LECTURE 4

PATHOPHYSIOLOGY OF THE GASTROINTESTINAL SYSTEM.
DISORDERS OF ESOPHAGUS AND STOMACH.

I. MANIFESTATIONS OF GI SYSTEM DISORDERS
   1. Altered digestion
   2. Altered bowel movements
   3. Gastrointestinal bleeding
   4. Abdominal pain

II. DISORDERS OF OESOPHAGUS
   1. Achalasia
   2. Gastroesophageal reflux (GERD)
   3. Hiatal hernia

III. DISORDERS OF STOMACH
   1. Gastritis
   2. Peptic ulcer
   3. Stress ulcers

I. MANIFESTATIONS OF GI SYSTEM DISORDERS

Upper GI complaints include chest pain, chronic and recurrent abdominal pain, dyspepsia, lump in the throat, halitosis, hiccups, nausea and vomiting, and rumination. Lower GI complaints include constipation, diarrhea, gas and bloating, abdominal pain and rectal pain, bleeding.

According to the digestive process that is altered, the manifestations of GI disorders are classified in:

(1) Manifestations of altered digestion:
   - Vomiting
   - Dysphagia (difficult swallowing)
   - Odynophagia (painful swallowing)
   - Anorexia (self-induced starvation, resulting in marked weight loss)

(2) Manifestations of altered bowel movements:
   - Diarrhea
   - Constipation
1.1 Dysphagia

Definition: dysphagia usually refers to the difficulty of swallowing = oropharyngeal dysphagia or it refers to the sensation that foods and or liquids are somehow hindered in their passage from the mouth to the stomach = esophageal dysphagia.

1.1.1 Oropharyngeal dysphagia: also called “high” dysphagia, due to an oral or pharyngeal location.

- Difficulty initiating swallow
- Nasal regurgitation
- Coughing
- Nasal speech
- Diminished cough reflex
- Choking (laryngeal penetration and aspiration may occur without concurrent choking or coughing).
- Dysarthria and diplopia (may accompany neurologic conditions that cause oropharyngeal dysphagia).
- Halitosis may be present in patients with a large residue-containing Zenker’s diverticulum, also with advanced achalasia or long-term obstruction with luminal accumulation of decomposing residue.

1.1.2 Esophageal dysphagia: also called “low” dysphagia, due to location in the distal esophagus, although some patients with esophageal dysphagia (i.e., achalasia) may describe it in the cervical region mimicking oropharyngeal dysphagia.

- Dysphagia that occurs equally with solids and liquids, often involves an esophageal motility problem. This suspicion is reinforced when intermittent dysphagia for solids and liquids is associated with chest pain.
- Dysphagia that occurs only with solids but never with liquids suggests the possibility of mechanical obstruction with luminal stenosis to diameter < 15 mm. If progressive, peptic stricture or carcinoma must be considered:
  - patients with peptic strictures usually have a long history of heartburn and regurgitation, but no weight loss.
  - patients with esophageal cancer tend to be older men with marked weight loss.

Causes of both types of dysphagia are listed in Table 1.

<table>
<thead>
<tr>
<th>Oropharyngeal dysphagia</th>
<th>Esophageal dysphagia</th>
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<tbody>
<tr>
<td>Mechanical and obstructive causes</td>
<td></td>
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<tr>
<td>Infections (e.g., retroperitoneal abscesses)</td>
<td></td>
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<tr>
<td>Mucosal diseases</td>
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<tr>
<td>Peptic stricture secondary to gastroesophageal reflux disease</td>
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</tbody>
</table>
1.2 Vomiting

- **Definition:** The *forceful expulsion of gastric content through the mouth*, caused by involuntary contraction of the abdominal musculature when the gastric fundus and lower esophageal sphincter are relaxed. It is both a **protective reflex** (prevents the extension of the disease and eliminates the harmful agents from the GIT) and a **GI symptom** (associated with nausea and retching).

- **Causes:**
  1. **Vomiting associated with GI disorders:**
     - alteration in the integrity of GI tract wall due to:
     - inflammatory changes (e.g., gastroenteritis, cholecystitis, appendicitis)
     - irritating substances (chemical – alcohol, biological - infections)
     - alteration in the motility of the GI tract (e.g., overdistension)
  2. **Vomiting associated with non-GI disorders:**
     - Neurological disturbances (meningitis, high intracranial pressure, cerebral ischemia)
     - Metabolic disorders (diabetic ketoacidosis, uremia, cholestasis)
     - Radio- and chemotherapy
     - Labyrinthine disorders (motion sickness) or severe pain (AMI)
  3. **Vomiting associated with non-pathologic causes:**
     - First trimester of pregnancy (*vomitus matutinus*).

- **Pathophysiology**
Vomiting is stimulated in certain areas of the brain (hypothalamus) and the cerebellum through sensory stimuli or injury. Vomiting is also provoked by certain labyrinthine signals, and from the chemoreceptive trigger zone located on the floor of the 4th ventricle close to area postrema. Vomiting is a coordinated sequence (by the vomiting centre in the medulla) of abdominal muscle contractions and reverse esophageal peristalsis:

1. Profound inspiration with closed epiglottis (respiration is blocked).
2. Peristaltic contractions in the stomach and small intestine stop and the pyloric sphincter closes.
3. Access to adjacent airways is cut off as:
   - the glottis closes the larynx’s opening,
   - the soft palate moves back to prevent nasal passage.
4. Somatomotor signals from the vomiting center induces an abrupt increase of abdominal pressure due to contraction of diaphragm, intercostal muscles and abdominal wall.
5. The high pressure applied to the stomach and its anti-peristaltic contractions will force the gastric content toward the esophagus.
6. Parasympathetic stimulation induces LES (lower esophageal sphincter) relaxation, which forces the gastric content into the esophagus and into the mouth.

N.B. Neurotransmitters/receptors = dopamine, serotonin / opioid receptors
- Dopamine antagonists (chlorpromazine): Abolish vomiting via stimulation of trigger chemoreceptor zone
- Serotonin antagonists (granisetron, ondansetron): Abolish vomiting due to radio/chemotherapy.

- **Complications**
  - **Short duration episodes**: minimal disturbances
  - **Prolonged or severe episodes**: serious systemic consequences:
    - Loss of fluid: hypovolemia and dehydration
    - Loss of electrolytes: hyponatremia, hypokalemia
    - Acid-base disturbance: metabolic alkalosis (loss of HCl leads to increased level of plasma HCO₃⁻)
    - Deficiencies of essential nutrients, especially vitamins: malnutrition and weight loss
    - Dental caries, due to acid
    - Bleeding into the esophageal lumen due to laceration (longitudinal tear) of the mucosa/submucosa of lower esophagus (the Mallory-Weiss syndrome)
    - Aspiration of vomitus: pulmonary damage = aspiration pneumonia:
      - Coma (alcoholic)
      - Deep anesthesia.

1.3 Diarrhea
- **Definition**: increased stool fluidity, increased volume of feces (> 200 g/day) or its frequency (> 2/days); it can be either acute (< 2 weeks) or chronic (> 4 weeks).
- **Cause:** *increased colonic fluid volume ➔ colonic distension ➔ the defecation reflex is activated.*

- **Etiopathogeny**

Normally, the small intestine and colon absorb 99% of fluid resulting from oral intake and GI tract secretions—a total fluid load of about 9-10 L daily. Thus, even small reductions (i.e., 1%) in intestinal water absorption or increases in secretion ➔ increase water content ➔ diarrhea.

**N.B. Absorption of water and electrolytes**

a) **At the small intestine level (= the major site of water retention):**

- **paracellular pathway:** passing of water and electrolytes through the tight junctions of the epithelial cells. The resistance of tight junctions is an important determinant of the relative degree that transcellular transport occurs, and this resistance varies throughout the intestine: Tight junctions are most leaky in the duodenum and jejunum, becoming progressively less leaky (tighter) in the ileum and colon.

- **transcellular pathway ➔ passing through the 2 membranes:**
  - apical membrane via 3 transporters:
    - **Anionic transporter Cl-HCO₃⁻ exchanger:** rapid transport ➔ net secretion of HCO₃⁻.
    - **Cationic transporter Na⁺-H⁺ exchanger.**
    - **Na-coupled glucose transporter (SGLT1)** takes up two Na⁺ ions with each glucose molecule. This property is central to the development of effective therapeutic oral rehydration solutions that contain glucose, Na⁺, Cl⁻, and HCO₃⁻ to enhance water and electrolyte uptake during severe diarrhea (eg, cholera).

  - **latero-basal membrane with ionic pomp:**
    - sodium pomp - ATP-ase Na⁺-K⁺ dependent.

b) **At the large intestine level:**

- Cationic transporter Na⁺-H⁺ exchanger is NOT present
- Anionic transporter Cl⁻-HCO₃⁻ exchanger is present
- The active absorption of Na⁺ is not influenced by glucose
- Sodium pomp from the latero-basal membrane induces an electrochemical gradient which leads to decreased absorption of K⁺ (increased K⁺ concentration in the feces)
- Water diffuses passively along the osmotic gradients

- **Causes** of diarrhea are listed in Table 2.

**Table 2. Most frequent causes of diarrhea.** (After The Merck Manual.


<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Norovirus, rotavirus</td>
</tr>
<tr>
<td>Viral infection</td>
<td>Salmonella, Campylobacter, or Shigella sp; Escherichia coli; Clostridium difficile</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>Giardia sp, Entamoeba histolytica, Cryptosporidium sp</td>
</tr>
<tr>
<td>Parasitic infection</td>
<td>Staphylococci, Bacillus cereus, Clostridium perfringens</td>
</tr>
<tr>
<td>Food poisoning</td>
<td>Laxatives, Mg-containing antacids, caffeine, antineoplastic drugs, many antibiotics, colchicine, quinine/quinidine, prostaglandin analogs, excipients (eg, lactose) in elixirs</td>
</tr>
<tr>
<td>Chronic</td>
<td></td>
</tr>
</tbody>
</table>
Drugs
Functional
Dietary factors
Inflammatory bowel disease
Surgery
Malabsorption syndromes
Tumors
Endocrine tumors
Endocrine

See Acute Irritable bowel syndrome Caffeine; fructose; hexitols, sorbitol, and mannitol; lactose; Mg. Ulcerative colitis, Crohn's disease Intestinal or gastric bypass or resection Celiac disease, pancreatic insufficiency Carbohydrate intolerance (particularly lactose intolerance) Colon carcinoma, lymphoma, villous adenoma of the colon Vipoma, gastrinoma, carcinoid, mastocytosis, medullar carcinoma of the thyroid Hyperthyroidism Diabetes (multifactorial concurrent celiac disease, pancreatic insufficiency, autonomic neuropathy)

4 basic mechanisms are responsible for most clinically significant diarrheas:

- **Secretory diarrhea**: active secretion of H\(_2\)O and inhibition of H\(_2\)O reabsorption.
- **Osmotic diarrhea**: osmosis, i.e. increased influx of water and sodium into the lumen of the bowel.
- **Exudative diarrhea**: exudation of water, proteins and mucus from the sites of intestinal inflammation into the lumen.
- **Diarrhea due to motility disturbances**: decreased/increased peristaltism.

_N.B. In many disorders, more than one mechanism is active. For example, diarrhea in inflammatory bowel disease results from mucosal inflammation, exudation into the lumen, and from multiple secretagogues and bacterial toxins that affect enterocyte function._

1.3.1 Secretory diarrhea

- **Definition**: enhanced water secretion and reabsorption inhibition into the intestinal lumen in response to irritation.
- **Causes**

  Secretory diarrhea occurs when Cl\(^-\) secretion of the small intestinal mucosa is activated.

  Within the mucosal cells, _Cl\(^-\) is secondarily actively enriched by a basolateral Na\(^+\)-K\(^+\)-2Cl\(^-\) symporter_ and _is secreted via luminal Cl\(^-\) channels_. These open more frequently when the intracellular concentration of cAMP rises. cAMP is formed in greater amounts in the presence of:

  - **bacterial enterotoxins**: Vibrio cholerae, E.coli, Staph. Aureus (most enterotoxins block Na\(^+\)-H\(^+\) exchange, which is an important driving force for fluid absorption in the small bowel and colon)
  - **laxatives**
  - **unabsorbed bile salts** (ileal resection with impaired recycling)
  - **overproduction of endogenous endocrine products**:
    - **VIP** (Vasoactive Intestinal Peptide) by pancreatic islet cell tumors
    - **Serotonin** by carcinoid tumors.

_Obs. Effects of increased [AMP\(_c\)_]:_
Inhibition of cationic transporter $\text{Na}^+\text{-H}^+$ decrease of $\text{Na}^+$ absorption

Stimulation of the anionic transporter $\text{Cl}^-\text{-HCO}_3^-$

NOT affected:

- $\text{Na}^*$ Glu transporter → administration of glucosate physiological serum allows the correction of hydro-electrolytes disturbances!
- $\text{Na}^+$ pomp from the latero-basal membrane.

1.3.2 Osmotic diarrhea

- Definition: increased amount of poorly absorbable, osmotic active solutes → remain in the bowel
  → retain water into the intestinal lumen, due to:
  - faulty digestion
  - impaired absorption
  - High intake of osmotically active solutes:
    - sorbitol (in “sugar free” sweets/medication)
    - fructose (lemonades, honey)
    - magnesium salts (antacids, laxatives)
    - anions (sulphate, phosphate, citrate).

1.3.3 Exudative diarrhea: exudation of water, mucus, proteins from the sites of active intestinal inflammation into the lumen.

E.g.: Inflammatory bowel disease - IBD (Crohn disease, ulcerative colitis).

1.3.4 Diarrhea due to motility disturbances

- Mechanisms:
  - peristaltism inhibition → intestinal stasis → bacterial proliferation.
  - decreased contact time of chyme with the absorptive surface → increased amount of fluid in the colon that overwhelms its absorptive capacity (diabetes mellitus, postgastrectomy dumping syndrome).
  - premature emptiness of the colon due to:
    - abnormal content (infectious diarrhea, hydroxylated fatty acids)
    - intrinsic irritability (irritable bowel syndrome).

- Complications may result from diarrhea of any etiology:
  - Fluid loss → dehydration, electrolyte loss (Na, K, Mg, Cl) → vascular collapse. Collapse can develop rapidly in patients who have severe diarrhea (e.g., patients with cholera) or are very young, very old, or debilitated.
  - $\text{HCO}_3^-$ loss → metabolic acidosis.
Hypokalemia can occur when patients have severe or chronic diarrhea or if the stool contains excess mucus.

Hypomagnesaemia after prolonged diarrhea → tetany.

### 1.4 Constipation

- **Definition:** constipation is a symptom which can be interpreted differently:
  - difficult or infrequent passage of stool,
  - hardness of stool, or
  - a feeling of incomplete evacuation.

Constipation is associated with abdominal pain, nausea, fatigue, anorexia that are actually symptoms of an underlying problem (eg, irritable bowel syndrome, depression).

- **Etiology**

Acute constipation suggests an organic cause, whereas chronic constipation may be organic or functional (see table 3).

In many patients, constipation is associated with sluggish movement of stool through the colon, due to

- drugs,
- organic conditions, or
- a disorder of defecator function (ie, pelvic floor dysfunction), or
- a disorder that results from diet (eg, all caffeine-containing beverages especially coffee with chicory; asparagus and cruciferous vegetables such as broccoli, cauliflower, cabbage, and Brussels sprouts; bran cereal, whole wheat bread, high-fiber foods; rice, bread, potatoes, pasta; bananas).

Patients with disordered defecation:

- do not generate adequate rectal propulsive forces,
- do not relax the puborectalis and the external anal sphincter during defecation, or both.

Excessive straining, perhaps secondary to pelvic floor dysfunction, may contribute to anorectal pathology (eg, hemorrhoids, anal fissures, and rectal prolapse) and possibly even to syncope.

Fecal impaction, which may cause or develop from constipation, is also common among elderly patients, particularly with prolonged bed rest or decreased physical activity. It is also common after barium has been given by mouth or enema.

<table>
<thead>
<tr>
<th>Table 3. Most frequent causes of constipation. (After The Merck Manual. [<a href="http://www.merckmanuals.com/professional/gastrointestinal_disorders/symptoms_of_gi_disorders/constipation.html">http://www.merckmanuals.com/professional/gastrointestinal_disorders/symptoms_of_gi_disorders/constipation.html</a>])</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causes</strong></td>
</tr>
<tr>
<td>Acute</td>
</tr>
<tr>
<td>Adynamic ileus</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
</tbody>
</table>
II. DISORDERS OF ESOPHAGUS

1.1 Achalasia

- **Definition.** Achalasia is a *neurogenic esophageal motility* characterized by a *loss of normal esophageal peristalsis* and *incomplete or abnormal relaxation of the lower esophageal sphincter* (LES). The LES must relax during swallowing, but if it does not and remains contracted, it will act as a barrier to the food destined to enter the stomach. *Secondary dilatation of the aperistaltic esophagus proximal to the constriction* occurs.

- **Etiopathogenesis**
  
  Achalasia is thought to be caused by a *loss of ganglion cells in the myenteric plexus of the esophagus* ➔ *denervation of esophageal muscle.*

  **Etiology of the denervation is unknown,** although a *viral cause is suspected,* and *certain tumors* may cause achalasia either by direct obstruction or as a paraneoplastic process.

  *Secondary achalasia* may occur *in Chagas disease* because of the *destruction of ganglion cells infected with Trypanosoma cruzi.*

- **Clinical features:**
  
  - Onset is insidious, and *progression is gradual* over months or years.
  - *Dysphagia for both solids and liquids* is the major symptom.
  - *Nocturnal regurgitation of undigested food:* in about 33% of patients ➔ *cough and pulmonary aspiration.*
  - *Chest pain* is less common but may occur on swallowing or spontaneously.
  - *Mild to moderate weight loss.*

  **Obs.** *When weight loss is pronounced,* particularly in elderly patients whose symptoms of dysphagia developed rapidly, *achalasia secondary to a tumor of the gastroesophageal junction* should be considered.

- **Complications:**
  
  *Pulmonary aspiration* and the presence of *cancer* are the determining prognostic factors!
− Nocturnal regurgitation and coughing suggest aspiration, with a high risk of pulmonary infectious complications which are difficult to manage.
− Incidence of esophageal cancer in patients with achalasia may be increased; this point is controversial.

1.2 Gastroesophageal reflux disease (GERD)

- **Definition.** *Reflux of gastric contents into the esophagus* is a common disorder, typically associated with *incompetence of the LES* (which in normal circumstances prevents the entry of the gastric contents into the esophagus).

- **Etiopathogeny**
GERD develops because of malfunction of the LES: *lowering of tension in the lower esophageal sphincter* ➔ gastric pressure drives acidic chyme into the esophagus.

Reflux may be caused by:
- *Temporary increase in intraabdominal pressure* (e.g., after overeating or drinking carbonated drinks),
- *Prolonged intraabdominal pressure* in pregnancy or obesity,
- *Protracted LES relaxation* and *uncoordinated contraction* due to the action of alcohol, fatty food, cigarettes, and drugs (e.g., morphine and diazepam),
- *Hiatal hernia*
- *Scleroderma* (Fibrous tissue replacing smooth muscle cells weakens the sphincter: in 70% of patients with scleroderma).

- **Clinical features:**
The most prominent symptom of GERD is *heartburn, with or without regurgitation* of gastric contents into the mouth.
- *Infants* present with *vomiting, irritability, anorexia*, and sometimes *symptoms of chronic aspiration*.
- Both *adults and infants with chronic aspiration* may have *cough, hoarseness, or wheezing*.
- *Esophagitis ➔ odynophagia* and even *esophageal hemorrhage*, which is usually occult but can be massive.
- *Peptic stricture ➔ gradually progressive dysphagia for solid foods*.
- *Peptic esophageal ulcers ➔ pain* usually localized to the xiphoid or high substernal region. Peptic esophageal ulcers heal slowly, tend to recur, and usually leave a stricture on healing.

- **Complications** of long-lasting GERD are:
  - *Esophagitis*
  - *Barrett esophagus* (columnar metaplasia of normal squamous epithelium of distal esophagus, with a high risk of adenocarcinoma)
  - *Esophageal bleeding* (with melena or hematemesis)
1.3 Hiatus hernia

- **Definition.** Hiatus (hiatal) hernia is a *protrusion of the stomach through the diaphragmatic hiatus.*
- **Etiology** is usually *unknown*, but a hiatus hernia is thought to be *acquired through stretching of the fascial attachments between the esophagus and diaphragm at the hiatus* (the opening through which the esophagus traverses the diaphragm).
- **Pathophysiology**

  Two forms are recognized:
  - **Sliding hernia** (90%): *gastroesophageal junction is pulled into the thorax* and is found *above the diaphragm.*
    - In most instances, it is *asymptomatic* and diagnosed accidentally during the workup of the patient for some other disease.
    - It may be associated with *GERD*, *heartburn*, and *dysphagia*.
  - **Paraesophageal hernia** (10%): *gastroesophageal junction is in the normal location*, but a portion of *the stomach rolls up beside it into the thorax.*
    - In most instances, it is *asymptomatic*, but the invaginated gastric mucosa may become strangulated by the diaphragm.

III. STOMACH DISORDERS

1.1 Gastritis

- **Definition:** *superficial inflammation of the stomach* lining *with mucosal injury/erosion*, but with *NO penetration of submucosa and muscularis*.
- **Classification**
  - Gastritis is classified as *erosive or nonerosive based on the severity of mucosal injury.*
  - It is also classified *according to the site of involvement* (ie, cardia, body, antrum).
  - Gastritis can be further classified histologically as *acute or chronic based on the inflammatory cell type.*

  N.B. No classification scheme matches perfectly with the pathophysiology; a large degree of overlap exists. Some forms of gastritis involve acid-peptic and *H. pylori disease*. Additionally, the term is often loosely applied to nonspecific (and often undiagnosed) abdominal discomfort and gastroenteritis.

1.1.1 Acute gastritis

- **Definition:** *superficial inflammation of gastric mucosa*, due to *PMN infiltration of the mucosa of the antrum and body.*
### Causes:
- **Ingested irritants:**
  - Alcohol
  - Aspirin / Nonsteroidal anti-inflammatory drugs (NSAIDs): acute gastritis combined with bleeding erosions of the mucosa → acute erosive gastritis
- **Acute ischemia:** stress, surgery, trauma, shock, burns.

#### 1.1.2 Chronic gastritis

- **Definition:** *inflammatory cell infiltration* with *gastric mucosal atrophy* and *loss of glands* (not evident to endoscopy).

It predominantly involves:
- the antrum → loss of G cells → *decreased gastrin secretion*, or
- the corpus → loss of oxyntic glands → *reduced acid, pepsin, and intrinsic factor*.

- **Classification**
  
  (1) **Chronic Atrophic Gastritis (type A) = autoimmune fundal gastritis: autoantibodies to parietal cells, intrinsic factor (IF) and gastrin receptor** with risk of:
  - decreased acid secretion → gastric adenocarcinoma
  - decreased absorption of vitamin B₁₂ → pernicious anemia
  - hyperplasia of enterochromaffin-like cells → neuroendocrine (carcinoid) tumors producing serotonin → flushing and diarrhea.

  (2) **Chronic Active Gastritis (type B) = infectious antral gastritis associated with H. pylori infection.**

In early stages of the disease, it is possible to distinguish type A from type B gastritis histologically, but in advanced stages, such a distinction is not always possible.

In the early stages of autoimmune gastritis, the *mucosa of the fundus and body is infiltrated* with *lymphocytes and plasma cells*.

Acute stages of *H. pylori infection* are associated with *infiltrates of neutrophils in the glands and the lamina propria*. H. *pylori* can be seen in the gastric glands, mostly *in the pyloric antrum*.

As the diseases progresses, both forms of chronic gastritis are accompanied by:
- Atrophy of gastric glands
- Intestinal metaplasia
- Lymphocytic follicles in the atrophic mucosa.

In this advanced stage of the disease, it is difficult to find *H. pylori*, which does not survive in the metaplastic intestinal glands. Reliable histopathologic distinction of type A from type B chronic gastritis becomes impossible in the disease’s later stages.

#### 1.2 Peptic Ulcer Disease
- Definition: disorders of the upper GI tract (esophagus, stomach, duodenum) appearing as localized erosions of mucosa with submucosa and muscularis penetration.

- Localization:
  - stomach and duodenum (98%)
  - rarely: small intestine (jejunum/ileum), esophagus.

- Pathogenesis
The pathogenesis of peptic ulcers is not fully understood. It is, however, generally accepted that the mucosal ulcerations are chemically mediated and develop because of the action of HCl and pepsin on a “weakened” or “susceptible” gastric or duodenal mucosa. Because the gastric acid of ulcer patients does not contain unusually high quantities of HCl or pepsin, it is postulated that the glands are damaged by a back-diffusion of hydrogen ions.

!!! In gastric ulcer the protective factors are decreased, i.e., mucosal defense mechanisms, while in duodenal ulcer the hostile factors are increased, i.e., hypersecretion of gastric acid and pepsin and too rapid gastric emptying.

(1) PROTECTIVE FACTORS. Normally, the GI mucosa is protected by several distinct mechanisms:

- The gastric mucosal barrier (mucus and bicarbonate): creates a pH gradient from the gastric lumen (low pH) to the mucosa (neutral pH). The mucus serves as a barrier to the diffusion of acid and pepsin.

- Epithelial cells remove excess hydrogen ions (H⁺) via membrane transport systems and have tight junctions (specialized membrane structures that join adjacent epithelial cells) which effectively block the diffusion of hydrogen ions back into the submucosa.

- Mucosal blood flow removes excess acid that has diffused across the epithelial layer.

- Several growth factors (eg, epidermal growth factor, insulin-like growth factor I) and prostaglandins have been linked to mucosal repair and maintenance of mucosal integrity.

(2) FACTORS THAT INTERFERE WITH THESE MUCOSAL DEFENSES:

- A. NSAIDs promote mucosal inflammation and ulcer formation (sometimes with GI bleeding) both topically and systemically:
  - inhibit prostaglandin production via blockage of the enzyme cyclooxygenase (COX) ➔ reduced gastric blood flow, reduced mucus and HCO₃⁻ secretion, and decreased cell repair and replication.
  - NSAIDs are weak acids and are nonionized at gastric pH ➔ diffuse freely across the mucus barrier into gastric epithelial cells, where H⁺ ions are liberated ➔ cellular damage.
  - Because gastric prostaglandin production involves the COX-1 isoform ➔ NSAIDs that are selective COX-2 inhibitors have fewer adverse gastric effects than other NSAIDs.
Ceasing the NSAIDs administration, antacid treatment and suppression of gastric acid with histamine-2 blockers promote healing of ulcers.

**B. Infection: *H. pylori*** is found in 90% of duodenal and 65% of gastric ulcer patients.

*H. pylori* is a spiral-shaped, *gram-negative organism* that has adapted to thrive in acid (*due to ammonia* produced by *H. pylori*) and colonizes the mucus layer & binds to surface epithelial cells.

Effects of *H. pylori* infection vary depending on the location within the stomach:

- **Antral-predominant infection** ➔ increased gastrin production, probably *via local impairment of somatostatin release* ➔ acid hypersecretion ➔ predisposition to prepyloric and duodenal ulcer.
- **Body-predominant infection** ➔ gastric atrophy and decreased acid production, possibly *via increased local production of IL-1β* ➔ predisposition to gastric ulcer and adenocarcinoma.
- Some patients have **mixed infection** of both antrum and body with varying clinical effects.
- **H. pylori** secretes *urease, protease, and phospholipases* ➔ mucosal injury and may serve as “**barrier breakers**” ➔ chemical injury of mucosal cells.

*Eradication of *H. pylori* infections contributes to the healing of peptic ulcers.*

**C. Neuroendocrine factors:** The secretion of gastric juices is under *neuroendocrine control*, which becomes *dysregulated in peptic ulcer patients*. Stress or endocrine disorders have been implicated in the pathogenesis of peptic ulcers, but the exact role of these putative insults is not known.

For example, the hypersecretion of corticosteroids and gastrin is associated with peptic ulcers in hormonal hypersecretion syndromes: *Cushing and Zollinger–Ellison syndromes*. However, there is no definitive evidence that these hormones play a role in the pathogenesis of “garden variety” solitary peptic ulcers.

*Vagotomy (excision of the vagus nerve) is used only in the treatment of complicated persistent ulcers resistant to other treatment modalities.*

**D. Alcohol, spicy food, and substances that stimulate acid secretion** may play a pathogenetic role.

*There is no evidence that dietary modification is helpful in the treatment of peptic ulcer disease.*

**E. Smoking:** reduces **blood flow and PG synthesis** ➔ mucosal defense is compromised.

*Peptic ulcers are twice as frequent in smokers and are associated with poor healing and increased recurrence.*

- **Clinical features**
  - Symptoms **depend on ulcer location and patient age**: many patients, particularly elderly patients, have few or no symptoms.

  **Pain** is most common, often **localized to the epigastrium** and relieved by food or antacids. The pain is described as burning or gnawing, or sometimes as a sensation of hunger.
The course is usually chronic and recurrent. Only about 1/2 of patients present with the characteristic pattern of symptoms.

- **Gastric ulcer** symptoms often do **not** follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

- **Duodenal ulcers** tend to cause more consistent pain. Pain is absent when the patient awakens but appears in mid-morning, is relieved by food, but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer.

In neonates, **perforation and hemorrhage may be the first manifestation of duodenal ulcer**! Hemorrhage may also be the first recognized sign in later infancy and early childhood, although repeated vomiting or evidence of abdominal pain may be a clue.

- **Complications**
  - (1) **Hemorrhage**: the most common complication.
    - **Minor hemorrhage** may present with melena ➔ iron deficiency anemia.
    - **Major hemorrhage** (in 10-20% of patients) may present as hematemesis (vomiting of fresh blood or “coffee ground” material); passage of bloody stools (hematochezia) or black tarry stools (melena). Can be associated with weakness, orthostasis, syncope, thirst, and sweating.

  - (2) **Perforation**
    It is found in approximately 10% of patients.
    Ulcers located in the anterior wall of the duodenum or, less commonly, in the stomach are typically associated with peritonitis and paralytic ileus. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output. Immediate surgery is required!

  - (3) **Gastric obstruction**
    Obstruction may be caused by scarring, spasm, or inflammation from an ulcer. Symptoms include recurrent, large-volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Loss of appetite with persistent bloating or fullness after eating also suggests gastric outlet obstruction. Prolonged vomiting ➔ weight loss, dehydration, and alkalosis. Typically involves the **gastric outlet at the pylorus** (ulcers may induce muscle spasm or hypertrophy).

  - (4) **Penetration**
    It includes extension of granulation tissue into the pancreas, typically as a complication of posterior wall duodenal ulcers. It is accompanied by dull pain and elevated serum amylase.

  - (5) **Stomach cancer**
Patients with *H. pylori*–associated ulcers have a 3- to 6-fold increased risk of gastric cancer later in life. There is no increased risk of cancer with ulcers of other etiology.

### 1.3 Stress Ulcers

- **Definition:** represent a form of *severe, acute gastritis; lesions are multiple and smaller than in peptic ulcers.*
- **Causes.** Wide variety of *acute systemic stresses:*
  - severe trauma: car accidents, crushing injuries
  - CNS damage
  - extensive skin burns
  - bacterial infections that spread through the blood
  - cardiovascular shock.
- **Pathogeny:**
  - Hypersecretion of acid — head trauma!
  - Defects in gastric glycoprotein mucus.
    - In critically ill patients, *increased concentrations of refluxed bile salts* or the presence of *uremic toxins ➔ denudation* of the *glycoprotein mucous barrier.*
    - Ischemia.
    - *Shock, sepsis, and trauma ➔ impaired perfusion of the gut.*

*Cushing and Curling ulcers* are typical types of gastric stress ulcers. Such ulcers are deeper than erosions and *may extend all the way to the muscularis mucosae.* Cushing ulcers are caused by *brain injury,* while Curling ulcers are found in *burn patients.*

### 1.4 Zollinger-Ellison syndrome

- **Definition:** *gastrin-secreting tumor (80% in the pancreas, 15% in the duodenum, and 5% in other sites).*
- **Clinical features**
  - *Hypergastrinemia* (demonstrable in blood)
  - *Peptic ulcers,* solitary or multiple.
- **Diagnosis** of Zollinger–Ellison syndrome suspected if ulcers are:
  - Multiple
  - Unusual site (e.g., jejunum and Meckel diverticulum)
  - Resistant to standard ulcer therapy
  - Occur in the setting of multiple endocrine neoplasia.