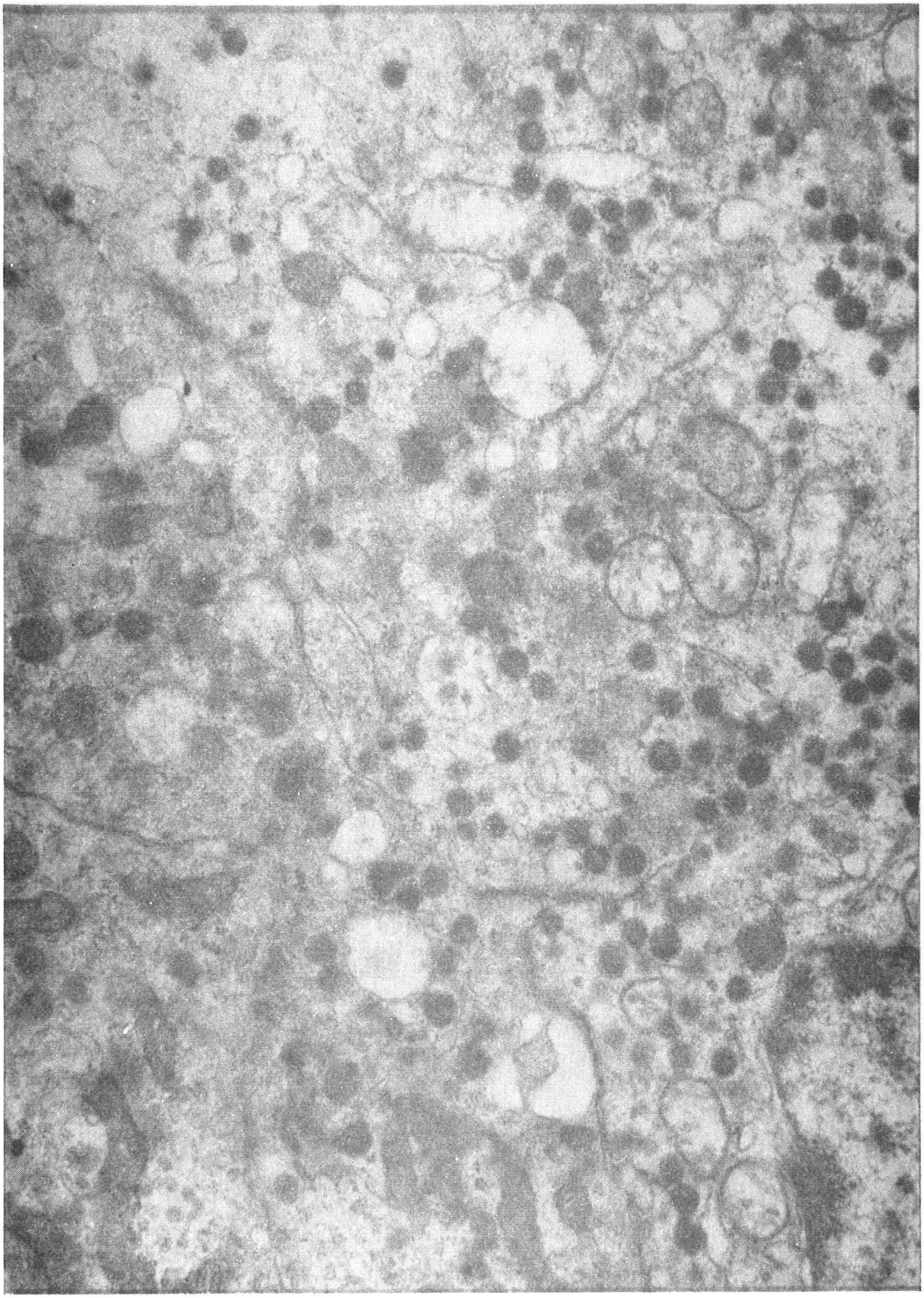
GI.

GASTRINOMA SYNDROME



INTERNAL MEDICINE GRAND ROUNDS

U.T.H.S.C.D., APRIL 26, 1984

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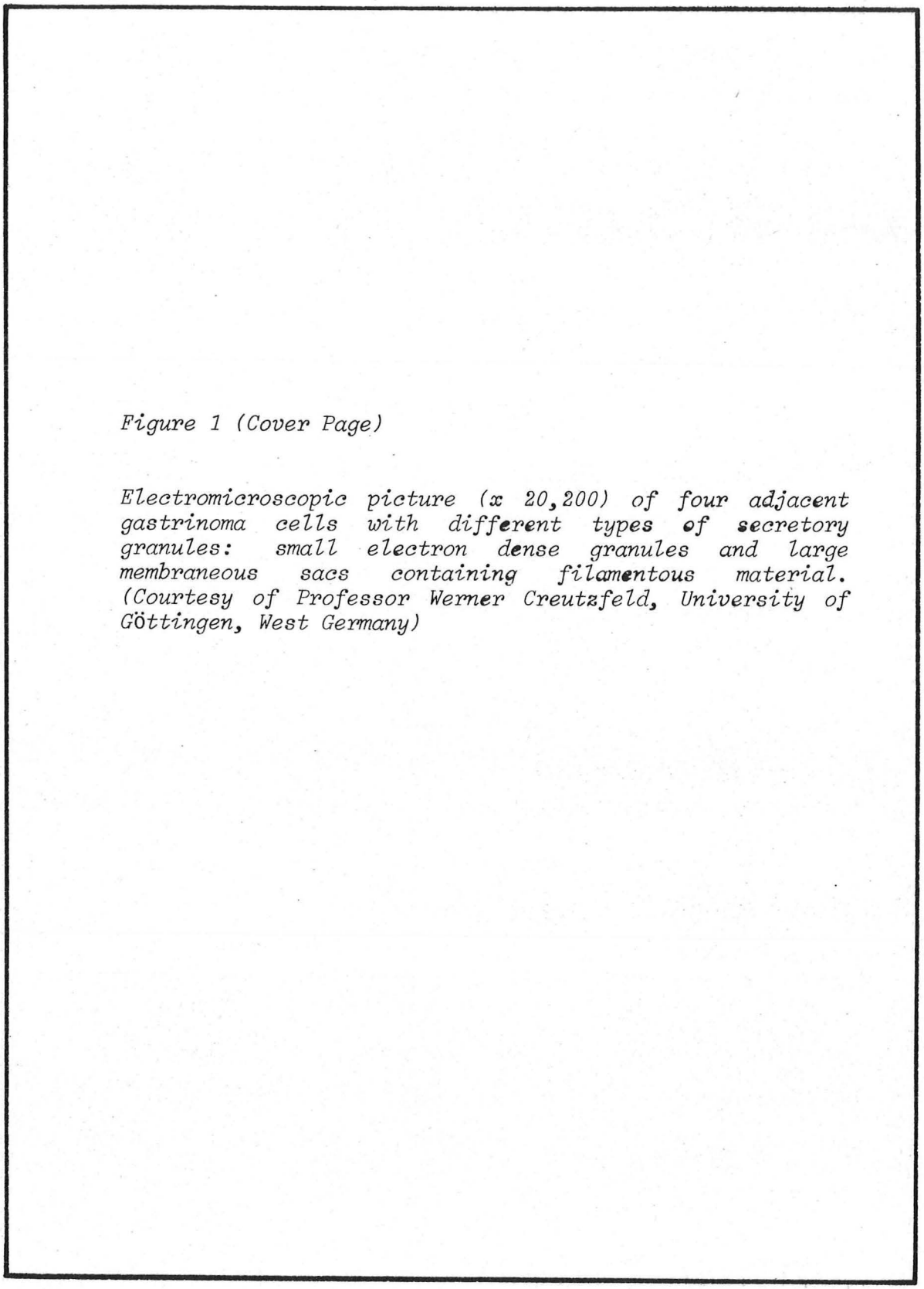

Figure 1 (Cover Page)

Electromicroscopic picture (x 20,200) of four adjacent gastrinoma cells with different types of secretory granules: small electron dense granules and large membraneous sacs containing filamentous material. (Courtesy of Professor Werner Creutzfeld, University of Göttingen, West Germany)

HISTORY

Although a number of case reports describing the occurrence of peptic ulcer in patients with islet cell tumor had been published earlier (1-4), it was Zollinger and Ellison, in 1955, (5) that furnished the correct hypothesis that pancreatic islet cell tumors may produce an ulcerogenic humoral factor. Thus, they suggested a new clinical entity consisting of hypersecretion, hyperacidity, and atypical peptic ulceration associated with noninsulin-producing islet cell tumors of the pancreas.

Figure 2 represents the complicated surgical history of Case I reported by Zollinger and Ellison (5). The patient had seven operations including segmental jejunal resection; abdominal vagotomy, jejunal segmental resection and gastrojejunostomy; subtotal gastrectomy; transthoracic vagotomy; excision of a marginal ulcer; surgical exploration of gastroentero-cutaneous fistula; and finally, total gastrectomy. The small pouch (Figure 2, Diagram 10) drained up to 4750 ml/day of gastric juice through a gastric-cutaneous fistula. Ultimately, the patient died of the complication of a duodenosophago-cutaneous fistula including intraabdominal abscesses. Autopsy showed a pancreatic islet cell adenoma (1 cm in diameter) in the central portion of the gland with similar encapsulated smaller nodules surrounding the major adenoma (Figure 2, Diagram 12).

The initial publication stimulated a wide interest in this syndrome, and many cases were found in subsequent years (6).

In 1960, Gregory and coworkers extracted from such a tumor a stimulant of acid secretion that behaved like gastrin, both in terms of how it was extracted and in terms of biological effects on acid secretion (7). The proof that the stimulant was indeed gastrin came with demonstration by Gregory and coworkers in 1969, that the amino acid composition of tumor gastrin and human antral gastrin were indistinguishable (8). Gastrins isolated from tumor tissue had different molecular weights. In addition to native gastrin, which has 17 amino acids, "minigastrins" and "big gastrins" were isolated (9,10).

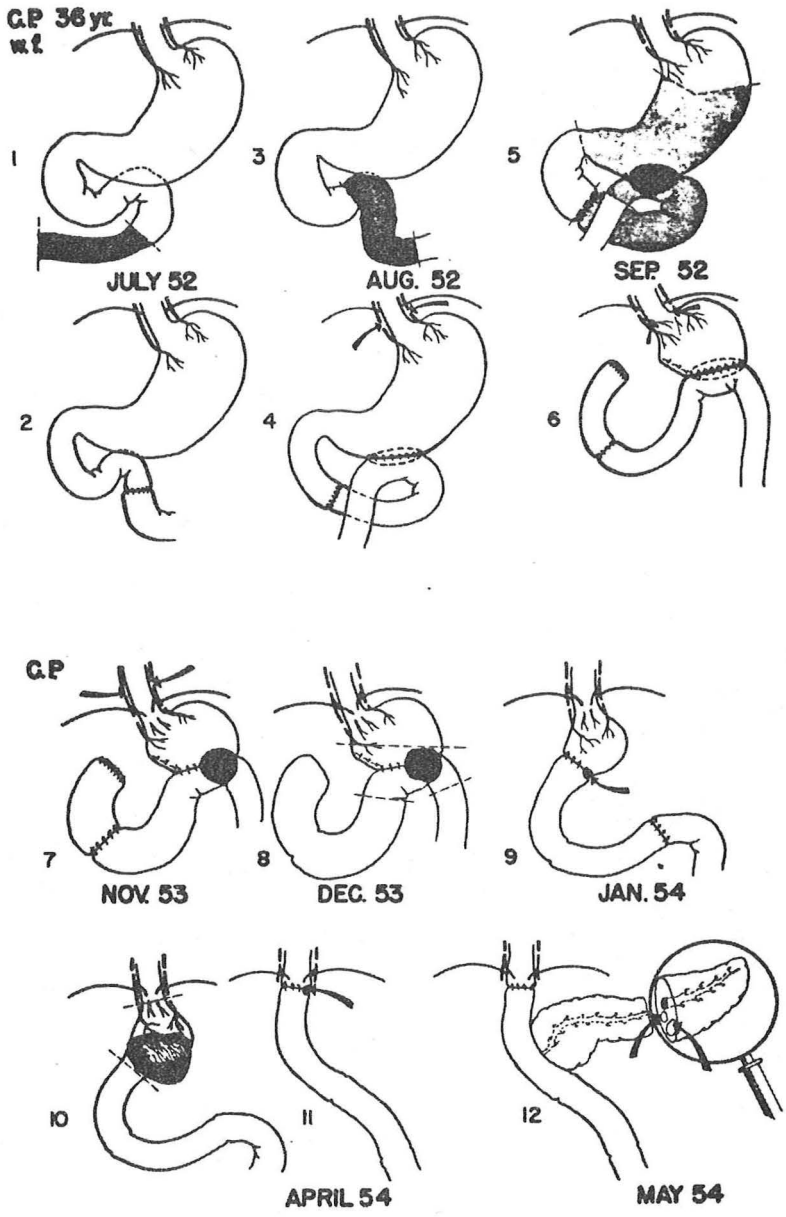

Figure 2: Surgical history of Case 1 described by Zollinger and Ellison in 1955 (5). The patient had 7 operations (see text page 3) starting with segmental resection of ulcerated jejunum and ending with total gastrectomy. Death occurred from complications of a duodenoesophago-cutaneous fistula. Autopsy (Diagram 12) showed pancreatic islet cell adenomas.

CASE REPORT

B.M. is a 34 year old Latin American female who was in good health until 1979, when she began to develop epigastric pain, vomiting, and diarrhea. She was examined at her local hospital and found to have a normal sonogram. She did fairly well on various symptomatic treatment regimens until February of 1983, when, during the ninth month of her third pregnancy, she developed severe nausea, vomiting, epigastric pain, diarrhea, and weight loss. A massive upper GI hemorrhage occurred with blood pressure drop to 60 systolic and a drop in hematocrit from 37 to 24%. On endoscopy (Dr. George Willeford, Austin, Texas) she was found to have multiple duodenal and esophageal ulcers. She was severely ill and had a stillbirth in the 35th week of her pregnancy. Serum gastrin was 2500 pg/ml (normal <200). She was started on cimetidine 600 mg q.i.d. and Pro-Banthine 15 mg b.i.d. and referred to Dallas for further investigation and treatment. The patient was admitted to the General Clinical Research Center of The University of Texas Health Science Center at Dallas.

Gastric acid analysis showed a basal acid output of 67 meq/l (normal <10) and a peak acid output (following pentagastrin injection) of 59 meq/h. Abdominal sonography was normal with well visualized pancreas. CT scan suggested a 2 cm hemangioma of the anterior part of the caudate lobe of the liver. The pancreas was normal.

Following intravenous secretin, serum gastrin rose from a basal level of 5670 pg/ml on that particular day to 52,500 pg/ml at five minutes following injection (laboratory of Dr. John Walsh, Los Angeles, California).

The patient underwent laparotomy at Parkland Memorial Hospital (Drs. Robert McClelland and Richard Thirlby). A 4 cm mass was seen in the caudate lobe adjacent to the falciform ligament, and a wedge resection was performed. Frozen section revealed metastatic carcinoma. There were two more small patches in the left lobe 3 and 4 mm in diameter, and those were left since the diagnosis of metastatic cancer appeared established.

The tail and the body of the pancreas were completely normal. However, there was some diffuse nodularity in the head of the pancreas which appeared abnormal. Resection would have entailed a pancreaticoduodenectomy, and this was not considered prudent since the diagnosis of metastatic cancer had been established. A proximal gastric vagotomy was performed. The final histology report confirmed islet cell tumor and electron microscopy revealed tumor cells with secretory granules consistent with gastrinoma (Dr. John Childers). Serum gastrin fell from 2500 preoperatively to a normal level of 95 pg/ml postoperatively. One year after surgery, the patient is doing well and is asymptomatic on ranitidine (150 mg t.i.d.). Her serum gastrin is elevated at a level of 500 pg/ml.

GASTRIN

Gastrin was discovered in 1905 (secretin, the first hormone described, was discovered in 1902). After several years of work on gastric physiology at a time when Pavlov's dogma prevailed that digestive glands are controlled solely by nerves, John Edkins reported to the Royal Society in London on May 18, 1905 (11):

> *On the analogy of what has been held to be the mechanism at work in the secretion of pancreatic juice by Bayliss and Starling, it is probable that, in the process of absorption of digested food in the stomach, a substance may be separated from the cells of the mucous membrane which, passing into the blood or lymph, later stimulates secretory cells of the stomach to functional activity.*

Edkins experiments were convincing. Only antral extracts stimulated acid secretion when injected intravenously in anesthetized cats. Fundic extracts and extracts of other tissue did not. Nevertheless, Edkins work was disputed for decades, primarily due to the discovery of histamine which confused matters. Komarov (1938) (12) and Grossman et al (1948) (13) provided further proof of a hormonal mechanism for gastric acid secretion. No significant progress in purification of gastrin came until Gregory and Tracy began their work in 1959 (14). Subsequently, gastrin was sequenced (15), and the synthesis was described in 1964 (16).

Gastrin is synthesized and stored in endocrine cells of the antrum called G-cells. The two most important molecular forms of gastrin are G17 (heptadecapeptide, "little gastrin") and G34 ("big gastrin"). Antral extracts contain about 90% G17 and 10% G34. Both smaller fragments (G14, G4) and larger molecules ("big-big gastrin") have also been identified, but they seem to have no major importance for gastric acid secretion (19-21). The most important circulating form of gastrin appears to be G17, which is several fold more potent than G34 as a stimulant of acid secretion. G17 is cleared from the circulation several times more rapid than G34. (Half-lives in the circulation are 5 min for G17 and 42 min for G34.) (22).

Another biological effect of gastrin is growth stimulation of gastrointestinal mucosa, most prominently in the oxyntic gastric mucosa. It is difficult to know whether gastrin normally regulates oxyntic gland growth. However, hypergastrinemia such as is seen in gastrinoma syndrome leads to an increase in parietal cell mass, and antral resection ("gastrin deficiency") may play a role in mucosal atrophy commonly seen in the remnant stomach after surgery.

Gastrin release occurs in response to luminal, humoral, and neuronal mechanisms. The most potent stimulants for release are protein products and amino acids in the lumen (23). Other stimulants for gastrin release are listed in Table 1.

TABLE 1

STIMULATION AND INHIBITION OF GASTRIN RELEASE FROM ANTRAL MUCOSA (from 22,24)

	Excitation	Inhibition
Vagal	Cholinergic Noncholinergic?	Cholinergic
Luminal	Food Calcium Distension	Acid Prostaglandin E_1 analogues
Chemical	Bombesin Epinephrine Calcium Prednisolone	Secretin, glucagon GIP, VIP Calcitonin Somatostatin

Inhibition of gastrin release occurs with low pH in the antrum. A pH of about 1 is required for maximal suppression, but even at pH 2.5 gastrin release in response to a test meal of amino acid is reduced by about 80% in normal subjects (25).

Radioimmunoassay

The carboxyl-terminal portion of the molecule contains the biologically active site. Antibody specificity is therefore directed against the C-terminus of gastrin. Most antibodies used in clinical laboratories have a similar affinity for both G17 and G34, and results are reported for total serum gastrin. For research purposes antibodies are available that can detect each of the two major molecular forms separately (22).

Normal basal serum gastrin is usually between 50 and 100 pg/ml with 200 pg/ml as the upper limit of normal.

Causes for hypergastrinemia are given in Table 2.

TABLE 2

CAUSES FOR HYPERGASTRINEMIA

GASTRINOMA

ATROPHIC GASTRITIS
(with or without pernicious anemia)

ANTRAL G-CELL HYPERPLASIA

RETAINED ANTRUM

PYLORIC STENOSIS

CHRONIC RENAL FAILURE

INTESTINAL RESECTION

VAGOTOMY

Atrophic Gastritis

In patients with atrophic gastritis but preserved antral mucosa, serum gastrin values are usually increased, sometimes 3 or 4 times the upper limit of normal. Since these patients are hypo- or achlorhydric, acid, as the physiological inhibitor of gastrin release, is absent. No pathophysiological significance has been ascribed to this "appropriate" hypergastrinemia (22,26).

Antral G-cell Hyperplasia

This entity has mainly been described in the European literature (27-31) and recognition in the United States followed later (22,32). Patients have peptic ulcers, increased acid secretion, increased basal serum gastrin, and a markedly exaggerated serum gastrin response to a meal. In response to intravenous secretin, serum gastrin concentration remains unchanged or decreases. Treatment consists of vagotomy and antrectomy or medical therapy with inhibitors of acid secretion.

Retained Antrum

Retention of antral mucosa in the duodenal stump during Billroth II partial gastrectomy was once an important cause of recurrent ulcer after surgery. Advances in surgery have made this complication virtually extinct. Hypergastrinemia is a result of absent acid inhibition of the isolated antral G-cells. Secretin led to a fall in serum gastrin in two such patients (22,33,34).

ISLET CELL TUMORS

Islet cell tumors (Table 3) are uncommon, occurring in less than one per 100,000 population (35). Endocrine pancreatic tumors may arise from any type of islet cell and produce insulin, glucagon, somatostatin, or pancreatic polypeptide (entopic hormones). A second group of tumors produces peptides that are not found in endocrine cells of the adult pancreas (ectopic hormones): gastrin, VIP, PHI, calcitonin, neurotensin, and corticotropin (36). Several attempts have been made to explain this ectopic peptide production by pancreatic tumors. One is based on the APUD concept (amine-precursor uptake and decarboxylation) (37) and another on dedifferentiation of neoplastic cells (38,39).

TABLE 3

ISLET CELL TUMOR SYNDROMES

I. Entopic Hormones

- Insulinoma
- Glucagonoma
- Somatostatinoma
- PPoma (Pancreatic Polypeptide)
- (Pancreatic Carcinoid)

II. Ectopic Hormones

- Gastrinoma
- VIPoma
- Calcitoninoma
- Neurotensinoma
- Parathyrinoma
- Corticotropinoma

III. "Candidate Tumor Syndromes" (not yet described)
Caused by Secretin, CCK, Motilin, GIP, Bombesin, Enkaphalin, and PYY.

GASTRINOMA

I. PATHOPHYSIOLOGY

1. Gastric Hypersecretion

The fundamental abnormality resulting in clinical disease in this syndrome is gastric acid hypersecretion as a result of continuous hypergastrinemia. Although considerable overlap exists with common duodenal ulcer patients, patients with gastrinoma often exceed a basal acid secretory rate of 10 meq/h, and their ratio of basal to peak (in response to pentagastrin) acid secretion is often more than 60%. Due to the trophic effect of gastrin on the oxyntic gland area, a true increase in parietal cell mass occurs (40).

2. Gastric Emptying

A. Dubois et al (41) have shown that patients with gastrinoma have an increased rate of gastric emptying (Fig. 3) which appears to be independent of acid hypersecretion and hypergastrinemia. The exact mechanism for this enhanced emptying is not known.

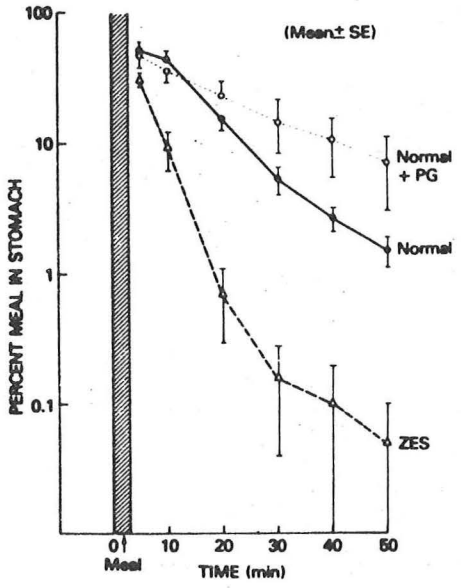

Figure 3: Percent of test meal remaining in the stomach. In gastrinoma patients (ZES), the meal is emptied significantly faster when compared to normals and normals whose acid secretion has been stimulated by pentagastrin (PG) (from 41).

3. Diarrhea

One third of patients with gastrinoma have diarrhea and 7% present with diarrhea alone (42,43). Diarrhea is of secretory nature (Table 4), i.e., stool electrolytes account for all of the osmolality of stool water (44,45).

TABLE 4

MAJOR CAUSES OF SECRETORY DIARRHEA (from 44)

1. Surreptitious laxative ingestion
2. Pancreatic cholera syndrome
3. Medullary carcinoma of the thyroid
4. Ganglioneuroma, ganglioneuroblastoma, neurofibroma
5. Zollinger-Ellison syndrome
6. Malignant carcinoid syndrome
7. Idiopathic secretory diarrhea (pseudopancreatic cholera syndrome)
8. Congenital choloridorrhea (in some cases)
9. Lethal familial protracted diarrhea
10. Secreting villous adenoma of the rectum
11. Total villous atrophy of small bowel mucosa
12. Collagen vascular diseases (scleroderma, systemic lupus erythematosus, mixed connective tissue disease)
13. Niacin deficiency
14. Ileocecal tuberculosis
15. Intestinal lymphoma
16. Giardiasis
17. Strongyloidiasis

Multiple factors appear to be related to the diarrhea, and they are listed in Table 5.

TABLE 5

FACTORS THAT MAY CAUSE DIARRHEA IN GASTRINOMA

1. Acid hypersecretion
2. Altered morphology of intestinal mucosa
3. Inhibition of intestinal absorption by high levels of circulating gastrin
4. Altered intestinal motility (rapid transit)

Gastric acid hypersecretion appears to be the paramount factor because diarrhea can be relieved by nasogastric suction, therapy with H_2-receptor antagonists, and total gastrectomy. Acid-induced mucosal injury may also play a role, and alterations in small bowel morphology have been described (46). These include abnormal shortening of villi, cellular infiltration of the

lamina propria with plasma cells and polymorphonuclear leukocytes, edema of the lamina propria and submucosa, epithelial microerosions, and gastric metaplasia of the surface epithelium (47). Alterations of the brush border by the abnormal acid milieu, not visible on light microscopy, has also been suggested. Gastrin can, by itself, reduce intestinal water and ion absorption (48,49), but this action of gastrin appears to be of no real clinical importance since diarrhea disappears when gastrin remains high after total gastrectomy (50). The large volume of acid delivered to the small bowel may cause mechanical and chemical stimulation of motility with shortened transit time (51). Pancreatic hypersecretion has also been reported in gastrinoma syndrome (52).

Rambaud et al (53) studied intestinal function of four patients with gastrinoma.

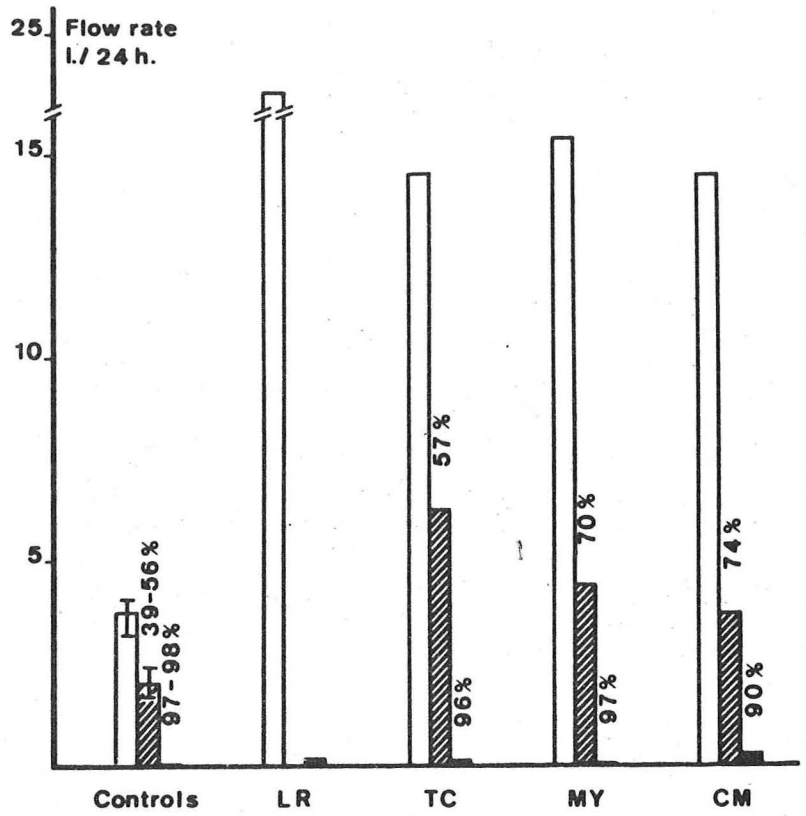

Figure 4: Twenty-four hour water flow rates at the ligament of Treitz (open columns), distal ileum (hatched bars), and feces (solid bars) in healthy controls and four subjects with gastrinoma. Flow rates in the proximal small bowel were abnormally high, but percentage decrease in the distal ileum was similar to controls (from 53).

Using the slow-marker perfusion technique (54), they found flow rates in the proximal small bowel between 15 and 24 liters/24 hours and proportionally high ileocecal transit volumes. They concluded that the high load of acidic fluid was the most important cause of diarrhea in patients with gastrinoma.

Steatorrhea in gastrinoma patients (usually in the range of 10 to 25 g fat per day) is thought to result from lipase inactivation due to the low luminal pH. Furthermore, bile salts may not be able to form micelles at low pH (55).

Our Patient B.M. (case report, see page 5) had severe disabling diarrhea, and while admitted to the GCRC, we were able to investigate intestinal water and ion movement. The results are shown in Figure 5.

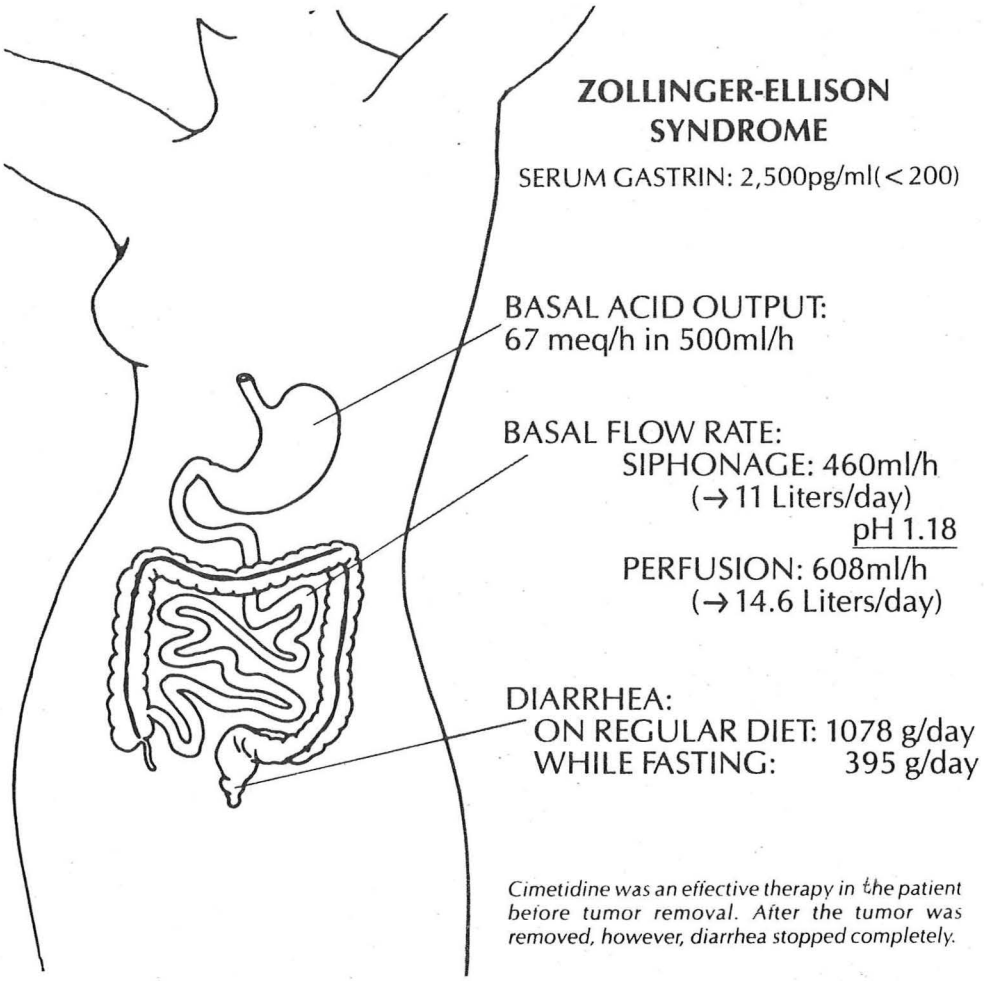

Figure 5: Synopsis of findings pertaining to the diarrhea in patient B.M. (from 56).

In normal subjects duodenal pH is above 7. Only in the duodenal bulb pH drops for short periods of time during gastric emptying (57). In patient B.M., pH in the proximal jejunum in the fasting state was 1.18. When luminal contents at the ligament of Treitz were drained by siphonage 460 ml/h were obtained. This calculated to a flow rate of 11 liters/day in the fasting state. When a more accurate method was used to estimate flow (intestinal perfusion with nonabsorbable volume marker) a flow rate of 608 ml/h was recorded (calculated 14.6 liters/day).

Jejunal water and electrolyte absorption in patient B.M. was studied by using the triple lumen perfusion technique (58-60). When a plasma-like electrolyte solution was perfused absorption rates for water and NaCl were normal in the jejunal test segment. Glucose absorption was likewise normal. In the mixing segment, pCO_2 was extremely high due to mixing of the bicarbonate-containing perfusate with the acidic fluid coming from above.

Thus, the major abnormality in intestinal water and ion movement in gastrinoma is an enormous influx of acidic fluid into the jejunum, in our patient close to 15 liters a day in the fasting state. While absorption of neutral solutions is not impaired, absorption of acidic salt solutions is (61,62). The high volume and the acidity of the fluid overwhelm absorptive capacity and diarrhea ensues.

II. CLINICAL FEATURES

1. Incidence, Age, Sex

The incidence of gastrinoma is estimated to be 0.05% per 100,000 population (or two new cases per year in DFW metroplex with a population of 4 million). For comparison, the incidence of pancreatic cancer is 10 and of colon cancer is 50 per 100,000 population.

In a review of 562 patients, Wilson (63) found 63% males and 37% females. In the Dallas series of 20 patients, 14 are male and 6 are female (64). Onset of the disease occurs at all ages but is most frequently seen in the fourth decade of life (63).

Gastrinoma syndrome has also been diagnosed in one dog with vomiting and weight loss (65). Endoscopy revealed duodenal ulcer. Gastric acid secretion was high (BAO 15, PAO 20 meq/h). Serum gastrin was 10 times the upper limit found in healthy dogs, and secretin stimulation was positive. Laparotomy revealed a pancreatic islet cell tumor metastatic to the liver.

2. Symptoms

Like with other islet cell tumors, symptoms are often present for several years prior to diagnosis. Zollinger (personal communication, 1984), in reviewing his own 40 cases, states that symptoms had been present for 5 to 9 years in most patients diagnosed prior to the introduction of gastrin radioimmunoassay. Wilson found symptoms present for a year or longer in 79% and 5 years or longer in 28% (of 685 patients reviewed) (63). Symptoms are those of peptic ulcer disease (pain, vomiting, hematemesis, melena, and diarrhea).

3. Diagnosis

   a. Barium Meal and Endoscopy (Table 6)

TABLE 6

TYPICAL X-RAY OR ENDOSCOPIC FINDINGS IN GASTRINOMA

1. Esophageal ulceration
2. Large gastric folds
3. Large amounts of fasting secretions (diluting barium)
4. Multiple duodenal ulcers
5. Ulcer distal to duodenal bulb and in jejunum
6. Widened duodenum
7. Large small bowel folds

b. Other Imaging

In search for a pancreatic mass or liver metastases, such imaging procedures as sonography, liver-spleen scan, CT scan, nuclear magnetic resonance, and angiography may be employed. Selective venous sampling, although advocated by some (66-68), is not recommended since the procedure is difficult and not without complications. Moreover, aberrant venous drainage of pancreatic islet cell tumors may lead to erroneous conclusions.

c. Serum Gastrin

The price for a serum gastrin determination is $42.00 (SMA-12 for comparison: $28.00) (Dr. Robert Putnam, personal communication). Some physicians recommend serum gastrin analysis as a routine test in any patient with newly diagnosed duodenal ulcer. Radioimmunoassay kits have made gastrin analysis almost as readily available as thyroid function tests.

Fasting values of higher than 200 pg/ml require further investigation (for other causes of hypergastrinemia, see Table 2, page 8). If serum gastrin is elevated and gastrinoma syndrome is suspected, a provocation test is indicated.

While calcium infusion has been used with relatively good success (69,70), the test of choice today entails serum gastrin measurements before and after intravenous secretin (71-74). While secretin inhibits gastrin release in normal subjects, secretin releases tumor gastrin and causes serum gastrin to peak within a few minutes after injection (50). Doubling of serum gastrin or a rise by $\geq$ 200 pg/ml is considered diagnostic for gastrinoma (71) (Fig. 6). False positive results have been reported with the use of impure secretin (76).

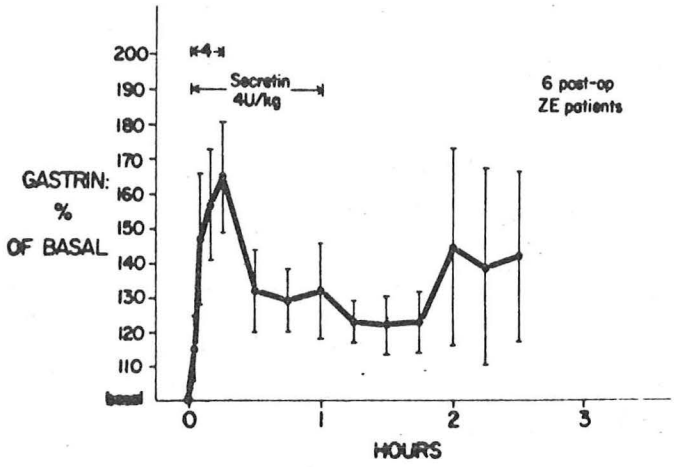

Figure 6: Increase in serum gastrin after intravenous secretin in 6 patients with remaining tumor after total gastrectomy (from 75).

c. Acid Secretion

Approximately two thirds of patients with gastrinoma have unstimulated gastric secretory rates that exceed 10 meq/h. Slightly more than half the patients secrete more than 15 meq of gastric acid in the basal state (77).

Stimulation of gastric secretion (pentagastrin) in gastrinoma patients often does not increase acid output much further. One half of patients with gastrinoma will have a ratio of basal to peak acid output of 60 or more percent.

There are a few patients with peptic ulcers who have high basal acid secretion but have a normal fasting serum gastrin concentration and a negative secretin test (52). The underlying mechanism for basal hypersecretion in these patients is poorly understood, the cause may be neuronal or hormonal in nature (78).

4. Gastrinoma as part of MEN I

Pancreatic endocrine tumors can be part of the multiple endocrine neoplasia syndrome, type I (MEN I), in which there is an hereditary predisposition to islet cell hyperplasia and islet cell tumor formation. Any islet cell tumor can occur in MEN; most commonly, however, tumors produce gastrin, VIP, and pancreatic polypeptide (36).

The incidence of MEN I in gastrinoma patients is about 25%. These patients should be considered as a separate group because they have better expectations of survival than patients with sporadic gastrinoma (79-82). This is contrary to what might be expected since the gastrinoma tends to be multiple throughout the pancreas in this group of patients.

These patients with MEN I present a greater challenge because of the multigland involvement and the tendency to develop additional endocrine tumors

after treatment for gastrinoma has been commenced. Parathyroid tumors are most commonly seen. In Zollinger's current series (1984, personal communication), 13 out of 40 patients with gastrinoma had MEN I. Of these, four had parathyroidectomy before operating for gastrinoma and 13 more parathyroidectomies were performed during 28 years of follow up. This includes patients with two to four recurrences of hyperparathyroidism and suggests that three and one-half of the parathyroids should be routinely removed at the initial operation.

Other tumors involve the pituitary and adrenals. Although pheochromocytomas have, in the past, not been expected in MEN I, Zollinger (personal communication, 1984) indicates a 10% incidence of pheochromocytoma in gastrinoma patients (83).

A "small endocrine screen" may include serum calcium and phosphorus, parathyroid hormone, prolactin, and cortisol, and urinary metanephrines. A "large endocrine screen" will also include serum pancreatic polypeptide, somatostatin, calcitonin, VIP, PHI, GIP, insulin, glucagon and neurotensin.

5. Variants of Gastrinoma Syndrome

The existence of a nongastrin gastric secretagogue released from an islet cell tumor is illustrated by the following case report.

W.S. was a 54 year old Swiss missionary who, while in Bolivia, developed severe hematemesis. A Billroth II subtotal gastrectomy was performed. Six months later hematemesis recurred, and in 1973 he returned to Zurich, Switzerland, for further investigation. Barium meal study revealed a large marginal ulcer. Acid secretion in the small gastric remnant revealed BAO of 12 and PAO of 13 meq/h. Serum gastrin levels (basal and during calcium infusion) were normal (measured by Dr. G. Feuerle, University of Göttingen, West Germany). When the patient's serum was used in a bioassay (rats with gastric fistula), the result was positive (laboratory of Dr. F. Halter, Berne, Switzerland). Hypoglycemia was also noted. First it occurred only during prolonged fasting for diagnostic tests, later it was continuous, requiring intravenous glucose infusion. Later, 10% glucose had to be given by central line. Interruption of the infusion for 4-5 minutes would result in hypoglycemic seizures. Serum insulin was not elevated (laboratory of Dr. E. R. Frösch, Zurich, Switzerland). Angiography revealed metastatic tumor in the liver which on percutaneous biopsy showed features of islet cell carcinoma. Thus, this tumor produced a peptide which caused gastric hypersecretion with severe peptic ulcer disease and hypoglycemia. However, the peptide was neither immunoreactive gastrin nor insulin. Unfortunately, the methods of peptide chemistry available at the time did not allow identification of the agent released by the tumor. The patient first showed a good response to chemotherapy with streptozotocin and was discharged. A year later he died of complications related to tumor mass.

Chey and coworkers (84) have recently observed two similar cases. Pancreatic islet cell tumors were associated with recurrent ulceration and hypersecretion of acid without hypergastrinemia. Tumor extracts caused acid secretion in a bioassay. It is anticipated that the rapid progress in peptide chemistry will soon allow identification of the peptide(s) responsible for hypersecretion in such patients.

6. Mixed Tumors

Radioimmunoassay and immunocytochemical techniques have demonstrated that more than half of all pancreatic islet cell tumors produce more than one peptide (85). Clinically, most patients with mixed pancreatic endocrine tumors present with symptoms characteristic of excess of only one hormone (86). Some of these mixed tumors are "clinically silent," or may only produce symptoms related to tumor mass and malignancy in general (anemia, weight loss). When symptoms are present, the immunocytochemical predominance of a certain cell type may not always correspond to the clinical picture. For instance, when gastrin-secreting cells constitute only 10% of the cell population in a tumor, the secretion of gastrin may, nevertheless, be sufficient to induce the Zollinger-Ellison syndrome (87). Sometimes the clinical syndrome may change during prolonged observation or following chemotherapy. In one case, transition from gastrinoma to insulinoma syndrome was noted without detectable ultrastructural changes within the tumor itself (88). In one patient symptoms of gastrinoma preceded those of a glucagonoma by seven years (89). In the patient in whom we described the somatostatinoma syndrome, symptoms of severe peptic ulcer disease with recurrent hematemesis were present for several years prior to detection of the somatostatinoma. However, during our investigations no abnormality related to gastrin was found (90).

7. Islet Cell Hyperplasia

Although a controversial subject, some endocrine syndromes related to pancreatic tumors have also been recognized in the setting of islet cell hyperplasia (rather than islet cell adenoma or carcinoma). For instance, the watery diarrhea hypokalemia hypochlorhydria syndrome has been associated with islet cell hyperplasia (91). PP cell and GIP cell hyperplasia have also been described (92,93).

In 20% of patients with clinical and laboratory evidence of gastrinoma, no tumor is found at surgery. Zollinger, Malagelada, and others (79,80) have emphasized the improved survival rate in these patients. Whether islet cell hyperplasia or a tumor too small to recognize is present in these patients is unresolved. It is conceivable that islet cell hyperplasia is a premalignant condition. This is at least suggested from follow-up studies in patients with MEN I where islet cell hyperplasia may precede development of an islet cell tumor (94,95).

8. Duodenal Wall Gastrinoma

When solitary gastrinomas are outside the pancreas the prognosis may be favorable since their removal is easily accomplished (see below, PROGNOSIS). Seven (15%) of Zollinger's 40 cases had duodenal wall gastrinomas. The ZES registry shows 103 such tumors of 800 gastrinoma patients (13%) (96).

PROGNOSIS

Therapy (see below) provides for cure in about 20% of patients, 10% die of complications of peptic ulcer disease, 50% die due to malignant progression of the tumor, and 20%, while having the syndrome, die for other reasons. In all gastrinoma patients together, Zollinger finds a 63% five-year survival and a 50% 10-year survival (79).

Factors that influence survival favorably are: 1) gastrinoma in the setting of MEN I, 2) inability to find a tumor at surgery, and 3) the presence of a duodenal wall (rather than pancreatic) tumor. Survival at 10 years is around 60% in these three subgroups. Unfavorable factors are the presence of metastases at surgery, however, the 10-year survival is still relatively high with 25%.

TREATMENT

The choice of therapy in gastrinoma patients is currently the most controversial subject pertaining to the whole syndrome. Three different schools can be recognized: "Aggressive Surgery," "Conservative Therapy," and an "Intermediate School." (Table 7).

TABLE 7

DIFFERENT TREATMENT PLANS IN PATIENTS WITH GASTRINOMA

School	Typical Representatives	Method	Ref
Aggressive Surgery	R. Zollinger, J. Thompson	Total gastrectomy, Tumor resection if feasible	Personal Communication, 97
Conservative Therapy	D. McCarthy	H_2-receptor blockers	98
Intermediate School	C. T. Richardson & Colleagues	Vagotomy, Tumor resection if feasible, H_2-receptor blockers	64

"Conservative Therapy"

Medical therapy with H_2-receptor antagonists has been shown to relieve symptoms in many but not all patients with gastrinoma. The mean failure rate (Table 8) is about 35% (80,99-102). Ranitidine and cimetidine have recently been compared in the treatment of gastrinoma patients. Ranitidine was three times more potent than cimetidine and caused less side effects (103). When H_2-receptor antagonists are given, suppression of acid secretion and clinical results can be improved by combination with an anticholinergic such as pirenzepine (104).

TABLE 8

TREATMENT FAILURES ON MEDICAL THERAPY

Total Patients Treated	Failed	Average Rx duration (mo)	Reference
13	5	-	99
16	10	12	100
26	6	-	101
20	10	36	102
18	2	22	80
Total 93	33 (35%)		

Omeprazole is a new antisecretory drug that inhibits hydrogen - potassium - ATPase, an enzyme located at the acid secretory surface of the parietal cell and involved in the final step of proton secretion (105). Omeprazole has now been used in seven gastrinoma patients who were cimetidine and/or ranitidine failures (106). On omeprazole, symptoms resolved in all patients. Their ulcers were healed at endoscopy, and gastric secretion remained inhibited by therapy during an average follow up of 14 months. Omeprazole is still an investigational drug and long-term safety has not been established.

Thus, since 35% of gastrinoma patients turn out to be treatment failures on medical therapy, we should not consider drug therapy alone as a satisfactory long-term treatment regimen.

"Aggressive Surgery"

Total gastrectomy represents the classical and traditional therapy for gastrinoma. This approach was designed at a time when the diagnosis was made late because a gastrin radioimmunoassay was not available, and H_2- receptor antagonists were not avialable as temporary or additional treatment.

Total gastrectomy may be associated with serious or incapacitating complications in 10-20% of patients (esophageal stricture, recurrent vomiting, blind loop, dumping, malnurishment, bone disease) (68,80). Operative mortality lies between 2 and 15% (107,108).

"Intermediate School"

Richardson and coworkers have designed a treatment compromise (Table 7) that entails proximal gastric vagotomy, tumor resection if feasible, and postoperative H_2-receptor therapy as needed. They have studied twenty patients in a careful and prospective manner (64). Tumors were found in eight patients and all visible tumors were removed from five of the eight. Fasting serum gastrin concentrations and serum gastrin responses to intravenous secretin were normal six weeks after surgery in four of these five patients and remain normal in two patients, two and one-half and four years after surgery. Follow up has ranged from six months to 19 years (median, two and a half years). Acid secretion was reduced after vagotomy in each patient, even when tumors were not found and serum gastrin concentrations remained elevated. The inhibitory effect of H_2-receptor antagonists on acid secretion was also enhanced by vagotomy. Doses of cimetidine or ranitidine have been reduced, compared to preoperative doses, in 18 patients, five of whom are taking no antisecretory drugs. Only three patients have had symptoms of ulcer disease. Complications such as bleeding, perforation or obstruction have not occurred in any patient. Endoscopy was performed in all patients and an ulcer was present in only one patient.

Based on these results, I would give my preference to the "Intermediate School." They have shown that laparotomy, vagotomy, and medical therapy with H_2-receptor antagonists is an effective treatment for patients with Zollinger-Ellison syndrome. The question that remains at this point concerns the aggressiveness with which visible or suspected tumor should be removed. For instance, should the pancreas be resected when a portion of it appears nodular without localized mass? Should a duodenopancreatectomy be performed in the presence of a single metastasis to a lymph node or to the liver?

Chemotherapy

If tumor mass becomes a problem in patients with advanced disease, chemotherapy with streptozotocin is effective in many but not all patients (109,110). The use of streptozotocin, which has nephrotoxicity is not indicated in localized but nonresectable tumors that cause no complications by compression or encroachment of adjacent organs. Streptozotocin therapy is given as palliative not curative therapy.

SUMMARY

Thirty years ago Zollinger and Ellison described a syndrome consisting of gastric acid hypersecretion and severe peptic ulcer disease associated with pancreatic islet cell neoplasia. Subsequent to the recognition of gastrin as the secretagogue released by the tumor, the pathophysiology of the syndrome has been elucidated.

Diagnosis is relatively easy due to the general availability of a radioimmunoassay for serum gastrin. Debate continues about the optional therapy for these patients. While total gastrectomy used to be the procedure of choice, recent data suggests that preference should now be given to a treatment approach combining vagotomy, tumor resection if feasible, and postoperative drug treatment with H_2-receptor antagonists.

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