Medical Pharmacology

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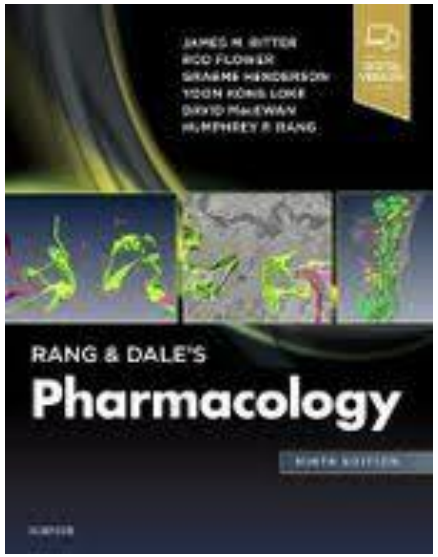
College of Medicine and Dentistry

JAMES COOK UNIVERSITY AUSTRALIA

Celebrating 50 YEARS 1970 - 2020

Gastrointestinal Pharmacology

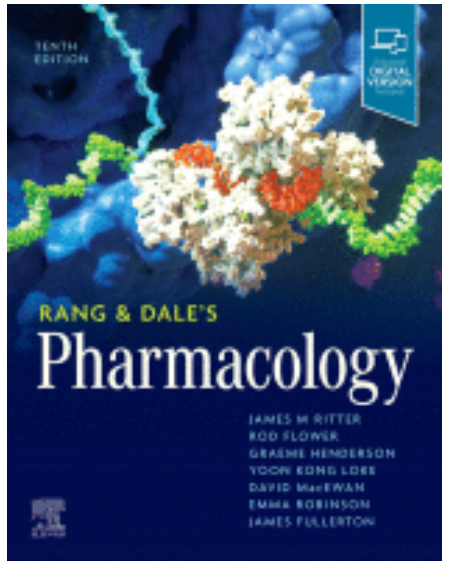
Lecture 2 – pharmacological agents for gastric acid suppression



Rang & Dale's Pharmacology

9th edn 2020

Chaps 31, 33



Rang & Dale's Pharmacology

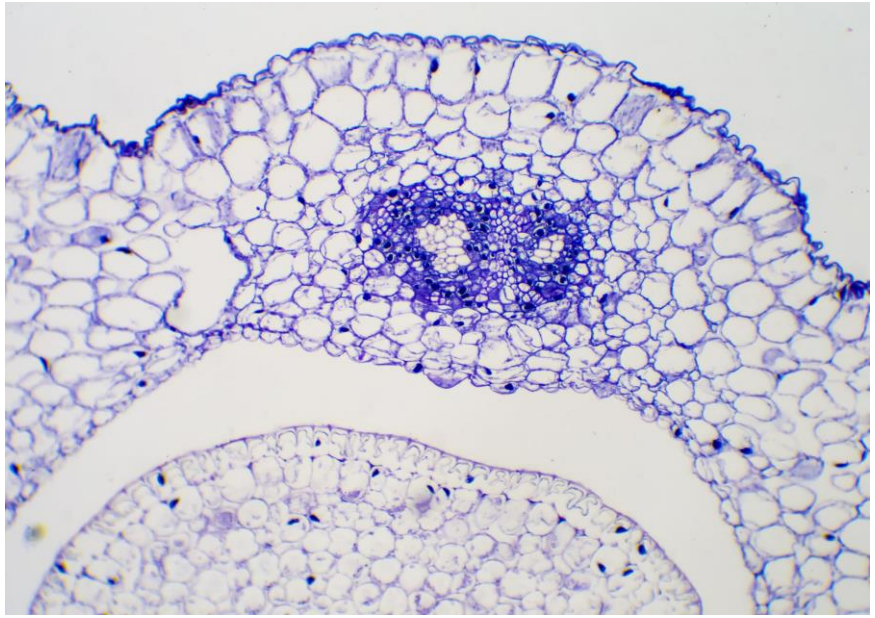
10th edn 2023

Chaps 30, 32

Learning Objectives

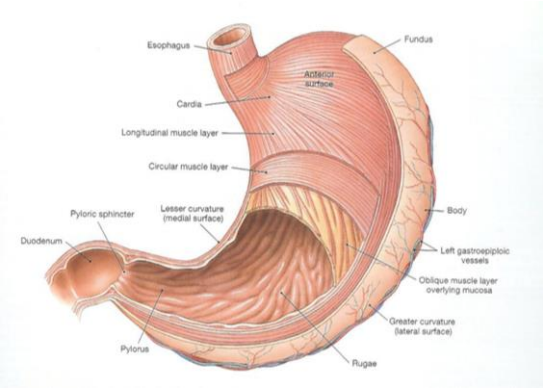
By the end of this module, students should be able to demonstrate and apply knowledge of:

- Mechanisms of gastric acid production
- Common gastric acid disorders- dyspepsia, GORD, PUD
- Pharmacology of agents for acid suppression
    1. H_2 receptor antagonists
    2. Proton Pump Inhibitors



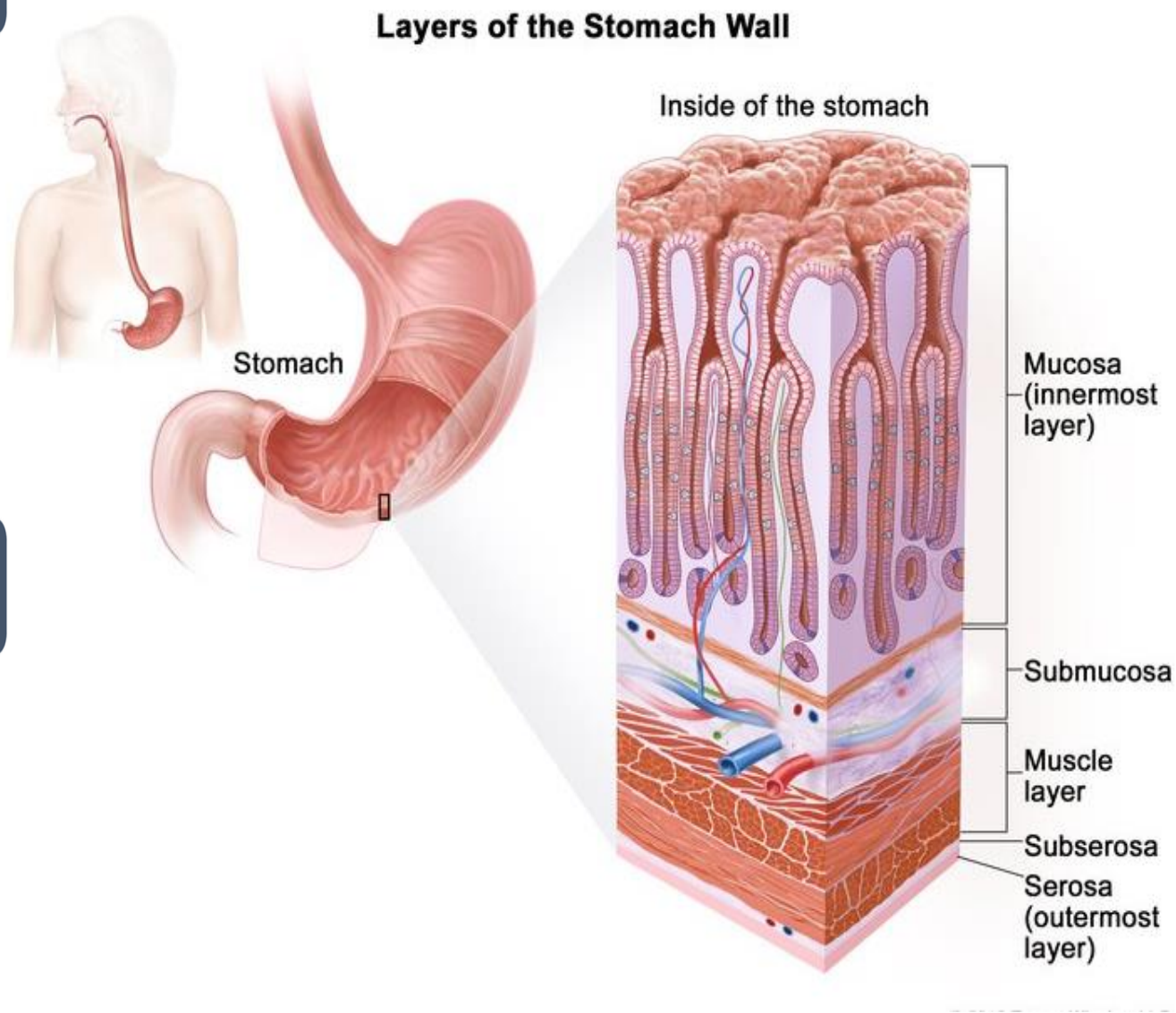
The stomach is divided into regions

- Fundic
- Cardiac
- Body
- Pyloric



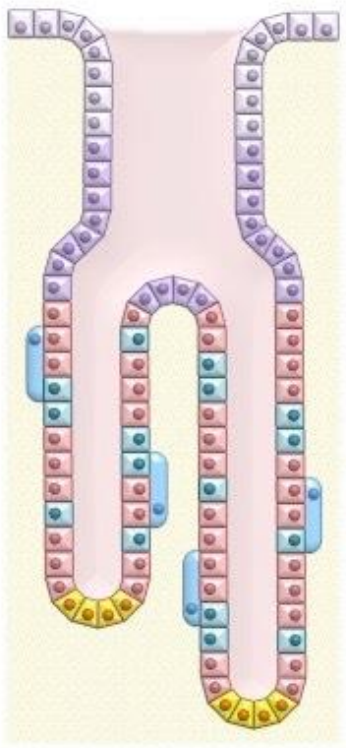
The stomach has four layers of tissue

- Serosa
- Muscularis
- Submucosal
- Mucosal



The innermost layer, the mucosa:

- Further divided into the surface epithelium, lamina propria and muscularis mucosa.
- In contact with food as it enters the stomach.
- Contains gastric pits and glands where specialised cells secrete substances important for the function of the stomach.
- Responsible for secreting digestive enzymes, hydrochloric acid (HCl^-) and protective mucous.



Cell Types	Substance Secreted
Goblet cells	Mucus (protects stomach lining)
Parietal cells	Gastric acid (e.g. hydrochloric acid)
Chief cells	Pepsinogen (protease precursor)
D cells	Somatostatin (inhibits acid secretion)
G cells	Gastrin (stimulates acid secretion)

Approximately ~2.5L of gastric juice is secreted daily.

- HCl- (from parietal cells)
- Pepsinogen (break down proteins)
- Mucous
- Intrinsic factor

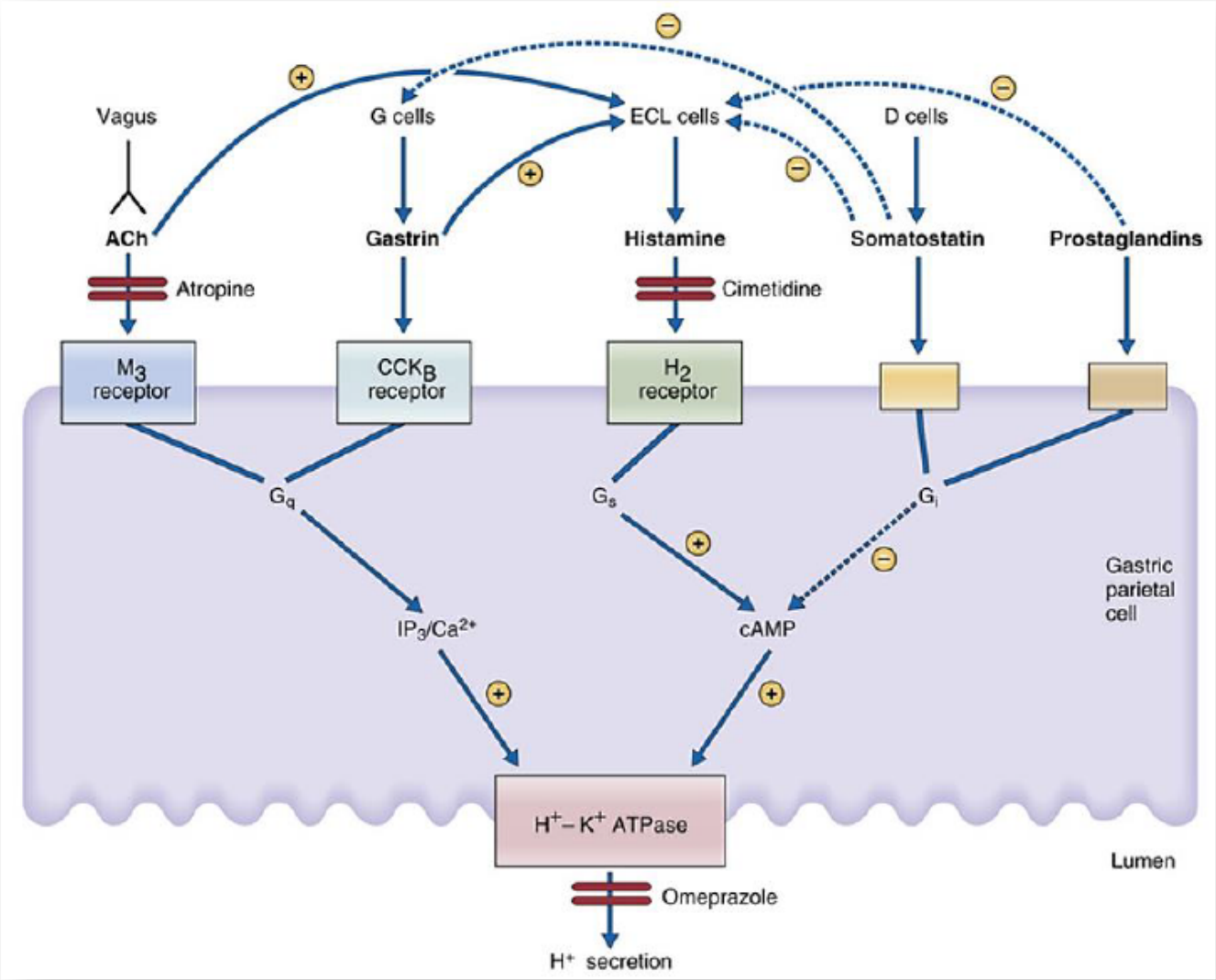
It is highly acidic- PH 1-2

- Proteolytic digestion of food.
- Conversion of pepsinogen (proenzyme) to pepsin.
- Killing of pathogens that prevents infection or sickness from occurring

Parietal cells are responsible for the release of H^+ ions via pump

- H^+/K^+ adenosine triphosphate (ATPase) proton pump.
- Uses energy derived from the cleavage of ATP to transport ions against a concentration gradient.
- Transports H^+ out of the parietal cell in exchange for K^+ ions.
- Receptor-mediated binding of secretagogues mediates activation of the proton pump

Regulation of Gastric Acid Secretion



Three main regulators of parietal cell secretion:

- ACh (Vagus - parasympathetic) via M3 receptors
- Gastrin (G cells) via GPCRs (CCK-B receptor)
- Histamine (ECL cells) via H2 receptors

Gastric mucosa secretes >3 L of gastric juice/day and are regulated by

- Neural Mechanisms
  - *Parasympathetic stimulation increases secretion*
  - *Sympathetic stimulation decreases secretion*
- Hormonal Mechanisms
  - *Gastrin stimulates enzyme and HCl secretion*
  - *Somatostatin – decreases gastric secretion*

Vagal Control of Gastric Secretions

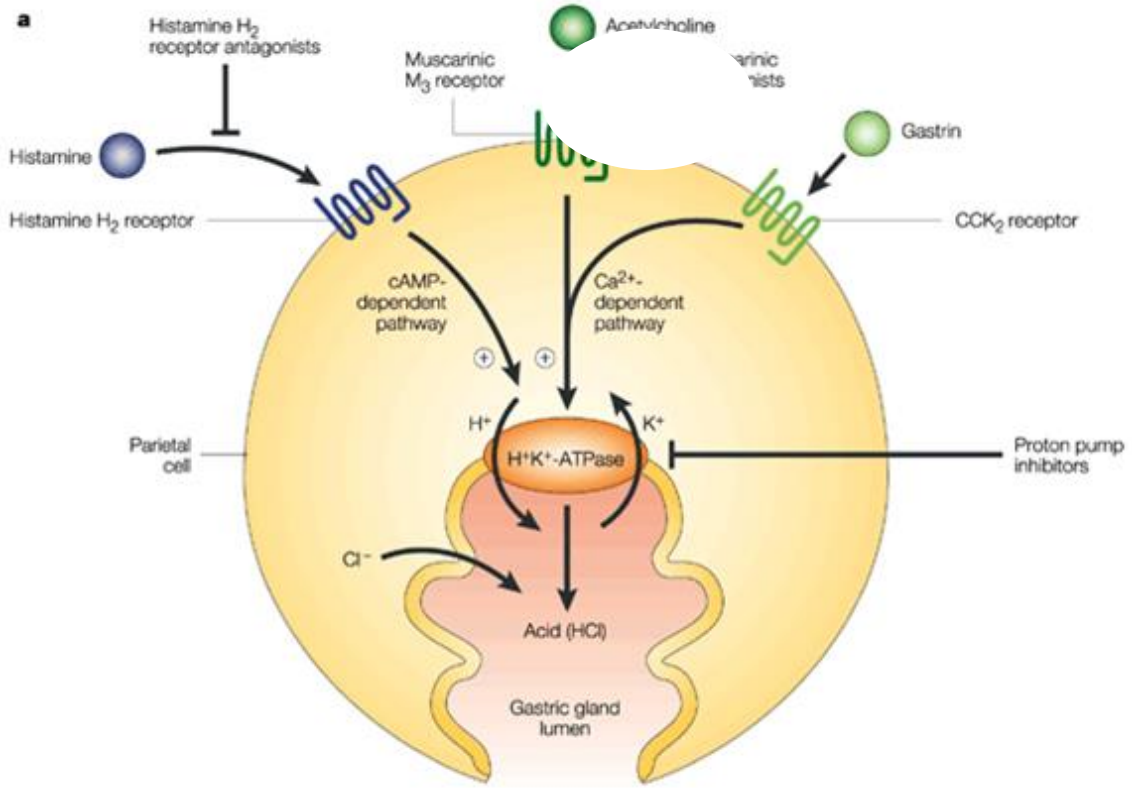
- *GRP (gastrin releasing peptide) stimulates gastrin release from G cells*
  - *Vagus stimulates GRP release*
- *Somatostatin inhibits gastrin release from G cell*
  - *Vagus inhibits somatostatin release*
- *Vagus potentiates the effects of gastrin and histamine*

Gastrin, acetylcholine and histamine potentiate the effects of the others

Regulation of gastric acid secretion

Three main regulators of parietal cell secretion:

- gastrin (G cells) via GPCRs
- ACh (parasymp NS) via M3 receptors
- histamine (ECL cells) via H2 receptors



Secretagogues are hormones or transmitters that stimulate acid secretion.

Gastrin

- Binds to CCK_2 receptors on parietal cells.
- Acts by inducing an increase in intracellular Ca^{2+} levels to activate the proton pump.
- Gastrin and ACh stimulate the release of histamine from ECL (enterochromaffin-like) cells.

Acetylcholine

- Binds to M_3 receptors on parietal cells.
- Acts by inducing an increase in intracellular Ca^{2+} levels to activate the proton pump.
- Gastrin and ACh stimulate the release of histamine from ECL cells.

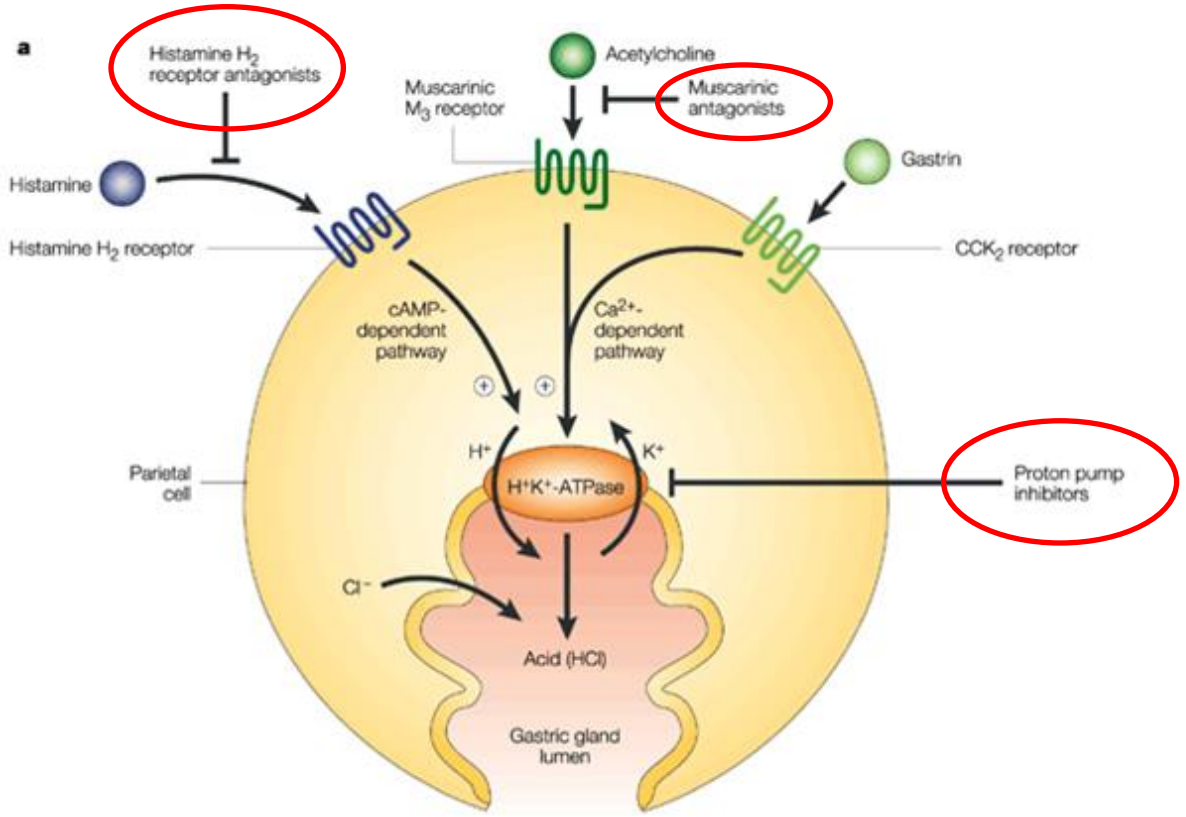
Histamine

- Binds to H_2 receptors on parietal cells.
- Binding causes activation of adenyl cyclase and the proton pump.

Regulation of gastric acid secretion

Three main regulators of parietal cell secretion:

- gastrin (G cells) via GPCRs
- ACh (parasymp NS) via M3 receptors
- histamine (ECL cells) via H2 receptors



Regulation of gastric acid secretion

- Prostaglandins (PGE_2 and I_2) bind to EP_3 prostaglandin receptors on parietal cells decreasing gastric acid secretion
- PGE_2 also stimulates the secretion of gastric cytoprotective mucus and bicarbonate ions.
- Goblet cells are mucous-secreting cells in mucosa layer and secrete bicarbonate ions (HCO_3-) and mucus.
- Somatostatin inhibits gastrin release and gastric acid production.
- Formation of gel-like layer (pH 6-7) protecting mucosa from being digested by acid and pepsin.
- Protective layer can be disrupted by alcohol or bile.

Disorders of Gastric Acid Secretion

Dyspepsia

- symptom complex - no clear definition
- symptoms include heartburn, acid regurgitation, bloating, nausea, chronic or recurrent pain, burning or discomfort centered in the upper abdomen
- Sensations of pain, fullness, early satiety.

Peptic Ulcer Disease (PUD)

- Includes gastric and duodenal ulcers.
- symptoms include epigastric pain or discomfort, bleeding, anaemia, weight loss, perforation.
- Helicobacter pylori (H. pylori) infection is present in 90% of duodenal ulcers and 80% of gastric ulcers; and is a risk factor for gastric cancer.
- Also associated with use of NSAIDs which reduce prostaglandin formation (removing secretion of mucus and bicarbonate ions while increasing acid secretion).
- More common with non-selective NSAIDS, less common with COX-2 selective agents

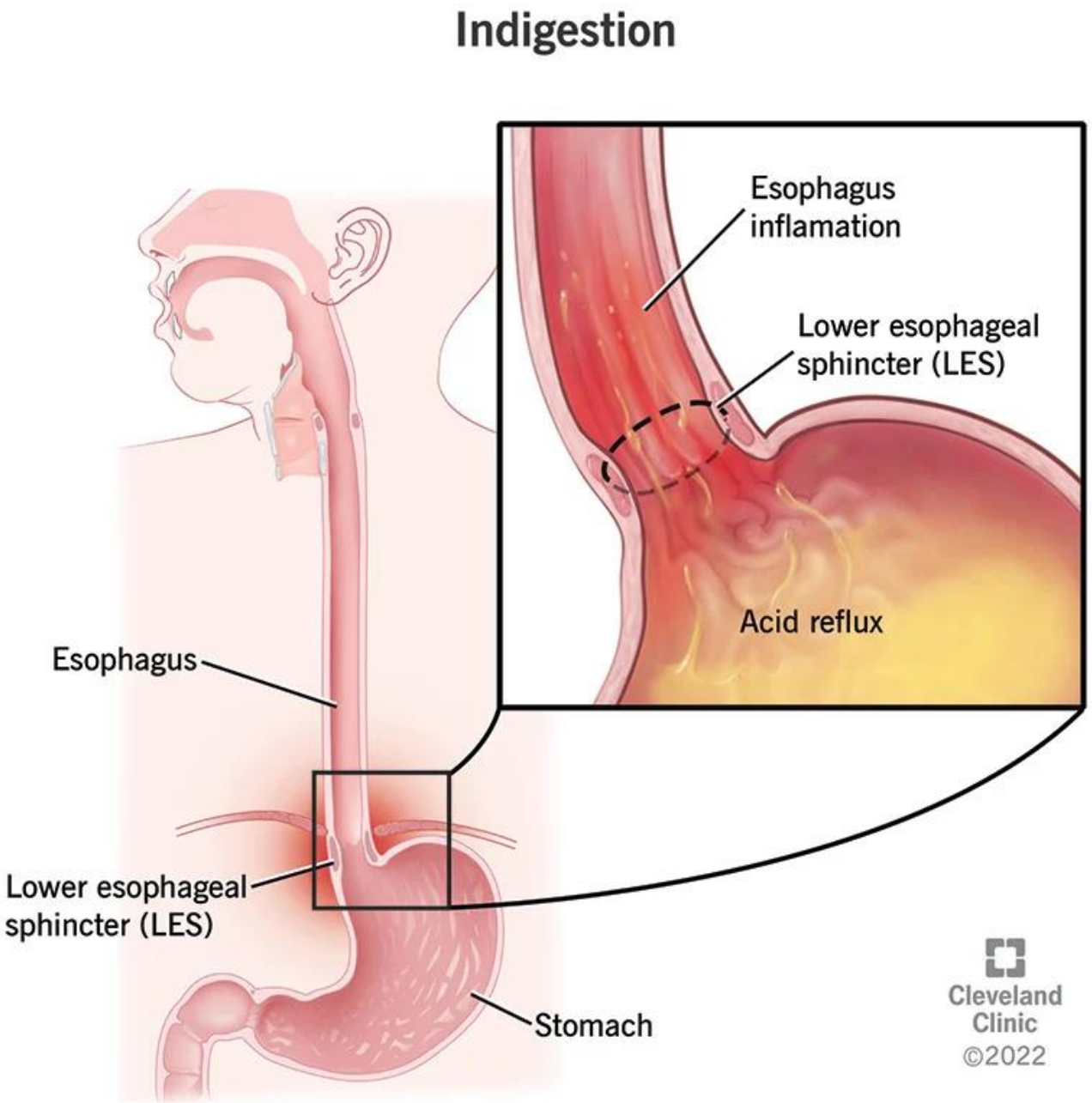
Disorders of Gastric Acid Secretion

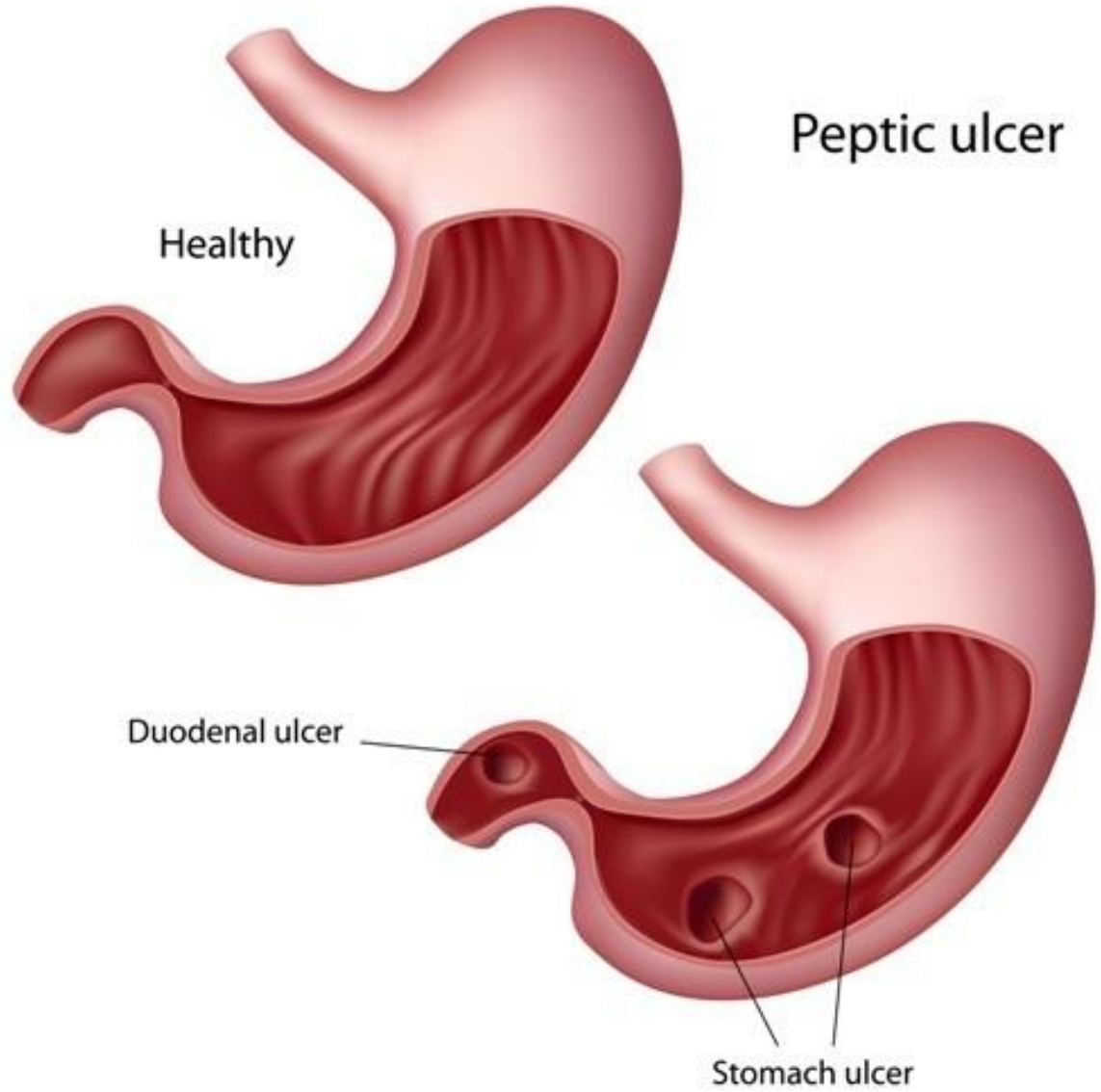
Gastro-oesophageal reflux disease (GORD)

- predominant symptom is chronic heartburn (retrosternal burning) due to acid regurgitation
- affects 10-20% of Australian adults
- GORD is present if symptoms are frequent (2 or more episodes per week) or severe enough to significantly impair quality of life, or if complications of GORD are present.
- can progress to serious oesophageal injury due to acidic reflux
    - esophagitis, Barrett's oesophagus, adenocarcinoma

Drug treatments

- these disorders are commonly treated with drugs that suppress stomach acid

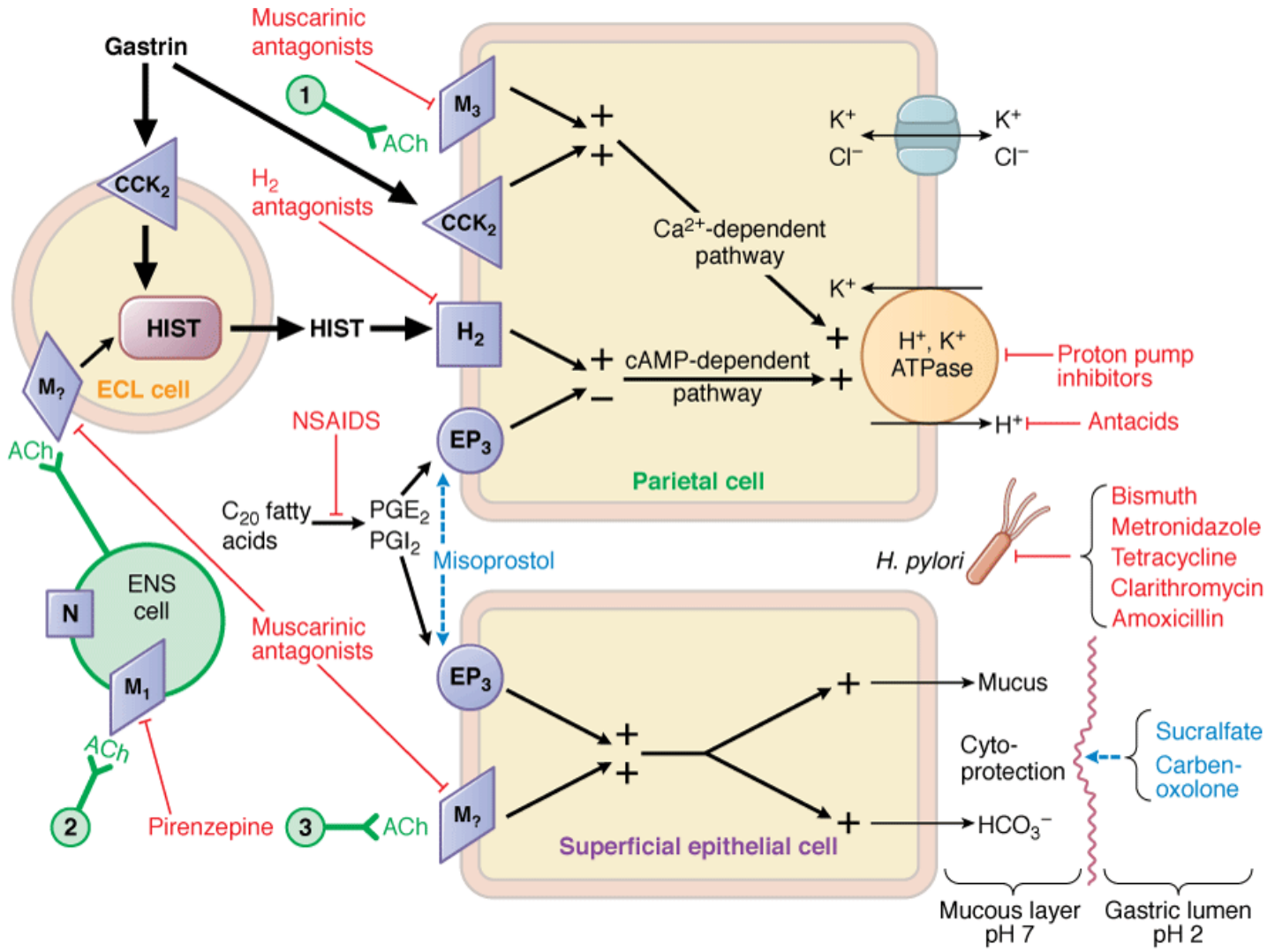

Indigestion
Esophagus inflamation
Lower esophageal sphincter (LES)
Acid reflux
Esophagus
Lower esophageal sphincter (LES)
Stomach
Cleveland Clinic
©2022


Peptic ulcer
Healthy
Duodenal ulcer
Stomach ulcer

Drugs for dyspepsia, reflux and peptic ulcers

main classes of drugs used

- Antacids
- H2 receptor antagonists
- Proton pump inhibitors
- protective agents



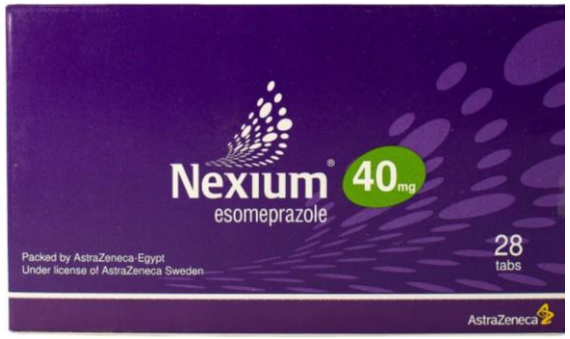
Treatment options- Dyspepsia, GORD, PUD

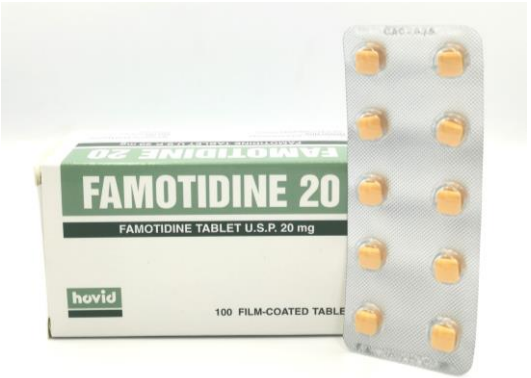
Drugs

- Inhibit the action of secretagogues
- Neutralize gastric acid: use basic salts to increase PH– Antacids
- Form a protective barrier, coat ulcers, limit acid diffusion – Cyto-protectives (Sucralfate, bismuth)
- Increase protective mucus, bicarbonate and prostaglandin – Cyto-protectives, Misoprostol
- Reduce gastric acid secretion – H_2 receptor antagonists and PPIs, Misoprostol
  - **H_2 receptor antagonists** block the effects of Histamine
  - **PPIs** inhibit proton pump activation by mediators Histamine, ACH and Gastrin

Other considerations

- Test for and treat *H. pylori*
- Cessation of causative agents (eg: NSAIDs)
- Lifestyle modification





Antacids

Indication

- symptomatic relief of mild reflux and dyspepsia

Mechanism of action

- neutralise acid in the stomach
- contain a variety of compounds including aluminium hydroxide, magnesium hydroxide, calcium carbonate, magnesium carbonate, sodium bicarbonate, alginates, simethicone

Adverse effects / Precautions / interactions

- can cause constipation / diarrhoea
- hyper-ionic changes in renal disease
- sodium bicarbonate preps can cause increased Na+ absorption
  - avoid in HF, hypertension etc

H_2 Receptor Antagonists

Mode of action

- H_2 receptor antagonists *competitively* and *reversibly* block endogenous histamine from binding to and stimulating the H_2 receptors on the basolateral membrane of parietal cells.
- Reduce gastric acid and pepsin secretion by ~70%.
- Increase pH by 1 unit (less effective than PPI).
- Used to treat dyspepsia, GORD and PUD.

2 April 2020

Following further investigation of this issue, the TGA has suspended the registration of all ranitidine medicines. Further information is available on: Medicines: Suspensions from the ARTG.

Practice Points

- Duration of action is 12 hours, dosing is twice daily.
- Drug names end in the suffix –tidine: famo*tidine* and niza*tidine* and cimet*idine*.
- Ranitidine containing products have been banned due to contamination with an impurity called N-nitrosodimethylamin (NDMA), a known carcinogen (2019).
- Promotes healing of ulcers but relapse can occur (need triple therapy)
- Can develop tolerance after chronic treatment
- Some (cimetidine) inhibit CYP3A4 enzyme

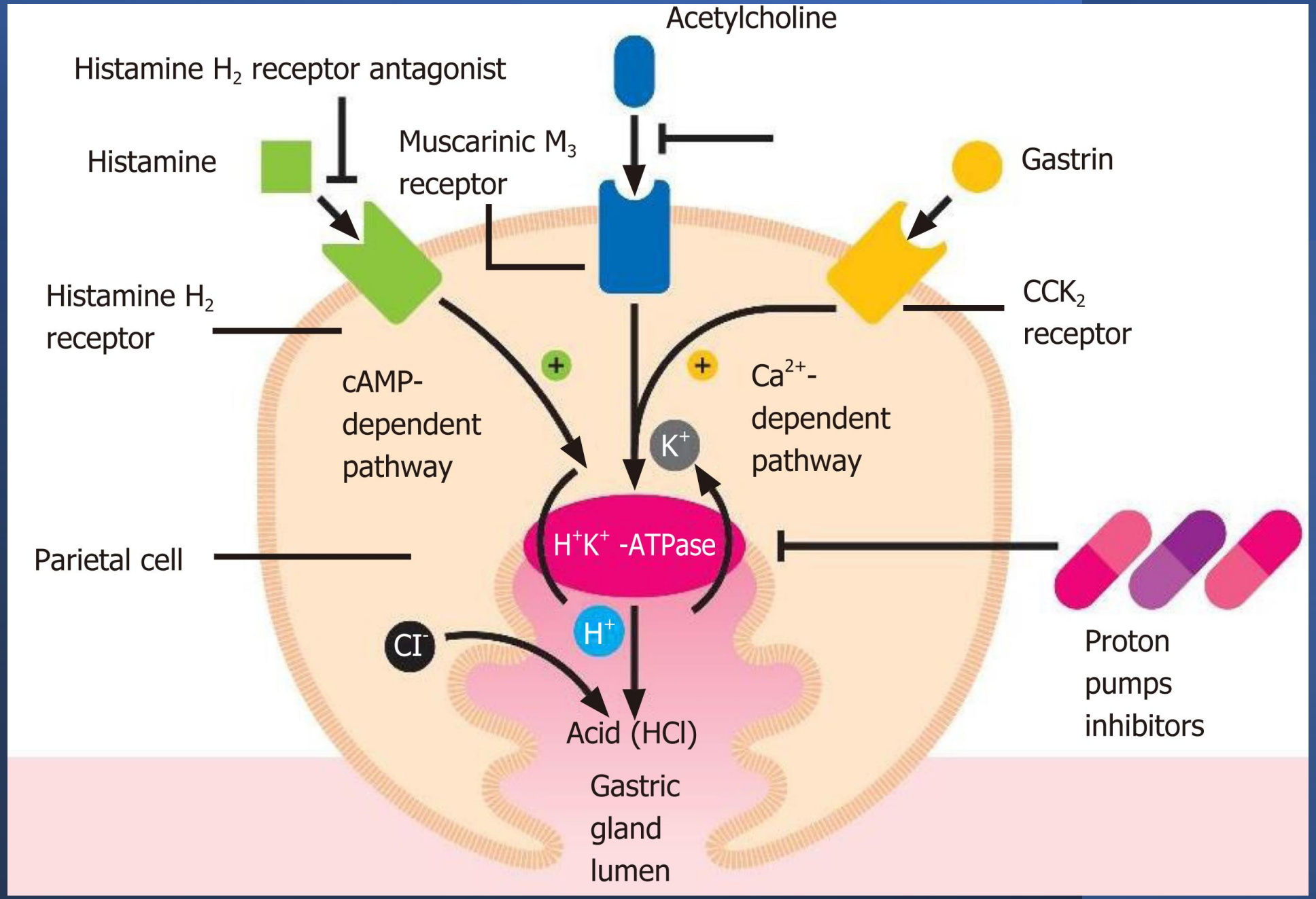
Proton Pump Inhibitors

Mode of action

- PPIs *irreversibly* bind to and inactivate the H^+/K^+ ATPase enzyme system (pump), inhibiting the activity of the pump at the secretory surface of gastric parietal cells.
- Are prodrugs and weak bases indicated for dyspepsia, GORD and PUD
- Degrade rapidly in low pH (the stomach) so enteric coating allows absorption from the small intestine into the blood then the drug accumulates in the parietal cell canaliculi where it is activated to the metabolite- a thiophilic sulphenamide.
- The active metabolite interacts covalently with the H^+/K^+ ATPase pump involved in H+ ion transport.
- Both basal and meal-stimulated gastric acid secretion is reduced.
- Most potent inhibitors of acid secretion (reduced by ~85%) as they affect the terminal step in the acid secretory pathway.
- Long duration of action- bind irreversibly, therefore a new H^+/K^+ ATPase must be synthesized
- Increase pH by 2-3 units.
- Very selective (therefore generally well tolerated)

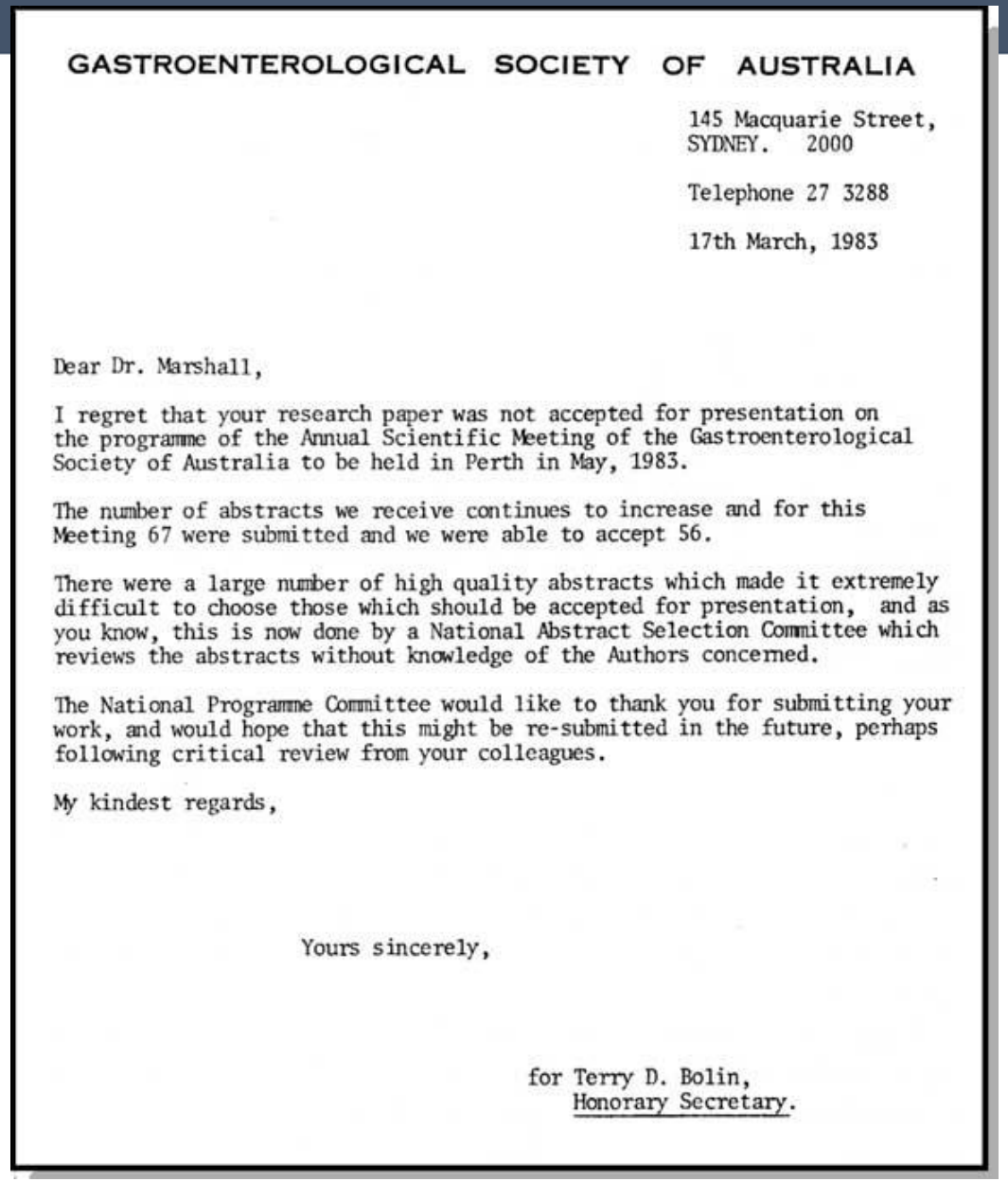
Practice Points

- Single daily dosing
- Names end in the suffix –razole: esomep*razole*, lansop*razole*, omep*razole*, pantop*razole* and rabep*razole*.
- Adverse effects: headache and diarrhoea (less than 2%), interstitial nephritis, hypomagnesaemia, reduced vitamin B_{12} absorption, increased risk of Clostridium difficile infection, CAP and fractures.


Acetylcholine
Histamine H_2 receptor antagonist
Histamine
Muscarinic M_3 receptor
Gastrin
Histamine H_2 receptor
CCK_2 receptor
cAMP-dependent pathway
Ca^{2+}-dependent pathway
K^+
Parietal cell
H^+K^+ -ATPase
H^+
Cl^-
Proton pumps inhibitors
Acid (HCl)
Gastric gland lumen

Eradication of *H. pylori*

From zero…



GASTROENTEROLOGICAL SOCIETY OF AUSTRALIA

145 Macquarie Street,
SYDNEY. 2000

Telephone 27 3288

17th March, 1983

Dear Dr. Marshall,

I regret that your research paper was not accepted for presentation on the programme of the Annual Scientific Meeting of the Gastroenterological Society of Australia to be held in Perth in May, 1983.

The number of abstracts we receive continues to increase and for this Meeting 67 were submitted and we were able to accept 56.

There were a large number of high quality abstracts which made it extremely difficult to choose those which should be accepted for presentation, and as you know, this is now done by a National Abstract Selection Committee which reviews the abstracts without knowledge of the Authors concerned.

The National Programme Committee would like to thank you for submitting your work, and would hope that this might be re-submitted in the future, perhaps following critical review from your colleagues.

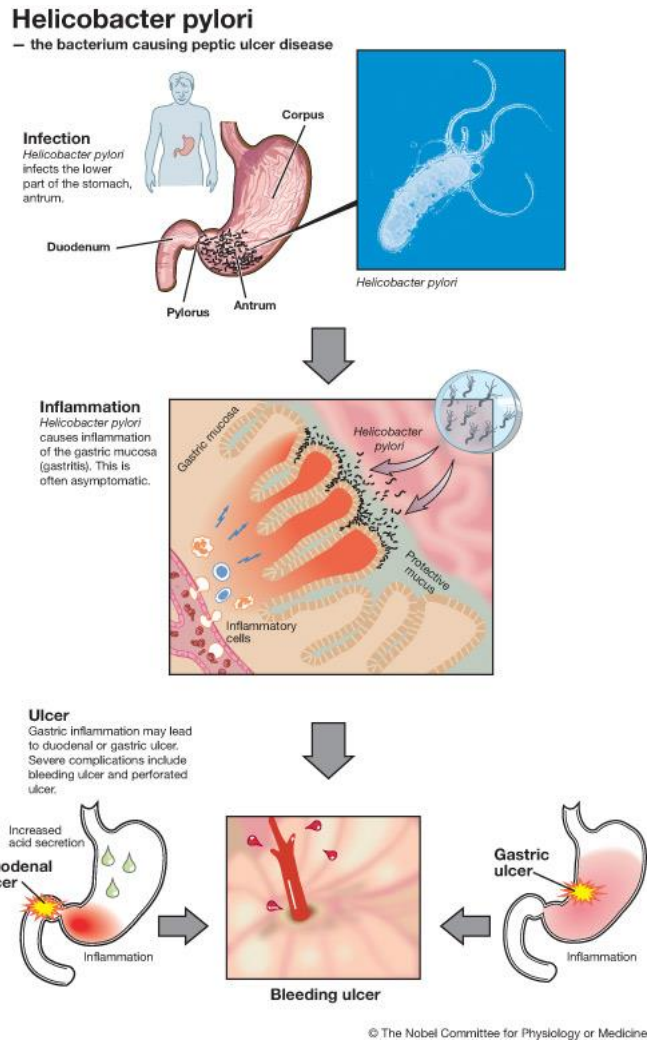
My kindest regards,

Yours sincerely,

for Terry D. Bolin,
Honorary Secretary.

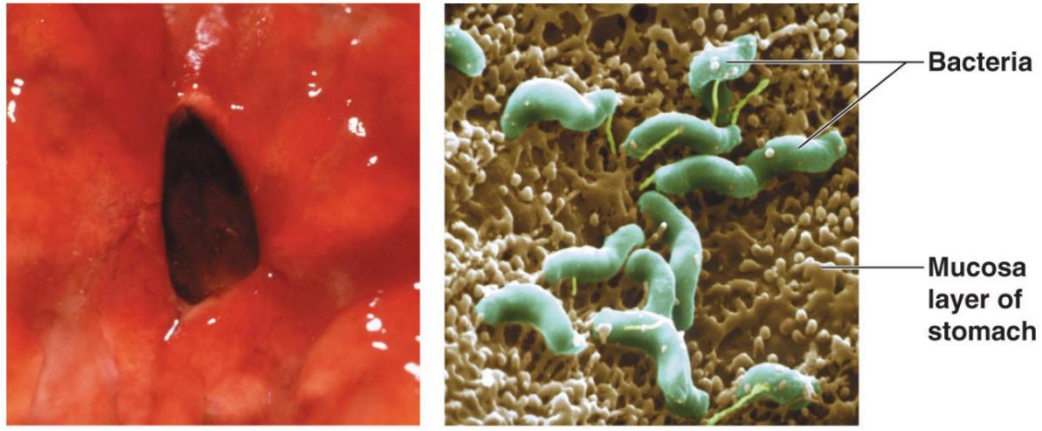
Eradication of *H. pylori*

…to hero !!!!!
2005 Nobel Prize - Australians
Barry Marshall and Robin Warren



Eradication of *H. pylori*

- Helicobacter pylori is a gram-negative bacterium that is prevalent in about 30-40% of adult Australians.
- *H. pylori* is a causal agent in the development of numerous conditions- duodenal and gastric ulcers, chronic gastritis and gastric cancer
- *H. pylori* itself converts gastric urea to ammonia (NH3) which raises the PH (more alkaline) to ensure it can survive



(a) A gastric ulcer lesion (b) *H. pylori* bacteria

- Eradication is essential for the successful treatment of an ulcer
- Diagnosis by urea breath test: patient given ^{13}C-urea orally, the urease in H.pylori metabolises it to release $^{13}CO_2$ and NH_3, the amount of CO_2 in the expired air is measure to confirm diagnosis
- Also may have antibody testing, endoscopy or biopsy

Eradication of *H. pylori*

Triple therapy

- First line treatment for eradication of *H. pylori:* two anti-bacterials and a PPI
- Amoxicillin + clarithromycin + PPI for 1-2 weeks.
- 80-90% eradication rate
- If hypersensitive to penicillin, amoxicillin is replaced with metronidazole.
- Side effects of triple therapy: nausea, diarrhoea, taste disturbance