GIS PATHOLOGY 3 online

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- The sheet is unexpectedly long, try to understand it well.

Overview:

Gastric diseases can be:

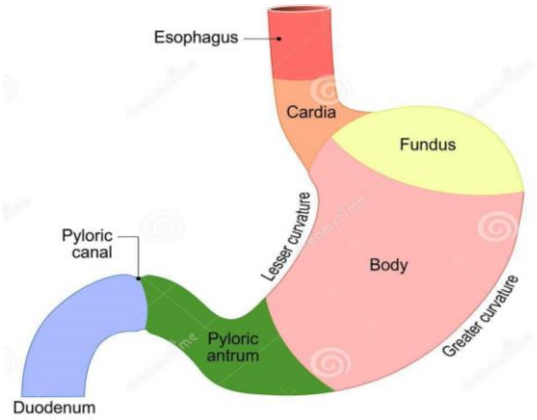
1-Inflammatory conditions 2-Neoplastic conditions.

Parts of the Stomach: Cardia, fundus, body, antrum, pylorus.

Before we start: Normal histology and anatomy of the stomach.

- **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 sphincter.

↳ Different areas of the stomach have different cellular populations 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.
  - Cellular component: Mainly parietal cells (HCL producing cells) and chief cells responsible for the production of a digestive enzyme of the stomach: **pepsin**.

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.**

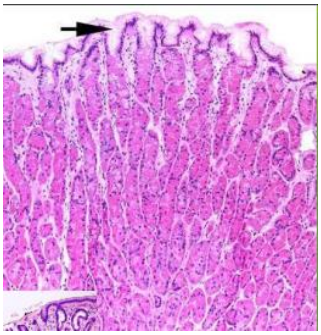
Microscopically: Sometimes it's difficult to find the G cells by H&E, so we use other histochemical stains.

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**

Parts of the stomach: **Proximally** it's connected to the **esophagus through the GEJ**. In the **distal part** it opens to the duodenum through the **pyloric canal (sphincter)**. The **lesser curvature** is the line between the GEJ and the GDJ **(inner curve)** from the right side, the **greater curvature (outer curve)** is from the left side.

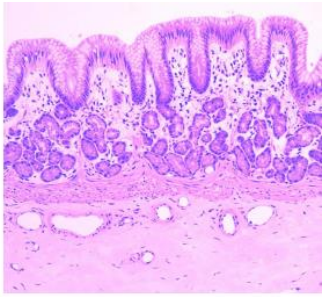
○ Normal histological sections of the stomach (H&E stain)



Body and Fundus Type Mucosa:

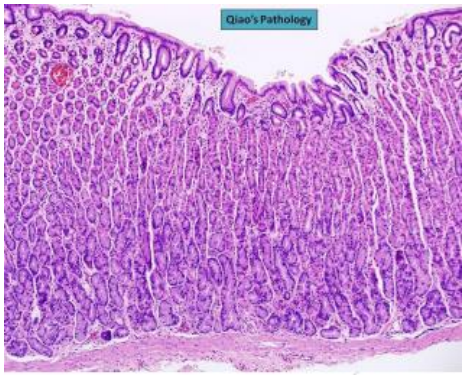
The **highly eosinophilic** cells seen here are the parietal cells, among them are cells with **bluish cytoplasm** and these are the chief cells.

↳ 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 .



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
You can see the that the thickness of mucosa here is different (less) than the other pictures.



Antral mucosa:

We can see many **antral glands** that **secrete mucus** but we don't see parietal 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:

Inflammatory conditions of the stomach are very common, and they're subdivided into 4 categories, some of which are acute and some are chronic:

› Acute conditions:
Acute gastritis.
Acute gastric ulcers.

› Chronic conditions:
Chronic gastritis.
Chronic peptic ulcers.

↳ **Peptic** means <u>any area that is exposed to the acid and pepsin from the stomach</u>. Like the stomach, distal esophagus, proximal duodenum, or other areas of the GI with ectopic gastric tissue producing acid or pepsin. So a "peptic" issue is **not necessarily in the stomach**.

○ Differentiation: 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.

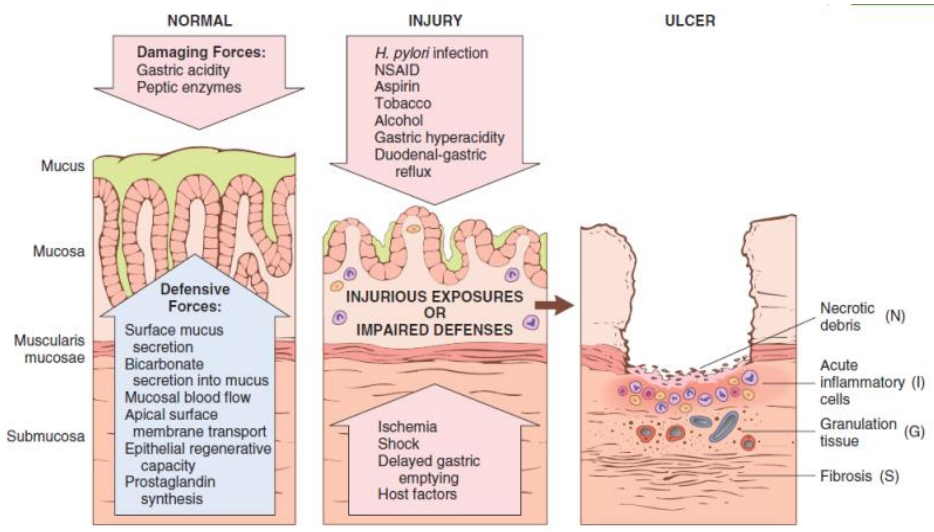
- **Acute gastritis:** Mucosal injury, **neutrophils** present.
- **Gastropathy:** regenerative changes in the mucosa due to damage, but no inflammation (and inflammatory cells).

<u>Causes for both:</u>

NSAIDs (they disrupt the protection of the mucosa- you remember from the NSAIDs material we took in MSS right? 😷), **alcohol**, **reflux of bile** from the duodenum into the stomach which could occur after certain surgical procedures which affect the competence of the pyloric sphincter, and **stress-induced** (by physiological stress like in surgical procedures and critically ill patients).

<u>Clinical features</u> (variable, related to the severity of the condition):
Asymptomatic or epigastric abdominal pain with nausea and vomiting.

<u>Pathogenesis</u>:
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.



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

○ 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:

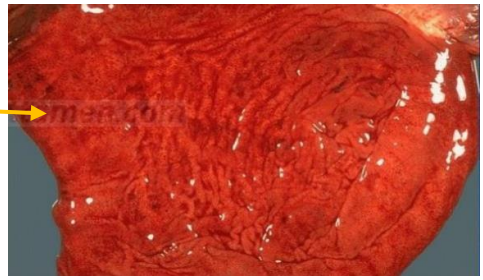
- Imbalance between protective and damaging forces

Main causes (damaging forces):

- **NSAIDs** → work 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.)
- **Uremic patients** (renal failure patients) and ***H. pylori* infected patients** (a bacterium that infects stomach). H. pylori produces urease enzyme that splits urea into ammonia, whose presence **interferes with the transport of bicarbonate** to the mucous layer.
  - Decreased concentration 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**.

➢ 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.

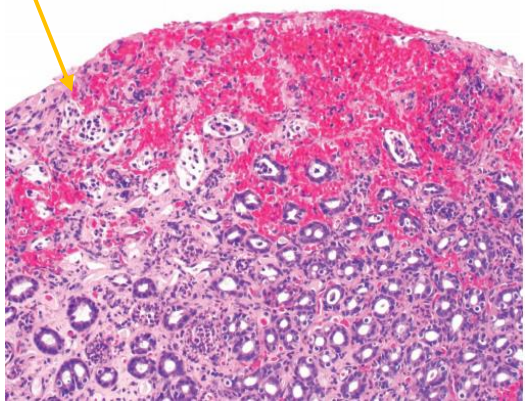
- Morphologic features of acute gastritis
  - They're non-specific and minor.



Endoscopically: **hyperemia mainly**

Microscopically:

- **Hyperemia**, **congestion of vessels** and **edema in the lamina propria.**
- Neutrophils (acute gastritis), lymphocytes and plasma cells but they are **not prominent**.
  - Presence of neutrophils is not a prerequisite to diagnose acute gastritis, it's mainly hyperemia, erythema and congestion.
  - Neutrophils are a sign of **active inflammation** and can be seen in acute or chronic gastritis.
- Intact surface epithelium.
  - In the Advanced cases: Erosions and hemorrhage can be seen. We call this: **acute erosive hemorrhagic gastritis.**



The image above shows a severe case with erosions on the surface and mild hemorrhage. There are also neutrophils attacking the glands in the lower part of the slide.

- Active inflammation (neutrophils) is **NOT necessary.**
  - 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:

Caused by severe physiologic stress:

- **Trauma** (pts. 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, patients with MI.**

  - 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.
- **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 → can rupture to the peritoneum and cause peritonitis.

Pathogenesis

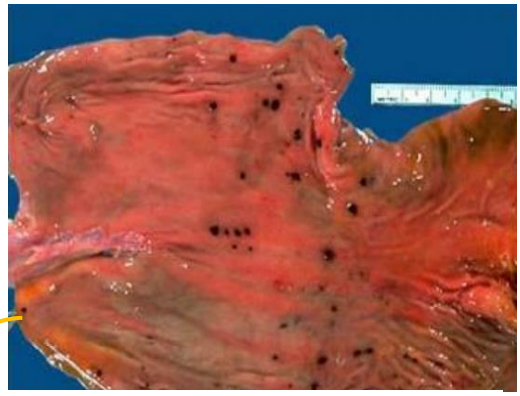
- Stress ulcers:
  - mainly due to **Local ischemia.** Which can follow:
    - Systemic hypotension or heart failure.
    - Locally reduced blood flow due to Splanchnic vasoconstriction. (blood supply to the GI)

  - **Systemic acidosis** → lower PH of cells → acidosis in the cells damage them.
    - ↳ COX2 expression is protective against stress ulcers.

- 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.**
- **usually 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 after removal of injurious factors.



→Look here

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**.

- 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.

CHRONIC GASTRITIS

- Common in out-patient and gastroenteric clinics and a major cause of upper endoscopic procedures performed on patients.
- Differs from the acute gastritis since the symptoms are less severe but the duration is prolonged.

Causes:

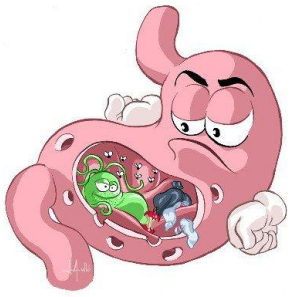
- *Helicobacter pylori* (G-ve bacillus bacteria) associated gastritis: most common.
- **Autoimmune atrophic gastritis**: less than 10% of cases.

Less common causes:

- Chronic NSAID use.
- Radiation injury.
- Chronic bile reflux.

Clinical features:

(somewhat similar to those of acute gastritis).



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

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.
- Can be seen on **gastric biopsy specimens** in the **mucus layer** overlying the mucosa. They've developed many protective and virulent factors to protect themselves from the acidic gastric juices. Can be demonstrated with H&E stain or other specialized stains like giemsa.
- Present in **almost all** duodenal ulcers. *It's present in the **stomach** of patients with 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.

↳ chronic gastritis is the disease responsible for all the symptoms.

› They prefer living in the antrum of the stomach and cause **Antral gastritis** which leads to **stimulation of the G-cells** of antrum with **increased gastrin** hormone production → activation of **parietal cells** → **increased acid** production >>>> **peptic ulcer.**

➢ Early on, *H. Pylori* causes only **antral gastritis**. However, in severe cases the inflammation can spread all over the stomach affecting even the body and the fundus causing **pangastritis** and damage to the **parietal cells**. This means that in severe cases the bacteria can cause hypo-secretion of acid.

➢ In severe cases: **Intestinal metaplasia** in the stomach and increased risk of **gastric cancer**
*In most cases gastric cancer is associated with a **background of chronic gastritis** and intestinal metaplasia. The intestinal metaplasia is then transformed into dysplasia and then adenocarcinoma.

- 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.**
Explanation: 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 → encodes (**CagA)** and aids in ulcer or cancer development by causing **damage to epithelial cells**.

o MORPHOLOGY of chronic gastritis:

When a patient presents with the symptoms of gastritis of 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.

↳ In duodenal ulcer or duodenitis, the bacteria would still be in the stomach, however the hyper acidity is what causes the problem.

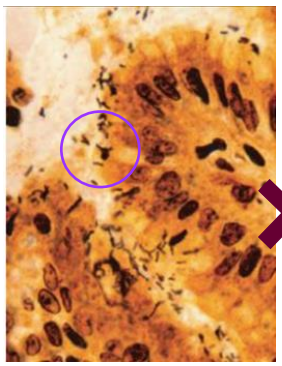
What we observe is an **inflammatory response** in the mucosa, predominated by

- **Neutrophils** within the lamina propria or attacking glands of antrum and causing small abscesses (in active disease).
- Plasma cells, lymphocytes & macrophages, also found in the lamina propria. The amount of these cells depends on **the severity of chronic gastritis.**
- In long standing disease we might see Intestinal metaplasia (intestinal epithelium with goblet cells), which can progress to dysplasia → increased risk of **adenocarcinoma.**

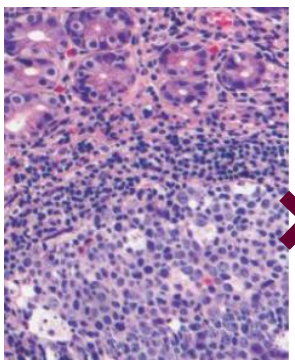
→ We can't find the bacteria in areas of intestinal metaplasia in cases of complication of chronic gastritis

- In more severe cases we can observe **Lymphoid aggregates** (lymphoid follicles with reactive germinal centers) as part of the mucosa associated lymphoid tissue. This means an increased risk of **MALT lymphoma**.

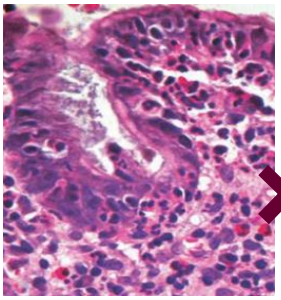
Histological description: all these slides are taken from the antrum



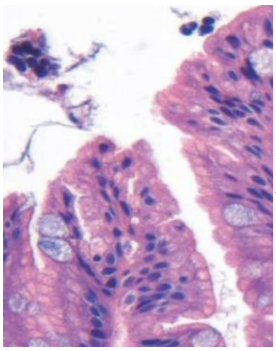
Warthin-starry silver stain, here we can see the **multiple curved bacilli** with **black discoloration** (these bacilli are H.pylori)



Lymphoid follicle with reactive germinal center, many lymphocytes 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.
The PMNs are even invading the surface epithelial cells.
Neutrophil presence is not diagnostic of the disease, it's rather a sign that there's an active disease taking place.



This specimen represents the feared complication of chronic gastritis associated with *H. pylori* infection with **intestinal metaplasia with goblet cells** that are characterized by mucus filled cytoplasm. (gray/bluish discoloration)
Associated with long term infection with *H. pylori* and it's important because it leads to dysplasia and adenocarcinoma of the stomach.

- Any patient who has chronic gastritis and shows intestinal metaplasia should be followed with consecutive endoscopic procedures and multiple biopsies to detect any dysplastic event before it progresses into an invasive malignancy, so we can pick it up earlier and save the patient.

○ Diagnosis of *H. pylori* chronic gastritis and treatment:

First, the patient presents with the symptoms discussed before. We first use the non-invasive methods to investigate, then we use the invasive investigations.

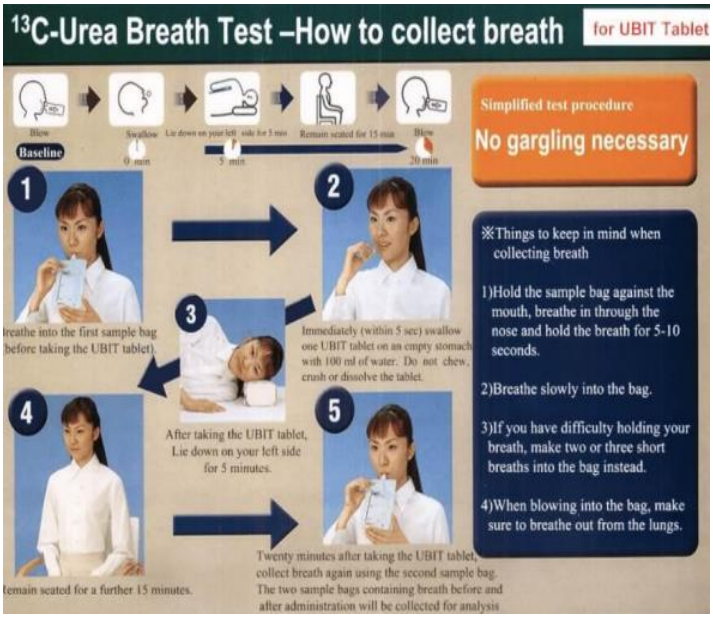
- Non-invasive:
  - Serologic test (blood test): anti-H. pylori antibodies (IgA, IgG).
  - The problem with this test is that it doesn't mean that the patient is having an active disease, previous infection can also cause the presence of antibodies.
  - Stool test for H. pylori
  - Urea breath test

- Invasive:
  - Upper Endoscopy to visualize the stomach of the patient.
  - Gastric biopsy is the best way to detect chronic gastritis or any inflammatory reaction and for visualizing H. pylori in the mucus layer.
    Bacterial culture (using the biopsy).
    PCR test for bacterial DNA (using the biopsy).

- Treatment: Eradication therapy for H. pylori which is formed by at least 2 antibiotics and proton pump inhibitors to decrease the acidity. (drug combinations)

- The treatment may need a long period of time for the patient to get rid of the organism. If the treatment was not completed, recurrence may take place. This recurrence may be because the bacteria was not completely eradicated with the first treatment or the individual may have been re-infected.

- Urease test:



We use this test to detect the **presence** of the products of **bacterial urease enzyme** in the breath.

How?

- ➲ the suspected patient is asked to drink a solution that contains the urea material which contains radiolabeled carbon.
- ➲ the patient is then left for twenty minutes, then **the radiolabeled carbon** is detected in the breath of the patient.

♦ As we know the urease enzyme of the bacteria is the responsible for splitting the urea into ammonia and carbon dioxide.

- Autoimmune (atrophic) Gastritis

↳ **Immune-mediated** disease directed against the **parietal cells** present in the body and the fundus, damage to these cells leads to loss of acid and intrinsic factor production and inactivation of the intrinsic factor directly.

- Characteristics associated with the disease:

› ABs against **parietal cells** and **intrinsic factor** **which can be detected in the serum as a clinical feature of the disease.**

↳ Intrinsic factor binds to vitamin B12 and aids in its absorption in the distal ilium.

› **Reduced serum pepsinogen I levels**, which is produced in the body and the fundus of the stomach, because of damage to these areas.

› As a response to the loss of acid production in the stomach, we will have a **reflex G-cell hyperplasia in the antrum (antral endocrine cell hyperplasia).**

↳ G cells produce gastrin which is produced as a response to the decrease in acid production (due to parietal cell damage).

› **Decreased intrinsic factor**>>> Vitamin B12 deficiency >>> **pernicious anemia** and **neurologic changes** ASSOCIATED with **autoimmune gastritis**.

› Impaired gastric acid secretion (**achlorhydria**), opposite to *H. pylori* gastritis.

› Typically AI gastritis **Spares the antrum** unlike *H.pylori* gastritis.

› Marked **hypergastrinemia.**

- Pathogenesis:

› **(immune mediated) Lymphocyte (T-cell) mediated loss of parietal cells** (with the production of auto-ABs against parietal cells) >>> reduction in acid and secretion.

- Acid reduction leads to reflex hypergastrinemia, which is mediated by hyperplasia of antral G cells.
- Reduction in intrinsic factor due to cells and auto-ABs directed against it.
- Deficient intrinsic factor >> deficient ileal VB12 absorption >> megaloblastic anemia which has many neurological manifestations.
  - Minority of patients develop this anemia, but it's a very important point to differentiate between autoimmune gastritis and helicobacter pylori gastritis.
- Some chief cells damage in the body of the stomach >> reduced pepsinogen production.

➢ Progression leads to loss of parietal cells in the mucosa, thinning and atrophy of the mucosa, and loss of the folds at these sites.

MORPHOLOGY

No *H. pylori* would be present in specimens (If present, it's NOT the cause).
Preferred biopsy site is the body or the fundus NOT the antrum.

- Damage of the oxyntic (acid-producing) mucosa→ parietal cell loss in the body/fundus.
- With time there'll be Diffuse atrophy, thinning of the wall and loss of rugal folds due to loss of acid producing cells and their damage.
- Lymphocytes, plasma cells, macrophages, and less likely neutrophils.
- In long standing cases: Intestinal metaplasia (due to achlorhydria) >>> dysplasia >> adenocarcinoma. *Risk is present in both types of chronic gastritis*
- Neuroendocrine (G-cell) cell hyperplasia as a reflex to reduced acid production>>> may transform into neuroendocrine tumors.
  (in *H. pylori* gastritis the risk is increased for MALT lymphoma).

Clinical features:

- Patients are in their 60s (higher age than *H. pylori* gastritis patients), slight female predominance.
- Often associated with other autoimmune diseases like *Hashimoto thyroiditis, type 1 DM*, or *Graves disease of the thyroid* – autoimmune diseases usually tend to cluster together, so when we find AI gastritis we should look for others.

Feature	*H. pylori*–Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin	Normal to markedly increased	Markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells (H^+,K^+-ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease; thyroiditis, diabetes mellitus, Graves disease

- Very important table summarizing all the differences between *H. pylori* associated gastritis and auto immune gastritis:

Notes:

- Location, of H. pylori associated gastritis is usually the antrum, in severe cases can transform into **pangastritis and cover the entire stomach.**
- In H. *pylori* associated gastritis, chronic inflammatory cells and neutrophils.
  In Auto-immune gastritis mainly chronic inflammatory cells. Focus on **lymphocytes**-they're pawns of pathogenesis.
- Decrease in acid can accompany severe cases of *H. pylori* pangastritis and it's only a slight decrease (remember originally in H. *pylori* associated gastritis there's an INCREASE in acid) not total achlorhydria unlike autoimmune gastritis.
- In H. *pylori* associated gastritis, gastrin would only be markedly increased in severe cases. In early cases the levels would remain normal.
- Sequelae (secondary results):
  In Helicobacter pylori associated gastritis it's **MALT lymphoma.**
  In autoimmune gastritis it's **Carcinoid tumors** (neuroendocrine tumors).

Good luck ☺