

The Consequences of Hypergastrinemia

Werner Creutzfeldt^a

Department of Medicine, Georg-August-University, Göttingen, Germany

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1. The only gastrin-dependent gastric endocrine cells are the fundic ECL cells. Excessive hypergastrinemia stimulates ECL cell proliferation in animals and man. The growth of other gastric endocrine cells is regulated by the gastric pH.
 2. Hypergastrinemia in man results in diffuse and linear hyperplasia of the ECL cells, while micronodular hyperplasia is correlated to the grade of corpus gastritis. ECL cell dysplasia and gastric carcinoids in man have been observed only in patients with gastrinoma as part of the MEN I syndrome and with pernicious anemia.
 3. Gastrin dependence of GI adenocarcinoma has not been established. Experimental findings may be explained by the presence of gastrin receptors and the role of gastrin as an autocrine growth factor.
 4. Epidemiological data do not support gastrin dependence of carcinoma of the stomach, the pancreas and the colon.
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INTRODUCTION

About nine years ago, Borch published his observations on an increasing number of gastric carcinoids in patients with pernicious anemia [1-3], and toxicologists, their findings of gastric carcinoids after life-long treatment with potent inhibitors of gastric secretion [4, 5]. These findings were immediately connected, called the achlorhydria carcinoid sequence and related to the accompanying hypergastrinemia [2, 6, 7, 8]. In the following years, the question has been frequently asked whether long lasting hypergastrinemia may initiate or promote tumor growth in man [9]. Hypergastrinemia occurs in man in the rare event of a gastrin-producing tumor, i.e., Zollinger-Ellison syndrome (gastrinoma) or more frequently as a consequence of hypo- or achlorhydria.

Any means of elevating the pH of the stomach content toward neutral leads to an increase of the serum concentration of gastrin, because the antral G-cell is inhibited by the acid pH in the gastric lumen, the so-called gastrin-acid-feedback regulation, or the acid brake [9]. This inhibition of the G-cells (which are usually stimulated by nutrients and nerves) is partially a direct effect of acid pH in the gastric lumen and partially mediated via paracrine secretion of somatostatin from the D-cells, which are stimulated by acid pH (Figure 1).

If the pH in the antral lumen becomes neutral by surgical or pharmacological elimination of acid secretion, the acid brake is lost. This leads to uninhibited gastrin secretion since G-cell stimulation by nerves and nutrients continues (Figure 2).

This review will discuss the consequences of hypergastrinemia for the growth of gastric endocrine cells and the possible role of hypergastrinemia for tumor growth in the stomach, the pancreas and the colon. While the growth of gastric endocrine cells in

^aTo whom all correspondence should be addressed: Professor W. Creutzfeldt, Zentrum für Innere Medizin, Robert-Koch-Straße, D-37075 Göttingen, Germany. Tel: (49) 551-396259; Fax: (49) 551-398943.

^bAbbreviations: ECL, enterochromaffin-like (cell); CCK, cholecystokinin; MEN I, multiple endocrine neoplasia, type I.

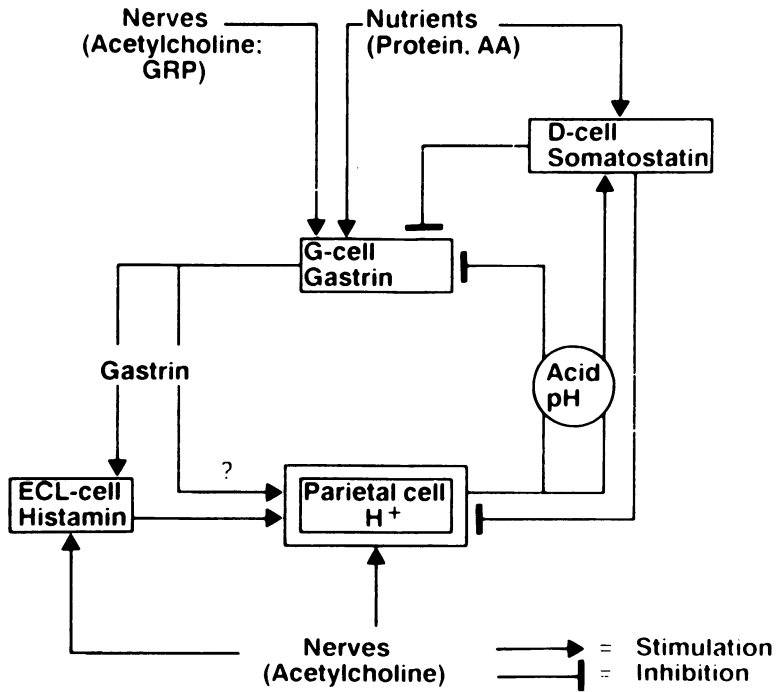


Figure 1. Scheme of the stimulating and inhibitory pathways regulating gastrin and acid secretion: the acid brake. From Ref. 9, with permission.

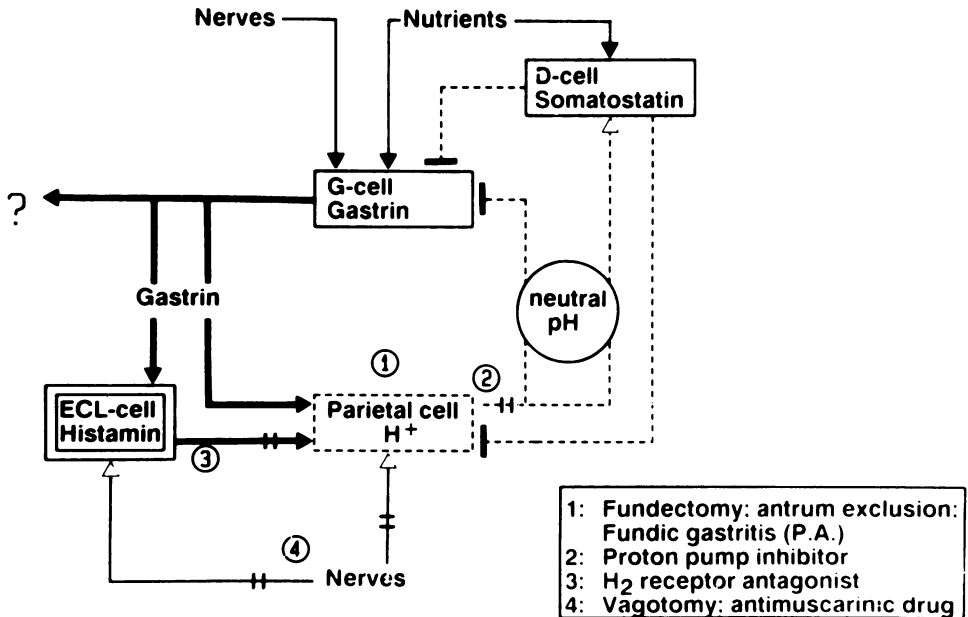


Figure 2. Scheme of the consequences of neutral pH in the gastric lumen. The loss of the acid brake results in uninhibited gastrin secretion if G cell stimulation by nerves and nutrients continues. Possible reasons for interruption of acid production are indicated in the lower right corner. From Ref. 9, with permission.

hypergastrinemic states has been extensively studied in man, the possible role of hypergastrinemia for tumor growth is a hypothesis that is poorly supported by the available clinical data.

GASTRIC ENDOCRINE CELL PROLIFERATION

The growth-promoting effect of gastrin on the histamine-producing enterochromaffin-like (ECL)^b cells, especially of rodents, is known from the work of Håkanson and co-workers [10] and is also found in other species, including man in case of atrophic type A (autoimmune) gastritis [3]. However, the development of gastric carcinoids described in a high percentage of female rats treated for two years with omeprazole [5] alarmed the scientific community and the authorities because a direct cancerogenic effect of omeprazole was suspected [7]. The finding was related to the occurrence of carcinoids in pernicious anemia, i.e., after excessive hypergastrinemia for more than ten years in five percent of patients with an autoimmune type gastritis [2] or in patients with the MEN I syndrome and hypergastrinemia due to a gastrinoma [11].

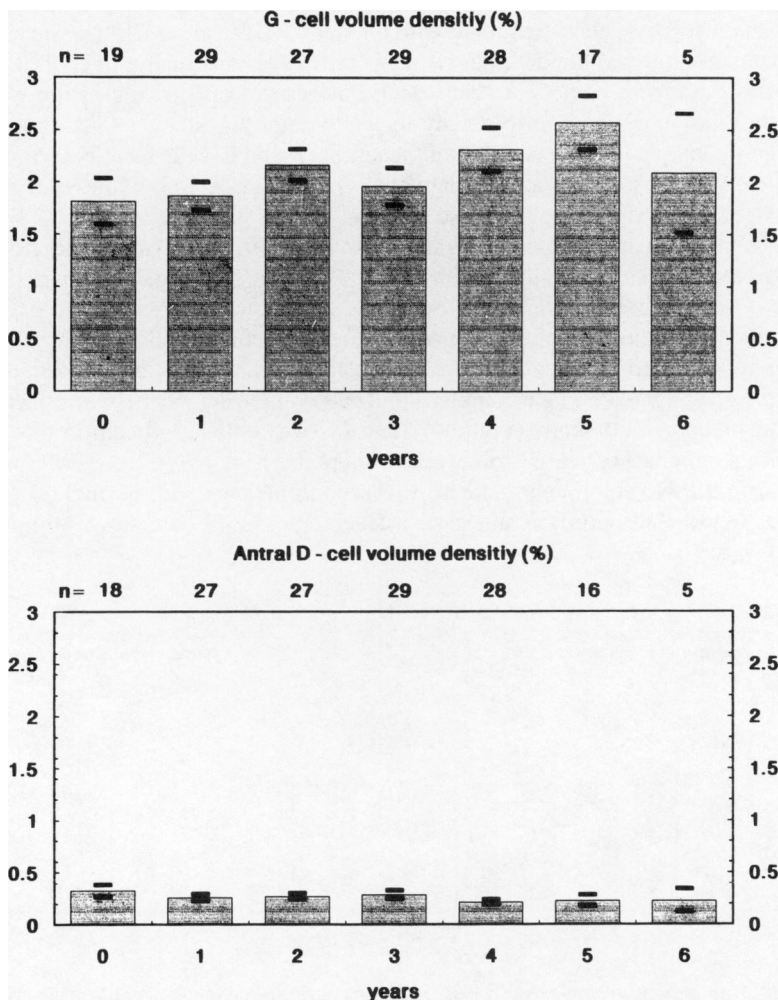


Figure 3. Volume density of G cells (top) and D cells (bottom) in the antral mucosa of patients under long-term omeprazole therapy. SEM values are indicated by horizontal bars. From Ref. 21, with permission.

However, in these two conditions, special factors are present: genetic predisposition in the multiple endocrine neoplasia syndrome [12] and immunological factors in pernicious anemia [8, 9]. The dependence of the carcinoid development in rats from the induction of hypergastrinemia via hypochlorhydria and not a specific drug has been convincingly shown by production of carcinoids by 75 percent corpectomy [13] or feeding with 2000 mg/kg ranitidine [14]. Also, other substances like the H₂ receptor antagonist loxidine [4] and the hypolipidemic compound ciprofibrate [15], which inhibits gastric secretion, have been shown to produce gastric carcinoids in rats. On the other hand, antrectomy prevents the omeprazole-induced ECL cell hyperplasia in rats, proving the mediator role of gastrin [16]. Despite this, some authors speculate on a direct cancerogenic effect of omeprazole [7] or on bacterial overgrowth in the achlorhydric stomach generating genotoxic N-nitroso compounds [17]. Since rats are prone to develop endocrine tumors and may serve as a model for MEN I syndrome [18], an inherited genetic trait might be a prerequisite for the development of gastric ECL cell carcinoids in rats with life-long hypergastrinemia.

In order to decide the question whether similar changes of the gastric endocrine cells occur in man during long-term treatment with omeprazole, the growth of gastric endocrine cells has been monitored, both quantitatively [9, 19, 20, 21] and qualitatively [20, 21, 22], in serial gastric biopsies of patients with ranitidine-resistant peptic ulceration who were treated with 20 to 40 mg omeprazole daily for up to eight years.

No significant quantitative changes of the antral G- and D-cells have been found even after years of high-dose omeprazole treatment (Figure 3) [19, 21], while after proximal selective vagotomy, a significant increase of antral G-cells has been reported [23]. In rats, the G-cell volume density doubled both quantitatively [9, 19, 20, 21] and qualitatively [20, 21, 22] after four weeks of treatment with omeprazole, reaching a plateau thereafter [24].

The evaluation of the ECL-cell growth has been done in sections of the oxyntic mucosa stained with the Grimelius-silver-impregnation technique [25]. Most of the argyrophil cells stained with this technique are ECL-cells. Morphometric assessment of biopsy samples showed an increase in gastric argyrophil cell volume density between the third and fifth year of omeprazole therapy (Figure 4), but this was only significant in the group of patients with the highest serum gastrin levels of more than 240 pg/ml (four times the upper normal limit) [20]. No significant increase was seen in patients with normal or moderately elevated (below 240 pg/ml) serum gastrin levels, i.e., in 77 percent of 66 unoperated

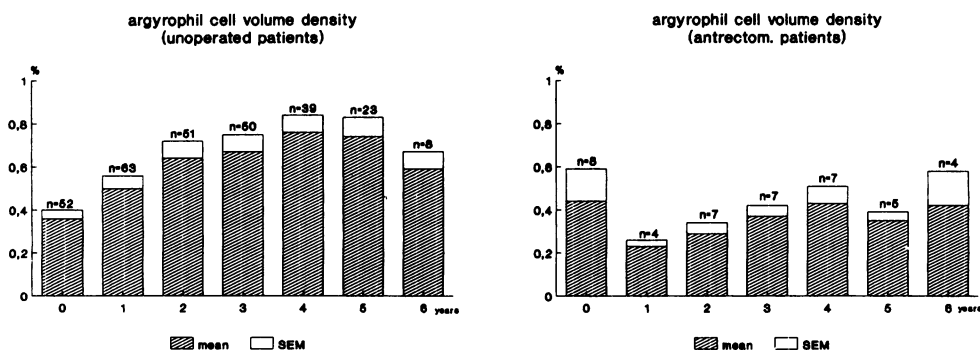


Figure 4. Volume density of argyrophil cells in the oxyntic mucosa of patients with ranitidine-resistant ulcerations under long-term omeprazole therapy (mean \pm SEM). The number of patients evaluated is given in each column. Left, unoperated patients; right, antrectomized patients. From Ref. 21, with permission

study patients (Figure 5). In eight antrectomized patients, no significant increase of the argyrophil cells has been found (Figure 4). Thus, the morphometric data support earlier findings [9] that an increase of the ECL-cell volume density is correlated to elevated fasting serum gastrin levels (Figure 6). A significant elevated volume density of argyrophil cells in the oxyntic mucosa has also been described in 31 patients after selective vagotomy (one to 15 years; median, four years earlier) together with elevated fasting serum gastrin levels [23].

The growth of the argyrophil cells has been also qualitatively graded according to the classification of Solcia et al. [26]. This classification distinguishes normal argyrophil cells (grade 0), diffuse hyperplasia (grade 1), linear hyperplasia (grade 2), micronodular hyperplasia (grade 3) and adenomatoid hyperplasia (grade 4). Addition of the findings in each patient revealed that significantly higher grades of hyperplasia occurred only in patients with serum gastrin levels greater than 240 pg/ml. In other words, linear and micronodular

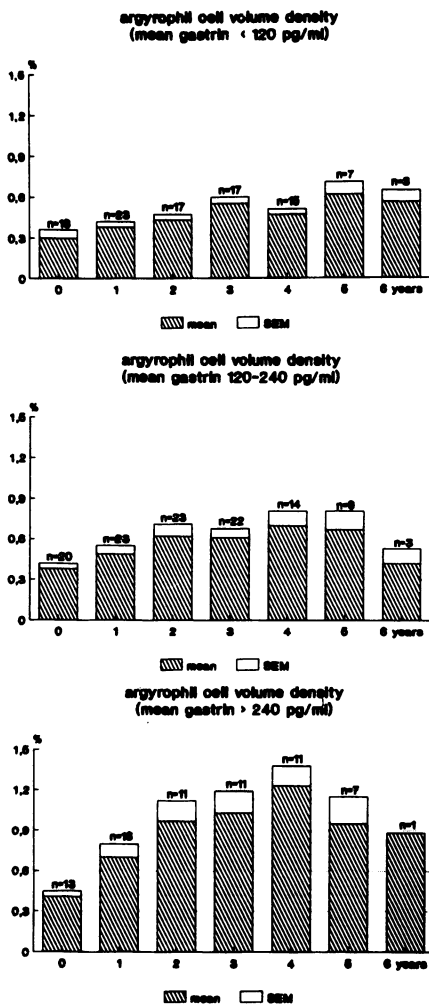


Figure 5. Argyrophil cell volume density in the nonantral gastric mucosa of patients with peptic ulceration undergoing long-term omeprazole therapy. The patients are divided into three groups according to the mean fasting serum gastrin levels. A significant increase in gastric argyrophil cell volume density occurs only in patients with mean serum gastrin levels greater than 240 pg/ml. From Ref. 20, with permission.

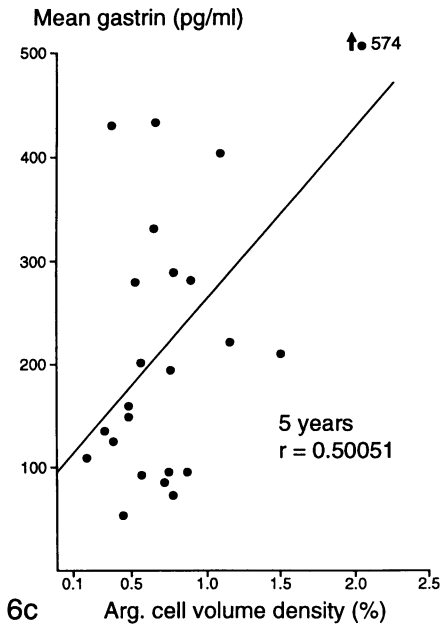
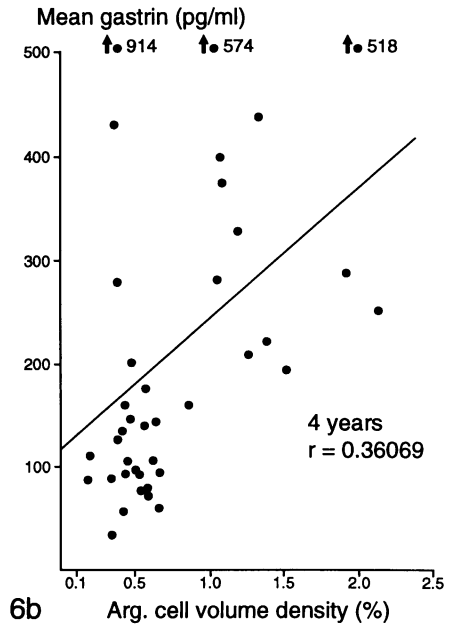
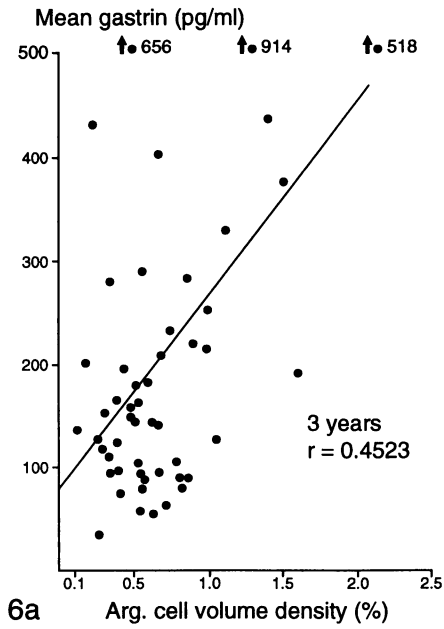


Figure 6. Correlation between argyrophil cell volume densities and individual mean serum gastrin concentrations throughout long-term omeprazole therapy. A, three years of continuous omeprazole therapy; B, four years; C, five years. From Ref. 21, with permission.

hyperplasia was confined to the group of patients with the highest serum gastrin levels [20]. Dysplasia (according to the classification of Solcia et al. [26]) has not been observed in any of the biopsies from 655 biopsy dates. This is in complete agreement with the finding in another study on more than 2000 biopsies from 448 patients treated with 20 mg omeprazole for up to four years [22].

During the qualitative assessment of the biopsies, a progressive increase in preatrophic and atrophic gastritis was noticed over the study period [9, 21, 22], and a correlation between different grades of atrophy of the oxyntic mucosa and argyrophil cell growth was established. By evaluating more than 3000 biopsies from 655 biopsy dates of 74 patients on long-term omeprazole treatment (up to eight years with 40 mg daily), it was found [20] that the prevalence of micronodular hyperplasia in superficial corpus gastritis was low (3.6 percent) and increased to 19.6 percent in interstitial gastritis and to 48 percent in atrophic gastritis (Figure 7). This finding is in agreement with an independent study on 2000 biopsies of patients treated with 20 mg daily for up to four years [22] and suggests a causal relationship between atrophic gastritis and micronodular hyperplasia. This relationship may partially be explained by condensation of the endocrine cells, caused by atrophy of the gastric glands and, thus, may not represent true hyperplasia [22, 26].

These observations suggest that the increased occurrence of argyrophil cell hyperplasia, especially the linear and micronodular form, in patients with the highest serum gastrin levels could as well be due to the more severe form of (atrophic) gastritis. This conclusion is supported by studies from Estonia in patients with long-standing, untreated gastric ulcer disease [28, 29]. None of these patients had ever received antisecretory therapy, and only 30 percent had hypergastrinemia. However, the majority (62 percent) had atrophic corpus

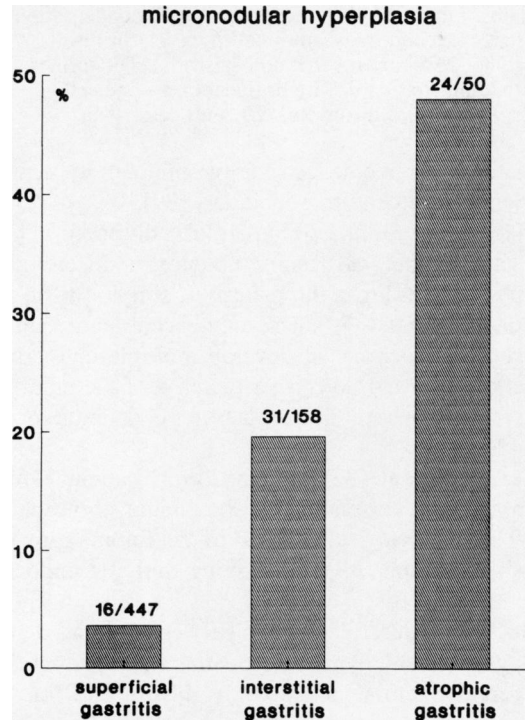


Figure 7. Prevalence of micronodular hyperplasia of argyrophil cells in 655 gastric biopsy dates (four to six biopsies per date) of 74 patients treated with long-term omeprazole, 40 mg daily. Absolute numbers are given on top of the columns. From Ref. 20, with permission.

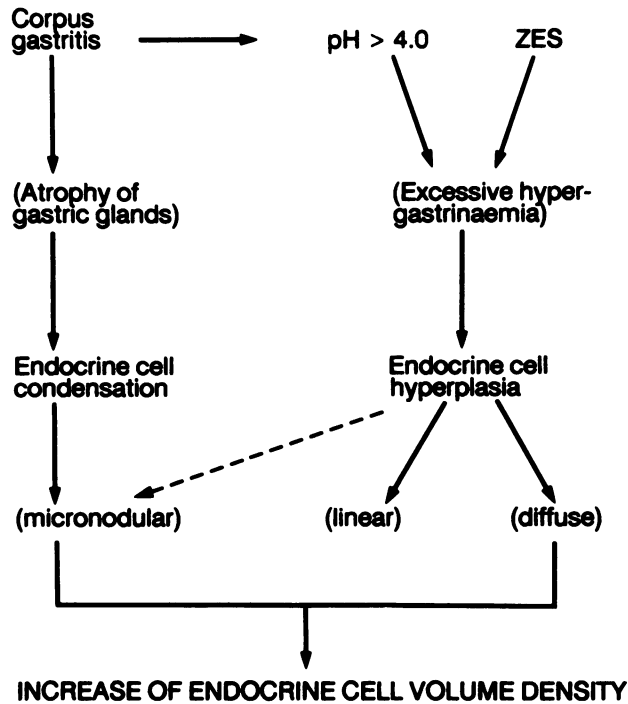


Figure 8. Flow sheet to explain the development of increased endocrine cell volume density by two different mechanisms. First, endocrine (argyrophil) cell condensation resulting from atrophy of gastric glands in gastritis; second, argyrophil cell hyperplasia resulting from hypergastrinemia (Zollinger-Ellison syndrome [ZES] or type A fundic gastritis). The former appears as micronodular hyperplasia, the latter predominately as diffuse or linear endocrine cell hyperplasia. The dotted line refers to ZES in patients with MEN I. From Ref. 20, with permission.

gastritis, which correlated to the incidence of argyrophil cell hyperplasia (45 percent simple, 18 percent linear and 37 percent micronodular) [29].

It is of interest that the argyrophil cell hyperplasia observed in hypergastrinemic subjects without corpus gastritis, i.e., gastrinoma patients, is different: in these patients the growth of the argyrophil cells follows the pattern of simple (diffuse) or linear hyperplasia, and no micronodules are found [30]. The only exception are patients with the MEN I syndrome, who are genetically prone to develop multiple endocrine tumors [11]. This growth pattern did not change, and no further increase of the number of argyrophil cells during high-dose omeprazole therapy of the gastrinoma patients for many years occurred [30, 31].

In a recent study, Cadiot et al. [32] described in 21 patients with gastrinoma, treated long-term with omeprazole, a correlation of the fundic argyrophil cell densities with serum gastrin levels. These were closely related to gastrinoma growth. Gastric carcinoids were found only in three patients, all three having multiple endocrine neoplasia type I (MEN I).

The available data on the interrelationship between increased argyrophil cell growth in the corpus mucosa, gastritis and hypergastrinemia can be summarized as follows: long-lasting excessive hypergastrinemia induces only diffuse and linear hyperplasia of the argyrophil cells in the oxyntic mucosa, while atrophic gastritis leads to micronodular hyperplasia [20] (Figure 8). Accordingly, a moderate hypergastrinemia in some patients

on high-dose omeprazole therapy is without consequence for the argyrophil cell growth and not responsible for micronodular hyperplasia.

HYPERGASTRINEMIA AND TUMOR GROWTH

Gastric ECL-cell carcinoids

The finding of carcinoids after life-long excessive hypergastrinemia in rats and patients with pernicious anemia established the so-called achlorhydria-hypergastrinemia-carcinoid sequence [8], and the question has been asked whether hypergastrinemia is dangerous [7]. No facts have been presented until now to support this contention.

It is now well established that gastric ECL-cell carcinoids are gastrin dependent. They have been observed only in patients with long lasting pernicious anemia or MEN I syndrome with gastrinoma. ECL-carcinoids arise exclusively in the non-antral mucosa and are relatively benign. In contrast, sporadic gastric carcinoids are mostly multihormonal tumors and gastrin independent, i.e., found in normogastrinemic patients without any background gastropathy [33]. They may be localized in the antrum as well as in the oxyntic mucosa. With their fast growth and metastasis, they behave like neuroendocrine carcinomas. The claim that diffuse gastric carcinomas are neuroendocrine gastrin-dependent tumors ("ECL-omas") [34] is pure speculation, because ECL-cells have not been convincingly identified in diffuse carcinomas [35], while the occurrence of some argyrophil cells is a frequent finding in gastric carcinomas.

Gastric adenocarcinoma

Gastrin dependence of gastric adenocarcinomas has not been established. As in many other tumors, gastrin receptors have been found on the cells of some gastric carcinomas. Also, growth stimulation by gastrin of such tumors has been described in vitro and in xenografts in vivo [36]. However, a clinical significance of this finding is not apparent from present epidemiological data.

The increased prevalence of pernicious anemia in patients with gastric adenocarcinoma [37] and of gastric carcinoma in patients with pernicious anemia [37, 38] has led to the speculation that hypergastrinemia may be responsible for this. However, a correlation to serum gastrin levels cannot be found in the majority of patients with gastric cancer, while a correlation to chronic atrophic gastritis is always present. Gastroscopic screening in achlorhydric patients revealed adenocarcinoma in four percent, but opposite to gastric carcinoids, no correlation to hypergastrinemia [1, 40].

The five-fold risk to develop stump carcinoma after antrectomy for treatment of recurrent ulcer disease [41, 42] occurs in the presence of even lower than normal gastrin levels and is identical to the cancer risk after vagotomy, i.e., in the presence of elevated serum gastrin levels [42].

Pancreatic adenocarcinoma

Despite the low affinity of gastrin to cholecystokinin A receptors of the pancreas, a possible role of gastrin for development and growth of pancreatic carcinoma has been discussed. In recent experiments, pancreatic hypertrophy and atypical acinar cell foci have been found in rats made hypergastrinemic by fundectomy for 14 months [43]. These changes were less marked than in rats with elevated plasma levels of CCK, induced by pancreatico-biliary diversion. Rats subjected to this procedure, but not fundectomized, also developed pancreatic adenoma.

These observations are in contradiction to short-term studies (up to 10 weeks) that did not show trophic effects of endogenous or exogenous gastrin on the pancreas [44, 45, 46]. Therefore, factors other than hypergastrinemia may have been responsible for the

pancreatic hypertrophy in the long-term fundectomized rats. The risk for cancer of the pancreas in 5161 hypergastrinaemic patients with pernicious anemia was lower than expected (standardized incidence ratio = 0.72) [39].

Adenocarcinoma of the colon

Contrary to the general opinion, gastrin has no trophic effects in the gastrointestinal tract outside the acid producing (oxyntic) mucosa [44, 45, 46]. This has been documented in chickens and several rodents. The belief that gastrin is a general trophic agent for the whole of the digestive tract and the pancreas [47, 48] is based largely on experiments with massive doses of pentagastrin. However, pentagastrin stimulates not only gastrin but also CCK_A receptors.

The numerous experimental data about the effect of (penta)gastrin on colon cancer cell lines in vitro or tumor transplants in vivo [49-52] are partly contradictory and can be explained with the frequent expression of gastrin receptors on tumor cells [53] (together with the expression of numerous other peptide and steroid receptors) and the possible role of gastrin as an autocrine growth factor in some of these tumors [9]. A recent paper demonstrated that omeprazol-induced hypergastrinemia did not influence the growth of a transplantable mouse colon carcinoma expressing gastrin receptors [52]. The growth-promoting effect of gastrin on a colon cancer cell line described in another recent publication [53] was achieved with supraphysiological gastrin concentrations and was not dose-dependent. The result may just indicate a conditioning role of gastrin for optimal growth.

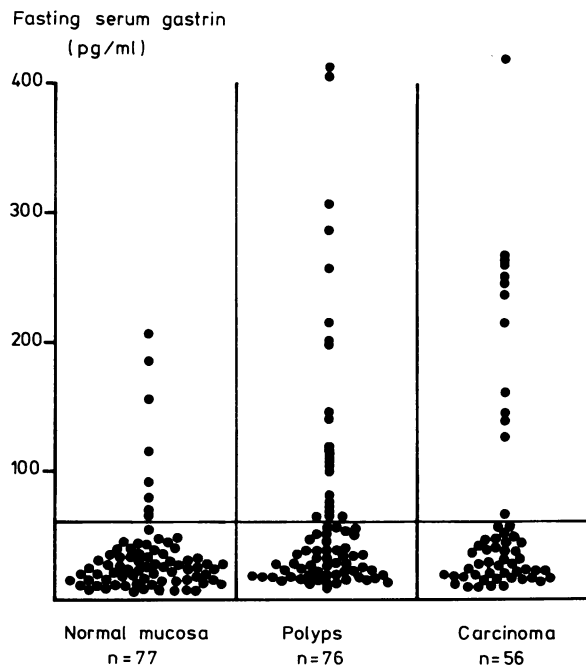


Figure 9. Individual values of fasting gastrin from 77 consecutive patients who underwent total colonoscopy and showed normal mucosa (mean age, 55 years), 76 patients with benign polyps of the colon (mean age, 62 years) and 56 patients with carcinoma of the colon (mean age, 66 years). The horizontal line indicates the upper limit of normal gastrin values. From Ref. 9, with permission.

The prevalence of pernicious anemia in 1777 patients with colon cancer was 0.2 percent, i.e., not significantly higher than in the general population of Denmark [37]. Also, the prevalence of colorectal carcinoma in patients with pernicious anemia was not significantly higher than expected in two historical studies [39, 55].

Several studies have been performed about plasma gastrin levels of patients with polyps and carcinoma of the colon, because in one small investigation, significantly higher fasting plasma levels of gastrin had been observed in patients with colon polyps and even higher levels in patients with colorectal adenocarcinoma than in matched controls with normal colon [56]. In the following studies [9, 57, 58, 59], no difference was found between matched controls with endoscopically normal colon and patients with polyps or carcinoma of the colon (Figure 9).

Two groups described elevated serum gastrin levels in a few patients with colon carcinoma. However, the elevated fasting [60] and postprandial [61] serum gastrin levels became normal after resection of the colon tumor, suggesting that the hypergastrinemia was a consequence and not the cause of the colon tumor. The expression of gastrin messenger RNA and the presence of progastrin and other G-17 precursors have recently been demonstrated in 12 colon carcinomas [62]. Only one tumor contained carboxyamidated, i.e., biologically active, gastrins. This finding would explain the elevated, and after tumor resection, normalized serum gastrin levels of patients, because some tumor cell lines secreted the gastrin precursors into the medium [62]. Gastrin antibodies used in the radioimmuno-assay do not distinguish gastrin precursors from G-17 or G-34.

In a recent study of 23 hypergastrinaemic patients with the Zollinger-Ellison syndrome, pancolonoscopy revealed four patients with small benign adenomas, and in one patient with a MEN I syndrome, an endocrine neoplasm of the colon [63]. This prevalence of colon adenomas is not higher than expected in this age group and was not related to the serum level of gastrin and the duration of the hypergastrinemia. The finding of the authors that in the hypergastrinaemic patients, the labeling index, using in vitro 5-bromodeoxyuridine incorporation in two colonic sites, was higher than in controls may not necessarily be evidence for a mitogenic effect of gastrin on the colonic mucosa [63], because the control group was highly selected regarding personal and family history, colonic function and exclusion of patients with adenomas. Similar studies are warranted in patients with pernicious anemia, because the results are in contradiction to experimental data in rodents [44, 45, 46].

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