NASPGHAN Physiology Series
Gastric Secretions

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H. Pylori *(*Slides 5-8)

H. pylori, flagellated organism, colonize the gastric epithelium of 50% of the world's population. Complications of infection include gastritis, peptic ulcers, mucosa-associated lymphoid tissue lymphoma (MALT), and gastric cancer. The flagella promote motility in the mucus layer. The organism binds to antigens on gastric epithelial cells, thus preventing mechanical clearance. The organism hydrolyzes urea locally resulting in an increase in gastric pH.

Acute infections cause hypochlorhydria due to inhibition of acid secretion. There are three mechanisms involved in acid inhibition; pro-inflammatory cytokine interleukin-1β, suppression of proton pump α-subunit promoter activity and interference in trafficking via tubulovessicles.

In chronic infection the stomach may have hypochlorhydria or hyperchlorhydria depending on the severity and location of involvement. Most patients have a ~~pangastritis~~pan gastritis and produce less than normal acid. Twelve percent of infected individuals have an antral dominant infection with inflammation. In antral dominant there is increased acid secretion due to reduced amounts of Somatostatin and increased gastrin. These patients are predisposed to develop a duodenal ulcer. Organism eradication results in normalization of acid, gastrin and Somatostatin.

Transmission is by person-to-person contact. Infections are very rare in infants, even if the mother is infected. Re-infection rates are low, but recrudescence (same strain in <12 months) is common.

Diagnosis is by one of several tests. Serum *H. Pylori* IgG indicates exposure. A positive test may indicate previous or acute infection. A urea breath test may be used to identify organisms with a sensitivity and specificity of 81-100% and 80-98%. It does require

physical coordination (blowing into a balloon) and thus can't be done easily in children younger than 7-9 years old, although some centers do have the capability. The rapid urease test (RUT) requires endoscopy and biopsy. The RUT has a sensitivity and specificity of 80–95% and 90–100%. Histological examination has a sensitivity of 83–95% and a specificity of 90–100%. Stool can also be used to assess for antigens with a sensitivity of 83–95% and a specificity of 93-96%.

Treatment is with triple therapy of a proton pump inhibitor and two antibiotics. Amoxicillin and Clarithromycin are the first line antibiotics. Flagyl, tetracycline and bismuth subsalicylate can be used in case of allergy. There are increasing numbers of resistant organisms.

Gastric Histology (Slides 10-12)
Gastric epithelium consists of two main gland types, oxyntic gland (parietal cell) and pyloric gland (G cell). Oxyntic glands are present in the fundus and body (80% of stomach) and pyloric glands are located in the antrum (20% of stomach). The parietal cell is the primary cell responsible for acid secretion.

There are many cells in the stomach involved in gastric secretions
1. Parietal cells: secrete acid, intrinsic factor, and leptin
2. Enterochromaffin-like cells (ECLs): secrete histamine
3. Chief cells: secrete pepsinogen, gastric lipase, and leptin
4. D cells: secrete somatostatin (paracrine control of parietal and G cells)
5. Enterochromaffin cells: produce ghrelin, obestatin, serotonin (5HT) and atrial natriuretic peptide (ANP).
6. Mucous cells: produce mucus and bicarbonate
7. G cells: secrete gastrin

The stomach secretes: (Slide 13)

–Water

–Electrolytes

–Hydrochloric Acid

–Glycoproteins

•Mucin

•Intrinsic Factor

•Enzymes

Acid Secretion (Slides 14-15)
Gastric acid is necessary for protein digestion, absorption of Ca^+, iron, vitamin B12 and thyroxin (when taken as an oral medication). Gastric acid also plays a role in prevention of bacterial overgrowth and enteric infections. It has been proposed that gastric acid also reduces or eliminates allergenicity of foods. Excess acid results in gastric and duodenal

inflammation and possible ulceration. Control of acid secretion is accomplished by a balance of neural, hormonal and paracrine pathways. Acid secretion is initiated directly by stimuli from brain as a reflex response to distension of the stomach and intestines. Following initiation there are many feedback loops that control levels.

The parietal cell is responsible for acid secretion. In the resting state the parietal cell is filled with vesicles. During acid secretion morphological changes occur to parietal cells, including the movement of the tubovesicles to the apical membrane with formation of secretory canaliculi. Activation of the parietal cell increases cytoplasmic calcium, followed by activation of a cAMP-dependent kinase cascade resulting in movement of the proton pump to the apical surface.

The proton pump, $H^+/K^-ATPase$, actively pumps H^+ ions in exchange for K^+. Parietal cell mitochondria provide ATP for ATP hydrolysis generating the necessary energy for the membrane embedded proton pump. Cessation of acid secretion is associated with the re-internalization of the $H^+/K^-ATPase$ pumps.

The protons are released following parietal cell stimulation when water and acid enter the cell and combine under the influence of carbonic anhydrase to form carbonic acid (H_2CO_3) and subsequently HCO_3- and H^+. The free H^+ are excreted on the apical side of the cell in exchange for potassium via the proton pumps. $H^+/K^-ATPase$ continues to exchange protons for K^+ resulting in gastric acidification. Bicarbonate ions are secreted on the basal side of the parietal cell in exchange for chloride. The HCO_3- secretion results in an alkaline tide, bringing bicarbonate to the surface for secretion by gastric mucous secreting cells. Cl^- is extruded down the electrochemical gradient through channels by a cAMP pump in the apical membrane which drives the Cl^-/HCO_3- exchange.

Parietal cells secrete HCl at a concentration of 160mM or at about a pH of 0.8. The median pH of the human stomach is 1.4. Newborns have an initial gastric pH of 6.0 to 8.0 which is followed by a burst of acid secretion in the 1st or 2nd day of life.   Acid secretion drops off again and reaches adult levels by 2 years of age. The average adult secretes 2-3 liters of acid rich fluid on a daily basis.

Control of Gastric Acid Secretion (Slides 16-29)
Gastric acid secretion is controlled by a balance of neurocrine, paracrine and hormonal pathways. The enteric nervous system (ENS) is vital to control of acid secretion with cholinergic and vagal inputs. Hormones are released into blood and reach targets via the bloodstream (i.e. gastrin). Paracrine agents are released into tissue and reach targets by diffusion (i.e. histamine and somatostatin). The primary stimulant of acid secretion is histamine, which is released from ECLs and acts in a paracrine mechanism.

Neural Control (Slides 18-23)
The ENS is composed of intrinsic neurons including the myenteric plexus and the submucosal plexus and extrinsic efferent and afferent neurons. The vagus accounts for 80-90% of the afferent neurons and 10-20% of the efferent neurons. Efferent fibers

synapse with postganglionic neurons in ENS. The neurologic input is most often divided into cephalic, gastric and intestinal phases.

The cephalic phase results from unconditioned reflexes (sight, smell, taste and swallowing), conditioned reflexes (thought of food) and vagal reflexes. It is responsible for 1/3 to 1/2 of gastric acid secretion and is mediated mainly by cholinergic and vagal mechanisms.
1. Afferent from vagus nerve to brainstem (sensory information)
2. Efferent output via the vagus nerve (motor limb of vagovagal reflex)

Vagal stimulation occurs via two pathways. The first is gastrin releasing peptide (GRP), which is also known as bombesin. Gastrin-releasing peptide (GRP) is released from vagal nerves stimulating G cells to release gastrin. The second involves acetylcholine (ACh) which acts directly on parietal cells in the body and fundus via M3 muscarinic receptors, increasing gastric acid secretion. In addition to the direct parietal cell stimulation there is indirect stimulation via decreased somatostatin (SST), produced in D cells. SST inhibits acid secretion with direct action on parietal cells. Therefore, decreases in SST, stimulate acid secretion.

The vagus nerve transmits the sensory information (dilation) from the stomach and intestines to the brainstem on afferent fibers. Efferent fibers from the motor limb of the vagal reflex secrete neurocrine agents (ACh and GRP) from nerve terminals. These agents reach their target by synaptic diffusion. This explains why following vagotomy there is limited acid secretion. Stretch receptors also stimulate the release of gastrin from G cells, stimulating enterochromaffin-like cells (ECLs) to release histamine. Parietal cells are stimulated by gastrin and by histamine to release HCl.

As food remains in the stomach, the stretch receptors remain stimulated resulting in continued gastrin secretion. G cells, found deep in the antral gastric glands are innervated by vagus nerve. Acetylcholine (ACh) acts directly on cells in the fundus and body of the stomach by binding to parietal cell muscarinic M3 receptors resulting in the release of gastric acid. The stomach also contains exocrine and endocrine-like neural regulatory cells, enterochromaffin cells (ECs). EC cells contain both serotonin (5HT) and atrial natriuretic peptide (ANP). ANP helps regulate antral somatostatin secretion, but the mechanisms regulating ANP secretion are not fully understood. ACh decreases release of ANP, which decreases D cell secretion of SST resulting in increased acid secretion. 5HT mainly affects gastric emptying and motility.

As food leaves the stomach the intestinal phase begins, although it plays a much smaller role in acid secretion due to decreased vagal stimulation as the stomach decompresses. SST is released as chyme enters the small intestine, directly inhibiting parietal cells and also inhibiting release of gastrin and histamine.

Hormone and Paracrine Control – Review (Slides 24-26)

Gastrin

Gastrin is the main hormone responsible for acid secretion.   It is secreted mainly by antral G cells, but also in small amounts in the non-antral stomach, duodenum, jejunum, ileum and pancreas. It is found outside of the GI tract in the brain, adrenal glands, respiratory tract and reproductive organs, although the role in these tissues is unknown. Gastrin is released primarily in response to meals. Proteins, peptides and amino acids are responsible for gastrin release. The primary mechanism of action for acid release is the gastrin stimulated release of histamine from ECL's. The stimulation is both direct and indirect. Direct stimulation occurs by diffusion to parietal cells where it activates the H2 receptors, which generate cAMP. This is followed by translocation and activation of H^+/K^+-ATPase (proton pump). The indirect stimulation of acid secretion occurs by activating H3 receptors inhibiting somatostatin release. Gastrin activity is closely controlled by the release of gastrin-releasing peptide (stimulatory) and somatostatin (inhibitory).

Gastrin is synthesized via post-translational modification of preprogastrin with cleavage of the dibasic arginine residue by convertase. Circulating gastrin is a mixture of several peptides with 95% α-amidated. 90% of gastrin production is gastrin-17 and 10% is gastrin-34. Gastrin-17 is cleared 10 times faster. This results in serum levels of gastrin-17 and gastrin-34 being similar.

The receptor for gastrin is the CCK-2 receptor, a G-protein coupled receptor containing seven membrane-spanning segments with an affinity for both gastrin and CCK. CCK-2 receptors are located on both parietal and ECL cells. CCK-2 receptors stimulation results in the release of histamine from ECL cells.

Gastrin has trophic effects on gastric oxyntic mucosa. This occurs via several different mechanisms to include: increased fibroblast growth factor, activation of epidermal growth factor receptors and mitogen-activated protein kinase.

Histamine

Histamine is present in both mucosal mast cells and enterochromaffin-like (ECL) cells in the oxyntic mucosa close to parietal cells. It is formed by decarboxylation of L-histadine by histadine decarboxylase. Histamine reaches receptors by interstitial diffusion or capillary transport. Gastrin is the primary trigger for histamine release from ECL cells. ECL cells are also stimulated by pituitary adenylate cyclase-activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP). Histamine release is inhibited primarily by somatostatin, as well as calcitonin gene-related peptide (CGRP), peptide YY, prostaglandins and galanin.

Gastrin stimulated ECLs degranulate, releasing histamine from vesicles. Gastrin has not been shown to result in histamine release from gastric mast cells. Stimulation of acid secretion is both direct and indirect. Direct stimulation of acid secretion occurs with stimulation of parietal cell H2 receptors, generating cAMP. This is followed by translocation and activation of H^+/K^+-ATPase (proton pump). The indirect stimulation of acid secretion occurs by activating H3 receptors resulting in inhibition of Somatostatin.

Secretion of histamine is increased by gastrin, aspirin, indomethacin, dexamethasone, IL-1, VIP, ghrelin and TNF. Secretion is decreased by somatostatin and prostaglandins.

Somatostatin (Slide 26)

Somatostatin is released from D cells found throughout the gastric mucosa. Somatostatin decreases acid secretion by direct inhibition of parietal cells. It also indirectly inhibits acid secretion by decreasing histamine secretion from ECLs and decreasing gastrin secretion from G cells. Somatostatin's primary effect is on the inhibition of histamine release from ECL cells.

Somatostatin release is stimulated by gastric acid secretion and the presence of gastrin providing a vital negative feedback loop. Luminal acid activates sensory calcitonin gene-related peptide (CGRP) neurons stimulating somatostatin release via an axon reflex. Somatostatin secretion is also affected by neural inputs, with suppression from cholinergic input and stimulation by VIP. Inhibitory effects of somatostatin on gastrin secretion are mediated by somatostatin subtype 2 receptor coupled to suppression of cAMP and to induction of menin.

Decreases in luminal acid (gastric atrophy, anti-secretory medications) result in a reduction of somatostatin resulting in increased gastrin. Hypergastrinemia induces ECL and parietal cell hyperplasia. Patients on prolonged PPI will have a rebound of acid secretion due to cellular hyperplasia from PPI use. Excess acid secretion reduces in 4-6 weeks.

Other neurotransmitters (Slide 27)

Postganglionic neurons contain many neurotransmitters including; acetylcholine (ACh), gastrin-releasing peptide (GRP), vasoactive intestinal polypeptide (VIP), nitric oxide, substance P and pituitary adenylate cyclase-activating polypeptide. As previously discussed, GRP is released initially in response to cephalic phase with additional release during the gastric and intestinal phases. VIP is also released at these times and increases acid secretion by transient stimulation of ECL histamine release. The more significant contribution from VIP is sustained somatostatin release, which decreases acid secretion. Finally, pituitary adenylate cyclase-activating polypeptide (PACAP) stimulates EC cells to release atrial natriuretic peptide (ANP) which increases histamine release and therefore acid secretion.

Acetylcholine (slide 28)

Acetylcholine (ACh) stimulates gastrin secretion. ACh is released from postganglionic nerves in Meissner's plexus where it binds to the M1 receptors on ECLs, stimulating histamine release. ACh also binds to M3 muscarinic receptors on parietal cells causing an **i**ncrease in intracellular calcium, which activates proton pumps. SST secretion is inhibited by activation of M2 and M4 receptors on D cells, which ultimately increases acid secretion.

Prostaglandins (PGE$_2$) (Slide 30)

Prostaglandins (PGE) are product of macrophages and capillary endothelial cells. PGE$_2$ inhibit acid and stimulates bicarbonate secretion. Surface receptors are found of both parietal and gastric mucous cells. Prostaglandins decrease histamine release and modulate the effects of histamine and parietal cells to reduce acid secretion.

Other Regulators of acid secretion

Control of acid secretion is complex and redundant. This allows for fine control of acid secretion but also makes pharmacologic inhibition challenging.

- Dietary fat reduces acid secretion by both CCK and secretin release. Fats also reduce acid secretion via stimulation of neural pathways.

- Transforming growth factor-alpha (TGF-alpha)   TGF-alpha is an epithelial cell mitogen that inhibits gastric acid secretion and increases gastric mucin. The exact mechanism is unknown. It may play a significant role in Menetrier's disease.

- Peptide YY is released post-prandially from ileal and colonic cells and inhibits the gastric phase of acid secretion. By binding to ECL cells Peptide YY blocks gastrin stimulated histamine release.

- Enterogastrones (Slide 36-39) are factors that inhibit acid secretion following arrival of nutrients in the intestine.   They include; CCK, Secretin, Neurotensin, GLP-1, Glicentin and Oxyntomodulin

- Cholecystokinin (CCK) (Slide 37) **decreases** acid secretion by binding to CCKa receptors on gastric mucosal D cells, increasing serotonin secretion. CCK also stimulates acid secretion by binding to CCKb receptors on parietal and ECLs. The inhibition of acid secretion dominates the two functions.

- Secretin (Slide 38) **is** released from duodenal cells in response to the arrival of gastric acid, bile salts and products of fat and protein digestion in the small

intestine lumen. Secretin decreases acid secretion by inhibiting gastrin release. It also stimulates pancreatic exocrine secretion of water and bicarbonate.

- Neurotensin is released by cells in the ileum and nerves in the myenteric plexus in response to intraluminal fat and plays a role in pancreatic secretions as well as blocking acid secretion. The mechanisms are not well understood.
- GLP-1, glicentin and oxyntomodulin are co-localized in L cells, which are present in increasing density in the small intestine. All three are released when lipids and carbohydrates are present in the lumen. Oxyntomodulin stimulates acid secretion from oxyntic glands, stimulates glucose uptake, regulates insulin secretion and decreases gastric emptying. More recent studies show it plays a large role in satiety. Glicentin's role in acid secretion is unknown at this time. GLP-1 stimulates somatostatin, but the larger role is in insulin regulation. Excess secretion of GLP-1 contributes to hypoglycemia in patients with accelerated gastric emptying.

Ghrelin (Slide 32)

Ghrelin is a motilin related peptide found in gastric mucosal endocrine cells. Secretion is increased with fasting and inhibited by eating. Ghrelin stimulates gastric motility, gastric emptying and gastric acid secretion. Increases in acid secretion are via vagal pathways resulting in increased histamine release. In addition, ghrelin stimulates growth hormone and insulin secretion.

Ghrelin is a natural ligand for the growth hormone secretagogue receptor located in the oxyntic mucosa. Small amounts are present in the antrum, small intestine and colon. Levels increase before meals and decrease after meals. It is thought that Ghrelin triggers pre-meal hunger and promotes eating.

Clinical correlations

- Ghrelin is suppressed following Roux-en-Y gastric bypass, decreasing hunger, leading to weight loss.

- Inhibited by both somatostatin and *H. pylori*. The precise mechanisms of action are unclear.

Leptin

Leptin is a hormone present in fundic glands and produced by adipose tissue. Leptin is an inhibitory granule of endocrine-type cells. It is mobilized following food ingestion after a fasting. It plays a role in satiety.

Orexin (Slide 33)

Orexin is present in the hypothalamus and gastric antrum along with its receptor. It functions by binding and activating two G protein-coupled receptors resulting in increased food intake. Orexin also stimulates gastric acid secretion.

Adrenomedullin (Slide 35)

Andrenomedullin, originally identified in pheochromocytoma tissue, is localized in ECLs of the gastric fundus. It stimulates gastric somatostatin release via a neural pathway decreasing levels of histamine and subsequently gastric acid secretion.

Clinical correlation

- Shown to be increased following mucosal injury.

- Proposed to play a role in mucosal defense and epithelial healing.

Acid Blockade (Slides 41-42)

Histamine-2 receptor antagonists (H2RAs) and **proton pump inhibitors** (PPIs) suppress gastric acid secretion via different actions on the parietal cell.

H2RAs inhibit the binding of histamine to specific (histamine-2) receptors on the basolateral surface. Activation of these receptors by histamine stimulates the parietal cell to secrete acid. Blockage of H2 receptors does not stop acid secretion, which can also be stimulated by ACh and Gastrin pathways.

Proton pump inhibitors (PPIs) cross the membrane of parietal cells and accumulate in the secretory canaliculus, where they bind to and inhibit active proton pumps. Inactivation of the proton pump also blocks the effects of histamine and other stimuli.

Clinical Correlation

- Tachyphylaxis is a problem with histamine blockers. H2RA tolerance may begin as early as 7 days following start of therapy. No tolerance has been identified in PPI therapy.

- Acid rebound after acid blockade can be clinically significant. Reduced somatostatin levels increase the number of parietal cells resulting in increased gastrin levels. Elevated gastrin induces ECL and parietal cell hyperplasia. Acid secretion is also amplified due to up regulation of histamine-independent stimulatory mechanisms mediated by vagal/cholinergic pathways.

- Rebound acid secretion is seen with both H2RA and PPI's. Rebound can occur following one month of therapy. Rebound acid can provoke symptoms. Symptoms can be seen 2-4 days after stopping therapy and typically stop after 4-6 weeks. Rebound acid secretion is more common in patients without *H. Pylori* infection.

- A double blind placebo controlled study with healthy volunteers found that 40% of subjects treated with PPI for 8 weeks had dyspepsia in the 4 weeks after cessation of therapy. Only 15% of placebo group experienced dyspepsia.

Measurement of acid secretion (Slide 45)

There is no practical or easy evaluation of gastric secretion. Currently there are four primary ways to evaluate stomach secretions.

1. Nasogastric tube placement with sampling of gastric fluid. This is the gold standard for evaluation of gastric secretions, however it is a complex and invasive.
2. A SmartPill records luminal pH, temperature and pressure during gastrointestinal transit. The technology allows for assessment pH levels in the stomach and intestine.
3. pH and pH Impedance have been used to assess gastric secretions.
4. A novel ^{13}C-labeled calcium carbonate breath test provides a potential noninvasive measurement of stimulated gastric acid secretion. Ingested calcium carbonate is converted to calcium chloride, CO2, and water by HCl. The CO2 is rapidly absorbed by the gastric mucosa and delivered through the bloodstream to the lungs where it is excreted in the breath. Measurement of excess ^{13}CO2 in the breath enables the amount of acid that has been secreted by the stomach to be calculated.

Other Gastric Secretions (Slides 49-53)

The stomach also secretes water and glycoproteins including mucin, intrinsic factor and enzymes.

1. Mucus
   a. Highly hydrated gel (95% H_2O, 5% mucin and electrolytes)
   b. Mucus cells on luminal surface and down into the glands
   c. Protects epithelium
   d. Prostaglandins and secretin stimulate secretion of bicarbonate into mucus

2. Gastric Lipase
   a. Initiates digestion of fats
      i. Hydrolyzes 20% of triglycerides
      ii. Resistant to acid
   b. Secreted by chief cells in the fundus
   c. Detectable by 10 weeks gestation

3. Pepsinogen
   a. Digestive enzyme secreted by gastric chief cells and mucus neck cells. Pepsinogen secreting chief cells are present in oxyntic mucosa
   b. Proenzyme converted by gastric acid to pepsin
   c. Necessary for protein digestion
   d. Stimulated by cephalic vagal input
   e. Secretion enhanced by ACh , CCK and gastrin
   f. Decreased secretion associated with anticholinergics, H_2 antagonists, and vagotomy

g. Present by 32-36 gestation
h. Increased levels of pepsinogen are associated with duodenal ulcers and gastrinomas. Atrophic gastritis associated with low levels.

4. Pepsin
   a. Enzyme product of pepsinogen
   b. Digestive enzyme necessary for protein digestion
   c. Mucolytic
   d. Ulcerogenic
   e. Pepsin can auto catalyze transition of additional pepsinogen to pepsin
   f. Inactivated by acidic environment (pH >4)

5. Intrinsic Factor (IF) (Slide 50)
   a. Meat, liver, fish, eggs and milk are high in Vitamin B12
   b. 1-5µg B_{12} absorbed daily (3-30µg in diet)
   c. Parietal cells (body and fundus) secrete
   d. Necessary for Vitamin B_{12} absorption
      i. Gastric pepsin and acid result in dietary B12 being released from peptide and protein complexes. It then attaches to IF and a second B12 binding protein, R-binder.
   e. Intrinsic Factor –Vitamin B_{12} complex
      i. Binds to Cubilin receptor in the ileal mucosa
      ii. Absorbed by endocytosis
      iii. In enterocytes,
         1. Cyanacobalamin transferred from IF to transcobalamin II
         2. Transports cyanacobalamin to plasma
         3. Cobalamin converted to active forms
            a. Methylcobalamin and 5-deoxyadenyosyl cobalamin

Clinical Correlation
- Autosomal recessive mutation of the cubulin receptor, Imerslund-Graesbeck syndrome, results in IF-Vitamin B_{12} malabsorption and megaloblastic anemia. Vitamin B_{12} deficiency can be caused by ileal resection, IF deficiency, bacterial overgrowth, pancreatic insufficiency or small intestinal disease resulting in megaloblastic anemia. Patients with hypochlorhydria due to acid blocking medications typically have enough IF to prevent Vitamin B_{12} deficiency.

Atrophic Gastritis (Slides 54-56)

Atrophic gastritis is a histologic diagnosis characterized by chronic inflammation, decreased glands and intestinal metaplasia. Typically limited to corpus-fundus mucosa and characterized by marked diffuse atrophy of parietal and chief cells. It can occur due to autoimmunity or chronic infection, such as *H. pylori*. Autoimmune gastritis is present

in 2% of the general population and 10% of patients with type I diabetes. Autoimmune atrophic gastritis is the most common cause of pernicious anemia in temperate climates. There is an associated 2.9 times increased risk of gastric adenocarcinoma. It is more frequent in individuals of northern European and African American descent.

Autoimmune gastritis is associated with serum anti-parietal and anti-intrinsic factor antibodies that result in deficiency of intrinsic factor (IF) and decreased availability of cobalamin (vitamin B-12). Pernicious anemia occurs due to low vitamin B-12. Cobalamin deficiency affects the hematological, GI, and neurologic systems.

- Constitutional:
    - Pale
    - Tachycardia
    - Slightly icteric skin and eyes.
- Hematologic manifestations:
    - Megaloblastic anemia
- GI manifestations:
    - Sore tongue.
    - Anorexia with weight loss
    - Diarrhea due to malabsorption associated with epithelium changes in the small intestine.
- Neurologic manifestations: These result from demyelination, followed by axonal degeneration and neuronal death.
    - Numbness and paresthesias
    - Weakness
    - Ataxia.
    - Mental function

Diagnosis is by histology from multiple gastric sites. Support for the diagnosis provided by presence of anti-parietal and anti-IF antibodies in the serum. Vitamin B-12 levels are low (< 100 pg/mL). Gastrin levels elevated due to achlorhydria. In addition, serum pepsinogen I levels are decreased and the ratio of pepsinogen I to pepsinogen II (< 20 ng/mL) has a sensitivity of approximately 96.2% and a specificity of 97% for detection of fundus atrophy.

Treatment is removal of organisms, *H. pylori*, if present. If atrophy is from autoimmunity, supplementation with vitamin B-12 is the therapy of choice at present.

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Board Review Questions:

1. A 17 yo Mexican immigrant child has worsening abdominal pain over several months and develops black, tarry stools. She is seen and evaluated in the emergency department. A smart GI fellow is concerned about an acute *H. Pylori* infection. What is the most cost-effective test to confirm the diagnosis?
   a. Upper Endoscopy with Biopsy for Histology
   b. Upper Endoscopy with Biopsy for rapid urease test
   c. Serum H. Pylori IgG
   d. Stool H Pylori antigen
   e. Urea Breath test

2. A patient has been taking a PPI for years and would like to stop therapy due to cost. You recommend they slowly wean off therapy to minimize what problem?
   a. Elevated serum histamine
   b. Acid hyper-secretion
   c. Development of gastritis
   d. Low serum gastrin
   e. Hypoglycemia

3. What substance is most important to acid release?
   a. Histamine
   b. Gastrin
   c. Somatostatin
   d. CCK

Answers:
1. D. Stool antigen is the most cost effective test for diagnosis, but does not have the highest sensitivity or specificity of all the tests.

2. B. Prolonged PPI use places patient at risk for acid hyper-secretion.

3. A. Histamine is required for acid secretion and thus is the most important. Gastrin and Somatostatin both affect histamine levels, but are not directly responsible for acid release.