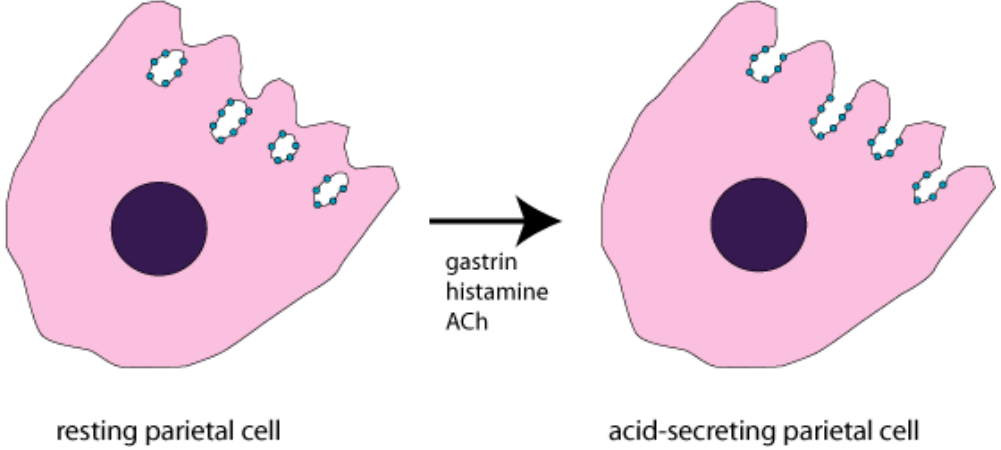
Drugs Used in the Treatment of Gastrointestinal Diseases.

Hamzeh Elayan, 2015.

Anything written in a “comic-sans-font” is a note added by the System team

First 3 slides are really physiology

Physiology of gastric Secretion



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

Parietal cells secrete **2** liters of acid/ day.

Optimal pH (between **1.8-3.5**) for the function of the digestive enzyme pepsin.

The H+/K+-ATPase (or **proton pump**) uses the energy derived from ATP hydrolysis to pump hydrogen ions into the lumen in exchange for potassium ions.

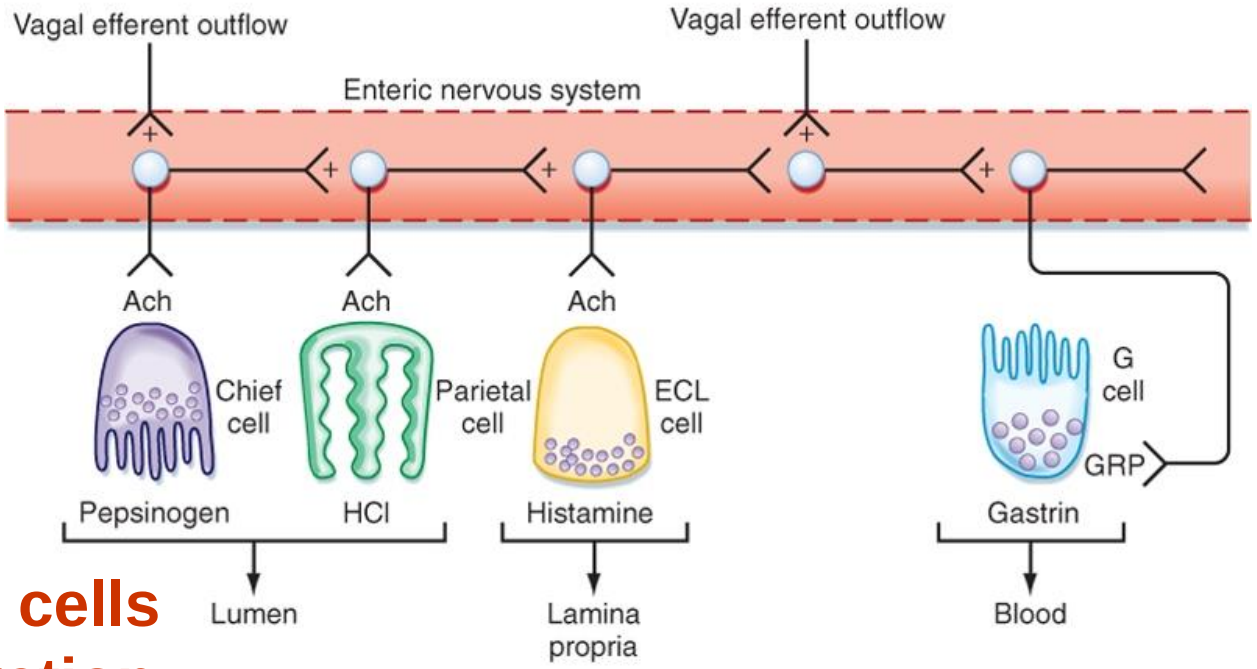
Chloride and hydrogen ions are secreted separately from the cytoplasm of parietal cells and mixed in the canaliculi.

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.**

Gastrin releasing peptide (**GRP**)

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.

Three phases in gastric acid secretion.

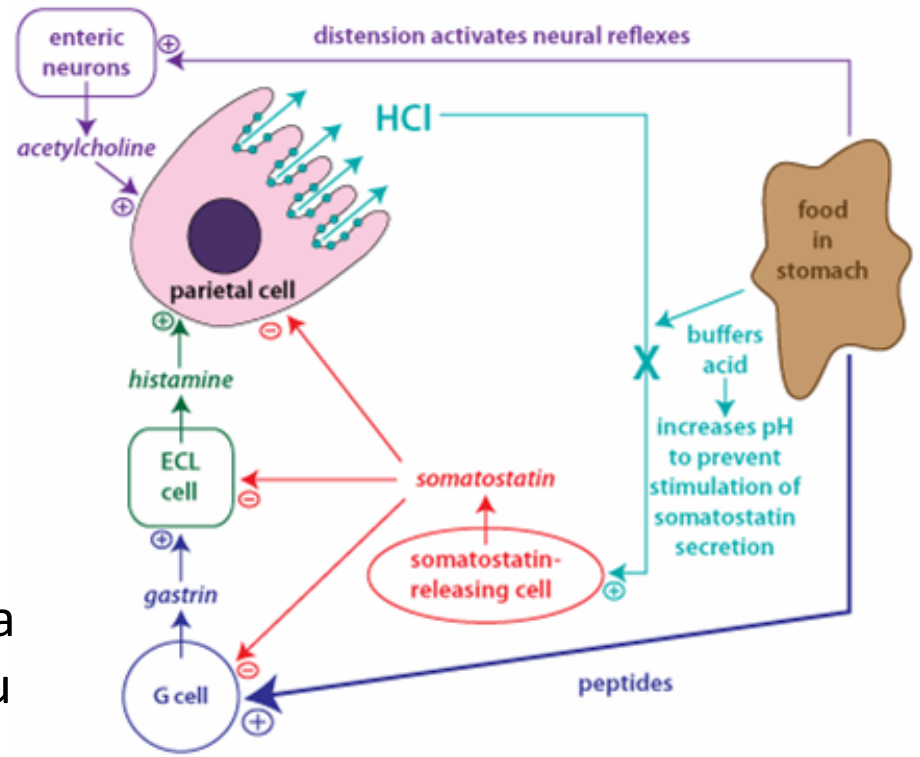
Cephalic Phase:

sight, smell, taste or thought of food,

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

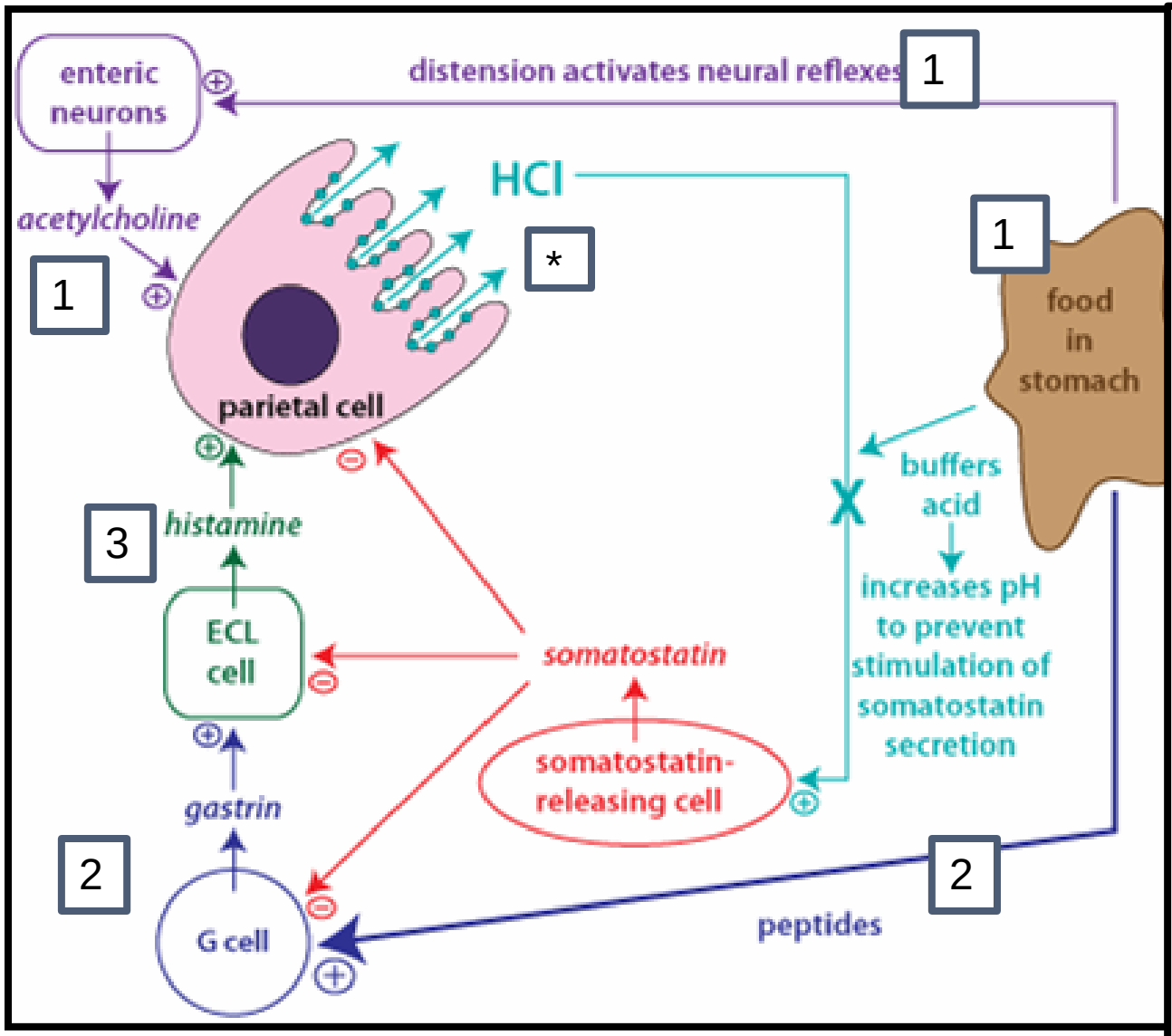
Gastric Phase:

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 .

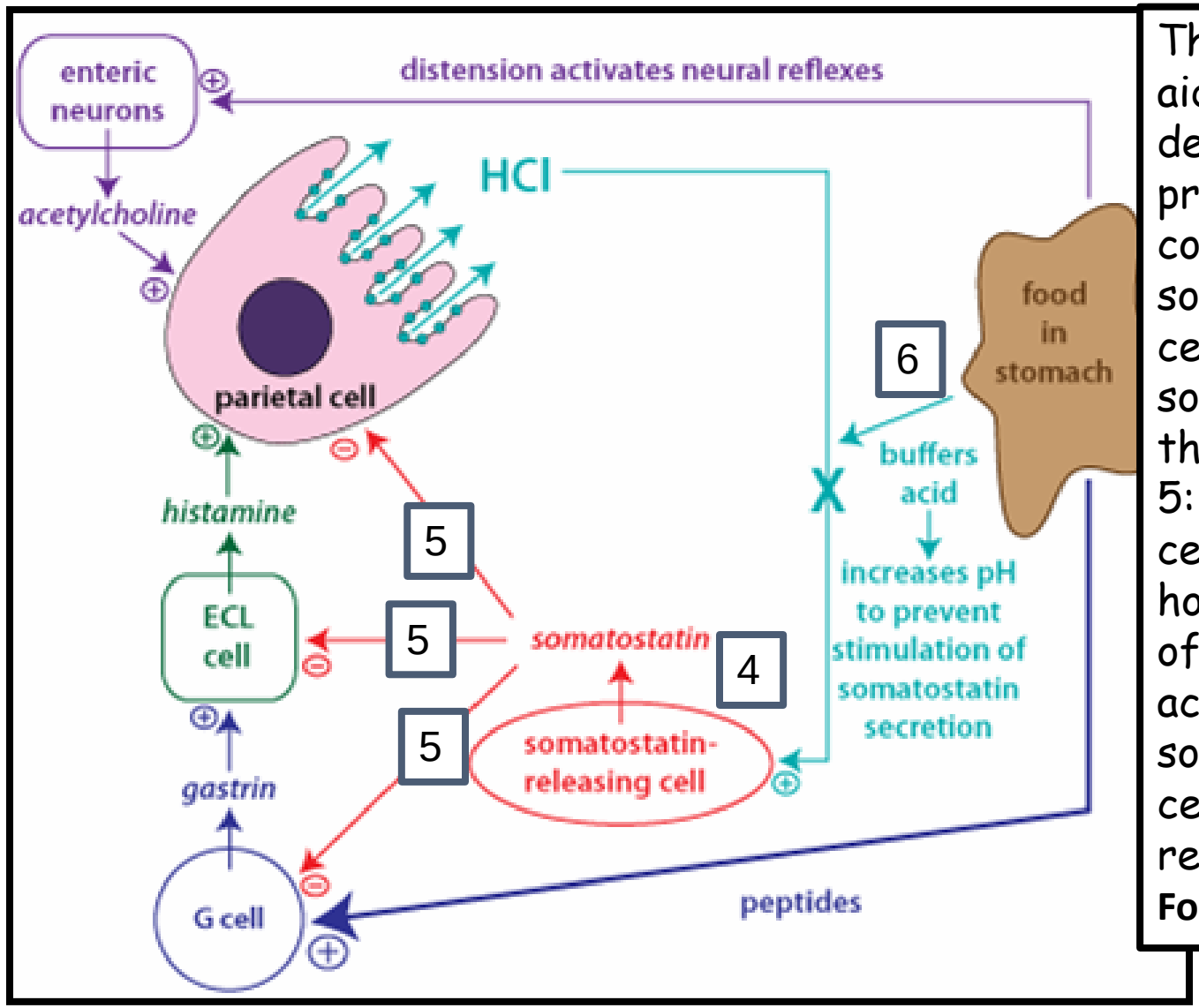


Intestinal Phase:

Once chyme enters the duodenum, it activa
negative feedback mechanisms to redu



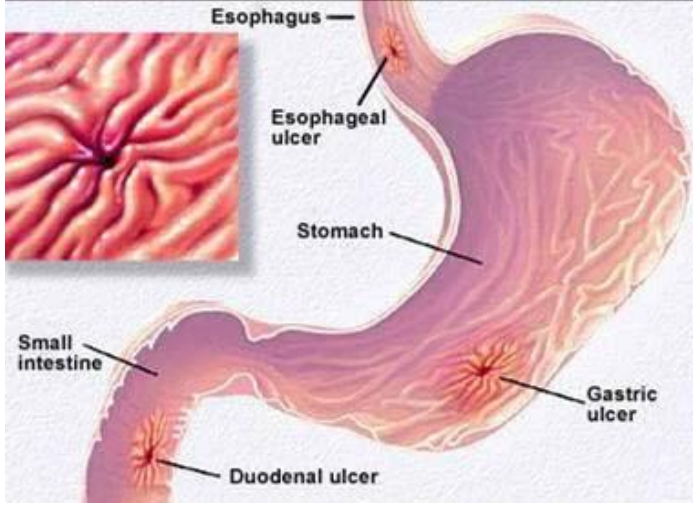
This figure summarize it all :
1:Presence of food in the stomach will lead to activation of neural reflex(by applying stretching and distension) that will end by secreting Ach from neurons which stimulate parietal cells to secrete HCl (indicated as *)
2:Presence of food in the stomach will also stimulate G cells to stimulate Gastrin
3:gastrin will stimulate enterochromaffin – like cells to secrete Histamine
that will also stimulate parietal cells to secrete HCl(*)



The HCl ,will:
aid in digestion and decrease the PH to provide the optimal conditions for somatastatin releasing cells to release somatostatin (4)
this
5: inhibits G-cells , ECL cells & parietal cells
however , the presence of food inhibits the action of HCl among somatostatin releasing cells & raise the PH (6)
remember ;
Food acts as a buffer

Peptic ulcer

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



Causes of Peptic Ulcer:

Helicobacter pylori (most common).

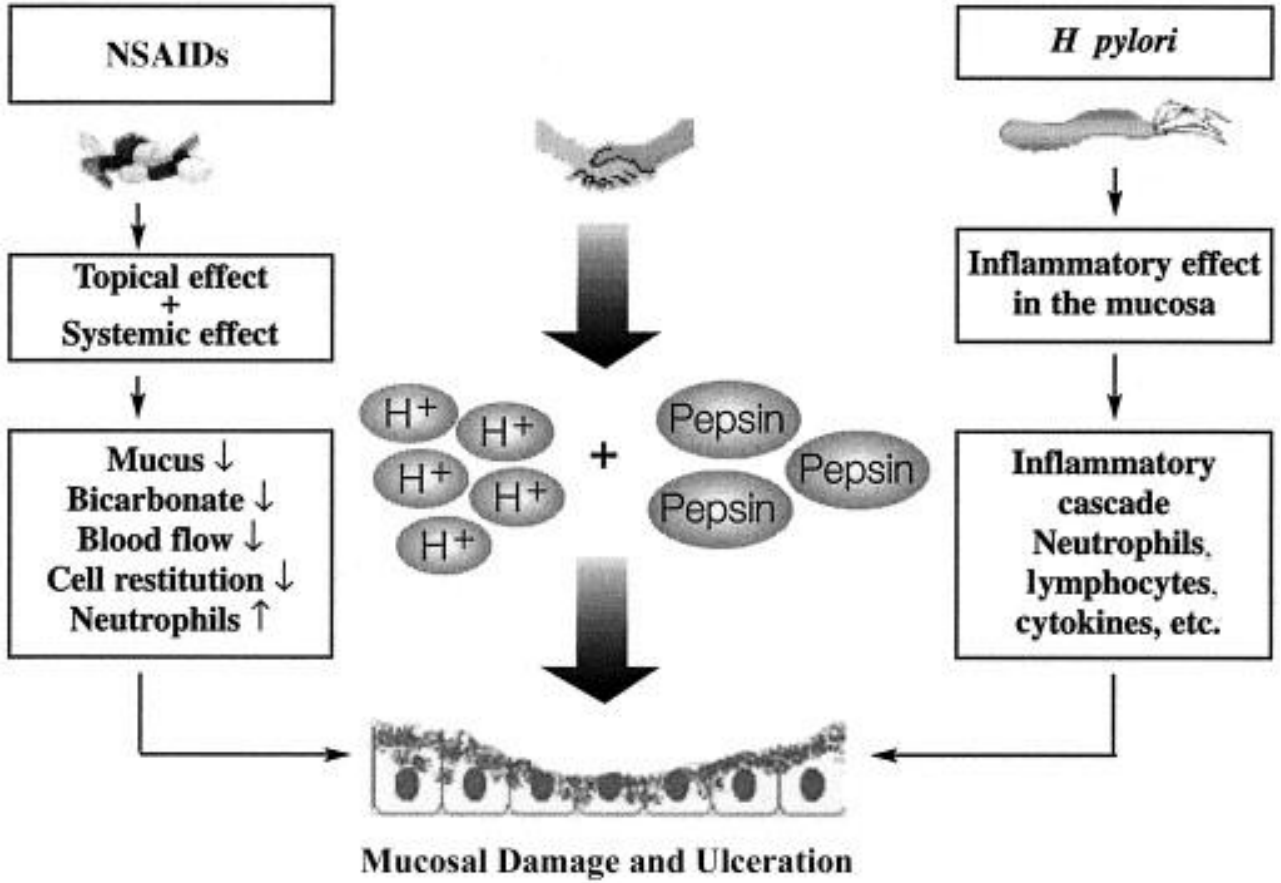
Drugs such as aspirin
& other NSAIDs*

Other factors:

Smoking,
Stress,
alcohol.
Gastrinomas

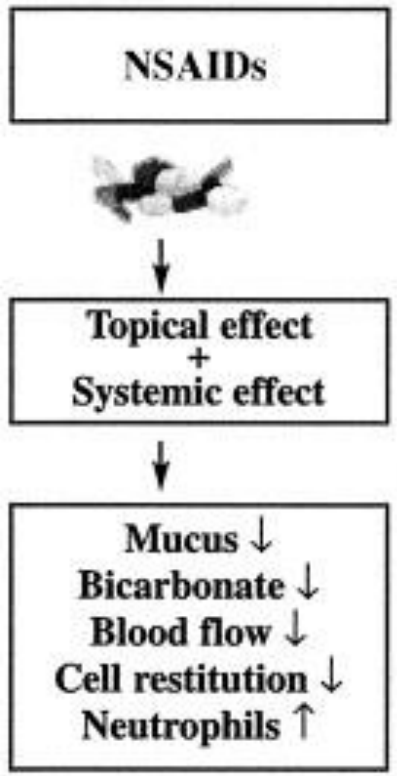
Zollinger Ellison syndrome

a rare gastrin-secreting tumors.



Regard
NSAIDs & Peptic ulcer

*NSAIDs= Non-Steroidal Anti Inflammatory Drugs
NSAIDs inhibit the secretion of Prostaglandins (PG) that normally play a vital role in protection & preservation of the stomach lining .
Inhibiting PG secretion by NASIDs will decrease (mucus secretion & the other things indicated in this figure)



Symptoms:

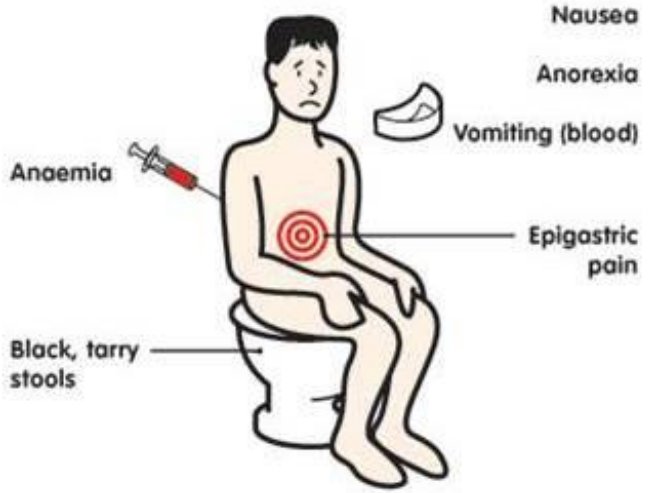
burning pain in stomach between meals or at night, bloating, heartburn, nausea or vomiting.

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 (discussed in details later)

- **Reduce** acid secretion (figure 1)
- **Neutralize** acid in the lumen (figure2)
- **Protect** the mucosa from acid destruction (figure3)
- **Antibiotics** to eradicate *Helicobacter pylori.* If this is successful then the ulcer should begin to heal on its own.(Figure4)

Figure 4

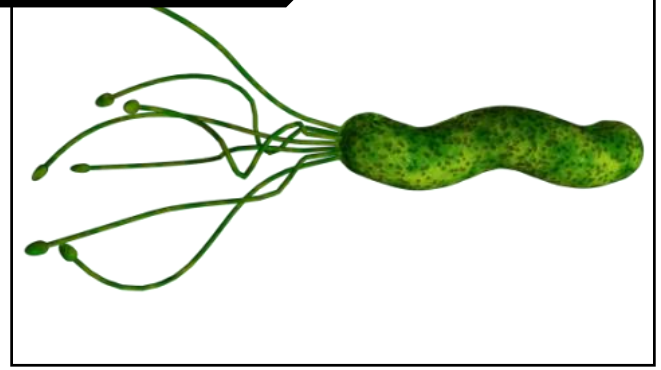
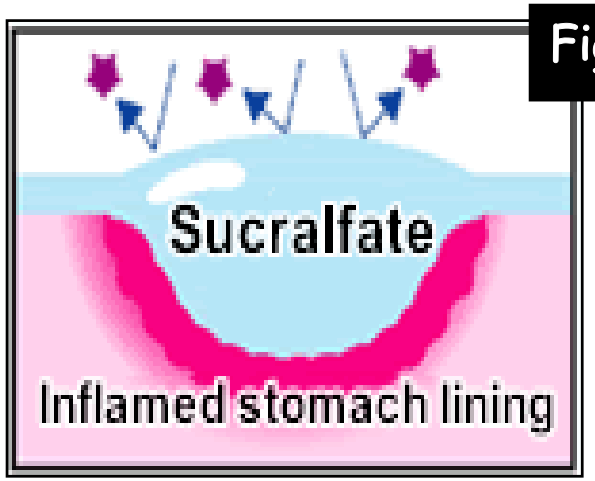


Figure 3



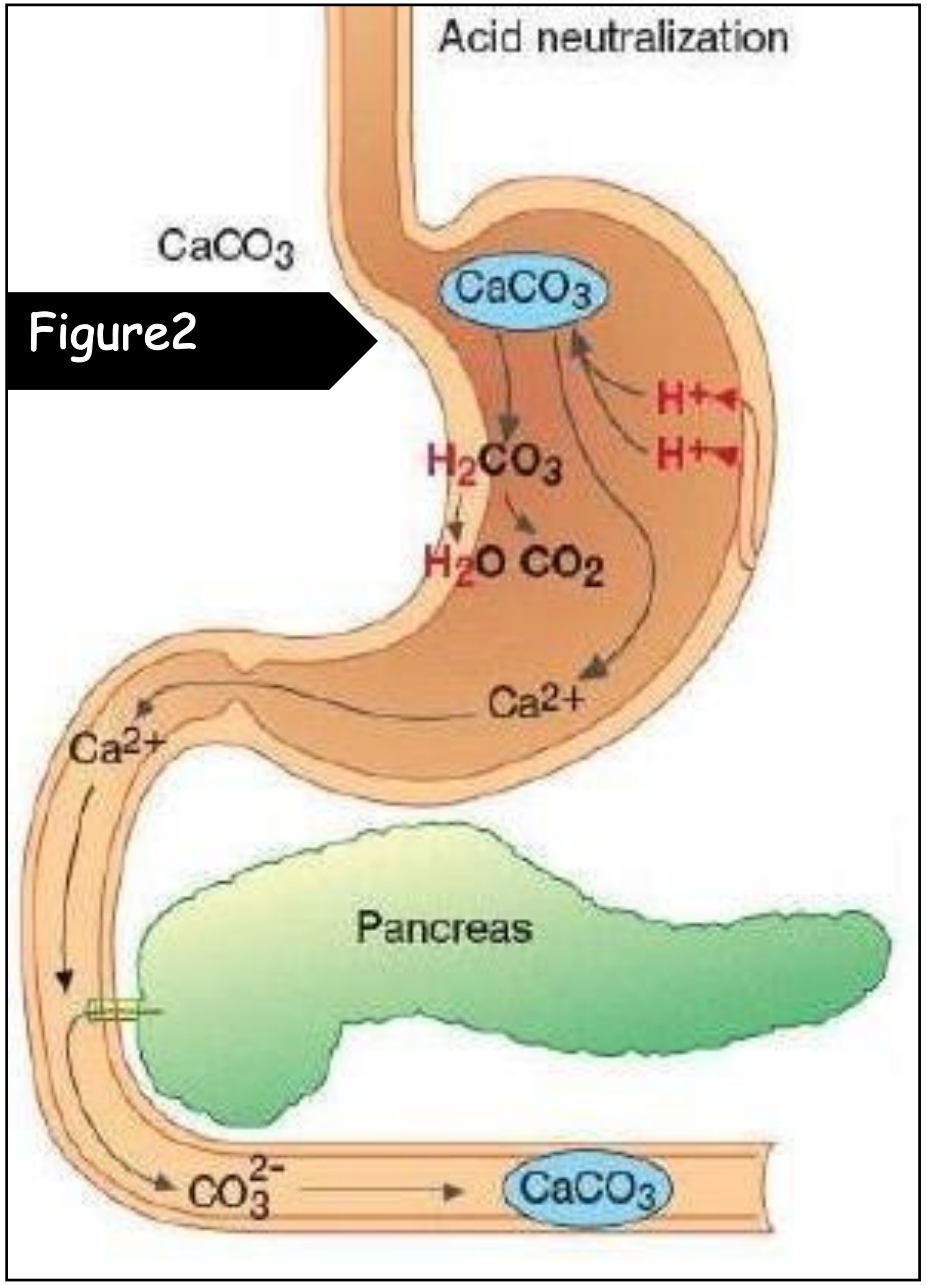


Figure2
Acid neutralization
CaCO3
CaCO3
H+
H+
H2CO3
H2O CO2
Ca2+
Ca2+
Pancreas
CO3 2-
CaCO3

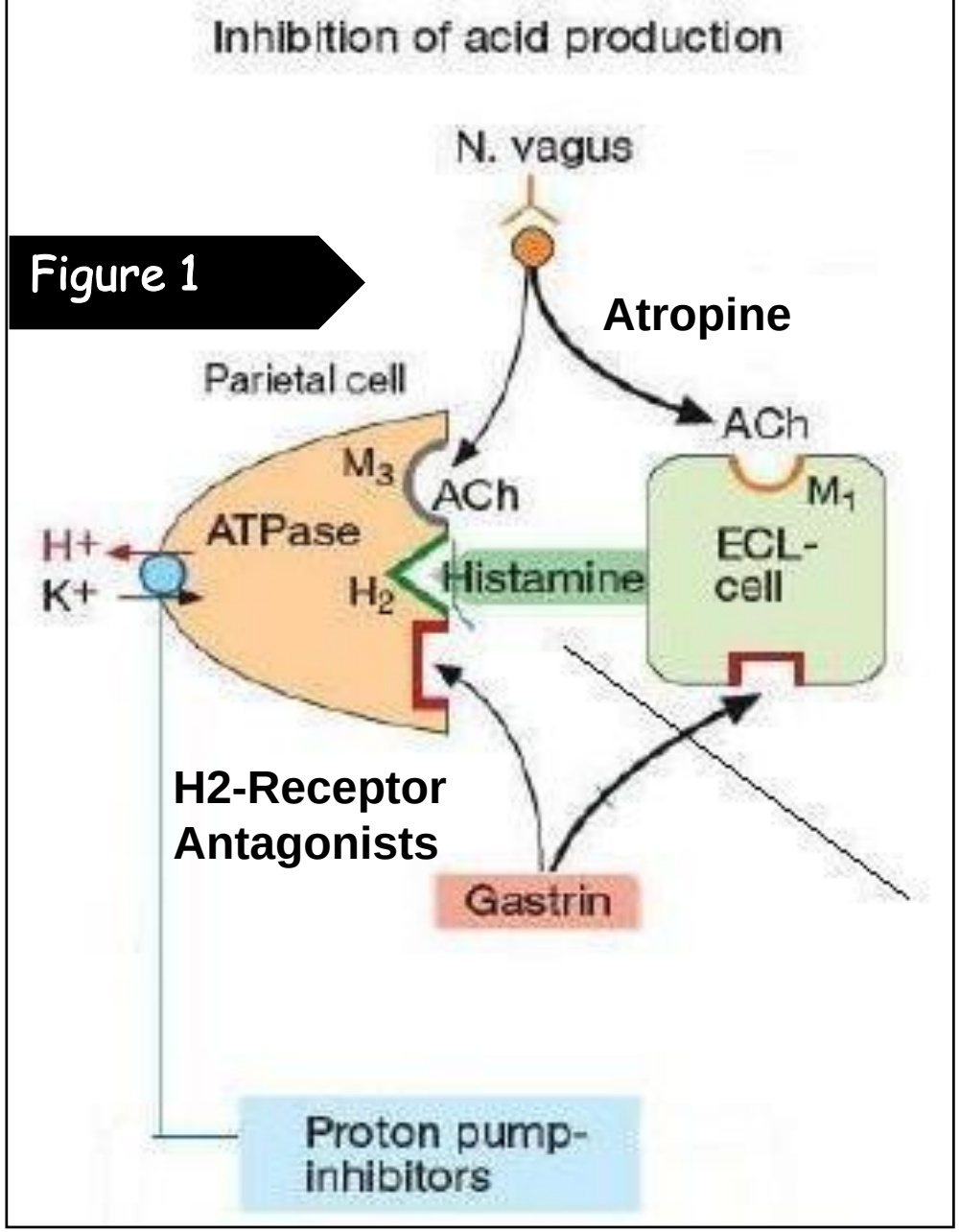


Figure 1
Inhibition of acid production
N. vagus
Atropine
Parietal cell
ACh
M3
ACh
M1
ATPase
H+
K+
H2
Histamine
ECL-
cell
H2-Receptor
Antagonists
Gastrin
Proton pump-
inhibitors

First Option
Neutralization of acid by Antacids

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.

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

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

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

2.Magnesium antacids have laxative action; diarrhea. ionic magnesium stimulates gastric release (acid rebound)

3.Magnesium trisilicate slow-acting antacid

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

5.Calcium carbonate

associated with "acid rebound"

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

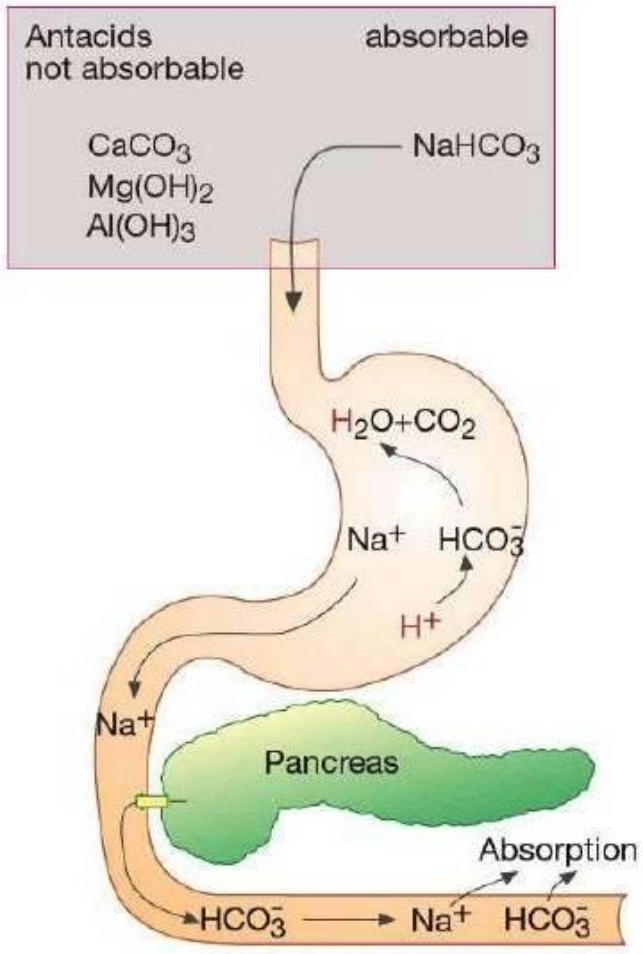
$2HCl + CaCO_3 \rightarrow CaCl_2 + \mathbf{CO_2} + H_2O$

These are not really preferred . The best Antiacid is a combination between Mg and Al

6.Sodium bicarbonate

should be avoided; aggravate CHF (Congestive heart failure) & counteracts diuretic therapy for hypertension, short duration of action, followed by acid rebound, highly absorbed, potentially causing metabolic alkalosis. CO2 results in gastric distention and belching.

$NaHCO_3 + HCl \rightarrow NaCl + H_2O + \mathbf{CO_2}$



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

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

$2HCl + CaCO3 \text{ ---> } CaCl2 + \mathbf{CO2} + H2O$

$NaHCO3 + HCl \rightarrow NaCl + H2O + \mathbf{CO2}$

The Antacid is a base(-OH) that will neutralize the HCl by "breaking" it.

Notice the release of CO2 in the last two formulas CO2 results in gastric distention and belching . (side effect = Not preferred)

Make sure You are familiar with these Terms:
acid rebound an increased rate of gastric acid secretion occurring 30 to 60 minutes after eating.
Metabolic alkalosis is a pH imbalance in which the body has accumulated too much of an alkaline substance, such as
bicarbonate, and does not have enough acid to effectively neutralize the effects of the alkali.

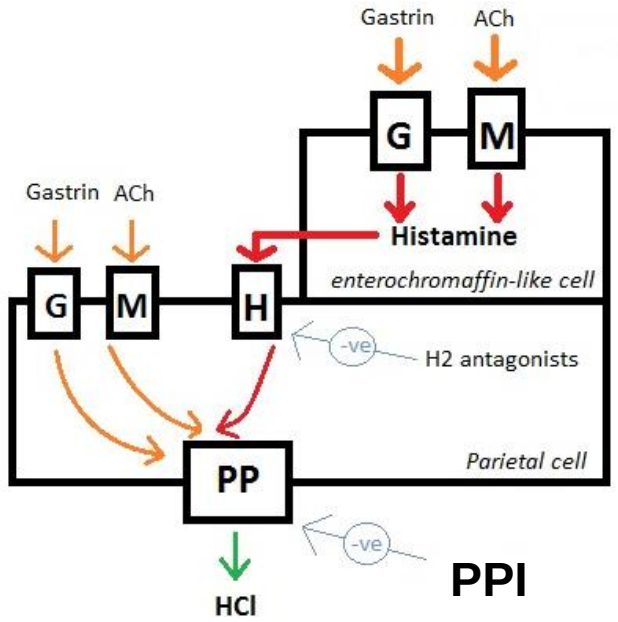
Second Option
reduce acid secretion by:
✓H2-Receptor Antagonists
✓Proton Pump Inhibitors (PPIs)

H2-Receptor Antagonists (checkout the note first)

Cimetidine, Ranitidine,

Famotidine Nizatidine.

(Mnemonic:Creepy Recipes to Form Nuggets)



Rapidly absorbed from intestine.

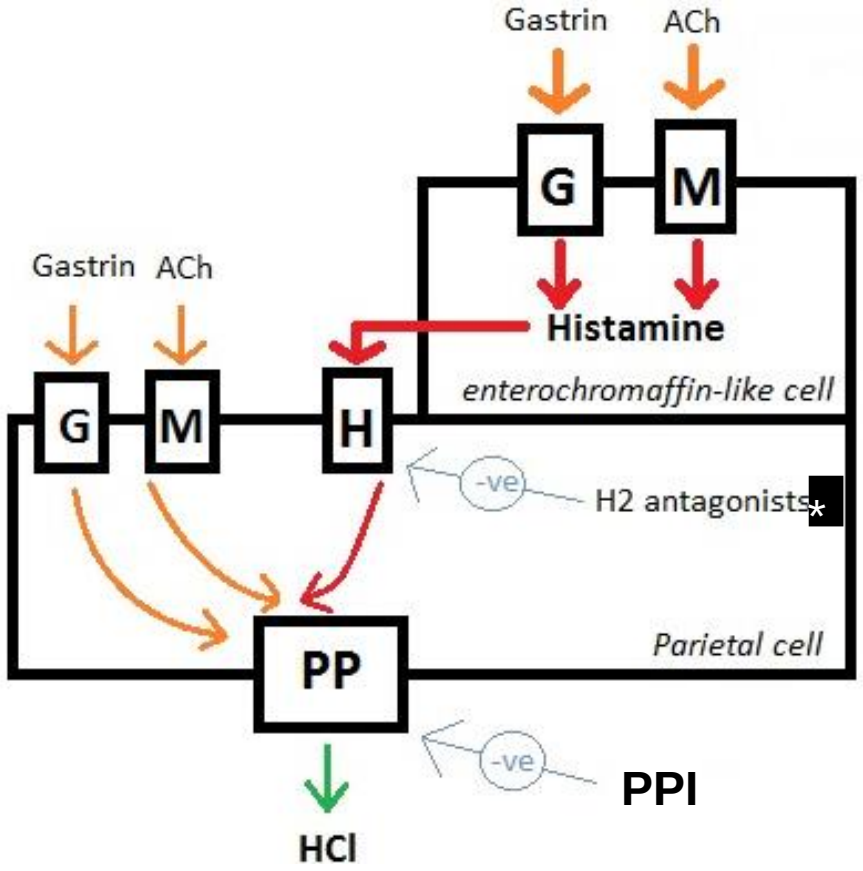
Cimetidine, ranitidine, famotidine

first-pass metabolism bioavailability 50%

Nizatidine has little first-pass metabolism.

Duration of action:6–10 hours, given twice daily.

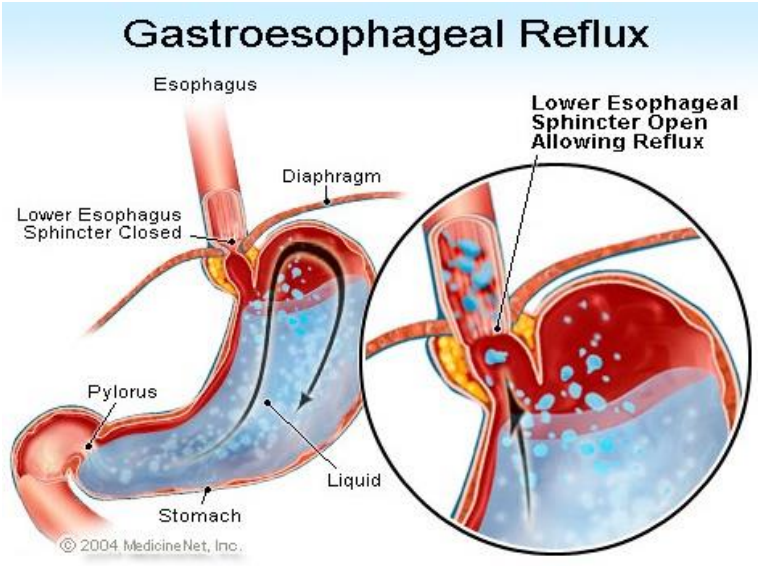
- Inhibit 90% of nocturnal acid (depends on histamine).
- Modest impact on meal-stimulated acid secretion (which is stimulated by gastrin, Ach and histamine)
- Inhibit 60% of day-time, meal stimulated acid.
- **Inhibit 60-70% of total 24-h acid secretion**.



H2-Receptor Antagonists
block the action of histamine at the histamine H2 receptors of the parietal cells in the stomach. This decreases the production of stomach acid.

*Remember at the very beginning we said that histamine will stimulate the parietal cells to release HCl (acid)
so they thought of making these antihistamines
the first generation was H1-receptos antagonists
then they found out that there's a different type of histamine receptors which is H2 receptors on the parietal cells >>so they produce them.

Clinical Uses of H2-Receptor Antagonists



Gastroesophageal Reflux Disease (GERD)

Taken prophylactically before meals.

In erosive esophagitis H2 antagonists healing is less than 50% hence **PPI** (discussed later) are preferred.

Non Ulcer Dyspepsia.

Over-the-counter agents for treatment of intermittent dyspepsia not caused by peptic ulcer.

Prevention of Bleeding from Stress-Related Gastritis

IV H2 antagonists are preferable over IV **PPI** because of their proven efficacy and lower cost.

Peptic Ulcer Disease:

Replaced by PPI.

- Healing rate more than 80-90% after 6-8 wks.
- Not effective in the presence of ***H. pylori.***
- Not effective if NSAID is continued.

Adverse Effects:

Extremely safe drugs. Diarrhea, headache, fatigue, myalgias, and constipation (3%).

Cimetidine may cause gynecomastia & impotence in men (antiandrogenic effects) and galactorrhea in women

*Antiandrogen: A drug that blocks the action of androgens (male sex hormones)

Drug Interactions:

Cimetidine inhibits cytochrome P450 enzymes so can increase half life of many drugs.

Ranitidine binds 4-10 times less.

Nizatidine and famotidine binding is negligible

Proton Pump Inhibitors (PPIs)

Among the most widely prescribed drugs worldwide due to their outstanding efficacy and safety (#1 selling drugs).

Omeprazole (oral).

Rabeprazole (oral).

Lanzoprazole (oral and IV).

Pantoprazole (oral and IV).

Esomeprazole (oral and IV).

Stupid mnemonic :P
Om Rabab is a Lady with Plastic Emotions

Prodrugs, released in the intestine (Destroyed by acid).

Immediate Release Suspension (contains sodium bicarbonate to protect the drug from acid degradation) results in rapid response.(furthered explanations next)

PPIs are prodrugs that need to be activated.
They are taken before meals .

These drugs can be Destroyed by the acids.
So to overcome this

- ✓ they are released in the small intestine not the stomach .
- ✓ contains sodium bicarbonate

Lipophilic weak bases, absorbed in small intestine and delivered to parietal cell through the blood.

Drug is protonated and “trapped” in acidic canaliculi.

Concentrated more than 1000-fold in the parietal cells.

Converted to the active form which covalently binds the H+/K+ ATPase enzyme and inactivates it.

Have short half lives but effect lasts for 24 hours.

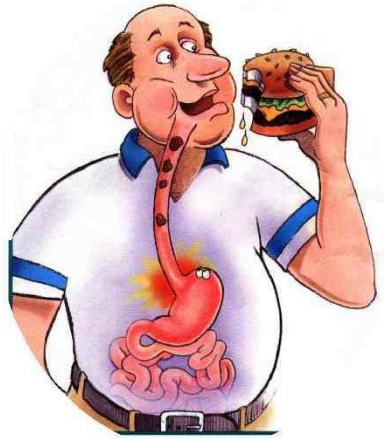
At least 18 hours are required for synthesis of new pump molecules.

Inhibit both fasting & meal-stimulated secretion

(90-98% of 24-hour secretion).

The full acid-inhibiting potential is reached in 3 to 4 days.

Clinical Uses of (PPIs) :



1.Gastroesophageal Reflux (GERD):

The most effective agents in all forms of GERD

2.Nonulcer Dyspepsia:

Modest activity.10-20% more beneficial than a placebo

3.Stress- Related Gastritis:

Oral immediate- release **omeprazole** administered by nasogastric tube.

For patients without a nasoenteric tube, **IV H_2- blockers** are preferred because of their proven efficacy.

4.Gastric acid hypersecretory states, including Zollinger -Ellison syndrome

Usually high doses of omeprazole are used.

5.Peptic Ulcer Disease:

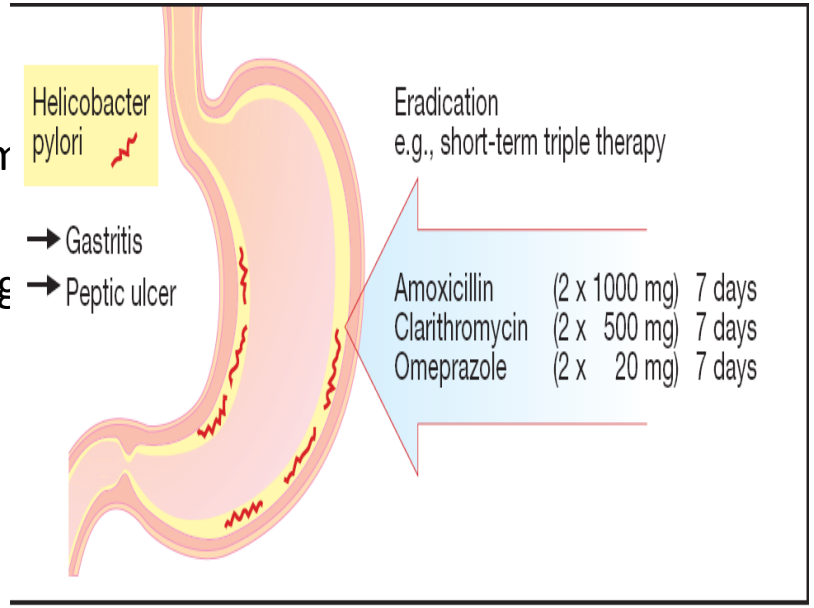
They heal more than 90% of cases within 4-6 weeks.

H.Pylori* - associated ulcers*:

PPI eradicate *H.pylori* by direct antimicrobial activity and by lowering MIC (minimal Inhibitory concentration) of the antibiotics.

***Triple Therapy*:**

PPI twice daily + Clarithromycin 500 m
twice daily +Amoxicillin 1gm
twice daily ,OR, Metronidazole 500mg
twice daily.



C. Helicobacter eradication

NSAID-associated ulcers

Healing despite continued NSAID use.

Also used to prevent ulcer of NSAIDs

Rebleeding peptic ulcer:

Oral or IV. High pH may enhance coagulation and platelet aggregation.

Adverse Effects of PPIs:

Well tolerated.

May cause headache, diarrhea, abdominal pain, nausea

& dizziness

Reduction of cyanocobalamine (Vitamine B12) absorption.

Increased risk of GI and pulmonary infection.

Increased serum gastrin levels causes:

Chronic inflammation in gastric body.

Atrophic gastritis and intestinal metaplasia.

NO CASES OF CANCER

Drug Interactions:

May affect absorption of drugs due to decreased gastric acidity like digoxin and ketoconazole.(these drugs need the acidity of stomach to act)

Third Option

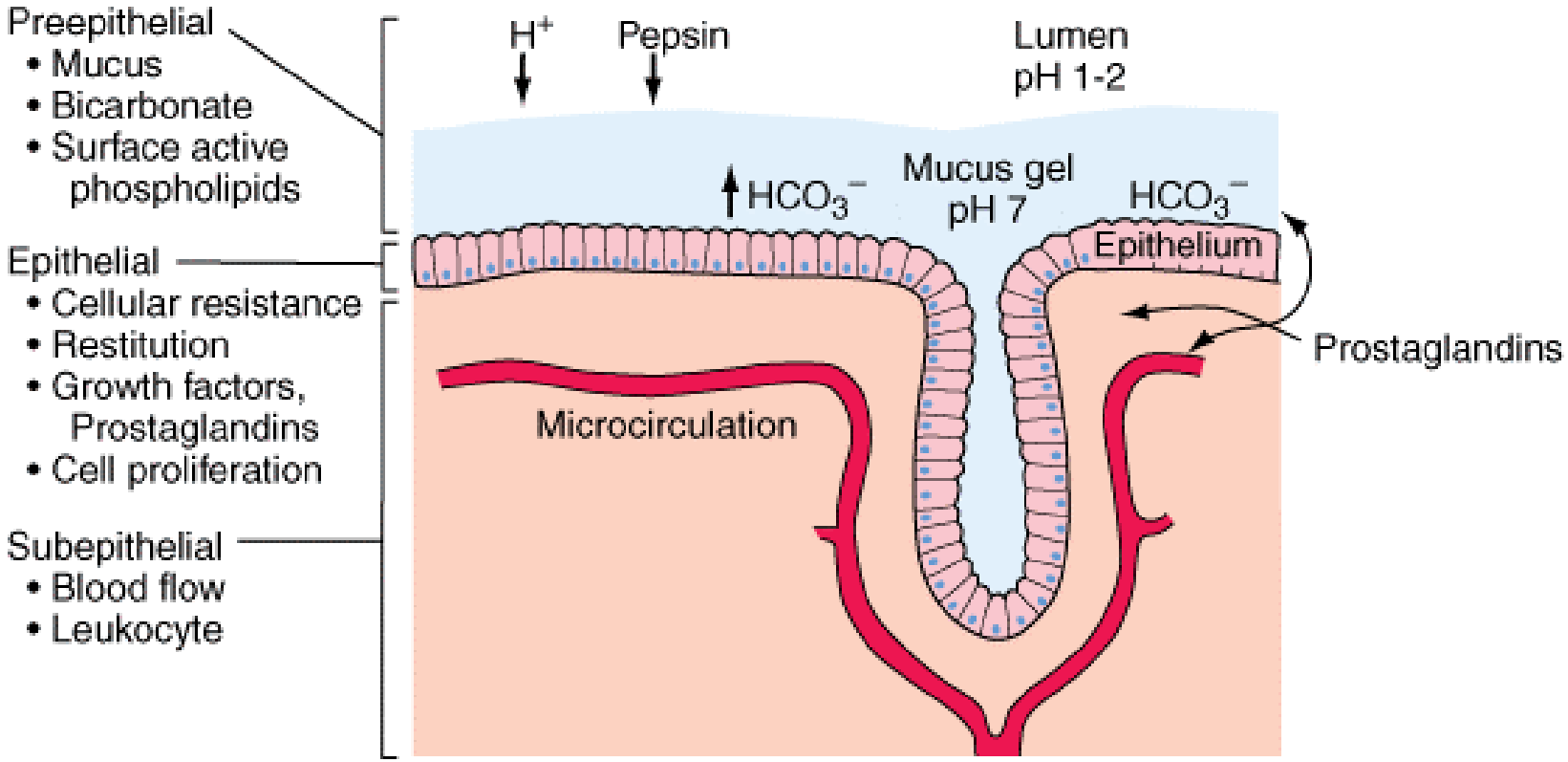
Protect the mucosa from acid destruction

(Mucosal Protective Agents)

- ✓ **Sucralfate**
- ✓ **Prostaglandin Analogs**
- ✓ **Bismuth Compounds**

Mucosal Protective Agents

To be continued.. つづく



1-Both mucus and epithelial cell-cell tight junctions restrict back diffusion of acid and pepsin.

2-Epithelial bicarbonate secretion

3-Blood flow carries bicarbonate

4- injured epithelium are repaired by **restitution**

5- Mucosal prostaglandins stimulates mucus and bicarbonate secretion and mucosal blood flow.