990. Cox, A. J., Jr. Stomach size and its relation to chronic peptic ulcer. Arch. Pathol *54*:407, 1952.
991. Moore, J. G., and Englert, E. Circadian rhythm of gastric acid secretion in man. Nature *226*:1261, 1970.
992. Shearman, D. J. C., Buckle, P. J., and Hetzel, D. J. The inhibition of nocturnal gastric acid secretion by omeprazole in patients with duodenal ulcer. Scand. J. Gastroenterol. *21*(suppl. 118):145, 1986.
993. Soll, A. H., Weinstein, W. M., Kurata, J. H., and McCarthy, D. Nonsteroidal anti-inflammatory drugs and peptic ulcer disease. Ann. Intern. Med. *114*:307, 1991.

Chapter 31

ZOLLINGER-ELLISON SYNDROME AND OTHER HYPERSECRETORY STATES

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ZOLLINGER-ELLISON SYNDROME

The syndrome that bears their name was defined by Zollinger and Ellison in 1955.[1] The triad they described includes severe ulcer disease, gastric acid hypersecretion, and non-beta islet cell tumors of the pancreas. They predicted, with extraordinary insight, that these tumors produced gastric acid hypersecretion and consequent ulcer disease by releasing a stimulatory secretagogue into the circulation. Their prediction was fulfilled by the subsequent demonstration that these tumors contain and release the most powerful gastric acid secretagogue presently known, the polypeptide hormone *gastrin,* leading to the current appropriate designation of these tumors as *gastrinomas.*[2–5] The brilliant clinical insight leading to their interpretation and definition of this syndrome is emphasized by our reflection that the only type of islet cell tumor appreciated at that time was insulinoma, known to arise from beta cells of the pancreatic islets. The contribution of Zollinger and Ellison represents not only a landmark in our knowledge of gastrointestinal (GI) hormonal tumors, but also an enormously potent catalyst to our rapidly accelerating knowledge of the biologic activities of GI hormones in health and disease.

The true incidence of the Zollinger-Ellison syndrome is not known. Although relatively rare, gastrinomas are the most common of all pancreatic islet cell tumors (Figs. 31–1 and 31–2). The Zollinger-Ellison syndrome has been estimated to be responsible for approximately one tenth of one per cent of all patients with duodenal ulcer. The Zollinger-Ellison syndrome has been reported to be slightly more common in males than in females.[6] Although detected from early childhood through the tenth decade of life, the initial clinical manifestations appear most commonly in patients from 30 to 50 years of age.[6, 7]

Etiology and Pathogenesis

Gregory and colleagues confirmed the prediction of Zollinger and Ellison, demonstrating a potent gastric acid secretagogue in extracts from these tumors five years after Zollinger and Ellison predicted that these islet cell tumors released a stimulant that was responsible for the ulcerogenic syndrome.[2] Subsequent investigations confirmed the suspicion that the secretagogue was gastrin by demonstrating large amounts of gastrin in Zollinger-Ellison tumors and in sera from patients with the Zollinger-Ellison syndrome.[3–5] Gastrin has been shown by immunocytochemistry to reside in numerous prominent secretory granules in the cytoplasm of gastrinoma cells.[8]

GASTRIN. The predominant biologically active molecular species of gastrin in gastrinomas, just as in the antral mucosa, is heptadecapeptide gastrin (G17).[5, 9, 10] The major form of biologically active gastrin in the blood of patients with gastrinoma is a larger form of gastrin con-

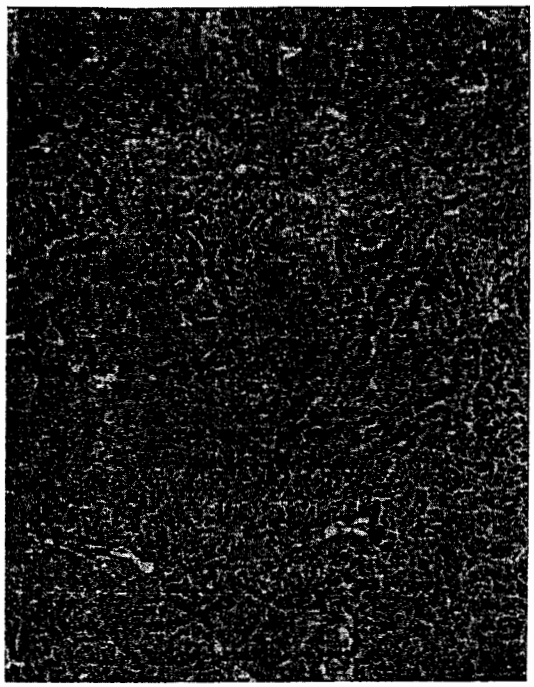

Figure 31–1. Pancreatic gastrinoma from patient with the Zollinger-Ellison syndrome. Hematoxylin and eosin stain, ×125. (Courtesy of Marie Greider, Ph.D.)

taining 34 amino acids (G34), the same principal species of gastrin in the circulation of normal individuals and patients with common peptic ulcer disease. Both sulfated (gastrin II) and nonsulfated (gastrin I) gastrin forms are present in sera of patients with gastrinoma as well as in normal subjects. The proportion of sulfated gastrin in sera of patients with the Zollinger-Ellison syndrome (mean 57 per cent) has been reported to be higher than in patients with common duodenal or gastric ulcer or in healthy subjects without ulcers (mean 37 per cent).[11] Evidence has been provided, using peptide region–specific gastrin antibodies, that the ratio of amino-terminal to carboxyl-terminal G17 gastrin immunoreactivity is increased in sera of patients with metastatic gastrinoma when compared with normal subjects and patients with nonmetastatic gastrinoma.[12] In addition to G17 and G34, smaller and larger forms of gastrin are found in sera and gastrinomas from Zollinger-Ellison patients.[10, 13] These include component I gastrin, a form of gastrin slightly larger than G34, which has not yet been characterized, as well as small amounts of gastrin fragments. These include the amino-terminal 1-13 fragment of G17 (which has no biologic activity) and the carboxyl-terminal tetradecapeptide amide ("minigastrin"), which has immunoreactivity and biologic activity similar to that of G17. Unprocessed progastrin and other precursor forms of gastrin have been found in high concentrations in gastrinoma tissue and plasma of patients with gastrinoma.[14] Glycine-extended biologically inactive forms of gastrin and progastrin are also present in abundance in gastrinoma tissue and plasma of gastrinoma patients and constitute the principal tissue and circulating immunoreactive gastrin forms in some patients with the Zollinger-Ellison syndrome.

The gastric parietal cell mass is expanded enormously in patients with the Zollinger-Ellison syndrome.[15] It has been estimated to be at least three to six times as large as in normal individuals and two to three times that of patients with common duodenal ulcer. Expansion of the parietal cell mass, which increases the capacity of the stomach to secrete hydrochloric acid, is caused by the trophic effects of hypergastrinemia on parietal cells. ECL cell hyperplasia and small multicentric noninvasive gastric carcinoid tumors composed of these cells are present in the gastric mucosa of some patients with gastrinoma and other causes of hypergastrinemia, including pernicious anemia.[16–19] These also appear to represent direct trophic effects of high circulating gastrin levels on this cell population.

GASTRINOMAS: ORIGIN, LOCATIONS, AND BEHAVIOR. There has been a lack of agreement as to the nature of the cells from which gastrinomas arise. Although gastrin-containing cells are known to be present in pancreatic islets of prenatal and newborn animals, little if any immunoreactive gastrin has been identified in the normal

Figure 31–2. Same tumor as in Figure 30–1, at higher magnification (×400). Cells are malignant. Hematoxylin and eosin stain. (Courtesy of Marie Greider, Ph.D.)

adult pancreas. For these reasons most investigators have viewed pancreatic gastrinomas as ectopic tumors. Recently, biologically active and inactive forms of progastrin and gastrin have been measured in pancreatic tissue from normal adult humans and patients with gastrinomas.[14] These observations suggest that gastrinomas arise from pancreatic islet cell populations already expressing gastrin gene products rather than as ectopic tumors, in which dedifferentiation of transcription mechanisms has been suggested to be responsible for aberrant hormone production. Although proposed earlier that the cells from which gastrinomas arise were derived from ectoderm, most recent evidence supports the conclusion that the cells from which these tumors develop are of endodermal origin.[20]

Gastrinomas in patients with the Zollinger-Ellison syndrome have been reported most often in the pancreas.[6, 15, 21–25] Contrary to earlier perceptions, pancreatic gastrinomas are most frequent in the head of the pancreas. Gastrinomas have also been identified in the hilus of the spleen, in the stomach or liver, in rare instances, and have been found frequently in regional parapancreatic and mesenteric lymph nodes. Gastrinomas are usually small but vary widely in size, ranging from approximately 0.1 to more than 20 cm in diameter.[6] In at least half the cases, gastrinomas are multiple.

More recent studies have suggested that as many as two thirds of patients with the Zollinger-Ellison syndrome have extrapancreatic gastrinomas.[26, 27] The most common site of extrapancreatic gastrinomas is the wall of the duodenum.[28–30] There is accumulating evidence that when gastrinomas are localized they are found at least as commonly (and perhaps more commonly) in the duodenum as in the pancreas. Duodenal wall gastrinomas are located principally in the submucosa and are easily overlooked at endoscopy or surgery. Duodenal gastrinomas are usually located in the first or second portion of the duodenum. Approximately 50 per cent of duodenal gastrinomas are solitary, and they may be as large as 1.5 cm or as small as 1 mm in diameter.[30, 31] The question has remained unanswered whether gastrinoma found only in lymph node tissue represents primary tumor or metastasis from undetected gastrinoma. However, there is accumulating evidence that undiscovered duodenal wall gastrinomas are most often the sites of occult gastrinomas in Zollinger-Ellison patients with isolated lymph node gastrinomas and in patients in whom no tumor is found at surgery.[30, 31]

At surgery, gastrinomas may be identified readily or, more often, they are difficult to localize or may not be identified at all.[32–35] When carefully sought for and finally located, approximately 90 per cent of gastrinomas are found within an anatomic triangle referred to as the *gastrinoma triangle* (Fig. 31–3). The gastrinoma triangle is defined anatomically by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially.[36] A small number of ovarian tumors have also been shown to be gastrinomas and may produce the Zollinger-Ellison syndrome.[37–40]

Approximately one half to two thirds of gastrinomas are malignant. There is poor correlation between the histologic appearance and the biologic activity of gastrinomas. The most reliable index of malignancy of gastrinomas is their biologic behavior, as expressed by the presence or absence of metastasis. Even when malignant, these tumors usually behave in a slow-growing, indolent manner. However, in a small proportion of patients with gastrinomas, the tumors may grow rapidly and metastasize early and widely. Sites of metastasis include regional lymph nodes, liver, spleen, bone, mediastinum, peritoneal surfaces, and skin.[6, 21] Duodenal gastrinomas commonly metastasize to regional lymph nodes and less often to the liver. Extended longitudinal studies of patients with the Zollinger-Ellison syndrome have verified differences in clinical course between patients in whom gastrinoma is found within lymph nodes and those with gastrinoma metastatic to the liver.[24] Death is rarely caused by tumor progression in patients found at surgery to have metastasis limited to lymph nodes. Patients with gastrinoma identified only in lymph nodes and not in the liver tend to live for long periods of time, often 25 years or more, without evidence of tumor progression. In fact, the clinical course of patients with gastrinoma identified in lymph nodes is indistinguishable from that of patients with gastrinoma in whom no tumor can be identified at surgery. In contrast, patients with hepatic metastases have a significantly shortened life expectancy, approximating eight years, usually with progressive tumor growth leading to liver failure.[24, 41]

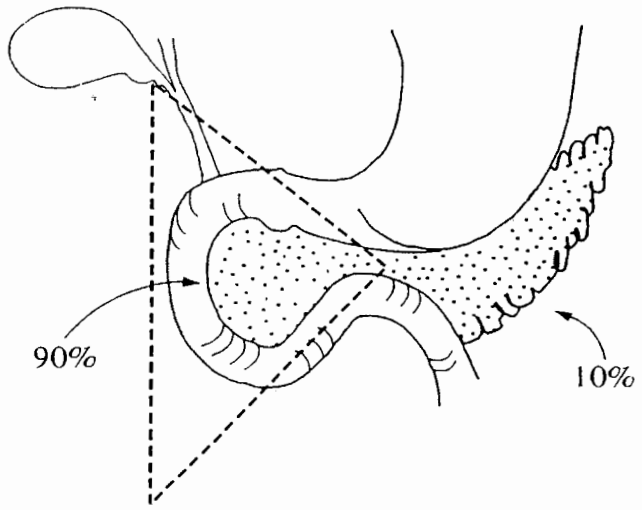

Figure 31–3. Gastrinoma triangle. More than 90 per cent of gastrinomas are found within limits of this anatomic triangle. (From Stabile, B., Morrow, D., and Passaro, E. The gastrinoma triangle: Operative indications. Am. J. Surg. *147*:25, 1984.)

Patients with proven metastatic gastrinoma often have increased serum levels of human chorionic gonadotropin (HCG) and its alpha and beta subunits.[42, 43] Twenty per cent of patients with malignant gastrinomas have increased serum α-HCG levels, and those with extensive metastatic gastrinoma are more likely to have strikingly increased α-HCG levels. Increased serum α-HCG levels have not been found in patients with benign gastrinoma.

Multiple Endocrine Neoplasia Type I (MEN I). It has been estimated in various studies that from 20 to 60 per cent of patients with gastrinomas have the multiple endocrine neoplasia type I (MEN I), which is composed of tumors or hyperplasia of parathyroid, pancreatic islet,

and pituitary glands.[44–50] MEN I is an autosomal dominant genetic disorder associated with a high degree of penetrance. The MEN I locus has been identified on chromosome 11.[51] It is probable that all patients with MEN I have involvement of all three organs (parathyroids, pancreatic islets, and pituitary), although not always with clinical expressions of excessive hormone release.[52]

Hyperparathyroidism is the most common manifestation of MEN I and is present in 90 to 100 per cent of these patients. Hyperparathyroidism in patients with MEN I is usually due to hyperplasia (80 per cent). Pituitary adenomas, usually prolactinomas, are believed to be present in all or almost all patients with MEN I, although they are symptomatic in only 30 per cent of these patients.[53] Unlike islet cell tumors, pituitary tumors are usually solitary in patients with MEN I. Islet cell tumors are expressed clinically in approximately 50 to 80 per cent of patients with MEN I. Islet cell tumors with MEN I are almost always multiple or multifocal in the pancreas or in other locations. Gastrinomas are found in 40 to 60 per cent of MEN I patients. Pancreatic tumors associated with MEN I often contain glucagon, pancreatic polypeptide, insulin, or somatostatin cells.[31] With increasing age, MEN I patients with hyperparathyroidism frequently progress to the Zollinger-Ellison syndrome. Hyperparathyroidism with resultant hypercalcemia may stimulate gastrin release and unmask latent gastrinoma in patients with MEN I.[54] Other hormones that are frequently elevated in sera of patients with MEN I include alpha-HCG, beta-HCG, ACTH, melanocyte-stimulating hormone (MSH), pancreatic polypeptide, and others.[55–60] In addition to parathyroid, islet cell, and pituitary abnormalities, thyroid nodules, carcinoid tumors, and hyperplasia of the adrenal cortices have been noted in a small number of MEN I family members. Gastrinomas in non–MEN I patients, at least currently, are considered to be sporadic.[48–50]

GASTRINOMA IN MEN I. Gastrinoma is by far the most common type of islet cell tumor in patients with MEN I. More than 60 per cent of patients with MEN I have been reported to have the Zollinger-Ellison syndrome or elevated serum gastrin levels.[44, 61–64] Islet cell tumors in patients with MEN I are usually multiple and multicentric.[62, 65] Gastrinomas are much more commonly extrapancreatic in patients with MEN I and are usually smaller than sporadic gastrinomas. It has been estimated that approximately 30 per cent of gastrinomas found in patients with MEN I are malignant. Gastrinomas frequently coexist with nonfunctioning endocrine tumors. Recent data indicate that all, or almost all, patients with MEN I have multiple endocrine tumors in the pancreas, but these tumors are not gastrinomas and are not usually responsible for clinical syndromes due to excessive hormone release.[31] Some authors have suggested that distant metastases are less common and that prognosis is better in patients with MEN I, although this is disputed by some other authors.[66]

DUODENAL GASTRINOMAS IN MEN I. Although in the past gastrinomas in MEN I patients have been thought to arise predominantly in the pancreas, recent data indicate that these tumors are found more often in extrapancreatic sites, especially in the wall of the proximal duodenum.[24, 31, 36, 67] It is clear that duodenal wall gastrinomas occur much more frequently in patients with MEN I than realized previously. The major features of duodenal gastrinomas in patients with MEN I are their extremely small size, their frequent multicentricity, and their submucosal location.[31] It is possible that duodenal tumors may be present in all patients with MEN I. MEN I gastrinomas are usually found in the first or second portion of the duodenum. Solitary tumors in the duodenum tend to be larger (6 to 20 mm), and when multiple, tumors tend to be smaller (2 to 6 mm) in these patients. Duodenal gastrinomas are usually solitary in Zollinger-Ellison patients with sporadic gastrinomas, whereas they are usually multiple in those with MEN I. Because of their small size and their location, duodenal wall gastrinomas have frequently escaped detection in patients with the Zollinger-Ellison syndrome. Duodenal wall gastrinomas in patients with sporadic gastrinomas are not usually associated with concomitant pancreatic gastrinomas. In patients with duodenal wall gastrinomas, islet cell tumors in the pancreas have been described which contain pancreatic polypeptide or glucagon cells or both and, in some instances, insulin and somatostatin cells.[31]

MULTIPLE POLYPEPTIDE HORMONES. When sought by means of immunocytochemical techniques, islet cell tumors in patients with the Zollinger-Ellison syndrome have been shown almost invariably to contain multiple polypeptide hormones.[31, 68–72] Gastrinomas have been described containing parathyroid hormone, antidiuretic hormone, growth hormone–releasing factor (GRF), vasoactive intestinal peptide, and pancreatic polypeptide, among other hormones. An islet cell carcinoma of the pancreas has been described which contained large amounts of gastrin, ACTH, melanocyte-stimulating hormone, and glucagon.[68] In general, although these islet cell tumors almost always contain multiple hormones and may release more than one hormone, there is usually a single dominant hormone released by the tumor that is responsible for the clinical manifestations. However, careful evaluation has indicated that 30 to 40 per cent of patients with the Zollinger-Ellison syndrome have laboratory or clinical evidence or both of excess release of additional peptide hormones, either from tumors in other locations, such as parathyroid or pituitary, or from the gastrinoma-containing islet cell tumor.[70] Patients with pancreatic islet cell tumors containing and releasing gastrin and glucagon have been reported with clinical manifestations of both Zollinger-Ellison and glucagonoma syndromes.[71]

The mechanism responsible for the development of tumors containing multiple peptides and the factors resulting in selective release of the dominant circulating peptide, with its associated pathophysiologic consequences, have not been elucidated. The most common additional hormone found in gastrinomas is ACTH: approximately 30 per cent of gastrinomas contain ACTH-like immunoreactivity. In most instances, biologically significant amounts are not released into the circulation. Increased serum ACTH levels producing Cushing's syndrome in patients with the Zollinger-Ellison syndrome may result from ACTH release from cells in the gastrinoma or ACTH release from pituitary tumors in patients with MEN I. Increased serum ACTH levels producing Cushing's syndrome were reported in 8 per cent of 75

patients with the Zollinger-Ellison syndrome.[72] Of these, three of 59 patients (5 per cent) with sporadic gastrinoma were found to have Cushing's syndrome. Each of these three patients had severe symptoms produced by ACTH secreted by the islet cell tumor, and each had metastatic gastrinoma, which responded poorly to chemotherapy and led to death within three years of diagnosis. Three of 16 MEN I patients (19 per cent) with the Zollinger-Ellison syndrome had Cushing's syndrome secondary to pituitary ACTH release. In general, Cushing's syndrome symptoms in those patients were mild. Gastrinomas were not metastatic and prognosis was excellent.

PANCREATIC POLYPEPTIDE. Increases in serum pancreatic polypeptide concentrations may be (1) caused by rare pancreatic polypeptide-secreting tumors, or (2) caused by release from pancreatic polypeptide cells within mixed endocrine cell tumors of the pancreas, or, most commonly, (3) associated with hyperplasia of pancreatic polypeptide cells, often accompanying islet tumors of the pancreas, including gastrinomas.[69, 71, 73, 74] Increased serum pancreatic polypeptide levels have not, as yet, been associated with production of a recognized characteristic clinical syndrome. Serum concentrations of pancreatic polypeptide are increased in 10 to 20 per cent of patients with gastrinoma. Although the increase in gastrinoma patients as a group is significant, the frequency of this increase is insufficient to make this determination a marker of value in identifying patients with gastrinoma.[75] In normal subjects, serum pancreatic polypeptide levels generally increase with age. This variation of pancreatic polypeptide level with age must be taken into consideration in assessing the significance of potentially increased serum pancreatic polypeptide levels.

Islet Cell Hyperplasia

Marked hyperplasia of the islets of Langerhans may be found in the pancreas of some patients with clinical features of the Zollinger-Ellison syndrome.[76] Islet cell hyperplasia is characterized by an increase in both the number and size of the islets of Langerhans in the pancreas; frequently, the islets are also densely cellular. Islet cell hyperplasia has been found in approximately 10 per cent of patients with the Zollinger-Ellison syndrome and has been observed in the presence or absence of demonstrated gastrinoma.[77] Islet cell hyperplasia appears to be associated with sporadic gastrinoma, but not with MEN I, in which multiple microadenomas (less than 5 mm in diameter) are present characteristically.[61, 62] The Zollinger-Ellison syndrome does not appear to be caused by islet cell hyperplasia, since removal of hyperplastic islet tissue does not result in resolution of the syndrome, nor does it decrease serum gastrin concentrations. Gastrin has not been shown to be present in hyperplastic islet cells. It is believed that islet cell hyperplasia in patients with Zollinger-Ellison syndrome is the result of, or is associated with, gastrinoma, which may or may not be identified.

Effects on the Small Intestine

In addition to ulcer disease, there are frequent functional and nonspecific morphologic abnormalities of the small intestine in patients with gastrinoma.[78, 79] These are believed to be caused by excessive quantities of acid in the lumen of the small intestine. The mucosa of the duodenum and proximal jejunum is often abnormal, with areas of denuded villi and infiltration of the lamina propria with polymorphonuclear leukocytes and eosinophils, frequently with accompanying edema, hemorrhage, and multiple superficial mucosal erosions. Remaining small intestinal mucosal villi are often broader and stunted. Brunner's glands, which are usually limited in distribution to the proximal duodenum, are increased in number and may be found as distal as the ligament of Treitz in patients with the Zollinger-Ellison syndrome.

Clinical Features

By far the most common clinical manifestations in patients with the Zollinger-Ellison syndrome are those of *peptic ulcer,* which is present in 90 to 95 per cent of patients with gastrinomas.[6, 15, 21, 22, 28, 77] Ulcer symptoms in patients with gastrinoma are often similar to those of patients with common peptic ulcer. However, symptoms may be more persistent, progressive, and less responsive to therapy. The distribution of ulcers in the upper gastrointestinal tract in patients with gastrinoma is similar, but not identical, to that of patients with common peptic ulcer. Approximately 75 per cent of ulcers in patients with the Zollinger-Ellison syndrome are located in the first portion of the duodenum or (much less commonly) in the stomach. Ulcers are usually solitary but may be multiple. In contrast to common peptic ulcer, ulcers associated with gastrinoma may be found in the second, third, or fourth portions of the duodenum or even the jejunum.[6, 15, 33] In a review of patients with the Zollinger-Ellison syndrome, 14 per cent of ulcers were found in the duodenum beyond its first portion, and 11 per cent were found in the jejunum.[6]

The ulcers in patients with gastrinomas are usually moderate or small in size (less than 1 cm in diameter). However, uncommonly, ulcers may be large, exceeding 2 cm in diameter. Recurrent ulcer, either at or distal to the anastomosis, is extremely frequent when usual gastric surgery for peptic ulcer is performed in Zollinger-Ellison patients harboring gastrinomas.[6, 7] This is accompanied commonly by severe complications such as hemorrhage or perforation, or both. Patients with gastrinomas may also develop reflux esophagitis, esophageal ulcerations, and esophageal strictures. Acid peptic reflux disease is more common and may be more severe in patients with the Zollinger-Ellison syndrome than appreciated initially.

Diarrhea occurs in more than one third of patients with gastrinoma and may precede ulcer symptoms by as much as eight years. In approximately 7 per cent of patients with gastrinoma, diarrhea occurs in the absence of clinical ulcer disease.[6] Diarrhea appears to be due principally to the effects of large amounts of hydrochloric acid in the upper gastrointestinal tract. Diarrhea may be reduced or eliminated by aspiration of gastric juice from the stomach. Although the major cause of diarrhea in patients with the Zollinger-Ellison syndrome is the large amount of concentrated hydrochloric acid passed into the small intestine, direct effects of circulating gastrin on the secretory

and absorptive properties of the small intestinal mucosa may play a role in producing diarrhea. Intravenous infusion of large amounts of gastrin increases intestinal secretion of potassium and reduces jejunal absorption of sodium and water, direct effects of gastrin which are not consequences of acidification of the intestinal contents.[80] It has been proposed that acid hypersecretion is necessary to produce diarrhea in these patients and that gastrin may contribute by its direct effects on small intestinal absorption and secretion. This hypothesis is supported by the absence of diarrhea in duodenal ulcer patients (without gastrinoma) with normal serum gastrin levels, who have gastric acid secretory rates similar to those of gastrinoma patients with diarrhea. Gastric acid hypersecretion is associated with increased pepsin secretion by gastric zymogen cells. Gastric acid hypersecretion in patients with the Zollinger-Ellison syndrome can produce pH values as low as 1 and 3.6 in the proximal and distal jejunum, respectively, converting pepsinogens to proteolytically active pepsins, which are believed to contribute to mucosal injury in the small intestine.

Steatorrhea, which is less common in gastrinoma patients than is diarrhea, is produced by several mechanisms.[78, 79] Pancreatic lipase is inactivated by enormous amounts of intraluminal acid in the upper small intestine. Pancreatic lipase is exquisitely susceptible to irreversible denaturation by acidification. Lipase inactivation results in failure to hydrolyze intraluminal triglycerides to their respective diglycerides, monoglycerides, and fatty acids for absorption. In addition, the low pH of the small intestine renders some primary bile acids insoluble, reducing formation of micelles, which are necessary for facilitation of fatty acid and monoglyceride absorption, therefore resulting in steatorrhea.

Patients with the Zollinger-Ellison syndrome may develop *vitamin B_{12} malabsorption,* which is not correctable by oral intrinsic factor.[79] Although gastric secretion of intrinsic factor is normal in these patients, the low intraluminal pH in the intestine interferes with intrinsic factor facilitation of active absorption of vitamin B_{12} by the distal ileum. The precise mechanism by which low pH within the small intestinal lumen reduces intrinsic factor activity is not known. However, when the intraluminal pH is adjusted upward to 7, inhibition of intrinsic factor–mediated vitamin B_{12} absorption is abolished.

Recognizing that clinical symptoms in patients with gastrinoma, especially initially, are usually not distinguishable from those of patients with common peptic ulcer, there are some situations in which heightened suspicion regarding the diagnosis is warranted. These include patients with multiple ulcers in the upper gastrointestinal tract; patients with ulcers distal to the first portion of the duodenum; patients in whom medical treatment with the usual doses and schedules for peptic ulcer disease is ineffective; patients with rapid ulcer recurrence following ulcer surgery; patients with unexplained diarrhea; those with a strong familial history of peptic ulcer; those with a personal or family history suggesting parathyroid or pituitary tumors; and, as will be described, patients with striking gastric acid hypersecretion and/or hypergastrinemia.

Diagnosis

The Zollinger-Ellison syndrome should be considered in patients with compatible clinical features, especially in those with substantially increased gastric acid secretion.

Gastric Acid Secretion. Hypersecretion of gastric acid, a direct effect of hypergastrinemia, is extremely frequent, although not universal in Zollinger-Ellison patients. However, it is sufficiently common and sufficiently impressive with gastrinoma that its presence provides valuable evidence in support of the diagnosis.[81] Most (>90 per cent) patients with the Zollinger-Ellison syndrome have unstimulated gastric acid secretory rates greater than 15 mEq/hr, and may be as high as 150 mEq/hr. Less commonly, however, acid secretory rates of Zollinger-Ellison patients may overlap those of patients with common duodenal ulcer and may even overlap those of normal subjects.

It has been proposed that comparing unstimulated acid output with acid output following maximal stimulation may be of value in identifying patients with gastrinoma.[81, 82] In normal individuals and patients with common peptic ulcer, basal acid output is usually less than 60 per cent of acid secreted after maximum stimulation (for example, with pentagastrin). Since their parietal cell mass is already stimulated by hypergastrinemia, patients with the Zollinger-Ellison syndrome, in response to further maximal stimulation, often increase their gastric acid secretion proportionately less than normal subjects or patients with common peptic ulcer. However, this comparison is of limited value in distinguishing patients with gastrinoma from those without because one half to two thirds of patients with gastrinoma have also been found to have ratios of unstimulated gastric acid output to maximum acid output that are less than 60 per cent.

Barium Contrast Radiographic Examination. Radiographic abnormalities may be of value in suggesting the diagnosis in patients with the Zollinger-Ellison syndrome (Figs. 31–4 and 31–5).[6, 15, 23] The gastric rugal folds are often conspicuously prominent, and the stomach may contain large amounts of fluid. Similar large gastric folds may be found in patients with Ménétrier's disease, gastric lymphoma, or other infiltrative processes. The normally fine small intestinal mucosal folds may be thickened and widened throughout the duodenum and, in some instances, in the jejunum. The duodenum may be dilated, and loops of small intestine may be abnormally separated from one another. Large amounts of fluid are present frequently in the lumen of the small intestine, causing irregular flocculation of barium. Gastrinomas in the pancreas are rarely identified by upper gastrointestinal barium examination. However, tumors arising within the wall of the duodenum may occasionally be visualized by barium studies.

Serum Gastrin. The most sensitive and specific method for identifying patients with the Zollinger-Ellison syndrome is demonstration of increased serum gastrin concentrations.[4, 83] In normal subjects and in patients with common duodenal ulcer, fasting serum gastrin concentrations average approximately 50 to 60 pg/ml (or less), with an upper limit of normal in most laboratories approximating 150 pg/ml.[84] Patients with gastrinoma almost al-

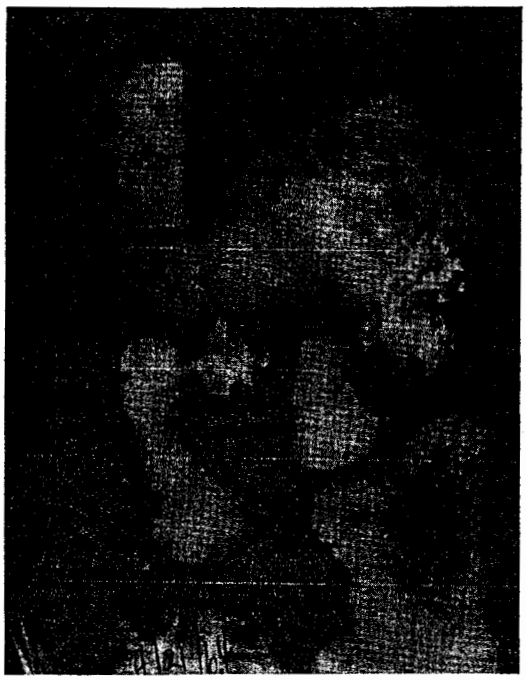

Figure 31–4. Large greater curvature and duodenal ulcers associated with the Zollinger-Ellison syndrome. Note also the edematous gastric and small bowel folds. (Courtesy of M. H. Sleisenger, M.D.)

ways have fasting serum gastrin levels greater than 150 pg/ml and may have serum gastrin concentrations as high as 450,000 pg/ml. Rare patients have been reported with fasting serum gastrin levels in the normal range.[85] Markedly increased fasting serum gastrin concentrations (greater than 1000 pg/ml) in patients with compatible clinical features and gastric acid hypersecretion establish the diagnosis of the Zollinger-Ellison syndrome. The magnitude of the increase in the fasting serum gastrin level in patients with gastrinoma has been found to correlate with the benign or malignant nature of the tumors.[86] Most patients with fasting serum gastrin levels greater than 1500 pg/ml are found to have metastatic gastrinoma. Aspiration of gastric juice has been reported to reduce serum gastrin concentrations in some patients with gastrinoma.[87] Reduction of hypergastrinemia by aspiration of gastric contents may be due to elimination of acid-induced stimulation of secretin release from the mucosa of the proximal small intestine.

It must be emphasized that marked hypergastrinemia is not specific for patients with gastrinoma. In fact, the most common cause of increased serum gastrin levels is reduced gastric acid secretion. The principal mechanism for inhibition of gastrin release in normal subjects is acidification of the antral contents; when the pH of antral contents is reduced to 3 (or lower), gastrin release is inhibited, and when the pH is reduced to 1.5, gastrin release is eliminated.[88] Mean serum gastrin concentrations in patients with pernicious anemia approximate 1000 pg/ml, and are in the same range as patients with gastrinomas.[89] In pernicious anemia the pH of the gastric contents, even in response to maximal stimulation, is not reduced below 6. Instillation of 0.1 M hydrochloric acid into the stomachs of patients with pernicious anemia reduces increased serum gastrin toward normal levels.[83] In general, in pernicious anemia the atrophic inflammatory process involves principally the mucosa of the body and fundus of the stomach with relative sparing of the antral mucosa, the normal residence of gastrin. In pernicious anemia, achlorhydria causes failure of the normal acid–gastrin feedback control mechanism, which is important in the regulation of antral gastrin release. Patients with other varieties of gastric atrophy with chronic gastritis and substantially reduced or absent gastric acid secretion also frequently exhibit increased serum gastrin levels. These include patients with chronic gastritis and hypochlorhydria or achlorhydria in the absence of pernicious anemia, as well as patients with gastric carcinoma with reduced or absent gastric acid secretion.[90–92] Serum gastrin concentrations in such patients tend to be lower than in patients with pernicious anemia, but higher than in normal subjects.

Elevated serum gastrin concentrations also have been reported in an assortment of other clinical states, including rheumatoid arthritis, vitiligo, and diabetes mellitus, in the presence or absence of gastroparesis. Increased fasting serum gastrin levels have also been described in patients and experimental animals with renal insufficiency, in patients with the retained and excluded antrum syndrome, and in some patients with massive resection of the small intestine.[93–96] Hypergastrinemia in patients with renal insufficiency, in general, correlates directly with the severity of renal impairment. Hypergastrinemia was believed originally to be secondary to reduced renal cortical degradation of gastrin. However, it is unlikely that this explanation is complete or correct, since anephric patients

Figure 31–5. Huge jejunal ulcer in Zollinger-Ellison syndrome after subtotal gastrectomy. (Courtesy of M. H. Sleisenger, M.D.)

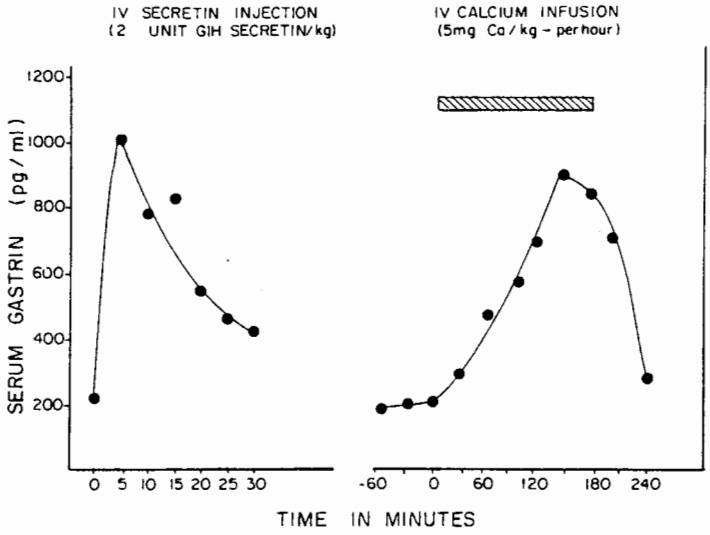

Figure 31–6. Serum gastrin responses to intravenous secretin injection *(left)* and to intravenous calcium infusion *(right)* in a patient with gastrinoma.

exhibit normal rates of gastrin clearance. Increased serum gastrin concentrations also have been described in patients with pheochromocytoma, in whom hypergastrinemia is believed to be secondary to catecholamine-stimulated gastrin release.[97] Increased serum gastrin levels may be found in a rare population of patients with duodenal ulcer disease caused by antral gastrin cell (G cell) hyperplasia and hyperfunction.

Provocative Tests. Several provocative tests have been applied to identify patients with the Zollinger-Ellison syndrome.[98–104] These tests are of greatest value in patients without striking hypergastrinemia because, as indicated previously, in patients with compatible clinical presentation, marked gastric acid hypersecretion, and fasting serum gastrin concentrations that exceed 1000 pg/ml, the diagnosis of the Zollinger-Ellison syndrome is established. However, in patients with a clinical course consistent with the Zollinger-Ellison syndrome and marginal or slightly increased serum gastrin concentrations (150 to less than 1000 pg/ml), provocative tests may be necessary in attempts to establish or exclude the diagnosis. Three major provocative tests have been used: (1) intravenous secretin injection, (2) intravenous calcium infusion, and (3) ingestion of a standard test meal, each performed with multiple measurements of serum gastrin concentrations.

The intravenous secretin injection test is clearly the provocative test of greatest value in identifying patients with gastrinomas. In normal individuals and in patients with common duodenal ulcer, intravenous secretin slightly decreases, has no effect, or slightly increases serum gastrin levels.[105] In contrast, in patients with the Zollinger-Ellison syndrome, intravenous secretin evokes often dramatic increases in serum gastrin concentrations.[101, 102] The following is recommended as a method for performance and interpretation of the intravenous secretin injection test in patients suspected to have the Zollinger-Ellison syndrome.[106] Pure porcine secretin (Kabi Group, Inc., Greenwich, CT), 2 units per kilogram, is given by intravenous injection over a 30-second interval. Serum samples are obtained for radioimmunoassay measurement of gastrin five minutes before administration of secretin, immediately before secretin administration, at two and five minutes, and then at five-minute intervals for a total of 30 minutes after secretin injection. In patients with gastrinoma, serum gastrin concentrations increase promptly by at least 200 pg/ml (usually at 2 minutes and virtually always by 10 minutes) after intravenous secretin injection (Fig. 31–6). The serum gastrin concentration then returns gradually to or toward the preinjection level. Boot's secretin should not be used in the secretin injection test for gastrinoma, in part because it is much less potent than Kabi secretin, but, more important, because it contains materials immunoreactive with many gastrin antibodies used for gastrin radioimmunoassay, and therefore may produce spuriously elevated serum gastrin levels and erroneous false-positive results.[107]

In the calcium infusion test, calcium, as calcium gluconate, has been given by constant intravenous infusion at a rate of 5 mg calcium per kilogram body weight per hour for a three-hour period.[98] Serum samples are obtained for gastrin radioimmunoassay 30 minutes before initiation of calcium infusion, at the time when calcium infusion is begun, and at 30-minute intervals thereafter for four hours. In most patients with the Zollinger-Ellison syndrome, intravenous calcium infusion evokes substantial increases in serum gastrin concentrations (i.e., usually more than a 400 pg/ml increase), with smaller increases in patients with common duodenal ulcer. Maximum serum gastrin concentrations are usually achieved during the final hour of intravenous calcium infusion.

A third provocative test that has been suggested is that of feeding a standard meal; one meal proposed for this purpose includes one slice of bread, 200 ml of milk, one boiled egg, and 50 gm of cheese. This meal contains 20 gm fat, 30 gm protein, and 25 gm carbohydrate. Serum samples for gastrin radioimmunoassay are obtained 15 minutes before and immediately before initiation of the meal, and then at 15-minute intervals for 90 minutes.

Interpretation of Serum Gastrin. The characteristic serum gastrin profile in patients with gastrinoma includes fasting hypergastrinemia (greater than 150 pg/ml), prompt and substantial increases in serum gastrin in response to intravenous secretin (increase by more

than 200 pg/ml), and substantial increases in serum gastrin with calcium infusion (increase by more than 400 pg/ml). The most frequent error in interpretation of fasting serum gastrin levels is the presumption of a diagnosis of gastrinoma on detection of hypergastrinemia. It bears emphasis that achlorhydria or hypochlorhydria is a vastly more common cause of hypergastrinemia than is gastrinoma. When fasting hypergastrinemia is identified, studies should be performed to determine the presence of gastric acid hypersecretion or, alternatively, achlorhydria or acid hyposecretion.[108] This determination should be performed before initiating any provocative tests (e.g., secretin stimulation). Achlorhydria or profound hypochlorhydria can readily account for strikingly increased fasting serum gastrin levels and can be associated with exaggerated gastrin release in response to secretin.[109] When achlorhydria or profound hypochlorhydria is found in association with hypergastrinemia, no further search for gastrinoma is justified.

The provocative tests in the Zollinger-Ellison syndrome are summarized in Table 31–1. With intravenous injection of secretin, a positive response (increase greater than 200 pg per milliliter) occurs in over 95 per cent of patients with proven gastrinoma.[106] False-positive tests with intravenous secretin, performed as suggested earlier and in Table 31–1, have been reported rarely. The calcium infusion test is less sensitive and less specific than the secretin injection test in identifying patients with gastrinomas. Exaggerated gastrin release in response to calcium infusion occurs in more than 80 per cent of patients with gastrinoma. In the absence of a positive gastrin release response to secretin exaggerated gastrin release with calcium infusion is unusual in patients with gastrinoma. Calcium infusion has been reported to amplify the serum gastrin response to secretin in some patients with gastrinoma. An exaggerated response to calcium, although rare in normal subjects or patients with common duodenal ulcer, may be found in some patients (approximately 50 per cent) with hypergastrinemia of antral origin (e.g., achlorhydria) in the presence or absence of pernicious anemia. For the reasons cited, the calcium infusion test does not have a major role in the clinical diagnosis of the Zollinger-Ellison syndrome and usually is not necessary.

In an extremely small proportion of patients with duodenal ulcer, gastric acid hypersecretion is accompanied by elevated serum gastrin concentrations, which appear secondary to antral gastrin cell (G cell) hyperplasia and hyperfunction.[104, 109, 110] This entity is much rarer than the Zollinger-Ellison syndrome. Serum gastrin levels in these patients are almost always less than 1000 pg/ml. In contrast to patients with gastrinomas, patients with antral gastrin cell hyperfunction show decreases, no change, or only slight increases in serum gastrin levels after intravenous secretin injection. Some authors have reported marked increases in serum gastrin concentrations (greater than 200 per cent increase) following the test meal in these patients. It has been suggested that this test may be of value in distinguishing these patients from those with the Zollinger-Ellison syndrome due to gastrinoma, who have been reported to release less gastrin in response to a test meal. Other investigators more recently have found similarly large gastrin release responses to the test meal in some patients with gastrinoma, suggesting that the meal stimulation test is of limited value in distinguishing patients with antral gastrin cell hyperplasia from those with the Zollinger-Ellison syndrome.[111] The meal stimulation test is not necessary or indicated in the evaluation of most patients in whom gastrinoma is considered and clearly provides less useful information than the secretin injection test.

Tumor Localization. Once the diagnosis of gastrinoma is established it is imperative to attempt to locate the tumor, recognizing that localization of gastrinomas is usually difficult and may be impossible. The tumors present substantial challenges in identification because of their usual small size, the many differing locations in which they may be found, and their frequent multiplicity or multicentricity. In approximately 40 to 45 per cent of patients in whom there is persuasive clinical and laboratory evidence of gastrinoma, the tumors cannot be identified at surgery.[32–36]

A variety of diagnostic techniques have been used to localize gastrinomas in patients with the Zollinger-Ellison syndrome.[112–118] Imaging studies that have been utilized in efforts to locate tumors have included selective arteriography, computerized axial tomography (CT scan), ultrasonography and magnetic resonance imaging (Figs. 31–7 and 31–8). Initial studies with selective arteriography in efforts to identify gastrinomas were disappointing. Only approximately 13 to 25 per cent of gastrinomas identified at surgery were detected by selective angiography, with a high frequency of false-positive studies (70 per cent). More recently, selective arteriography has been reported to detect about one third of patients with clinical and biochemical evidence of gastrinoma (approximately

TABLE 31–1. COMPARISON OF SERUM GASTRIN RESPONSE

DISORDER	SECRETIN INJECTION	CALCIUM INFUSION	TEST MEAL
Zollinger-Ellison syndrome (gastrinoma)	Substantial increase in serum gastrin (increase is usually greater than 200 pg/ml)	Exaggerated release of gastrin (usually serum gastrin increases by more than 400 pg/ml)	Variable increases in serum gastrin (from minimal/absent to 200 per cent increase)
Antral G-cell hyperfunction	Decrease, no change, or slight increase in serum gastrin (no increase greater than 200 pg/ml)	May or may not have increase in serum gastrin greater than 400 pg/ml	Exaggerated release of gastrin in response to feeding (increase by >200 per cent)
Common duodenal ulcer	Decrease, no change, or slight increase in serum gastrin (no increase greater than 200 pg/ml)	Small increase in serum gastrin (less than 400 pg/ml)	Moderate increase in serum gastrin (often slightly more than normal, but less than in G-cell hyperfunction)

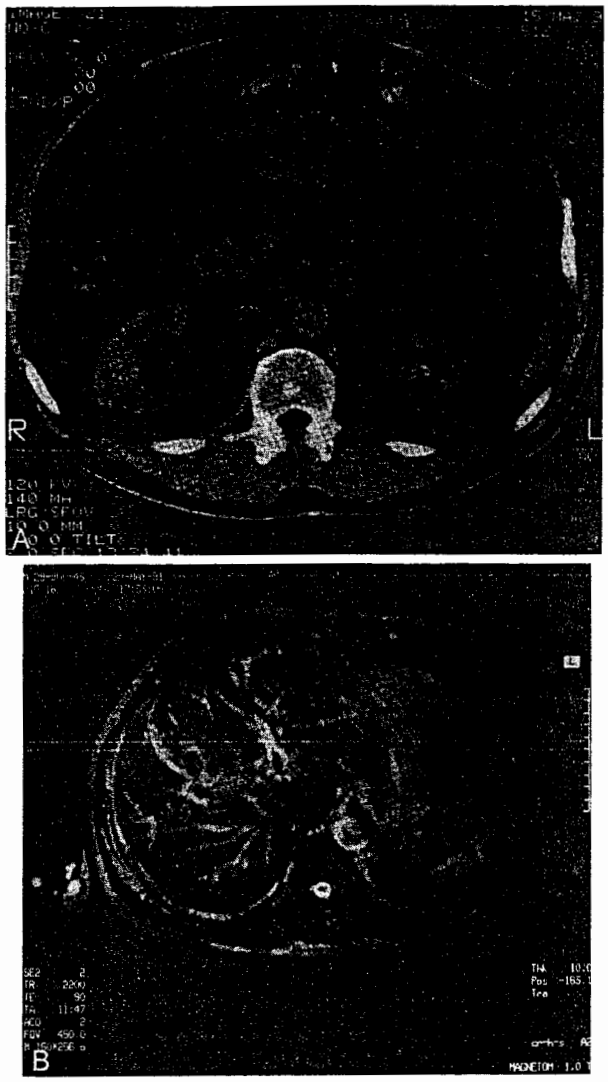

Figure 31–7. Computerized axial tomography (CT) scan. *A*, Demonstrating thickened gastric folds and increased secretions in stomach (supine position). Gastrinoma is seen as circular mass anterior and to left of aorta. *B*, Magnetic resonance imaging (MRI) study demonstrates enormously thickened gastric wall in the same patient.

60 per cent of gastrinomas that were found at surgery). When identified by arteriography, gastrinomas appear as focal areas of dye uptake during the later arterial and capillary phases. It is not possible arteriographically to distinguish intrapancreatic tumors from tumors located in the wall of the immediately adjacent duodenum. Selective celiac and hepatic artery angiography has proved to be the best technique for identifying and characterizing hepatic metastasis in patients with gastrinoma. Computed tomography is successful in identifying gastrinoma in approximately 30 per cent of cases. Ultrasound has been found to be less sensitive, being positive in only about 15 per cent of patients with evidence of gastrinoma. Intravenous bolus-enhanced, thin-section computed tomography has been suggested as the optimal computed tomographic technique. Performance of both selective arteriography and computed tomography has been reported to detect 44 per cent of gastrinomas in Zollinger-Ellison patients and 80 per cent of gastrinomas that were located at surgery.[35] Unfortunately, neither visceral arteriography nor computed tomography is sufficiently sensitive to identify tumors less than approximately 1.5 cm in diameter.

Magnetic resonance imaging (MRI) has been disappointing in detecting gastrinomas and appears, thus far, to be less effective than computed tomography.[115–117] Magnetic resonance imaging is approximately as effective as abdominal ultrasound in identifying gastrinomas. The ability of MRI to identify extrahepatic gastrinomas is related to tumor size. This procedure does not detect tumors less than 1 cm in diameter and has been reported to detect only 50 per cent of tumors 3 cm or larger. MRI has not been found to be as effective as selective angiography or computed tomography in detecting intrahepatic metastatic gastrinoma. Newer magnetic imaging techniques currently under evaluation may prove to be of greater value in localizing gastrinomas. It has been proposed that the initial evaluation for localization of gastrinoma in patients with the Zollinger-Ellison syndrome include computed tomography, ultrasound, and MRI fol-

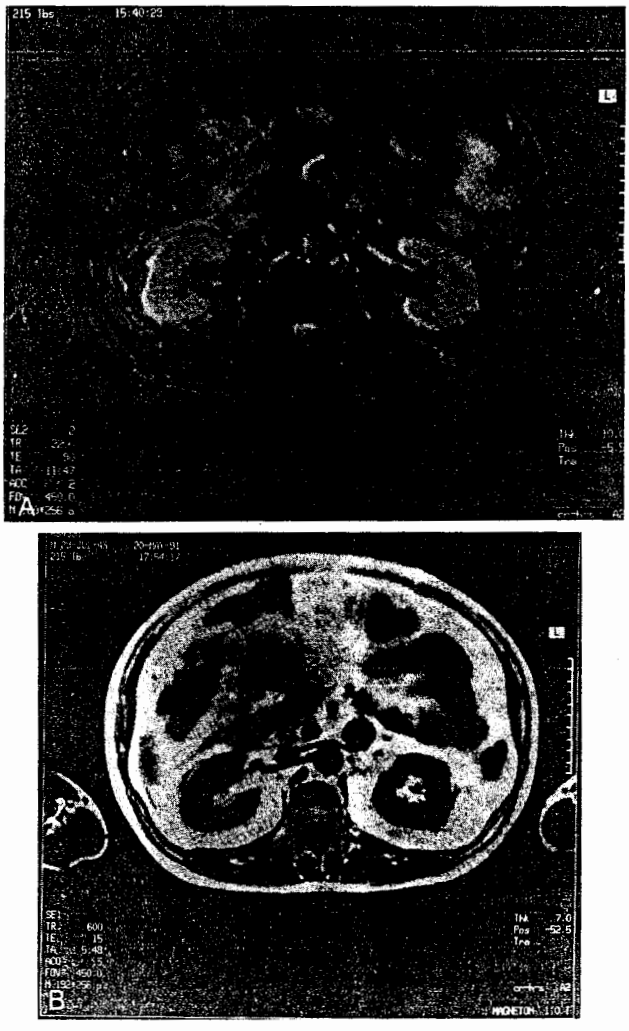

Figure 31–8. Same patient as in Figure 31–7. MRI studies using different parameter settings. In both *A* and *B*, gastrinoma (as in Fig. 31–7) is seen anterior and to left of aorta. In *B*, slender, darkly contrasting vein extends to the right from the gastrinoma.

lowed by selective arteriography. The frequency of gastrinomas in the wall of the proximal duodenum also supports the role of upper endoscopy in efforts to localize gastrinomas in these patients.

Transhepatic portal venous sampling with identification of localized serum gastrin gradients in the portal vein and its tributaries, a technically demanding procedure, has also been utilized in efforts to localize gastrinoma. Results with transhepatic portal venous sampling for gastrinoma localization have varied. Some authors have found the procedure to be comparable to results with computed tomography, whereas others have reported localization of gastrinomas with portal venous sampling in approximately 63 per cent of patients when all imaging studies were negative.[35, 114, 119, 120]

Most recently, localization of gastrinomas by selective injection of secretin into the gastroduodenal, splenic, and superior mesenteric arteries with measurements of hepatic vein serum gastrin concentrations has been reported.[121] The selective arterial secretin injection (SASI) test involves injection of 20 to 30 units of secretin by catheter into the superior mesenteric artery, gastroduodenal artery, or splenic artery. Blood for gastrin radioimmunoassay is obtained from the hepatic vein before and 20, 40, 60, 90, and 120 seconds after secretin injection. Gastrinoma localization by selective arterial injection of secretin is based on consideration of the blood supply provided by the arteries into which secretin is injected. The gastroduodenal artery feeds the upper half of the head of the pancreas and upper duodenum. The splenic artery feeds the body and tail of the pancreas. The inferior pancreaticoduodenal artery, a branch of the superior mesenteric artery, feeds the lower half of the head of the pancreas and the lower duodenum. Positive responses for gastrinoma localization are characterized by hepatic vein serum gastrin increases by more than 80 pg/ml within 40 seconds of secretin injection to a level at least 20 per cent greater than the preinjection serum gastrin level. The selective secretin arterial injection test has been reported to localize gastrinomas that were not identified by computed tomography, ultrasound, and selective arteriography.[121]

Treatment

Selection of appropriate therapy for individual patients with the Zollinger-Ellison syndrome must be individualized. Considerations regarding treatment selection in patients with gastrinoma include those related to ulcer disease and/or diarrhea secondary to gastrin-mediated gastric acid hypersecretion and to those related to the potentially malignant properties of the tumor. The principal threat to life in patients with the Zollinger-Ellison syndrome is not complications of ulcer disease, as it was originally for these patients, but rather malignant invasion by these tumors. Present data suggest that 50 per cent or more of patients with gastrinoma not resected will die from direct invasive effects of the gastrinoma. Choice of best treatment in individual patients may be difficult and, in some instances, controversial. Both medical and surgical treatment alternatives must be considered carefully on behalf of each patient with Zollinger-Ellison syndrome.

Surgical Treatment. For more than 20 years following the original description of the Zollinger-Ellison syndrome, total gastrectomy was considered by virtually all experts to be the treatment of choice in the management of patients with the Zollinger-Ellison syndrome.[6, 7, 15, 21, 22, 80] This conclusion was based on recognition that mortality was lowest in patients in whom total gastrectomy was the initial surgical procedure, as opposed to total gastrectomy that followed earlier ulcer operation (or, more commonly, operations). Total gastrectomy, which removes the major target organ for gastrin, clearly is effective in curing ulcer disease in patients with the Zollinger-Ellison syndrome. At present, however, total gastrectomy is seldom necessary or indicated in the management of these patients. Potent antisecretory agents are now available which reduce acid secretion effectively, eliminating the need for total gastrectomy when the gastrinoma cannot be removed surgically.

Surgical resection, when possible, is the optimal treatment for patients with the Zollinger-Ellison syndrome.[24–27, 33, 110] The primary goal for treatment of these patients is complete surgical removal of the gastrinoma, which eliminates the source of excessive gastrin release responsible for gastric acid hypersecretion and ulcer disease and protects the patient against the life-threatening effects of the malignant properties of these tumors, now the major cause of death in patients with gastrinoma. Early reviews of experience in the surgical treatment of patients with the Zollinger-Ellison syndrome suggested that only a small proportion of gastrinomas, probably less than 5 per cent, could be resected successfully. It has been estimated that using presently available diagnostic and surgical methods, it should be possible to resect gastrinomas completely with cure in approximately 30 to 40 per cent of patients with gastrinomas.[24, 25, 33, 34, 122–125] Ellison and colleagues reviewed results in 60 patients with the Zollinger-Ellison syndrome identified and treated before or after 1970, at which time radioimmunoassay measurement of gastrin became available, thereby permitting earlier and more precise diagnosis.[124] Striking differences were observed in the two groups. The prevalence of metastatic disease at the time of diagnosis decreased from 56 per cent to 23 per cent after 1970. The opportunity for cure in these patients with the Zollinger-Ellison syndrome increased from 4 per cent to 30 per cent after 1970. The 5-year survival rate increased from 44 per cent to 82 per cent, and the 10-year survival rate increased from 40 per cent to 64 per cent after 1970.

Patients with the Zollinger-Ellison syndrome should have a careful preoperative evaluation in an attempt to localize the gastrinoma. Surgical exploration with intent to resect the gastrinoma should be performed in all patients with the Zollinger-Ellison syndrome except those in whom surgery is contraindicated and those with metastatic disease judged to be unresectable. Surgery with intent to resect tumor should be undertaken even in those instances in which the tumor is not identified by preoperative localization efforts. The knowledge, experience, and skill of the surgeon in the careful and complete examination and resection of gastrinoma in patients with the Zollinger-Ellison syndrome are absolute requirements

for success in the surgery of these patients. The surgeon should perform a careful examination of the pancreas, duodenum, and stomach as well as the mesenteric and retroperitoneal areas, liver, remainder of the small intestine, and pelvis. All masses, nodules, or potentially involved lymph nodes should be removed for histologic examination. Duodenotomy and intraluminal examination must be integral components of the surgical procedure in these patients, since duodenal gastrinomas, the most common form of extrahepatic gastrinoma, are excellent candidates for complete cure by resection. If gastrinoma is identified at surgery and is resectable, complete surgical removal of the gastrinoma is recommended. When this is performed successfully, it is not necessary to include gastrectomy. All lymph nodes containing gastrinoma should be removed. Recent studies indicate successful gastrinoma resection in approximately 21 to 45 per cent of patients, with cure rates from 12 per cent to 36 per cent.[53] Complete tumor removal is more often possible with extrapancreatic gastrinomas, approximately half of which can be resected completely.[28, 36, 126] Surgery for gastrinomas found in the pancreas should be enucleation when possible, but when the gastrinoma is located in the tail of the pancreas, the tail should be resected. In most instances, because of its excessive morbidity and mortality in patients with the Zollinger-Ellison syndrome, pancreatoduodenectomy (Whipple's procedure) is not recommended and should be a consideration only when there appears to be great likelihood for cure and a lesser surgical procedure cannot be performed. Blind distal pancreatectomy and total pancreatectomy are not recommended in patients with the Zollinger-Ellison syndrome. Duodenal wall gastrinomas, usually solitary in patients with sporadic gastrinomas and multiple in patients with MEN I, are usually small, readily resectable, and benign, and even when malignant their metastases are usually to local lymph nodes. Occult duodenal wall gastrinomas probably account for the majority of gastrinomas found in peripancreatic lymph nodes when no gastrinoma had been identified in the pancreas.

If metastasis is not found at abdominal exploration or if metastasis is confined to lymph nodes, it is unlikely that the patients will succumb to metastatic disease, whereas hepatic metastasis is an ominous finding in patients with gastrinoma.[24, 125] In these patients invasive tumor extension usually continues until the patient dies. Aggressive resection of metastatic gastrinoma in the liver with favorable clinical responses has been reported.[127] If metastatic gastrinoma in the liver is completely and safely resectable, it probably should be resected. Patients may also have rare primary hepatic gastrinomas, which have been cured by complete removal of the hepatic tumor.[126]

If gastrinomas cannot be located and/or resected at operation, surgical options include total gastrectomy and proximal gastric vagotomy. Partial gastric resection should not be considered. Patients with the Zollinger-Ellison syndrome treated by total gastrectomy are subject to the same complications as any patient who has undergone total gastrectomy. They do live longer and have less severe metabolic consequences than do patients who have undergone total gastrectomy for carcinoma of the stomach. After total gastrectomy, these patients require intramuscular administration of vitamin B_{12} (100 μg per month). Oral administration of calcium and vitamin D is recommended to reduce the severity of osteoporosis and osteomalacia, which occur commonly after total gastrectomy. Proximal gastric vagotomy in patients with gastrinoma has been reported to reduce substantially gastric acid secretion and to reduce required doses of H_2 receptor antagonist.[34] In a small portion of patients with gastrinoma, antisecretory drugs were not required after proximal gastric vagotomy. Total pancreatectomy is rarely, if ever, justified in patients with the Zollinger-Ellison syndrome.

MEDICAL TREATMENT. Until *H_2 receptor antagonists* became available, there had been no effective medical therapy for patients with the Zollinger-Ellison syndrome. The development of H_2 receptor antagonists provided therapeutic agents that proved effective in producing symptom relief, reducing acid secretion, and healing ulcers.[128–130] Cimetidine, the first H_2 receptor antagonist shown to be effective, decreased gastric acid secretion, improved clinical symptoms, and healed ulcers in 80 to 85 per cent of patients with the Zollinger-Ellison syndrome. Ranitidine and famotidine have been shown to be as effective as, or more effective than, cimetidine in the treatment of patients with the Zollinger-Ellison syndrome. Doses of H_2 receptor antagonists required in the treatment of patients with the Zollinger-Ellison syndrome have exceeded substantially those used to treat common duodenal ulcer. Average total daily doses of H_2 receptor antagonists required to reduce gastric acid secretion to satisfactory levels (less than 10 mEq/hr) in patients with the Zollinger-Ellison syndrome have been 7.8 gm (range 1.2 to 13.2 gm) for cimetidine, 2.1 gm (range 0.6 to 3.6 gm) for ranitidine, and 0.24 gm (range 0.08 to 0.48 gm) for famotidine.[130] There is no evidence that treatment with H_2 receptor antagonists influences serum gastrin levels either adversely or favorably, nor is there evidence that such treatment influences the biologic behavior of the gastrinoma.

It is not unusual for Zollinger-Ellison patients who were initially responsive to become resistant to treatment with H_2 receptor antagonists. With long-term treatment and extended observation, as many as 50 per cent of patients with the Zollinger-Ellison syndrome have been reported to fail H_2 receptor antagonist treatment.[131] Symptoms do not correlate well with ulcer healing or ulcer recurrence in Zollinger-Ellison patients treated with H_2 receptor antagonists.[132] Ulcer disease may continue or recur in the absence of symptoms. For this reason, it has been proposed that the dose of H_2 receptor antagonist or other antisecretory agent be used which reduces gastric acid output to less than 10 mEq/hr for the hour that immediately precedes the next scheduled dose of the antisecretory medication.[126, 130] Anticholinergic agents have occasionally been used to increase the effectiveness of concurrent administration of H_2 receptor antagonists in reducing gastric acid secretion in Zollinger-Ellison patients. Intravenous infusion of H_2 receptor antagonists is of value in the stabilization and in the preoperative and perioperative management of patients with gastrinomas.

The development of *omeprazole* has provided a powerful antisecretory agent that strikingly reduces gastric acid secretion and produces ulcer healing and symptom relief in patients with the Zollinger-Ellison syndrome.[133–135]

Omeprazole is a substituted benzimidazole that inhibits hydrogen potassium ATPase, the proton pump that constitutes the terminal step in parietal cell secretion of hydrogen ions (see Ch. 27). Omeprazole reduces gastric acid secretion by 77 to 100 per cent in patients with the Zollinger-Ellison syndrome and has been found to be effective in the treatment of patients whose ulcers and symptoms were not controlled adequately by high doses of H_2-receptor antagonists. Treatment with omeprazole has produced ulcer healing within two weeks in more than 60 per cent of patients with the Zollinger-Ellison syndrome, with 90 to 100 per cent healing at four weeks.

Currently, when medical therapy is indicated, omeprazole is the drug of choice for the treatment of patients with the Zollinger-Ellison syndrome. The dose required in most patients is 60 to 80 mg per day, which can be administered in a single daily oral dose in approximately 70 per cent of patients with gastrinoma. During treatment of patients with the Zollinger-Ellison syndrome with omeprazole, gastric acid secretion should be maintained at levels less than 10 mEq/hr. An initial dose of 60 mg is recommended. In most patients, 60 mg omeprazole is effective in substantially reducing gastric acid secretion, in reducing symptoms, in curing ulcer, and in preventing ulcer recurrence. If the 60-mg dose of omeprazole does not reduce gastric acid secretion to less than 10 mEq/hr by 24 hours after the initial dose, it is recommended that dosage be increased to 80 mg per day. If a dose greater than 80 mg omeprazole per day is required, it is suggested that the dosage be divided into two doses per day. If omeprazole at 60 mg per day induces achlorhydria, the dose should be reduced to 40 mg per day.

Omeprazole is indicated as initial treatment of patients with the Zollinger-Ellison syndrome, during diagnosis and evaluation, and for prolonged treatment of patients who are poor candidates for gastrinoma resection. It is the antisecretory medical treatment of choice for patients in whom attempted resection of tumor has been unsuccessful and total gastrectomy is not performed. When instituted for long-term management of patients with the Zollinger-Ellison syndrome, omeprazole treatment should not lapse or be interrupted, since its discontinuance often is followed by ulcer recurrence, frequently with complications such as hemorrhage, perforation, or both.

Two subsets of patients with gastrinoma have been reported to require maintenance of gastric acid secretion at levels less than 5 mEq/hr. These include patients with *partial gastric resection*, with or without vagotomy, and patients with moderately severe or *severe acid–reflux disease* involving the esophagus.[136, 137] The frequency and potential severity of acid–reflux disease in patients with the Zollinger-Ellison syndrome has been appreciated only relatively recently. Approximately 25 per cent of patients with gastrinoma have clinically significant reflux esophagitis, and about 15 per cent have severe erosive esophagitis, many with esophageal strictures. In order to protect the esophageal mucosa from serious damage, these patients may require reduction of gastric acid secretion with omeprazole to rates even less than 1 mEq/hr.[136] Requirements for greater reduction in acid secretion in patients with severe gastroesophageal reflux disease reflects the limitations of esophageal mucosal defense mechanisms against the corrosive effects of refluxed acid–peptic gastric juice. Gastrinoma patients with partial gastric resection with Billroth II anastomosis may develop stomal ulcer unless gastric acid secretion is reduced to less than 5 mEq/hr, and in some instance to less than 1 mEq/hr.[137] There is no adequate explanation available for the enhanced requirements for antisecretory medications in patients who have undergone partial gastric resection.

Somatostatin reduces gastric acid secretion by its direct inhibitory effects on parietal cells and indirectly by inhibiting gastrin release. Use of native somatostatin as a therapeutic agent has been limited by its brief half-life. A synthetic analog of somatostatin, with a much longer duration of biologic action, has been administered to patients with the Zollinger-Ellison syndrome.[138, 139] This long-acting somatostatin analog (octreotide, Sandostatin) has a half-life of approximately two hours. Octreotide is administered subcutaneously in doses from 100 to 250 μg three times a day. This somatostatin analog has been reported to reduce serum gastrin levels substantially for 16 hours and to decrease gastric acid secretion for as long as 18 hours. Octreotide is approved for treatment of patients with carcinoid tumors and with VIPomas but not for patients with the Zollinger-Ellison syndrome. The drug appears to have no clear long-term treatment advantage over omeprazole, but it may be of use in selected instances requiring short-term parenteral administration of an antisecretory agent.

Patients with metastatic gastrinomas have been treated with a variety of chemotherapeutic agents, including streptozotocin, streptozotocin with 5-fluorouracil, or both agents with doxorubicin.[140–142] Decreases in both metastatic tumor mass and serum gastrin levels have been reported in more than half the patients treated by intra-arterial administration of streptozotocin. Some authors favor early treatment of patients with documented metastatic disease, whereas most others advocate chemotherapy only for symptoms from tumor mass or organ replacement, almost always involving the liver. There is no support for use of chemotherapy in patients with metastatic gastrinoma confined to lymph nodes. Chemotherapy has no primary therapeutic role in attempts to reduce gastric acid hypersecretion and consequent ulcer disease associated with gastrinoma, which can be treated effectively with omeprazole. Chemotherapy in patients with metastatic gastrinoma appears to have its major benefit in reducing tumor size and improving symptoms due to invasive or mass effects of the tumor.

In a small number of patients, tumor infarction produced by hepatic arterial embolization has been used as palliative treatment for reduction of metastatic hepatic tumor mass and associated symptoms.[143] Hepatic arterial embolization of metastatic gastrinoma involving the liver has been reported to be associated with a direct 10 to 14 per cent mortality, as well as additional mortality secondary to hepatic abscess and infection. The benefits of hepatic arterial embolization have yet to be proved in patients with gastrinoma. Therefore, at this time the procedure probably should not be recommended.

Decisions for Treatment. Decisions regarding selection of therapy for patients with gastrinoma are influenced by recognition that these tumors are often multifocal, usually malignant (although of highly variable biologic invasiveness), and frequently metastatic at the

time of diagnosis. In addition, tumors, even after careful preoperative evaluation and examination at surgery, often cannot be located.

The following are proposed as general guidelines for the selection of therapy in patients with the Zollinger-Ellison syndrome. Omeprazole is effective treatment for gastric acid hypersecretion and ulcer in Zollinger-Ellison patients and should be used during evaluation and for preoperative control. It should be used as indefinitely extended treatment of gastrinoma patients in whom surgery is not possible and/or when tumor cannot be found or resected. Intravenous H_2 receptor antagonists may also be of value and be required for stabilization during patient evaluation and in the perioperative period. After careful evaluation in attempts to localize the gastrinoma, surgical exploration with the intention to resect the tumor should be performed in all patients with the Zollinger-Ellison syndrome, except in those in whom tumor is clearly not resectable or surgery is refused or contraindicated. When a solitary gastrinoma is found and appears to be resected completely, there is no need for total gastrectomy. All lymph nodes containing tumor should be removed. Aggressive surgical removal of metastatic gastrinoma in the liver may benefit selected patients and should be considered when metastatic disease may be safely and completely removed.

When the diagnosis of gastrinoma appears certain and it is not possible to locate the tumor despite maximum efforts, the physician and patient have several therapeutic alternatives. Options include lifelong treatment with an antisecretory agent, e.g., omeprazole. For patients in whom lifelong treatment with omeprazole is not possible or accepted and in whom complete gastrinoma resection is not possible, total gastrectomy or proximal vagotomy should be considered.

Prognosis

Complete tumor removal is followed promptly by reductions in serum gastrin to normal levels, elimination of gastric acid hypersecretion, and disappearance of ulcer disease and/or diarrhea and is associated with an otherwise normal life expectancy. Complete surgical removal of the gastrinoma is achieved in approximately 30 per cent of patients with gastrinoma. With earlier diagnosis and better medical therapy for ulcer disease, eventual malignant invasion by tumor has replaced ulcer complications as the major factor responsible for mortality in patients with gastrinoma. Treatment with omeprazole almost always induces substantial reduction in gastric acid secretion, disappearance of ulcer symptoms and diarrhea, and ulcer healing in patients with the Zollinger-Ellison syndrome. When initiated for an indefinite time, omeprazole treatment should not be discontinued or allowed to lapse, because of the potential for frequent, prompt, and often aggressive ulcer recurrence after discontinuance. The 5-year survival estimates for all patients with gastrinoma have been reported form 62 to 75 per cent. Five-year survival in patients with metastatic gastrinoma in the liver is estimated to be approximately 20 per cent and the 10-year survival is approximately 10 per cent.

When the gastrinoma cannot be resected but proximal gastric vagotomy is performed, it should be possible to reduce the dose of omeprazole required for ulcer healing. After total gastrectomy, with removal of the target organ, symptoms in patients with gastrinoma improve dramatically and ulcers disappear. In most patients, serum gastrin concentrations remain unchanged after total gastrectomy. In approximately one third of Zollinger-Ellison patients, there may be modest decreases in serum gastrin levels after total gastric resection.[85] This may reflect the absence of secretin-stimulated release of tumor gastrin due to elimination of contact of acid with secretin-secreting small intestinal mucosa. In a small number of patients with metastatic gastrinoma, regression of primary tumor and/or metastases has been reported after total gastrectomy.[85] The explanation of this distinctly unusual event after total gastrectomy is not understood, although ablation of trophic influences on the gastrinoma exerted by the stomach has been suggested.

Management of patients with the Zollinger-Ellison syndrome should be considered an indefinite or lifelong program. Recognizing that the nature and frequency of patient surveillance should be individualized, the following is a potential format for continued monitoring of patients with the Zollinger-Ellison syndrome. Annual evaluation is suggested to include history and physical examination, measurement of fasting serum gastrin, and measurement of gastric acid secretion (for one hour during the hour before the next dose is due) if the patient is being treated with antisecretory agents (e.g., omeprazole). Substantial progressive increases in serum gastrin concentrations should alert the physician to the likelihood of metastatic tumor progression. The secretin stimulation test is of value in identifying recurrence of gastrinoma after apparently successful surgical resection. It is suggested that a secretin stimulation test be performed every two to three years after resection of gastrinoma to assess potential tumor recurrence. In addition, in patients in whom the tumor has not been found or has not been completely resected, it is suggested that periodic evaluation be performed, at approximately two- to three-year intervals, including, for example, computed tomography, selective angiography, or portal venous sampling in order to attempt to localize the gastrinoma for subsequent surgical resection. The possibility of gastrinoma should be considered in all first-degree members of families with MEN I, in whom fasting serum gastrin levels should be measured and intravenous secretin provocative tests performed. These measures provide a satisfactory method for identifying latent or overt gastrinoma in this population.

OTHER HYPERSECRETORY STATES

The Zollinger-Ellison syndrome constitutes the major prototype for states of gastric acid hypersecretion with associated peptic ulcer disease. In addition to common duodenal ulcer, often but not consistently associated with excessive gastric acid secretion, several other entities are frequently accompanied by gastric acid hypersecretion.

Systemic Mastocytosis

Systemic mastocytosis is a disease in which there is mast cell infiltration of multiple organs including the skin, GI tract, lymph nodes, bone marrow, spleen, and liver.[144-147] Hypersecretion of gastric acid is found in approximately one third of patients with systemic mastocytosis produced by increased serum levels of histamine, released from the numerous infiltrating mast cells. Gastric acid secretory rates, when elevated, may approach those of patients with the Zollinger-Ellison syndrome but characteristically are not as substantially increased as those of patients with gastrinoma.[148] Twenty-five per cent of the patients with systemic mastocytosis have been reported to have basal acid output rates of 15 mEq/hr or greater, values found in more than 95 per cent of patients with the Zollinger-Ellison syndrome. Doses of H_2 receptor antagonists successful in the treatment of patients with duodenal ulcer or duodenitis with mastocytosis have included cimetidine (mean, 1 gm/day; range, 0.9 to 1.2 gm/day) and ranitidine (mean, 0.6 gm/day; range, 0.3 to 1.2 gm/day).[148]

Nongastrinoma Ulcerogenic Islet Cell Tumors

A small number of islet cell tumors, ampullary and pancreatic carcinomas, have been described in patients with marked gastric acid hypersecretion, peptic ulcer, and/or diarrhea in the absence of hypergastrinemia and without significant gastrin content in these tumors.[149-151] Clinical manifestations are indistinguishable from those of patients with gastrinomas and the Zollinger-Ellison syndrome. These nongastrinoma ulcerogenic islet cell tumors are frequently malignant. Plasma extracts from patients with these nongastrinoma ulcerogenic tumors and extracts from these tumors have shown secretagogue activity, in that they stimulate gastric acid secretion in experimental animals. The nature of the secretagogue(s) contained in and released by these tumors is not known. The secretagogue is believed to be a small acidic peptide with a molecular weight approximating 2000 to 3000 daltons. Unlike gastrin, the material in these tumors responsible for stimulation of acid secretion is destroyed by trypsin.[151] As with gastrinoma, pepsin output in response to this secretagogue is relatively low. Similar to stimulation by gastrin, the gastric acid secretory response to the nongastrin secretagogue is inhibited by atropine.[151, 152] A nongastrinoma ampullary carcinoma has been described as containing motilin, insulin, somatostatin, pancreatic polypeptide, and pancreatic cancer–associated antigen in addition to the unknown secretagogue.[150]

DIAGNOSIS AND MANAGEMENT. These patients are identified by verification of an islet cell tumor with hypersecretion of gastric acid and no evidence of hypergastrinemia or gastrin in the tumor. Secretin does not stimulate gastrin release in these patients. Management recommended for these distinctly unusual patients with nongastrinoma ulcerogenic tumors is similar to that recommended for patients with gastrinoma.

Hyperparathyroidism and Peptic Ulcer Disease

Some investigators have suggested an increased incidence of peptic ulcer disease in patients with hyperparathyroidism. At present, however, an increased association of peptic ulcer disease with hyperparathyroidism, separate from the association with MEN I and gastrinoma, remains controversial.[153-155] When peptic ulcer occurs with hyperparathyroidism and is not associated with gastrinoma, as in MEN I, the clinical features are those of common peptic ulcer. In contrast to the Zollinger-Ellison syndrome, striking gastric hypersecretion is not present. A substantial portion of patients with hyperparathyroidism and peptic ulcer may harbor gastrinomas, particularly those with elevated fasting serum gastrin concentrations. In order to detect possible gastrinoma, it is recommended that the secretin stimulation test be performed in patients with hyperparathyroidism and peptic ulcer. In general, in the absence of associated gastrinoma or other causes for hypergastrinemia, patients with hyperparathyroidism do not have increased serum gastrin levels. Treatment of peptic ulcer associated with hyperparathyroidism is that indicated for treatment of the two individual diseases (see Chs. 9 and 30).

Massive Resection of the Small Intestine (see Ch. 61)

Increases in serum gastrin and gastric acid output, sometimes accompanied by peptic ulcer, have been noted in patients who have undergone massive small intestinal resection.[96] Consistent increases in gastric acid secretion have been produced after major resection of the small intestine in experimental animals. Several investigators have shown that the degree of gastric acid hypersecretion can be related directly to the amount of small intestine resected. Antrectomy has been shown to abolish acid hypersecretion following intestinal resection, and vagotomy enhances acid hypersecretion under these circumstances. These observations have been consistent with a role for gastrin and hypergastrinemia in postresection acid hypersecretion. The mechanism for the usually transient hypergastrinemia that is reported in some patients who have undergone massive intestinal resection has not been defined. However, it does not appear to be due exclusively to reduced intestinal degradation of gastrin.[96] It is more likely that small intestinal resection removes the site of release of intestinal hormone(s) that normally inhibit gastrin release. The usually transitory nature of acid hypersecretion suggests adaptation by the remaining small intestine, thereby reversing the functional abnormalities leading to gastric acid hypersecretion. The recommended treatment for patients with ulcer disease caused by gastric acid hypersecretion following massive intestinal resection includes antisecretory agents such as H_2 receptor antagonists or omeprazole.

Gastrin Cell Hyperplasia/Hypertrophy

In a small proportion of patients with duodenal ulcer, gastric acid hypersecretion is accompanied by elevated

serum gastrin concentrations, which appear to be produced by antral gastrin cell (G cell) hyperplasia and hyperfunction.[103, 104] Elevated serum gastrin levels in these patients are usually less than 1000 pg/ml. The mechanism responsible for gastrin cell hyperplasia in these patients has not been identified. In experimental animals, a combination of an elevated antral pH and passage of food over the pyloric gland area produces gastrin cell hyperplasia. Increased gastric acid secretion as seen in patients with the gastrin cell hyperplasia syndrome suggests a dysfunction in the relationship between intragastric pH and the regulation of the antral gastrin cell population. These subjects may be distinguished from those with gastrinomas by measurements of serum gastrin after secretin infusion and after the test meal. In contrast to patients with gastrinomas, patients with antral gastrin cell hyperfunction show decreases, no change, or only slight increases in serum gastrin levels after intravenous secretin injection. Following the test meal, most of these patients exhibit marked increases in serum gastrin concentrations (greater than 200 per cent increase); these increases exceed those of most normal subjects and patients with common duodenal ulcer or gastrinoma. Antral G cell hyperplasia and hyperfunction, therefore, are usually characterized by gastric acid hypersecretion, elevated fasting serum gastrin concentration, exaggerated gastrin release in response to feeding, and serum gastrin levels that do not increase dramatically after intravenous injection of secretin.

Antrectomy has frequently been required and successful in reducing serum gastrin levels and gastric acid hypersecretion with resultant healing and nonrecurrence of the ulcer disease.[110] Treatment of patients with antral gastrin cell hyperplasia and acid hypersecretion can in some instances be successful by use of H_2 receptor antagonists. It is also probable that success would be achieved with treatment of such patients with omeprazole.

REFERENCES

1. Zollinger, R. M., and Ellison, E. H. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann. Surg. *142*:709, 1955.
2. Gregory, R. A., Tracy, H. J., French, J. M., and Sircus, W. Extraction of gastrin-like substance from pancreatic tumour in case of Zollinger-Ellison syndrome. Lancet *1*:1045, 1960.
3. Gregory, R. A., Grossman, M. I., Tracy, H. J., and Bentley, P. H. Nature of gastric secretagogue in Zollinger-Ellison tumors. Lancet *2*:543, 1967.
4. McGuigan, J. E., and Trudeau, W. L. Immunochemical measurement of elevated levels of gastrin in the serum of patients with pancreatic tumors of the Zollinger-Ellison variety. N. Engl. J. Med. *278*:1308, 1968.
5. Gregory, R. A., Grossman, M. I., Tracy, H. J., and Bentley, P. H. Amino acid constitution of two gastrins isolated from Zollinger-Ellison variety. N. Engl. J. Med. *278*:1308, 1968.
6. Ellison, E. H., and Wilson, S. D. The Zollinger-Ellison syndrome: reappraisal and evaluation of 260 registered cases. Ann. Surg. *160*:512, 1964.
7. Wilson, S. D., and Ellison, E. H. Total gastric resection in children with the Zollinger-Ellison syndrome. Arch. Surg. *91*:165, 1965.
8. Greider, M. H., Rosai, J., and McGuigan, J. E. The human pancreatic islet cells and their tumors. II. Ulcerogenic and diarrheogenic tumors. Cancer *33*:1423, 1974.
9. Yalow, R. S., and Berson, S. A. Size and charge distinctions between endogenous human plasma gastrin in peripheral blood and heptadecapeptide gastrins. Gastroenterology *58*:609, 1970.
10. Rehfeld, J. F., Stadil, F., and Vikelsoe, J. Immunoreactive gastric components in human serum. Gut *15*:102, 1974.
11. Andersen, B. N., Petersen, B., Borch, K., and Rehfeld, J. F. Variations in the sulfation of circulating gastrins in gastrointestinal disease. Scand. J. Gastroenterol. *18*:565, 1983.
12. Kothary, P. C., Fabri, P. J., Gower, W., O'Dorisio, T. M., and Ellis, J. Evaluation of NH2-terminus gastrins in gastrinoma syndrome. J. Clin. Endocrinol. Metab. *62*:970, 1986.
13. Dockray, G. J., and Walsh, J. H. Amino terminal gastrin fragment in serum of Zollinger-Ellison syndrome patients. Gastroenterology *68*:222, 1975.
14. Bardram, L. Gastrin in non-neoplastic pancreatic tissue from patients with and without gastrinomas. Scand. J. Gastroenterol. *25*:945, 1990.
15. Zollinger, R. M., and Moore, F. T. Zollinger-Ellison syndrome comes of age. JAMA *204*:361, 1968.
16. Morgan, J. E., Kaiser, C. W., Johnson, W., et al. Gastric carcinoid (gastrinoma) associated with achlorhydria (pernicious anemia). Cancer *51*:2332, 1983.
17. Mendelsohn, G., De La Monte, S., Dunn, J. L., and Yardley, J. H. Gastric carcinoid tumors, endocrine cell hyperplasia, and associated intestinal metaplasia: histologic, histochemical, and immunohistochemical findings. Cancer *60*:1022, 1987.
18. Müller, J., Kirchner, T., and Müller-Hermelink, K. Gastric endocrine cell hyperplasia and carcinoid tumors in atrophic gastritis type A. Am. J. Surg. Pathol. *11*(12):909, 1987.
19. Berendt, R. C., Jewell, L. D., Shnitka, T. K., Manickavel, V., and Danyluk, J. Multicentric gastric carcinoids complicating pernicious anemia: origin from the metaplastic endocrine cell population. Arch. Pathol. Lab. Med. *113*:399, 1989.
20. Sidhu, G. The endodermal origin of digestive and respiratory tract APUD cells: histopathologic evidence and review of the literature. Am. J. Pathol. *96*:5, 1979.
21. Way, L., Goldman, L., and Dunphy, J. E. Zollinger-Ellison syndrome: an analysis of twenty-five cases. Am. J. Surg. *116*:293, 1968.
22. Thompson, J. C., Reeder, D. D., and Villar, H. V. Natural history and experience with diagnosis and treatment of the Zollinger-Ellison syndrome. Surg. Gynecol. Obstet. *140*:5, 1975.
23. Zollinger, R. M., Ellison, E. C., Fabri, P. J., Johnson, J., Sparks, J., and Carey, L. C. Primary peptic ulcerations of the jejunum associated with islet cell tumors: twenty-five year appraisal. Ann. Surg. *192*:422, 1980.
24. Stabile, B. E., and Passaro, E., Jr. Benign and malignant gastrinoma. Am. J. Surg. *149*:144–150, 1985.
25. Kaplan, E. L., Horvath, K., Udekwu, A., Straus, F., II, Schark, C., Ferguson, D. J., and Skinner, D. B. Gastrinomas: a 42-year experience. World J. Surg. *14*:365, 1990.
26. Norton, J. A., Doppman, J. L., Collen, M. J., et al. Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann. Surg. *204*:468, 1986.
27. Howard, T. J., Zinner, M. J., Stabile, B. E., and Passaro, E. Gastrinoma excision for cure: a prospective analysis. Ann. Surg. *211*:9, 1990.
28. Hofmann, J. W., Fox, P. S., and Wilson, S. D. Duodenal wall tumors and the Zollinger-Ellison syndrome. Surgical management. Arch. Surg. *107*:334, 1973.
29. Delcore, R., Hermreck, A. S., and Friesen, S. R. Selective surgical management of correctable hypergastrinemia. Surgery *106*:1094, 1989.
30. Thompson, N. W., Vinik, A. I., and Eckhauser, F. E. Microgastrinomas of the duodenum: a cause of failed operations for the Zollinger-Ellison syndrome. Ann. Surg. *209*:396, 1989.
31. Pipeleers-Marichal, M., Somers, G., Willems, G., Foulis, A., Imrie, C., Bishop, A. E., Polak, J. M., Häcki, W. H., Stamm, B., Heitz, P. U., and Klöppel, G. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N. Engl. J. Med. *322*:723, 1990.
32. Thompson, J. C., Lewis, B. G., Weiner, I., and Townsend, C. M., Jr. The role of surgery in the Zollinger-Ellison syndrome. Ann. Surg. *197*:594, 1983.
33. Malagelada, J. R., Edis, A. J., Adson, M. A., van Heerden, J. A., and Go, V. L. Medical and surgical options in the management of patients with gastrinoma. Gastroenterology *84*:1524, 1983.

34. Richardson, C. T., Peters, M. N., Feldman, M., et al. Treatment of Zollinger-Ellison syndrome with exploratory laparotomy, proximal gastric vagotomy, and H_2-receptor antagonists. A prospective study. Gastroenterology *89*:357, 1985.
35. Cherner, J. A., Doppman, J. L., Norton, J. A., et al. Selective venous sampling for gastrin to localize gastrinomas. Ann. Intern. Med. *105*:841, 1986.
36. Stabile, B. E., Morrow, D. J., and Passaro, E., Jr. The gastrinoma triangle: operative implications. Am. J. Surg. *147*:25, 1984.
37. Cocco, A. E., and Conway, S. J. Zollinger-Ellison syndrome with ovarian mucinous cystadenocarcinoma. N. Engl. J. Med. *393*:485, 1975.
38. Primrose, J. N., Maloney, M., Wells, M., Bulgim, O., and Johnston, D. Gastrin-producing ovarian mucinous cystadenomas: a cause of the Zollinger-Ellison syndrome. Surgery *104*:830, 1988.
39. Heyd, J., Livni, N., Herbert, D., Mor-Josef, S., and Glaser, B. Gastrin-producing ovarian cystadenocarcinoma: sensitivity to secretin and SMS 201–995. Gastroenterology *97*:464, 1989.
40. Maton, P. N., Mackem, S. M., Norton, J. A., Gardner, J. D., O'Dorisio, T. M., and Jensen, R. T. Ovarian carcinoma as a cause of Zollinger-Ellison syndrome. Gastroenterology *97*:468, 1989.
41. Passaro, E., Jr., Stabile, B. E., and Howard, T. J. Contributions of the Zollinger-Ellison syndrome. Am. J. Surg. *161*:203, 1991.
42. McCarthy, D. M., Weintraub, B. D., and Rosen, S. W. Subunits of human chorionic gonadotropin in malignant gastrinoma. Gastroenterology *76*:1198, 1979.
43. Stabile, B. E., Braunstein, G. D., and Passaro, E., Jr. Serum gastrin and human chorionic gonadotropin in the Zollinger-Ellison syndrome. Arch. Surg. *115*:1090, 1980.
44. Ballard, H. S., Frame, B., and Hartsock, R. J. Familial multiple endocrine adenoma-peptic ulcer complex. Medicine *43*:481, 1964.
45. Wermer, P. Multiple endocrine adenomatosis: multiple hormone producing tumors, a familial syndrome. *In* Bonfile S. (ed.). Endocrine-Secreting Tumors of the Gastrointestinal Tract. London, W. B. Saunders Company, 1974, p. 671.
46. Creutzfeldt, W., Arnold, R., Creutzfeldt, C., and Track, N. S. Pathomorphologic, biochemical, and diagnostic aspects of gastrinomas (Zollinger-Ellison syndrome). Hum. Pathol. *6*:47, 1975.
47. Friesen, S. R. Treatment of the Zollinger-Ellison syndrome: a 25 year assessment. Am. J. Surg. *143*:331, 1982.
48. Lamers, C. B., Stadil, F., and Van Tongeren, J. H. Prevalence of endocrine abnormalities in patients with the Zollinger-Ellison syndrome and in their families. Am. J. Med. *64*:607, 1978.
49. Wolfe, M. M., and Jensen, R. T. Zollinger-Ellison syndrome: current concepts in diagnosis and management. N. Engl. J. Med. *317*:1200, 1987.
50. Zollinger, R. M. Gastrinoma: the Zollinger-Ellison syndrome. Semin. Oncol. *14*:247, 1987.
51. Larsson, C., Skogseid, B., Öberg K., et al. Multiple endocrine neoplasia type I gene maps to chromosome 11 and is lost in insulinoma. Nature *332*:85, 1988.
52. Majewski, J., and Wilson, S. The MEA-I syndrome: an all or none phenomenon? Surgery *86*:475, 1979.
53. Mozell, E., Stenzel, P., Woltering, E., Rösch, J., and O'Dorisio, T. M. Functional endocrine tumors of the pancreas: clinical presentation, diagnosis, and treatment. *In* Wells, S. (Editor-in-Chief). Current Problems in Surgery. St. Louis, Mosby-Year Book, Inc., 1990, 309–385.
54. Gogel, H. K., Buckman, M. T., Cadieux, D., and McCarthy, D. M. Gastric secretion and hormonal interactions in multiple endocrine neoplasia type I. Arch. Intern. Med. *145*:855, 1985.
55. Heitz, P., Kasper, M., Kloppel, G., et al. Glycoprotein-hormone alpha-chain production by pancreatic endocrine tumors. A specific marker for malignancy. Immunocytochemical analysis of tumors of 155 patients. Cancer *51*:277, 1983.
56. Kahn, C., Rosen, S., Weintraub, B., et al. Ectopic production of chorionic gonadotropin and its subunits by islet-cell tumors: a specific marker for malignancy. N. Engl. J. Med. *297*:565, 1977.
57. Lyons, D., Eisen, B., Clark, M., et al. Concurrent Cushing's and Zollinger-Ellison syndrome in a patient with islet cell carcinoma: case report and review of the literature. Am. J. Med. *76*:729, 1984.
58. Law, D., Liddle, G., Scott, H., et al. Ectopic production of multiple hormones (ACTH, MSH, and gastrin) by a single malignant tumor. N. Engl. J. Med. *273*:292, 1965.
59. Polak, J., Adrian, T., Bryant, M., et al. Pancreatic polypeptide in insulinomas, gastrinomas, VIPomas and glucagonomas. Lancet *1*:328, 1976.
60. Oberg, K., and Wide, L. hCG and hCG subunits as tumour markers in patients with endocrine pancreatic tumors and carcinoids. Acta Endocrinol. *98*:256, 1981.
61. Thompson, N. W., Lloyd, R. V., Nishiyama, R. H., et al. MEN 1 pancreas: a histological and immunohistochemical study. World J. Surg. *8*:561, 1984.
62. Klöppel, G., Willemer, S., Stamm, B., Häcki, W. H., and Heitz, P. U. Pancreatic lesions and hormonal profile of pancreatic tumors in multiple endocrine neoplasia type 1: an immunocytochemical study of nine patients. Cancer *57*:1824, 1986.
63. Friesen, S. R., Kimmel, J. R., and Tomita, T. Pancreatic polypeptide as screening marker for pancreatic polypeptide apudomas in multiple endocrinopathies. Am. J. Surg. *139*:61, 1980.
64. Öberg, K., Wälinder, O., Boström, H., Lundqvist, G., and Wide, L. Peptide hormone markers in screening for endocrine tumors in multiple endocrine adenomatosis type 1. Am. J. Med. *73*:619, 1982.
65. Brandi, M. L., Marx, S. J., Aurbach, G. D., and Fitzpatrick, L. A. Familial multiple endocrine neoplasia type 1: a new look at pathophysiology. Endocr. Rev. *8*:391, 1987.
66. Zollinger, R. M., Ellison, E. H., O'Dorisio, T. M., et al. Thirty years' experience with gastrinoma. World J. Surg. *8*:427, 1984.
67. Stamm, B., Hedinger, C. E., and Saremaslani, P. Duodenal and ampullary carcinoid tumors: a report of 12 cases with pathological characteristics, polypeptide content and relation to the MEN 1 syndrome and von Recklinghausen's disease (neurofibromatosis). Virchows Arch. [A] *408*:475, 1986.
68. O'Neal, L. W., Kipnis, D. M., Luse, S. A., Lacy, P. E., and Jarret, L. Secretion of various endocrine substances by ACTH-secreting tumors—gastrin, melanotropin, norepinephrine, serotonin, parathormone, vasopressin, glucagon. Cancer *21*:1219, 1968.
69. Tomita, T., Kimmbel, J. R., Friesen, S. R., Doull, V., and Pollock, H. G. Pancreatic polypeptide in islet cell tumors. Morphologic and functional correlations. Cancer *56*:1649, 1985.
70. Bardram, L., and Stage, J. G. Frequency of endocrine disorders in patients with the Zollinger-Ellison syndrome. Scand. J. Gastroenterol. *20*:233, 1985.
71. Dawson, J., Bloom, S. R., and Cockel, R. A unique apudoma producing the glucagonoma and gastrinoma syndromes. Postgrad. Med. J. *59*:315, 1983.
72. Maton, P. N., Gardner, J. D., and Jensen, R. T. Cushing's syndrome in patients with the Zollinger-Ellison syndrome. N. Engl. J. Med. *315*:1, 1986.
73. Lamers, C. B. H., Diemel, J., and Roeffen, W. Serum levels of pancreatic polypeptide in Zollinger-Ellison syndrome, and hyperparathyroidism from families with multiple endocrine adenomatosis type 1. Digestion *18*:297, 1978.
74. Schwartz, T. W. Pancreatic-polypeptide (PP) and endocrine tumours of the pancreas. Scand. J. Gastroenterol. *14*:93, 1979.
75. Byrnes, D. J., Marjason, J., Henderson, L., Gallagher, N., and Fabricatorian, D. Is pancreatic polypeptide estimation of value in diagnosing gastrinomas (Zollinger-Ellison syndrome). Aust. N.Z. J. Med. *9*:364, 1979.
76. Bloodworth, J. M. B., Jr., and Elliott, D. W. The histochemistry of pancreatic islet cell lesions. JAMA *183*:1011, 1968.
77. Fox, P. S., Hofmann, J. W., Wilson, S. D., and Decosse, J. J. Surgical management of the Zollinger-Ellison syndrome. Surg. Clin. North Am. *54*:395, 1974.
78. Wright, H. K., Hersh, T., Floch, M. H., and Weinstein, L. D. Impaired intestinal absorption in the Zollinger-Ellison syndrome independent of gastric hypersecretion. Am. J. Surg. *119*:250, 1970.
79. Shimoda, S. S., Saunders, D. R., and Rubin, C. E. The Zollinger-Ellison syndrome with steatorrhea. Mechanisms of fat and vitamin B_{12} malabsorption. Gastroenterology *55*:705, 1968.
80. Mansbach, C. M., Todd, J. E., Moore, S. W., and Beal, J. M. Zollinger-Ellison syndrome with interesting variations. Am. J. Surg. *112*:807, 1966.
81. Ayogi, T., and Summerskill, W. H. J. Gastric secretion with ulcerogenic islet cell tumor: importance of basal acid output. Arch. Intern. Med. *117*:667, 1966.

82. Marks, I. N., Selzer, G., Louw, J. H., and Bank, S. Zollinger-Ellison syndrome in Bantu woman, with isolation of gastrin-like substance from primary and secondary tumors. I. Case report. Gastroenterology *41*:77, 1961.
83. Yalow, R. S., and Berson, S. A. Radioimmunoassay of gastrin. Gastroenterology *58*:1, 1970.
84. Trudeau, W. L., and McGuigan, J. E. Serum gastrin levels in patients with peptic ulcer disease. Gastroenterology *59*:6, 1970.
85. Yanda, R. J., Ostroff, J. W., Ashbaugh, D. D., Guis, M. S., and Goldberg, H. I. Zollinger-Ellison syndrome in a patient with normal screening gastrin level. Dig. Dis. Sci. *34*:1929, 1989.
86. Sanzenbacher, L. J., King, D. R., and Zollinger, R. M. Prognostic implications of calcium-mediated gastrin levels in the ulcerogenic syndrome. Am. J. Surg. *125*:116, 1973.
87. Stadil, F., Rehfeld, J. F., and Hess Thaysen, E. Gastric juice as gastrin-releasing factor in the Zollinger-Ellison syndrome. Lancet *2*:102, 1971.
88. Unvas, B. Discussion of Schofield B. Inhibition by acid of gastrin release. *In* Grossman, M. I. (ed). Gastrin (UCLA Forum in Medical Sciences No. 5). Berkeley, University of California Press, 1966, p. 186.
89. McGuigan, J. E., and Trudeau, W. L. Serum gastrin concentrations in pernicious anemia. N. Engl. J. Med. *282*:358, 1970.
90. Korman, M. G., Strickland, R. G., and Hansky, J. Serum gastrin in chronic gastritis. Br. Med. J. *2*:16, 1971.
91. Ganguli, P. C., Cullen, D. R., and Irvine, W. J. Radioimmunoassay of plasma-gastrin in pernicious anemia, achlorhydria without pernicious anemia, hypochlorhydria, and in controls. Lancet *1*:155, 1971.
92. McGuigan, J. E., and Trudeau, W. L. Serum and tissue gastrin concentrations in patients with carcinoma of the stomach. Gastroenterology *64*:22, 1973.
93. Korman, M. G., Scott, D. H., Hansky, J., et al. Hypergastrinanemia due to an excluded gastric antrum: a proposed method of differentiation from the Zollinger-Ellison syndrome. Aust. N.Z. J. Med. *3*:266, 1972.
94. Korman, M. G., Laver, M. C., and Hansky, J. Hypergastrinanemia in chronic renal failure. Br. Med. J. *1*:209, 1972.
95. Davidson, W. D., Springberg, P. D., and Falkinburg, N. R. Renal extraction and excretion of endogenous gastrin in the dog. Gastroenterology *64*:955, 1973.
96. Straus, E., Gerson, C. D., and Yalow, R. S. Hypersecretion of gastrin associated with the short bowel syndrome. Gastroenterology *66*:175, 1974.
97. Hayes, J. R., Ardill, J., Kennedy, T. L., et al. Stimulation of gastrin release by catecholamines. Lancet *1*:819, 1972.
98. Trudeau, W. L., and McGuigan, J. E. Effects of calcium on serum gastrin in the Zollinger-Ellison syndrome. N. Engl. J. Med. *281*:862, 1969.
99. Basso, N., and Passaro, E., Jr. Calcium-stimulated gastric secretion in the Zollinger-Ellison syndrome. Arch. Surg. *101*:3399, 1970.
100. Passaro, E., Jr., Basso, N., Sanchez, R. E., and Gordon, H. E. Newer studies in the Zollinger-Ellison syndrome. Am. J. Surg. *120*:138, 1970.
101. Isenberg, J. I., Walsh, J. H., Passaro, E., Jr., et al. Unusual effect of secretin on serum gastrin, serum calcium, and gastric acid secretion in a patient with suspected Zollinger-Ellison syndrome. Gastroenterology *62*:626, 1972.
102. Kolts, B. E., Herbest, C. A., and McGuigan, J. E. Calcium- and secretin-stimulated gastrin release in the Zollinger-Ellison syndrome. Ann. Intern. Med. *81*:758, 1974.
103. Straus, E., and Yalow, R. S. Differential diagnosis in hyperchlorhydric hypergastrinemia. Gastroenterology *66*:867, 1974.
104. Ganguli, P. C., Elder, J. B., Polak, J. E., et al. Antral-gastrin cell hyperplasia in peptic-ulcer disease. Lancet *1*:1288, 1974.
105. Hansky, J., Soveny, C., and Korman, M. G. Effect of secretin on serum gastrin as measured by immunoassay. Gastroenterology *61*:62, 1971.
106. McGuigan, J. E., and Wolfe, M. M. Secretin injection test in the diagnosis of gastrinoma. Gastroenterology *79*:1324, 1980.
107. Brady, C. E., Johnson, R. C., Williams, J. R., and Boran, K. False-positive serum gastrin stimulation due to impure secretin. Gastroenterology *76*:1106, 1979.
108. Spindel, E., Harty, R. F., Leibach, J. R., and McGuigan, J. E. Decision analysis in evaluation of hypergastrinemia. Am. J. Med. *80*:11, 1986.
109. Feldman, M., Schiller, L. R., Walsh, J. H., Fordtran, J. S., and Richardson, C. T. Positive intravenous secretin test in patients with achlorhydria-related hypergastrinemia. Gastroenterology *93*:59–62, 1987.
110. Clark, C. G., Chowcat, N. L., Lewin, M. R., Gilbert, J. M., Gelister, J. S. K., and Boulos, P. B. Surgery for peptic ulceration associated with hypergastrinaemia. Br. J. Surg. *73*:248, 1986.
111. Mills, S. R., Doppman, J. L., Dunnick, N. R., and McCarthy, D. M. Evaluation of angiography in Zollinger-Ellison syndrome. Radiology *131*:317, 1979.
112. Damgaard-Petersen, K., and Stage, J. G. CT Scanning in patients with Zollinger-Ellison syndrome and carcinoid syndrome. Scand. J. Gastroenterol. *53*:117, 1979.
113. Roche, A., Raisonnier, A., and Gillon-Savouret, M. C. Pancreatic venous sampling and arteriography in localizing insulinomas and gastrinoma: procedure and results in 55 cases. Radiology *198*:621, 1982.
114. Doppman, J. L., Shawker, T. H., and Miller, D. L. Localization of islet cell tumors. Gastroenterol. Clin. North Am. *18*:793, 1989.
115. Frucht, H., Doppman, J. L., Norton, J. A., Miller, D. L., Dwyer, A. J., Frank, J. A., Vinayek, R., Maton, P. N., and Jensen, R. T. Gastrinomas: comparison of MR imaging with CT, angiography, and US? Radiology *171*:713, 1989.
116. Vinayek, R., Frucht, H., Chiang, H. C. V., Maton, P. N., Gardner, J. D., and Jensen, R. T. Zollinger-Ellison syndrome: Recent advances in the management of the gastrinoma. Gastroenterol. Clin. North Am. *19*:197, 1990.
117. London, J. F., Shawker, T. H., Doppman, J. L., Frucht, H. H., Vinayek, R., Stark, H. A., Miller, L. S., Miller, D. L., Norton, J. A., Jensen, R. T., Gardner, J. D., and Maton, P. N. Zollinger-Ellison syndrome: prospective assessment of abdominal US in the localization of gastrinomas. Radiology *178*:763, 1991.
118. Burcharth, F., Stage, J. G., Stadil, F., Jensen, L. I., and Fischermann, K. Localization of gastrinomas by transhepatic portal catheterization and gastrin assay. Gastroenterology *77*:444, 1979.
119. Glowniak, J. V., Shapiro, B., Vinik, A. I., Glaser, B., Thompson, N. W., and Cho, K. J. Percutaneous transphepatic venous sampling of gastrin: value in sporadic and familial islet-cell tumors and G-cell hyperfunction. N. Engl. J. Med. *307*:293, 1982.
120. Imamura, M., Takahashi, K., Isobe, Y., Hattori, Y., Satomura, K., and Tobe, T. Curative resection of multiple gastrinomas aided by selective arterial secretin injection test and intraoperative secretin test. Ann. Surg. *210*:710, 1989.
121. Deveney, C. W., Deveney, K. E., Stark, D., Moss, A., Steing, S., and Way, L. W. Resection of gastrinomas. Ann. Surg. *198*:546, 1983.
122. Howard, T. J., and Passaro, E., Jr. New medical and surgical approaches. Surg. Clin. North Am. *69*:667, 1989.
123. Andersen, D. K. What's new in general surgery: current diagnosis and management of Zollinger-Ellison syndrome. Ann. Surg. *210*:685, 1989.
124. Ellison, E., Carey, C., Sparks, J., et al. Early surgical treatment of gastrinomas. Am. J. Med. *82*:17, 1987.
125. Norton, J. A., Sugarbaker, P. H., Doppman, J. L., et al. Aggressive resection of metastatic disease in selected patients with malignant gastrinoma. Ann. Surg. *203*:352, 1986.
126. Wolfe, M. M., Alexander, R. W., and McGuigan, J. E. Extrapancreatic, extraintestinal gastrinoma: effective treatment by surgery. N. Engl. J. Med. *306*:1533, 1982.
127. Norton, J. A., Sugarbaker, P. H., Doppman, J. L., et al. Aggressive resection of metastatic disease in selected patients with malignant gastrinomas. Ann. Surg. *149*:144, 1985.
128. McCarthy, D. M. Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology *74*:453, 1978.
129. Bonfils, S., Nignon, M., and Gratton, J. Cimetidine treatment of acute and chronic Zollinger-Ellison syndrome. World J. Surg. *3*:597, 1979.
130. Howard, J. A., Chermos, A. N., Collen, M. J., et al. Famotidine, a new, potent, long-acting histamine H_2-receptor antagonist: comparison with cimetidine and ranitidine in the treatment of Zollinger-Ellison syndrome. Gastroenterology *88*:1026, 1985.
131. Stabile, B. E., Ippoliti, A. F., Walsh, J. H., and Passaro, E., Jr. Failure of histamine H_2-receptor antagonist therapy in Zollinger-Ellison syndrome. Am. J. Surg. *145*:17, 1983.

132. Raufman, J. P., Collins, S. M., Pandol, S. J., et al. Uncertainties in the management of the Zollinger-Ellison syndrome. Gastroenterology *84*:108, 1983.
133. Lamers, C. B. H. W., Lind, T., Moberg, S., et al. Omeprazole in Zollinger-Ellison syndrome: effects of a single dose and of long-term treatment in patients resistant to histamine H_2-receptor antagonists. N. Engl. J. Med. *310*:758, 1984.
134. McArthur, K. E., Collen, M. J., Maton, P. N., et al. Omeprazole: effective convenient therapy for Zollinger-Ellison syndrome. Gastroenterology *88*:939, 1985.
135. Maton, R. N., Lack, E., McArthur, K. E., et al. Effects of long term omeprazole on gastric acid secretion and mucosal histology in patients with Zollinger-Ellison syndrome (ZES). Gastroenterology *94*:A288, 1988.
136. Miller, L. S., Frucht, H., Saeed, Z. A., et al. Esophageal involvement in Zollinger-Ellison syndrome (ZES). Gastroenterology *94*:A304, 1988.
137. Maton, P. N., Frucht, H., Vinayek, R., et al. Medical management of patients with Zollinger-Ellison syndrome who have had previous gastric surgery: a prospective study. Gastroenterology *94*:294, 1988.
138. Ellison, E. C., O'Dorisio, T. M., Sparks, J., et al. Observations on the effect of a somatostatin analog in the Zollinger-Ellison syndrome: implications for the treatment of apudomas. Surgery *100*:437, 1986.
139. Woltering, E. A., Mozell, E. J., D'Orisio, T. M., Fletcher, W. S., and Howe, B. Supression of primary and secondary peptides with somatostatin analog in the therapy of functional endocrine tumors. Surg. Gynecol. Obst. *167*:453, 1988.
140. Moertel, C. G., Hanley, J. A., and Johnson, L. A. Streptozotocin alone compared with streptozotocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N. Engl. J. Med. *303*:1189, 1980.
141. Kvols, L. K., and Buck, M. Chemotherapy of metastatic carcinoid and islet cell tumors. A review. Am. J. Med. *82*(Suppl 5B):77, 1987.
142. Von Schrenck, T., Howard, J. M., Doppman, J. L., et al. Prospective study of chemotherapy in patients with metastatic gastrinoma. Gastroenterology *94*:1326, 1988.
143. Clouse, M. E., Lee, R. G., Duszlak, E. J., Lokich, J. J., and Alday, M. T. Hepatic artery embolization for metastatic endocrine-secreting tumors of the pancreas. Gastroenterology *85*:1183, 1983.
144. Dermis, D. J. The mastocytosis syndrome. Ann. Intern. Med. *59*:194, 1963.
145. Roberts, L. J., Sweetman, B. J., Lewis, R. A., Austen, K. F., and Oates, J. A. Increased production of prostaglandin D_2 in patients with systemic mastocytosis. N. Engl. J. Med. *303*:1400, 1980.
146. Parker, C., Jost, R. J., Bauer, E., Haddad, J., and Garza, R. Systemic mastocytosis. Am. J. Med. *61*:671, 1976.
147. Webb, T. A., Li, C. Y., and Yam, L. T. Systemic mast cell disease: a clinical and hematopathologic study of 26 cases. Cancer *49*:927, 1982.
148. Cherner, J. A., Jensen, R. T., Dubois, A., O'Dorisio, T. M., Gardner, J. D., and Metcalfe, D. D. Gastrointestinal dysfunction in systemic mastocytosis: a prospective study. Gastroenterology *95*:657, 1988.
149. Chey, W. Y., Chang, T. M., Park, H. J., et al. A non-gastrin secretagogue in ulcerogenic tumors of the pancreas. Ann. Intern. Med. *101*:7, 1984.
150. Chey, W. Y., Chang, T. M., Lee, K. Y., et al. Ulcerogenic tumor syndrome of the pancreas associated with a non-gastrin acid secretagogue. Ann. Surg. *210*:139, 1989.
151. Sloas, D. D., Hirschowitz, B. I., and Chey, W. Y. A nongastrin malignant ampullary tumor causing gastric acid and pepsin hypersecretion. Gastroenterology *92*:1644, 1987.
152. Hirschowitz, B. I., Molina, E., Ou, T. L., and Helman, C. A. Effects of very low doses of atropine on basal acid and pepsin secretion, gastrin and heart rate in normals and DU. Dig. Dis. Sci. *29*:790, 1984.
153. Black, B. H. Hyperparathyroidism. Springfield, IL, Charles C. Thomas, 1953.
154. Ellis, C., and Nicoloff, D. M. Hyperparathyroidism and peptic ulcer disease. Arch. Surg. *96*:114, 1968.
155. Ostrow, J. D., Blandshard, G., and Gray, S. J. Peptic ulcer in primary hyperparathyroidism. Am. J. Med. *29*:769, 1960.