Hyperplastic Proliferations of the ECL Cells

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Enterochromaffin-like (ECL) cells are the dominant endocrine cell type in the oxytic mucosa. Normally regarded as histamine-producing cells, they are exquisitely sensitive to the trophic action of gastrin and undergo a hyperplastic increase in a variety of hypergastrinemic conditions.

A hyperplasia-neoplasia sequence of ECL-cell proliferations has been recently proposed, following the realization that increasingly severe degrees of ECL-cell hyperplasias over a period of several years can progress to ECL-cell carcinoids. Such carcinoids arising in patients with chronic hypergastrinemia differ both in their clinical and pathologic profiles from the sporadic carcinoids that occur in normogastrimic individuals and, therefore, need to be distinguished from them. This distinction is particularly important for their clinical management, since antrectomy appears to be of benefit in ECL carcinoids of hypergastrinemic patients.

INTRODUCTION

As part of the overall structural and functional organization of the gastrointestinal mucosa, the oxytic (acid-producing) portion of the human gastric mucosa is generously endowed with endocrine cells. Ultrastructural studies have identified at least six distinct cell types in this endocrine cell population: the enterochromaffin (EC) cells, the enterochromaffin-like (ECL) cells, the D cells, the D1 cells, the P, and the X cells.

Located chiefly in the middle and lower third of the mucosal thickness, the vast majority of these cells are randomly interspersed between the parietal and chief cells lining the oxytic glands. While occasional endocrine cells can also be identified between mucus neck cells in the superficial third of the mucosa, rare stray endocrine cells may, in addition, be seen associated with nerve fibers and Schwann cells (neuroendocrine complexes) in the lamina propria [1,2]. Even though these various cell types have a random spatial distribution, it is of interest that the ECL cells are preferentially located adjacent to the chief cells [3,4], and that their cell density within the mucosa normally shows little, if any, regional variation. Some workers have, however, observed the D and ECL cells to show significant age- and gender-related variations in their total numbers [5].

These cells show immunoreactivity for such markers of neuroendocrine differentiation as chromogranin A, neuron-specific enolase, synaptophysin, pancreostatin, and the like. Histochemically, while these cells are argyrophil in nature, not all of them can be simultaneously identified by any one argyrophil stain. Thus the

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Abbreviations:
EC: enterochromaffin (cells)  ECL: enterochromaffin-like (cells)  H&E: hematoxylin and eosin (stains)  HCG: human chorionic gonadotropin  MEN-1: multiple endocrine neoplasia type I  ZE: Zollinger-Ellison (syndrome)

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Grimelius stain identifies all oxyntic endocrine cells except the D cells that show argyrophilia only with the Hellerstrom-Hellman technique. The Sevier-Munger technique for argyrophilia, on the other hand, selectively stains the ECL cells and a small subset of the EC and D₁ cells. Since, however, the relative proportion of the EC and D₁ cells stained by this technique is negligible, the Sevier-Munger stain is currently relied upon for visualization of ECL cells in formalin-fixed, paraffin-embedded tissues processed for light microscopy.

Although immunohistochemical techniques using antibodies against secretory products of endocrine cells have now supplanted the histochemical stains for their specific identification, this technique is applicable only when the secretory product of a particular cell type is known and present in detectable quantities. Since histamine is either leached out, destroyed, or otherwise rendered non-immunoreactive after formalin fixation and paraffin embedding, immunohistochemical visualization of ECL cells requires special procedural modifications (freeze-drying, vapor-fixation, and cryostat sectioning). This necessity has severely impaired our ability to study the human ECL cells in routinely processed surgical pathology material, and our current knowledge of these cells is therefore based on a composite derived from their histochemical, immunohistochemical, and ultrastructural characteristics. Table 1 summarizes the relative numbers, secretory products (when known), histochemical, immunohistochemical, and ultrastructural characteristics of various endocrine cells in the human oxyntic mucosa.

Interest in the pathology of oxyntic endocrine cells was serendipitously sparked when tumors were seen to develop in the oxyntic mucosa of rats, following the long-term administration of high doses of potent anti-secretory agents [6-10]. Originally regarded as adenocarcinomas, these tumors were reclassified as ECL-cell carcinoids when Sevier-Munger stains showed the tumor cells to be argyrophil. Such studies further showed that these ECL-cell carcinoids were accompanied by a concomitant hyperplasia of ECL cells in the adjacent non-tumorous oxyntic mucosa [6,7,8,11]. Subsequent workers paved the way for the gradual acceptance of the idea that not only were these ECL-cell carcinoids derived from the ECL-cell hyperplasia diffusely present in the oxyntic mucosa of these rats, but also that the histogenesis of both the hyperplastic and neoplastic ECL-cell proliferations was related to the chronic hypergastrinemia, induced by the prolonged suppression of acid secretion in these animals (Fig. 1).

Following the accurate categorization of these tumors and the elucidation of the role of chronic hypergastrinemia in the pathogenesis of ECL-cell proliferations in the rat model, attention swiftly shifted toward a systematic study of the human ECL cells in order to determine if similar lesions might also develop in patients on long-term anti-secretory therapy. This attention represented a very genuine and pertinent concern, since these pharmacologic agents are being increasingly prescribed not only for the treatment and long-term management of duodenal ulcer disease, gastroesophageal reflux disease, and the Zollinger-Ellison (ZE) syndrome but are also being recommended as adjuvant treatment for the eradication of *H. pylori* infection [12,13]. So much scientific attention and inquiry is currently focused on ECL cells and their proliferative lesions that these cells are now the most extensively studied endocrine cell type in the oxyntic mucosa.
| Cell Type | Relative % | Secretory Product | CG Stain | Grimelius Stain | S-M Stain | H-H Stain | M-F Stain | Ultrastructural Characteristics |
|-----------|------------|-------------------|----------|-----------------|-----------|-----------|-----------|---------------------------------|
| ECL       | 30-50      | Histamine         | +        | +               | +         | -         | -         | Round to elongated granules, up to 300 nm in diameter; moderately electron-dense cores with wide halo |
|           |            | Calbindin         |          |                 |           |           |           |                                  |
|           |            | Gastrocalcin      |          |                 |           |           |           |                                  |
|           |            | ?α-HCG            |          |                 |           |           |           |                                  |
| D         | 10-20      | Somatostatin      | +        | -               | -         | +         | -         | Variably sized round granules (250-400 nm in diameter), with weakly to moderately dense cores and tightly bound limiting membrane |
| EC        | 5-15       | Serotonin         | +        | +               | ±         | -         | +         | Small- to medium-sized oval granules (200-300 nm in diameter), with variable electron-dense cores |
| D₁        | 5-10       | Unknown           | +        | +               | ±         | -         | -         | Small, round, pleomorphic granules (140-200 nm in diameter), with highly electron-dense cores and a thin halo; may represent a consortium of several different cells yet to be categorized |
| P         | 5-10       | Bombesin?         | +        | (+)              | -         | -         | -         | Very small, round granules (90-150 nm in diameter), with electron-dense cores and thin peripheral halo; closely similar to those of D₁ cells |
| X         | 1-5        | Unknown           | +        | +               | -         | -         | -         | Medium-sized granules up to 250 nm in diameter, with moderately dense cores |

CG = chromogranins; S-M = Sevier-Munger stain for argyrophilia; H-H = Hellerstrom-Hellman stain for argyrophilia; M-F = Masson-Fontana stain for argentaffinity; + = positive; (+) = weakly positive; – = negative; ± = few cells positive.
Long-Term Administration of Gastric Anti-secretory Agents (Ranitidine, Cimetidine, Omeprazole, etc.) to Rats

Prolonged Hypo-/Achlorhydria

Secondary Induction of Chronic Hypergastrinemia

Hyperplastic Proliferation of ECL Cells in Oxyntic Mucosa

Progression to ECL-Cell Carcinoids

FIG. 1. Sequence of events in the induction of ECL-cell carcinoids in rats following lifelong administration of anti-secretory agents.

ENTEROCHROMAFFIN-LIKE (ECL) CELLS

In humans and all vertebrate species studied so far, the ECL cells are normally confined to the oxyntic mucosa of the stomach, where they constitute its predominant endocrine cell type [11,14]. Scattered randomly in the lower and intermediate third of the mucosal glands, these cells are preferentially associated with chief cells. In each of the species studied, ECL cells have been shown to produce histamine [15]. In man and in several other mammalian species, the ECL cells have also been claimed to produce calbindin, a 28 kDa calcium-binding protein; gastrocalcin, a hormone that lowers blood calcium; and the alpha subunit of human chorionic gonadotropin (HCG) [16,17,18]. At the tissue level, ECL cells in humans are essentially identified by their topographic distribution in the oxyntic mucosa, their ability to stain with the Sevier-Munger technique for argyrophilia, and the ultrastructural features of their secretory granules. One of the most significant biologic characteristics of the ECL cells is their exquisite sensitivity to the trophic influence of gastrin. These cells, therefore, frequently undergo hyperplasia in chronically hypergastrinemic states.

ECL-CELL HYPERPLASIA

Hyperplasia denotes a non-neoplastic (non-autonomous) proliferation of a given cell type and implies an increase in its total cell mass. It is a morphologic phenomenon and requires morphologic criteria for its recognition and documentation. In the context of gastrointestinal endocrine cells in general and ECL cells in particular, hyperplasia is currently defined as the presence of increased numbers (beyond twice the standard deviation in age- and gender-matched controls) of cells per unit area of mucosa [19].

PROBLEMS RELATED TO THE STUDY OF ECL-CELL HYPERPLASIA

In sharp contrast to other gastrointestinal endocrine cell types, ECL-cell hyperplasias have traditionally been difficult to recognize clinically because they lack corre-
tion with a specific clinical syndrome or biochemical abnormality attributable to their hyperfunction. Even though we now know that such hyperplasias are commonly associated with certain clinical conditions, they are hard to detect, since they do not produce any distinctive, endoscopically recognizable lesions that can be biopsied. Histologically, too, they can be easily missed on routine hematoxylin and eosin (H&E) stains unless they are specifically sought for by special histochemical and immunohistochemical stains. In certain conditions (e.g., chronic atrophic gastritis, pernicious anemia, and so on) associated with such hyperplasias, the involved gastric mucosa is significantly atrophied, and it is difficult to establish if the observed increase represents a genuine hyperplasia or a mere overcrowding related to decreased mucosal volume. Similarly, in conditions such as the Zollinger-Ellison syndrome, its presence may be masked by the generalized oxyntic mucosal hypertrophy. Confusion related to documentation of endocrine cell hyperplasia has also resulted from differences in the morphometric methodologies and the frames of reference employed by earlier workers. Thus some workers have counted individual cells, while others have used computerized point-counting techniques, and still others have quantitated the hyperplastic population by measuring absorbance of light and the fractional surface area of the tissue section in which such absorbance occurs [20,21]. Results, too, have been expressed in such variable terms as absolute cell counts per mm² of mucosa, cells per unit length of mucosa, high-power field, gland, or crypt as the frames of reference [20].

MECHANISMS OF ECL-CELL HYPERPLASIA

Hyperplasias of ECL cells could theoretically result from a number of different mechanisms, such as prolongation of their half-life, differentiation of a larger fraction of pluripotent stem cells into ECL cells, or the augmented self-replication of functionally mature ECL cells. Since these mechanisms are not mutually exclusive, ECL-cell hyperplasias could result from a combination of these mechanisms. Each such mechanism could be triggered by a release from the normal restraining influence of an inhibitor of endocrine cell proliferation, an interruption of the normal physiologic negative feedback mechanism governing their status, the trophic stimulation by specific regulatory peptides (e.g., gastrin) and secretagogues (e.g., calcium), or by autocrine mechanisms whereby cells secreting an endogenous hormone-like growth factor, for which they themselves have surface receptors, could self-stimulate their proliferative activity [6,7,22–26]. Furthermore, the local tissue and intraluminal microenvironment (for example, gastric motility, distention, and the intraluminal pH of the stomach) could, by influencing any one or more of these triggering mechanisms, also play an important role in the initiation, maintenance, and progression of the hyperplasias.

With gradual improvements in our understanding of their normal physiologic role, their interrelationships with other endo- and exocrine cell types, and their status in various diseases, we have now come to realize that, although ECL-cell proliferations generally do not produce a dramatic clinical syndrome, ECL-cell hyperplasias can occur in a variety of clinical conditions. It must, however, be mentioned that, although such hyperplasias could either be a primary event or be secondarily induced, only secondary hyperplasias of the ECL cells have been described so far.

Hyperplastic and neoplastic ECL-cell proliferation have been best documented in rodents—most notably in the Mastomys sp., where they give rise to histamine-
induced gastric and duodenal ulcers [27], and in rats, following the long-term administration of various anti-secretory agents (e.g., ranitidine, cimetidine, omeprazole, and so on) [6-10]. Whereas, in the Mastomys, these lesions are related to the genetic predisposition of this species to develop spontaneous tumors in the glandular stomach and other viscera, the ECL-cell hyperplasia observed in rats is, on the other hand, due to the sustained hypergastrinemia induced secondarily by suppression of acid secretion [7,26,28-30]. In fact, in the rat model not only does the severity of hypergastrinemia correlate with the intensity of ECL-cell hyperplasia [6,7,23,29], but these hyperplasias also undergo regression after correction of the hypergastrinemia [31]. Recent reports that ECL-cell hyperplasias, with or without ECL-cell carcinoids, also develop in rats rendered chronically hypergastrinemic by partial corpectomy or by exogenous gastrin infusion further support this inductive role for hypergastrinemia [11,32-34]. Gastrin induces its well-known trophic influence on oxyntic mucosa by promoting both DNA synthesis and mitotic activity in the epithelial cells, and consequently causes increased growth and weight of the mucosa [30,33,35-38]. Cell kinetic studies in rats and dogs have shown that, while hypergastrinemia increases the labeling index in both the pluripotent stem cells of the proliferative zone and the functionally mature ECL cells, this increase is more pronounced in the latter [6,23,30,37,38]. These studies thus confirm that the ECL cells are preferentially influenced by the mitogenic effects of gastrin, and that ECL-cell hyperplasia results more from a replication of mature ECL cells than their augmented derivation from uncommitted progenitor cells.

In man, ECL-cell hyperplasias and ECL-cell carcinoids have been recognized only recently and were first observed in patients with chronic atrophic gastritis, pernicious anemia, and the ZE syndrome [39-47]. More recently, these lesions have also been observed in patients receiving anti-secretory therapy with H₂ blockers or the proton pump inhibitor omeprazole [48,49]. In these patients, the ECL-cell hyperplasia appears to result from hypergastrinemia that is secondarily induced by those therapeutic agents [41]. In the oxyntic mucosa of these patients, argyrophil stains show a spectrum of hyperplastic lesions ranging from a diffuse increase in argyrophil cell numbers at one end, through linear and nodular aggregates, to frank carcinoids [4,20,50-52]. As in rats, a parallel correlation between the degree of hypergastrinemia and the severity of ECL-cell hyperplasia has also been observed in these patients [51]. Such a progression from diffuse hyperplasia, through linear and micronodular hyperplasia, to carcinoid tumors has recently been formalized into a hyperplasia-neoplasia sequence [19] (Table 2). In this sequence, the earliest stage (simple hyperplasia) is characterized by the presence of increased numbers of endocrine cells scattered singly or in clusters of up to three or four cells per gland deep in the oxyntic mucosa (Fig. 2). When quantitated morphometrically, the number of such cells per mm² of the oxyntic mucosa is seen to exceed 2 standard deviations over the normal range in age- and gender-matched controls [53]. With increasing degrees of hyperplasia, the proliferating endocrine cells align themselves in a linear or daisy-chain-like fashion along the basement membrane of the gland; this phase is designated as the stage of linear hyperplasia (Fig. 3). The next recognizable stage (micronodular hyperplasia) in this scheme is the earliest stage that can be seen under the H&E stain and is characterized by the presence of small nodular endocrine cell clusters located in the base of the oxyntic glands, abutting the muscularis mucosae (Fig. 4). These solid micronodular clusters, with the same
average diameter as that of a gastric gland (100–150 μm), represent clonal proliferations of intraglandular ECL cells, since they are bounded by an intact basement membrane contiguous with that of the gland. Aggregates of several such micronodular lesions, each with its intact basement membrane, constitute the stage of *adenomatoid hyperplasia* (Fig. 5). Enlargement of each micronodule, with breakdown of its basement membrane, presence of cytologic atypia, increased nuclear-cytoplasmic ratio, and a reduction in the intensity of argyrophilia is the hallmark of the *dysplastic (pre-carcinoid) lesions*. These lesions, ranging between 150 microns and 0.5 mm in diameter, can show a variety of morphologic variations such as *enlarging micronodules*.

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**TABLE 2**

Classification of Oxyntic Endocrine Cell Proliferations

| Hyperplasia                      |
|----------------------------------|
| Simple (diffuse)                 |
| Linear                           |
| Micronodular                     |
| Adenomatoid                      |

| Dysplasia (Pre-Neoplastic Stage) |
|----------------------------------|
| Enlarging micronodule            |
| Fusing micronodule               |
| Microinvasive lesion             |
| Nodule with newly formed stroma  |

| Carcinoid (Neoplastic Stage)     |
|----------------------------------|
| Intramucosal carcinoid           |
| Invasive carcinoid               |

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**FIG. 2.** Simple hyperplasia of argyrophil endocrine cells in the oxyntic mucosa of a patient with chronic atrophic gastritis type A. Note the increased numbers of argyrophil cells dispersed singly or in small clusters of up to three or four cells in the closely packed glands (Grimelius stain with methyl green counterstain) (from [20]).
FIG. 3. Linear hyperplasia of argyrophil endocrine cells in the oxyntic mucosa of a patient with chronic atrophic gastritis type A. The markedly increased numbers of argyrophil cells are arranged in a linear daisy-chain-like fashion along the basement membrane of the glands (Grimelius stain with methyl green counterstain) (from [20]).

(when nodular aggregates measure more than 150 microns in diameter), fusing micronodules (when several adjacent micronodules fuse together to form a large island of cells), microinvasive lesions (when clusters of atypical cells infiltrate the lamina propria between the glands or show incipient extension into the adjacent muscularis mucosae), and nodules with newly formed stroma (when the nodules

FIG. 4. Micronodular hyperplasia of argyrophil endocrine cells in a patient with chronic atrophic gastritis, type A. Focal nodular clusters of five to 25 endocrine cells, ranging up to 100 microns in size and not exceeding the diameter of the gastric glands, are seen deep in the lamina propria, abutting the muscularis mucosae. A few glands also show linear hyperplasia of the endocrine cells (Grimelius stain with methyl green counterstain) (from [20]).
HYPERPLASTIC PROLIFERATIONS OF THE ECL CELLS

Fig. 5. Adenomatoid hyperplasia, showing a collection of several micronodules deep in the oxyntic mucosa of a patient with chronic atrophic gastritis type A. Note that, though the micronodules are in close proximity to each other, their basement membranes are still intact (Grimelius stain with methyl green counterstain) (from [20]).

acquire a lobular or trabecular pattern) (Fig. 6). Conceptually, the dysplastic stage is highly significant, since it marks the borderland between the clearly hyperplastic stages preceding it and the neoplastic (carcinoid) stage following it in the sequence. The carcinoid stage is characterized by the presence of nodular infiltrating growths greater than 0.5 mm in diameter. Though these lesions are completely intramucosal

Fig. 6. Dysplastic lesion, showing large irregular clusters of proliferating endocrine cells deep in the lamina propria. These clusters lack a basement membrane; the cells are only faintly argyrophilic and show nuclear atypia (Grimelius stain with methyl green counterstain) (from [20]).
at first, they gradually extend intramurally and, with time, invade vascular or lymphatic channels to produce nodal and distant metastases (Fig. 7).

This hyperplasia-neoplasia sequence of ECL-cell proliferation is relevant for its implication in assessing the neoplastic potential of ECL-cell hyperplasias in different clinical conditions and for the prognostic evaluation of patients at risk of developing gastric carcinoids. The validity and reproducibility of this qualitative system of diagnosing and grading ECL-cell hyperplasias has been confirmed in a comparative study, wherein ECL cells in gastric mucosal biopsies were quantitated morphometrically as well as independently graded for hyperplasia by the above-mentioned criteria. It was seen that not only were the cell counts (mean ± SEM = 8.3 ± 1.2 cells/mm²) in the earliest stage (simple hyperplasia) well above the 2 standard deviations of the corresponding value of 1.6 ± 0.2 cells/mm² in age- and gender-matched controls, but also that there was close to complete concordance between the two techniques [53].

The co-existence of ECL-cell carcinoids with various grades of ECL-cell hyperplasias in the oxyntic mucosa of hypergastrinemic patients strongly reinforces the belief that the different hyperplastic lesions represent sequential steps in the evolution of gastric ECL-cell carcinoids (Fig. 8). While ECL-cell carcinoids most frequently occur in patients with chronic atrophic gastritis and pernicious anemia [4,14,39,40,43,50,54–58], they are very uncommon in the Zollinger-Ellison syndrome, even though these patients have a more severe degree of hypergastrinemia and frequently have ECL-cell hyperplasia in the oxyntic mucosa [14,46,54,59–61]. The few ZE patients who have developed ECL-cell carcinoids have all had the multiple endocrine neoplastic type 1 (MEN-1) syndrome [14].

While development of ECL-cell hyperplasia in MEN-1 patients may be linked to genetic factors, it could also be due to the antral G-cell hyperplasia that these
patients are known to have. Thus, MEN-1 patients may already have some degree of secondary ECL-cell hyperplasia even before they develop hypergastrinemia from their gastrinomas [62]. The non-familial ZE patients, on the other hand, have normal antropyloric G-cell counts [63] and therefore develop ECL-cell hyperplasia only after the onset of their tumor-induced hypergastrinemia. Since there is a long evolutionary period of several years (apparently more than ten) in the progression of hyperplasia to neoplasia, it is possible that some of these patients may undergo a gastrectomy in the interim [64]. Nevertheless, the occasional reports of such tumors developing in patients with non-familial ZE syndrome indicate that ECL-cell carcinoids can develop in these patients as well [14,47,56,65,66]. This development is particularly germane for clinical management, since increasing numbers of ZE patients are now being managed medically on long-term therapy with gastric acid inhibitors and are having their gastrectomies postponed for longer and longer periods. Furthermore, it is quite likely that, in the future, ECL-cell hyperplasias and ECL-cell carcinoids will be detected in a variety of other chronic hypergastrinemic states as well [67].

Clinical Relevance of ECL-Cell Hyperplasias

ECL-cell hyperplasia is seen in nearly 10 percent of patients undergoing endoscopy for upper gastrointestinal symptoms [50]. Since these lesions are asymptomatic, they are most often detected incidentally or when co-existent carcinoids or polyps produce symptoms. Histologically, too, the early lesions remain undetected, unless their presence is specifically sought for by special stains. Because these hyperplastic lesions have the ability to develop into carcinoids which are potentially malignant tumors, it has been suggested that ECL-cell hyperplasias should be regarded as
FIG. 9. Gastric oxyntic mucosa. Several small micronodular aggregates of closely packed neuro-
endocrine cells are located deep in the mucosa, abutting the muscularis mucosae. These clusters were argyrophilic by both the Grimelius and the Sevier-Munger techniques, and strongly immuno-
reactive for both neuron-specific enolase and chromogranins (hematoxylin and eosin stains) (from [20]).

pre-neoplastic lesions [19]. Since, however, the clinical risk lies not in the presence of these lesions but in their progression to invasive carcinoids, it is important to bear in mind that not all hyperplasias progress to carcinoids, and even the few that do take several years to do so. In the absence of carcinoid tumors, these lesions should be managed conservatively by periodic endoscopy and biopsy to monitor their progression. It should, however, be noted that the early hyperplastic lesions are radiologically and endoscopically undetectable [55], and even the earliest lesions (micronodular hyperplasia) visible on routine light microscopy are located deep within the mucosa (Fig. 9). Quite often, they are not even included in mucosal biopsies obtained by the usual 2–3 mm biopsy forceps. It is therefore important that multiple full-thickness mucosal biopsies with “jumbo” biopsy forceps be obtained when patients at risk for endocrine cell hyperplasia are being evaluated. When a carcinoid tumor develops, management should be dictated by clinical symptomatology, and tempered by pathologic features (size, number, location, local invasion, and so on) of the tumors.

Clinical Relevance of ECL-Cell Carcinoids

In the past, gastric carcinoids accounted for 3–5 percent of all gastrointestinal carcinoids and for 0.3 percent or less of all gastric tumors [68]. Recent studies indicate that they now comprise between 11–30 percent of all gastrointestinal carcinoids [69,70]. This increase in the overall incidence of gastric carcinoids, especially in hypergastrinemic patients, may be multifactorial: the first factor relates mainly to whether the tumors arising in patients with chronic atrophic gastritis and pernicious anemia may have been under- or misdiagnosed in the past. Carcinoids arising in these patients are radiologically and endoscopically indistinguishable from the hyperplastic and adenomatous polyps so commonly encountered in these patients [71] and may indeed even co-exist with such polyps. Since, in the pre-
TABLE 3

| Conditions Associated with Increased Risk for Multicentric Gastric Carcinoids |
|--------------------------------------------------------------------------------|
| Chronic Atrophic Gastritis (type A)                                               |
| Zollinger-Ellison (familial and non-familial) Syndrome                            |
| Patients on Pharmacologic Gastric Acid Blockade                                    |
| (H2-receptors, proton pump inhibitors)                                            |
| Chronic Renal Failure (± hemodialysis)                                            |
| Pernicious Anemia                                                                |
| Autoimmune Disorders:                                                           |
| Diabetes mellitus, type 1 (IDDM)                                                 |
| Polyglandular autoimmune syndrome                                                |
| Rheumatoid arthritis                                                             |
| Sjogren's syndrome                                                               |
| Addison's disease                                                                |
| Myxedema                                                                         |

IDDM: insulin-dependent diabetes mellitus

endoscopy era, such polyps were never biopsied, their true nature may never have been established. Second, gastric carcinoids generally exhibit a solid, trabecular, or mixed (glandular and trabecular) architecture different from that of the more common appendiceal and ileal carcinoids [72,73]. Since these lesions are indistinguishable from poorly differentiated adenocarcinomas, it is possible that some of them may have been misdiagnosed as such [74,75]. In a retrospective analysis of 140 gastric tumors originally diagnosed as adenocarcinoma, 7 percent of the tumors were eventually reclassified as carcinoids [76]. The third factor relates to the more widespread use of histochemical, immunohistochemical, and ultrastructural techniques, all of which have substantially improved our ability to diagnose these tumors more accurately and subclassify them as to their constituent cell type. Last, but not least important, is our increased awareness of the higher potential of these tumors to develop in a variety of hypergastrinemic states. Perhaps the most significant factor in this regard is the emergence of an enlarging pool of a heterogeneous group of hypergastrinemic patients who are at higher risk for developing gastric carcinoids. Such a pool would include patients with duodenal ulcer or ZE syndrome undergoing long-term therapy with anti-secretory agents [48,49,77,78], patients with chronic renal failure, and those with such autoimmune disorders as insulin-dependent diabetes mellitus (diabetes mellitus, type 1), Addison’s disease, Sjogren’s syndrome, rheumatoid arthritis, autoimmune thyroiditis, the polyglandular autoimmune syndrome, and so on (Table 3). A significant proportion of patients with some of these disorders have chronic atrophic gastritis and hypergastrinemia [42,44,79–85], while others additionally have antibodies to parietal cells and intrinsic factor in their circulation [80,81,86,87]. In fact, several reports documenting the association of gastric carcinoids, achlorhydria, and hypergastrinemia in patients with diabetes mellitus and Addison’s disease have already appeared in the literature [42,44,84,88]. It is very likely, therefore, that in the future as more of those at risk are carefully screened, both ECL-cell hyperplasias and tumors will be encountered with greater frequency in a wider variety of hypergastrinemic states than is currently recognized [67].

Despite the close similarities in their clinical, histologic, histochemical, and immunohistochemical profiles, hypergastrinemia-associated gastric carcinoids differ
Comparative Profile of Gastric Carcinoids in Hyper- and Normogastrinemic Patients

| Hypergastrinemia-Associated Gastric Carcinoids | Sporadically Occurring Gastric Carcinoids |
|-----------------------------------------------|-------------------------------------------|
| Number                                        | Usually multicentric                       | Invariably single                           |
| Size                                          | Usually less than 2 cm                     | Generally more than 3 cm                    |
| ECL-Cell Hyperplasia                          | Diffusely present                          | Absent                                      |
| Neuroendocrine Markers                        |                                           |                                             |
| Chromogranin A                                | Diffusely positive                         | Diffusely positive                          |
| Synaptophysin                                 | Diffusely positive                         | Diffusely positive                          |
| Pancreastatin                                 | Diffusely positive                         | Diffusely positive                          |
| NSE, and so on                                | Diffusely positive                         | Diffusely positive                          |
| Argyrophilia                                  | Diffusely positive                         | Diffusely positive                          |
| Grimelius                                     | Diffusely positive                         | Variably positive                           |
| Sevier-Munger                                 | Diffusely positive                         | Heterogeneous                               |
| Regulatory Peptides                           | Most cells negative, some positive for 5-HT, gastrin, and so on | Variably positive for 5-HT, 5-HTP, ACTH, BMSH, and so on |
| Ultrastructure                                | Secretory granules are vacuolated and have small eccentric cores. Granulated cores with thin halo Agranulated cells with few D₁ or P-type granules | Very variable                               |
| Clinical Features                             | Endocrinologically silent “Atypical carcinoid syndrome” (Histamine) | Endocrinologically silent “Atypical carcinoid syndrome” (5-HTP and 5-HT, Cushing’s syndrome, ACTH) |
| Biological Behavior                           | Less aggressive                            | More aggressive                             |
| Nodal metastasis                              | 16%                                       | 55%                                        |
| Liver metastasis                              | 4%                                        | 24%                                        |
| Five-year survival                            | ?                                         | 50%                                        |

significantly in their biologic behavior and ultimate outcome from those arising sporadically in normogastrinemic patients (Table 4). Thus, carcinoids in both groups are usually asymptomatic and are generally detected incidentally during radiologic, endoscopic, or surgical evaluation for unrelated symptoms. Tumors in hypergastrinemic patients are usually multiple, while those occurring sporadically in normogastrinemic patients are invariably solitary [14,56]. The multicentric carcinoids in hypergastrinemic patients arise in a background of ECL-cell hyperplasia, while the solitary ones in normogastrinemic patients do not. Quite often, the adjacent mucosa does not even show any inflammatory or metaplastic changes. Irrespective of whether they are solitary or multiple, carcinoids arising in oxyntic mucosa are argyrophil by both the Grimelius and Sevier-Munger techniques, but are non-argentaffin. Tumor cells are immunoreactive for such neuroendocrine markers as neuron-specific enolase, chromogranins, synaptophysin, and so on, but are usually negative for all of the common gastrointestinal regulatory peptides and biogenic amines. Occasional tumors may, however, show immunoreactivity for serotonin, gastrin, somatostatin, and the like in up to 10 percent of the cells [72,89–91]. In the hypergastrinemic patients with chronic atrophic gastritis and pernicious anemia, the occasional non-ECL-cell tumors arising from co-existent foci of pyloric and intestinal
metaplasia show a mixed population of cells that are immunoreactive for intestinal hormones [42,50]. Ultrastructurally, the tumor cells in ECL-cell carcinoids of hypergastrinemic patients show morphologically heterogeneous secretory granules that do not resemble those of normal or hyperplastic ECL cells. They either have a wide halo and small, eccentric, electron-dense cores, or show moderately electron-dense cores with a granular interior and a thin halo [64,92]. The non-ECL-cell tumors arising in normogastrinemic patients, on the other hand, contain granules identical to those in normal D₁ or P cells, while the mixed tumors, referred to earlier, show cells that are either agranular or contain granules similar to those in normal or neoplastic EC and ECL cells [14,42,50].

Of far greater significance are the clinical and biological differences between the two groups of tumors. Although the vast majority of gastric carcinoid tumors are endocrinologically silent, approximately 7 percent of such tumors in hypergastrinemic patients are associated with an atypical carcinoid syndrome that is due to excessive histamine production by the tumor cells [66,93,94]. The atypical carcinoid syndrome associated with sporadic carcinoids in normogastrinemic patients is clinically different and is due to the overproduction of 5-HT and 5-HTP by the tumor cells [95,96]. The Cushing's syndrome sometimes seen in these patients is due to excessive production of ACTH [97]. Biologically, too, the sporadic tumors appear to have a much more aggressive clinical course. Thus, the incidence of regional lymph node metastasis (55 percent) and hepatic metastasis (24 percent) and an overall five-year survival rate of 50 percent seen in gastric carcinoids in general [98] is in sharp contrast to the corresponding figures of 16 percent and 4 percent for those arising in hypergastrinemic patients [14]. While survival figures for this latter group are not yet available, follow-up data indicates that their prognosis, even in the presence of metastasis, is superior to that of the sporadic group [40,44,51,99–101]. Even when such tumors have been incompletely excised, they have been seen, at re-exploration several years later, not to have grown or metastasized [99]. Thus, because of differences in their clinical and biological behavior, hypergastrinemia-associated carcinoids need to be differentiated from those occurring sporadically in normogastrinemic patients. This task is easily accomplished on the basis of their clinical and pathological features. 

**Role of Gastrin in the Histogenesis of ECL-Cell Carcinoids**

Considerable clinical and experimental evidence has now accumulated to indicate that prolonged hypergastrinemia is an important, if not the primary, causative factor in the histogenesis of ECL-cell hyperplasias and the multicentric ECL carcinoids [4,6–10,14,23,41,45,50,51,54,57,58,102]. Since gastric carcinoids develop in normogastrinemic patients as well, it is clear that not all gastric carcinoids are gastrin-dependent for their histogenesis [4,50]. Since carcinoids in normogastrinemic patients do not arise from an antecedent endocrine cell hyperplasia, it is likely that they are either only partly gastrin-dependent or are dependent on factors other than gastrin for their histogenesis [4,50]. Although clarification of the role of hypergastrinemia in ECL-cell proliferations has enhanced our understanding of how multicentric gastric carcinoids develop, it has also fueled controversy regarding their clinical management. The most pertinent issues revolve around whether an antrectomy performed for such tumors has any
beneficial effects on the reversibility of ECL-cell hyperplasias and whether it influences the biological progression of these hyperplastic lesions to carcinoidogenesis. In this context, two factors need to be borne in mind. First, not all endocrine cell hyperplasias inevitably evolve into carcinoids, and even the few that do are slow to do so. Second, while hypergastrinemic patients are inherently at risk for developing such proliferative lesions in their oxyntic mucosa, it has not been conclusively shown that patients on prolonged anti-secretory therapy are rendered more prone to develop these tumors as a result of such therapy. Neither has it been shown that the few tumors that have developed in such patients [77,78] are any more aggressive biologically than those developing in patients with hypergastrinemia from other causes. Furthermore, since only a small number of patients have received long-term therapy with these agents, their annual or cumulative risk for developing gastric carcinoids cannot be assessed, as yet. The situation needs to be carefully monitored and shall, it is hoped, be clarified as more data become available in the future.

The Role of Antrectomy in Clinical Management of ECL-Cell Hyperplasias and Carcinoids

Antrectomy is now known to lead to a regression or complete disappearance of both ECL-cell hyperplasias and gastric carcinoids in hypergastrinemic patients [58,90,103,104]. A recent report even documents a spontaneous regression of these tumors [105]. Antrectomy, either performed surgically or through pharmacologic manipulations using somatostatin or its synthetic analogs, is therefore being advocated for the treatment of gastrin-dependent carcinoid tumors. On account of its inhibitory action on gastrin release, therapy with somatostatin or its long-acting synthetic analog appears to hold promise in hypergastrinemic patients. Although a variety of gastrointestinal and pancreatic endocrine tumors have been treated with these agents [106,107], their effects on ECL-cell hyperplasias have not been studied as yet. Surgical antrectomy, on the other hand, is based on sound physiologic principles and would appear to be an appropriate treatment for these lesions.

Since, however, the sporadic non-ECL cell, and the metaplastically derived mixed-cell carcinoids of the oxyntic mucosa are not gastrin-dependent, antrectomy would not be the most appropriate therapy for these tumors. Because these latter tumors can be easily differentiated from the gastrin-dependent ones by their histochemical, immunohistochemical, and electron microscopic profiles, and the presence or absence of ECL-cell hyperplasia in the adjacent non-tumorous mucosa, a detailed work-up of gastric carcinoids should be routinely performed before any therapeutic decisions are undertaken.

To be of benefit, antrectomy should, therefore, be considered in patients with advanced stages of ECL-cell hyperplasia alone, and those in whom ECL-cell carcinoids occur in a background of ECL-cell hyperplasia. On the basis of our current knowledge, it would appear that antrectomy should ideally be performed before carcinoids have developed. The latest stage in which surgical antrectomy may have an interceptive effect on the development of gastric ECL-cell carcinoids would probably be the stage of adenomatoid hyperplasia, and surgery should definitely be performed before invasive carcinoids have developed. Histological differentiation between adenomatoid nodules and small carcinoid tumors can, at times, be difficult, and all such lesions need to be interpreted with caution.
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