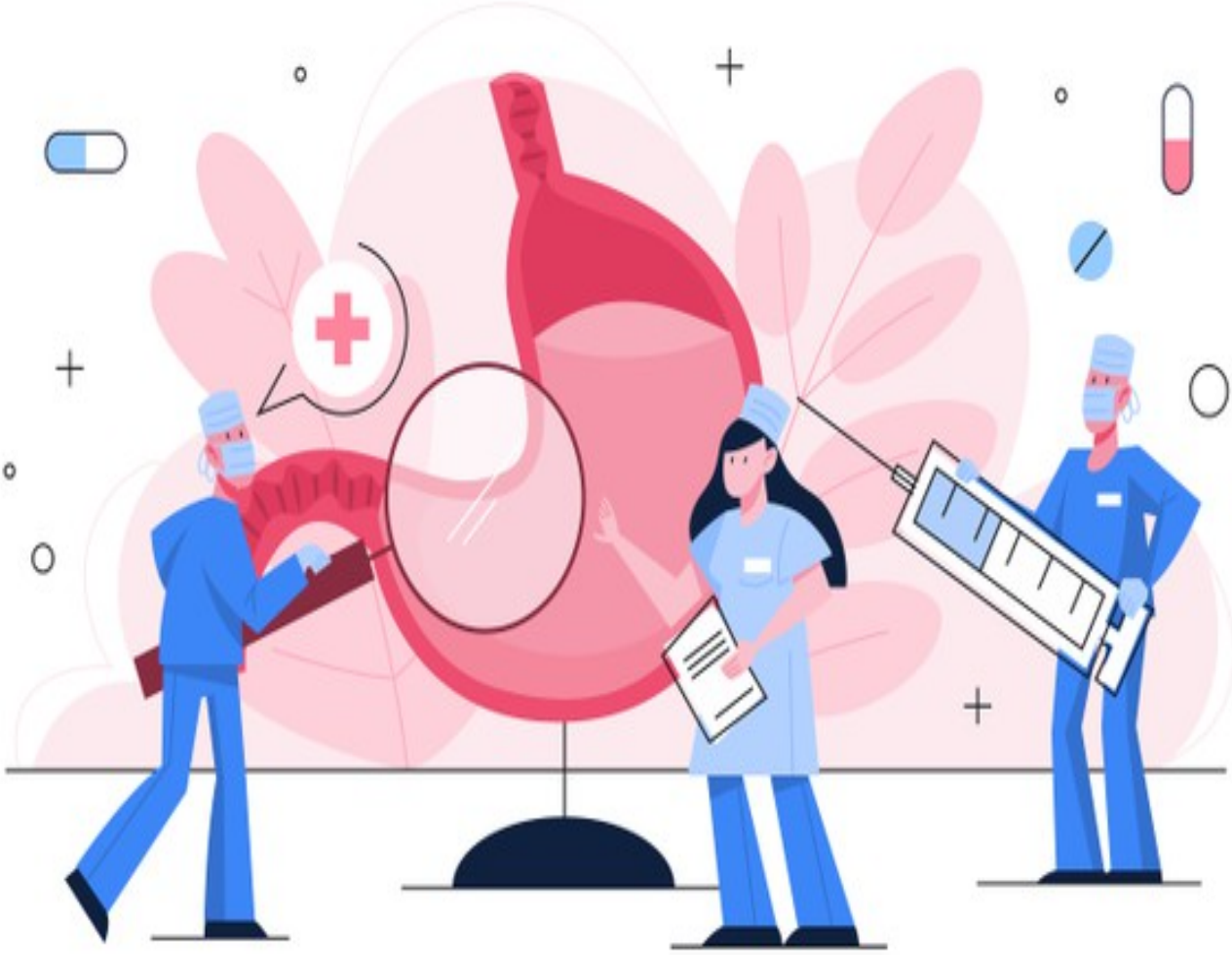
GIS.

Sheet no.3

Pathology



Done by: Sham Alsalim.

Correction: Sham Alsalim.

Doctor: Manar Hajeer.

Hope you all are doing great!
In this sheet we'll start our journey in the pathology of the stomach, put your seatbelt and let's go! Another thing **PINK** is for the doctor…

Overview:

Gastric diseases can be:

1-Inflammatory conditions (acute or chronic: acute/chronic gastritis**).**
2-Neoplastic conditions.

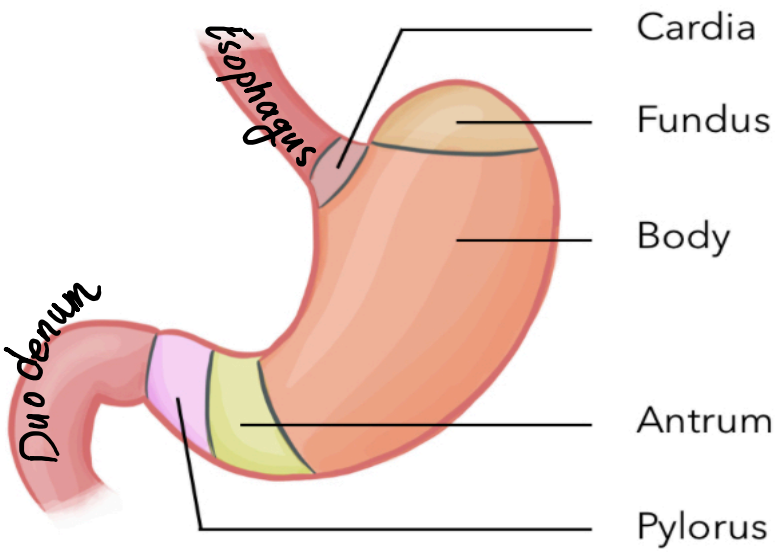
Parts of the Stomach:

Cardia, fundus, body, antrum, pylorus.

Let's begin with the normal anatomy and histology of the stomach…

Anatomy:

- **The Cardia:** The first part after the gastroesophageal junction, just below the esophagus.
- **The Fundus:** Upper part of the stomach.
- **The Body:** constitutes most of the surface area of the stomach.
- **The Antrum, Pylorus:** Through which the stomach communicates with the duodenum through the **gastroduodenal junction** or pyloric canal/sphincter.



Different areas of the stomach have different histology with different functions within the mucosa.

Histology:

- The Cardia: Mucin-secreting foveolar cells are the prominent cellular component at this site.

Thickness of the cardia is usually less than the thickness of mucosa at other sites of the stomach.

- The Body and the Fundus: Mucosa here is **thicker** than the cardia.

Has mainly parietal cells (HCL producing cells**), chief cells responsible for the production of digestive enzyme for the stomach: PEPSIN.**

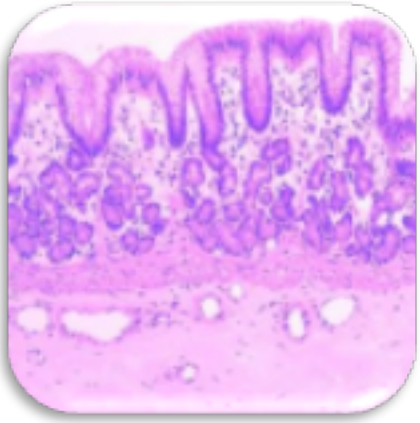
We have four layers of the stomach:
- **Mucosa(**with different compositions throughout**):**
*Muscularis mucosa, separates mucosa from the sub mucosa.
- **Sub mucosa**
- **Muscularis propria (**externa**).**
- **Adventitia and serosa.**

Microscopically:
Parietal cells have abundant **eosinophilic granular cytoplasm** and **chief cells** have abundant **bluish cytoplasm.**

- The Antrum: There are the **antral glands** and **neuroendocrine G cells** which are scattered throughout the crypts and are responsible for the **production of gastrin.**

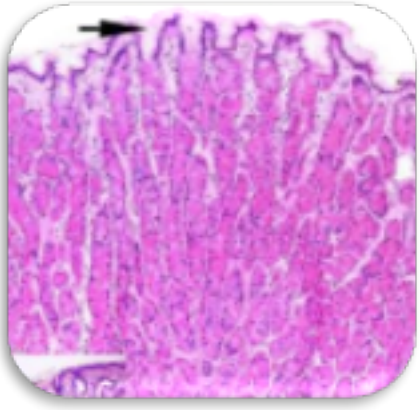
Sometimes it's difficult to find the G cells by H&E, so we use other histochemical stains.

#Here are some histological sections of the stomach(H&E stain**):**



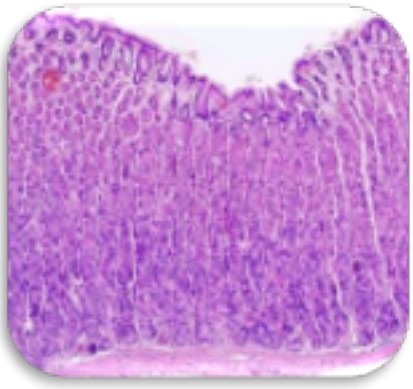
Cardial mucosa:

You can see that the surface epithelium is **highly mucinous**; it contains cytoplasmic mucin.
These are called the **foveolar cells** of the cardia(that produce mucus).
The thickness of mucosa here is different (less) than the other pictures.



Body and Fundus Type Mucosa:

The **highly eosinophilic** cells seen here are the **parietal cells** (that produce HCL), among them are the cells with **bluish cytoplasm** and these are the **chief cells** (that produce Pepsinogen).
-We can see a lot of parietal cells in the **body** and the **fundus**, this is important because in some cases of gastritis we can lose these cells and this feature can be used as a hint to diagnose the disease .

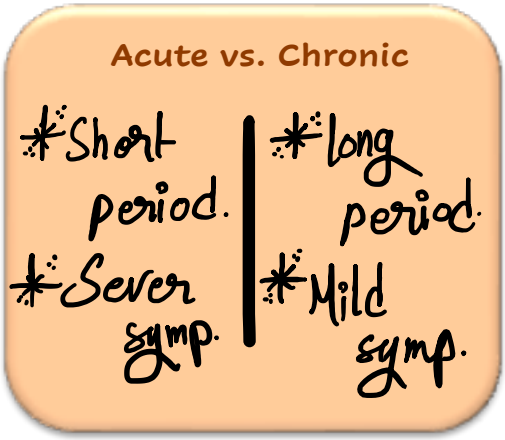


Antral mucosa:

We can see many **antral glands** that **secrete mucus** but we **don't** see parietal cells **nor** chief cells here.
We can see neuroendocrine cells (**G-cells**)(that produce gastrin), but they are better highlighted by some stains.

Inflammatory conditions of the stomach:

As we've said previously it's subdivided into ACUTE & CHRONIC, and it's very common among individuals:



1.Acute conditions:
-Acute gastritis. -Acute gastric ulcers.
2.Chronic conditions:
-Chronic gastritis. -Chronic peptic ulcers.

-Peptic means any area that is exposed to the acid and pepsin from the stomach, so peptic ulcers is **NOT** necessarily in the stomach.
-It can happen in **Meckel's diverticulum** in the terminal ileum/ **Lower part of the esophagus**…
-However, it's **commonly** found in the **stomach**.

Acute gastritis and gastropathy:

These two terms are related to similar conditions. However, the main difference between them is in the morphology under the microscope when we take gastric biopsies.

- Acute gastritis: **Mucosal injury(**prominent as congestion/hemorrhage…**)**, neutrophils present(but **NOT** prominent).
- Gastropathy: **regenerative** changes in the mucosa due to damage, but **NO** inflammation at all **NOR** inflammatory cells.

Causes for both:

Top 1

1.NSAIDs (they disrupt the protection of the mucosa).
2.Alcohol.
3.Bile reflux.(from the **duodenum** into the **stomach** which could occur after certain surgical procedures that affect the competence of the pyloric sphincter, and **stress-induced** by physiological stress like in surgical procedures and critically ill patients).

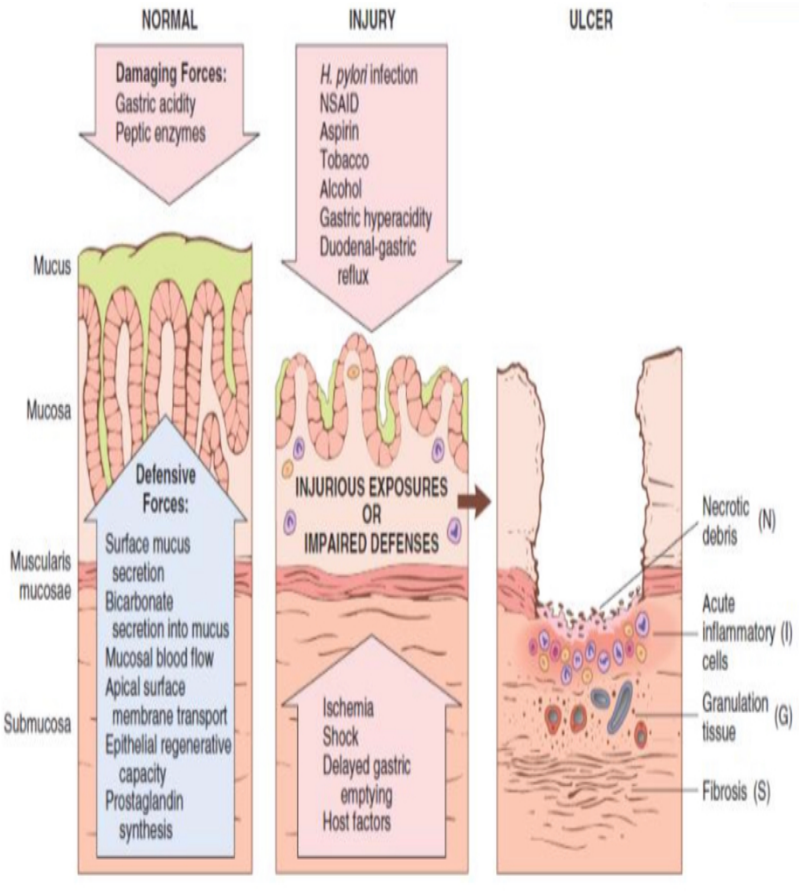
Clinical features:

-Variable, related to the severity of the condition.
*Asymptomatic. *Mainly.
*Epigastric abdominal pain with nausea and vomiting.

Pathogenesis:

-The mechanism of acute gastritis, gastropathy or even chronic gastritis and peptic ulcer disease, are all inter-related in one way or another because the underlying triggers are almost the same.

-In acute or chronic gastritis there's an imbalance between these different forces that are naturally present in the stomach(the protective forces**) and the injurious stimuli.**



The media in the stomach is very acidic (low pH),this along with pepsin is a damaging factor in its nature and can cause damage to the gastric mucosa if it comes in direct contact with it.
However, the mucosa has developed many defensive

Protective factors in the stomach:

› **The mucous secretions** of the surface epithelial cells which form a mucous layer on the surface of epithelial cells, protecting them from the damage of **acid** and **pepsin**.

› **Bicarbonate ions** buffer this solution (the mucus layer) because bicarbonate ions produce a nearly **alkaline medium** near the epithelium (also produced by epithelial cells).
This mucous layer rich in bicarbonate offers high protection for the mucosa.

› **We have very good mucosal blood flow** all the time to the GI tract, which keeps the regenerative capacity of the GIT very high.

› **Prostaglandin synthesis** as you know they're produced from **arachidonic acid** through the different pathways of COX enzyme (1-2).
-Prostaglandins offer protection by: **increasing mucus secretion and bicarbonate production and increasing blood flow** to the gastric mucosa.
Any interference with prostaglandin secretion in the stomach (like NSAIDs, mainly non- selective forms**) can cause reduction of PG synthesis and thus reduce these protective effects on the gastric mucosa leading to larger damage.**

The injurious stimuli:

Exogenous: NSAIDs including aspirin, H.pylori bacteria, tobacco, alcohol, gastric hyper acidity, and duodenal-gastric reflux (bile reflux).
Endogenous: Ischemia, shock, delayed gastric emptying and host factors (like autoimmunity)
-In general for chronic, acute gastritis & peptic ulcers to develop we must have an **imbalance between the protective and damaging factors** of the stomach.
-**Reduction in protection** or **increase in injurious stimuli** would lead to one of the mentioned problems.

Pathogenesis of acute gastritis and gastropathy:

-Imbalance between protective and damaging forces:

#Main causes in details (damaging forces**):**

- **NSAIDs** → by inhibiting COX → decrease PGs synthesis (which work as protective factors).

-Both non-selective and selective COX-2 inhibitors can cause damage, but the effect is higher with non-selective, like aspirin, ibuprofen, and naproxen.

-We recommend for the long time intake, *ProtonPumpInhibitors.

- **Uremic patients** (renal failure patients) and **H. pylori infected patients** (main cause for chronic gastritis 90%).

-It can cause acute gastritis BUT mainly it's unnoticed.

-H. pylori produces urease enzyme that splits urea into ammonia, whose presence interferes with the transport of bicarbonate to the mucous layer.

Decreased conc. of bicarbonate→decreased protective effect.

- **Old age**, because mucus and bicarbonate secretions are decreased.
- **Hypoxia** whether caused by ischemia or high altitude.

-Hypoxia and decreased oxygen supply to the mucosa would lead to a decrease in the protective factors.

- **Harsh chemicals** cause direct epithelial injury and damage.

-Like acids or bases in suicidal attempts or accidental ingestion.

- **Alcohol, NSAIDs, and radiation therapy** cause direct injury to epithelial cells.
- **Chemotherapy.**

-By Interference with DNA synthesis and mitotic capacity it affects the GIT through decreasing proliferation of cells or causing direct damage.

Again.. these factors cause damage, either by inflicting direct injury to the epithelium of the stomach or by reducing the protective factors already present in it.

Morphologic features of acute gastritis:

-They're non-specific and minor.

1. Endoscopically/Macroscopically يعني تنظير:
   hyperemia(red in color**)** mainly.
   -It can be in combined with hemorrhage.
2. Microscopically/Biopsy:
   Hyperemia, **congestion of vessels** and **edema**. (in lamina propria)
   -We can see neutrophils (acute gastritis**), lymphocytes and plasma cells but they are NOT prominent.**
   -When we say acute gastritis we see DAMAGE as it is so obvious NOT neutrophils.
   -In the Advanced cases: Erosions and **hemorrhage** can be seen.
   -We call this: **acute erosive hemorrhagic gastritis.**
   -Active inflammation (neutrophils) is NOT necessary.

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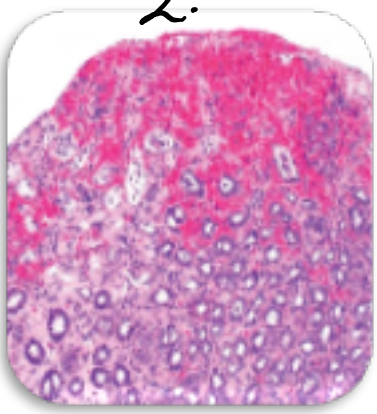


- The difference between acute and chronic is mainly the **duration**.
- Neutrophils can be used to differentiate between gastropathy (negative/ not present) and acute gastritis (positive).

Stress-Related Mucosal Disease:

- Acute Gastric Ulcers:

-Acute gastritis mainly complicated by it.

-Caused by severe physiologic stress:

- **Trauma** (After road traffic accidents).
- **Extensive burns** (a large area of the skin is involved).
- **Intracranial disease** (increased intracranial pressure).
- **Major surgery.**
- **Serious/severe medical disease.**
- **Critically ill patients**(ICU patients…)

Types of Acute Gastric Ulcers:

-There are different types according to cause and location.

▪ **Stress ulcers:** Occurs in critically ill patients with shock, severe hyper-tension, sepsis, or severe trauma.
-Decreases blood flow → loss of one protective factor…
▪ **Curling ulcers:** peculiar, proximal duodenum, **severe burns** or trauma.

▪ **Cushing ulcers:** In the stomach, duodenum, or esophagus. Associated with increased **intracranial pressure**, high risk of perforation.
-Increases the vagal stimulation→ Increases acid secretion→ ULCER.

-Always put in your mind that the acid secretion is strongly related to ulcers; NO ACID = NO ULCERS and vice versa.

Let's get more in depth!

Stress ulcers:

-Mainly due to Local ischemia. Which can follow:

- **Systemic hypotension or heart failure.**
- **Locally reduced blood flow due to Splanchnic vasoconstriction. (blood supply to the GI)**
- **Systemic acidosis→lower PH of cells→acidosis in the cells damage them.**

-COX2 expression is protective against stress ulcers which it produces PGs.

Cushing ulcers:

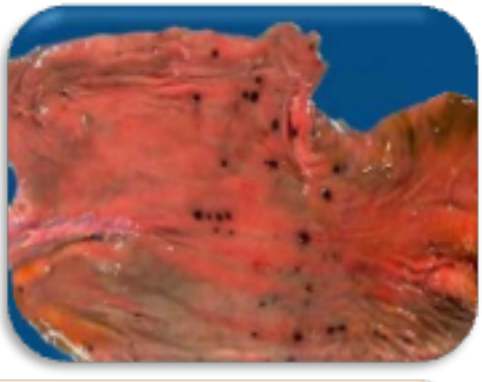
- **Direct vagal nerve stimulation,** like in cases of increased intracranial pressure, causes acid hypersecretion.

Morphology (micro or macroscopic):

-Usually diagnosed by endoscopy and clinical manifestations (hematemesis, gastric pain),**NOT** BIOPSIES.

› **Multiple** (**unlike chronic peptic ulcers**).
› Acute ulcers are rounded, variable in size but typically **less than 1 cm in diameter.**
› Shallow to deep.
› **Normal** adjacent/ surrounding **mucosa.**

› Ulcers' bases are **brown to black**, due to the effect of gastric juices on the blood.
› Can occur **anywhere** in stomach.
› No scarring (**a characteristic of these ulcers, unlike chronic peptic ulcers**).
› Healing with complete re-epithelialization occurs days or weeks **WITHOUT** intervention **NOR** scaring **after removal of injurious factors.**



Features of acute gastric ulcers:
› Multiple, black or brownish, small and distributed ulcers
› Normal uninflamed gastric mucosa around the ulcers
› Typical History: A patient in this case is usually critically ill, in the ICU, has an underlying stressful condition, or had trauma.

Clinical features:
› Severely and critically ill patient in the ICU, or traffic road accidents.
› Nausea, vomiting with dark blood bits (**due to the action of acidic juices on fresh blood**) (**Coffee-ground hematemesis**).
› Melena (**black stool caused by upper GI bleeding**).
› Some cases have a higher degree of hemorrhage and need blood transfusions, **BUT** it occurs in a minority of patients→ Perforation complication.

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-The best way to deal with acute gastric ulcers is Prophylaxis with proton pump inhibitors (decrease acid secretion and protect the mucosa**) for patients at risk (**mentioned above**).**

-Outcome depends on severity of underlying cause. If we treat the underlying cause, complete healing and re-epithelialization takes place.

-Acute ulcers→sudden onset→acute symptoms→predisposing factor→nausea/hematopoiesis/melena/vomiting are the most common to see.

-It's not necessarily to see all of the symptoms to give the diagnosis.

Chronic gastritis:

-Gradual onset for a long period of time and it's less severe than acute gastritis.

#Causes:

- **Helicobacter pylori**(G-ve bacillus bacteria)associated gastritis: most common 90% of cases.
- **Autoimmune atrophic gastritis** less than 10% of cases.

#Less common causes:

- **Chronic NSAID use.**

-It's the primary cause in acute gastritis.

- **Radiation injury.**
- **Chronic bile reflux.**

Clinical features:

-Somehow it's similar to those of acute gastritis.

- Less severe but more prolonged symptoms.
  - **Nausea** and **upper-abdominal discomfort.**
  - **Vomiting.**
  - **Hematemesis is UNCOMMON.**

Let's study on a closer look the little villain😈, the most common cause of chronic gastritis: Helicobacter pylori.

-This little devil caused a revolution in medicine after finding out the association between it and the peptic ulcer disease, as before this discovery it was not thought that chronic gastritis was caused by a pathogen.

- Spiral or curved, G-ve, bacilli.
- Not invasive(seen in the mucus layer overlying the mucosa **NOT** inside the cell).
- Most commonly live in the antrum of the stomach(Antral gastritis with increased acid production).

-Stimulation of the G-cells of antrum with increased gastrin hormone production →activation of parietal cells → increased acid production >>>> peptic ulcer.

-We clinicians recommend to take the biopsy from the antrum otherwise, if we see all the stomach is red and inflamed…

›In severe cases the inflammation can spread all over the stomach affecting even the body and the fundus causing **pangastritis.**

-In those patients they develop what we call *HYPERCHLORHYDRIA*; it damages even the parietal cells(acid producing cells**), thus it decreases acid production.**

›They've developed many protective and virulent factors to protect themselves from the **acidic gastric juices.**

›Present in **ALL** duodenal ulcers.

› Majority of gastric ulcers or chronic gastritis,**BUT** other causes are present.

› Acute infection is subclinical.

-It's usually acquired in childhood through the ingestion of contaminated food and water and it's common in places of poor sanitation and crowding and poverty.

› Intestinal metaplasia in the stomach and increased risk of gastric cancer.

- The intestinal metaplasia is then transformed into dysplasia and then adenocarcinoma.

-SO HERE IT IS A CANCER FORMED FROM A BACTERIA.

Epidemiology of gastritis caused by H. pylori:

-There's a very well noticed difference in the prevalence of H. pylori associated gastritis in **different geographical locations** and **populations.**

-More common with **poverty**, **household crowding**, **limited education**, **poor sanitation**.

-The infection is typically acquired in childhood through ingestion, then it persists for years to adult-life without causing any symptom, at some point in life the bacteria can *trigger irritation to the stomach* and cause the *chronic gastritis* especially when the patient reaches the adult life.

-Colonization rate varies according to geographic locations from as much as 10% of the population to 80% of it.

Pathogenesis:

-Multiple acquired characteristics aid in protecting the bacteria form the protective mechanisms of the stomach and for pathogenesis.
-H. pylori adapted to live in the mucus layer, and it's usually non-invasive.
-Invasion is NOT the mechanism by which it causes the disease, it can cause the disease while still in the mucus layer.
-It has developed many mechanisms to **protect** itself from the **acidic environment** like:

- Flagella: Allow motility.
- Urease: A very peculiar feature of it: Urease splits urea into **ammonia** (alkaline media), which in turn protects bacteria from the acidic pH of the stomach.
- Adhesins: Bacterial adherence to foveolar cells of the stomach.
- Toxins: The main toxin is the cytotoxin associated **gene A** →aids in **ulcer** or **cancer** development by causing damage to epithelial cells.

Morphology of chronic gastritis:

-When a patient presents with the symptoms of gastritis as nausea, vomiting and epigastric pain, a gastroenterologist would perform an endoscopy to visualize gastric mucosa, and a biopsy can be obtained, both presenting certain features.

- Endoscopically → Most important feature is ***hyperemia***.
- Microscopically → H. pylori would be present in the ***mucus layer***, ***antrum*** is the ***best place*** to obtain a biopsy because H.pylori prefers to live there and attach to foveolar cells, however it's presence isn't documented in the acid producing region (fundus, body) except in very severe cases.

-What we observe is an ***inflammatory response*** in the ***SURFACE*** mucosa, predominated by:

- Neutrophils: within the lamina propria (in sever cases).
- Plasma cells, lymphocytes & macrophages.

-The amount of these cells depends on the severity of chronic gastritis.

- Intestinal metaplasia: In long standing disease we might see (intestinal epithelium with goblet cells), which can progress to ***dysplasia***→increased risk of ***adenocarcinoma***.

-We CAN'T find the bacteria in areas of intestinal metaplasia in cases of complication of chronic gastritis.

- Lymphoid aggregates: In more severe cases we can observe (lymphoid follicles with reactive germinal centers) as part of the mucosa associated lymphoid tissue.

-This means an increased risk of MALT lymphoma.

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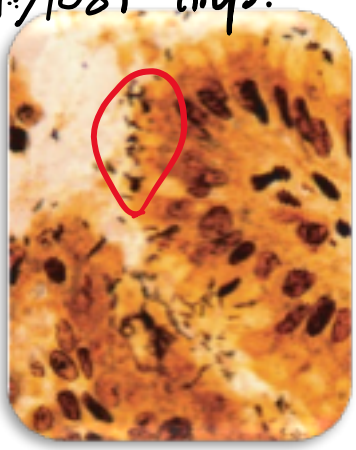
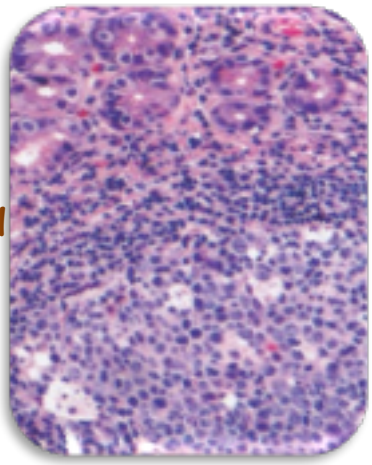
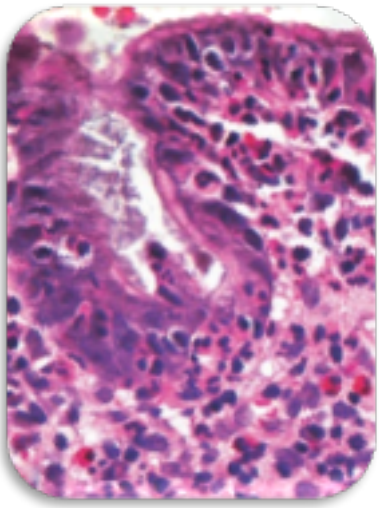


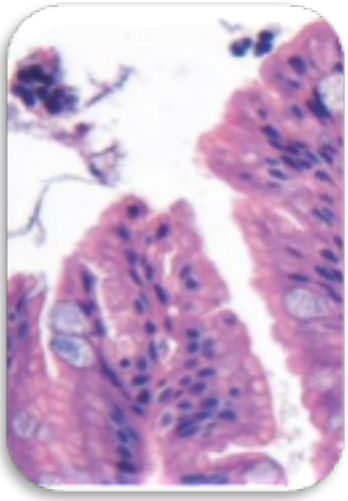
We can see the H.pylori; multiple curved bacilli with black discoloration.



Many lymphocytes aggregates infiltrating between the gastric glands in the lamina propria, which indicates chronic gastritis.



This section has many neutrophils which indicates an active state of the chronic disease.
Neutrophil presence is NOT diagnostic of the disease, it's rather a sign that there's an active disease taking place.



This one is intestinal metaplasia with *goblet cells* that are characterized by mucus filled cytoplasm. (gray/bluish discoloration).

-H.pylori can cause TWO types of cancers in the stomach; Lymphoma(lymphoid aggregates**) & Adenocarcinoma(**Intestinal metaplasia**).**

Best wishes!

made with love