

## Pathobiology and Management of Hypergastrinemia and the Zollinger-Ellison Syndrome

BASIL I. HIRSCHOWITZ, M.D.

*Division of Gastroenterology, University of Alabama at Birmingham,  
Birmingham, Alabama*

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Gastrin is both stimulatory and trophic to the cells of the gastric fundus—parietal and peptic cells, and enterochromaffin-like (ECL) cells which are major intermediaries of the gastrin effect. Gastrin (from the antrum) and acid (from the fundus) represent the interactive positive and negative limbs of a feedback loop. The nature and extent of sub-loops, perhaps involving the vagus, acetylcholine, histamine, and other peptides and cell products are at present unclear or unknown.

Loss of either gastrin or acid has predictable consequences. Absent acid, as in pernicious anemia or as a result of omeprazole, leads to hypergastrinemia. In rats, such hypergastrinemia (gastrin > 1,000 pg/ml) causes fundic ECL hyperplasia and, eventually, carcinoids; in humans with pernicious anemia, hypergastrinemia causes ECL-cell hyperplasia, which may progress to carcinoids that are reversible upon withdrawal of gastrin, illustrated by three cases described here. Loss of gastrin by antrectomy for duodenal ulcer leads to fundic involution and marked reduction in basal acid output, maximal acid output, and fundic histamine. An uncontrolled excess of gastrin, as from a gastrinoma outside the negative feedback loop, causes acid and pepsin hypersecretion with upper GI mucosal damage, the Zollinger-Ellison syndrome. This paper summarizes the abnormal regulation of gastrin and the biology, natural history, diagnosis, and management of ZE syndrome by medical and surgical means.

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### INTRODUCTION

As with other hormones (e.g., ACTH, TSH), gastrin has two functions, stimulation and trophism (Fig. 1). Moreover, gastrin has multiple targets. The most evident target for these actions of gastrin is the parietal cell of the gastric fundus, the product of which, acid, completes the negative feedback loop by inhibiting the source of gastrin, the G cell. Trophism of parietal cells is presumably controlled by the same feedback mechanism, namely acid, even though stimulation and trophism may not result from the same cellular mechanisms. It is not clear whether parietal cell hyperplasia continues under the influence of hypergastrinemia while acid secretion is inhibited by proton pump inhibitors, i.e., whether the replication and function signals interact.

A second target of gastrin is the enterochromaffin-like (ECL)-cell population of the gastric fundus, a function brought to light by the recent finding that profound

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*Abbreviations:* APUD: amine precursor uptake and decarboxylation BAO: basal acid output DU: duodenal ulcer ECL: enterochromaffin-like GI: gastrointestinal MAO: monoamine oxidase MEN-I: multiple endocrine neoplasia syndrome PA: pernicious anemia PAO: peak acid output ZE: Zollinger-Ellison (syndrome)

Address reprint requests to: Basil I. Hirschowitz, M.D., Div. of Gastroenterology, University of Alabama at Birmingham, Birmingham, AL 35294

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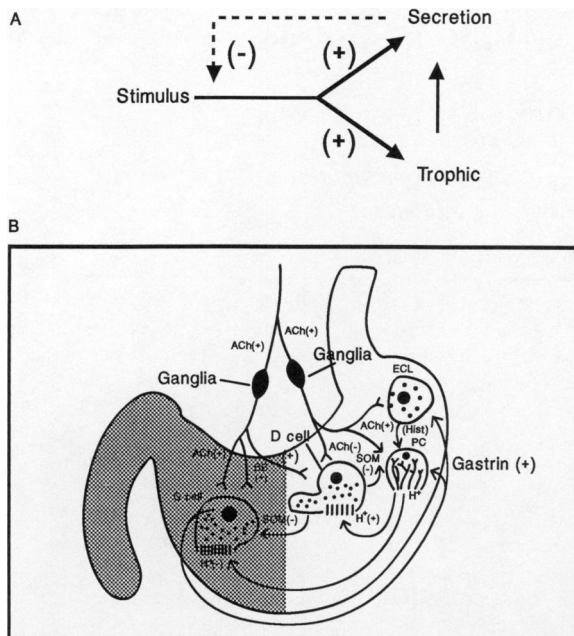


FIG. 1. **Top:** Simple feedback loop model incorporating a dual effect of a stimulus on the target cell population. For the stomach, the stimulus is gastrin, the target the parietal cell, and the feedback product acid. **Bottom:** Expanded stimulus and feedback loops for the stomach, to include the antrum (shaded area), the vagus, ECL cells, and D cells interacting with G cells and parietal cells. ACh: acetylcholine; BB: bombesin; ECL: enterochromaffin-like cell; Hist: histamine; PC: parietal cell; SOM: somatostatin; G cell: gastrin cell; H: hydrochloric acid; (-) = inhibition; (+) = stimulation.

acid suppression by the proton-pump inhibitor omeprazole or high-dose  $H_2$  antagonists [1] or near total fundectomy [2] in rats causes marked hypergastrinemia, leading to ECL-cell proliferation that eventually results in the development of ECL carcinoids. It is not yet clear whether ECL cells represent a separate target or an intermediate target—the pathway by which gastrin stimulates the parietal cell through the release of histamine [3,4]. In the latter case, the feedback loop model can be expanded (Fig. 1B); the eventual target product, acid, would serve as the single negative link for stimulation and trophism of both ECL and parietal cells. In addition to the gastric mucosa, gastrin is also trophic to the duodenal mucosa and the pancreas, all of which can be sustained in hypophysectomized rats by gastrin alone. It is not known what if any feedback products or loops are involved in these trophic functions of gastrin, but it is clear that neither duodenal mucosa nor the pancreas are subject to hyperplasia due to hypergastrinemia.

It is also not known whether there are any sub-loop direct feedbacks involved (e.g., between parietal cells and ECL cells), and whether other intermediaries such as somatostatin, or the vagus, should be included in a further expanded model of the feedback loop (Fig. 1B). It is, however, known from experimental and clinical data that interruption or overactivity of the loop at either end (acid or gastrin) has predictable consequences.

### ACID AND THE ANTRUM

Gastrin, the product of antral G cells (source product) reaches its targets via the circulation (i.e., hormonal), while the ultimate target product, acid, reaches the G cell via the gastric lumen. This simple two-product closed loop may be disrupted at either end. Thus, if acid is removed or diverted from the G cells, G cells will both multiply and secrete gastrin in an unregulated manner, with resulting hypergas-

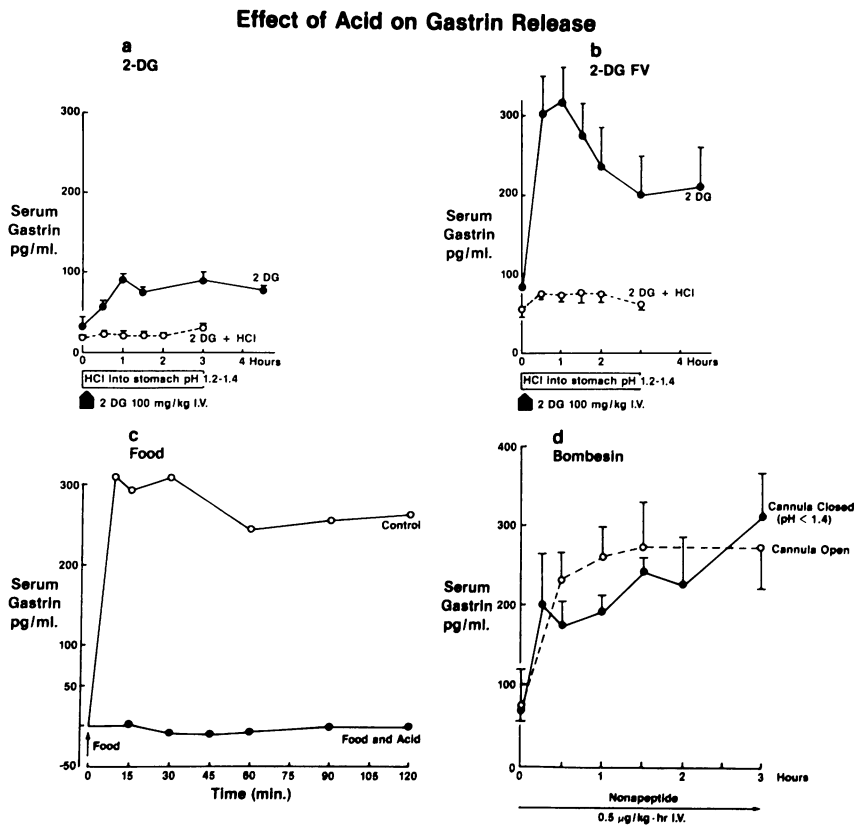


FIG. 2. Effects of antral acidification (HCl) on gastrin release stimulated via vagal activation by 2-DG (2-deoxy-d-glucose) in the intact stomach [panel (a)], or after fundic vagotomy (FV) [panel (b)]. In panel (c), the effect of food without and with acid instilled in the stomach, and in panel (d) the lack of effect of acid in the stomach on the stimulation of gastrin release by the bombesin nonapeptide analog given intravenously. All experiments performed in conscious gastric fistula dogs ( $n = 4$ , mean  $\pm$  SEM).

trinemia. Effective loss of acid results if parietal cells are lost (e.g., pernicious anemia) or are rendered incapable of secreting acid by powerful inhibitors such as omeprazole; the same outcome results if the antrum is removed from exposure to acid experimentally by transplantation to the colon or the duodenum with acid diversion [5,6]. In either case, the antrum still retains the essential mechanisms for responding to acid suppression.

Implicit in this model is that acid is both antisecretory and antitrophic for antral G cells, but neither of the mechanisms driving G-cell secretion and trophism nor those mediating the antisecretory effects of acid on gastrin release are known. Acid (pH < 2.0) inhibits gastrin release caused by food in the lumen, which is the major stimulus of the G cell, as well as that produced by strong vagal stimulation (by the compound 2-DG) in the dog (Fig. 2); however, gastrin release induced by the neurotransmitter bombesin is insensitive to acid (Fig. 2). By contrast, somatostatin inhibits bombesin- but not food-stimulated gastrin release [7], implying that there is more than one antisecretory mechanism for the G cell and making it unlikely that acid suppresses food-stimulated gastrin release via somatostatin from D cells. Since

the G cell has a microvillous border opening to the lumen [8], it is possible that both the stimulus (food, amines, peptides, and so on) and inhibitor (acid) act on this surface. The cellular transduction pathways for either food or acid acting on this cell surface membrane have not yet been described. Other negative feedback mechanisms whereby acid inhibits gastrin release apparently originate in the duodenum. Those would appear to be hormonal as well, since they reduce gastrin produced by a colon-transplanted antral pouch [6].

To find a role for the intimately and strategically located inhibitory antral D (somatostatin) cell, which is also an "open" type of cell with a luminal microvillous border as opposed to the closed D cells of the fundus [8], one could imagine the G cell to be constitutively active but restrained by the antral D cell. Inhibition of the D cell could then result in gastrin release, but, as argued above, acid does not seem to act via the D cell, since somatostatin does not inhibit food-stimulated gastrin release [7]. Since gastrin also stimulates the D cell, there may be a direct sub-loop by which local release of gastrin stimulates the D cell [9] and so additionally modulates gastrin secretion. The role of bombesin and acetylcholine, both stimuli of the D cell as well as the G cell (probably with different sensitivity) in regulating and modulating G-cell secretion and proliferation, remains incompletely understood [9].

### HYPERGASTRINEMIA AND THE FUNDUS

As displayed in Fig. 3, two principal gastric consequences arise from unregulated hypergastrinemia: (1) With an atrophic fundus as in pernicious anemia in which parietal cells are destroyed by an autoimmune process (Fig. 3a), ECL-cell hyperplasia results, in some patients progressing to ECL carcinoids. In this case, the hypergastrinemia is secondary to the loss of the normal acid feedback loop. (2) In the presence of a gastrinoma, with a normal stomach, hypersecretion of acid and hyperplasia of parietal cells define the Zollinger-Ellison syndrome (Fig. 3b).

#### *ECL-Carcinoid in Pernicious Anemia*

Serum gastrin levels in pernicious anemia commonly exceed 1,000 pg/ml. As in omeprazole-treated achlorhydric rats (Fig. 3a) with similarly high and unremitting serum gastrin [1], ECL hyperplasia is common in patients with pernicious anemia and about 5 percent develop multi-centric carcinoids [10]. Because a small proportion of these may metastasize [11,12], total gastrectomy is often advised [13]. Two reports [14,15] of regression of multi-centric carcinoids after removal of the gastrin source by antrectomy, however, led us to recommend the same operation in three similar patients [16]. All three patients (two males age 59 and 73 years and one female age 45 years) had serum gastrin levels of approximately 1,500 pg/ml and had been known to have carcinoids for six months to four years. Antrectomy was performed in each, and serum gastrin fell to the normal range with a half-life of 40–60 minutes. In all three patients, carcinoids regressed rapidly, disappearing in two at six weeks and in the third by four months. In all three, a micro-focus of carcinoid was found at 14–18 months post-antrectomy but not in later follow-up, up to 36 months after surgery. No ECL hyperplasia remained in any of the three patients.

These results strongly support the concept that ECL-cell hyperplasia and carcinoid are totally dependent on hypergastrinemia. This concept derived from the evidence of ECL hyperplasia in rats due to hypergastrinemia induced by different

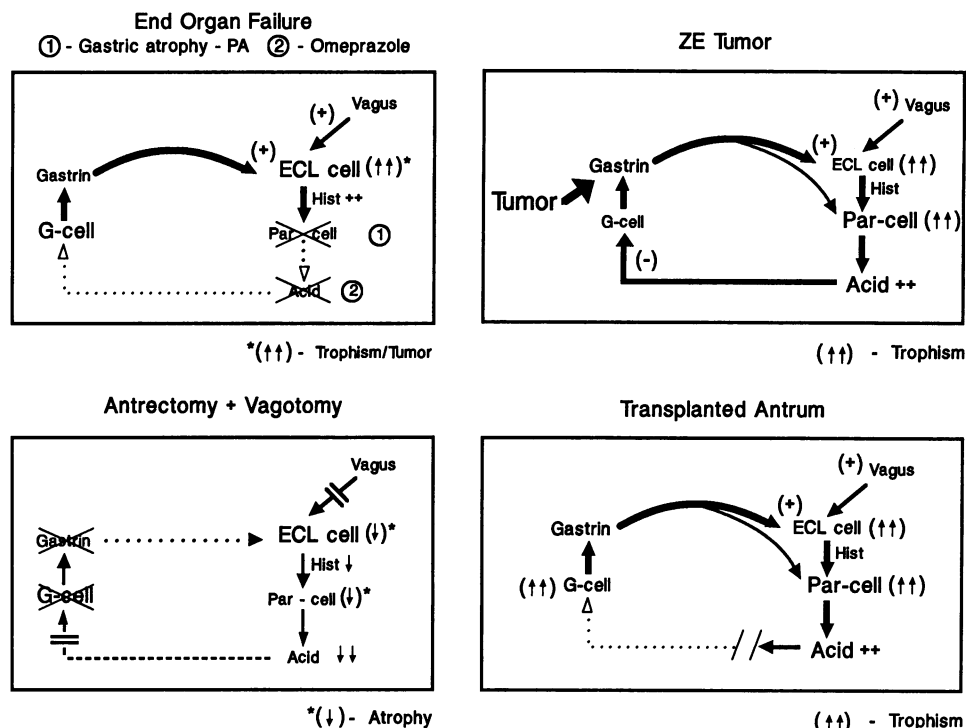


FIG. 3. Four clinical or experimental models demonstrating the consequences of removal or of excess of acid or gastrin on the stimulus targets ECL and parietal cells or the acid-feedback target, the G cells. A role for the vagus is illustrated in each case. **a.** Loss of acid secretion through inhibition by omeprazole (2) or the loss of parietal cells in pernicious anemia (PA) (1) leads to gastrin excess and ECL-cell hyperplasia or even carcinoid tumor. **b.** The effect of unregulated excess of gastrin from a gastrinoma (ZE) tumor on ECL and parietal cell number and function. The tumor is not subject to acid feedback. **c.** Antrectomy removes gastrin with consequent involution of the ECL and parietal cell targets. Vagotomy augments the effect. **d.** If the antrum is transplanted out of the acid feedback, e.g., to the colon in the dog [5,6], gastrin is secreted in an unregulated manner. Antral exclusion in man produces the same result. **Par:** parietal cell; **Hist:** histamine.

acid-suppressing drugs [1,17] or by fundectomy [2]. ECL hyperplasia and carcinoids were prevented by antrectomy [1] and were reversed upon removal of the stimulus, either by stopping omeprazole or by antrectomy after one year [1,18]. Surprisingly, unilateral vagotomy apparently blocks development of ECL-cell hyperplasia on the ipsilateral fundic half [17], suggesting a modulating or permissive role for either acetylcholine or other neurotransmitter of the vagus (Fig. 3).

#### *Zollinger-Ellison Syndrome*

The essential fact in Zollinger-Ellison (ZE) syndrome is that the hypergastrinemia due to gastrinoma is engrafted on to a normal gastrointestinal (GI) tract and that complete removal of the tumor allows the resumption of the normal state. Careful study of such reversal would allow us to understand the effects of constant hypergastrinemia on the otherwise normal stomach. Adequate inhibition of acid secretion by omeprazole first allowed us to understand what the acid and pepsin hypersecretion of ZE do to the GI tract. Complex duodenal ulcer, esophagitis, and diarrhea due to

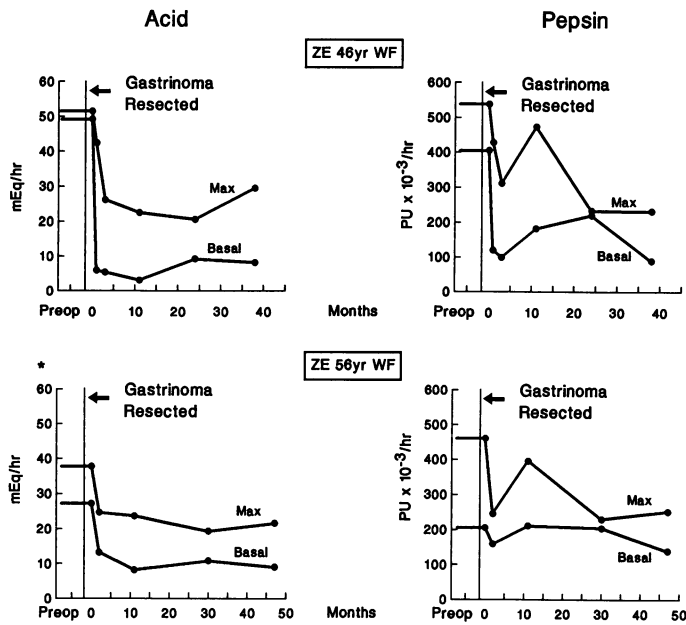


FIG. 4. Acid and pepsin output in two patients before and at intervals after resection of tumor and normalization of serum gastrin to levels below 60 pg/ml.

acid inactivation of pancreatic enzymes and damage to the jejunum are readily reversed by omeprazole, as discussed below. These consequences of excessive acid and pepsin secretion perhaps define more clearly the role of acid and pepsin in a GI tract that is not affected by the partly genetically determined duodenal ulcer disease syndrome. Since, in ZE, hyperplasia of the fundic mucosa is the result of the action of gastrin on previously normal mucosa, it might be expected that removal of the tumor would reverse the trophic effects of the hypergastrinemia. Gastric secretion was studied before and after removal of an apparently single functioning gastrinoma in two women aged 46 and 56 years with two and three years, respectively, of clinical symptoms (Fig. 4). Basal acid output (BAO) fell from 49 to 5.4 mEq/hour in one and from 27 to 8.2 mEq/hour in the other. Peak acid output (PAO) (representing parietal cell mass) [19] fell from 51.5 to 20.6 mEq/hour and from 37.8 to 19.3 mEq/hour, respectively (normal female BAO < 8 mEq/hour and PAO < 38 mEq/hour,  $n = 50$  [unpublished]). These figures suggest that parietal cell mass had been doubled in these two patients. Maximum pepsin outputs showed an equally sharp decline in both. It is not known whether maximum pepsin output reflects peptic cell populations, and limited data exist for peptic cell populations in either normals or in patients with ulcer or gastrinoma. Apoptotic cell death [20] would equally well explain the rapid reversal, upon withdrawal of gastrin, of parietal cell hyperplasia induced by the hypergastrinemia in the ZE patient, who is essentially normal without the gastrinoma. Similar rapid reversals occur after withdrawal of stimuli in experimentally induced hyperplasia in the adrenal cortex, liver, kidney, and pancreas of mammals [20].

It should be noted that an equally great fall (25–50 percent) occurs in PAO after vagotomy in patients with duodenal ulcer (DU) (Fig. 5), despite increased serum gastrin to between 100 and 200 pg/ml. It is not clear whether that represents loss of a separate trophic effect of the vagus or a necessary gastrin/vagal interaction.

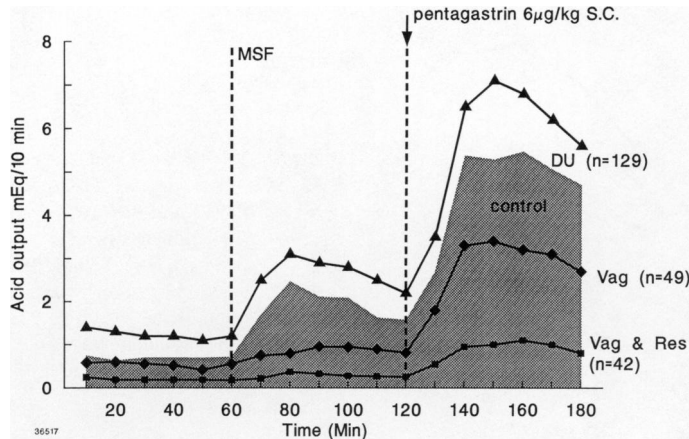


FIG. 5. Gastric acid secretion in the basal fasting state (0–60 minutes), after vagal stimulation (60–120 minutes) by modified sham feeding (MSF) for 15 minutes (60–75 minutes) and after pentagastrin injection (120–180 minutes) in 129 patients with duodenal ulcer (DU), normal controls ( $n = 39$ ), duodenal ulcer after vagotomy (Vag) without resection, or after vagotomy and antrectomy (Vag & Res).

Whether the ECL cells of the fundus represent a separate or an intermediate target for gastrin (Fig. 1) is not clear. In acid-secreting fundus, ECL hyperplasia due to hypergastrinemia also occurs—ECL-cell counts are increased by 100 to 200 percent in ZE [21]—but more advanced manifestations, i.e., ECL carcinoid, are rare and, when present, are almost exclusively seen in the multiple endocrine neoplasia (MEN-I) syndrome. When contrasted with the greater prevalence of advanced ECL hyperplasia and carcinoid in pernicious anemia (PA) or in achlorhydric rats, it is tempting to conclude that there might be a sub-loop feedback between parietal cells and ECL cells via acid or some other parietal cell product such as  $\text{HCO}_3^-$ , that is antitrophic. It is unlikely that a product of the ECL cells themselves, such as histamine, could be the feedback agent, since in the anacid mucosa of pernicious anemia, progressive ECL hyperplasia leading to carcinoid is more prominent than in the acid-secreting mucosa of ZE.

#### *Systemic Mastocytosis*

One interesting model that might shed light on other possible antral and fundic feedback loops is systemic mastocytosis, in which there is both an excess of histamine and basal acid hypersecretion, as well as elevated maximum acid output, i.e., an increased parietal cell mass. There should be suppression of antral G cells, serum gastrin, and fundic ECL cells.

#### REDUCED GASTRIN AND THE FUNDUS

One of the puzzling results of antrectomy in experimental animals or in DU has been the marked reduction in monoamine oxidase (MAO), which is much greater than that after vagotomy (Fig. 5). Combining both surgical procedures produces even more profound reduction in MAO (Fig. 5). Reduced MAO might result from reduction in the number of parietal cells but could result from reduction (involution)

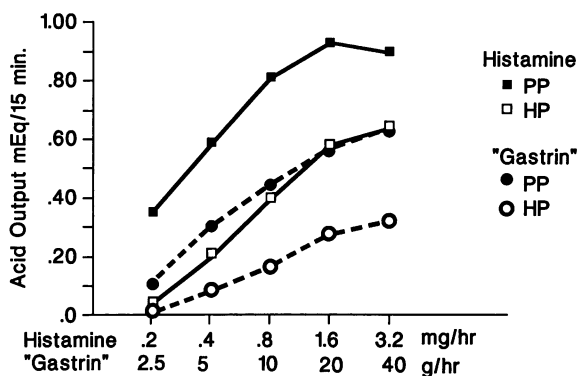


FIG. 6. Acid output stimulated by histamine or gastrin from innervated (PP) and denervated (HP) fundic gastric pouches in dogs after antrectomy. In each case, histamine elicited greater responses than gastrin, and the innervated pouches (PP) responded better than the denervated pouch (HP). From [22].

of the ECL-cell population (Fig. 3c) [18], through which gastrin may be acting [3,4]. In support of such a possibility, Fig. 6 shows a higher response to histamine than to gastrin in the antrectomized dog from both innervated and denervated fundic pouches [22]. Both responses are lower in the denervated (Heidenhain) pouch. The effect of antrectomy in reducing ECL-cell counts supports this concept [1,17]. Further recent evidence comes from quantitative studies of ECL number and function [18]. A role for the vagus in ECL hyperplasia has been suggested by the finding that unilateral vagotomy retards or prevents ECL hyperplasia in rats given large doses of omeprazole [17]. The implication is not only that ECL-cell hyperplasia is vagus-dependent, but that ECL function may also be vagus-dependent [17]. That hypothesis could explain why vagotomy of the fundus depresses the response to pentagastrin but not histamine [23]. Moreover, restoration of the effectiveness of pentagastrin after vagotomy by acetylcholine [23] clearly implicates a combined role for gastrin and acetylcholine in ECL function as well as in hyperplasia. Presumably by having a direct effect on the parietal cells, histamine bypasses this step.

#### CLINICAL IMPLICATIONS OF THE ZE SYNDROME

Though reported to be relatively uncommon—estimates of yearly incidence vary from 0.1 to 3 per million population [21]—the ZE syndrome is probably more common than generally realized because it is not routinely sought or tested for. ZE syndrome comprises two principal forms. A sporadic form, in which gastrinoma is the only tumor, accounts for 80 percent of cases. The remaining 20 percent of cases occur where gastrinoma is part of a (familial) multiple endocrine neoplasia syndrome (MEN-I) in which other endocrine adenomas, especially parathyroid, co-exist.

##### *Sporadic Gastrinomas*

The sporadic form of gastrinoma is due to a single adenoma in 20–50 percent of cases, and to more than one tumor in the rest. Gastrinomas occur in the gastrinoma triangle, an anatomic location bounded by the junction of the cystic and common ducts, the junction of the head and body of pancreas, and the junction of the second and third part of the duodenum [24]. Although traditionally thought to be a pancreatic tumor, as many as 30 percent of gastrinomas are located outside the pancreas, largely in the duodenal wall or peripancreatic lymph nodes, in which they may be primary rather than metastatic [21,24]. In a significant number of cases, perhaps up to 30 percent, no tumor can be found at surgery; however, more



meticulous surgery and experience have reduced this number to less than 10 percent [21]. Even so, the belief that ZE syndrome could result from islet cell hyperplasia (nesidioblastosis) is no longer valid. Rare cases of gastrinomas elsewhere, such as the ovary, have been reported. It is reported that one-third of gastrinomas have metastases at diagnosis [21], and earlier reports described an even higher prevalence of metastases. Metastases are usually described in localized lymph nodes (where they may be primary, since excision may eliminate the hypergastrinemia), or the liver, where they may stabilize (in one of my patients, multiple hepatic metastases have remained stable for 21 years). In rapidly spreading tumors, there is spread as well to bone [25] or skin. Rapid spread is invariably associated with fatal outcome in less than two years and is usually manifest early in the course of the disease. The significance of the spread to lymph nodes or even to liver is not quite clear because of the variable rate of progression. By contrast with the 34 percent of metastases found at initial surgery for ZE syndrome at the NIH [21], only five of 50 patients (10 percent) in our own institution have died of malignancy in a two- to 25-year follow-up.

Gastrinomas resemble carcinoids and are classified as APUDomas (amine precursor uptake and decarboxylation). The stem cell from which they derive is unknown. No gastrin cell is normally found in the pancreas. Gastrinomas have a heterogeneous morphology, and it is usually not possible to distinguish, histologically, malignant from non-malignant tumors. Many, if not most, gastrinomas also contain one or more other GI hormones, though those are seldom clinically significant. They include insulin, human pancreatic polypeptide, glucagon, somatostatin, neurotensin, ACTH, and gastrin-releasing peptide (bombesin), which can all be demonstrated immunocytochemically [26]. It is also possible to find gastrin associated with insulinomas, but without clinical ZE manifestations.

Gastrinomas contain various molecular forms of gastrin, predominantly G-17. Other products vary from big-big gastrin (larger than 34 amino acids) to G-34 [27], to fragments of gastrin and incompletely processed post-translational products such as glycine-extended gastrin [28]. In all likelihood, these products represent variable processing by the tumor cells. Blood concentrations of G-34 exceed those of G-17, even though the tumors contain less, because of a longer half-life of G-34. The ratio of G-34: G-17 has not been shown to have any clinical significance.

### *MEN-I*

About 20 percent of patients with ZE syndrome have familial MEN-I [21,29]. The associated endocrine tumors are parathyroid (80 percent), beta cell islet (insulin) (20 percent), and, less commonly, glucagonoma, VIPoma, and others (<5 percent) [26]. Pituitary adenomas occur in 50–60 percent and adrenal tumors in 27–36 percent, although many are non-functional. The most typical finding, related to hyperparathyroidism, is an elevated serum calcium, which may be independently symptomatic and commonly presents with renal stones. Removal of the parathyroid adenomas with normalization of serum calcium may lead to normalization of gastrin and resolution of the gastric hypersecretor status. Note that one of the provocative tests for gastrinoma employs calcium infusion [30].

### *Clinical Presentation*

The classical ZE syndrome presents most frequently with persistent, often multiple, symptomatic duodenal ulcers which may be complicated by bleeding, perforation, or fistula. Gastric ulcer is rare and was found in only 2 percent of our own series. Over 40 percent of cases are associated with esophagitis, and as many as one-third also have diarrhea; either may be the primary or sole presenting problem. Previously, when gastric surgery for ulcer was being performed more frequently, ZE patients often presented as cases of recurrent complicated marginal ulcers within weeks of gastrectomy. Today the widespread use of acid-suppressing medications frequently blunts the presenting features, and most ZE patients resemble ordinary duodenal ulcer (DU). Some may have rather more resistant or more rapidly recurring DU. The average duration of ulcer symptoms before diagnosis in the 165 patients studied at the NIH [21] was 6.4 years. This fact supports my contention that the syndrome is underdiagnosed because it is not being aggressively sought, even by gastroenterologists, with the result that only full-blown cases are being recognized.

Except for those with advanced metastatic disease, all the GI pathology and symptoms are due to acid and pepsin hypersecretion. These, in turn, are due to unregulated hypergastrinemia, which is secreted by the gastrinoma that is out of the acid-dependent feedback loop. Moreover, it seems reasonable to assume that acid stimulation of the duodenum acts as a continuing positive feedback by releasing more secretin from the duodenum. There does not seem to be a functional *negative* feedback from the acidified duodenum in ZE, such as there is in the dog with transplanted antrum [4]. After total gastrectomy or in ZE patients who are totally acid-suppressed, as well as in patients with pernicious anemia who have high gastrin and no acid, there are no symptoms attributable to hypergastrinemia. Therefore, the entire clinical syndrome results from gastric hypersecretion. This fact allows a highly rational approach to ZE syndrome. Adequate control of gastric secretion (to be defined below) will therefore eliminate the clinical syndrome; malignancy is a separate problem. Before appropriate drugs were available, total gastrectomy was the only certain way of achieving this goal [31,32]. With H<sub>2</sub> antagonists, the goal could be achieved in some but not in all, but with proton pump inhibitors (omeprazole, lansoprazole) this goal is now fully achievable. The clinical syndromes that demand treatment are:

*Esophageal* Fully 40 percent of ZE patients have significant esophagitis, some with stricture. While the duodenal component may be (partly) treatable by H<sub>2</sub> blockers, the esophagitis requires much more potent acid suppression. Therefore, in an unrecognized ZE under treatment for DU, esophagitis, which is harder to control, may progress due to undertreatment.

Peptic ulcer in ZE presents almost invariably (98 percent) as DU, frequently classical DU, but often with features of slow healing or rapid recurrence, especially after gastric surgery. Many present as cases of multiple ulcers, some more distal in the duodenum and complicated by bleeding in some. The picture may be confused by concomitant aspirin abuse, which may also cause treatment resistance, multiple ulcers, and rapid recurrence, as described above [33].

*Intestinal* Hypersecretion of acid results in a low pH for a variable distance down the jejunum, with injury to the jejunal mucosa, consequent diarrhea, and malabsorption which may be severe. Inactivation of pancreatic enzymes at low pH

contributes to diarrhea through maldigestion of food. Such patients may lose a great deal of weight.

Elimination of acid hypersecretion leads to cure of all three categories of upper GI pathology.

### *Natural History*

Survival has been studied by several centers, with an average reported survival of 62–75 percent at five years and 50 percent at ten years and for all cases. These findings have been broken down by Jensen and Gardner [21] in two alternative analyses. (a) For those operated on for tumor diagnosis and resection where possible: as expected, unresectable tumors had the worst prognosis, with an average 40 percent survival at five years; but with no tumor found or tumor resected there was 60–100 percent survival at ten years. (b) According to MEN-I status: for patients with MEN-I, there was 62–85 percent survival at ten years and for non-MEN patients 40–65 percent survival at ten years. Apart from malignancy and fatal metastatic disease (~10 percent of my patients), most ZE syndromes may kill the patient from complications of upper GI mucosal disease—bleeding or perforation, stricture of the esophagus, severe malnutrition. Patients with ZE syndrome are at great risk from the often misguided and inadequate surgical procedures undertaken without proper pre-operative diagnosis or preparation.

### *Diagnosis*

Every patient presenting with esophagitis, duodenal ulcer, or chronic diarrhea should have a fasting serum gastrin measured. The measurement should be made before beginning antisecretory treatment, but can be obtained after treatment has begun. If mildly elevated to between 100 and 150 pg/ml (normal <100 pg/ml), the test should be repeated after medication is withdrawn.

There are many causes for elevated gastrin [34]. The most common confounding cause is food in the stomach, whether from non-fasting or from gastric retention. Other causes particularly include hypochlorhydria or achlorhydria (e.g., pernicious anemia) in which serum gastrin may reach 6,000 pg/ml.

If, in the correct clinical setting, an elevated gastrin is found, a gastric analysis should be obtained. The usual finding is a basal (fasting) one-hour acid output (BAO) of  $\geq 15$  mEq/hour, though a number of unoperated ZE patients have lower values. After gastric surgery for ulcer disease,  $\text{BAO} \geq 5$  mEq/hour is supportive of the diagnosis. Even if a gastric analysis cannot be obtained, an untreated gastric content pH  $> 3.5$  rules out hypersecretion. It must be emphasized that any gastric acid studies must be performed after the patient is more than two days off  $\text{H}_2$  blockers and more than eight days off omeprazole.

When serum gastrin is  $> 250$  pg/ml and acid output is appropriate, no further tests need to be done. When gastrin levels are 100–250, and gastric acid output elevated, even if BAO is under 15 mEq/hour, a provocative test for gastrinoma is generally required. Two tests can be used—secretin or intravenous calcium provocation, and of these the secretin test is easier to perform, better standardized, and is generally preferred [30]. Duplicate fasting values are obtained before intravenous bolus injection of secretin, with measurement of gastrin at 2, 5, 10, 15, and 20 minutes. A rise of  $> 110$  pg/ml at two or five minutes was positive evidence of gastrinoma in 93 percent of ZE patients [30]. Jensen and Gardner [21] recommend a rise of  $\geq 200$

pg/ml to rule out false-positives. None of 72 duodenal ulcer patients in my laboratory, however, had a serum gastrin rise of  $> 100$  pg/ml. Therefore, we feel that a rise  $\geq 100$  pg/ml, especially when combined with typical gastric hypersecretion, would be adequate for the diagnosis of gastrinoma. A small number of patients with gastrinoma may have a normal basal serum gastrin, though these are also generally secretin-positive. Meal stimulation may increase serum gastrin significantly ( $> 100$  percent) in as many as 30 percent of ZE patients. Thus, the test is of little value in the differential diagnosis of antral G-cell hyperplasia and gastrinoma. The increased gastrin response to food in *H. pylori*-infected stomachs adds further confusion to the picture, but apparently *H. pylori* does not cause acid hypersecretion, since eradication leads to reduction of gastrin but no change in acid output. Acid secretion studies are essential to evaluate properly the significance of an elevated serum fasting gastrin.

Hypersecretion of acid  $\geq 15$  mEq/hour is considered the hallmark of ZE syndrome. In 100 patients with DU, and BAO  $> 15$  mEq/hour, whom we studied, however, 67 did not have evidence for gastrinoma. The greater majority of the non-ZE hypersecreting patients (95 percent) were men, and in those in whom a vagotomy was performed, BAO was reduced to  $< 3$  mEq/hour [35]. Three of the non-ZE hypersecretors had hyperhistaminemia (systemic mastocytosis in two and basophilic leukemia in one). All hypersecretors require continuous therapy, however, as do those whose hypersecretion is due to gastrinemia. The non-ZE hypersecretors are amenable to treatment by fundic vagotomy as an alternative to long-term acid-suppressing therapy [35], whereas vagotomy in ZE is only of modest benefit, and does not eliminate the need for continuous medical treatment.

### *Treatment*

Even though most ZE syndrome patients can be partly or even wholly controlled with  $H_2$  antagonists, many required large doses (up to 10–12 g of cimetidine/day and a four-hour dose schedule) or the addition of anticholinergics [21]. Generally it was considered adequate to reduce gastric acid to  $< 10$  mEq/hour before the next dose, but that level frequently failed to heal esophagitis when present and allowed very little therapeutic margin, with often severe symptomatic relapse occurring within one to two days of interruption of treatment. Because of the much greater efficacy of the proton pump inhibitors (e.g., omeprazole) and their longer duration of action, *it is no longer reasonable to use  $H_2$  antagonists in ZE syndrome. There is also no residual role in ZE for anticholinergics, sucralfate, prostaglandins, or somatostatin.* Though patients may use occasional doses of antacid, continued need for antacid signifies inadequate acid control.

Omeprazole binds irreversibly to the proton pump enzyme  $H^+ - K^+$  ATPase located on the apical (luminal) membrane of the parietal cell. Because this is the final step in acid secretion, omeprazole is highly effective and long-lasting; however, the optimum dose may vary widely from 20 to  $> 120$  mg/day and needs to be individualized. If the long-term management of a ZE patient is to be undertaken, facilities for measuring acid secretion are essential. The objective of acid control is to maintain acid output at  $< 5$  mEq/hour in the intact stomach and  $< 1$  mEq/hour post-gastrectomy in the hour before the next dose. Even more stringent control may be required for those with significant esophagitis. To achieve this goal, omeprazole is given at an initial dose of 60 mg each morning, with adjustments of dose down or up at intervals of one

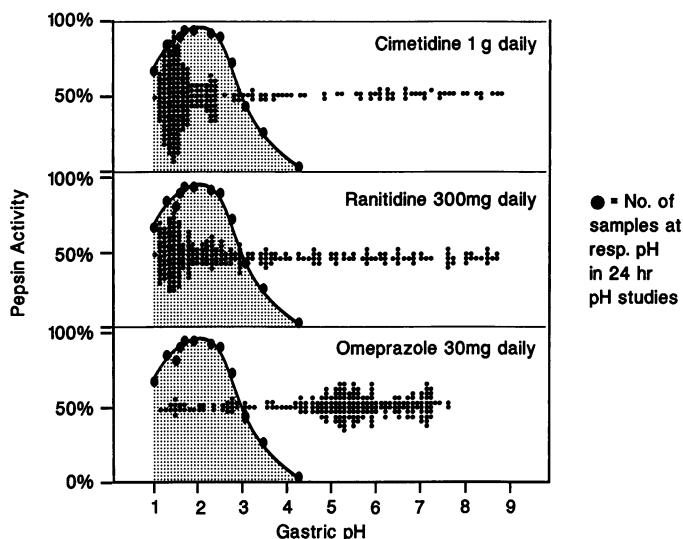


FIG. 7. Distribution of individual hourly gastric pH values in ten volunteers, each tested over 24 hours while being treated with cimetidine, ranitidine, and omeprazole (after Walt et al. [43]). The shaded area enclosed by the large circles connected by a solid line represents the pH profile of the proteolytic activity of pepsin (100 percent = maximum activity).

to two weeks. If the dose required is 80 mg/day, it should be split and given every 12 hours. In our patients, the median dose for men was 60 mg/day and women 40 mg/day for the above targets.

In general, a dose established by this means remains stable in the long term, but the patient should be retested three to six months after the first dose adjustment has been completed. If the patient is still stable, the next test should be done at 12 months, and then at yearly intervals. It is likely that lesser doses might be effective in maintaining remission after initial healing, but that possibility has not yet been established. Endoscopy should be performed as indicated for the presenting lesions in order to be sure that ulcers or esophagitis are healed. Beyond that, the lack of symptoms, the resolution of diarrhea, and gain in weight can be expected in patients with secretion adequately controlled. Any anemia should resolve spontaneously. In those who have bled, aspirin should be avoided entirely.

Esophagitis is common in ZE, being present in over 40 percent of cases, and requires even more stringent reduction of acid than does the duodenal ulcer. Thus, omeprazole has been found to be superior to  $H_2$  antagonists in esophagitis. Since pepsin may play an unrecognized but probably dominant role in esophagitis [36], the ability of omeprazole but not  $H_2$  antagonists to elevate gastric juice pH for most of the 24-hour day to levels outside the optimal proteolytic range of pepsin (Fig. 7) provides the necessary environment for healing.

Esophageal strictures should be dilated, cautiously at first while the mucosa is inflamed, and progressively as healing is complete, to a final diameter of 20 mm. Mucosal healing may require suppression of BAO to  $< 1$  mEq/hour. After complete resolution of the esophagitis, it may be possible to reduce the dose of omeprazole to allow BAO to drift up to 2–5 mEq/hour.

### *Side Effects*

Long-term treatment of patients with omeprazole [21,34] for up to eight years has so far led to no known side effects attributable to the drug, including those seen in female rats made achlorhydric by omeprazole [1]. Mice and other species that do not develop such high gastrin levels with achlorhydria do not develop tumors under similar circumstances [1,34]. Gastrinoma patients have increased numbers of ECL cells in the gastric mucosa, as do patients with elevated gastrins due to pernicious anemia [34]. The incidence of carcinoids in ZE syndrome is very low, however, and probably confined to those with MEN-I [37], whose primary tumors are in fact also carcinoids. There are no data to implicate omeprazole in the promotion of ECL-cell hyperplasia or carcinoids in man.

It is still important before the issue is considered closed to follow, carefully, medically treated ZE cases for the development of gastric carcinoids; however, no cases were found in one prospective study over four years [38]. Annual endoscopy is recommended for this purpose as well as to rule out acid/peptic mucosal damage.

### *Special Situations*

Where patients cannot take oral medications, e.g., after abdominal or other surgery requiring nothing-by-mouth status, or if comatose, vomiting, and the like, omeprazole cannot be given via the nasogastric tube because the granules dissolve at neutral pH (in the suspending solution) and the drug is then destroyed by acid in the stomach. In these cases, intravenous  $H_2$  antagonists in adequate doses need to be given to control secretion (intravenous omeprazole is not yet available). Testing for adequate control is mandatory; one of our patients who was placed on a respirator for an unrelated acute illness at another institution died of a perforated DU within days of admission because of failure to control acid secretion.

### *Surgical Management*

Surgical management of ZE syndrome is of two kinds: (a) for control of secretion [39] or treatment of ulcer complications and (b) for tumor removal [40,41]. In no instance should surgery be undertaken, except for emergencies, until the ulcer syndrome has been brought under control medically and the patient recovered for a period of two to three months.

*For Ulcer Manifestations* There is no indication at present for a primary operation to control acid secretion—neither vagotomy [39] nor total gastrectomy, which before  $H_2$  antagonists was sometimes the only method available for effective control of acid secretion. Total gastrectomy can only be considered for those who cannot or will not take omeprazole [32,37]. It is clear that any lesser resection is an invitation to disaster, and no elective ulcer or esophagitis surgery should be undertaken without absolute knowledge of gastrinoma status. Any patient undergoing emergency surgery for perforation or bleeding duodenal ulcer should be studied at the earliest opportunity using the aspirate for (titrated) acid output (not pH alone) per unit time and for serum gastrin, the level of which is valid even if intravenous  $H_2$  antagonists are being given post-operatively. Repair of gastrocolic fistulas in ZE patients should not be undertaken until the secretion has been controlled and nutrition improved.

*Tumor Control* MEN-I In patients with hypercalcemia and ZE syndrome,

parathyroidectomy is indicated and may reduce the level of gastrin and of acid output in most [40]. Gastrinomas, seldom if ever malignant in this syndrome, however, are usually multiple, and are not amenable to attempted curative resection. Subtotal pancreatectomy or Whipple's procedure is never curative and is clearly contraindicated. It is not reported that any resection of gastrinoma leads to reduction in clinical status of other co-existing over-acting endocrine tumors.

*Primary Gastrinoma Resection* In sporadic ZE syndrome (not MEN-I), the optimal treatment would be excision of the responsible tumor. Even under ideal circumstances, this approach is only completely successful in restoring normal secretion in 20 percent of cases. Long-term follow-up of such cases is important because of recurrence or persistence of hypersecretion requiring medication in as many as two-thirds of the cases [41]. As mentioned above, MEN-I patients, who comprise about 20 percent of all ZE syndrome patients, are not amenable to surgical treatment except for parathyroidectomy when indicated [40]. Of the remaining 80 percent, more than one-third already have metastases at presentation and are also not amenable to curative resection [21], leaving a little over 55 percent, of whom 30 percent have no identifiable tumor found at surgery.

Pre-operative diagnostic workup should include ultrasound, abdominal CT scan, and pancreatic and hepatic angiography. Other techniques include selective portal venous sampling, which, though providing an improved yield, carries significant risks and should be practiced only in highly specialized centers [42]. Magnetic resonance imaging has yet to be shown to be useful. Theoretically, scanning for uptake of radiolabeled gastrin antibody or stable somatostatin analogs might localize tumors, but this approach has not so far been adequately studied. Multiple intra- or extra-hepatic metastases are a contraindication to surgery. Ideally, if a single tumor can be identified and removed, the chance of cure is good. Recently it has been recognized that gastrinomas are frequently extrapancreatic, commonly in the duodenal wall and peripancreatic and periduodenal nodes. Special attention to these areas, including transillumination of the duodenum at surgery, allows identification of some tumors, and increases the yield [21,41]. Endoscopic-associated ultrasound may prove to be quite useful in the detection of tumors in the duodenal wall and in periduodenal and peripancreatic nodes.

It is my practice at present to recommend surgery only for those patients in whom a solitary gastrinoma has been demonstrated by computed tomography or angiography. It is not clear whether the aggressive search for a resectable tumor results in an eventual reduction in death from metastasis, since it is not even determinable histologically whether a particular tumor is malignant. Partial pancreatectomy and Whipple's operation are not recommended, even for unresectable gastrinoma in the pancreas. One should separate the objective of curing the functional disorder (hypergastrinemia) from the malignant metastasis prevention. It is apparent that successful surgery would be a therapeutic convenience, freeing the patient from the need for medication, but the equal goal can be readily accomplished by adequate doses of omeprazole. Successful intervention for prevention of potentially fatal metastatic disease has yet to be shown to be achieved by this approach.

### *Metastatic Gastrinoma*

No chemotherapy is indicated in patients who have metastases only to regional lymph nodes. Moreover, chemotherapy has been almost universally ineffective in

curing the tumor, controlling the clinical syndrome, or even substantially retarding the growth of established metastases [21]. At the same time, cases have been reported of long-standing stable hepatic or lymph node metastases without therapeutic intervention.

## CONCLUSION

In conclusion, this review first deals with the feedback loop between gastrin and the acid-secreting parietal cell. The ECL cell of the fundus is an additional target of gastrin. Loss or over-production of gastrin on the one hand or of acid secretion on the other has predictable consequences, and each of these is illustrated in appropriate clinical models. These models include gastrinoma with unregulated gastrin over-production and consequent hypersecretion and hyperplasia of parietal cells. Loss of acid, as in pernicious anemia, promotes gastrin cell hyperplasia, and hypergastrinemia, which leads to ECL hyperplasia and eventually carcinoids. This effect is reversible upon removal of the gastrin.

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