Gastrointestinal drugs

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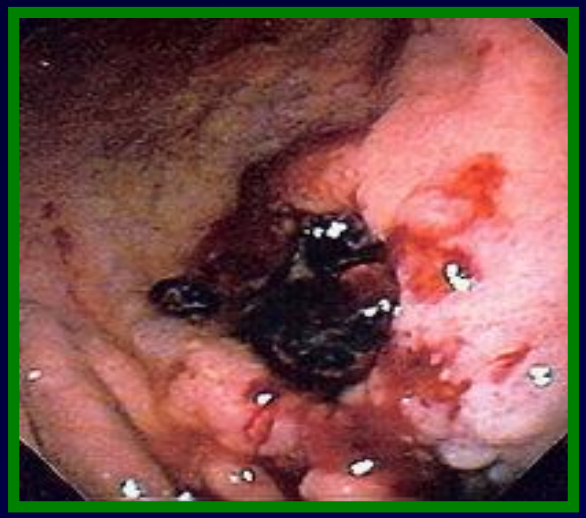
Peptic ulcer

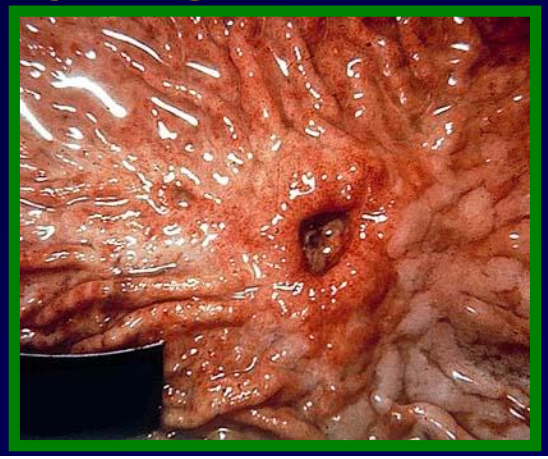
Gastric mucosa -
a sensitive balance of factors preventing self-digestion

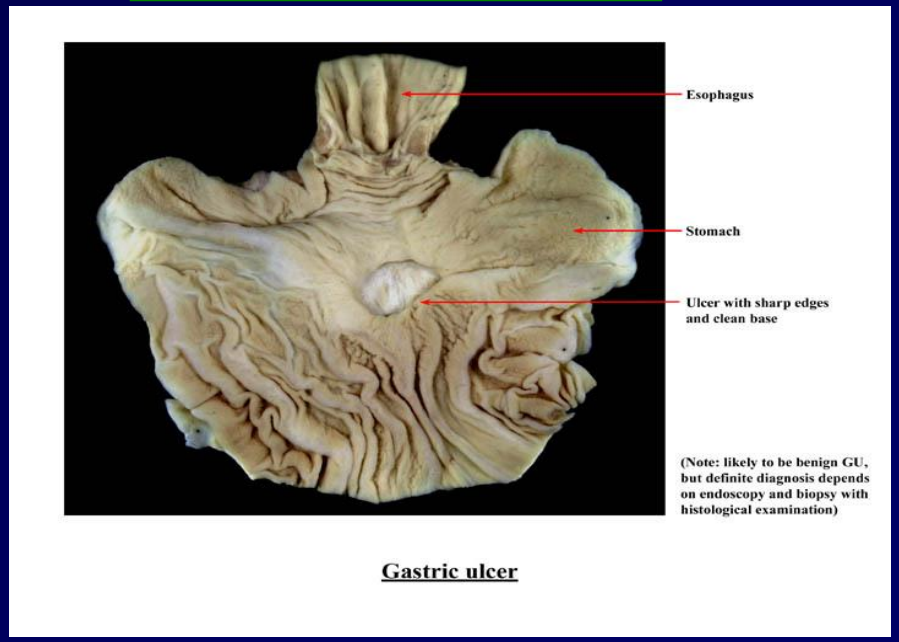
Protective factors
- **bicarbonate**
- **mucus**
- **blood supply**
- **epithelial cell regeneration**

Aggressive factors
- **HCl**
- **pepsin**
- **bile acids**
- **H. pylori**
- **ROS**

Gastric ulcer in antrum of stomach with overlying clot.







Peptic ulcer – *cont.*

H. pylori

Bile reflux

Stress

Prostaglandin synthesis inhibitors

Glucocorticoids

Alcohol

Smoking

Blood flow disturbancy

Regulation of gastric acid secretion

gastric acid is secreted by parietal cells is controled by:

- gastrin ⇧
- histamine ⇧
- acetylcholine ⇧
- prostaglandins E_2, I_2 ⇩

Non-pharmacological therapy

- sleep, stress
- diet /avoid „aggressive“ food, coffeine/
- smoking

Drugs used to treat peptic ulcer

1. Drugs used to diminish effect of HCl

- antisecretory drugs (H_2-blockers, PPI, parasympaticolytics)

- antacids (aluminium hydroxide, magnesium hydroxide, calcium carbonate, sodium bicarbonate)

2. Cytoprotective agents

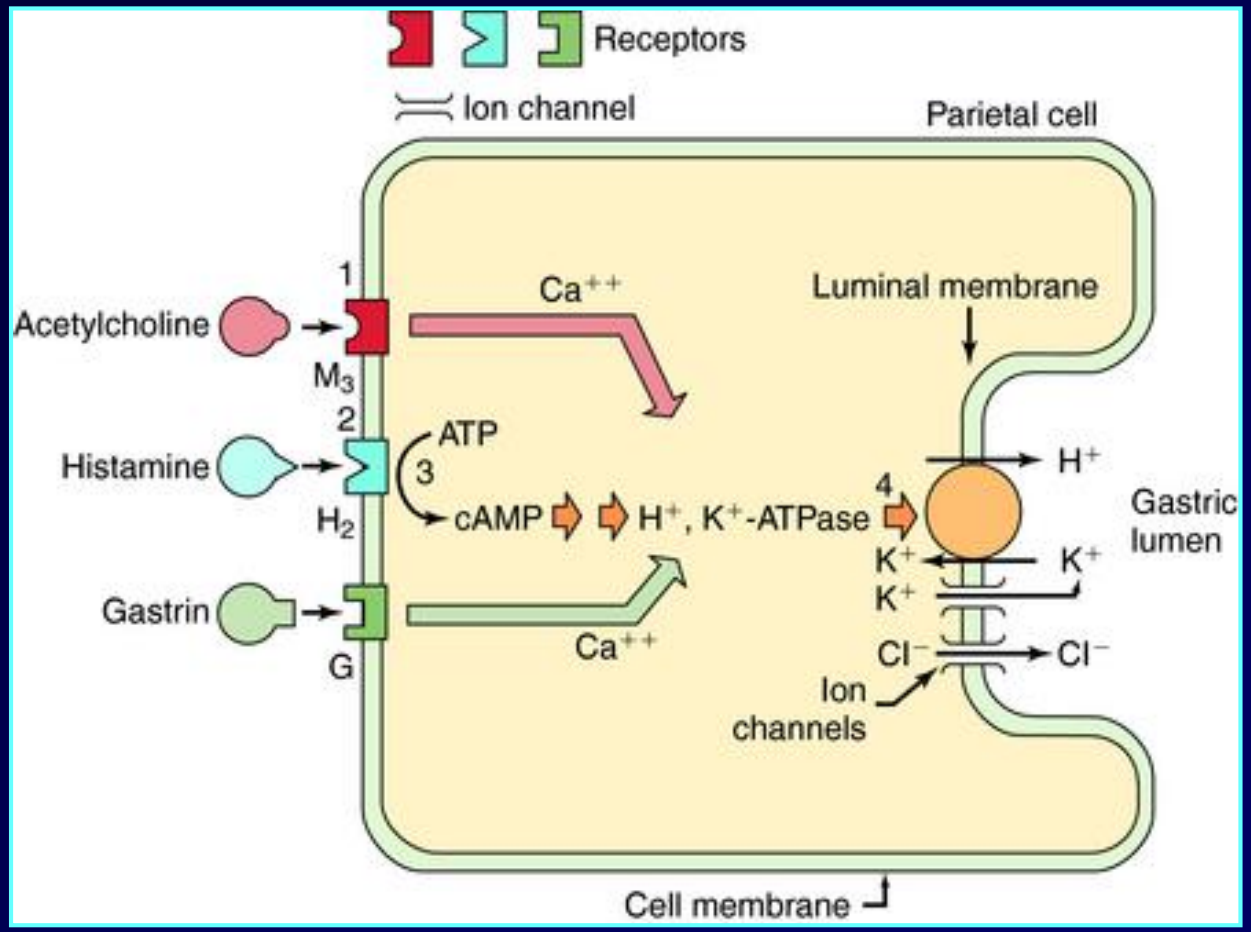
prostaglandins

sucralfate

colloidal bismuth

3. Anti-Helicobacter pylori drugs

Parietal cell



Histamine H_2 receptor blockers

cimetidine, ***ranitidine, nizatidine, famotidine***

- **competetively block the H_2 histamine receptor - decrease basal and food-stimulated acid secretion by 90 % or more**
- **completely inhibit histamine stimulated secretion**
- **partialy inhibit secretion stimulated by gastrin, and acetylcholine**

Pharmacokinetic aspects

- taken orally are well absorbed
- they are distributed widely throughout the body - including breast milk and placenta
- cimetidine has a short serum half-life, blocks cytochrome P_{450}
- ranitidine has longer half-life, 5x more potent than cimetidine, does not inhibit cytochrome P_{450}

- famotidine - similar to rantidine in its action, 20-160x more potent than cimetidine and 3-20x more potent than ranitidine
- nizatidine - similar to ranitidine in action and potency; little first-pass effect - near 100% bioavailability
- ranitidine - oral doses twice daily
- nizatidine and famotidine - once a day

Therapeutic uses

peptic ulcers

- **all agents are equally effective in promoting healing of gastric and duodenal ulcer**

Zollinger-Ellison syndrome

- **rare conditions; gastrin-producing tumor; hypersecretion of gastric acid**
- **however, more effective are PPI**

Acute stres ulcers

- **in patients with acute stress ulcer associated with major physical trauma or great surgery in patients in intensive care units**

***Gastroesophageal reflux disease* (heatburn)**

- **low doses of H_2-antagonist are effective for prevention and treatment of heatburn**
- **they may relieve symptoms for at least 45 minutes**

Unwanted effects

- are usually minor
- diarrhoea, dizziness, muscle pain

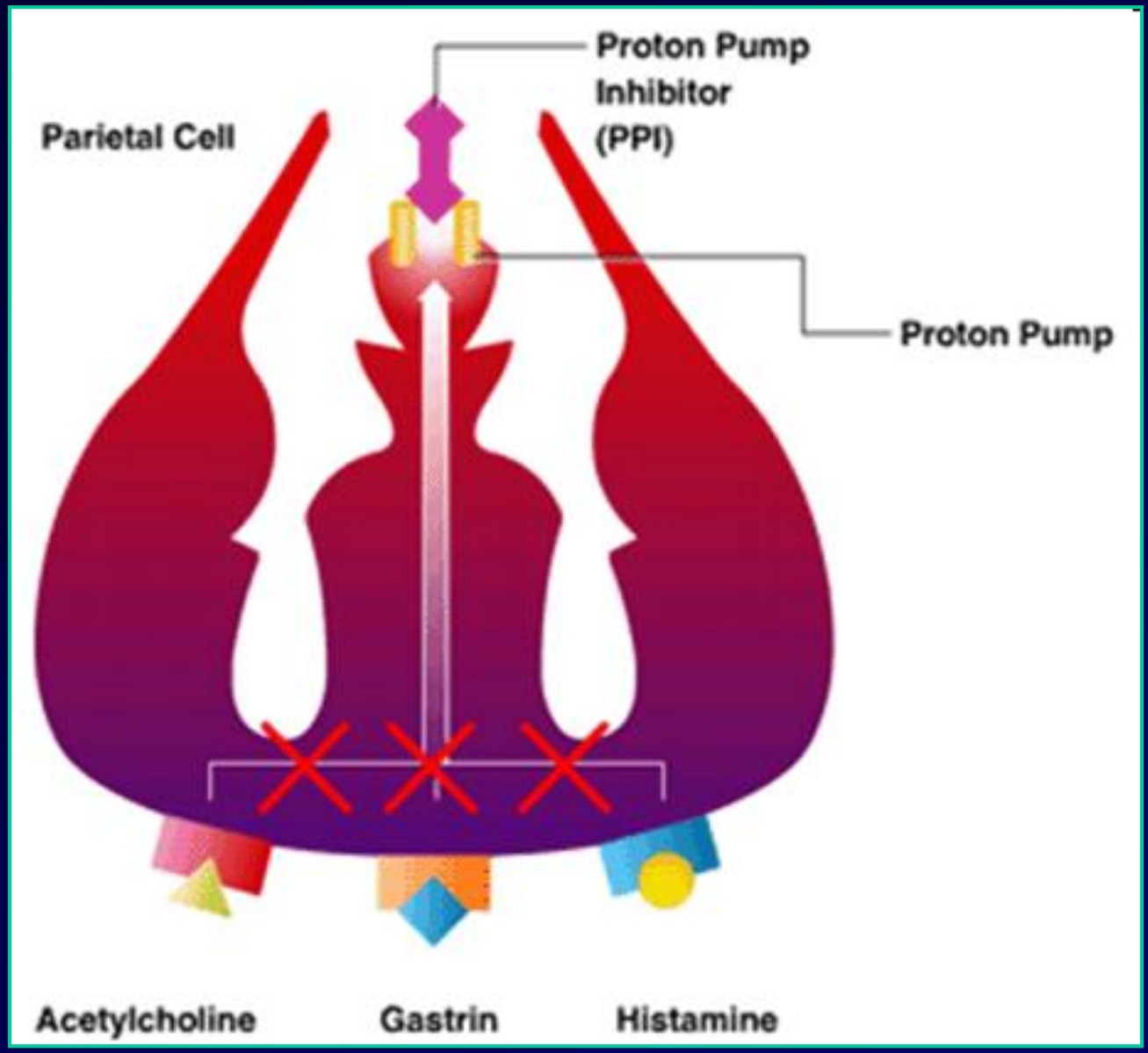
- cimetidine: gynecomastia in men, decrease in sexual function, inhibition of cytochrome P-450

- ranitidine has lower affinity to the androgen receptors and cytochrome P-450
- H_2-antagonists appear to be safe drugs

Proton-pump inhibitors (PPI)

omeprazole, lansoprazole, pantoprazole …

- **they block (irreversible) H^+/K^+-ATPase - the final step in the acid secretory pathway**
- **inhibit basal and stimulated acid secretion more than 90%**
- **acid suppression begins within 1-2 hours with lansoprazole and slightly erlier with omeprazole**
- **they are inactive at neutral pH and they are activated at pH lower than 3**


Proton Pump
Inhibitor
(PPI)
Parietal Cell
Proton Pump
Acetylcholine
Gastrin
Histamine

PPI: Mechanism of Action

- PPI are activated in the acidic compartments of parietal cells
- THUS, they only inhibit actively secreting proton pumps

Pharmacokinetic aspects

- given orally are well absorbed
- they are enteric-coated pills to protect them from premature activation
- after absorption in duodenum - transport to the parietal cells
- single daily dose affects acid secretion about 2-3 days
- they are rapidly and completly eliminated by biotransformation to inactive products
- metabolites are excreted in urine and feces

Therapeutic uses

- proton-pump blockers are useful in patient resistant to other types of antisecretory drugs

Zollinger-Ellison syndrome

- they are extremly valuable in patients with Zollinger-Ellison syndrome

Erosive esophagitis

- used for short-term therapy
- ***Peptic ulcer and gastroesophageal reflux***
- use in peptic ulcer - healing of 90-100% patients after 4 weeks therapy

Unwanted effects

- headache, diarrhea & abdominal pain.
- achlorhydria
- hypergastrinaemia.
- gastric mucosal hyperplasia
  - increased bacterial flora
  - increased risk of community-acquired respiratory infections & nosocomial pneumonia

Long term use:

- Vitamin B_{12} deficiency

Muscarinic-receptor antagonists

pirenzepine, telenzepine - main parasympatholytic antisecretory drugs

- the main effects of parasympathetic stimulation - increase in motility and secretion activity
- muscarinic M1 receptor blockade
- telenzepine - anti-secretory effect 4-10 x ⇧

M-receptor antagonists – *cont.*

- all are given orally
- therapeutic doses - inhibitory effect at other M-receptors - unwanted effects
- pirenzepine shows a greater specificity
- about 20% of patients - dry mouth and blurred vision
- telenzepine – 3-10x more potent than prirenzepine

Antacids

- weak bases that neutralize gastric acid
- they do not decrease acid secretion
- neutralisation of gatric acid results in two therapeutic effects:
  - decrease in total acid delivered to the duodenum
  - inhibition of pepsin activity
- less effective than H_2-blockers or PPI

Antacids – *cont.*

a) systemic - are higly soluble and are rapid absorbed from the gut

sodium bicarbonate

- **act rapidly - ⇧ gastric pH to about 7.4**
- **carbon dioxide is liberated - belching**
- **CO_2 stimulates gastrin release - secondary rise in acid secretion**
- **can be absorbed in intestine and ⇧ blood pH (metabolic alkalosis) and alkalinize urine**
- **sodium bicarbonate should not be prescribed for the long-term therapy of peptic ulcer**

Antacids – *cont.*

b) non-systemic - are less soluble and exert their antacid action locally in the GIT

- they are preferred because of safety and longer duration of action
- non-systemic antacids usually contain calcium, aluminium or magnesium ions

Antacids – *cont.*

aluminium hydroxide - **neutralises HCl forming insoluble aluminium chloride and water**

- **⇧ the gastric juice pH to about 4**
- **it also absorb pepsin**
- **long-continued use can cause constipation**
- **it binds to phosphate - it may lead to phosphorus deficiency**
- **in patients with renal failure - cumulation of aluminium - toxic effects ?**

Antacids – *cont.*

- ***magnesium hydroxide*** **- neutralises gastric acid forming insoluble magnesium chloride**
- **some unchanged drug passes into duodenum - diarrhea**
- **many antacids combine both aluminium and magnesium hydroxides to prevent diarrhea (caused by magnesium) and obstipation (caused by aluminium ions)**
- **rapid onset of action**

- ***calcium carbonate*** **- relatively rapid onset of action - calcium chloride**
- **pH is usually raised to only 4-5**
- **about 10 % of $CaCl_2$ is absorbed - hypercalcemia**

- **calcium ions can stimulate acid secretion, resulting in „acid rebound“**

Mucosal protective agents

- protection of gastric mucosa by:

  formation a barrier over the gastric surface

  stimulation of bicarbonate secretion

  both

Prostaglandins

- antisecretory and cytoprotective actions on the gastric and duodenal mucosa
- in parietal cells inhibit adenylyl cyclase stimulation by histamine - inhibition of essential step in histamine-stimulated acid secretion
- they are more effective in reducing NSAIDs-induced mucosal damage than cimetidine
- *misoprostol* - a synthetic analogue of PGE_2 - causes ulcer healig - comparable with cimetidine effectivity

Sucralfate

- complex of aluminium hydroxide and sulphated sucrose
- selectively binds to necrotic ulcer tissue
- it acts as a barrier to HCl and pepsine and is effective in ulcer healing
- it also stimulates production:
  - mucus
  - bicarbonate
  - prostaglandine

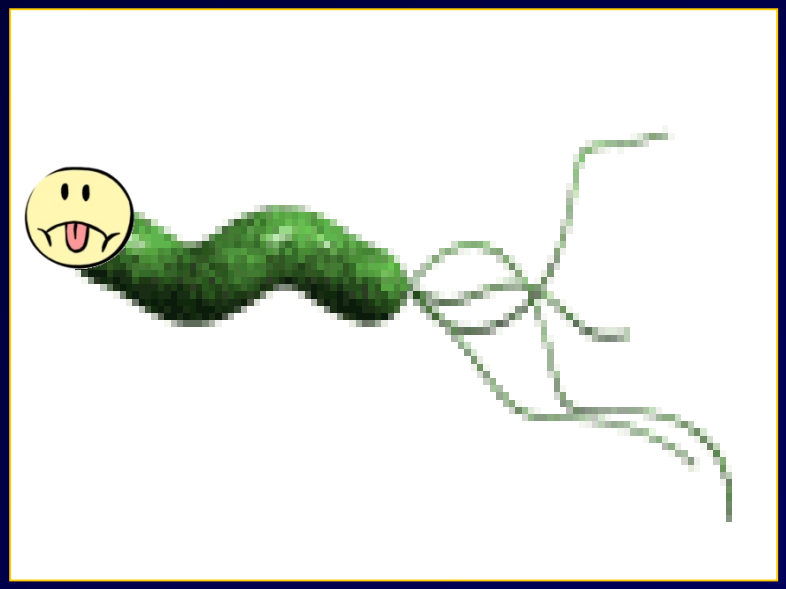
Sucralfate – *cont.*

- it requires an acidic pH for activation - it should not be administered with antacids
- it is administerd orally, 4 times daily before meals
- about 30 % is present in the stomach 3 hours after administration
- only small amount is absorbed systemicaly
- unwanted effects are rare - obstipation

Colloidal bismuth

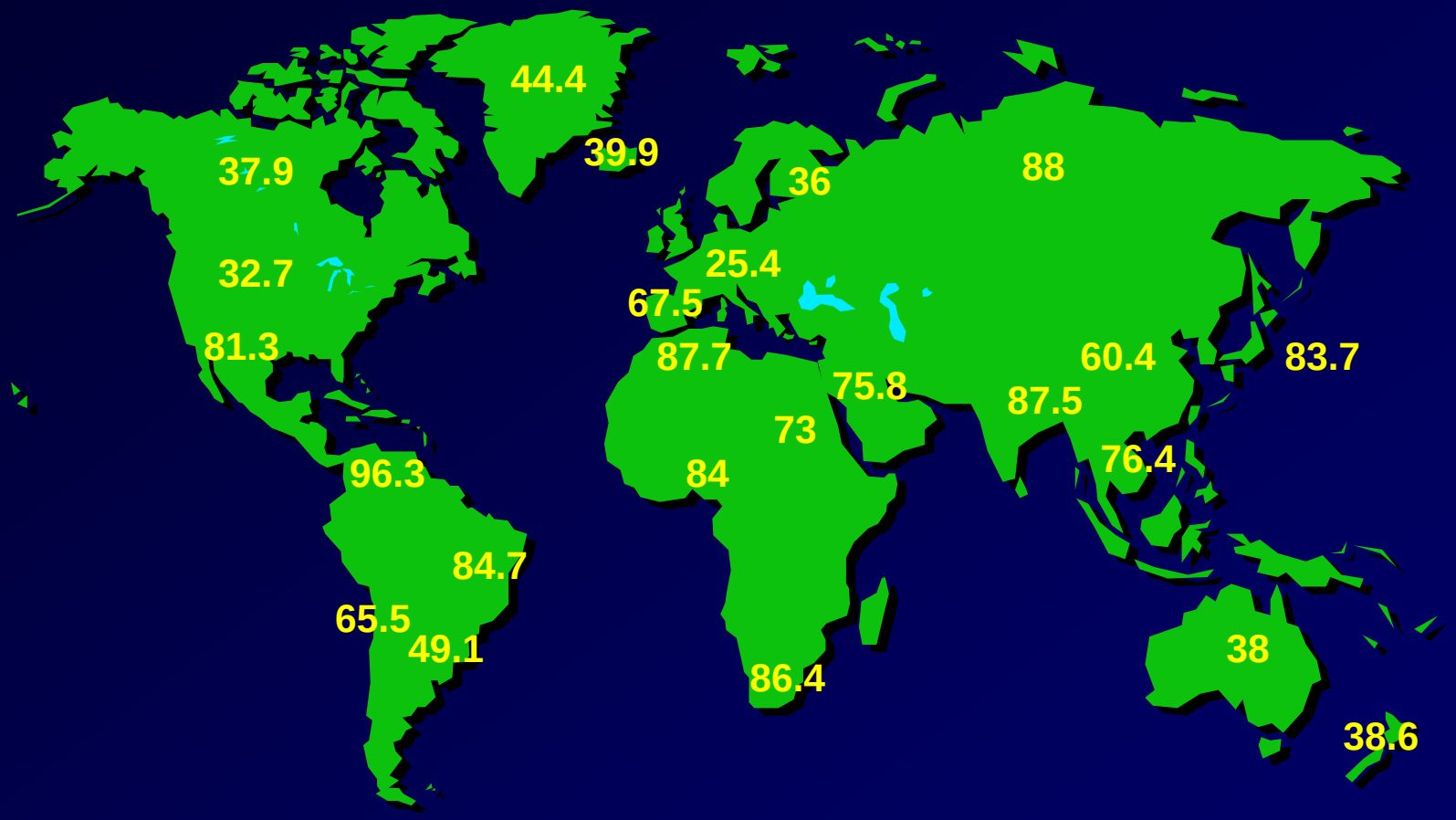
- it may act by coating of ulcer and protecting it
- it is also bactericidal against *Helicobacter pylori*
- *H. pylori* - has been implicated in the pathogenesis of peptic and particularly duodenal ulcer
- erradication - significantly lowers the relapse rate
- colloidal bismuth causes darkening of the faeces and stains tongue and teeth black
- it should not be used in severe renal failure - encephalopathy

Helicobacter pylori



- Gram negative bacterium
- Spiral shaped
- Colonizes human stomach
- High prevalence
- Associated with gastritis, peptic ulcer and gastric cancer

World Prevalence



Percent of the Population Infected with *H. pylori*

Helicobacter pylori

- ***H.pylori*** **- discovered by Marshall and Warren at 1983**

- **2005 – Nobel Prize (Medicine and Physiology)**

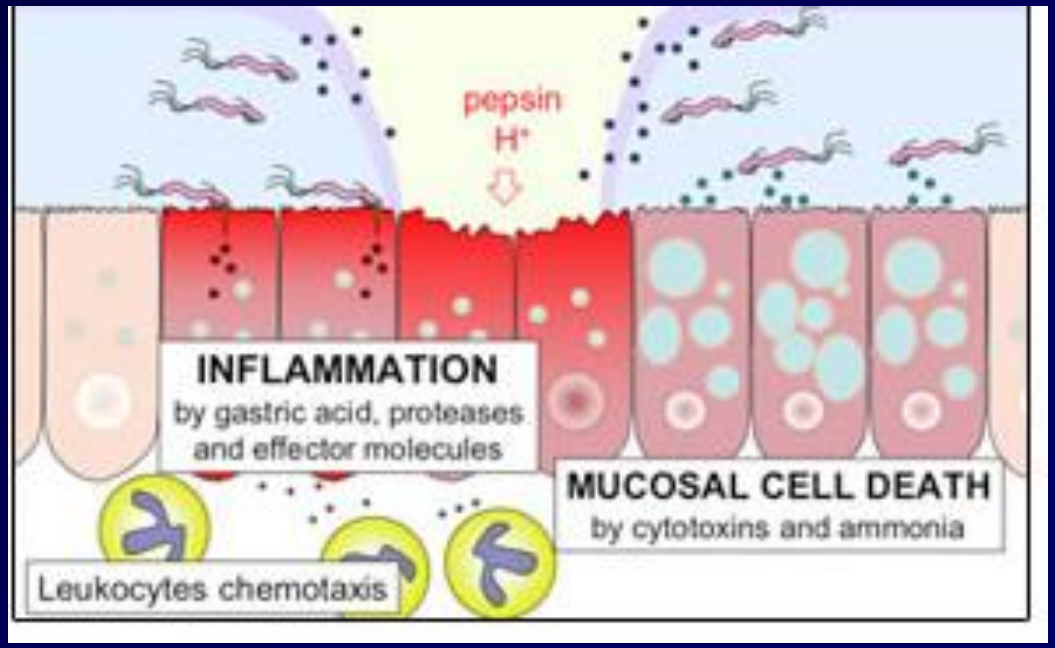
H. pylori-positive ulcers

Mechanisms of gastric mucosa injury in HP+

- **decrease of mucus production**
- **amonia production**
- **liposacharides of HP - stimulation of HCl and pepsin secretion**
- **ROS**
- **phagocytes**

H. pylori

- Secret proteins and toxins that interact with the stomach's epithelial cells
- Leads to inflammation and damage



Treatment

- Goal of treatment to eradicate infection

- **Triple therapy regimens** consist of one anti-secretory agent and two antimicrobial agents for 10 to 14 days

- Triple therapy regimens must
  - have cure rate of approximately 80%
  - be without major side effects
  - minimal induction of resistance

Drugs used for HP erradication

- **Antibiotics:** metronidazole, tetracycline, clarithromycin, amoxicillin
- **Proton pump inhibitors:** omeprazole, lansoprazole
- **Stomach-lining protector:** bismuth subsalicylate

Antidiarrheals

and

laxatives

Diarrhea

Acute diarrhea

- sudden onset in a previously healthy person
- lasts from 3 days to 2 weeks
- self-limiting
- resolves without sequelae

Diarrhea (cont'd)

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

bacterial

viral

drug induced

nutritional

protozoal

Chronic diarrhea

tumors

diabetes

Addison's disease

hyperthyroidism

irritable bowel syndrome

Antidiarrheals: mechanism of action

Adsorbents

- coat the walls of the GI tract
- bind to the causative bacteria or toxin, which is then eliminated through the stool
- examples: bismuth subsalicylate, kaolin-pectin, activated charcoal

Antidiarrheals: mechanism of action (cont'd)

Anticholinergics

- decrease intestinal muscle tone and peristalsis of GI tract
- result: slowing the movement of fecal matter through the GI tract
- examples: belladonna alkaloids, atropine, hyoscyamine

Antidiarrheals: mechanism of action (cont'd)

Opioids

- decrease bowel motility
- decrease transit time through the bowel, allowing more time for water and electrolytes to be absorbed
- opioids are effective in the treatment of moderate-to-severe diarrhea!
- examples: opium tincture, loperamide, diphenoxylate

Opioids (cont'd)

- ***diphenoxylate*** **is about an order of magnitude more potent than morphine**
- ***loperamide*** **acts predominantly on μ receptors in the GI tract, it is 40 to 50 times more potent than morphine; penetrates the CNS very poorly**
- **can be given alone or in combination with antimicrobials (trimethoprim, trimethoprim-sulfamethoxazole, fluoroquinolones)**

Antidiarrheals: mechanism of action (cont'd)

Octreotide, the synthetic analog of ***somatostatin***

1. ↓ of gastric acid and pepsinogen secretion
2. ↓ of intestinal fluid and bicarbonate secretion
3. ↓ of smooth muscle contractility

- must be administered parenterally
- it is useful in treating the symptoms of tumors of the GI tract (carcinoid, VIPoma, glucagonoma, gastrinoma, insulinoma)
- diarrhea refractory to other treatment (*e.g.*, AIDS-related diarrhea)

Antidiarrheals: mechanism of action (cont'd)

Intestinal flora modifiers

- bacterial cultures of *Lactobacillus* organisms work by:
  - supplying missing bacteria to the GI tract
  - suppressing the growth of diarrhea-causing bacteria
- example: *L. acidophilus*

Antidiarrheal agents: side effects

Adsorbents

- constipation, dark stools
- confusion, twitching
- hearing loss, tinnitus, metallic taste, blue gums

Antidiarrheal agents: side effects (cont'd)

Anticholinergics

- urinary retention, dry mouth
- headache, dizziness, confusion, anxiety, drowsiness
- dry skin, rash, flushing
- blurred vision, photophobia, increased intraocular pressure
- hypo-, hypertension, brady-, tachycardia

Antidiarrheal agents: side effects (cont'd)

Opiates

- drowsiness, sedation, dizziness, lethargy
- nausea, vomiting, anorexia, constipation
- respiratory depression
- bradycardia, palpitations, hypotension
- urinary retention
- flushing, rash, urticaria

Antidiarrheal Agents: Interactions

- adsorbents decrease the absorption of many agents, including digoxin, clindamycin, quinidine, and hypoglycemic agents
- antacids can decrease effects of anticholinergic antidiarrheal agents

Laxatives

Constipation

- abnormally infrequent and difficult passage of feces through the lower GI tract
- symptom, not a disease
- disorder of movement through the colon and/or rectum
- can be caused by a variety of diseases or drugs

Laxatives: Mechanism of Action

a) retention of fluid in colonic contents, thereby:

- **increasing bulk and softness**
- **facilitating transit**

b) direct and indirect decrease of net absorption of water and NaCl

c) increased intestinal motility, causing:

- **decreased absorption of salt and water**
- **decreased transit time**

Laxatives classifications

- bulk forming
- emollient
  - stool softeners
  - lubricants
- hyperosmotic
- saline
- stimulant

Laxatives: mechanism of action

- Dietary fiber and bulk forming
- high fiber
- absorbs water to increase bulk
- distends bowel to initiate reflex bowel activity
- examples:
  - psyllium, carboxymethylcellulose
  - dextrose, plant gums

Bulk forming laxatives –*cont.*

- **Must be followed with a large amount of fluid**
  - **If chewed or taken in dry powder form, these agents can cause esophageal obstruction and/or fecal impaction.**

Laxatives: mechanism of action

Stool softeners

- detergent-like drugs:
  - permit mixing of fats and fluids with the fecal mass
  - stool becomes softer and is passed much easier
  - takes several days to work
- example: docusate salts

Laxatives: mechanism of action

Lubricant laxatives

- **oils lubricate the fecal material and intestinal walls, thereby promoting fecal passage**
  - prevent fat-soluble vitamins from being absorbed

- **Example**
  - mineral oil (liquid petroleum)
    - Not digested or absorbed

Laxatives: mechanism of action

Hyperosmotic

- increase fecal water content
- result: bowel distention, increased peristalsis, and evacuation
- examples:
  - polyethylene, glycol sorbitol
  - glycerin, lactulose

Hyperosmotic – cont.

- **Lactulose** - digested in the colon by bacteria to form acids substances
  - acid substances cause water to be drawn into the colon
- **Polyethylene glycol** - must consume 4 liters/3 h
  - Causes a large volume of water to be retained in the colon
  - Acts within one hour, produces a diarrheal state

Laxatives: Mechanism of Action (cont'd)

Saline

- increase osmotic pressure within the intestinal tract, causing more water to enter the intestines
- result: bowel distention, increased peristalsis, and evacuation
- examples:
  - magnesium sulfate, magnesium hydroxide
  - magnesium citrate, sodium phosphate

Laxatives:
Mechanism of Action (cont'd)

Stimulants

- increases peristalsis via intestinal nerve stimulation
- examples:
  - castor oil, senna
  - Cascara, bisacodyl, phenolphthalein

Laxatives: Indications

Laxative Group	
Bulk forming	❑ acute and chronic constipation ❑ irritable bowel syndrome
Emollient	❑ softening of fecal impaction

Laxatives: Indications (cont'd)

Laxative Group	
Hyperosmotic	❑ chronic constipation ❑ diagnostic and surgical preparation ❑ constipation
Saline	❑ diagnostic and surgical preparation ❑ removal of helminths and parasites

Laxatives: Indications (cont'd)

Laxative Group	
Stimulant	❑ acute constipation ❑ diagnostic and surgical bowel preparation

Laxatives: Side Effects

Bulk-forming laxatives have few side effects and minimal systemic effects:

- **allergic reactions (*plant gums*)**
- **flatulence**
- **systemic retention of Na^+ and H_2O *(psyllium, carboxymethylcellulose)***
- ***dextrose* should be avoided in diabetic patients**
- ***cellulose* can reduce the absorption of many drugs**

(cardiac glycosides, salicylates, nitrofurantoin)

- ***psyllium* may bind coumarin derivatives**

Laxatives: Side Effects (cont'd)

Saline laxatives

- up to 20% of the salt is absorbed
- Mg^{2+} - toxicity in patients with impaired renal function
- Na^{+} salts should not be used in patients with CHF or renal disease
- phosphate laxatives can cause hyperphosphatemia and a reduction of plasma Ca^{2+}
- hypertonic salt solutions can produce significant dehydration and must be administered with sufficient water to ensure that no net loss of body water occurs

Laxatives: Side Effects (cont'd)

Hyperosmotic

- ***lactulose:*** flatulence, cramps, abdominal discomfort
- excessive dosage can cause diarrhea, loss of fluid and K^+, hypernatremia, exacerbation of hepatic encephalopathy

Contraindications

- patients requiring a galactose-free diet must not use ***lactulose***
- patients with diabetes must be cautious in using ***lactulose***

Stimulants

- fluid and electrolyte deficits (overdosage)
- they can damage enterocytes (inflammatory response in the colon)
- allergic reactions, osteomalacia
- protein- losing gastroenteropathy
- possible pink coloring of the urine and feces *(phenolphthalein)*
- *an excessive laxative effect and abdominal pain (senna, cascara)*

All laxatives can cause electrolyte imbalances!

Long-term use

- Long-term use of laxatives often results in decreased bowel tone and may lead to dependency.

- Encourage
  - A healthy, high-fiber diet
  - Increased fluid intake

Prokinetic agents

Mechanisms of action

- direct M_2-receptor agonists ***(bethanechol)***
- AChE inhibitors ***(neostigmine)***
- inhibitory presynaptic D_2-receptor blockers ***(metoclopramide)***
- excitatory presynaptic 5-HT_4-receptor agonists ***(cisaprid)***
- excitatory motilin receptor activators ***(erythromycin)***

Clinical usefulness

- prokinetic drugs increase gastric emptying
- they increase tone of the lower esophageal sphincter
- they exhibit antiemetic activity ***(metoclopramide)***
- they improve coordination of gastroduodenal contractions

Adverse effects

- cholinergic agonists have variety of muscarinic side effects (excess GI secretions, cramps, salivation, sweating, urination, lacrimation, defecation)
- dopamine-receptor antagonists can induce dystonia, parkinsonism, hyperprolactinemia (gynecomastia, galactorhea)