PEPTIC ULCER

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PART – 1

CLINICAL AND PATHOPHYSIOLOGICAL ASPECT

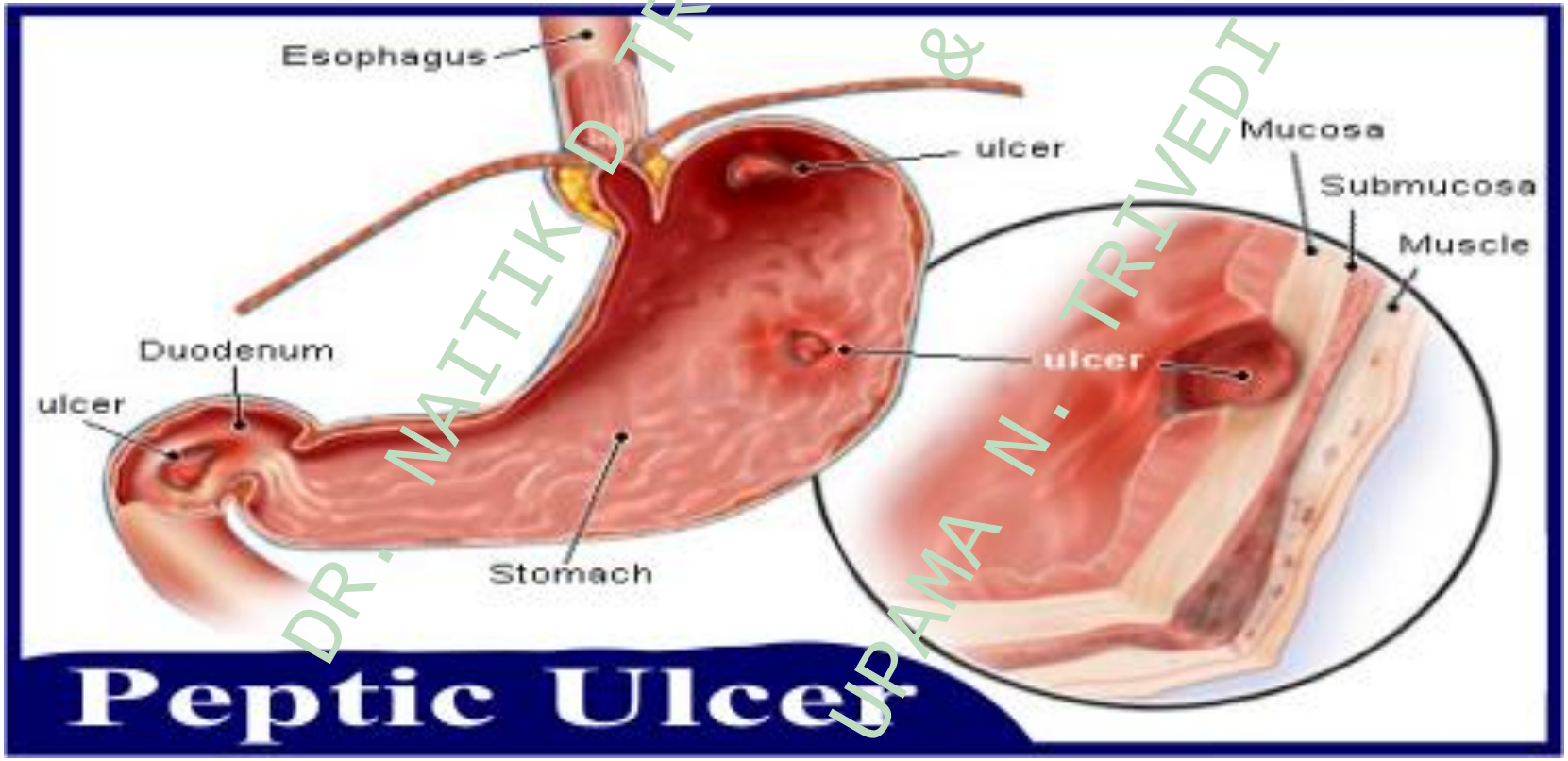
INTRODUCTION:

- Peptic ulcer disease (PUD) is one of the most common diseases affecting the GI tract. It causes inflammatory injuries in either the gastric or duodenal mucosa, with extension beyond the submucosa into the muscularis mucosa.
- A **peptic ulcer** is a distinct breach in the mucosal lining of the stomach (gastric ulcer) or the first part of the small intestine (duodenal ulcer),[1] a result of corrosive effects of acid and pepsin in the lumen.
- Histologically, peptic ulcer is identified as necrosis of the mucosa which produces lesions equal to or greater than 0.5 cm (1/5").
- The etiologies of this condition are multifactorial and are rarely related simply to excessive acid secretion.
- Helicobacter pylori is one of the most common causes of peptic ulcer. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.
- Even though gastric ulcer is a common disease, a diagnosis can be difficult because it has a wide spectrum of clinical presentations, ranging from asymptomatic to vague epigastric pain, nausea, and iron-deficiency anemia to acute life-threatening hemorrhage.

- Ref.: 1. "Peptic ulcer". *Medline Plus*. National Institutes of Health. Retrieved 10 April 2014.

DEFINATION:

- Peptic ulcer disease refers to painful sores or ulcers in the lining of the stomach or first part of the small intestine, called the duodenum.[2]

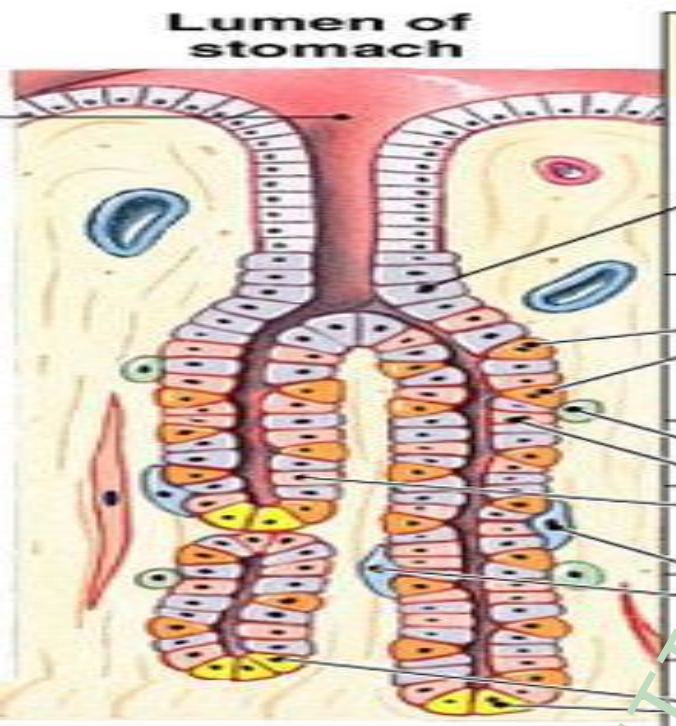


Ref. :2. http://www.webmd.com/digestive-disorders/digestive-diseases-peptic-ulcer-disease

GASTRIC ANATOMY:

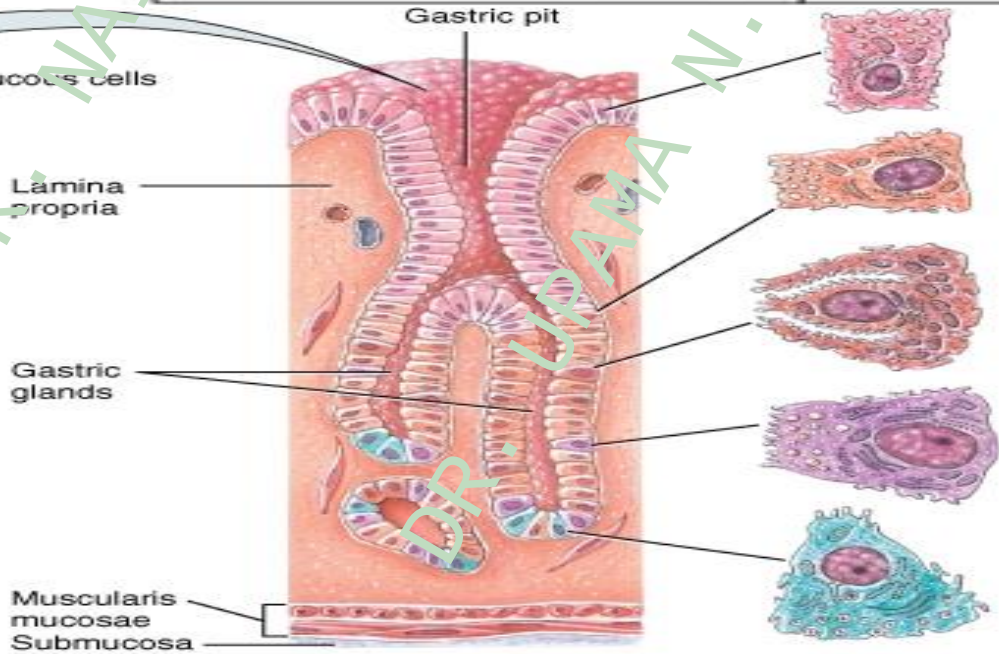
Gastric glands have several types of secreting cells:

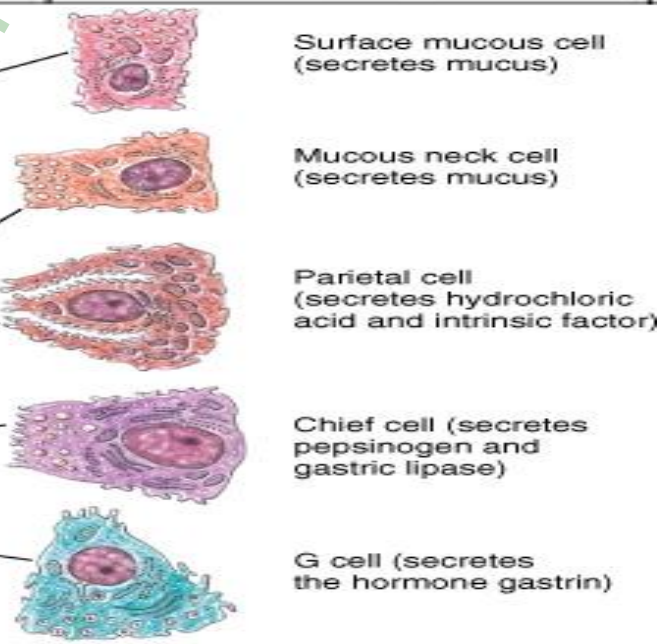
- Goblet cells : secrete mucus
- Surface mucous cells and mucous neck cells : secretes mucus
- Parietal cells : secretes hydrochloric acid
- Chief (or Zymogenic) cells : secrete pepsinogen , inactive form of the protein– digesting enzyme pepsin.
- Enteroendocrine cells (Argentaffin cells) : secrete serotonin and histamine as autocrine regulators.
- G-cells : secrete the hormone gastrin into the blood.
- In addition to these products, the gastric mucosa (probably the parietal cells) secretes a polypeptide called intrinsic factor, which is required for absorption of vitamin B12 in the small intestine.



Cell Types	Substance Secreted
Mucous neck cell	Mucus (protects lining)
	Bicarbonate
Parietal cells	Gastric acid (HCl)
	Intrinsic factor (Ca++ absorption)
Enterochromaffin-like cell	Histamine (stimulates acid)
Chief cells	Pepsin(ogen)
	Gastric lipase
D cells	Somatostatin (inhibits acid)
G cells	Gastrin (stimulates acid)

Stomach mucosa



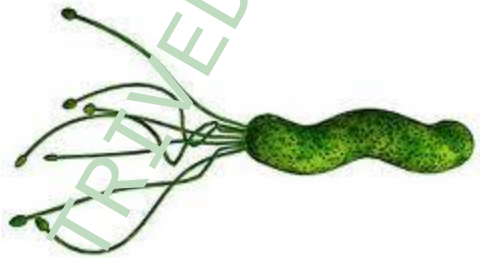


SYMPTOMS OF PEPTIC ULCER:

- A burning pain in the gut is the most common symptom. The pain
  - feels like a dull ache
  - comes and goes for a few days or weeks
  - starts 2 to 3 hours after a meal
  - comes in the middle of the night when your stomach is empty
  - usually goes away after you eat
- Other symptoms are
  - losing weight
  - not feeling like eating
  - having pain while eating
  - feeling sick to your stomach
  - vomiting
  - Bleeding from ulcers
- If blood loss is slow, it may not be obvious. People suffering from slow bleeding may feel tired and weak. If the bleeding is heavy, blood will appear in vomit or stool. Stools containing blood appear tarry or black.
- Melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin)

ETIOLOGY:

- Nonsteroidal Antiinflammatory Drugs (NSAIDs)
  - Peptic ulcers occur in 5-20% of longterm NSAID use
- Helicobacter Pylori
  - Duodenal Ulcer: 90-100% Prevalence
  - Gastric Ulcer: 70-90% Prevalence
- Acid Induced Ulcers
  - Idiopathic
  - Zollinger-Ellison Syndrome
- Chronic Disease
  - Stress Ulcers in chronic debilitated conditions
  - Chronic Obstructive Pulmonary Disease
  - Cystic Fibrosis
  - Alpha-1-Antitrypsin Deficiency
  - Systemic Mastocytosis
  - Basophilic Leukemia
  - Chronic Renal Failure
  - Cirrhosis



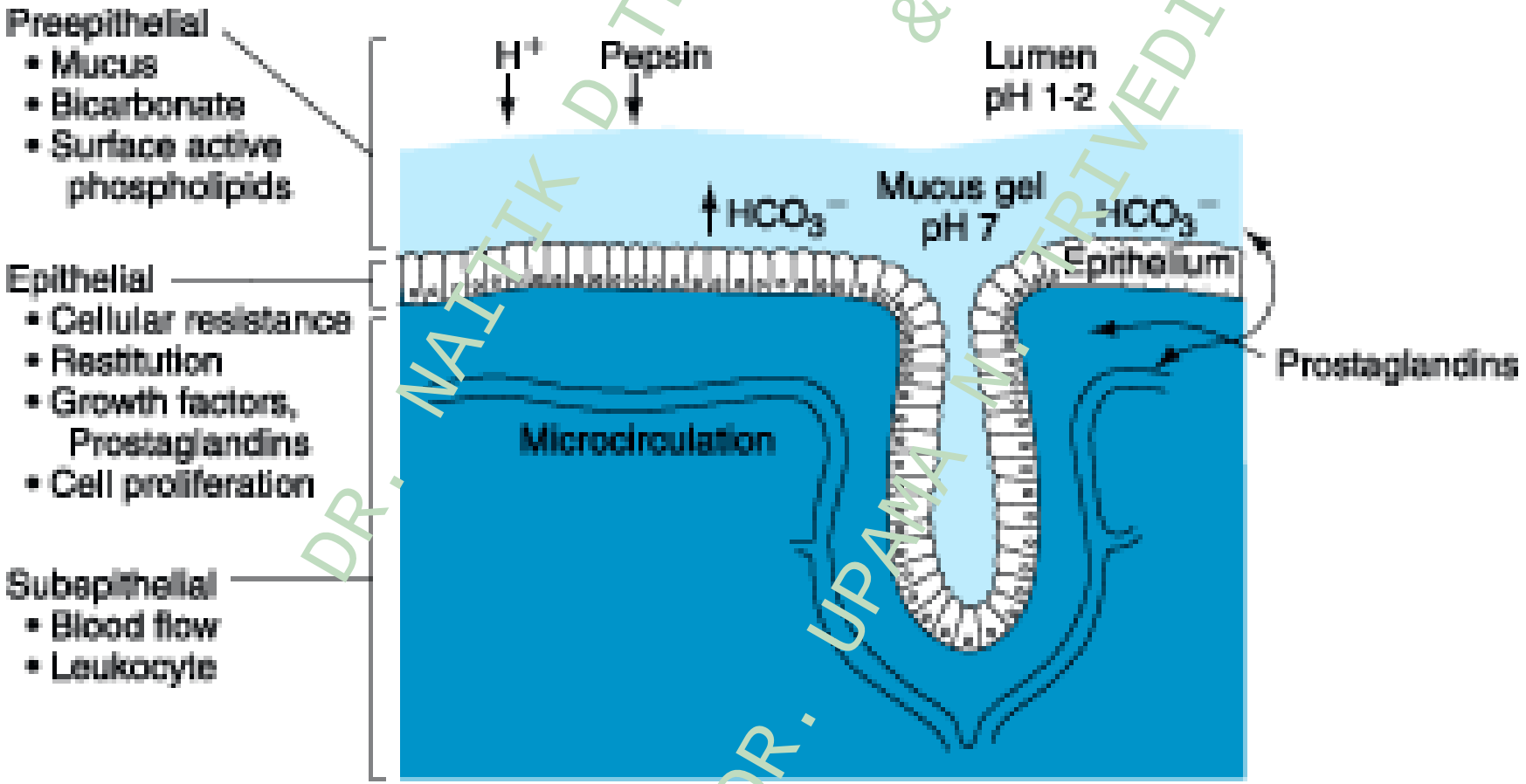
PATHOPHYSIOLOGY:

- Peptic ulcer disease occurs due to the imbalance between the aggressive factors and local mucosal defensive mechanisms.

Aggressive factors	Local mucosal defensive mechanisms
1.Endogenous factors a. gastric acid secretion b.pepsin secretion **2.Exogenous factors** a.NSAIDs b.alcohol c.caffeine d. H.pylori infection, e.smoking f.occupation, stress and trauma	mucin, prostaglandin, nitric oxide, growth factors, bicarbonate, chemical agents, hydrophobic cell membrane, rapid cell turnover, restitution, blood flow, Angiogenesis

PATHOPHYSIOLOGY:

- MUCOSAL DEFENCE:



- The gastric epithelium is under a constant assault by a series of endogenous noxious factors including HCl, pepsinogen/pepsin, and bile salts. In addition, a steady flow of exogenous substances such as medications, alcohol, and bacteria encounter the gastric mucosa.
- A highly intricate biologic system is in place to provide defense from mucosal injury and to repair any injury that may occur. The mucosal defense system can be envisioned as a three-level barrier, composed of preepithelial, epithelial, and subepithelial elements.
- **The first line of defense** is a mucus-bicarbonate layer, which serves as a physicochemical barrier to multiple molecules including hydrogen ions.
- Mucus is secreted in a regulated fashion by gastroduodenal surface epithelial cells. It consists primarily of water (95%) and a mixture of lipids and glycoproteins.
- Mucin is the constituent glycoprotein that, in combination with phospholipids (also secreted by gastric mucous cells), forms a hydrophobic surface with fatty acids that extend into the lumen from the cell membrane.
- The mucous gel functions as a nonstirred water layer impeding diffusion of ions and molecules such as pepsin. Bicarbonate, secreted by surface epithelial cells of the gastroduodenal mucosa into the mucous gel, forms a pH gradient ranging from 1 to 2 at the gastric luminal surface and reaching 6 to 7 along the epithelial cell surface. Bicarbonate secretion is stimulated by calcium, prostaglandins, cholinergic input, and luminal acidification.

- **Surface epithelial cells provide the next line of defense** through several factors, including mucus production, epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production, and intracellular tight junctions.
- If the preepithelial barrier were breached, gastric epithelial cells bordering a site of injury can migrate to restore a damaged region (*restitution*).
- This process occurs independent of cell division and requires uninterrupted blood flow and an alkaline pH in the surrounding environment. Several growth factors including epidermal growth factor (EGF), transforming growth factor (TGF) a, and basic fibroblast growth factor (FGF) modulate the process of restitution.
- Larger defects that are not effectively repaired by restitution require cell proliferation
- Epithelial cell regeneration is regulated by prostaglandins and growth factors such as EGF and TGF-a.
- In tandem with epithelial cell renewal, formation of new vessels (*angiogenesis*) within the injured microvascular bed occurs.
- Both FGF and vascular endothelial growth factor (VEGF) are important in regulating angiogenesis in the gastric mucosa.
- An elaborate microvascular system within the gastric submucosal layer is the key component of the subepithelial defense/repair system.
- A rich submucosal circulatory bed provides HCO3-, which neutralizes the acid generated by parietal cell secretion of HCl.
- Moreover, this microcirculatory bed provides an adequate supply of micronutrients and oxygen while removing toxic metabolic by-products.

- Prostaglandins play a central role in gastric epithelial defense/repairs. The gastric mucosa contains abundant levels of prostaglandins. These metabolites of arachidonic acid regulate the release of mucosal bicarbonate and mucus, inhibit parietal cell secretion, and are important in maintaining mucosal blood flow and epithelial cell restitution.
- Prostaglandins are derived from esterified arachidonic acid, which is formed from phospholipids (cell membrane) by the action of phospholipase A2. A key enzyme that controls the rate-limiting step in prostaglandin synthesis is cyclooxygenase (COX), which is present in two isoforms (COX-1, COX-2), each having distinct characteristics regarding structure, tissue distribution, and expression. COX-1 is expressed in a host of tissues including the stomach, platelets, kidneys, and endothelial cells. This isoform is expressed in a constitutive manner and plays an important role in maintaining the integrity of renal function, platelet aggregation, and gastrointestinal mucosal integrity.
- In contrast, the expression of COX-2 is inducible by inflammatory stimuli, and it is expressed in macrophages, leukocytes, fibroblasts, and synovial cells.
- The beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on tissue inflammation are due to inhibition of COX-2; the toxicity of these drugs (e.g., gastrointestinal mucosal ulceration and renal dysfunction) is related to inhibition of the COX-1 isoform. The highly COX-2-selective NSAIDs have the potential to provide the beneficial effect of decreasing tissue inflammation while minimizing toxicity in the gastrointestinal tract.

PATHOPHYSIOLOGY:

- **AGGRESIVE FACTORS:**

1. Endogeneous secretions:

a. Gastric acid secretion

b. Pepsinogen secretion

2. Exogeneous factors

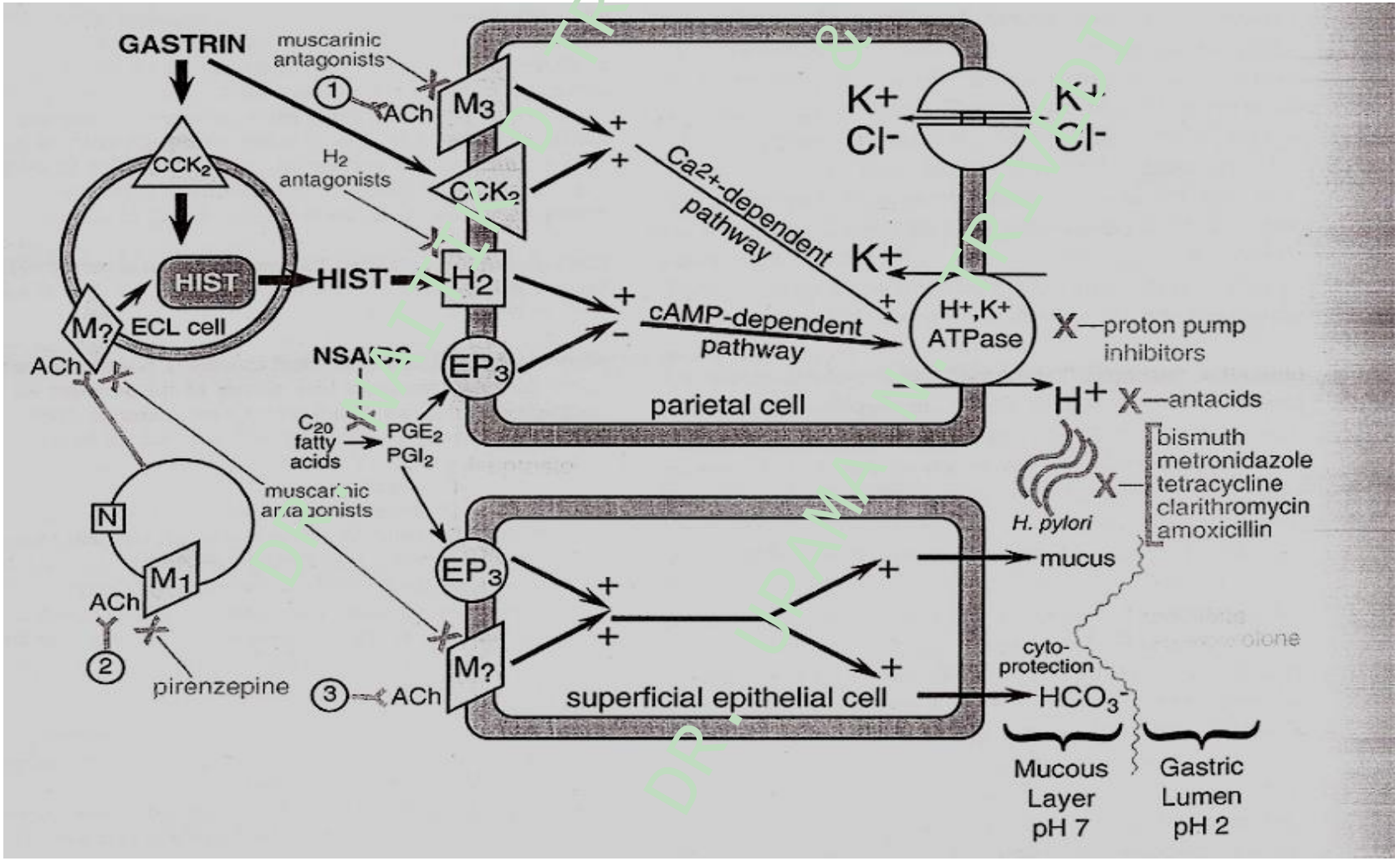
ENDOGENEOUS SECRETIONS:

A. Physiology of gastric acid secretion

- ***Cephalic phase*** – this results from the thought, sight, smell or taste of food. Neural stimuli arise in the cerebral cortex, appetite centre or hypothalamus and are transmitted through the vagus.
- ***Gastric phase*** – food entering the stomach elicits long vasovagal reflexes, local enteric reflexes and release of gastrin. This phase accounts for about 70% of total gastric secretion.
- ***Intestinal phase*** – food mixed with gastric secretions (chyme) entering the proximal small intestine can stimulate modest gastric secretion. Mechanisms include duodenal gastrin release, absorbed amino acids, other hormones and reflexes.

ENDOGENEOUS SECRETIONS:

A. Physiology of gastric acid secretion



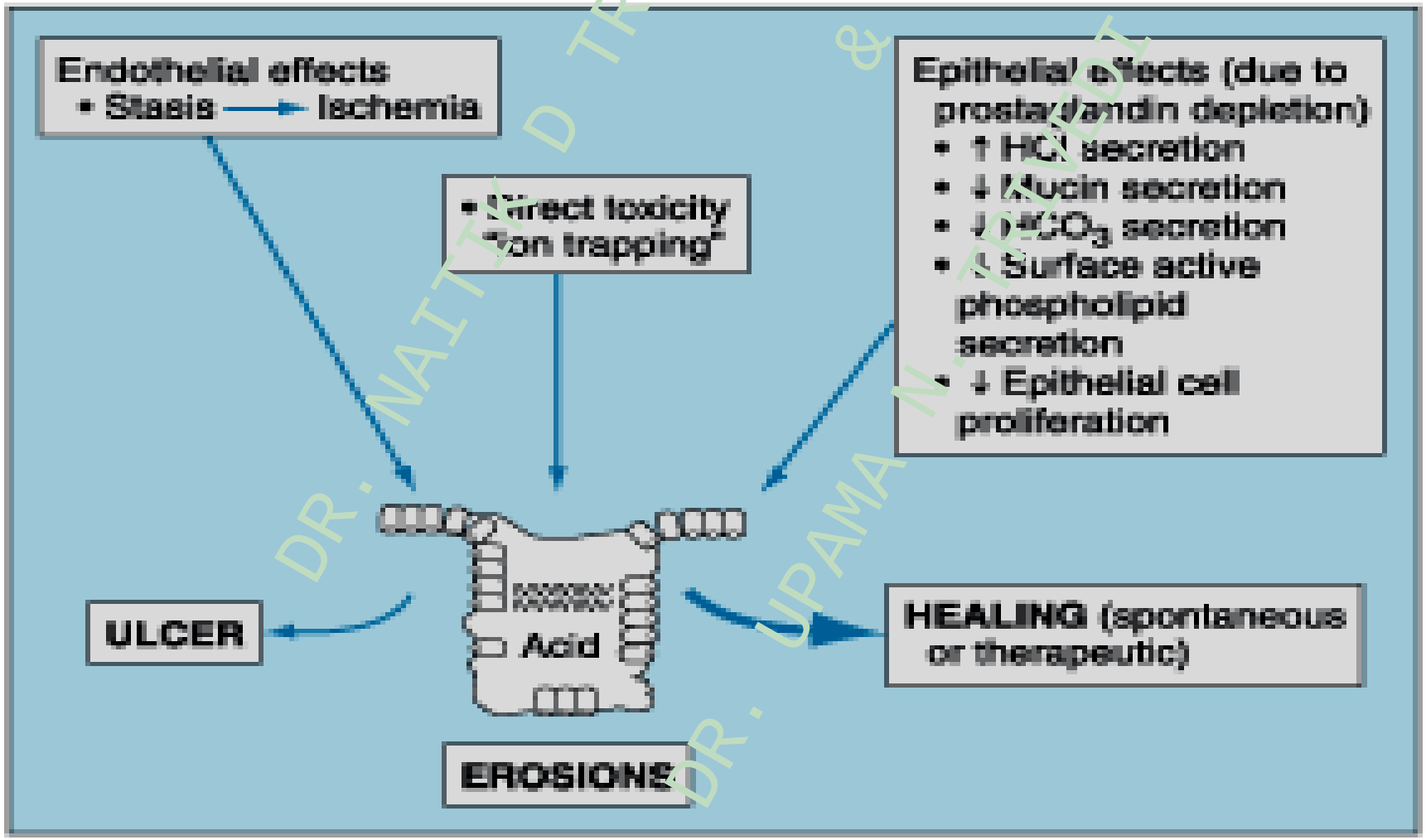
ENDOGENEOUS SECRETIONS:

B) Pepsinogen secretion:

- The chief cell, found primarily in the gastric fundus, synthesizes and secretes pepsinogen, the inactive precursor of the proteolytic enzyme pepsin. The acid environment within the stomach leads to cleavage of the inactive precursor to pepsin and provides the low pH (<2.0) required for pepsin activity. Pepsin activity is significantly diminished at a pH of 4 and irreversibly inactivated and denatured at a pH of more than 7. Many of the secretagogues that stimulate acid secretion also stimulate pepsinogen release. Pepsinogen is released in response to neural stimulation and in the presence of gastric acid.

EXOGENEOUS FACTORS:

A) Role of NSAIDs:



EXOGENEOUS FACTORS:

B) Role of H.Pylori:

- It can cause damage by:

1) Direct mechanisms

2) Inflammatory mechanisms/immune mechanism

3) Alteration of gastric acid and gastric physiology

- Gastrin levels may rise
- Somatostatin levels may drop (impairing negative feedback)

1. ***Bacterial factors*:** Urease, which allows the bacteria to reside in the acidic stomach, generates NH3, which can damage epithelial cells.

❖ The bacteria produce surface factors that are chemotactic for neutrophils and monocytes, which in turn contribute to epithelial cell injury .

❖ *H. pylori* makes proteases and phospholipases that break down the glycoprotein lipid complex of the mucous gel, thus reducing the efficacy of this first line of mucosal defense.

❖ *H. pylori* express adhesins, which facilitate attachment of the bacteria to gastric epithelial cells.

EXOGENEOUS FACTORS:

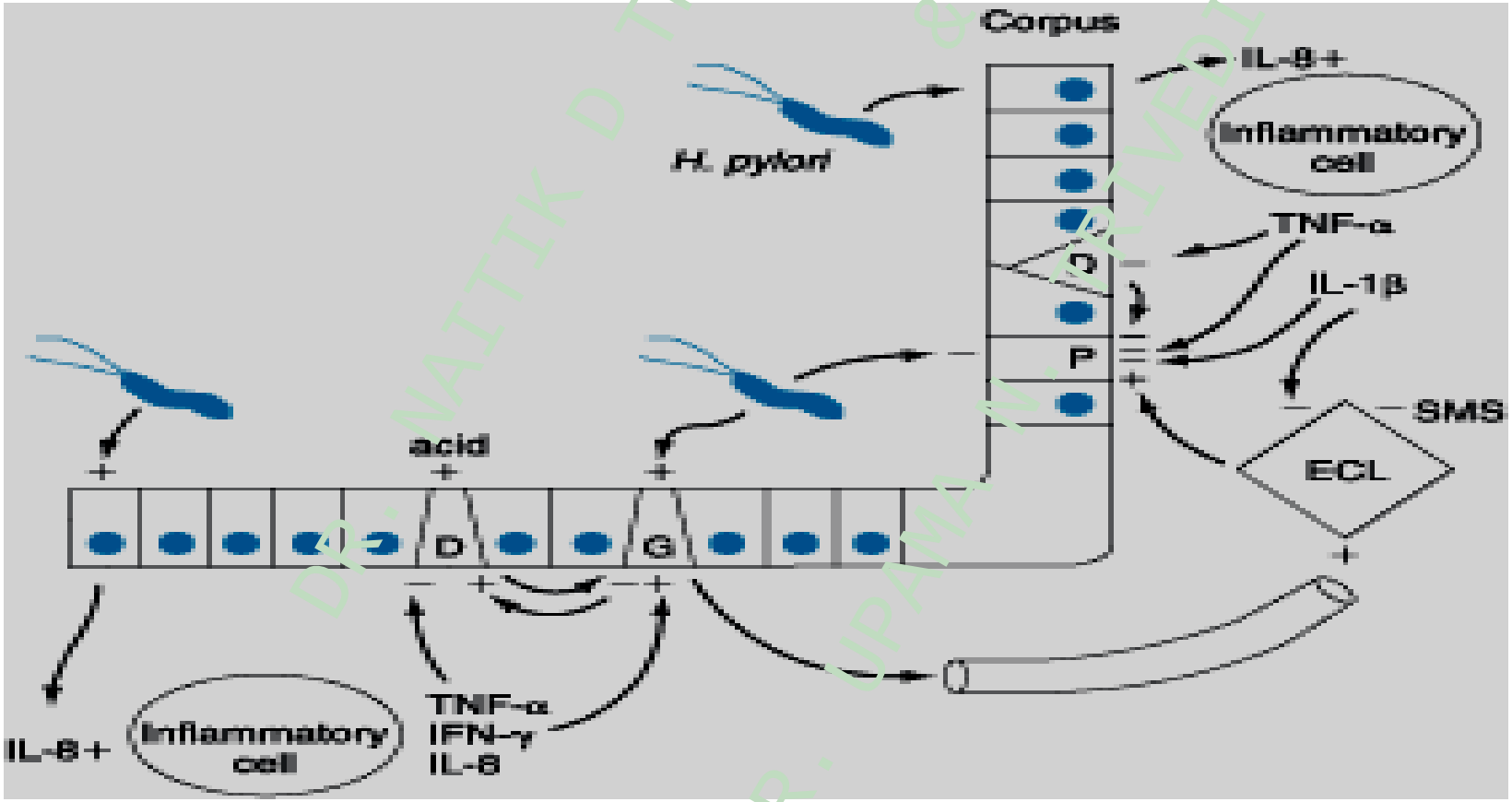
B) Role of H.Pylori:

2. *Host factors*:

- The host responds to *H. pylori* infection by mounting an inflammatory response, which contributes to gastric epithelial cell damage without providing immunity against infection.
- T lymphocytes and plasma cells are components of the chronic inflammatory infiltrate, supporting the involvement of antigen-specific cellular and humoral responses.
- A number of cytokines are released from both epithelial and immune modulatory cells in response to *H. pylori* infection including the proinflammatory cytokines tumor necrosis factor (TNF)a, interleukin (IL)1a/b, IL-6, interferon (IFN)g, and granulocyte-macrophage colony stimulating factor.
- Several chemokines such as IL-8 and growth-regulated oncogene (GRO) a, involved in neutrophil recruitment/activation have been observed in *H. pylori*-infected mucosa.

EXOGENEOUS FACTORS:

B) Role of H.Pylori:



EXOGENEOUS FACTORS:

C) Cigarettes

* Cigarette smoking impairs ulcer healing and promotes recurrence
* Thought to stimulate gastric acid secretion
* May alter blood flow or gastric motility
* May cause bile reflux or reduce production of prostaglandins

D) Alcohol

Acute ingestion may cause gastritis, gastric mucosal damage, and GI bleeding, however not considered a risk factor for PUD

E) Caffeine

Caffeine acts synergistically with histamine (but not pentagastrin) to stimulate secretion. It also enhances the secretion of pepsin.

F) Stress induced ulcer:

- psychological stress
- physiological stress as in
  - Shock
  - Severe Trauma
  - Septicemia
  - Extensive burns (Curling's ulcers in the posterior aspect of the first part of the duodenum).
  - Intracranial lesions (Cushing's ulcers developing from hyperacidity following excessive vagal stimulation).

DIAGNOSIS:

- Physical examination
- Lab test
- Other test for H.pylori detection

PHYSICAL EXAMINATION

- Epigastric pain described as a burning or gnawing discomfort can be present in both DU and GU. The discomfort is also described as an ill-defined, aching sensation or as hunger pain. The typical pain pattern in DU occurs 90 min to 3 h after a meal and is frequently relieved by antacids or food. Pain that awakes the patient from sleep (between midnight and 3 A.M.) is the most discriminating symptom.
- Dyspepsia that becomes constant, is no longer relieved by food or antacids, or radiates to the back may indicate a penetrating ulcer (pancreas). Sudden onset of severe, generalized abdominal pain may indicate perforation. Pain worsening with meals, nausea, and vomiting of undigested food suggest gastric outlet obstruction. Tarry stools or coffee ground emesis indicate bleeding.

PHYSICAL EXAMINATION

- **Endoscopy** is a common and efficient diagnostic method that allows clinicians to see the GI tract. Not only does it detect more than 90% of all ulcers, but it is also very safe and well tolerated, even by the elderly. Endoscopy can identify H. pylori-positive individuals and differentiate among various types of ulcers. This procedure is performed under sedation and involves inserting an endoscope - a small, flexible tube with a tiny camera on the end - down throat and into the stomach and duodenum. It allows the doctor to see the lining of the esophagus, stomach, and duodenum to check for possible ulcers, inflammation, or food allergies. The endoscope can also be used to perform **tissue tests** to detect the presence of H. pylori.
- The endoscopy is often used in conjunction with a test called a **pH probe**, in which a small wire is inserted into the lower part of the esophagus to measure the amount of acid going into that area.

PHYSICAL EXAMINATION

- **Upper gastrointestinal (upper GI) X-ray.** Your doctor may begin with this test, which outlines your esophagus, stomach and duodenum. During the X-ray, you swallow a white, metallic liquid (containing barium) that coats your digestive tract and makes an ulcer more visible. An upper GI X-ray can detect some ulcers, but not all.

LAB TEST:

- 1. Blood test may show hypochromic anemia.

- 2. Stool test may detect occult blood if the ulcer is chronic.

TEST FOR IDENTIFICATION OF H.PYLORI

- INVASIVE TEST:
  - Biopsy: Identification of the organism in an endoscopically obtained biopsy specimen remains the criterion standard for diagnosis of *H pylori* infection. Routinely, 2 biopsy samples are obtained from the antrum and the body of the stomach. Gastritis is apparent on routine histological slides stained with hematoxylin and eosin; however, special staining with Giemsa or Warthin-Starry silver stain provides almost 100% accurate results. False-negative results can occur in patients with active gastrointestinal bleeding and in patients taking antisecretory agents.
  - Culture: This is the most specific method; however, it is not routinely performed in clinical practice because of the fastidious nature of the organism.
  - Rapid urease test: This test contains urea-impregnated agar and a pH indicator that changes color if urease is present in the biopsy sample. This test is quick and accurate, with a sensitivity and specificity of higher than 90%.

TEST FOR IDENTIFICATION OF H.PYLORI

- NON-INVASIVE TEST:
  - Antibody testing: Serological testing is simple, inexpensive, and widely available, although it is of limited value because positive results cannot be used to differentiate between past exposure and active infection.
  - Urea breath testing (UBT): This test is useful for documenting the eradication of *H pylori* after treatment. *H pylori* produce a large amount of urease. Patients ingest carbon-labeled urea (i.e., carbon 13 or carbon 14) that is broken down by urease with release of the labeled carbon. A failure to detect exhaled labeled carbon dioxide confirms the eradication of the bacteria. UBT should be performed 4 weeks after *H pylori* eradication to prevent false-negative results.
  - Stool antigen: This test, approved by the FDA, helps identify bacterial antigens in stool. The test has been shown to be extremely accurate with a sensitivity of 89-98% and with a specificity of greater than 90% in helping to diagnose infection or to document eradication. To assess for eradication of *H pylori,* stool antigen should be checked only after 8 weeks of completion of therapy.

TREATMENT:

- Life style modification
- Drug treatment
- Surgery

LIFE STYLE MODIFICATION

- **Diet**
- Large amounts of food should be avoided because stretching or swelling of the stomach can result in painful symptoms.
- *Take Fruits and Vegetables.* Stop *Milk,Coffee and Carbonated Beverages,Spices and Peppers*
- **Exercise**
- **Addiction:** Stop alcohol and stop smoking

- **Stress Relief**
- Stress relief programs have not been shown to promote ulcer healing, but they may have other health benefits.

DRUG TREATMENT:

Drugs Used in the Treatment of Peptic Ulcer Disease

Drug Type/Mechanism	Examples	Dose
Acid-suppressing drugs		
Antacids	Mylanta, Maalox, Tums, Gaviscon	100-140 meq/l, 1 and 3 h after meals and hs
H_2 receptor antagonists	Cimetidine	800 mg hs
	Ranitidine	300 mg hs
	Famotidine	40 mg hs
	Nizatidine	300 mg hs
Proton pump inhibitors	Omeprazole	20 mg/d
	Lansoprazole	30 mg/d
	Rabeprazole	20 mg/d
	Pantoprazole	40 mg/d
Mucosal protective agents		
Sucralfate	Sucralfate	1 g qid
Prostaglandin analogue	Misoprostol	200 μg qid
Bismuth-containing compounds	Bismuth subsalicylate (BSS)	See anti-*H. Pylori* regimens (Table 285-7)

DRUG TREATMENT:

Regimens Recommended for Eradication of *H. pylori* Infection

Drug	Dose
TRIPLE THERAPY	
1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin *or* metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole *or*	500 mg bid
Amoxicillin	1 g bid
QUADRUPLE THERAPY	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

DRUG TREATMENT:

Recommendations for Treatment of NSAID-Related Mucosal Injury

Clinical Setting	Recommendation
Active ulcer	
NSAID discontinued	H_2 receptor antagonist or PPI
NSAID continued	PPI
Prophylactic therapy	Misoprostol
	PPI
	Selective COX-2 inhibitor
H. pylori infection	Eradication if active ulcer present or there is a past history of peptic ulcer disease

NOTE: PPI, proton pump inhibitor; COX-2, isoenzyme of cyclooxygenase.

SURGERY:

Endoscopy

- *The Procedure*. Endoscopic treatment of bleeding generally involves the following:
- The physician places an endoscope (a thin, flexible plastic tube) into the patient's mouth and down the esophagus (food pipe) into the stomach.
- The surgeon passes a probe through an endoscopic tube and applies electricity, heat, or small clips to coagulate the blood and stop the bleeding.
- An injection of epinephrine (commonly known as adrenaline) directly into the ulcer increases the effectiveness of endoscopic treatments and may reduce rebleeding. Epinephrine plus a combination of blood clotting factors termed fibrin glue may prove to be even more effective.
- The use of proton-pump inhibitors after endoscopy appears to reduce the risk for rebleeding.
- A repeat endoscopy performed by experienced doctors may be effective in controlling bleeding about 75% of cases.

SURGERY:

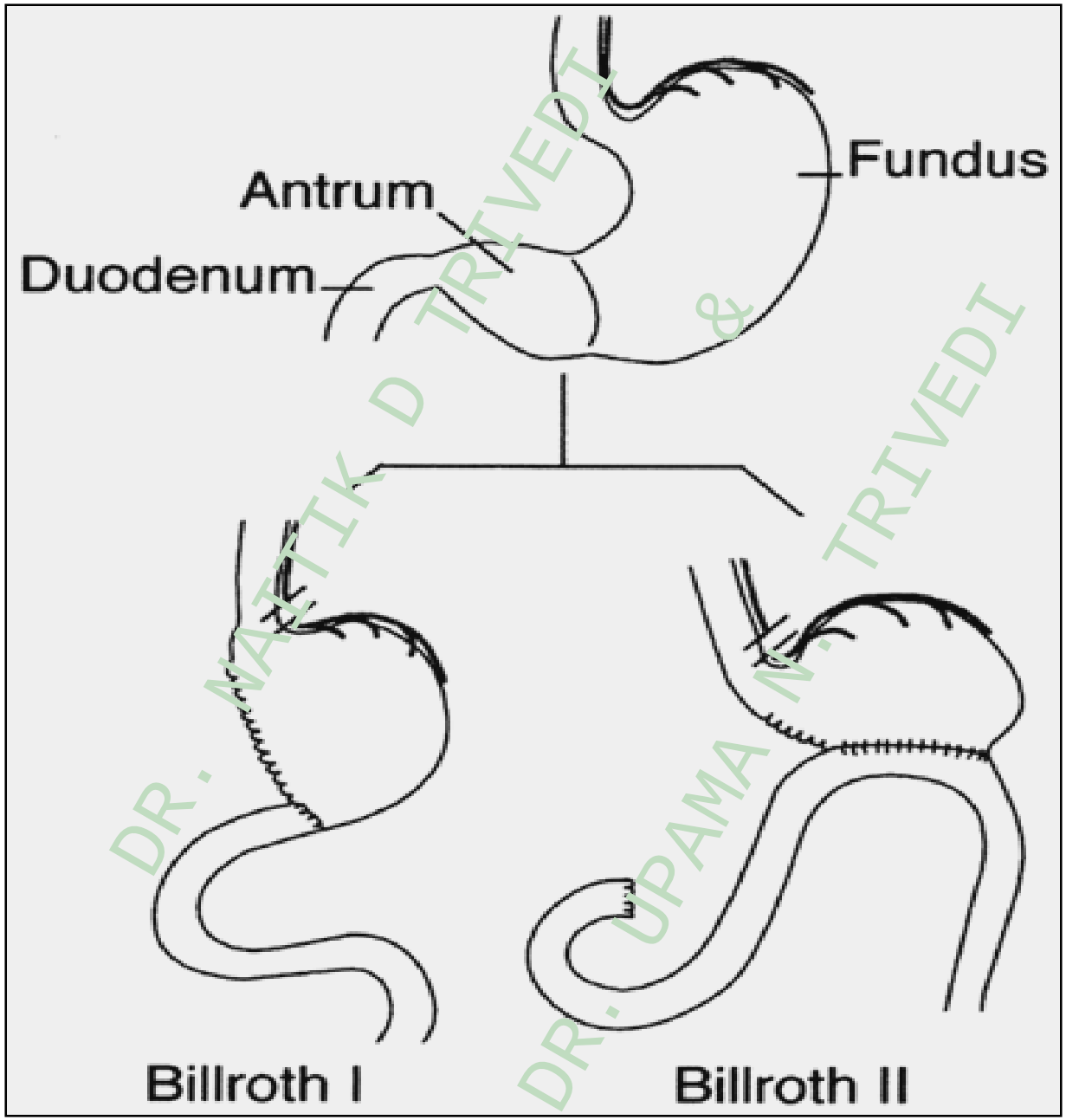
Major Abdominal Surgery

- **Vagotomy** cuts the vagus nerve and interrupts messages from the brain that stimulate acid secretion in the stomach. This surgery may impair stomach emptying; a recent variation that cuts only parts of the nerve may reduce this complication.
- **Antrectomy** removes the lower part of the stomach, which manufactures the hormone responsible for stimulation of digestive juices.
- **Pyloroplasty** enlarges the opening into the small intestine so that stomach contents can pass into it more easily.
- **Total gastrectomy:**Removing the entire stomach is done only for resistant Zollinger-Ellison syndrome or extensive cancers.
- **Billroth I and II**

  After removing a piece of the stomach, the remainder must be reattached to the rest of the bowel. Simply joining the upper stomach back to the duodenum is called a Billroth I or gastroduodenostomy. It is sometimes better to attach the stomach with another piece of bowel (the jejunum), creating a "y" with the bile drainage and the duodenum forming the second branch of the "y." This part of the procedure is called a gastrojejunostomy. A gastroenterostomy is a more general term for connecting the stomach with any piece of bowel.

  A selective **vagotomy** can be done alone. A complete vagotomy requires either a pyloroplasty or antrectomy. An antrectomy must be reconnected with either a Billroth I or a Billroth II.

- Some of these procedures are now being done through a laparoscope.



SURGERY:

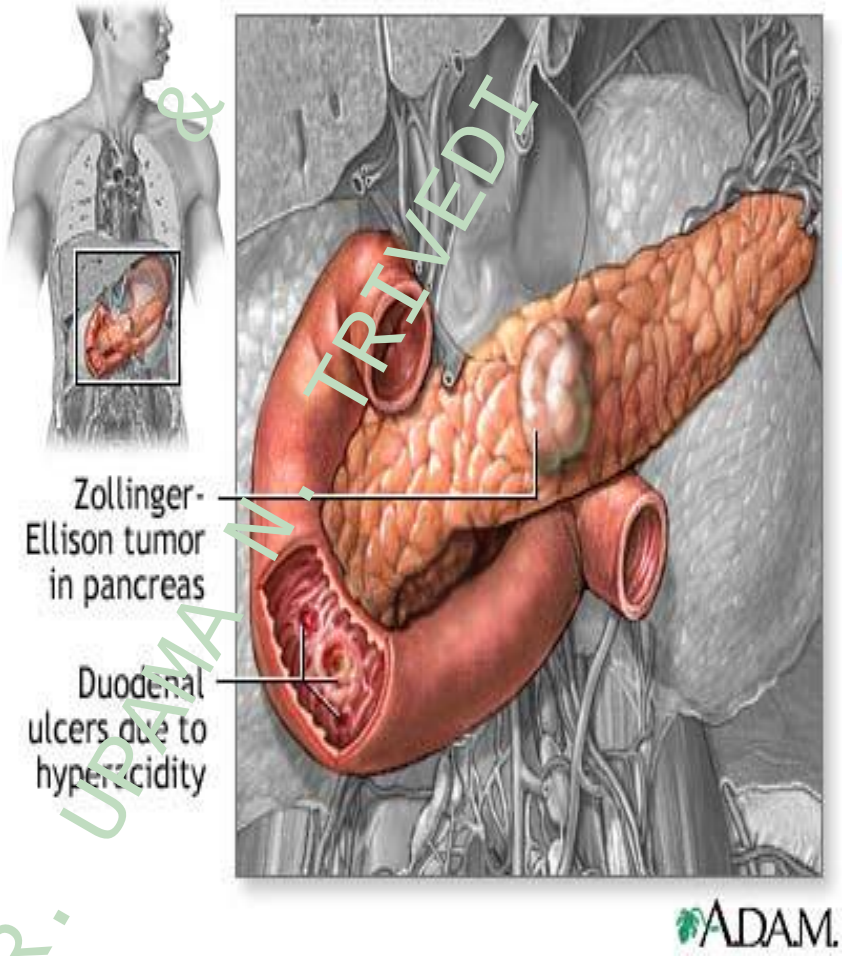
RISKS

- All of these procedures carry risks, generally in proportion to their benefits. The more extensive surgeries such as vagotomy and antrectomy with Billroth II reconnection have the highest success rate and the highest complication rate.
- Complications include:
- Diarrhea after a meal
- Dumping syndrome occurring after a meal and characterized by sweating, abdominal **pain**, vomiting, light-headedness, and diarrhea
- Hypoglycemia after a meal
- Alkaline reflux **gastritis** marked by abdominal pain, vomiting of bile, diminished appetite, and iron-deficiency anemia
- Recurrence of an ulcer

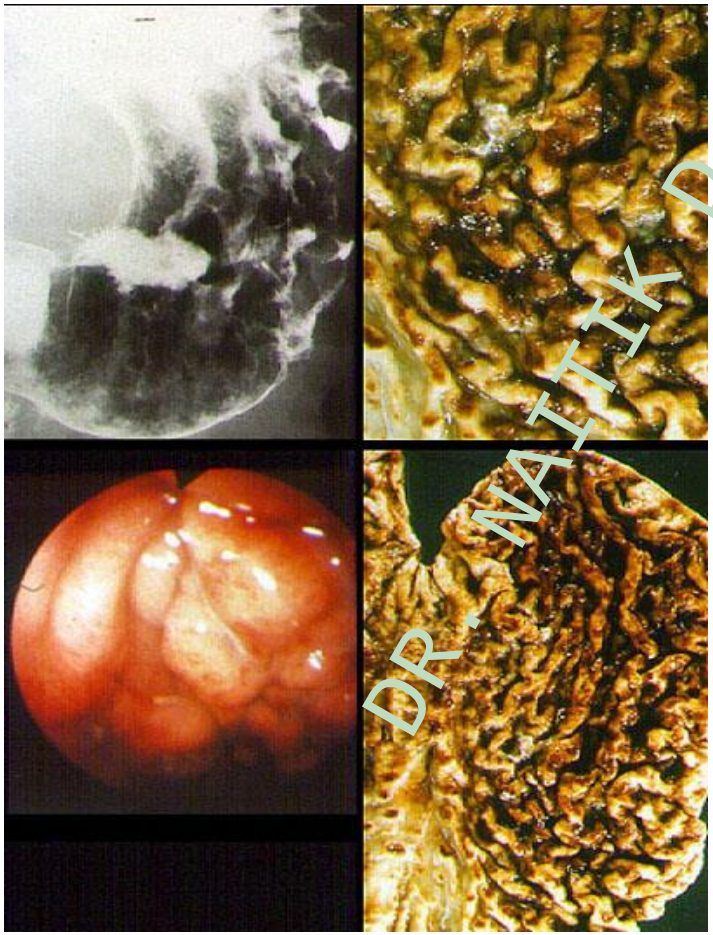
RELATED DISEASES:

ZOLLINGER-ELLISON SYNDROME

- Severe peptic ulcer diathesis secondary to gastric acid hypersecretion due to unregulated gastrin release from a non-b cell endocrine tumor (gastrinoma) defines the components of the ZES.



RELATED DISEASES:



MENETRIER'S DISEASE

- Ménétrier's disease causes giant folds of tissue to grow in the wall of the stomach. The tissue may be inflamed and may contain ulcers. The disease also causes glands in the stomach to waste away and causes the body to lose fluid containing a protein called albumin. Ménétrier's disease increases a person's risk of stomach cancer.

RELATED DISEASES:

GASTRITIS:

- Chronic or acute inflammation of the stomach, especially of the mucous membrane of the stomach. Gastritis commonly refers to inflammation of the lining of the stomach, but the term is often used to cover a variety of symptoms resulting from stomach lining inflammation and symptoms of burning or discomfort.

PART – 2

PHARMACOLOGICAL ASPECT

CLASSIFICATION OF DRUGS

- **1. Reduction of gastric acid secretion:**

  A. H_2 Antihistamines: Cimetidine, Ranitidine, Famotidine, Nizatidine

  B. Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole, Esomeprazole

  C. Anticholinergics: Pirenzepine, Propentheline, Oxyphenonium

  D. Prostaglandin analogues: Misoprostol, Enprostil, Rioprostil

- **2. Neutralization of gastric acid (Antacids):**

  A. Systemic: Sodium bicarbonate, Sodium citrate

  B. Nonsystemic: Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide, Magaldrate, Calcium carbonate

- **3. Ulcer protectives:** Sucralfate, Colloidal bismuth subcitrate (CBS)
- **4. Ulcer healing drugs:** Carbenoxolone sodium
- **5. Anti-H. pylori drugs:** Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline.

H_2 ANTIHISTAMINES

Cimetidine, Ranitidine, Famotidine, Nizatidine

- **MECHANISM OF ACTION:**

❖ H_2 receptor antagonist inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on basolateral membrane of parietal cells.

❖ Also they cause suppression of stimulated (feeding, gastrin, hypoglycemia, or vagal stimulation) acid production.

H_2 ANTIHISTAMINES

PHARMACOKINETICS:

- They are absorbed rapidly from oral administration, with peak serum concentration reached within 1 to 3 hours.

- Very little amount of drug undergo metabolism in liver.

- Both metabolized and unmetabolized products are excreted by kidney by both filtration and renal tubular secretion.

H_2 ANTIHISTAMINES

ADVERSE REACTION:

- Diarrhea, headache, drowsiness, fatigue, muscular pain, and constipation.
- With I.V. administration CNS effects like confusion, delirium, hallucination, slurred speech occurs.
- Also cause various cytopenias including reduction in platelet count.
- With cimetidine gynecomastia in men and galactorrhea in women occur due to binding of cimetidine to androgen receptors and inhibition of the cytochrome P450-catalyzed hydroxylation of estradiol.
- Also with cimetidine reduction in sperm count and reversible impotence is reported in men.

H_2 ANTIHISTAMINES

INTERACTION:

- 1. Cimetidine inhibits cytochrome P450 and thus alter metabolism of drugs like warfarin, phenytoin, b-blockers, quinidine, caffeine, etc.
- 2. Cimetidine inhibits renal tubular secretion of procainamide and its active metabolite N-acetylprocainamide.

THEREPEUTIC USES:

- 1. DU and GU.
- 2. ZES.
- 3. GERD (Gastroesophageal reflux disease).
- 4. As prophylactic in stress ulcers.

H_2 ANTIHISTAMINES

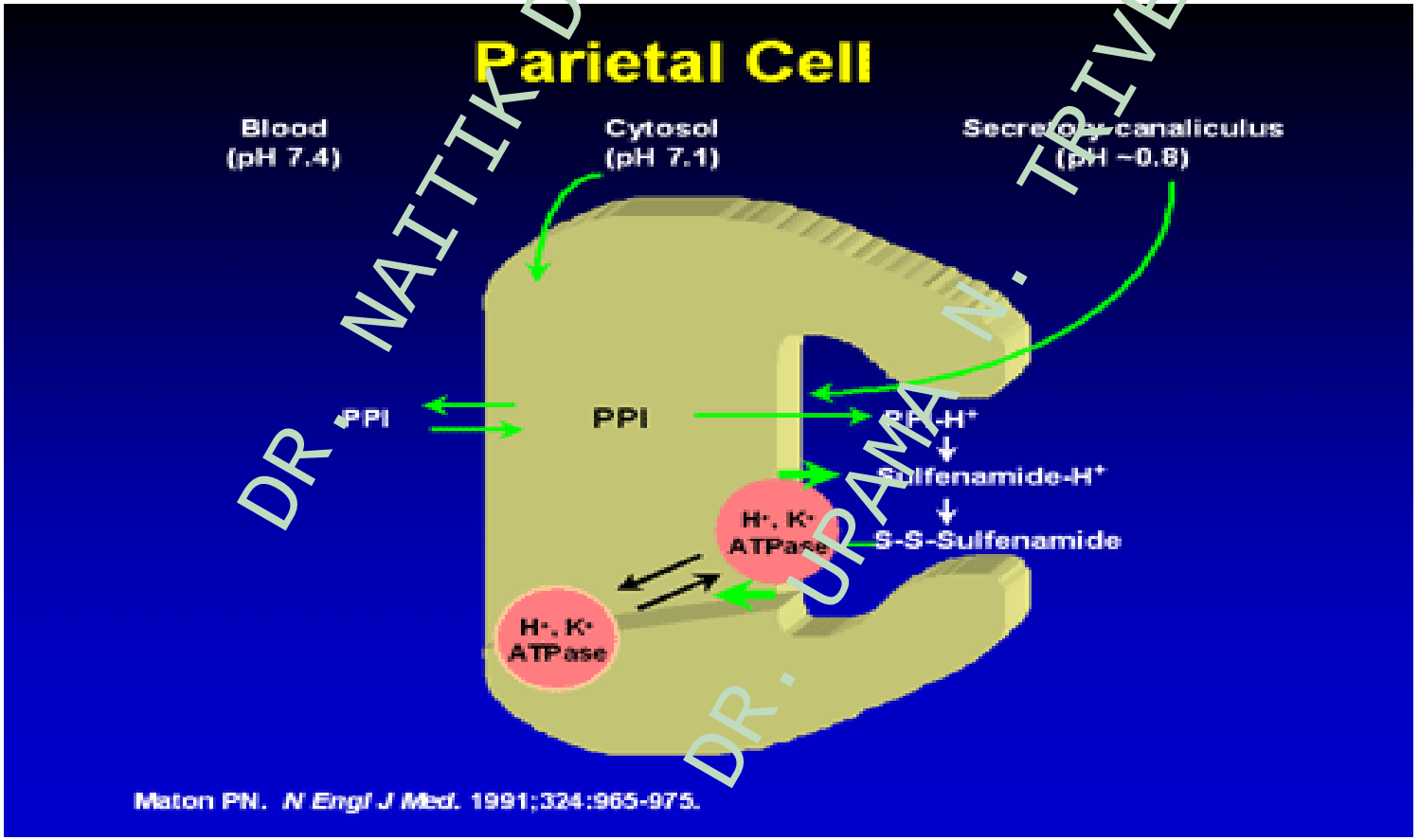
- **COMPARISION OF PROPERTIES OF H_2 RECEPTOR ANTAGONISTS:**

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability (%)	80	50	40	>90
Relative potency	1	5-10	32	5-10
Plasma half life (hours)	1.5-2.3	1.6-2.4	2.5-4	1.1-1.6
Duration of effect (hours)	6	8	12	8
Relative effect on CYT.P450	1	0.1	0	0

PROTON PUMP INHIBITORS

Omeprazole, Lansoprazole, Pantoprazol, Esomeprazole

- **MECHANISM OF ACTION:**



PROTON PUMP INHIBITORS

PHARMACOKINETICS:

- 1. They are unstable at low pH. Thus given in form of enteric coated granules, which dissolves only in alkaline pH.
- 2. They are rapidly absorbed orally, highly protein bound and is extensively metabolized in liver by cytochrome P450 system.
- 3. The sulfated metabolites are excreted in urine and feces.
- 4. Plasma half life is about 1-2 hours.

NOTE: Pantaprazole is relatively more acid stable.

PROTON PUMP INHIBITORS

ADVERSE REACTION:

- 1. Nausea, abdominal pain, constipation, flatulence and diarrhea.
- 2. Subacute myopathy, arthralgia, headache, and skin rashes are also reported.
- 3. Hypergastrinemia.
- 4. On long term usage omeprazole decrease absorption of vit. B_{12}.

INTERACTION:

- 1. They inhibit activity of cytochrome P450 enzyme and thus alter metabolism of various drugs like warfarin, phenytoin, diazepines,etc.

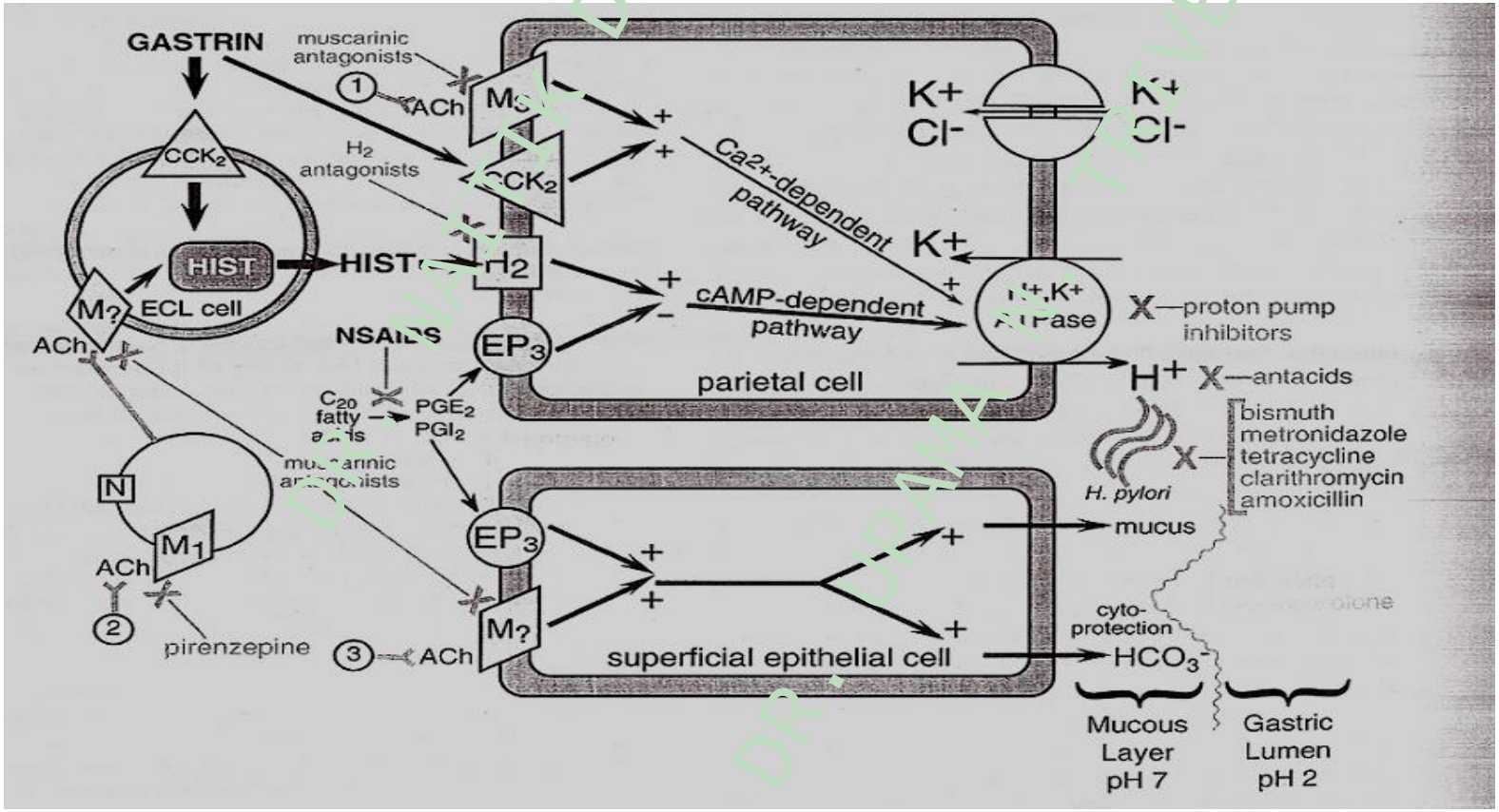
THEREPEUTIC USES:

- 1. DU and GU.
- 2. ZES.
- 3. GERD (Gastroesophageal reflux disease).

PROSTAGLANDIN ANALOGS

Misoprostol.

- **MECHANISM OF ACTION:**



PROSTAGLANDIN ANALOGS

PHARMACOKINETICS:

- 1. It is rapidly absorbed orally.
- 2. Undergoes extensive and rapid first past metabolism to form Misoprostol acid, the principle active metabolite of drug.
- 3. After a single dose, inhibition of secretion is seen within 30 minutes, peak at 60-90 minutes, and last for 3 hours.
- 4. The elimination half life of active metabolite is 20-40 minutes, and is excreted in urine.

PROSTAGLANDIN ANALOGS

ADVERSE REACTION:

- 1. Dose dependent diarrhea with or without abdominal pain.
- 2. Causes abortion during pregnancy by increasing uterine contractility, thus contraindicated.

INTERACTION:

- Food and antacids decrease the rate of absorption of Misoprostol, resulting in decreased plasma concentration of Misoprostol acid.

THEREPEUTIC USES:

- In preventing mucosal injury caused by NSAIDs.

ANTACIDS

They neutralize the acid present in stomach by simple acid base reaction.

A) SYSTEMIC ANTACIDS:

- Sodium bicarbonate, Sodium citrate
- They are water soluble, act instantly, but the duration is short.
- $NaHCO_3$ is rapidly cleared from stomach and presents both an alkali and a sodium load.

PROBLEMS ASSOCIATED:

1. Large doses will induce systemic alkalosis.
2. Produce CO_2 in stomach- distension, discomfort, belching, risk of ulcer perforation.
3. Acid rebound.
4. Increases Na ion load: worsen edema and CHF, contraindicated in cardiac disease, HT.

USES:

1. Quick symptomatic relief in heart burn.
2. Alkalization of urine and to treat acidosis.

ANTACIDS

B) NONSYSTEMIC ANTACIDS:

Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide,Magaldrate, Calcium carbonate

- The various cations released from the formulations like Ca2+, Mg2+ and Al3+ provides fast and sustained neutralizing capacity. Magaldrate is a hydroxy-magnesium aluminate complex that is rapidly converted in gastric acid to $Mg(OH)_2$ and $Al(OH)_3$, which are poorly absorbed and thus provides a sustained antacid effect with balanced effect on intestinal motility.
- Simethicone, a surfactant that may decrease foaming and hence esophageal reflux, is included in many antacid preparation.

ANTACIDS

SIDE EFFECTS:

- Aluminum hydroxide: may lead to the formation of insoluble aluminum-phosphate-complexes, with a risk for hypophosphatemia and osteomalacia. Although aluminum has a low gastrointestinal absorption, accumulation may occur in the presence of renal insufficiency. Absorbed aluminium leads to osteoporosis, encephalopathy and proximal myopathy. Aluminum-containing drugs may cause constipation.

- Magnesium hydroxide: has laxative properties. Magnesium may accumulate in patients with renal failure leading to hypermagnesemia, with cardiovascular and neurological complications.

ANTACIDS

- **Carbonate:** regular high doses may cause alkalosis, which in turn may result in altered excretion of other drugs, and kidney stones. A chemical reaction between the carbonate and hydrochloric acid may produce carbon dioxide gas. This causes gastric distension, nausea, flatulence and belching which may not be well tolerated.

- **Calcium:** compounds containing calcium may increase calcium output in the urine, which might be associated to renal stones. Calcium salts may cause constipation.

ANTACIDS

- **Sodium:** increased intake of sodium may be deleterious for arterial hypertension, heart failure and many renal diseases.

- **Milk-alkali syndrome:** Caused when large doses of $NaHCO_3$ and/or $CaCO_3$ are given together with milk or cream. The syndrome results from large quantity of Ca2+ and absorbable alkali; effect consisit of hypercalcemia, reduced secretionof parathyroid hormone, retension of phosphate, precipitation of Ca2+ salt in kidney and renal insufficiency.

ANTACIDS

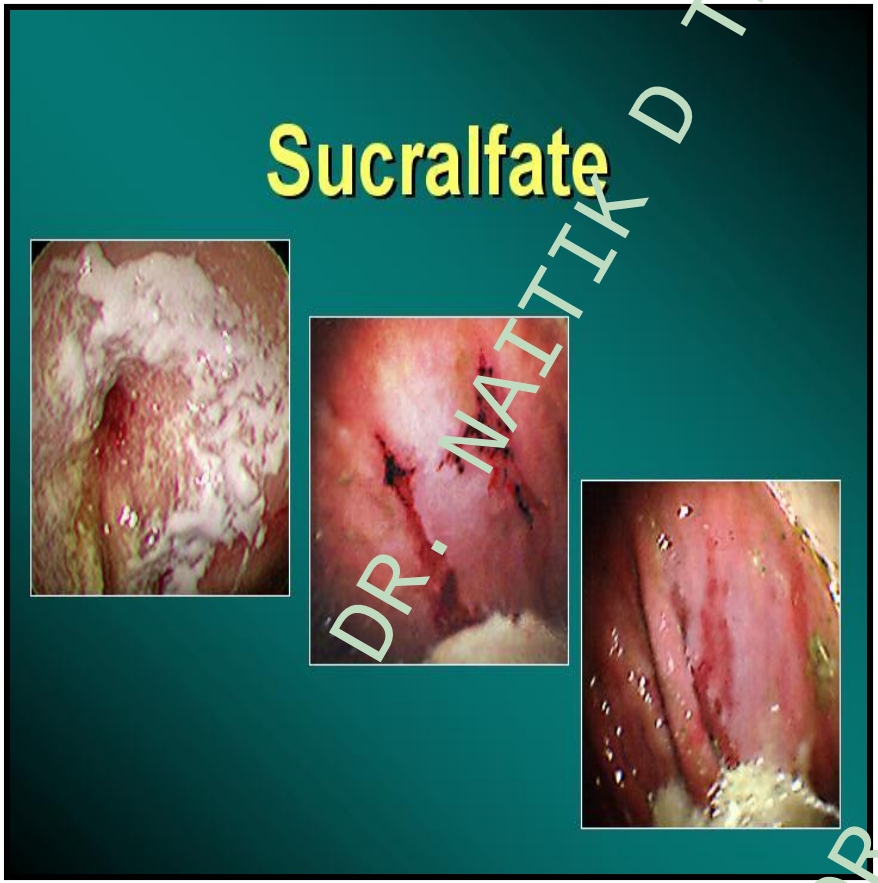
INTERACTION:

- 1. Altered pH or complex formation may alter the bioavailability of other drugs, such as tetracycline.
- 2. Urinary excretion of certain drugs may also be affected.

THEREPEUTIC USES:

- 1. Intercurrent pain relief and acidity.
- 2. Nonulcer dyspepsia and episodes of heartburn.

SUCRALFATE



MECHANISM OF ACTION:

- It mainly acts by three modes:
  1. Gel formation
  2. Cytoprotective effect
  3. Action on bile salt

SUCRALFATE

ADVERSE REACTION:

- 1. Most common side effect is constipation.
- 2. Causes aluminium overload in case of renal failure.

INTERACTION:

- Sucralfate forms a viscous layer in stomach, it may inhibit absorption of other drugs like phenytoin, digoxin, Cimetidine, ketoconazole, and flouroquinolones. Thus it is recommended that Sucralfate be taken atleast 2 hours after intake of drugs.

THEREPEUTIC USES:

- 1. Prophylaxis of stress ulcer.
- 2. Bile reflux and gastritis.

COLLOIDAL BISMUTH SUBCITRATE

MECHANISM OF ACTION:

It acts by various mechanism:

- 1. Increased secretion of mucus and bicarbonate through stimulation of mucosal PGE2 production.
- 2. CBS and mucus forms a glycoprotein-Bi complex which coats the ulcer and acts as a diffusion barrier for HCl.
- 3. Detaches H.pylori from surface of mucosa and directly kills this organism.

COLLOIDAL BISMUTH SUBCITRATE

PHARMACOKINETICS:

- 1. Most of the ingested CBS passes in feaces.
- 2. Small amount absorbed is excreted in urine.

ADVERSE REACTION:

- 1. Diarrhoea, dizziness, headache.
- 2. Prolong use cause osteodystrophy and encephalopathy due to bismuth toxicity.
- 3. Also cause blackening of toungue, dentures and stool.

THEREPEUTIC USES:

- Only used as a component of triple drug anti H.pylori regimen.

OTHER AGENTS

- 1. Anticholinergic compound Pirenzepine and telenzepine are antagonist of the M1 cholinergic receptor and may act to suppress neural stimulation of acid production.

- 2. Rebamide has cytoprotective effect including increasing prostaglandin generation in gastric mucosa as well as by scavenging reactive oxygen species.

- 3. Carbenoxolone, a component of liquorice root alter the composition and quantity of mucin and thus acts as cytoprotective.

THERAPY FOR H.PYLORI

Regimens Recommended for Eradication of *H. pylori* Infection

Drug	Dose
TRIPLE THERAPY	
1. Bismuth subsalicylate *plus*	2 tablets qid
Metronidazole *plus*	250 mg qid
Tetracycline	500 mg qid
2. Ranitidine bismuth citrate *plus*	400 mg bid
Tetracycline *plus*	500 mg bid
Clarithromycin *or* metronidazole	500 mg bid
3. Omeprazole (lansoprazole) *plus*	20 mg bid (30 mg bid)
Clarithromycin *plus*	250 or 500 mg bid
Metronidazole *or*	500 mg bid
Amoxicillin	1 g bid
QUADRUPLE THERAPY	
Omeprazole (lansoprazole)	20 mg (30 mg) daily
Bismuth subsalicylate	2 tablets qid
Metronidazole	250 mg qid
Tetracycline	500 mg qid

THERAPY FOR H.PYLORI

SIDE EFFECTS OF TRIPLE THERAPY:

- Bismuth may cause black stools, constipation, or darkening of the tongue.
- The most feared complication with amoxicillin is pseudomembranous colitis, but this occurs in <1 to 2% of patients. Amoxicillin can also lead to antibiotic-associated diarrhea, nausea, vomiting, skin rash, and allergic reaction.
- Tetracycline has been reported to cause rashes and very rarely hepatotoxicity and anaphylaxis.

THERAPY FOR H.PYLORI

SIDE EFFECTS OF TRIPLE THERAPY:

- Clarithromycin is a macrolide and is the most expensive of the antibiotics used against *H. pylori*. It is also very effective, but there is growing bacterial resistance to this drug.

- Tetracycline is effective, but tetracyclines have unique side effects among antibiotics, including skin reactions to sunlight, possible burning in the throat, and tooth discoloration. Pregnant women cannot take it.

- Metronidazole was the mainstay in initial combination regimens for *H. pylori*. As with clarithromycin, however, there continues to be growing bacterial resistance to the drug (about 25% to 35% of *H. pylori* bacteria).

THERAPY FOR H.PYLORI

QUADRUPLE THERAPY:

- Failure of *H. pylori* eradication with triple therapy is usually due to infection with a resistant organism.
- Quadruple therapy where clarithromycin is substituted for metronidazole (or vice versa) should be the next step.
- If eradication is still not achieved in a compliant patient, then culture and sensitivity of the organism should be considered.

NEW DRUG

RABEPRAZOLE: It is a newer proton pump inhibitor. Its advantages over other PPIs are as follows:

- It has been shown that rabeprazole achieve more rapid and profound inhibition of acid secretion and they sustain this suppression to provide acid control and symptom relief over 24 hours.

- Faster symptom relief with the first dose and within the first days of treatment.
- Daytime and night-time heartburn.

- Rabeprazole may play an important role in restoring a patient's quality of life by providing fast and effective relief from severe heartburn as a major GORD-related symptom.

- Moreover, the balanced hepatic metabolism of rabeprazole, involving both cytochrome P450 (CYP)-mediated reactions in the liver and non-enzymatic reactions, appears to confer an advantage over older PPIs, in that genetic polymorphisms for CYP 2C19 do not significantly influence rabeprazole clearance.

Every man is superior in some ways, In that I learn from him.

Thank you…

Formal education will make you a living; self-education will make you a fortune.

~ Abraham Lincoln