GERD

Reflux Esophagitis	Symptoms of mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.
GERD	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.

Reflux Esophagitis

Causes	Pathophysiology	Morphology	Symptoms
▪ Fungal infection (Candida albicans) ▪ Viral infections of the esophagus (herpes simplex and cytomegalovirus) in AIDS patient ▪ Bacterial infection. ▪ Irradiation. ▪ Chemical.	**Abnormal lower esophageal sphincter:** **The most common cause of GERD:** ▪ Functional (frequent transient LES relaxation) ▪ Mechanical (hypotensive LES) **Decrease the pressure of the LES:** ▪ Foods (e.g., coffee) ▪ Medications (eg, calcium channel blockers) ▪ Hiatal hernia **Increased Abdominal Pressure:** ▪ Obesity ▪ Pregnancy ▪ Increased gastric volume	Mild: Unremarkable **Sever:** ▪ **Eosinophils** ▪ **Basal zone hyperplasia** ▪ Elongation of lamina propria papillae	**Most common:** – **Heartburn.** – **Dysphagia.** – **Regurgitation** **Atypical:** – **Coughing.** – **Chest pain.**

Complicationss

Erosive esophagitis	Stricture	Barrett's esophagus
Red mucosa with erosions leading to hematemesis and melena.	Result of healing of erosive esophagitis	Intestinal metaplasia of the esophagus, Associated with the development of adenocarcinoma. **Pathophysiology:** ▪ Acid damages lining of esophagus and causes chronic esophagitis. ▪ Damaged area heals in a metaplastic process and abnormal columnar cells replace squamous cells.

Peptic Ulcers

Ulcers	A breach in the mucosa of the alimentary tract that may extend through muscularis mucosa into submucosa or deeper
Types of ulcers	**1. Peptic ulcers 2. Stress ulcers (acute gastric ulcers)**

Acute Peptic Ulcer

Pathophysiology

- **As part of an acute gastritis,** Due to:
  Excessive alcohol consumption, NSAIDs, Radiation therapy or Chemotherapy.
- **As a complication of a severe stress response:**
  - Curling ulcers (severe burns), Cushing ulcers (Major Trauma) and Cerebrovascular accidents.
- **As a result of extreme hyperacidity: Zollinger-Ellison syndrome**

Morphology

Small and multiple
They range in depth from very superficial lesions (erosion) to deeper lesions that involve the entire mucosal thickness (true ulceration).

Chronic Peptic Ulcer

Pathophysiology

- NSAIDs and aspirin stop prostaglandin synthesis.
- Cigarette smoking: impairs mucosal blood flow and healing.
- Chronic renal failure, and hyperparathyroidism are associated with hypercalcemia
- Psychological stress (can increase gastric acid secretion).

Locations

- Any portion of the GI tract exposed to acidic gastric juices.
- 98% located in **first portion of duodenum or stomach**
- Esophagus
- Gastric mucosa within a **Meckel diverticulum**
- In **Zollinger-Ellison syndrome**

Info

Chronic, recurring lesions that occur most **without** obvious precipitating conditions, other than chronic gastritis.

The most common cause of chronic gastritis is infection with the bacillus Helicobacter pylori

Gastric ulcers

The mucosal defences against acid attack consist of:

- Mucus-bicarbonate barrier: When Duodeno-gastric reflux (bile) occurs → Ulcer.
- The surface epithelium:
  - NSAIDs & H. pylori infection

Thus peptic ulcers in the stomach caused by breakdown of mucosal defense more than excessive acid production.

Duodenal ulcers

- Increased production of acid assumes more importance in the pathogenesis of duodenal ulceration
- *H. pylori*-infected individuals secrete 2-6 times as much acid as non-infected persons.
- *Helicobacter* colonizes areas of gastric metaplasia in duodenal ulceration because there is gastric metaplasia in response to excess acid. Gastric metaplasia paves the way for colonization by *Helicobacter.*

Pancreatitis

Acute	A group of reversible lesions characterized by inflammation of the pancreas ranging in severity from edema and fat necrosis to parenchymal necrosis with severe haemorrhage
Chronic	Defined by irreversible destruction of exocrine pancreatic parenchyma

Acute Pancreatitis

Etiology	Common causes
• ***Metabolic:*** Alcoholism, Hyperlipoproteinemia, Genetic & Hypercalcemia • ***Vascular:*** Shock, Atheroembolism & Polyarteritis nodosa • ***Infectious:*** Mumps, Coxsackievirus & Mycoplasma pneumoniae • ***Mechanical:*** Trauma, Perioperative injury, Gallstones, Iatrogenic injury & Endoscopic procedures with dye injection	80% Biliary tract disease or alcoholism **35% to 60% Gallstones.** Obstruction of the pancreatic duct system Medications, Metabolic disorders Acute ischemia, Infections, Trauma, Inherited mutations

Morphology

(1) Microvascular leakage.
(2) Necrosis of fat.
(3) An acute inflammatory reaction.
(4) Proteolytic destruction.
(5) Destruction of blood vessels with hemorrhage.

Microscopically	**Mild**	**Interstitial edema. & Focal areas of fat necrosis.**
	Severe	Such as acute necrotizing pancreatitis. **Necrosis & Vascular damage**
	Most Severe	Which is hemorrhagic pancreatitis. **Extensive necrosis + diffuse hemorrhage**
Gross	▪ Red-black hemorrhagic areas interspersed with foci of yellow-white, chalky fat necrosis. ▪ The peritoneum contains a serous, slightly turbid, brown-tinged fluid with globules of fat.	

Pathogenesis

1. Duct obstruction. 2. Acinar cell injury 3. Defective intracellular transport

Clinical features

- **Abdominal pain**. (constant and intense and is often referred to the **upper back)**
- Leukocytosis.
- Hemolysis.
- Fluid sequestration.
- Acute respiratory distress syndrome.
- Diffuse fat necrosis.
- Disseminated intravascular coagulation.
- Peripheral vascular collapse and shock.
- **Laboratory findings:** Marked elevation of serum amylase levels during the first 24 hours, followed by a rising serum lipase level, which happens within 72 to 96 hours.

Chronic Pancreatitis

Characterized by

Inflammation of the pancreas with **destruction of exocrine parenchyma**, **fibrosis**, and, in the late stages, the destruction of **endocrine** parenchyma.

Causes

The **most common** cause of chronic pancreatitis is **long-term alcohol abuse and biliary tract disease**

Pathogenesis

Three hypotheses are proposed:
Ductal obstruction., Toxic-metabolic & Oxidative stress.

Morphology

Microscopically

- Characterized by:
  - **Parenchymal fibrosis.**
  - **Reduced number and size of acini.**
  - **Variable dilation of the pancreatic ducts.**
- Chronic inflammatory infiltrate around lobules and ducts.

Grossly: Gland is hard, sometimes with extremely dilated ducts and visible calcification

Clinical Features

- **Silent or repeated attacks of abdominal pain, or persistent abdominal and back pain.**
- **Repeated bouts of jaundice.**
- **Vague indigestion.**
- **Gallstone-induced obstruction.**
- **Calcifications.**
- **Weight loss** and **hypoalbuminemic.**

Complications

- Severe pancreatic exocrine insufficiency.
- Chronic malabsorption
- Severe chronic pain.
- Pancreatic pseudocysts.
- Diabetes mellitus.

Pancreatic Pseudocysts

Morphology

- Commonly **attached** to the surface of the gland and involve peripancreatic.
- **Solitary** and range in size.
- Either spontaneously resolve, or become secondarily infected.
- They can produce abdominal pain and predispose to **intraperitoneal hemorrhage or peritonitis.**

Info

- **Localized** collections of **liquefied necrotic-hemorrhagic material rich in pancreatic enzymes.**
- Such cysts **lack** an epithelial lining (hence the prefix "pseudo"), and they account for majority of cysts in the pancreas.
- Usually arise after an episode of acute pancreatitis, or of chronic alcoholic pancreatitis.
- **Traumatic injury** to the abdomen can also give rise to pseudocysts.

Malabsorption

Malabsorption	Characterized by defective absorption of fats, fat- and water-soluble vitamins, proteins, carbohydrates, electrolytes and minerals, and water. Presents most commonly as chronic diarrhea.
Malabsorption Syndrome	Inability of the intestine to absorb nutrients adequately into the bloodstream. Impairment can be of single or multiple nutrients depending on the abnormality.

Causes	Pathophysiology	Clinical Features
▪ Inadequate digestion. ▪ Deficient bile salt. ▪ Inadequate small intestine. ▪ Lymphatic obstruction	**Inadequate digestion:** Stomach: ○ Postgastrectomy ○ Zollinger-Ellison syndrome. Bile: ○ Obstructive jaundice. ○ Terminal ileal resection. Pancreas: ○ Deficiency of pancreatic lipase. ○ Chronic pancreatitis. ○ Cystic fibrosis. ○ Pancreatic resection. **Small intestine abnormalities:** Mucosa: Celiac disease, Tropical sprue, Whipple's disease & Giardiasis. Inadequate small intestine: Intestinal resection & Crohn's disease. Lymphatic obstructions: Intestinal lymphangiectasia & Malignant lymphoma	General: Abnormal stools: Steatorrhea & Stools become soft, yellow, malodorous, greasy and float on top of the water in the toilet. Depending on the deficient nutrient: Protein → Edema , Muscles wasting. B12, folic acid and iron deficiency → Anemia Vitamin D, calcium → Muscle cramps, Osteomalacia and osteoporosis.

Celiac Disease

Definition	Complications	Morphology	Presentation
An immune reaction to **gliadin** fraction of the wheat protein gluten in genetically predisposed persons.	Osteopenia, osteoporosis, Infertility in women, Short stature, delayed puberty, anemia & Risk for GI lymphoma.	▪ Mucosa is flattened with marked villous atrophy. ▪ Increased intraepithelial lymphocytosis. ▪ Crypt elongation or hyperplasia.	**Infants**: GI symptoms & failure to thrive **Children**: Minor GI symptoms, inadequate rate of weight gain. **Young adults**: Anemia, **Adults**: GI symptoms

Association	Pathology	Diagnosis
Class II HLA DQ2 & DQ8	Loss of the villous surface in the small intestine.	▪ Stool has ↑ Fat. Biopsy = villous atrophy. ▪ Serology is +ve for IgA to tissue transglutaminaseor IgG. ▪ Improvement on gluten free diet.

Lactose intolerence			
Definition	**Causes**	**Diagnosis**	**Clinical Features**
Low or absent activity of the enzyme lactase	**Inherited Lactase Deficiency:** Childhood-onset and adult-onset lactase deficiency (Common) Congenital lactase deficiency (rare) **Acquired Lactase Deficiency (post Infectious)** Transient, secondary lactase deficiency due to intestinal mucosal injury by an infectious, allergic, or inflammatory process	Empirical treatment with a lactose-free diet, which results in the resolution of symptoms. - Hydrogen breath test	• Bloating. • Abdominal discomfort. • Flatulence.

Tropical sprue			
Definition	**Seen in**	**Etiology**	**Clinical Features & Morhology**
A chronic and progressive malabsorption syndrome without a definable cause	Seen in patients who live or have lived in the **tropics**, and in **absence of other intestinal disease or parasites**. Occurs mainly in the West Indies and Asia.	Unclear, **toxigenic Escherichia coli.**	Resemble coeliac disease. However, a gluten-free diet has little beneficial effect.

Bacterial Overgrowth			
Definition	**Causes**	**A result of**	**Clinical Features & Management**
Malabsorption secondary to excessive bacteria in the small intestine, usually the jejunum.	• Excessive entry of Bacteria. • Stagnant region. • Disturbed motility • Defective immune-mechanisms.	• Deconjugation of bile salts by the bacteria. • Damage to the small intestinal mucosa. • Binding of vitamin B12 by bacteria. • Diarrhea is both secretory and osmotic	Weight loss, diarrhea and anaemia (due to vitamin B12 deficiency). **Management:** Antibiotic therapy and surgical resection for a localized abnormality, e.g. stricture, fistula.

Diarrhea

Diarrhea	3 or more loose or liquid stools per day. There is abnormal high fluid content in the stool more than 200-300 gm/day.

Acute Diarrhea

Pathophysiology

Secretory	▪ Increase in the active secretion. High stool output. Lack of response to fasting. ▪ It has a normal or low stool osmotic gap < 100 mOsm/kg. ▪ The most common cause of this type of diarrhea is a **bacterial toxin** (E. coli, cholera) ▪ Also seen in Endocrine tumors. Rotavirus and norwalk virus.Rectal villous adenoma.
Osmotic	▪ Excess amount of poorly absorbed substances that exert osmotic effect. ▪ Stool output is usually not massive. Fasting improves the condition. Stool osmotic gap is high, > 125 mOsm/kg. ▪ Can be the result of: Malabsorption, Osmotic laxatives or Hexitols.
Exudative (inflammatory	▪ Results from the outpouring of blood protein, or mucus from an inflamed or ulcerated mucosa. ▪ Presence of blood and pus in the stool. Persists on fasting ▪ Occurs with inflammatory bowel diseases, and invasive infections. ▪ Some bacterial infections cause damage by invasion of the mucosa. ▪ The main organisms that may cause bacterial dysentery are: ***Campylobacter*** causes ulceration and acute inflammation, ***Salmonella typhi, S. paratyphi A, B,* and *C, Shigella*** infections are mainly seen in young childre. & ***E. coli***
Motility -related	▪ Caused by the rapid movement of food through the intestines (hypermotility). ▪ IBS: Causes abdominal pain and altered bowel habits with diarrhea: Increased serotonin & No inflammation in bowel mucosa.

Etiology	Antibiotic-Associated Diarrhea
▪ Infections, Viral gastroenteritis, Food poisoning & Drugs. ▪ Clinically person become dehydrated with electrolyte disturbance and low bicarbonate in blood	Diarrhea occurs in 20% of patients receiving broad-spectrum antibiotics; about 20% of these diarrheas are due to Clostridium difficile. Leading to pseudomembranous colitis

Chronic Diarrhea

Can be due to	Infectious Causes	Complications
▪ Malabsorption, Post-infectious, Infection. ▪ Endocrine diseases, Inflammatory bowel disease ▪ Colon cancer, Irritable bowel syndrome	▪ Giardia Lamblia ▪ Cryptosporidiosis in AIDS	▪ Fluids → Dehydration, Persistent → Malnutrition ▪ Electrolytes → Electrolytes imbalance ▪ Sodium bicarbonate → Metabolic acidosis.

Polyps

Hyperplastic

- Asymptomatic.
- > 50% are located in the **rectosigmoid.**
- **Sawtooth** surface.
- **Star shaped** crypts.
- Well-formed glands and crypts lined by differentiated goblet or absorptive cells.

Hamartomatous

Juvenile Polyps

- Developmental malformations affecting the glands and lamina propria.
- Children under 5 years old in the rectum.
- In adult called retention polyp.
- No malignant potential.
- Could lead to polyposis in the colon or stomach.
- Cronkhite-Canada syndrome.

Peutz-Jeghers syndrome

- Rare, autosomal dominant
- Mainly it's dilated glands + smooth muscles in the lamina propria, blood in stool, pigmentation in oral mucosa + gentile skin + face and lips
- large pedunculated polyps.

Inflammatory

- Longstanding IBD, especially in **chronic ulcerative colitis**.
- Represent an exuberant reparative response to longstanding mucosal injury called **pseudopolyps.**

Familial Polyposis Syndrome

- **Genetic defect of Adenomatous polyposis coli (*APC*).**
- *APC* gene located on the long arm of chromosome 5 (5q21).
- Innumerable neoplastic polyps in **the colon**.

Gardner's syndrome

Polyposis coli, multiple osteomas, epidermal cysts, and fibromatosis.

Turcot syndrome

Polyposis coli, glioma and fibromatosis

Adenomatous

- Occur mainly in large bowel.
- Epithelium proliferation and **dysplasia**

Tubular: < 25% villous architecture

- Represents 75% of all neoplastic polyps.
- 75 % occur in the distal colon and rectum
- Sigmoid colon most common site.

Villous adenoma: > 50%

- The least common, largest and the most ominous.
- Age: 60 to 65 years, 75% located in rectosigmoid area
- Present with rectal bleeding or anemia, large ones may secrete copious amounts of mucoid material rich in protein and potassium
- Large tumors can produce hypoalbuminemia and hypokalemia

Tubulovillous adenoma: between 25 and 50%.

- 20%–30% of polyps
- Intermediate in size, degree of dysplasia and malignant potential.

Tumors

Adenocarcinoma

- Most common.
- The small intestine is an uncommon site for benign and malignant tumors.
- Constitutes 98% of all cancers in the large intestine.
- 60 to 70 years of age.

Predisposing factors

IBD, adenomas, polyposis syndrome & Diet

Carcinogenesis

The APC/β-catenin pathway (85%)

Chromosomal instability that results in stepwise accumulation of mutations in a series of oncogenes and tumor suppressor genes, *TP53* → mutated late & Mutation in *APC* tumor suppressor gene.

The DNA mismatch repair genes pathway

There is accumulation of mutations (as in the *APC/B-catenin schema*), DNA mismatch repair genes (**MSH2, MSH6, MLH1,** PMS1 & PMS2) & ***(HNPCC) syndrome.***

Colorectal Carcinoma

Morphology

- Left-sided carcinomas tend to be annular, encircling lesions with early symptoms of **obstruction**.
- Right-sided carcinomas tend to grow as polypoid, fungating masses, obstruction is uncommon. (Mostly presents with anemia).

Signs & Symptoms

- Close to the anus: change in bowel habit, feeling of incomplete defecation, PR bleeding.
- Bowel obstruction, if the tumor was large enough.
- Right-sided lesions are more likely to bleed while left-sided tumors are usually detected later and could present with bowel obstruction.

Tumor markers

- CEA & CA19-9 detect late stage of the disease, elevated in:

CEA	Some **non-neoplastic** conditions like ulcerative colitis pancreatitis, cirrhosis COPD, Crohn's disease as well as in smokers.
CA19-9	Colon cancer, pancreatic cancer, esophageal cancer and hepatocellular carcinoma. Apart from cancer, pancreatitis, cirrhosis.

- Tissue inhibitor of metalloproteinases 1 (TIMP1) = Early as well as late stage disease

Carcinoid Tumors

Info

Called "carcinoid" because they are slower growing.

Neoplasms arising from **endocrine cells**.

- The peak incidence: 60s, but they may appear at any age.

Clinical Features

Ultrastructural features: neurosecretory electron dense bodies in the cytoplasm

Clinical features:

- Asymptomatic. May cause obstruction, intussusception or bleeding.

Carcinoid Syndrome

- Paroxymal flushing, asthma-like wheezing, right-sided heart failure, watery diarrhea, abdominal pain.
- The principal chemical mediator is **serotonin.** Associated with ileal carcinoids with **hepatic metastases.**

Crohn's Disease

Characterized by

Most commonly affects the **ileum** and colon but has the potential to **involve any part of the gastrointestinal** tract

Clinical Features

- **Acute phase:** fever, diarrhea, and right lower quadrant pain may mimic acute appendicitis.
- **Chronic disease:** remissions and relapses over a long period.
- Thickening → an ill-defined mass in the abdomen.

Morphology

Microscopically

- Distortion of mucosal crypt architecture with mucosal inflammation.
- **Transmural inflammation.**
- **Epithelioid granulomas [60%].**
- Fissure-ulcers and fistulas can be seen microscopically.

Grossly

- Segmental (discontinuous or skip lessions
- **Marked fibrosis**, **Fissures** & **Fistulas**
- Cobblestone effect.

Complications

Intestinal obstruction, Fistula formation., Extraintestinal manifestations (arthritis and uveitis) & Slight increased risk of development of carcinoma of the colon—much less than in ulcerative colitis.

Ulcerative Colitis

Characterized by

Chronic relapsing ulceroinflammatory disease of undetermined etiology. a disease of the **rectum, and the colon**. The ileum is not involved as a rule

Clinical Features

- In the acute phase and during relapse, the patient has fever, leukocytosis, lower abdominal pain (relieved by defecation), bloody diarrhea and mucus in the stool.
- The disease usually has a chronic course, with remissions and exacerbations. Smoking may partially relieve symptoms.

Morphology

Microscopically

- Restricted to the mucosa.
- In the active phase → neutrophils (Cryptits, crypt abscess).
- In the chronic phase → crypt atrophy and distortion.
- Absent granulomas.

Grossly

- **Mucosa** (diffuse hyperemia with **numerous superficial ulcerations** in the acute phase.
- Diffuse hyperemia & No skip lesions.

Complications

Acute phase: Severe bleeding & Toxic megacolon**. Chronic ulcerative colitis:** Increase risk of developing colon carcinoma & The presence of high-grade dysplasia in a mucosal biopsy imposes a high risk of cancer and is an indication for colectomy.
Extraintestinal manifestations: Arthritis, Uveitis, Skin lesions & Sclerosing cholangitis, leading to obstructive jaundice.

Cirrhosis

- Most common cause is **alcohol abuse and viral hepatitis**.
- Defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.

Pathophysiology	Morphology			
When hepatocytes get inflamed they start secreting cytokines that activate **stellate cells** (normally store vitamin A) → activated Stellate cells transform into **myofibroblast-like cells** → types I and III collagen are deposited in the perisinusoidal space in the lobule (Fibrosis), creating delicate or broad septal tracts.	Gross	The nodules are larger than 3 mm and, hence, this is an example of "macronodular" cirrhosis. Micronodular cirrhosis: The regenerative nodules are quite small, averaging less than 3 mm in size.	Microscopic	Regenerative nodules of hepatocytes are surrounded by fibrous connective tissue that bridges between portal tracts. Collagenous tissue, lymphocytes as well as a proliferation of bile ducts.

Chronic Hepatitis	Alcoholic Liver Disease
Morphology	**Morphology**
▪ Hepatocyte injury, necrosis, and regeneration ▪ Portal tract Inflammation ▪ Fibrosis ▪ HBV: "ground-glass" hepatocytes, "sanded" nuclei ▪ HCV: bile duct damage, lymphoid aggregate formation ▪ Cirrhosis: end-stage.	Macrovesicular steatosis, involving most regions of the hepatic lobule. The intracytoplasmic fat is seen as clear vacuoles. Early fibrosis is present (Masson trichrome). Alcoholic hepatitis. Necrotic hepatocyte, A Mallory bodies & Diffuse nodularity.

Portal Hypertension

Definition	Pathogenesis	Leads to
Resistance to blood flow.	↑ resistance to portal flow by fibrosis and expanded parenchymal nodules.	**Portosystemic venous shunts formation:** Rectum → hemorrhoids. Abdominal wall → caput medusa. Cardioesophageal junction → **esophagogastric varices.**

Ascites

Definition	Pathogenesis
Accumulation of excess fluid in the **peritoneal cavity**	• Sinusoidal hypertension and **hypoalbuminemia** → drives fluid into the extravascular space of Disse • Leakage of hepatic lymph into the peritoneal cavity → protein-rich fluid • Could also be due to sodium and water retention due to secondary hyperaldosteronism.

Esophageal Varices

Definition	Pathogenesis
Congested subepithelial and submucosal venous plexus within the distal esophagus.	Portal HTN → induce the development of collateral channels → enlargement of the subepithelial and submucosal venous plexi → varices.

Clinical Features & Morhology

- Detected by **venogram** **as: tortuous** dilated veins lying primarily within the **submucosa** of the distal esophagus and proximal stomach.
- Venous channels directly beneath the esophageal epithelium may also become massively dilated.
- Variceal rupture results in **hemorrhage** into the lumen or esophageal wall, in which case the overlying mucosa appears **ulcerated and necrotic.**
- If rupture has occurred in the past, venous thrombosis, inflammation, and evidence of prior therapy may also be present.

Clinical features: Asymptomatic but if it ruptures → massive hematemesis and death.

Factors that lead to rupture:

Inflammatory erosion of thinned overlying mucosa, ↑ tension in dilated veins & ↑ **vascular hydrostatic pressure** associated with vomiting.

Treated by any of several methods: Sclerotherapy, Endoscopic balloon tamponade & Endoscopic rubber band ligation.

Splenomegaly

- Long-standing congestion may cause congestive splenomegaly (1000 gm or less).
- Massive splenomegaly may induce Hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or pancytopenia.

Pulmonary hypertension & Hepatopulmonary syndrome

Pulmonary arterial hypertension associated with liver disease or portal hypertension.

- **Causes:** Portal hypertension & Changes in pulmonary blood flow occurring **secondary to hepatic failure.**
- **Clinical features:** the most common clinical manifestations are **dyspnea on exertion and clubbing of the fingers**, followed by palpitations and chest pain.

Liver Faliure

Jaundice & Icterus	Cholestasis
Jaundice, a yellow discoloration of skin and sclerae (icterus). Causes: Bilirubin overproduction, hepatitis, **obstruction** of the flow of bile and hemolytic anemia. Occurs when bilirubin production and clearance is disrupted.	Defined as systemic **retention** of bilirubin and other solutes which are eliminated in bile. (particularly bile salts and cholesterol). Causes: impaired bile flow. ↑ Alkaline phosphatase in hepatocytes is a characteristic.

Hepatic Encephalopathy

Definition	Pathogenesis
Spectrum of disturbances in consciousness, ranging from subtle behavioral abnormalities to deep coma and death.	• There are only **minor morphologic changes** in the brain, such as edema and an astrocytic reaction. • In acute setting → ↑ blood ammonia levels), which impair neuronal function and promote generalized brain edema. • In chronic setting → deranged neurotransmitter production → neuronal dysfunction.

Clinical Features

Rigidity, hyperreflexia, nonspecific electroencephalographic changes, and, rarely, seizures. **Characteristic is asterixis (flapping tremor)**

Hepatorenal Syndrome

Definition	Pathogenesis
Appearance of renal failure in individuals with **severe chronic liver disease without** any primary abnormalities of the kidneys themselves.	▪ The syndrome is heralded by ↓ urine output & ↑ blood urea nitrogen and creatinine values. ▪ The ability to concentrate urine is retained, producing a hyperosmolar urine low in sodium.

Morhology

- There will be **no intrinsic morphologic or functional causes** for the renal failure.
- The cause of failure is decreased renal perfusion pressure due to **systemic vasodilation** and activation of the renal sympathetic nervous system with vasoconstriction of the afferent renal arterioles.
- Increased synthesis of **renal vasoactive mediators** will **decrease glomerular filtration**.

Cancers of Liver & Pancreas

Hepatocellular carcinoma

Risk Factors	Important factors
Viral infection (HBV, HCV), Cirrhosis, Food contaminants, & others	Inflammation and regeneration, Acquired mutations in specific oncogenes (such as *β-catenin*) and tumor suppressors, Acquired defects in DNA repair & **HBV-X gene**.

What do we see?

- Develops from **small-cell, high-grade dysplastic nodules** in cirrhotic livers.
- Tumors may arise from both **mature hepatocytes and progenitor cells**
- **Nodule vascularization**.
- **The presence of structural and numeric chromosomal abnormalities**.

Morphology

Grossly	**Unifocal** mass	**Multifocal**, multiple nodules	A **diffusely infiltrative** cancer.
	All three patterns may cause liver enlargement. **All patterns of hepatocellular carcinomas have a strong propensity for invasion of vascular channels**.		
Microscopically	Range from well-differentiated to highly anaplastic undifferentiated lesions.		
	Moderate & well	**Bile pigment** is usually present. The malignant cells may be **positive for alpha-fetoprotein**	
	Poorly	Pleomorphic appearance with numerous anaplastic giant cells.	
Findings	Extensive intrahepatic metastases may occur, Invasion of the portal vein (Snakelike masses) & Lymph node metastases.		

Fibrolamellar carcinoma

- More in males, has no association with HBV or cirrhosis, and has a **better prognosis.**
- Presents as a **single large, hard "scirrhous" tumor** with fibrous bands coursing through it.
- Microscopically, it is composed of **well-differentiated** polygonal cells growing in nests or cords and separated by parallel lamellae of dense collagen bundles.

Clinical Features

- Ill-defined upper abdominal pain, malaise, fatigue, weight loss, and feeling of abdominal fullness.
- Enlarged liver can be felt on palpation.
- More often encountered in persons with **symptomatic cirrhosis of the liver**. In these persons, a rapid ↑ in liver size, worsening of ascites, or the appearance of bloody ascites, fever, and pain.

Laboratory Findings	Diagnosis	Prognosis
Elevated levels of serum *α*-fetoprotein	Radiologic screening of patients with cirrhosis at 6-month intervals, looking for dysplastic nodules or early, small HCCs	Grim, overall, death usually occurs from Cachexia, Gastrointestinal or esophageal variceal bleeding, Liver failure or Rupture of the tumor with fatal hemorrhage

Cholangiocarcinoma

Risk Factors	Info
Primary sclerosing cholangitis, Previous exposure to Thorotrast, & congenital fibropolycystic diseases of the biliary system	A malignancy of the biliary tree, arising from bile ducts within and outside of the liver. Occur mostly in persons of 50 to 70 years of age. Extrahepatic cholangiocarcinomas constitute approximately 2/3 of these tumors and may develop at the hilum (known as Klatskin tumors) or more distally in the biliary tree. ▪ Several consistent genetic changes have been noted in these tumors, including activating mutations in the *KRAS* and *BRAF* oncogenes and loss-of-function mutations in the *TP53* tumor suppressor gene.

Morphology

Microscopically	▪ Most are well to moderately differentiated. Rarely bile stained. ▪ Mixed variants occur. Hematogenous metastases to the lungs, bones (mainly vertebrae), adrenals, brain. Lymph node metastases to the regional lymph nodes are also found
Intrahepatic	▪ Occur in the **non-cirrhotic** liver and may track along the intrahepatic portal tract system to create **a treelike tumorous mass** within the liver or a massive tumor nodule. Lymphatic and vascular invasion are **common**.
Extrahepatic	▪ Relatively small at the time of diagnosis. ▪ May spread to extrahepatic sites. Has a greater propensity for extrahepatic spread than does hepatocellular carcinoma.

Clinical Features

- **Intrahepatic cholangiocarcinoma** is usually **detected late** in its course.
- Symptoms and signs arising from **extrahepatic cholangiocarcinomas** result from biliary obstruction.
- **Poor prognosis.** Alpha-fetoprorein is **not elevated.** Elevated serum levels of **alkaline phosphatase and aminotransferases**

Metastatic tumors

Info

- Metastatic involvement of the liver is far **more common** than primary neoplasia.
- Most common primaries producing hepatic metastases are those of the breast, lung, and colon.
- Multiple nodular metastases are found that often cause striking **hepatomegaly** and may replace over 80% of existent hepatic parenchyma.

Angiosarcoma

- Consists of pleomorphic **endothelial cells** with large hyperchromatic nuclei, giant cells in frequent mitosis and **irregular anastomosing vascular channels.**
- Cells may appear spindle shaped and cirrhosis is present in 20% to 40% of the cases. These have also been linked to vinyl chloride and thorostrast exposure.

Pancreatic carcinoma

Risk Factors	Info
Smoking., Chronic pancreatitis, Diabetes mellitus & Inherited genetic defects.	▪ Has one of the highest mortality rates of any cancer. ▪ It is carcinoma of the exocrine pancreas. It arises from ductal epithelial cells. ▪ It occurs in the 6th to 8th decade, blacks more than whites, males more than females, diabetics more than non-diabetics.

Morphology

Microscopically		Moderately to poorly differentiated adenocarcinoma forming abortive tubular structures or cell clusters and exhibiting an aggressive, deeply infiltrative growth pattern Dense stromal fibrosis and a proclivity for perineural invasion within and beyond the organ. Lymphatic invasion also is commonly seen.
Ductal adenocarcinomas	Two features are characteristic:	1. It is **highly invasive.** 2. It elicits an intense non-neoplastic host reaction called a **"desmoplastic response".**
Involvement		Peripancreatic, gastric, mesenteric, omental, and portahepatic lymph nodes are frequently involved. Distant metastases occur.
Carcinoma	Head	**Most obstruct the distal common bile duct.** In 50% of such cases, there is marked distention of the biliary tree, and patients typically exhibit jaundice.
	Body & tail	**Do not impinge on the biliary tract and hence remain silent for some time. They may be quite large and widely disseminated by the time they are discovered.**

Pathogenesis

There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive precursor lesions, to invasive carcinoma.

- Both intraductal papillary mucinous neoplasms and mucinous cystic neoplasms can progress to invasive adenocarcinoma and are thus considered bona fide precursors of cancer.
- The most common antecedent lesions of pancreatic cancer arise in small ducts and ductules, and are called **pancreatic intraepithelial neoplasias (PanINs).**
- Four genes are **most commonly** affected by somatic mutations in this neoplasm: **KRAS, CDKNA2A/p16, SMAD4, and TP53.**

Clinical Features

- Remain **silent** until it **extends to other structures.**
- **Pain.**
- **Obstructive jaundice.**
- Weight loss, anorexia, generalized malaise and weakness are manifestations of **advanced** disease.
- **Migratory thrombophlebitis** (*Trousseau syndrome*)

Cholecystitis

Gallstones	Majority (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades.
Types of gallstones	**1. Cholesterol stones (**crystalline cholesterol monohydrate) **2. Pigment stones (**bilirubin calcium salts).

Cholesterol stones

Pathophysiology

- When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleates into solid cholesterol monohydrate crystals.
- Cholesterol gallstone formation involves **four simultaneous defects:**
  - Supersaturation of bile with cholesterol.
  - Gallbladder hypomotility ensues.
  - Cholesterol nucleation in bile is accelerated.
  - Mucus hypersecretion in the gallbladder traps the crystals.
- **Prolonged fasting**, pregnancy, rapid weight loss, total parenteral nutrition, and spinal cord injury also promote stone formation.

Risk factors

Northern Europeans, North and South Americans, Native Americans, Mexican Americans, Advancing age, Female sex hormones, Female gender, Oral contraceptives, Pregnancy, Obesity and metabolic syndrome, Rapid weight reduction, Gallbladder stasis, Inborn disorders of bile acid metabolism & Hyperlipidemia syndromes

Morphology

Arise exclusively in the gallbladder and are composed of cholesterol. Pale yellow, round to ovoid to faceted, and have a finely granular, hard external surface. **Stones composed largely of cholesterol are radiolucent; only 10% to 20% of cholesterol stones are radio-opaque.**

Pigment stones

Pathophysiology

- Pathogenesis of pigment stones is based on the presence in the biliary tract of unconjugated bilirubin (which is poorly soluble in water) and precipitation of calcium bilirubin salts.
- Thus, infection of the biliary tract, as with *Escherichia coli* or *Ascaris lumbricoides* or by the liver fluke *Opisthorchis sinensis*, increases the likelihood of pigment stone formation.

Risk factors

Asians more than Westerners, rural more than urban, Chronic hemolytic syndromes, Biliary infection, Gastrointestinal disorders: ileal disease, ileal resection or bypass & cystic fibrosis with pancreatic insufficiency

Morphology

- "Black" pigment stones are found in sterile gallbladder.
- "Brown" pigment stones are found in infected intrahepatic or extrahepatic bile ducts, greasy.
- Both are soft and usually multiple.
- **Because of calcium carbonates and phosphates, approximately 50% to 75% of black stones are radio-opaque.**

Cholesterolosis

Clinical features	Complications
• Most remain asymptomatic throughout their lives. • Symptoms: spasmodic or "colicky" upper quadrant pain, which tends to be excruciating. • It usually follows a fatty meal which forces a stone against the gall bladder outlet leading to increased pressure in the gall bladder causing pain. Pain is localized to right upper quadrant or epigastrium that may radiate to the right shoulder or the back • It is usually due to obstruction of bile ducts by passing stones.	• Empyema, perforation, fistulas, inflammation of the biliary tree (cholangitis), obstructive cholestasis and pancreatitis. • Occasionally a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction **("gallstone ileus" or Bouveret syndrome).** • Gallstones are associated with an increased risk of gallbladder carcinoma

Info

mucosal surface is studded with minute yellow flecks, producing the "strawberry gallbladder

Acute Cholecystitis

Pathophysiology	Risk factors	Morphology	Clinical features
Results from chemical irritation and inflammation of the obstructed gallbladder.	Occurs in the absence of gallstones, generally in severely ill patient	• Gallbladder is usually enlarged and tense, and bright red to green-black. • The serosal covering is frequently layered by fibrin and, in severe cases, by exudate. • The gallbladder lumen is filled with a cloudy or turbid bile that may contain fibrin and frank pus, as well as hemorrhage. When the contained exudate is virtually pure pus, the condition is referred to as **empyema of the gallbladder**. • In mild cases, the gallbladder wall is thickened, edematous, and hyperemic. • In more severe cases, it is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**, with small-to-large perforations.	• Progressive right upper quadrant or epigastric pain, frequently associated with mild fever, anorexia, tachycardia, sweating, and nausea and vomiting. The upper abdomen is tender. Most patients are free of jaundice • **Acute calculous cholecystitis** may appear with remarkable suddenness and constitute an acute surgical emergency or may present with mild symptoms that resolve without medical intervention. • Clinical symptoms of **acute acalculous cholecystitis** tend to be more insidious, since symptoms are obscured by the underlying conditions precipitating the attacks.

Chronic Cholecystitis

Pathophysiology	Risk factors	Morphology	Clinical features
May be a sequel to repeated bouts of mild to severe acute cholecystitis, but in many instances, it develops in the apparent absence of antecedent attacks.	It is associated with cholelithiasis in over 90% of cases.	• Gall bladder may be contracted (fibrosis), normal in size or enlarged (from obstruction). The wall is variably thickened. Stones are frequent. • On histology, the degree of inflammation is variable. Outpouchings of the mucosal epithelium through the wall (**Rokitansky-Aschoff sinuses**) may be quite prominent. • Rarely, extensive dystrophic calcification within the gallbladder wall may yield a **porcelain gallbladder**. • **Xanthogranulomatous cholecystitis** is also a rare condition in which the gallbladder is shrunken, nodular, fibrosed and chronically inflamed with abundant lipid filled macrophages. • Finally, an atrophic, chronically obstructed gallbladder may contain only clear secretions, a condition known as **hydrops of the gallbladder**.	• The symptoms of **calculous chronic cholecystitis** are similar to those of the acute form and range from biliary colic to indolent right upper quadrant pain and epigastric distress. • Patients often have **intolerance** to fatty food, belching and postprandial epigastric distress, sometimes include nausea and vomiting.

Complications of both Acute & Chronic

- Bacterial superinfection with cholangitis or sepsis
- GB perforation & local abscess formation
- GB rupture with diffuse peritonitis
- Biliary enteric (cholecystenteric) fistula with drainage of bile into adjacent organs, and potentially gallstone-induced intestinal obstruction (ileus)
- Aggravation of pre-existing medical illness, with cardiac, pulmonary, renal, or liver decompensation.