EXPECTATIONS...????
It's Quiz Time!
1. What is the function of GIT..?
2. Mention three pathologies involving the GIT..?
3. What do we mean by peptic ulcer..?
4. Mention two drugs used for treatment of peptic ulcer..?
5. What is the mechanism of action of Cimetidine..?
OBJECTIVES:

By the end of this lecture student should be able to:

1. Define the term peptic ulcer.
2. Mention the way by which acid secretion is controlled.
3. Explain different mechanisms for peptic ulcer therapy.
4. Explain how to choose the appropriate treatment for specific patients.
• What is the main function of the GIT..?

• The gastrointestinal tract is one of the major endocrine systems in the body and has its own integrative neuronal network, *The enteric nervous system*, which contains almost the same number of neurons as the spinal cord.
• It is also the site of many common pathologies.

• Medicines for treating these gastrointestinal disorders comprise some 8% of all prescriptions.
Other functions of the gastrointestinal tract that are important from the viewpoint of pharmacological intervention are:

1. Gastric secretions.
2. Emesis.
4. The formation and excretion of bile.
GASTRIC SECRETION

• The stomach secretes about 2.5 liters of gastric juice daily.

• The principal exocrine components are proenzymes such as prorennin and pepsinogen elaborated by the chief or peptic cells, and hydrochloric acid (HCl) and intrinsic factor secreted by the parietal or oxyntic cells.
• The production of acid is important for promoting proteolytic digestion of foodstuffs, iron absorption and killing pathogens.

• Mucus-secreting cells also abound among the surface cells of the gastric mucosa. Bicarbonate ions are secreted and trapped in the mucus.
Disturbances in these secretory and protective mechanisms are thought to be involved in the pathogenesis of peptic ulcer, and indeed in other types of gastric damage such as gastro-esophageal reflux disease (GERD) and injury caused by non-steroidal anti-inflammatory drugs (NSAIDs).
THE REGULATION OF ACID SECRETION BY PARIETAL CELLS

• The regulation of acid secretion is important in the pathogenesis of peptic ulcer, and constitutes a particular target for drug action.
• The principal mediators that directly- or indirectly-control parietal cell acid output are:

1. **Histamine** (a stimulatory local hormone).
2. **Gastrin** (a stimulatory peptide hormone).
3. **Acetylcholine** (a stimulatory neurotransmitter).
4. **Prostaglandins E2** and **I2** (local hormones that inhibit acid secretion).
5. **Somatostatin** (an inhibitory peptide hormone).
**Combined neurocrine, endocrine and paracrine events in the activation of gastric HCl secretion**

- **Acetylcholine** (ACh) neural input
- **Histamine** (H/K) release of histamine receptor
- **Gastrin** hormonal input
- **PARIETAL cell**
- **ECL cell** (enterochromaffin-like cell)
- **G cell** (gastrin-secreting cell)

**HOW IT WORKS AT THE RECEPTOR LEVEL**

- **Transduction-activation events**
- **ECL cell** = enterochromaffin-like cell
- **G cell** = gastrin-secreting cell
Combined neurocrine, endocrine and paracrine events in the activation of gastric HCl secretion

Acetylcholine $\circ$ neural input neurocrine

ACh receptor

histamine receptor

histamine - secreting cell

PARIETAL cell

ECL cell

histamine - secreting cell

gastrin receptor

Gastrin $\bigtriangleup$ hormonal input endocrine

paracrine release of histamine $\n$ $\n$

transduction-activation events

H/K P

HCl secretion

G cell

H-2 receptor blockers
Tagamet
Zantac
Pepcid
Prilosec
Nexium
Aciphex

H/K ATPase pump inhibitors

neural input

circulation

chemical input
DRUGS USED TO INHIBIT OR NEUTRALISE GASTRIC ACID SECRETION

• The principal clinical indications for reducing acid secretion are *peptic ulceration* (both duodenal and gastric), *GERD* (in which gastric juice causes damage to the esophagus) and the *Zollinger-Ellison syndrome* (a rare condition that is caused by a gastrin-producing tumor).
• Therapy of peptic ulcer and reflux esophagitis aims to decrease the secretion of gastric acid with H$_2$ receptor antagonists or proton pump inhibitors, and/or to neutralize secreted acid with antacids.

• These treatments are often coupled with measures to eradicate *H. pylori*. 
HISTAMINE H$_2$ RECEPTOR ANTAGONISTS

- H$_2$ receptor antagonists competitively inhibit histamine actions at all H$_2$ receptors.
- Their main clinical use is as inhibitors of gastric acid secretion.
- Inhibit histamine- and gastrin-stimulated acid secretion.
- Pepsin secretion also falls with the reduction in volume of gastric juice.
• These agents not only decrease both basal and food-stimulated acid secretion by 90% or more, but numerous clinical trials indicate that they also promote healing of gastric and duodenal ulcers. However, relapses are likely to follow after cessation of treatment.
The drugs used are *Cimetidine, Ranitidine* (sometimes in combination with bismuth) *Nizatidine* and *Famotidine*. There is little difference between them.
The drugs are generally given orally and are well absorbed, although preparations for Intramuscular and Intravenous use are also available (except Famotidine).

Dosage regimens vary depending on the condition under treatment. Low-dosage over-the-counter formulations of Cimetidine, Ranitidine and Famotidine are available for short-term uses, without prescription, from pharmacies.
• *Unwanted effects* are rare.

• Diarrhea, dizziness, muscle pains, alopecia, transient rashes, and confusion in the elderly have been reported.
• Cimetidine sometimes causes *Gynaecomastia* in men and, rarely, a decrease in sexual function.

• Cimetidine also *inhibits cytochrome P450*. 
PROTON PUMP INHIBITORS

• The first proton pump inhibitor was Omeprazole, which irreversibly inhibits the 
  $\text{H}^+/$$\text{K}^+$ ATPase (the proton pump), the terminal 
  step in the acid secretory pathway

• Both basal and stimulated gastric acid 
  secretion are reduced.

• The drug is a weak base, and accumulates in 
  the acid environment of the canaliculi of the 
  stimulated parietal cell where it is activated.
• Other proton pump inhibitors (all of which are very similar) include *Esomeprazole, Lansoprazole, Pantoprazole* and *Rabeprazole*.
• Oral administration is the most common route of administration, although some injectable preparations are available.

• Omeprazole is given orally, but as it degrades rapidly at low pH, it is administered as capsules containing enteric-coated granules. It is absorbed and, from the blood, passes into the parietal cells and then into the canaliculi.
• Increased doses give disproportionately higher increases in plasma concentration (possibly because its inhibitory effect on acid secretion improves its own bioavailability).
• Although its half-life is about 1 h, a single daily dose affects acid secretion for 2-3 days, because it accumulates in the canaliculi and inhibits H\(^+\)-K\(^+\)-ATPase irreversibly.

• With daily dosage, there is an increasing antisecretory effect for up to 5 days, after which a plateau is reached.
• *Unwanted effects* of this class of drugs are uncommon.

• They may include headache, diarrhea (both sometimes severe) and rashes. Dizziness, somnolence, mental confusion, impotence, gynaeecomastia, and pain in muscles and joints have been reported.
• Proton pump inhibitors should be used with caution in patients with liver disease, or in women who are pregnant or breastfeeding. The use of these drugs may 'mask' the symptoms of gastric cancer.
ANTACIDS

• Antacids are the simplest way to treat the symptoms of excessive gastric acid secretion.
• They directly neutralize acid, which also has the effect of inhibiting the activity of peptic enzymes, which practically ceases at pH 5.

• Given in sufficient quantity for long enough, they can produce healing of duodenal ulcers but are less effective for gastric ulcers.
• Most antacids in common use are salts of magnesium and aluminium.

  • *Magnesium salts* = diarrhea
  • *Aluminium salts* = constipation

  • *So mixtures of these two can, happily, be used to preserve normal bowel function.*

• Some preparations of these substances contain high concentrations of sodium.
• *Magnesium hydroxide* is an insoluble powder that forms magnesium chloride in the stomach. It does not produce systemic alkalosis, because Mg\(^{2+}\) is poorly absorbed from the gut.
• *Magnesium trisilicate* is an insoluble powder that reacts slowly with the gastric juice, forming magnesium chloride and colloidal silica. This agent has a prolonged antacid effect, and it also adsorbs pepsin.
• Aluminium hydroxide gel forms aluminium chloride in the stomach; when this reaches the intestine, the chloride is released and is reabsorbed.

• Aluminium hydroxide raises the pH of the gastric juice to about 4, and also adsorbs pepsin. Its action is gradual, and its effect continues for several hours.
• Colloidal aluminium hydroxide combines with phosphates in the gastrointestinal tract, and the increased excretion of phosphate in the faeces that occurs results in decreased excretion of phosphate via the kidney. This effect has been used in treating patients with chronic renal failure.
Alginates

- **Alginates or Simethicone** are sometimes combined with antacids. Alginates are believed to increase the viscosity and adherence of mucus to the esophageal mucosa, forming a protective barrier, whereas Simethicone is an anti-foaming agent, intended to relieve bloating and flatulence.
TREATMENT OF HELICOBACTER PYLORI INFECTION

• *H. pylori* infection has been implicated as a causative factor in the production of gastric and, more particularly, duodenal ulcers, as well as a risk factor for gastric cancer.
Certainly, eradication of *H. pylori* infection promotes rapid and long-term healing of ulcers, and it is routine practice to test for the organism in patients presenting with suggestive symptoms.
• If the test is positive, then the organism can generally be eradicated with a 1 or 2 week regimen of 'triple therapy' comprising a proton pump inhibitor in combination with the antibacterial agents **Amoxicillin** and **Metronidazole** or **Clarithromycin**, 

• other combinations are also used.
• Bismuth-containing preparations are sometimes added.
• While elimination of the bacillus can produce long-term remission of ulcers, reinfection with the organism can occur.
Some agents, termed Cytoprotective, are said to enhance endogenous mucosal protection mechanisms and/or to provide a physical barrier over the surface of the ulcer.
• *Bismuth chelate* is used in combination regimens to treat *H. pylori*.

• It has toxic effects on the bacillus, and may also prevent its adherence to the mucosa or inhibit its bacterial proteolytic enzymes.
• It is also believed to have other mucosal protecting actions, by mechanisms that are unclear, and is widely used as an over-the-counter remedy for mild gastrointestinal symptoms.
• Very little is absorbed, but if renal excretion is impaired, the raised plasma concentrations of bismuth can result in encephalopathy.

• *Unwanted effects* include nausea and vomiting, and blackening of the tongue and faeces.
• **Sucralfate** is a complex of aluminium hydroxide and sulfated sucrose, which releases aluminium in the presence of acid.

• The residual complex carries a strong negative charge and binds to cationic groups in proteins, glycoproteins, etc.
• It can form complex gels with mucus, an action that is thought to decrease the degradation of mucus by pepsin and to limit the diffusion of $\text{H}^+$. 
• Sucralfate can also inhibit the action of pepsin and stimulate secretion of mucus, bicarbonate and prostaglandins from the gastric mucosa.

• All these actions contribute to its mucosal protecting action.

• Given orally.
• It reduces the absorption of a number of other drugs, including **Fluoroquinolones**, **Theophylline**, **Tetracycline**, **Digoxin** and **Amitriptyline**.
• Because it requires an acidic environment for activation, antacids given concurrently or prior to its administration will reduce its efficacy.

• *Unwanted effects* are few, the most common being constipation. Less common effects include dry mouth, nausea, vomiting, headache, and rashes.
• **Misoprostol**: Prostaglandins of the E and I series have a generally protective action in the gastrointestinal tract, and a deficiency in endogenous production (after ingestion of a NSAID, for example) may contribute to ulcer formation.

• Misoprostol is a stable analogue of prostaglandin E₁.
• It is given orally and is used to promote the healing of ulcers or to prevent the gastric damage that can occur with chronic use of NSAIDs.
• It exerts a direct action on the ECL cell (and possibly parietal cell) inhibiting the basal secretion of gastric acid as well as the stimulation of production seen in response to food, pentagastrin and caffeine.

• It also increases mucosal blood flow and augments the secretion of mucus and bicarbonate.
• *Unwanted effects* include diarrhea and abdominal cramps.

• uterine contractions can also occur, so the drug should not be given during pregnancy (unless deliberately to induce a therapeutic abortion).
Guidelines for Peptic Ulcer treatment
So..

Don't Forget...
Pink Bismuth Tablets

- Fast Acting
- Soothing Coating Action
- Provides relief for indigestion, upset stomach, heartburn, diarrhea and nausea

Sodium Free

30 Chewable Tablets
Omeprazole
Delayed Release Tablets 20 mg
Acid Reducer

Treats Frequent Heartburn!
Occurring 2 Or More Days A Week

42 Tablets
Three 14-day courses of treatment

Perrigo®
NDC 45802-888-55
PlusPHARMA
SIMETHICONE 80 mg

Anti Gas
Acts fast to relieve:
✓ Bloating
✓ Discomfort
✓ Pressure

Compare to the active ingredient in Mylanta® Gas®

This product is not manufactured or distributed by Johnson & Johnson • Merck Consumer Pharmaceuticals Co., owner of the registered trademark Mylanta®.

100 CHEWABLE TABLETS • 80 mg
THAT'S THE END

IF YOU HAVE ANY QUESTIONS PLEASE FEEL FREE TO ASK??
ANY QUESTIONS...???
THANKS