The Effect of Zollinger-Ellison Syndrome and Neuropeptide-secreting Tumors on the Stomach

Joseph R. Pisegna, MD

Address
Division of Gastroenterology and Hepatology (111C), VA Greater Los Angeles Health Care System, CURE: VA/UCLA Digestive Diseases Center, Building 115, Room 316, 11301 Wilshire Boulevard, Los Angeles, CA 90073, USA.

Current Gastroenterology Reports 1999, **1**:511–517
Current Science Inc. ISSN 1522–8037

Zollinger-Ellison syndrome (ZES) is caused by a tumor that secretes gastrin and is the most common of the malignant islet cell tumors. ZES leads to hypergastrinemia, which, in turn, causes an overproduction of gastric acid and results in complications of peptic ulcer disease. Of all the islet cell tumors, gastrinoma tumors have undergone the most extensive study, providing a model of tumor management. Increased awareness and improved biochemical and radiologic techniques mean that these disorders are being recognized in more patients. Advances in the management of gastric acid secretion and new localization methods have significantly reduced the morbidity and mortality associated with ZES. The use of intravenous proton pump inhibitors such as pantoprazole will make surgical and perioperative management more favorable for patients. Radiologic and nuclear medicine studies permit the detection of the majority of islet cell tumors and improve the ability for surgical resection. With the recent cloning of the gene for multiple endocrine neoplasia type I (*MEN-I*) and the recognition of tumor markers associated with the development of islet cell tumors, early detection of these tumors may someday be possible.

Introduction

Neuroendocrine tumors (NET) of the gastrointestinal tract can be broadly divided into either carcinoid tumors or islet cell tumors. NETs are a heterogeneous group of tumors comprised of argentaffin cells possessing granules that stain positive for chromogranins, synaptophysins, or neurotensin [1,2]. The tumors are thought to arise from a common ancestral cell belonging to the amine precursor uptake and decarboxylation (APUD), and under the light microscope they are virtually indistinguishable. Histologically, the NETs are noted to contain monotonous sheets of cells with small compact nuclei. By electron microscop (EM), the cells can be seen to contain electron-dense granules that may have either biologically active amines or peptides. In general, EM is not of clinical utility for determining the specific hormone contained in the granules. A more useful evaluation is to perform immunohistochemistry with specific antibody stains of the tumor. These studies provide more definitive pathologic evaluation. In general, a combination of a chromogranin A, neuron specific enolase, and/or synaptophysin will lead to a positive diagnosis of NET in the majority of cases. In addition to these studies, anti-gastrin, glucagon, somatostatin, pancreatic polypeptide, and VIP (vasoactive intestinal polypeptide) can be used for more definitive diagnosis of tumors that secrete these hormones. In findings from one study, a combination of these evaluations had a predictive value of 92% [3].

The particular syndrome associated with NETs is identified by the class of hormone overproduction that determines the clinical syndrome. The majority of the tumors secrete multiple hormones that may result in symptoms, and some neither result in hormone hypersecretion nor a clinical syndrome. These tumors therefore pose a significant diagnostic challenge to clinicians because of the variable clinical syndromes that are encountered. Because the diagnosis is difficult and often delayed, a high index of suspicion is required. Following diagnosis, confirmation of the hormone hypersecretory state is necessary by means of serum and/or urine biochemical markers. In most instances, because the tumors are small, localization with standard radiologic studies is needed. Biopsy is not generally useful for their diagnosis.

With respect to overall prevalence, NETs are rare an account for less than 1% of malignant tumors. The overall prevalence of NETS in the population is approximately 10 persons per million [4]. The most common of the NETs in the gastrointestinal tract are gastrinomas, excluding inulinomas. Gastrinomas account for the extant ZES and are malignant in the majority of cases, representing approximately 0.2 cases per 100,000-population (Table 1) [3].

Table 1 Classification of Neuroendocrine Tumors

Name	Hormone	Syndrome	Diagnosis
Gastrinoma	Gastrin	ZES	Elevated fasting gastrin, gastric acid hypersecretion, secretin test
Glucagonoma	Glucagon	Glucagonoma	Elevated serum glucagon, rash, diarrhea
VIPoma	VIP	VIPoma	Profuse watery diarrhea, hypokalemia, elevated serum VIP
Carcinoid	Serotonin	Carcinoid	Diarrhea, flushing, 24-hr 5-HIAA levels elevated

VIP—vasoactive intestinal polypeptide; ZES—Zollinger-Ellison syndrome.

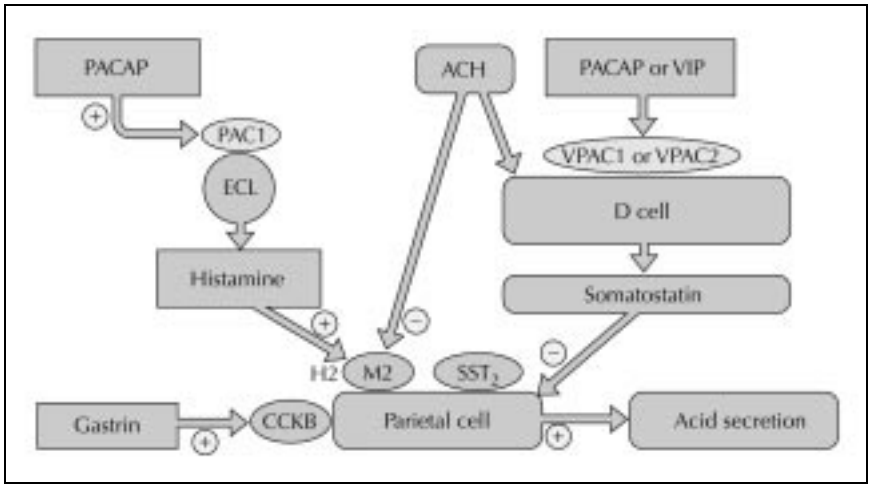

Figure 1. Depiction of the multiple neuronal and hormonal factors influencing the regulation of gastric acid secretion. ACH—acetylcholine; ECL—enterochromaffin-like cells; H2—histamine 2 receptor; M2—muscarinic receptor; PACAP—pituitary adenylate cyclase activating polypeptide; SST—somatostatin. VIP—vasoactive intestinal polypeptide.

Zollinger-Ellison Syndrome (Gastrinoma)

Zollinger-Ellison syndrome was first described in 1955 by two surgeons who proposed that the syndrome could be accounted for by a tumor secreting gastrin. Following the first description of the gastrin radioimmunoassay nearly a decade later, the hormone causing this syndrome was confirmed. Since the discovery of ZES, it is now estimated that the syndrome occurs in approximately one patient per million in the United States. Thus, for a large metropolitan area such as that of New York City, it can be estimated that there will be seven to ten patients with ZES [5]. The mean age at the time of ZES diagnosis is 50, and there is no predilection for males or females.

A diagnosis of ZES can be considered in any patient who presents with severe duodenal ulcer disease associated with diarrhea and abdominal pain. The cause of these symptoms is the high rate of gastric acid output b the stomach caused by excessive gastrin secretion by the gastrinoma tumor. Gastrin acts at the level of the parieta cell to stimulate the H+-K+ATPase. As shown in Figure 1, multiple hormone and receptor targets are located within the gastric mucosa.

Multiple neuronal and hormonal factors influence the regulation of gastric acid secretion (Fig. 1). Adrenergic neurons (ADR) have effects at the level of the mast cell that inhibit histamine-induced gastric acid secretion, whereas ADR projections stimulate the D cell of the stomach to release somatostatin. Histamine from enterochromaffin-like (ECL) cells stimulates the release of gastric acid by acting directly at the histamine 2 (H2) receptor expressed on the parietal cell. Acetylcholine (ACH) fro vagal efferent nerves stimulates acid secretion by acting at the muscarinic receptor (M2) expressed on the parietal cell. The newly discovered receptor for pituitary adenylate cyclase activating polypeptide (PACAP), named PAC1, has been shown to be expressed on the surface of the ECL cell and is now seen as an important neuropeptide that regulates gastric acid secretion. PAC1 is expressed on gastric ECL cells, and the receptor for VIP is expressed on the D cells to regulate the release of both histamine and somatostatin, respectively, to influence gastric acid secretion. Gastrin, acting at the recently cloned CCKB receptor on the surface of the ECL cell, stimulates release of histamine, which acts in a paracrine manner at the H2 receptor expressed on the parietal cell [6,7,8••

Diagnosis of Zollinger-Ellison syndrome

The diagnosis of Zollinger-Ellison syndrome is clinicall made once it is determined that the patient has an elevated level of fasting serum gastrin in the absence of achlorhydria and either a positive secretin test or histologically proven NET (Fig. 2). The physical examination is normal in the majority of patients and is therefore not useful in the diagnosis of ZES.

The diagnosis is made biochemically when the fasting serum gastrin (>100 pg/mL) is found in the absence of achlorhydria (Fig. 1). Patients with gastrinoma usually have levels greater than 500 pg/mL, and a level greater than

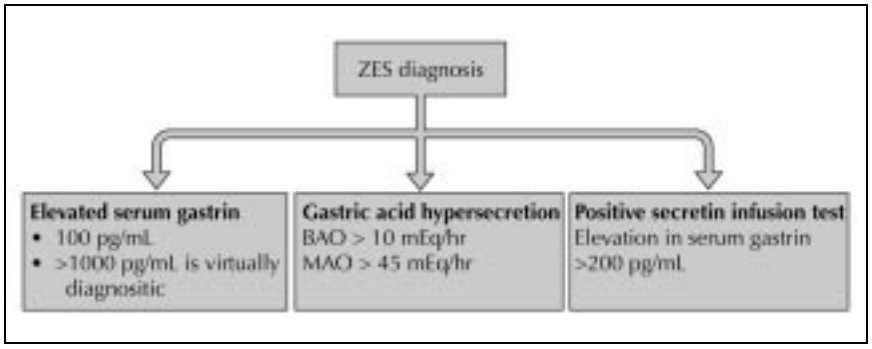

Figure 2. Diagnosis of Zollinger-Ellison syndrome. BAO—basal acid output; MAO—maximal acid output.

1000 pg/mL is nearly diagnostic of ZES. With the recent use of potent gastric acid antisecretory medications such as omeprazole and lansoprazole over the past decade, it has become increasingly clear that a large number of patients without ZES have elevated fasting serum gastrin levels. In order to overcome this problem, it is recommended that, in patients being evaluated for ZES, the proton pump inhibitor should be discontinued for at least 1 week and the serum gastrin repeated. In practice, patients can generally be safely switched to a high dose of an H2 receptor antagonist during this period of time in order to control symptoms. The H2 receptor antagonist should be discontinued for 36 hours before the serum gastrin is measured under fasting conditions

Gastric analysis is an important part of the diagnosis and management of patients with ZES. It is performed by placement of a nasogastric tube in the dependent portion of the stomach. Placement is achieved by the water recovery method, by which more than 90% of instilled water is recovered under suction. The basal acid output (BAO) is a reflection of the basal secretion of acid, which is measured following the collection of four 15-minute samples. Th maximal acid output (MAO) is performed following th administration of pentagastrin subcutaneously. The concentration of acid is measured by the titration method, wherein 0.1 N NaOH is used to titrate the sample of gastric juice to pH 7.0. Acid output is determined by the product of the volume of titrant required and the volume of gastric juice collected. For diagnosis of gastric acid hypersecretion, the BAO is generally greater than 10 mEq/hr.

In patients with elevated gastrin values being evaluated for ZES, a secretin provocative test has a diagnostic sensitivity of 87% to 93% [9]. To perform this test, secretin (2 units/kg) is administered intravenously followin the collection of two basal serum gastrin measurements. A positive test is defined by a rise in serum gastrin greate than 200 pg/L within 15 minutes following the infusion. In the past, a calcium infusion test was recommended for confirmation, but it has been replaced by the secretin test in clinical practice.

In general, ZES can be broadly divided into two major groups of patients: sporadic and MEN-I–associated. This classification is important because it underscores the major differences in epidemiology and tumor biology and dictates treatment. Patients with the sporadic form of the disease do not have specific genetic markers, and there is no family history. This lack of familial transmission suggests that the syndrome results from a spontaneous mutation in this group of patients. Patients with the sporadic form of ZES generally have pancreatic tumors that are larger at the time of surgery and have a greater predisposition for the development of metastatic disease compared with patients who have ZES associated with MEN-I syndrome (Table 2). Consequently, in those patients with the sporadic form of ZES, a significant reduction is seen in 20-year survival.

Significantly, ZES is associated with MEN-I in approximately one third of patients [10]. This high association emphasizes the importance of determining at initial evaluation whether a positive family history is present for endocrinopathy, MEN-I, and nephrolithiasis. Although the survival rate for patients with ZES associated with MEN-I is high, because the tumors tend to be multifocal, surgical resection almost never results in surgical cure.

Control of gastric acid secretion in patients with Zollinger-Ellison syndrome

Following diagnosis of Zollinger-Ellison syndrome, the control of gastric acid secretion is the next most important step in management of these patients [11]. Adequate control of gastric acid secretion will reduce the incidence of PUD and its complications. In practice, this can be achieved by maintaining the level of acid secretion at less than 10 mEq/hr. The majority of patients will require continued gastric acid antisecretory medications, even following curative gastrinoma resection [12]. For patients with MEN-I syndrome, GERD (gastroesophageal reflux disease), or prior gastric acid–reducing surgery, the basal acid output should be maintained at less than 1–2 mEq/hr [13]. Control of gastric acid secretion, especially for patients with gastric hypersecretory disorders such as ZES, has been revolutionized over the past decade by the development of the substituted benzimidazoles (proton pump inhibitors) that inhibit the activity of the H+-K+ATPase, the final step i gastric acid production [14].

As shown in Table 3, the proton pump inhibitors are more effective in the management of gastric acid hypersecretion for patients with ZES. In general, the H2 receptor antagonists have a lower efficacy and shorter duration of action and

Table 2 Table 2. Comparison of Sporadic ZES an MEN-I–associated ZES

Feature	Sporadic ZES	MEN-I–associated ZES
Genetic predisposition	No	Yes
Tumor location	Pancreatic> duodenal	Duodenal> pancreatic
Size of tumor	Large (>2 cm)	Small (<2 cm)
Metastatic potential	High	Low
20-year survival	<70%	>90%

MEN—multiple endocrine neoplasia; ZES—Zollinger-Ellison syndrome.

Table 3 Median Dose of Antisecretory Agents Used in Gastrinoma Patients

Agent	Median dose (range)
H+-K+ ATPase inhibitor	
Omeprazole	60 mg/d (20–60 mg bid)
Lansoprazole	60 mg/d (30–60 mg bid)
H2 blockers	
Cimetidine	3.6 g/d (1.2–12.6)
Ranitidine	1.2 g/d (0.45–6)
Famotidine	0.25 g/d (0.05–0.8)

require high doses to be administered for the adequate control of gastric acid secretion. For example, the median dose of ranitidine required to fully control gastric acid secretion is approximately 1.2 g/d in four divided doses. At present, in patients with ZES who are pregnant, ranitidine has been shown to be safe [15••]. Another instance in which H2 antagonists are useful is in their intravenous administration for acute control of gastric acid secretion. In these situations, for example, during the perioperative period, in acute gastrointestinal hemorrhage, or during chemotherapy, ranitidine infu sion at a dose of 1 mg/kg/hr effectively controls acid secretion in the majority of patients [16]. More recently, an intravenous formulation of another substituted benzimidazole, pantoprazole, has been under investigation for the management of gastric acid hypersecretion in ZES. Intravenous pantoprazole has been shown to rapidly (<30 min) and effectively control gastric acid secretion in patients with ZES (BAO<10 mEq/hr) for up to 16 hours following a single 40-mg infusion (Fig. 3 [17••,18]. The use of an intravenous pantoprazole in the clinical setting of ZES will provide significant advantages over the currently available intravenous H2 receptor antagonists.

Diagnostic imaging of gastrinoma tumors

After the diagnosis of Zollinger-Ellison syndrome is established (sporadic vs MEN-I) and management of the gastric acid hypersecretion is initiated, localization of the gastrinoma tumor is required (Fig. 4). Recent development of both radiologic and nuclear medicine studies has increased the capability for determining tumor locale in the majority of patients with ZES. Localization permits the evaluation of tumor extent and provides guidance in intraoperative resection of the gastrinoma. Therefore, it is critical that every effort be made prior to surgical resection to identify the site of tumor involvement. In addition, should evidence of metastatic disease be determined, chemotherapy and hormonal or radiologic intervention should be considered.

In one study, magnetic resonance imaging (MRI) had the highest detection rate for hepatic metastases compared with computerized tomography (CT) and angiography (Angio). For the detection of primary tumors, however, the angiogram has proven more sensitive [19]. More recently, endoscopic ultrasonography (EUS) has replaced the angiogram as the most sensitive imaging modality. By EUS, the tumors generally are identified as round, homogeneous, and slightl hypoechoic. Because nearly half of gastrinomas occur in the duodenal wall and these tend to be small (<1 cm), EUS may prove to be an important imaging modality for their detection. Similarly, Octreoscan (somatostatin receptor scintigraphy; manufactured by Mallincrkrodt Med., St. Louis, MO has shown an improved sensitivity for detection of hepatic and extrahepatic gastrinomas. Spiral CT is preferred over standard CT and may have a sensitivity for detecting hepatic metastases that is similar to those of MRI and Octreoscan; however, no studies have yet compared the sensitivity of these imaging modalities with others for the detection of islet cell tumors (Table 4)

Surgical management of Zollinger-Ellison syndrome

The most definitive treatment of the gastrinoma tumor that causes sporadic Zollinger-Ellison syndrome is by surgical resection. Following adequate control with gastric acid hypersecretion and tumor localization studies, surgical resection is recommended for any patient with the sporadic form of the disease. Surgical management should be directed at complete tumor resection for these patients. A successful surgical resection will result in cure and prevent the development of metastases [20]. It should be emphasized therefore that all patients with sporadic ZES undergo surgical exploration and resection after the appropriate imaging studies are performed [21••]. For patients with ZES and MEN-I, however, surgical resection almost never results in cure [22]. In our series of 10 patients with ZES and MEN-I, only one patient had a short-term cure lasting 3 months as determined by serum gastrin levels (Unpublished data)

Surgical exploration should include a duodenotomy and transillumination of the duodenum to identify tumor in this region [23]. Approximately 50% of gastrinoma tumors identified at the time of surgery will be localized to the wall of the duodenum. The majority of these tumors will be submucosal, making endoscopic extirpation dangerous because of the risk for perforation [24]. If presurgical endoscopic or EUS examination suggests that a duodenal nodule may be a gastrinoma, performance of a fine needle aspiration is recommended rather than attempted removal of the nodule

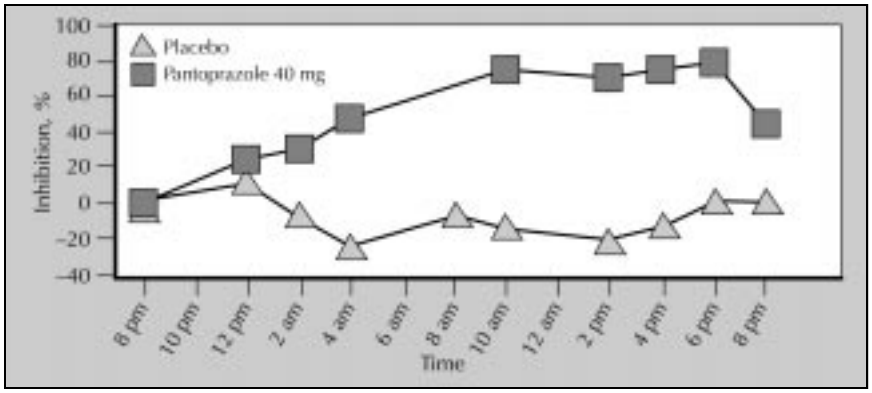

Figure 3. Percentage of inhibition of pentagastrin-stimulated gastric acid secretion by intravenous pantoprazole.

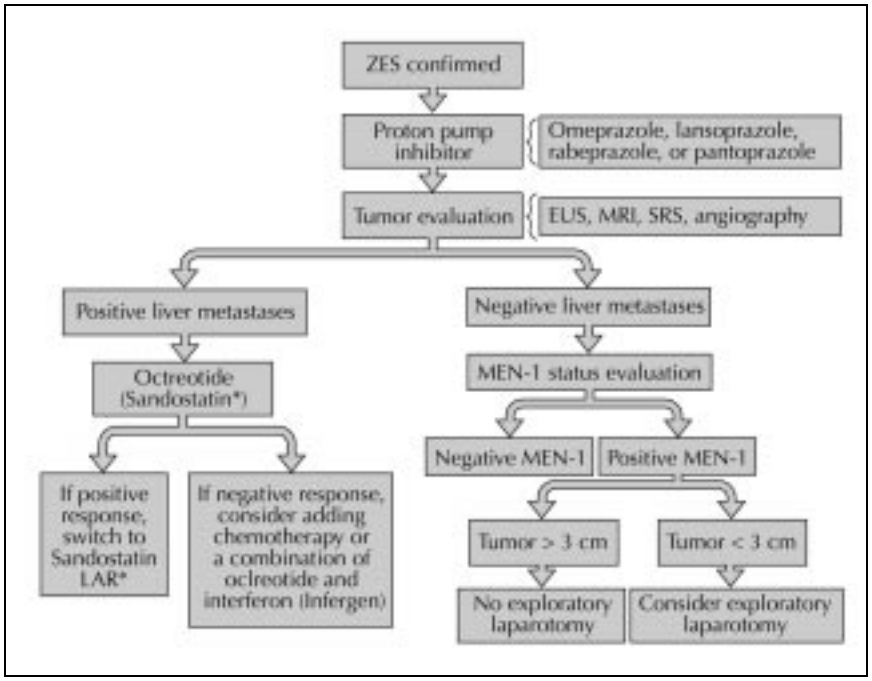

Figure 4. Model for confirmation of Zollinger-Ellison syndrome. Infergen—interferon alfacon-1 (Amgen, Thousand Oaks, CA).

Table 4 Localization of Hepatic Metastases

Diagnostic study	Sensitivity
Magnetic resonance imaging	83%
Endoscopic ultrasonography	50%
Computed tomography	56%
Angiography	61%

[25]. The other 50% of the identified gastrinomas occur either in the pancreas or in the peripancreatic lymph nodes. Intraoperative ultrasonography is suggested to identify gastrinoma tumor in the pancreatic parenchyma, but this modality may not be useful in extrapancreatic sites [23]. Total gastrectomy should be considered only in patients whose ulcer disease is refractory to medical therapy and who are unable to undergo resection of the tumor.

For patients presenting with sporadic ZES in whom there is evidence of metastatic involvement of the liver, resection should be considered for limited disease. More recently, with the development of cryosurgical techniques, a number of patients with metastatic NET have undergone cryosurgical resections, but no large case–control studies have been undertaken comparing their efficacy with that of medical therapy or liver transplantation. Ultimately, liver transplantation should be considered in those patients who have undergone complete resection of the primary tumors.

Nonsurgical management of metastatic gastrinoma tumors

Radiation therapy

The role of radiation therapy is in the relief of bony pain associated with metastatic tumor. In general, bone metastases occur in the setting of more advanced disease and result in significant debilitation. In patients with these symptoms, radiation therapy results in adequate symptom control but does not significantly alter the natural history of the disease [26].

Chemotherapy and hormone therapy

The types of medical therapy used for management of the metastases that occur in more advanced stages of Zollinger-

Ellison syndrome include chemotherapy, hormonal therapy, immunomodulating agents, and high-dose radioactive octreotide therapy. These agents have undergone extensive study in patients with metastatic gastrinoma, and some general recommendations can be made. Although these agents may cause a reduction in hormone levels (gastrin), in the majority of cases they either have a transient effect on tumor regression or prevent growth for a short time period. Thus, no single agent has a reproducible effect in preventing tumor progression. In general, it is best to begin with the agent with the least side effects and proceed t chemotherapy for those tumors that have a limited response to these less toxic agents.

The somatostatin analogue Sandostatin (Sandoz, Hanover, NJ) has only minimal response when used alone. More recently this agent has been reformulated into a long-acting form (Sandostatin LAR) that can be administered on a monthly basis. Somatostatin reduces gastric acid secretion directly by its inhibitory effects on parietal cells and indirectly by inhibiting gastrin release. Although Sandostatin is effective for symptomatic treatment of the inappropriately released hormones in patients with NETs, it is not yet approved for the management of metastatic disease. Recent studies have demonstrated that pancreatic islet cell tumors express somatostatin receptors, suggesting that somatostatin analogues may have a role in inhibiting tumor growth. A reduction in tumor growth has been demonstrated in vitro and in animal studies [27,28]. Moreover, two large phase II trials demonstrated that octreotide significantly inhibits tumor growth in 37% to 50% of patients with advanced islet cell tumors, but this effect is short lasting [29,30]. The emerging use of radiolabeled somatostatin for therapeutic benefit is currently under investigation.

Interferons are a family of naturally occurring proteins that have been shown, in vitro and in vivo, to bind to specific membrane receptors and activate human T lymphocytes with a Th-1 pattern of cytokine production. These cells are known to be the effectors of immune response directed against intracellular parasites, such as viruses and tumoral cells. Human recombinant interferon-α has been reported to be effective in patients with NETs, but the responses have been variable[31]. In one study (*N*=22), 77% of the patients had an objective tumor response, including three of the four patients with metastatic gastrinoma as defined by greater than 50% reduction in tumor mass or greater than 50% reduction in serum hormone or tumor marker levels [32]. In contrast, another study showed only a minimal response to the administration of interferon-α alone [33].

Although somatostatin and interferon have shown some efficacy when used as monotherapy, they have even greater efficacy when used in combination. In small open studies, treatment with the combination of Sandostatin and interferon-α had a synergistic antiproliferative effect in patients unresponsive to Sandostatin alone [34,35]. In one European study,21 patients with metastatic islet cell tumor were treated with a combination of Sandostatin (200μg IU three times daily) and human recombinant interferon-α Intron A (Schering, Kenilworth, NJ) at a dose of 5 million IU three times weekly; inhibition of tumor growth was observed in 14 patients (67%), and complete regressio was seen in one patient that lasted for up to 52 month [36]. The regimen was generally well tolerated, and side effects included fever, weight loss, and diarrhea.

The role of chemotherapy and hormonal therapy has been extensively studied in patients with metastatic gastrinoma and should be used for patients with advanced disease or in those patients who are unresponsive to hormonal therapy. The most effective of these agents are streptozocin, 5-fluorouracil, and doxorubicin (Adriamycin; Pharmaci and Upjohn, Kalamazoo, MI) [37]. Combination of these three agents results in a response rate that is short-lasting and is associated with significant toxicity [38].

Conclusions

Since the discovery of Zollinger-Ellison syndrome, the management of the disease has focused on preoperative localization followed by attempts at surgical care. We now kno that, for patients with sporadic ZES, every effort should be directed at surgical resection, whereas for patients with MEN-I, there is almost no role for surgical resection. Despite the successes in surgical cure afforded to sporadic ZES patients, little success has been achieved in the management of metastatic disease. One study with promising results suggests that interferon, when used in combination with octreotide, may prevent metastatic tumor growth. The future management of metastatic disease therefore deserves further attention. Newer potent proton pump inhibitors that can be administered intravenously, such as pantoprazole, provide a significant improvement in the acute management of gastric acid hypersecretion, especially in the perioperative period, and should reduce morbidity associated with surgery in these patients.

References and Recommended Reading

Recently published papers of particular interest are highlighted as:

- • Of importance
- •• Of major importance

1. O' Conner DT, Deftos LJ: **Secretion of chromogranin A by peptide-producing endocrine neoplasms.** *N Engl J Med* 1986, **314:**1145–1151.
2. Del Valle, J, Yamada T: **Zollinger-Ellison Syndrome.** In *Textbook of Gastroenterology.* Edited by Yamada T. Philadelphia: JB Lippincott; 1991:1912–1928.
3. Lam KY, Lo CY: **C-erb-2 protein expression in oesophageal squamous epithelium from esophageal squamous cell carcinomas, with special reference to histological grade of carcinoma and pre-invasive lesion** *Eur J Surg Oncol* 1997, **23** 36–42.
4. Boden G: **Insulinoma and glucagonoma.** *Semin Oncol* 1987, **14:**253–262.

5. Hirschowitz BI: **Zollinger-Ellison syndrome: pathogenesis diagnosis, and management.** *Am J Gastroenterol* 1997, **92(suppl):**44S–48S.
6. Pisegna JR, de Weerth A, Huppi K, *et al.*: **Molecular cloning of the human brain and gastric cholecystokinin receptor: structure, functional expression and chromosomal localization.** *Biochem Biophys Res Comm* 1992, **189:**296–303.
7. Wank SA, Pisegna JR, de Weerth A: **Molecular cloning of the rat cholecystokinin type B receptor: structure, and functional expression.** *Proc Natl Acad Sci* 1992, **89:** 8691-8695.
8. •• Zeng N, Kang T,Wong H, *et al.*: **The pituitary adenylate cyclase activating polypeptide type 1 receptor (PAC1) is expressed on gastric ECL cells: evidence by immunocytochemistry and RT-PCR.** *Ann N Y Acad Sci* 1998, **865:**147–156.

This study demonstrates that the novel neuropeptide, PACAP, has a significant role in the regulation of gastric acid secretion.

9. Bloom SR, Long RG, Bryant MG, *et al.*: **Clinical, biochemical and pathological studies on 62 VIPomas.** *Gastroenterology* 1980, **78:**1143.
10. Fishbeyn VA, Norton JA, Benya RV, *et al.*: **Assessment and prediction of long-term cure in patients with the Zollinger-Ellison syndrome: the best approach.** *Ann Intern Med* 1993, **119:**199–206.
11. Fass R, Rosen HR, Walsh JH: **Zollinger-Ellison syndrome: diagnosis and management.** *Hosp Pract* 1995, **30:**73–80.
12. Pisegna JR, Norton JA, Slimak GG, *et al.*: **Effects of curative gastrinoma resection on gastric secretory function and antisecretory drug requirement in the Zollinger-Ellison syndrome.** *Gastroenterology* 1992, **102:**767–778.
13. Metz DC, Pisegna JR, Fishbeyn VA, *et al.*: **Currently used doses of omeprazole in Zollinger-Ellison syndrome are too high.** *Gastroenterology* 1992, **103:**1498–1508.
14. Frucht H: **Use of omeprazole in patients with Zollinger-Ellison syndrome.** *Dig Dis Sci* 1991, **36:**394.
15. •• Stewart CA, Termanini B, Sutliff VE, *et al.*: **Management of the Zollinger-Ellison syndrome in pregnancy.** *Am J Obstet Gynecol* 1997, **176:**224–233.

This study is the first to demonstrate the safety of ranitidine during pregnancy.

16. Maton, PN: **Zollinger-Ellison syndrome: recognition and management of acid hypersecretion.** *Drugs* 1996, **52:**33–44.
17. •• Metz DC, Lew E, Forsmark CE, *et al.*: **Intravenous (IV) pantoprazole (PANTO) rapidly and effectively controls acid output (AO) in patients with Zollinger-Ellison syndrome (ZES).** *Gastroenterology* 1998, **114:**G0926.

This study is important for its examination of the acute management of gastric acid hypersecretion in patients with ZES. The authors demonstrate that the new proton pump inhibitor, pantoprazole, can be safely used to treat patients with ZES.

18. Pisegna JR, Huang, M, Asvar C, *et al.*: **Inhibition of pentagastrin-induced gastric acid hypersecretion by single-dose intravenous pantoprazole compared with single-dose intravenous famotidine and placebo in healthy subjects.** *Gastroenterology* 1998, **114:**G1065.
19. Pisegna JR, Doppman JL, Norton JA, *et al.*: **Prospective comparative study of ability of MR imaging and other imaging modalities to localize tumors in patients with Zollinger-Ellison syndrome.** *Dig Dis Sci* 1993, **38:**1318–1328.
20. Townsend CM, Thompson JC: **Surgical management of tumors that produce gastrointestinal hormones.** *Ann Rev Med* 1985, **36:**111–124.
21. •• Norton JA, Fraher DL, Alexander R, *et al.*: **Surgery to cure: th Zollinger-Ellison syndrome.** *N Engl J Med* 1999, **341:**635–644.

This report describes one of the most complete clinical studies examining the role of surgery to cure ZES. The authors have significant experience in the surgical management of this syndrome and offer a review of the most up-to-date methods for surgical cure of these patients.

22. Thompson NW: **Surgical treatment of the endocrine pancreas and Zollinger-Ellison syndrome in the MEN 1 syndrome.** *Henry Ford Hosp Med J* 1992, **40:**195–198.
23. Frucht H, Norton JA, London JF, *et al.*:**Detection of duodenal gastrinomas by operative endoscopic transillumination: a prospective study.** *Gastroenterology* 1990, **99:1622–**1627.
24. Straus E, Raufman JP, Samuel S, *et al.*: **Endoscopic cure of the Zollinger-Ellison syndrome.** *Gastrointest Endosc* 1992, **38:**709–711.
25. Benya RV, Metz DC, Hijazi YM, *et al.*: **Fine needle aspiration cytology of submucosal nodules in patients with Zollinger-Ellison syndrome.** *Am J Gastroenterol* 1993, **88:**258–265.
26. Barton JC, Hirschowitz BI, Maton PN, *et al.*: **Bone metastases in malignant gastrinoma.** *Gastroenterology* 1986, **91:**1179–1185.
27. Reubi JC, Kvols LK, Nagorney DM, *et al.*: **Detection of somatostatin receptor in surgical and percutaneous needle biopsy of samples of carcinoid and islet cell carcinomas.** *Cancer Res* 1990, **50:**5969–5977.
28. Redding TW, Schally AV: **Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones.** *Proc Natl Acad Sci U S A* 1984, **84:**248–252.
29. Saltz L, Trochanowski B, Buckley M, *et al.*: **Octerotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors.** *Cancer* 1993, **72:**244–248.
30. Arnold R, Trautmann ME, Creutzfeldt W, *et al.*: **Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours.** *Gut* 1996, **38:**430–438.
31. Anderson JV, Bloom SR: **Treatment of malignant endocrine tumors with human leukocyte interferon.** *Lancet* 1987, **1:**97.
32. Eriksson B, Alm G, Lundqvist G, *et al.*: **Treatment of malignant endocrine pancreatic tumors with human leukocyte interferon.** *Lancet* 1986, **2:**1307–1309.
33. Pisegna JR, Slimak GG, Doppman JL, *et al.*: **An evaluation of human recombinant alpha interferon in patients with metastatic gastrinoma.** *Gastroenterology* 1993, **105:**1179–1183.
34. Creutfeldt W, Bartsch HH, Jacubaschke U, *et al.*: **Treatment of gastrointestinal endocrine tumors with interferon-alpha and octreotide.** *Acta Oncol* 1991, **30:**529–535.
35. Nold R, Frank M, Kajdan U, *et al.*: **Combined treatment of metastatic endocrine tumors of the gastrointestinal tract with octreotide and interferon-alpha.** *Gastroenterology* 1994, **32:**193–197.
36. Frank M, Klose KJ, Wied M, *et al.*: **Combination therapy with octreotide and a-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors.** *Am J Gastroenterol* 1999, **94:**1381–1387.
37. Moertel CG: **Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma.** *N Engl J Med* 1992, **326:**519–523.
38. von Schrenck T, Howard JM, Doppman JL, *et al.*: **Prospective study of chemotherapy in patients with metastatic gastrinoma.** *Gastroenterology* 1988, **94:**1326–1334.