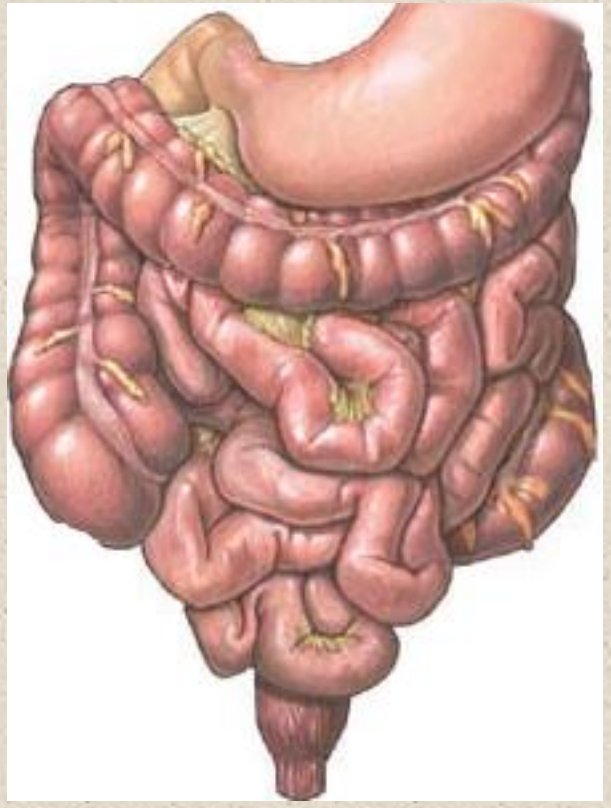
Gastrointestinal Drugs



Dr. Manoj Sharma

✓In addition to its main function of digestion and absorption of food, the gastrointestinal tract is one of the major endocrine systems in the body and has its own integrative neuronal network, the enteric nervous system.

✓which contains almost the same number of neurons as the spinal cord.

THE INNERVATION AND HORMONES OF THE GASTROINTESTINAL TRACT :-

•The blood vessels and the glands (exocrine, endocrine and paracrine) that comprise the gastrointestinal tract are under both neuronal and hormonal control

1. NEURONAL CONTROL:-

There are two principal intramural plexuses in the tract:

- ***Myenteric*** **plexus (Auerbach's plexus): B/W outer, longitudinal and middle, circular muscle layers, and**
- ***Submucous*** **plexus (Meissner's plexus): on the lumenal side of the circular muscle layer.**

✓**These plexuses are interconnected, and their ganglion cells receive preganglionic parasympathetic fibres from the vagus, which are mostly cholinergic and excitatory, although a few are inhibitory.**

✓**Incoming sympathetic fibres are largely postganglionic, and these, in addition to innervating blood vessels, smooth muscle and some glandular cells directly, may terminate in these plexuses, where they inhibit acetylcholine secretion.**

✓**The neurons within the plexuses constitute the *enteric nervous system* and secrete not only acetylcholine and noradrenaline (norepinephrine), but also 5-hydroxytryptamine, purines, nitric oxide and a variety of pharmacologically active peptides.**

✓**The enteric plexus also contains sensory neurons, which respond to mechanical and chemical stimuli.**

2. HORMONAL CONTROL :-

- The hormones of GIT include both:-

    1. Endocrine secretion and
    2. Paracrine secretions.

- The endocrine secretions (i.e. substances released into the bloodstream) are mainly peptidic in nature and are synthesised by endocrine cells in the mucosa. e.g. gastrin and cholecystokinin.

- The paracrine secretions include many regulatory peptides released from special cells found throughout the wall of the tract.

- These hormones act on nearby cells, and in the stomach: mainly is histamine.

- Some of these paracrine factors also function as neurotransmitte.

✓Orally administered drugs are absorbed in the GIT .

✓The main functions of GIT that are important from the viewpoint of pharmacological intervention are:

- Gastric Secretion
- Vomiting (emesis)
- Motility of the bowel and the expulsion of the faeces
- Formation and excretion of bile

GASTRIC SECRETION:-

- The stomach secretes about 2.5 litres of gastric juice daily.

- The principal exocrine secretions are proenzymes such as
  - *Prorennin* and P*epsinogen* from *chief* or *peptic* cells, and
  - hydrochloric acid (HCl) and intrinsic factor secreted by the *parietal* or *oxyntic* cells.

- Mucus-secreting cells abound among the surface cells of the gastric mucosa.

- Bicarbonate ions are also secreted and are trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6-7 in the face of a much more acidic environment (pH 1-2) in the lumen.

- Alcohol and bile can disrupt this layer.

- Locally produced 'cytoprotective' prostaglandins stimulate the secretion of both mucus and bicarbonate.

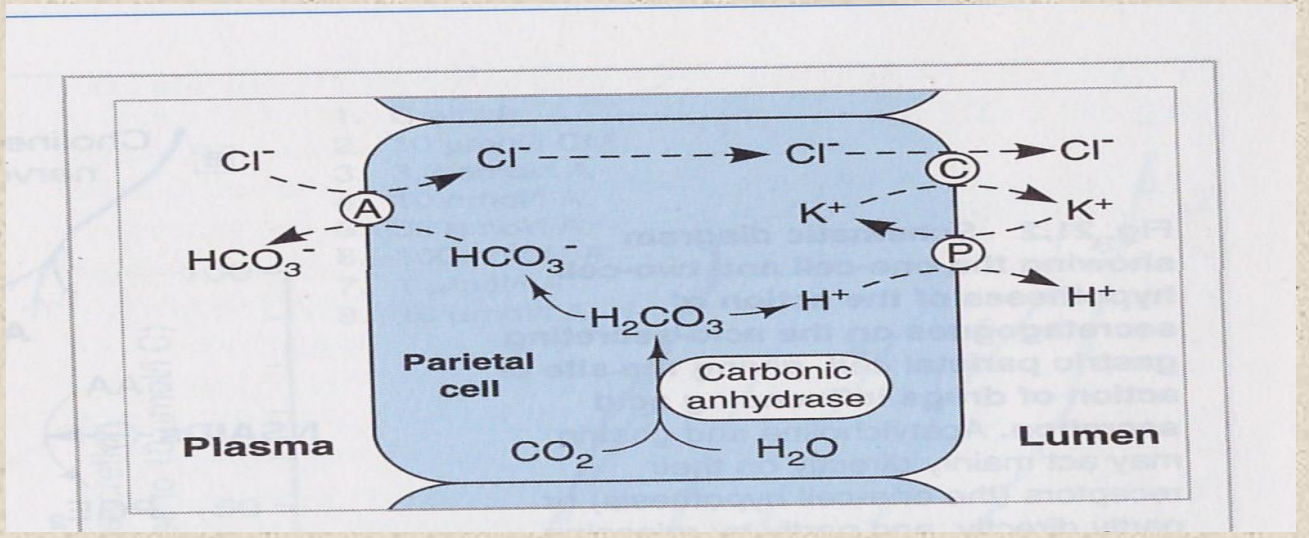
- Disturbances in these secretory and protective mechanisms are thought to be involved in the pathogenesis of peptic ulcer, and the therapy of this condition includes drugs that modify each of these factors.

THE REGULATION OF ACID SECRETION BY PARIETAL CELLS :-

•The regulation of acid secretion by parietal cells is especially important in the pathogenesis of peptic ulcer, and constitutes a particular target for drug action.

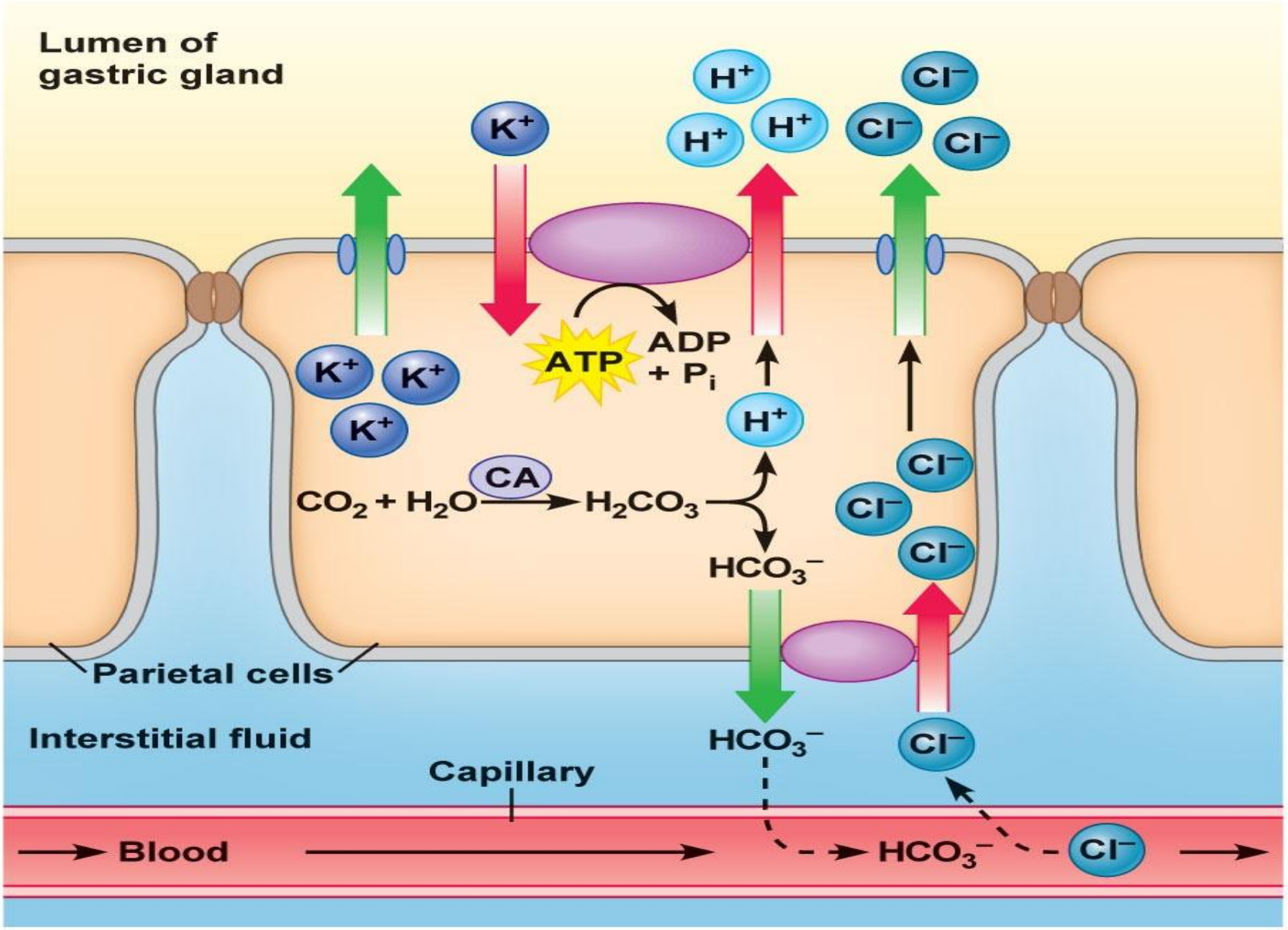
• The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH < 1,

•The concentration of hydrogen ions being more than a million times higher than that of the plasma.



•The Cl^- is actively transported into *canaliculi* in the cells that communicate with the lumen of the gastric glands and thus with the stomach itself.

• This Cl^- secretion is accompanied by K^+, which is then exchanged for H^+ from within the cell by a K^+/H^+ ATPase ($^+$ and bicarbonate ions. The latter exchanges across the basal membrane of the parietal cell for Cl^-.



- **The principal stimuli acting on the parietal cells are:**
  - **Gastrin (a stimulatory hormone)**
  - **Acetylcholine (a stimulatory neurotransmitter)**
  - **Histamine (a stimulatory local hormone)**
  - **Prostaglandins E_2 and I_2 (local hormones that inhibit acid secretion**

Gastrin :-

Gastrin is a peptide hormone synthesised in endocrine cells of the mucosa of the gastric antrum and duodenum, and secreted into the portal blood.

Its main action is stimulation of the secretion of acid by the parietal cells, but there is controversy about the precise mechanism of stimulatory action.

Gastrin also indirectly increases pepsinogen secretion, stimulates blood flow and increases gastric motility.

Release of this hormone is controlled both by neuronal transmitters and blood-borne mediators, as well as the chemistry of the stomach contents.

Gastrin secreation is inhibited when PH of the gastric content falls to2.5 or lower.

Acetylcholine:

It is released from (e.g. vagal) neurons and stimulates specific muscarinic receptors on the surface of the parietal cells and on the surface of histamine-containing cells.

Histamine:

- Histamine play important role in gastric secretion.

- Within the stomach, mast cells (or histamine-containing cells similar to mast cells) lying close to the parietal cell release a steady basal release of histamine, which is further increased by gastrin and acetylcholine.

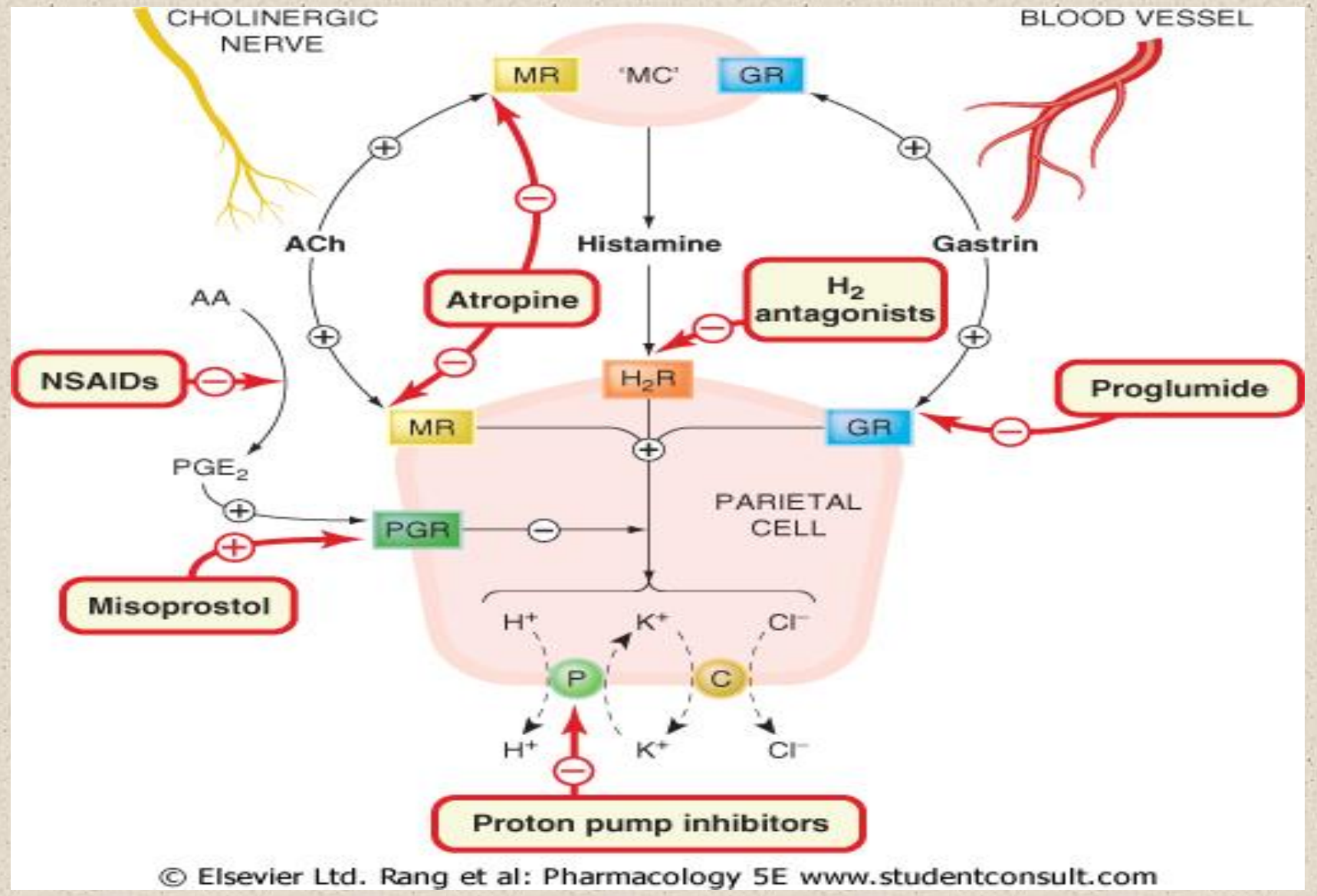
- The hormone acts on parietal cell H_2 receptors, which are responsive to histamine concentrations that are below the threshold required for vascular H_2 receptor activation

The coordinated role of acetylcholine, histamine and gastrin in regulating acid secretion :-

Secretion of gastric acid, mucus and bicarbonate

- The control of the gastrointestinal tract is through nervous and humoral mechanisms.
  - Acid is secreted from gastric parietal cells by a proton pump (K^+/H^+ ATPase).
  - The three endogenous secretagogues for acid are histamine, acetylcholine and gastrin.
  - Prostaglandins E_2 and I_2 inhibit acid, stimulate mucus and bicarbonate secretion, and dilate mucosal blood vessels.

- The genesis of peptic ulcers involves:
  - infection of the gastric mucosa with *Helicobacter pylori.*
  - an imbalance between the mucosal-damaging (acid, pepsin) and the mucosal-protecting agents (mucus, bicarbonate, prostaglandins E_2 and I_2, and nitric oxide


CHOLINERGIC NERVE
BLOOD VESSEL
MR
'MC'
GR
ACh
Histamine
Gastrin
Atropine
H2 antagonists
AA
NSAIDs
H2R
Proglumide
MR
GR
PGE2
PARIETAL CELL
PGR
Misoprostol
H+
K+
Cl−
P
C
H+
K+
Cl−
Proton pump inhibitors
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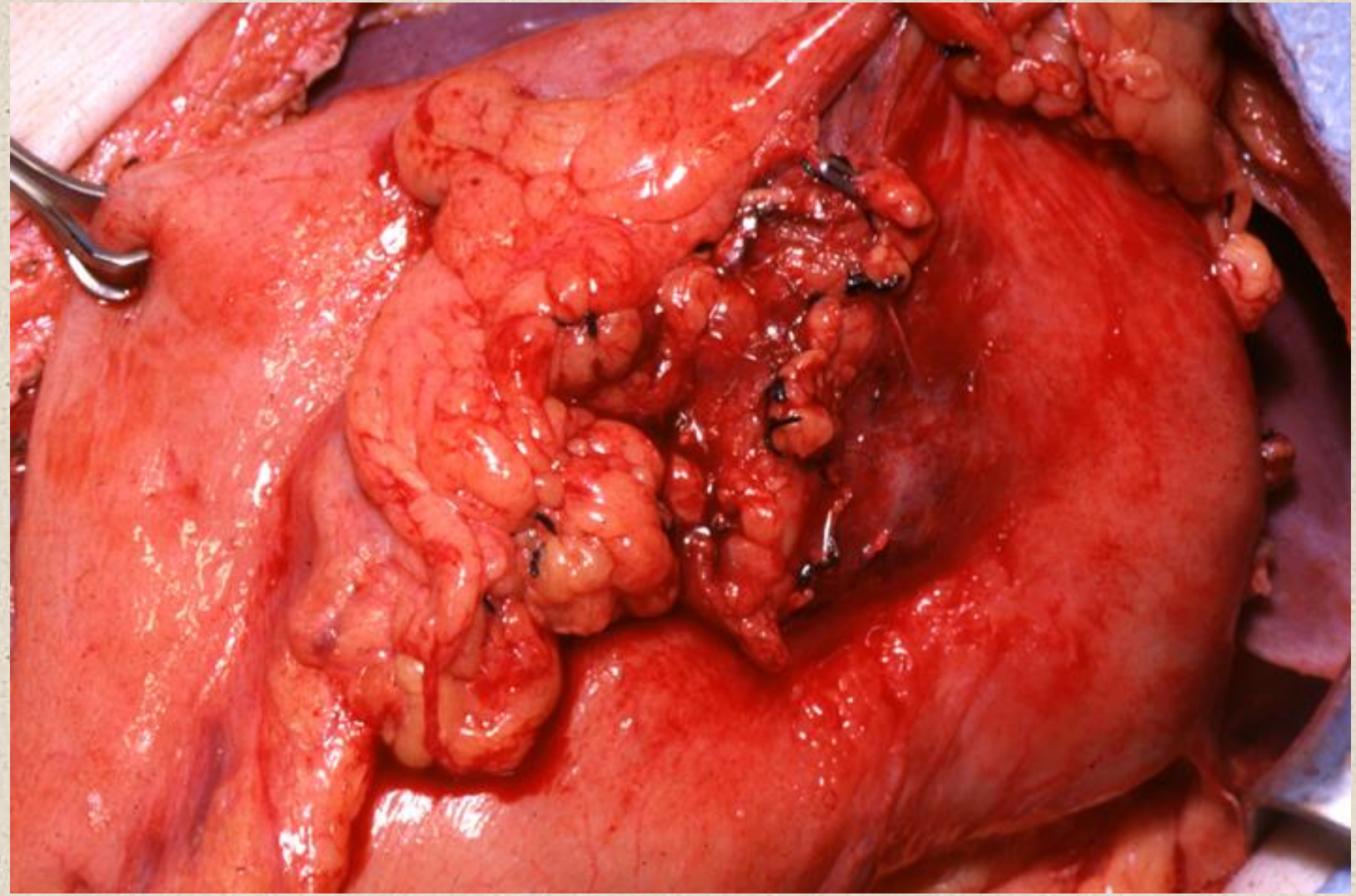
A Gastric Peptic Ulcer



Therapy of peptic ulcer and reflux oesophagitis:-

- **Aims to decrease the secretion of gastric**

Antacids are the simplest of all the therapies for treating the symptoms of excessive gastric acid secretion. They directly neutralise acid, thus raising the gastric pH; this also has the effect of inhibiting the activity of peptic enzymes, which practically ceases at pH 5. Given in sufficient quantity for long enough, they can produce healing of duodenal ulcers but are less effective for gastric ulcers.

Most antacids in common use are salts of magnesium and aluminium. Magnesium salts cause diarrhoea and aluminium salts constipation, so mixtures of these two can, happily, be used to preserve normal bowel function. Some preparations of these substances (e.g. magnesium trisilicate mixture and some proprietary aluminium preparations) contain high concentrations of sodium and should not be given to patients on a sodium-restricted diet. Numerous antacid preparations are available; a few of the more significant are given below.

Magnesium hydroxide is an insoluble powder that forms magnesium chloride in the stomach. It does not produce systemic alkalosis, because Mg^{2+} is poorly absorbed from the gut. Another salt, **magnesium trisilicate**, is an insoluble powder that reacts slowly with the gastric juice, forming magnesium chloride and colloidal silica. This agent has a prolonged antacid effect, and it also adsorbs pepsin

Aluminium hydroxide gel forms aluminium chloride in the stomach; when this reaches the intestine, the chloride is released and is reabsorbed. Aluminium hydroxide raises the pH of the gastric juice to about 4, and also adsorbs pepsin. Its action is gradual, and its effect continues for several hours.[2] Colloidal aluminium hydroxide combines with phosphates in the gastrointestinal tract, and the increased excretion of phosphate in the faeces that occurs results in decreased excretion of phosphate via the kidney. This effect has been used in treating patients with chronic renal failure (see Ch. 24, p. 382).

•Sodium bicarbonate acts rapidly and is said to raise the pH of gastric juice to about 7.4. Carbon dioxide is liberated, and this causes eructation (belching). The carbon dioxide stimulates gastrin secretion and can result in a secondary rise in acid secretion. Because some sodium bicarbonate is absorbed in the intestine, large doses or frequent administration of this antacid can cause alkalosis, the onset of which can be insidious. To avoid this possibility, sodium bicarbonate should not be prescribed for long-term treatment, nor should it be given to patients who are on a sodium-restricted diet.

Alginates or **simeticone** are sometimes combined with antacids. The former are believed to increase the viscosity and adherence of mucus to the oesophageal mucosa, forming a protective barrier (see also below), whereas the latter is a surface active compound that, by preventing 'foaming', can relieve bloating and flatulence.

THE MOTILITY OF THE GASTROINTESTINAL TRACT:-

Drugs that alter the motility of the gastrointestinal tract include:

- **Purgatives, which accelerate the passage of food through the intestine**
- **Agents that increase the motility of the gastrointestinal smooth muscle without causing purgation**
- **Antidiarrhoeal drugs, which decrease motility**
- **Antispasmodic drugs, which decrease smooth muscle tone**

PURGATIVES:-

- **The transit of food through the intestine may be hastened by several different types of drugs, including –**
  - ***Laxatives,***
  - ***Faecal softeners* and**
  - ***Stimulant Purgatives.***
- **These agents may be used to relieve constipation or to clear the bowel prior to surgery or examination.**

➢Bulk and osmotic laxatives

The *bulk laxatives* include

- **Methylcellulose** and
- Certain plant extracts such as **Sterculia**, **Agar**, **Bran** and **Ispaghula husk**.

• These agents are polysaccharide polymers that are not broken down by the normal processes of digestion in the upper part of the GIT.

•They form a bulky hydrated mass in the gut lumen promoting peristalsis and improving faecal consistency.

•They may take several days to work but have no serious unwanted effects.

•The *osmotic laxatives* consist of –

poorly absorbed solutes-the **saline purgatives-and lactulose.**

•The main salts in use are magnesium sulfate and magnesium hydroxide.

•By producing an osmotic load, these agents trap increased volumes of fluid in the lumen of the bowel, accelerating the transfer of the gut contents through the small intestine.

• This results in an abnormally large volume entering the colon, causing distension and purgation within about an hour. Abdominal cramps can occur..

Faecal softeners:-

•**Docusate sodium** is a surface-active compound that acts in the gastrointestinal tract in a manner similar to a detergent and produces softer faeces.
•It is also a weak stimulant laxative.
• Other agents that achieve the same effect include **arachis oil**, which is given as an enema, and **liquid paraffin**, although this is now seldom used.

Stimulant laxatives

The stimulant laxative drugs act mainly by increasing electrolyte and hence water secretion by the mucosa, and also by increasing peristalsis-possibly by stimulating enteric nerves. Abdominal cramping may be experienced as a side effect with almost any of these drugs.

•**Bisacodyl** may be given by mouth but is often given by suppository. In the latter case, it stimulates the rectal mucosa, inducing defecation in 15-30 minutes.
• **Glycerol** suppositories act in the same manner.
• **Sodium picosulfate** and **docusate sodium** have similar actions. The former is given orally and is often used in preparation for intestinal surgery or colonoscopy.

•**Senna** and **dantron** are anthroquinone laxatives. The active principle (after hydrolysis of glycosidic linkages in the case of the plant extract, senna) directly stimulates the myenteric plexus, resulting in increased peristalsis and thus defecation.

•Another member of the family is dantron. As this drug is a skin irritant and may be carcinogenic.

DRUGS THAT INCREASE GASTROINTESTINAL MOTILITY

Domperidone is primarily used as an antiemetic. but it also increases gastrointestinal motility (although the mechanism is unknown).

Clinically, it increases lower oesophageal sphincter pressure (thus inhibiting gastro-oesophageal reflux), increases gastric emptying and enhances duodenal peristalsis.

It is useful in disorders of gastric emptying and in chronic gastric reflux.

Metoclopramide (also an antiemetic) stimulates gastric motility, causing a marked acceleration of gastric emptying.

It is useful in gastro-oesophageal reflux and in disorders of gastric emptying, but is ineffective in paralytic ileus.

Cisapride stimulates acetylcholine release in the myenteric plexus in the upper gastrointestinal tract through a 5-HT_4 receptor-mediated effect.

This raises oesophageal sphincter pressure and increases gut motility.

The drug was used for treating reflux oesophagitis and in disorders of gastric emptying.

ANTIDIARRHOEAL AGENTS :-

- Diarrhoea is the frequent passage of liquid faeces, and this is generally accompanied by abdominal cramps and sometimes nausea and vomiting.

- It may be viewed as a physiological mechanism for rapidly ridding the gut of poisonous or irritating substances.

- There are numerous causes, including underlying disease, infection, toxins and even anxiety
- It may also arise as a side effect of drug or radiation therapy.

During an episode of diarrhoea, there is an increase in the motility of GIT, accompanied by an increased secretion coupled with a decreased absorption of fluid, which leads to a loss of electrolytes (particularly Na^+) and water.

Cholera toxins and some other bacterial toxins produce a profound increase in electrolyte and fluid secretion by irreversibly activating the guanine nucleotide regulatory proteins that couple the surface receptors of the mucosal cells to adenylate cyclase

There are three approaches to the treatment of severe acute diarrhoea:

- **maintenance of fluid and electrolyte balance**
- **use of anti-infective agents**
- **use of spasmolytic or other antidiarrhoeal agents.**

The maintenance of fluid and electrolyte balance by means of oral rehydration is the first priority, and wider application of this cheap and simple remedy could save the lives of many infants in the developing world.

Many patients require no other treatment. In the ileum, as in parts of the nephron, there is cotransport of Na^+ and glucose across the epithelial cell. The presence of glucose (and some amino acids) therefore enhances Na^+ absorption and thus water uptake.

Preparations of sodium chloride and glucose for oral rehydration are available in powder form, ready to be dissolved in water before use.

ANTIMOTILITY AND SPASMOLYTIC AGENTS

The main pharmacological agents that decrease motility are opiates and muscarinic receptor antagonists.
Agents in this latter group are seldom employed as primary therapy for diarrhoea because of their actions on other systems, but small doses of atropine are used, combined with diphenoxylate.

The main opiates used for the symptomatic relief of diarrhoea are-

- **Codeine (a morphine congener),**
- **Diphenoxylate and**
- **Loperamide**

(both pethidine congeners that do not readily penetrate the blood-brain barrier and are used only for their actions in the gut).

All may have unwanted effects including constipation, abdominal cramps, drowsiness and dizziness. Paralytic ileus can also occur. They should not be used in young (< 4 years of age) children.

Loperamide is the drug of first choice for traveller's diarrhoea and is a component of several proprietary antidiarrhoeal medicines.

It has a relatively selective action on the gastrointestinal tract and undergoes significant enterohepatic cycling. It reduces the frequency of abdominal cramps, decreases the passage of faeces and shortens the duration of the illness.

•Muscarinic receptor antagonists decrease spasm by inhibiting parasympathetic activity.

•Agents available include atropine, hyoscine, propantheline and dicycloverine. The last named is thought to have some additional direct relaxant action on smooth muscle.

•Mebeverine, a derivative of reserpine , has a direct relaxant action on gastrointestinal smooth muscle. Unwanted effects are few

Adsorbents:-

Adsorbent agents are used extensively in the symptomatic treatment of diarrhoea,

The main preparations used contain
kaolin, pectin, chalk, charcoal, methyl cellulose and magnesium/ aluminium silicate).

It has been suggested that these agents may act by adsorbing micro-organisms or toxins, by altering the intestinal flora or by coating and protecting the intestinal mucosa,

They are often given as mixtures with other drugs (e.g. kaolin and morphine mixture).

DRUGS AFFECTING THE BILIARY SYSTEM:-

- The commonest pathological condition of the biliary tract is cholesterol *cholelithiasis*,
- i.e. the formation of gallstones with high cholesterol content.
- Surgery is generally the preferred option, but there are orally active drugs that dissolve non-calcified 'radiolucent' cholesterol gallstones.
- The principal agent is Ursodeoxycholic acid, a minor constituent of human bile (but the main bile acid in the bear, hence *urso*).
- Diarrhoea is the main unwanted effect.

Drugs affecting biliary spasm :-

Biliary colic, the pain produced by the passage of gallstones through the bile duct, can be very intense, and immediate relief may be required.

Morphine relieves the pain effectively, but it may have an undesirable local effect because it constricts the *sphincter of Oddi* and raises the pressure in the bile duct.

Buprenorphine may be preferable.

- Pethidine has similar actions, although it relaxes other smooth muscle, e.g. ureter.
- Atropine is commonly employed to relieve biliary spasm because it has antispasmodic action and may be used in conjunction with morphine.
- The nitrates can produce a marked fall of intrabiliary pressure and may be used to relieve biliary spasm

VOMITING :-

The act of vomiting is a physical event that results in the forceful evacuation of gastric contents through the mouth.

It is often preceded by *nausea* (a feeling of 'queaziness' or of impending vomiting) and can be accompanied by *retching* (repetitive contraction of the abdominal muscles with or without actual discharge of vomit).

Vomiting can be a valuable (indeed life-saving) physiological response to the ingestion of a toxic substance (e.g. alcohol),

but it is also an unwanted side-effect of many clinically used drugs, notably in patients receiving cancer chemotherapy.

Vomiting also occurs in early pregnancy, in the form of motion sickness and accompanies numerous disease states (e.g. migraine) and also bacterial and viral infections.

THE REFLEX MECHANISM OF VOMITING

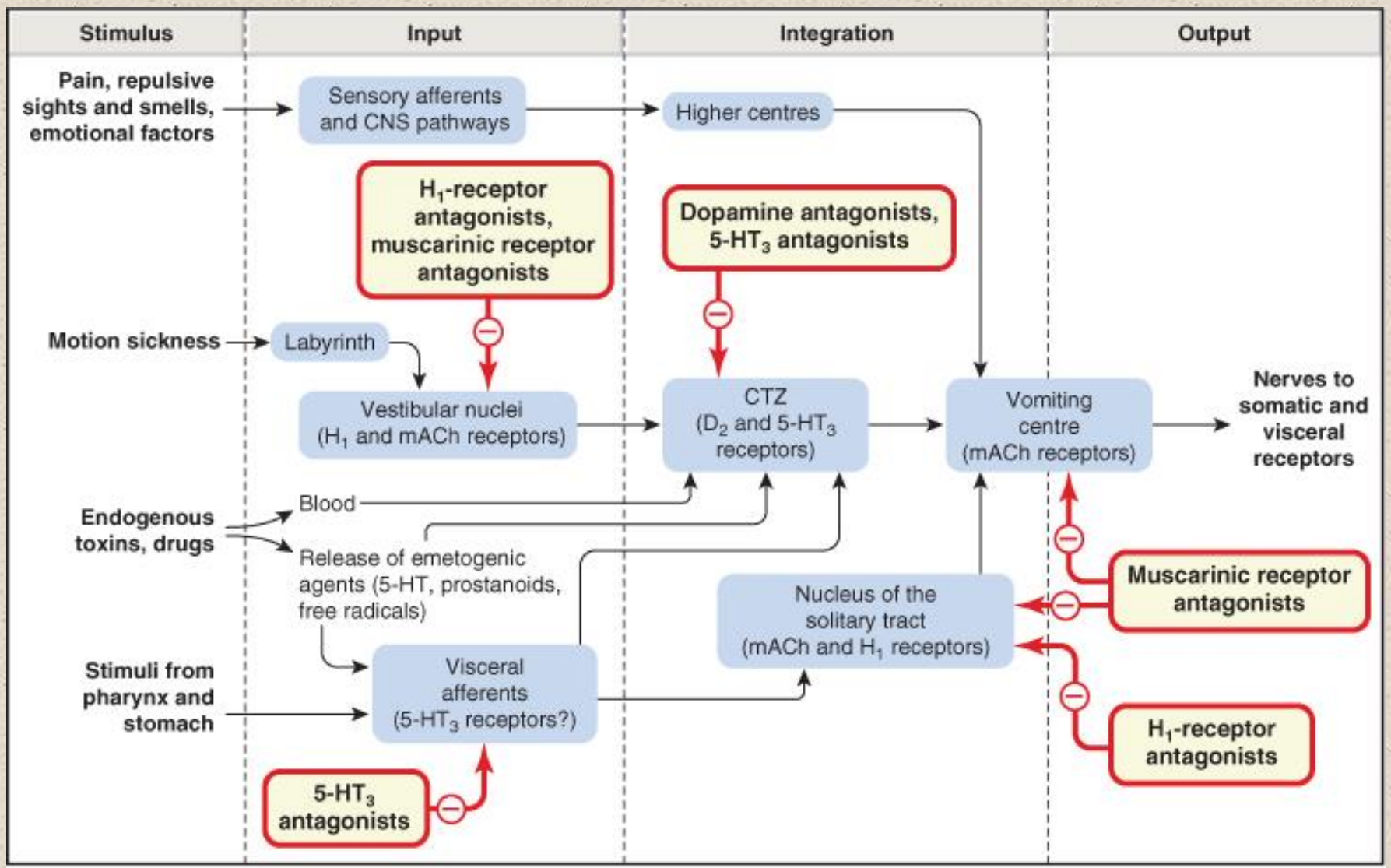
The central neural regulation of vomiting is vested in two separate units in the medulla.

(1) *vomiting centre* and

(2) the *chemoreceptor trigger zone* (CTZ).

- **Emetic stimuli include**
  - **chemicals in blood**
  - **neuronal input from gastrointestinal tract, labyrinth and CNS.**

- **Impulses from chemoreceptor trigger zone, and various CNS centres relay to the vomiting centre.**
-
- **Chemical transmitters include: histamine, acetylcholine, dopamine and 5-hydroxytryptamine, acting on H_1-, muscarinic, D_2- and 5-HT_3-receptors, respectively.**



EMETIC DRUGS:

- In some circumstances, such as when a toxic substance has been swallowed, it may be necessary to stimulate vomiting.
- This should never be attempted if the patient is not fully conscious or if the substance is corrosive
- The drug usually used to produce vomiting is ipecacuanha, which acts locally in the stomach.
- Its irritant action results from the presence of two alkaloids *emetine* and *cephaeline*.
- In cases of poisoning, activated charcoal can also be given to sequester the toxic drug.

•ANTIEMETIC DRUGS:

•Different antiemetic agents are used for different conditions, though there may be some overlap.

•Antiemetic drugs are of particular importance as an adjunct to cancer chemotherapy to combat the nausea and vomiting produced by many cytotoxic drugs.

•These agents can cause almost unendurable nausea and vomiting.*

•In using drugs to treat the morning sickness of pregnancy, the problem of potential damage to the fetus has to be borne in mind. In general, all drugs should be avoided, if possible, during the first 3 months of pregnancy.

1. H_1-receptor antagonists : Meclizine, Cinnarizine, Cyclizine, Dimenhydrinate, Promethazine and Diphenydramine

2. Muscarinic antagonists : (effective treatments for motion sickness and vomiting caused by the presence of irritants in the stomach)
   hyoscine (Scopolamine)
   for prophylaxis and treatment of motion sickness and is often administered as a transdermal patch.

3. 5-HT_3-receptor antagonists :- Ondansetron, Granisetron, Tropisetron and Dolasetron
   particular value in preventing and treating vomiting caused either by radiation therapy in cancer patients or by administration of cytotoxic drugs

4. D_2-receptor antagonists :- Thiethylperazine, Metoclopramide, Domperidone

Antipsychotic phenothiazines, such as chlorpromazine, prochlorperazine and trifluoperazine, are effective antiemetics

5. Cannabinoids (e.g. nabilone & dronabinol)

6. Steroids : - High-dose glucocorticoids (particularly Dexamethasone & Methylpreednisolone can have antiemetic action

7. neurokinin-1 antagonists.

- Main side-effects of principal antiemetics include:
  - drowsiness and antiparasympathetic effects (hyoscine, nabilone > cinnarizine)
  - dystonic reactions (thiethylperazine > metoclopramide)
  - general CNS disturbances (nabilone)
  - headache, gastrointestinal tract upsets (ondansetron

Who Gets Peptic Ulcers

- Peptic Ulcer Disease Affects All Age Groups
  - Can occur in children, although rare
  - Duodenal ulcers tends to occur first at around the age 25 and continue until the age of 75
  - Gastric ulcers peak in people between the ages of 55 and 65
- Men Have Twice The Risk as Women Do
- Genetic Factors
  - High levels of acid production, weakness in mucosal layer, abnormal nonprotective mucus production
- Increase Acid Production and/or Decrease in Bicarbonate and PG Production
  - Caffeine, Cigarettes, Alcohol, Fruit Juices, Stress

What Causes Peptic Ulcer Disease

- *Helicobacter Pylori (H. pylori)*
  - Most ulcers are the result of infection with *H. pylori*
  - *Not all of those infected with H. pylori develop ulcers*
  - *H. pylori MAY* result in a weakening of the mucosal defense systems, allowing for development of ulcer subsequent to acid/pepsin aggression;

What Causes Peptic Ulcer Disease

- NSAIDs

  Long term use of nonsteroidal anti-inflammatory drugs. NSAIDs block COX enzymes and decrease prostaglandins (PGs).

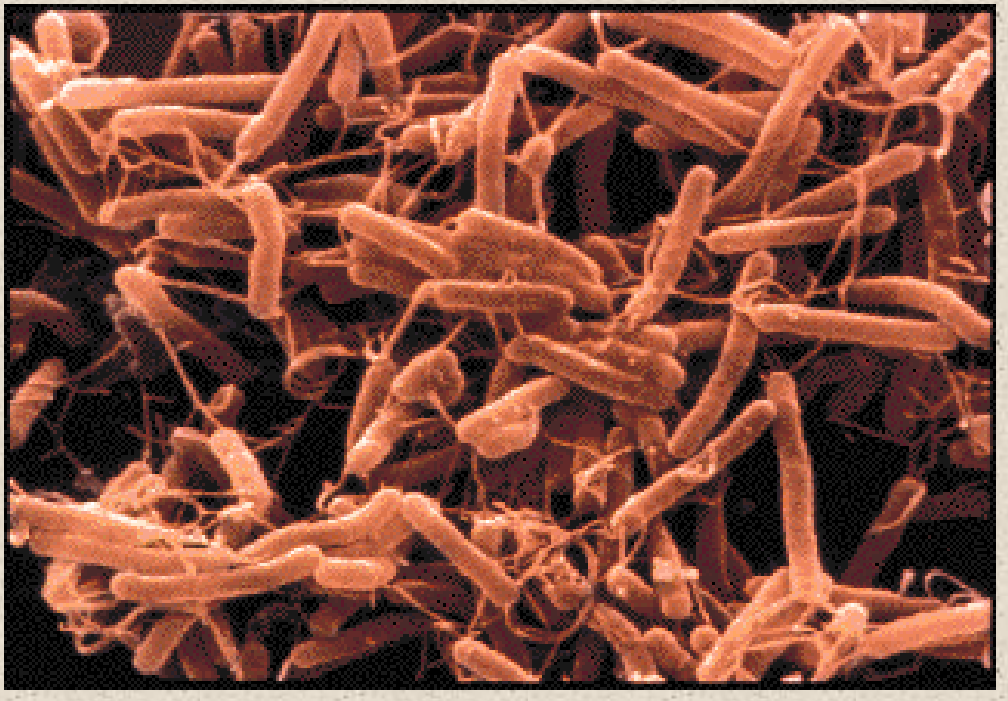
- Gastrinoma (Zollinger-Ellison Syndrome)

  Tumors of the duodenum or pancreas and secrete abnormally high amounts of gastrin which stimulates gastric acid.

- Stress ulcers

  Result of physical trauma (i.e., burn patients).

Helicobacter pylori



Spiral shaped, flagellated, Gram negative bacterium

Omeprazole (Prilosec)

- ***Prototype*** **H^+, K^+-ATPase inhibitor; A prodrug that needs a low pH to be active;**

- ***Irreversible (forms a covalent bond with the proton pump)*** **- long lasting inhibition of acid production;**

- **Profound reduction of gastric acid - elevates gastric pH significantly (20mg/day for 7days will decrease acid by 95%);**

- **Highly protein bound; Metabolized by CYP2C & CYP3A; plasma half life of 1 to2 hours but long duration of action; Should be taken just prior to a meal and should NOT be taken with other acid-suppressing agents.**

Esomeprazole (Nexium)

Simply the S-isomer of omeprazole;

H^+, K^+-ATPase inhibitor;

Given orally.

Rabeprazole (Aciphex)

Lansoprazole (Prevecid)

H^+, K^+-ATPase inhibitor;

Given orally.

Pantoprazole (Protonix)

H^+, K^+-ATPase inhibitor;

An acid-stable form and can be given by i.v.

Proton Pump Inhibitors (PPI)

Well Tolerated

Hypergastrinemia

(can lead to tumor growth in the GI)

Nausea

Headaches, skin rashes

Histamine Receptors

- **H_1 receptors**
  - Smooth muscle
  - Nerves
- **H_2 receptors**
  - Parietal cells

Histamine H_2 Antagonists

- **Cimetidine (Tagamet)**
- **Ranitidine (Zantac)**
- **Famotidine (Pepcid)**
- **Nizatidine (Axid)**

Drugs for Acid-Peptic Disorders
- Cimetidine (Tagamet)

- Competitive H_2 receptor Antagonist;
- Markedly inhibits basal acid secretion *including nocturnal secretion*;
- Readily absorbed after oral administration;
- Relatively brief duration of action (4-8 hr)
  - Given on a multiple dosing schedule;
  - (300-400 mg, 2-4 times daily);
  - Typical therapy is for 4-8 weeks.

Drugs for Acid-Peptic Disorders - Cimetidine (Tagamet)

- **Side effects include *inhibition of the microsomal metabolism of other drugs***

  results in higher blood levels and enhancement of their effects

  – Interactions have been shown with:

Diazepam	Chlordiazepoxide
Theophylline	Phenytoin
Warfarin	Propranolol
Meperidine	Pentobarbital
Lidocaine	and many others...

Drugs for Acid-Peptic Disorders - Ranitidine (Zantac), Famotidine (pepcid), Nizatidine (Axid)

- Same mechanism of action as Cimetidine but a longer duration of action (8 to 12 hrs);
- Can be given less frequently;

  150 or 300 mg, 1-2 times daily
- Less interactions at P450 than Cimetidine.

Drugs for Acid-Peptic Disorders - Anticholinergics

- Blockade of acetylcholine at muscarinic (M_3/M_1) receptors
  - Effectively blocks acid secretion (30 to 40%)
  - Limited by side-effects

- Side-effects are typical of anticholinergics such as atropine
  - Dry mouth
  - Tachycardia
  - Blurred vision
  - Bowel discomfort (constipation)
  - Difficulty in urination

Drugs for Acid-Peptic Disorders - Anticholinergics

- ***General muscarinic receptor antagonists***

  (block all types of muscarinic receptors)

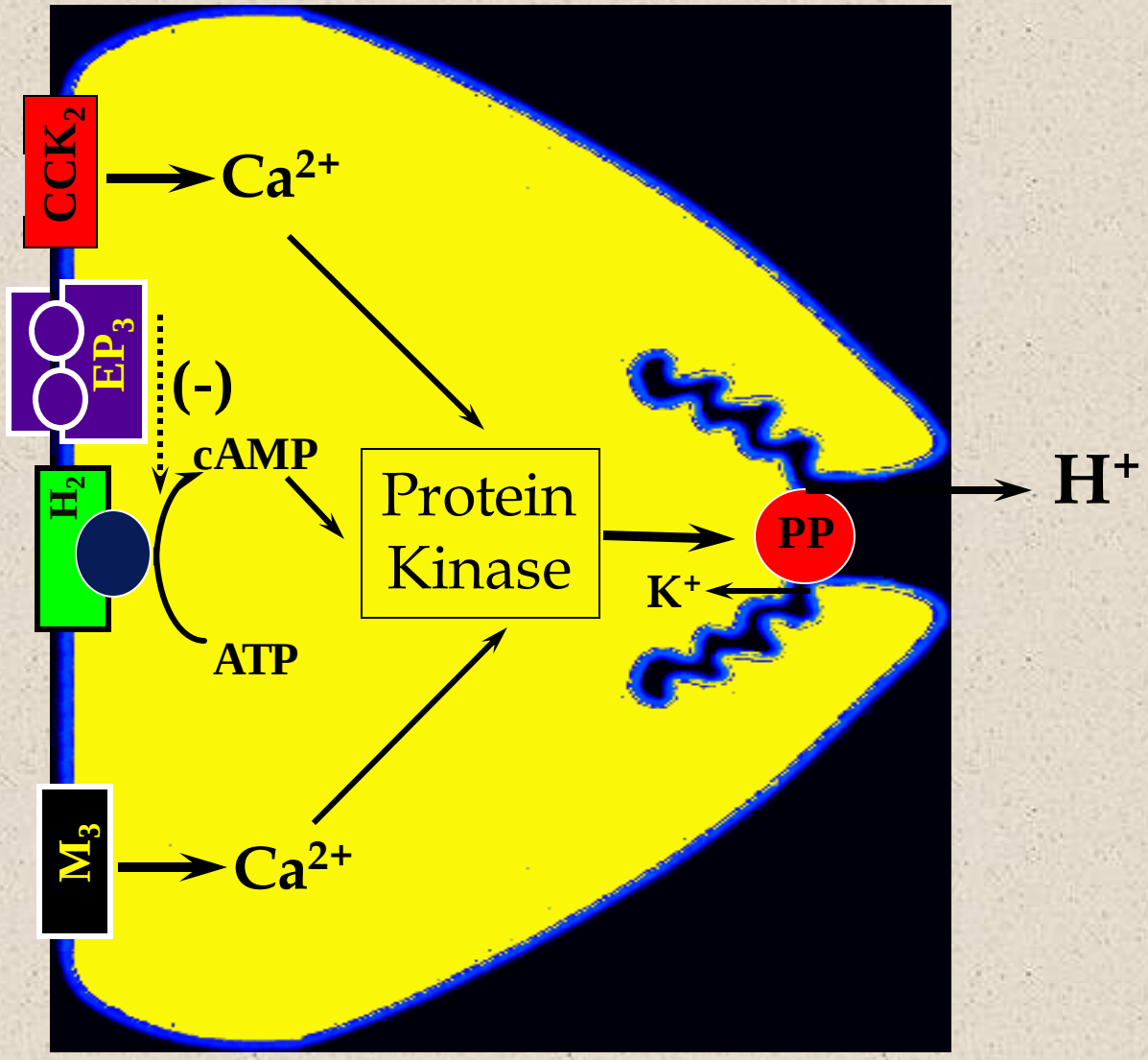
  - Atropine
  - Propantheline (Pro-Banthine)
  - Dicyclomine (Bentyl)

- ***Selective M_1 receptor antagonists***

  - Pirenzepine
  - Telenzepine

Strategies for Inhibiting Parietal Cell Acid Secretion

Prostaglandin Agonists



Drugs for Acid-Peptic Disorders - Prostaglandins

Misoprostol (Cytotec):

- Synthetic Analog of Prostaglandin E_1
- Anti-acid secretory
- 0.1 to 0.2 mg results in 85% to 95% acid reduction
- Prevention of NSAID gastric ulcers

Side Effects

- Diarrhea
- Abortion
- Exacerbate IBD and should not be given

Drugs for Acid-Peptic Disorders - Antacids

- Antacids are weak bases that neutralize HCl in the stomach;
- They do not decrease the secretion of acid, and in some cases increase secretion;
- *They do not suppress nocturnal acid secretion*

1. Neutralize acid
2. Decrease acid load to duodenum
3. Diminish pepsin activity

Drugs for Acid-Peptic Disorders - Antacids

- Magnesium hydroxide
- Magnesium trisilicate
- Magnesium-aluminum mixtures
- Calcium carbonate
- Sodium bicarbonate

Characteristics of Common Antacids

Feature	Sodium Bicarbonate	Calcium	Magnesium Hydroxide	Aluminum
Onset of action	rapid	intermediate	rapid	slow
Duration of action	short	moderate	moderate	moderate
Systemic alkalosis	yes	?	no	no
Effect on stool	---	constipating	laxative	constipating

Drugs for Acid-Peptic Disorders – Sucralfate (Carafate)

- Sucralfate is a basic aluminum salt of sucrose octasulfate;
- In the presence of acid (pH < 3-4) some of the aluminum ions dissociate and the resulting negatively charged molecule polymerizes to form a viscous paste-like substance;
- This substance adheres strongly to gastric and duodenum mucosa and adheres even more strongly to partially denatured proteins such as those found at the base of the ulcer.

Drugs for Acid-Peptic Disorders - Sucralfate (Carafate)

- This compound does not decrease the concentration or total amount of acid in the stomach;
- Sucralfate protects the gastric and duodenal mucosa from acid/pepsin attack.

Side effects:

- The compound is not really absorbed and, therefore, side-effects are minimal:
  - constipation
  - diarrhea
  - nausea

Role of H. pylori in Peptic Ulcer Disease

- Treatment
  - If *H. pylori* detected, e*radication of the bacteria*, along with inhibition of acid.
  - Eradication of *H. pylori* is a cure as reinfection rates in Western countries is less than 1%.

Role of H. pylori in Peptic Ulcer Disease

- *Combination therapy with Omeprazole and Amoxycillin*

Eradication of H. pylori reduces the rate of duodenal ulcer relapse

Study	Year	Follow up (months)	Ulcer relapse (%) *H. pylori*	
			Positive	Negative
Coghlan et al.	1987	12	76	10
Lambert et al.	1987	6	76	0
Marshall et al.	1988	12	81	12
Smith et al.	1988	18	80	0
Borody et al.	1988	12-25	100	0
Rauws & Tyt gat	1990	12	81	0
Blum et al.	1990	6	41	0
George et al.	1990	12-48	0	0

H. pylori Eradication Rates with Either Dual, Triple or Quad Therapy (1999)

Treatment	Pooled Eradication Rate
Dual Therapy	72%
Triple Therapy	85%
Quad Therapy	90%

H. pylori Eradication Rates with Either Dual, Triple or Quad Therapy (1999)

GENERIC NAME	DOSING	DURATION	CURE RATE (%)
Dual therapies			
omeprazole	500 mg TID	14 days	70-80
amoxycillin	1,000 mg TID	14 days	
ranitidine	400 mg BID	28 days	73-84
clarithromycin	500 mg TID	14 days	
lansoprazole	30 mg TID	14 days	66-77
amoxycillin	1,000 mg TID	14 days	

H. pylori Eradication Rates with Either Dual, Triple or Quad Therapy (1999) Cont.

GENERIC NAME	DOSING	DURATION	CURE RATE (%)
Triple therapies			
lansoprazole	**30 mg BID**	**14 days**	**86-92**
amoxycillin	**1,000 mg BID**	**14 day**	
clarithromycin	**500 mg BID**	**14 days**	

H. pylori Eradication Rates with Either Dual, Triple or Quad Therapy (1999) Cont.

GENERIC NAME	DOSING	DURATION	CURE RATE (%)
Quad therapies			
bismuth subsalicylate	Two tablets 525 mg QID	7 days	85-95
metronidazole	250 mg QID	7 days	
tetracycline	500 mg QID	7 days	
omeprazole	20 mg BID	7 days	
or			
lansoprazole	30 mg BID	7 days	

New Strains of H. pylori

- Recently a more virulent genetic strain of H. Pylori known as cytotoxin-associated gene A (cagA) has been found in some people with peptic ulcers

Drugs for Acid-Peptic Disorders

Drugs	Stage I GERD (sporadic)	Stage II GERD (> 2-3 episode /wk)	Stage III GERD (Chronic)	Gastric & Duodenal Ulcers	Major Side Effects
Proton Pump Inhibitors		+	++	++	CYP450 Hypergastr.
Antibiotics				++	
H_2 Antagonists	+	+		+	CYP450 Antiandrogen
Anticholinergics				non-U.S.?	Parasym. ANS
Prostaglandins				NSAID +	diarrhea
Antacids	+			+?	↑ GI Ca^{+2}
Sucralfate				Stress +	GI

Topics for Discussion

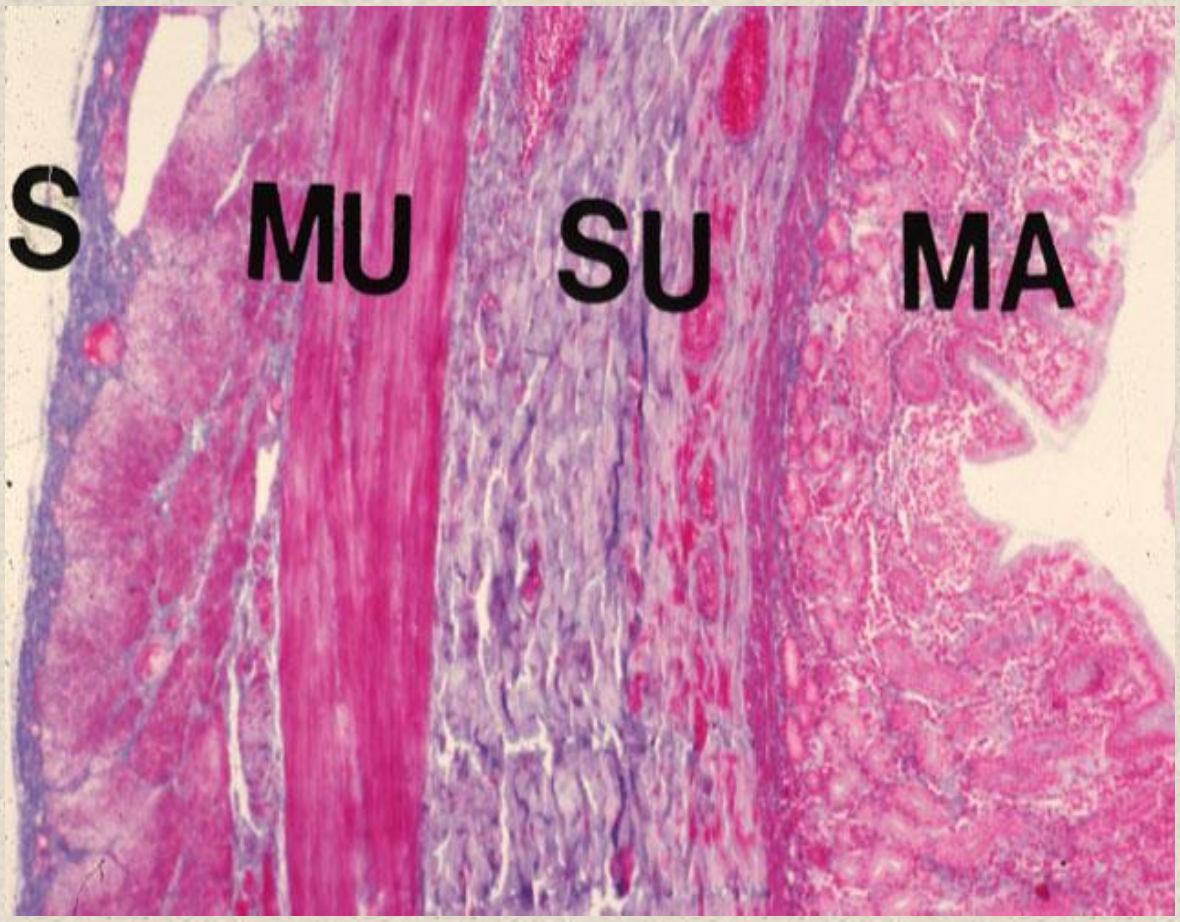
- **Drugs for Acid-Peptic Disorders**
  - Eradication of *Helicobacter pylori* (Antibiotic/Inhibition of Acid)
  - Proton Pump Inhibitors (Omeprazole)
  - Histamine (H2) Receptor Antagonists (Cimetidine, Ranitidine)
  - Anticholinergics
  - Prostaglandins (Misoprostol)
  - Antacids
  - Mucoprotective Drugs (Sucralfate)
- **Drugs for Motility Disorders**
  - Prokinetics (Metoclopramide)
  - Laxatives (Bran)
  - Antidiarrheals (Opioids)

Structure of the GI Tract

MU = Muscularis Mucosa

Consists of:

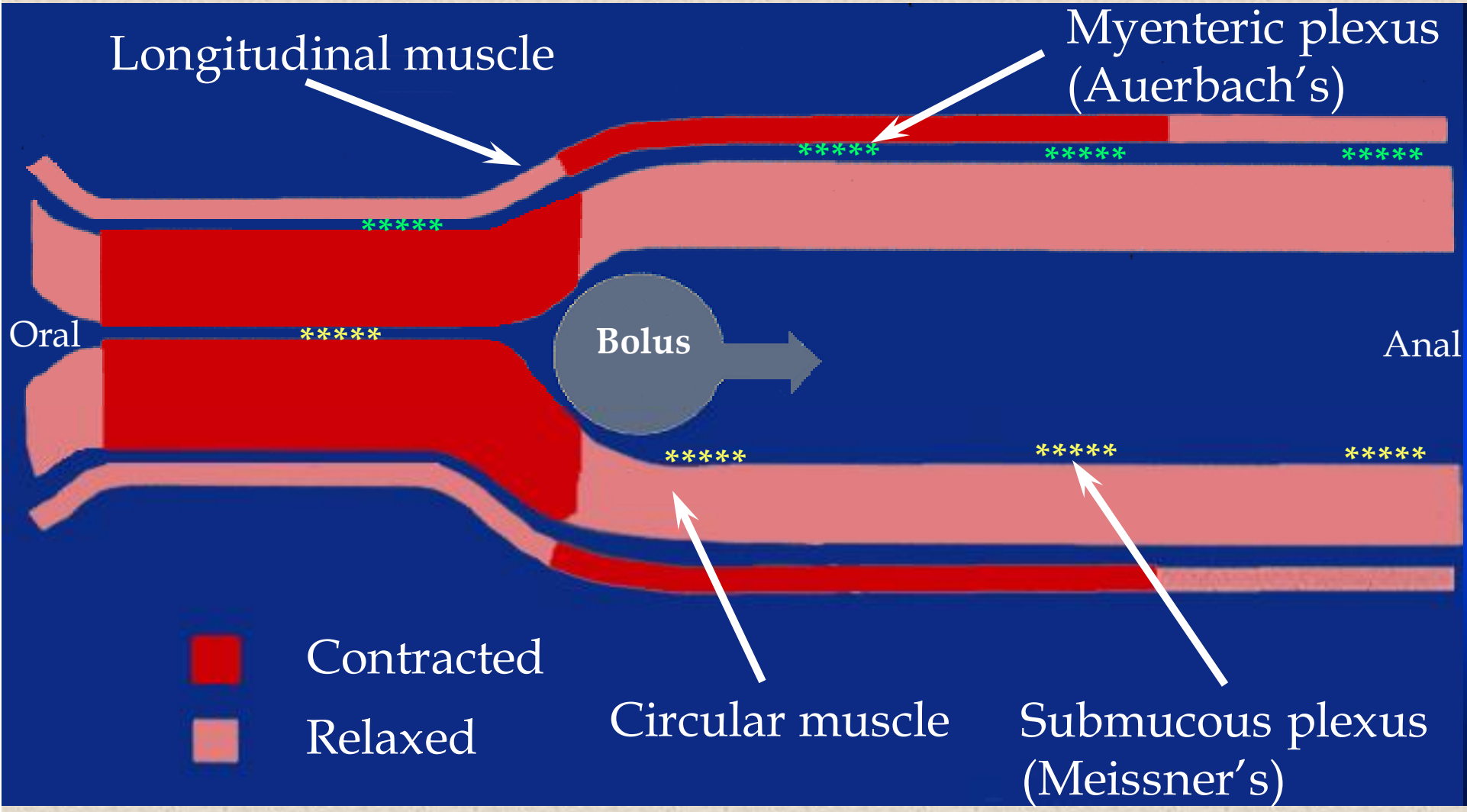
- **inner circular layer**
- **outer longitudinal layer**



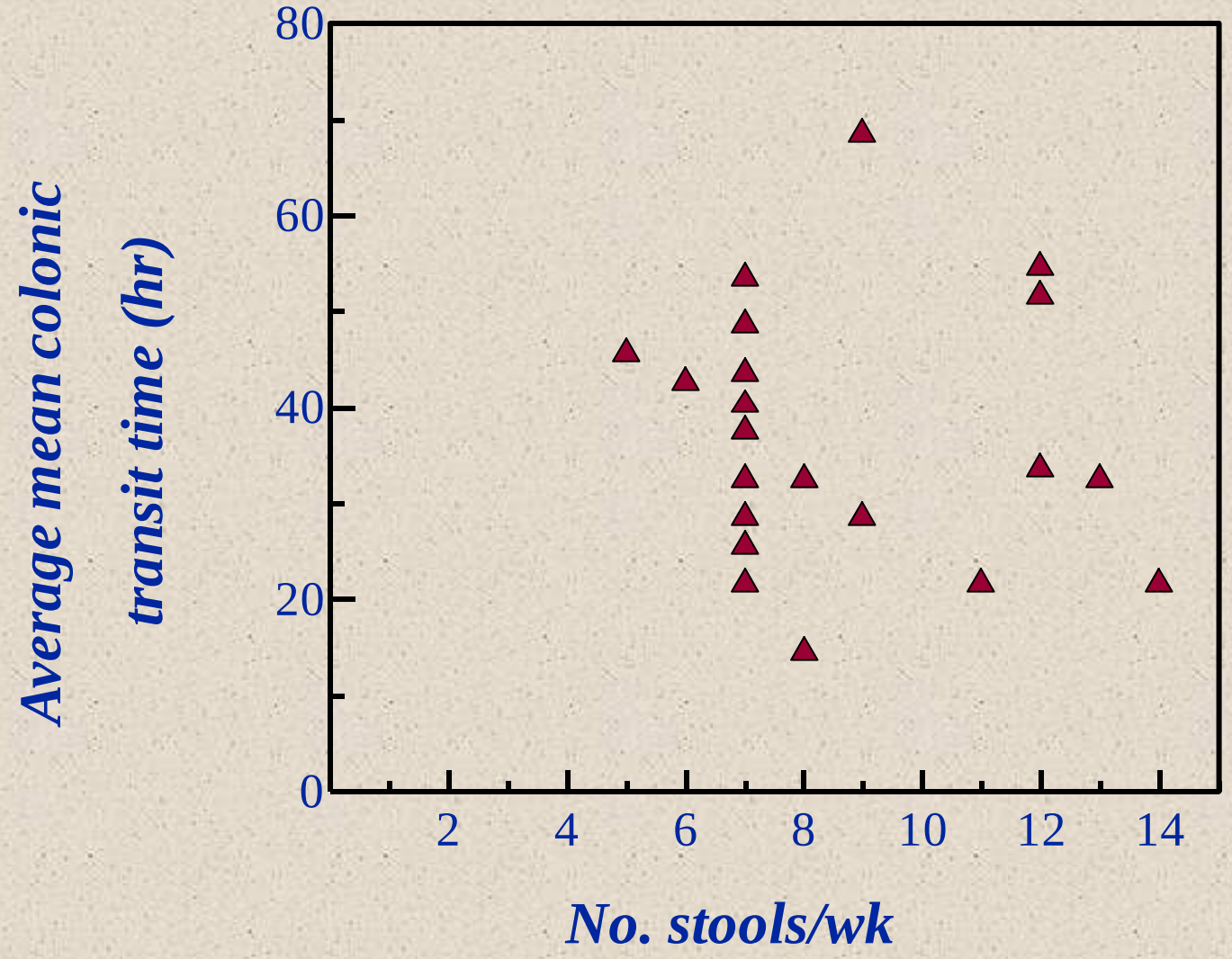
Functional Disorders of the GI

- Contractions may be *propulsive* - i.e., proximal to distal contractions called “mass action” contractions;
- Contractions may be non-propulsive - *segmenting or mixing* contractions which increase luminal fluid to mucosal surface to promote absorptive action of the colon.

Peristalsis Produced by Coordinated Contraction and Relaxation of Muscle Coats



Colonic Transit and Stool Frequency in Healthy Volunteers



Functional Disorders of the GI

- Pharmacotherapy (prescription and non-prescription) amounts to *$5 to $6 billion annually* for real or perceived disorders of colonic motility;
- Patients seek medical care because they are not experiencing presumed "normal" pattern of bowel movement (one per day) or stool consistency;
- Complaints are highly subjective and personal, and difficult to quantify and validate.

Functional Disorders of the GI

- Primary
  - infection, inflammation, congenital defects (disorders of the neuronal/muscular activity);
- Secondary
  - metabolic disorders (hypo- or hyper-parathyroidism, hypercalcemia), neurologic (diabetes mellitus - damage to vagal and sympathetic extrinsic nerves, intrinsic nerves; MS, heavy metal toxicity, carcinoma);
- Examples of colonic dysfunction:
  - IBS; chronic constipation; Hirschsprung's disease (agangliosis of myenteric plexus); sphincter dysfunction, etc.

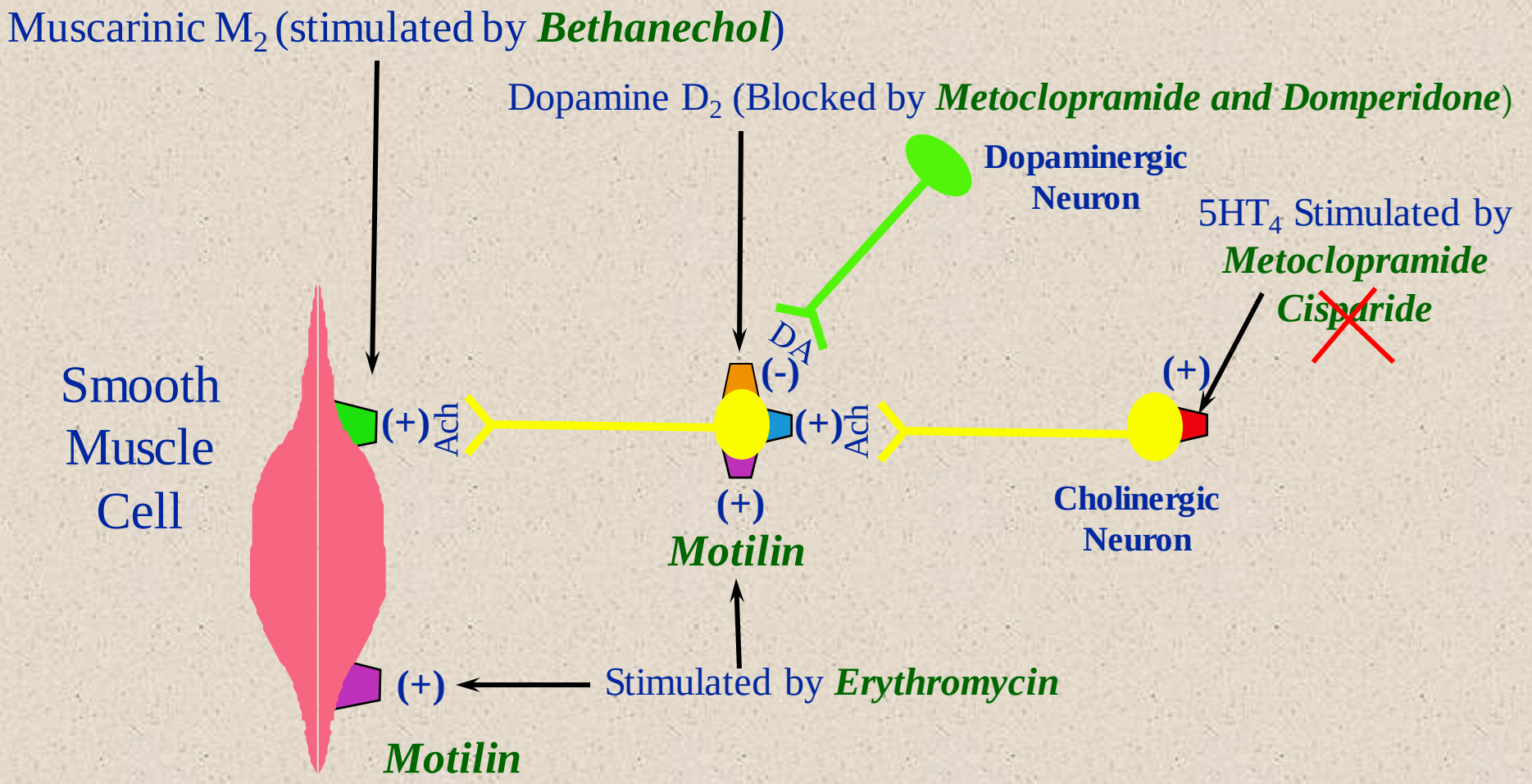
Prokinetic Drugs are Often Used for:

- Gastroesophageal reflux disease (GERD)
- Gastroparesis
- Nighttime heartburn
- Severe refractory constipation (sometimes caused by irritable bowel syndrome (IBS))

Prokinetic Drugs

- Substances which enhance transit of materials through the GI tract;
  - Increase neuromuscular transmission

Prokinetic Drugs Act on Enteric Nerves to Increase Cholinergic Stimulation



- Indirect effects are mediated by M_2 muscarinic receptors
- Metoclopramide crosses the blood-brain barrier

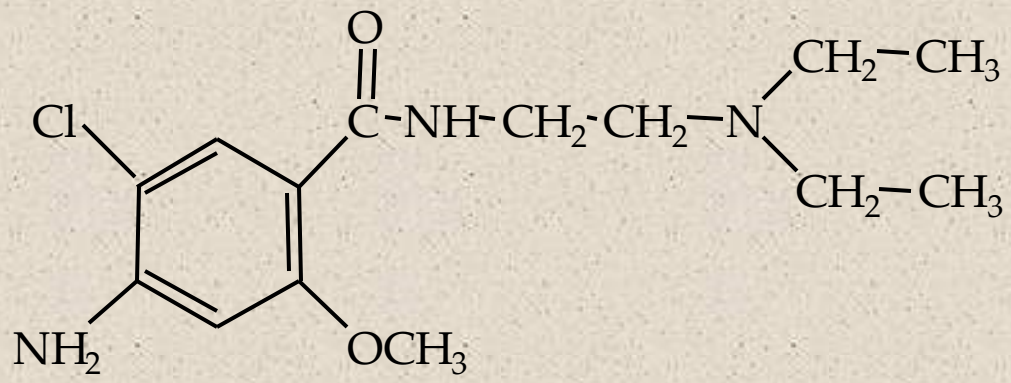
Prokinetic Drugs - Cholinomimetics *(Carbachol; Bethanechol)*

- **Actions**
  - Muscarinic receptor agonist
  - Increase force of contraction
  - Little effect on intestinal transit

- **Adverse Side-effects**
  - Cardiovascular (hypotension, bradycardia)
  - Urinary Bladder (increase voiding press., decrease capacity)
  - Exocrine Glands (increase secretions)
  - Eye (pupil constriction and loss of accommodation)

Prokinetic Drugs – Metoclopramide (Reglan)

- Metoclopramide is an antiemetic and improves gastric emptying – indirectly releases acetylcholine
  - **Actions**
    - **Dopamine D_2 receptor antagonist**
    - **5-HT_4 receptor agonist**
    - **Ganglionic stimulant**
  - **Pharmacokinetics**
    - Oral bioavailability
    - Crosses blood-brain barrier
  - **Adverse Side-effects**
    - Sedation
    - Dystonic reactions
    - Anxiety reactions
    - Gynecomastia
    - Galactorrhea



Prokinetic Drugs – Domperidone (Motilium)

- Domperidone is an antiemetic and improves gastric emptying – Not very effective for GERD
  - **Actions**
    - Dopamine receptor antagonist
    - Ganglionic stimulant
  - **Pharmacokinetics**
    - Low oral bioavailability
    - Does not cross blood-brain barrier
  - **Adverse Side-effects**
    - Headaches
    - Gynecomastia
    - Galactorrhea

Prokinetic Drugs - Cisapride (Propulsid)

- **Actions**

  5-HT_4 agonist; other unknown actions.

- **Adverse Side-effects**

  Serious cardiovascular problems including arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation and QT prolongation

  As of December 1999, 80 deaths

  Janssen Pharmaceutical Inc. has stopped making cisapride in the US as of 2000

Prokinetic Drugs - Additional Compounds

- Erythromycin
  - Motilin agonist
  - Antibacterial
  - Diarrhea
- Motilin (22 amino acid active peptide)
  - Agonist for the Motilin receptor
  - Stimulates gastric emptying

Comparison of Gastric Prokinetic Drugs

Pharmacological Class	Specific Drugs	Mechanism of Action
Cholinergic	Bethanechol	Muscarinic Receptors M_3
Dopamine Antagonist	Metoclopramide Domperidone	D_2
Serotonin Agonist	Metoclopramide	5-HT_4
Motilin Agonist	Erythromycin	Motilin Receptor

Laxatives

Three general mechanisms of action:

- Hydrophilic or osmotic properties *promote retention of water* in the colon - increase bulk and softness and facilitate transit;

- Act on colonic mucosa to *decrease absorption* of water;

- *Increase intestinal propulsive motility*, decreasing absorption of fluid secondary to decreased transit time.

Laxatives

Secretory agents:

- Increase secretion of fluid in the intestine, probably by opening chloride channels;
- *Castor oil*, *cascara* and *senna (Senokot)* are naturally occurring substances. *Phenolphthalein (Ex-Lax)*, and *bisacodyl (Dulcolax, Correctol)* are popular OTC substances.
- Active ingredient in Ex-Lax is now Senna.

Laxatives

Saline Agents:

- Contain a cation (magnesium) or anion (sulfate or phosphate) that carries obligatory water of hydration and is poorly absorbed from the intestinal lumen;

- Retain fluid in the bowel to promote flow. Examples include *magnesium hydroxide (Milk of Magnesia)*, *sodium phosphate* and *sodium sulfate;*

- Disadvantage is rapid delivery of a large pressure head to the distal colon and anal sphincter - *difficult to time and control.*

Laxatives

Emollients:

- Nonabsorbed lubricants which enhance flow.
- *Dioctyl sodium sulfosuccinate (Colace, Doxinate, Surfak)* - these are anionic surfactants. They produce softening of the stool over a period of 1-3 days. Details of pharmacology are uncertain.
- *Mineral oil* is also used - difficult to contain by the anal sphincter - can be socially distressing (kind of like *Olestra*).

Laxatives

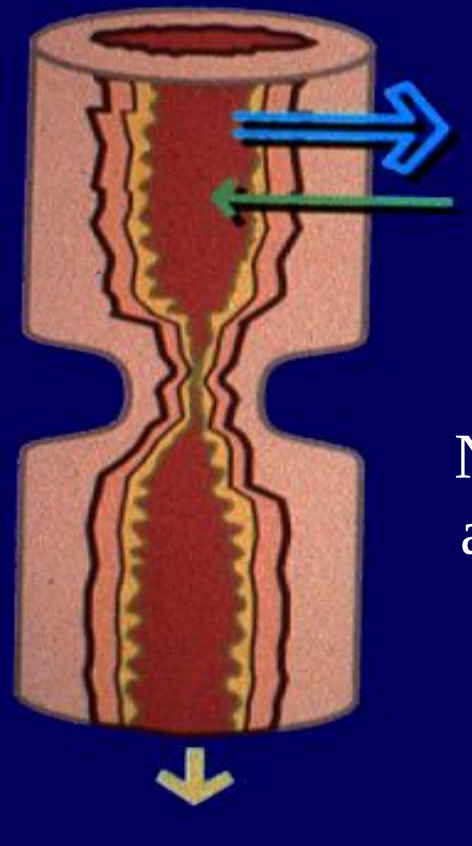
Bulk-forming agents:

Bran, *methylcellulose* and *psyllium (Metamucil)*.
Innocuous, inexpensive and recommended.


SOMETIMES I FEEL THAT I HAVE THE WORST JOB IN THE WORLD!
YA...RIGHT!

Diarrhea is Associated with Excessive Flow Through the Lumen of the Bowel

Normal

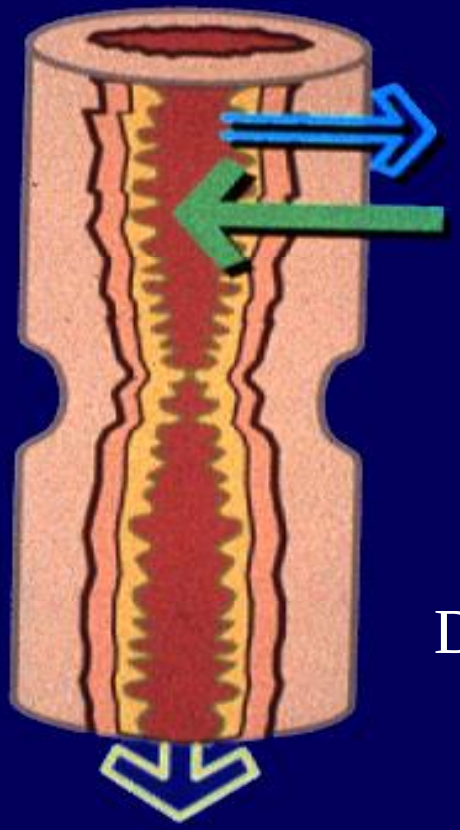


Net fluid absorption

Normal mixing and propulsive contractions

Normal Flow

Diarrhea



Net fluid accumulation

Increased propulsive contractions

Decreased mixing contractions

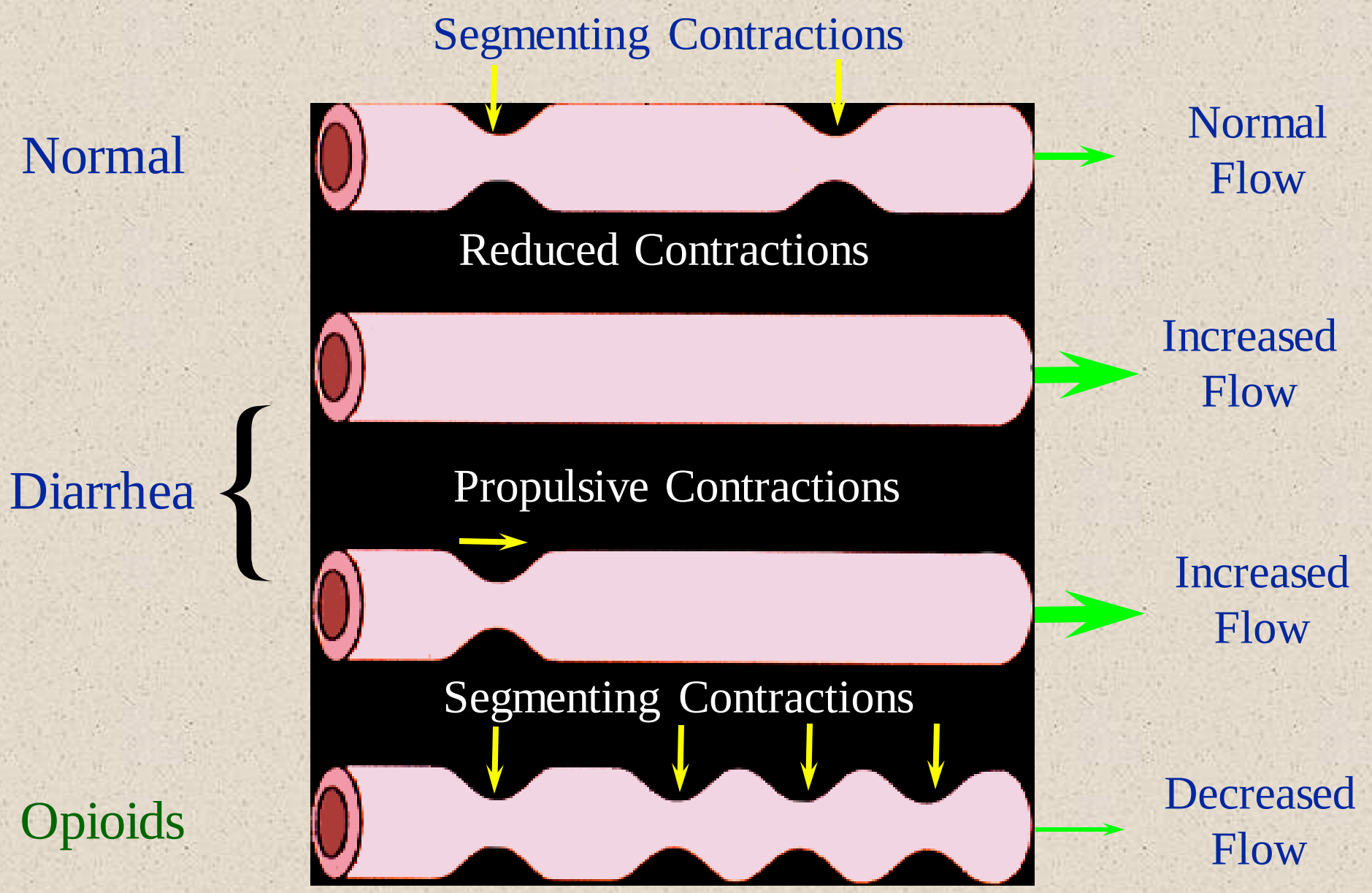
Increased Flow

The Goals of Antidiarrheal Therapy are to Correct the Pathophysiology

Goals:

- Eliminate cause;
- Decrease fluid accumulation in lumen;
- Decrease propulsive contractions;
- Increase mixing contractions.

Opioids and Intestinal Motility



Antidiarrheal Agents - Opioids

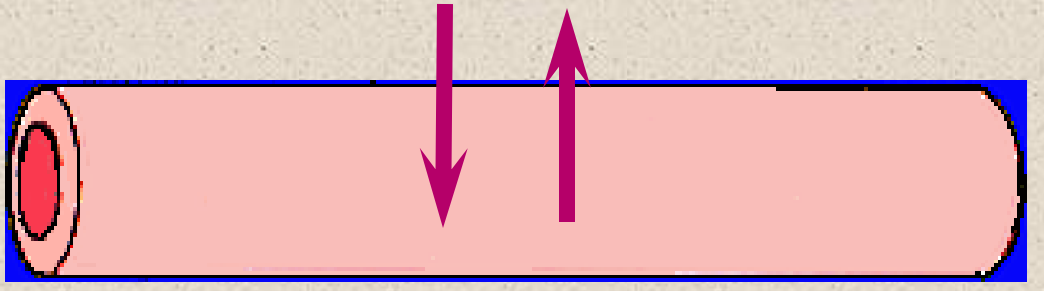
- Agonist at mu opioid receptors;
- Decreases fluid secretion;
- Increases fluid absorption;
- Decreases propulsive contractions;
- Increases segmenting contractions;
- Delays gastric emptying.

Adverse Side Effects:

- Constipation
- CNS effects

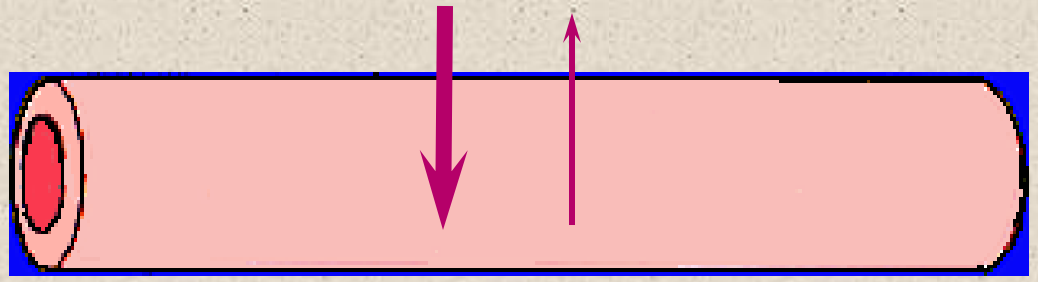
Opioids and Mucosal Transport of Salt and Water

Normal



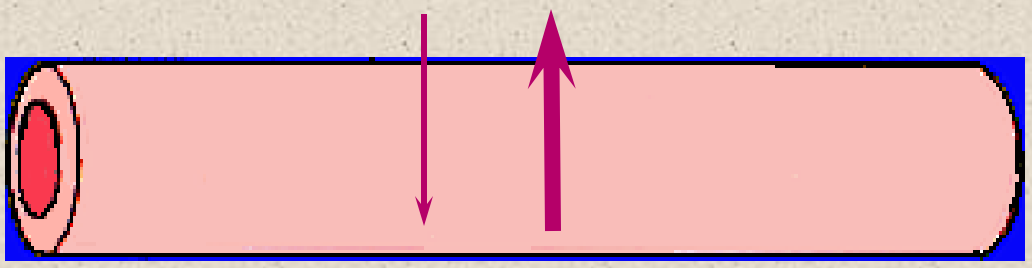
Physiological Balance

Diarrhea



Net Fluid Accumulation

Opioids



Net Fluid Absorption

Analgesics that can be used as Antidiarrheal Agents

- Morphine
- Codeine

Antidiarrheal Agents - Loperamide (Imodium)

Mu opioid agonist

Very little distribution into CNS

Low addiction liability

Side Effect

Constipating

Some Opioid Drugs Act Both in the CNS and on Enteric Nerves, Others Act Only on Enteric Nerves

Drug	Central Nervous System	Enteric Nerves
Morphine	+++	+++
Codeine	+++	+++
Diphenoxylate	+	+++
Loperamide	**0**	+++

Loperamide does not effectively cross the blood-brain barrier after oral administration and exerts mainly peripheral effects

Antidiarrheal Agents - Anticholinergics

Muscarinic antagonists

Decrease propulsive contractions

Decrease cholinergic secretions

Side Effects

Produce typical antimuscarinic side-effects

- Dry mouth
- Tachycardia
- Blurred vision
- Bowel discomfort (constipation)
- Difficulty in urination

Antidiarrheal Agents - Clonidine (Catapres)

Alpha$_2$ agonist

Decreased release of secretagogues

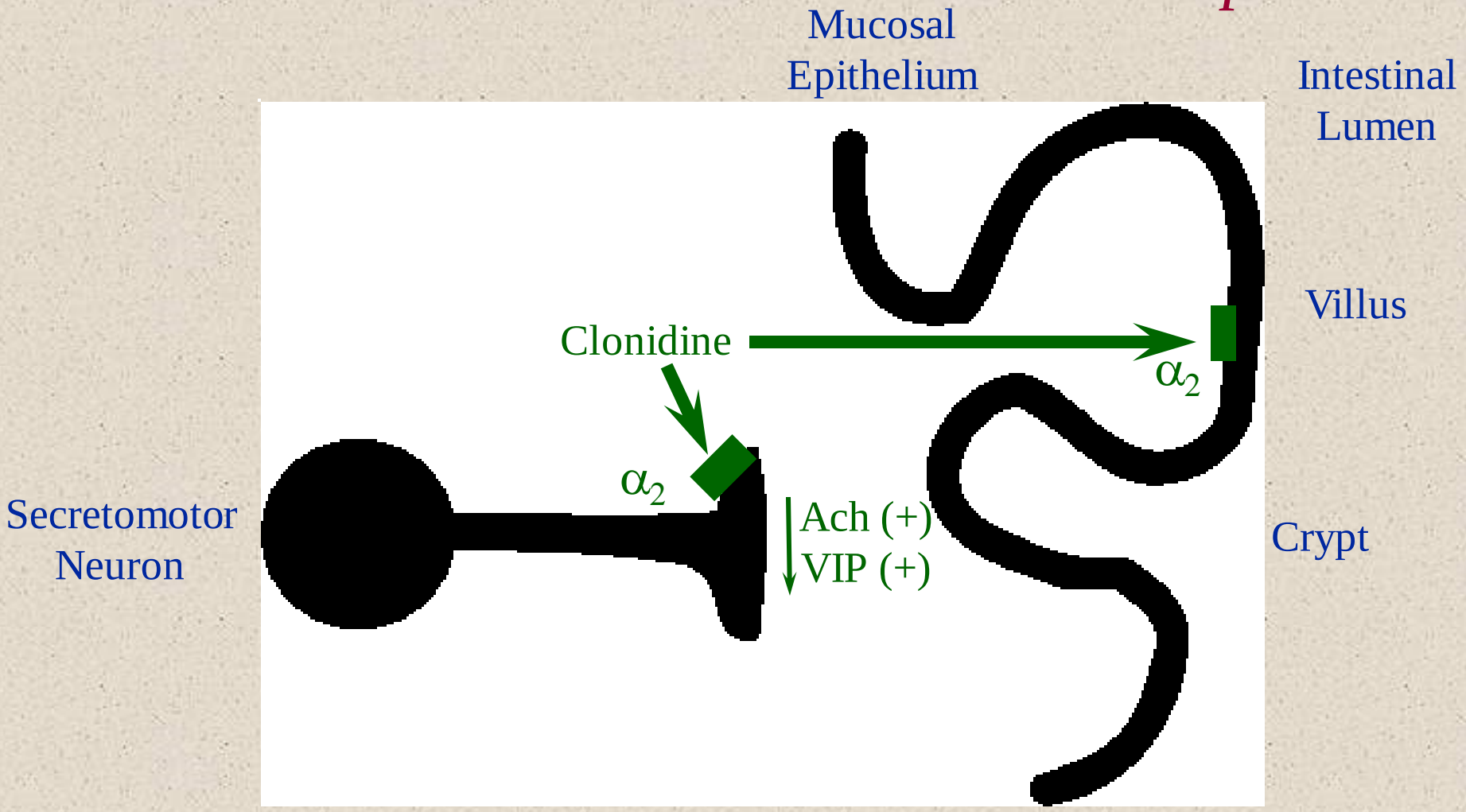
Action on villus cells

increase fluid and electrolyte absorption

Side Effect

Induces hypotension

Clonidine Acts at Alpha-2 Adrenergic Receptors to Decrease Secretion and Increase Absorption



Clonidine acts at neural α_2 receptors to inhibit release of secretory neurotransmitters and at epithelial α_2 receptors to stimulate absorption

Antidiarrheal Agents - Bismuth Subsalicylate

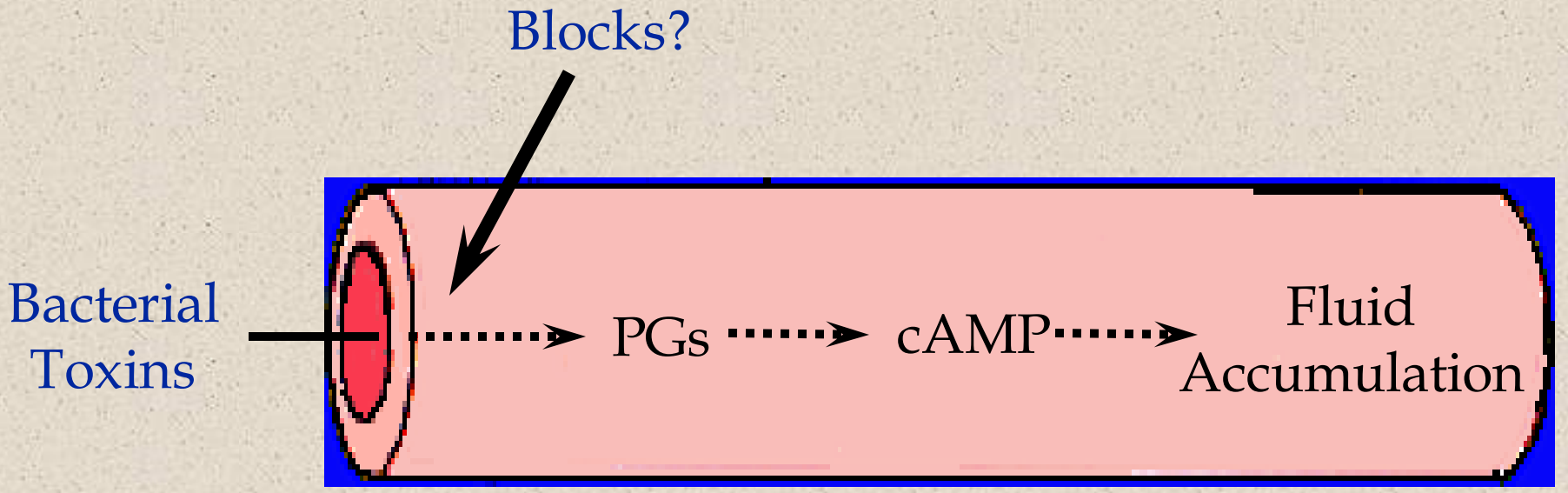
Bismuth Subsalicylate (Pepto-Bismol)

Binds bacterial toxins

Reduces formation of prostanoids

Antibacterial

Bismuth Subsalicylate



Antidiarrheal Agents - Gel Forming Agents

Attapulgite - natural clay

Kaolin - natural clay

Pectin - citrus pulp (Kaopectate)

ineffective

Bile Acid Catharsis

Cholestyramine (anion-exchange resin)
Lowers LDL cholesterol

Side Effects

Not well absobed

Constipation

Antidiarrheal Drugs Act By a Variety of Mechanisms

Drugs	Inhibit propulsive contractions	Stimulate nonpropulsive contractions	Decrease fluid secretion*	Enhance fluid absorption	Bind luminal secretagogues
Opioids	+++	+++	+++	++	
α_2 agonists			+++	+	
Anticholinergics	+++		++		
Somatostatin (Octreotide)	+		+++		
Bismuth subsalicylate					+++
Cholestyramine					+++

* Stimulated by secretagogues

What type of therapy is recommended for a person diagnosed with peptic ulcer disease and *H. pylori* positive?

1. Tagamet with Omeprazole
2. Antacid with Amoxicillin
3. Amoxicillin with Metronidazole
4. Omeprazole with Amoxicillin
5. Omeprazole

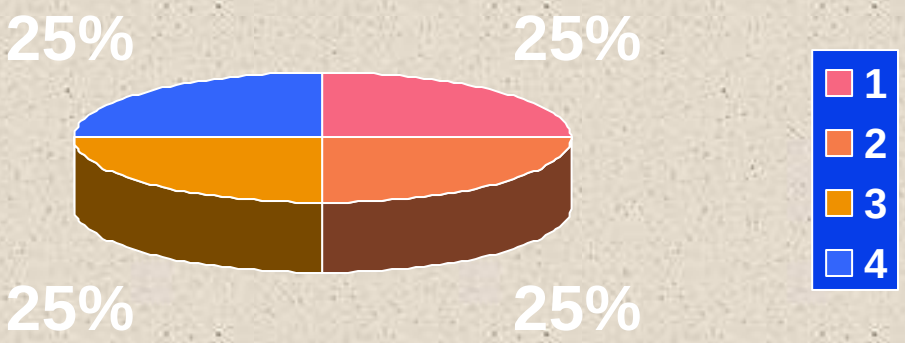
The drug Misoprostol (Cytotek®) will:

1. Decrease the production of acid
2. Increase the mucosal barrier
3. Is “cyto-protective”
4. Is often used for NSAID induced gastric ulcers
5. All of the above
6. 2 and 3 only

10

Propantheline works by what mechanism to reduce gastric acid:

1. Directly blocks the proton pump
2. Act at the nicotinic receptors to stop Ach interactions
3. Block Ach activity at the M3/M1 receptors on parietal cells
4. Act as an agonist at M3/M1 receptors to decrease acid production from parietal cells



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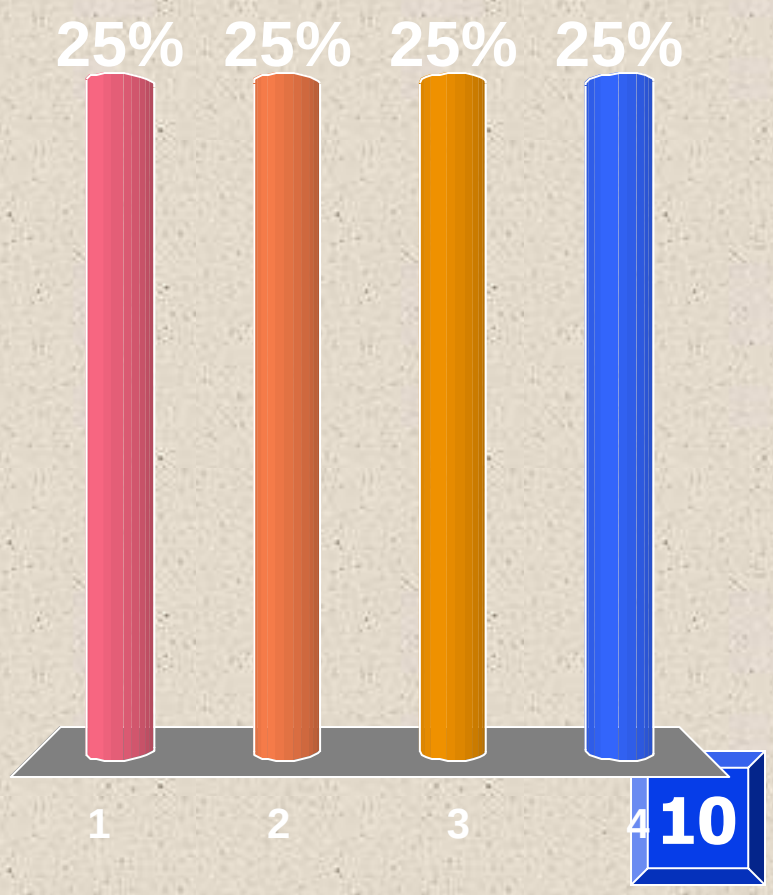
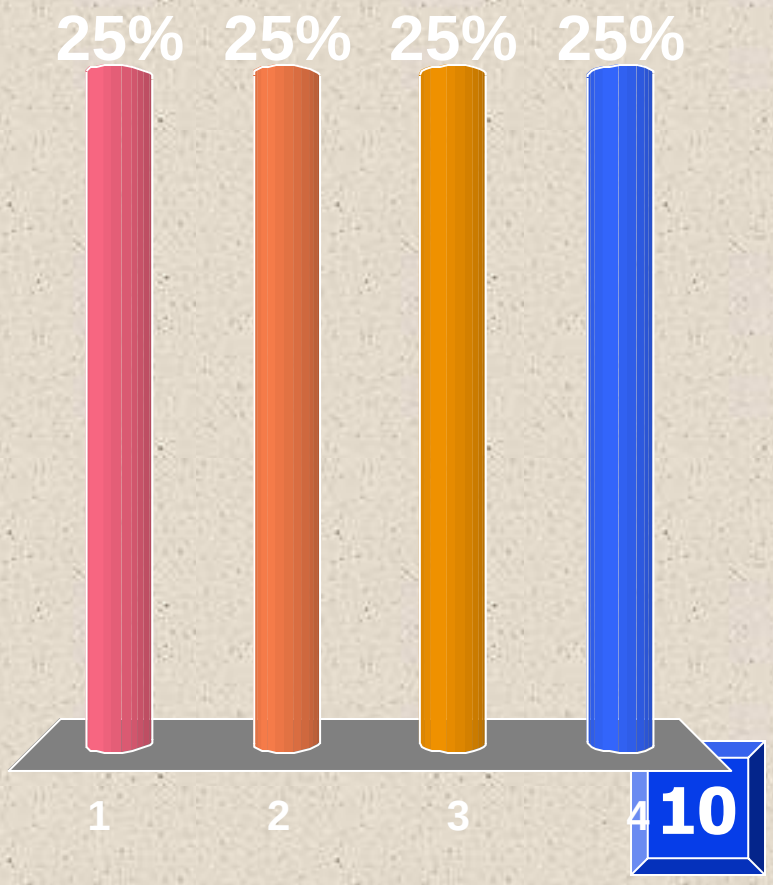
What type of antacid may result in a laxative side effect?

1. Calcium based antacids
2. Sodium Bicarbonate Antacids
3. Magnesium based antacids
4. Aluminum based antacids



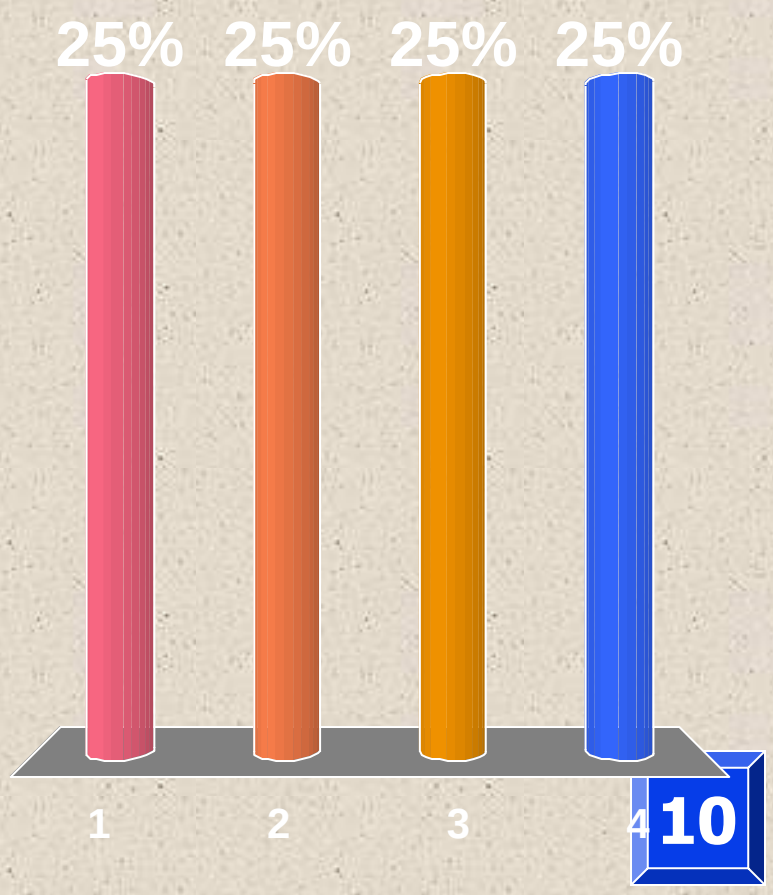
Prokinetic drugs result in:

1. A decrease in propulsive contractions
2. An increase in mixing contractions
3. Increase fluidity within the lumen of the GI tract
4. Improve antroduodenal coordination



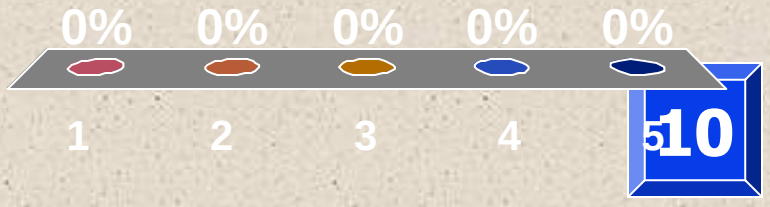
Metoclopramide acts as a prokinetic by:

1. Directly acting on the smooth muscle to increase propulsive contractions
2. By acting as an agonist at 5HT4 receptors to increase the release of Acetylcholine
3. By acting as an agonist at D2 receptors to increase the release of Acetylcholine
4. By releasing Motilin to increase propulsive contractions



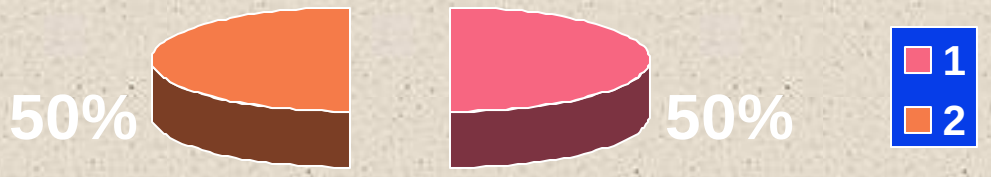
Sucralfate (Carafate®) is a basic aluminum salt of sucrose octasulfate. It is used for peptic ulcers due to its ability to:

1. Complexes with proteins at the ulcer site
2. Decreases back diffusion of hydrogen ions
3. Binds to pepsin and bile salts
4. None of the above
5. All of the above



Laxatives work by decreasing secretions into the lumen

1. **True**
2. **False**



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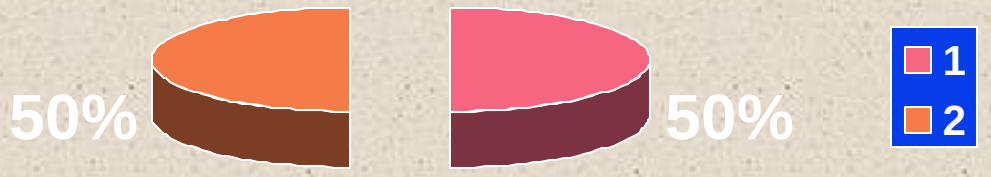
The antidiarrheal drug that is best for "bug"-induced diarrhea is bismuth subsalicylate

1. **True**
2. **False**



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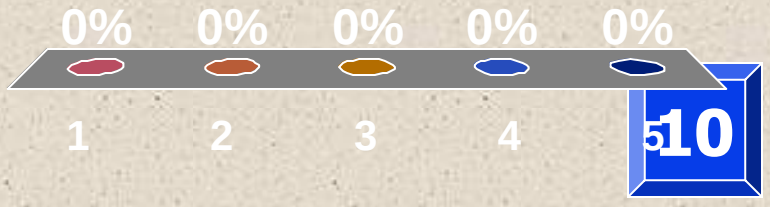
An opioid such as Loperamide is useful as an antidiarrheal drug since it can:

1. Increase segmenting contractions of the GI
2. Decrease propulsive contractions of the GI
3. Results in contents remaining in the GI longer for more fluid retention
4. 1 and 2 only
5. All of the above



GI CASE I

MedPharm, Fall 2004
John D. Palmer, Ph.D. M.D.

A 79 year old man

Chief Complaint: Chest Pain, ten episodes of bright red vomiting
and maroon and black colored stools.

PROBLEM LIST:

- Ischemic cardiomyopathy – CHF
- Myocardial infarction
- Gout
- Hiatus hernia
- Erosive esophagitis

MEDICATIONS:

- Allopurinol
- Furosemide
- Metolazone
- Spironolactone
- Omeprazole
- Clopidogrel
- Warfarin
- Aspirin
- Carvedilol

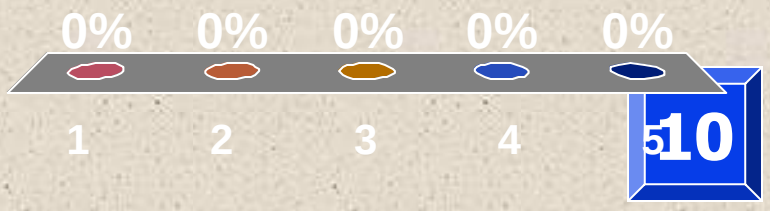
Laboratory:

Hemoglobin/Hematocrit 6.6/19.7 (normal = 14/44)

PT/INR 26.4/5.2

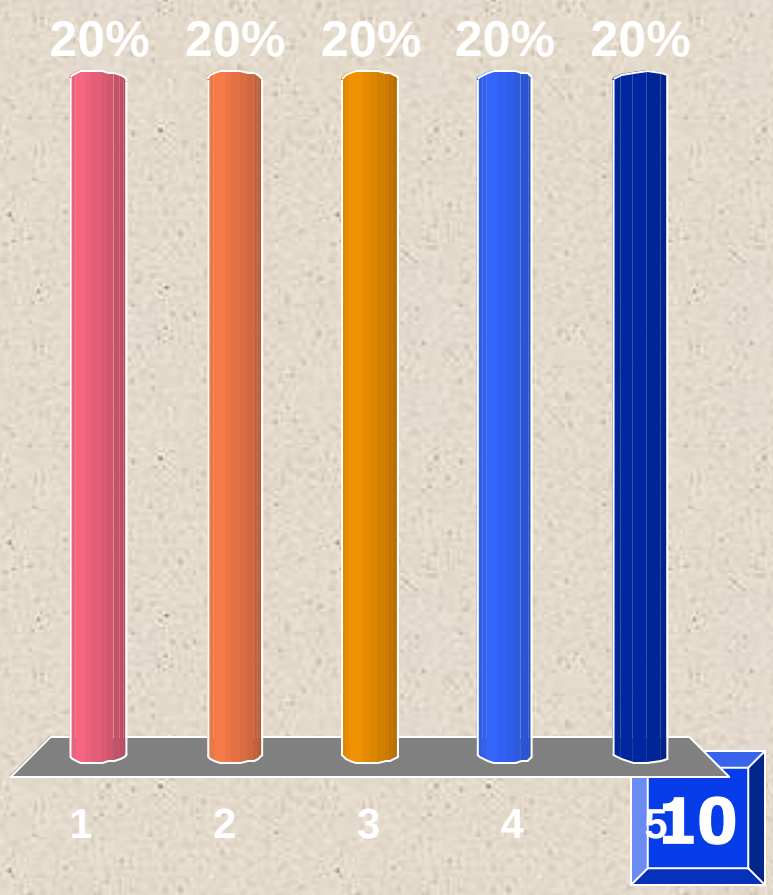
What is the most likely diagnosis?

1. NSAID induced ulcer
2. Food and Stress induced ulcer
3. H. pylori induced ulcer
4. Acute Myocardial Infarction
5. Gastric Cancer



How would you Treat such a patient

1. Proton pump inhibitor
2. Antibiotic
3. H2 receptor antagonist & sucralfate
4. Proton pump inhibitor & antibiotic
5. Prostaglandins (Misoprostol)



GI – CASE II

A 55 year old man

Chief Complaint: Nausea, black tarry stools with diarrhea and vomiting of blood

PROBLEM LIST:

Psoriasis with arthritis
Obesity
Sleep apnea
Chronic bronchitis
History of peptic ulcer disease

MEDICATIONS:

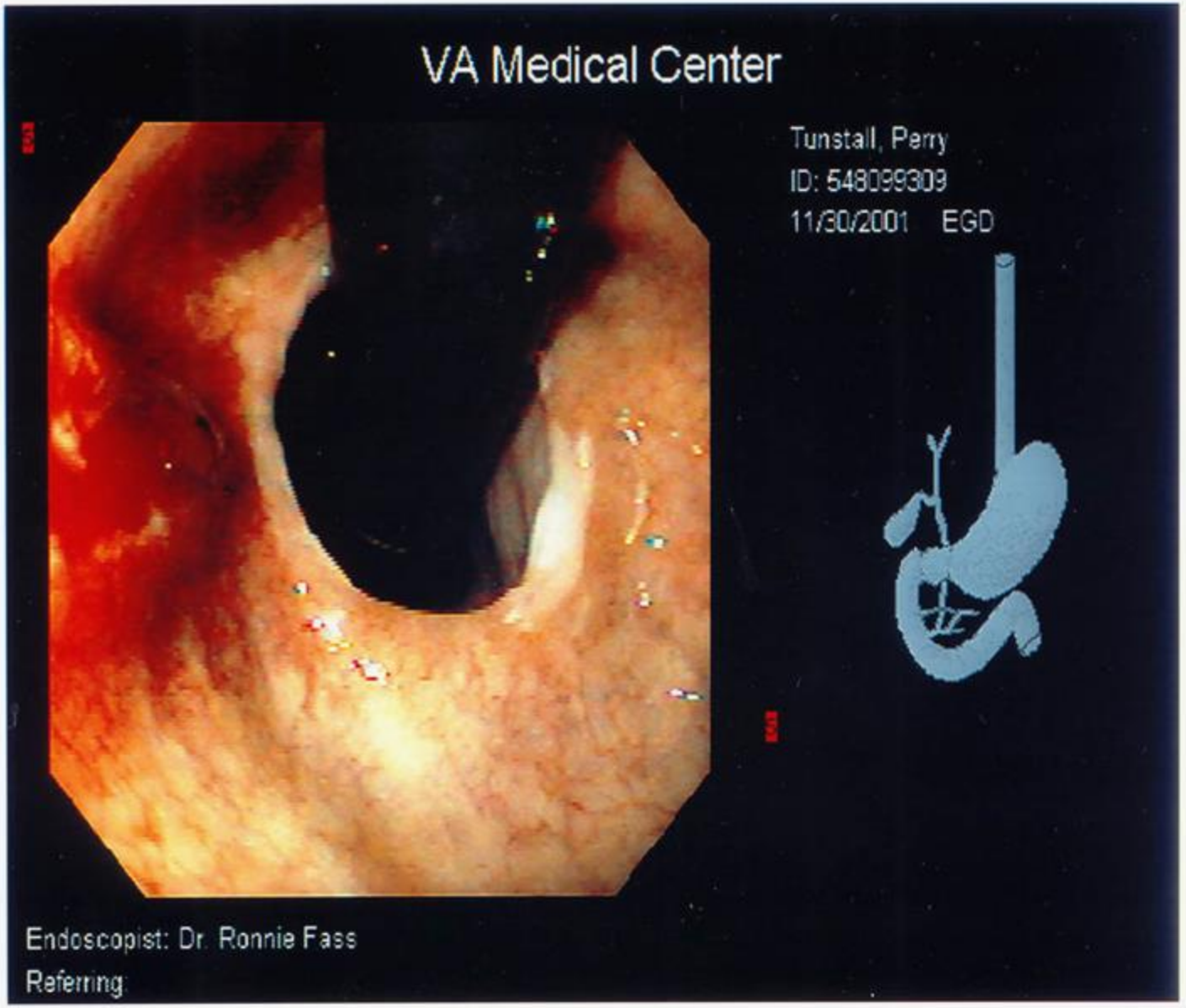
Acetaminophen & hydrocodone
Folic acid
Methotrexate
Salsalate

No Alcohol used

Vital signs: BP 106/45 Pulse 106 Resp 20

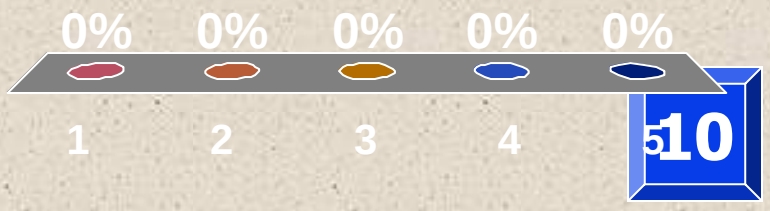
Laboratory:

PT/INR 13.8/-
Hemoglobin/Hematocrit 13.6/38


VA Medical Center
Tunstall, Perry
ID: 548099309
11/30/2001 EGD
Endoscopist: Dr. Ronnie Fass
Referring

What is the most likely diagnosis?

1. NSAID induced ulcer
2. Food and Stress induced ulcer
3. H. pylori induced ulcer
4. Zollinger Ellison Syndrome
5. Gastric Cancer



GI – CASE III

A 47 year old man

Chief Complaint: worsening abdominal pain and generalized weakness,

Complains of a 3 month history of stomach discomfort and indigestion, little relationship to mealtime.

noted a recent black, tar-like bowel movement, which he attributed to eating too many black beans.

PROBLEM LIST: occult blood (a small amount of blood not visible to the naked eye) on a stool test (Hemoccult),

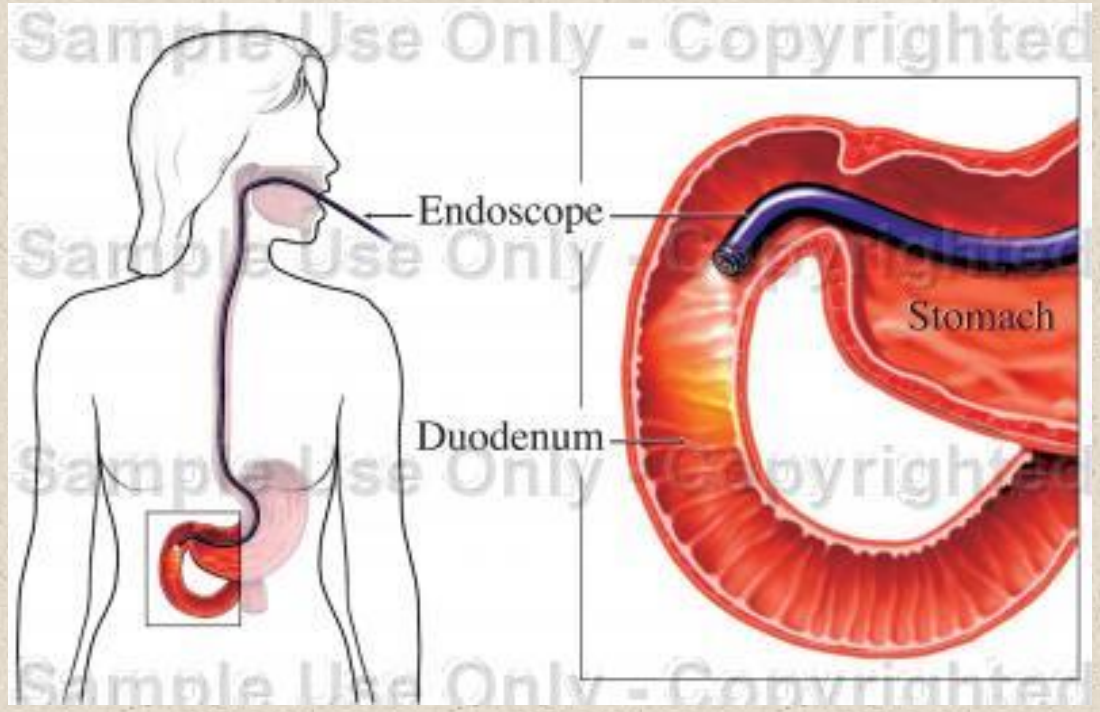
his red blood cell count was lower than normal (anemia).

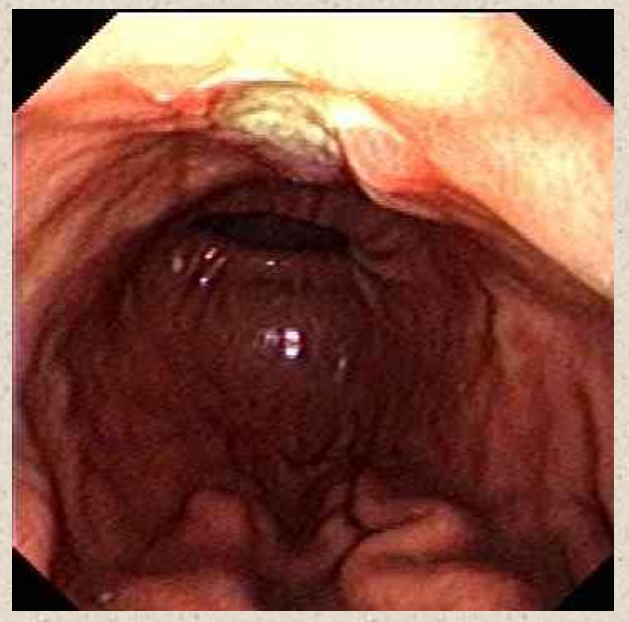
MEDICATIONS: Antacids

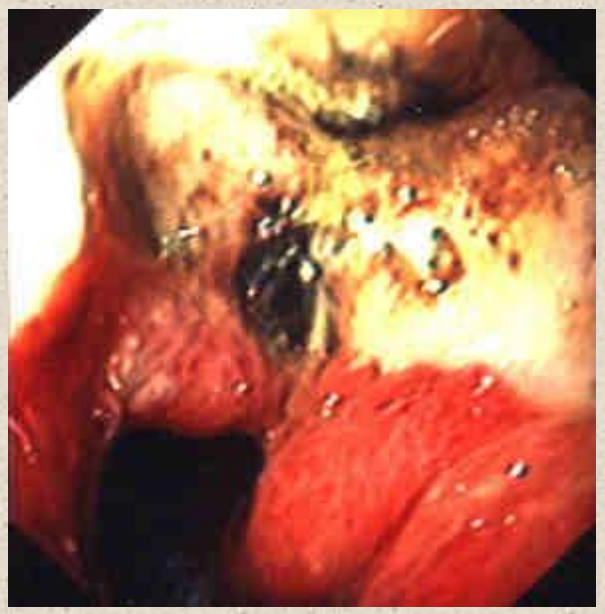
Vital signs: BP 110/55 Pulse 90 Resp 20

Laboratory: Endoscopy exam revealed a large ulcer in the bottom of his stomach with some evidence of recent bleeding,

Biopsy of the stomach demonstrated bacteria, Helicobacter pylori.

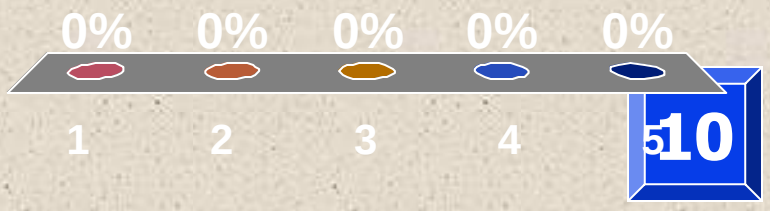

Endoscope
Stomach
Duodenum





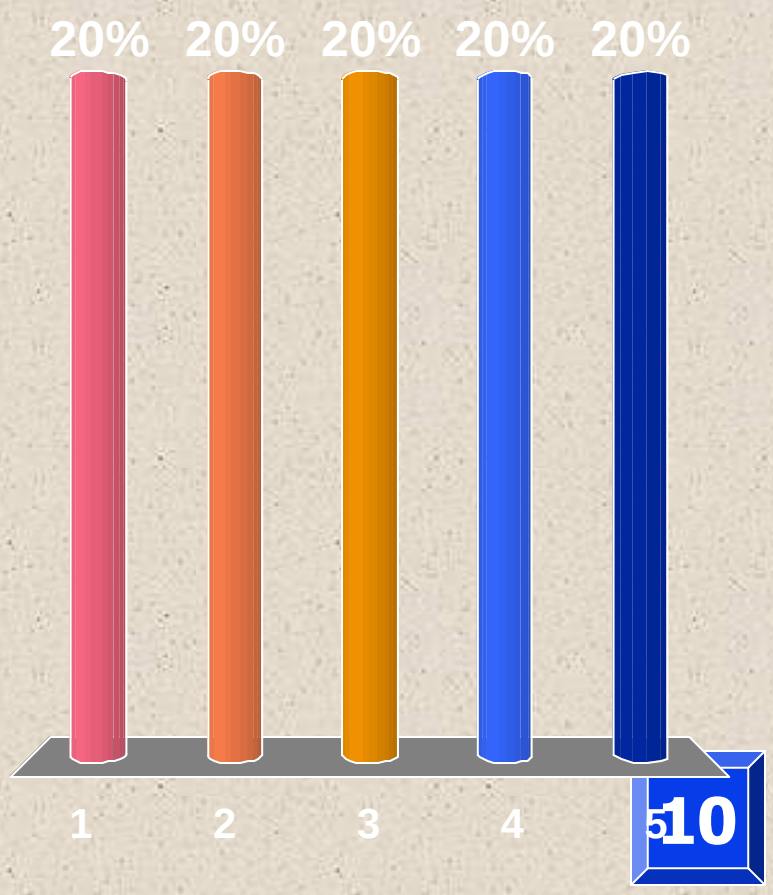
What is the most likely diagnosis?

1. NSAID induced ulcer
2. Food and Stress induced ulcer
3. H. pylori induced ulcer
4. Zollinger Ellison Syndrome
5. Gastric Cancer



How would you Treat such a patient

1. Proton pump inhibitor & antacids
2. Antibiotic
3. H2 receptor antagonist & sucralfate
4. Proton pump inhibitor & antibiotic
5. Prostaglandins (Misoprostol)



GI – CASE IV

A 68 year old man

Chief Complaint: Chest pain with vomiting of bright red blood for several days.

PROBLEM LIST: Chronic renal insufficiency and Osteoarthritis.

MEDICATIONS: Ibuprofen

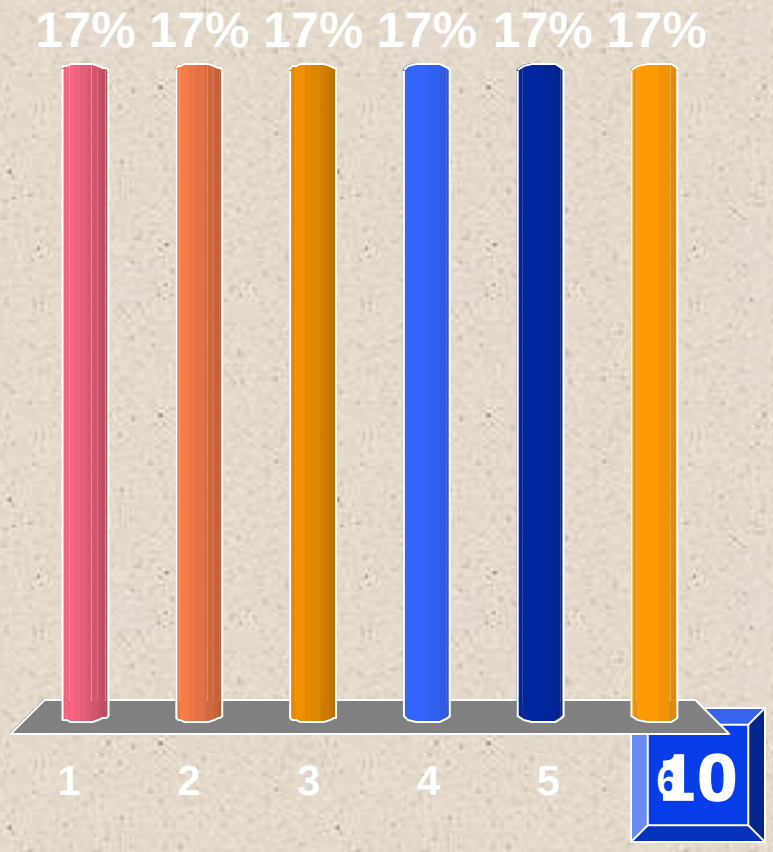
Vital signs: BP 110/55 Pulse 80 Resp 20

Physical Exam: Tender in epigastrium

Laboratory: Hgb/Hct 15/44 PT/aPTT-WNL
Gastric aspiration- negative for blood
Stool negative for blood

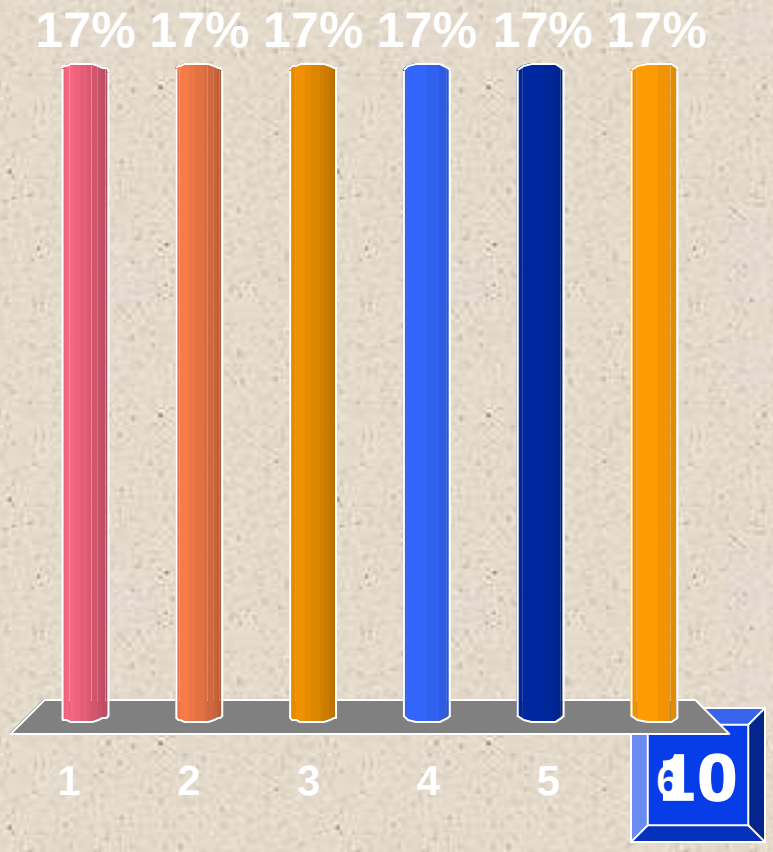
What are the possible causes?

1. NSAID induced ulcer
2. Bleeding into bowel from an aortic aneurysm
3. H. pylori induced ulcer
4. Cardiovascular event
5. Gastric Cancer
6. All of the above



Further laboratory evaluation, what test(s) do you want?

1. Liver cell test
2. EGD
3. H. pylori induced breath test
4. EKG & Cardiac enzymes
5. Abdominal X-rays
6. All of the above



Hospital Course

- **All Laboratory Tests Within Normal Limits**
- **GI Consult**
- **Did Not Meet Criteria for EGD**
- **Discharged With Instructions to Discontinue Use of NSAIDs**

Return to ER

- **36 Hours later With History of vomiting bright red blood and copious maroon colored stools**
- **Physical Exam:**
  - Apperance- pale and sweaty

VS: BP 90/50 pulse 100 R 18

Epigastric tenderness

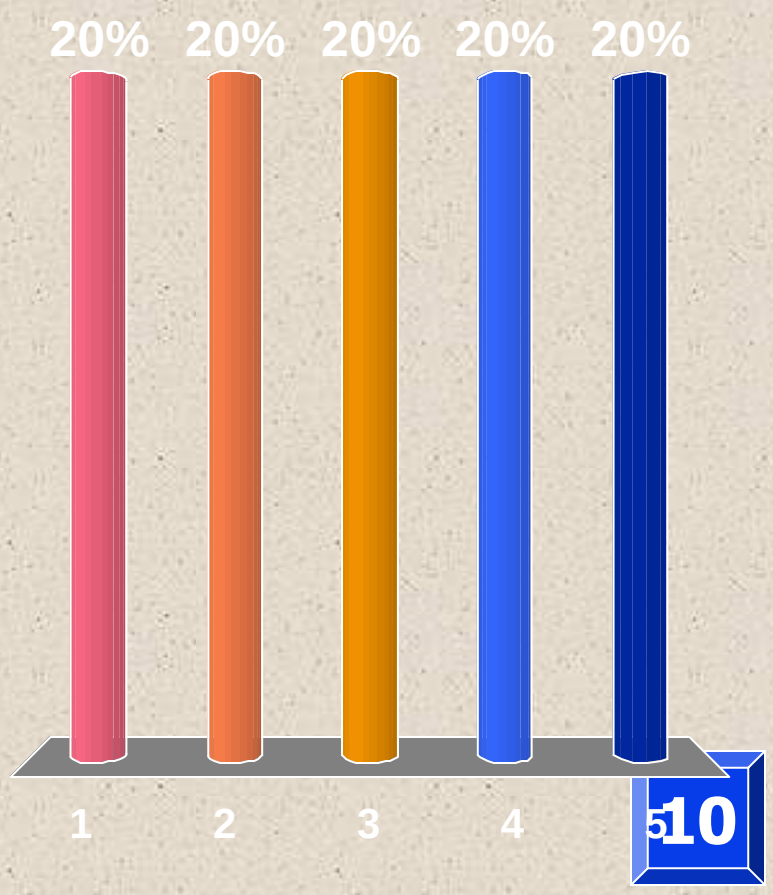
Lab Hgb/Hct 9/30

Hospital Course

- **Admitted to ICU**
- **Stabilized with IV fluids**
- **GI Consult Requested**
- **GI agrees to perform EGD**
- **GI starts procedure with conscious sedation using local anesthesia and midazolam**
- **Patient expels large volume of blood from the mouth that can not be controlled with suction**

What is going on? Differential diagnosis would include all of the following EXCEPT

1. Massive bleeding peptic ulcer
2. Hemrroidal bleeding
3. Bleeding colon cancer
4. Communication between GI tract and aorta
5. Hemorrhagic gastritis

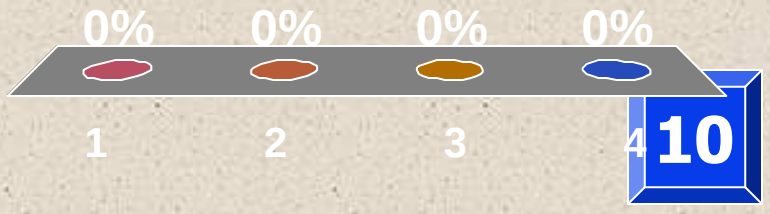


Post-mortem

- **Pathologist finds communication between third portion of duodenum and abdominal aortic aneurysm**
- **Microscopic exam: no evidence of inflammation seen in duodenal wall**

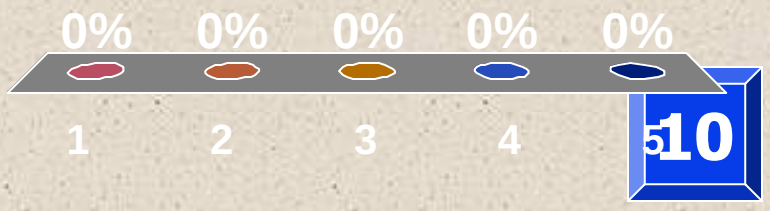
How does *H. pylori* contribute to peptic ulcer disease?

1. Increases prostaglandin synthesis
2. Decreases the mucosal barrier
3. Increases the synthesis of HCL
4. Increases pepsin production



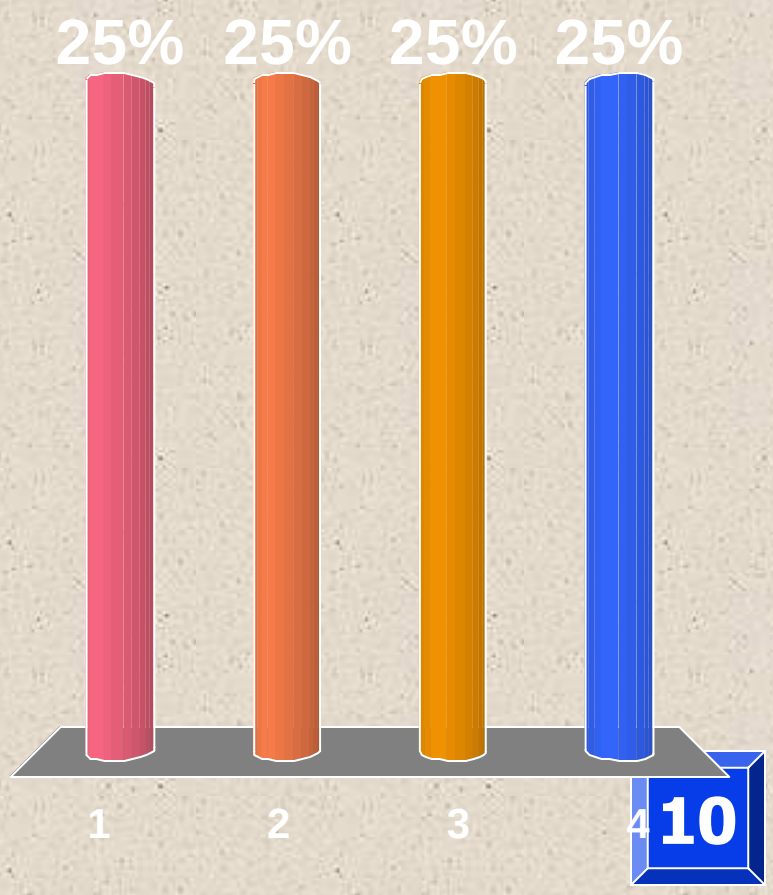
The three major pathways regulating parietal cell acid secretion include:

1. Vagal nerve stimulation
2. Endocrine stimulation via gastrin
3. Paracrine stimulation via histamine
4. 1 an 2
5. All of the above



Cimetidine, an H2 antagonist, is effective at reducing acid but has several side effects EXCEPT:

1. Inhibition of drugs metabolized by CYP450's
2. An antiandrogen effect
3. Can result in hypergastrinemia
4. Can cause confusion and disorientation in the elderly



Therapeutic Strategy for Peptic Ulcer Disease

- Old Therapeutic Strategy:
  - *USED TO BE "no acid, no ulcer".*
  - Accomplished by reduction of acid production *OR* improvement of the integrity of the mucosal barrier, or both.

- Current Therapeutic Strategy:
  - Now "*no NSAID damage, no Zollinger Ellison syndrome, no H. pylori, no ulcer*".