Fathology Doctor 2017 Medicine JU GI	
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*Please review the sections of the human stomach because their importance presents itself in the fact that each disease usually occurs in the same area each time.

Stomach landmarks and their histology:

- **Cardia**: First part of the stomach directly after the GEJ. **Histologically**: Thinner mucosa than other parts of the stomach. The main cellular component is *foveolar* cells that secrete mucin.
- Fundus & Body: Make most of the stomach, and they are very similar in histological structure. The fundus is slightly bulged upward. Histologically: *Parietal Cells* which are pink in color with H&E stain, they secrete HCL. *Chief Cells* characterized by a bluish cytoplasm; they secrete Pepsin.
- Pyloric antrum: Opens into the duodenum through the GDJ. Histologically: Thicker than cardia, composed mainly of mucin secreting *Antral Glands*. It also contains *Neuroendocrine G Cells*, interspersed between the *Antral Glands*, for the secretion of <u>gastrin Hormone</u>. Gastrin is transferred in the blood to the parietal cells of the body & fundus to stimulate acid (HCL) secretion.
- **Lesser curvature**: On the right side of the stomach.
- **Greater curvature**: On the left side of the stomach.





Foveolar cells: notice the whitish appearance which indicates <u>mucus</u> secretion.



Parietal cells: have abundant pink eosinophilic cytoplasm and secrete HCl.

Chief cells: have bluish cytoplasm and secrete <u>pepsin</u>.



Gastric diseases:

- Neoplastic (*discussed later*)
- Inflammatory:
 - o Gastritis
 - Acute (commonly caused by NSAIDs)
 - Chronic
 - *H. pylori* related (90%!)
 - Autoimmune gastritis (10%)
 - Peptic Ulcer: Acute or Chronic

The stomach contains gastric acid secretions and pepsin, both are considered as natural damaging factors. If these secretions come in direct contact with the mucosa of the stomach, the mucosa will be damaged (Self-digestion).

Damaging factors could be:

- Intrinsic (Natural):
 - Acid secretions \rightarrow pH 1 \rightarrow HIGHLY acidic
 - Peptic enzymes.
 - Extrinsic or acquired:
 - NSAIDs (mainly in acute gastritis, and function by inhibiting PG synthesis)
 - *H. pylori* infections (mainly in chronic gastritis/ulcers)
 - Alcohol use
 - o Duodenal-Gastric reflux
 - Ischemia (causes loss of protective forces → ulcers)

On the other hand, we have natural protective mechanisms of the stomach to protect the mucosa from the acid and pepsin effect, these include:

- Surface mucous secretion, it acts as a protective layer between the acid and the epithelium.
- Bicarbonate secretion, from the foveolar cells, buffers the acidity near the epithelium.
- Rich blood supply to the gastric mucosa that:
 - $\circ\;\;$ Removes protons that diffuse back into the lamina propria and
 - Helps regenerate any damaged epithelium (High regenerative capacity)
- Prostaglandins synthesis (by COX) and secretions, always present in the stomach, which stimulates all the above mechanisms (Mainly PGE2).

Use of NSAIDs, either as a large sudden dose or chronic use, reduces the protective factors of the stomach due to inhibition of COX, thus prostaglandins synthesis, makes the patient more prone to gastritis and gastric ulcers.

IN SUMMARY: For any gastric injury to occur, and imbalance must develop between the protective and damaging forces of the stomach, either the protective factors decrease, or the damaging factors increase.



13:00 This was all a slight revision on the first online lecture which talked in depth about the acute inflammatory gastric diseases and chronic gastritis. In the rest of this sheet we shall talk about the last form of gastric disease, chronic ulcers, and some of the gastric neoplasms

Peptic Ulcer Disease (chronic ulcers):

A very common disease that usually affects the first portion of the duodenum and the lower antrum of the stomach (site of H. *pylori* associated chronic gastritis which is the main cause of these peptic ulcers). PUD is more common in a chronic gastritis background.

The term peptic does not necessarily mean gastric, it can denote all areas in the GIT that are exposed to high acidity and pepsin, namely the **lower esophagus** (by GERD), **stomach** (obviously), the first part of the **duodenum** which receives the highly acidic juices of the stomach (anterior wall of duodenum), or even if **ectopic gastric mucosa** developed anywhere along the rest of the small intestine, common examples are in the esophagus or a Meckel diverticulum (*see below*). Remember that ectopic tissue means a type of tissue that grew in an unusual place, therefore, ectopic gastric epithelium in a place other than the stomach will damage that area by its acidic secretions and enzymes, ultimately causing peptic ulcers.

Outside info: Meckel's diverticulum is an outpouching or bulge in the terminal ilium. The bulge is congenital and is a leftover of the umbilical cord. Meckel's diverticulum is the most common congenital defect of the GIT.

Pathogenesis:

- Gastric acid is fundamental in the pathogenesis (no acid, no ulcer).
- >70% of PUD cases are associated with H. *pylori* infections, yet ONLY 5-10% of H. *pylori* infected individuals develop ulcers.

HYPERACIDITY \rightarrow an imbalance between protective and damaging forces \rightarrow damage to the epithelial mucosa and submucosa \rightarrow ulcers.

Causes of hyperacidity:

- *H. pylori* infections (70%)
- Parietal cell hyperplasia
- Excessive secretory response (vagal)
- Hypergastrinemia (excessive gastrin release)
 ex. Zollinger-Ellison syndrome which is characterized by multiple ulcers in the stomach, duodenum, and even jejunum, caused by uncontrollable release of gastrin by a tumor and the resulting massive acid production.

NSAIDs use is also a common cause of PUD, not by causing hyperacidity but by causing an imbalance between protective and damaging gastric forces directly, due to inhibition of prostaglandin synthesis.

Cofactors: smoking, chronic NSAIDs use, high-dose corticosteroids (mechanism is also by inhibiting PG synthesis), alcoholic cirrhosis, COPD (Chronic Obstructive Pulmonary Disease), CRF (Chronic Renal Failure), and hyperparathyroidism (HPT).

- Mechanism of CRF: It causes hypocalcemia $\rightarrow \uparrow$ PTH $\rightarrow \uparrow$ Gastrin release \rightarrow Hyperacidity.
- Mechanism of HPT: \uparrow PTH $\rightarrow \uparrow$ Gastrin release \rightarrow Hyperacidity.

<u>Epidemiology</u>: remember from the online lecture that *H. pylori* infections are more common in developing areas, therefore *H. pylori*-caused ulcers are on the drop in places like the USA and Europe while NSAIDs-caused ulcers are on the rise, especially in older adults who use aspirin for daily prophylaxis against heart disease.

Note: *H. pylori* most commonly causes gastritis not PUD, only 5-10% of infected individuals develop ulcers.

Morphology:

• Peptic ulcers are four times more common in the proximal duodenum (anterior wall) than in the stomach (4:1), and that is expected because the **duodenum has much weaker protective factors**.

Note: **100% of duodenal ulcers are caused by** *H. pylori* **mediated gastritis**, not because *H. pylori* is present in the duodenum but because of the hyperacidity caused by *H. pylori* in the stomach. *H. pylori* causes only 70-80% of gastric ulcers. Other causes of gastric ulcers are mentioned above in the cofactors.

- Peptic ulcers are **solitary** (unlike acute ulcers which are usually multiple) in more than 80% of patients.
- Round/Oval, sharply punched-out defect in the epithelial surface.
- The base of peptic ulcers is smooth and clean as a result of peptic digestion of exudate.
- Histologic examination reveals that the base is composed of richly vascular granulation tissue in attempts of healing.
- Haemorrhage and perforation are life-threatening complications. Perforation can cause peritonitis which is an emergency state that requires immediate surgery.



Fig. 15.15 Peptic ulcer disease. (A) Endoscopic view of typical antral ulcer associated with NSAID use. (B) Gross view of a similar ulcer that was resected due to gastric perforation, presenting as free air under the diaphragm. Note the clean edges. (C) The necrotic ulcer base is composed of granulation tissue overlaid by degraded blood. (Endoscopic image courtesy of Dr. Ira Hanan, The University of Chicago, Chicago, Illinois.)

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Clinical Features:

- Epigastric burning or aching pain.
- Nausea, vomiting, bloating, and belching may be present.
- The pain tends to occur 1 to 3 hours after meals during the day, it worsens at night, and is relieved by alkali or food (causes patients to become overweight), which reduces the hyperacidity.
- Complications include haemorrhage or perforation as previously discussed, while extreme blood loss due to haemorrhage can cause iron deficiency anaemia.

<u>Tx</u>:

- Current therapies are aimed at H. pylori eradication with antibiotics and neutralization of gastric acid, usually through use of proton pump inhibitors (PPIs).
- Surgical management is reserved for treatment of severe ulcers with uncontrollable bleeding or perforation.
- Eradication course takes a long time, 4 weeks.
 Antibiotics during the first 2 weeks then continuation of the treatment by taking PPIs. Some patients are incompliant, so bacteria stay and becomes more resistant to further treatments which leads to recurrence of the infection.

SUMMARY

ACUTE AND CHRONIC GASTRITIS

- Gastritis is a mucosal inflammatory process. When inflammatory cells are absent or rare, the term gastropathy can be applied.
- The spectrum of acute gastritis ranges from asymptomatic disease to mild epigastric pain, nausea, and vomiting. Causative factors include any agent or disease that interferes with gastric mucosal protection. Acute gastritis can progress to gastric ulceration.
- The most common cause of chronic gastritis is H. pylori infection; most remaining cases are caused by NSAIDs, alcohol, or autoimmune gastritis.
- *H. pylori* gastritis typically affects the antrum and is associated with increased gastric acid production.
- H. pylori gastritis induces mucosa-associated lymphoid tissue (MALT) that can give rise to B-cell lymphomas (MALTomas).
- Autoimmune gastritis causes atrophy of the gastric body oxyntic glands, which results in decreased gastric acid production, antral G-cell hyperplasia, achlorhydria, and vitamin B₁₂ deficiency. Anti-parietal cell and anti-intrinsic factor antibodies are typically present.
- Intestinal metaplasia develops in both forms of chronic gastritis and is a risk factor for development of gastric dysplasia and adenocarcinoma.
- Peptic ulcer disease can be caused by *H. pylori* chronic gastritis and the resultant hyperchlorhydria or NSAID use. Ulcers can develop in the stomach or duodenum and usually heal after suppression of gastric acid production, discontinuation of NSAID use, or, if present, *H. pylori* eradication.

Gastric Polyps and Tumours

- Gastric Polyps:
 - Inflammatory and Hyperplastic Polyps
 - o Gastric Adenoma
- Gastric Adenocarcinoma
 - o Intestinal
 - Diffuse
- Lymphoma
 - o MALToma
- Neuroendocrine (Carcinoid) Tumor
- Gastrointestinal Stromal Tumor (GIST)

Gastric Polyps:

Polyp: any mass protruding above the level of the mucosa. Polyps may develop as a result of foveolar epithelium or stromal cell hyperplasia, inflammation, ectopia, or neoplasia. (Hyperplastic)

- Inflammatory and Hyperplastic Polyps (benign):
 - Constitute about **75%** of all gastric polyps.
 - Are also called reactive polyps because they arise in response to chronic gastritis (MUST have chronic gastritis background).



- There is a high risk of dysplasia/malignancy if the polyps reach a size larger than **1.5 cm**.
- **Treatment is by eliminating the cause of the chronic gastritis**, therefore, if it is associated with *H. pylori* gastritis, polyps may regress after H. *pylori* eradication.
- Gastric Adenomas:
 - Uncommon, unlike colonic adenomas, constitute only 10% of all gastric polyps.
 - Increased incidence with age.
 - Males are affected three times more often than females (3:1).
 - Adenomas almost always occur on a **background of chronic gastritis** with atrophy and intestinal metaplasia in the stomach.
 - All gastrointestinal adenomas exhibit epithelial dysplasia, this is their characteristic feature. Their dysplasia can be classified as low- or high-grade.
 - The risk of developing adenocarcinoma from gastric adenomas is related to the size of the lesion and is particularly elevated with lesions greater than 2 cm in diameter.
 - Gastric adenomas have a much higher risk of developing into carcinomas than colonic adenomas. Carcinoma may present in 30% of gastric adenomas.

Gastric Adenocarcinoma:

- **90%** of all gastric cancers.
- Early symptoms resemble those of chronic gastritis, including epigastric pain, nausea, and vomiting. As a result, the cancer is often diagnosed at advanced stages when clinical manifestations such as weight loss, melena, hematemesis, and cachexia trigger diagnostic evaluation.

Gastric adenocarcinomas are similar to oesophageal adenocarcinomas in how they have late presentation and are not often diagnosed until late stages. Screening is a method used for early detection but can be expensive on a large scale.

- Occur in a background of chronic gastritis, mucosal atrophy and intestinal metaplasia.
- Since adenocarcinomas have a chronic gastritis background, it isn't peculiar that their incidence distribution is similar to that of chronic gastritis.
 Rates vary markedly with geography. Japan, Costa Rica, Chile are places where adenocarcinomas are very common.

Furthermore, since the most common cause of chronic gastritis, *H. pylori*, is decreasing in the US, so is the incidence of adenocarcinomas (in other words: USA has less *H. pylori* $\rightarrow \downarrow$ chronic gastritis $\rightarrow \downarrow$ adenocarcinomas).

- Ulcers of PUD don't increase the risk of gastric cancer and won't transform to become malignant. Remember that both PUD and adenocarcinomas have chronic gastritis background.
- There are two main types of adenocarcinoma:
 - Intestinal: forms glands like those of the intestinal mucosa
 - Diffuse: is composed of single cells that infiltrate the whole wall of the stomach.

We will continue on adenocarcinomas in the next lecture, good luck! $\ensuremath{\textcircled{\odot}}$