INORGANIC PHRMACEUTICAL CHEMISTRY

GASTROINTESTINAL AGENTS

The stomach secretes:

-Hydrochloric acid(HCL)

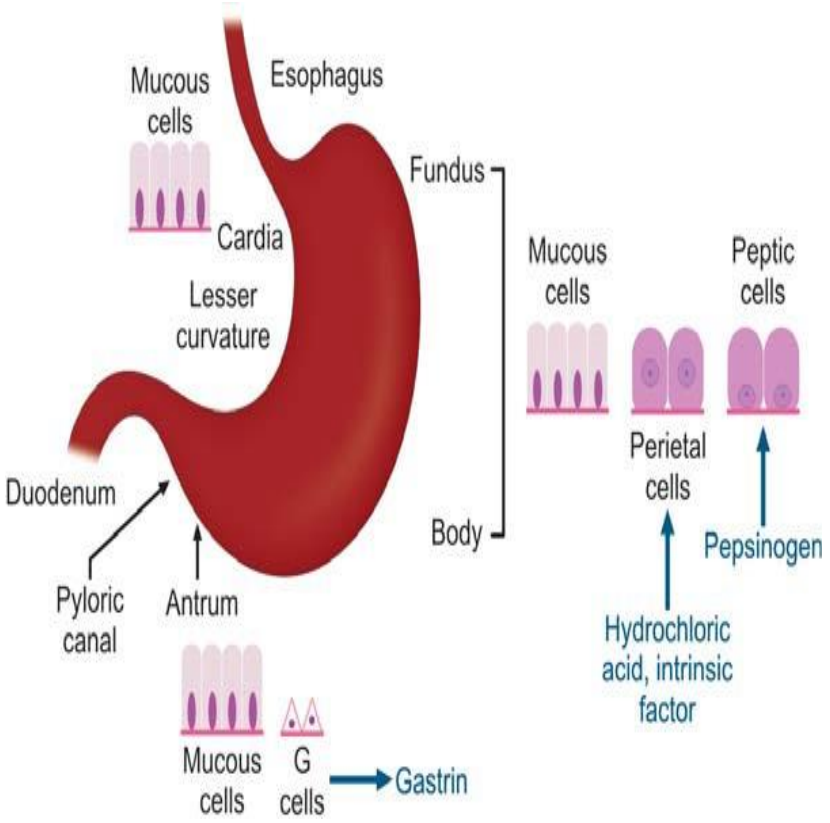
-Bicarbonate

-Pepsinogen

-Intrinsic factors

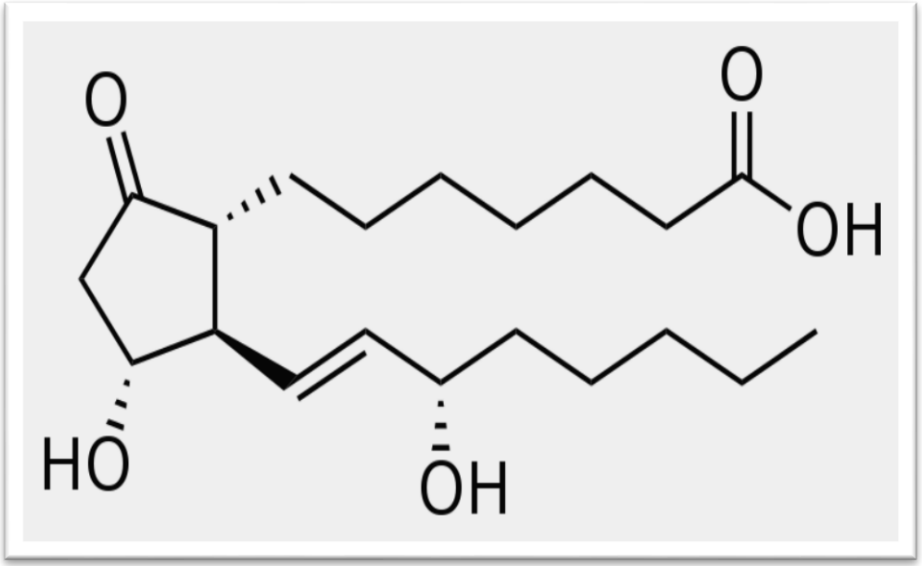
-Mucus

-Prostaglandins



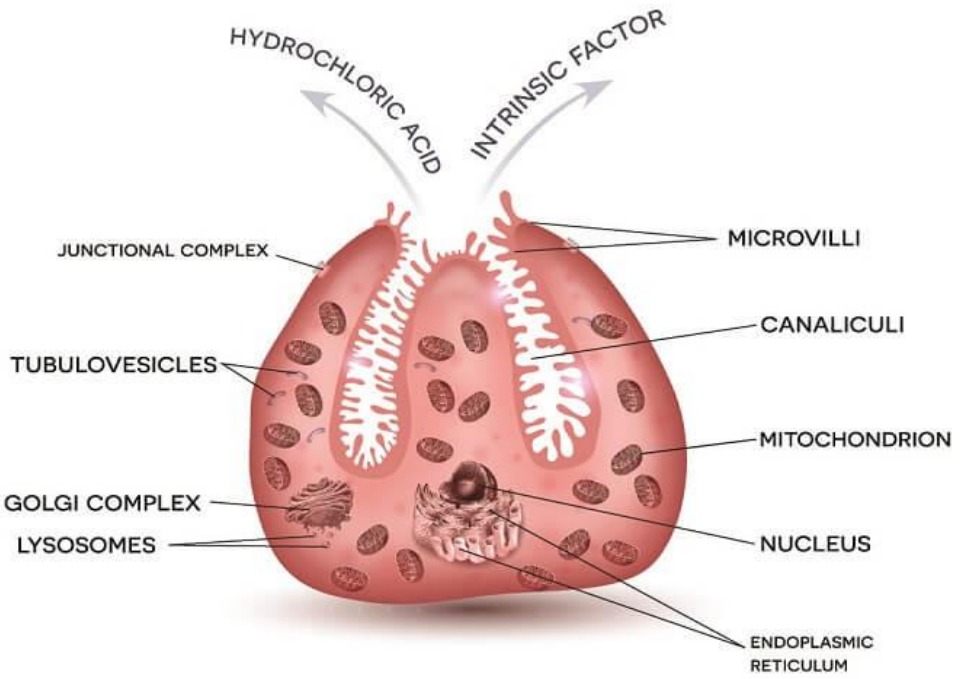
prostaglandins

The prostaglandins are a lipid compounds having hormone-like effects formed by **the gastric mucosa**. Prostaglandins have been shown to protect against gastric and duodenal mucosal damage in animals and humans.



Intrinsic factor (IF), **cobalamin binding intrinsic factor**, also known as gastric intrinsic factor (GIF), is a glycoprotein produced by the parietal cells (in humans) of the stomach. It is necessary for the absorption of vitamin $B_{12.}$

parietal cell



Cells in the Gastric Gland

Parietal Cells

Produce and secrete HCl

Primary site of action for many acid controller drugs.

Chief cells (peptic cells)

Secrete pepsinogen, a pro enzyme

Pepsinogen becomes pepsin when activated by exposure to acid

Pepsin breaks down proteins (proteolytic)

Mucoid cells

Mucus-secreting cells (surface epithelial cells), secrete mucus and bicarbonate, This mucus-bicarbonate barrier is an important first line of defence against damage by gastric acid and pepsin

Hydrochloric Acid

- Secreted by the parietal cells when stimulated by food
- Maintains stomach at pH of 1 to 4
- **Secretion also stimulated by:**

✓ Large fatty meals
✓ Excessive amounts of alcohol
✓ Emotional stress

Acid Related Disease

ACHLORHYDRIA

is the medical term for a lack of stomach acid (hydrochloric acid) due to the failure of the parietal cells to produce gastric acid. Patient with achlorhydia suffering from epigastric pain, frequent bowel movement and diarrhea

Causes

1-**Gastric atrophy**

This is a result of chronic inflammation of the gastric mucosa and there is a loss of glandular gastric cells.

2-Chronic gastritis

usually due to ***Helicobacter Pylori*** (*H. pylori*) infection.

3-Autoimmune gastritis

as a result of antibodies against the parietal cells which seen in pernicious anemia.

4-Drugs

Long term use or excessive use of the following drugs may result in iatrogenic achlorhydria.

1-Proton Pump Inhibitors (PPI's)

These drugs work by inhibiting the **H+/K+ ATPase enzyme** pump which is responsible for transporting hydrogen and the subsequent production of HCl.

2-Histamine H2-Receptor Antagonist

Also known as H2 blockers, decrease gastric acid secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells, thereby inhibiting the binding and activity of the endogenous ligand histamine.

5-Tumors

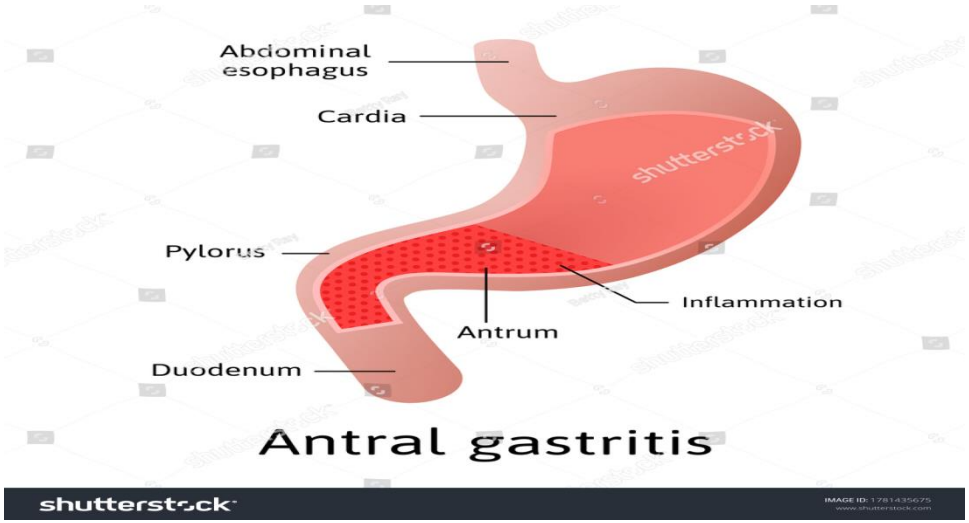
Gastric cancer

Tumors that affect the fundus of the stomach are more likely to result in achlorhydria as it destroys the parietal cells which are responsible for the secretion of HCl.

6-Surgery

Gastric resection for the treatment of certain stomach conditions like antroctomy or certain types of weight loss surgery

Achlorhydria treated by use 0.1 N HCL



HYPERACIDITY (OVERPRODUCTION OF HCL)

Caused by

-imbalance of the three cells of the gastric gland and their secretions.

-H. pylori

-Bacterium found in GIT

Symptoms of hyperacidity are:

- Burning sensation in the chest (heartburn), usually after eating, which might be worse at night or while lying down.
- Regurgitation of food or sour liquid.
- Upper abdominal or chest pain.
- Trouble swallowing (dysphagia).
- Sensation of a lump in the throat

Gastric mucosal defense mechanisms

Secretion of :

1-**M**ucus: protective barrier against HCL

2-**B**icarbonate: helps buffer acidic properties of HCL

3-**P**rostaglandins:prevent activation of proton pump which result in decrease HCL production

Types of Acid-Controlling Agents

1-Antacids 2-H2 antagonists 3-Proton pump inhibitors

Antacids: Mechanism of Action

-Antacids **DO** neutralize the acid once it's in the stomach

-Antacids **DO NOT** prevent the over-production of acid and not cause systemic alkalosis

-Reduction of pain associated with acid-related disorders

-Raising gastric pH from 1.3 to 1.6 neutralizes 50% of the gastric acid

-Raising gastric pH (1.3 to 2.3) neutralizes 90% of the gastric acid

Generally ideal antacid buffer in the pH range 4- 6

Used alone or in combination

Antacids: Aluminum Salts

- Have constipating effects
- Often used with magnesium to counteract constipation
- Delay onset, but long duration of action
- Contraindication for patient with hypophosphatemia

Examples : Aluminum carbonate, Hydroxide salt combination products (aluminum and magnesium): **Gaviscon, Maalox.**

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O$$

Antacids: Magnesium Salts

Forms: carbonate, hydroxide, oxide, trisilicate

-In addition to the GI irritation magnesium salts cause watery **d**iarrhea, usually used with other agents to counteract this effect

-Contraindicated with **R**enal failure because the patients cannot excrete extra magnesium leading to **H**ypermagnesemia

-Delay onset but long duration of action

-Combination products such as Maalox, Gaviscon (aluminum and magnesium).

$$Mg(OH)_2 + 2HCl \rightarrow MgCl_2 + 2H_2O$$

Antacids: Calcium Salts

-Forms many, but carbonate is most common.

-May cause constipation, kidney stones and renal failure in addition to the hyperphosphatemia

-Delay onset, but long duration of action

Example: calcium carbonate

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2CO_3$$

$$H_2CO_3 \rightarrow H_2O + CO_2$$

Milk-alkali syndrome: is a condition in which there is a high level of calcium in the body as a result, there can be a loss of kidney function.

Burnett syndrome is occur due to prolong used of calcium containing antacid.

Antacids: Sodium Bicarbonate

-Highly soluble

-Buffers the acidic properties of HCl

-Quick onset, but short duration

-May cause metabolic alkalosis

-Sodium content may cause problems in patients with HF, hypertension, or renal insufficiency (fluid retention)

$$NaHCO_3 + 1HCl \rightarrow NaCl + H_2CO_3$$

The ideal neutralizing capacity of an antacid should be at least 5 meq. of HCL per dosage unit

Antacids and Antiflatulents

Antiflatulents: used to relieve the painful symptoms associated with gas, several agents are used to bind or alter intestinal gas by reducing the surface tension of bubbles in the stomach and are often added to antacid combination products.

Examples

Activated charcoal and simethicone

Alter elasticity of mucous-coated bubbles causing them break

Antacids side effect:

1- Aluminum and calcium = Constipation

2-Magnisum = diarrhea

3-Calcium carbonate produces gas and belching; often combined with simethicone

Antacids contraindictions

1-Fluid imbalances 2- Heart Failure 3-Renal disease
4-GI obstruction 5-Pregnancy 6-Allergy

-Patients with HF or hypertension should use low-sodium antacids.

-Use with caution with other medications due to the many drug interactions.

-Most medications should be given 1 to 2 hours after giving an antacid.

-Antacids may cause premature dissolving of enteric-coated medications, resulting in stomach upset.

-Be sure that chewable tablets are chewed thoroughly, and liquid forms are shaken well before giving.

-Caffeine, alcohol, harsh spices, and black pepper may aggravate the underlying GI condition.

Antacid: Drug interactions

-Adsorption of other drugs reduces the ability of these drugs to be absorbed into the body

- Chelation

Chemical binding or inactivation of another drug produces insoluble complexes, result in reduce drug absorption

Antidiarrheals

Diarrhea: abnormal frequent passage of loose stool or abnormal passage of stools with increased frequency, fluidity, or increased stool water excretion

Antidiarrheal drugs act as adsorbents:

-Coat the walls of GIT

-Bind to the causative agents(bacteria or toxins) and eliminated them with stool *examples:* **B**isumth subsalicylate, **K**aolin-pectin, **A**ctivated charcoal(**Kaopectate**)

Side Effects

-Increased bleeding time

-Constipation, dark stools

-Confusion, twitching

Hearing loss, tinnitus, metallic taste

Interactions

Adsorbents decrease the absorption of many drugs including digoxin, clindamycin, quinidine, and hypoglycemic agents

Adsorbents cause increased bleeding time when given with anticoagulants.

Types of diarrhea

1-Acute diarrhea

Sudden onset in a previously healthy person lasts from 3 days to

2 weeks, self-limiting

2-Chronic diarrhea

Lasts for more than 3 weeks

Associated with recurring passage of diarrheal stools, fever, loss of appetite, nausea, vomiting, weight loss, and chronic weakness

Causes of Diarrhea:

Acute Diarrhea	Chronic Diarrhea
Bacterial	Tumors
Viral	Diabetes
Protozoal	Addison's disease
Drug induced	Hyperthyroidism
Nutritional	Irritable bowel syndrome

Laxatives(Cathartics)

Constipation

Abnormally infrequent and difficult passage of feces through the lower GI tract due to the disorder of movement in the colon and/or rectum

It is not a disease can be caused by a variety of diseases or drugs

Laxatives act by:

1-Bulk forming

-Absorbs water to increase bulk

-Distends bowel to initiate reflex bowel activity

Examples:

psyllium (Metamucil)

methylcellulose (Citrucel)

Polycarbophil (FiberCon)

2-Emollient

Stool softeners and lubricants Promote more water and fat in the stools(docusate salts)

Lubricate fecal material and intestinal walls (mineral oil)

3-Hyperosmotic

Increase fecal water content

Bowel distention, increased peristalsis and evacuation, examples:

Polyethylene glycol

Sorbitol(increases fluid movement into intestine)

Glycerin

Lactulose

4-Saline

Increase osmotic pressure within the intestinal tract causing more water to enter the intestines

bowel distention, increased peristalsis, and evacuation, should not be given to patient with low sodium diet.

Examples:

magnesium sulfate

magnesium hydroxide

magnesium citrate

sodium phosphate

5-Stimulant

Increases peristalsis via intestinal nerve stimulation leading to local irritation of intestinal tract.

Examples:

castor oil

senna

cascara

Indications for each type of laxatives

✓ **Bulk forming**

Acute and chronic constipation and Irritable bowel syndrome

✓ **Emollient**

Softening of fecal impaction; facilitation of BMs in anorectal conditions

✓ **Hyperosmotics**

Chronic constipation

Diagnostic and surgical preps

Indications for each type of laxatives

✓**Saline**

Removal of helminths and parasites

Diagnostic and surgical preps

✓**Stimulant**

Acute constipation

Diagnostic and surgical bowel preps

Side Effects of each type of laxatives:

✓ **Bulk forming**

Impaction

Fluid overload

✓ **Emollient**

Skin rashes

Decreased absorption of vitamins

✓ **Hyperosmotic**

Abdominal bloating

Rectal irritation

Side Effects of each type of laxatives:

✓ **Saline**

Excessive loss of body fluid in form of watery stools
Magnesium toxicity (with renal insufficiency)
Cramping
Diarrhea
Increased thirst

✓ **Stimulant**

Nutrient malabsorption
Skin rashes
Gastric irritation
Rectal irritation

All laxatives can cause electrolyte imbalances