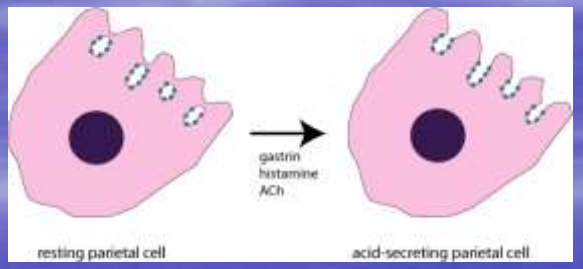
Drugs Used in the Treatment of Gastrointestinal Diseases.

Manar Zraikat

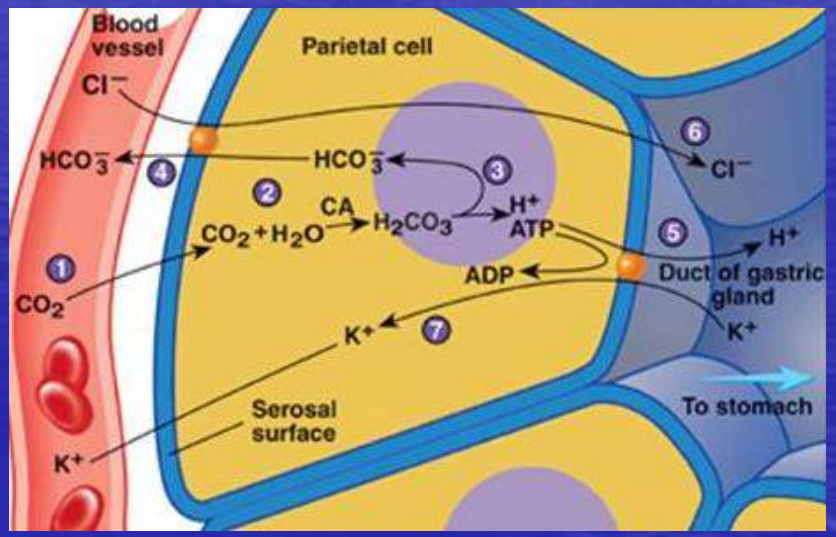
Physiology of gastric Secretion



Parietal cells secrete **2** liters of acid/ day.
Optimal pH (between **1.8-3.5**) for the function of the digestive enzyme pepsin.

Stimulation of acid secretion involves **translocation** of **H+/K+-ATPase** to the apical membrane of **parietal cell.**

H+/K+-ATPase (**proton pump**) uses the energy derived from ATP hydrolysis to pump H+ into the lumen in exchange for potassium ions.
Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi.



Stimulants of acid secretion:

1-**Ach** from **enteric neurons**.

2-Histamine from **ECL** (**enterochromaffin - like**) **cells**.

3-Gastrin released by **G cells.**

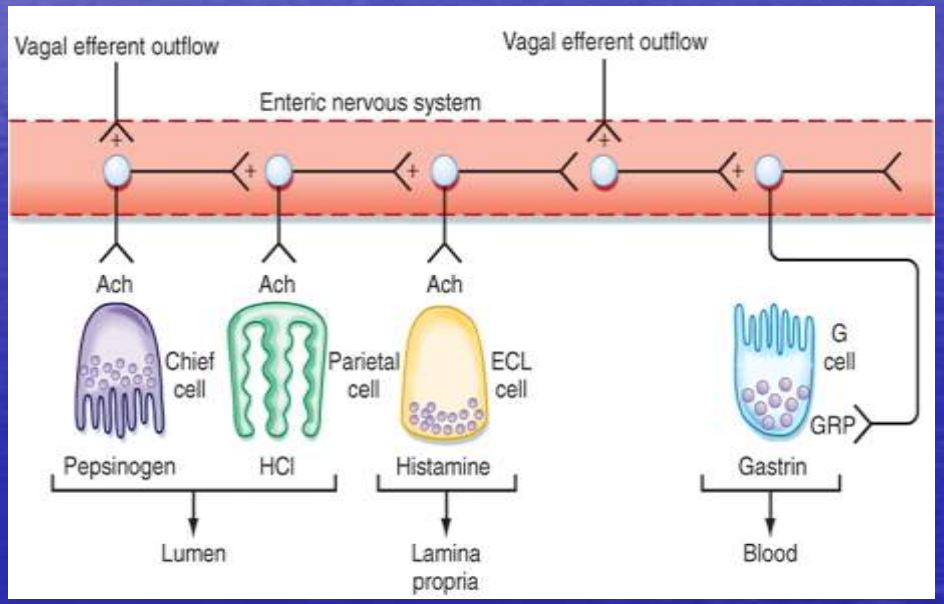
Somatostatin in **D cells inhibits acid secretion.**

Gastric pH < 3 --> gastric D cells release somatostatin

It inhibits acid secretion by:

1-direct effects on parietal cells.

2- inhibiting release of histamine & gastrin.



Gastrin releasing peptide (**GRP**)

Three phases in gastric acid secretion.

Cephalic Phase:

sight, smell, taste or thought of food,

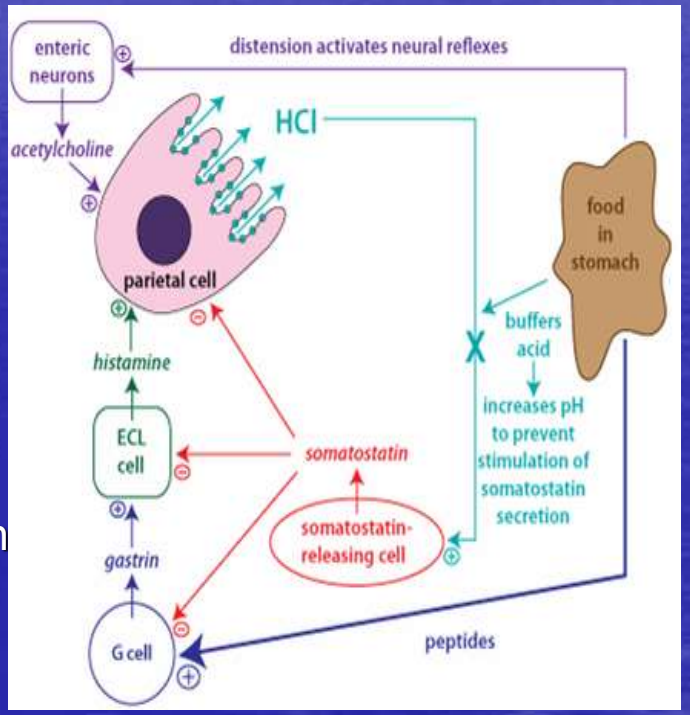
activate enteric neurons. In humans, the major effect of **gastrin** is indirect through the release of histamine from ECL cells not through direct parietal cell stimulation.

Gastric Phase:

Food stretch stomach walls
activating a neural reflex
to stimulate acid secretion.
Peptides & amino acids stimulate
G cells to release gastrin.
Food acts as a buffer, raising the
pH & thus removing the stimulus
for somatostatin secretion .

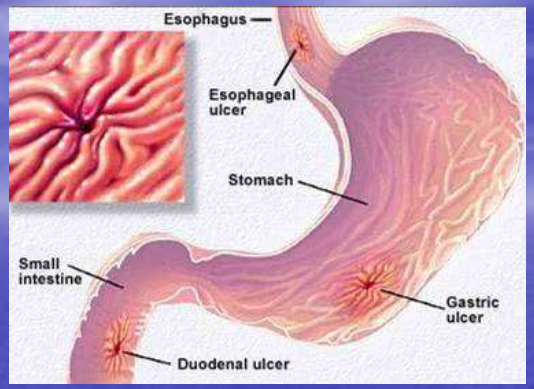
Intestinal Phase:

Once chyme enters the duodenum, it activates negative feedback mechanisms to reduce acid secretion



Peptic ulcer

A defect in the lining of the stomach or the duodenum.



Causes of Peptic Ulcer:

Helicobacter pylori (most common).

Drugs such as aspirin & other NSAIDs

Other factors:

Smoking,

Stress,

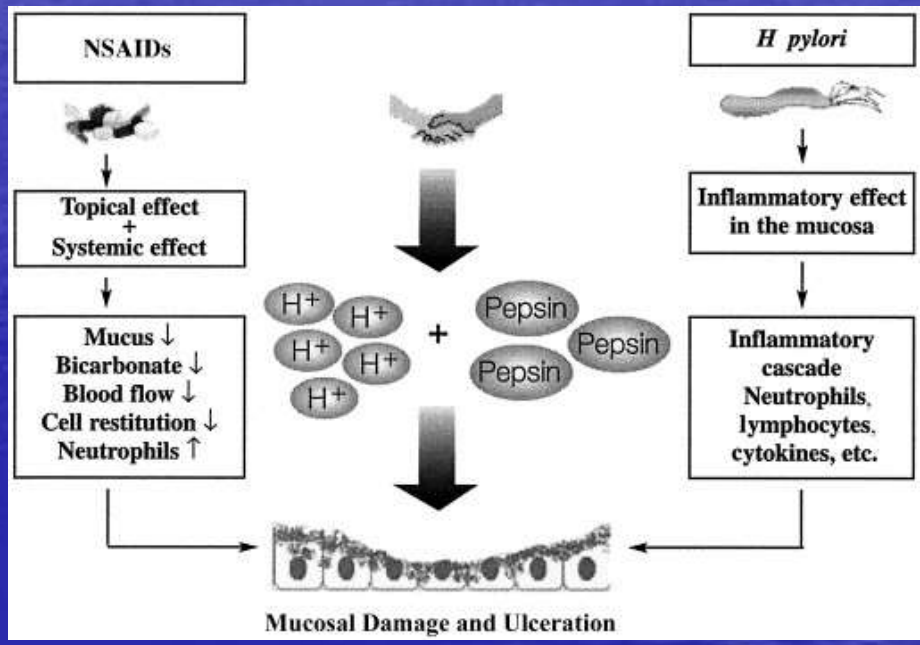
alcohol.

Gastrinomas

Zollinger Ellison syndrome

a rare gastrin-secreting tumors.

Gastrinomas are neuroendocrine tumors characterized by the secretion of gastrin with resultant excessive gastric acid production causing severe peptic ulcer disease and diarrhea, a combination referred to as the Zollinger-Ellison syndrome (ZES)

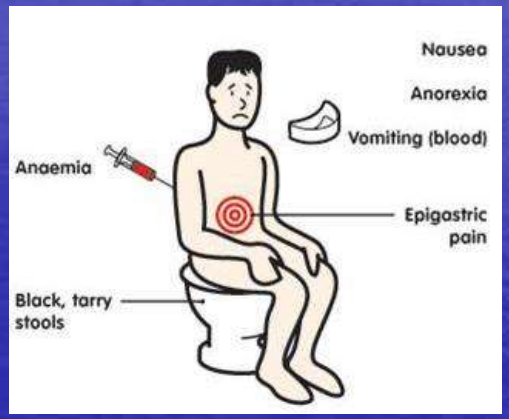


Symptoms:

burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.

In severe cases, symptoms include:

Dark or black stool (due to bleeding)
Vomiting blood
Weight loss & severe pain
in the mid to upper abdomen.

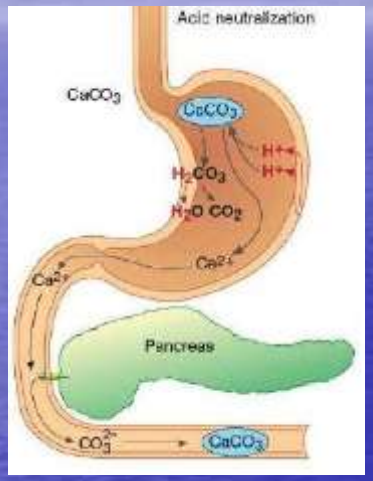


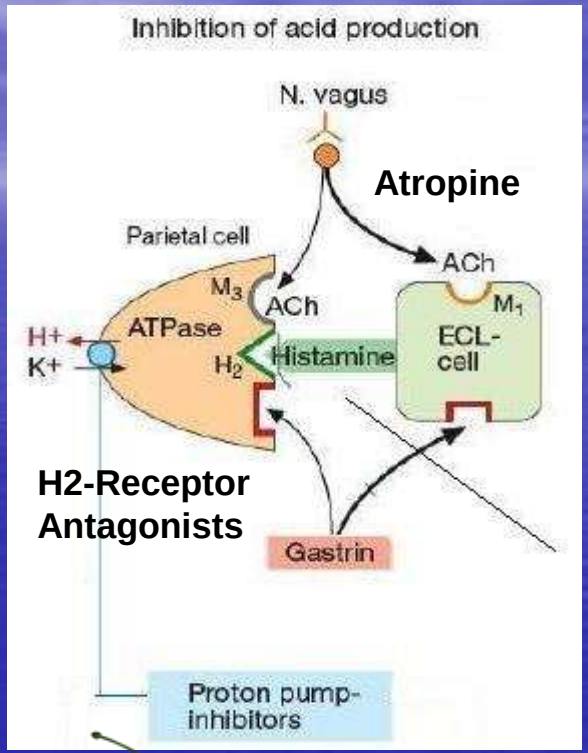
Complications of peptic ulcer

Gastrointestinal bleeding.
(Sudden large bleeding can be life threatening).
Cancer (Helicobacter pylori as the etiological factor)
Perforation (hole in the wall) Penetration.

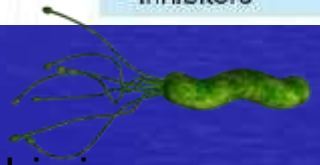
Treatment options

Reduce acid secretion or
Neutralize acid in the lumen





Protect the mucosa from acid destruction



Antibiotics to eradicate *Helicobacter pylori.* If this is successful then the ulcer should begin to heal on its own.

Neutralization of acid (Antacids)

Nonprescription remedies for treatment of heartburn & dyspepsia.

Given 1 hour after a meal effectively neutralizes gastric acid for up to 2 hours.

$$AL(OH)3 + HCl \text{ -----> } ALCl3 + H2O$$

$$2HCl + Mg(OH)2 \text{ ----> } MgCl2 + 2H2O$$

Aluminum antacids cause constipation, interfere with absorption of many drugs.

Magnesium antacids have laxative action; diarrhea.

ionic magnesium stimulates gastric release (acid rebound)

Magnesium trisilicate slow-acting antacid

Combination of Magnesium & aluminum antacids are most commonly used (No diarrhea or constipation).

Antacids

- Magnesium Hydroxide.
- Aluminum Hydroxide.
  - React slowly and without gas formation.
  - Metabolic alkalosis is also uncommon.
  - Mg salts cause diarrhea.
  - Aluminum salts cause constipation.
  - Usually given in combination.
  - Contraindicated in renal insufficiency.

Calcium carbonate

associated with "acid rebound"

with excessive chronic use, it may cause milk-alkali syndrome with elevation of serum calcium, phosphate , urea, nitrogen, creatinin & bicarbonate levels.

$2HCl + CaCO_3 \rightarrow CaCl_2 + CO_2 + H_2O$

Sodium bicarbonate

-Should be avoided as it counteracts diuretic therapy for hypertension,

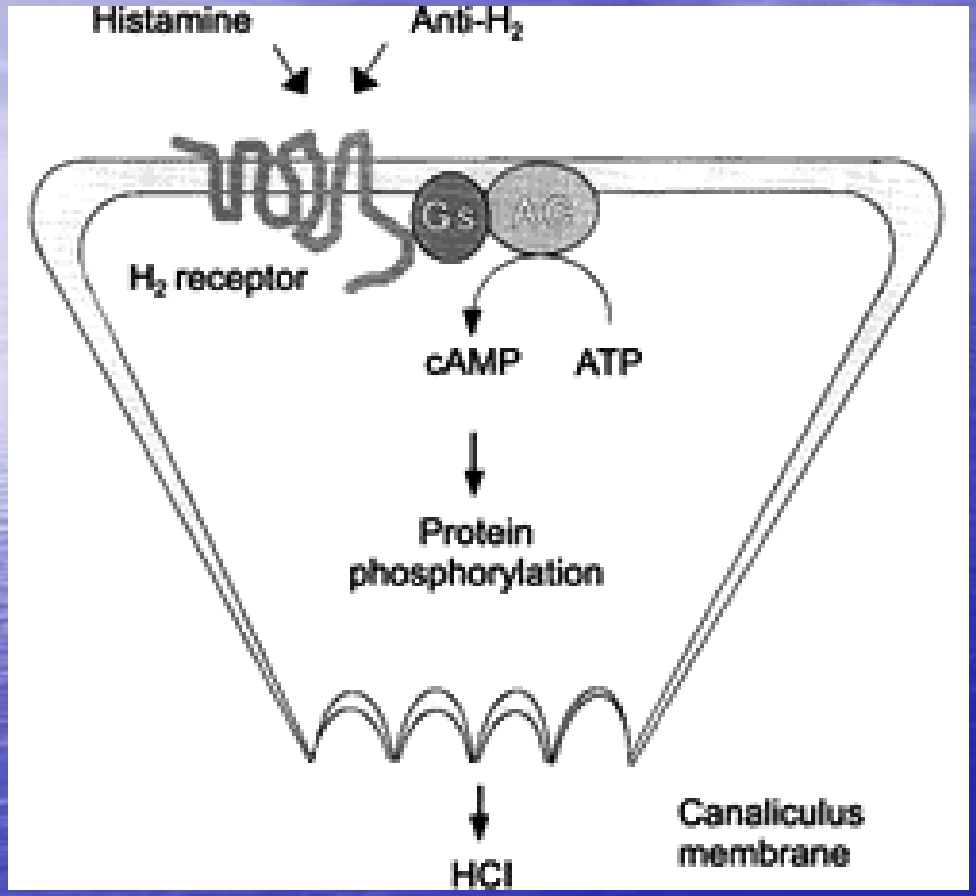
-Short duration of action, followed by acid rebound.

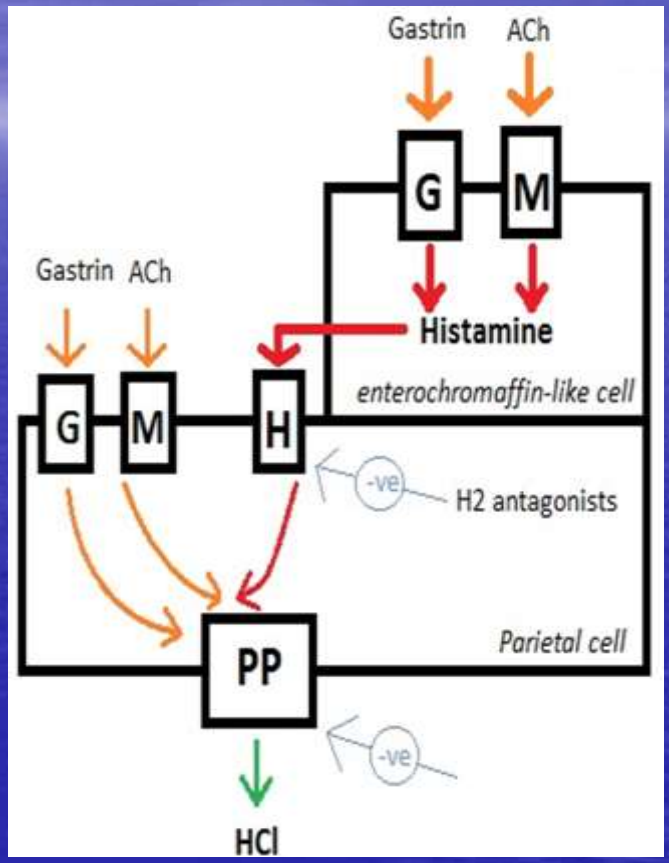
-Highly absorbed, potentially causing metabolic alkalosis.

- CO_2 results in belching.

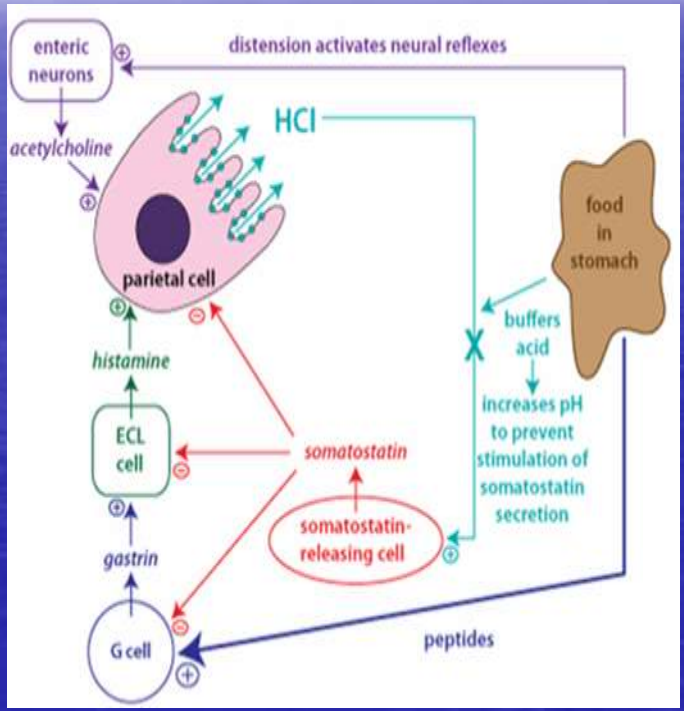
$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$

H_{2-} Receptor Antagonists





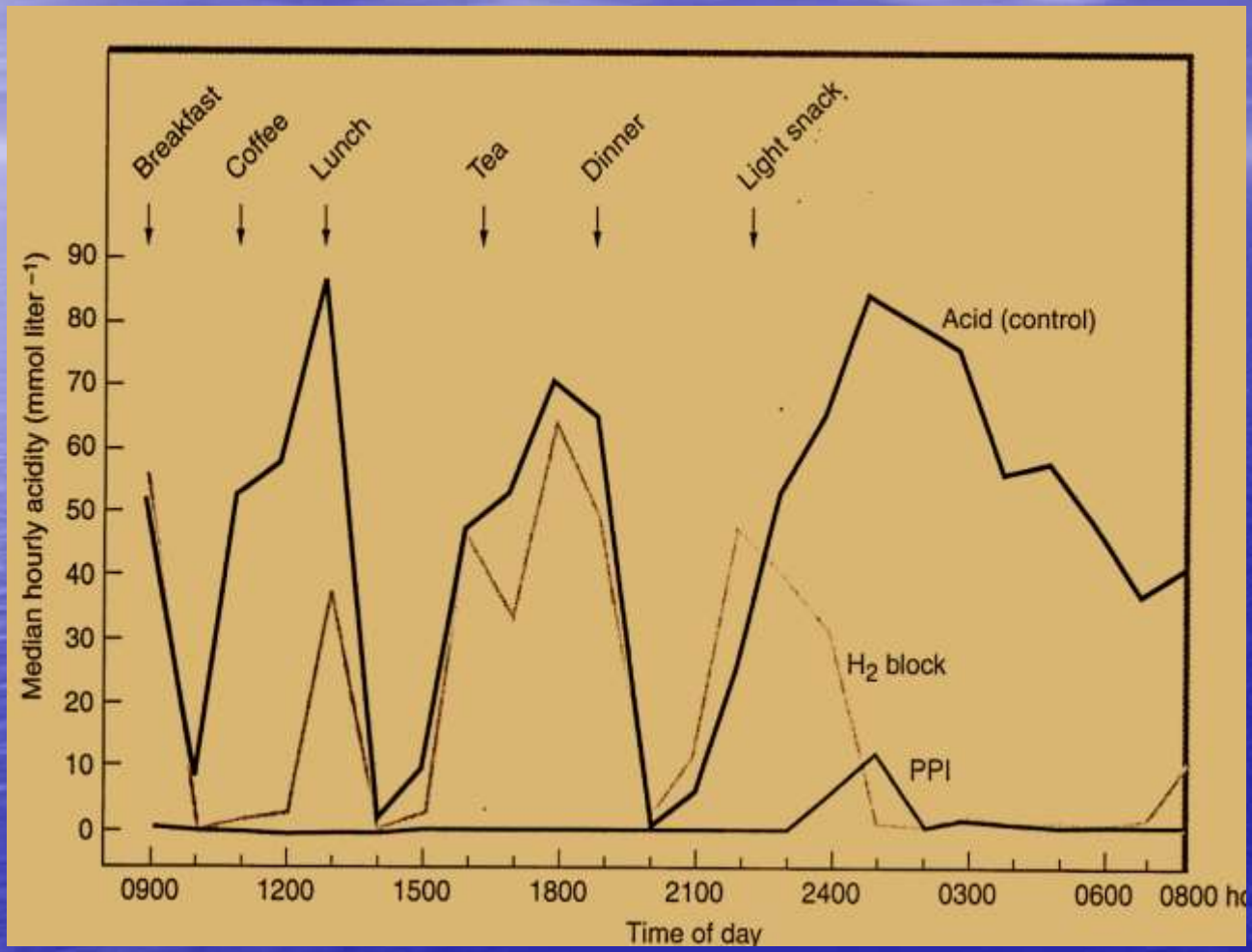
Selective competitive inhibitors of the parietal cell H2 receptor and suppress basal and meal-stimulated acid secretion in a dose-dependent manner. Also decrease volume of secretion and pepsin concentration.



H_2- Receptor Antagonists(1970s-1990s)

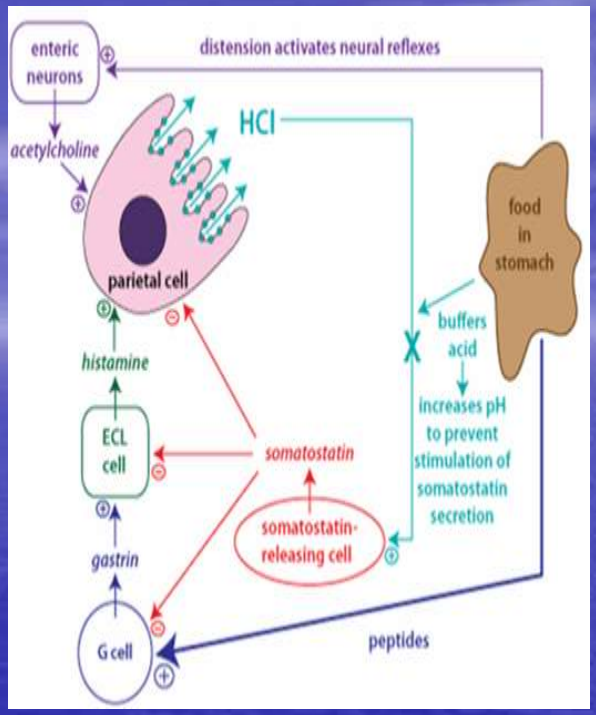
Were the most commonly
prescribed drugs in the world.

- Cimetidine, prototype, many problems.
- Ranitidine.
- Famotidine.
- 50% first-pass metabolism bioavailability
- Nizatidine
- has little first-pass metabolism


Breakfast
Coffee
Lunch
Tea
Dinner
Light snack
Median hourly acidity (mmol liter⁻¹)
90
80
70
60
50
40
30
20
10
0
Acid (control)
H2 block
PPI
0900
1200
1500
1800
2100
2400
0300
0600
0800 h
Time of day

H_2 Receptor Antagonists(1970s-1990s)

- Decrease secretion stimulated by:
  - Histamine.
  - Gastrin.
  - Acetylcholine.
- Duration of action: 12 hours.
- Inhibit 60-70% of total 24-h acid secretion.
  - 90% of nocturnal acid.
  - 60% of day-time, meal stimulated, acid.



Nocturnal acid is the presence of intragastric pH < 4 during the overnight period for at least 60 continuous minutes

H_2- Receptor Antagonists

- **Clinical Uses:**
- Gastroesophageal Reflux:
  - Prophylactically, before meals.
  - Afford healing for erosive esophgitis in less than 50% of patients.
  - Proton pump inhibitors are preferred.
- Non Ulcer Dyspepsia.
- Stress- Related Gastritis:
  - Can prevent bleeding, usually given IV.

Esophagitis is an inflammation of the lining of the esophagus

H_2- Receptor Antagonists

- **Peptic Ulcer Disease:**
  - Replaced by PPI.
  - Healing rate greater than 80-90% after 6-8 weeks.
  - Not effective in the presence of *H. pylori* infection.
  - Not effective if NSAID is continued.

H_2- Receptor Antagonists

Adverse Effects:

- Extremely safe drugs, but can (in 3% of patients) cause diarrhea, headache, fatigue, myalgia and constipation.
- CNS:
  - Confusion, hallucinations occur only with IV cimetidine to elderly patients in ICU.
- Endocrine Effects:
  - Again only with cimetidine, can inhibit estradiole metabolism, and can increase prolactin serum levels.

H_2- Receptor Antagonists

Adverse Effects:

- Pregnancy and Nursing Mothers:
  - Can cross placental barrier and appear in breast milk.
- Other Effects:
  - Rarely can cause bradycardia and hypotension.

H_2- Receptor Antagonists

Drug Interactions:

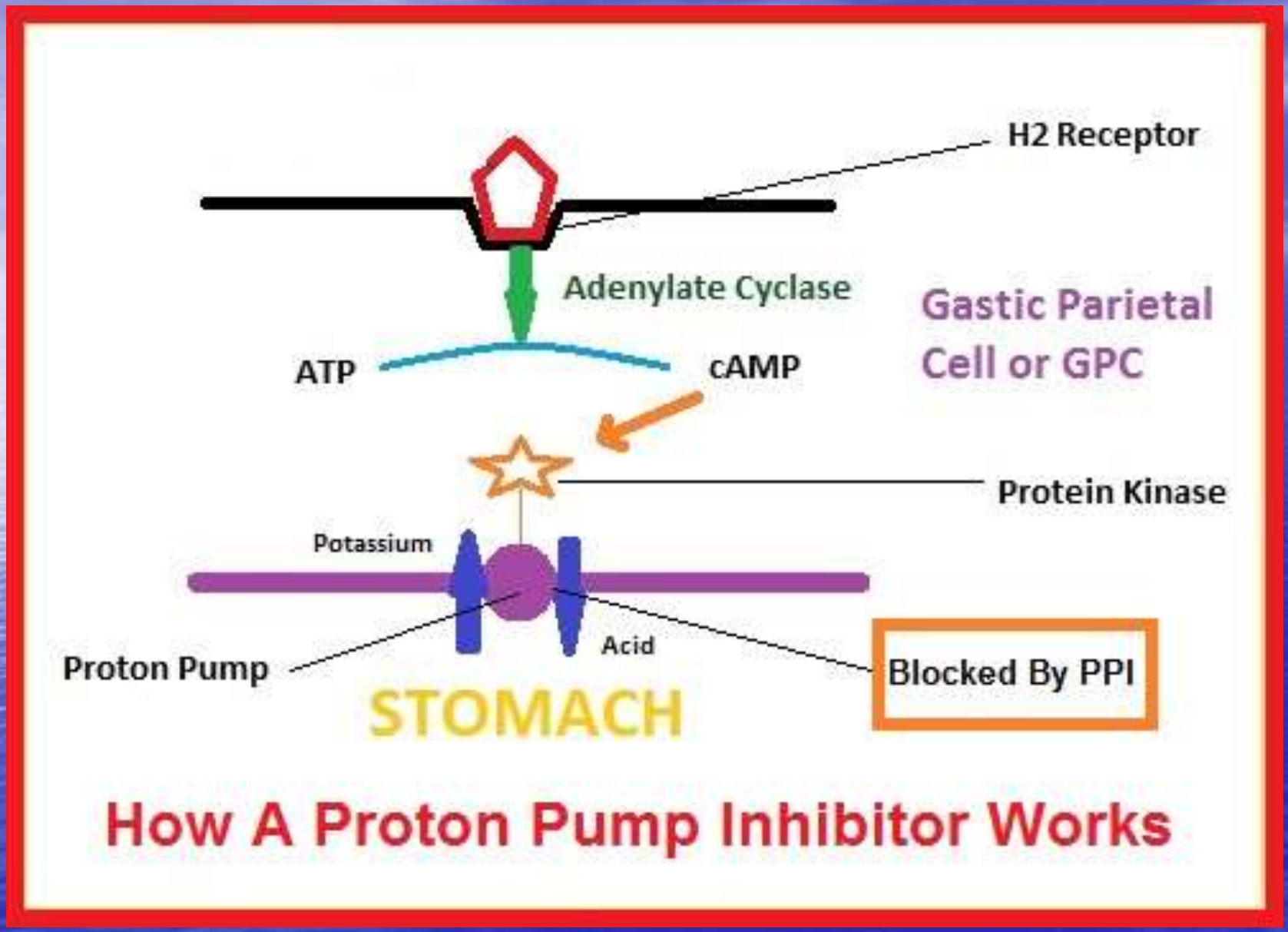
- Cimetidine can inhibit cytochrome P450 enzymes(CYP1A2, CYP2C9, CYP2D6, and CYP3A4), so can increase half life of many drugs.
- Ranitidine binds 4-10 times less.
- Nizatidine and famotidine binding is negligible.

Proton Pump Inhibitors

Proton Pump Inhibitor Drugs

Proton Pump Inhibitors, PPI(1990s)

- Very efficacious and safe drugs.
- Omeprazole (oral).
- Rabeprazole (oral).
- Lanzoprazole (oral and IV).
- Pantoprazole (oral and IV).
- Esmoprazole (oral and IV).
- Formulated as a prodrug which is released in the intestine.
- Immediate Release Suspension results in rapid response.


H2 Receptor
Adenylate Cyclase
Gastic Parietal
Cell or GPC
ATP
cAMP
Protein Kinase
Potassium
Proton Pump
Acid
Blocked By PPI
STOMACH
How A Proton Pump Inhibitor Works

PPI

Pharmacokinetics:

- They are lipophilic weak bases (pKa 4-5).
- After intestinal absorption, they diffuse across lipid membranes into acidified compartments such as the parietal cell canaliculus.
- The prodrug becomes protonated and concentrated more than 1000-fold within the parietal cells.
- There, it undergoes a molecular conversion to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.

PPI

Pharmacokinetics:

Rabeprazole has immediate release omeprazole have faster onsets of action.

- Should be given one hour before meal.
- Have short half lives but effect lasts for 24 hours due to irreversible inhibition.

PPI

- **Pharmacodynamics:**
- **Inhibit both fasting and meal-stimulated secretion because they block the final common pathway of acid secretion (90-98% of 24-hour secretion).**

PPI

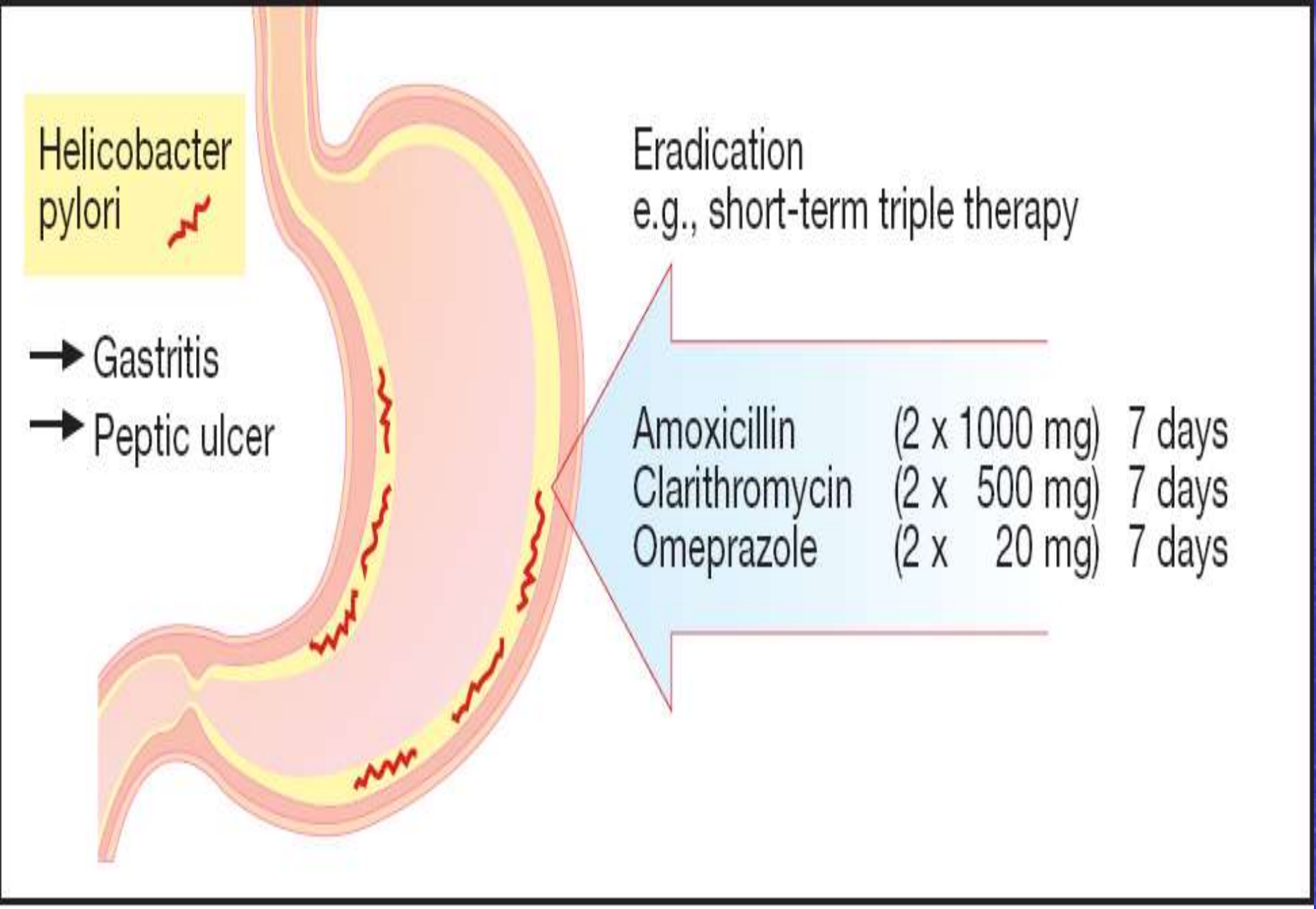
- **Clinical Uses:**
- **Gastroesophageal Reflux (GERD):**
  - **They are the most effective agents in all forms of GERD and complications.**
- **Nonulcer Dyspepsia:**
  - **Modest activity.**
  - **10-20% more beneficial than a placebo.**

PPI

- **Stress- Related Gastritis:**
  - Oral immediate- release omeprazole administered by nasogastric tube.
  - For patients without a nasoenteric tube, IV H_2-antagonists are preferred because of their proven efficacy.
- **Gastrinoma and other Hypersecretory Conditions:**
  - Usually high doses of omeprazole are used.

PPI

- **Peptic Ulcer Disease:**
  - **They heal more than 90% of cases within 4-6 weeks.**
  - ***H.pylori*- associated ulcers:**
    - **PPI eradicate *H.pylori* by direct antimicrobial activity and by lowering MIC of the antibiotics.**
    - ***Triple Therapy*:**
      - **PPI twice daily.**
      - **Clarithromycin 500mg twice daily.**
      - **Amoxicillin 1gm twice daily ,OR, Metronidazole 500mg twice daily.**



C. Helicobacter eradication

PPI

- **Peptic Ulcer Disease:**
  - **NSAID-associated ulcers:**
    - **PPIs promote ulcer healing despite continued NSAID use.**
    - **Also used to prevent ulcer complications of NSAIDs.**
  - **Rebleeding peptic ulcer:**
    - **Oral or IV.**
    - **High pH may enhance coagulation and platelet aggregation.**

PPI

- **Adverse Effects:**

General:

- **Diarrhea, headache, abdominal pain, not teratogenic in animals, but not used in pregnancy.**

Reduction of cyanocobalamine absorption.
Increased risk of GI and pulmonary infection.

Vitamin B12 can help balance immune responses to better fight viral and bacterial infections

PPI

- **Adverse Effects:**

Increased serum gastrin levels:

Hyperplasia of ECL cells.

Carcinoid tumors in rats.

Increase proliferative rate of colonic mucosa.

Chronic inflammation in gastric body.

Atrophic gastritis and intestinal metaplasia.

Gastritis is a general term for a group of conditions with one thing in common: Inflammation of the lining of the stomach.

A change of cells to a form that does not normally occur in the tissue in which it is found

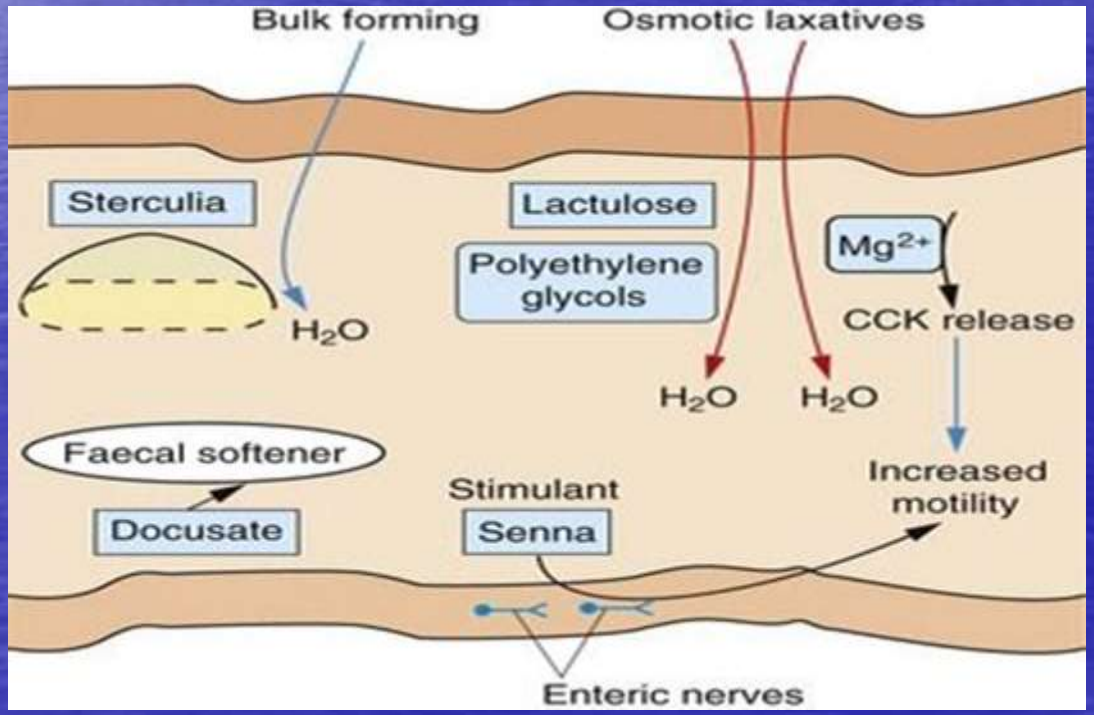
PPI

- **Drug Interactions:**
  - May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.
  - Omeprazole can inhibit metabolism of drugs such as diazepam and phenytoin.
  - Rabeprazole and pantoprazole have no significant interaction.

Drugs Affecting GI Motility

- **Laxative Agents.**

- **Antidiarrheal Agents.**



Laxatives

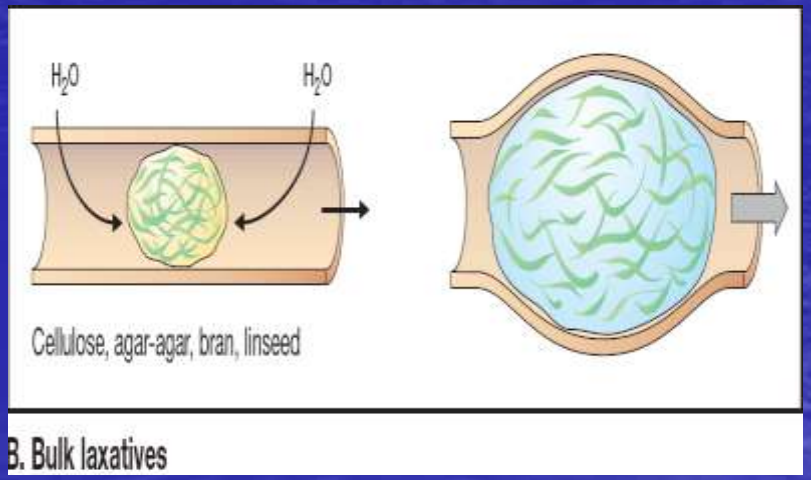
Nonpharmacologic Remedies:

- High fiber diet.
- Adequate fluid intake.
- Regular exercise.
- Responding to nature's call.

Laxatives

Bulk-Forming Laxatives:

- Are indigestible, hydrophilic colloids that absorb water, forming a bulky, emollient gel that distends the colon and promotes peristalsis.
- Can cause bloating and flatus.
- Natural Plant Products:
  - Psyllium.
  - Sterculia "Normacol"
  - Methylcellulose.
- Synthetic Fibers:
  - Polycarbophil.



Laxatives

Stool Surfactant Agents(Softeners):

- They permit water and lipids to penetrate.
- Given orally or rectally.
- Docusate.
- Glycerin suppository.
- Mineral oil:
  - Clear viscous oil that lubricates fecal material, retarding water absorption from the stool.
  - Used to prevent and treat fecal impaction.
  - Aspiration can cause lipoid pneumonia.
  - Can impair absorption of fat-soluble vitamins.

Aspiration pneumonia occurs when food or liquid is breathed into the airways or lungs, instead of being swallowed.

Laxatives

Osmotic Laxatives(Purgatives):

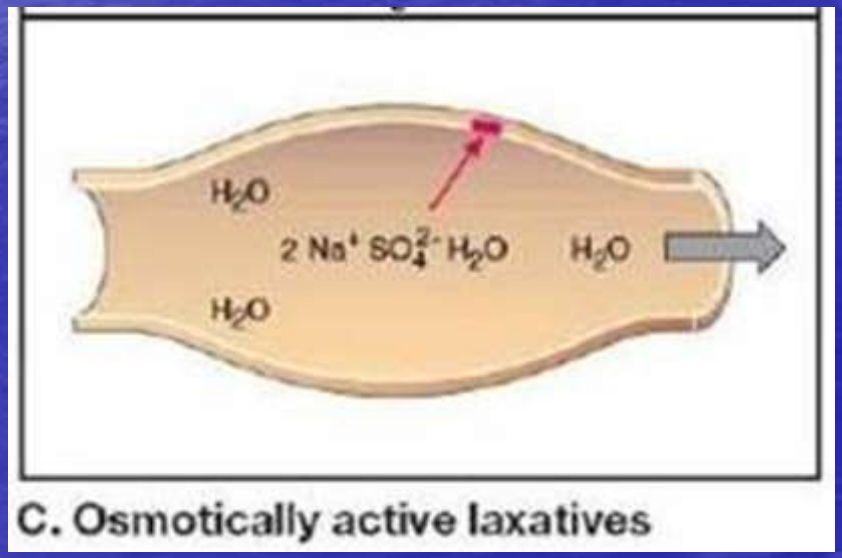
- Soluble nonabsorbable compounds that result in increased stool liquidity due to an obligate increase in fecal fluid.

- Magnesium oxide (Milk of Magnesia):
  - Can cause hypermagnesemia.
  - Large doses of magnesium citrate and sodium phosphate can cause Purgation: rapid bowel evacuation within1-3 hours. This might cause volume depletion.

Laxatives

Osmotic Laxatives:

- Sorbitol.
- Lactulose.
  - Sugars metabolized by bacteria producing severe flatus and cramps.



C. Osmotically active laxatives

Laxatives

Osmotic Laxatives:

- **Balanced Polyethylene Glycol:**
  - Safe solution: no intrvascular fluid or electrolyte shifts. Does not cause cramps or flatus.
  - Used for complete colonic cleansing before endoscopy.
  - PEG is an inert, nonabsorbable, osmotically active sugar.
  - Sodium sulfate, chloride, bicarbonate and potassium chloride.
  - For colonic cleansing, it should be ingested rapidly(4 L over 2-4hs).
  - For chronic constipation, PEG powder is mixed with water or juice.

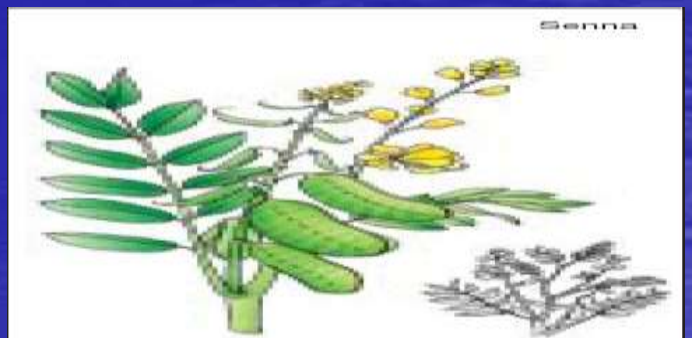
Laxatives

Stimulant Laxatives(Cathartics):

- Direct stimulation of the enteric system.
- Colonic electrolyte and fluid secretion.
- Can lead to dependence and destruction of the myenteric plexus resulting in colonic atony and dilation.
- May be needed in neurologically impaired patients and in bed- bound patients in long term care facilities.

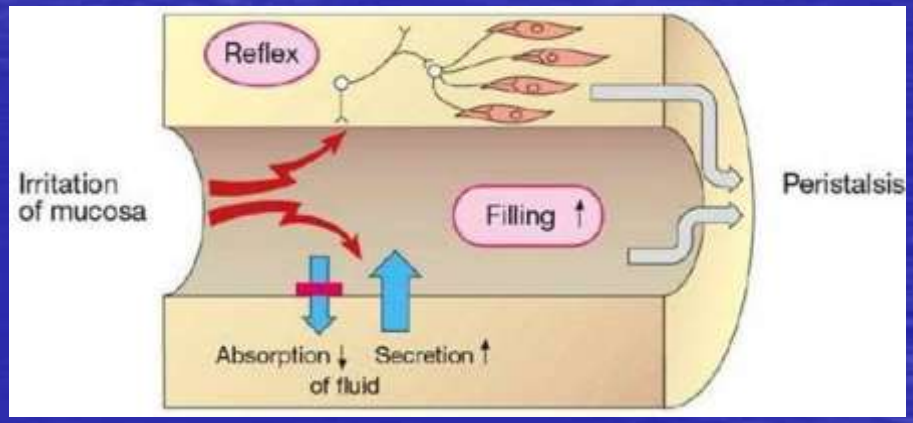
Laxatives

- **Stimulant Laxatives(Cathartics):**
- **Anthraquinone Derivatives:**
  - Aloe.
  - Senna.
  - Cascara.
    - Poorly absorbed .
    - After hydrolysis, produce bowel movement in (6-12) hours.
    - Cause brown pigmentation of the colon" Melanosis Coli".
    - Not carcinogenic.



Laxatives

- **Stimulant Laxatives(Cathartics):**
- **Castor Oil:**
  - **Hydrolyzed in upper intestine into ricinoleic acid which is a local irritant.**
  - **Was used as purgative to clean the colon before procedures.**

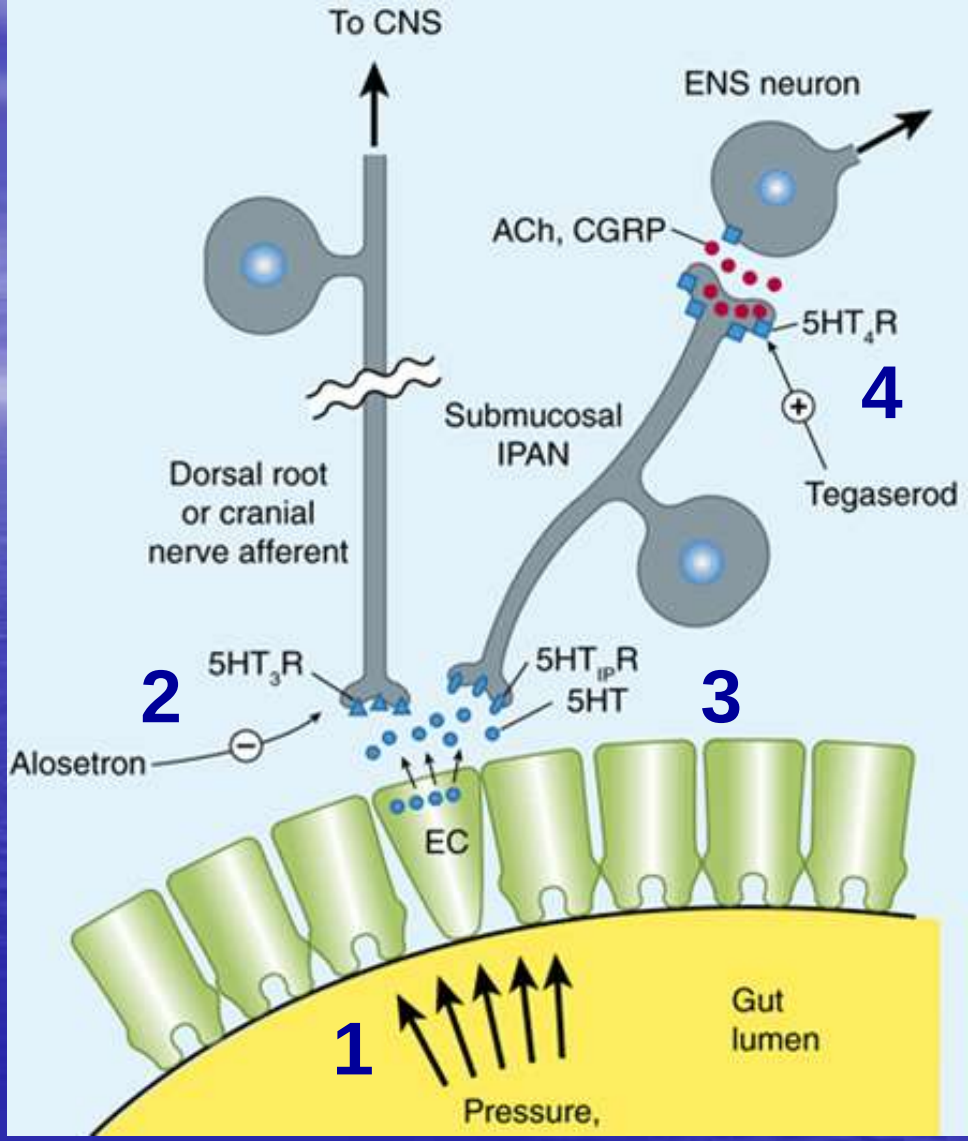


Normal situation

1-Gut distention stimulates 5-HT release from EC cells.

2-Stimulation of **5-HT3** receptors on the extrinsic afferent nerves, stimulate **nausea, vomiting**, or **abdominal pain**.

3- 5-HT also stimulates **5-HT1P** receptors of the intrinsic primary afferent nerves (IPANs) which activate the enteric neurons responsible for **peristaltic and secretory reflex activity.**



4- Stimulation of 5-HT4 receptors (5-HT4R) on presynaptic terminals of IPANs enhances release of **ACh** & calcitonin gene related peptide (**CGRP**), promoting reflex activity.

Laxatives

Tegaseroid:

- Is a serotonin 5-HT_4 partial agonist, which are presynaptic receptors of the submucosal intrinsic primary afferent nerves which enhance the release of their neurotransmitters.
- These neurones stimulate proximal bowel contraction(via ACh and substance P) and distal relaxation(via nitric oxide and VIP).
- The drug promotes gastric emptying and small and large bowel transit but has no effect on esophageal motility.
- Also stimulates cAMP-dependent chloride secretion leading to increased stool liquidity.

Laxatives

Tegaseroid:

Clinical Uses:

Chronic constipation.

Nonulcer dyspepsia.

Gastroparesis.

Irritable bowel syndrome.

Adverse Effects:

Extremely safe drug.

Diarrhea occurs in 9% of patients but resolves within days.

Expensive.

Laxatives

Tegaseroid:

Antidiarrheal Agents

Can be used in mild to moderate acute diarrhea.

Should not be used in the presence of infective diarrhea.

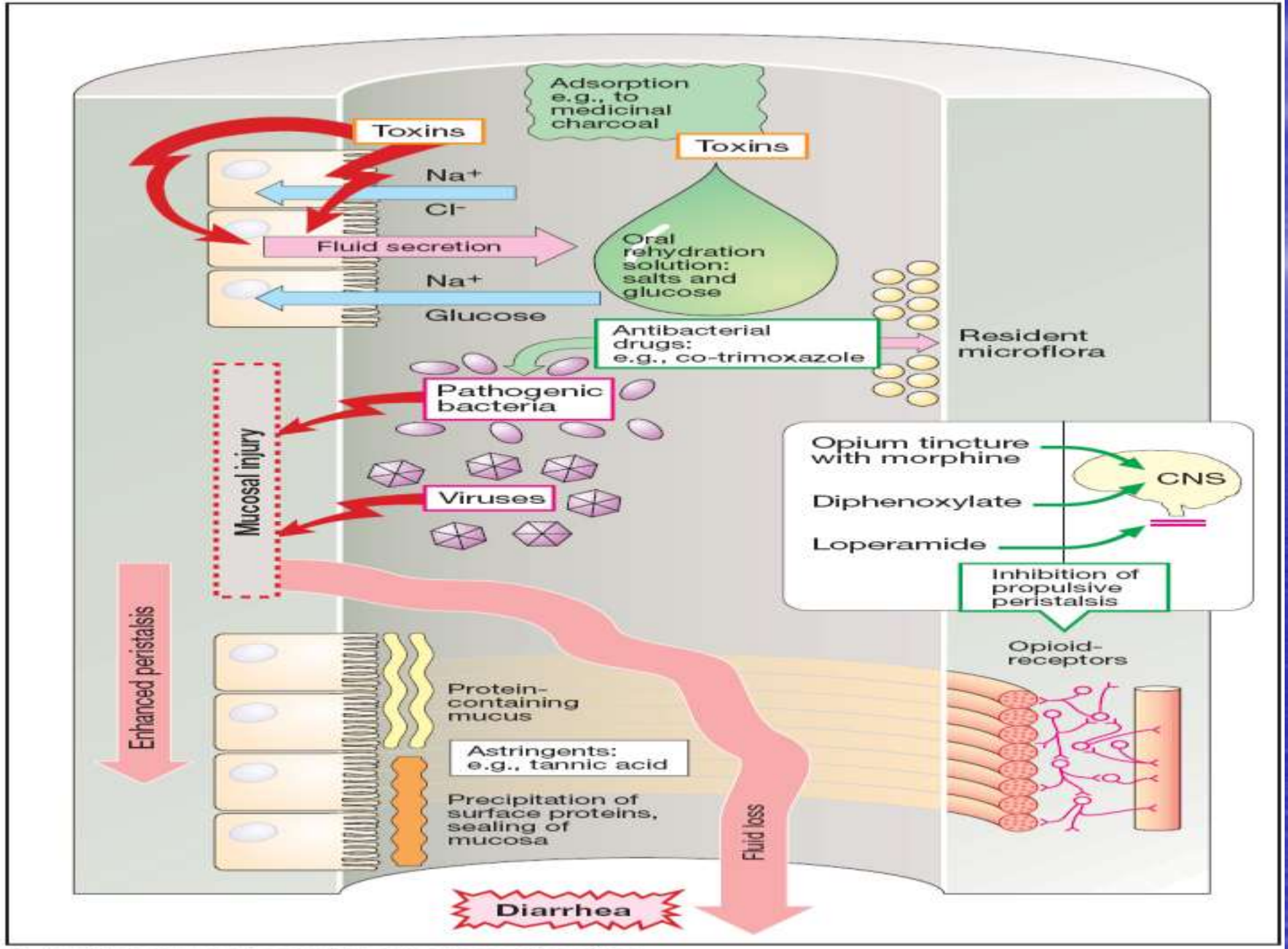
Can be used to control chronic diarrhea, like in irritable bowel syndrome or inflammatory bowel disease.

Antidiarrheal Agents

Opioid Agonists:

Have significant constipating effects:

- **Inhibit presynaptic cholinergic nerves, leading to increased colonic transit time and increased fecal water absorption.**
- **Decrease mass colonic movements and gastrocolic reflex.**
- **Can have CNS effects and addiction potential.**
- **Usually combined with atropine to reduce dependence.**



A. Antidiarrheals and their sites of action

Antidiarrheal Agents

Opioid Agonists:

Loperamide:

Does not cross BBB.

No analgesic or addiction potential.

Diphenoxylate:

Can have CNS effects and dependence.

Antidiarrheal Agents

Kaolin and Pectin:

Kaolin is a naturally occurring hydrated magnesium silicate.

Pectin is an indigestible carbohydrate derived from apples.

Both act to absorb bacteria, toxins and fluid.

Usually combined, e.g. Kaopectate.

Taken far from other medications.

Antidiarrheal Agents

Bile salt-binding resins:

- **Cholestyramine**
- **Colistipol.**
- **Malabsorption of bile salts (e. g .after surgical resection), can cause diarrhea.**

The drugs can bind bile salts.

Can cause bloating, flatulence, constipation and fecal impaction.

Also, drug and fat malabsorption.

Antidiarrheal Agents

Octreotide:

Is a synthetic octapeptide with actions similar to somatostatin.

Somatostatin is a 14 amino acid peptide released in the GIT and pancreas as well as from the hypothalamus:

1. Inhibits release of many hormones.
2. Reduces intestinal fluid and pancreatic secretions.
3. Slows GIT motility and gallbladder contraction.
4. Contracts blood vessels.
5. Inhibits secretion of some anterior pituitary hormones.

Antidiarrheal Agents

Octreotide:

Clinical Uses:

1. **Inhibition of endocrine tumor effects:**

   Carcinoid can cause secretory diarrhea and systemic symptoms like flushing and wheezing.

2. **Diarrhea due to vagotomy or dumping syndrome or and AIDS.**

3. **In small doses can stimulate motility in small bowel bacterial overgrowth or intestinal pseudo-obstruction secondary to scleroderma.**

4. **pituitary tumors and GI bleeding.**

vagotomy usually means cutting the branch of the vagus nerve that tells your stomach to secrete gastric acid

Dumping syndrome is a condition in which food, especially food high in sugar, moves from your stomach into your small bowel too quickly after you eat

Scleroderma is an uncommon condition that results in hard, thickened areas of skin

Drugs Used in the Treatment of Irritable Bowel Syndrome

IBS is an idiopathic chronic,
relapsing disorder characterized
by: Abdominal discomfort
pain, bloating, distention, or cramps with alterations in bowel habits
diarrhea, constipation, or both.

Pharmacologic therapies for **I**BS are directed at relieving abdominal pain and discomfort and improving bowel function.

Drugs used in Irritable Bowel Syndrome

- **Antispasmodic or Anticholinergic Agents:**
  - **Dicyclomine**
  - **Hyoscyamine.**
    - Spasm is not an important symptom in IBS.
    - They inhibit muscarinic cholinergic receptors in the enteric plexus and on smooth muscle.
    - At usual low doses, have minimal side effects.

Drugs used in Irritable Bowel Syndrome

- **Serotonin 5-HT_3- Receptor Antagonists:**
  - **Alosterone:**
    - 5-HT_3 receptors are present in the afferent pain fibers in the extrinsic sensory neurons. Also present on the terminals of the enteric cholinergic neurons. Centrally, 5-HT_3 is involved in the central response to visceral afferent stimulation.

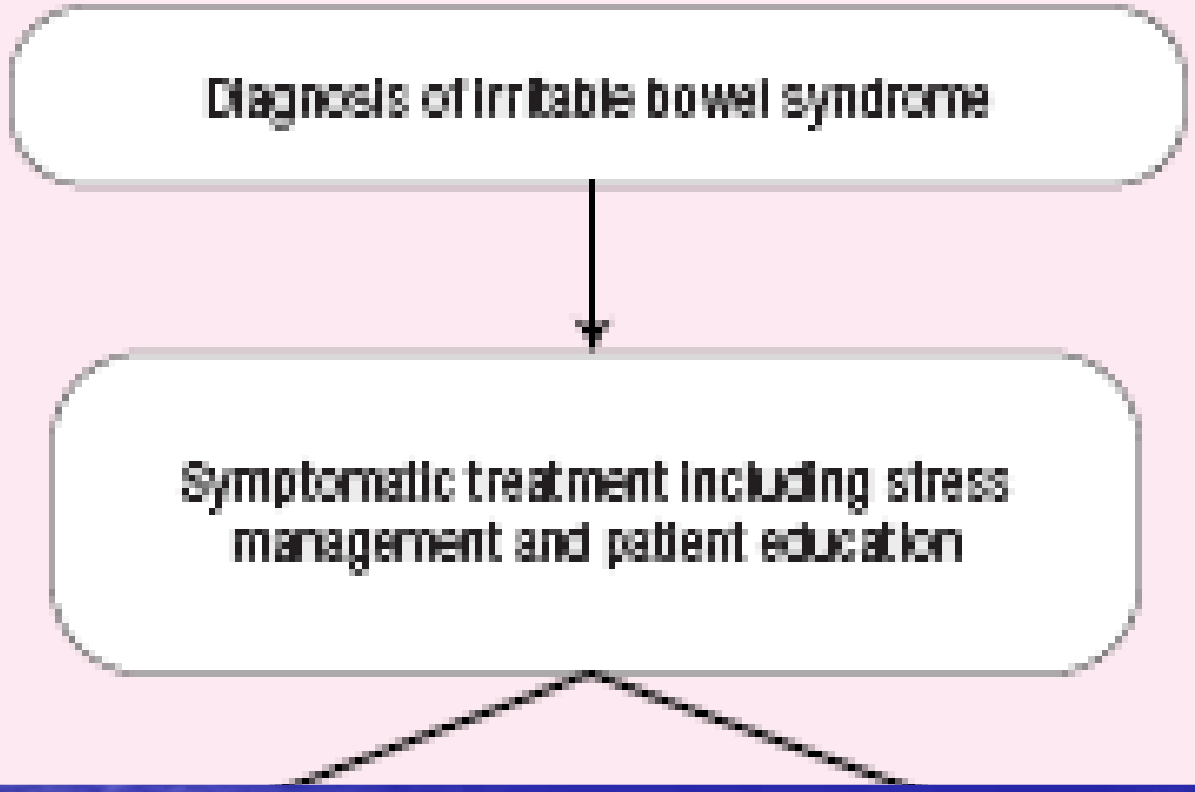
Drugs used in Irritable Bowel Syndrome

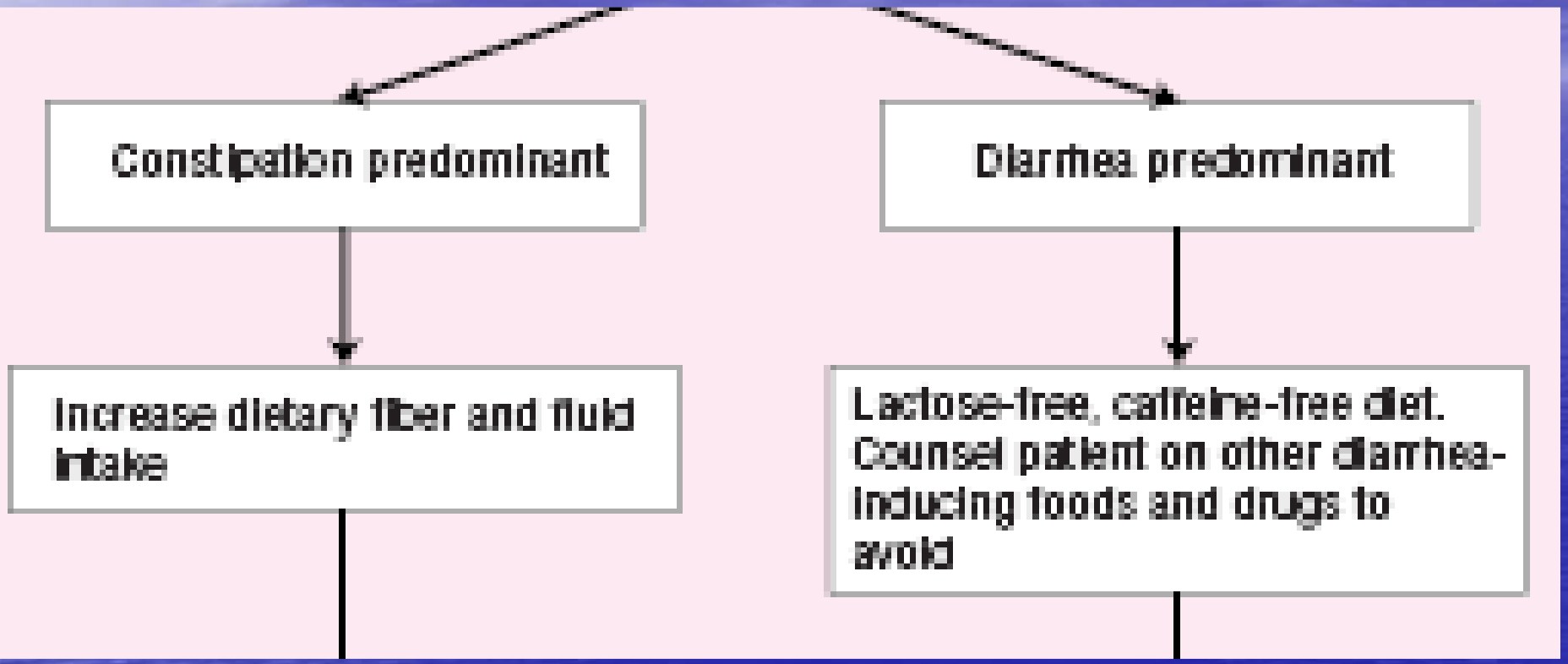
- **Serotonin 5-HT_3- Receptor Antagonists:**
- **Alosterone:**
  - Selective antagonist of 5-HT_3 receptors.
  - Has long duration of action.
  - Approved for **women** with severe IBS in whom diarrhea is the prominent symptom.
  - Efficacy in men is not established.
  - Can cause ischemic colitis, severe constipation requiring hospitalization and surgery

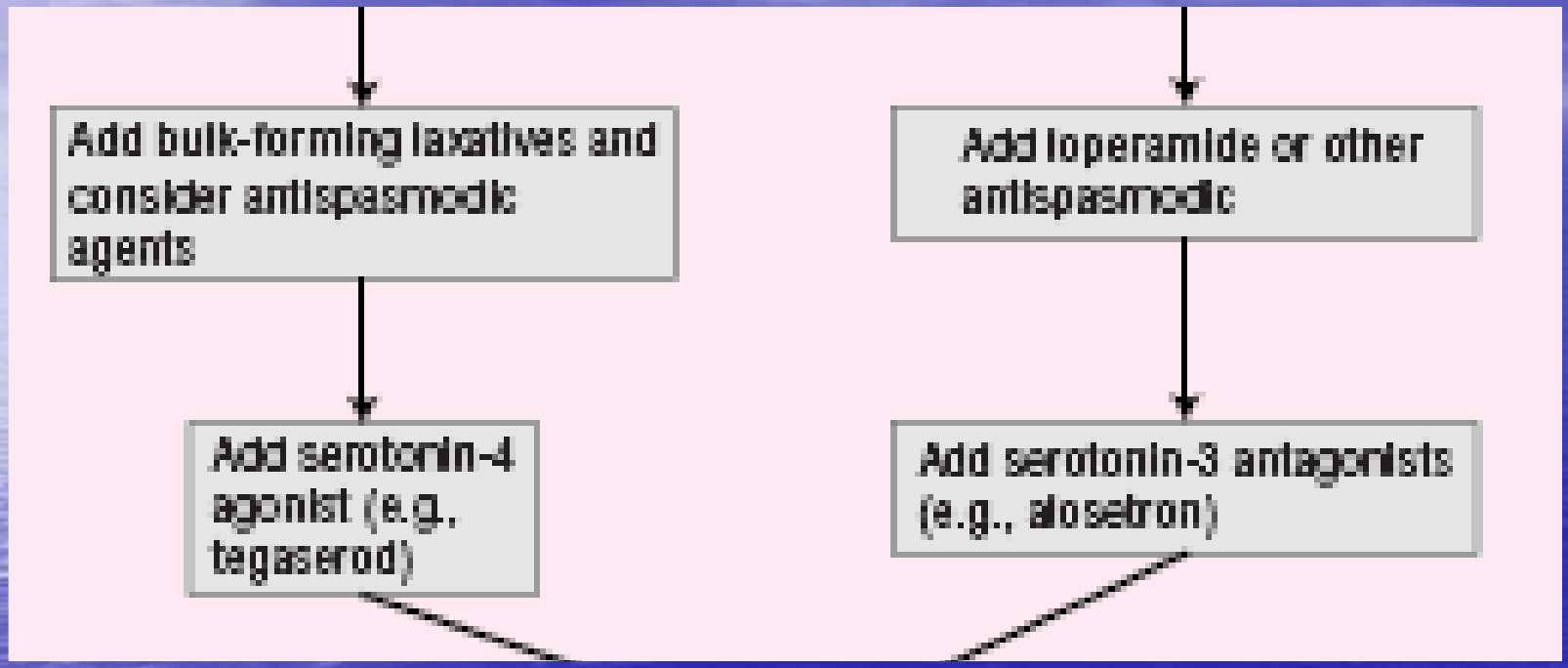
Ischemic colitis occurs when blood flow to part of the large intestine is temporarily reduced

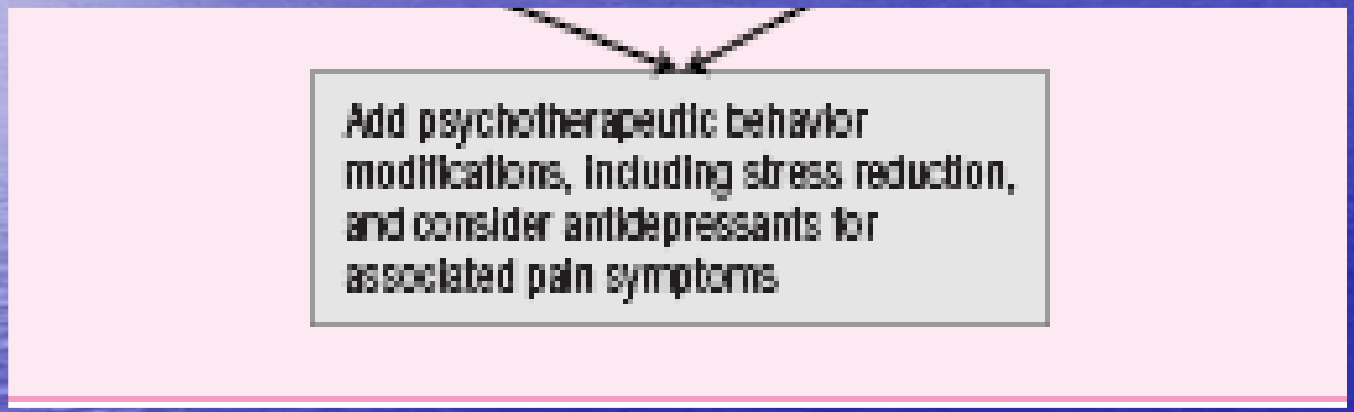
Drugs used in Irritable Bowel Syndrome

- **Serotonin 5-HT $_3$- Receptor Agonists:**
- **Tagaserod:**
  - Approved for short term treatment of **women** with IBS who predominantly have constipation.
  - Reduces pain, bloating and hardness of stool.
  - Expensive.


Diagnosis of irritable bowel syndrome
Symptomatic treatment including stress management and patient education


Constipation predominant
Diarrhea predominant
Increase dietary fiber and fluid intake
Lactose-free, caffeine-free diet. Counsel patient on other diarrhea-inducing foods and drugs to avoid


Add bulk-forming laxatives and consider antispasmodic agents
Add loperamide or other antispasmodic
Add serotonin-4 agonist (e.g., tegaserod)
Add serotonin-3 antagonists (e.g., alosetron)


Add psychotherapeutic behavior modifications, including stress reduction, and consider antidepressants for associated pain symptoms

Antiemetic Agents

Nausea and vomiting may be manifestations of a wide variety of conditions, including:

Adverse effects of medications.

systemic disorders or infections.

Pregnancy.

Vestibular dysfunction.

CNS infection or increased pressure.

Peritonitis.

Hepatobiliary disorders.

Radiation or chemotherapy.

GIT obstruction, dysmotility, or infections.

Pathophysiology

The brainstem "**vomiting center**" coordinates vomiting through interactions with cranial nerves **VIII** and **X** and neural networks in the **nucleus tractus solitarius** that control respiratory, salivatory, and vasomotor Centers.

Vomiting center contains high concentrations of:

M1 receptors.

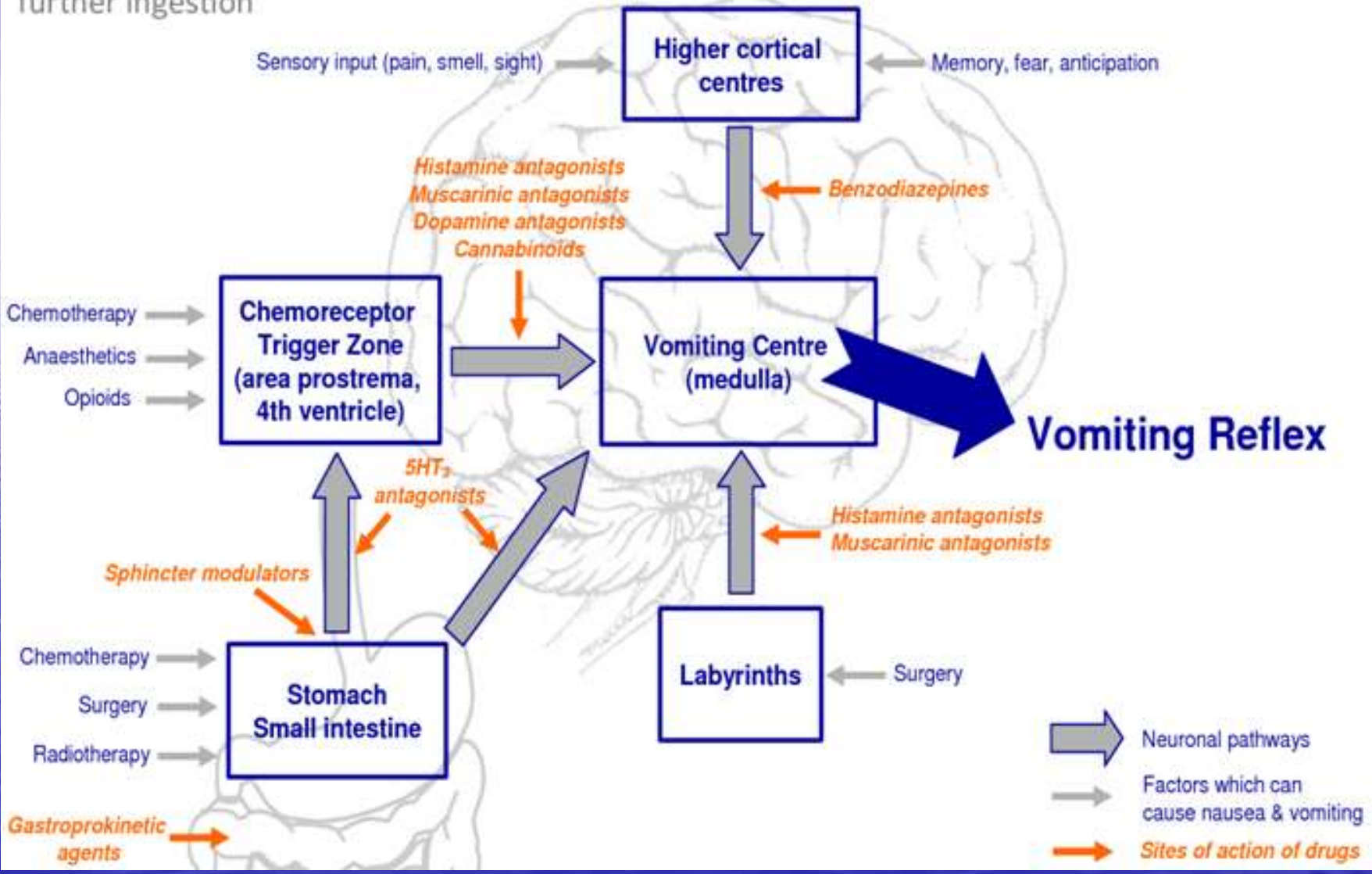
H1 receptors.

Neurokinin 1 (NK1) receptors.

5-HT3 receptors.

Antiemetic Agents

Vomiting :The act of vomiting and the sensation of nausea that accompanies it are protective reflexes that serve to rid the stomach and intestine of toxic substances and prevent their further ingestion



Serotonin 5-HT3 Antagonists

Ondansetron

Granisetron

Block central 5-HT3 and peripheral (main effect) 5-HT3 receptors.

Prevent emesis due to vagal stimulation and chemotherapy.

Other emetic stimuli such as motion sickness are poorly controlled.

Uses

Prevention of acute chemotherapy-induced nausea and emesis and postoperative nausea and vomiting.

Their efficacy is enhanced by combination therapy with **dexamethasone** and **NK1-receptor antagonist.**

Adverse effects: Headache, dizziness, and constipation.

Neurokinin 1 Receptor (NK1) Antagonists

Block central **NK1receptors** in the area postrema.

Aprepitant

Used in combination with **5-HT3-receptor antagonists** and **corticosteroids** for the prevention of acute and delayed nausea and vomiting from chemotherapy.

Cannabinoids

Dronabinol, Nabilone

Psychoactive agents.

Used for chemotherapy-induced vomiting.

Mechanisms for these effects are not understood.

Adverse effects

Euphoria, dysphoria, sedation, hallucinations, dry mouth, and increased appetite.

Antipsychotic drugs

Prochlorperazine

Promethazine

Droperidol

Antiemetics due to blocking dopamine and muscarinic receptors.

Sedative effects due to antihistamine activity.

Benzodiazepines

Lorazepam

Diazepam

Reduce vomiting caused by anxiety.

Antiprotozoal drugs

- Protozoal and helminthic infections are a major cause of disease in many parts of the world.

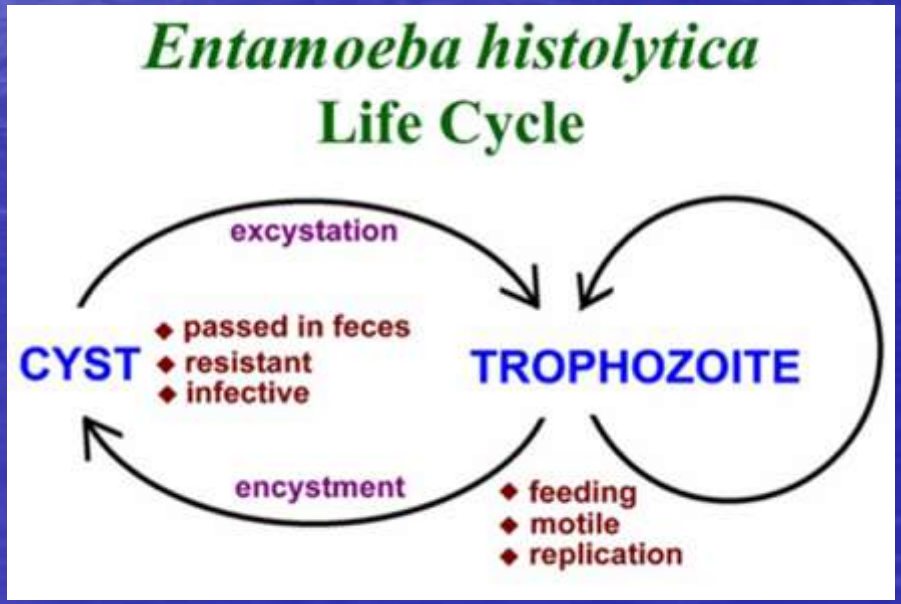
<u>some of these diseases</u>

- in migrant workers
- or individuals returning from an endemic area

Selected PROTOZOAL DISEASES

Amebiasis

- The protozoan Entamoeba histolytica causes amebiasis, an infection that is endemic in parts of the United States
- The parasite can be present in the host as either an encysted or a trophozoite form.



- Initial ingestion of the cyst may result either in no symptoms or in severe amebic dysentery characterized by the frequent passage of bloodstained stools.
- symptom occurs after invasion of the intestinal mucosa by the actively motile and phagocytic trophozoite form of the protozoan.

•Trophozoites may spread to the liver through the portal vein and produce acute amebic hepatitis

•Many patients continue to excrete cysts for several years after recovery from the acute disease and therefore are a hazard to themselves and other persons

Entamoeba histolytica.

This organism can cause:

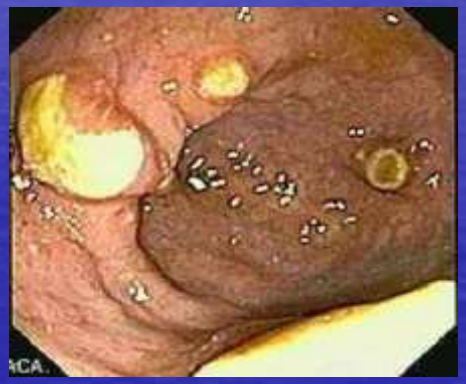
Asymptomatic intestinal infection.

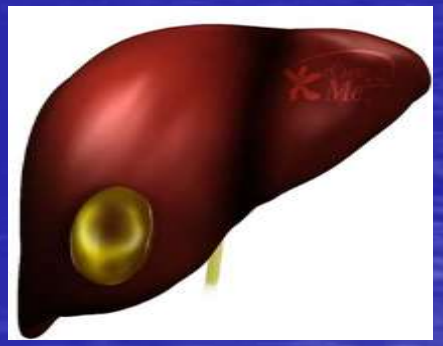
Mild to moderate colitis.

Severe intestinal infection (dysentery).

Ameboma (a tumor-like mass in the intestines in amebiasis which results in a large local lesion of the bowel).

Liver abscess and other extraintestinal infection





Treatment of Specific Forms of Amebiasis

Asymptomatic Intestinal Infection

Asymptomatic carriers are treated with a **luminal amebicide**.

Standard luminal amebicides are:

Diloxanide furoate, Iodoquinol, and Paromomycin.

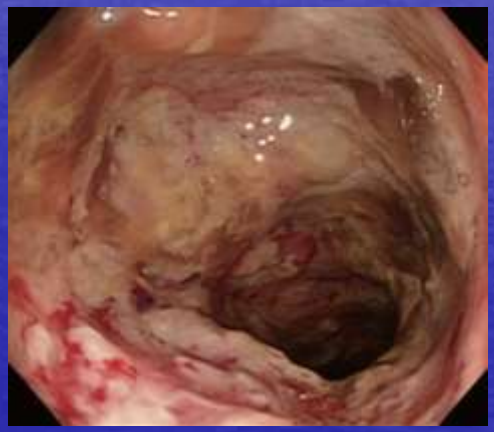
Therapy with a luminal amebicide is also required in the treatment of all other forms of amebiasis.

Amebic Colitis

Metronidazole + a luminal amebicide is the treatment of choice.

Tetracyclines and **erythromycin** are alternative drugs for moderate colitis but are not effective against extraintestinal disease.

Dehydroemetine or emetine can also be used, but are best avoided because of toxicity.



Amebic Colitis

Balantidium coli

- the largest of the protozoans that infect humans
- trophozoite form is covered with cilia, which impart mobility
- Infection is acquired through the ingestion of cyst-contaminated soil, food, or water.

Balantidium coli

- The trophozoite causes superficial necrosis or deep ulceration in the mucosa and submucosa of the large intestine
- healthy persons commonly exhibit nausea, vomiting, abdominal pain, and diarrhea
- nutritionally stressed patients may develop severe dysentery.

Classes of oral antiprotozoal drugs

Commonly used oral antiprotozoal drugs can be generally classified into two main groups:

- *antimalarial drugs*
- *miscellaneous antiprotozoals.*

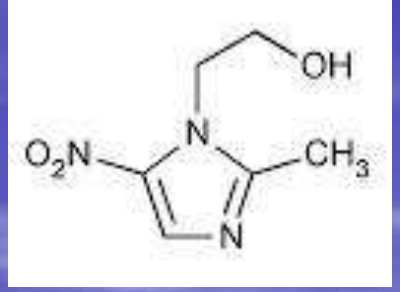
In addition to their use as antiprotozoals, some of them such as metronidazole and doxycycline are also used for treating bacterial infections.

antiprotozoals

Commonly used miscellaneous antiprotozoals include

- metronidazole,
- tinidazole and
- nifuratel.

Metronidazole

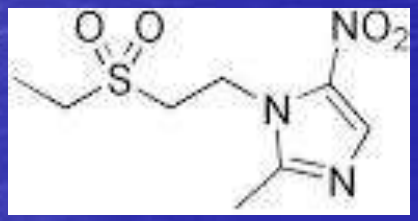


Drug of choice in the treatment of extraluminal amebiasis.

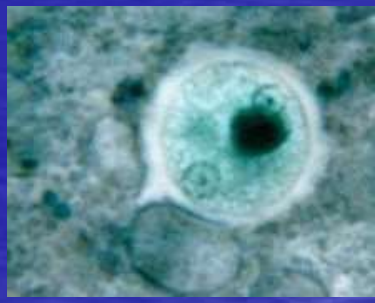
It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal & extraintestinal tissue infections.

Trophozoite of Entamoeba histolytica in intestine.

Tinidazole



Similar activity & better toxicity profile than metronidazole.



Cysts of *E histolytica*

Metronidazole

- Metronidazole (*Flagyl, Metrogel*)
- exerts activity against most anaerobic bacteria and several protozoa.

- The drug freely penetrates protozoal and bacterial cells but not mammalian cells.

Metronidazole

- The enzyme, pyruvate-ferredoxin oxidoreductase, found only in anaerobic organisms, reduces metronidazole and thereby activates the drug.

- Reduced metronidazole disrupts replication and transcription and inhibits DNA repair.

Clinical Uses

Amebiasis

Metronidazole

The drug of choice in the treatment of all tissue infections with *E histolytica*. (hepatic abscess; intestinal wall/ extraintestinal infections)

- Not effective against luminal parasites and so **must be used with a luminal amebicide to ensure eradication of the infection**. kills trophozoites but not cysts

Giardiasis

Metronidazole is the treatment of choice

Efficacy after a single treatment is about 90%

Tinidazole is equally effective.

Trichomoniasis

Metronidazole is the treatment of choice.

A single dose of 2 g is effective.

Trichomonas vaginalis

Adverse Effects & Cautions

Common:

Nausea, headache, dry mouth, metallic taste.

Infrequent adverse effects:

vomiting, diarrhea, insomnia, weakness, dizziness,.

Rare:

Pancreatitis and severe central nervous system toxicity Tinidazole is better tolerated.

Metronidazole is best avoided in pregnant or nursing women, although congenital abnormalities have not clearly been associated with use in humans.

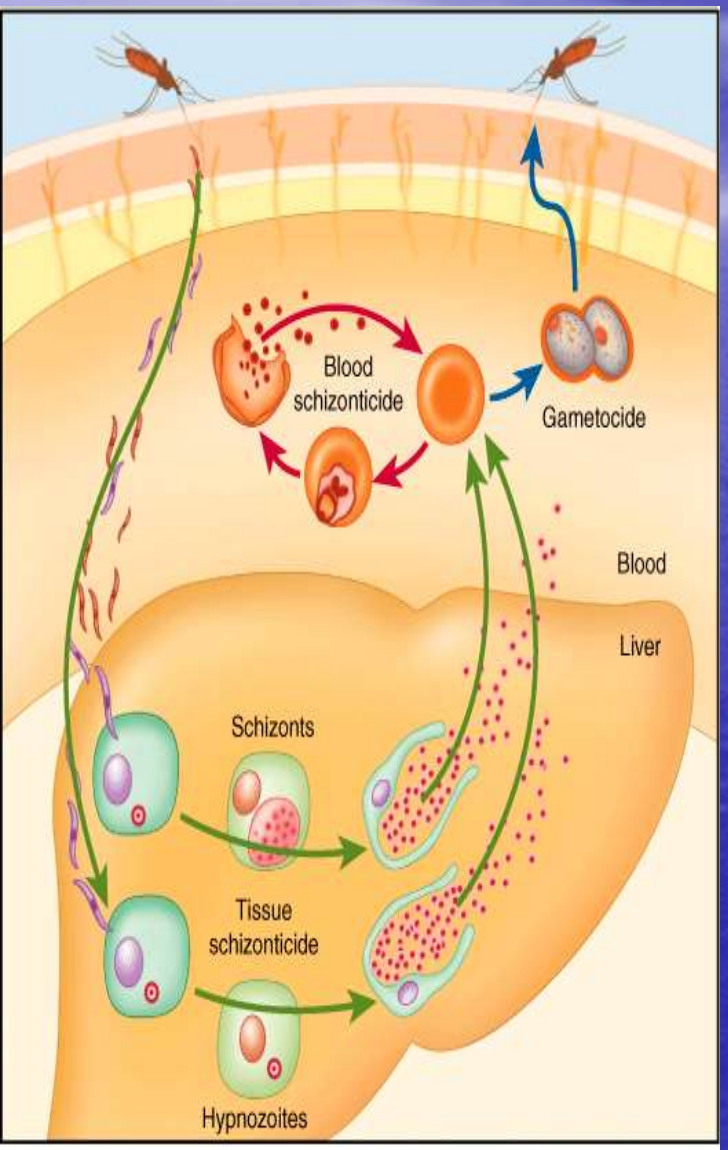
Tinidazole

Tinidazole works as well as metronidazole and has many of the same side effects, but it can be given in a single dose. Whereas, nifuratel can be used as an alternative to metronidazole or tinidazole in the treatment of trichomoniasis.

Antimalarial Drugs

- **Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a group of single-celled microorganism) belonging to the genus Plasmodium.**

Life Cycle of Malaria Parasites



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

- Malaria transmitted by the bite of infected female *Anopheline mosquitoes.*
- *From the* mosquito salivary glands enter the circulation
- localize *in* hepatocytes to multiply, and develop
- Asymptomatic for 5 to 15 days, depending on the *Plasmodium*
- Tissue schizonts rupture,
- releasing thousands of merozoites that enter the circulation, invade erythrocytes where mature schizonts form
- Schizont-containing erythrocytes rupture, each releasing 6 to 32 merozoites this process that produces febrile attacks.

Antimalarial Drugs

- **Chloroquine:**
  - **Most useful agent to terminate an acute attack.**
  - **Available as oral, IV, and IM preparation.**
  - **Resistance develops.**
  - **Causes N, headache, and is teratogenic.**

Antimalarial Drugs

- **Quinine:**
  - **Oldest drug, from Cinchona tree.**
  - **Many actions**
  - **Toxic**
  - **Still used, no resistance to its action**
- **Artemisinin:**
  - **New drug, from Sweet wormwood, الشيح**
- **Doxycycline**
- **Pyrimethamine**

Anthelmintics

Infection by *helminths* (worms)

- May be limited solely to the intestinal lumen

- May involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue.

helminths have either

- a simple cycle of egg deposition and development of the egg to produce a mature worm,
- others must progress through one or more hosts and one or more morphological stages, each metabolically distinct from the other, before emerging as an adult

Pathogenic helminths can be divided into the following

- *cestodes* (flatworms),
- *nematodes* (roundworms),
- *trematodes* (flukes)
- *Acanthocephala* (thorny-headed worms).

CESTODES : general properties

- Flat worms, tape-like, Segmented parasites
- Length range from mm to meters
- Scolex (Head) provided with suckers, Hooks +/-
- Adult worms are in Gastrointestinal tract
- Digestive tract is absent, absorb nutrients from body wall
- Hermophrodites, Reproductive system, Excretory & Nervous systems present
- complete chain of segments known as ***strobila,*** Segment – **Proglottid**
- Life span – 5 to 25 years

Nematode
the roundworms

- The body of a nematode is long and narrow, resembling a tiny thread in many cases, and this is the origin of the group's name
- Most living roundworms are microscopic, On the other hand, one species of parasitic nematode can reach 13 meters in length

Trematodes

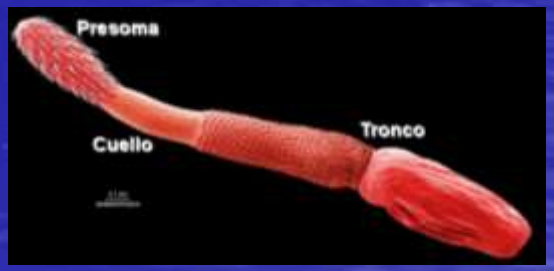
الديدان المثقوبة

- Trematode infections occur worldwide.
- Trematodes, also called flukes, cause various clinical infections in humans.
- The parasites are so named because of their conspicuous suckers, the organs of attachment

مشوكات الرأسAcanthocephala

•Thorny-headed worms, are parasites that live in the gut of vertebrates and - earlier in their life cycle - within invertebrates.

• Acanthocephalans lack a mouth or alimentary canal. Adult stages live in the intestines of their host and uptake nutrients which have been digested by the host, directly, through their body surface.



Anthelmintics

- are drugs that act either locally to expel worms from the gastrointestinal tract or systemically to eradicate adult helminths or developmental forms that invade organs and tissues

Most available anthelmintic drugs exert their antiparasitic effects by interference with

(1)energy metabolism,

(2)neuromuscular coordination,

(3) microtubular function

(4) cellular permeability

TREATMENT FOR INFECTIONS CAUSED BY NEMATODES

Piperazine

- Prolonged treatment and might need a purgative
- Piperazine (Vermizine) contains a heterocyclic ring that lacks a carboxyl group.

Piperazine

- It acts on the musculature of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. this results in expulsion of the worm.
- Piperazine acts as an agonist at gated chloride channels on the parasite muscle.

Diethylcarbamazine

- It interferes with the metabolism of arachidonic acid and blocks the production of prostaglandins,
- resulting in capillary vasoconstriction and impairment of the passage of the microfilaria

Mebendazole"Vermox":

- Widely used, wide spectrum, safe drug.
- Threadworm: *Enterobius vermicularis*, simple teatment: single dose, can be repeated after 3 weeks.

Hockworm: *Ankylostomiasis*: 2tablets*3days.

Roundworm: *Ascaris lumbricoidis*

TREATMENT FOR INFECTIONS CAUSED BY CESTODES

Niclosamide

- Niclosamide is amchlorinated salicylamide that inhibits the production of energy derived from anaerobic metabolism
- Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite

Niclosamide

- The drug affects the scolex and proximal segments of the cestodes,
- resulting in detachment of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel.

TREATMENT FOR INFECTIONS CAUSED BY TREMATODES

Praziquantel

- The neuromuscular effects of praziquantel (Biltricide) appear to increase parasite motility leading to spastic paralysis.
- The drug increases calcium permeability through parasite-specific ion channels, so that the muscle cells of the parasite accumulate calcium

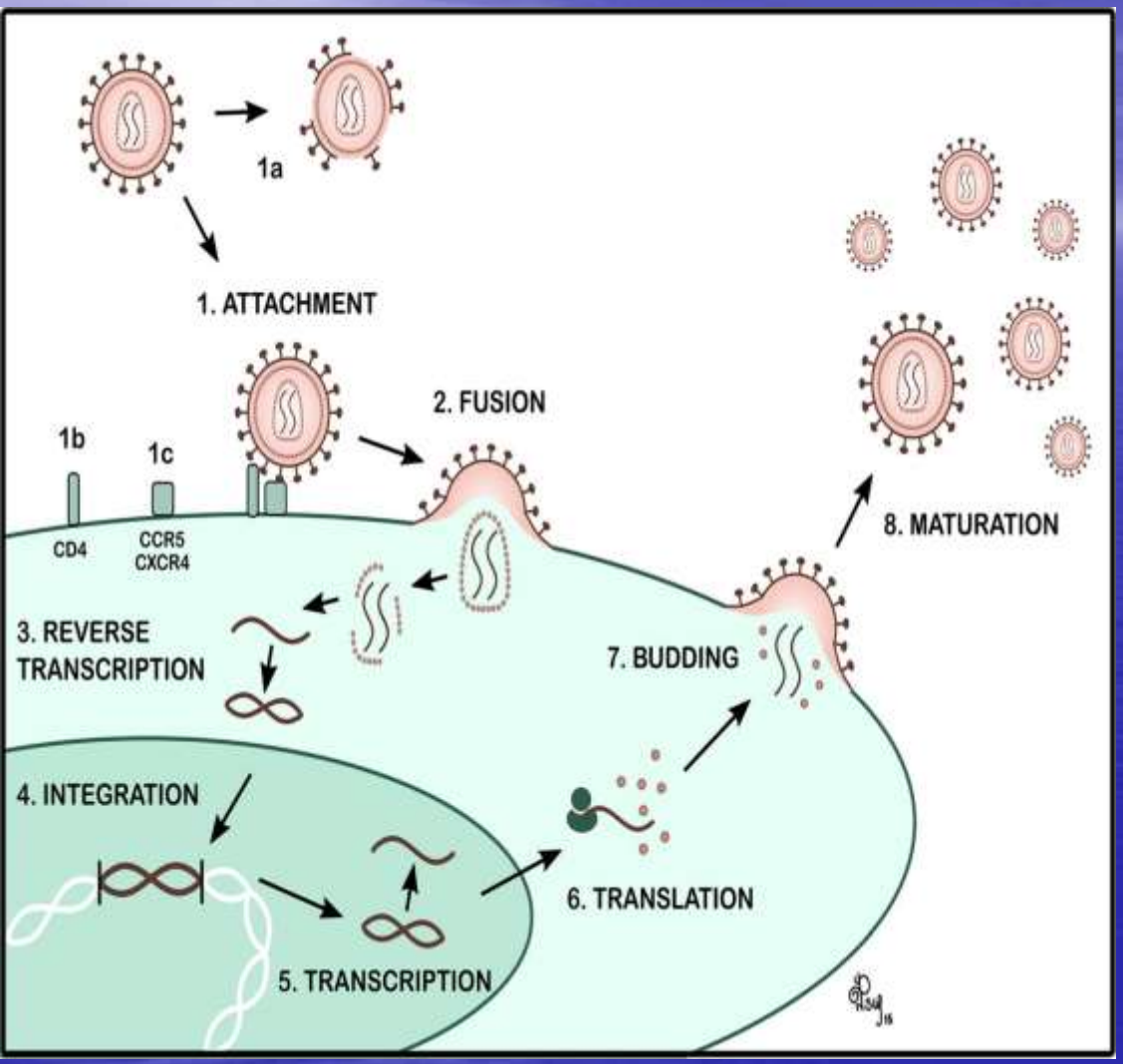
Praziquantel

- This action is followed by exposure of hitherto masked tegmental antigens, lipid anchored protein, and actin.
- Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault.

Antiviral Agents

- Viruses are obligate intracellular microbes
- use many of the host cell's biochemical mechanisms and products to sustain their viability

- A mature virus(virion) can exist outside a host cell and still retain its infective properties.



- the virus

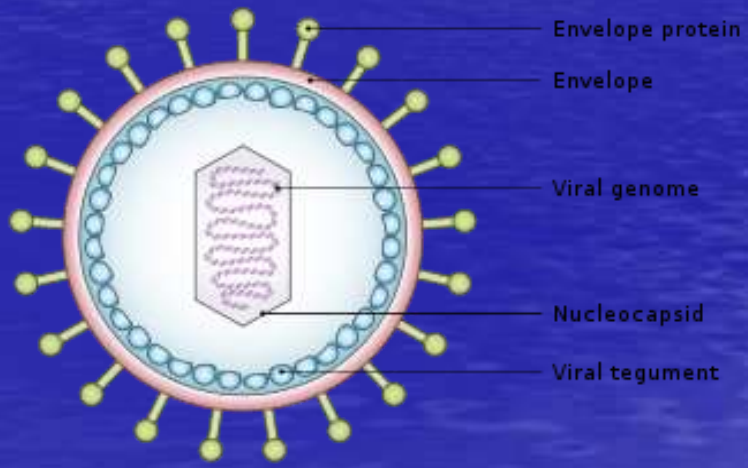
must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles

Classification of Viruses

- Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid).

- Many viruses possess an outer envelope of protein or lipoprotein.

- Viral cores can contain either DNA or RNA



- viruses may be classified as DNA viruses or RNA viruses.

- Further classification is usually based on morphology, cellular site of viral multiplication, or other characteristics.

DNA viruses

- adenoviruses (colds, conjunctivitis)
- hepadnaviruses (hepatitis B);
- herpesviruses (cytomegalovirus chickenpox)
- papillomaviruses (warts)

RNA viruses

- arborviruses (yellow fever)
- arenaviruses (meningitis);
- orthomyxoviruses(influenza);
- paramyxoviruses (measles, mumps);
- picornaviruses (meningitis, colds);
- rubella virus (German measles)
- retroviruses (AIDS).

Antiviral Agents

Viruses live intracellular, so drugs should be able to enter the human cells.

The most encountered viral infections of the GI tract

Cytomegalovirus (CMV)

- CMV is a highly prevalent infection globally and is capable of producing severe systemic disease mostly in neonates, elderly and immunocompromised patients.
- However, immunocompetent patients can also be affected.
- CMV involvement of the GI tract is the most common manifestation of an active CMV infection.
- Primary CMV infection often cause an asymptomatic syndrome.
- CMV can remain latent in the macrophages after the primary infection leading to reactivation at a later time

Herpes simplex virus (HSV)

- HSV most commonly involve the esophagus and the anorectal region; however it can cause infections throughout the GI tract.
- Although most immunocompetent patients have self-limited disease, immunocompromised patients are at risk of disseminated infection.
- Patients with HSV esophagitis often present with acute onset nausea and vomiting, chest pain and less commonly GI bleeding.
- Immunocompromised patients are at risk of severe complications such as esophageal perforation

Adenovirus

- Enteric Adenovirus types 40 and 41 is transmitted through fecal oral route and primarily affects infants and young children.
- Severe adenovirus infection with high mortality rate can affect immunocompromised patients or transplant recipients.
- Patients often present with watery diarrhea lasting 5–12 days.
- Adenovirus can cause lymphoid hyperplasia leading to obstruction particularly in the pediatric population.

Gastroenteritis Caused by Rotaviruses

- Rotaviruses are double-stranded RNA viruses in the family Reoviridae.
- They are responsible for common diarrheal illness,
- although prevention through vaccination is becoming more common.
- The virus is primarily spread by the fecal-oral route

- These viruses are widespread in children, especially in day-care centers.
- The CDC estimates that 95% of children in the United States have had at least one rotavirus infection by the time they reach age five.
- Due to the memory of the body's immune system, adults who come into contact with rotavirus will not contract the infection or, if they do, are asymptomatic.
-

- The elderly, however, are vulnerable to rotavirus infection due to weakening of the immune system with age,
- so infections can spread through nursing homes and similar facilities.
- In these cases, the infection may be transmitted from a family member who may have subclinical or clinical disease.
- The virus can also be transmitted from contaminated surfaces, on which it can survive for some time.

- Infected individuals exhibit fever, vomiting, and diarrhea.
- The virus can survive in the stomach following a meal, but is normally found in the small intestines, particularly the epithelial cells on the villi.
- Infection can cause food intolerance, especially with respect to lactose.
- The illness generally appears after an incubation period of about two days and lasts for approximately one week (three to eight days).
- Without supportive treatment, the illness can cause severe fluid loss, dehydration, and even death.

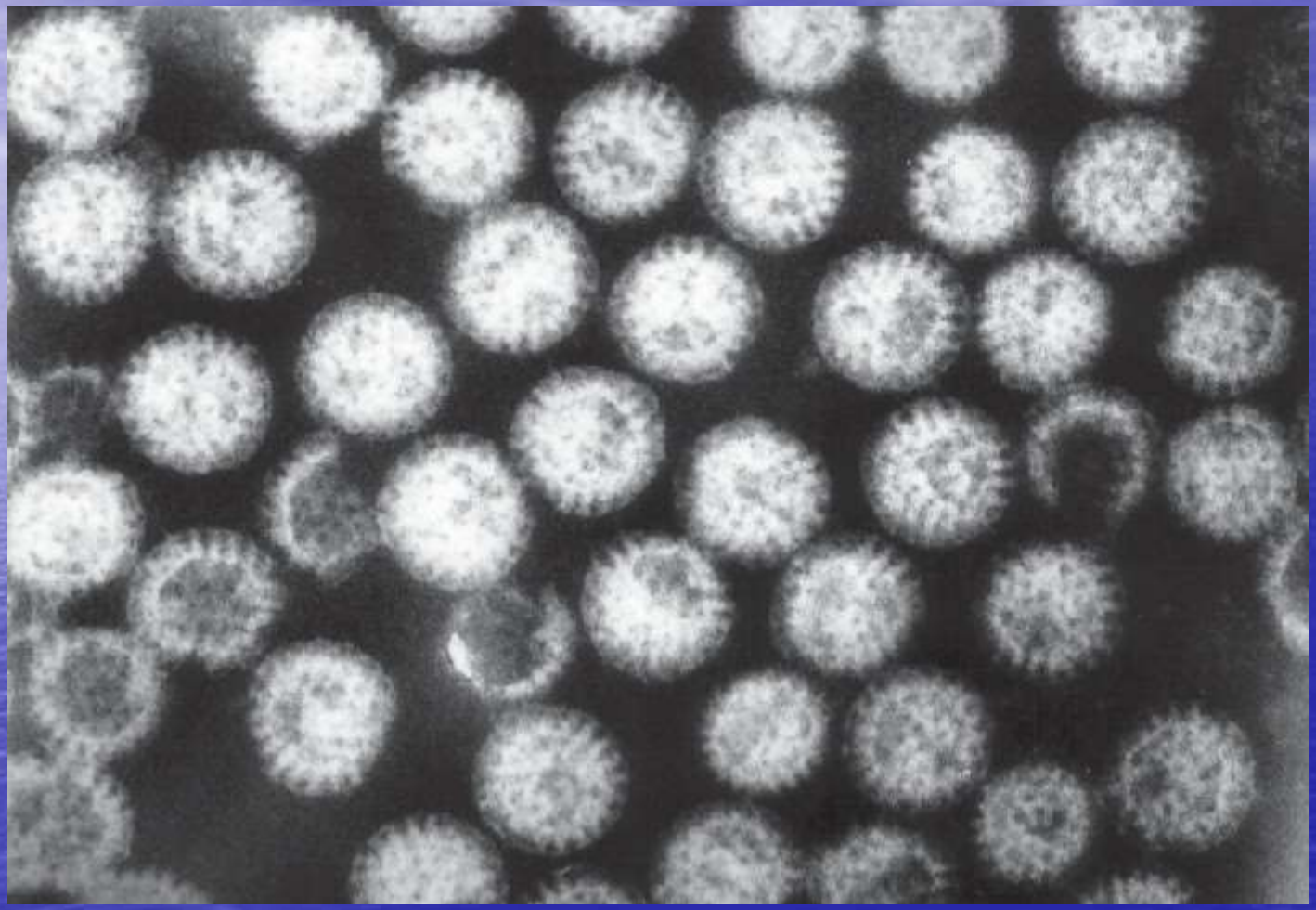
- Even with milder illness, repeated infections can potentially lead to malnutrition, especially in developing countries,
- where rotavirus infection is common due to poor sanitation and lack of access to clean drinking water.
- Patients (especially children) who are malnourished after an episode of diarrhea are more susceptible to future diarrheal illness, increasing their risk of death from rotavirus infection.

diagnosis

- The most common clinical tool for diagnosis is enzyme immunoassay, which detects the virus from fecal samples.
- Latex agglutination assays are also used. Additionally, the virus can be detected using electron microscopy and RT- PCR.

Treatment

- supportive with oral rehydration therapy.
- Preventive vaccination is also available.
- In the United States, rotavirus vaccines are part of the standard vaccine schedule and administration follows the guidelines of the World Health Organization (WHO).
- The WHO recommends that all infants worldwide receive the rotavirus vaccine, the first dose between six and 15 weeks of age and the second before 32 weeks.



Rotaviruses in a fecal sample are visualized using electron microscopy

Gastroenteritis Caused by Noroviruses

- Noroviruses, commonly identified as Norwalk viruses, are caliciviruses.
- Several strains can cause gastroenteritis.
- There are millions of cases a year, predominately in infants, young children, and the elderly.
- These viruses are easily transmitted and highly contagious.
- They are known for causing widespread infections in groups of people in confined spaces, such as on cruise ships.

- The viruses can be transmitted through direct contact, through touching contaminated surfaces, and through contaminated food.
- Because the virus is not killed by disinfectants used at standard concentrations for killing bacteria, the risk of transmission remains high, even after cleaning.

- The signs and symptoms of norovirus infection are similar to those for rotavirus,
- with watery diarrhea, mild cramps, and fever. Additionally, these viruses sometimes cause projectile vomiting.
- The illness is usually relatively mild, develops 12 to 48 hours after exposure, and clears within a couple of days without treatment. However, dehydration may occur.

- Norovirus can be detected using PCR or enzyme immunoassay (EIA) testing.
- RT-qPCR is the preferred approach as EIA is insufficiently sensitive.
- If EIA is used for rapid testing, diagnosis should be confirmed using PCR.
- No medications are available, but the illness is usually self-limiting. Rehydration therapy and electrolyte replacement may be used.
- Good hygiene, hand washing, and careful food preparation reduce the risk of infection.

Viral Causes of Gastroenteritis					
Disease	**Pathogen**	**Signs and Symptoms**	**Transmission**	**Diagnostic Tests**	**Vaccine**
Norovirus gastroenteritis	Noroviruses	Fever, diarrhea, projectile vomiting, dehydration; generally self-limiting within two days	Highly contagious via direct contact or contact with contaminated food or fomites	Rapid enzyme immunoassay confirmed with RT-qPCR	None
Rotavirus gastroenteritis	Rotaviruses	Fever, diarrhea, vomiting, severe dehydration; recurring infections can lead to malnutrition and death	Fecal-oral route; children and elderly most susceptible	Enzyme immunoassay of stool sample, latex agglutination assays, RT-PCR	Preventive vaccine recommended for infants