

Zollinger-Ellison Syndrome and Acid Hypersecretion

Core Curriculum Conference

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Zollinger-Ellison Syndrome

- First described by Robert Zollinger and Edwin Ellison in the Annals of Surgery, October 1955.
- Presented 2 cases with jejunal ulcers demonstrating marked gastric hypersecretion and hyperacidity.
- Refractory to surgical therapy necessitating total gastrectomy.
- In 1968, McGuigan and Trudeau showed elevated gastrin levels in patients with ZES.

Zollinger-Ellison Syndrome

- Classic Triad of ZES:
 - Severe peptic ulcer disease
 - Gastric acid hypersecretion
 - Nonbeta cell gastrin producing tumor of pancreas

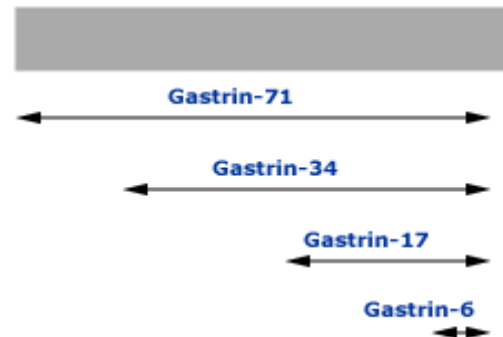
Gastrin Physiology



In the endoplasmic reticulum, the signal peptide (blue) of preprogastrin is cleaved resulting in progastrin



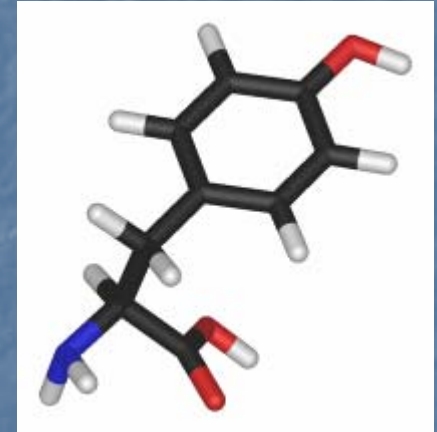
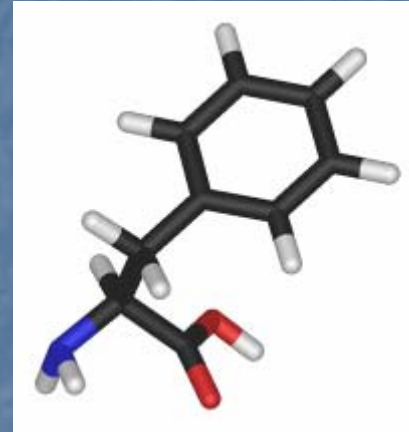
Further enzymatic modification of progastrin in the Golgi generates products that are packaged into secretory granules



Post-translational processing produces many active forms of gastrin

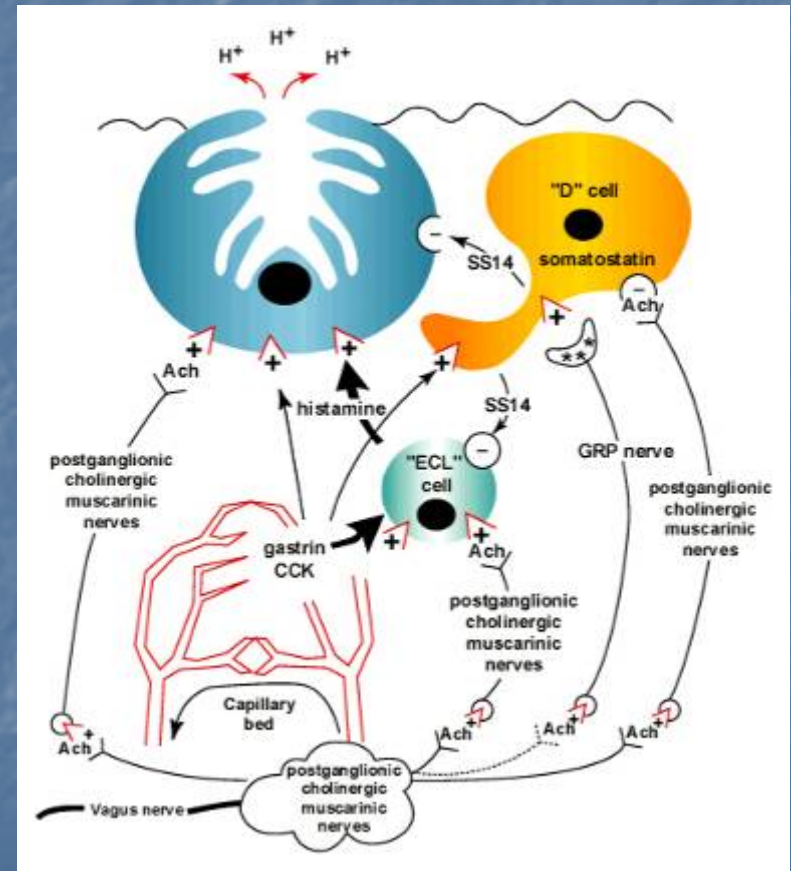
Gastrin Physiology

- Stimulants of Gastrin:
 - Luminal amino acids
 - Elevated gastric pH



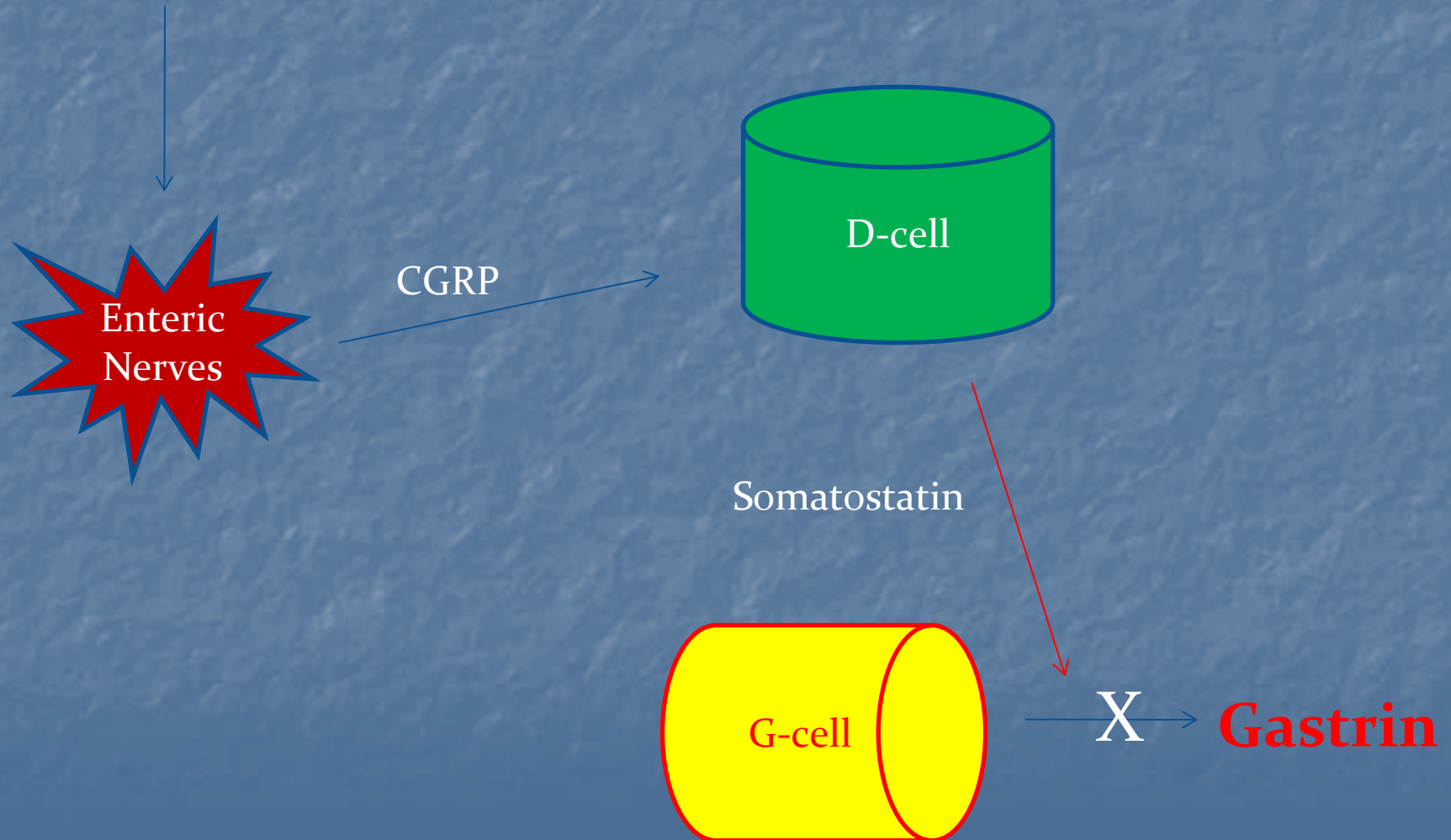
Gastrin Physiology

- Gastrin stimulates fundic enterochromaffin like (ECL) cells to secrete histamine.
- Histamine acts on parietal cells to release H^+ .



Acidic Gastric pH

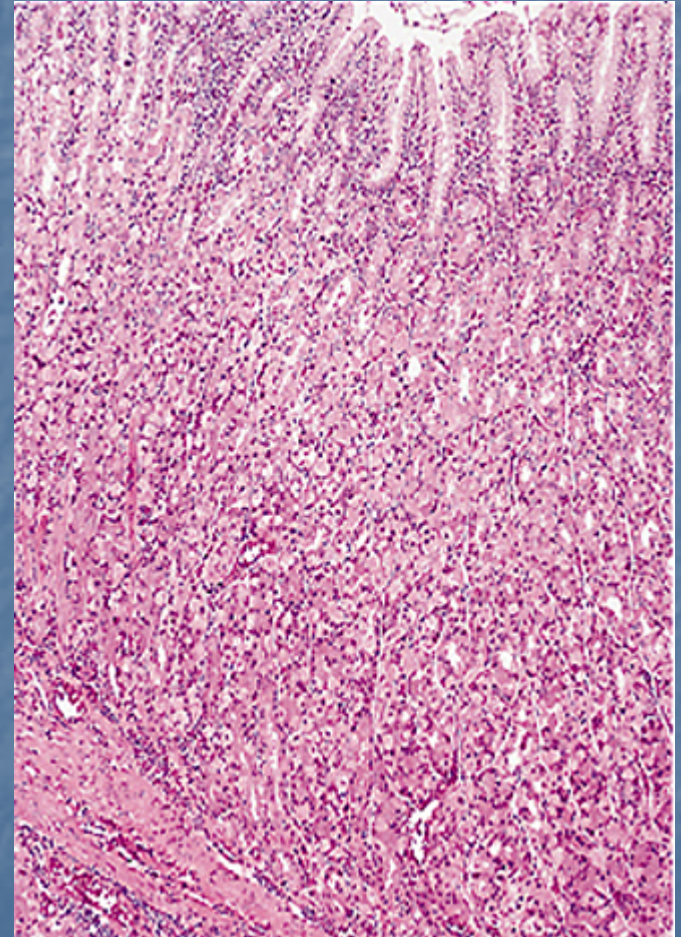
Negative Feedback to Gastrin



CGNP=Calcitonin gene-related peptide

Pathology

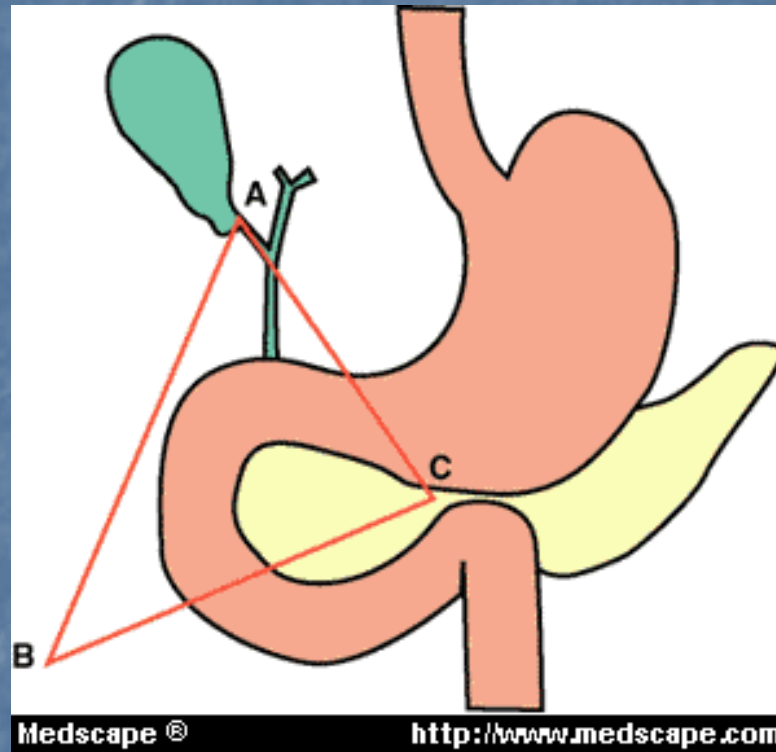
- Gastrinomas are derived from multipotential stem cells of endodermal origin.
- Like other neuroendocrine tumors, typically stain positive for chromogranins, neuron specific enolase, and synaptophysins.
- Expanded glandular compartment due to excess parietal cells



Pathology

- Most gastrinomas occur in the pancreas and duodenum in "Gastrinoma Triangle".
- Duodenum (50-70%)
 - Often multiple, < 2cm, and less malignant
 - More than 90% in 1st or 2nd portion
- Pancreas (25%)
 - Solitary, >2 cm, and more malignant
- Lymph node adjacent to the pancreas (5%)

Gastrinoma Triangle





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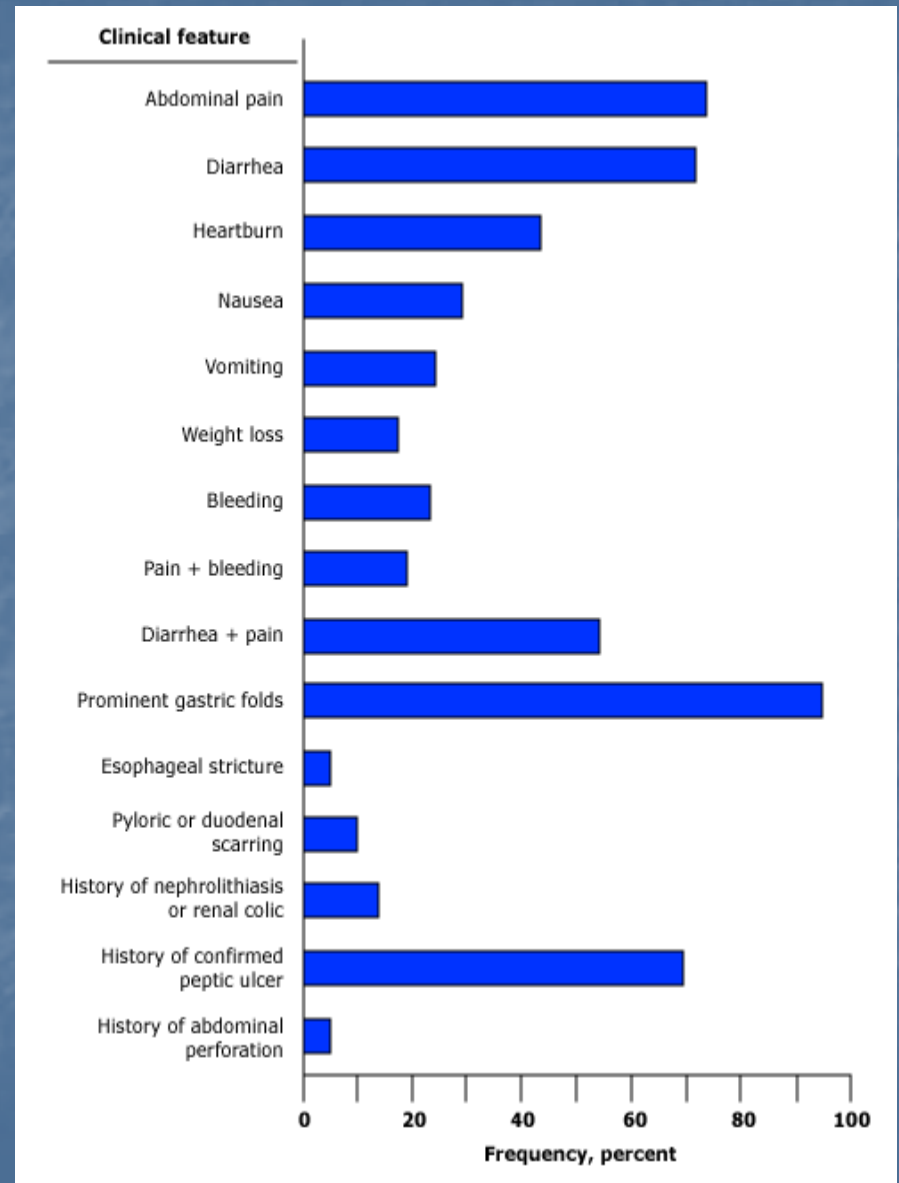
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DUDY NOBLE FIELD / POLK - DEMENT STADIUM

Epidemiology

- 0.1 to 3 patients per million
- Mean age at time of diagnosis is 41 yrs.
- 1.5:1 to 2:1 - Male:Female
- Sporadic 78%, MEN-I 22%
- *H. pylori* (+) – 10-50%
- Localized disease – 70%
- Mean delay of diagnosis – 5.2 yrs.

Presentation



Data from Roy, PK, Venzon, DJ, Shojaamenes, H, et al, Medicine (Baltimore) 2000; 79:379

Presentation

- Clinical features suspicious for ZES
 - Postbulbar duodenal ulcer
 - Multiple duodenal or jejunal ulcers
 - PUD with chronic diarrhea
 - PUD refractory to medical therapy
 - History of PUD and nephrolithiasis
 - Recurrent PUD in absence of H.pylori or NSAIDS
 - Family history of PUD and hypercalcemia

Diagnosis

- Fasting serum gastrin concentration
- Secretin stimulation test
- Gastric acid secretion studies

Fasting Serum Gastrin

- Upper limit of normal is 110 pg/ml
- Gastrin of > 1000 in setting of gastric pH of less than 5 is highly specific for ZES.
- 2/3 have gastrin levels 150-1000 pg/ml
- False positive with PPI's - must be off more than one week.
- Chronic atrophic gastritis or severe *H. pylori* can give false positive

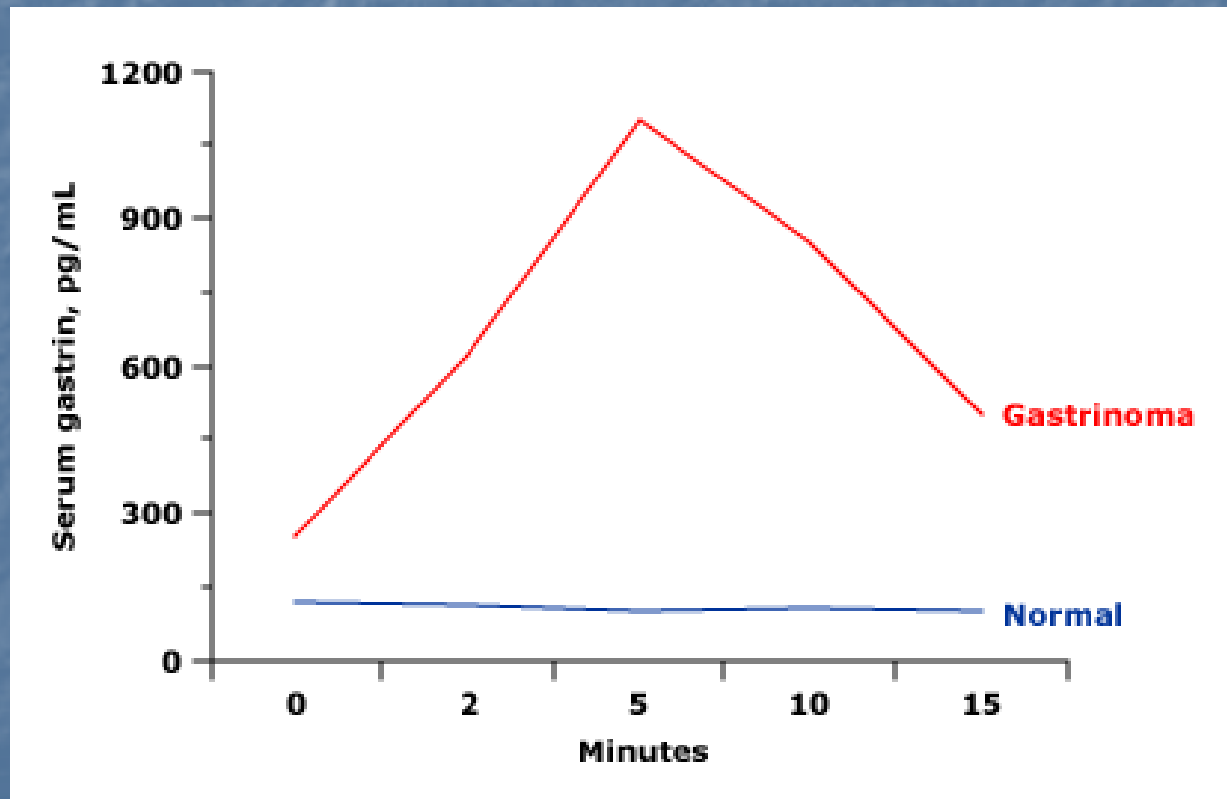
Secretin Stimulation Test

- Useful for confirmation of ZES in patients with indeterminate gastrin levels
- Secretin stimulates gastrin release from gastrinomas
- Secretin inhibits normal G-cells

Secretin Stimulation Test

- Secretin 0.4 µg/kg IV over 1 minute
- Measure baseline gastrin twice and then 2, 5, 10, 15, and 20 minutes post infusion
- Traditionally - positive if gastrin increases by 200pg/mL or more
 - Sens 83%, Spec 100%
- Using a cut off of 120pg/mL increases
 - Sens 94%, Spec 100% ⁽¹⁾
- Peak at about 5-10 minutes

Secretin Stimulation Test

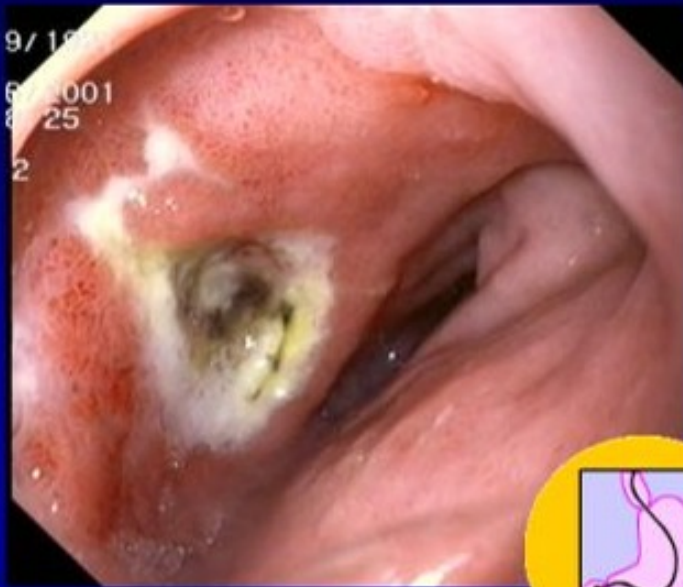


Other Tests

- Chromogranin A
 - General marker for neuroendocrine tumors
 - Level correlates with tumor volume
 - Less sensitive and specific than secretin, but can be used for confirmation

Endoscopic Findings

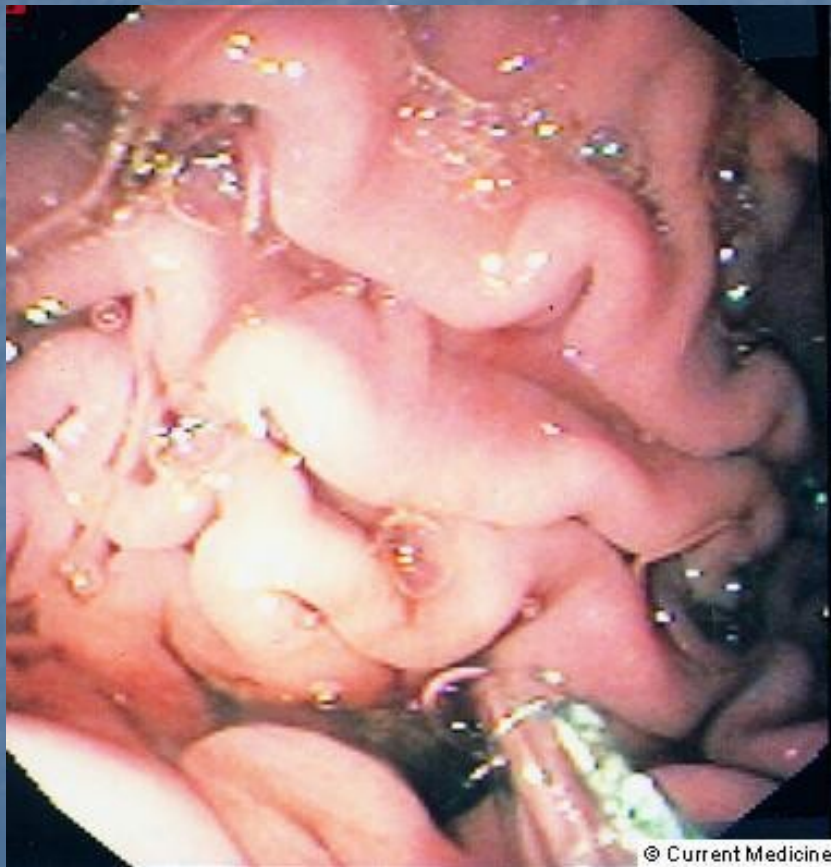
Duodenal Ulcer (DU)



Gastric Ulcer (GU)



Endoscopic Findings



© Current Medicine



Differential Diagnosis of Hypergastrinemia

- Acid-suppressive medications
- Chronic atrophic gastritis
- Diabetes mellitus
- Foregut carcinoid (histamine)
- Gastrin cell hyperplasia/hyperfunction
- Gastric outlet obstruction
- H. pylori infection
- Idiopathic
- Increased intracranial pressure
- Massive small bowel resection
- Ovarian cancer
- Pernicious Anemia
- Pheochromocytoma
- Renal insufficiency
- Retained gastric antrum
- Rheumatoid arthritis
- Systemic mastocytosis
- Vitiligo
- ZE



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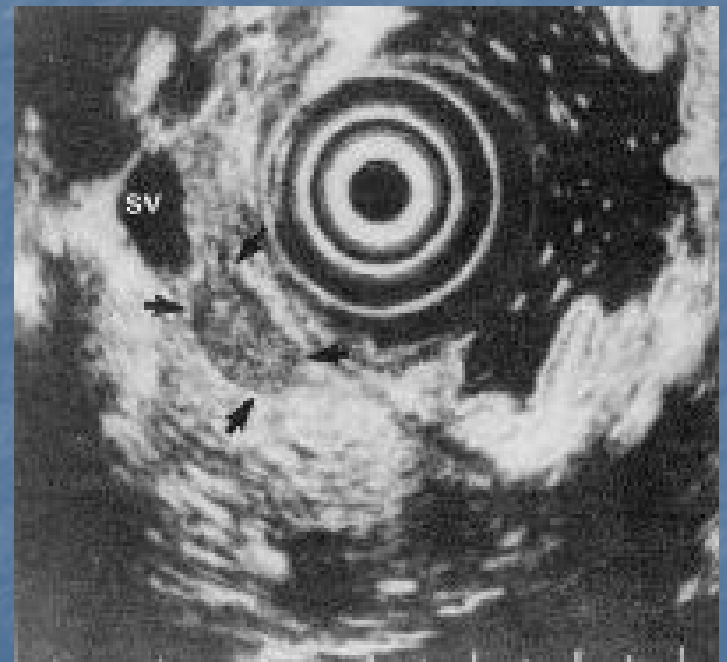
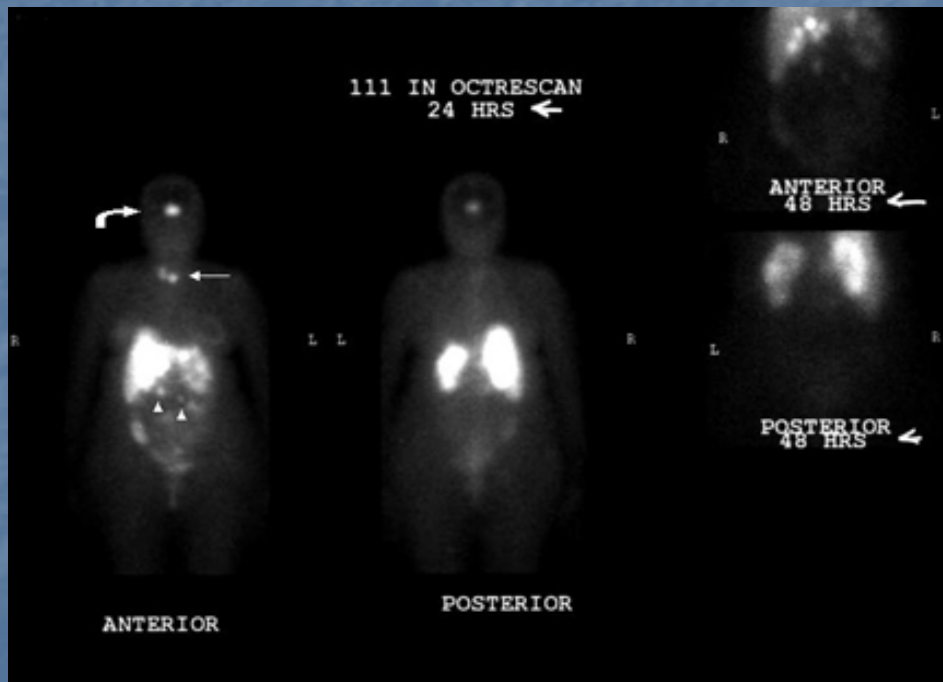
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DAVIS WADE STADIUM AT SCOTT FIELD

Tumor Localization

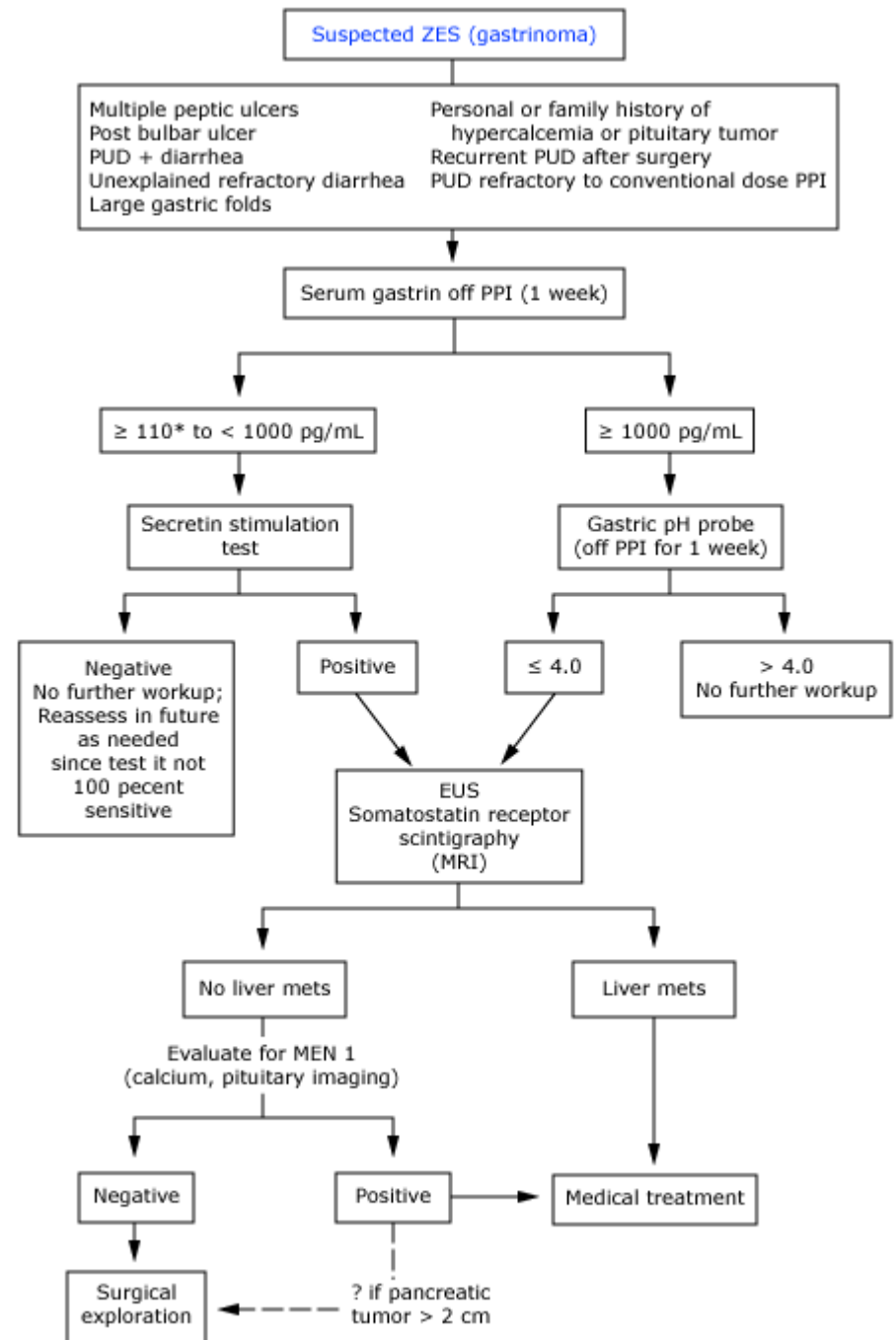
- Two main modalities are octreotide scan and EUS
- >90% of tumors are identified if both modalities are used
- Alternatives:
 - Helical CT, MRI, angiography, arterial stimulation, venous sampling, and laparotomy

Tumor Localization



Gastrinoma

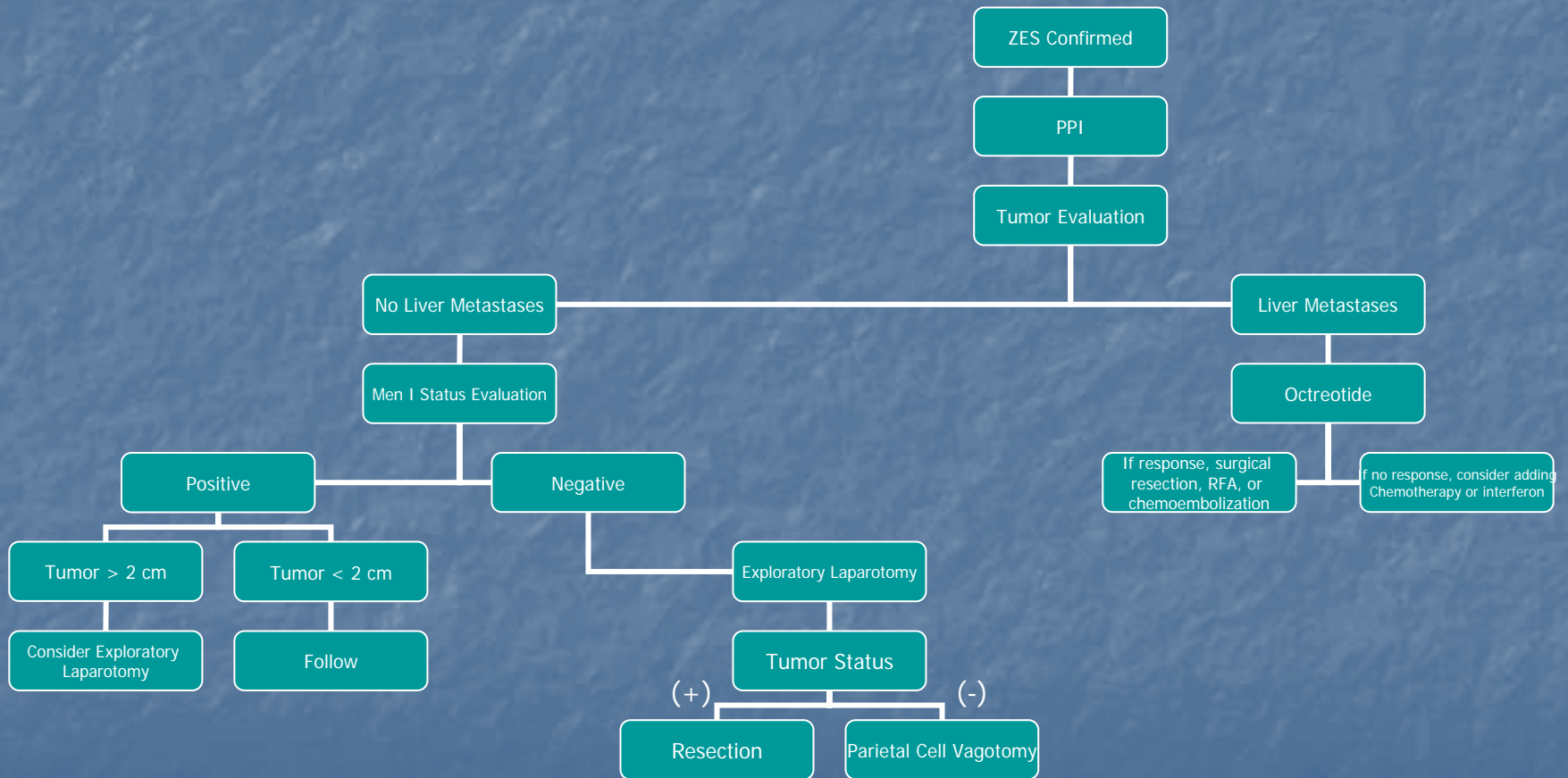
ZES Algorithm



Prognosis of ZES

- Most important factor is presence or absence of liver metastasis
 - Patients with liver metastases had a 10-year survival of only 30 percent compared to a 15-year survival of 83 percent in those without liver metastases
- Lower cure rates with MEN I
- Cushing's syndrome from ectopic ACTH release by gastrinoma associated with aggressive disease

Management



Medical Management

- Goal: Limit complications of disease
- Proton pump inhibitors
 - Omeprazole 60 mg QD – BID (or its equivalent) is sufficient in 95% of patients
 - Esomeprazole 120 mg QD-BID
 - Lansoprazole 45 mg QD-BID
 - Rabeprazole 60 mg QD-BID
 - Pantoprazole 120 mg QD-BID

Medical Management

- Histamine 2 receptor antagonists (also effective)
 - Require higher dosing
 - Cimetidine – 3.6 g/day
 - Ranitidine - 1.2 g/day
 - Famotidine – 0.25 g/day
- MEN-1 patients seem to be more resistant to medical treatment

Surgical Management

- Acid reducing surgery such as gastrectomy and vagotomy are rare since the introduction of PPI's.
- Consider curative surgery if tumor size is less than 2 cm.

Metastatic Disease

- Tumors spread to liver first, then bone (spine and sacrum)
- Treatment options
 - Octreotide can decrease fasting serum gastrin levels
 - Hepatic lobectomy in the absence of bilobar disease
 - Hepatic arterial embolization
 - Radiofrequency ablation, cyroablation
 - Liver transplant (investigational)
 - Chemotherapy – response rate 10-40%

MEN I (Wermer's Syndrome)

- Primary hyperparathyroidism
- Pituitary adenomas
- Pancreatic islet cell/gastrointestinal adenomas (ZE, insulinomas, non-functioning pancreatic tumors)

MKSAP 14

- A 33-year-old woman has a 3-week history of burning epigastric pain, nausea, intermittent vomiting of partially digested food, and early satiety. The pain improves slightly with antacids. Medical history includes a duodenal ulcer that was treated with an H₂-receptor antagonist. She is otherwise healthy and takes no medications.

MKSAP 14

- Physical examination is normal except for mid-epigastric tenderness to palpation. Upper endoscopy shows several gastric antral ulcers with some narrowing of the pyloric channel and a moderate amount of retained food. The fasting serum gastrin level is 420 pg/mL (420 ng/L).

MKSAP 14

- Which of the following is the most appropriate next step in managing this patient?
 - A. Endoscopic ultrasonography of the pancreas
 - B. Fasting serum gastrin measurement after pyloric dilation
 - C. Helical CT scan of the abdomen
 - D. Somatostatin receptor scintigraphy
 - E. Surgical exploration for a primary tumor

Questions?

