ZOLLINGER - ELLISON SYNDROME:

NATURE'S EXPERIMENT IN HYPERGASTRINEMIA

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HISTORICAL OVERVIEW

About 50 years ago, Sailer and Zinniger first described the syndrome of severe peptic ulcer disease, gastric hypersecretion, and a non-insulin-secreting islet cell tumor of the pancreas (1). Ten years later, the pathologist, R.M. Zollinger, and the surgeon, R.H. Ellison, expanded the clinical and pathological description of this syndrome, and hypothesized that the tumor secreted a humoral factor which caused the peptic ulceration (2). The term Zollinger-Ellison syndrome became immediately popular and widely known, not because the syndrome was common, but because physicians recognized that the syndrome was an unusual and exciting natural experiment in the physiology of acid secretion and the pathophysiology of ulcer disease. In 1960, Gregory was able to isolate the newly described peptide hormone gastrin from a pancreatic tumor (3), directly linking a tumor product with the acid hypersecretion and ulcers suffered by patients with Zollinger-Ellison syndrome. Because acid hypersecretion caused devastating ulcer disease complicated by bleeding and perforation in most patients, treatment was aimed primarily at removing the stomach and only partially at an attempt at cure by resecting tumor which was successful only about 5% of the time in the original studies (4).

Developed about 20 years ago, the radioimmunoassay for serum gastrin by both McGuigan (5) and Yalow (6) was a great boon to the diagnosis and long-term follow-up of Zollinger-Ellison syndrome patients, as well as a major research tool in the study of gastric physiology and peptic ulcers in general. It was soon realized that not all patients with Zollinger-Ellison syndrome secreted large amounts of gastrin into the blood stream. Several provocative tests designed to cause tumor release of gastrin were developed to increase diagnostic accuracy; the best of these is the secretin test (7), which will be discussed in more detail later. Zollinger-Ellison syndrome is now known to occur in two major forms; in about 25% of patients, the syndrome is part of a more generalized familial endocrine disorder of parathyroid, pancreas and pituitary glands (Multiple Endocrine Neoplasia Type I or MEN-I). In the other 75% of patients, gastrinomas appear without involvement of other endocrine glands; this is usually referred to as sporadic gastrinoma or sporadic Zollinger-Ellison syndrome.

Medical therapy for Zollinger-Ellison syndrome became possible shortly after the development of the radioimmunoassay. After the first histamine H_2-receptor antagonists became available (first metiamide and then cimetidine), it became quickly apparent that few patients needed total gastrectomy; if not cured of tumor, they could be managed on medication indefinitely. Increasingly potent and longer-acting H_2-receptor antagonists were developed until their use was largely supplanted by the proton pump inhibitor omeprazole. Now patients not only could be treated with medication, but in most cases could take this medication only once a day. Each medication developed was generally tried in patients with Zollinger-Ellison syndrome, and then became much more widely used for the other peptic conditions so common in general practice, gastric and duodenal ulcers and gastroesophageal reflux disease.

The success of medical therapy for the acid hypersecretion in Zollinger-Ellison syndrome has actually increased concern for management of tumor. Since essentially no one diagnosed with Zollinger-Ellison syndrome should die of peptic disease, then all patients are exposed to

the potential consequences of tumor growth and metastasis. In addition, long-term medical therapy carries a considerable burden for cost and compliance. Current issues in management of Zollinger-Ellison syndrome focus primarily on improved detection and resection of tumor, better treatment of unresectable/metastatic tumor, and possible surgical approaches to decreasing acid secretion and long-term drug requirements.

PHYSIOLOGY OF GASTRIN IN NORMAL PATIENTS

Gastrin is a peptide synthesized and stored by specialized endocrine cells called gastrin or G-cells (8). These cells are located in the gastric antrum and in the proximal duodenum. Gastrin primarily exists in two physiologically important sizes, a 17 amino acid form (little gastrin), which accounts for 90% of gastrin from the antrum and 40% from the duodenum, and a 34 amino acid form (big gastrin which makes up most of the remaining circulating gastrin. Both forms can be synthesized as sulfated or nonsulfated forms. Normally, gastrin is released by luminal components in the diet such as amino acids and peptides after meals. These components act primarily on G-cells, but may also activate some neural pathways which release gastrin. Gastrin released by G-cells travels through the circulation to interact with gastric parietal cells which release acid into the lumen. Gastrin release after a meal in a normal person explains almost all of the acid secretion stimulated by the gastric phase of digestion. The interaction of G-cells and parietal cells in the stomach are modulated by a third cell, the D-cell of the pyloric gland. These interactions are summarized in Table 1 (Adapted from reference (9)). D-cells release the inhibitory peptide somatostatin (SS) which inhibits gastrin release from G-cells. The principal physiologic stimulant of somatostatin release is low gastric Ph. Cholinergic nerves stimulate G-cells to release gastrin, parietal cells to release acid, while inhibiting somatostatin release from D-cells. Nerves using the peptide GRP as a neurotransmitter stimulate gastrin release while nerves using the peptide VIP stimulate D-cell release of somatostatin.

Table 1. Interactions of G-cells, D-cells and parietal cells in the stomach.

	G-cell	D-cell	Parietal cell
High Ph	gastrin ↑		Acid ↑
Low pH		SS ↑	Acid ↓
Luminal nutrients	gastrin ↑		Acid ↑
Cholinergic nerves	gastrin ↑	SS ↓	Acid ↑
GRP nerves	gastrin ↑		Acid ↑
VIP nerves		SS ↑	Acid ↓

Gastrin interacts with two major classes of receptors; the gastrin receptor itself and the

closely related cholecystokinin (CCK) receptor. CCK can interact with gastrin receptors as well as CCK receptors. Not surprisingly, these two receptors share about 50% of their amino acid residues, and both linked to GTP-binding proteins which stimulate phospholipase C to produce diacylglycerol and inositol 1,4,5 triphosphate. This pathway increases intracellular calcium concentrations and activates protein kinase C. Because the gastrin and CCK receptors are so similar, they are now often referred to as CCK-A (CCK-preferring) and CCK-B (gastrin-preferring) receptors. These two types of receptors are present in different proportions in different cell types. The actions of gastrin and CCK depend on the cells that possess the receptors, as summarized in Table 2 (Adapted from reference (9)).

Table 2. Distribution of gastrin and CCK receptors.

Location	Cell Type	Receptor	Action
Stomach	Parietal Cell	Gastrin	Acid secretion
	D Cell	Gastrin, CCK	Somatostatin Release
	ECL Cell	Gastrin	Histamine Release, Histadine Decarboxylase Activation
	Stem Cell	? Gastrin	Proliferation
Pancreas	Acinar Cell	CCK	Enzyme Secretion Growth
Gallbladder	Smooth Muscle Cell	CCK	Contraction
Intestine	Nerves	CCK	Peristalsis
Brain	Cortex Brainstem	Gastrin CCK	Unknown ? Satiety

PHYSIOLOGY OF GASTRIN IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME

In patients with Zollinger-Ellison syndrome, clinical effects of hypergastrinemia outside the stomach are not generally apparent. In addition to gastrin's ability to stimulate gastric acid from parietal cells in the fundus of the stomach, gastrin has a major role as a trophic factor for the cells of the stomach and pancreas, as well as for endocrine cells in the stomach and duodenum. Some of the gastric acid hypersecretion is due to the continual stimulation of the parietal cell by high circulating concentrations of gastrin produced by the tumor, while some

acid hypersecretion is due to the gradual hypertrophy of the gastric mucosa including the acid-producing parietal cells (10). In the last few years, the discovery that gastrin also causes hypertrophy of enterochromaffin-like cells in the gastric mucosa has led to the interesting association of Zollinger-Ellison syndrome with gastric carcinoid tumors (11,12). Chronic hypergastrinemia clinically is much more likely to be associated with low acid secretion and high gastric pH, as occurs with chronic atrophic gastritis, thus most clinically apparent gastric carcinoids occur in association with chronic atrophic gastritis (13). Less commonly, long-acting, potent antisecretory drugs such as omeprazole cause significant hypergastrinemia. To date, the association of drug therapy in patients with gastric carcinoid tumors is quite rare. The ability of gastrin to stimulate acid secretion in both normal people and in patients with Zollinger-Ellison syndrome is not necessarily related to its ability to stimulate mucosal growth. This is because acid secretion by the parietal cell is controlled in a complex fashion involving stimulation or inhibition by several receptors. Agents which inhibit acid secretion by interacting with receptors other than gastrin do not affect mucosal growth (14), as summarized in Table 3 (Adapted from reference (9)). In contrast, agents which interfere with gastrin binding inhibit both acid secretion and mucosal growth.

Table 3. Relationship between gastrin-stimulated acid secretion and gastrin-stimulated mucosal growth.

Agent	Interaction with parietal cell	Inhibition of acid	Inhibition of growth	Inhibition of gastrin binding
Atropine	Inhibitor that binds to cholinergic receptor	Yes	No	No
Prostaglandin	Binds to receptor linked to inhibitory G-protein	Yes	No	No
H_2-blocker	Inhibitor that binds to histamine receptor	Yes	No	No
Omeprazole	Inhibitor that blocks H_+,K^+-ATPase at luminal surface	Yes	No	No
CCK	Competes with gastrin for gastrin receptor (weak agonist)	Yes	Yes	Yes
Proglumide	Competes with gastrin for gastrin receptor (weak antagonist)	Yes	Yes	Yes

DIAGNOSIS OF ZOLLINGER-ELLISON SYNDROME

Although Zollinger-Ellison syndrome is much easier to diagnose now with the wide availability of the gastrin radioimmunoassay, diagnosis is still frequently delayed due to the relative rarity of the syndrome compared to the great frequency of peptic disease in the general population. Zollinger-Ellison syndrome only accounts for about 0.1 percent of cases of duodenal ulcer disease. Males are probably slightly more likely than females to have this syndrome, which can present from the first through the tenth decade of life. Most patients with Zollinger-Ellison syndrome are diagnosed between the ages of 30 to 50 years. Duodenal ulcers are still the most common manifestation of Zollinger-Ellison syndrome (15). While gastric ulcers certainly occur, they are usually in association with duodenal ulcers. Similarly, severe esophagitis with reflux symptoms is common, but is rarely the only manifestation of Zollinger-Ellison syndrome. About 10-20% of patients with Zollinger-Ellison syndrome may present with watery diarrhea as the major manifestation. Clinical manifestations that suggest gastrinoma and Zollinger-Ellison syndrome are summarized in Table 4.

Table 4. Clinical features that suggest Zollinger-Ellison syndrome.

Ulcer disease
Multiple duodenal or gastric ulcers
Ulcers in unusual locations (e.g. post-bulbar)
Ulcers without history of NSAID use or presence of H. pylori infection
Ulcers resistant to medical therapy
Frequent, rapid recurrence of ulcers after therapy stopped
Recurrent ulcer after apparently adequate ulcer surgery
Diarrhea
Watery diarrhea
Steatorrhea
Metabolic abnormalities
Hypercalcemia
Basal hyperchlorhydria
Family history
Extensive family history of ulcer disease
Family history of tumors of pancreas, pituitary or parathyroid

Certainly any of these features should prompt the physician to consider a diagnosis of Zollinger-Ellison syndrome. In addition, patients with complications of duodenal ulcer disease for whom surgery is being considered should be evaluated for Zollinger-Ellison syndrome. A reasonably simple and economical screening test is a fasting serum gastrin determination. In the great majority (but not all) of patients with Zollinger-Ellison syndrome, fasting gastrin

concentration will be abnormal (> 100 pg/ml). The next step should be measurement of gastric acid secretion. This is because hypergastrinemia due to gastric achlorhydria is more common than hypergastrinemia due to Zollinger-Ellison syndrome. Conditions associated with low rates of acid secretion and hypergastrinemia are listed in Table 5.

Table 5. Conditions associated with low rates of gastric acid secretion and elevated serum gastrin.

Condition	Occurrence
Treatment related	
H^+,K^+-ATPase inhibitors	Most patients with long-term treatment
H_2-receptor antagonists	Uncommon, minor elevations
Postvagotomy	Occasional
Chronic type A atrophic gastritis	
Idiopathic or autoimmune pernicious anemia	Up to 5% of population; 70% of these patients develop hypergastrinemia
Chronic renal failure	50% of patients with creatinine > 3; 80% of these have normal or low gastric acid

Usually, consideration of the clinical setting will allow one to exclude these factors before more extensive (and expensive) evaluation is performed. The presence of gastric ulcer without duodenal ulcer in a patient with hypergastrinemia should alert the clinician to the possibility of an ulcerating gastric cancer in a possibly hypo- or achlorhydric patient; careful evaluation with endoscopy and multiple biopsies of the ulcer will generally lead to an accurate diagnosis. If the patient has active peptic ulcer disease, then a course of anti-secretory treatment can and should be given to allow healing before stopping medications for measurement of acid secretion. This course of action is considered in more detail later. Basal gastric acid secretion in Zollinger-Ellison syndrome is > 15 mmol/h, or > 5 mmol/h in patients with prior successful vagotomy. Several other conditions can cause both hypergastrinemia and basal acid hypersecretion, as summarized in Table 6 (adapted from reference (9)).

Table 6. Conditions associated with high rates of gastric acid secretion and elevated serum gastrin.

Condition	Occurrence
Zollinger-Ellison syndrome	About 250 new cases per year in U.S.
Excluded gastric antrum after gastric surgery	Very rare with modern surgical techniques
Gastric outlet obstruction	About 2% of patients with duodenal ulcer disease or gastric cancer, due to retained food or distension
Chronic renal failure	50% of patients with creatinine > 3; 15% of these have normal or high gastric acid but even fewer have elevated serum gastrins
? Antral G-cell hyperplasia	Rare
? H. Pylori infection	May elevate gastrin 1.5-2 fold, acid secretion is usually normal but may be elevated. Acid hypersecretion persists after H. pylori eradication.

When a patient has elevated basal gastric acid secretion in conjunction with a fasting serum gastrin > 1000 pg/ml, the diagnosis of Zollinger-Ellison syndrome is secure and treatment and/or evaluation for tumor can proceed. However, in about half of patients, serum gastrin will be between 100 and 1000 pg/ml. In these patients, the provocative intravenous administration of secretin will be useful. In a positive test, serum gastrin will increase by 200 pg/ml. Smaller increases may be seen in normal subjects and those with duodenal ulcer disease. Other provocative tests such as intravenous calcium infusion or test meal administration are less accurate or associated with more side effects. Occasionally even achlorhydric patients may have a positive secretin test (16) which points out the importance of measuring gastric acid before making a diagnosis of Zollinger-Ellison syndrome. Results of secretin testing in three groups of patients with hypergastrinemia are shown in Figure 1.

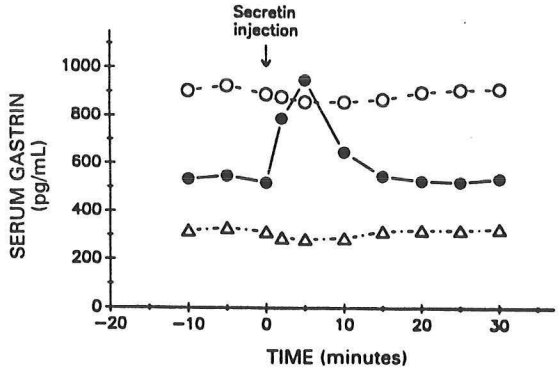


Figure 1. Serum gastrin concentrations after intravenous administration of secretin in patients with chronic atrophic gastritis (open circles), gastrinoma (closed circles) or duodenal ulcer with gastric outlet obstruction (open triangles). From reference (15).

About 15% of patients will have a negative secretin test in conjunction with acid hypersecretion and the clinical features of Zollinger-Ellison syndrome (17); after considering the other causes of gastric acid hypersecretion, a clinical diagnosis of Zollinger-Ellison syndrome can be safely made. The diagnosis of G-cell hyperplasia has historically been made when the patient has a modestly elevated gastrin, a negative secretin test, and an exaggerated gastrin response to a test meal. Some patients with the diagnosis of G-cell hyperplasia may have had either minute duodenal gastrinomas which were not detected or elevated gastrins from H. pylori infection.

MANAGEMENT OF ACID HYPERSECRETION IN ZOLLINGER-ELLISON SYNDROME.

When the diagnosis of Zollinger-Ellison syndrome appears likely, based on the clinical picture, acid hypersecretion and an elevated fasting gastrin, treatment should immediately focus on management of acid hypersecretion. In patients with active ulcers, stopping medication (unless nasogastric suction is performed) is associated with a real risk of complications of bleeding or perforation. There is rarely any clinical urgency in making a diagnosis of Zollinger-Ellison syndrome which has probably existed for months or years prior to the current presentation of the patient. The great majority of patients with Zollinger-Ellison syndrome can now be managed easily on oral medication. This has led some physicians to neglect measurement of acid secretion both for initial diagnosis and subsequent management. This leads either to either inadequate treatment or overtreatment often at great expense in a sizeable proportion on patients. If one is unable to provide acid secretory measurements for a patient with Zollinger-Ellison syndrome, referral should be made to one of many centers for such measurements, which

after initial evaluation will only need to be done on a very infrequent basis. Patients with acid hypersecretion frequently require larger than average doses of antisecretory medications. A reasonable initial drug regimen for oral therapy is omeprazole, 60 mg/day in a single dose. An alternative strategy is to start with a more potent H_2-receptor antagonist such as ranitidine 150 mg four times/day. Acid secretion should be measured for an hour at the end of the dose interval to ensure that secretion is $<$ 10 mmol/h (or $<$ 5 mmol/h in patients with partial gastrectomies). When using H^+,K^+-ATPase inhibitors, such as omeprazole, bioavailability will increase with better control of acid secretion (18), so dose adjustments after the acute phase should be made at about one week intervals. Patients who are unable to tolerate medication by mouth can be started on intravenous H_2-receptor antagonist, such as ranitidine, 100 mg as a bolus followed by an infusion of 0.5 mg/kg/h. In this situation, acid secretion can be measured every four hours and the dose of H_2-receptor antagonist increased until secretion is $<$ 10 mmol/h. An infusion of ranitidine, 1 mg/kg/h will control acid secretion in about 70% of patients (19,20). If necessary, rates of up to 4-5 mg/kg/h can be used.

Once the active peptic ulcer is cured, oral H_2-receptor antagonists should be stopped for three days and omeprazole or other H^+,K^+-ATPase inhibitor should be stopped for one week prior to measuring of acid secretion. The purpose of obtaining acid secretory measurements off all medication is to obtain a baseline to evaluate the effectiveness of subsequent surgical therapy aimed at cure or long-term reduction of acid secretion. In the occasional hypersecretory patient who develops vomiting or diarrhea after stopping medication, intravenous H_2-receptor antagonists can be used up to 24 h prior to testing. The very occasional patient will require nasogastric suction and intravenous fluids for the 12-24 h prior to testing. An initial strategy for diagnosis and treatment is outlined in Fig. 2 and 3.

FIG.2. INITIAL DIAGNOSIS AND TREATMENT OF ZES

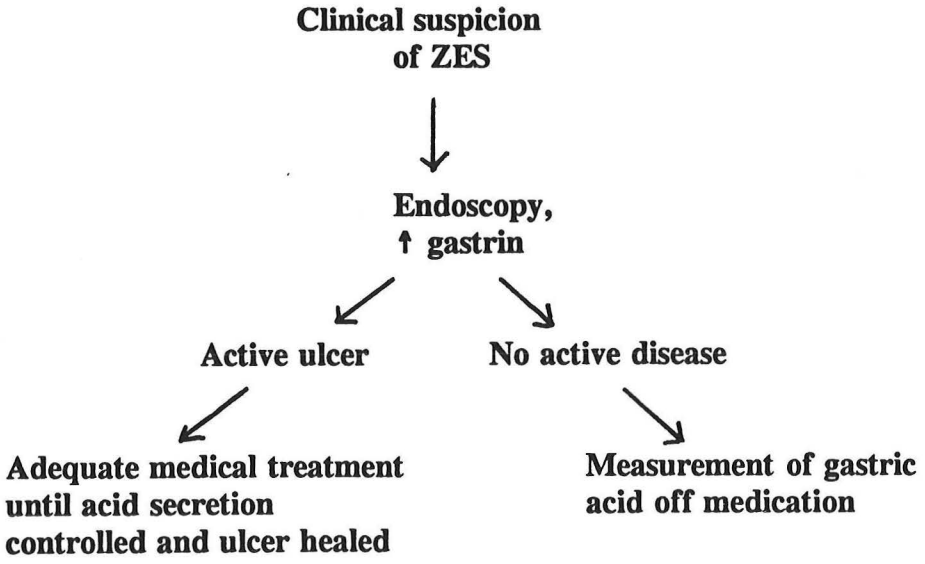
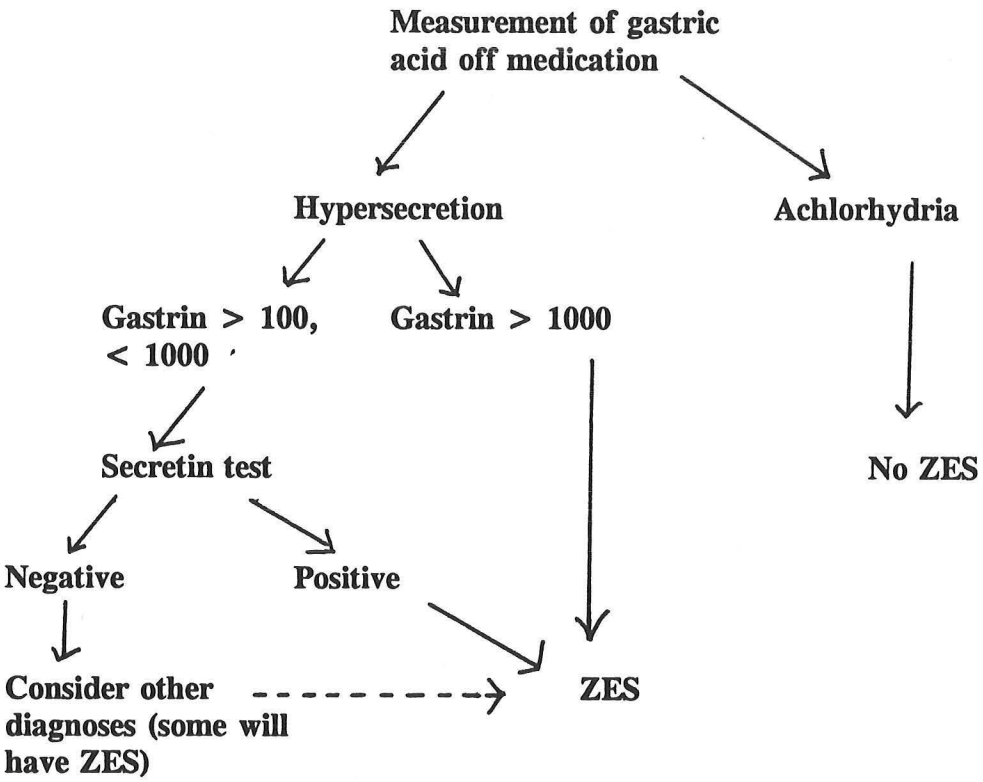


FIG. 3. INITIAL DIAGNOSIS AND TREATMENT OF ZES



EVALUATION FOR TUMOR IN ZOLLINGER-ELLISON SYNDROME

Anatomic and pathological factors. Over the last 15 years, with improvement in diagnostic techniques and in surgery directed at tumor localization, our concepts regarding the gastrinomas of Zollinger-Ellison syndrome have changed considerably. Probably only about a third of gastrinomas are located in the pancreas itself, while the most common site for gastrinomas is actually in the wall of the duodenum. Thus gastrinomas are not actually "islet cell tumors" but tumors arising from endocrine cells in a variety of locations. About 90% of gastrinomas do arise from a well-localized area called the "gastrinoma triangle," illustrated in Fig. 4.

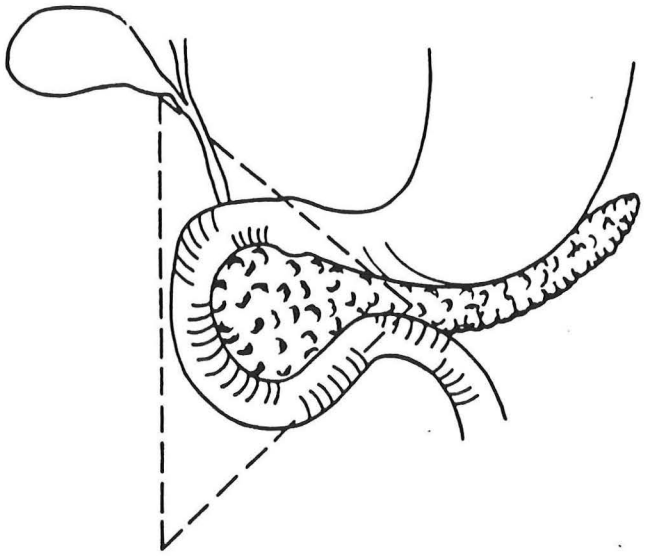


Fig. 4. The gastrinoma triangle. From reference (21).

This is the area bordered superiorly by the junction of the cystic and common bile ducts, inferiorly by the second and third portions of the duodenum, and medially by the junction of the head and body of the pancreas. Of considerable interest is the now well-documented occurrence of apparently primary gastrinomas occurring in lymph nodes or liver. To date, in the most current surgical series, gastrinoma is found at laparotomy in only about 70% of patients. We assume that we are missing very small gastrinomas which are still capable of making large amounts of gastrin to produce the clinical manifestation of acid hypersecretion. The frequency of gastrinoma localizations is summarized in Table 7. Of gastrinomas found at surgery, histology is almost always of a benign appearance, with nests of fairly monotonous cells often forming glandular structures. This benign appearance does not correlate well with the actual behavior of the tumor, which can be defined as "malignant" by the presence of metastases, most often to the liver or to regional lymph nodes, but occasionally to bone, brain or other distant organs. It is estimated that about half to two thirds of gastrinomas have metastases, but even patients with metastases tend to do very well with prolonged clinical courses of 5 - 15 years or longer. The presence of hepatic metastases is associated with a survival averaging eight years (22,23). A fairly small proportion of patients with documented gastrinomas will have a much more rapid downhill course with widespread metastases.

Table 7. Anatomic localization of documented gastrinomas.

Location	Frequency of occurrence
Duodenum	40%
Pancreas	30%
Lymph Nodes	10-20%
Liver	Unusual
Hilum of Spleen	Unusual
Stomach	Unusual
Ovary	Rare

Fig. 5 shows survival in a group of patients with a variety of localizations of gastrinoma at the time of surgery. Attempts at curative resection were attempted, but residual tumor was often left behind.

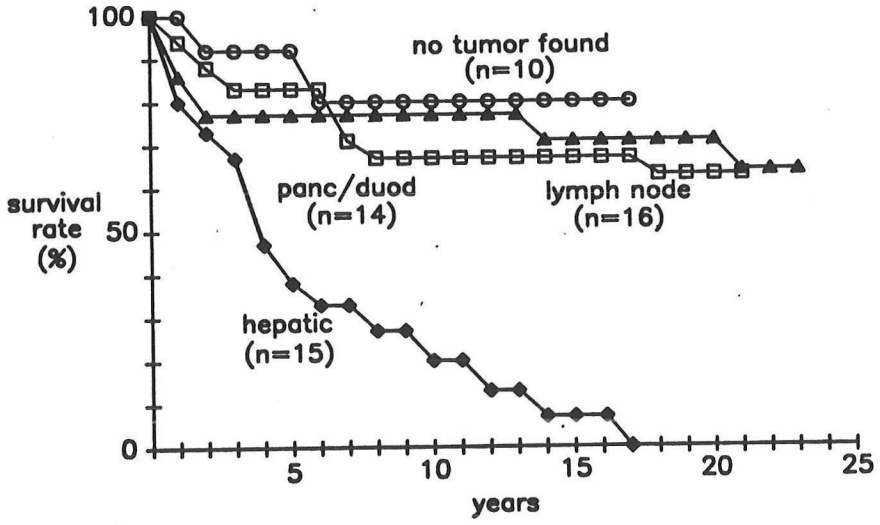


Fig. 5. Life table analysis of survival in 62 patients with gastrinoma. From reference (21).

Preoperative studies. Preoperative localization of tumor in Zollinger-Ellison syndrome with diagnosis of metastases is highly desirable. Since 50% or more of patients will have metastases, these patients should ideally be spared an extensive exploratory laparotomy. Several techniques have been widely used and data exists to evaluate their benefit. A well-done **abdominal CAT scan** with intravenous contrast is useful in localizing about half of primary tumors and about 60% of metastatic tumors (24). This is considerably better than ultrasound, which is not generally useful. As expected, CAT scans detect almost all tumors greater than 3 cm in size and almost no tumors less than 1 cm in size. **Selective abdominal arteriography** is probably somewhat better in highly experienced hands, but taking all published reports as a whole, does not routinely add to the diagnostic accuracy of the CAT scan. It currently seems reasonable to use angiography as an adjunct to CAT scan when results are equivocal or when the angiography is deemed useful in planning some specialized surgical technique such as segmental hepatic resection. **Magnetic resonance imaging (MRI)** disappointingly is currently inferior to the CAT scan for detection of both primary gastrinomas or metastases. The usefulness of these techniques is compared in Table 8.

Table 8. Comparison of several preoperative imaging techniques to detect primary and metastatic gastrinomas.

	Primary Tumor		Metastatic Tumor	
Imaging Technique	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Ultrasound	23	92	14	100
CAT with contrast	50	90	54	99
Angiography	68	89	62	98
MRI	21	33	67	100

Adapted from reference (25).

Several studies have evaluated the ability of functional studies to localize gastrin preoperatively. These have included portal venous sampling (26,27). In this technique, blood is taken from the various tributaries of the portal vein and gastrin concentrations are measured. The technique is time-consuming, expensive and fairly invasive and uncomfortable for the patient. It suffers most from the fact that it can only localize the gastrinoma to a certain area; the unique anatomy of gastrinoma localization already ensures that about 90% of gastrinomas will be within the gastrinoma triangle described earlier; thus the procedure adds no real value to the imaging studies described earlier. More recently, the technique of injecting small amounts of secretin selectively into various arteries during arteriography has been tried (28). Venous samples are taken from the right hepatic vein and a peripheral vein. This is a new technique for which

limited data is available. It is likely to suffer from the same disadvantages as portal venous sampling; it is relatively invasive and can only localize the gastrinoma to a general area.

Zollinger-Ellison syndrome and MEN-I. Patients with Zollinger-Ellison syndrome as part of MEN-I syndrome need special consideration. Patients with MEN-I syndrome probably make up about 25% of all patients with Zollinger-Ellison syndrome. MEN-I syndrome is an autosomal dominant genetic disorder with tumors in parathyroid and pituitary as well as in the gastrinoma triangle (29). Parathyroid hyperfunction, generally due to hyperplasia rather than adenoma is present in almost all patients (30). "Islet cell" tumors occur in about 50% of patients; most of these tumors are gastrinomas. Symptomatic solitary pituitary tumors occur in about 30% of patients.

Historically, these patients have been felt to be incurable but to have a generally more benign and prolonged course compared to patients with sporadic Zollinger-Ellison syndrome. More recent studies cast some doubt on both of these beliefs. The poor rate of cure in MEN-I is generally ascribed to the multiple gastrinomas these patients often have; more recently, it has been suggested that up to 50% have duodenal primaries while only 10% have pancreatic adenomas and about 20% have gastrinomas in lymph nodes. Increased attention to the duodenal area may lead to improved cure rates. Several recent studies with careful followup of patients with MEN-I syndrome and gastrinoma have shown that life expectancy in these patients is about the same as in patients with sporadic Zollinger-Ellison syndrome (8,31,32). It is clear that control of gastric acid hypersecretion is greatly facilitated in these patients by parathyroidectomy to reduce hypercalcemia. Normocalcemia is associated with decreases in basal acid secretion and fasting serum gastrin concentrations, and improves response to antisecretory medication (33,34).

DECISIONS FOR SURGERY

Surgery to reduce gastric acid secretion. Before considering attempts at tumor resection, it is reasonable to consider whether surgery aimed at control of acid secretion is indicated in patients with Zollinger-Ellison syndrome. It has been only 10 - 15 years since these patients were routinely treated with total gastrectomy. The advent of medical therapy has made this surgical approach virtually obsolete. If the diagnosis of Zollinger-Ellison syndrome is known or suspected, the patient should definitely **not** have a partial gastric resection such as antrectomy with gastroduodenostomy or jejunostomy. Removing the antrum, containing normal G-cells, will have absolutely no impact on the hypergastrinemia of a gastrinoma, and now the acid secretion from the fundus will pour into a relatively unprotected anastomosis. In fact, this is the reason that ulcer patients should have a fasting serum gastrin concentration to eliminate the diagnosis of Zollinger-Ellison syndrome prior to elective antrectomy. In patients who inadvertently have had antrectomy with reanastomosis, as mentioned previously, acid secretion must be even more substantially reduced (to < 5 mmol/h) than in a patient with an intact stomach.

A safe, effective way to reduce acid secretion in a patient with Zollinger-Ellison syndrome is a proximal gastric vagotomy (also called a highly selective vagotomy or parietal cell

vagotomy. This operation denervates the fundus of the stomach, containing the parietal cells, without interfering significantly with gastric emptying. In the earlier days of medical therapy, a "medical vagotomy" was often used in the form of anticholinergic medication to reduce the requirement of H_2-receptor antagonist in patients with requirements for large doses of drug. Of course the anticholinergic drugs, although quite effective, often produced systemic side effects and are rarely used now in patients with Zollinger-Ellison syndrome. We have performed a long-term study of the effectiveness of proximal gastric vagotomy at this institution in 22 patients with Zollinger-Ellison syndrome (35). Recently, we have performed further follow-up studies. Table 9 shows the characteristics of the 22 patients entered into the study. None had known metastatic disease upon entry into the trial.

Table 9. Characteristics of 22 patients on entry (1978-1984).

Male/Female	16/6
Age (years)	12-64
Duodenal Ulcer	20
Chronic diarrhea with no ulcers	2
MEN-I	3

All patients underwent an exploratory laparotomy; easily resectable tumors were removed and then a proximal gastric vagotomy was performed. Of the 22 patients, tumor was found in 9, was completely resectable in 6, and partially resectable in 3. No tumor was found in the remaining 13 patients. Patients have now been followed up to 14 years. Using the Kaplan-Meier life-table method, the survival rate at 10 years is 81%. Of the four deaths, 3 were related to gastrinoma and 1 was from suicide in a patient with a strong family history of depression and suicide. In the six patients with complete tumor resection, only one required antisecretory medication at last followup. In the 11 surviving patients of the 13 in whom no tumor was found, 2 now require no medication, while the remainder require relatively modest doses of H_2-receptor antagonist or H^+,K^+-ATPase inhibitor. This is due to the prolonged fall in acid secretion of more than 50%. Based on these results, it seems highly reasonable to a proximal gastric vagotomy on any patient with Zollinger-Ellison syndrome who requires surgery for tumor. An occasional patient who requires very high doses of antisecretory medication might be a candidate for proximal gastric vagotomy. Some centers do not agree with this, citing the possible side effects of adhesions or increased esophageal reflux (15). However, in a patient already having an extensive exploratory laparotomy, no additional adhesions are likely. Also, all Zollinger-Ellison syndrome patients despite the type of surgery received need medication dose adjusted by acid secretory measurements. Significant reflux is rarely a problem when acid secretion is well-controlled, and if a small increase in dose is required for reflux, it is unlikely to exceed the dose the patient needed preoperatively.

Surgery to remove tumor. Patients can be divided into several categories to assist in making a decision for surgery. Based on the information presented, it is clear that there is almost never any urgency to perform surgery since long-term survival is common in most patients despite their tumor status. This does not mean that surgery is not often highly desirable and helpful in managing these patients, only that it is more important to complete a careful, thoughtful workup and to locate a surgeon with sufficient experience in gastrinoma resection than to perform surgery in the days, weeks or sometimes even months after initial diagnosis. Surgical decisions usually made are summarized in Table 10.

Table 10. Tumor Surgery in Patients with ZES

ZES	Metastases	Surgery
Sporadic	Absent	Exploratory lap for cure, PGV
	Present	Rarely
Plus MEN-I	Absent	Perhaps exploratory lap for ?cure/debulking, PGV
	Present	Rarely if ever

PGV = proximal gastric vagotomy

Group 1. Patients with sporadic Zollinger-Ellison syndrome; primary tumor is not found or is localized but not metastatic on preoperative evaluation. This is the most straightforward group to consider. These patients should all go to surgery if their medical condition permits. A minority of these patients will have metastasis at surgery or technically unresectable tumor. However, if tumor can be completely resected, 5 to 10 year survival rates of 90 - 100% are reported in more recent studies (36,37). Even patients with partially resectable or unresectable tumors do moderately well (36,38). At the time of surgery, a proximal gastric vagotomy should be performed to reduce acid secretion, since even in the best of cases, a long-term cure rate of only about 30 to 45% can be expected in this group.

Group 2. Patients with sporadic Zollinger-Ellison syndrome; metastases are found on preoperative evaluation. In almost all cases, these patients should not undergo exploratory laparotomy for cure. Despite the presence of even bulky tumor, these patients may have a long-term survival; as mentioned earlier, the mean survival is about 8 years in this group. One exception is the patient with no primary visualized on preoperative imaging who has a solitary lesion. Very occasionally, this "solitary metastasis" may actually be a liver primary. Some centers have attempted aggressive partial hepatic resections for fairly localized metastases; it is not clear that this improves survival, and it almost never produces a cure. In one center, only

5 of 20 patients with hepatic metastases had disease localized well enough for an attempt at complete resection (39). Complete resection was performed in only 3 of the 20. All patients received chemotherapy postoperatively; 2 had normal fasting gastrins and negative secretin tests after 14 and 32 months of followup. This type of treatment should probably be undertaken only in a major center with an ongoing research interest in metastatic gastrinoma. Proximal gastric vagotomy should be performed to reduce acid secretion in patients who have metastases diagnosed during an exploratory laparotomy. These patients should of course be considered for chemotherapy as outlined in the next section.

Group 3. Patients with Zollinger-Ellison syndrome as a part of MEN-I syndrome, no metastases on initial evaluation. As mentioned previously, these patients will almost always have hyperparathyroidism; if so, parathyroidectomy should be performed before any abdominal surgery. In general, this group of patients has not been treated with attempts at curative resection because of the frequency of multiple tumors. This concept is currently being reexamined. Currently, some centers will operate if a patient has a large tumor, resecting the tumor along with the pancreatic body and tail in an effort to debulk the patient of tumor and perhaps prevent metastases (40). It is unclear whether this improves quality of life or prolongs survival. Other groups have attempted curative resection of patients without tumor visible on preoperative imaging if portal venous sampling demonstrated localized regional secretion (41). In four such patients, basal serum gastrin concentrations remained low for a mean followup of 7 years, although secretin tests were often positive. In contrast, another major center found that removing a gastrinoma from the region of a gastrin gradient on portal venous sampling did not result any cures based on repeated fasting gastrin concentrations or secretin tests (42). It is now clear that many MEN-I patients have duodenal wall tumors, often small and multiple, rather than pancreatic tumors. Theoretically, resecting the entire pancreas and duodenum would result in cure, but the morbidity of such an approach in contrast to the relatively long life and good quality of life in the average unoperated patient prevents the use of such aggressive surgery. Currently, it seems reasonable to operate on younger patients in an attempt to prolong life, while older patients should probably be left on medical therapy. Surgery for proximal cell vagotomy should be performed only if the patient needs surgery for other reasons. This is a group of patients, who if operated, greatly need a surgeon experienced in gastrinoma surgery.

Group 4. Patients with Zollinger-Ellison syndrome as a part of MEN-I syndrome, metastases are found on initial evaluation. Again, these patients will almost always have hyperparathyroidism; if so, parathyroidectomy should be performed to reduce acid secretion and requirements for antisecretory drugs. These patients almost never should have exploratory laparotomy. Surgery for proximal cell vagotomy should be performed only if the patient needs surgery for other reasons.

Surgical technique and intraoperative imaging. As mentioned previously, the patient who appears to be a surgical candidate should be evaluated by a surgeon with specific experience in gastrinoma surgery. This may mean referring the patient to another hospital or city, but it is well worth the extra time and expense in terms of better surgical outcome. Two intraoperative techniques are now used by experienced surgeons in an attempt to improve detection of

gastrinomas at the time of surgery; intraoperative ultrasound and endoscopic transillumination of the duodenum. **Intraoperative ultrasound** is performed by inserting the ultrasound transducer into a long, sterile, plastic sheath and then filling the abdominal cavity with warm saline. Multiple passes with the transducer combined with palpation are made to find suspicious lesions, defined as sonolucent masses in both transverse and longitudinal imaging planes. All suspicious areas are then biopsied or removed. In a study including 36 patients with Zollinger-Ellison syndrome (43), palpation and intraoperative ultrasound generally found the same lesions, but in about 10% of cases, ultrasound found gastrinomas missed by palpation. This 10% advantage must be weighed against the considerable cost of the equipment and the extra time spent on the procedure. Table 11 summarizes the results of this study.

Table 11. Palpation versus intraoperative ultrasound in localizing gastrinomas at surgery.

	Pancreatic Gastrinoma		Extrapancreatic Gastrinoma	
	Palpation	Ultrasound	Palpation	Ultrasound
True-positive	21	22	12	7
True-negative	5	1	0	2
False-positive	4	8	5	3
False-negative	2	1	0	5
Sensitivity	91%	95%	100%	58%

From reference (43).

The role if **endoscopic transillumination of the duodenum** was evaluated more recently. Norton et al. recently reported results of 10 years of surgery for curative resection in sporadic Zollinger-Ellison syndrome performed on 73 of 121 consecutive patients referred to the National Institutes of Health (44). No patients with preoperative diagnoses of MEN-I or hepatic metastases were included. In patients operated between 1980 and 1987, a laparotomy was performed with exploration of the liver, pelvis, small intestine, pancreas, stomach, duodenum, mesenteric and retroperitoneal regions of the upper abdomen. The pancreatic head and duodenum were examined after mobilization of the ascending colon and hepatic flexure, while the body and tail were examined by opening the gastrocolic ligament, exposing the lesser sac, and mobilizing the splenic flexure of the colon. The ovaries were palpated in women. After 1982, intraoperative ultrasound was used to examine the pancreas and duodenum. In group 2, endoscopic transillumination of the duodenum to look for duodenal wall adenomas was performed. Any suspicious areas were removed after duodenotomy. Addition of endoscopic transillumination made a significant difference in the ability of the surgeon to detect and resect small (average size 6 mm) duodenal gastrinomas. Duodenal gastrinomas were found in only 4/36 patients in Group

1, but 16 of 37 patients in Group 2. Impact on surgical findings is summarized in Table 12.

Table 12. Ability to find gastrinomas based on use of duodenal transillumination.

Result of surgery	Group 1 (n=36) (Transillumination not done)	Group 2 (n=37) (Transillumination done)
Gastrinoma found	23 (64%)	34 (92%)
Gastrinoma not found	13 (36%)	3 (8%)

Adapted from reference 1253.

Unfortunately, this improved ability to find primary gastrinomas was counterbalanced by the tendency of duodenal gastrinomas to have lymph node or hepatic metastases, illustrated in Table 13.

Table 13. Metastasis associated with primary gastrinoma of duodenum or pancreas.

Location of primary	Number with metastases (%)
Pancreas (23)	5 (22%)
Duodenum (20)	11 (55%)

Adapted from reference 1253.

This finding is contradiction to reports in smaller groups of patients, in which duodenal gastrinomas were felt to confer a better prognosis (45-47). However, since the total rate of detection of duodenal gastrinoma increased four-fold while only half of these patients had metastases, the overall cure rate increased somewhat for the entire patient group. This appears to be a useful technique.

TREATMENT OF HEPATIC METASTASES

The prolonged survival of patients with Zollinger-Ellison syndrome due to improved anti-secretory drug therapy has led to a larger group of patients with metastatic disease who require treatment. The options currently available include chemotherapy, surgical removal of metastatic disease, hepatic artery embolization, treatment with the somatostatin analog octreotide, and even treatment with alpha-interferon.

Chemotherapy is the most widely used treatment, and has been extensively reviewed in

a number of series (25,30,36,48,49). The most common protocol is streptozotocin combined with 5-fluorouracil and sometimes doxorubicin. Chemotherapy probably reduces tumor size by an average of 20-60%. Due the rarity of the disease, it is hard to be definitive about the best treatment. Sometimes gastrinomas are included with other islet cell tumors to increase the numbers of patients in a trial. In one such trial of 105 patients (49), either streptozotocin plus doxorubicin or chlorozotocin were superior to streptozotocin plus 5-fluorouracil. Although many patients with hepatic metastases will die in the first 3 to 5 years, some untreated patients will be stable for as long as 20 years. The most conservative approach is to use chemotherapy only for symptomatic patients, but these patients will almost always have extensive, bulky disease. Others follow the patient for 3 - 6 months after diagnosis, and only use chemotherapy for enlargement of metastases on imaging study, usually CAT scan. Still others treat all patients as soon as they are diagnosed. The relative benefits of these approaches has not been studied. Treatment only for enlarging metastases seems reasonable, and spares patients with stable disease the side effects of chemotherapy that may not be helpful. Changes in serum gastrin concentrations and basal acid secretion do not correlate with changes in tumor size.

Surgical removal of metastatic disease is an original idea of Zollinger, but has not been studied in a controlled fashion. As described earlier, Norton was able to achieve at least a temporary "cure" by secretin tests in 2/20 patients evaluated with extensive disease (39). This 10% rate may be deceptively low if patients can be selected better prior to surgery, since the cure rate in the patients in whom he actually attempted complete resection was 2/5. There are other very small series or case reports in which surgery for metastasis appears to have been helpful in individual patients, but based on our current knowledge, this type of treatment cannot be recommended outside centers studying this specific problem.

Hepatic artery embolization for islet cell type tumors was developed for metastatic carcinoid. Much less is known about this treatment for gastrinomas. No data currently exists that determines whether this treatment prolongs life, and it has the potential for serious complications, with 10 - 14% of patients dying of complications of the procedure in two studies (50,51). In the 12% of patients with hepatic metastases who have been reported to have bony metastases (52), hepatic artery embolization would be completely useless. Like surgical removal of extensive hepatic metastases, this type of treatment cannot be recommended outside centers studying this specific problem.

Octreotide showed promise in treating carcinoids, and is attractive because of its simplicity of administration (subcutaneously, often by the patient at home). It is fairly expensive however, and in a recent study of 9 patients with gastrinoma treated for 1 to 11 months, tumor regression did not occur (53).

Alpha-interferon is the latest treatment attempted (54). In 22 patients with islet cell tumors of various types, 18/22 refractory to chemotherapy, 17/22 showed a decrease in tumor size or tumor markers of at least 50%. Only 4 of these patients had gastrinomas, of which 2 responded. Therefore, not enough data exists to evaluate this treatment.

LONG-TERM MEDICAL THERAPY IN ZOLLINGER-ELLISON SYNDROME

It is fairly clear at this point that long-term cure rates of at best 25-30% can be expected in sporadic Zollinger-Ellison syndrome, and probably no more that 5% in patients with gastrinoma associated with MEN-I. Thus, the majority of patients will require long-term antisecretory therapy. Fortunately, we now have a variety of safe and effective medications for this purpose, as outlined previously. After surgery, whether or not tumor was resected, the patient should remain on the dose of medication determined prior to surgery to adequately control acid secretion. After about 3 months, in patients with tumor resection and normal serum gastrins, medication can usually be stopped and basal and stimulated acid secretion measured to assess the possibility of cure. Generally, after 3 - 6 months, in a biochemically normal patient, basal acid output will decrease by about 75% while stimulated acid output decreases about 50%; levels generally remain constant after this unless the patient again becomes hypergastrinemic. In all patients, particularly after proximal gastric vagotomy, attempts to reduce medication can be made based on acid secretory response. As described before, basal acid secretion should be maintained at < 10 mmol/h in the last hour before the next dose of medication. When the patient's dose has been adjusted, yearly evaluation of response to medication is sufficient in the absence of symptoms; this involves only a one hour basal acid measurement the last hour before the next dose of medication is due.

One expects a gradual decline in acid secretion after curative resection as the trophic effects of chronic hypergastrinemia disappear. Most studies report that biochemical cures with the expected decline in acid secretion allow the great majority of patients to discontinue medication. There is one interesting report that in patients with curative resections, only 5/20 patients were able to discontinue medication 3 - 6 months after cure; in followup for up to 4 years, about the same proportion (25-30%) were able to remain off medication (55). Mean ranitidine dose did decline from 1597 mg/day to 535 mg/day at 3 - 6 months and about 300 mg/day at 1 - 4 years, as illustrated in Fig. 6. This may be because of the study design; drugs were used in all patients with basal hypersecretion, without an attempt to see if symptoms recurred without medication. In men, 80% had basal hypersecretion (> 15 mmol/h) a year after surgery, in women, basal hypersecretion persisted in about 50%. This hypersecretion was mild, always just over the upper limit of normal. In addition, drugs were restarted in patients with normal acid secretion with peptic symptoms; it is not clear if these symptoms were associated with mucosal changes or represented the nonspecific dyspepsia so common in the general population. These data are somewhat surprising, but if confirmed by further studies, would strengthen a role for proximal gastric vagotomy at the time of exploratory laparotomy.

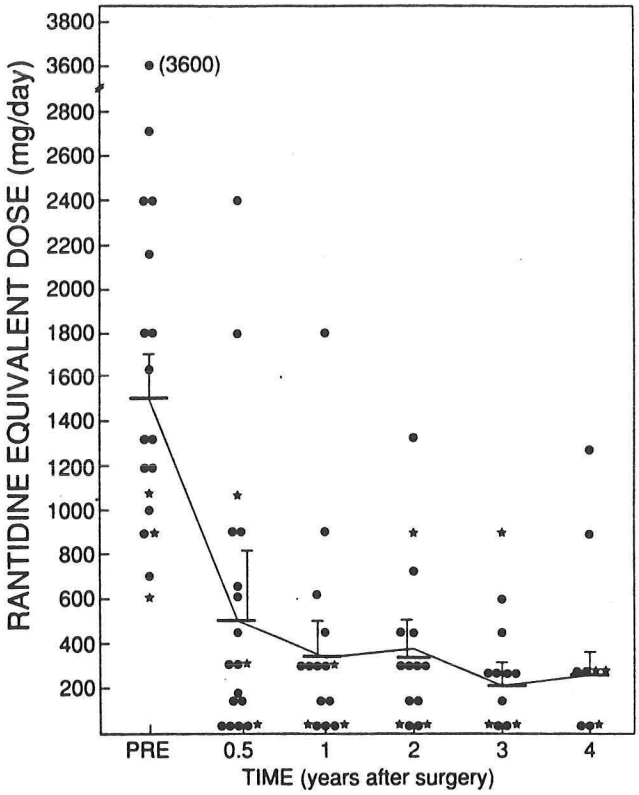


Fig. 6. Daily antisecretory drug dose preoperatively and at various times after curative resection of gastrinoma. From reference (55).

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