The Pathobiology of the Human Enterochromaffin-Like Cell

I.M. MODLIN, M.D., Ph.D., AND A.K. NANGIA, M.D.

Gastrointestinal Pathobiology Research Unit, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

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The significance of the enterochromaffin-like (ECL) cell as a critical endocrine regulator of gastric fundic mucosal function has only recently been recognized. Although the percentage of these cells present in the human fundic mucosa is less than that in rodents, the observation that they secrete histamine and are probably important modulators of parietal cell function has resulted in their attaining some considerable biological significance. The further identification of gastrin and somatostatin receptors on the surface of the ECL cells has suggested that other neurohormonal influences may be significant in the regulation of parietal cell function, utilizing the ECL cell as an intermediate modifier. While abnormalities of ECL cells in the human stomach (hyperplasia/neoplasia) have been mostly confined to observations in patients with pernicious anemia and atrophic gastritis, the recent recognition of hyperplasia in pharmacothe-rapeutically induced achlorhydric or hypochlorhydric states has excited considerable interest. It has been proposed that the generation of luminal hypo- or achlorhydria by powerful acid inhibitory pharmacotherapy may result in hypergastrinemia. This condition is responsible initially for the development of hyperplasia and, subsequently, possibly even neoplasia of the ECL system of the fundic mucosa. This phenomenon seems to be prevalent in rodents but has so far been only rarely observed in humans, e.g., pernicious anemia, atrophic gastritis. In particular, patients with the gastrinoma component of the multiple endocrine neoplasia type I syndrome exhibit ECL-cell hyperplasia and neoplasia after exposure to acid inhibitory pharmacotherapy. It is therefore likely that an underlying genomic phenomenon is necessary prior to the induction of hyperplasia and subsequent neoplastic transformation. The scientific evaluation of the relationship between gastrin, ECL-cell function, and the development of hyperplasia and neoplasia may provide some important information in regard to the molecular evolution of gastrointestinal neuroendocrine disease states. It is possible that the future pharmacotherapy of acid secretory disease may require regulation not only of parietal cell but of ECL-cell function.

INTRODUCTION

The possible relationship of the enterochromaffin-like (ECL) cells to gastric pathobiology has recently generated considerable interest since the recognition of a relationship between gastric carcinoidosis and hypochlorhydric states. It is probable that ECL cells play a major role in the regulation of parietal cell function, and it seems likely that ECL cells, in addition, exhibit a trophic regulatory function on the gastric mucosa.

Of particular interest is the observation that pharmacotherapeutic agents which

Abbreviations: CAG/A: chronic atrophic gastritis type A  EC: enterochromaffin (cells)  ECL: entero-
chromaffin-like (cells)  FGF: fibroblast growth factor  5-HT: 5-hydroxytryptamine  MEN-1: multiple
endocrine neoplasia type 1  PA: pernicious anemia  ZES: Zollinger-Ellison syndrome

Address reprint requests to: I.M. Modlin, M.D., Ph.D., Dept. of Surgery, Yale University School of
Medicine, 333 Cedar Street, New Haven, CT 06510

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are associated with profound and sustained acid inhibition may have a role in the generation of ECL-cell hyperplasia. This phenomenon has also been noted in human disease states in which a significant decrease in acid secretion is evident, namely, chronic atrophic gastritis type A (CAG/A), with or without pernicious anemia (PA). Of further significance is the observation that patients with gastrinomas and multiple endocrine neoplasia type 1 (MEN-1) also exhibit ECL-cell hyperplasia and neoplasia (gastric carcinoid or ECLoma) after the induction of profound and sustained inhibition of acid secretion with proton pump inhibitors. The likelihood of a genetic component in the genesis of human gastric neuroendocrine disease is therefore probable.

HISTORY

The first description of peptide hormone-producing endocrine cells in the gastric mucosa was in 1870, by Heidenheim, who described chromaffin cells in the dog gastric mucosa [1]. In 1907, Ciacco introduced the term “enterochromaffin” (EC) cells [2]. The endocrine nature of the EC cells, and their difference from adrenal chromaffin cells, was first recognized in 1914 by Masson, who utilized silver impregnation to demonstrate their argentaffin characteristics (capacity to generate and accumulate metallic silver precipitates by reducing silver nitrate solution). Erspamer and Asero, in 1952, identified 5-hydroxytryptamine (5-HT) as the endogenous substance in the argentaffin (chromaffin) cells which reduced silver and chromium [3].

Kull, in 1913, noted that the gastrointestinal tract contained cells with a morphology similar to that of chromaffin cells, which were unable to reduce silver nitrate (i.e., lacked argentaffinity). These cells were originally thought to be progenitors of the EC cells. Dawson, in 1948, was the first to develop a method of staining these gastric non-EC cells, utilizing a silver nitrate solution together with exogenous reducing agents. This technique stained EC cells and many other endocrine cells [4] and reflects the ability of secretory granules to accumulate and retain the resulting silver precipitates (argyrophilia).

In 1966, Hakanson and Owan identified cells in the rat oxyntic mucosa that were capable, like EC cells, of amine precursor uptake and decarboxylation [5]. In 1967, they further reported that these cells were identical to histamine-containing cells of the oxyntic mucosa [6,7] and introduced the term “enterochromaffin-like” (ECL) cell. Capella et al., in 1969, reserved the term “enterochromaffin-like” for a distinct oxyntic endocrine cell type identified by the characteristic electron microscopic appearance of its individual secretory granules [8].

MORPHOLOGY-BIOLOGY

Seven different endocrine cell types and their respective secretory products have been identified in the human stomach: the enterochromaffin (EC), somatostatin (D), P/D₁, A (fetus and newborn), X, gastrin (G), and ECL cells. Gastrin (G)-secreting cells are limited to antral mucosa, with the remainder predominantly distributed in the oxyntic mucosa [9]. In gastric biopsies from ten healthy volunteers (five males, five females), endocrine cells accounted for approximately 1.2 percent of the epithelial volume and 0.9 percent of the mucosal volume [10]. By electron microscopy criteria, ECL cells account for 30–35 percent of the endocrine cell mass of the oxyntic mucosa [10,11], a value which is substantially higher than that reported
TABLE 1
Relative Frequency of Different Endocrine Cells in Oxyntic Mucosa of Rat and Man

| Cell Type | Percentage of Total Endocrine Cell Mass |
|-----------|----------------------------------------|
| ECL cells | Rat 65 Man 35 Man* 30 |
| EC cells  | 0  25  7 |
| D cells   | 10  26  22 |
| P cells   | 24  |
| D1 cells  | 24b  14b  9 |
| X cells   | 0.6 |

*Morphometry performed by electron microscopy (others by light microscopy)
*Combined percentage of P + D1 + X

Data from [1,2,6]

utilizing light microscopy (4 percent) [12]. D'Adda and Bordi noted that P and D cells accounted for approximately 24 percent and 22–26 percent of the endocrine cells in the same region, respectively. There is some disagreement as to whether ECL cells represent the majority of the endocrine cell population of the fundus [13]. In the rat, endocrine cells represent ± 2 percent of the normal oxyntic mucosa [14], and ECL cells account for 65 percent of this population [15] (Table 1).

Identification and classification of the gastric neuroendocrine cells have been based largely on the different staining characteristics and the ultrastructural morphology of their secretory granules, as determined by electron microscopy [9]. ECL cells are argyrophilic, stain positively with Grimelius and Sevier-Munger techniques, but negatively with Hellerstrom-Hellman and Masson stains [9]. These cells lack demonstrable monoamines and therefore are non-argentaffin (with the exception of the cat and the rabbit [16]). At the light microscopic level, human ECL cells are small, irregularly shaped cells with pale cytoplasm and nuclei with fine nuclear membranes and chromatin [17]. Ultrastructurally, they exhibit either vesicular granules with an irregular argyrophilic core eccentrically located in a wide space, or a round, relatively compact (or coarsely granular) argyrophilic core surrounded by a membrane of wavy appearance and forming a thin clear space [9].

ECL cells are scattered in oxyntic glands, especially in the deep and intermediate regions. No ECL cells have been identified in the gastric pits or in the epithelium covering the luminal surface, and very few are present in the neck region. The cells lack contact with the lumen of the gland, thereby forming a "closed configuration," and thus do not appear to be influenced directly by luminal gastric secretions [9]. The possibility of dendritic protrusions accessing the luminal surface has not been excluded.

The exact function and precise peptide/amine content of the human ECL cells has not been completely determined. To date, a number of putative agents have been proposed to occur in human ECL cells. As in other mammals, histamine has been detected, but the number of histamine-storing granules in human ECL cells appears to be moderate or low [16], as evaluated by the relatively low histidine decarboxylase
activity identified [18]. The secretory granules of the ECL cell contain chromogranin A, which appears to be involved in the mechanism of amine storage and silver binding [19]. Human ECL cells, in addition, have been reported to exhibit immunoreactivity for both the alpha subunit of chorionic gonadotropin and calbindin [20,21]. Gastrin and somatostatin receptors have been identified on rodent (mastomys) ECL cells [22] and may therefore exist in the human ECL-cell system. Somatostatin receptors have been identified on the cells of human carcinoid samples [23].

A putative role for calcium in the secretory regulation and pathobiology of ECL cells has been proposed, but the details remain controversial. Calbindin, a 28 kDa calcium-binding protein, has been identified in ECL cells of lower mammalian species and in human ECL cells [23,24]; however, the function is unclear. Calbindin has been demonstrated in a number of neuroendocrine cells, including: parathyroid C cells, secretin- and enteroglucagon-containing cells, pancreatic glucagon/insulin/PP cells, adrenal medullary cells, and enteric neurons [23,25]. It seems likely that calbindin may be involved in mechanisms of calcium-mediated endocrine cell secretion or in intra- or extracellular calcium homeostasis [23].

Antral gastrin has been postulated to influence calcium metabolism [26,27] by release of gastrocalcin, a putative hypocalcemic peptide found in ECL cells of the gastric fundus [28]. Gastrocalcin secreted by ECL cells, under gastrin stimulation, may interact with calbindin in the gastric modulation of calcium homeostasis.

Overall, the ECL system requires to be better defined in terms of its cell biology and molecular physiology. It is quite likely that a number of significant regulatory peptides important in gastric secretion are present within this cell, and the elucidation of their function may be of critical concern in understanding mucosal biology. Of particular importance would be the identification of tropic regulatory peptides, particularly the trefoil group, since the relationship between endocrine regulation of mucosal growth and the development of neoplasia in a cell system of a different phenotype may be of considerable pertinence.

**ECL-CELL FUNCTION**

The previous concept of the regulation of acid secretion held that gastrin was a primary modulator of parietal cell function. In addition, histamine was hypothesized to play an important role in acid secretion, also via a direct effect on the parietal cell. The source of histamine was controversial. Initially, mast cells and, more recently, ECL cells were proposed as putative sources. The vagus was felt to modulate acid secretion via the effect of acetylcholine on the parietal cell. Receptors for all three chemical messengers had been identified on the parietal cell, and their presence was consistent with a triumvirate modulation of acid secretion. The dominant inhibitory effect of H$_{2}$-receptor blockade suggested that histamine was the prime modulator of acid secretion. More recently, the three-receptor model of acid secretion has been reevaluated, and the ECL cell has assumed a more dominant role. Current understanding would indicate that gastrin primarily drives the ECL cell to generate histamine, which is the dominant activator of parietal cell acid secretion (Fig. 1). This scenario is consistent with experimental observations that, in the isolated parietal cell system, gastrin alone is a poor stimulant of parietal cell function. Conversely, histamine alone is a powerful agonist of acid secretion, and the addition of gastrin results in only a mild augmentation of acid secretion. Similarly, states of hypergastrinemia result in substantial hyperplasia of ECL cells and augmented levels of
Histamine production. The role of the vagus and acetylcholine seems to be less substantial but of some importance. In essence, the ECL cell may be the major local regulator of parietal cell function and, in addition, subserve an as yet poorly identified role in the trophic regulation of gastric fundic cell lineage.

DEVELOPMENTAL AND AGE-RELATED CHANGES IN HUMAN ECL-CELL POPULATIONS

The origin of neuroendocrine cells and, in particular, ECL cells is still disputed—with endodermal or neuroectodermal origin debated. Endocrine cells first appear in fetal development in the ninth to tenth week. Enterochromaffin (EC) and somatostatin D cells mature first, and fundic ECL cells appear later, at approximately 14 weeks [9]. Few studies have addressed the question of ECL-cell changes with age/sex or during development. In general, neuroendocrine cells have been reported to decrease with advancing age [29], but Stachura et al. in 1987 noted that, in the rat, the number of ECL cells increased with age [30]. Human data indicates that ECL-cell density declines with age in males, whereas, in females, no significant difference in cell density between young and old was evident [31]. Older females exhibited a higher rate of asymptomatic gastritis with associated increased levels of
gastrin and ECL-cell number. This finding was interpreted as evidence of the trophic effect of gastrin on ECL cells [31,32].

The situation as regards the regulation of ECL-cell growth and proliferation is not definitely understood. Clearly the relationship of an endocrine cell system which changes with age is important in an organ where the genesis of neoplasia is not understood, and it appears related to alterations in acid secretion and mucosal turnover that occur with age. The specific local and distant regulatory factors of ECL-cell proliferation require identification.

**ECL PATHOBIOLOGY IN HUMAN DISEASE PROCESSES**

Although the cellular mechanism of ECL-cell function is poorly understood, its involvement in several pathophysiological states is evident. ECL-cell pathology has been reported in human diseases predominantly associated with trophic effects of hypergastrinemia. Such conditions may occur secondary to tumor (gastrinoma with or without MEN-1), or low acid secretory states (e.g., chronic atrophic gastritis type A), pernicious anemia, or peptic ulcer management associated with prolonged and profound acid inhibition by pharmacological or surgical interventions.

Gastric endocrine tumors (carcinoids) account for approximately 3 percent of all gastrointestinal carcinoids [33,34], but only 0.3 percent of all gastric neoplasms [35]. More recently, Solcia et al. reported that gastric carcinoids account for up to 30 percent of all carcinoids in the gastrointestinal tract and suggested that this fact may reflect the introduction of improved diagnostic techniques [36]. In the same series, 41 out of 46 endocrine growths were identified in the oxyntic mucosa. Most gastric argyrophilic carcinoids investigated ultrastructurally have proved to be ECL tumors or to contain a predominant ECL-cell component [37]. Pure or mixed “ECLomas” account for 63 to 84 percent of all gastric endocrine tumors found in CAG/A and gastrinoma with or without MEN-1 [36,38]. Rogers and Murphy, in 1979, reported that 7 percent of routinely diagnosed gastric malignancies, previously classified as adenocarcinoma, were carcinoids or mixed tumors [39].

The delineation of the precise morphology of neuroendocrine malignancies of the gastrointestinal tract is difficult. Light microscopy and immunocytochemistry provide a morphological description of a tumor, but fail to define either its lineage, biological behavior, or even the potential for alteration of phenotype. Considerable difficulty has been experienced in the identification of the change from hyperplasia to neoplasia. A number of different markers of both nuclear and cytoplasmic domains have been suggested as providing criteria for identification of the change to neoplasia; these are dealt with by Solcia et al. elsewhere in this symposium. A particular issue is the exact cell type involved and the issue of whether cell phenotype may change at a particular level of hyperplasia. Thus the identification of a neoplasm which has progressed from ECL-cell hyperplasia to either a pure ECLoma or to an ECLoma which exhibits EC cells is an important issue. In general, it is felt that ECLomas follow a benign course, whereas tumors which are mixed or contain EC cells behave in a far more malignant and unpredictable fashion.

**Peptic Ulcer Management and ECL-Cell Pathobiology**

Recent surveys have estimated the annual incidence of chronic duodenal and gastric ulceration to be ten to 20 per 1,000 adult population. A lifetime prevalence of chronic peptic ulcer disease approaches 10 percent of the population [40].
A significant number of patients may require prolonged and profound suppression of acid secretion, especially in the management of chronic peptic ulcers or reflux esophagitis. Maintenance therapy to prevent recurrence may extend over many years. Acid suppression may also be required in patients who have undergone vagotomy with or without resection of the gastrin-secreting antrum. In clinical experience, H₂-receptor blockers, vagotomy, and the use of omeprazole have been reported to result in acutely increased levels of circulating gastrin [41–44], but a consistent effect on ECL-cell hyperplasia was not demonstrated.

The potential risk of developing gastric carcinoid/carcinoma with prolonged pharmacologic suppression of acid secretion was initially raised in 1979 by Elder et al. [45]. Hawker, in 1980, also reported gastric carcinomas in patients receiving cimetidine for benign gastric ulcers, confirmed by negative endoscopic biopsies of the stomach [46]. In 1983, Colin-Jones et al. reported a surveillance study of 9,928 patients treated with cimetidine versus age- and sex-matched controls. In this study, gastric carcinoma was found in 74 cimetidine-treated patients versus eight in the control group; however, in the majority of the 74 in the treated group, the occurrence of gastric carcinoma could not be attributed to cimetidine therapy (23 carcinomas diagnosed before treatment; 29 had advanced malignant tumor with less than six months' treatment) [47]. A large study from Copenhagen, of 17,000 patients on cimetidine, demonstrated a tenfold increased risk of developing gastric cancer versus controls, but also noted that the risk declined with age in conjunction with the declining risk of other malignancies studied in this cohort [48]. The newer, more potent competitive H₂-receptor blockers, such as ranitidine and famotidine, and the H-K ATPase blocker, omeprazole, have not been utilized for a sufficient time in a clinical setting to draw any firm conclusions regarding their effect on the pathogenesis of gastric carcinoma/carcinoid.

Quantitative studies of patients on omeprazole (20 to 60 mg/day) for resistant peptic ulcer disease/reflux esophagitis for a period of up to three years have noted an increase in circulating gastrin levels (from 81.5 to 206 pg/ml in one study). No significant hyperplasia of gastric endocrine cells, especially ECL cells, was noted, however, nor was there evidence of dysplasia or neoplasia [49–51]. Solcia et al. reported mild hyperplasia in only 11 to 19 percent of patients on long-term omeprazole (mean period of treatment was 13 months). This result was attributed to associated atrophic gastritis present. The focal changes were unrelated to gastrin levels or length of omeprazole treatment [52]. Conversely, however, Bordi et al. have reported that, although the entire endocrine population of the oxyntic mucosa remains unchanged following omeprazole, the mean volume fraction of ECL cells was increased by 64 percent as compared with normal values. They also noted that the granule content in the ECL cells was lower than comparable normal values [53]. It is noteworthy that, in the large cohort studies on cimetidine, endocrine cell hyperplasia and carcinoids have not been documented.

While cautious evaluation continues in regard to the role of acid-suppressing agents in the biology of gastric adenocarcinoma, the evaluation of experimental data in animal studies has revealed an increased incidence of gastric carcinoids when treated with agents which both inhibit acid and are associated with hypergastrinemia. It appears that significant acid inhibition and prolonged periods of therapy seem necessary to generate such lesions [14,54–58]. An increased predilection in female
animals has been noted, suggesting either a hormonal or genetic influence on the evolution of ECL pathology.

The relationship between peptic ulcer disease and ECL-cell pathobiology is clearly an area of considerable importance. It is as yet not clear whether ECL-cell function is altered due to the peptic ulcer disease itself or, alternatively, reflects changes initiated by the use of acid inhibitory therapy. A study which addresses this question would provide important information. As the situation currently stands, the relationship of ECL-cell proliferation to peptic ulcer disease and its management needs to be monitored carefully on an ongoing basis.

Chronic Atrophic Gastritis and Pernicious Anemia

ECL-cell pathobiology in animal models has been well characterized [59] but has only been studied in detail in two human pathological conditions: gastrinoma (see below) and chronic atrophic gastritis type A (CAG/A). Both these conditions exhibit a diffuse qualitative and quantitative oxyntic argyrophilic cell hyperplasia.

CAG/A is characterized by chronic inflammation of the oxyntic mucosa, often autoimmune, resulting in progressive atrophy of oxyntic glands and achlorhydria. The antral mucosa is unaffected by the inflammatory changes, and gastrin G cells (with no negative feedback by acid, due to the achlorhydria) generate hypergastrinemia and secondary fundic mucosal ECL-cell hyperplasia. CAG/A is a common finding in autoimmune pernicious anemia, but may exist independently [60].

Bordi, Solcia et al. have described in detail the qualitative relationship between hypergastrinemia and oxyntic argyrophilic cell hyperplasia, detailing the histological pattern, and have proposed a classification for this hyperplasia [9,61,62]. In Western countries, post-atrophic gastritis carcinoid tumors may account for up to 43 percent of gastric carcinoids, of which 63 percent are usually associated with pernicious anemia [63]. Of interest is the observation that the prevalence of gastric carcinoids in pernicious anemia without CAG is 1.2–8 percent [64]. In a survey of 55 cases (from three studies) of CAG-related gastric carcinoids, all were found in the fundus, and qualitatively most constituted ECL cells [63]. Forty-two percent of these ECLomas were noted to be multiple, 18 percent exhibited hepatic metastases, but none were associated with the carcinoid syndrome. A primary observation of this study was the association of the gastric carcinoid lesions with massive hypergastrinemia of antral G-cell origin: 15 to 57 times the upper limit of normal [63]. The survey also noted that the age of patients with gastric carcinoids secondary to CAG appeared lower than the age of CAG patients with hyperplasia alone (no tumor) and that the gastrin levels were significantly higher in the tumor patients versus the hyperplasia group [63]. Some ECLomas have been reported to regress following antrectomy, with subsequent normalization of gastrin levels [65–68].

The mucosal histamine content in CAG has been found to be increased and significantly correlated to the number of argyrophilic ECL cells [69]. The functional significance of histamine associated with ECL-cell hyperplasia in humans is still unclear, but sustained local release of histamine may contribute to excessive acid hypersecretion associated with gastrinoma. Thus the likelihood of histamine playing a significant role in the evolution of the fundic hypersecretory state in patients with gastrinoma may reflect a local augmented release of histamine. In support of this hypothesis is the fact that significant ECL-cell hyperplasia has been noted in the fundic mucosa of patients with Zollinger-Ellison syndrome [70]. Of particular
relevance, however, is the recent observation that histamine itself may exert mitogenic effects. Further support of this observation in the stomach is born out by the inhibition of ECL-cell hyperplasia engendered by hypergastrinemia when the animals are exposed to a histamine 1 receptor blocker. It is therefore possible that histamine may function not only as a secretory agent in the fundic mucosa but also participate in a feedback inhibition loop within the ECL system responsible for trophic regulation.

Zollinger-Ellison Syndrome (Gastrinoma) and Multiple Endocrine Neoplasia

Zollinger-Ellison syndrome (ZES) provides a useful model to evaluate the effects of chronic hypergastrinemia on human oxyntic endocrine cells [70]. The association between ZES and hyperplasia of these cells was initially recognized by Bordi et al. in 1974 [70]. Morphometry of gastric endocrine cells in patients with ZES has revealed that the volume density of endocrine cells is approximately 3.2 percent of the mucosal epithelial component—a 168 percent increase over normal subjects. In the ZES group, ECL cells comprised greater than 50 percent of the entire endocrine cell mass. The mean volume fraction of the ECL cell in ZES was 65 percent—a 119 percent increase over normal controls [71]. The majority of patients with ZES have low-grade ECL-cell hyperplasia, whereas those with MEN-1 exhibit high-grade (linear-micronodular) hyperplasia or carcinoid tumors. Thus, 15 ZES patients—six of eight with MEN-1 compared with only four of nine without MEN-1—demonstrated high-grade hyperplasia "precarcinoid" [36,72].

Interest in MEN-1 relates to the underlying genetic predisposition of such individuals to develop endocrine tumors, including gastric carcinoid. The MEN-1 gene has been identified on chromosome 11, and it is probable that clinical MEN-1 results from two mutational events affecting the MEN-1 locus, with the gene for MEN-1 functioning as a growth suppressor in normal cells [73–75]. Two initiation models demonstrate that an inherited tumor results from the unmasking of a recessive gene at the disease locus [74]. The first mutation is carried in the germ line, while the second mutation serves to eliminate the remaining wild-type allele at this locus [74]. In MEN-1 patients with gastrinoma, it is possible that gastrin or some other trophic factors increase the mitotic rate of the ECL cell and thereby exponentially increase the probability of occurrence of the second mutational event. This hypothesis is consistent with the higher incidence of argyrophil cell hyperplasia elicited by hypergastrinemia in combined ZES/MEN-1 patients, compared to patients with ZES alone. Possible alternative trophic agents include fibroblast growth factor (FGF), which has been demonstrated in plasma of MEN-1 patients and shown to be mitogenic for parathyroid tissue [76,77]. A cooperative role between classic growth factors and gastrin may exist in the genesis of argyrophil cell lesions. Such an interaction may be responsible for tumor promotion. The role of FGF as a mitogen may be related to the positive association between gastric carcinoid and hyperparathyroidism (in the absence of ZES or MEN) [78–80]. The relationship between parathyroid hormone, ECL-cell function, and antral G cells requires further evaluation [20,81].

While modern therapeutic strategy in ZES is directed toward the eradication of the tumor process [82], only 60–80 percent of patients with duodenal wall gastrinomas and 15–20 percent of pancreatic gastrinomas may be viable surgical candidates [83]. Thus, in the majority, acid hypersecretion has been managed by either total
gastrectomy or potent anti-secretory agents. A concern of the latter therapy has been raised by the result of experimental animal studies, which have revealed major increases in plasma gastrin levels and gastric carcinoid formation [54,57,84,85]. Lehy et al. in 1989 demonstrated in a study of 22 ZES patients that 77 percent exhibited argyrophil cell hyperplasia (versus normal controls), regardless of the acid-suppressive agent used (ranitidine, omeprazole, SMS 201995, pirenzepine with or without ranitidine) [86]. This result was similar to that reported by Bradram and colleagues, who noted that 79 percent of ZES patients (15 of 19 cases) exhibited argyrophil hyperplasia independent of the type of treatment (omeprazole or ranitidine). These data were not compared with controls, and seven of the 19 cases demonstrating hyperplasia were untreated ZES patients [87]. Bradram et al. in this semiquantitative study demonstrated no significant difference in the degree of hyperplasia between ZES patients with or without acid suppression treatment (ranging between eight and 84 months) [87]. HELander, in a quantitative study of 14 ZES patients before and after 6–21 months of omeprazole treatment, confirmed this observation and reported no significant change in endocrine cell density over the time course of treatment (on successive biopsies) [88]. Lehy et al. noted a positive correlation between argyrophil cell density and duration of omeprazole treatment, but indicated that seven of ten patients showed no significant increase in cell density within the initial 18 months [86]. Both Bradram and Lehy reported a positive correlation between the degree of hyperplasia and the fasting gastrin level.

THE ROLE OF GASTRIN IN HUMAN ECL-CELL PATHO BIOLOGY

The role of gastrin in the pathogenesis of human gastric carcinoid formation has been studied both in a clinical setting and in experimental animal models. Studies have been based on two models: hypergastrinemia secondary to achlorhydria and hypergastrinemia secondary to gastrin-producing tumors. The former is associated in humans with CAG with or without PA, whereas, in animal models, the effect has been demonstrated using potent acid-suppressing agents, fundectomy, antral exclusion, or portal systemic shunting.

A number of investigators have demonstrated in humans that, in the hypochlorhydric/achlorhydric conditions found in CAG/PA, serum gastrin levels are elevated and correlate with endocrine cell (especially ECL-cell) hyperplasia and carcinoid formation. In animal models, sustained and potent acid suppression has generated a similar outcome. In several of these animal models, predominantly the rat, it has been shown that either withdrawal of the drug or antrectomy results in a normalization of hypergastrinemia and reversal of the hyperplastic/carcinoid state [56,65,89].

The second “model” which further defines the role of gastrin on the ECL-cell population is the ZES/MEN-1 patient group. The ECL-cell hyperplasia associated with ZES correlates with the serum gastrin level (see above), except in cases of ZES associated with MEN-1, where an additional genetic factor (agent) and not hypergastrinemia alone may interact in the generation of a severe hyperplasia/carcinoid state. This fact poses the question as to whether sustained hypergastrinemia alone is the risk factor in the development of gastric carcinoid tumors. Alternatively, associated chemical regulators, growth factors, or genetic events need to be identified in order to define the cellular mechanism of action by which the neoplastic process is initiated.

Gastrin has at least two major biological effects: stimulation of gastric acid
secretion and promotion of gastric mucosal growth— in particular, the promotion of self-replication of ECL cells [90–93]. The interaction between gastrin, ECL cells, histamine, and parietal cells has been studied in an attempt to delineate regulatory events in the histogenesis of the gastric mucosa. Two events appear of critical importance. First, the effect of gastrin on the ECL cell and parietal cell and, second, the influence of gastrin on the release of histamine. A trophic role for histamine in gastric mucosal histogenesis may also be a plausible alternative, since ECL cells in a number of species, including man, produce histamine, which has known mitogenic properties [16]. The direct action of gastrin on parietal cells, as an acid secretagogue, appears unlikely, and in numerous experimental preparations histamine is a more efficient acid secretagogue [94]. Sandvik et al. have reported that gastrin produces immediate and concentration-dependent histamine release in an isolated stomach preparation. They also noted that gastrin-induced histamine release is sufficient to explain the acid-stimulatory effect of gastrin [95,96]. Thus, the general trophic effect of gastrin on the gastric mucosa might either be direct or mediated via alternative agents (PYY, enteroglucagon, or histamine) released from ECL cells.

Crean et al., in 1969, demonstrated a specific and marked trophic effect of gastrin on parietal cells in the rat [97]; however, since gastrin, at least in the rat, exerts its effect by releasing histamine [96], maximal gastrin-stimulated acid secretion may not only reflect parietal cell mass, but also the histamine-releasing capacity of ECL cells. In this review, the effect of endogenous hypergastrinemia on ECL-cell density has been noted. Waldum et al. have extended these studies and reported that rats treated for 90 days with omeprazole with or without astemizole not only exhibit a serum gastrin increase, but also gastrin-stimulated histamine release. This histamine release correlates with the increase in ECL-cell density reported elsewhere [98].

*Mastomys natalensis*, an African rodent, is a useful model to study the role of chromosomal abnormalities in gastric carcinoid formation, since this animal spontaneously produces gastric carcinoids in 16–24 months but, unlike ZES with MEN in humans, does not naturally exhibit hypergastrinemia [99]. When hypergastrinemia is induced by achlorhydria secondary to irreversible H2 blockade, however, gastric carcinoids form in four to six months [58]. This species clearly provides evidence of a genetic factor facilitating the effects of hypergastrinemia.

Hypergastrinemia in non-antral atrophic gastritis was initially noted in 1970 by Yalow and Berson and related to achlorhydria [100]. Endocrine cell proliferation in the atrophic mucosa of such patients has been well described [62,63,101,102], with a correlation demonstrated between serum gastrin levels and gastric carcinoid formation in patients with CAG [101].

Atrophic gastritis has been noted in patients with peptic ulcer disease [101]. Solcia et al. have reported that, in 122 patients with peptic ulcer disease, none had gross hypergastrinemia, yet 19 percent of patients demonstrated ECL-cell hyperplasia (no dysplasia/neoplasia was evident) [103]. This finding may suggest that dysplastic or neoplastic lesions do not develop in areas of atrophic gastritis unless gross hypergastrinemia exists for a number of years, as in pernicious anemia [64]. In experimental reports, Solcia and Lundell both noted that antrectomy in patients with gastric carcinoids secondary to PA resulted in complete regression of tumor and normalization of serum gastrin levels [67,104]. This reversible process suggests that an irreversible initiation event (e.g., genetic damage) may not be involved.

Acid suppression using either H2-receptor blockers or proton pump inhibitors
causes a dose-dependent increase in gastrin levels in humans [104]. Omeprazole (40 mg/day) resulted in a rapid rise in serum gastrin from 81 pg/ml to 220 pg/ml in two to three months, with a constant level maintained over the next 37–56 months. A survey of 241 patients on omeprazole, with regular monitoring by endoscopic biopsies and serum gastrin levels, noted the following: antrectomy patients exhibited a low volume density of argyrophilic cells in the oxyntic mucosa, and the volume density in patients on 40 mg/day of omeprazole increased slightly (just reaching a level of significance) in the first year, less markedly in the subsequent three years. Large variations between individuals and even within the same individual also existed [105]. No severe hyperplasia was evident. A positive correlation between individual serum gastrin levels and ECL-cell volume densities was noted.

The failure to correlate severe hyperplasia in long-term omeprazole treatment with gastric carcinoids found in patients with CAG with or without PA, or carcinoids found in animal models may be explained in two ways. First, endocrine cell hyperplasia in humans progresses very slowly, as demonstrated by a serial gastric biopsy study by Roucayrol and Cattan. In patients with CAG, serum gastrin slowly increases over a mean period of five years [106]. Thus gastric carcinoids in PA may take up to ten years or more to develop. A second explanation for the discrepancy between omeprazole and CAG with PA patients and carcinoid outcome may reflect the different levels of gastrin in the two patient groups. The latter exhibit a much higher and more sustained level than that observed in those on omeprazole. This suggestion has been evaluated in studies of 24-hour intragastric acidity and plasma gastrin concentrations before and during treatment with ranitidine (2 × 150 mg/day) or omeprazole (20 mg/day) versus patients with PA. Median gastrin concentrations in PA patients were approximately tenfold greater than in either treatment group [107].

The current consensus is that high-dose therapy with omeprazole causes only moderate hyperplasia in man, and prolonged treatment has not been shown to increase further the gastrin level or to cause progression of the hyperplasia. Data from MEN-1 and PA patients reviewed in conjunction with animal studies indicate that a substantial level of hypergastrinemia, with or without possible genetic predisposition/initiation, may be a prominent mechanism in gastric carcinoid tumorigenesis.

While it is likely that gastrin is a primary player in the relationship between ECL-cell hyperplasia and neoplasia, it is probable that other agents are also involved. The gastric mucosa is a major source of trefoil peptides, which themselves are important regulators of cell proliferation. Similarly, histamine has been reported to exert mitogenic effects. Furthermore, the parietal cell itself is known to possess a number of agents with trophic activities, suggesting that a complex cascade involving gastrin and a number of other chemical messengers are components of the regulation of the ECL-cell cycle.

**PHARMACOTHERAPY AND ECLOMAS**

The pharmacotherapy of peptic ulcer disease and ZES has principally involved methods of controlling acid secretion. Although peptic ulcer disease was first described in the late eighteenth century, it was not until 1886 that hyperchlorhydria was offered as the cause of ulcers [108]. Early approaches to treatment included diet
modification and surgical intervention, such as gastric resection and truncal vagotomy.

The first pharmacological intervention involved the use of antacids to neutralize the acid. Subsequently, anticholinergics were utilized to inhibit acid production. In 1976, the introduction of the H₂ histamine receptor antagonist class of agents established a significant advance in the treatment of peptic ulcer disease, reflux esophagitis, and ZES. More potent and/or longer acting H₂-receptor antagonists can produce a profound and long-lasting suppression of intragastric acidity. The anti-secretory effect of drugs such as loxtidine, SK94482, and sulfotidine extend over an entire 24-hour dosing interval, unlike the short-term effects noted with more commonly used H₂ blockers (cimetidine, ranitidine, and nizatidine). This pattern is similar to that exhibited by omeprazole—a proton pump inhibitor. Both loxtidine and sulfotidine were withdrawn from clinical development subsequent to the development of gastric carcinoids during animal studies. To date in the U.S.A., omeprazole is licensed by the FDA for acute treatment of severe gastro-esophageal reflux disease unresponsive to antacids or H₂ antagonist therapy and long-term usage in erosive esophagitis and chronic treatment of ZES. The profound and sustained inhibition of acid secretion by omeprazole results in achlorhydria in over 90 percent of patients [109] and is associated with more rapid ulcer healing than ranitidine or famotidine [110]. Based on the efficacy of the class of agents (substituted benzimidazoles), further agents of their type have been designed (e.g., lansoprazole [111] and AG1749 [112]). Animal data demonstrating the correlation between lifelong hypergastrinemia (secondary to acid suppression) and gastric carcinoid formation has not been reconciled with the apparent lack of similar results in human studies [54,57,84,85,91]. Overall, animal data indicate that substantial and/or prolonged administration of any potent acid suppressor is associated with hypergastrinemia, and the evolution of a carcinogenic process. The major issue in humans is that studies utilizing such agents have not yet been evaluated over long time periods. It is possible that periods of 15 to 20 years of exposure (constant or intermittent) may be necessary for valid correlations to emerge.

Creutzfeldt and colleagues have proposed that, because of the critical importance of hypergastrinemia in the scheme for development of gastric mucosal neoplasia, monitoring of serum gastrin levels in patients undergoing long-term acid suppression, especially omeprazole, is advisable. In addition, gastric biopsies may also be necessary in the management of such patients. They further suggested that serum gastrin levels five times above the upper limit of normal may be an indication for reduction of the omeprazole dose. For the present, however, neither a critical gastrin concentration nor a maximum treatment period beyond two years has been established. Longer observation periods and larger patient numbers are necessary to define these limits [50].

The perspectives for new anti-secretory drugs with unique mechanisms of action are being identified at present. Garner has proposed the future use of short-acting or reversible H-K ATPase inhibitors as well as hybrid molecules comprising a gastrin antagonist linked to an unsurmountable H₂ antagonist [113,114]. Clearly the role of the ECL cell in the physiology of acid secretion and in the pathobiology of the gastric mucosa is only now becoming apparent. It is likely that the role of the gastric neuroendocrine system may achieve critical importance in the future management of gastric disease processes.
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