

# Pathology

Doctor 2017 | Medicine | JU | GI

Number >>

4

Doctor

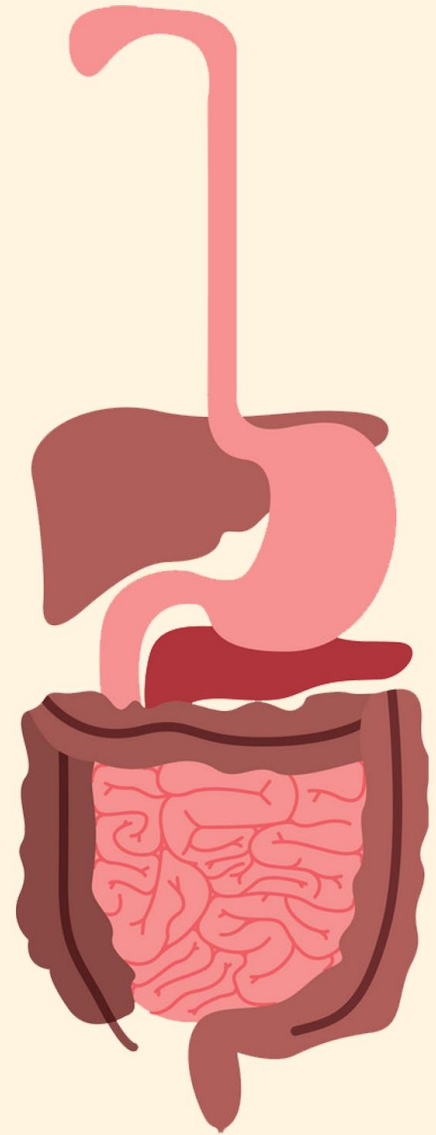
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2<sup>nd</sup> system - GI



## Today we will be talking about

- Gastric Tumors (malignancies)
- Intestinal pathology.

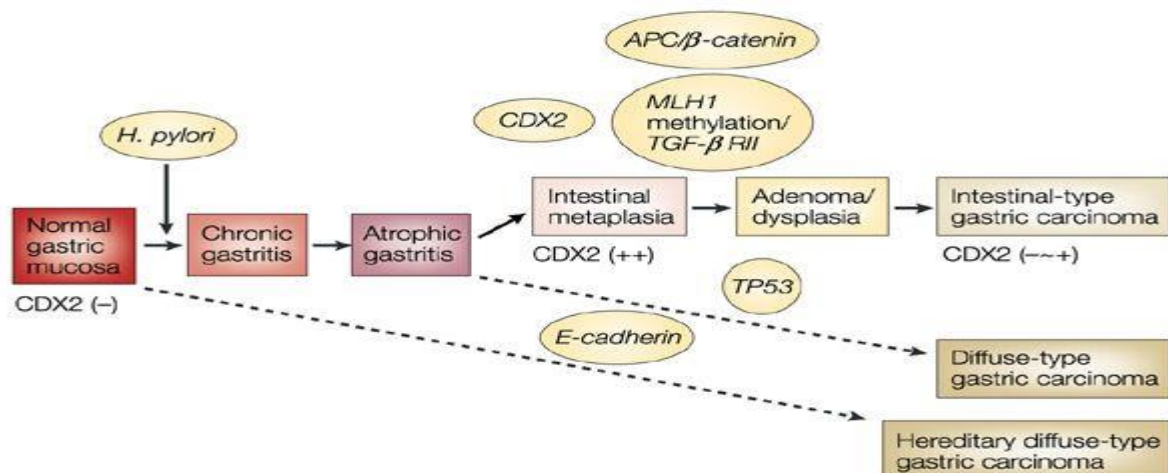
Last time we said that the most common gastric tumor is **gastric adenocarcinoma**:

- 90% of all gastric cancers
- Most of the time happens in the background of **chronic gastritis** whatever the cause.
- 2 types of gastric cancer:
  1. Intestinal type: looks like intestinal mucosa with glands and mucus production.
  2. Diffused type: (which we will be talking about in a while.)
- **Intestinal type only** is complicated by intestinal metaplasia → dysplasia → adenocarcinoma

we divided gastric cancers into 2 types because they differentiate in the morphology, pathogenesis and behavior.

## Pathogenesis of gastric adenocarcinoma

- Genetic alterations due to
  1. H. Pylori associated chronic gastritis
  2. Lesser extent: autoimmune gastritis, Epstein-Barr virus (EBV) (10%).
- Most cases are sporadic (Acquired with underlying cause of disease).
- Familial cases are only 10%.



Nature Reviews | Cancer

## Intestinal Adenocarcinoma

- **Familial** intestinal type, with **FAP**:  
**APC gene mutation.**

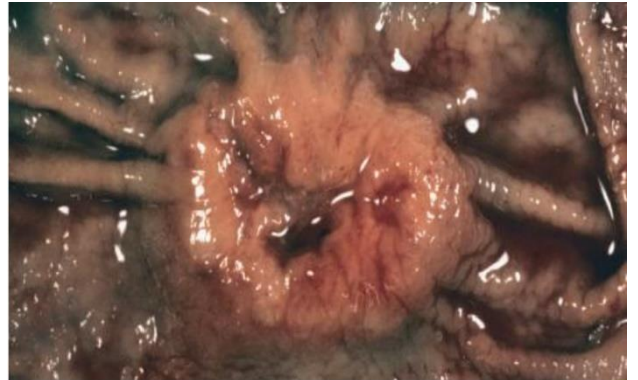
Patients with FAP, in addition to colon cancer and cancer polyps they will have gastric Adenocarcinoma.

- **Sporadic** intestinal type, lots of mutations.

Most common:

1. B-Catenin
  2. Microsattelite instability: problem with DNA repair genes.
- Ulcerated Mass with chronic gastritis background.

1. **APC Gene:** Adenomatous Polyposis Coli Gene
2. **FAP:** Familial Adenomatous Polyposis Syndromes, people with multiple hundreds of colon polyps and increases the risk of early onset colon cancer.



## Diffuse Adenocarcinoma

- **Familial** diffuse type: Mutation in **E-Cadherin gene (CDH1).**
- **Sporadic** diffuse type:
  1. **E-Cadherin gene mutation in 50% of cases.**
  2. **Methylation in the rest.** E-Cadherin is **inactivated.**

- Gross image of Diffuse type gastric cancer is different than intestinal type, due to absence of e-cadherin, cells are dis-cohesive. Intestinal type looks like colonic adenocarcinoma.
- **Linitis Plastica** is a lumen without masses, might be flat mucosa. However, the wall is very thick.
- Might be called leather bottle appearance.

- **E-Cadherin Gene:** Adhesion molecule
- E-Cadherin gene encodes the cadherin which is an adhesion molecule that allows cells to adhere to each other if it was mutated, cells will lose the adhesion.

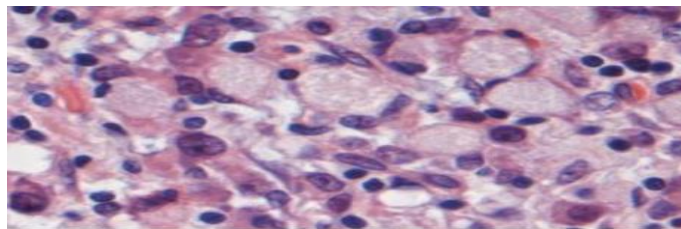


**P-53** which is a tumor suppressor gene, is involved in both types.  
and it is the most commonly mutated genes in all cancers.

## Morphology of both types

- Lauren classification: separates gastric cancers into intestinal and diffuse types.
  1. **Intestinal type**:
    - a. Bulky (Mass).
    - b. Exophytic mass or ulcer. Localized with its most common site in the antrum
    - c. Form glands.
  2. **Diffuse gastric cancers**
    - a. Infiltrative growth pattern
    - b. Absence of a mass, diffuse thickening in stomach wall, making it very thick. And so we call it linitis plastica
    - c. Tricky
    - d. Discohesive cells (signet ring cells), due to loss of E-Cadherin, leading to absence of glands, and mucus cell production.
    - e. Desmoplastic reaction (thick wall, linitis plastica), fibrosis collagen deposition. And very rigid wall.

f. Signet ring cells: large **mucin vacuoles** that expand the cytoplasm and push the nucleus to the periphery



- Cells are very tricky, and it is very hard to diagnose diffuse type adenocarcinoma, even with biopsy since it might be too small to examine, and few cells are not enough for diagnosis
- Diffused adenocarcinoma is not associated with the preceding intestinal metaplasia, dysplasia and H. Pylori, and so it has a different pathway and pathogenesis.

## Clinical Features

<u>Intestinal Type</u>	<u>Diffuse Type</u>
<b>High Risk Areas</b> Costa Rica, Japan	Incidence <b>uniform across countries.</b> because the problem is not a predisposing factor, it is a mutation.
<b>Develops from precursor</b> (adenoma, dysplasia)	<b>No precursor lesions.</b>
<b>Mean age 55 yrs.</b>	<b>Younger age.</b> Typically in 30-40's And it will be very bad since cells can metastasize everywhere and treatment is very difficult
<b>M:F 2:1</b>	<b>M:F 1:1</b>

- The **drop** in the gastric adenocarcinoma rate (US, UK) was in the **intestinal type** only NOT diffused type.
- Most powerful in **prognosis** is the **stage**.
- **TNM stage**
  - T: depth of invasion
    - Depth in mucosa, submucosa, muscularis, serosa. (worse last)
  - N: lymph node status
  - M: distant metastasis
- Gastric cancer can metastasize to the ovaries, it can lead to Krukenberg tumor, and it is a typical scenario and it is a marker of distant metastasis worsening the prognosis.
- **Treatment** of gastric cancer is
  1. Surgery
  2. +/- Chemotherapy
  3. Radiotherapy
  4. Targeted therapy
  5. Anti-HER2 (if mutation was present)



- Gastric cancer expresses a surface epidermal growth factor receptor molecule HER2.
- If patient has HER2 mutation, they can take an advancement treatment of gastric cancer which includes Anti-HER2.

## Other type of gastric tumors

### Lymphoma

- Tumor of lymphoid **tissue**
- 5% of all gastric malignancies
- Most common site is lymph nodes; however, the GI tract (**stomach**) is a count site for **extra nodal lymphoma**.
- **Most common lymphoma: MALToma, indolent**, low grade malignancy.
- Extra nodal marginal zone B-cell lymphomas
- Mucosa associated lymphoid tissue
- Background of H. Pylori gastritis.
- **Second most common lymphoma: diffuse large B cell lymphoma (aggressive).**



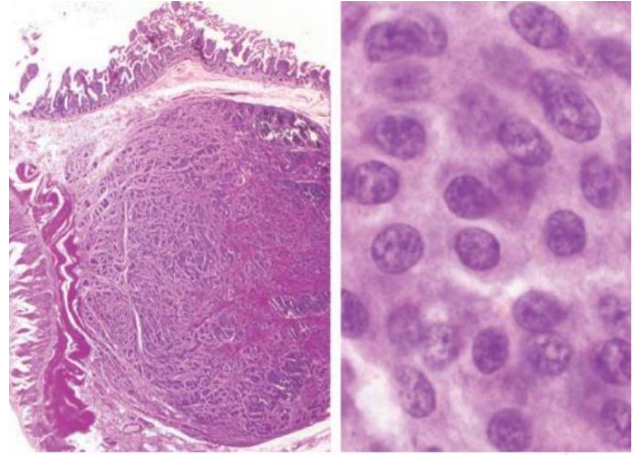
Doctor said she will not focus on details much, just memorize the indolent and the aggressive tumors

### Neuroendocrine (Carcinoid) Tumors

- **Slowly growing tumor**
- Better prognosis than carcinoma which is why it is called carcinoid.
- Commonly seen in GI tract, **> 40% occur in the small intestine**.
- Coming from neuroendocrine cells which is occurs in the proliferation of autoimmune gastritis due to absence of acids causing growth of gastrin producing cells in antrum leading to a tumor, like Gastrinoma.
- Associated with endocrine cell hyperplasia, chronic atrophic gastritis, and Zollinger- Ellison syndrome (Gastrinoma, pancreas, duodenum)



- carcinoid is in the **submucosa** or within the muscle and projects as a nodule or a mass to the lumen in the stomach
- Gastroenterologist might remove it thinking it is a polyp and then will realize it is a neuroendocrine cell
- **Well circumscribed**
- Nesting: cells are gathered in a nest
- uniform cells with scant, pink granular cytoplasm and
- **salt and pepper chromatin**, no prominent nucleolus.
- **Carcinoid tumors can be associated with carcinoid syndrome.**



### Carcinoid syndrome:

- Due to release **vasoactive amines** from carcinoid tumor
- Since it is present in the GI tracts, vasoactive amines are metabolized in the liver and so effect of vasoactive amines will disappear.
- **Observed in metastatic disease**, and so the vasoactive amines produced in metastatic site will not go to the liver and so implying its effect.
- Seen in 10% of cases.
- **Cutaneous flushing**, sweating, **bronchospasm**, colicky abdominal pain, **diarrhea**; vasoactive amines increase peristaltic movements in the bowel. and right-sided **cardiac valvular fibrosis**.

Up until now we have discussed the tumors of the stomach.

# Intestinal pathology

- Please note that part of this lecture is recorded, and it covers:
  1. Intestinal obstruction
  2. Vascular disorders mainly hemorrhoids
  3. Malabsorptive diseases and infectionsinfections are not covered in pathology

## inflammatory bowel diseases

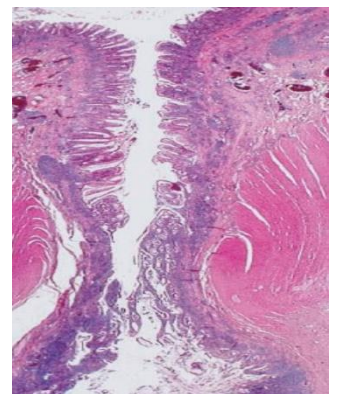
- Very common on real life
- Subdivided into
  1. **Diverticular disease (diverticulitis).**
  2. **Chronic inflammatory bowel disease (CIBD).**
    - a. Ulcerative colitis
    - b. Crohn's disease
- Immune mediated disorders.

### Diverticulitis (انبعاث):

Wall of the intestine is similar to the stomach with the presence of the mucosa, submucosa, muscularis propria, and serosa. Small intestine has a thinner wall, with smaller lumen than the large intestine.



- Outpouchings of colonic mucosa and submucosa.
- Acquired.
- **Diverticulum commonly takes place in large intestine** principally in sigmoid and rectum (rectosigmoid column).
- Occurs in people with recurrent constipation, which leads to **elevated intraluminal pressure in the sigmoid colon** (people associated with **low fiber diet**). So, **exaggerated peristaltic contractions** take place to propel the stool and so intraluminal pressure increases, due to constipation, stool is not propelled,





and so patient will have **elevated intraluminal pressure** leading to the mucosa exiting through weak bowel points.

- Weak bowel points: entering points of nerves and vessels through muscle fibers
- Mucosa and submucosa enter bowel wall and reached muscle layer and might reach serosal surface and with time they will be attenuated, thin and weak.
- The neck is an opening allowing the exit of diverticulum, if obstruction took place due to presence of stool, there will be an infection in the diverticulum. Obstruction will allow the growth of bacteria in the stool causing diverticulitis which causes rupture in diverticulum. The patient will complain of acute abdomen (Intermittent lower abdominal pain) and peritonitis.
- Diverticulum takes place in **old age people**.
- If the patient had a recurrent diverticulitis, in the end they will have strictures with Risk of perforation and narrowing in the bowel wall which increases constipation.
- **Treatment:**
  1. If **not complicated** → high fiber diet
  2. If **complicated**:
    - a. diverticulitis → antibiotics
    - b. Perforations → surgery
    - c. strictures → surgery

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### Chronic Inflammatory Bowel Disease

- Characterized by inappropriate activation of the mucosal immune responses with insignificant irritation.
- In normal individuals, stool's mass is composed nearly of 50% bacteria. They also have protective bacteria in the bowel protecting us against pathogenic bacteria. If the beneficial bacteria's function is altered or affected the pathogenic bacteria will cause irritation or damage to the mucosa. This is **associated with genetic predisposition, having mutations in certain genes**. When they experience any kind of bacteria, they will undergo exaggerated mucosal response/inflammation and therefor; symptoms of chronic inflammatory bowel disease.



*Healthy Colon*



*Ulcerative Colitis*

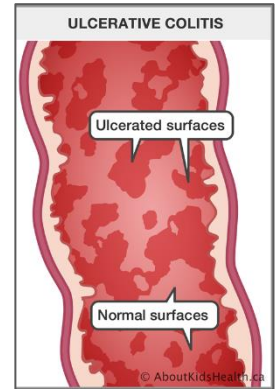


*Crohn's Disease*

- **Inflammatory bowel diseases** are composed mainly of 2 types:

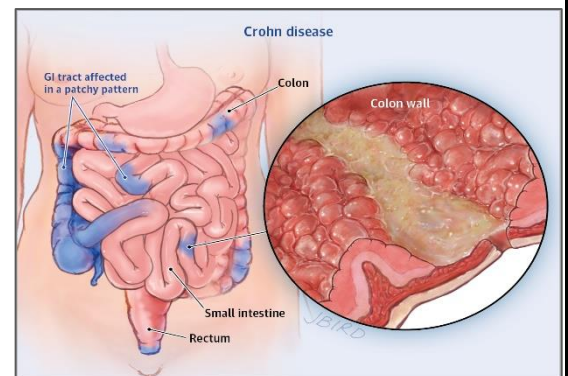
### 1. **Ulcerative colitis:**

- characterized by ulcerations and inflammation **ONLY** in the colon. (rectum, sigmoid, descending, transverse, ascending colon, cecum).
- Inflammation is only relative to the mucosa, and submucosa.
- Disease always starts in rectum and then proximal continuous extension takes place.
- Characterized by ulcerations
- Areas that are not affected by ulcerations appear as pseudo-polyps, inflamed mucosa, above the level of the surrounding mucosa.
- The genes of ulcerative colitis are unknown, and their role is less than the genetic role in Crohn's disease.

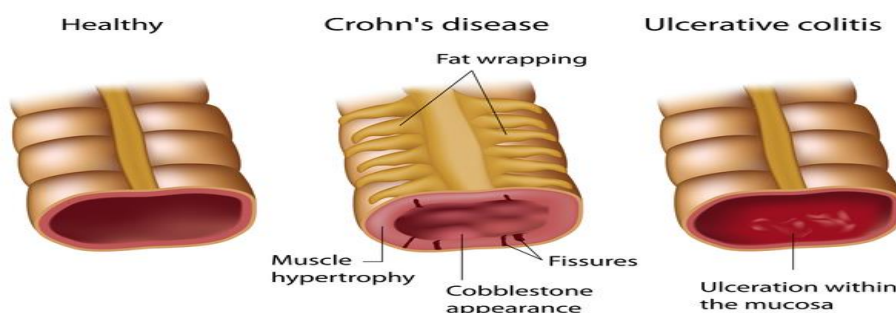


### 2. **Crohn's Disease:**

- Any **area in the GI tract** from mouth to anus can be affected.
- Regional Enteritis:** **most common site** is the ileocecal valve, terminal ileum and cecum. (40% of people, only affected site)
- Inflammation is transmural**, existing or occurring across the entire wall, thus the entire bowel is affected (mucosa, submucosa, muscularis, serosa)
- Genes play a very important role >>> ulcerative colitis
- Skip lesions**, normal areas between inflamed areas. This is not seen in ulcerative colitis.



### **Inflammatory Bowel Disease**



## Epidemiology

-2 peaks-

1. Young adults and Adolescence
2. Peak in 5<sup>th</sup> decade

- Geographic variations. Relating to hygienic hypothesis.

In places with intensive hygienic care, especially for children where they are not exposed to pathogens. Inflammatory bowel disease is more likely to occur in people that are less exposed to pathogens, which also makes them more vulnerable to allergic diseases and immune mediated diseases later on.

They will respond to any trivial infection or insignificant insult in an exaggerated way.

- Making inflammatory bowel disease more common in **developed countries** in which people are extra cautious about child-pathogen exposure.

-there is no firm evidence to support this theory-

## Pathogenesis

- Combination of factors

1. Genetically predisposed

- a. Crohn's disease → 200 gene associated

- b. Ulcerative colitis → few genes with low concordance rates

2. **Alterations in host interactions** with intestinal microbiota

Exaggerated reactions

3. Abnormality in **intestinal epithelial function**

4. **Exaggerated immune response**

5. **Altered in composition of gut microbiome** (normal flora in gut)

Some patients can respond to treatment by yogurt containing normal flora or even microbiome transplant. And so, they assumed that the microbiome composition is different in patients.

- Doctor said she will not concentrate about pathogenesis much because it will be taught in the clinical part. She will concentrate on the clinical presentations, symptoms and how to treat the disease.

## Genetics

Genetic factors play an important role and people with inflammatory bowel disease always show family history with one of his siblings having inflammatory bowel disease and they showed that concordance rates of monozygotic twins, 50% concordance rate for Crohn's disease, and 16% in ulcerative colitis (much less).

- **NOD2** (nucleotide oligomerization binding domain 2):
  1. Susceptibility gene in Crohn disease.
  2. This gene is present in normal individuals. When mutated, it alters the defense of the body against bacteria.  
Bacteria will start entering epithelia causing inappropriate activation and damage of the epithelium.
- Autophagy genes

## Mucosa immune responses

- Immunosuppressive and immunomodulatory agents are mainstays of IBD therapy.
- Excessive immune activation by intestinal microbes; In both Crohn's disease and Ulcerative colitis.
- Excessive inflammatory cell infiltrate in mucosa, mainly derived from T-cells.  
TH-1 → Crohn's Disease  
TH-2 → Ulcerative colitis
- biopsy will be associated with a mucosa full of inflammatory cells.
- Defects in intestinal epithelial tight junction barrier function >>>> in Crohn disease.
- Barrier dysfunction causes activation in innate and adaptive immunity.
- mucosal immunity >>> sensitize subjects to disease.

Good luck.

Don't hesitate to ask any questions.