Chapter 31

ZOLLINGER-ELLISON SYNDROME
AND OTHER HYPERSECRETORY STATES

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ZOLLINGER-ELLISON SYNDROME

The syndrome that bears their name was described by Zollinger and Ellison in 1955. 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. 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 biological 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 all patients with duodenal ulcer. The Zollinger-Ellison syndrome has been reported to be slightly more common in males than in females. 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.

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. 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. Gastrin has been shown by immunocytochemistry to reside in numerous prominent secretory granules in the cytoplasm of gastrinomas cells.

GASTRIN. The predominant biologically active molecular species of gastrin in gastrinomas, just as in the antral mucosa, is heptadecapeptide gastrin (G17). The major form of biologically active gastrin in the blood of patients with gastrinoma is a larger form of gastrin con-
increased in sera of patients with metastatic gastrinoma when compared with normal subjects and patients with nonmetastatic gastrinoma. In addition to 
G17 and G34, smaller and larger forms of gastrin are found in sera and gastromomas from Zollinger-Ellison patients. 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 I-13 fragment of G17 (which has no biologic activity) and the carboxy-terminal tetra-
decapeptide 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 gastrino-
mosa tissue and plasma of patients with gastrinoma. 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. 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, when 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 gastrin 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. These also appear to represent direct trophic effects of high circulating gastrin levels on this cell pop-
ulation.

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

Figure 31-2. Same tumor as in Figure 30-1. at higher magnification (X 400). Cells are malignant. Hematoxylin and eosin stain. (Courtesy of Male Greider, Ph.D.)
adult pancreas. For these reasons most investigators have viewed pancreatic gastrinomas as e-topic tumors. Recently, insulinoma and gastrin have been measured in pancreatic tissue from normal adult humans and patients with gastrinomas. 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 these tumors may arise from endocrine neoplasia of endocrine mesenchyme, most recent evidence supports the conclusion that the cells from which gastrinomas arise were derived from endoderm of origin.\textsuperscript{9}

Gastrinomas in patients with the Zollinger-Ellison syndrome have been reported most often in the pancreas.\textsuperscript{10, 11} Contrary to earlier perceptions, pancreatic gastrinomas are now 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 may vary widely in size, ranging from approximately 0.1 to more than 20 cm in diameter.\textsuperscript{12} 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.\textsuperscript{12, 13} The most common site of extrapancreatic gastrinomas is the wall of the duodenum.\textsuperscript{14, 15} There is accumulating evidence that when gastrinomas are localized they are found at least as commonly in the stomach and perhaps more commonly in the duodenum as in the pancreas. Duodenal wall gastrinomas are located principally in the submucosa and are easily overlooked. These gastrinomas are usually located in the first or second portion of the duodenum. Approximately 30 per cent of duodenal gastrinomas are solitary, and they may be as large as 15 cm or as small as 1 mm in diameter.\textsuperscript{15, 16} The question has remained unanswered whether gastrinomas found only in lymph node tissue represent primary tumors or metastases from undetected gastrinomas. However, there is accumulating evidence that undiagnosed duodenal wall gastrinomas are more often the situs of occult gastrinomas in Zollinger-Ellison patients with isolated lymph node gastrinomas and in patients in whom no tumor is found at surgery.\textsuperscript{16, 17}

At surgery, gastrinomas may be identified readily or, more often, they are difficult to localize or may not be identified at all.\textsuperscript{17-22} 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. 3). The gastrinoma triangle is defined anatomicall by the junction of the cecum and the duodenum. The first point of the triangle is the junction of the second and third portions of the duodenum, the second junction of the second and third portions of the duodenum inferiorly, and the third junction of the neck and body of the pancreas medially.\textsuperscript{20} A small number of duodenal tumors have also been shown to be gastrinomas and may produce the Zollinger-Ellison syndrome.\textsuperscript{3}

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, mesenteric, perigastric, and splenic nodes, and skin.\textsuperscript{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.\textsuperscript{22} Death is rarely caused by tumor progression in patients found at surgery to have metastasis limited to lymph nodes. Patients with gastrinomas 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, approaching eight years, usually with progressive tumor growth leading to liver failure.\textsuperscript{23, 24}

Patients with proven metastatic gastrinoma often have increased serum levels of human chorionic gonadotropin (HCG) and its alpha and beta subunits.\textsuperscript{23-25} Twenty per cent of patients with malignant gastrinomas have increased serum beta-HCG levels, and those with extensive metastatic gastrinoma are more likely to have strikingly increased alpha-HCG levels. Increased serum alpha-HCG levels have not been found in patients with benign gastrinoma.\textsuperscript{23, 24} MULTIPLE ENDODINE NEPLAOSIS TYPE I (MEN I).\textsuperscript{25} It has been estimated in various studies that from 20 to 50 per cent of patients with gastrinomas have the multiple endocrine neoplasia type 1 (MEN I), which is composed of tumors or hyperplasia of parathyroid, pancreatic islet,
an oral and oropharyngeal glands. MEN I is an autosomal dominant genetic syndrome characterized by a high degree of endocrine hyperplasia. The MEN I locus has been identified on chromosome 11. It is probable that all patients with MEN I have hyperplasia of all three endocrine organs (parathyroid, pancreatic islets, and pituitary), although not always with clinical expression of excessive hormone release. Hyperparathyroidism is the most common manifestation of MEN I and is present in 90 to 100 percent of these patients. Hyperparathyroidism in patients with MEN I is usually due to hyperplasia (80 percent). In MEN IIa, adenomas, usually pheochromocytomas, are believed to be present in 50 to 60 percent of patients with MEN I. In MEN IIa and IIb, pituitary tumors are usually solitary in patients with MEN I, although they are more prevalent in women. In MEN IIb, pituitary adenomas are more prevalent in patients with MEN IIb. Unlike islet cell tumors, pituitary tumors are usually solitary in patients with MEN I, although they may be multiple and are often bilateral. Unlike islet cell tumors, pituitary tumors are usually solitary in patients with MEN I, although they may be multiple and are often bilateral.

In MEN I, islet cell tumors are not usually associated with concomitant diabetic pancreatic islet cell tumors. 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. Multiple endocrine neoplasia (MEN) II and MEN III (MEN IIa, MEN IIb) are described in detail in other sections of this text.
patients with the Zollinger-Ellison syndrome. Of these, three of 59 patients (5 per cent) with sporadic gastrinomas were found to be of the Cushings' 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. None of 36 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 in these patients was mild. Gastrinomas were not metastatic and prognosis was excellent.

**Pancreatic Polypeptide** Increases in serum pancreatic polypeptide-secreting tumors, or (2) caused by release from pancreatic polypeptide cells within mixed islet-endocrine tumors of the pancreas, or, most commonly, (3) associated with hyperplasia of pancreatic polypeptide cells, often accompanying islet tumors of the pancreas, including gastrinoma. 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 is a group is significant, the frequency of this increase is insufficient to make this determination a matter of value in identifying patients with gastrinoma.

In normal subjects, serum pancreatic polypeptide levels generally increase with age. This variation of pancreatic polypeptide level with age must be taken into consideration when 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. 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 disordered and 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 of absence of demonstrated gastrinoma. 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. The Zollinger-Ellison syndrome does not appear to be caused by islet cell hyperplasia, since removal of hyperplastic islet cells 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 microscopic morphologic abnormalities of the small intestine in patients with gastrinoma. 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 intact villi and the disappearance of the tuft of villi proper with polymorphonuclear leukocytes and eosinophils, frequently with accompanying edema, hemorrhage, and multiple superficial mucosal erosions. Remaining small intestinal mucosal villi are often broader and longer than Brunner's glands, which are usually limited in distribution to the proximal duodenum. The number and may be found in 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. Ulcer symptoms in patients with gastrinomas 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 in the duodenum or stomach are found in 75 per cent of patients with the Zollinger-Ellison syndrome. In a review of patients with the Zollinger-Ellison syndrome, 14 per cent of ulcers were found in the duodenum beyond the first part, and 11 per cent were found in the jejunum.

The ulcers in patients with gastrinoma are usually multiple, with no ulcers in less than 1 per cent of patients. However, uncommonly, ulcers may be large, exceeding 2 cm in diameter. Recurrent ulcer, either at or distal to the antrum, is extremely frequent when usual gastric surgery for peptic ulcer is performed in Zollinger-Ellison patients harboring gastrinomas. This is accompanied 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 anticipated initially.

Diabetes 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, diabetes occurs in the absence of clinical ulcer disease. Diabetes appears to be due principally to the effects of large amounts of hydrochloric acid in the upper gastrointestinal tract. Diabetes may be reduced or eliminated by aspiration of gastric juice from the stomach. Although the major cause of diabetes 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. 46 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 pepin secretion by gastric zymogen cells. Gastric acid hypersecretion in patients with the Zollinger-Ellison syndrome can produce pH values as low as 1.5 and 3.6 in the proximal and distal jejunum, respectively, converting pepinogens to proteolytically active pepins, which are believed to contribute to mucosal injury in the small intestine.

Statovicea, which is less common in gastrinoma patients than is diarrhea, is produced by several mechanisms. 47, 48 Pancreatic lipase is inactive by enor- mous amounts of intraluminal acid in the upper small intestine. Pancreatic lipase is exquisitely susceptible to irreversible denaturation by acidification. Lipase inactiva- tion results in failure to hydrolyze intraluminal triglycer- erides 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 the facilitation of fatty acid and monoglyceride absorption, therefore resulting in steatorrhea.

Patients with the Zollinger-Ellison syndrome may de- velop vitamin B12 malabsorption, which is not correctable by intramuscular factor. 49 Although gastric secretion of intrinsic factor is normal in these patients, the low intra- luminal pH in the intestine interferes with intrinsic factor facilitation of active absorption of vitamin B12 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 B12 absorption is abolished.

Recognizing that clinical symptoms in patients with gastrinoma, especially initially, are usually not distin- guishable 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 follow- ing 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 chronic peptic ulcer disease, especially in those with substantially increased gastric acid secretion. Gastric Acid Secretion. Hyperscretion of gastric acid, a diagnostic feature of the syndrome, is extremely frequent, although not universal in Zollinger-Ellison pa- tients. However, it is sufficiently common and sufficiently impressive with gastrinoma that its presence provides valuable evidence in support of the diagnosis. 50 Most (>90 per cent) patients with the Zollinger-Ellison syn- drome have a stimulated gastric acid secretion rate 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 normal 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 gas- trinoma. 51, 52 In normal individuals and patients with common peptic ulcer, basal acid output is usually less than 60 per cent of acid secreted after maximum stimu- lation (for example, with pentagastrin). Since their pari- etal 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 also have 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 syn- drome (Fig. 41-14 and 31-35), which suggest true 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 gastric disease, gastric lymphoma, or other infiltrative processes. The normally fine small intestinal mucosal folds may be thickened and indented throughout the duodenum and, in some in- stances, 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 flattening of barium. Gastrinomas in the pan- creas are rarely identified by upper gastrointestinal bar- ium 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. 53, 54 In normal subjects and in patients with common duodenal ulcer, fasting serum gastrin concentra- tions average approximately 30 to 60 pg/ml (or less), with an upper limit of normal in most laboratories approxi- mately 150 pg/ml. 55 Patients with gastrinoma almost al-
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. Mark-
edly 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-Ellenon 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. 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. Reduction of hypergastrinemia by aspira-
tion 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. Mean serum gastrin concentrations in patients with pernicious anemia approximate 1000 pg/ml, and are in the same range as patients with gastrinoma. 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. In general, in pernicious anemia the atrophic inflammatory process involves principally the mucoza of the body and fundus of the stomach with relative sparing of the antral mucosa, the normal residence of gastrin. In perni-
cious anemia, achlorhydria causes failure of the normal acid-gastrin feedback control mechanism, which is im-
portant in the regulation of gastric secretions. Patients with other varieties of gastric atrophy with chronic gas-
tritis 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 perni-
cious anemia, as well as patients with gastric carcinoma with reduced or absent gastric acid secretion. 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 re-
ported in an assortment of other clinical states, includ-
ing 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 insuffi-
ciency, in patients with the retained and excluded crypt syndrome, and in some patients with massive resection of the small intestine. Hypergastrinemia in patients with renal insufficiency, in general, correlates directly with the severity of renal impairment. Hypergastrinemia was be-
lieved originally to be secondary to reduced renal cortical degradation of gastrin. However, it is unlikely that this explanation is complete or correct, since septic patients...
exhibit normal rates of gastrin clearance. Increased serum gastrin concentrations also have been described in patients with phaeochromocytoma, in whom hypergastrinemia is believed to be secondary to catecholamine-stimulated gastrin release. 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. 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) injection 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. In contrast, in patients with the Zollinger-Ellison syndrome, intravenous secretin evokes dramatic increases in serum gastrin concentrations. 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. 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. 31-5-6). The serum gastrin concentration then returns gradually to or toward the preinjection level. Bowell'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.

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. 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 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 prominent error in interpreting 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 listing hypergastrinemia is identified, studies should be performed to determine the presence of gastric acid hypersecretion or, alternatively, achlorhydria or acid hyposecretion.19 This determination should be performed before initiating any provocative tests (e.g., secretin stimulation). 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 percent of patients with proven gastrinoma.20 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 gastrinoma. Exaggerated gastrin release in response to calcium infusion occurs in more than 80 percent of patients with gastrinoma. In the absence of a positive gastrin release response to secretin, exaggerated gastrin release, serum calcium infusion is unusual in patients with gastrinoma.

Calcium infusion has been reported to amplify the serum gastrin response 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 percent) 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.20, 21 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 hyperplasia 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 percent 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 also 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.14 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 percent of patients in whom there is persuasive clinical and laboratory evidence of gastrinoma, the tumor cannot be identified at surgery.21-26 A variety of diagnostic techniques have been used to localize gastrinomas in patients with the Zollinger-Ellison syndrome. 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 percent of gastrinomas identified at surgery were detected by selective angiography, with a high frequency of false-positive studies (70 percent). More recently, selective arteriography has been reported to detect about one third of patients with clinical and biochemical evidence of gastrinoma (approximately

<table>
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<tr>
<th>DISORDER</th>
<th>SECRETIN INJECTION</th>
<th>CALCIUM INFUSION</th>
<th>TEST MEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zollinger-Ellison syndrome (gastrinoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral G-cell hyperfunction</td>
<td>Substantial increase in serum gastrin</td>
<td>Exaggerated release of gastrin (usually serum gastrin increases by more than 400 pg/ml)</td>
<td>Viscibly increases in serum gastrin (from normal to almost to 2000 pg/ml increase)</td>
</tr>
<tr>
<td>Common duodenal ulcer</td>
<td>Decrease, no change, or slight increase in serum gastrin (no increase greater than 200 pg/ml)</td>
<td>Small increase in serum gastrin (less than 100 pg/ml)</td>
<td>Exaggerated release of gastrin in response to flushing (increase by &gt;2000 pg/ml)</td>
</tr>
</tbody>
</table>

19. This determination should be performed before initiating any provocative tests (e.g., secretin stimulation).
20. 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 gastrinoma.
21. In the absence of a positive gastrin release response to secretin, exaggerated gastrin release, serum calcium infusion is unusual in patients with gastrinoma.
22. A variety of diagnostic techniques have been used to localize gastrinomas in patients with the Zollinger-Ellison syndrome. 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 percent of gastrinomas identified at surgery were detected by selective angiography, with a high frequency of false-positive studies (70 percent). More recently, selective arteriography has been reported to detect about one third of patients with clinical and biochemical evidence of gastrinoma. (approximately
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 paracrine tumors from tumors located in the wall of the immediatelv adjacent duodenum. Selective celiac and hepatic artery angiography has proved to be the best technique for identifying and characterizing hepatic metastases 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. Unfortunately, neither 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. Magnetic resonance imaging is approximately as effective as abdominal ultrasound in identifying gastrinomas. The ability of MRI to identify extrapancreatic 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 36 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 gastrinomas in patients with the Zollinger-Ellison syndrome include computed tomography, ultrasound, and MRI fol-
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 to detect gastrinomas. 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% of patients when all imaging studies were negative. 20, 104, 139, 148

Most recently, localization of gastrinomas by selective injection of secretin into the gastrroduodenal, splenic, and superior mesenteric arteries with measurements of hepatic vein serum gastrin concentrations has been reported. 112, 113 The selective arterial secretin injection (SASI) test involves injection of 20 to 30 units of secretin by catheter into the superior mesenteric artery, gastrroduodenal 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 gastrroduodenal 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 pg/ml greater than the preinjection serum gastrin level. The selective secretin arterial injection test has been reported to detect gastrinomas that were not identified by computed tomography, ultrasound, and selective arteriography. 113

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 30% 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. 1, 5, 10, 20, 21, 34, 35, 36, 38, 40 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 controlling 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. 20, 22, 30, 34, 40 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. 20, 22, 30, 34, 40, 109 Zollinger 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. 44 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 62 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 the 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 be aware that duodenum, the stomach as well as the mesenteric and retroperitoneal areas, liver, remainder of the small intestines, and lymph nodes as well as accessory 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 gastritis, the most common form of extragastric gastritis, arc excellent candidates for complete cure by biopsy. If gastritis 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 gastric cyst. All lymph nodes containing gastrinoma should be removed. Recent studies indicate successful gastrinoma resection in approximately 21% of patients with, cure rates from 12% to 26%. Complete tumor removal is more often possible with extragastric gastrinomas, approximately half of which can be resected completely.26,108 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, pancreaticoduodenectomy (Whipple’s procedure) is not recommended and should be a consideration only when there appears to be a greater likelihood for cure and a lesser surgical procedure cannot be performed. Biopsy of gastrinoma and total pancreatectomy are not recommended in patients with the Zollinger-Ellison syndrome. Duodenal wall gastrinomas, which are a second source of gastrin when multiple in patients with MEN I, are usually small, readily resectable, and benign, and even when malignant their metastatic potential is limited. Gastrinoma in duodenal wall gastrinomas probably account for the majority of gastrinomas found in peripancreatic lymph nodes who no gastrinoma has 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. 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. If metastatic gastrinoma in the liver a completely and safely resectable, it probably should be resected. Patients may also harbor primary hepatic gastrinomas, which have been cured by complete removal of the hepatic tumor.116 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 with 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 B12 (30 μg per month). Oral administration of calcium and vitamin D is recommended. Patients with osteoporosis and low serum calcium, which occur commonly after total gastrectomy. Proximal gastric vagotomy in patients with gastrinoma has been reported to result in reduced acid secretion and to reduce required doses of H2 receptor antagonists. 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 H2 receptor antagonists became available, there had been no effective medical therapy for patients with the Zollinger-Ellison syndrome. The development of H2 receptor antagonists provided therapeutic agents that proved effective in producing symptom relief, reducing acid secretion, and healing ulcers.109-112 Cimetidine, the first H2 receptor antagonist shown to be effective, decreased gastric acid secretion, improved clinical symptoms, and healed ulcers in 85% 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 H2 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 H2 receptor antagonists required to reduce gastric acid secretion to satisfactory levels (less than 10 mEq/hr) in patients with Zollinger-Ellison syndrome have ranged from 0.8 g (Zollinger-Ellison syndrome without MEN I) to 1.2 to 13.2 g (cimetidine, 2.1 g (range 0.6 to 3.6 g) for ranitidine, and 0.24 g (range 0.06 to 0.48 g) for famotidine. There is no evidence that treatment with H2 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 treatment with H2 receptor antagonists. With long-term treatment and extended observation, as many as 50% of patients with the Zollinger-Ellison syndrome have been reported to fail H2 receptor antagonist treatment.113 Symptoms do not correlate well with ulcer healing or ulcer recurrence in Zollinger-Ellison patients treated with H2 receptor antagonists.114 Ucer disease may continue or recur in the absence of symptoms. For this reason, it has been proposed that the dose of H2 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.115 Anticholinergic agents have occasionally been used to increase the effectiveness of concurrent administration of H2 receptor antagonists in patients with Zollinger-Ellison syndrome. Intravenous infusion of H2 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 decreases gastric acid secretion and produces ulcer healing and symptomatic relief in patients with the Zollinger-Ellison syndrome.116-118
Omeprazole is a substituted benzimidazole that inhibits the H+/K+-ATPase ion pump that constitutes the terminal step in parietal cell secretion of hydrogen ions (see Ch. 27). Omeprazole reduces gastric acid secretion by 90% to 100% 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 H2-receptor antagonists. Treatment with omeprazole has produced ulcer healing within two weeks in more than 50% of patients with Zollinger-Ellison syndrome, with 90 to 100% cure 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 as 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 is discontinued and reactivated by food or sedative, the dose should be reduced to 40 mg per day.

Omeprazole is indicated as initial treatment of patients with Zollinger-Ellison syndrome during diagnosis and evaluation, and for prolonged treatment of patients who are poor candidates for gastrinoma resection. It is the appropriate treatment of patients in whom attempted resection of tumours has been unsuccessful and total gastrectomy is not performed. When instituted for prolonged treatment of patients with Zollinger-Ellison syndrome, omeprazole treatment should not lapse or be interrupted, since its discontinuance often is followed by relapse or by 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.16,17 The frequency and 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.16 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 may use histamine 2 agonists, but gastrinoma patients who develop somatostatin resistance unless gastric acid secretion is reduced to less than 5 mEq/hr, and in some instances to less than 1 mEq/hr.18 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 halflife. A synthetic analog of somatostatin, with a much longer duration of biologic action, has been administered to patients with Zollinger-Ellison syndrome.19,20 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 select 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 in combination. Chemotherapy with actinomycin D is used to treat metastatic tumor mass and serum gastrin levels have been reported in more than half the patients treated by intravenous administration of streptozotocin. Some authors favor early treatment of patients with documented metastatic disease, whereas most others advocate chemotherapy only for patients with liver metastases. Chemotherapy has no primary therapeutic role in attempts to reduce gastric acid hypersecretion and consequent ulcer disease occurring as a result of gastrin secretion. Therefore, chemotherapy is used effectively with omeprazole. Chemotherapy in patients with metastatic gastrinoma appears to have a 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 infusion has been used as palliative treatment for reduction of metastatic hepatic tumor mass and associated symptoms.18 Hepatic arterial embolization of metastatic gastrinoma involving 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 multicentric, usually malignant (although of highly variable biologic aggressiveness), and frequently metastatic at the
time of diagnosis. In addition, tumors, even after careful preoperative localization 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 H₂-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 options. 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% 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 discontinuation.

The 5-year survival estimates for all patients with gastrinoma have been reported at from 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 control hypergastrinemia and ulcer. The incidence of peptic ulcer disease is reduced during long-term therapy. 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. This may reflect the absence of secretin-stimulated release of tumor gastrin due to elimination of contact of acid with secretin- and somatostatin-sensitive intestinal mucosa. In a small number of patients with metastatic gastrinoma, regression of primary tumor and metastases has been reported after total gastrectomy. 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 levels are suggestive of metastatic tumor progression. The secretin stimulation test is of value in identifying recurrence of gastrinoma in 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 gastrinomas 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 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. 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. Twenty-five per cent of the patients with systemic mastocytosis have been reported to have basal acid output rates of 15 mEq/l or greater. Values found in more than 95 per cent of patients with the Zollinger-Ellison syndrome. Doses of H2 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 gmday) and ranitidine (mean, 0.8 0.9 gmday; range, 0.3 to 1.2 gmday). 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 gastric content in these tumors. 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 destroyable by trypsin. As with gastrinoma, pepinulin output in response to this secretagogue is relatively low. Similar to stimulation by gastrin, the gastric acid secretory response to the nongastrinoma secretagogue is inhibited by atropine. 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.

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 gastric release in these patients. Management is 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. 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 hyperscrection 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. 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. It is more likely that small intestinal resection removes the site of release of intestinal hormone(s) that normally inhibit gastric release. The usually transient 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 H2 receptor antagonists or omeprazole.

Gastrin Cell Hyperplasia/Hyperplasia

In a small proportion of patients with duodenal ulcer, gastric acid hypersecretion is accompanied by elevated
between endogenous human plasma gastrin in peripheral blood and hepaticoduodenal gastrin. Gastroenterology 88:609, 1980.


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