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Diseases of the stomach

-Lining epithelium of the stomach lumen is glandular-columnar type epithelium that is composed of tubular cells and glands (crypts)

-The stomach is divided into four major anatomic regions: the cardia, fundus, body, and antrum

The difference between antrum and body of the stomach is mucosa type; as the body of the stomach has additional cells which are the parietal cells and chief cells which secrete HCL and Pepsin

**Book:**

- Cardia is lined mainly by mucin secreting foveolar cells that form shallow glands
- Antral glands are similar but they also contain endocrine cells, such as G cells, which secrete gastrin to stimulate luminal acid secretion by parietal cells within the fundus and body

Well developed glands of the body and fundus contain chief cells that produce and secrete digestive enzymes such as pepsin.

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**Gastropathy and Acute Gastritis**

Gastritis: is a mucosal inflammatory process.

When neutrophils are present, the lesion is referred to as acute gastritis.

When inflammatory cells are rare or absent, the term gastropathy is applied; marked by gastric injury or dysfunction
Gastritis : inflammation of the stomach could either be:
A) acute --> acute inflammatory cells are present which are neutrophils and polymorphonuclear cells
B) chronic --> chronic inflammatory cells are present which are mononuclear cells (macrophages, lymphocytes) and plasma cells

Gastropathy : gastric injury without inflammatory cell infiltration

Both gastritis and gastropathy have similar presentations

- Pathogenesis:

The gastric lumen has a pH of close to 1, this harsh environment contributes to digestion but also has the potential to damage the gastric mucosa.

Esophagus is not as tolerable to this environment as the stomach is; which explains why acidic reflux injures the esophagus

- Multiple mechanisms have evolved to protect the gastric mucosa:

Mucin and phospholipids secreted by surface foveolar cells.
bicarbonate ion secretion by surface epithelial cells.
a continuous layer of gastric epithelial cells forms a physical barrier.

Complete replacement of the surface foveolar cells every 3 to 7 days is essential for both the maintenance of the epithelial layer and the secretion of mucus and bicarbonate from these cells.

Both goblet cells and foveolar cells secrete mucin but the difference is:
goblet cells are situated in the small and large intestine, they secrete acidic mucin.
foveolar cells are situated in the stomach, they secrete neutral mucin.

An additional protective mechanism is prostaglandin secretion which increases mucin production; helps in forming a protective layer.
Gastropathy, acute gastritis, and chronic gastritis can occur following disruption of any of these protective mechanisms.

- Causes of acute and chronic gastritis:

NSAIDs: inhibit COX dependent synthesis of PG E2 and I2, Although COX-1 plays a larger role than COX-2, both isoenzymes contribute to mucosal protection.

Phospholipases act on phospholipids of the cell membrane to release arachidonic acid, arachidonic acid is substrate for two enzymes, either: Cyclooxygenase enzymes (COX) which produce prostaglandins OR lipooxygenase enzymes (LOX) which produce leukotriens.

Prostaglandins normal function is --> vasodilation, increase vascular permeability and increase mucin production.

NSAIDs are anti-inflammatory, they are not considered broad spectrum drugs as they only inhibit one specific enzyme which is the cyclooxygenase enzyme. There are two types of cyclooxygenase enzymes:

COX-1: found normally in tissues
COX-2: induced by inflammation

COX-1 is more commonly associated with gastritis.
Inhibition of COX enzymes inhibits prostaglandins production which leads to decreased mucin production, which increases the susceptibility of gastritis.

The anti-inflammatory effect of corticosteroids is stronger than that of NSAIDs; because corticosteroids inhibit phospholipase.

- **uremic patients** and those infected with **urease secreting H. pylori**: may be due to inhibition of gastric bicarbonate transporters by ammonium ions.
- **older adults**: Reduced mucin and bicarbonate secretion
- **high altitudes**: Decreased oxygen delivery

- Ingestion of **harsh chemicals** (acids or bases), excessive **alcohol** consumption, **NSAIDs**, **bile reflux**, **radiation** therapy, **chemotherapy**: direct cellular damage.

- **chemotherapy**: inhibit DNA synthesis or the mitotic apparatus—— insufficient epithelial renewal.

**Stress-Related Mucosal Disease**

- **Stress ulcers**: are most common in individuals with shock, sepsis, or severe trauma.
- **Curling ulcers**: Ulcers occurring in the proximal duodenum and associated with severe burns or trauma.
- **Cushing ulcers**: Gastric, duodenal, and esophageal ulcers arising in persons with intracranial disease.

Pathogenesis:

**local ischemia** due to systemic hypotension or reduced blood flow caused by **stress-induced splanchnic vasoconstriction**.

Cushing ulcers Thought to be caused by **direct stimulation of vagal nuclei**, which causes hypersecretion of gastric acid.

Unlike peptic ulcers, which arise in the setting of chronic injury, acute stress ulcers are found **anywhere in the stomach** and are most often **multiple**.
Both gastropathy and acute gastritis may be asymptomatic or cause variable degrees of epigastric pain, nausea, and vomiting.

In more severe cases there may be mucosal erosion, ulceration, hemorrhage hematemesis, melena, or, rarely, massive blood loss.

Symptoms aren’t specific unlike chronic gastritis. Hematemesis (upper GI bleeding) which gives a clue that it’s an acute injury.

**Chronic Gastritis.**

The most common cause of chronic gastritis is infection with the bacillus *H. pylori.*

Autoimmune gastritis, the most common cause of diffuse atrophic gastritis, represents less than 10% of cases of chronic gastritis, but is the most common form of chronic gastritis in patients without *H. pylori* infection. Less common causes of chronic gastritis include:

- radiation injury,
- chronic bile reflux,
- mechanical injury (e.g. an indwelling nasogastric tube),
- involvement by systemic diseases, such as Crohn disease, amyloidosis, or graft-versus-host disease.
- **Helicobacter pylori Gastritis**
  - H. pylori present in gastric biopsy specimens of almost all patients with duodenal ulcers as well as most individuals with gastric ulcers or chronic gastritis.
  - H. pylori organisms are present in 90% of individuals with chronic gastritis affecting the antrum.

*H. pylori* is a rod shaped bacteria (spiral shaped or curved bacilli), its located in the stomach specifically in the antral type mucosa in the epithelium.

- **Pathogenesis:**
  - H. pylori infection most often presents as a predominantly antral gastritis with normal or increased acid production.
  - When inflammation remains limited to the antrum, increased acid production results in greater risk of **duodenal peptic ulcer**.
  - Gastritis may progress to involve the gastric body and fundus. This multifocal atrophic gastritis is associated with patchy mucosal atrophy, reduced parietal cell mass and acid secretion, intestinal metaplasia, and increased risk of **gastric adenocarcinoma**.

**Complications:**
- Increased gastric acid secretion leads to chronic ulcers that could either be duodenal or gastric ulcers.

*Duodenal ulcers* form by the transportation of the HCL from the stomach to the duodenum, nearly 100% of all duodenal ulcers are caused by *H. pylori* gastritis. *Gastric ulcers*: 90% of them are caused by *H. pylori* gastritis.

If the patient is **not treated** and **heavy colonization** of *H. pylori* occurs it will also be found in the body and fundus type mucosa. This results in atrophy in gastric mucosa of body and fundus which leads to reduced parietal cells and chief cells, this reduces gastric acid secretion (Hypochlorohydria) which progresses to *intestinal metaplasia* (no *H. pylori* are present here) ---> dysplasia ---> adenocarcinoma.

If we take a biopsy from each the stomach and the duodenum, only the stomach would provide the appropriate environment for *H. pylori* growth.
*H pylori can only grow in the stomach as it requires gastric type mucose, this explains why it's not found in intestinal metaplasia

**Reasons why H pylori complications differ from one person to the other:**
1) Host factors
2) Types of H. pylori

1) Host factors

The course of H. pylori gastritis is the result of interplay between host factors (gastroduodenal mucosal defenses, inflammatory responses), and bacterial virulence factors.

**Host factors:**

Genetic polymorphisms that lead to increased expression of the proinflammatory cytokines (TNF, IL-1β) or decreased expression of the antiinflammatory cytokine (IL-10) are associated with development of pangastritis, atrophy, and gastric cancer.

due to **genetic polymorphisms (different genes makeup)**

if someone genetically has:
- increased proinflammatory cytokines, and
- decreased anti-inflammatory cytokines

this means that the disease will be more severe in this individual.

2) Different types of H pylori

- bacterial virulence factors:
  
  Flagella—motile in viscous mucus
  Urease—generates ammonia from urea, +pH, bacterial survival
  Adhesins—adherence
  Toxins/cytotoxin-associated gene A (CagA)—disease progression

For example, CagA gene present in 90% of H. pylori isolates found in populations with elevated gastric cancer risk. This may, in part, be because CagA expressing strains can effectively colonize the gastric body and cause multifocal atrophic gastritis.
Cytotoxin associated gene A (CagA) is not found in all H pylori and its responsible for disease progression (progression to atrophy, intestinal metaplasia, adenocarcinoma)

Lymphoid aggregates, some with germinal centers, are frequently present and represent an induced form of mucosa-associated lymphoid tissue, or MALT, that has the potential to transform into B cell lymphomas (MALTomas).

- MORPHOLOGY:

H. pylori display tropism for gastric epithelia and are generally not found in association with intestinal metaplasia or duodenal epithelium.

Within the stomach, H. pylori are most often found in the antrum. Thus, an antral biopsy is preferred for evaluation of H.pylori gastritis.

Long-standing H. pylori gastritis may extend to involve the body and fundus, and the mucosa can become atrophic, with loss of parietal and chief cells. The development of atrophy is typically associated with the presence of intestinal metaplasia and increased risk of gastric adenocarcinoma.

Histology of H. pylori:
rod shaped bacteria that is present only on the surface area, it's not found in the crypts.
Stained with:
A)H&E stain
B)Silver stain in which they appear as a black material(its more clear to see)
In addition to histologic identification of the organism, several diagnostic tests have been developed including:

- A noninvasive serologic test for antibodies to H. pylori
- Fecal bacterial detection
- The urea breath test based on the generation of ammonia by the bacterial urease.

Gastric biopsy specimens can also be analyzed by the rapid urease test, bacterial culture, or bacterial DNA detection by PCR.

Clinical Features:

Acute H. pylori infection does not produce sufficient symptoms to come to medical attention in most cases; it is the chronic gastritis that ultimately causes the individual to seek treatment.

In contrast to acute gastritis, the symptoms associated with chronic gastritis are typically less severe but more persistent. Nausea and upper abdominal pain are typical, sometimes with vomiting, but hematemesis is uncommon.

- Effective treatments for H. pylori infection include combinations of antibiotics and proton pump inhibitors.
- Individuals with H. pylori gastritis usually improve after treatment, although relapses can occur after incomplete eradication or reinfection, which is common in regions with high endemic colonization rates.

Treatment—>antibiotics and either proton pump inhibitors or histamine H2 receptor antagonists.
Autoimmune gastritis:

**Autoantibodies** attack the parietal cells, destruction of the parietal cells leads to **decreased intrinsic factor** which results in **vitamin B12 deficiency**.

Destruction of parietal and chief cells leads to decreased gastric acid production.

Inflammation is mainly in the body and fundus.

Increased risk of acidic metaplasia and acidic gastritis.

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**Table 17-2 Characteristics of Helicobacter pylori–Associated and Autoimmune Gastritis**

<table>
<thead>
<tr>
<th></th>
<th>H. pylori–Associated</th>
<th>Autoimmune</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Antrum</td>
<td>Body</td>
</tr>
<tr>
<td><strong>Inflammatory Infiltrate</strong></td>
<td>Neutrophils, subepithelial plasma cells</td>
<td>Lymphocytes, macrophages</td>
</tr>
<tr>
<td><strong>Acid production</strong></td>
<td>Increased to slightly decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Gastrin</strong></td>
<td>Normal to decreased</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Other lesions</strong></td>
<td>Hyperplastic/inflammatory polyps</td>
<td>Neuroendocrine hyperplasia</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>Antibodies to <em>H. pylori</em></td>
<td>Antibodies to parietal cells (<em>H+,K+-ATPase, Intrinsic factor</em>)</td>
</tr>
<tr>
<td><strong>Sequelae</strong></td>
<td>Peptic ulcer, adenocarcinoma, MALToma</td>
<td>Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor</td>
</tr>
<tr>
<td><strong>Associations</strong></td>
<td>Low socioeconomic status, poverty, residence in rural areas</td>
<td>Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease</td>
</tr>
</tbody>
</table>

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**Book**

Autoimmune gastritis leads to achlorhydria while *H pylori* gastritis leads to Hypochlorhydria.
• Uncommon Forms of Gastritis:
  - Eosinophilic Gastritis
  - Lymphocytic Gastritis
  - Granulomatous Gastritis

Each form has different manifestations.

Complications of Chronic Gastritis

• Peptic Ulcer Disease
• Mucosal Atrophy and Intestinal Metaplasia
• Dysplasia
• Gastritis Cystica

Gastritis cystica—cyst like invagination in the submucosa and muscularis propria due to mainly trauma (such as stomach surgery) or H. pylori infection.

*Formation of mucin cysts in the muscle layers of the gut lining*

**Peptic ulcer disease (PUD)**

• PUD refers to chronic mucosal ulceration affecting the duodenum or stomach.

• Nearly all peptic ulcers are associated with H. pylori infection, NSAIDs, or cigarette smoking.

PUD is a type of ulcer that could be found in the stomach, duodenum or esophagus.

a duodenal ulcer is 100% caused by H pylori

gastric ulcers are caused by NSAIDS, smoking, H pylori

• The most common form of peptic ulcer disease (PUD) occurs within the gastric antrum or duodenum as a result of chronic, H. pylori induced antral gastritis, which is associated with increased gastric acid secretion, and decreased duodenal bicarbonate secretion.

• PUD within the gastric fundus or body is usually accompanied by lesser acid secretion as a result of mucosal atrophy (associated with some cases of H. pylori-induced or autoimmune chronic gastritis. And generally protected from antral and duodenal ulcers.
PUD may also be caused by acid secreted by ectopic gastric mucosa within the duodenum or an ileal Meckel diverticulum.

PUD may also occur in the esophagus as a result of GERD or acid secretion by esophageal ectopic gastric mucosa.

**Ectopic gastric mucosa:**
mucosa found in an abnormal location such as esophagus or duodenum

**MORPHOLOGY:**
Peptic ulcers most common in the *proximal duodenum*, and involve the anterior duodenal wall. Gastric peptic ulcers are predominantly located along the *lesser curvature* near the interface of the body and antrum.

Peptic ulcers are solitary in more than 80% of patients.

**PUD has specific morphology unlike stress induced ulcers**
they are also most commonly solitary unlike stress induced ulcers

- Size and location do not differentiate between benign and malignant ulcers. However, the gross appearance of chronic peptic ulcers is virtually diagnostic. The classic peptic ulcer is a round to oval, *sharply punched-out defect*. In contrast, heaped-up margins are more characteristic of cancers.

- Malignant transformation of peptic ulcers occurs rarely, if ever, and reports of transformation probably represent cases in which a lesion thought to be a chronic peptic ulcer was actually an ulcerated carcinoma from the start.
Most common complication of PUD is bleeding.

- Clinical Features:

  - The majority of peptic ulcers come to clinical attention because of **epigastric burning or aching pain**. The pain tends to occur 1 to 3 hours after meals during the day, is worse at night (usually between 11 PM and 2 AM), and is relieved by alkali or food.

  - Nausea, vomiting, bloating, belching, and significant weight loss are additional manifestations.

  - Significant fraction present with complications such as iron deficiency anemia, hemorrhage, or perforation

    - The recurrence rate is now less than 20% following successful clearance of H. pylori.

    - The success of proton pump inhibitors and H. pylori eradication has relegated surgical intervention to treatment of bleeding or perforated peptic ulcers.
Mucosal Atrophy and Intestinal Metaplasia

- Long-standing chronic gastritis that involves the body and fundus may ultimately lead to significant loss of parietal cell mass.
- May be associated with intestinal metaplasia, recognized by the presence of goblet cells, and is strongly associated with increased risk of gastric adenocarcinoma.
- Achlorhydria of gastric mucosal atrophy permits overgrowth of bacteria that produce carcinogenic nitrosamines.
- The risk of adenocarcinoma is greatest in autoimmune gastritis.

Dysplasia

- Chronic gastritis exposes the epithelium to inflammation related free radical damage and proliferative stimuli. Over time this combination of stressors can lead to the accumulation of genetic alterations that result in carcinoma.