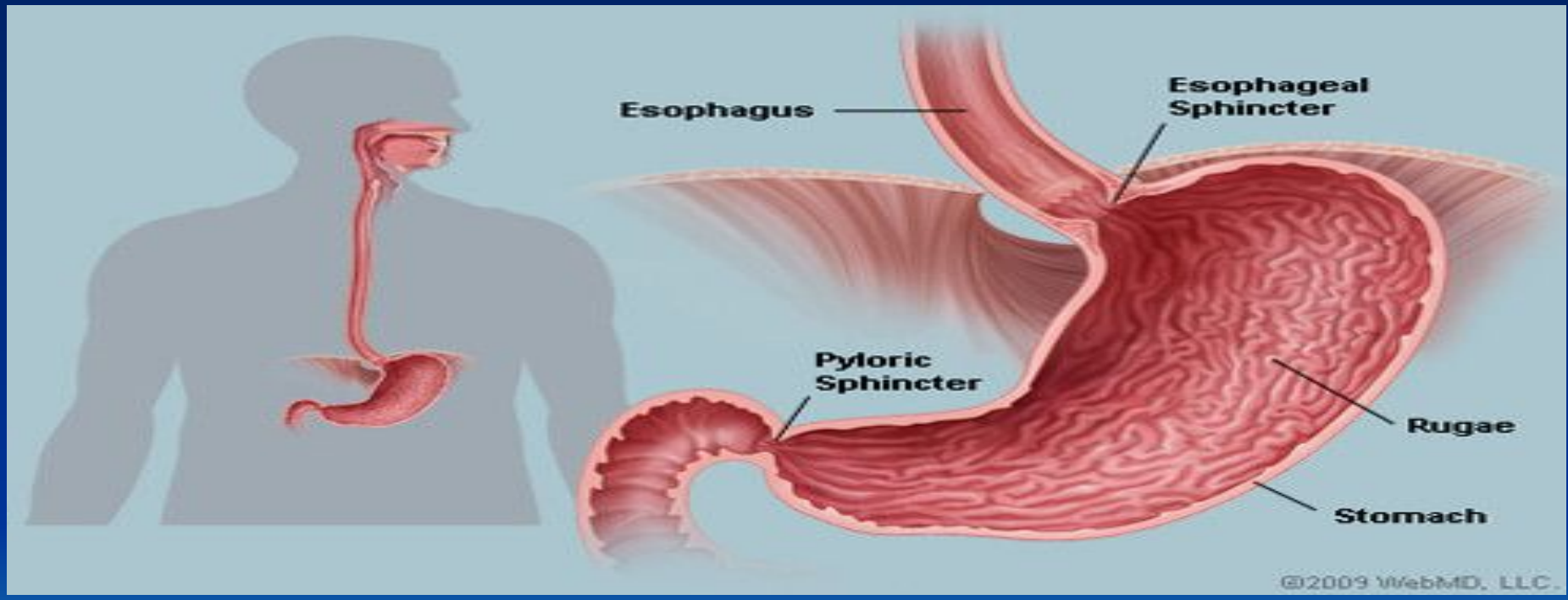
DRUGS USED IN GIT L1



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:This lecture contain 2 parts

1st part for your informations

2nd part is the objectives

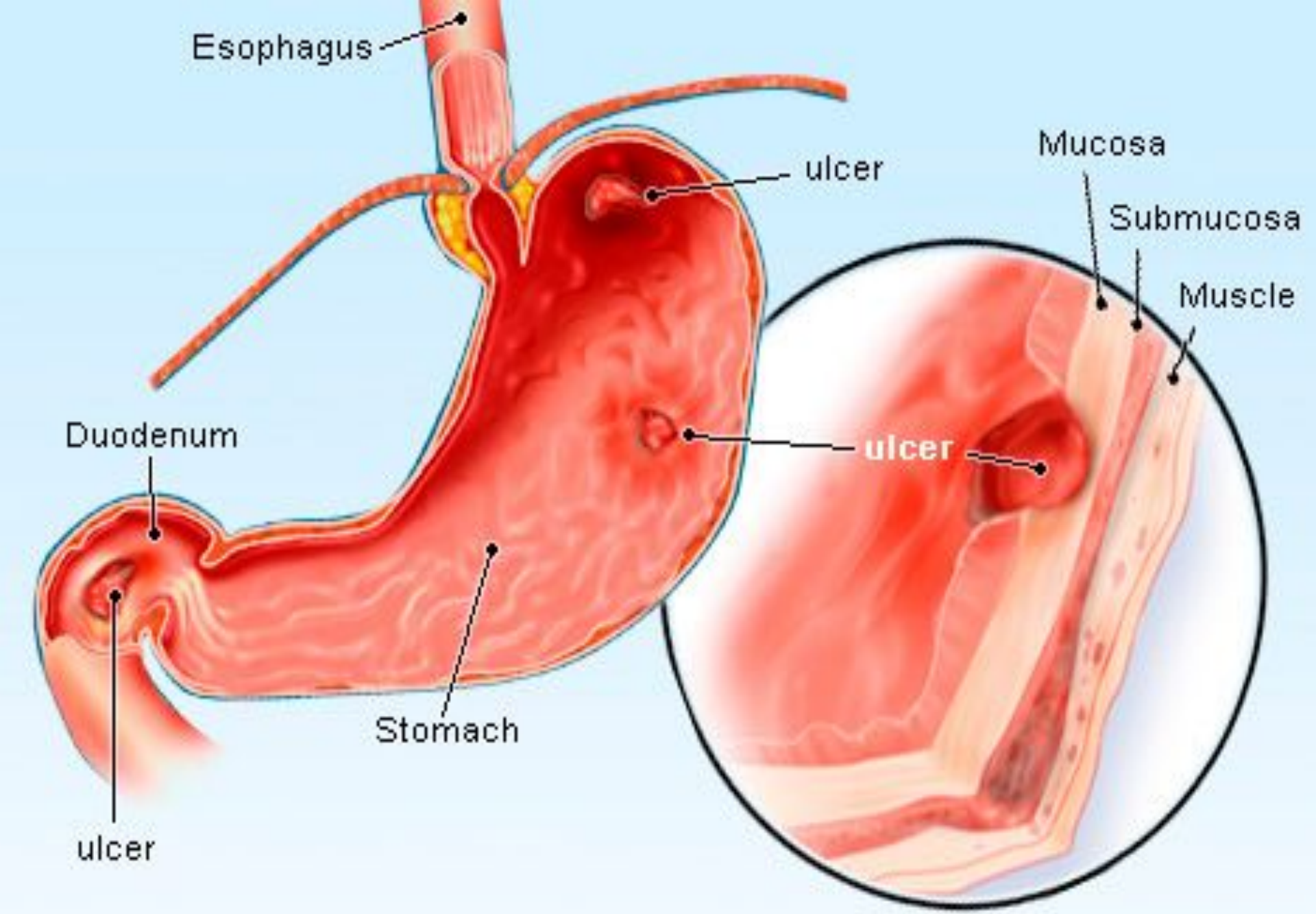
Part 1

Peptic ulcer: is a defect in the gastric or duodenal wall that extends through the muscularis mucosa into the deeper layers of the wall; which is of **2 types**: duedenal .and gastric ulcer

Measures for maintaining the integrity of gastric mucosa:

Acid and pepsin production (**destructive** factors) -1

Mucosal resistance (**protective** factors) -2



Normally (acid and pepsin) and mucosal resistance are present in balance

Acid and pepsin  mucosal resistance

peptic ulcers are **produced** when the **balance** between (**acid and pepsin**) and the mucosal resistance is . **disturbed**

This occurred either by **increase** acid and pepsin or **decrease** mucosal resistance

:Protecting measures of the mucosa

PG (prostaglandin) is responsible for protecting mucosa, thus PG :functions are

.Secretion of **mucus** and **bicarbonate** ion -1

.**Impermeability** to H ion -2

.increase **Blood** flow of mucosa -3

Capacity to **replacement** of the damaged -4 .epithelial cells

:Factors play role in the formation of ulcer

A: **Common** causes

. **Genetic** -1

:Environmental factors include -2

Helicobacter pylori infection in 90% of ptatient(gram-negative) ..1

NSAIDs (decrease PG) ..2

:Smoking: **effects include** ..3

. **Acceleration** of gastric **emptying** (A)

.Promotion of **duodenogastric** reflux (B)

.**Inhibition** of pancreatic **bicarbonate** secretion (C)

.**Reduction** in mucosal **blood** flow (D)

.**Inhibition** of mucosal **PG** production (E)

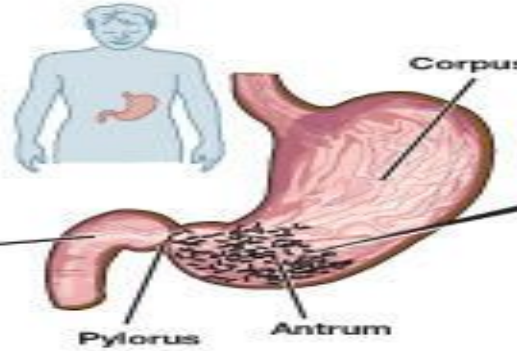
others: food, psychological -3

B: **Uncommon** causes: like tumour, radiation, viral infection and Zollinger Ellison .disease

Helicobacter pylori

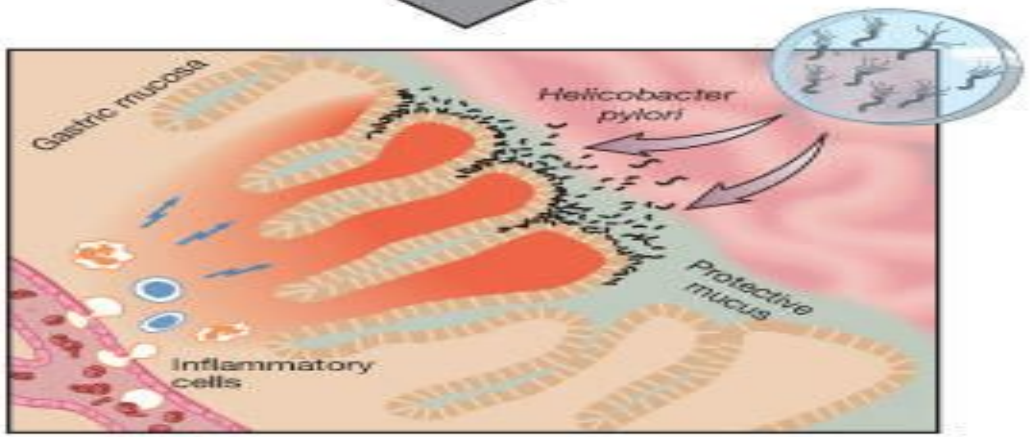
— the bacterium causing peptic ulcer disease

Infection
Helicobacter pylori infects the lower part of the stomach, antrum.

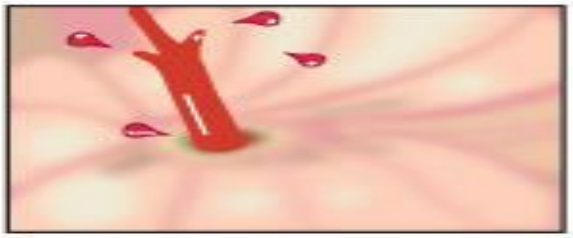


Helicobacter pylori

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.

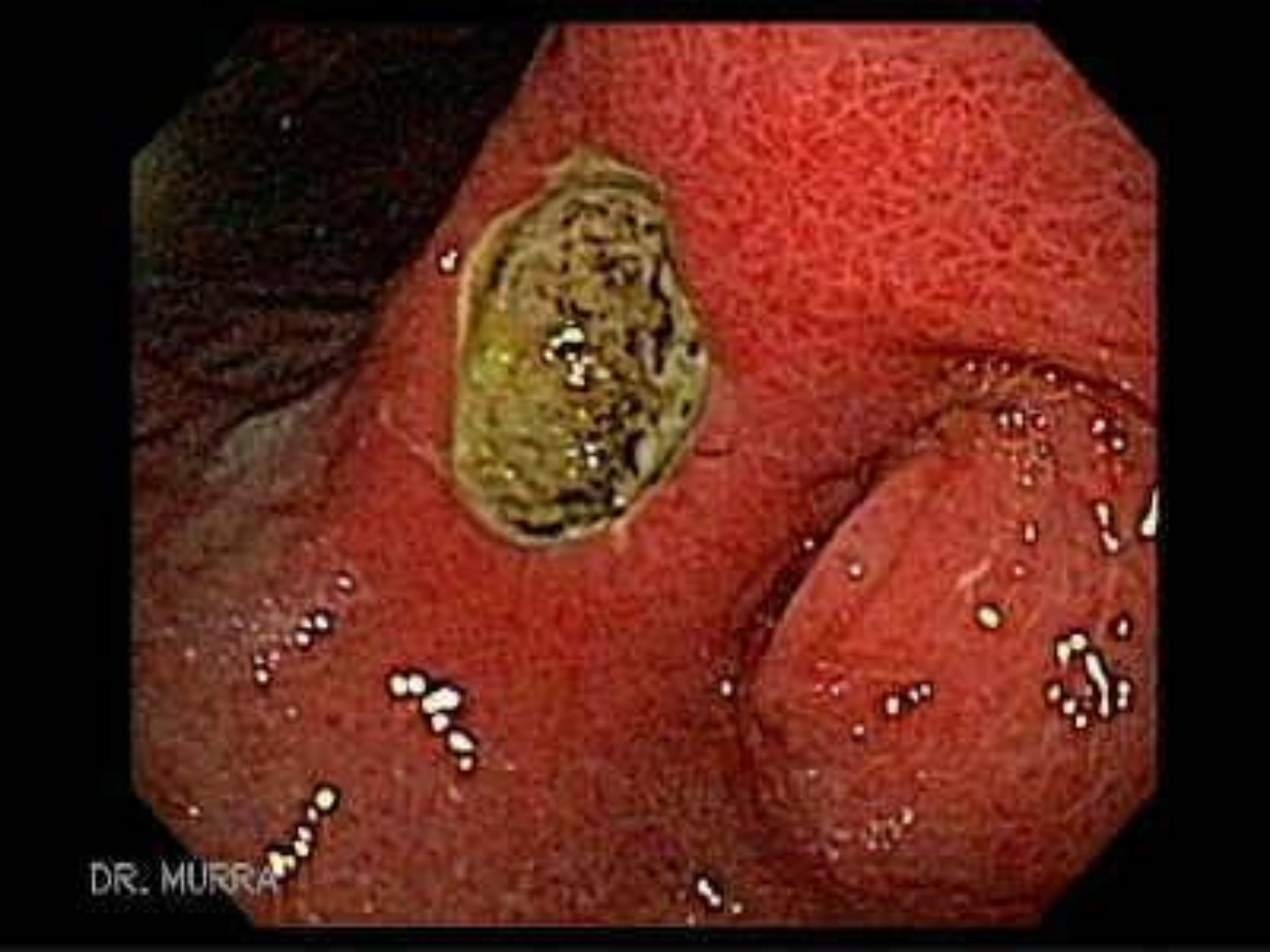


Bleeding ulcer

Table 2. Mechanism for *Helicobacter pylori* Mucosal Injury

Hypergastrinemia
Negative feedback loop for gastrin release is halted; therefore, more acid is secreted
Direct Mucosal Damage
Increased production of cytotoxins increases the production of ammonia, which may be toxic to epithelial cells within the gastric region
Inflammatory Response
Influx of macrophages and neutrophils trying to phagocytose the bacterial products or the bacteria themselves; directly due to cell-mediated response mechanisms

Source: Reference 3.


DR. MURRA

Part 2

Lines of treatment in patient with peptic :ulcer

A- General measures (smoking, spicy food……., should be avoided)

:B- Drug

:Reduction of acid secretion by .1

.A- Histamine H 2 receptor antagonists

.B- Proton pump inhibitors

.C- Antimuscarinic drugs

.Direct neutralization of acid by antacids .2

Protecting the mucosa by increase mucosal resistance .3 :by

.A. Protecting the **base** of peptic ulcer

.B. Increase **PG** (Cytoprotection)

C. **Eradication helicobacter** pylori infection by :antimicrobials

levofloxacin(the drug of choice)

Currently, quadruple therapy of bismuth subsalicylate, metronidazole, and tetracycline plus a PPI is a recommended first-line option

Triple therapy consisting of a **PPI** + **amoxicillin** + **clarithromycin** is a .preferred treatment when rates of **clarithromycin** resistance are low

Classification of drugs used to treat peptic ulcer disease

ANTIMICROBIAL AGENTS

Amoxicillin GENERIC ONLY
Bismuth compounds PEPTO-BISMOL, KAOPECTATE
Clarithromycin BIAXIN
Metronidazole FLAGYL
Tetracycline GENERIC ONLY

H_2 – HISTAMINE RECEPTOR BLOCKERS

Cimetidine TAGAMET
Famotidine PEPCID
Nizatidine AXID
Ranitidine ZANTAC

PROTON PUMP INHIBITORS

Dexlansoprazole DEXILANT
Esomeprazole NEXIUM
Lansoprazole PREVACID
Omeprazole PRILOSEC
Pantoprazole PROTONIX
Rabeprazole ACIPHEX

PROSTAGLANDINS

Misoprostol CYTOTEC

ANTIMUSCARINIC AGENTS

Dicyclomine BENTYL

ANTACIDS

Aluminum hydroxide GENERIC ONLY
Calcium carbonate TUMS
Magnesium hydroxide MILK OF MAGNESIA
Sodium bicarbonate ALKA-SELTZER

MUCOSAL PROTECTIVE AGENTS

Bismuth subsalicylate PEPTO-BISMOL
Sucralfate CARAFATE

Parietal cell: This cell contains receptors for histamine , Ach, PG and gastrin

Histamine
Ach
Gastrin

stimulat acid secretion

Histamine by stimulating H2 → adenylate cyclase → stimulate protein kinase → .proton pump → secretion of acid

Ach and gastrin .secretion → Ca+ and IP3 → increase gastric acid

PGs → inhibit adenylate cyclase → .inhibition of acid secretion

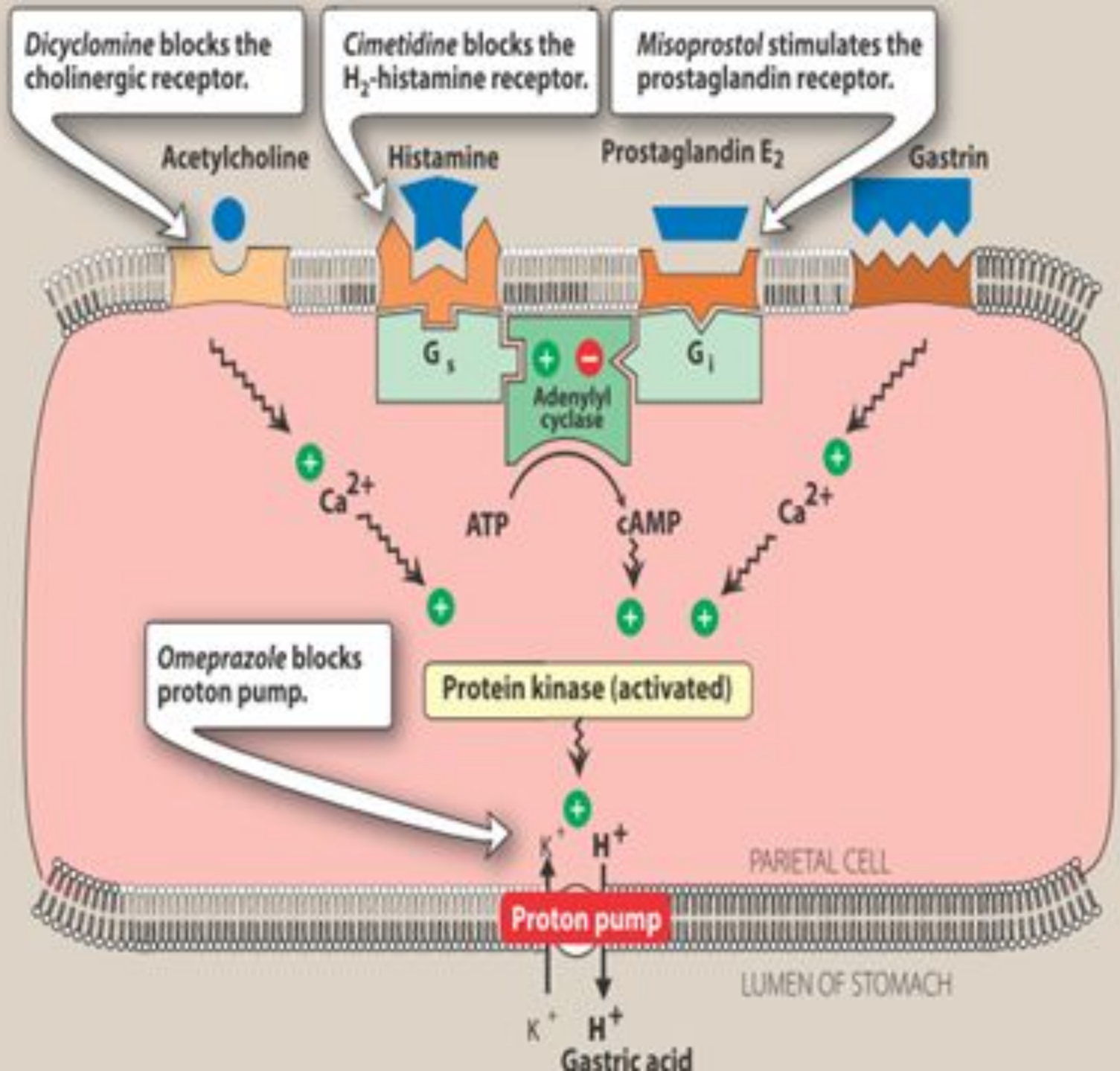
Proton pump is the **final stage** in acid secretion, so .if we block it, all acid secretion will be blocked

If these receptors blocked they will **inhibit** basal, food-stimulated, and nocturnal secretion of gastric acid, reducing acid secretion by approximately .**70%**

Gastrin is a hormone that is produced by **'G' cells** in the lining of** the stomach and upper small intestine, and released into the blood circulation

Note

Gastrin increase in response to reduction of HCl, for this reson gastrinoma due to gastric cell proliferation occur if there is long time reduction of HCl


Dicyclomine blocks the cholinergic receptor.
Cimetidine blocks the H_2-histamine receptor.
Misoprostol stimulates the prostaglandin receptor.
Acetylcholine
Histamine
Prostaglandin E_2
Gastrin
G_s
G_i
Adenylyl cyclase
Ca^{2+}
ATP
cAMP
Ca^{2+}
Omeprazole blocks proton pump.
Protein kinase (activated)
K^+
H^+
PARIETAL CELL
Proton pump
LUMEN OF STOMACH
K^+
H^+
Gastric acid

1- Reduction of Acid secretion:by

A. H2 receptor antagonists:

-Cimetidine.

-Ranitidine.

-Famotidine

-nizatidine

:Mechanism of Action

H2 receptors selective blockers (not act on H1 receptor) act by **competitive blocking of H2 receptors in the gastric mucosa leading to** inhibition of gastric acid .secretion

Pharmacokinetics

orally effective -1

.**Antacids decrease** their **absorption** -2

.**Peak** serum concentration (**1-2** hrs) after **oral** dose -3

:**Distribute widely** throughout the body -4

.All cross **BBB** and **placenta**-

.They are **excreted** in breast **milk**-

Excreted mainly in the **urine**-5

They have **different bioavailability**: all **bioavailabilities** -6 **decreased** by 30 -50% differently, while bioavailability of **nizatidine** is 90-100%

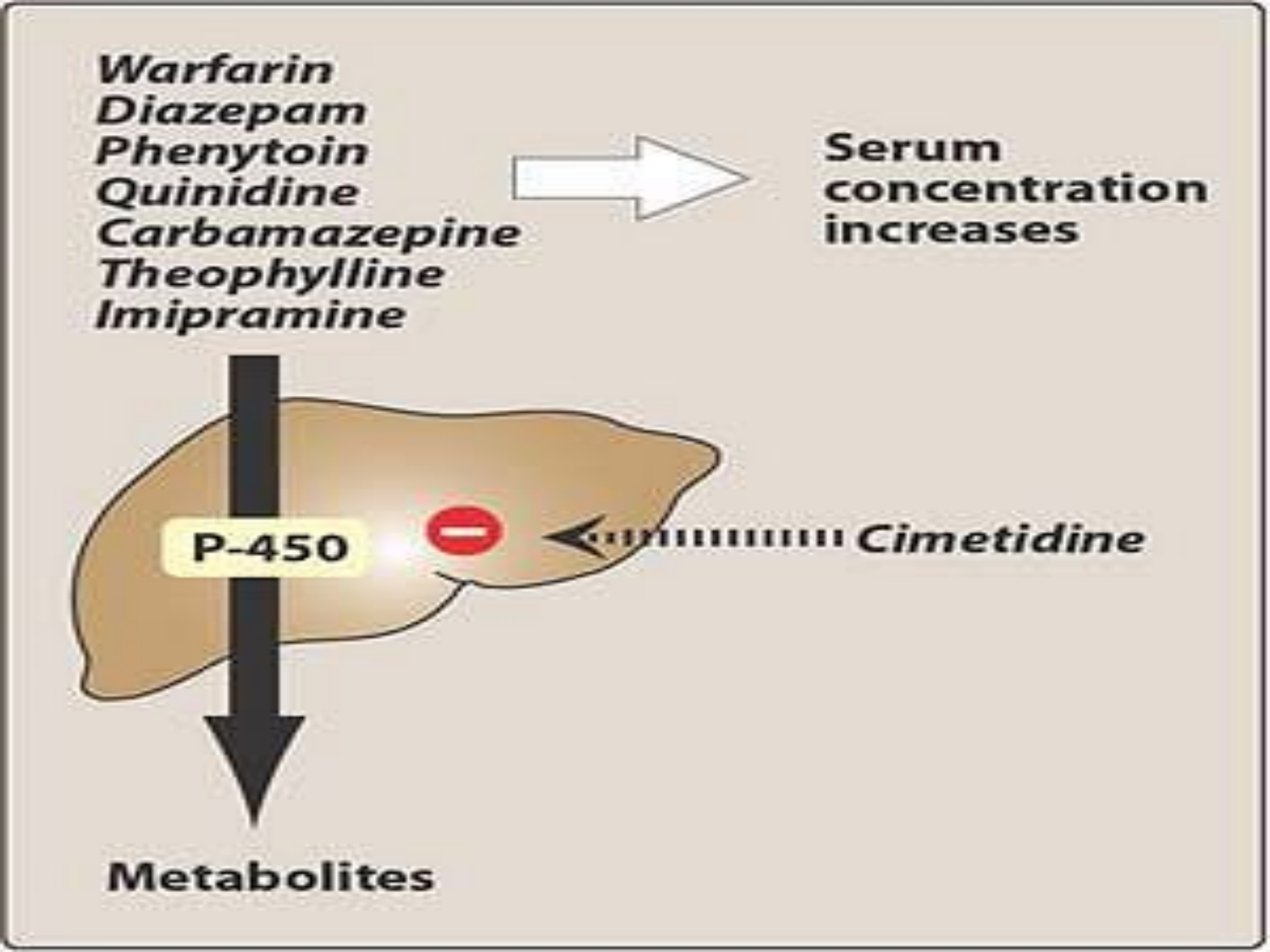
.**Efficacy** is the **same** for all -7

•

Cimetidine, ranitidine, and famotidine are -8
available in **intravenous** formulations

H_2 receptor antagonists may **reduce the efficacy** of drugs -9
that **require an acidic environment** for absorption, such as
ketoconazole

Cimetidine is an **inhibitor** of CYT P450, so it leads to **increase** -10
plasma level of many drugs (like: warfarin, Ca- channel blockers and
diazepam). **Ranitidine** has **less** effect than cimetidine on
CYT P45o


Warfarin
Diazepam
Phenytoin
Quinidine
Carbamazepine
Theophylline
Imipramine
Serum concentration increases
P-450
Cimetidine
Metabolites

:Side Effects

:Minor , include

.A- constipation and muscular pain

B- CNS disturbances in old age like headache and ……,dizziness

C-**Cimetidine** has **1- weak anti-androgenic** effect and it **increase prolactin** secretion leading to **gynecomastia** and **sexual dysfunction** in males (other **H2** antagonists have no .anti-androgenic effects)

Bradycardia (after I.V. injection) -2

.**Inhibits** CYT P450 -3

D- **Allergic** reaction like **Pruritis** by **Nizatidine**

Uses of H2-receptor antagonists

GERD

.Peptic ulcer disease

.Gastric stress ulcer

.NSAID ulcers if the NSAID is discontinued

But use of **PPI** decrease using of these agents

:B.Muscarinic antagonist

selective antagonists acting on (M1 receptors) like .**pirenzepine**, **telenzepine** , **Dicyclomin** are useful

These selective drugs act **mainly on** **M1** receptors ('less .effect on M2 and M3 receptors)

M1 receptors are found in the intramural neurons and in the enterochromaffin like cells which are responsible for .secretion of histamine

:Side Effects

Same of atropine

:Kinetics

Dose is 100-150 mg/d for pirenzepine -1

t1/2 =11 hrs -2

.**Poorly absorbed** from the stomach -3

.It is **excreted unchanged** in **urine** and **bile** -4

.**Selectivity** is **lost** with increasing the dose -5

:C. Proton pump inhibitors (PPI)

: Are

,Omeprazole (the **prototype)**

,lansoprazole

dexlansoprazole

,pantoprazole

rabeprazole and

esomprazole

Chemical features: They are

They are substituted **benzimidazole** containing -
.sulfahydryl group

.**weak bases** -

,At **neutral PH**, **they** are **stable** and **lipid** soluble-

.so they have no **inhibitory** activity

:MOA

They **irreversibly** inhibit **H -K ATPase**

inhibit the exchange of H and K
(at the **final** step of acid secretion)

: Note

H -K ATPase found on **apical** membrane of parietal cells in the stomach and this enzyme primarily responsible for the **acidification** of the stomach contents and the **activation** of the digestive .enzyme pepsin

:Mechanism of inhibition

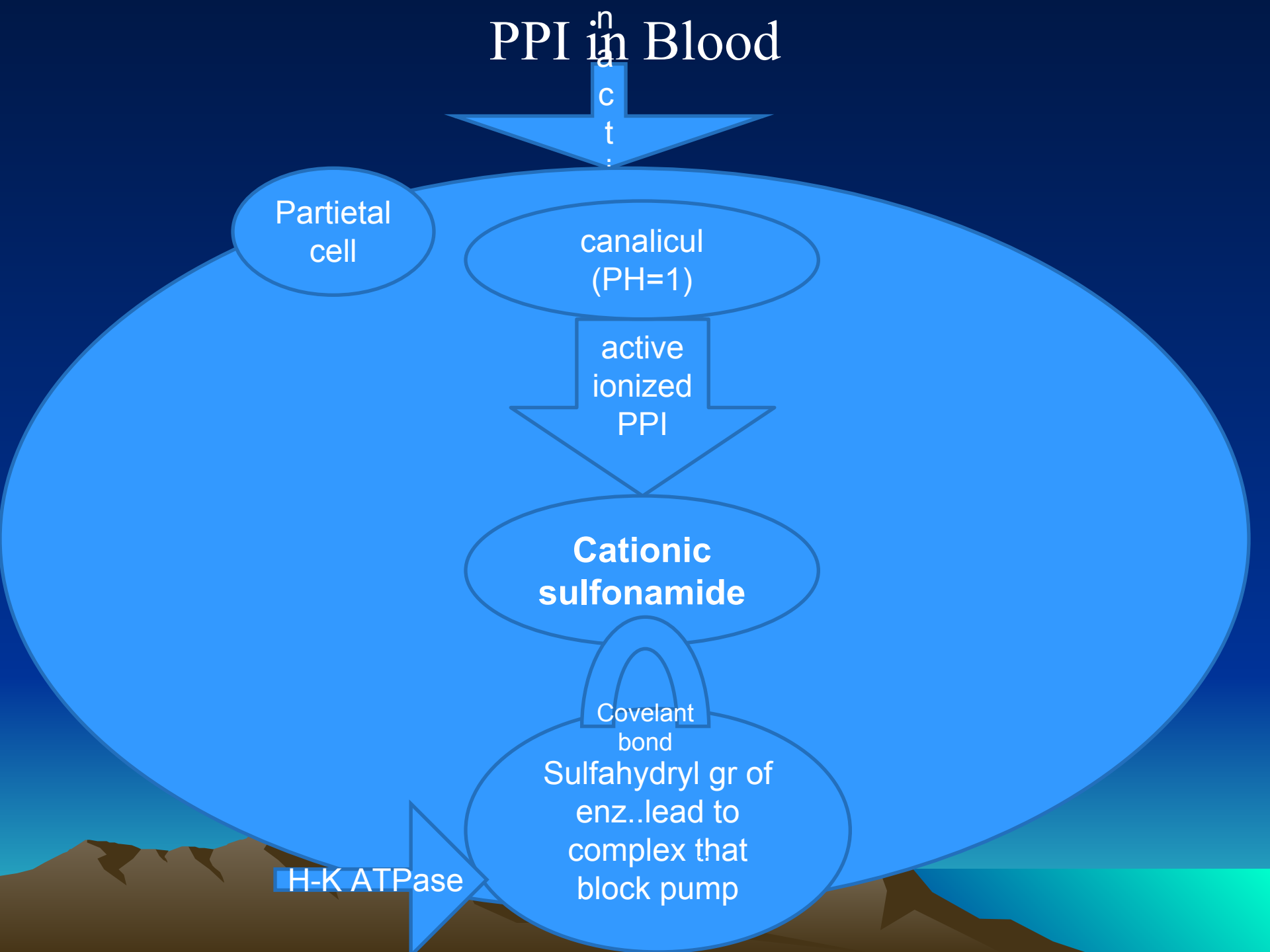
PPI agents are **prodrugs** with an acid-resistant **enteric coating** to protect them from **premature** .**degradation** by gastric acid

The **coating** is **removed** in the **alkaline** duodenum, and the prodrug, a weak base, is absorbed and .transported to the parietal cell canaliculus

when they are in the **canaliculi** of parietal cells they .become **active (**where **PH** is **about 1)**

In the canaliculi they are **ionized** to form a **cationic sulfonamide** which forms **covalent bonds** with the **sulfahydryle** group at the critical site of the H-K ATPase **.**enzyme, they form a **complex block the pump**

PPI in Blood


Partietal cell
canalicul (PH=1)
active ionized PPI
Cationic sulfonamide
Covelant bond
Sulfahydryl gr of enz..lead to complex that block pump
H-K ATPase

Thank you