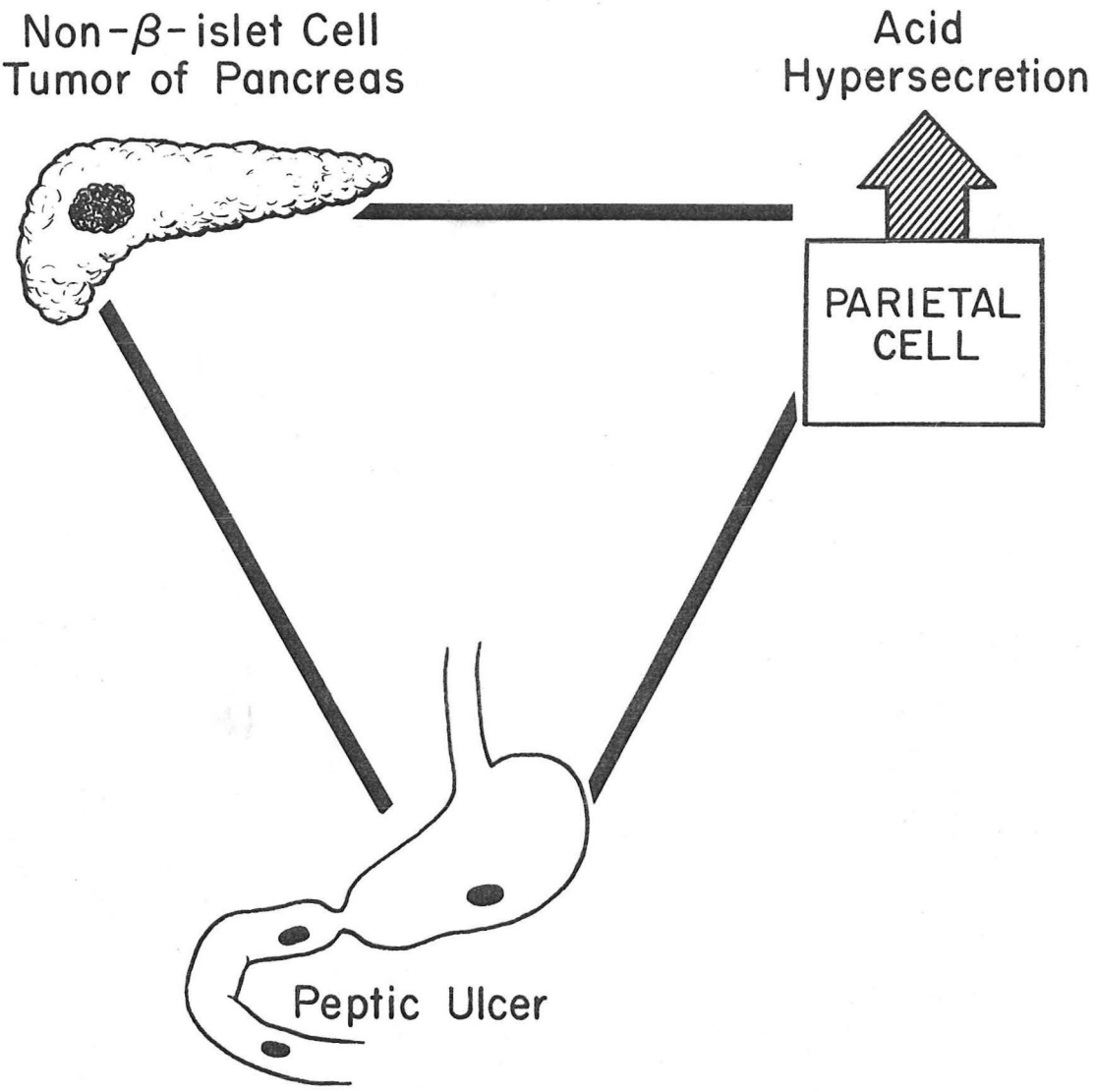
# PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT OF ZOLLINGER-ELLISON SYNDROME




## MEDICAL GRAND ROUNDS

July 28, 1977

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In 1955, Zollinger and Ellison presented a paper before the American Surgical Association in which they described two patients.[1] They proposed a new clinical syndrome consisting of the following triad:

1. Ulcerations in unusual locations, i. e. second or third portions of the duodenum, upper jejunum or recurrent stomal ulcers following any type of gastric surgery short of total gastrectomy.

2. Gastric hypersecretion of gigantic proportions persisting despite adequate conventional medical, surgical or irradiation therapy.

3. Non-specific islet cell tumors of the pancreas.

They postulated that "an ulcerogenic humoral factor of pancreatic islet cell origin was responsible for the peptic ulcer diathesis." The following case summary is one of Zollinger and Ellison's original patients.

| | |
|---|---|
| | J. M., 19 y/o lady. |
| July, 1951-Jan., 1952 | Unexplained upper abdominal pain. |
| Feb., 1952 | Exploratory laparotomy. No abnormality found. |
| July, 1953 | Acute adominal pain. Pre-op diagnosis - perforated viscus. Exploratory laparotomy - two jejunal ulcers identified and oversewn. |
| Oct., 1953 | Weight loss - 180 to 121 lbs. |
| Jan., 1954 | Admitted to University Hospital, Columbus, Ohio with chief complaint of vomiting and abdominal pain. Abdominal pain subsided after naso-gastric suction. |
| | UGI - duodenal ulcer and jejunal ulcer plus coarse duodenal folds. |
| | 12 hr. gastric aspiration: Vol. - 2800 ml. Free HCl - 308 meq. |

| | |
|---|---|
| Jan., 1954 (continued) | A radical gastrectomy and fundusection with end-to-end gastroduodenostomy were performed to control gastric hypersecretion. |
| | Post-op. 12 hr acid secretion:<br>Vol. - 570 ml.<br>Free HCl - 28 meq. |
| Feb., 1954 | Severe right upper quadrant pain and hematemesis. |
| | Pain and bleeding subsided with antacid therapy. |
| Feb.-July, 1954 | Mid-epigastric burning pain in spite of medication and diet. |
| July, 1954 | 12 hr acid secretion:<br>Vol. 2000 ml.<br>Free HCl - 32 meq. |
| | UGI - ? marginal ulcer; coarsening and widening of duodenal folds. |
| | Radiation therapy instituted to control hypersecretion and to avert a total gastrectomy. |
| August, 1954 | Hospitalized because of nausea and severe burning epigastric pain. |
| Aug.-Oct., 1954 | Daily pain and vomiting. |
| Oct., 1954 | Hospitalized for the sixth time in nine months. |
| | UGI - gastroesophageal ulcer and a penetrating stomal ulcer at the gastroduodenal junction. |
| | Total gastrectomy was performed. |

Since the total gastrectomy in 1954, the patient has had two children and is living and well and works as a dental assistant.

## *Pathogenesis of Z-E Syndrome*

Signs and symptoms associated with Z-E Syndrome are related to non - β islet cell tumors of the pancreas and their products. In their original presentation, Zollinger and Ellison suggested that glucagon might be the humoral factor responsible for the clinical syndrome. However, several years later, gastrin was shown to be the humoral substance. Therefore, the term, "gastrinoma," is a more exact designation for the

non - β islet cell tumor causing the Z-E Syndrome.

GASTRINOMA

Location and Size. Characteristically, gastrinomas are slow growing neoplasms; however, they have an unusually high disposition for multiple primary sites and frequently are biologically malignant. Because of the propensity for multiple primary sites, it is often difficult to ascertain whether in an individual patient multiple tumors represent metastases or multiple primary sites. Table 1 outlines the location of gastrinomas in 624 Z-E patients.[2]

Table 1

*Location of Gastrinoma in 624 Z-E Patients*

| | |
|---|---|
| Pancreas: 426 patients | |
| Multiple or metastatic tumor sites | 296 |
| Coexisting islet-cell hyperplasia | 21 |
| Single, localized tumor | 109 |
| Duodenal wall: 103 patients | |
| With associated pancreatic and/or metastatic tumor sites | 50 |
| Coexisting islet-cell hyperplasia | 5 |
| Localized duodenal wall tumor | 48 |
| Islet-cell hyperplasia alone: | 40 |
| Metastatic tumor site alone: | 55 |

Only 109 out of 426 patients had a single tumor in the pancreas. When tumors are localized to the pancreas, they are most often located in the head or tail and least commonly in the body. The ratio is 4:1:4, head: body: tail. Tumors may also be located in the pancreas, stomach or duodenal wall, hilus of the spleen and regional lymph nodes.[3] They vary in size, ranging from 2 mm. up to 20 cm. or more in diameter.

Cellular Structure. Cells of hormone secreting tumors probably have a common embryologic origin and arise from precursor cells in the neuroectoderm.[4,5] These cells share common cytochemical properties, including the ability to take up and decarboxylate certain amino acids. Therefore, these cells are classed as "APUD" or "amine percursor uptake and decarboxylation" cells.

Although "APUD" cells share a common embryologic background, similar cytochemical properties, and similar secretory products (amines and polypepties), they differ in the type of secretory granules and the composition and function of secretory hormones. For example, the pancreatic islets contain at least three different hormone secreting cells. The α cells secret glucagon, the β cells secret insulin and the δ cells secret gastrin. Gastrinomas are thought to be composed of δ cells.

Histology. On light microscopy, islet tumor cells are well differentiated and occur in trabecular patterns or in sheets or nests. The cells are small, uniform in size, and have eosinophilic cytoplasm. It is impossible to distinguish by light microscopy a gastrinoma from carcinoid tumors or insulinomas. It is also impossible to distinguish a benign from a malignant tumor by light microscopy.

GASTRIN

The first major achievement in determining the nature of the hormonal substance responsible for Z-E Syndrome occurred in 1961. Gregory, Tracy and their colleagues documented that a tumor extract contained a substance which had similar chemical and physiological properties as the antral hormone, gastrin.[6] When injected subcutaneously into conscious dogs, this substance stimulated gastric acid secretion.

The cells which contain gastrin are called G-cells and are found in the gastric antrum. A small number of G-cells are also found in the upper small intestine. There is controversy as to the presence of G-cells in the pancreas.[7] If present, they are rare. Although the ultrastructure of gastrinoma cells is typical of endocrine cells, the secretory granules frequently are not identical of those found in antral G-cells.

The amount of gastrin per gram of tissue extracted from a normal pancreas is small and only slightly higher than that extracted from control tissue. The amount of gastrin that can be extracted from a gastrinoma is quite high and is similar to concentrations found in antral mucosa.

Chemical Structure and Activity. So far, six biologically active forms of gastrin have been isolated and characterized.[8] The principle forms of gastrin found in antral extracts and in most tumor extracts are the monosulfated and sulfated heptadecapeptides G-17-I and G-17-II, also known as little gastrins I and II (See Fig. 1 and Table 2).[9]

Fig. 1 (Ref. 9)

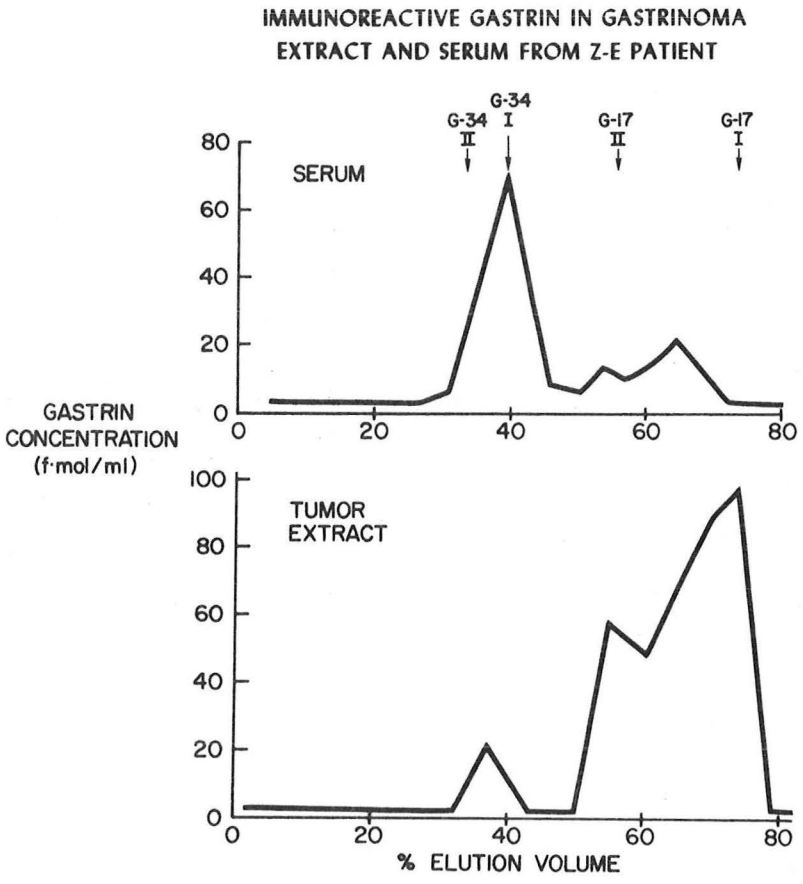


Table 2

*Molecular forms of Gastrins*

| | GASTRIN PEPTIDES | | | |
|---|---|---|---|---|
| | G-34 | G-17 | G-14 | |
| Residues | 34 | 17 | 14 | |
| Molecular Weight (I) | 3839 | 2098 | 1833 | |
| (II) | 3919 | 2178 | 1913 | |
| | Glp | | | 34 |
| | Leu | | | 33 |
| | Gly | | | 32 |
| | Pro | | | 31 |
| | Gln | | | 30 |
| | Gly | | | 29 |
| | His | | | 28 |
| | Pro | | | 27 |
| | Ser | | | 26 |
| | Leu | | | 25 |
| | Val | | | 24 |
| | Ala | | | 23 |
| | Asp | | | 22 |
| | Pro | | | 21 |
| | Ser | | | 20 |
| | Lys | | | 19 |
| | Lys | | | 18 |
| | Gln | Glp | | 17 |
| | Gly | Gly | | 16 |
| | Pro | Pro | | 15 |
| | Trp | Trp | Trp | 14 |
| | Leu | Leu | Leu | 13 |
| | Glu | Glu | Glu | 12 |
| | Glu | Glu | Glu | 11 |
| | Glu | Glu | Glu | 10 |
| | Glu | Glu | Glu | 9 |
| | Glu | Glu | Glu | 8 |
| | Ala | Ala | Ala | 7 |
| | Tyr-R | Tyr-R | Tyr-R | 6 |
| | Gly | Gly | Gly | 5 |
| | Trp | Trp | Trp | 4 |
| | Met | Met | Met | 3 |
| | Asp | Asp | Asp | 2 |
| | Phe-$NH_2$ | Phe-$NH_2$ | Phe-$NH_2$ | 1 |

R = H (gastrin-I).
R = $SO_3H$ (gastrin-II).

The next most abundant forms in tissue, and the most common forms in serum in the stimulated state and in serum of gastrinoma patients are nonsulfated and sulfated big gastrins, G-34-I and G-34-II (See Table 2). It can be seen from Table 2 that G-17 molecules are shorter fragments of G-34. It is assumed that all gastrin is originally synthesized in the form of G-34 and subsequently converted to G-17. In vitro, this occurs after digestion of G-34 with trypsin. Cleavage occurs at the LYS-GLN

bond forming G-17. The significance of the sulfate group in gastrin-II is not known. No biologic differences have been noted between sulfated and nonsulfated forms.

The carboxy-terminal region of the gastrin molecule has all the biologic actions of the whole molecule.[10] Traces of activity are seen with fragments as small as the C-terminal dipeptide amine. Removal of the C-terminal amide to form the free acid results in complete loss of activity.

Measurement. Prior to radioimmunoassay, gastrin concentrations were quantified by bioassay. Extracts of tissue or serum were infused into experimental animals, and the acid secreting potential of the extract quantified. Sensitive and specific radioimmunoassays have been developed for gastrin, and extensive studies have been performed analyzing different molecular forms of gastrin in plasma and tissues.

Fasting serum gastrin concentrations very among different laboratories using different assay methods and different standards. The normal mean values for basal serum gastrin concentration ranges between 30 and 200 pg/ml with a few normal subjects having values in the range of 200-300 pg/ml.[11] Normal values for laboratories in the Dallas area are shown in Table 3.

Table 3

| | Normal Serum Gastrin (pg/ml) |
|---|---|
| Parkland | <200 |
| V. A. | 50-200 |
| Baylor | <200 |
| St. Paul | 80-170 |
| Presbyterian | <200 |
| Bio-Assay | <300 |
| Swiss Avenue | 0-150 |
| Specialized Biomedical | 0-150 |
| Southwest Medical Labs. | 0-150 |
| Harris Hospital | 50-275 |

Gastrin Release. The release of gastrin is initiated by various chemicals that act on the G-cells (Table 4). These chemicals are delivered to G-cells by blood, by release from nerve endings at the G-cells, or by contents of the stomach bathing the microvilli on the luminal surface of G-cells.[8]

Table 4

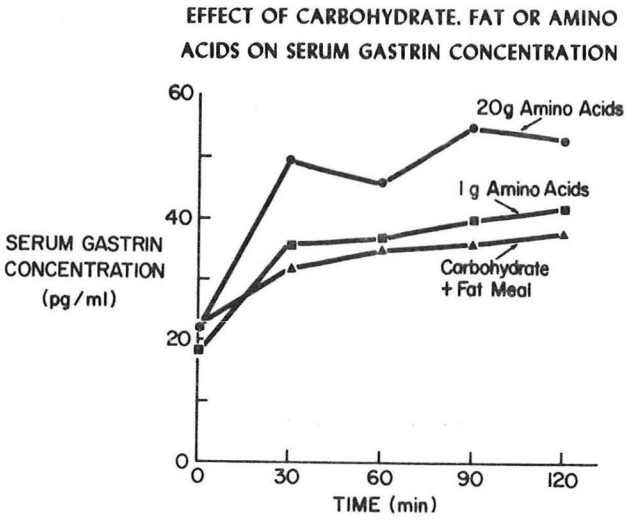
*Regulation of Release of Gastrin**
*(from Walsh and Grossman, Ref. 8)*

| Stimulation | Inhibition |
|---|---|
| Luminal stimulants | Luminal |
| PEPTIDES & AMINO ACIDS | ACID |
| Neural stimulants | Blood Borne |
| VAGAL CHOLINERGIC | Secretin, gip, vip, |
| Blood-borne stimulants | glucagon, calcitonin |
| Calcium | |
| Epinephrine | |

*Factors thought to operate under physiologic conditions are capitalized

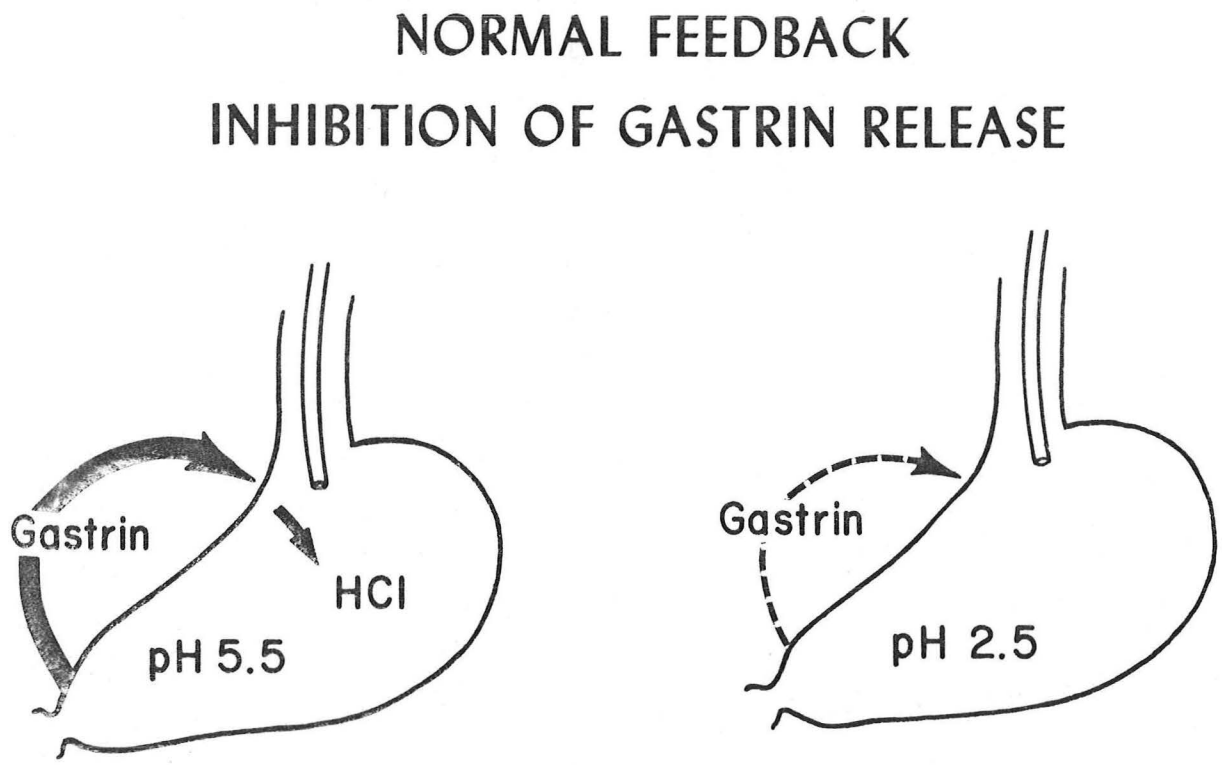
One of the most potent physiological stimulants for gastrin release is amino acids (See Fig. 2).[14]

Fig. 2




Inhibition of Gastrin Release. Release of gastrin is controlled by a negative feedback mechanism in which gastric acid bathing antral mucosa inhibits the release of gastrin (See Fig. 3).[15] All stimulants for gastrin release are inhibited by acid. A pH of about 1 is required for maximal supression, but even at pH 2.5, gastrin release in response to a test meal of amino acids is reduced by about 80 per cent in normal human subjects.[15]

Fig. 3



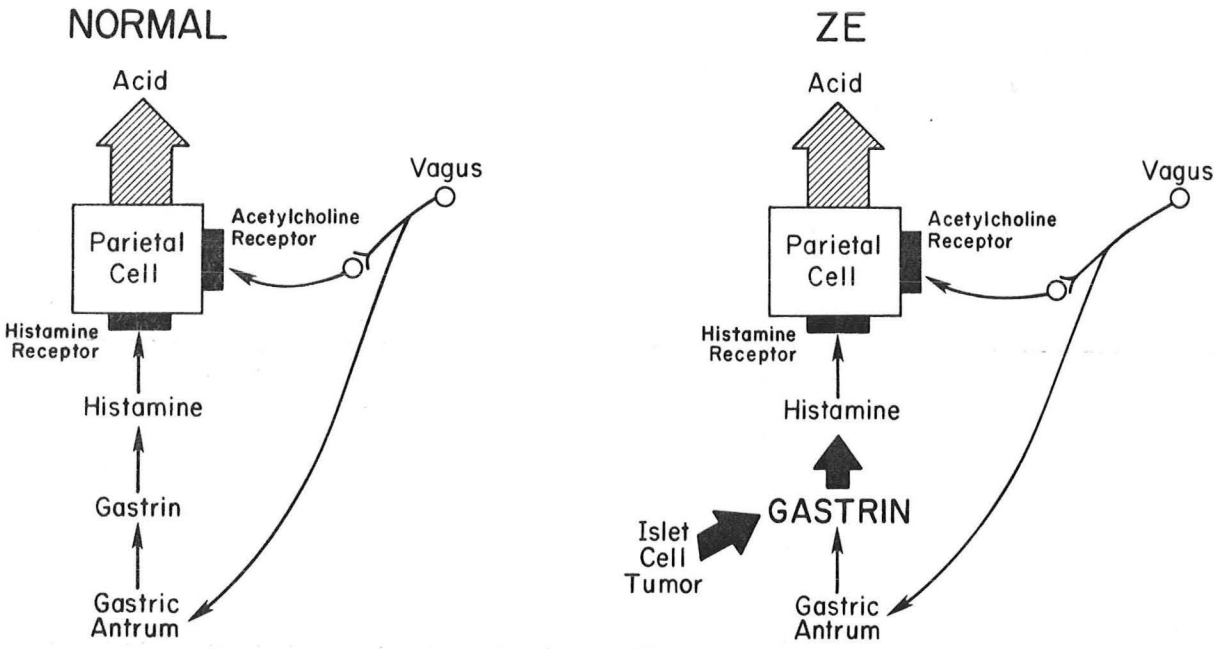
*Pathophysiology of Z-E Syndrome*

The disordered physiology and pathology in Z-E Syndrome is related primarily to hypersecretion of gastric acid which is secondary to increased levels of circulating gastrin.

Acid Secretion - Normal Physiology.

In normal humans, there are three major stimuli to acid secretion - gastrin, acetylcholine and histamine. The interaction between these stimuli and the exact mechanism by which they stimulate acid secretion by the parietal cell is not known. A theoretical model is shown in Fig. 4.

Fig. 4




Neural stimulation of acid secretion occurs primarily via the vagus nerve (cephalic phase). In addition, there are local cholinergic reflexes in the wall of the stomach that are involved in the stimulation of acid secretion. Cholinergic stimulation of acid secretion is mediated by acetylcholine.

Antral gastrin is also an important stimulant of acid secretion. Whether gastrin stimulates parietal cells to secrete acid by acting through histamine release as shown in Fig. 4 or whether gastrin acts on a separate parietal cell receptor (i.e. a gastrin receptor) is not known. Histamine stimulation of acid secretion per se is most likely mediated through the histamine $H_2$ - receptor.

## Acid Secretion - Z-E Syndrome

A theoretical model for the stimulation of acid secretion in Z-E patients is shown in Fig. 4, right. The sequence of events leading to acid secretion are probably the same in patients with Z-E Syndrome as they are in normal subjects. However, the parietal cells are under a constant state of stimulation because of increased levels of circulating gastrin. Therefore, even in the basal state patients with Z-E Syndrome have increased acid secretion and this increased acid secretion leads to other pathophysiological events.

## Parietal Cell Hyperplasia

Gastrin has a trophic effect on gastric parietal cells and causes parietal cell hyperplasia in patients with Z-E Syndrome.[16] Hyperplasia of the gastric mucosa can be produced experimentally in rats by large doses of pentagastrin given repeatedly over a period of several weeks.[17] In patients with Z-E Syndrome both hypergastrinemia and increased parietal cell mass contribute to hypersecretion of acid.[18]

## Gastric Emptying

Patients with Z-E Syndrome have an increased rate of gastric emptying (Fig. 5).[19] Increased gastric emptying does not appear to be related to acid hypersecretion since an increased fractional rate of emptying persisted despite abolition of gastric hypersecretion by a histamine $H_2$-receptor antagonist. Also, it is probably not related to hypergastrinemia since an increased rate of emptying could not be duplicated in normal subjects by giving pentagastrin. Increased gastric emptying is one of the few pathophysiological events that does not appear to be related to increased acid or gastrin. An undefined neural or humoral factor is postulated as the cause.

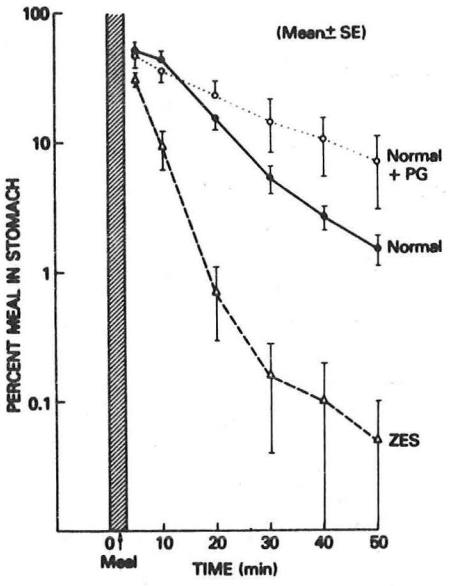



Fig. 5. Per cent of meal remaining in stomach. (from Dubois, et al, Ref. 19)

## *Clinical Presentation*

### Incidence, Sex and Age at Onset

The absolute incidence of patients with Z-E Syndrome in the general population is unknown. Neither a geographic nor a racial distribution has been demonstrated. The number of patients recognized as having Z-E Syndrome has increased dramatically with the availability of gastrin radioimmunoassay.

The sex incidence is 63% males and 37% females.[20] The onset of symptoms may occur at any age, but the highest incidence occurs in the third through the fifth decade (Fig. 6). Gastrinomas have also been reported in children and in the elderly.

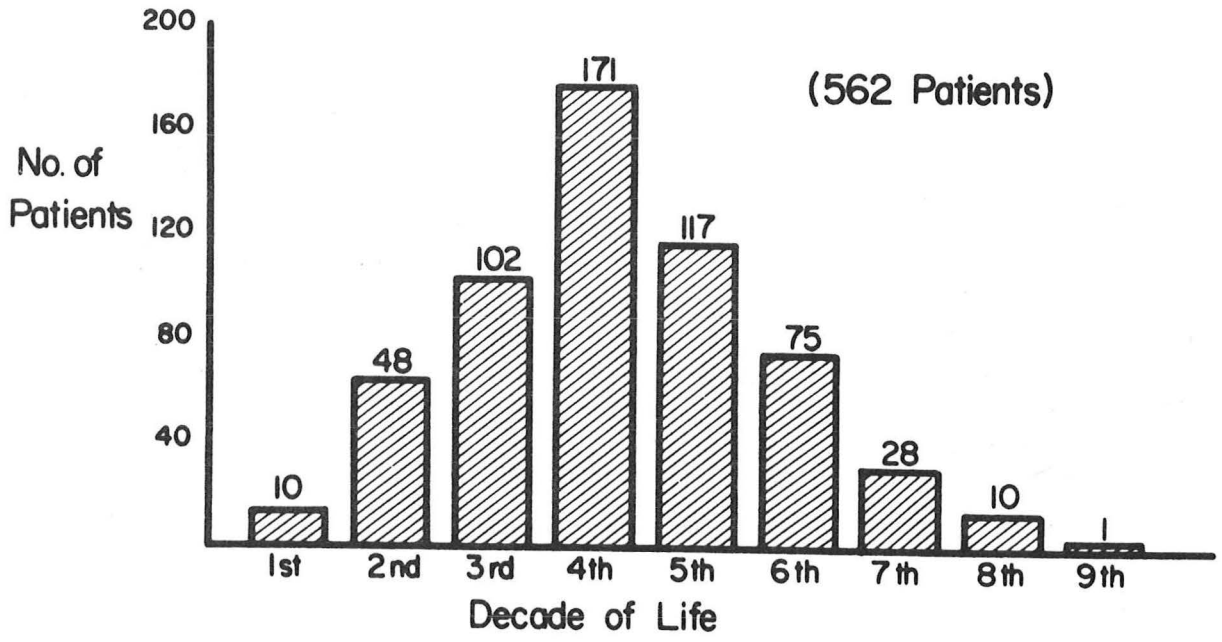



Fig. 6. Age of onset of symptoms of Z-E Syndrome (from Wilson, S. D. Ref. 20)

### Symptoms

Patients usually present with abdominal pain secondary to ulcer disease. However, as shown in Table 5 other symptoms may also be present. In 79%

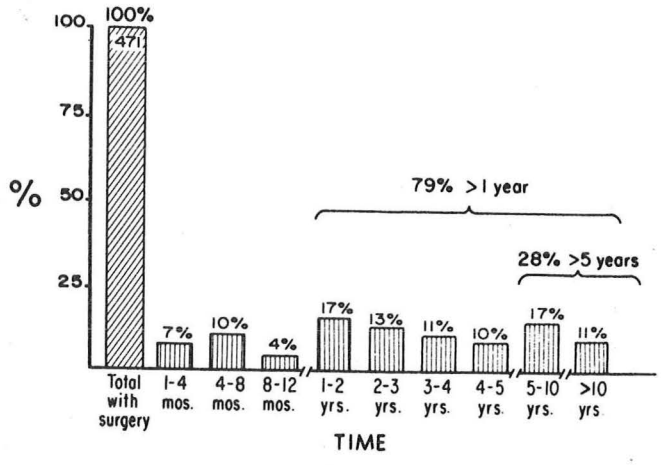
Table 5

*Symptoms in 685 Patients with Z-E Syndrome (from Wilson, S. D. Ref. 20)*

| | % of Patients |
|---|---|
| Ulcer pain | 72 |
| Diarrhea | 30 |
| Melena | 29 |
| Vomiting | 29 |
| Hematemesis | 23 |
| Perforation | 14 |
| Endocrine Disorders | 12 |
| Cramps and Diarrhea | 8 |

of patients (See Fig. 7) symptoms are present for a year or longer prior to surgery.

Fig. 7. Time from onset of symptoms to surgical procedure (from Wilson, S.D. Ref. 20)




Ulcer Symptoms. Symptoms secondary to ulcer disease may be persistent, progressive and unresponsive to conventional medical therapy. This is illustrated by the next case.

J. S. is a 45 y/o man who presented with severe epigastric pain. He had, had indigestion intermittantly for several years, but the symptoms had always responded to antacids. He was hospitalized one year ago for UGI bleeding and a duodenal ulcer was seen on x-ray.

One month ago the frequency of indigestion increased and gradually became persistent and no longer responsive to antacids. He was hospitalized and placed at bed rest. Hourly antacids and anticholinergics, q 6 h were prescribed. Pain persisted. The dose of antacid was increased but this did not help.

Acid Secretory Studies - BAO - 45 meq/hr.
- PAO - 60 meq/hr.

UGI - Hypertrophic gastric folds; thickened duodenal folds.

Serum Gastrin Concentration - 800 pg/ml.

Diagnosis of Z-E Syndrome was made and because of unremitting pain, a total gastrectomy was performed.

Diarrhea. Diarrhea may be the most prominent symptom in some patients with Z-E Syndrome and may occur in the absence of ulcer symptoms. Diarrhea is closely related to gastric acid hypersecretion since it can be relieved or eliminated by nasogastric suction or total gastrectomy.[21-24]

Other factors also contribute to the development of diarrhea. For example, gastrin decreases salt and water absorption from the small intestine[25, 26] and may also effect small bowel motility.[27,28] Changes in small bowel morphology have also been reported in Z-E Syndrome and these changes are probably related to acid hypersecretion.[29]

In summary, diarrhea is caused by multiple factors including:[30]

1. Delivery of excessive amounts of gastric acid to the duodenum.

2. Damage to the small bowel mucosa by acid gastric juice.

3. Decreased small bowel absorption of water and electrolytes secondary to gastrin and/or mucosal damage.

4. Increased intestinal motility.

Diarrhea usually can be controlled by nasogastric suction, total gastrectomy or antisecretory drugs (See Therapy).

Diarrhea in Z-E Syndrome must be distinguished from diarrhea secondary to pancreatic cholera or the WDHA Syndrome (watery diarrhea, hypokalemia and achlorhydria). The distinction can usually be made by gastric acid secretory studies. Acid secretion in Z-E is markedly elevated; whereas, acid secretion in WDHA is very low or non-existent. Also, serum gastrin concentration is normal in the WDHA Syndrome.

Steatorrhea. Many patients with Z-E Syndrome have steatorrhea and in some instances the finding of steatorrhea may lead initially to a wrong diagnosis. This is illustrated by the next case.

E. L. is a 48 y/o lady who presented several years ago with weight loss, severe diarrhea, and cramping abdominal pain.
Laboratory Studies: Stool fat - 18 gms/24 hr.
D-Xylose - 3 gms. (nl >5)

Small Bowel Biopsy - Decreased villi and increased inflammatory cells

Diagnosis: Celiac Disease
Treatment: Gluten Free Diet

Symptoms persisted in spite of therapy.

The patient was seen by a gastroenterologist in Dallas for further evaluation.

UGI - Large rugal folds; duodenal ulcer.
Acid Secretory Studies - BAO - 30 meq/hr.
PAO - 40 meq/hr.

Serum Gastrin Concentration - 600 pg/ml.

The diagnosis of Z-E Syndrome in this patient was delayed for two years because the presence of steatorrhea and small bowel biopsy abnormalities was misleading. Z-E Syndrome should at least be included in the differential diagnosis of steatorrhea.

There are at least three causes for steatorrhea in Z-E Syndrome:

1) Inactivation of pancreatic lipase by acid in the duodenum, 2) small bowel mucosal damage and 3) precipitation of bile salts especially glycine conjugates.

Clinical Diagnosis: Summary. Z-E Syndrome should be considered immediately if any of the following are present.

1. Fulminant ulcer diathesis in a patient who is very young or very old.

2. Severe ulcer symptoms with perforation or hemorrhage occurring in the immediate postpartum period or soon after a standard ulcer operation.

3. Severe and persistent diarrhea accompanied by steatorrhea and gastric hypersecretion.

4. Ulcer symptoms associated with other evidence of polyglandular involvement.

5. Family history of ulcer disease, endocrine disorders or both.

## *Diagnostic Evaluation*

### Upper Gastrointestinal X-ray

Because most patients present with ulcer like symptoms, one of the first diagnostic tests usually performed is an UGI series. If any of the following are seen on UGI, a diagnosis of Z-E should be considered.

1. Hypertrophic gastric folds

2. Appearance of less dense or granular barium (due to increased fluid secretion)

3. Thickened duodenal folds with or without duodenal dilatation

4. Multiple duodenal ulcers

5. Post-bulbar ulcer

6. Ulcerations past the ligament of Treitz

7. Malabsorption pattern in the small bowel

Acid Secretory Studies

Until the recent development of a sensitive radioimmunoassay for gastrin, the diagnosis of Z-E Syndrome depended on the documentation of acid hypersecretion. Even now, more often than not, an acid secretory test is the first diagnostic test performed. The acid secretory criteria that have been used to make a diagnosis of Z-E Syndrome are listed below:

1. Nocturnal gastric secretion (12 hr.) - >1000 ml and 100 meq. HCl[31, 32] (with the availability of 1 hour basal acid output and histamine or pentagastrin stimulated peak acid output, 12 hr. overnight secretory studies should not be performed.)

2. Basal acid output - >15 meq/hr.[33] (This test should not be performed without also including peak stimulation. In addition, a number of patients have a BAO >15 meq/hr. and do not have Z-E. Therefore, increased BAO alone does not mean that a patient has Z-E.)

3. Basal Acid Output:Peak Acid Output - >60%[34]

   Example: BAO = 30 meq/hr.
   PAO = 40 meq/hr.
   BAO/PAO = 75%

   (This is the best acid secretory criteria for diagnosing Z-E)

Serum Gastrin Determination

Now that serum gastrin assays are available (See page 6 and Table 3), serum gastrin concentration should be measured in every patient suspected of having Z-E Syndrome. As stated previously (See Table 3), because of different assay methods and standards, the normal values for basal serum gastrin concentration vary from laboratory to laboratory. To determine the degree of variability not only for normals but also for Z-E patients, a serum sample from a normal subject and a known Z-E patient was sent to several laboratories in the Dallas area (the sample sent to each lab was from the same syringe). The results are shown in Table 6.

Table 6

*Results of Serum Gastrin Determinations (pg/ml) Performed in Dallas Area Laboratories*

| | Normal for Laboratory | K. C. (normal subject) | W. W. (Z-E patient) |
|---|---|---|---|
| Biomedical Testing | <150 | 145 | 450 |
| Bio-Assay | <150 | 160 | 220 |
| Baylor | <200 | 140 | 228 |
| Parkland | <200 | 170 | 685 |
| V. A. | <200 | 140 | >800 |
| Southwest Medical | <150 | 125 | 180 |
| Walsh (Los Angeles) | <150 | 100 | 465 |

*Differential Diagnosis Based on Acid Studies and Serum Gastrin Concentration*

As shown in Table 7, there are a few diseases that are associated with either increased gastrin or increased acid but not with both. For example, patients with pernicious anemia have increased gastrin. Therefore, based on this one test, Z-E Syndrome might be suspected. However, if an acid secretory study is performed also, pernicious anemia can easily be distinguished from Z-E Syndrome. All patients suspected of having Z-E Syndrome should have gastrin and acid secretion measured.

Table 7

| Decreased or 0 Acid Increased Gastrin | Increased Acid Normal Gastrin | Increased Acid Increased Gastrin |
|---|---|---|
| Pernicious Anemia[35] | Idiopathic Basal Hypersecretion[38] | Z-E |
| Atrophic Gastritis[36,37] | | Retained Antrum |
| | | ? Antral G-cell hyperplasia[39-44] |
| | | ? Gastric Outlet Obstruction[45] |
| | | ? Short Bowel Syndrome[46] |

The diseases associated with both increased acid and increased gastrin are shown in Table 7, last column. If a patient has a high gastrin (>600 pg/ml) and acid hypersecretion (BAO:PAO >60%), Z-E Syndrome is by far the most likely diagnosis. There are, however, four other conditions associated with increased acid and increased gastrin but they are extremely rare. These have been labled

nontumorous hypergastrinemic hyperchlorhydrias.

Retained antrum. This is an unusual condition that occurs after antrectomy and gastrojejunostomy when the duodenal stump contains antral mucosa. Gastric hypersecretion develops because the cuff of antral mucosa is no longer exposed to normal inhibitory action by gastric acid but instead is exposed to an alkaline environment. Careful surgical techniques usually prevent retained antrum from occurring. However, if it does occur, it can lead to confusion with Z-E in the postoperative patient with recurrent ulceration. (Retained antrum can usually be ruled out by reviewing the path report. If brunners glands were reported at the distal end of the resected antral specimen, retained antrum should not be considered.)

Gastric Outlet Obstruction and Short Bowel Syndrome. These are rare and questionable causes of increased acid and increased gastrin. They should not cause a diagnostic problem.

Antral G-cell Hyperplasia. Several patients have been described that have basal acid hypersecretion, moderately increased fasting serum gastrin and markedly accentuated serum gastrin response to a meal.[39, 40] An additional four patients were described who had elevated fasting serum gastrin, profound antral G-cell hyperplasia (based on immunofluorescence analysis), and no tumor or islet cell hyperplasia. The major finding that distinguishes these patients from patients with Z-E Syndrome is an accentuated gastrin response to a test meal.*

Some investigators question the existence of G-cell hyperplasia. It may be that G-cell hyperplasia does not represent a separate entity but instead represents an accentuation of functional G-cell hyperactivity found in the general population of patients with duodenal ulcer. In a review of 400 patients with recurrent ulceration after surgery or peptic ulcer with hypergastrinemia, only three patients were found that had findings suggestive of G-cell hyperplasia.[47]

If antral G-cell hyperplasia occurs, it is rare and should be easily distinguishable from Z-E Syndrome by measuring the serum gastrin response to a standard test meal.

Indeterminate Serum Gastrin Concentration. As stated previously, if serum gastrin concentration is >600 pg/ml and BAO:PAO is >60%, Z-E Syndrome is a very likely diagnosis. A diagnostic problem arises, however, if the serum gastrin concentration is slightly elevated, i.e. between 200-600 pg/ml. There are two provocative tests that should be used in patients who have a gastrin concentration in this range.

Secretin Infusion Test. In normal subjects and patients with duodenal ulcer, secretin produces either no change or a decrease in basal gastrin (Fig. 8) In contrast, about 75% of patients with Z-E Syndrome respond to secretin infusion with a rapid

*Test meal - 6 oz ground sirloin and two pieces of toast or orange juice and two boiled eggs

increase in serum gastrin.[48-50] As shown in Fig. 9, a peak response is usually achieved 5-10 minutes after secretin injection.

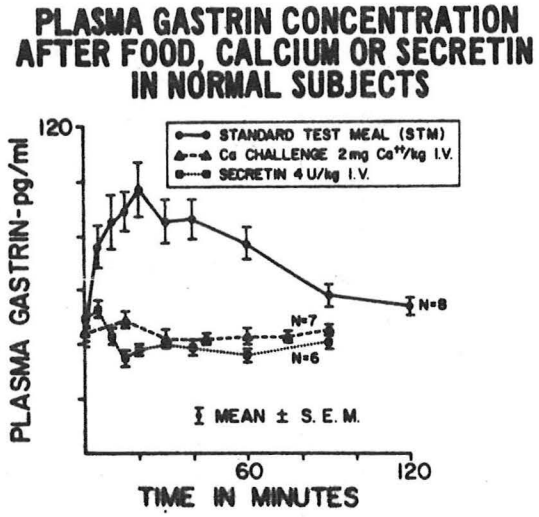



Fig. 8
(from Straus, E. and Yalow, R.S. Differential Diagnosis of Hypergastrinemia. Gastrointestinal Hormones. ed. J. C. Thompson, Univ. of Texas Press, 1975.)

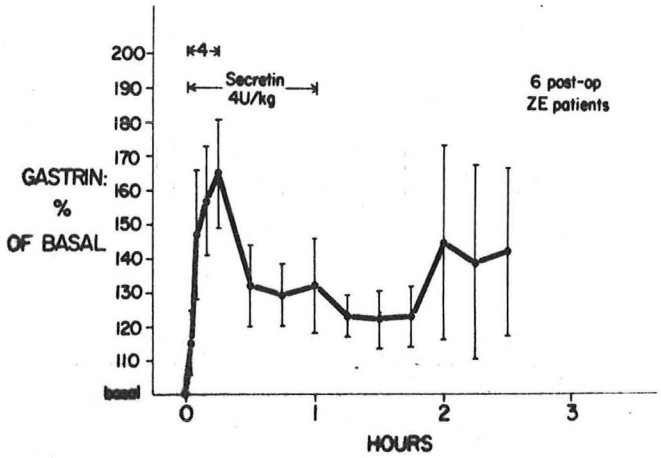



Fig. 9
Effect of secretin infusion on serum gastrin concentration in Z-E (from Ref. 49)

*Test Procedure:*

1. Obtain blood sample for basal serum gastrin determination.
2. Secretin, 2 u/kg, diluted in 8-10 ml normal saline - inject slowly I.V. push.
3. Obtain samples for serum gastrin at 2, 5, 10, 15 and 30 minutes.

*Positive Results.* Doubling of serum gastrin concentration strongly suggests gastrinoma. According to one study, a rise of >100 pg/ml is diagnostic.[51]

Calcium Infusion Test. Patients with Z-E Syndrome have an exaggerated acid secretory and serum gastrin response to calcium infusion (Fig. 10).[52-54] However, a calcium infusion test is more difficult to perform and may be less specific than a secretin infusion test.

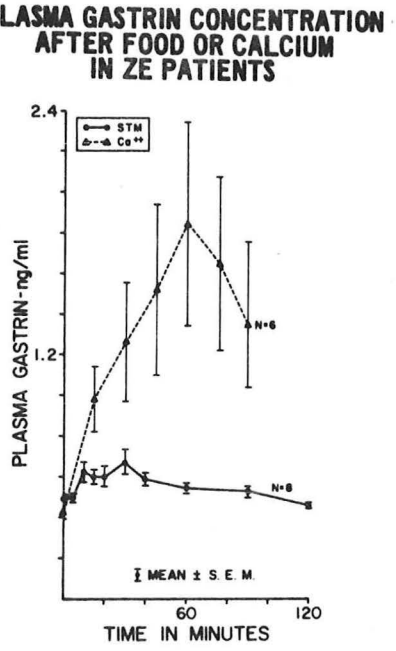



Fig. 10
(from Straus, E. and Yalow, R. S. Differential Diagnosis of Hypergastrinemia. Gastrointestinal Hormones. ed. J. C. Thompson, Univ. of Texas Press, 1975.)

*Test Procedure:*

1. Obtain blood samples for basal serum gastrin determination.
2. Calcium, 4 mg/kg/hr. as calcium gluconate - infuse intravenously for three hours.
3. Obtain samples for serum gastrin at 30, 60, 90, 120, 150 and 180 minutes.

*Positive Results.* A rise of >450 pg/ml in serum gastrin concentration strongly suggests Z-E Syndrome. In one study false negative results occurred in several patients.[51] If a rise of >450 pg/ml does not occur and Z-E Syndrome is strongly suspected, the test should be repeated, or preferably, a secretin infusion test should be performed.

In summary, if secretin is available, a secretin infusion test appears to be the best provocative test.

Idiopathic Basal Hypersecretion. There are a few patients who have increased basal acid secretion (BAO:PAO >40-50%) but who have a normal fasting serum gastrin concentration, a negative secretin test and a negative calcium infusion test. These patients are suspected of having Z-E Syndrome because of basal acid hypersecretion and therefore present a diagnostic dilemma. This is illustrated by the next case.

M. C., 32 y/o man
1969 Severe epigastric pain; hematemesis
UGI x-ray: Duodenal ulcer; large duodenal folds
BAO - 43 meq/hr. BAO:PAO = 74%
PAO - 58 meq/hr.
Serum Gastrin - 153 pg/ml (nl <250)
Calcium Infusion Test - non-diagnostic for Z-E

Total gastrectomy considered. Because of conflicting data (acid results vs. gastrin) it was decided to follow patient on medical therapy.

1969-1977 Patient followed. Intermittant symptoms usually relieved by antacids.

1977 BAO - 34 meq/hr BAO:PAO - 50%
PAO - 68 meq/hr.
Serum Gastrin - 89 pg/ml

The cause of basal acid hypersecretion in this and similar subjects is not known. Bioassay of plasma extracts from patients with normogastrinemic, acid hypersecretion has suggested the presence of a circulating nongastrin gastric secretogogue.[55]

In summary, if a patient has Idiopathic Basal Hypersecretion a total gastrectomy should not be performed. The patient should be treated medically (See Treatment of Z-E) and surgery performed only for complications of ulcer disease.

Other Diagnostic Tests

Angiography. Celiac angiography has been used as an ancillary diagnostic test in patients with suspected Z-E Syndrome in an attempt to localize the tumor and/or metastases. However, a tumor is found in less than 60% of cases (only 30% in one series).[56,57]

*Should an angiogram be performed in all patients with suspected Z-E?* An angiogram should not be performed as a primary diagnostic test. In fact, a textbook entitled Endocrine Surgery states "angiographic demonstration and localization of these tumors is no longer indicated since the diagnosis rests upon the measurement of gastric secretion and serum gastrin."[58] Angiography, however, may be indicated in designing a therapeutic approach. For example, if an isolated tumor is seen in the tail of the pancreas, an exploratory laporatomy should be performed. If an isolated tumor is found, then the tumor should be removed (see Therapy).

Sonography. Sonography may also be used as an ancillary diagnostic test in an attempt to localize the tumor.

## *Therapy of Z-E Syndrome*

Therapy of Z-E Syndrome has undergone dramatic change during the past two-three years. In 1973, a review article stated "As a general rule, patients with Z-E Syndrome respond poorly to medical therapy."[30] However, with the advent of histamine $H_2$ receptor antagonists, medical therapy has provided an alternative to surgery and a number of patients are currently being treated medically.

Immediate Management

When patients present, they usually can be divided into two categories based on the severity of their illness.

1) Patients with symptoms of peptic ulcer disease and/or diarrhea and steatorrhea. These patients may have had previous surgery but other than their symptoms are in reasonably good health.

| | |
|---|---|
| | J. H., 45 y/o lady. |
| Oct., 1971: | Bleeding D. U. and diarrhea |
| March, 1972: | Bleeding D. U. |
| June, 1973: | Ulcer pain; large rugal folds and D. U. on x-ray. |
| | 12 hr. secretory rate - 200 meg.<br>Serum gastrin - 750 pg/ml. |
| | Refused total gastrectomy.<br>Laparotomy: no tumor found<br>Vagotomy and pyloroplasty performed. |
| Nov., 1974: | Recurrent D. U. |
| March, 1975: | Referred to Parkland Hospital<br>Persistent epigastric pain<br>No weight loss |
| | BAO - 31 meq/30'<br>PAO - 33 meq/30'<br>Serum gastrin - 680 pg/ml |

2) Patients with severe peptic ulcer symptoms, weight loss, malnutrition, and multiple complications of ulcer disease. When they present, they require more intensive therapy.

| | |
|---|---|
| | C. S., 38 y/o lady |
| 1972 | Severe watery diarrhea, epigastric pain weight loss (10 lbs) |
| 1973 | Persistent pain, diarrhea, and continued weight loss |
| Nov., 1974 | UGI bleeding |
| June, 1975 | Diarrhea, epigastric pain, 30 lb weight loss. Severe volume depletion. |

Reduction of volume and acidity of gastric juice is the major goal of treatment for all patients with Z-E Syndrome. Patients in the second category, however, require additional supportive therapy such as hospitalization, fluid replacement and perhaps I.V. hyperalimentation. Nasogastric suction may be necessary during the early period of hospitalization as an additional method

of reducing the volume of gastric acid.

Reduction of Volume and Acidity of Gastric Juice. Histamine $H_2$ - receptor antagonists, especially in combination with an anticholinergic drug, should be used to reduce gastric acid secretion (See Fig 11). Anticholinergic drugs, alone, are usually not effective. Antacids also should be given to further reduce gastric acidity.

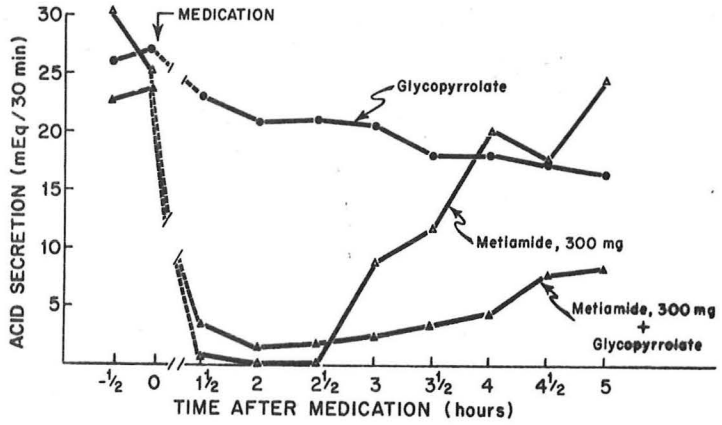



Fig. 11

Dosage. *Cimetidine*. The oral dose is 300 mg. four times daily (with meals and at bedtime). In Z-E patients, the dose may be increased to 300 mg. q 4 h while awake (2 gms. daily).

Cimetidine may also be given intravenously. The I.V. dose is the same as the oral dose.

*Anticholinergic*. An anticholinergic drug should be given with cimetidine. For example, one tablet (Probanthine, Robinul, Quarzan, etc.) should be given with each cimetidine tablet. If anticholinergic side effects develop, the dose or frequency of administration should be reduced.

*Antacid*. Antacid should be given every hour, initially. If adequate inhibition of acid secretion is achieved with cimetidine plus anticholinergic, antacids can be reserved for recurrent symptoms.

Immediate Management Summarized. Antisecretory therapy with cimetidine and anticholinergic is the treatment of choice for initial therapy. This is especially important in patients who are severely ill and in whom a total gastrectomy would be hazardous.

Long Term Management.

In designing long-term management, one must remember that the morbidity and mortality in Z-E patients are related to the pathophysiological effects of continuous excessive gastrin release and not to the invasiveness of the tumor. In spite of frequent metastases, tumor invasion is usually not responsible for death. Morbidity and death are usually associated with complications of ulcer disease.

Surgical Therapy. Soon after the first description of Z-E Syndrome, it was recognized that sub-total gastrectomy or vagotomy and drainage procedure were invariably followed by complications, recurrent surgery and in many instances death. Therefore, total gastrectomy evolved as the surgical procedure of choice.

From the standpoint of reducing morbidity and mortality, results of total gastrectomy have been reasonably good especially when compared with

lesser procedures.[59] Table 8 compares the per cent survival after total gastrectomy with the per cent survival after lesser surgical procedures.

Table 8 (from Fox, et al, Ref. 60)

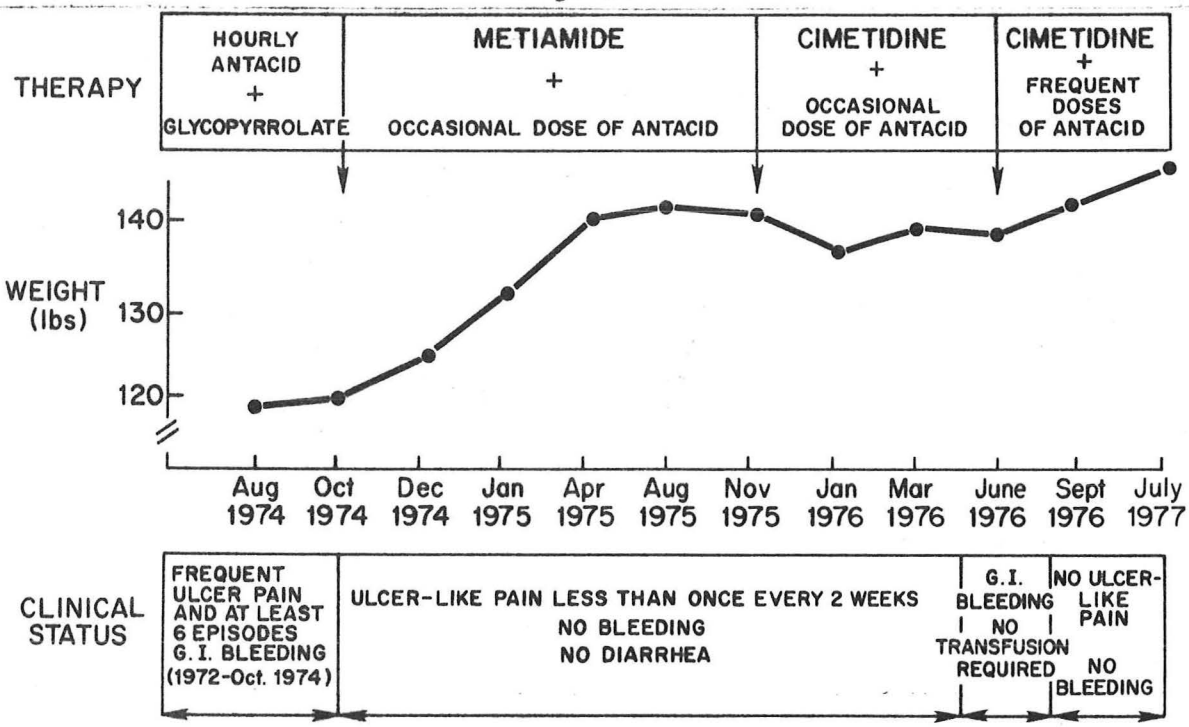
| | % Survival | | |
|---|---|---|---|
| | 1 year | 5 years | 10 years |
| Total Gastrectomy | 75% | 55% | 42% |
| Lesser Surgical Procedures | 51% | 27% | 18% |

Occasionally, an isolated gastrinoma will be found in the distal port of the pancreas or in the duodenum. When these are found, they should be removed, and a total gastrectomy should not be performed (See Medical Therapy).

In summary, there are only two types of surgical procedures that should be performed in patients with Z-E: 1) Total gastrectomy and 2) resection of an isolated pancreatic or duodenal gastrinoma without total gastrectomy.

Medical Therapy - Antisecretory. $H_2$ receptor antagonists play an important role in the short-term management of Z-E Syndrome, and their role in the long-term management is currently under investigation.[61,62] Preliminary studies are promising. Several patients have now been treated with metiamide or cimetidine for over two years, and in each case the clinical results have been excellent. We have treated two patients with $H_2$ receptor antagonists plus a anticholinergic for 33 and 28 months, respectively. The clinical course of one patient is shown in Fig. 12. Both patients continue to do extremely well.

Fig. 12




A total of 61 patients have been treated with $H_2$ receptor antagonists and 23 have been treated for longer than one year.[63] The results have been excellent.

*Treatment Regimen*. Cimetidine, 300 mg. four times daily (with meals and at bedtime). The frequency of medication may need to be increased to q. 4 h. while awake (2-2.4 gms. daily). An anticholinergic should be given with cimetidine. Antacids may be needed if symptoms develop on the above regimen.

Medical Therapy - Chemotherapy. Patients with metastatic gastrinoma have been treated with streptozotocin.[64,65] A decrease in serum gastrin concentration and reduction in tumor mass have been reported in a few patients. However, the results have not been uniformly favorable. Chemotherapy is not recommended as an alternative to surgical or antisecretory therapy although it may play an adjunctive role in tumor chemotherapy in those patients with invasive and metastatic gastrinoma.

Is long-term antisecretory therapy an alternative to total gastrectomy?

To evaluate the role of antisecretory agents in relation to total gastrectomy, several questions need to be answered.

1) *Do gastrinomas regress after total gastrectomy?* It has been postulated that removal of the target organ by total gastrectomy causes regression of tumor. In a review of 267 patients after total gastrectomy, tumor regression was documented in only four patients.[66] In three of the patients tumor reoccurred after reported regression and in the fourth patient tumor regression was not related temporarily to total gastrectomy.

   If tumor regression occurs, it is rare and should not be used as an indication for total gastrectomy.

2) *What is the chance of resecting the tumor?* As stated previously isolated tumors may occur in the tail of the pancreas or the duodenum. If they are found and there is no evidence of metastasis or secondary tumors, the isolated gastrinoma should be removed. The chance of finding an isolated tumor may be frequent enough to justify an exploratory laporatomy.

3) *What is the mortality rate with total gastrectomy?* In a review of over 800 cases of Z-E Syndrome, the overall operative mortality with total gastrectomy was approximately 20%.[67] This ranged from 5% in elective cases to 50-70% where bleeding or perforation required emergency surgery.

4) *What is the long-term morbidity associated with total gastrectomy?* Data on the long-term effects of total gastrectomy in Z-E patients are difficult to find. A number of patients develop metabolic bone disease and some develop post-gastrectomy diarrhea. On the other hand, a number of patients do well as illustrated by the first case.

Conlcusions:

1. Based on the above answers and the good results, so far, with cimetidine, antisecretory therapy is a rational alternative

to total gastrectomy. The drugs must be given in adequate doses and patients must be cooperative and willing to take medication as prescribed.

2. If diagnostic tests, i.e. liver scan and arteriography, show no evidence of metastasis or no evidence of multiple tumors, an exploratory laparotomy should be performed. If an isolated tumor is found in the pancreas or duodenum, it should be removed. If no tumor or multiple tumors are found, there are two alternatives: a) total gastrectomy or b) close the incision and treat with cimetidine and an anticholinergic.

*Relationship to MEA-I*

(See Multiple Endocrine Adenoma - Peptic Ulcer Syndrome, Medical Grand Rounds, Joseph L. Goldstein, M. D., Jan. 30, 1975) Whether every patient with Z-E Syndrome is part of Multiple Endocrine Adenomatosis (MEA) - Type I Syndrome has not been established. Because of the close embryologic origin of hormone secreting tumors, it seems likely that gastrinomas are part of MEA. However, several patients have been seen at Parkland and at the Dallas Veterans Administration Hospital who do not have evidence of other endocrine abnormalities. In addition, the family of one of these patients has been extensively studied, and so far, none of the family members have evidence of endocrine tumors. There are at least three possible explanations for why Z-E Syndrome appears to occur as an isolated finding: first, the syndrome may occur as an entity separate from MEA; second, isolated cases may represent new dominant mutations; and third, the families of isolated cases may not have been studied completely.

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