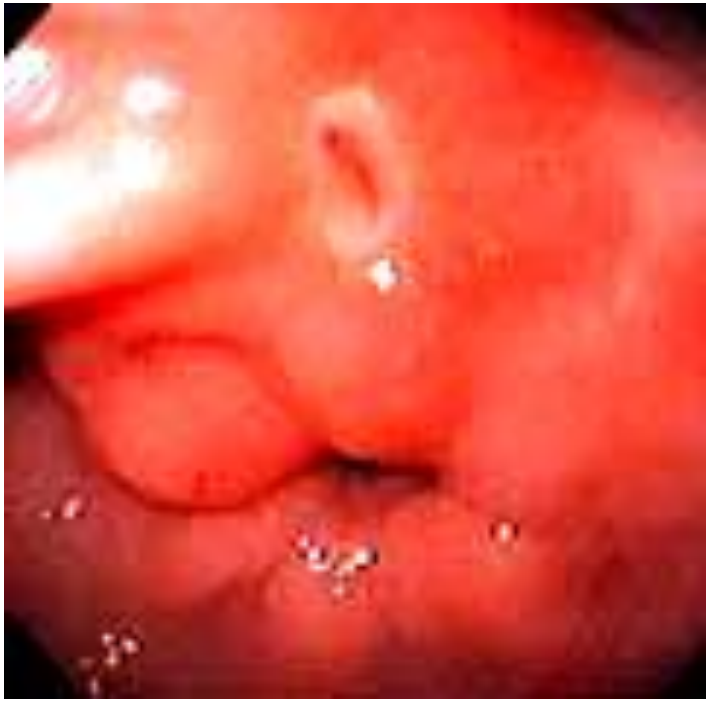


THERAPY OF GASTRIC ULCER

EPIDEMIOLOGY OF GASTROINTESINAL BLEEDING

- Bleeding from upper gastrointestinal tract is life-threating; the mortality is **5–20%.**

- The frequency of acute gastrointestinal bleeding in Western Europe and USA is **60-100/100 000 person/year** (In Hungary: 140/100 000 person/year).

- A stress ulcer can develope in patients in intensive care units. Mortality due to gastric bleeding associated with stress ulcer can reach, even exceed **50%.**

Stress ulcer in humans

ULCER - TYPE I.

In case of distal, antral and duodenal ulcers hypersecretion is observed

DOMINANCY OF AGRESSIVE FACTORS

ULCER - TYPE II.

In case of upper gastric ulcers the acid secretion is normal or decreased

(tends to malignant transformation!)

DECREASED DEFENSIVE MECHANISMS

WHY STOMACH DOES NOT DIGET ITSELF?

Davenport, 1957

INTEGRITY OF GASTRIC MUCOSA DEPENDS

Not on the luminal H^+ ion concentration, but on the amount of back-diffused H^+ ions.

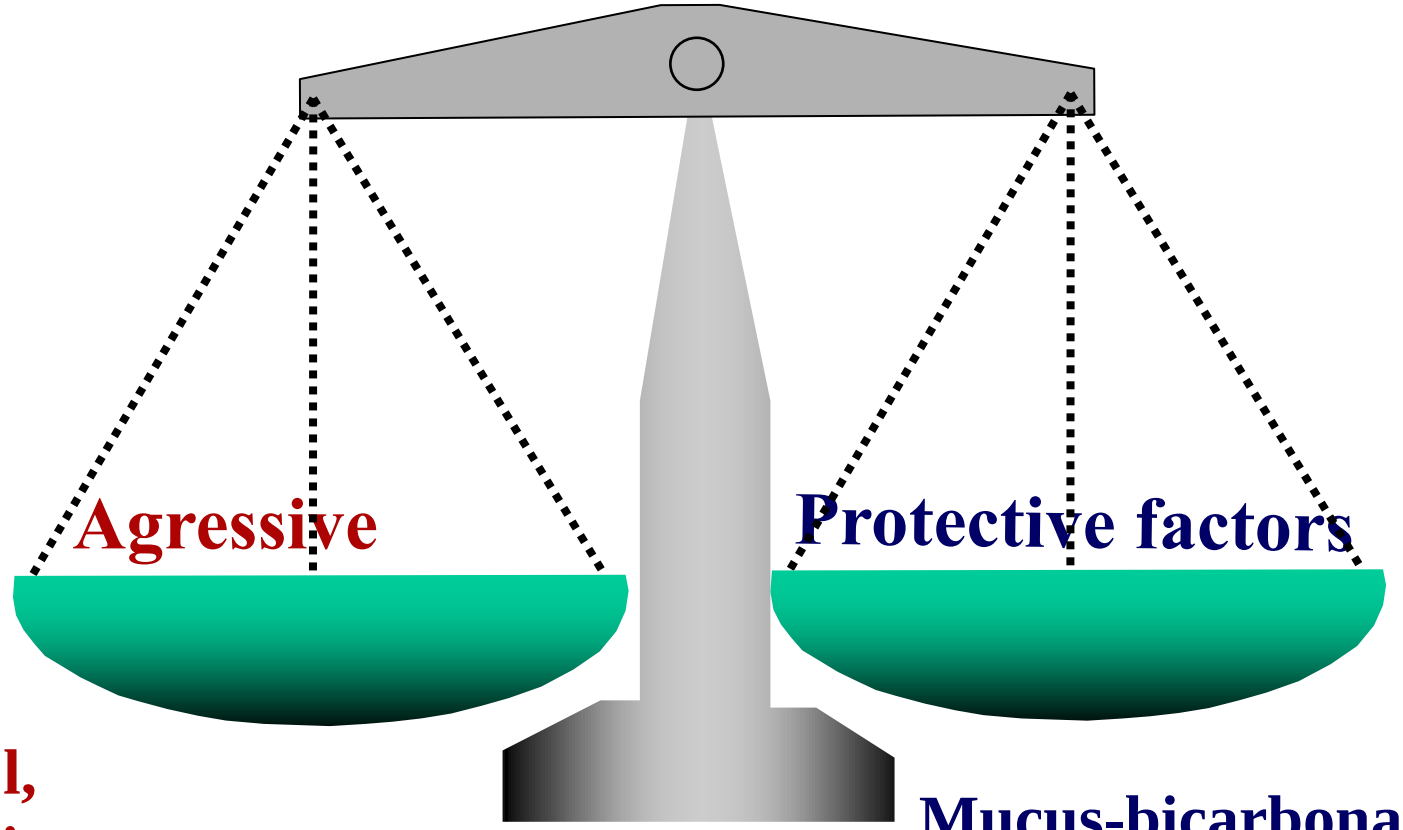
This is determined by

MUCOSAL BARRIER

MUCOSAL RESISTENCE

MUCOSAL MICROCIRCULATION

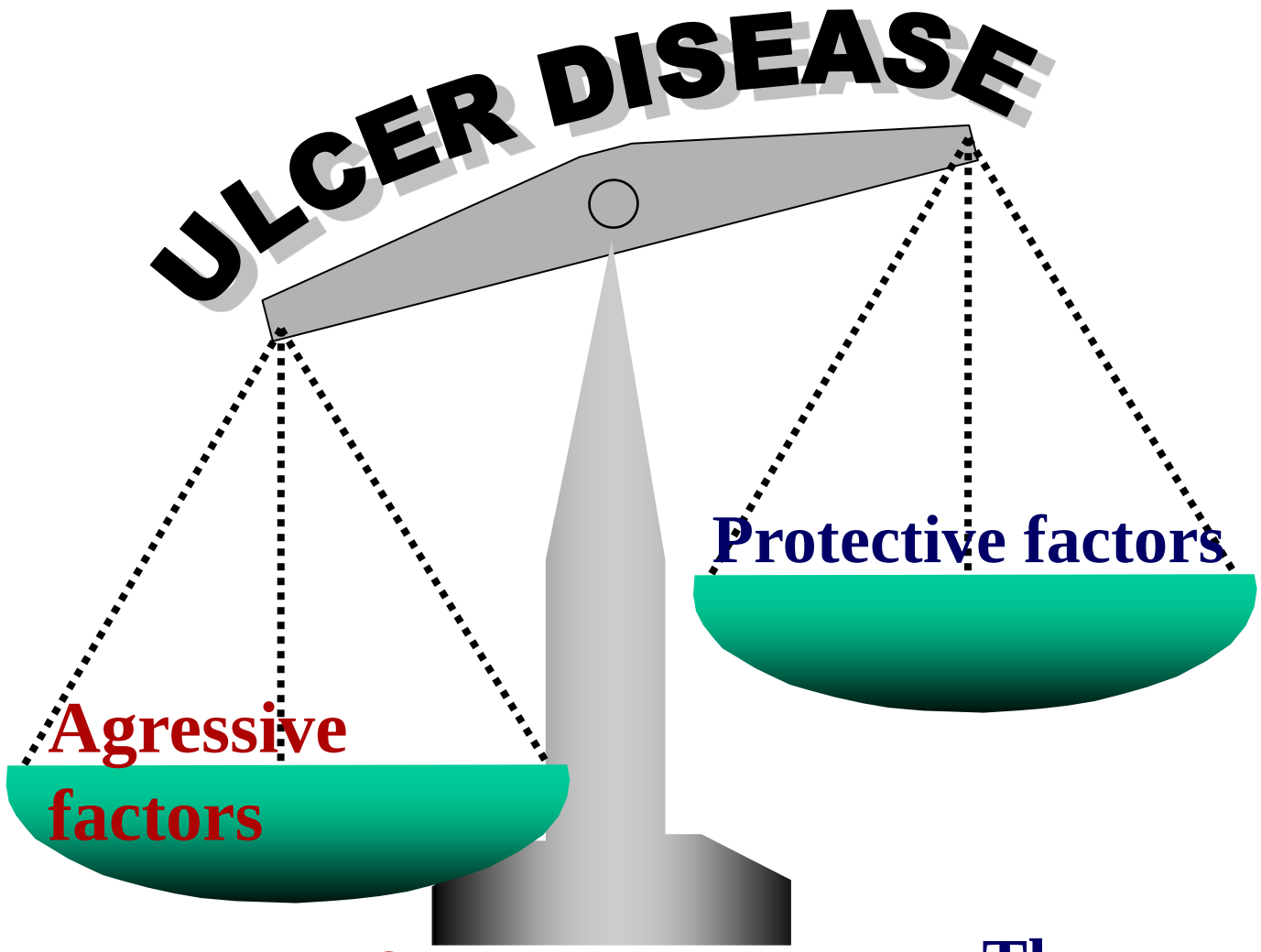
INTEGRITY OF GASTRIC MUCOSA



HCl,
Pepsin,
H. pylori

Mucus-bicarbonate layer

PG, NO
CGRP?

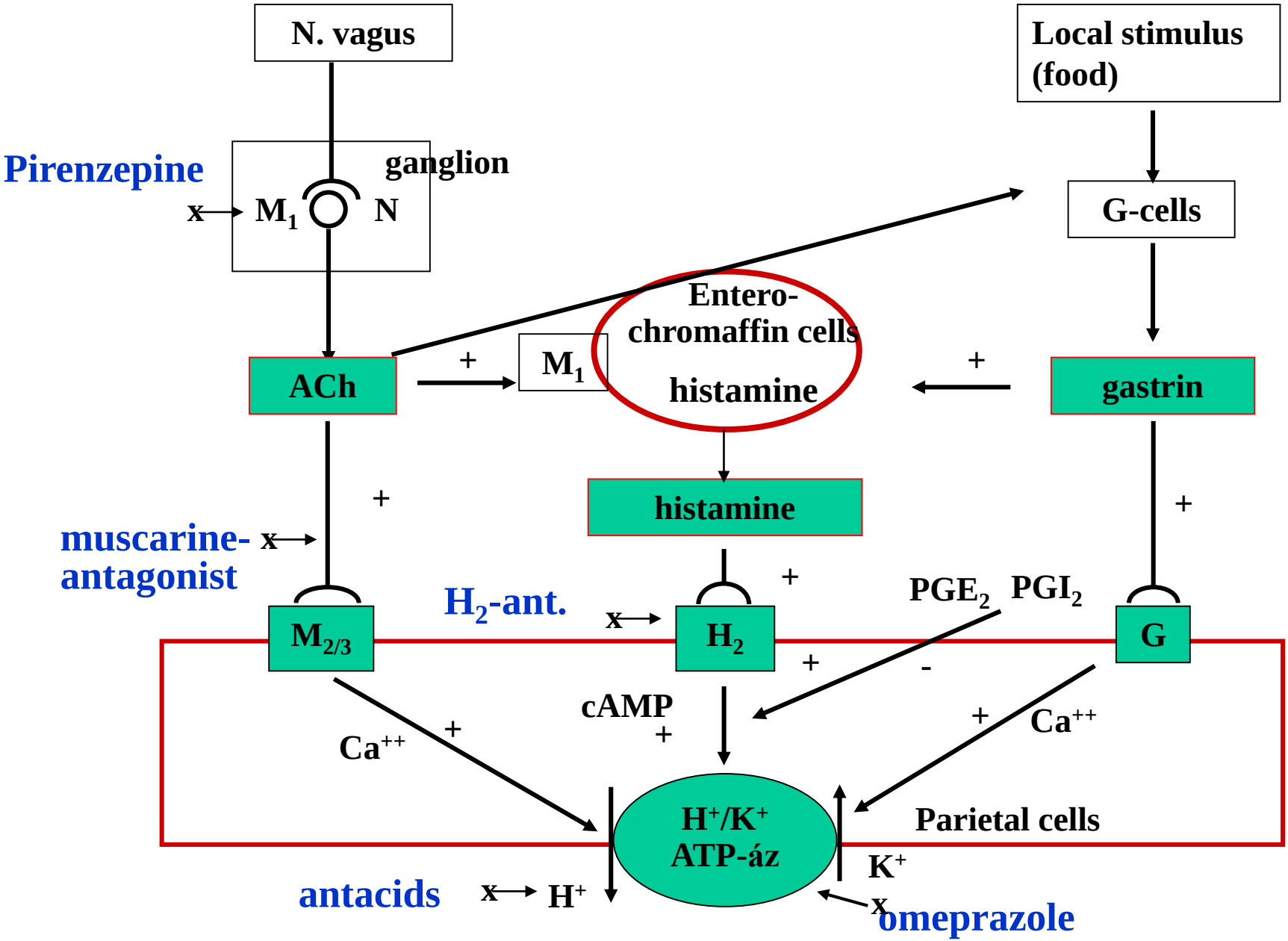


Therapy: inhibition of acid secretion, antibacterial agents

Therapy: sucralphate ??

I. AGRESSIVE FACTORS

GASTRIC ACID SECRETION



ULCER THERAPY

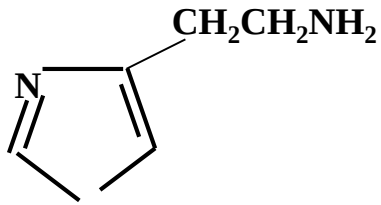
- **INHIBITION OF AGRESSIVE FACTORS**
- **Anti-secretory agents**
- **H2 blocking drugs**
- **Proton pump inhibitors**
- **Anticholinergic drugs**
- **Antacids**

- **INCREASE OF MUCOSAL RESISTENCE**
  - **Sucralfat**
  - **Prostaglandins**
  - **Bismuth salts**

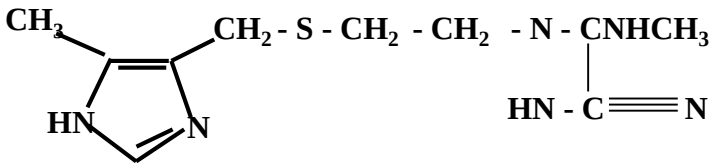
- **ERADICATION OF HELICOBAECTER PYLORI**

I. ANTI-SECRETORY AGENTS

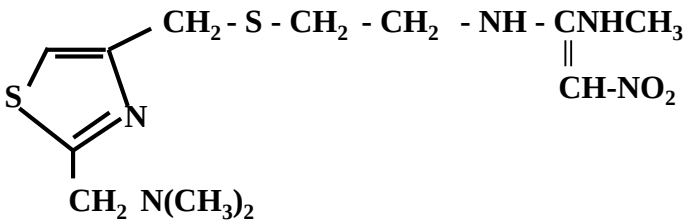
1. HISTAMINE H_2 RECEPTOR ANTAGONISTS



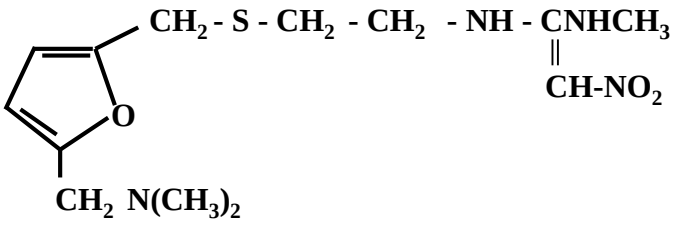
Histamine



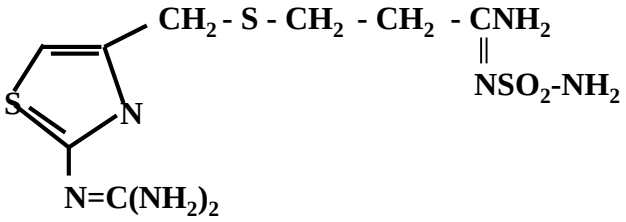
Cimetidine



Nizatidine



Ranitidine



Famotidine

EFFECTS

1. INHIBITION OF GASTRIC SECRETION

Inhibits stimulated (muscarin agonist, gastrin) gastric acid secretion (both at ECL-cells and at parietal cells)
histamine final common mediator?

pepsin, intrinsic factor secr.

2. OTHER:

enhanced immune response (?)

antagonism of certain effects of histamine on heart and vessels

ABSORBTION

good absorbtion from the stomach (but: food, antacids)

INDICATION

PEPTIC ULCERATION

1000 mg cimetidine/day: 50% reduction of secretion
300 mg ranitidine/day: 70% -”- “-”

Peptic ul DUODENAL ULCER
85-90% are healed after 8 weeks treatment

GASTRIC ULCER

50-70% are healed after 8 weeks
- Zollinger-Ellison syndrome high doses are needed
- Other condition: reflux oesophagitis
stress ulcers
preanesthetic use in emergency

Indications

- GERD: twice/day less than 3 heartburn/ week

  (erosive oesophagitis: PPI!!)

- Peptic ulcer disease: largely replaced by PPI

  suppression of nocturnal acid secretion stimulates healing of ulcer: bedtime administration results in 80-90% healing in 6-8 weeks

- NSAID: with atcive ulcer: PPI
- H.Pylori associated acute ulcer: PPI
- Stress ulcer: without nasoenteric tube, ileaus: preferred over PPI
- Perianaesthetic medication in emergency

SIDE EFFECTS

1. headache, dizzeness

2. nausea, diarrhea, constipation, myalgia

3. skin rashes, pruritus

4. only cimetidine:loss of libido, gynecomastia, impotentia (binds to androgen receptors)

5. only cimetidine: binds to cytochrome P-450; inhibit the activity of hepatic microsomal

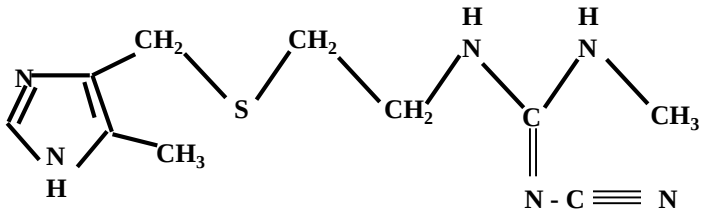
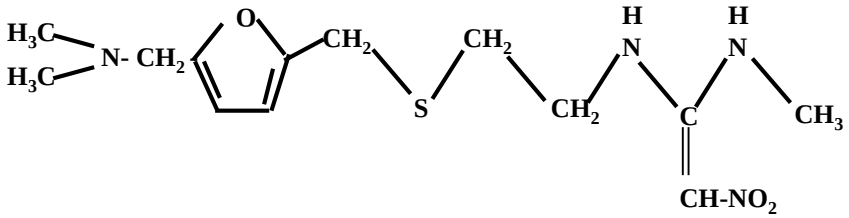
6. CNS disturbance (in elderly people)

7. Rare effects: thrombo-leukocytopenia
hepato-renal toxicity
i.v. inj.: bradycardia

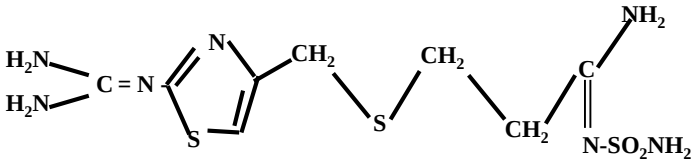
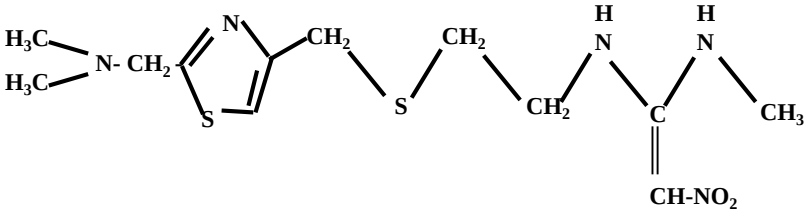
8. Hypochlorohydria
a) favours the survival of bacteria; candidal peritonitis
b) growth of bacteria that form from ingested nitrates
carcinogen nitrosamines (??)

9. Diagnosis of gastric cancer can be retarded in the presence of H_2 blockers

H_2 RECEPTOR BLOCKING DRUGS

Drugs	Bioavailability (Oral)	Vd	$t_{1/2\beta}$	Elimination
Cimetidine 	30-80 %	0.8-1.2 L/kg	1.5-2.3 hr, increased in severe renal failure	Mostly renal Major metabolite, S-oxide.
Ranitidine  desmethyl	30-88 %	1.2-1.9 L/kg	1.6-2.4 hr, increased in severe renal failure	Mostly renal. Small amounts of S-oxide, N-oxide, and N- metabolites.

H_2 RECEPTOR BLOCKING DRUGS (cont.)

Drugs	Bioavailability (Oral)	Vd	$t_{1/2\beta}$	Elimination
Famotidine 	37-45 %	1.1-1.4 L/kg	2.5- 4 hr,in-creased in severe renal failure	Mostly renal. Major metabolite, S-oxide.
Nizatidine  desmethyl	75-100 %	1..2-1.6 L/kg	1.1-1.6 hr, increased in severe renal fail-ure	Mostly renal. Small amounts of S-oxide, N-oxide N-metabolites.

Comparison of histamine H_2 receptor blocking drugs

Characteristics	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailibility(%)	80	50	40	>90
Relatíve potency	1	5-10	32	5-10
Duration (h)	6	8	12	8
Relatíve potency on cytochrom P-450	1	0,1	0	0
Daily dose in peptic ulcer	800 mg or 2x400 mg	300 mg or 2x150 mg	40 mg or 2x 20 mg	300 mg evening or 2x150 mg
Daily dose in gastroesophageal reflux	2x800 mg	2x150 mg	2x20 mg	2x150 mg

DOSES:

cimetidine:	800 mg at bedtime 4 x 200 mg 2 x 400 mg
ranitidine:	300 mg at bedtime 2 x 150 mg
famotidine:	40 mg at bedtime 2 x 20 mg
nizatidine:	300 mg at bedtime 2 x 150 mg

2. PROTON-PUMP INHIBITORS

OMEPRAZOLE (pro-drug)

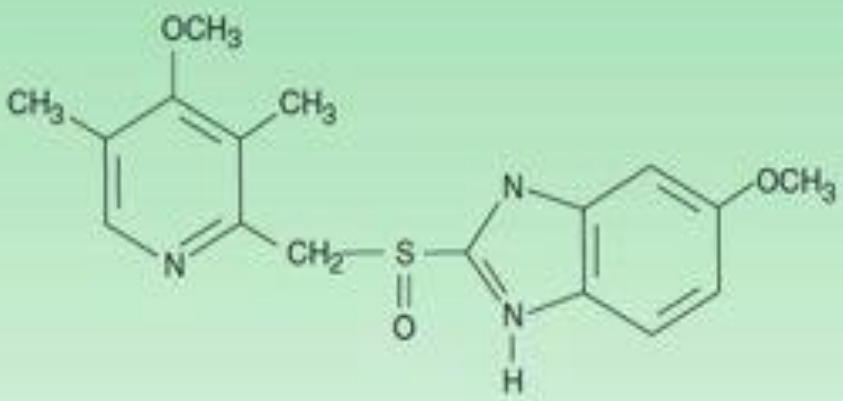
PANTOPRAZOLE

LANSOPRAZOLE

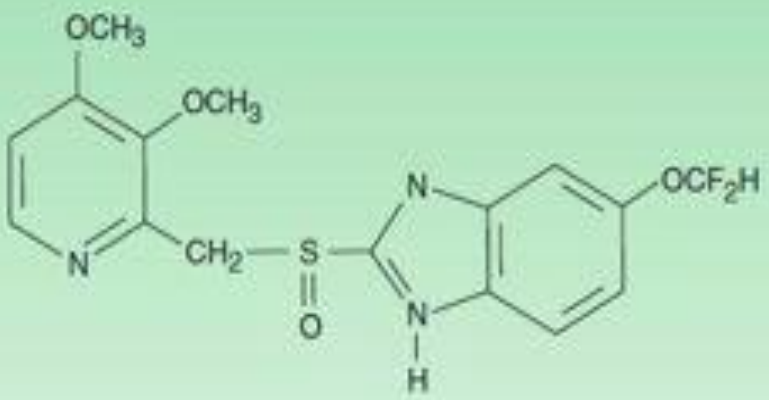
DEXLANSOPRAZOLE

ESOMEPRAZOLE

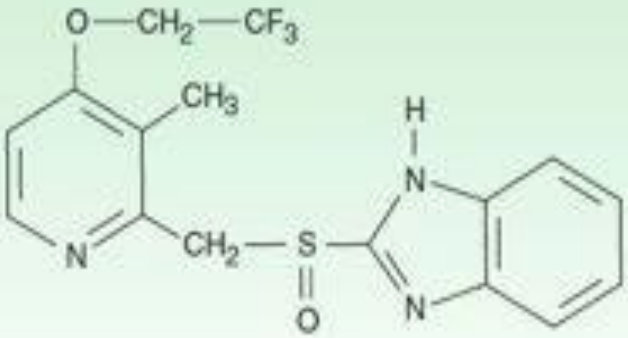
RABEPRAZOLE



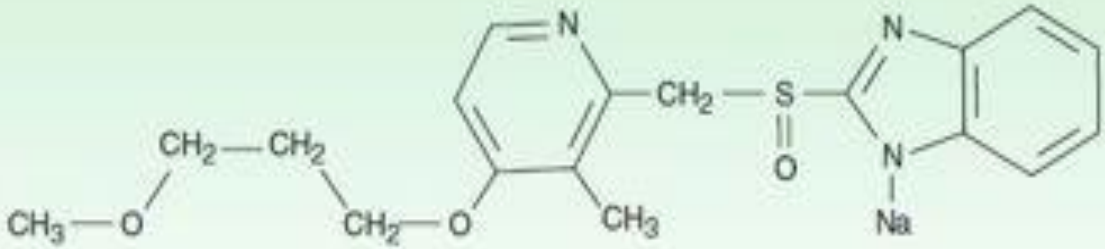
Omeprazole



Pantoprazole



Lansoprazole



Rabeprazole

MECHANISM:

H^+-K^+-ATP-ase: final step in gastric acid secretion inhibited by substituted benzimdazole: Omeprazole and derivatives

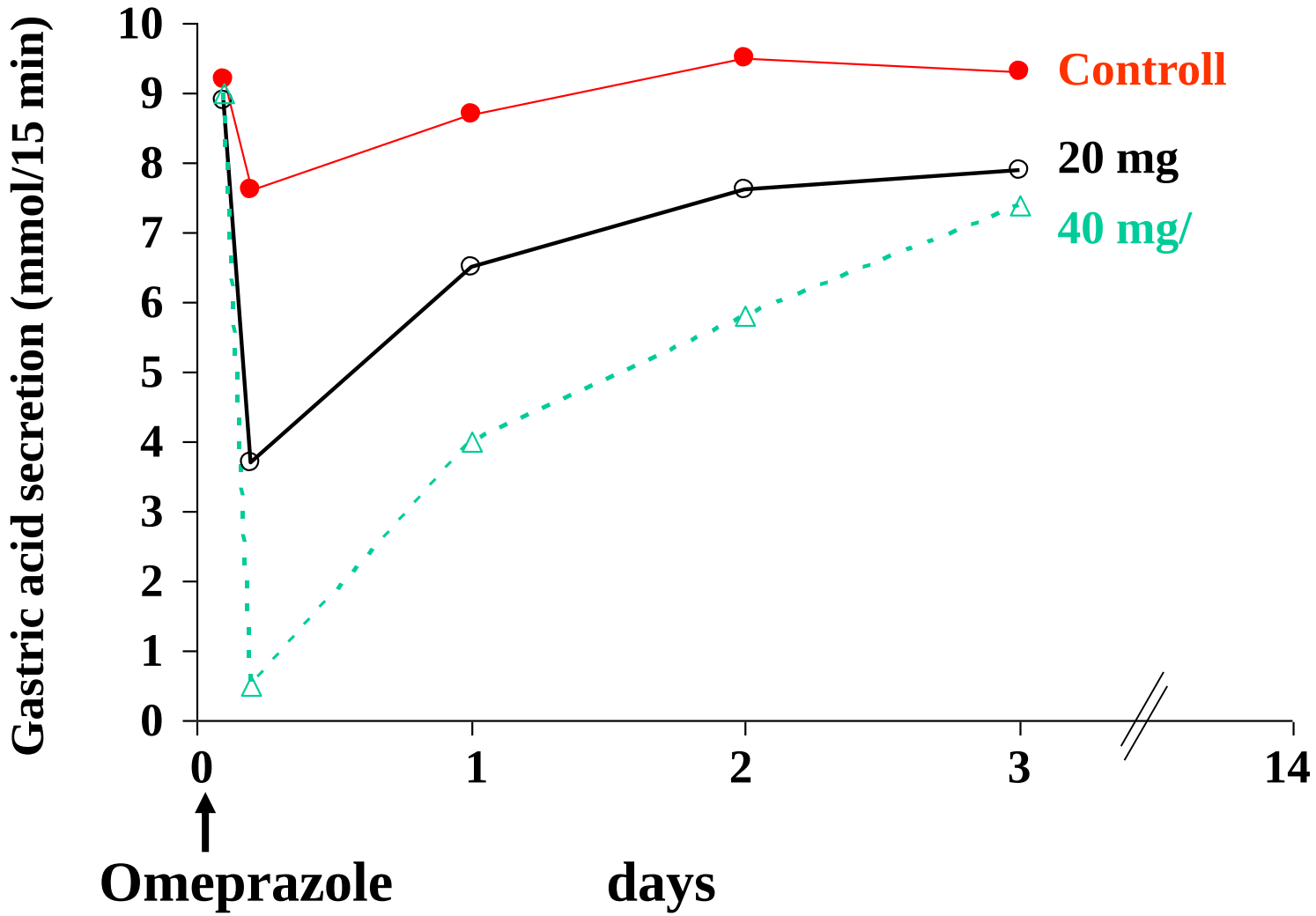
Lipophillic, weak bases, pro-drugs, formulated as delayed release, acid resisistant enteric coated capsules – aganst acid.

Omeprazole: also as powder (with bicarbonate) , immediate release

After absorbtion in parietal cell in canaliculi are formed the active form, reactive thiphillic, sulfenamid cation, forms a disulfide covalent bound with H^+/K^+ ATP-ase

EFFECTS

- Inhibits both basal and meal-stimulated acid secretion
- Inhivits acid secetion by 90-98+ for 24h


Gastric acid secretion (mmol/15 min)
10
9
8
7
6
5
4
3
2
1
0
0
1
2
3
14
Controll
20 mg
40 mg/
Omeprazole
days

Indications

- GERD:

  Non-erosive reflux: H2 blocking intermittant course of PPI

  Erosive oesophagitis: PPI, once daily (healing: 80%),
  twice daily (healing: 15%)
  Extra-oeophageal reflux: twice daily

- Peptic ulcer disease

  80-90% healing after 6-8 weeks gastric, after 4 week
  treatment duodenal ulcer

- NSAID:

  to stop with NSAID, NSAID with active ulcer PPI once or twice

  Prevention of ulcer formation, or complications: once daily

  (10-20 % asymptomatic ulcer, 1-2 % bleeding perforation)

INDICATIONS

- Stress ulcer: PP by nasogastric tube, i.v. : omeprazol – immediately release twice than once/day)

COMPARISON OF PROTON PUMP INHIBITORS

	Bioavailability (%)	Half life (h)	Daily dose
Omeprazole	40-65	0.5-1	20 mg
Esomeprazole	50-89	1.2	20-40 mg
Lansoprazole	80-90	1.5	30 mg
Pantoprazole	77	1.9	40 mg
Rabeprazole	52	0.7-2.0	20 mg

SIDE EFFECTS

- **Hypergastrinaemia**
  (hyperplasia of ECL-cells, carcinoid tumor in rats)
- **Potential risk:** bacterial overgrowth
  Rarely: gastrointestinal disturbance
- **CNS:** headache, dizziness skin rash, leukopenia, acute interstitial nephrits

SIDE EFFECTS

- **Community aquired and nosocomial *pneumonia***
- **Diarrhoe induced by** clostridium difficile and aditional bacteria (Salmonella, Shigella, E coli, Campylobacter)
- **Nutrition problem** with impaired absorbtion of vitamin B12 iron, calcium
- **Long term use: osteoporosis,** increased risk of hip, spin, wrist fracture

INTERACTION

Omeprazol inhibits the *clopidogrel-induced antiaggregation*

Mechanism: the active metabolite of clopidogrel and omeprazol is produced by the enzimm CYP (CYP2C19).

.

3. M_1 MUSCARIN RECEPTOR ANTAGONIST

Pirenzepine **Telenzepine**

gastric secretion is blocked in lower doses than other cholinergic functions

Absorbtion: **poorly absorbed**
Indication: **duodenal ulcer 2x 50 mg/day**
gastric ulcer 3x 50 mg/day
Side effects:
blurred vision less frequently dry mouth
constipation-diarrhoea frequently
headache frequently
CNS frequently

ANTACIDS

1. Sodium compounds

Sodium bicarbonate, sodium citrate

$NaHCO_3 + HCl = NaCl + H_2O + CO_2$

Systemic alkalosis!!!

Fluid retention (Na)

2. Magnesium hydroxyde

$Mg(OH)_2 - 2HCl = MgCl_2 + 2H_2O$

poor solubility, prolonged neutralizing effect

cathartic effect

3. Aluminium compounds

Aluminium hydroxyde, Basic Al carbonate gel,
Al phosphate gel

$Al(OH)_3 + 3HCl = ALCl_3 + H_2O + CO_2$

$AlCl_3$: insoluble, slow action
constipation
binds e.g. to tetracyclins, phosphate
if absorbed: encephalopathy, Alzheimer?

4. Calcium carbonate

$CaCO_3 + 2HCl = CaCl_2 + H_2O + CO_2$

10% CaCl2 is absorbed: hypercalcaemia
milk-alkali syndrome

only for short treatment

5. Combination: Magaldrate: $Mg(OH)_2 + Al(OH)_3$

II. ENHANCEMENT OF GASTRIC MUCOSAL DEFENSE

1. Bismuth chelate (De-Nol)

Mechanism: **a. chelating with protein forms coating**
b. antipeptic activity

Indication: **gastric, duodenal ulcer**
(= with H_2 blocking drugs, <u>less relapse</u>)

Dose: **4x120 mg (30’ min before meals 2^h after last meal)**

Adverse effect: **- darkening of oral cavity**
- encephalopathy, osteodistrophy: only: if renal damage!!

2. Sucralfate

basic aluminium salt of sucrose octasulphate

Mechanism: **a. the (-) sucrose octasulphate bind to (+)protein molecules: gel**
b. decrease the back-diffusion of H^+
c. stimulation of PG synthesis

Indication: **gastric ulcer duodenal**

Dose**: 4x1 g 1 h before meal**
Adverse effect**: obstipation**

Interaction: **antacids, H_2 antagonist should not be taken simultaneously (sucralfate is effective only in acidic einviroment)**

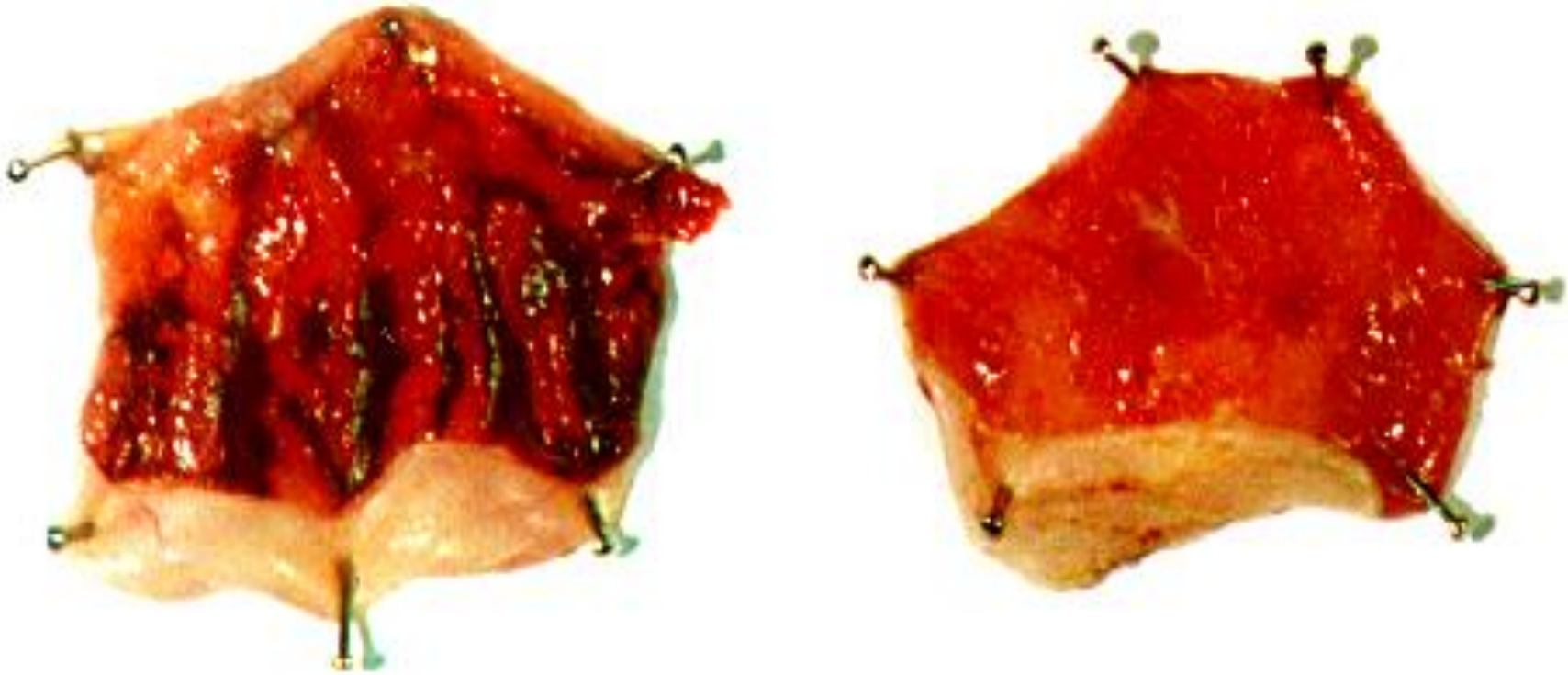
3. Prostaglandins

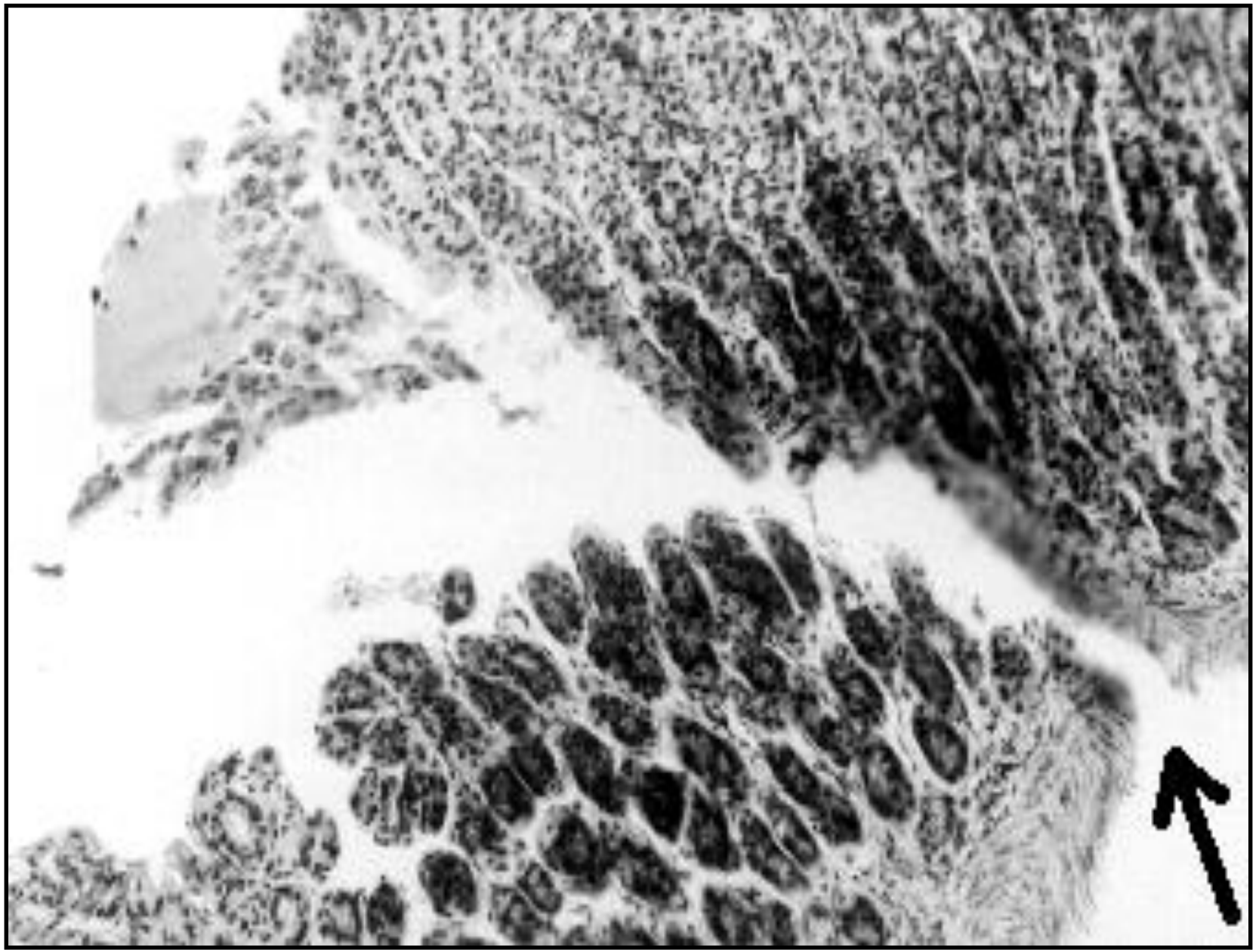
misoprostol (2-3x0.1 mg)

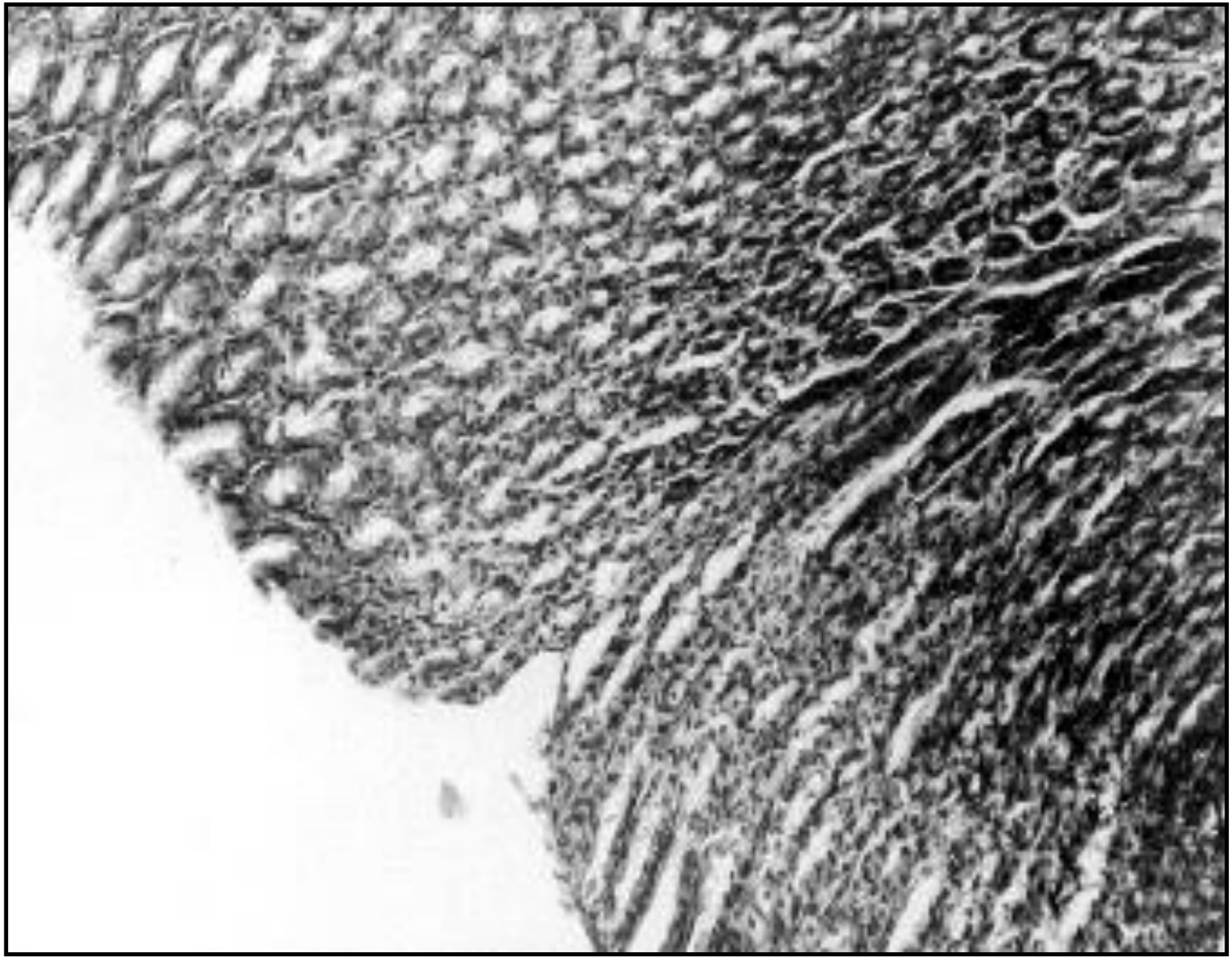
Mechanism: **a. stimulation of mucus secretion**
b. enhanced mucosal blood flow
b. prevents H^+ back-diffusion
c. enhanced cell replication
d. inhibition of acid secretion!
(inhibition of cAMP)

Indication: **NSAID-induced GI mucosal damage**

Adverse effect: **diarrhea**
uterus contraction (pregnancy!)







Profilaxis of NSAID-induced gastric mucosal damage

- Risk factors: GI ulcer!!, age, smoking
  parallel steroid drugs
- Selective COX-2 inhibitors
- Misoprostol
- Proton pump inhibitors: for gastric but
  not intestinal mucosal injury

HELICOBACTER PYLORI

- 1983: Marschall and Warren isolated from gastric mucosa of chronic gastritis.

- Later from epithelium of gastric ulcer and cancer.

A HELICOBACTER PYLORI

Urease production

↓

Urea → **NH_3+CO_2**

↓

NH_4Cl: gastric acid neutralisation

↓

OPTIMAL MICROENVIROMENT FOR BACTERIA

GASTRIC EPITHELIAL DAMAMGE

- **Cytotoxin**
- **Ammonia and derivatives (urease)**
- **Phospholipase A_2 és C activity**
- **Leukotrien release**
- **PAF release**
- **Endotoxin-induced endothel damage**

ERADICATION OF HELICOBACTER PYLORI

1. TRIPLE THERAPY

Metronidazol (2-3 x 400-500 mg)

Bismuth salts (bismuth citrate, 4x 120 mg)

Tetracycline (4x500 mg)/ amoxycillin (3-4x500 mg)

Duration: **14 days**

Side effect**: 80 %**

+ omeprazol

Duration: **7 days**

- **2. MODIFIED TRIPLE THERAPY**

  poton pump inhibitor
  claritromycin (2x500 mg)
  metronidazol (2-3x400-500 mg)
- ***Duration:*** **7 days**
- ***Side effect*** **: 15 %**

- **3. ALTERNATIVE TRIPLE THERAPY**

  poton pump inhibitor
  claritromycin (2x500 mg)
  amoxycillin(2x1000 mg)
- ***Duration*** **: 7 DAYS**
- ***Side effect*****: 30%**

“Rescue” therapy

- PPI 2x
- Amoxicillin 2 x 1,0g
- Levofloxacin 500 mg / 10 nap

OR

- Rifabutin 300 mg

Or

- furazolidon 400 mg/10 nap