PHARMACOLOGY OF GASTROINTESTINAL TRACT

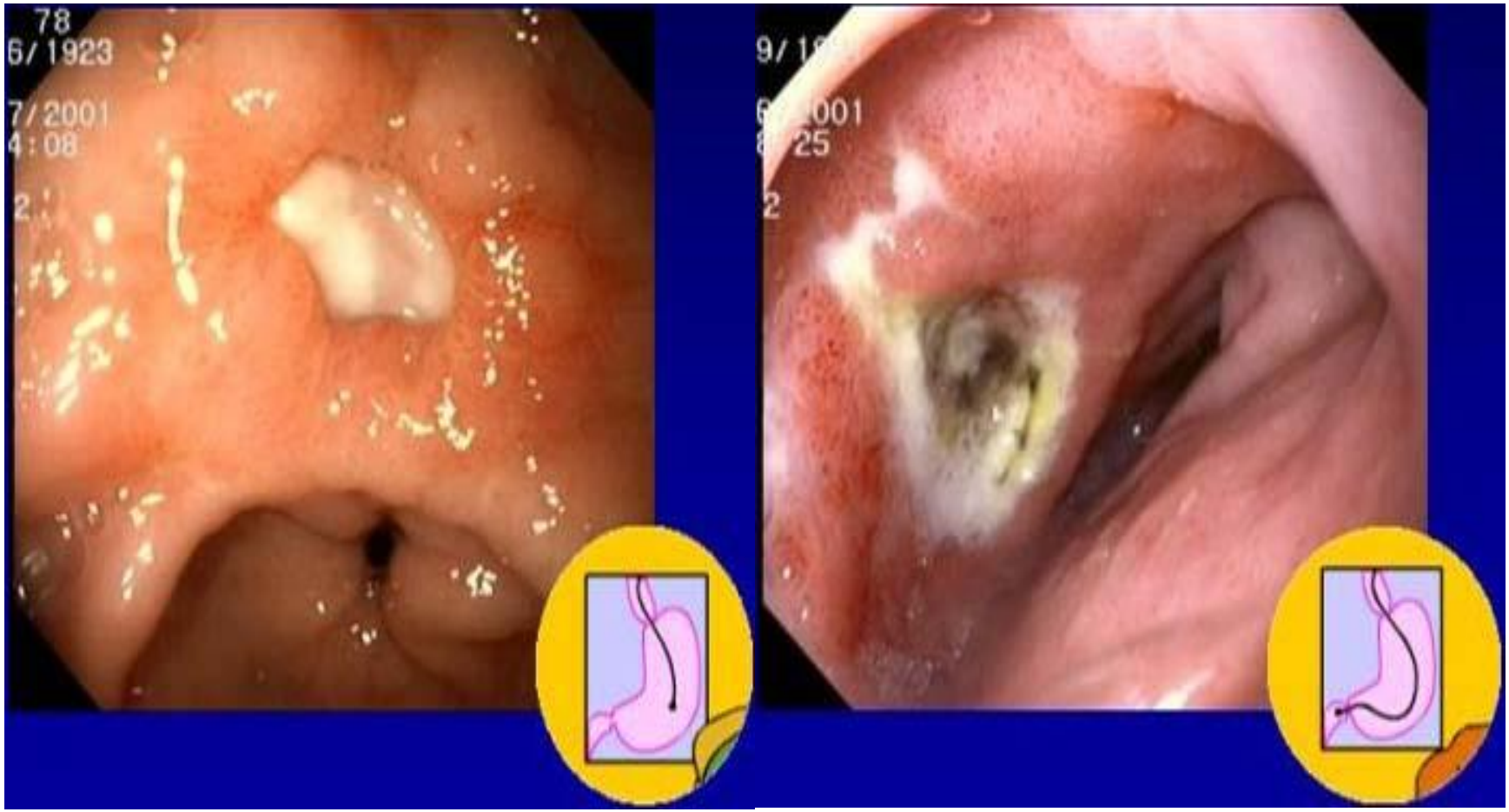
TREATMENT OF ULCER DISEASE

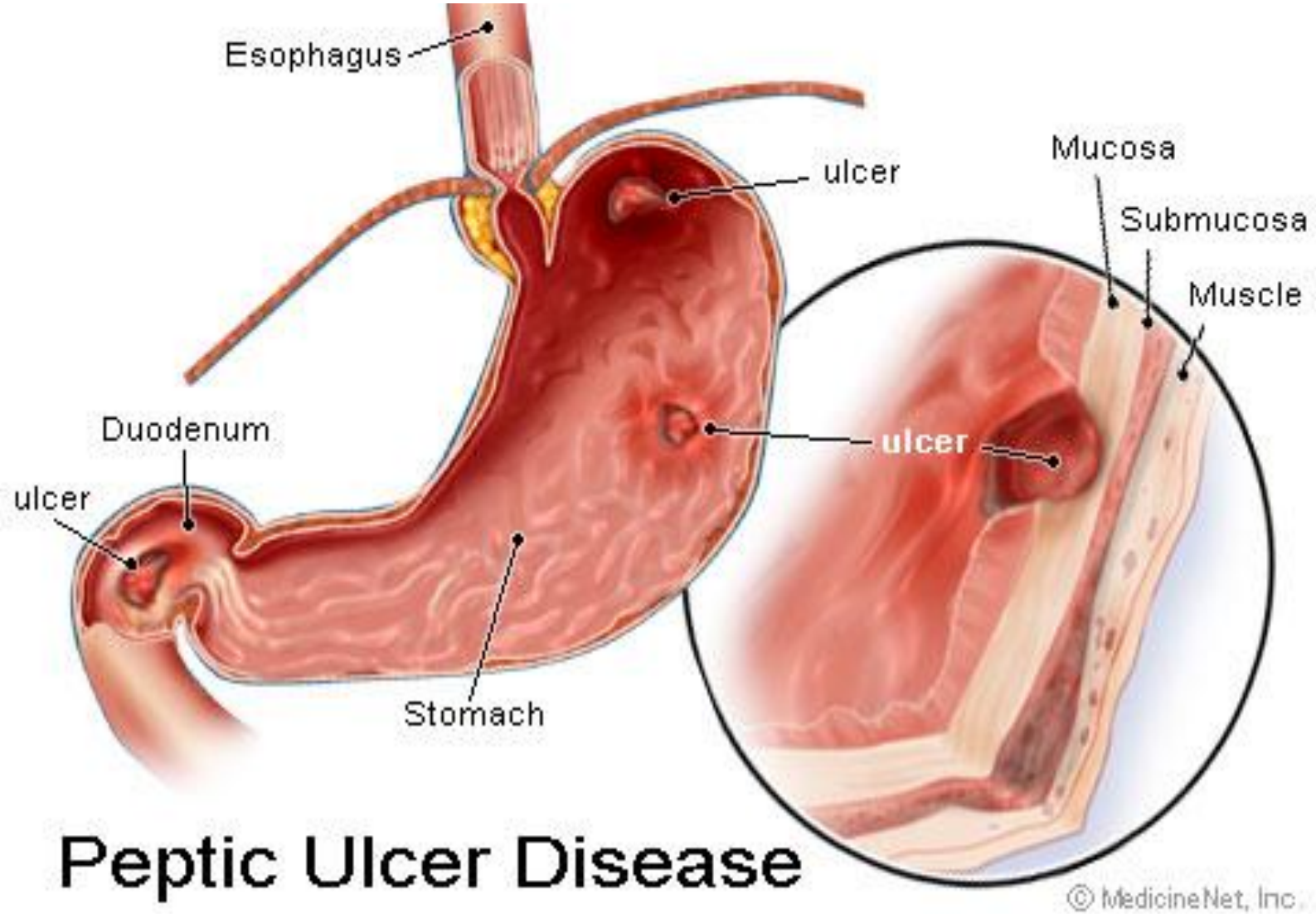
Definition

A circumscribed ulceration of the gastrointestinal mucosa occurring in areas exposed to acid and pepsin and most often caused by *Helicobacter pylori* infection.

(Uphold & Graham, 2003)

Peptic Ulcers:
Gastric & Dudodenal




Esophagus
ulcer
Mucosa
Submucosa
Muscle
Duodenum
ulcer
ulcer
Stomach
Peptic Ulcer Disease
© MedicineNet, Inc.

Duodenal ulcers

- duodenal sites are 4x more common than gastric sites
- most common in middle age
  - peak 30-50 years
- Male to female ratio—4:1
- Genetic link: 3x more common in 1st degree relatives
- more common in patients with blood group „0“
- *H. pylori* infection - very frequent
  - up to 95%

Gastric Ulcers

- common in late middle age
  - incidence increases with age
- Male to female ratio—2:1
- More common in patients with blood group A
- Use of NSAIDs - associated with a three- to four-fold increase in risk of gastric ulcer
- Less related to *H. pylori* than duodenal ulcers – about 80%
- 10 - 20% of patients with a gastric ulcer have a concomitant duodenal ulcer

Ulcer disease etiology

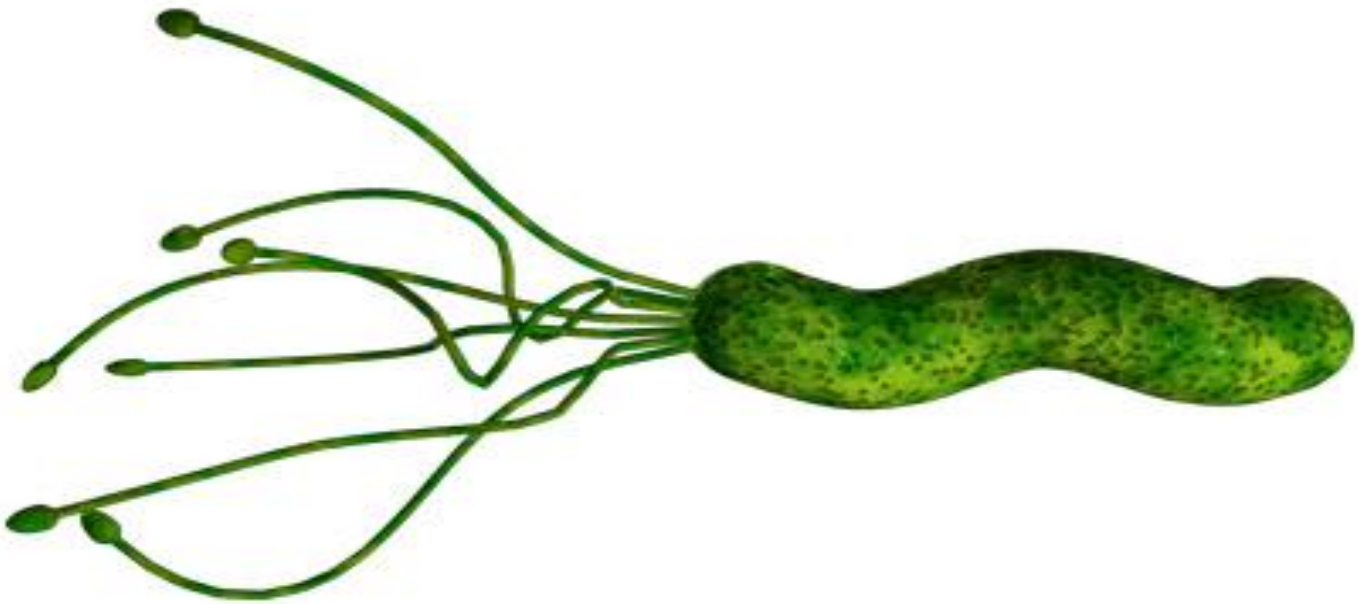
↓ **Protective factors**

- mucus, bicarbonate
- mucosal blood flow
- ↓ prostaglandins

↑ **Agressive factors**

- HCl, pepsin
- drugs, ethanol, stress
- *H. pylori*

Helicobacter pylori



Barry J Marshall

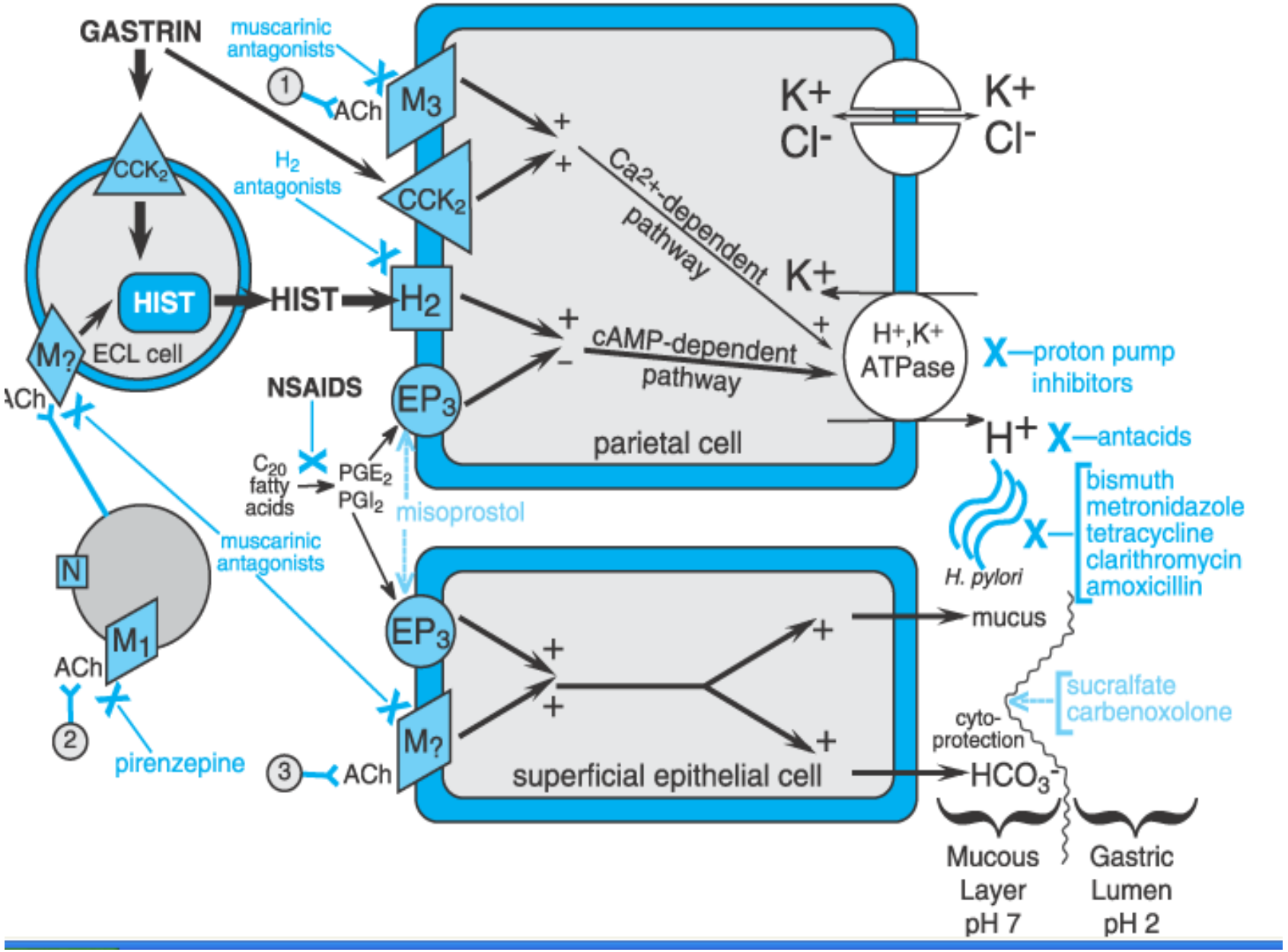
Nobel prize
Medicine – 2005

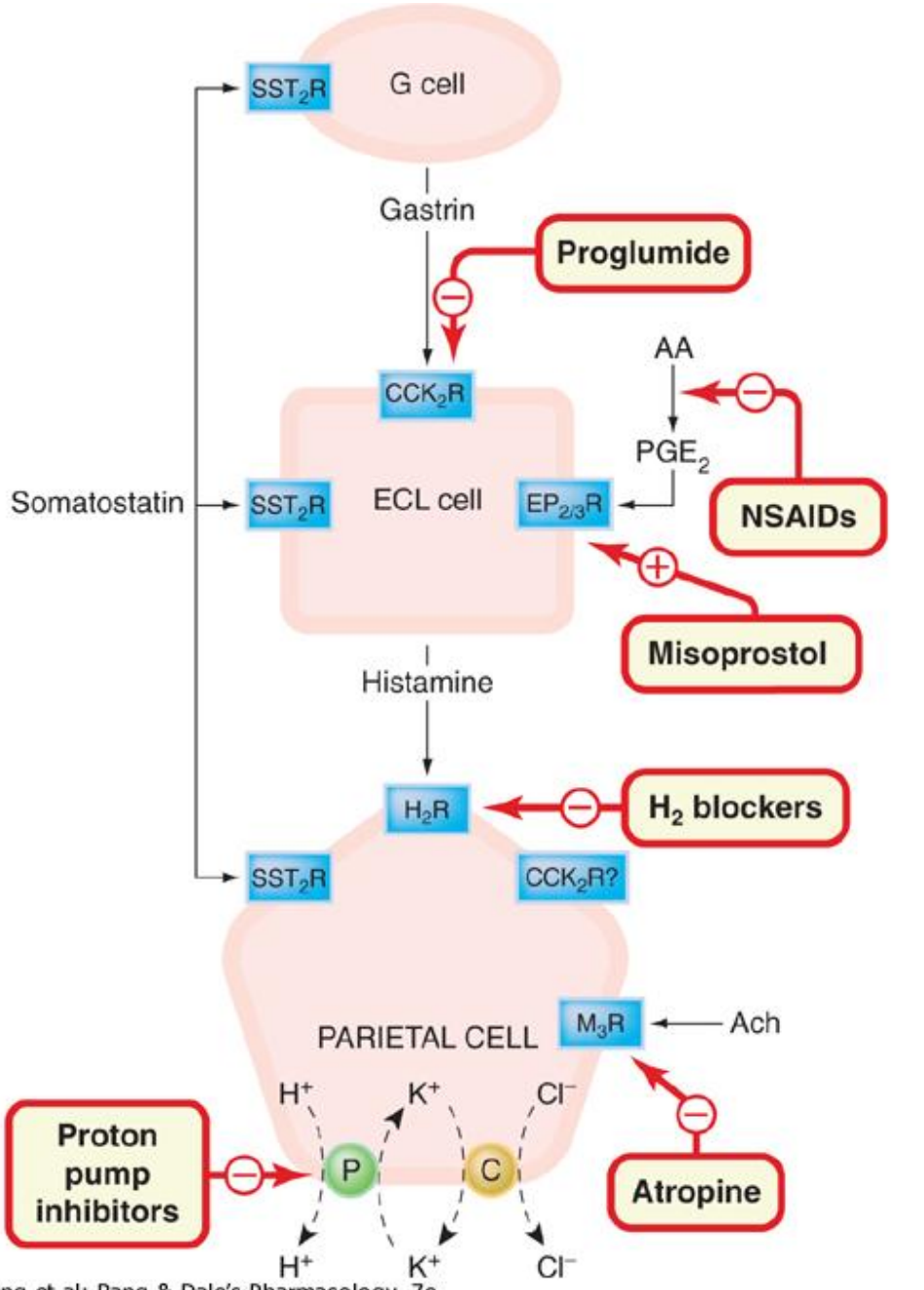
J. Robin Warren

Discovery of *H. pylori* & its role in ulcer

Treatment

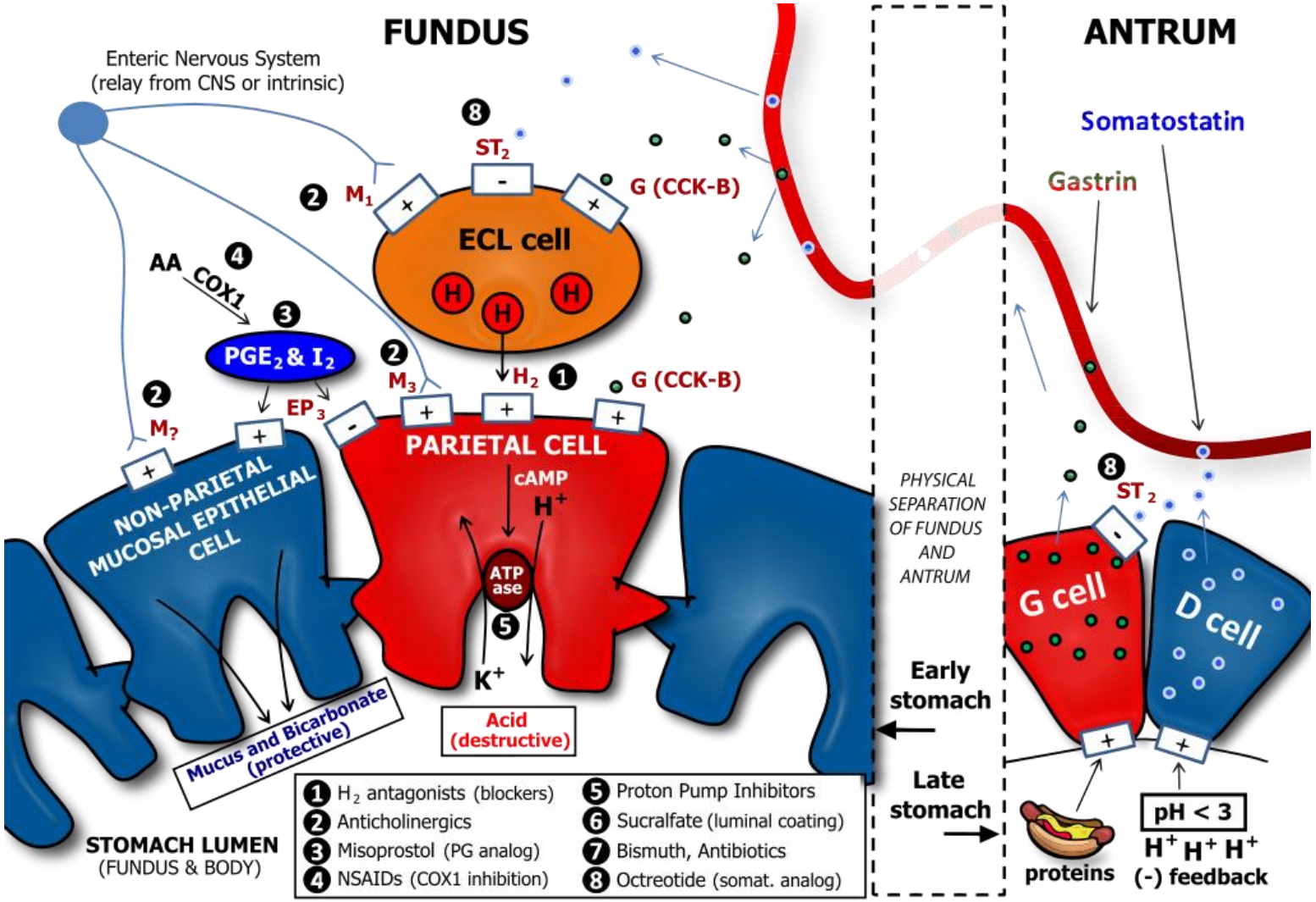
- Diet
- ↓ risk factors (NSAID, corticosteroids)
- **Pharmacotherapy**
  1. ↓ HCl production and secretion
  2. neutralisation of pH (antacides)
  3. mucous membrane protection
  4. eradication *H. pylori* (antibiotics)


GASTRIN
muscarinic antagonists
1
ACh
M3
CCK2
H2 antagonists
CCK2
HIST
HIST
H2
M?
ECL cell
ACh
NSAIDS
EP3
C20 fatty acids
PGE2
PGI2
misoprostol
parietal cell
Ca2+-dependent pathway
cAMP-dependent pathway
K+
Cl-
K+
Cl-
K+
H+,K+ ATPase
X—proton pump inhibitors
H+
X—antacids
H. pylori
X—
bismuth
metronidazole
tetracycline
clarithromycin
amoxicillin
mucus
sucralfate
carbenoxolone
cyto-protection
HCO3-
muscarinic antagonists
N
M1
ACh
2
pirenzepine
EP3
M?
3
ACh
superficial epithelial cell
Mucous Layer pH 7
Gastric Lumen pH 2



Rang et al: Rang & Dale's Pharmacology, 7e

Diagram depicting the major determinants of gastric acid secretion, with inclusion of drug targets for peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD).



http://en.wikipedia.org/wiki/Gastric_acid

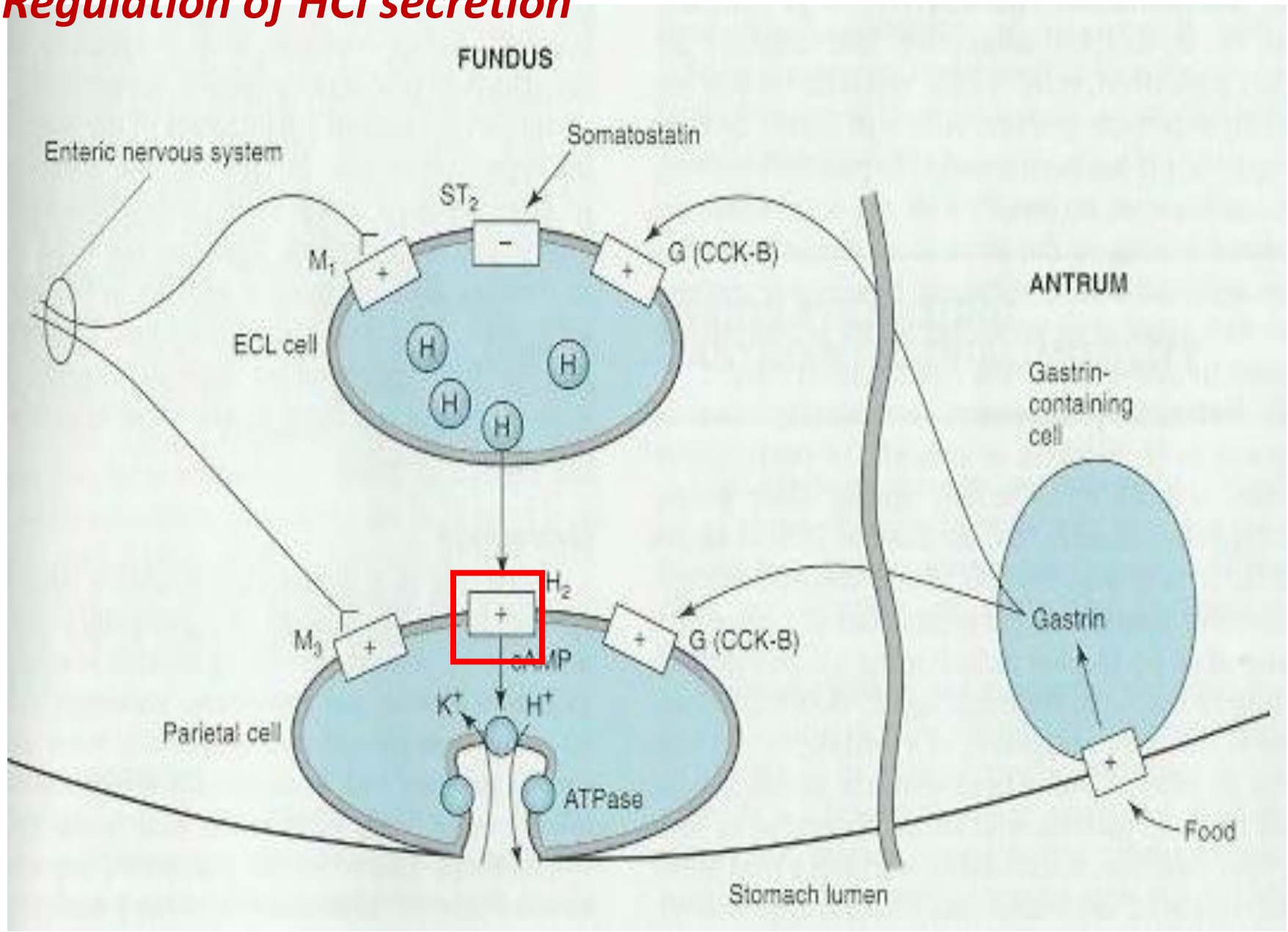
Secretion of gastric acid, mucus and bicarbonate - pathophysiological issues

- **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
  - somatostatin inhibits all phases of parietal cell activation.
- **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).

1. Suppressors of gastric acid secretion

- Inhibitors of proton pump
- Antagonists of histamine (H_2) receptors
- Antagonists of muscarinic (M) receptors

Regulation of HCl secretion

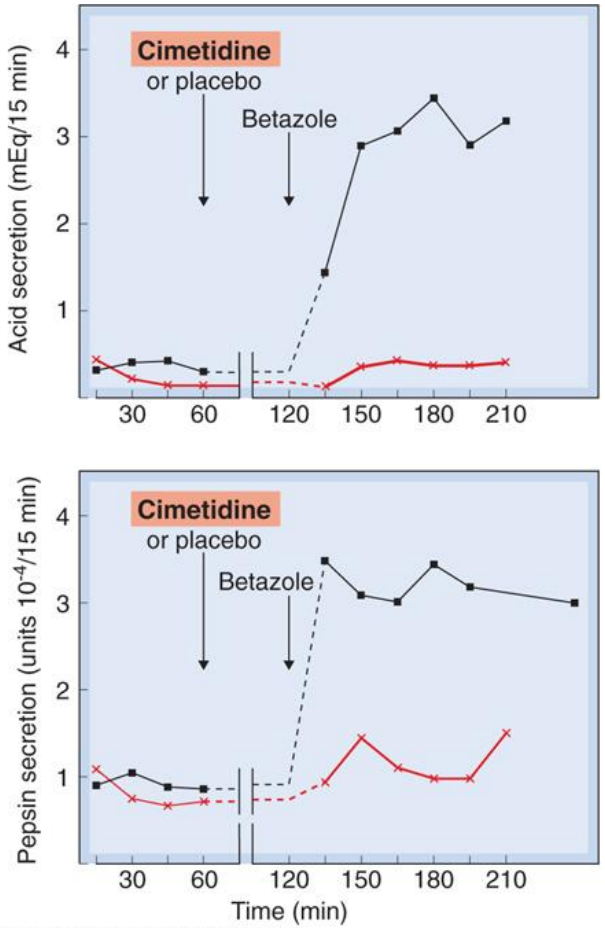


H_2 receptors antagonists

- Competetive antagonists of H_2 receptors of parietal cells

- Cimetidine – TAGAMET, BELOMET, PRIMAMET
- Ranitidine – ULCOSAN, RANISAN, RANITAL, ZANTAC
- Famotidine – ULFAMID, PEPCID, QUAMATEL
- Nizatidine - AXID

Effect of cimetidine on acid and pepsin secretion



The effect of cimetidine on betazole-stimulated gastric acid and pepsin secretion in humans. Either cimetidine or a placebo was given orally 60 min prior to a subcutaneous injection (1.5 mg/kg) of betazole, a relatively specific histamine H_2-receptor agonist that stimulates gastric acid secretion. (Modified from Binder H J, Donaldson R M 1978 Gastroenterology 74: 371-375.)

Therapeutic uses

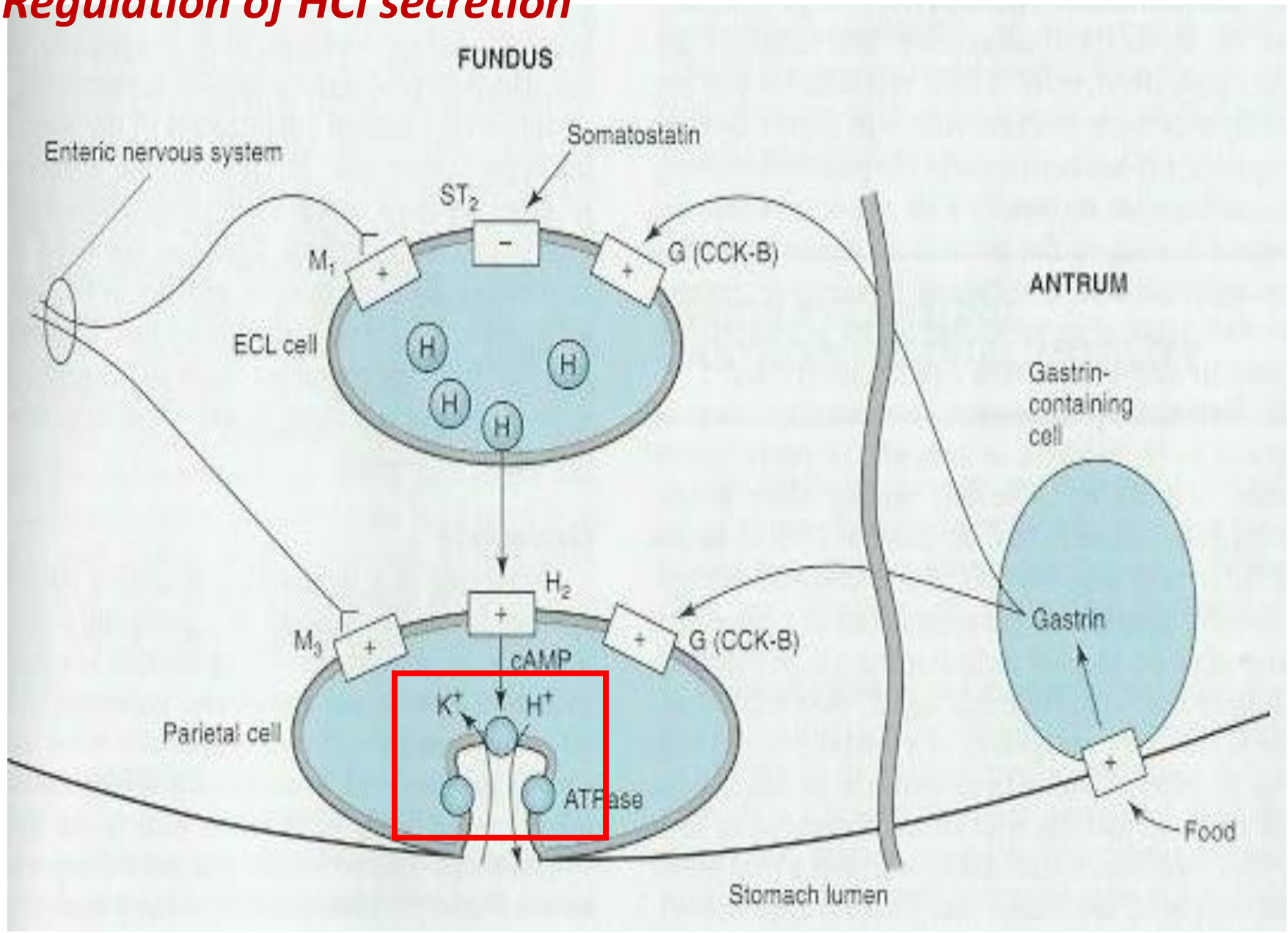
- promote healing of gastric and duodenal ulcers
- to treat uncomplicated GERD
- to prevent the occurrence of stress ulcers
- ↓ pH during pancreatic enzymes substitution

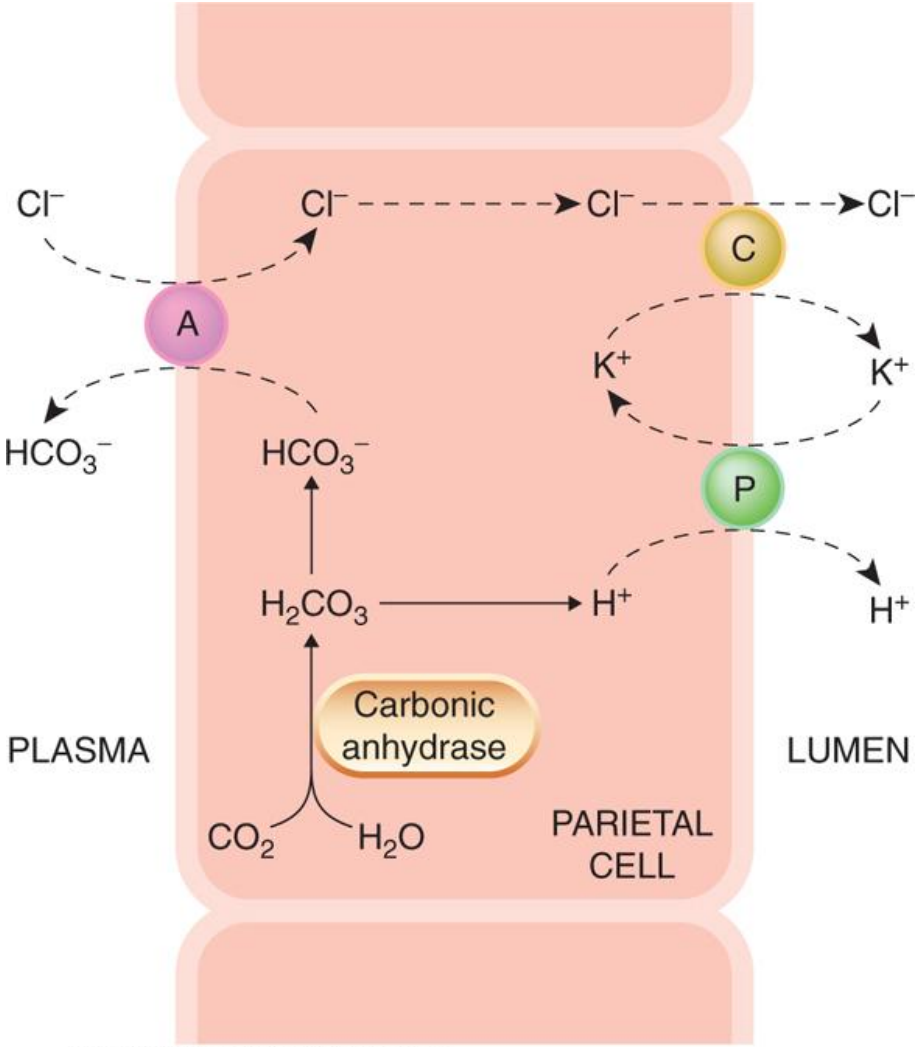
Adverse effects

- diarrhea, constipation
- muscular pain
- CNS (confusion, delirium, hallucinations, slurred speech) i.v. elderly
- Tolerance – rebound effect

- **CIMETIDINE !!!!**
  - Anti-androgenic effect, inhibits estradiol hydroxylation
  - galactorrhea in women
  - gynecomastia, reduced sperm count, impotence in men
  - inhibits CYPs (*e.g.*, CYP1A2, CYP2C9, and CYP2D6) – **interactions!!!**

Regulation of HCl secretion



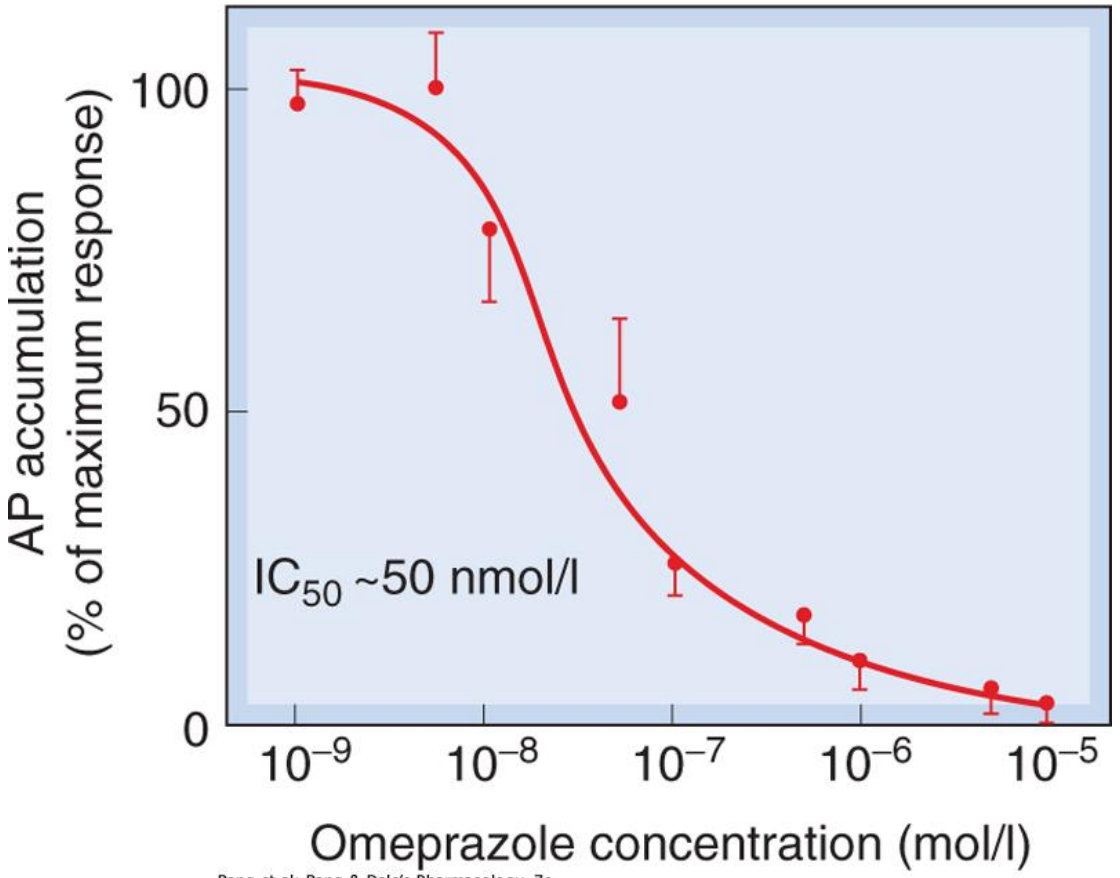


Secretion of hydrochloric acid by the gastric parietal cell. Secretion involves a proton pump (P), which is an H^+-K^+-ATPase, a symport carrier (C) for K^+ and Cl^-, and an antiport (A), which exchanges Cl^- and HCO_3^-.

Proton Pump Inhibitors

- Irreversible inhibitor of H^+-K^+ ATPase
- Prodrugs requiring activation in acid environment
- Accumulate in canaliculi of parietal cell
- Activated in canaliculi & bind covalently to extracellular domain of H^+-K^+ ATPase
- Acid secretion resumes only after synthesis of new molecules

Omeprazol action on acid secretion



The inhibitory action of omeprazole on acid secretion from isolated human gastric glands stimulated by 50 µmol/l histamine. Acid secretion was measured by the accumulation of a radiolabelled weak base, aminopyrine (AP), in the secretory channels. The data represent the mean and standard error of measurements from eight patients. (Adapted from Lindberg P et al. 1987 Trends Pharmacol Sci 8: 399-402.)

Proton pump inhibitors

- Omeprazole – LOSEC, ULTOP, PRILOSEC
- Pantoprazole – CONTROLOC, PROTONIX
- Lansoprazole – LANZUL, PREVACID
- Esomeprazole – NEXIUM
- Rabeprazole – ACIPHEX, ZULBEX

Therapeutic uses

- gastric and duodenal ulcers
- **g**astro**e**sophageal **r**eflux **d**isease (GERD)
- Zollinger-Ellison`s syndrome
- Treatment and prevention of recurrence NSAiD associated gastric ulcers
- reducing the risk of duodenal ulcer recurrence associated with *H. pylori* infections

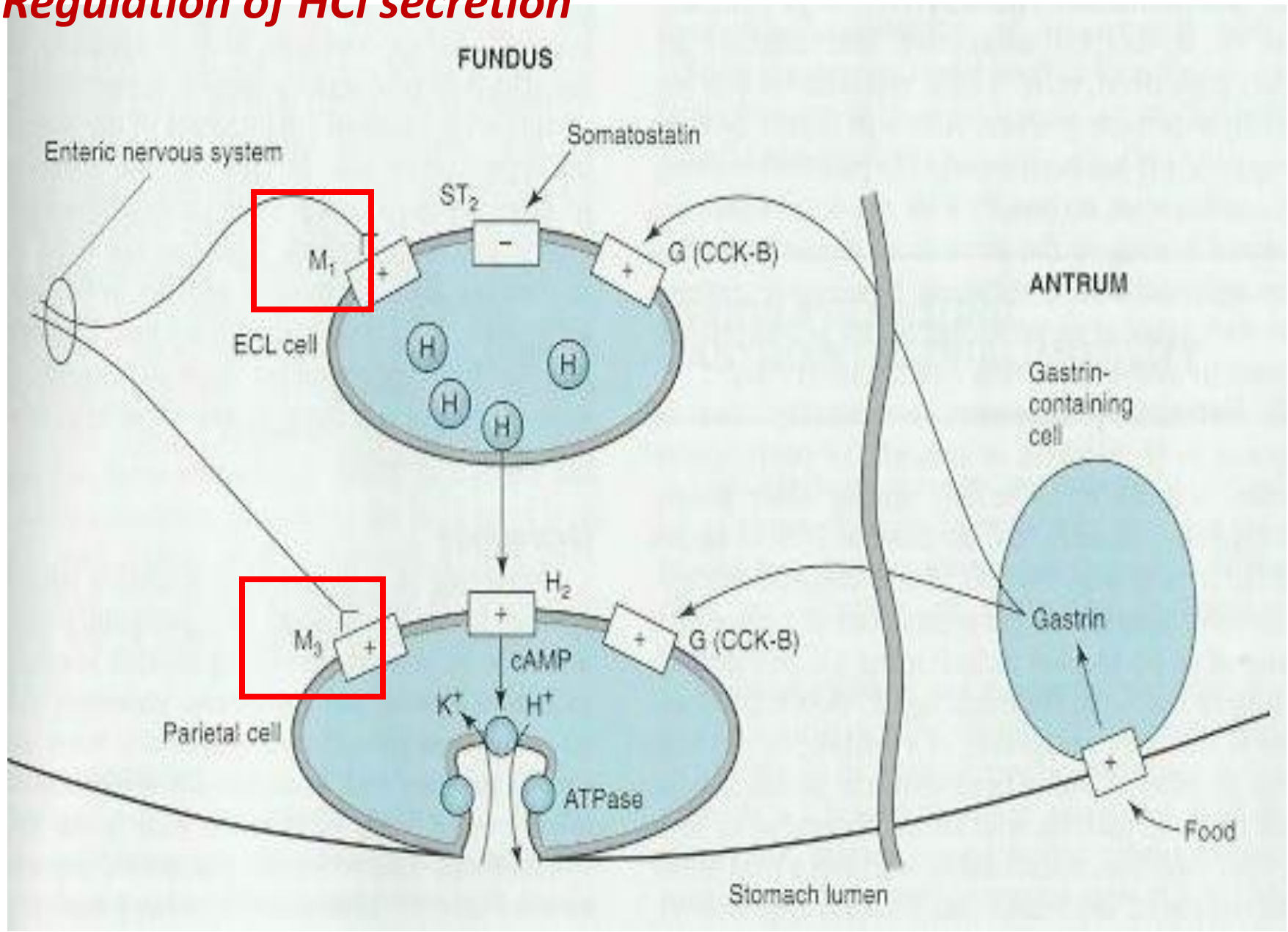
Treatment Plan: H. Pylori

- Medications: **Triple therapy** for 14 days is considered as a treatment of choice.
  - Proton Pump Inhibitor + clarithromycin (metronidazol) + amoxicillin
  - In the setting of an active ulcer, continue proton pump inhibitor therapy for additional 2 weeks.
- Goal: complete elimination of H. Pylori. Once achieved - reinfection rates are low
- Compliance of patient is essential!

Side effect of PPI

- nausea, abdominal pain, constipation,
- flatulence, diarrhea
- interference with cytochrome P450 metabolism
  - (inhibition of CYP2C19 and CYP3A4)
- Allergic reaction
- Hypergastrinemia (rebound fenomen)

Regulation of HCl secretion



Antagonists of M receptors

- Inhibition of M1 and M3 receptors in parietal cells
- Therapeutic use:
  - ulcer disease ??? (duodenal ulcers)
  - NSAID, corticosteroids gastropathy
- SE: anticholinergic effect
  - dry mucous membranes,
  - Mydriasis
  - Tachycardia
  - „atropine fever“

- **Pirenzepine – GASTROZEPIN, GASTROZEM**

Antacids

- HCl neutralisation
- ↑ stomach pH - ↓pepsin activity

- **Magnesium salts (Mg^{2+})**
  - MILK OF MAGNESIA
  - ACIX
  - GASTROGEL

- $MgCl_2$ - production - diarrhoea
- hypermagnesemia - risk of AE- kidney, heart disease

Antacids

- **Aluminium salts - Al^{3+}**
  - GASTERIN
  - TALCID

- formation of insoluble aluminium-phosphate-complexes
- hypophophatemia, osteomalacia
- constipation
- renal insufficiency

Antacids

- **Calcium salts - Ca^{2+}**
  - MAALOX, tbl.
  - TUMS
- hyperkalciemia
- kidney stones
- milk-alkali syndrom
- acid rebound (hyperacidity rebound)

- **Sodium bicarbonate - $NaHCO_3$**
- quick onset - short duration.
- metabolic alkalosis.
- Sodium content - !!!patients with hypertension or renal insufficiency

Antacids

- Preexisting conditions that may restrict the use of antacids
- ↓ AE – salts combination
- Use with caution with other medications due to many drug interactions (absorption)
- Most medications should be given 1 to 2 hours after giving antacid
- Long-lasting administration – more AE

Combined antacids

- Ca^{2+}, Mg^{2+}
  - RENNIE
- Ca^{2+}, Mg^{2+}, Al^{3+}
  - GASTROGEL
  - TALCID
- Mg^{2+}, Al^{3+}
  - MYLANTA
  - GELUSIL
  - ANACID

Mucosal Protective Agents

- Sucralfate
- Misoprostol
- Colloidal Bismuth compounds

Sucralfate

- In acidic pH polymerise to viscous gel that adheres to ulcer
- Taken on empty stomach 1 hr. before meals

- ↓ phosphate absorption from GIT- therapy of hyperphosphatemia
- Contains small amount of Al^{3+} - kidney disease,
- Combinations with Al^{3+} antacides

  - ULCOGANT, ALSUCRAL, VENTER

Misoprostol

- PGE_1 analogue
- Stimulates mucus & bicarbonate secretion
- Enhances mucosal blood flow
- Prevention of NSAiD induced ulcer
- AE (30 % of patients)
  - Diarrhoea
  - Abdominal pain
- Contraindication:
  - Pregnancy
  - IBD

  - CYTOTEC

Colloidal Bismuth Compounds

- Coats ulcer, stimulates mucus & bicarbonate secretion
- Direct antimicrobial activity against *H. pylori*
- May cause black discoloration of stools & tongue
- Not used for long periods – bismuth toxicity

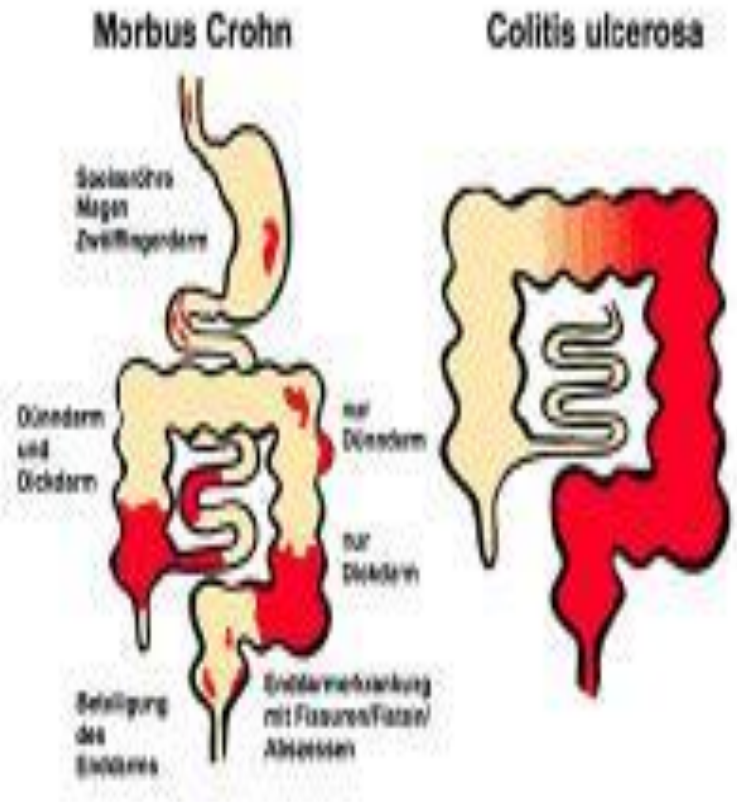
- Available compounds :
  - Bismuth subsalicylate – in USA (PEPTO-BISMOL)
  - Bismuth subcitrate – in Europe (DE-NOL, JATROX)

PHARMACOLOGY OF GASTROINTESTINAL TRACT

Treatment of inflammatory bowel disease

Inflammatory Bowel Disease

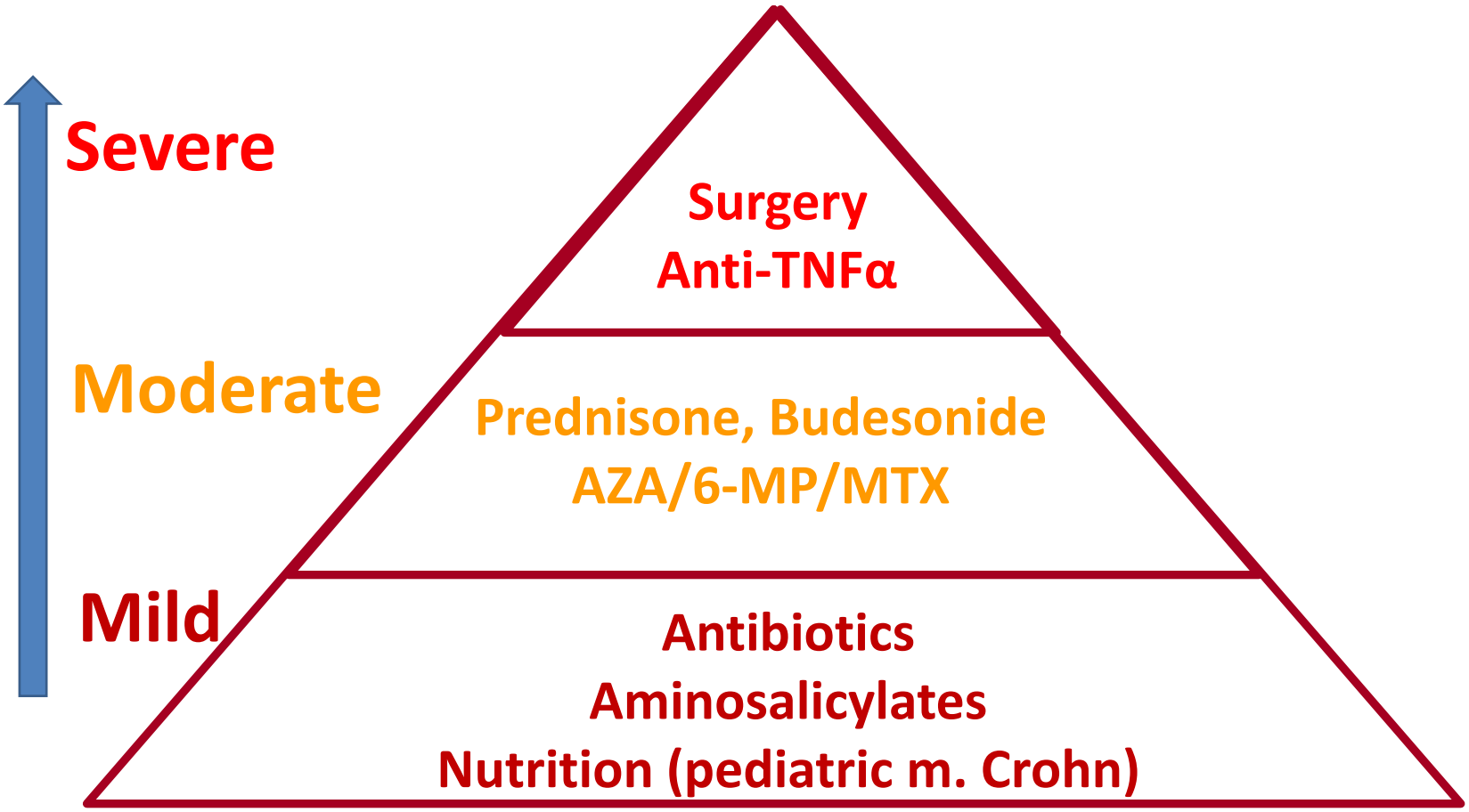
- Inflammation and ulceration of the lining of the intestines:
  - **Ulcerative colitis** – begins in the rectum and extends upward
  - **Crohn's disease** or regional enteritis – can effect any area



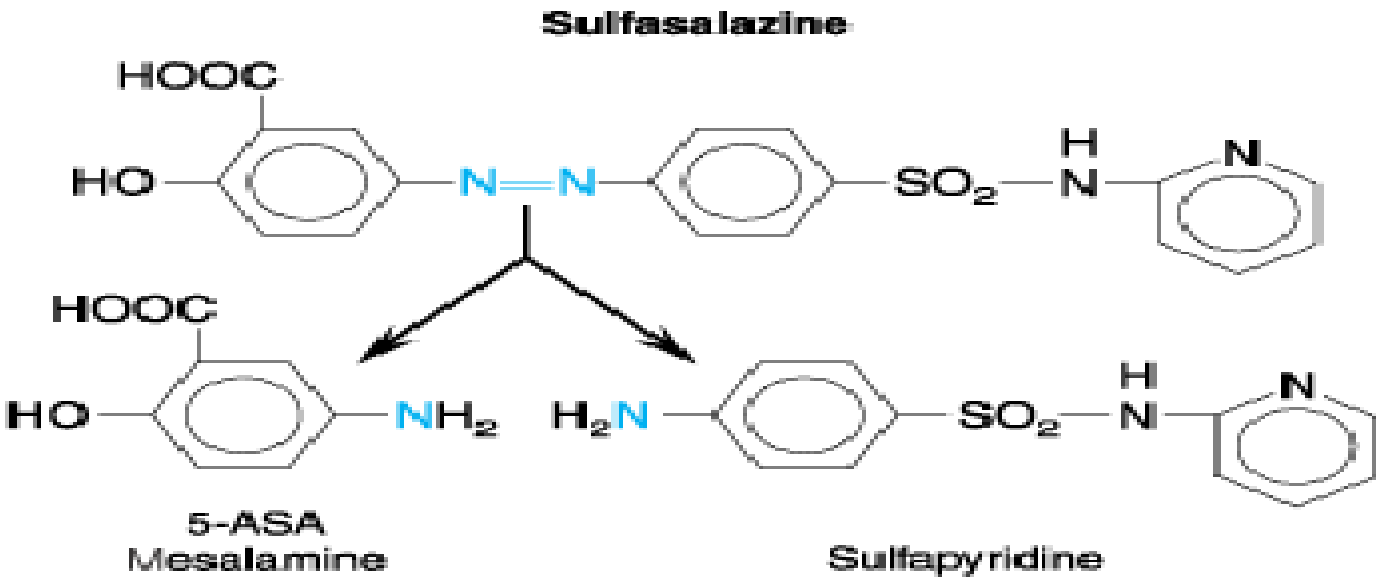
Clinical manifestation

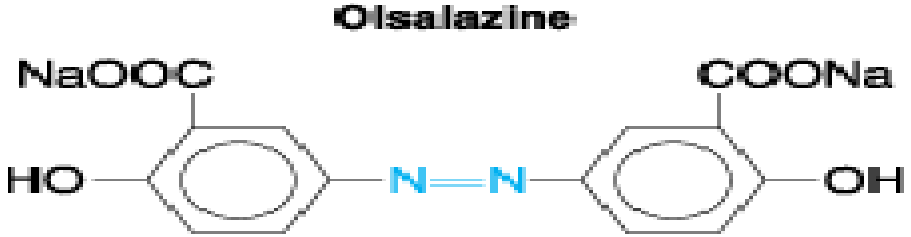
- Diarrhoea
- Blood in stool
- Fever
- Decreased hemoglobin
- Abdominal pain

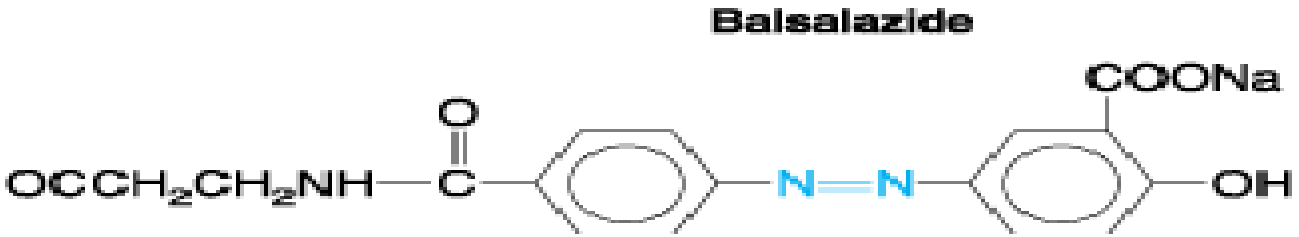
Treatment of IBD



Derivatives of 5-ASA



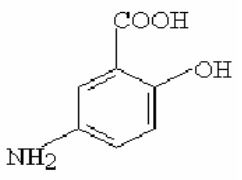




Sulfasalazine

- 5-ASA linked to sulfapyridine
- ↓ AA products (PG, LT), IL-1, TNF-alfa
- scavenger of oxygen radicals
- SE:
  - GIT distrubances
  - Hepatotoxicity
  - Neuropathy
  - Allergic reaction...

Mesalamine (5-ASA, mesalazine)



- p.o. (!! absorption)
- SE
  - allergic reactions
  - GIT
  - Headache
  - Hepatitis
  - Hemolytic anemia
  - Bone marrow suppression
- inhibits intestinal folate absorption

  - ROWASA – enema (rectal suspension)
  - CANASA – suppositories

Second generation of 5-ASA derivatives

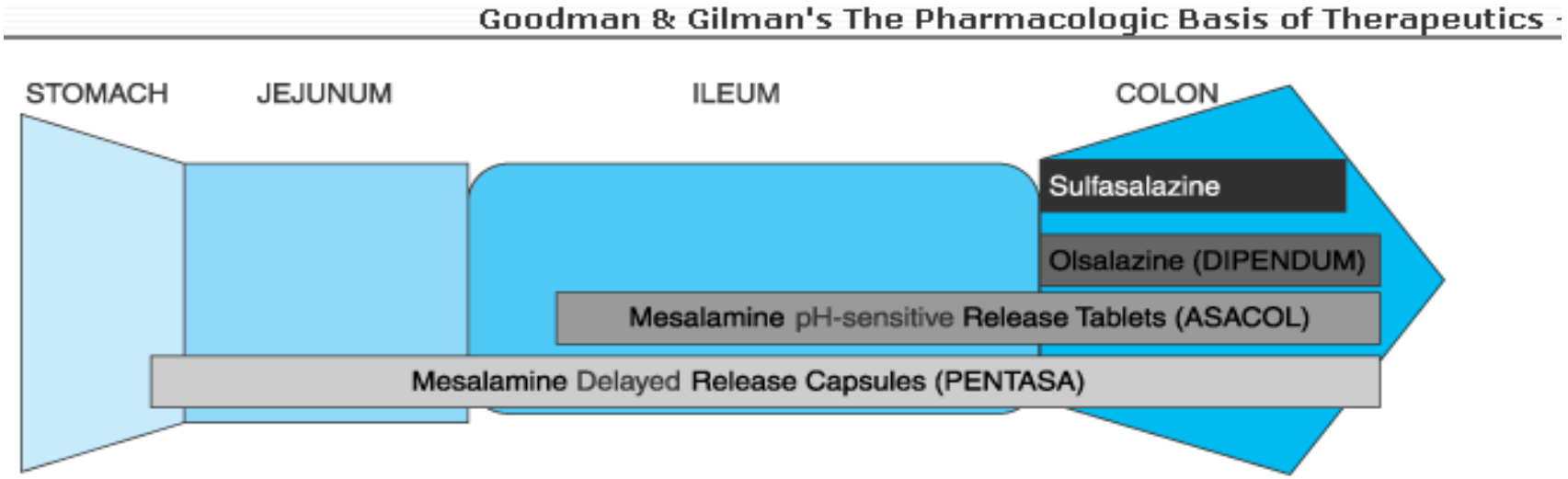


Figure 38-4. *Sites of release of mesalamine (5-ASA) in the GI tract f*

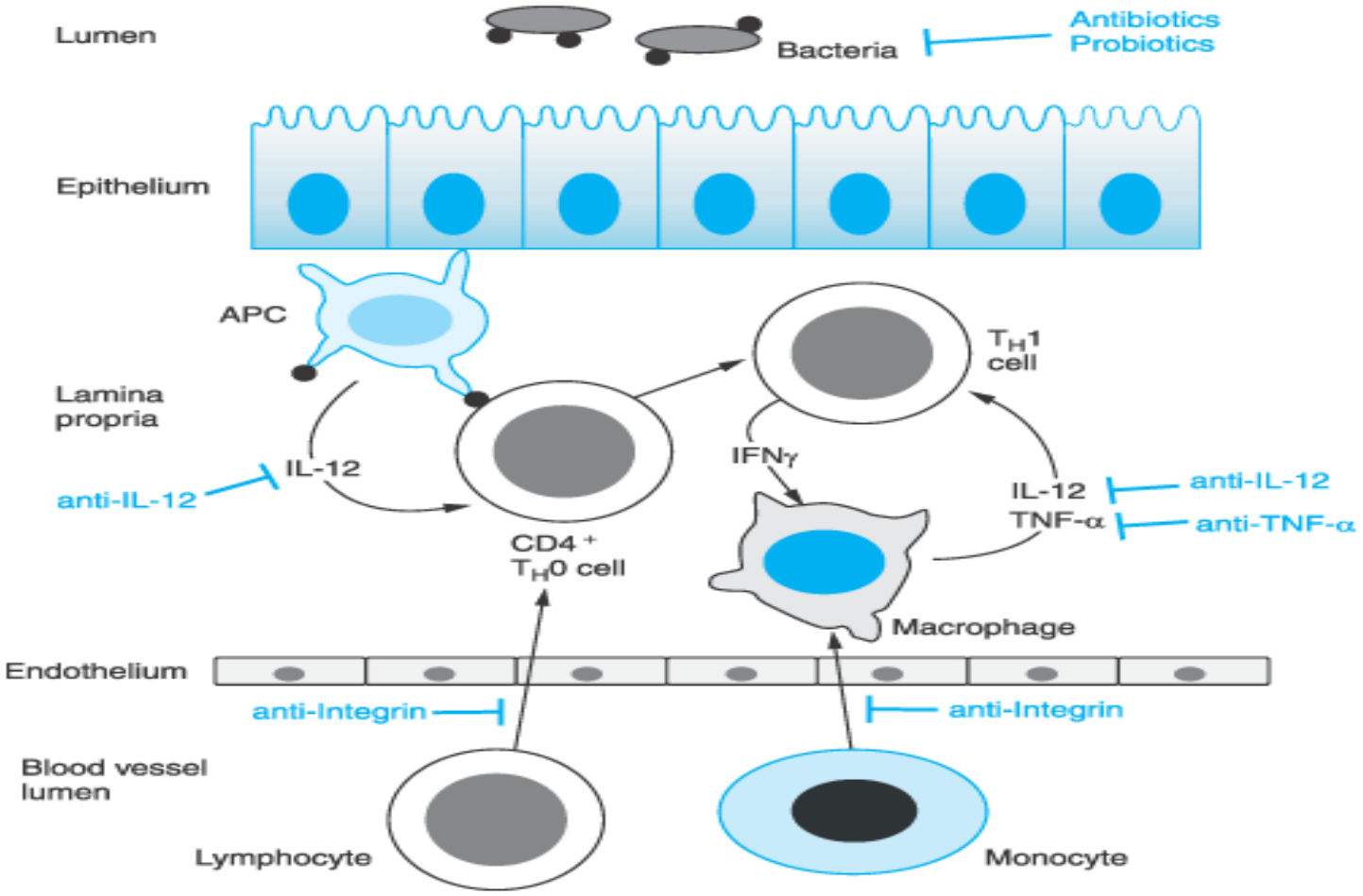
***Prodrug** – olsalazine (DIPENDIUM), balsalazide (COLAZIDE)*

***Modified tbl.** – ASACOL, PENTASA, SALOFALK*

Combined therapy

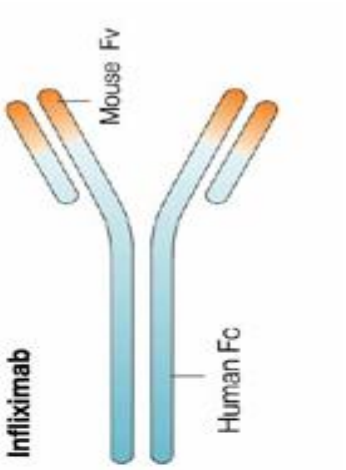
- Antimicrobial
  - metronidazol, ciprofloxacine
- Glucocorticosteroids
  - Prednisolone (p.o.)
  - Budesonide (locally)
- Other Immunosuppressive drugs
  - Azathioprine
  - 6-mercapto-purine

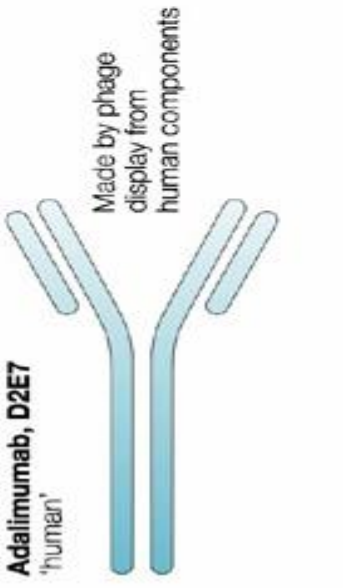
Anti TNF-α therapy

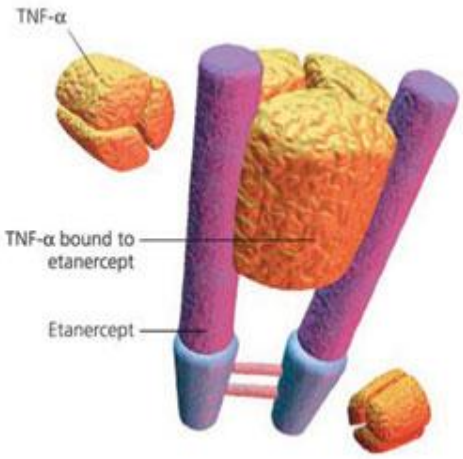


Anti TNF-α therapy

- **Infliximab – REMICADE**
- **Adalimumab – HUMIRA**







Etanercept – ENBREL