

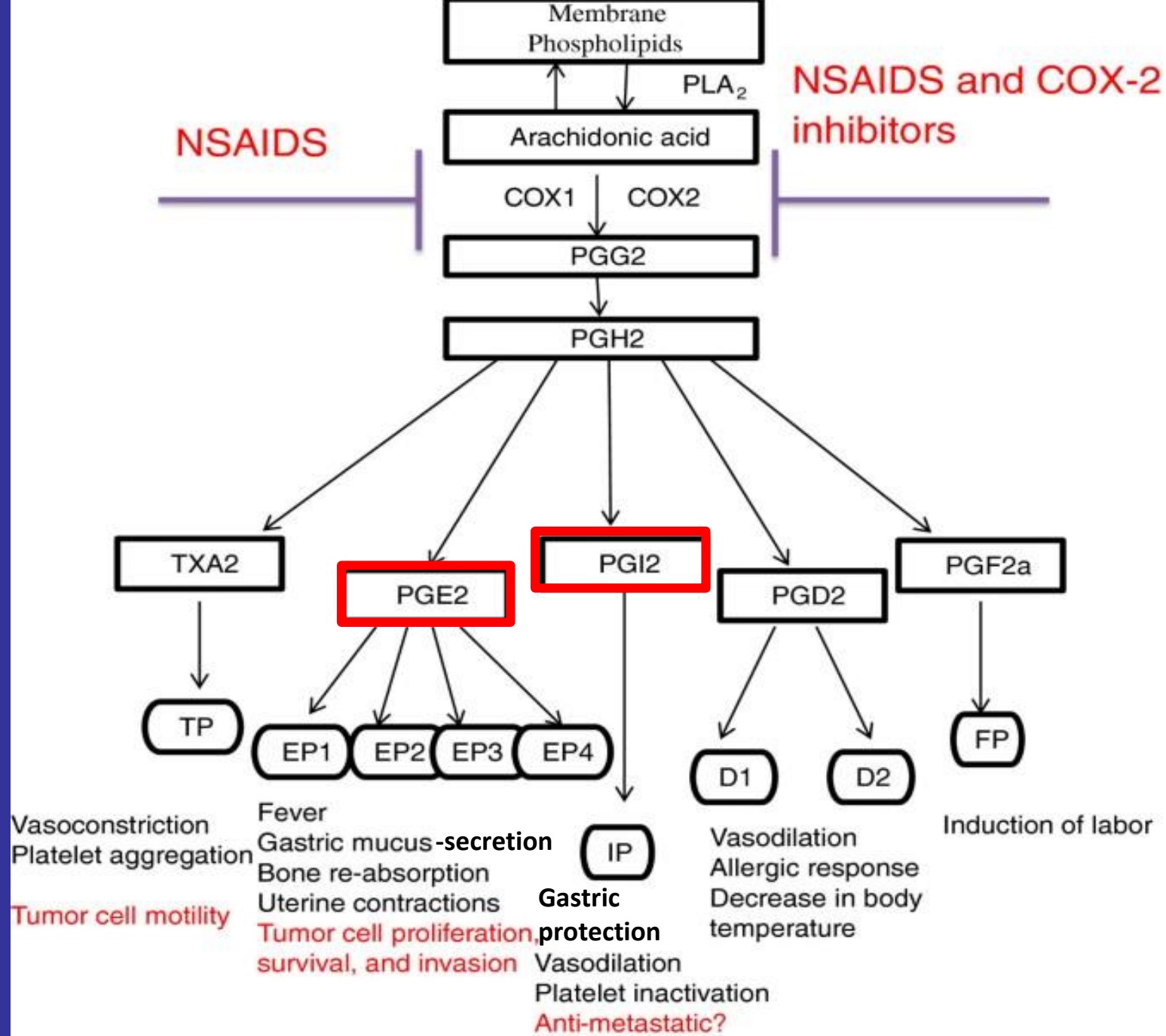
Gastrointestinal Apparatus Drugs

(ulcer, reflux, vomiting, diarrhea, constipation)

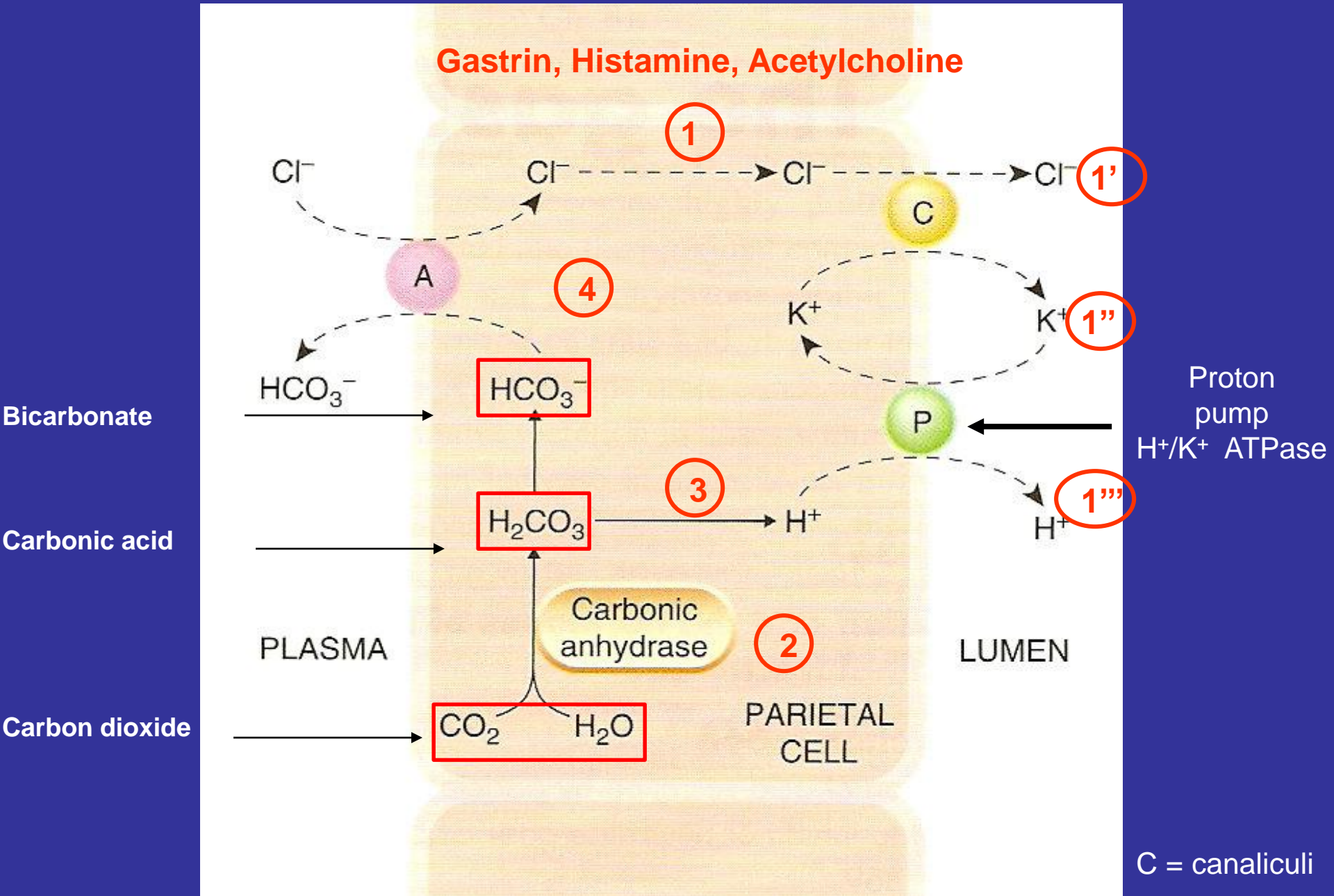
Secretion of gastric acid, mucus and bicarbonate



- 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).



Secretion of hydrochloric acid in gastric parietal cells



Drugs for ulcer

One cell and two cell hypothesis

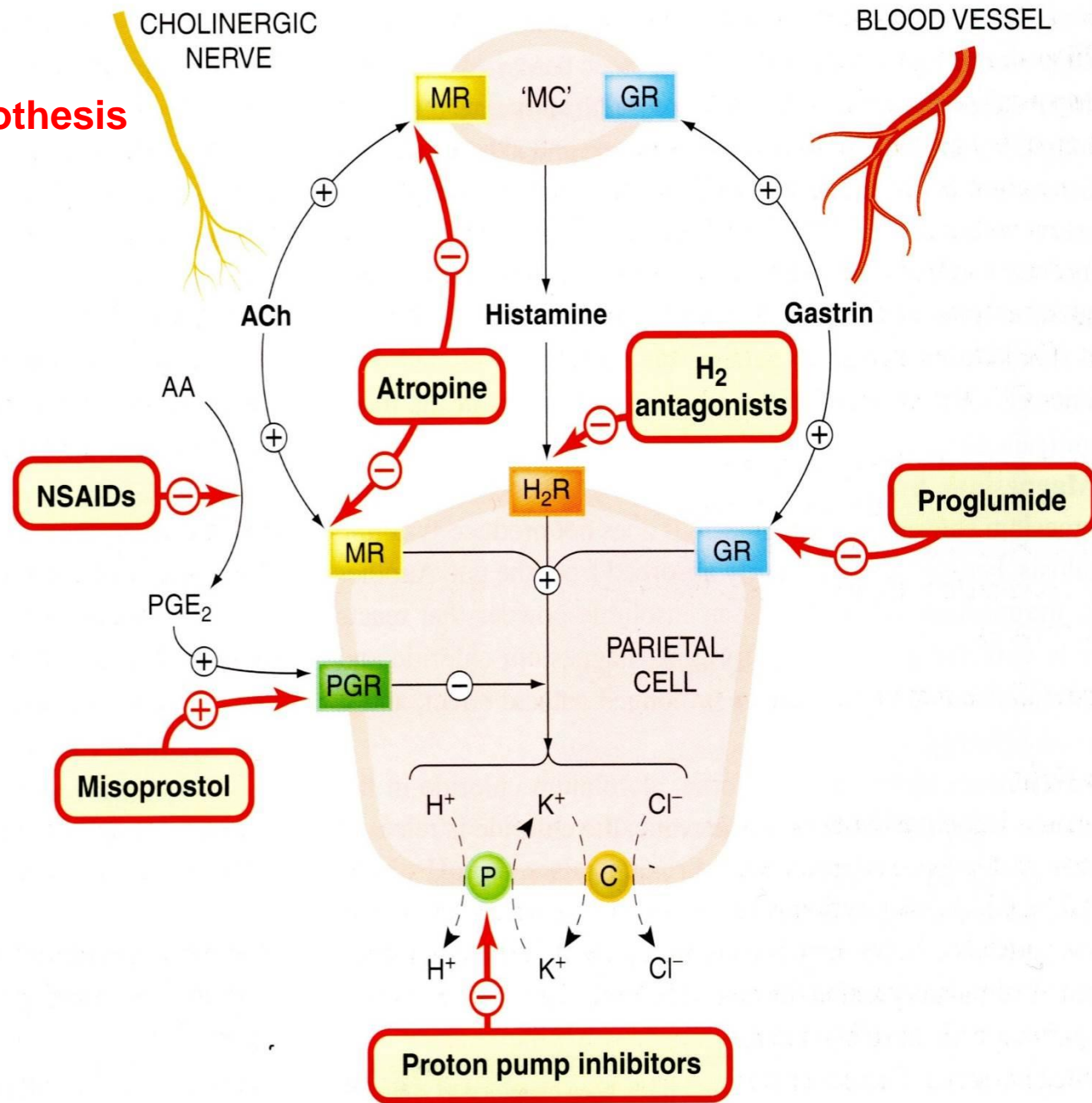


Fig. 25.2 Schematic diagram showing the one-cell and two-cell hypotheses of the action of secretagogues on the acid-secreting gastric parietal cell, illustrating the site of action of drugs influencing acid secretion. Acetylcholine and gastrin act either directly on their receptors (the one-cell hypothesis) or partly directly and partly indirectly by releasing histamine (the two-cell hypothesis).

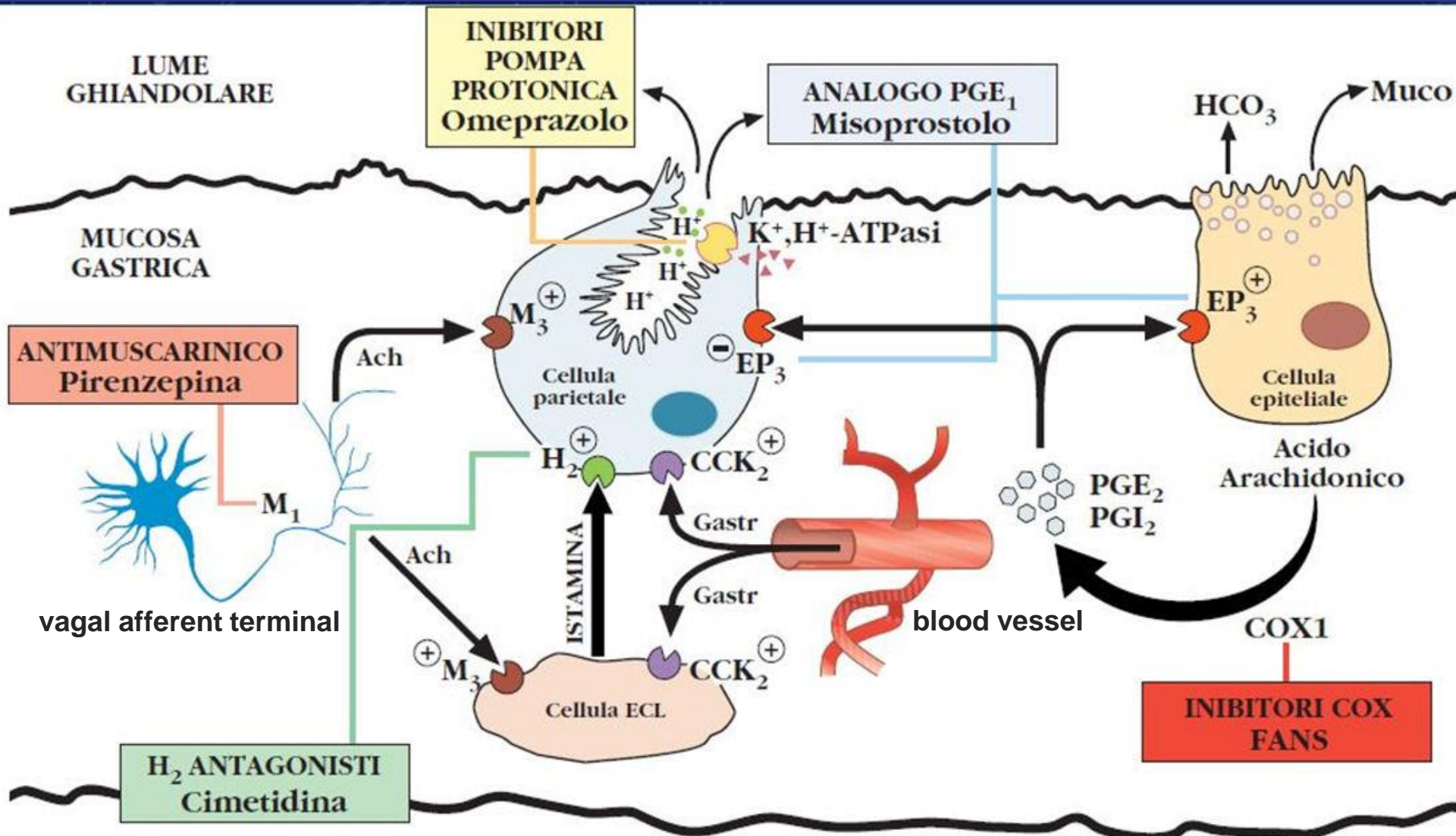
AA, arachidonic acid; ACh, acetylcholine; C, symport carrier for K⁺ and Cl⁻; GR, gastrin receptor; H₂R, histamine H₂ receptor; Hist, histamine; MC, mast cell-like histamine-secreting cell; MR, muscarinic receptor; NSAIDs, non-steroidal anti-inflammatory drugs; P, proton pump (H⁺/K⁺ ATPase); PGE₂, prostaglandin E₂; PGR, prostaglandin E₂ receptor.

Clinical use of agents affecting gastric acidity



- Histamine H₂ receptor antagonists (e.g. **ranitidine**):
 - *peptic ulcer*
 - *reflux oesophagitis*.
- Proton pump inhibitors (e.g. **omeprazole**, **lansoprasole**):
 - *peptic ulcer*
 - *reflux oesophagitis*
 - as one component of therapy for *Helicobacter pylori* infection
 - *Zollinger–Ellison* syndrome (a rare condition caused by gastrin-secreting tumours)
- Antacids (e.g. **magnesium trisilicate**, **aluminium hydroxide**, **alginates**):
 - *dyspepsia*
 - symptomatic relief in *peptic ulcer* or (alginate) *oesophageal reflux*.
- **Bismuth chelate**:
 - as one component of therapy for *H. pylori* infection.

Control of acid secretion



ECL= enterochromaffin cell; EP = endoperoxide receptors

Helicobacter Pylori

Incidence of helicobacter pylori infection in ulcerative pathologies

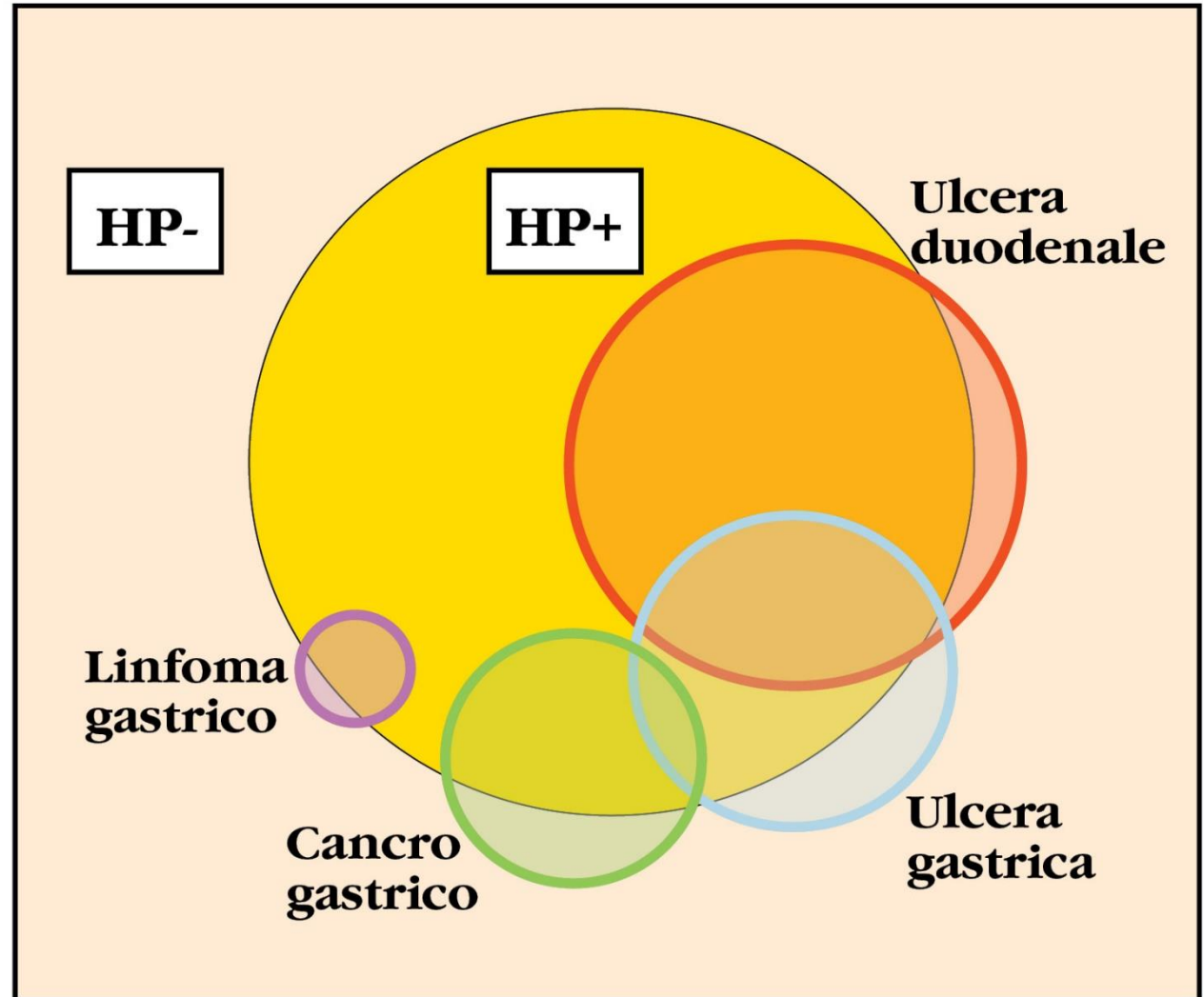
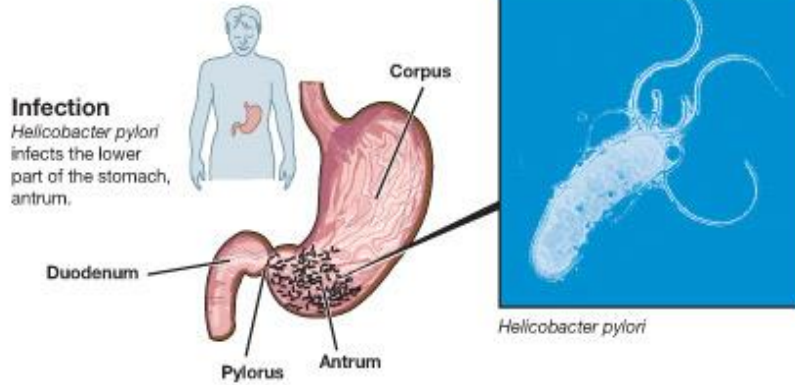


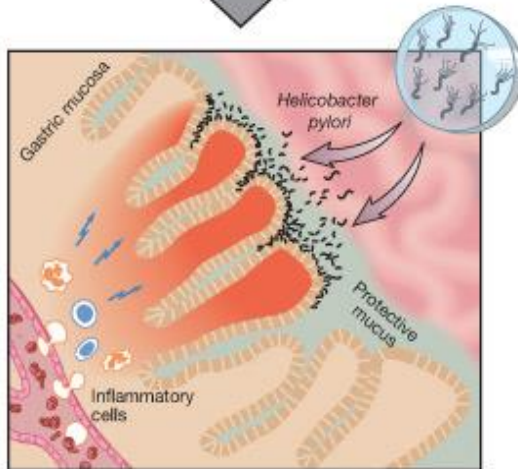
Figura 53.8. Incidenza dell'infezione da *H. pylori* e correlazione con le patologie ulcerose: l'area gialla individua la quota di popolazione costituita da pazienti positivi all'*H. pylori* (HP^+) mentre l'area rosa pallido individua la quota di popolazione di pazienti negativi al batterio (HP^-).

Helicobacter pylori associated with gastric mucosae

Gram negative, microaerophilic and acidophilic bacterium (acid resistant)

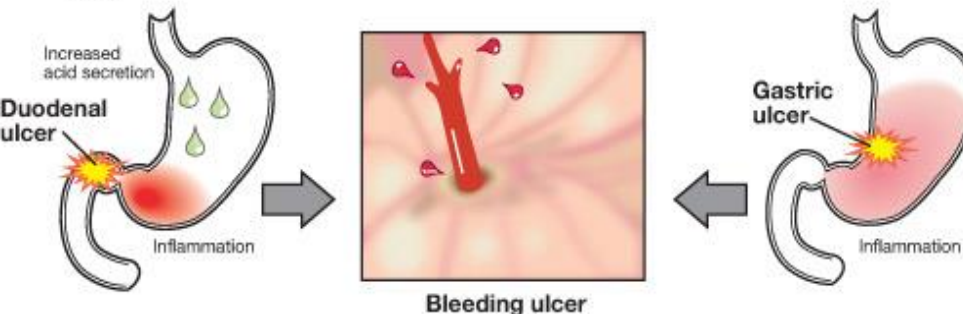


Inflammation
Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.



Ulcer

Gastric inflammation may lead to duodenal or gastric ulcer. Severe complications include bleeding ulcer and perforated ulcer.



Bizzozero 1893
Warren e Marshall (Nobel 2005)

Antimicrobials

- *Amoxicillina*
- Composti del bismuto
- *Clarithromicina*
- *Metronidazolo*
- *Tetraciclina*

H2R antagonists

- Cimetidina*
- Famotidina*
- Nizatidina*
- Ranitidina*

Proton Pump Inhibitors

- Esomeprazolo*
- Lansoprazolo*
- Omeprazolo*
- Pantoprazolo*
- Rabeprazolo*

Prostaglandins

- └ *Misoprostolo*

Drugs for ulcer
and peptic ulcer

Recommended therapy and dosage for the eradication of helicobacter pylori

FARMACO	DOSAGGIO	DURATA
Triplice Terapia		
Claritromicina +	500 mg bid	14 giorni
Amoxicillina +	1 g bid	
IPP	20-40 mg bid	
Quadruplica Terapia con Bismuto		
Bismuto subcitrato +	120-300 mg qid	10-14 giorni
Metronidazolo o tinidazolo +	500 mg tid-qid	
Tetraciclina +	500 mg qid	
IPP	20-40 mg bid	
Triplice Terapia con Levofloxacina		
levofloxacina +	500 mg una volta id	10-14 giorni
Amoxicillina +	1 g bid	
IPP	20-40 mg bid	

Dosaggio standard degli IPP: 20 mg bid esomeprazolo; 30 mg bid lansoprazolo; 20 mg bid omeprazolo; 40 mg bid pantoprazolo; 20 mg bid rabeprazolo.

Bismuth = inhibits pepsin, increases mucus secretion, protective layer

Anti H₂ Drugs

Antimicrobials

Amoxicillina

Composti del bismuto

Clarithromicina

Metronidazolo

Tetraciclina

H2R antagonists

Cimetidina

Famotidina

Nizatidina

Ranitidina

Proton Pump Inhibitors

Esomeprazolo

Lansoprazolo

Omeprazolo

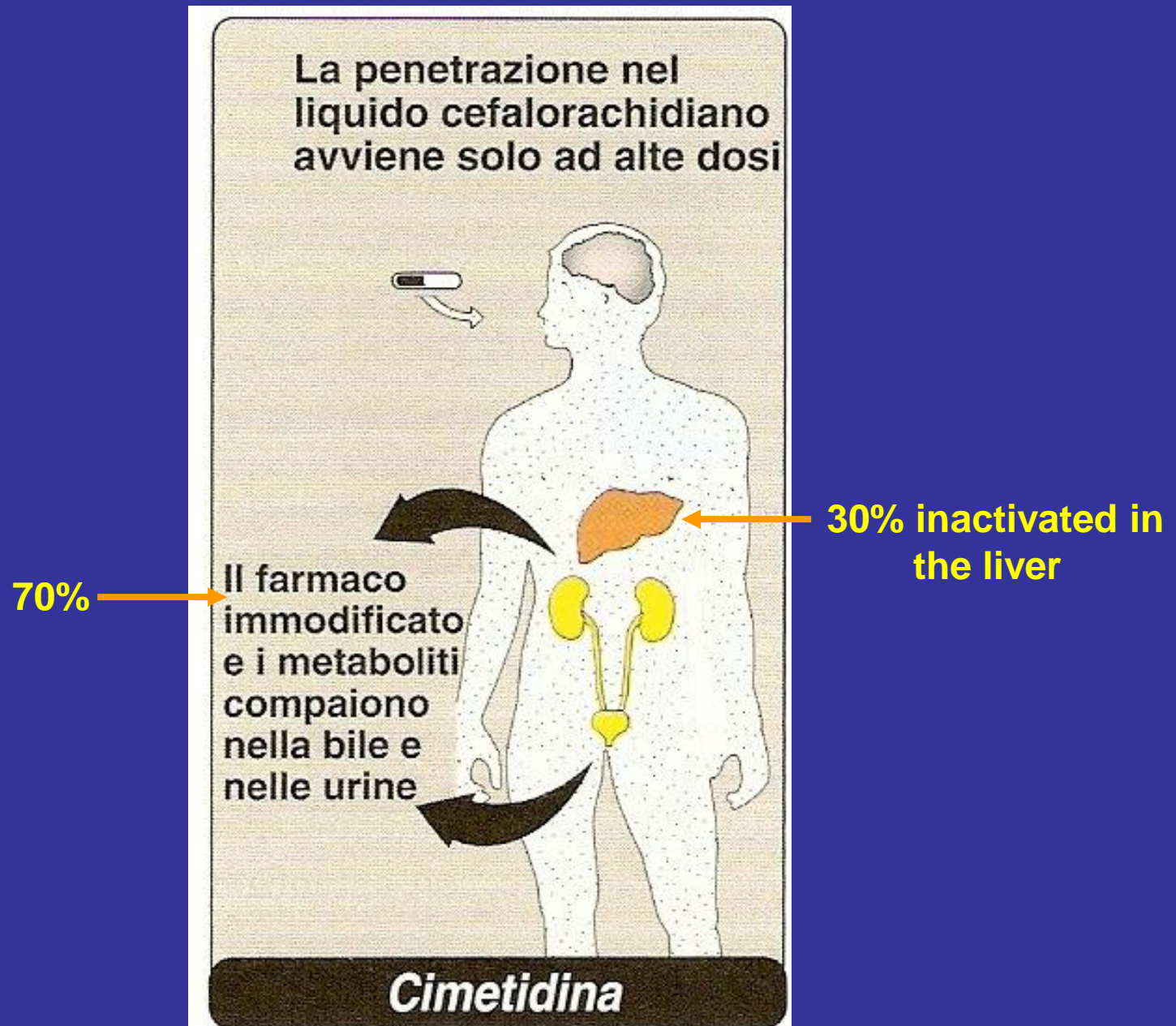
Pantoprazolo

Rabeprazolo

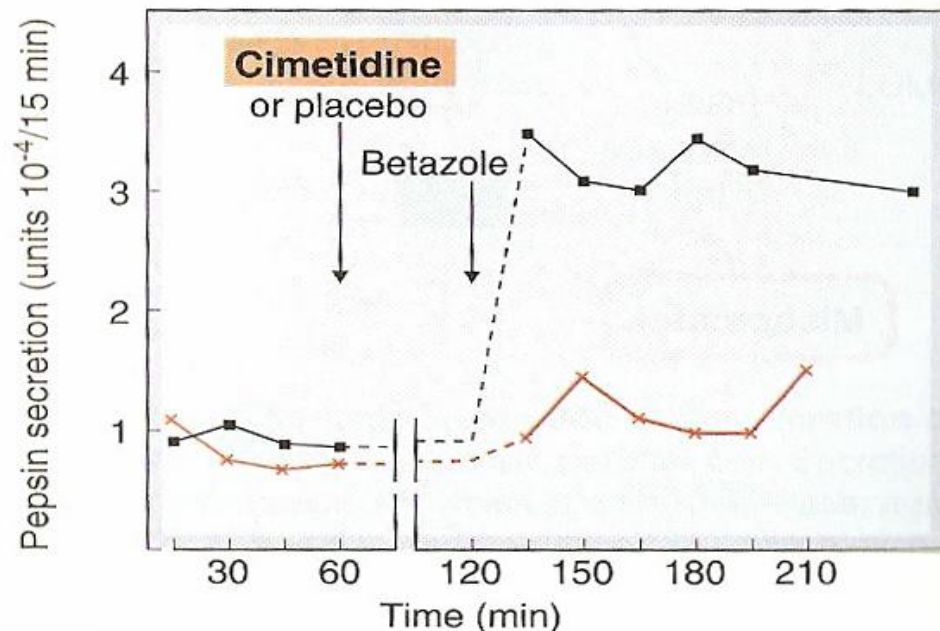
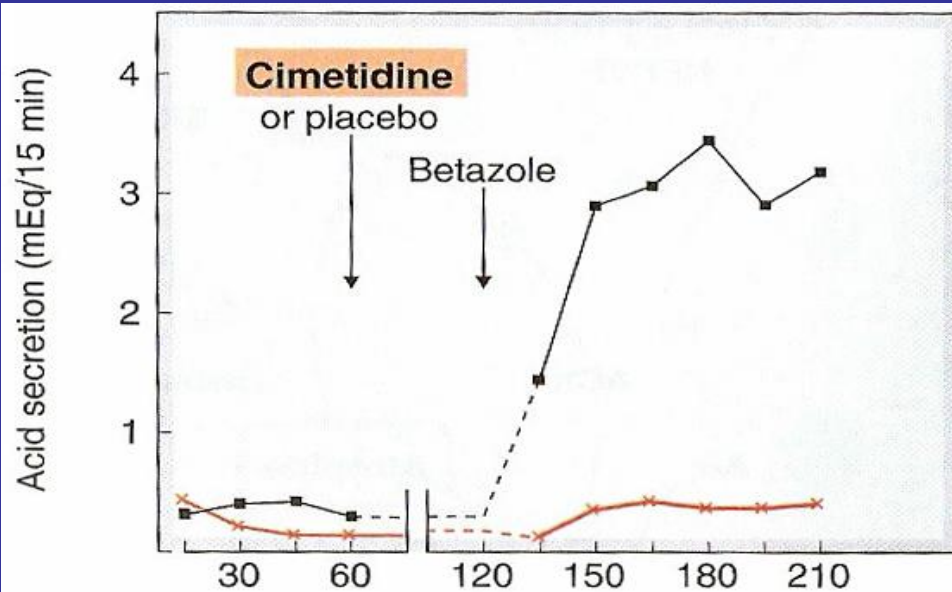
Prostaglandins

Misoprostolo

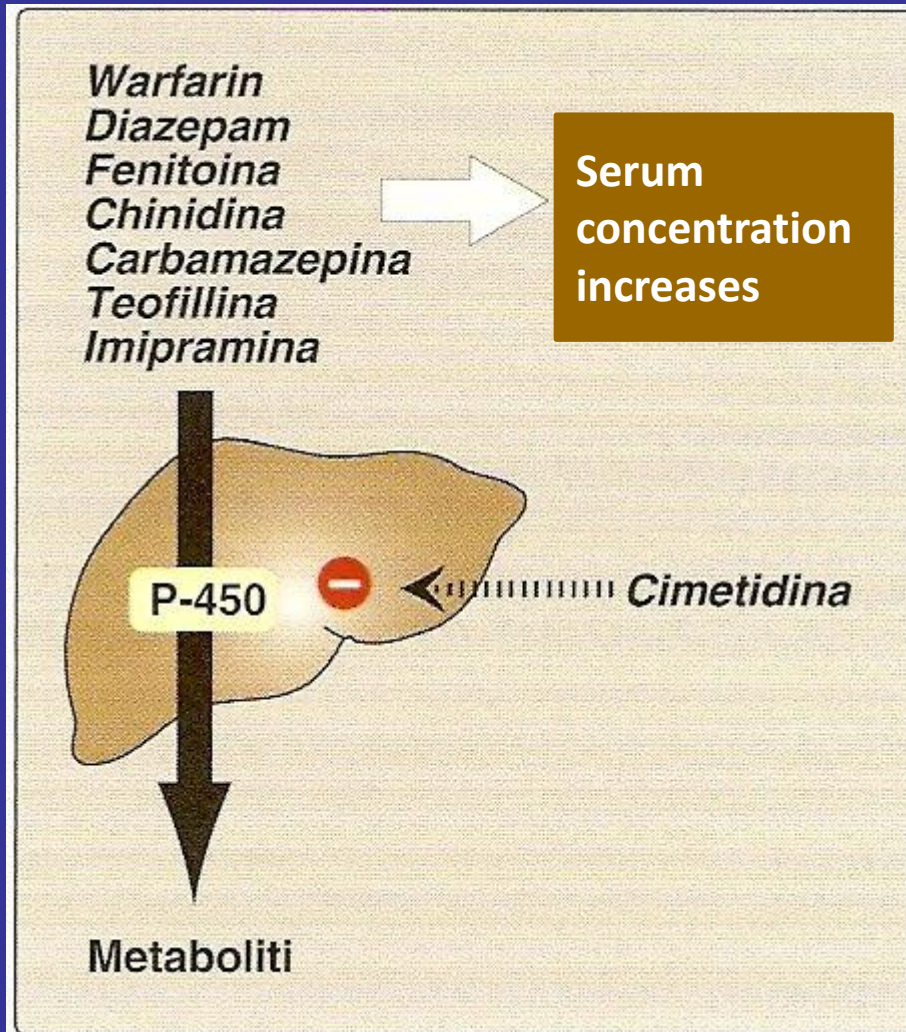
Administration and fate of cimetidine



Effect of cimetidine on the stimulation mediated by betazole of gastric acid and pepsin secretion



Drug interactions with *cimetidine* and side effects



Side effects

Headache, dizziness, diarrhea, muscle pain, confusion-hallucinations (in the elderly), antiandrogen (gynecomastia-galactorrhoea, sperm reduction)

↓ absorption of ketoconazole

Proton Pump Inhibitors (PPI)

Antimicrobials

Amoxicillina

Composti del bismuto

Clarithromicina

Metronidazolo

Tetraciclina

H2R antagonists

Cimetidina

Famotidina

Nizatidina

Ranitidina

Proton Pump Inhibitors

Esomeprazolo

Lansoprazolo

Omeprazolo

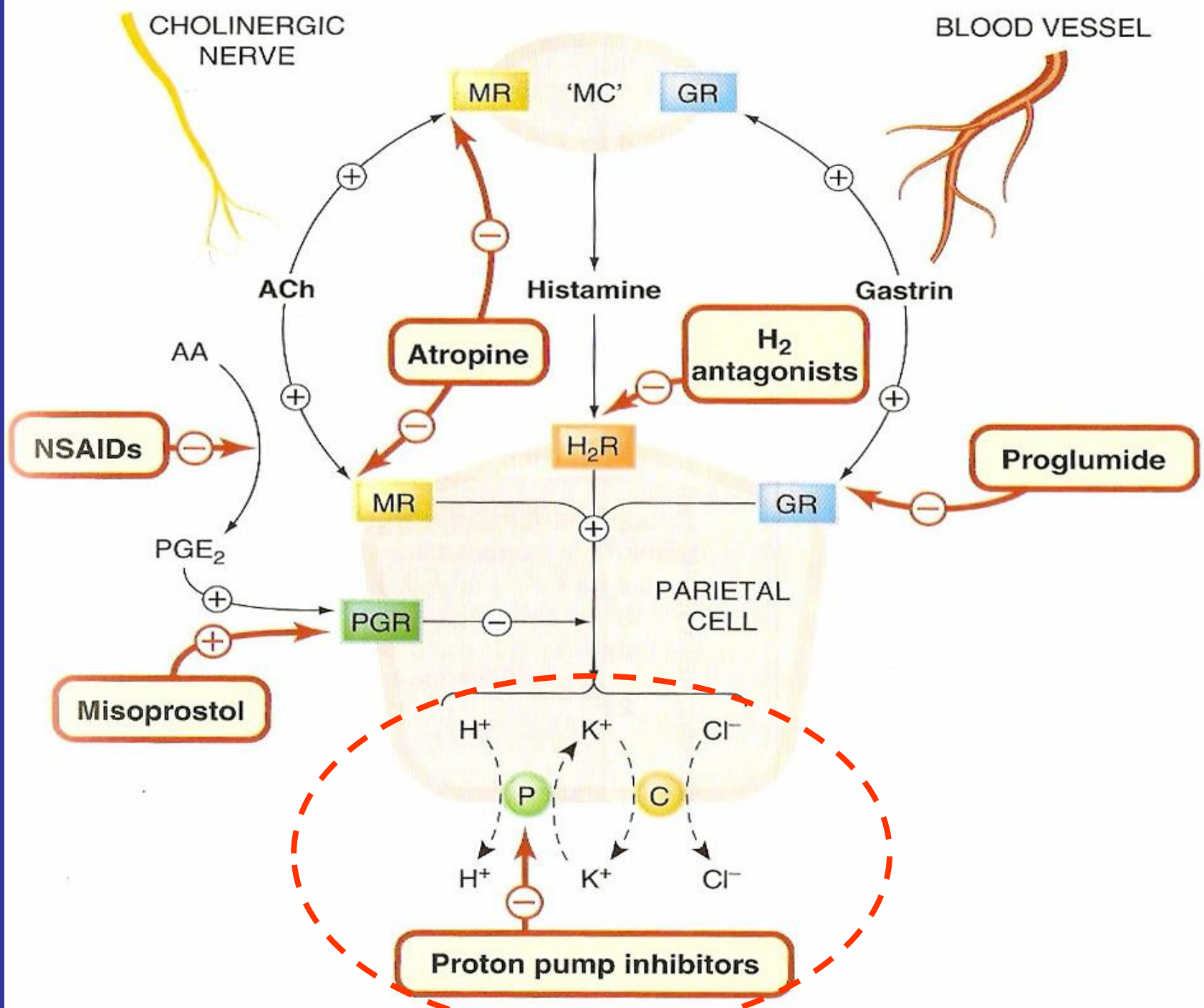
Pantoprazolo

Rabeprazolo

Prostaglandins

Misoprostolo

- Intake: meal concomitance (peak of maximum activation proton pump)
- Unstable in an acid environment
- Tablets (weak base), with acid resistant coating, removed in duodenum
- Absorbed in duodenum



Recommended dosage schedules for the eradication of helicobacter pylori

FARMACO	BIODISPONIBILITÀ %	EMIVITA (ORE)	INTERFERENZE METABOLICHE	POSOLOGIA PER MRGE E UP
Esomeprazolo	64* (89 al 5° giorno di terapia)	1.2	Inibizione CYP2C19	20-40 mg/die
Lansoprazolo	80	1.3-1.7	Induzione CYP1A2	30 mg/die
Omeprazolo	30* (65 al 5° giorno di terapia)	0.5-1.0	Inibizione CYP2C19	20 mg/die
Pantoprazolo	77	1.0-1.9	—	40 mg/die
Rabeprazolo	52	1.0-2.0	—	20 mg/die

MRGE: Malattia da reflusso gastro-esofageo; UP: ulcera peptica; * la biodisponibilità al 5° giorno di terapia aumenta per inibizione degli enzimi metabolici.

Drug interactions and side effects

- Increased bacteria in the stomach
- Increased pH in stomach, gastrin secretion and hypochlorhydria (Tumors)
- Low levels of vit. B12 (intrinsic factor)
- Increased hip fracture risk

Omeprazole interferes with oxidation of:
warfarin, phenytoin, diazepam, cyclosporin

Prostaglandin drugs

Antimicrobials

Amoxicillina

Composti del bismuto

Clarithromicina

Metronidazolo

Tetraciclina

H2R antagonists

Cimetidina

Famotidina

Nizatidina

Ranitidina

Proton Pump Inhibitors

Esomeprazolo

Lansoprazolo

Omeprazolo

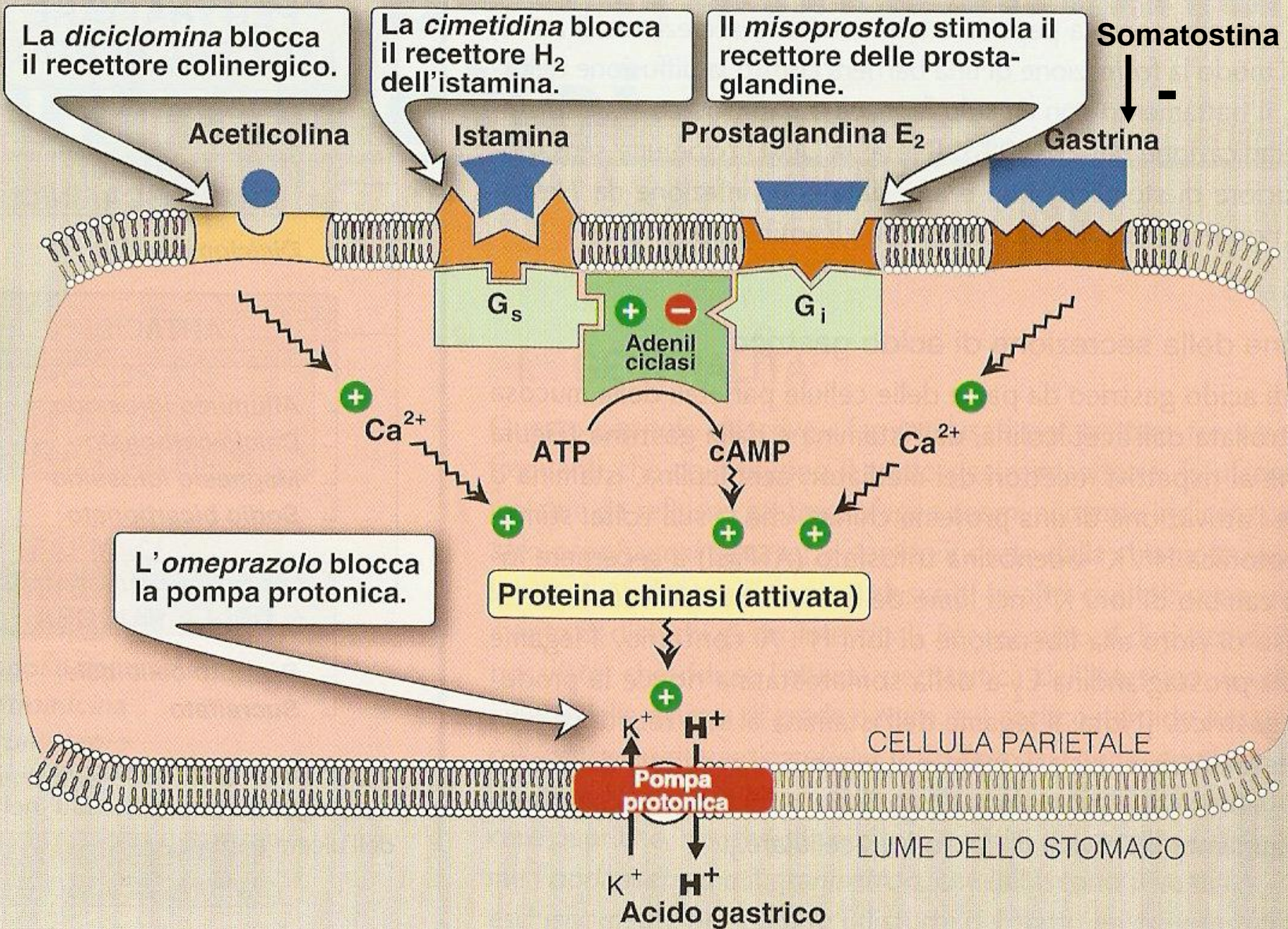
Pantoprazolo

Rabeprazolo

Prostaglandins

Misoprostolo

Modulation of gastric acid secretion



Antacid drugs and protective agents

Antacid and protective agents

Antiacids

Alluminio idrossido

Calcio carbonato

Magnesio idrossido

Sodio bicarbonato

Alginati

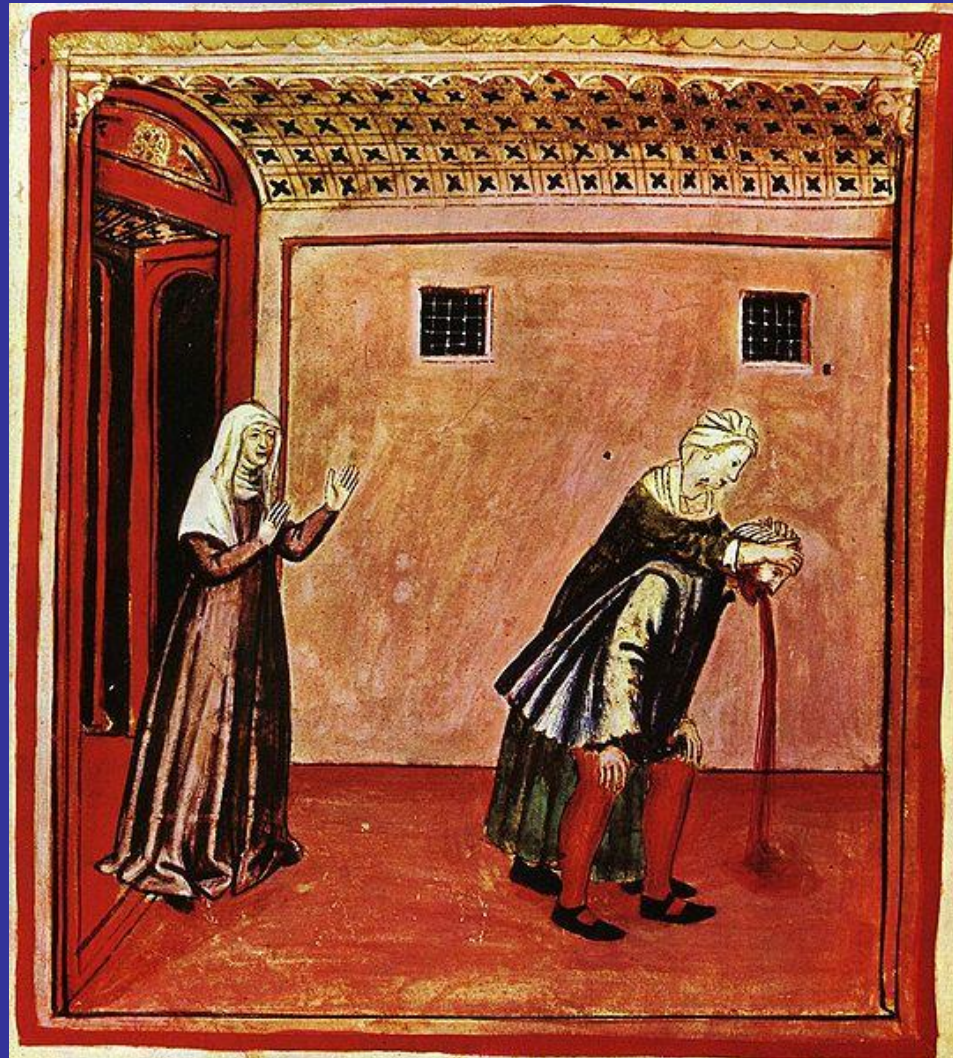
Protective of the mucosa

Bismuto colloidale

Sucralfato (alluminio idrossido + sucrosio solfato)

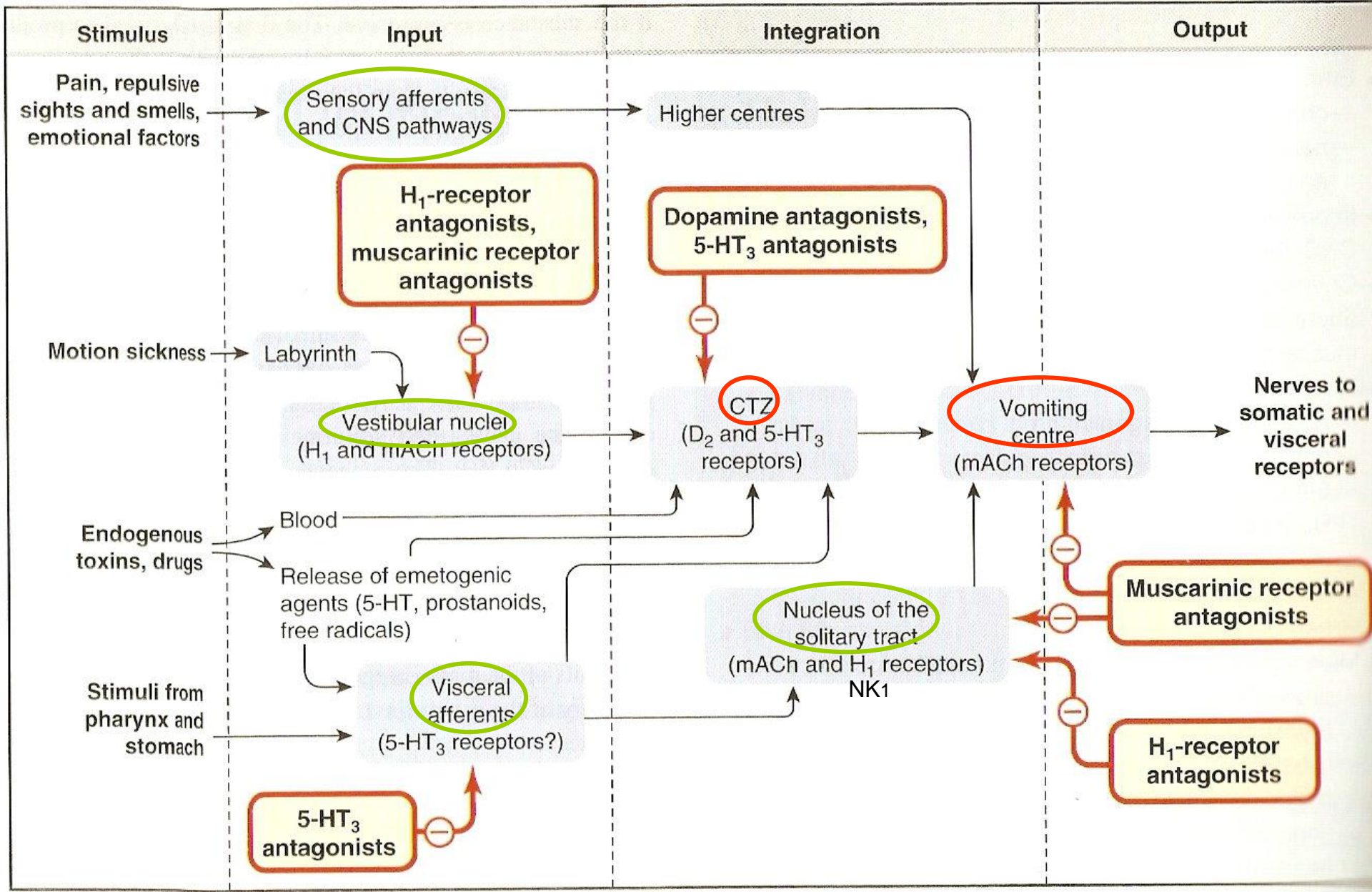
Dyspepsia,
Gastroesophageal reflux

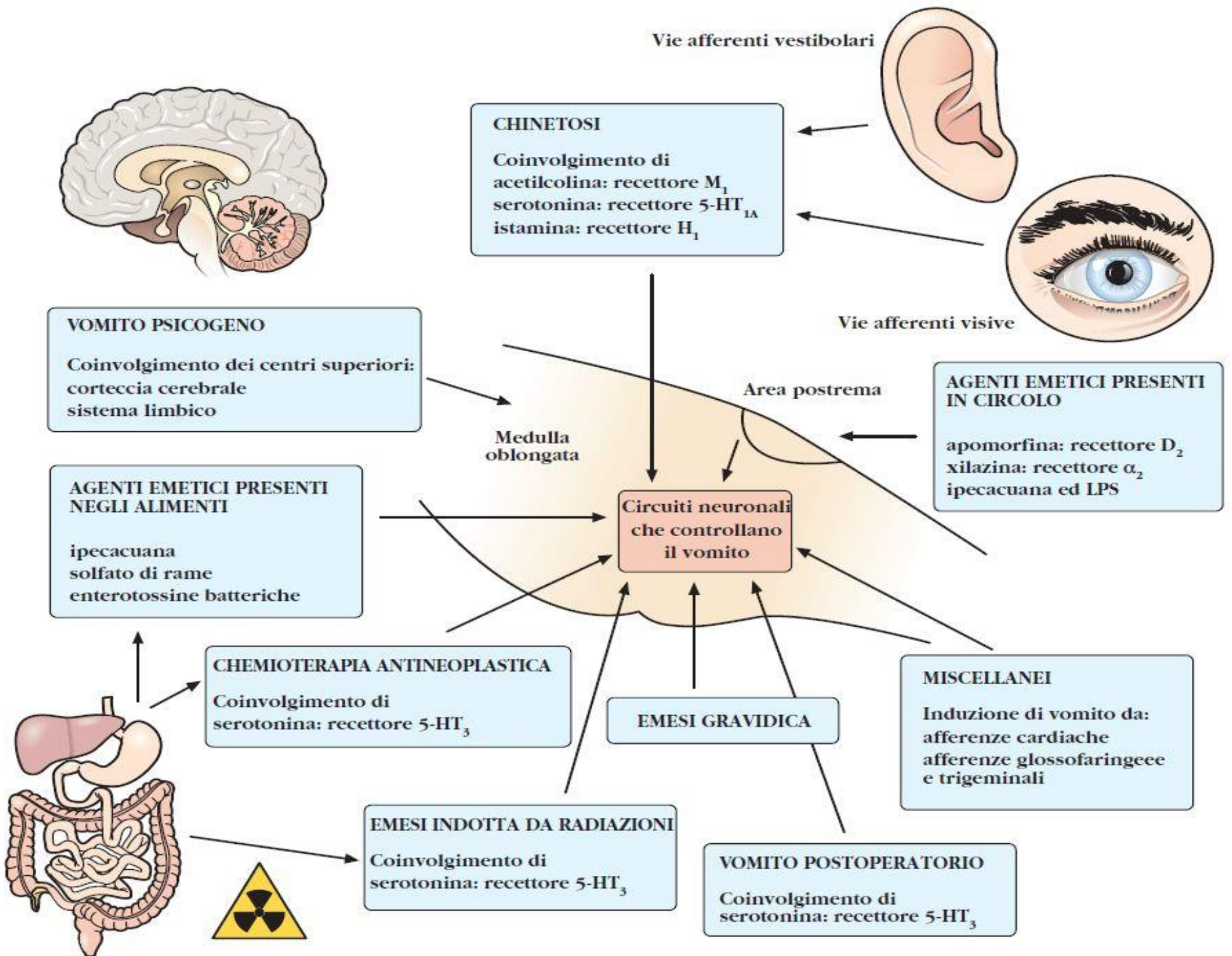
Drugs used in the control of vomiting



Taccuino sanitatis
XIV secolo

Factors that influence vomiting





Vie afferenti vestibolari

CHINETOSI

Coinvolgimento di
 acetilcolina: recettore M_1
 serotonina: recettore $5-HT_{1A}$
 istamina: recettore H_1

Vie afferenti visive

VOMITO PSICOGENO

Coinvolgimento dei centri superiori:
 corteccia cerebrale
 sistema limbico

Area postrema

AGENTI EMETICI PRESENTI IN CIRCOLO

apomorfina: recettore D_2
 xilazina: recettore α_2
 ipecacuana ed LPS

Medulla oblongata

Circuiti neuronali
 che controllano
 il vomito

AGENTI EMETICI PRESENTI NEGLI ALIMENTI

ipecacuana
 solfato di rame
 enterotossine batteriche

MISCELLANEI

Induzione di vomito da:
 afferenze cardiache
 afferenze glossofaringee
 e trigeminali

CHEMIOTERAPIA ANTINEOPLASTICA

Coinvolgimento di
 serotonina: recettore $5-HT_3$

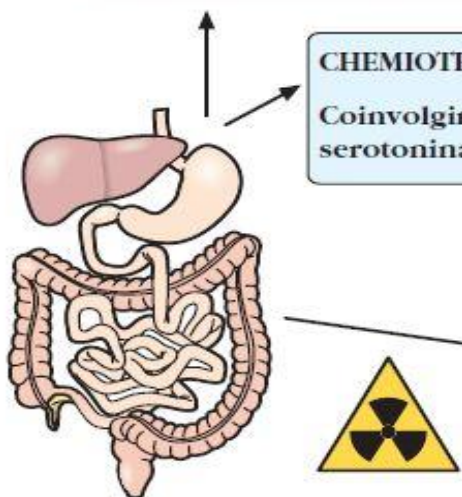
EMESI GRAVIDICA

EMESI INDOTTA DA RADIAZIONI

Coinvolgimento di
 serotonina: recettore $5-HT_3$

VOMITO POSTOPERATORIO

Coinvolgimento di
 serotonina: recettore $5-HT_3$



- 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.
- Antiemetic drugs:
 - H_1 -receptor antagonists (e.g. cyclizine)
 - muscarinic antagonists (e.g. hyoscine)
 - $5-HT_3$ -receptor antagonists (e.g. ondansetron)
 - D_2 -receptor antagonists (e.g. thiethylperazine, metoclopramide)
 - cannabinoids (e.g. nabilone).
 - neurokinin-1 antagonists.
- Main side-effects of principal antiemetics include:
 - drowsiness and antiparasymphathetic effects (hyoscine, nabilone > cinnarizine)
 - dystonic reactions (thiethylperazine > metoclopramide)
 - general CNS disturbances (nabilone)
 - headache, gastrointestinal tract upsets (ondansetron).

Mechanism of vomiting

Classic drugs used to treat nausea and vomiting

H1 receptor blockers

Cinnarizine, cyclizine, promethazine, diphenhydramine

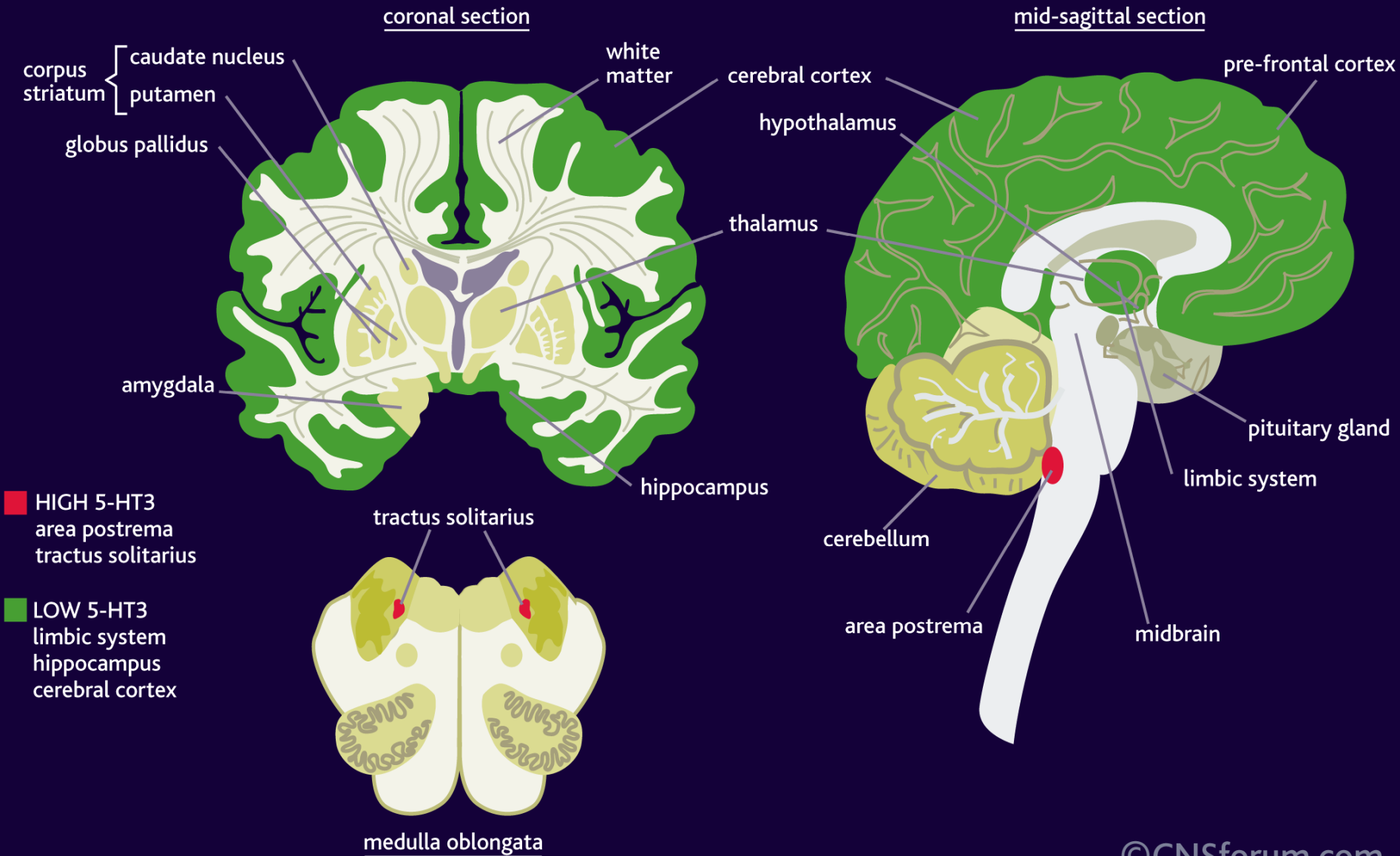
Muscarinic receptor blockers

Scopolamine

5HT₃, D₂ receptor blockers

Ondansetron, metoclopramide, domperidone

5HT₃ receptors and vomiting



FENOTIAZINE

Prochlorperazina

Tietilperazina

BLOCCANTI DEI RECETTORI 5-HT₃

Dolasetron (idrossidolasetron)

Granisetron

Ondansetron

Palonosetron

BENZAMIDI SOSTITUITE

Metoclopramide

BUTIRROFENONI

Domperidone

Droperidolo

Drugs used to control nausea and vomiting

Accessory drugs

BENZODIAZEPINE

Alprazolam

Lorazepam

CORTICOSTEROIDI

Desametasone

Metilprednisolone

CANNABINOIDI

Dronabinolo

Nabilone

BLOCCANTE DEL RECETTORE DELLA NEUROCHININA-1/SOSTANZA P

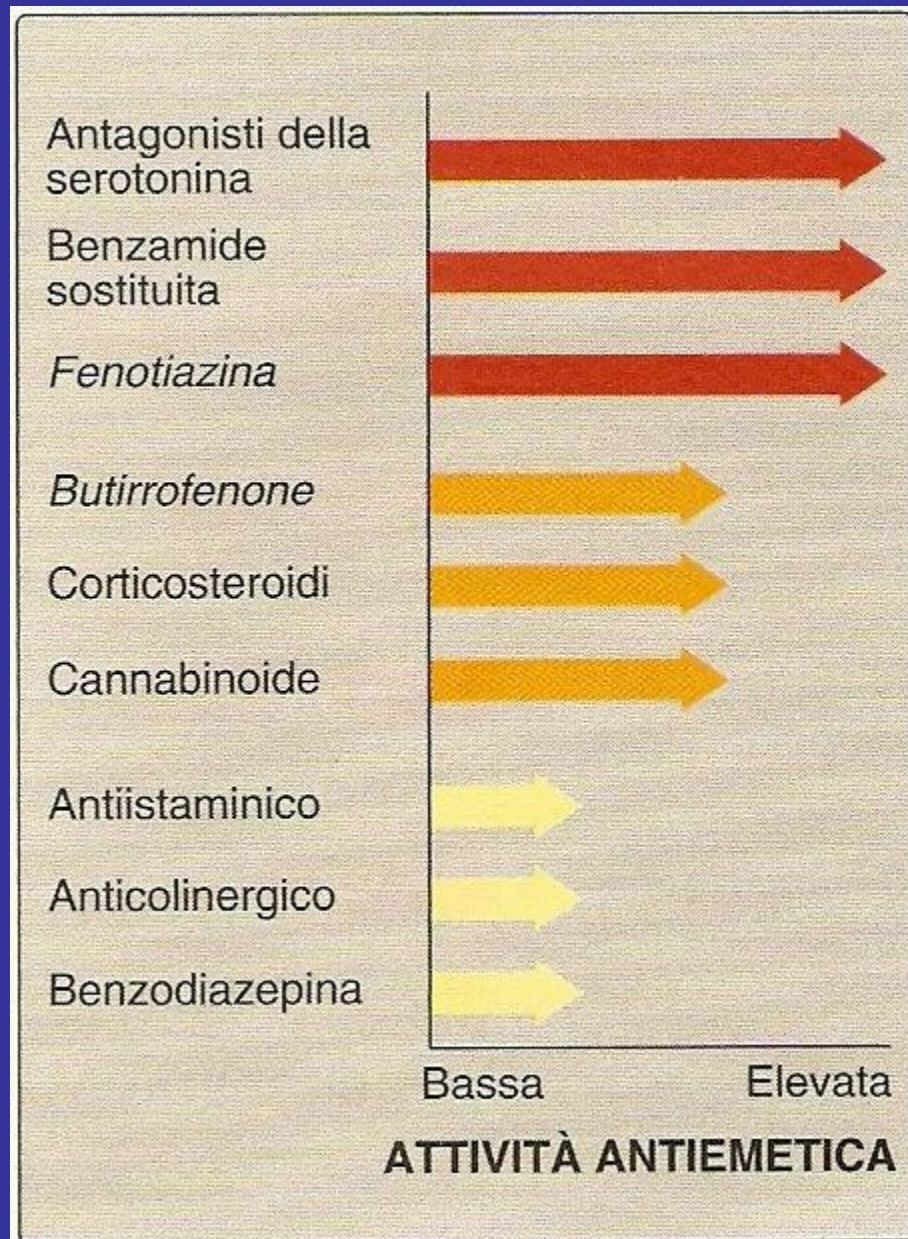
Aprepitant

Clinical use of anti-emetic drugs



- Histamine H₁-receptor antagonists:
 - cyclizine: **motion sickness**, meclizine, dimenhydrinate, diphenhydramine
 - cinnarizine: motion sickness, vestibular disorders (e.g. Ménière's disease)
 - promethazine: severe morning sickness of pregnancy (but only if absolutely essential).
- Muscarinic receptor antagonists:
 - hyoscine: **motion sickness**
- Dopamine D₂-receptor antagonists:
 - phenothiazines (e.g. prochlorperazine): vomiting caused by uraemia, radiation, viral gastroenteritis; severe morning sickness of pregnancy (but only if absolutely essential)
 - metoclopramide: vomiting caused by uraemia, radiation, gastrointestinal disorders, cytotoxic drugs.
- 5-Hydroxytryptamine 5-HT₃-receptor antagonists (e.g. ondansetron): vomiting caused by cytotoxic anticancer drugs; postoperative vomiting; radiation-induced vomiting.
- Cannabinoids (e.g. nabilone) for vomiting caused by cytotoxic anticancer drugs.

Comparison of the potency of antiemetic drugs



Drugs used in the treatment of diarrhea and constipation

Drugs and gastrointestinal tract motility



- Purgatives include:
 - bulk laxatives (e.g. **ispaghula** husk, first choice for slow action)
 - osmotic laxatives (e.g. **lactulose**)
 - faecal softeners (e.g. **docusate**)
 - stimulant purgatives (e.g. **senna**).
- Drugs that can increase motility without purgation:
 - **domperidone**, used in disorders of gastric emptying.
- Drugs used to treat diarrhoea:
 - oral rehydration with isotonic solutions of NaCl plus glucose or starch-based cereal (important in infants)
 - antimotility agents, for example **loperamide** (unwanted effects: drowsiness and nausea)
 - absorbents (e.g. **magnesium aluminium silicate**).

Antidiarrheal

Attapulgate attivata

Bismuto subsalicilato

Caolino

Difenossilato

Indometacina




Loperamide

Metilcellulosa

Pectina

Silicato di magnesio e alluminio

Drugs used in the treatment of diarrhea

-  antimotility
-  adsorbent
-  PG inhibition, transport of liquids and electrolytes

Drugs used in the treatment of constipation

Laxative

Aloe

Bisacodile

Colloidi idrofili

Crusca

Docusato sodico

Fenolftaleina

Glicole polietilenico *

Idrossido di magnesio

Lattulosio

Metilcellulosa

Olio di ricino

Olio minerale

Semi di psillio

Senna

Solfato di magnesio

Supposte di glicerina



emollients



stimulants, irritants



mass increase, osmotic