j.1365-2036.2000.00752.x.
49. Creutzfeldt, W. The consequences of hypergastrinemia. Yale J. Biol. Med. 1994, 67, 181–194.
50. Cadiot, G.; Lehy, T.; Ruszniewski, P.; Bonfils, S.; Mignon, M. Gastric endocrine cell evolution in patients with Zollinger-Ellison syndrome. Influence of gastrinoma growth and long-term omeprazole treatment. Dig. Dis. Sci. 1993, 38, 1307–1317, doi:10.1007/bf01296083.
51. Ryberg, B.; Mattsson, H.; Carlsson, E. Effects of omeprazole and ranitidine on gastric acid secretion, blood gastrin levels and [3H]-thymidine incorporation in the oxyntic mucosa from dogs and rats. Digestion 1988, 39, 91–99, doi:10.1159/000199611.
52. McGuigan, J.E. Immunochemical studies with synthetic human gastrin. Gastroenterology 1968, 54, 1005–1011.
53. Rehfeld, J.F. Gastrins in serum. A review of gastrin radioimmunoanalysis and the discovery of gastrin heterogeneity in serum. Scand. J. Gastroenterol. 1973, 8, 577–583.
54. Trudeau, W.L.; McGuigan, J.E. Relations between serum gastrin levels and rates of gastric hydrochloric acid secretion. New Engl. J. Med. 1971, 284, 408–412, doi:10.1056/nejm197102252840803.
55. Borch, K.; Renvall, H.; Liedberg, G. Gastric endocrine cell hyperplasia and carcinoid tumors in pernicious anemia. Gastroenterology 1985, 88, 638–648.
56. Solcia, E.; Capella, C.; Fiocca, R.; Rindi, G.; Rosai, J. Gastric argyrophil carcinoidosis in patients with Zollinger-Ellison syndrome due to type 1 multiple endocrine neoplasia. A newly recognized association. Am. J. Surg. Pathol. 1990, 14, 503–513.
57. Bordi, C. Carcinoid (ECL cell) tumor of the oxyntic mucosa of the stomach, a hormone dependent neoplasm? Prog. Surg. Pathol. 1988; 8, 177–195.
58. Solcia, E.; Rindi, G.; Silini, E.; Villani, L. Enterochromaffin-like (ECL) cells and their growths: Relationships to gastrin, reduced acid secretion and gastritis. Baillieres Clin. Gastroenterol. 1993, 7, 149–165, doi:10.1016/0950-3528(93)90035-q.
59. Lee, L.; Ramos-Alvarez, I.; Ito, T.; Jensen, R.T. Insights into Effects/Risks of Chronic Hypergastrinemia and Lifelong PPI Treatment in Man Based on Studies of Patients with Zollinger-Ellison Syndrome. Int. J. Mol. Sci. 2019, 20, doi:10.3390/ijms20205128.

60. Procter Gamble Company/Astra Zeneca LP. Omeprazole magnesium tablets. NDA (New Drug Application) 2000;21:229.

61. Lahner, E.; Esposito, G.; Pilozzi, E.; Purchiaroni, F.; Corleto, V.D.; Di Giulio, E.; Annibale, B. Occurrence of gastric cancer and carcinoids in atrophic gastritis during prospective long-term follow up. Scand. J. Gastroenterol. 2015, 50, 856–865, doi:10.3109/00365521.2015.1010570.

62. Murphy, G.; Dawsey, S.M.; Engels, E.A.; Ricker, W.; Parsons, R.; Etemadi, A.; Lin, S.W.; Abnet, C.C.; Freedman, N.D. Cancer Risk After Pernicious Anemia in the US Elderly Population. Clin. Gastroenterol. Hepatol. 2015, 13, 2282–2289, doi:10.1016/j.cgh.2015.05.040.

63. Weise, F.; Vieth, M.; Reinhold, D.; Haybaeck, J.; Goni, E.; Lippert, H.; Ridwelski, K.; Lingohr, P.; Schildberg, C.; Vassos, N.; et al. Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research. United Eur. Gastroenterol. J. 2020, 8, 175–184, doi:10.1177/2050640619891580.

64. Antonodimitrakis, P.; Tsolakis, A.; Welin, S.; Kozlovacki, G.; Oberg, K.; Granberg, D. Gastric carcinoid in a patient infected with Helicobacter pylori: A new entity? World J. Gastroenterol. 2011, 17, 3066–3068, doi:10.3748/wjg.v17.i25.3066.

65. Sato, Y.; Iwafuchi, M.; Ueki, J.; Yoshimura, A.; Mochizuki, T.; Motoyama, H.; Sugimura, K.; Honma, T.; Narisawa, R.; Ichida, T.; et al. Gastric carcinoid tumors without autoimmune gastritis in Japan: A relationship with Helicobacter pylori infection. Dig. Dis. Sci. 2002, 47, 579–585.

66. Strickland, R.G.; Bhathal, P.S.; Korman, M.G.; Hansky, J. Serum gastrin and the antral mucosa in atrophic gastritis. Br. Med. J. 1971, 4, 451–453, doi:10.1136/bmj.4.5785.451.

67. Jensen, R.T. Management of the Zollinger-Ellison syndrome in patients with multiple endocrine neoplasia type 1. J. Intern. Med. 1998, 243, 477–488, doi:10.1046/j.1365-2796.1998.00281.x.

68. Cadiot, G.; Vissuzaine, C.; Potet, F.; Mignon, M. Fundic argyrophil carcinoid tumor in a patient with sporadic-type Zollinger-Ellison syndrome. Dig. Dis. Sci. 1995, 40, 1275–1278, doi:10.1007/bf02065537.

69. Feurle, G.E. Argyrophil cell hyperplasia and a carcinoid tumour in the stomach of a patient with sporadic Zollinger-Ellison syndrome. Gut 1994, 35, 275–277, doi:10.1136/gut.35.2.275.

70. Cavalcoli, F.; Zilli, A.; Conte, D.; Ciafardini, C.; Massironi, S. Gastric neuroendocrine neoplasms and proton pump inhibitors: Fact or coincidence? Scand. J. Gastroenterol. 2015, 50, 1397–1403, doi:10.3109/00365521.2015.1054426.

71. Jianu, C.S.; Fossmark, R.; Viset, T.; Qvigstad, G.; Sordal, O.; Marvik, R.; Waldum, H.L. Gastric carcinoids after long-term use of a proton pump inhibitor. Aliment. Pharmacol. Ther. 2012, 36, 644–649, doi:10.1111/apt.12012.

72. Haga, Y.; Nakatsura, T.; Shibata, Y.; Sameshima, H.; Nakamura, Y.; Tanimura, M.; Ogawa, M. Human gastric carcinoid detected during long-term antiulcer therapy of H2 receptor antagonist and proton pump inhibitor. Dig. Dis. Sci. 1998, 43, 253–257, doi:10.1023/a:1018881617038.

73. Nandy, N.; Hanson, J.A.; Strickland, R.G.; McCarthy, D.M. Solitary Gastric Carcinoid Tumor Associated with Long-Term Use of Omeprazole: A Case Report and Review of the Literature. Dig. Dis. Sci. 2016, 61, 708–712, doi:10.1007/s10620-015-4014-0.

74. Mattsson, H.; Havu, N.; Bräutigam, J.; Carlsson, K.; Lundell, L.; Carlsson, E. Partial gastric corpectomy results in hypergastrinemia and development of gastric enterochromaffinlike-cell carcinoids in the rat. Gastroenterology 1991, 100, 311–319, doi:10.1016/0016-5085(91)90197-s.

75. Bordi, C.; Senatore, S.; Missale, G. Gastric carcinoid following gastrojejunostomy. Am. J. Dig. Dis. 1976, 21, 667–671, doi:10.1007/bf01071964.

76. Rindi, G.; Luinetti, O.; Cornaggia, M.; Capella, C.; Solcia, E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: A clinicopathologic study. Gastroenterology 1993, 104, 994–1006, doi:10.1016/0016-5085(93)90266-f.

77. Lahner, E.; Esposito, G.; Pilozzi, E.; Galli, G.; Corleto, V.D.; Di Giulio, E.; Annibale, B. Gastric cancer in patients with type I gastric carcinoids. Gastric Cancer 2015, 18, 564–570, doi:10.1007/s10120-014-0393-8.

78. Sjöblom, S.M.; Sipponen, P.; Miettinen, M.; Karonen, S.L.; Jrvinen, H.J. Gastroscopic screening for gastric carcinoids and carcinoma in pernicious anemia. Endoscopy 1988, 20, 52–56, doi:10.1055/s-2007-1018130.

79. Parra-Medina, R.; Moreno-Lucero, P.; Jimenez-Moreno, J.; Parra-Morales, A.M.; Romero-Rojas, A. Neuroendocrine neoplasms of gastrointestinal tract and secondary primary synchronous tumors: A systematic review of case reports. Casualty or causality? PLoS ONE 2019, 14, e0216647, doi:10.1371/journal.pone.0216647.

80. Qvigstad, G.; Qvigstad, T.; Westre, B.; Sandvik, A.K.; Brenna, E.; Waldum, H.L. Neuroendocrine differentiation in gastric adenocarcinomas associated with severe hypergastrinemia and/or pernicious anemia. Apmis: Acta Pathol.

Microbiol. Et Immunol. Scand. 2002, 110, 132–139, doi:10.1034/j.1600-0463.2002.100302.x.

81. Qvigstad, G.; Sandvik, A.K.; Brenna, E.; Aase, S.; Waldum, H.L. Detection of chromogranin A in human gastric adenocarcinomas using a sensitive immunohistochemical technique. Histochem. J. 2000, 32, 551–556.
82. Martinsen, T.C.; Skogaker, N.E.; Fossmark, R.; Nordrum, I.S.; Sandvik, A.K.; Bendheim, M.O.; Bakkelund, K.E.; Waldum, H.L. Neuroendocrine cells in diffuse gastric carcinomas: An ultrastructural study with immunogold labeling of chromogranin A. Appl. Immunohistochem. Mol. Morphol.: Aimm 2010, 18, 62–68, doi:10.1097/PAI.0b013e3181b70594.
83. Waldum, H.L.; Sordal, O.F. Classification of Epithelial Malignant Tumors-the Differentiation Between Adenocarcinomas and Neuroendocrine Carcinomas: Why Rely on Nonspecific Histochemistry and Dismiss Specific Methods Like Immunohistochemistry and In Situ Hybridization? Appl. Immunohistochem. Mol. Morphol.: Aimm 2016, 24, 309–312, doi:10.1097/pai.0000000000000190.
84. Sordal, O.; Qvigstad, G.; Nordrum, I.S.; Sandvik, A.K.; Gustafsson, B.I.; Waldum, H. The PAS positive material in gastric cancer cells of signet ring type is not mucin. Exp. Mol. Pathol. 2014, 96, 274–278, doi:10.1016/j.yexmp.2014.02.008.
85. Bakkelund, K.; Fossmark, R.; Nordrum, I.; Waldum, H. Signet ring cells in gastric carcinomas are derived from neuroendocrine cells. J. Histochem. Cytochem.: Off. J. Histochem. Soc. 2006, 54, 615–621, doi:10.1369/jhc.5A6806.2005.
86. Tahara, E.; Haizuka, S.; Kodama, T.; Yamada, A. The relationship of gastrointestinal endocrine cells to gastric epithelial changes with special reference to gastric cancer. Acta Pathol. Jpn. 1975, 25, 161–177, doi:10.1111/j.1440-1827.1975.tb00855.x.
87. Prade, M.; Bara, J.; Gadenne, C.; Bognel, C.; Charpentier, P.; Ravazzola, M.; Caillou, B. Gastric carcinoma with argyrophilic cells: Light microscopic, electron microscopic, and immunochemical study. Hum. Pathol. 1982, 13, 588–592, doi:10.1016/s0046-8177(82)80277-3.
88. Kanomata, N. Neuroendocrine and mucinous differentiation in signet ring cell carcinoma of the stomach: Evidence for a common cell of origin in composite tumors. Hum. Pathol. 2012, 43, e1344, doi:10.1016/j.humpath.2012.03.017.
89. Qvigstad, G.; Falkmer, S.; Westre, B.; Waldum, H.L. Clinical and histopathological tumour progression in ECL cell carcinoids ("ECLomas"). Apmis: Acta Pathol. Microbiol. Et Immunol. Scand. 1999, 107, 1085–1092.
90. Calvete, O.; Reyes, J.; Zuniga, S.; Paumard-Hernandez, B.; Fernandez, V.; Bujanda, L.; Rodriguez-Pinilla, M.S.; Palacios, J.; Heine-Suner, D.; Banka, S.; et al. Exome sequencing identifies ATP4A gene as responsible of an atypical familial type I gastric neuroendocrine tumour. Hum. Mol. Genet. 2015, 24, 2914–2922, doi:10.1093/hmg/ddv054.
91. Fossmark, R.; Calvete, O.; Mjones, P.; Benitez, J.; Waldum, H.L. ECL-cell carcinoids and carcinoma in patients homozygous for an inactivating mutation in the gastric H(+) K(+) ATPase alpha subunit. Apmis: Acta Pathol. Microbiol. Et Immunol. Scand. 2016, 124, 561–566, doi:10.1111/apm.12546.
92. Rogers, L.W.; Murphy, R.C. Gastric carcinoid and gastric carcinoma. Morphologic correlates of survival. Am. J. Surg. Pathol. 1979, 3, 195–202, doi:10.1097/00000478-197906000-00001.
93. Ishiwata, N.; Ikeda, T.; Tokushima, K.; Tozuka, S.; Sakamoto, S.; Marumo, F.; Aida, S.; Sato, C. Gastric adenocarcinoma producing neuron-specific enolase. Dig. Dis. Sci. 1998, 43, 971–974, doi:10.1023/a:1018814330919.
94. Mjønes, P.; Sagatun, L.; Nordrum, I.S.; Waldum, H.L. Neuron-Specific Enolase as an Immunohistochemical Marker Is Better Than Its Reputation. J. Histochem. Cytochem.: Off. J. Histochem. Soc. 2017, 65, 687–703, doi:10.1369/0022155417733676.
95. Miyaoka, Y.; Kadowaki, Y.; Ishihara, S.; Ose, T.; Fukuhara, H.; Kazumori, H.; Takasawa, S.; Okamoto, H.; Chiba, T.; Kinoshita, Y. Transgenic overexpression of Reg protein caused gastric cell proliferation and differentiation along parietal cell and chief cell lineages. Oncogene 2004, 23, 3572–3579, doi:10.1038/sj.onc.1207333.
96. Oue, N.; Mitani, Y.; Aung, P.P.; Sakakura, C.; Takeshima, Y.; Kaneko, M.; Noguchi, T.; Nakayama, H.; Yasui, W. Expression and localization of Reg IV in human neoplastic and non-neoplastic tissues: Reg IV expression is associated with intestinal and neuroendocrine differentiation in gastric adenocarcinoma. J Pathol 2005, 207, 185–198, doi:10.1002/path.1827.
97. Waldum, H.L.; Hauso, O.; Sordal, O.F.; Fossmark, R. Gastrin May Mediate the Carcinogenic Effect of Helicobacter pylori Infection of the Stomach. Dig. Dis. Sci. 2015, 60, 1522–1527, doi:10.1007/s10620-014-3468-9.
98. Uemura, N.; Okamoto, S.; Yamamoto, S.; Matsumura, N.; Yamaguchi, S.; Yamakido, M.; Taniyama, K.; Sasaki, N.; Schlemper, R.J. Helicobacter pylori infection and the development of gastric cancer. New Engl. J. Med. 2001, 345, 784–789, doi:10.1056/NEJMoa001999.
99. Tanimoto, H.; Yoshida, K.; Yokozaki, H.; Yasui, W.; Nakayama, H.; Ito, H.; Ohama, K.; Tahara, E. Expression of basic fibroblast growth factor in human gastric carcinomas. Virchows Arch. B Cell Pathol. Incl. Mol. Pathol. 1991, 61, 263–

267, doi:10.1007/bf02890427.

100. Hyodo, M.; Yumoto, E.; Wakisaka, H.; Mori, T.; Takada, K. Gastric scirrhous carcinoma as a rare cause of aggressive fibromatosis in the neck. Am. J. Otolaryngol. 2001, 22, 38–42, doi:10.1053/ajot.2001.20697.

101. Azzopardi, J.G.; Pollock, D.J. Argentaffin and argyrophil cells in gastric carcinoma. J. Pathol. Bacteriol. 1963, 86, 443–451.

102. Chejfec, G.; Gould, V.E. Malignant gastric neuroendogrinomas. Ultrastructural and biochemical characterization of their secretory activity. Hum. Pathol. 1977, 8, 433–440, doi:10.1016/s0046-8177(77)80007-5.

103. Soga, J.; Tazawa, K.; Aizawa, O.; Wada, K.; Tuto, T. Argentaffin cell adenocarcinoma of the stomach: An atypical carcinoid? Cancer 1971, 28, 999–1003

104. Soga, J.; Tazawa, M.D.; Ito, H. Ultrastructural demonstration of specific secretory granules of Mastomys gastric carcinoids. Acta. Med. Et Biol. 1969, 17, 119–124.

105. Kubo, T.; Watanabe, H. Neoplastic argentaffin cells in gastric and intestinal carcinomas. Cancer 1971, 27, 447–454

106. Ooi, A.; Mai, M.; Ogino, T.; Ueda, H.; Kitamura, T.; Takahashi, Y.; Kawahara, E.; Nakanishi, I. Endocrine differentiation of gastric adenocarcinoma. The prevalence as evaluated by immunoreactive chromogranin A and its biologic significance. Cancer 1988, 62, 1096–1104

107. Blumenfeld, W.; Chandhoke, D.K.; Sagerman, P.; Turi, G.K. Neuroendocrine differentiation in gastric adenocarcinomas. An immunohistochemical study. Arch. Pathol. Lab. Med. 1996, 120, 478–481.

108. Ali, M.H.; Davidson, A.; Azzopardi, J.G. Composite gastric carcinoid and adenocarcinoma. Histopathology 1984, 8, 529–536, doi:10.1111/j.1365-2559.1984.tb02362.x.

109. Caruso, M.L.; Pilato, F.P.; D'Adda, T.; Baggi, M.T.; Fucci, L.; Valentini, A.M.; Lacatena, M.; Bordi, C. Composite carcinoid-adenocarcinoma of the stomach associated with multiple gastric carcinoids and nonantral gastric atrophy. Cancer 1989, 64, 1534–1539

110. Levendoglu, H.; Cox, C.A.; Nadimpalli, V. Composite (adenocarcinoid) tumors of the gastrointestinal tract. Dig. Dis. Sci. 1990, 35, 519–525, doi:10.1007/bf01536929.

111. Miguchi, M.; Iseki, M.; Shimatani, K. Advanced gastric neuroendocrine carcinoma with an adenocarcinoma component. Case Rep Gastroenterol 2012, 6, 52–57, doi:10.1159/000336320.

112. Mjones, P.; Nordrum, I.S.; Sordal, O.; Sagatun, L.; Fossmark, R.; Sandvik, A.; Waldum, H.L. Expression of the Cholecystokinin-B Receptor in Neoplastic Gastric Cells. Horm. Cancer 2018, 9, 40–54, doi:10.1007/s12672-017-0311-8.

113. Goetze, J.P.; Eiland, S.; Svendsen, L.B.; Vainer, B.; Hannibal, J.; Rehfeld, J.F. Characterization of gastrins and their receptor in solid human gastric adenocarcinomas. Scand. J. Gastroenterol. 2013, 48, 688–695, doi:10.3109/00365521.2013.783101.

114. Chen, J.N.; He, D.; Tang, F.; Shao, C.K. Epstein-Barr virus-associated gastric carcinoma: A newly defined entity. J. Clin. Gastroenterol. 2012, 46, 262–271, doi:10.1097/MCG.0b013e318249c4b8.

115. Chan, W.Y.; Liu, Y.; Li, C.Y.; Ng, E.K.; Chow, J.H.; Li, K.K.; Chung, S.C. Recurrent genomic aberrations in gastric carcinomas associated with Helicobacter pylori and Epstein-Barr virus. Diagn. Mol. Pathol. 2002, 11, 127–134, doi:10.1097/00019606-200209000-00001.

116. Tahara, E. Genetic pathways of two types of gastric cancer. Iarc. Sci. Publ. 2004, 327–349.

117. Guilford, P.; Hopkins, J.; Harraway, J.; McLeod, M.; McLeod, N.; Harawira, P.; Taite, H.; Scoular, R.; Miller, A.; Reeve, A.E. E-cadherin germline mutations in familial gastric cancer. Nature 1998, 392, 402–405, doi:10.1038/32918.

118. Fox, J.G.; Wang, T.C. Inflammation, atrophy, and gastric cancer. J. Clin. Investig. 2007, 117, 60–69, doi:10.1172/jci30111.

119. Graham, D.Y.; Zou, W.Y. Guilt by association: Intestinal metaplasia does not progress to gastric cancer. Curr. Opin. Gastroenterol. 2018, 34, 458–464, doi:10.1097/mog.0000000000000472.

120. Wong, B.C.; Lam, S.K.; Wong, W.M.; Chen, J.S.; Zheng, T.T.; Feng, R.E.; Lai, K.C.; Hu, W.H.; Yuen, S.T.; Leung, S.Y.; et al. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: A randomized controlled trial. Jama 2004, 291, 187–194, doi:10.1001/jama.291.2.187.

121. Take, S.; Mizuno, M.; Ishiki, K.; Kusumoto, C.; Imada, T.; Hamada, F.; Yoshida, T.; Yokota, K.; Mitsuhashi, T.; Okada, H. Risk of gastric cancer in the second decade of follow-up after Helicobacter pylori eradication. J. Gastroenterol. 2020, 55, 281–288, doi:10.1007/s00535-019-01639-w.

122. Kishikawa, H.; Ojiro, K.; Nakamura, K.; Katayama, T.; Arahata, K.; Takarabe, S.; Miura, S.; Kanai, T.; Nishida, J. Previous Helicobacter pylori infection-induced atrophic gastritis: A distinct disease entity in an understudied population without a history of eradication. Helicobacter 2020, 25, e12669, doi:10.1111/hel.12669.
123. Stathis, A.; Chini, C.; Bertoni, F.; Proserpio, I.; Capella, C.; Mazzucchelli, L.; Pedrinis, E.; Cavalli, F.; Pinotti, G.; Zucca, E. Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. Ann. Oncol.: Off. J. Eur. Soc. Med Oncol. 2009, 20, 1086–1093, doi:10.1093/annonc/mdn760.

Retrieved from https://encyclopedia.pub/entry/history/show/14033