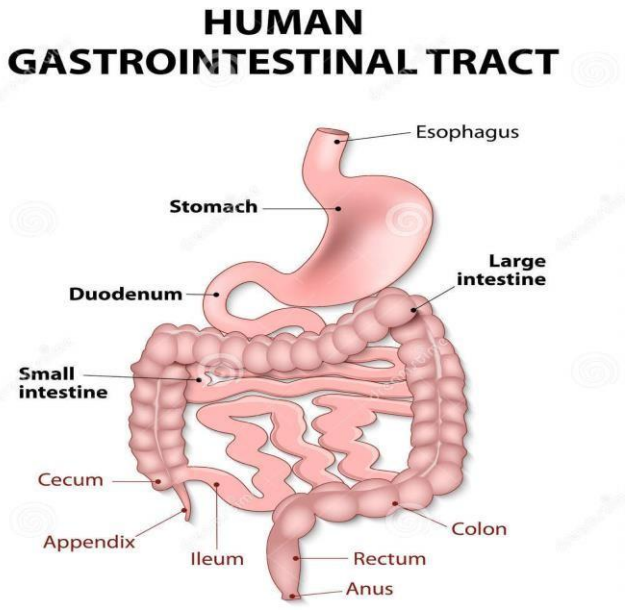
Pathophysiology of the Gastrointestinal Tract (GIT)

The gastrointestinal tract (GIT) is a hallow tube extending from the oral cavity to the anus that consists of anatomically distinct segments, including:

- Esophagus
- Stomach
- Small intestine
- Large intestine, colon
- Rectum
- Anus

General function of the GIT:

1. Regulate the intake of nutrients
2. Processing the nutrients through digestion
3. Absorption of ingested nutrients
4. Disposal of waste products



Pathological disorders of the GIT:

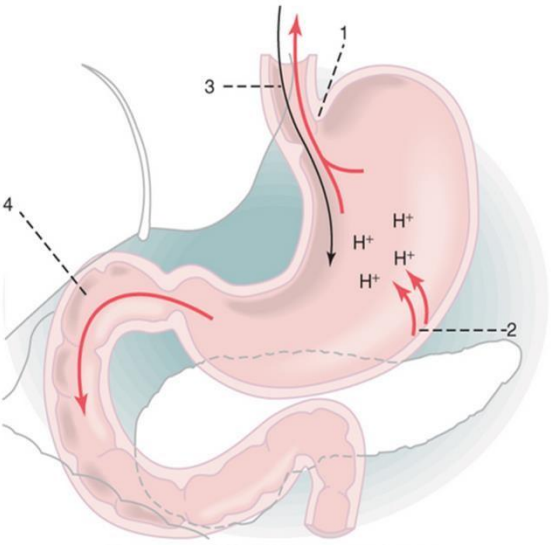
1. **Esophagus:**
    - Esophageal obstruction
    - Achalasia
    - Mallory-weiss tears
    - Esophagitis
    - Gastroesophageal varices
    - Barrette esophagus
    - Esophageal adenocarcinoma
    - Esophageal squamous cell carcinoma
2. **Stomach:**
    - Acute gastritis
    - Chronic gastritis (peptic ulcer)
    - Zollinger – Ellison syndrome
    - Gastric polyps and tumors
    - Gastric adenocarcinoma
3. **Small and large intestine and rectum:**
    - Hernia
    - Malabsorption and diarrhea
    - Gastroenteritis
    - Irritable bowel syndrome (IBS)
    - Inflammatory bowel disease (IBD)
    - Intestinal polyps (benign and malignant)
    - Appendicitis (acute and chronic)
    - Hemorrhoids

Esophagitis (Gastroesophageal reflex disease GERD):

Reflux of gastric contents into the lower esophagus is the most frequent cause of esophagitis. It occurs when the amount of gastric juice that refluxes into the esophagus exceeds the normal limit, causing symptoms with or without associated esophageal mucosal injury.

- **Etiology:**
    a. Transient relaxation of the lower esophageal sphincter
    b. Certain type of food like coffee and alcohol
    c. Medications like doxycycline, alendronate and calcium channel blockers
    d. Hiatal hernia
    e. Obesity
    f. Pregnancy (mechanical and hormonal)
    g. Increased gastric volume

- **Pathogenesis:**
    1. impaired lower esophageal sphincter: low pressures or frequent transient lower esophageal sphincter relaxation
    2. hypersecretion of acid
    3. decreased acid clearance resulting from impaired peristalsis
    4. Delayed gastric emptying or duodeno-gastric reflux of bile salts and pancreatic enzymes.



- **Morphological changes:**
    1. Redness of the mucosa in mild cases
    2. Recruitment of eosinophils and neutrophils into the squamous mucosa in severe cases
    3. Hyperplasia of the epithelial layer

- **Clinical features:**
    1. Common symptoms: heartburn (retrosternal burning discomfort), and regurgitation (effortless return of gastric contents into the pharynx)
    2. Atypical symptoms: dry cough, chest pain and wheezing

Esophageal adenocarcinoma and squamous cell carcinoma:

1. **Adenocarcinoma:**
   It is benign tumor of the esophagus, usually occurs in the distal third of the esophagus and may invade the adjacent gastric cardia. It accounts for less than 10% of all cases

    - **Etiology:**
        - Barrett esophagus (most common cause)
        - Chronic GERD
        - Tobacco smocking
        - Obesity
        - Age (usually over 60 years)
        - Gender (men more than women)
        - Ethnicity (Africans more than Caucasians)

    - **Pathogenesis:**
      Chronic GERD → squamous epithelium injury → Barrett metaplasia → dysplasia → Adenocarcinoma

- **Morphological changes:**
  - Grossly: appearing as flat or raised patches in intact mucosa, large masses of 5 cm or more in diameter may develop (nodules). Alternatively, tumors may infiltrate diffusely or ulcerate and invade deeply.
  - Microscopically: Barrett esophagus is frequently presented adjacent to the tumor. Tumors most commonly produce mucin and form glands, often with intestinal-type morphology.

- **Clinical Features:**
  - Pain and difficulty in swallowing
  - Progressive weight loss
  - Chest pain
  - Hematemesis
  - Vomiting
  - Survival rate usually 5 years or less

2. **Squamous cell carcinoma:**

   It is malignant cancer of the esophagus, usually occurs in the middle third of the esophagus in which the tumor cells resembles stratified squamous epithelium (squamous dysplasia). It accounts for 90% of all the cases.

   - **Etiology:**
     - Esophageal disorders (chronic esophagitis, achalasia … etc)
     - Tobacco smocking
     - Alcohol drinking
     - Deficiency in vitamins and minerals
     - Fungal contamination of food
     - High content in nitrite/nitrosamines

- Genetic predisposition
- Age (over 60 years)
- Gender (men more than women
- Ethnicity (Africans more than Caucasians)
- Previous radiation therapy
- HPV (human papilloma virus)

- **Pathogenesis:**
  The molecular pathogenesis of esophageal squamous cell carcinoma remains incompletely defined, but recurrent abnormalities include:
  - Over transcription factor gene SOX2 (believed to be involved in cancer stem cell self-renewal and survival);
  - Over expression of the cell cycle regulator cyclin D1;
  - Loss of tumor suppressors P53, E-cadherin, and NOTCH1.

- **Morphological Changes:**
  - Grossly: Early lesions appear as small, gray-white, plaque-like thickenings. Over months to years they grow into tumor masses that may be polypoid, or exophytic, and protrude into and obstruct the lumen. Other tumors are either ulcerated or diffusely infiltrative lesions that spread within the esophageal wall and cause thickening, rigidity, and luminal narrowing.
  - Microscopically: Most squamous cell carcinomas are moderately to well differentiated; seen as intracellular bridges, epithelial pearls and keratinization.

- **Clinical features:**
  - Dysphagia
  - Odynophagia (pain and difficulty in swallowing)
  - Obstruction
  - Prominent weight loss
  - Hemorrhage
  - Sepsis
  - Survival rate usually 5 years or less

Gastritis (Acute and Chronic):

An inflammation of the gastric mucosa and it is mostly a histological term that needs biopsy to be confirmed. It is classified into two types:

1. **Acute gastritis:** usually short term of inflammation with neutrophilic infiltration and no fibrosis
2. **Chronic gastritis:** usually long term of inflammation with infiltration of mono-nucleated cells especially monocytes and lymphocytes and there is always fibrotic tissue formation

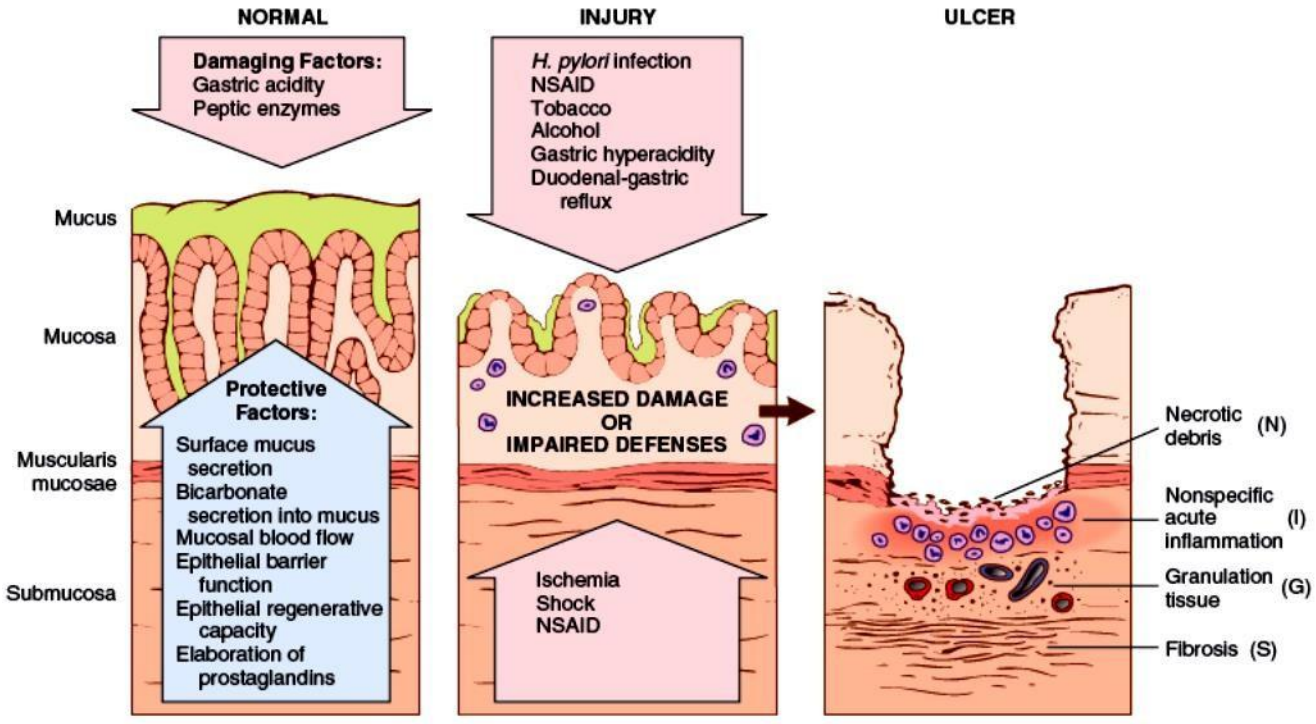


Figure (1): mechanism of injury and protection of gastric mucosa

- **Acute Gastritis:**
  Usually short term of inflammation of the gastric mucosa with neutrophilic infiltration and no fibrosis

  - **Etiology:**
    - Long term use of non-selective NSAIDs (specifically non-selective COX2 inhibitors like aspirin, ibuprofen, diclofenac, naproxen … etc.)
    - Excessive alcohol consumption and tobacco smocking
    - Chemotherapeutic agents
    - Severe stress and trauma
    - Ischemia, shock and uremia
    - Distal gastrectomy

  - **Pathogenesis:**
    - Increased acid secretion with back diffusion
    - Decreased production of bicarbonate buffer
    - Decreased secretion and disrupt adherence of mucus to the mucosal layer
    - Reduced blood flow
    - Reduced in prostaglandins (PG-E_2 and PG-I_2)
    - Direct damage to the epithelium

  - **Morphological Changes:**
    - Grossly: Acute ulcers are rounded and less than 1 cm in diameter. The ulcer base is frequently stained brown to black by acid digestion of extra-vasated blood and may be associated with transmural inflammation and local serositis.
    - Microscopically: acute ulcers are sharply demarcated, with essentially normal adjacent mucosa. There may be a suffusion of blood into the mucosa and submucosa and an associated inflammatory reaction.

- **Clinical Features:**
  - Stomach upset and nausea
  - Abdominal pain
  - Vomiting usually hematemesis
  - Indigestion
  - Loss of appetite
  - Sometimes black, tarry stool

- **Chronic Gastritis:**

  Usually long term of inflammation with infiltration of mono- nucleated cells especially monocytes and lymphocytes and there is always fibrotic tissue formation.

  Chronic Gastritis usually referred to the term peptic ulcer which is of two types:

  a. Gastric ulcer; the site of injury or ulcer formation is the stomach
  b. Duodenal ulcer; the site of injury or ulcer formation is the duodenum

  - **Etiology:**
    - *Helicobacter pylori* infection (most common)
    - Autoimmune gastritis (accounts for 10% of all cases)
    - Radiation therapy
    - Chronic bile reflex
    - Mechanical injury (eg: nasogastric tube)
    - Systemic disorders (eg: Crohn disease)

- **Pathogenesis:**
  - Same as that of acute gastritis
  - **In case of *H pylori* infection**; the bacteria secretes an enzyme called urease which converts endogenous urea into ammonia and thus increase gastric acidity
  - **In case of autoimmune gastritis**; there is increased antibodies production against parietal cells (responsible for acid and intrinsic factor production)

- **Morphological Changes:**
  - Grossly: the lesions are either round or oval, about (0.3cm – 0.6cm) in diameter and likely to be deeper. The mucosal margin may overhang the base slightly, but is usually level with the surrounding mucosa.
  - Microscopically: thin layer of fibrinoid debris with predominantly neutrophilic inflammatory infiltrate. Beneath this, granulation tissue infiltrated with mononuclear leukocytes and a fibrous or collagenous scar forms the ulcer base

- **Clinical Features:**
  - Epigastric burning sensation or aching pain referred to the back or the left upper quadrant of the abdomen
  - Iron deficiency anemia
  - Hemorrhage or perforation
  - Nausea and vomiting
  - Bloating
  - Belching
  - Significant weight loss

Inflammatory Bowel Disease:

It is s a chronic condition resulting from inappropriate mucosal immune activation. It comprises two types of disorders:

1. **Ulcerative colitis:** limited to the colon and rectum and extends only into the mucosa and submucosa.
2. **Crohn disease:** may involve any area of the GI tract and is typically transmural.

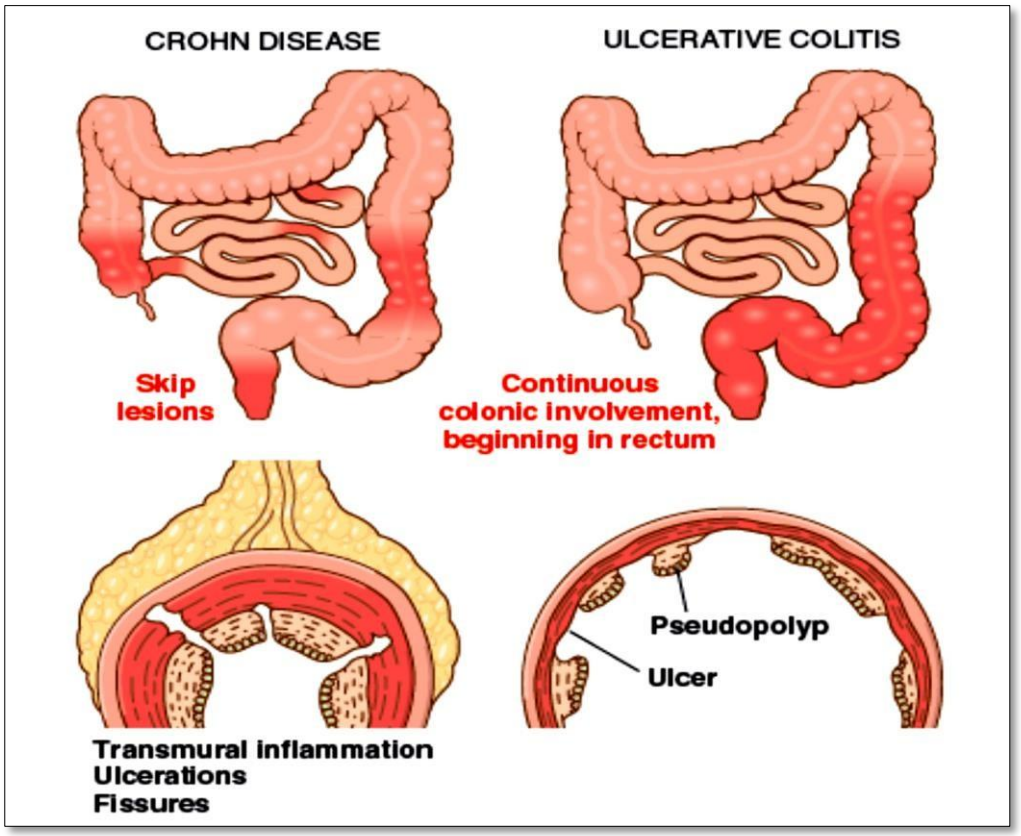


Figure (2): Distribution of lesions in inflammatory bowel disease. The distinction between Crohn disease and ulcerative colitis is primarily based on morphology.

- **Etiology:** it remains largely unknown but it involves a complex interaction between:
  - Genetic abnormalities
  - Environmental factors

- Microbial factors
- The immune responses

- **Pathogenesis:**
  - Alteration in host interactions with intestinal microbiota (genetic polymorphism)
  - Intestinal epithelial dysfunction
  - Abnormal mucosal immune responses
  - Altered composition of the gut normal flora (microbiome)

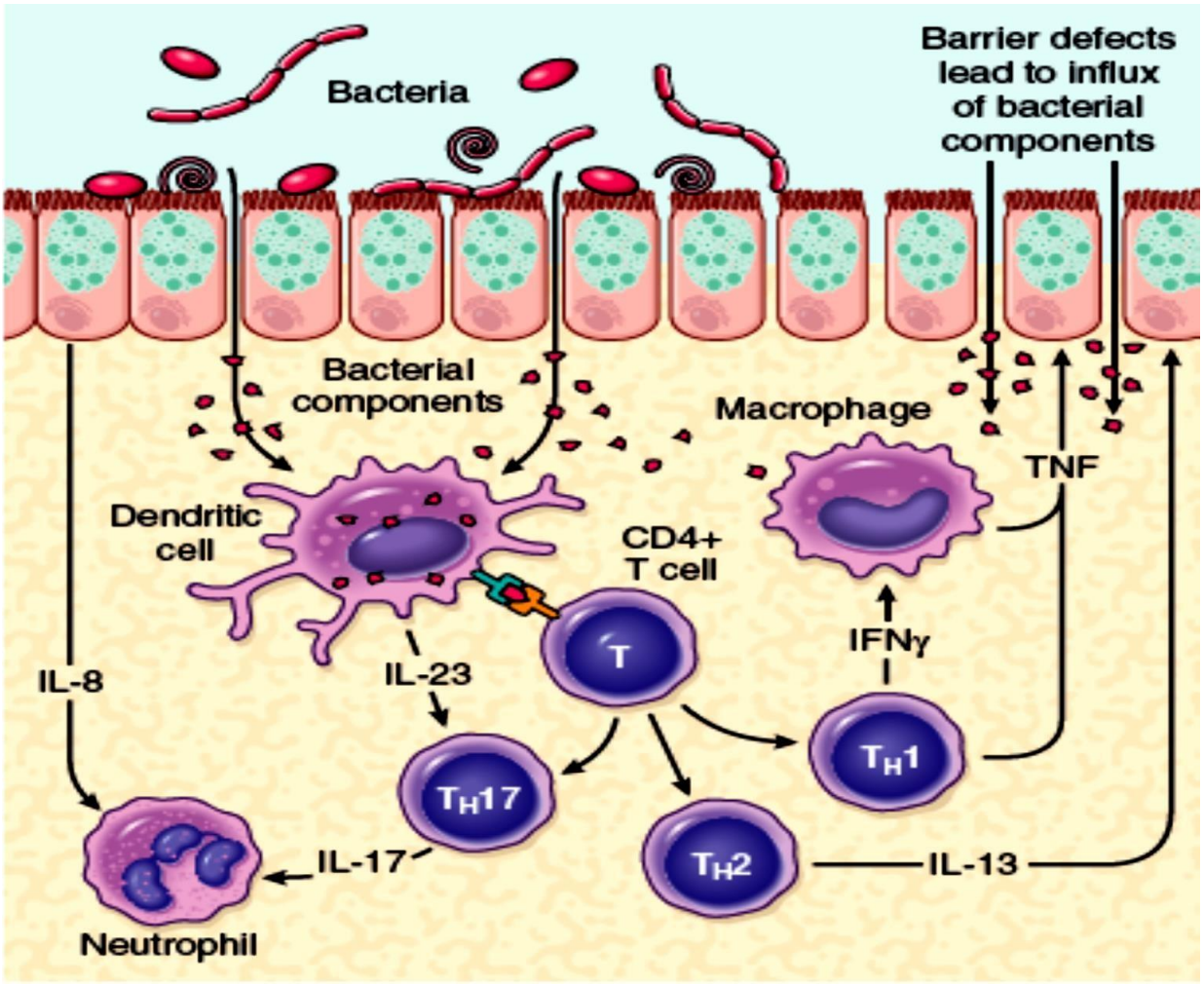


Figure (3): One model of IBD pathogenesis. Aspects of both Crohn disease and ulcerative colitis are shown.

- **Morphological Changes:**
  - **Crohn disease:**
    - Grossly: there is a multiple elongated ulcerative and patchy lesions on the surface, the texture is cobblestoned, Fissures frequently develop between mucosal folds and may extend deeply to become perforations
    - Microscopically: transmural edema, inflammation, submucosal fibrosis, and hypertrophy of the muscularis propria
  - **Ulcerative colitis:**
    - Grossly: usually affects the proximal colon and rectum; the mucosa has a friable granular appearance and shows superficial ulcers.
    - Microscopically: increased or altered distribution of cell types present in the colorectal mucosa, infiltration of inflammatory cells in the mucosa (acute and chronic inflammation)

- **Clinical Features:**
  - Abdominal pain and cramping
  - Diarrhea
  - Blood in stool
  - Fever and fatigue
  - Reduced appetite
  - Weight loss