I. MALABSORPTION SYNDROMES
1. Definition and etiology
   - Definition: defective digestion and/or absorption of one or more dietary nutrients.
   - Etiology
     (1). Defective digestion:
     - Lack of pancreatic enzymes: severe pancreatic failure, obstruction of pancreatic ducts
     - Lack of bile: severe liver failure, obstruction of the bile ducts, ileal resection
     - Abnormal intestinal motility: intestinal obstruction, paralytic ileus
     - Bacterial overgrowth determines:
       - Impairment of bile salts cycling ➔ bile deficiency
       - Enhancement of osmotic water movement to the intestinal lumen ➔ diarrhea
2. Consequences of malabsorption of major dietary nutrients

(a) Malabsorption of carbohydrates
Normally, the *pancreatic enzyme amylase* and *brush border enzymes* on microvilli lyse carbohydrates and disaccharides (eg, lactase, maltase, isomaltase, sucrase) → monosaccharides.

In pathological conditions, the undigested disaccharides cause an osmotic load → water and electrolytes are attracted into the bowel → osmotic diarrhea + subsequent loss of $\text{HCO}_3^-$ → metabolic acidosis. *Bacterial fermentation of carbohydrates* in the colon produces gases ($\text{H}_2$, $\text{CO}_2$, and methane), and *short-chain fatty acids* (butyrate, propionate, acetate, and lactate) → excessive flatus, bloating/distension, and abdominal pain.

(b) Malabsorption of fats
Normally, the pancreatic enzymes (*lipase and colipase*) split long-chain triglycerides → fatty acids and monoglycerides, which combine with bile acids and phospholipids to form micelles required for the intestinal absorption. At the level of enterocytes, fatty acids generate *triglycerides* that will combine with *apoproteins and phospholipids* to form chylomicrons that are transported by the lymphatic system.
In pathological conditions, malabsorption of fats is characterized by fatty stools (steatorrhea) ➔ weight loss from a lack of these high-caloric components of food. Unabsorbed fats trap fat-soluble vitamins (A, D, E, K) and some minerals, causing deficiency with:

- easy bruising and bleeding: due to vitamin K deficiency
- bone pain, a predisposition to the development of fractures and tetany: due to vitamin D and calcium deficiency
- hyperkeratosis and night blindness: due to vitamin A deficiency
- macrocytic anemia and glossitis: due to folic acid deficiency
- hypochromic anemia: due to iron deficiency.

(c) Malabsorption of proteins

Normally, gastric pepsin initiates digestion of proteins in the stomach (and also stimulates release of cholecystokinin that is critical to the secretion of pancreatic enzymes). Enterokinase, a brush border enzyme, activates trypsinogen into trypsin, which converts many pancreatic proteases into their active forms.

Active pancreatic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids.

In pathological conditions, malabsorption of proteins can lead to muscular atrophy and weight loss, while hypoproteinemia is responsible for the decreased colloid-osmotic pressure and edema.

3. Postgastrectomy malabsorption

- Etiopathogenesis

Surgical treatments for gastric disorders include:

- gastric resection (Billroth I/II, or Roux) in gastric tumors
- selective/non-selective vagotomy (VT) in treatment-resistant gastric ulcers

Surgical reduction of gastric volume and impaired relaxation reflexes after VT increase gastric wall tension when ingesting a normal meal; this is responsible for premature satiety, nausea, and vomiting as well as rapid gastric emptying.

Consequences of rapid gastric emptying are:

(a) Early dumping syndrome (occurring 30–60 min after food intake) is due to the:

- high chyme volume per time unit that distends the intestinal wall and causes nausea, vomiting, cramps, and vasomotor reactions: cutaneous vascular dilation (flush), palpitations/tachycardia, and orthostatic hypotension.
- hypertonicity of chyme that is emptied too quickly; the osmotically obliged water secretion into the intestinal lumen will result in:
  - diarrhea
• further cardiovascular reactions due to resulting hypovolemia.

(b) Late dumping syndrome occurs in the presence of high concentrations of carbohydrate into the chyme that leads to the rapid absorption of glucose \( \Rightarrow \) hyperglycemia that peaks at 90–180 minutes after food intake followed by reactive hypoglycemia due to the rapid release of insulin (confusion, loss of consciousness).

(c) Rapid gastric emptying also exceeds the digestive capacity of the upper small intestine \( \Rightarrow \) distal small intestine will take part in the digestion and absorption of nutrients, i.e. distal shift of digestion and absorption occurs.

(d) Billroth II gastrectomy can lead to the blind loop syndrome = stasis in the afferent loop with bacterial proliferation.

(e) Gastric resection (reduction of parietal cells) is also responsible for the: i) reduced H+ secretion into the stomach \( \Rightarrow \) decreases the liberation of iron from food and the absorption of Fe(II) \( \Rightarrow \) iron-deficiency anemia and ii) decreased secretion of intrinsic factor (if it falls below 10% of its normal value) impairment of cobalamin absorption \( \Rightarrow \) cobalamin deficiency \( \Rightarrow \) anemia is further aggravated (long term).

4. Malabsorption due to bacterial overgrowth

Under normal conditions, the proximal small bowel contains \(< 10^5 \) bacteria/mL, mainly gram-positive aerobic bacteria. This low bacterial count is maintained by the normal peristalsis & normal gastric acid secretion, mucus, secretory IgA, and an intact ileocecal valve.

- Etiopathogenesis

Small-bowel bacterial overgrowth can occur from: i) alterations in intestinal anatomy, ii) abnormal GI motility, and iii) decreased gastric acid secretion due to:

- strictures or partial obstruction
- postgastrectomy states (especially in the afferent loop of a Billroth II resection)
- intestinal motility disorders associated with diabetic neuropathy, systemic sclerosis, amyloidosis, hypothyroidism can also impair bacterial clearance
- hypochlorhydria and idiopathic changes in intestinal motility \( \Rightarrow \) bacterial overgrowth in elderly people.

- Consequences

(a) Excessive consumption of nutrients, including carbohydrates and vitamin B₁₂ \( \Rightarrow \) caloric deprivation and vitamin B₁₂ deficiency. However, because the bacteria produce folate, this deficiency is rare!

(b) Bacteria deconjugate bile salts \( \Rightarrow \) failure of micelle formation \( \Rightarrow \) fat malabsorption.

(c) Severe bacterial overgrowth also damages the intestinal mucosa.

Fat malabsorption and mucosal damage \( \Rightarrow \) diarrhea, steatorrhea, bloating, and excess flatulence.

- Diagnosis is by breath test or quantitative culture of intestinal fluid aspirate.
Treatment is with oral antibiotics that cover both aerobic and anaerobic enteric bacteria.

5. Malabsorption due to lactase deficiency: lactose intolerance

Lactase is an enzyme at the apical cell membrane of intestinal villi responsible for lactose hydrolysis \( \rightarrow \) lactase deficiency will lead to milk/dairy products intolerance. Intolerance to dairy products is associated with osmotic diarrhea and malabsorption. Diagnosis may be suggested by typical occurrence of diarrhea after ingesting milk or cheese and is confirmed by a lactose tolerance test.

- **Classification**
  Lactase deficiency can be primary or secondary.
  (1) Primary lactase deficiency (primary adult hypolactasia) is the most common form of carbohydrate intolerance.
  (2) Secondary lactase deficiency occurs in conditions that damage the small bowel mucosa (eg, celiac disease, acute intestinal infections).

Recovery from the underlying disease is followed by an increase in activity of the enzyme!

- **Consequences**
  Undigested lactose cause an osmotic load that attracts water and electrolytes into the bowel \( \rightarrow \) osmotic diarrhea.
  Bacterial fermentation of carbohydrates in the colon produces gases (H\(_2\), CO\(_2\), and methane) \( \rightarrow \) excessive flatus, bloating, distension, and abdominal pain.

- **Diagnosis** is suggested by typical occurrence of diarrhea after ingesting milk or cheese and is confirmed by a lactose tolerance test.

- **Treatment**: dietary restriction.

N.B. Symptoms typically require ingestion of more than the equivalent of 250 to 375 mL of milk.

6. Malabsorption due to gluten enteropathy (celiac disease, non-tropical sprue)

- **Definition**: Celiac disease is an immune mediated disease occurring in genetically susceptible people, characterized by intolerance to gluten, a protein component of wheat (and rye, barley, oats), leading to mucosal inflammation and villous atrophy, responsible for malabsorption.

- **Etiopathogenesis**
  The exact pathogenesis of celiac disease is not fully understood, several factors being involved:

  (1) **Genetic factors**:
  - there is familial occurrence: 15% of first-degree relatives may be affected
- the presence of Ag HLA DQ2 and DQ8 with an essential role in the immunological recognition of gliadin (presentation to T lymphocytes)

(2) Toxic factors:

- normally, gluten is split by peptidases in small peptides and amino acids. In celiac disease, the incomplete hydrolysis of gluten, due to a deficit of transglutaminase, leads to accumulation of gliadin and large, toxic polypeptides → direct effect in damaging the intestinal mucosa.

(3) Immune factors. Gluten and its degradation products induce an immune reaction at the intestinal mucosa level, with activation of:

A. Cell immunity, with the:

- proliferation of cytotoxic lymphocytes (CD8) with T cells infiltration in lamina propria of intestinal mucosa and subsequent release of cytokines, responsible for:
  - Mucosa lesions: villous atrophy and crypt hyperplasia
  - Activation of plasmocytes with antibodies (Ab) secretion

- favorable response to corticotherapy

B. Humoral immunity, with the:

- Synthesis of anti-gliadin Ab (present in 90% of the patients) and also, of anti-transglutaminase Ab

- Consequences:
  - Maldigestion: abdominal bloating, pain, gas, diarrhea, steatorrhea, and weight loss
  - Malabsorption with deficiency of fat-soluble vitamins (A, D, E, and K)
  - A severe skin rash called dermatitis herpetiformis
  - Iron deficiency anemia (low blood count)

- Diagnostic: gold standard – endoscopy with biopsy that reveals typical mucosal changes.

- Treatment: gluten-free diet.

  N.B. Elimination of gluten leads to gradual restoration of intestinal structure and normal absorption!

II. GASTROINTESTINAL INFLAMMATION

1. Appendicitis

- Definition: acute inflammation of the vermiform appendix, with the highest incidence in the range of 10-20 years
  - It is the most common cause of abdominal surgery in children.

- Etiology

  The lumen of the appendix becomes obstructed due to:
  - Fecaliths (inspissated fecal material)
- Submucosal lymphoid tissue hyperplasia (in viral infections)
- Pinworms, carcinoid tumors (and other less common causes)

**Pathophysiology**
The **obstruction blocks mucus outflow** → pressure in the distended appendix increases, restricting blood flow to the organ and causing **severe abdominal pain**. Inflammation may lead to **infection, clotting, tissue decay**, and **perforation** of the appendix. If the appendix ruptures or perforates, the **infected content spills into the abdominal cavity** → **peritonitis**.

**Clinical features**
The classic symptoms of acute appendicitis are **epigastric or periumbilical pain** followed by **nausea** and **vomiting**; after a few hours, the pain **shifts to the right lower quadrant**. Pain increases with cough and motion. **Low-grade fever** (rectal temperature 37.7 to 38.3°C) is common.

2. **Peritonitis**

**Definition:** inflammation of the peritoneum

**Etiology:**
- perforation of an inflamed abdominal organ
- bleeding from the GI tract
- acute pancreatitis, acute intestinal obstruction, acute diverticulitis
- abdominal wounds: surgical or traumatic
- perforation of the colon’s wall due to an invading tumor
- ruptured ovarian cyst, ectopic pregnancy, torsion of ovary, acute salpingitis

**Pathogenesis:** **peritoneal inflammation at the point where peritoneum overlays an inflamed abdominal organ** with:
- Formation of fibrinous exudate on the respective peritoneal surface
- Generation of an abscess in the case of:
  - delayed clearance of exudates + pus
  - colonic perforation
- Post-inflammatory scarring that may induce:
  - **adhesions/strictures** → **obstruction** of normal intestinal motility

**Manifestations** – **acute abdomen syndrome**:
- acute onset pain
- fever
- severe vomiting

**Complications:**
- **perforation** of an adjacent pelvic structure → **fistula** *(abnormal connection or passage way between two epithelium-lined organs or vessels)*
- widespread involvement → **generalized peritonitis**
3. Diverticular disease

 Terms and definition

➢ Diverticula, in which the mucosal and submucosal layers herniate through the muscle layers of the colon, are located primarily in the sigmoid colon but can affect any part of the large bowel.

➢ Diverticulosis is a disease characterized by the appearance of diverticula in the colon. These outpouchings of the GI wall occur presumably because of increased pressure in the large intestine related to straining during defecation.

 Etiopathogenesis

Diverticulosis results from an acquired deformity of the colon in which the mucosa and submucosa herniate through the underlying muscularis. Its incidence increases with age, starting from about 40 years. Diverticula probably result from high intraluminal pressure on an area of weakness in the GI wall where blood vessels enter.

Most acquired diverticula occur in the colon: the descending colon and sigmoid are involved in > 90% of cases. Acquired abnormalities in colonic wall connective tissue are believed to be the structural basis of diminished resistance to mucosal and submucosal herniation. The functional abnormality is believed to be related to chronic constipation, most likely related to the change in dietary habits: decreased dietary fibers makes forward propulsion of feces at normal transmural pressures more difficult ➔ increased muscle contraction ➔ development of diverticular disease with abdominal pain (the cardinal symptom of uncomplicated diverticular disease). The pain may last hours to days, with sudden relief on passing flatus or feces.

 Complications

About 1/5 of patients with diverticular disease develop one of the two major complications, diverticulitis and diverticular bleeding.

(1) Diverticulitis: is the most common complication of diverticulosis. It develops when a focal area of inflammation occurs in the wall of a diverticulum in response to irritation by fecal material (undigested food and bacteria accumulate in the diverticular sac) ➔ blood supply to the thin walls of the sac is cut off ➔ high susceptibility to bacteria attack ➔ inflammation ➔ perforation, abscess, peritonitis, obstruction, or hemorrhage. Occasionally, the inflamed colon segment adheres to the bladder or other organs ➔ fistula.

(2) Diverticular bleeding. Diverticula are a source of bleeding in 3–5% of patients with diverticulosis. Branches of the colonic intramural arteries (vasa recta) are closely associated with the diverticular sac, presumably leading to occasional rupture and bleeding. This is the
most common cause of lower GI bleeding in the elderly. Diverticular bleeding is typically painless and no association with inflammation occurs.

4 Inflammatory bowel disease (IBD)

- Definition
The term inflammatory bowel disease is used to denominate two related inflammatory intestinal disorders: Crohn’s disease and ulcerative colitis.

- The common features:
  - Unknown etiopathogenesis
  - Basic pathology: chronic inflammation of the colon
  - Genetic predisposition
    - Close blood relatives of affected persons have increased incidence of both disorders in approximately 20% of cases
    - Can occur in the same family
  - Extraintestinal manifestations
    - Arthritis
    - Eye lesions (iritis and episcleritis)
    - Primary sclerosing cholangitis
    - Skin lesions such as erythema nodosum

- Etiopathogenesis
A combination of genetic risk and environmental factors are recognized in the pathogenesis of inflammatory bowel disease.
In the past years, several susceptibility genes for both Crohn's disease and ulcerative colitis have been discovered.
Many environmental factors have been speculated to contribute to the development of Crohn’s disease:
  - defective immune response
  - microorganisms (bacteria and viruses)
  - dietary factors
  - psychosocial factors.
The normal gut is able to modulate frank inflammatory responses to its constant bombardment with dietary and microbial antigens in the lumen. This modulation may be defective in Crohn’s disease, resulting in uncontrolled inflammation. Cytokines, such as interleukins and tumor necrosis factor, secreted by $T_H1$ and $T_H17$ lymphocytes are central to the pathogenesis of Crohn’s disease.

The common features to all forms of inflammatory bowel disease are mucosal ulceration and inflammation of the GI tract.
a. Crohn's disease (regional enteritis)

- **Definition:** Crohn's disease, also known as regional enteritis or granulomatous colitis, is a *localized inflammation of any part of the GI tract* (usually the terminal ileum), *extending through all layers of the intestinal wall*. It may also involve *regional lymph nodes* and the *mesentery*.

- **Pathophysiology**
  In Crohn's disease, *inflammation spreads slowly and progressively*. 
  
  *Enlarged lymph nodes block lymph flow* in the submucosa → edema, mucosal ulceration and *fissures, abscesses*, and sometimes *granulomas*. Mucosal ulcerations are called *skipping lesions* because they are not continuous, as in ulcerative colitis (i.e., sharply demarcated, granulomatous lesions are surrounded by normal-appearing mucosal tissue). Subsequent *fibrosis thickens the bowel wall → stenosis*, or *narrowing of the lumen*. The *serous membrane* becomes *inflamed* (serositis), inflamed bowel loops may adhere to other diseased or normal loops, and *diseased bowel segments become interspersed with healthy ones*. Finally, *diseased parts of the bowel become thicker, narrower, and shorter*; the combination of deep mucosal ulceration and submucosal thickening gives the involved mucosa a characteristic "*cobblestone*” appearance.

- **Clinical features**
  - Steady, colicky pain in right lower quadrant
  - Cramping, tenderness
  - Weight loss
  - Diarrhea, steatorrhea, bloody stools
  - Low-grade fever

- **Complications**
  Frequent complications of Crohn's disease are *perforation, fistula, abscess*, and small intestinal *obstruction*, due to the full-thickness involvement of the bowel wall. Frank *bleeding from the mucosal ulcerations* and *protein-losing enteropathy* can occur.

  Patients with Crohn's disease also present *extraintestinal symptoms*: arthritis (most commonly), inflammation of skin (*erythema nodosum*), eye (*uveitis, iritis*), mucous membranes (*aphtous ulcers* of the buccal mucosa), bile ducts (*sclerosing cholangitis*), and liver (*autoimmune chronic active hepatitis*).

  Renal disorders, especially *nephrolithiasis*, are observed in 1/3 of patients with Crohn's disease, probably related to increased oxalate absorption associated with steatorrhea. *Amyloidosis* is a serious complication of Crohn’s disease, as is the *thromboembolic disease*. Both of these complications are probably reflections of the systemic character of the inflammatory process. Patients are often malnourished and show evidence of *nutrient deficiency states*.

  Another important complication is an increased incidence of *intestinal cancer*. 


b. Ulcerative colitis

- **Definition**
  Ulcerative colitis is a *continuous inflammatory disease* that affects the *mucosa of the colon and rectum*. It invariably *begins in the rectum and sigmoid colon*, and commonly *extends upward into the entire colon*, rarely affecting the small intestine, except for the terminal ileum. Ulcerative colitis produces *edema* (leading to mucosal friability) and *ulcerations*. Severity ranges from a mild, localized disorder to a fulminant disease that may cause a *perforated colon* → potentially fatal *peritonitis* and *toxemia*. The disease cycles between exacerbation and remission.

- **Pathophysiology**
  *Inflammation of the mucosal layer of the large intestine* is responsible for the appearance of *erosions* that coalesce generating *ulcers*, with *congestion*, *edema*, and *hemorrhage*. In contrast to Crohn's disease, *inflammation in ulcerative colitis is restricted to the mucosa of the colon and rectum.* Abscesses in the mucosa drain purulent pus, become necrotic, and ulcerate. Sloughing causes bloody, mucus-filled stools. As abscesses heal, *scarring and thickening* may appear in the bowel's inner muscle layer. As *granulation* tissue replaces the muscle layer, *the colon narrows, shortens*, and *loses its characteristic pouches* (hiatal folds).

**Clinical features**
- onset more abrupt than in Crohn's disease
- bloody diarrhea and rectal bleeding leading to serious fluid and electrolyte losses
- abdominal pain
- bouts of remission separate the attacks.

**Complications:**

Because ulcerative colitis generally is limited to the mucosa, *obstruction, perforation*, and *fistula formation* are not typical complications. *Toxic megacolon* is the one complication of ulcerative colitis that carries a high risk of perforation. Its cause is unknown.

For unknown reasons, the *risk of carcinoma appears even higher* in ulcerative colitis than in Crohn's disease.

### 3. INTESTINAL OCCLUSION (OBSTRUCTION)

- **Definition**: the *impairment of movement of intestinal contents* in the usual oral to anal direction.
- **Causes**
  1. Intraluminal causes
  - Tumors (most often carcinoma of the large intestine)
- Foreign bodies
- Intussusception of the intestinal loops (invagination of one loop into another)

_N.B. Intussusception develops most often under two conditions:_

- In small children with very active peristalsis: In these children, one small intestinal loop invaginates into another, like the finger of an inverted glove. The loop is said to be “telescoped into another loop” (because the loops resemble the old navigators’ telescopes), and intussusceptum is strangulated by the out-sided intussuscipient. The inner loop may become necrotic unless the invagination is everted surgically (or spontaneously, as may sometimes occur).
- In the presence of tumors: Small pedunculated tumors carried by peristalsis may pull forward the loop to which such a tumor is attached.

(2) Intramural causes
- Chronic inflammation and fibrosis
- Hematomas
- Complications of surgery

(3) Extraintestinal causes
- Hernia
- Adhesions
- Volvulus (a complete twisting of the bowel on an axis formed by its mesentery)
- Metastases of the mesentery

- **Classification**

According to their mechanism, 2 types of intestinal occlusion may occur.

(1) **Mechanical ileus** can result from *intrinsic or extrinsic causes* that encroach on the patency of the bowel lumen. Mechanical bowel obstruction may be a **simple obstruction** in which there is *no alteration in blood flow*, or a **strangulated obstruction** in which the *impairment of blood flow* and *necrosis of bowel tissue* occur.

(2) **Adynamic ileus** results from *neurogenic or muscular impairment of peristalsis* with 2 forms:

a. **Paralytic ileus**

- **Causes:**
  - Abdominal stimuli:
    - pain after abdominal surgery
    - peritonitis
    - appendicitis
    - severe trauma (e.g., spinal fractures)
    - acute distension of an abdominal organ (e.g., ureters)
✓ Systemic conditions:
  - infections
  - renal disease
  - electrolyte imbalances (hypokalemia)

- **Mechanism:** a neurogenic reflex is responsible for the **paralysis** of the intestinal muscles.

**b. Vascular ileus**

- **Causes:**
  - Thrombosis
  - ATS
  - Compression of mesenteric vessels supplying the intestine

- **Mechanism:** a compromised blood supply is responsible for the focal loss of motility ➔ risk of infection, necrosis and gangrene

- **Pathophysiology**

  The major effects of intestinal obstruction are **abdominal distension** and loss of fluids and electrolytes. If untreated, the distention tends to perpetuate itself by causing atony of the bowel and further distension. Both forms of obstructions eventually may lead to strangulation (i.e., interruption of blood flow), gangrenous changes, and ultimately, perforation of the bowel.

- **Clinical features:** vary with the location, duration and the degree of obstruction.

In acute obstruction, the onset usually is sudden and dramatic, while in chronic obstructions, the onset is gradual.

- **Upper obstruction** (e.g., pyloric stenosis, proximal/jejunal obstruction):
  - Pain
  - Vomiting
  - Dehydration ➔ hypovolemic shock
  - Electrolyte depletion

- **Lower obstruction** (e.g., distal obstruction/ileus, colon obstruction):
  - Pain
  - Constipation or obstipation (extreme, persistent constipation)
  - Massive abdominal distension
  - Less fluid/electrolyte losses
  - Stasis & bacterial proliferation ➔ risk for bowel necrosis, perforation and peritonitis.

In mechanical obstruction the **pain is severe and colicky**, while in paralytic ileus is **continuous**.
- **Complications**
  
  **Strangulation** with **necrosis** of the bowel may occur → **perforation, peritonitis, and sepsis**, and may increase the mortality rate associated with intestinal obstruction to approximately 25% if surgery is delayed.

- **Diagnosis** is based on history and physical findings. Abdominal x-ray studies reveal a gas-filled bowel.

- **Treatment** depends on the cause and type of obstruction: most cases of adynamic obstruction respond to decompression of the bowel through nasogastric suction and correction of fluid and electrolyte imbalances. Strangulation and complete bowel obstruction require surgical intervention.