UNIT – 4 🔬 PATHOPHYSIOLOGY

B. PHARMACY 2nd SEMESTER

POINTS TO BE COVERED IN THIS TOPIC

- ➤ INFLAMMATORY BOWEL DISEASES 🦠
- ➤ JAUNDICE 🟡
- ➤ HEPATITIS (A, B, C, D, E, F) 🦠
- ➤ ALCOHOLIC LIVER DISEASE 🍺
- ➤ DISEASES OF BONES & JOINTS 🦴
- ➤ RHEUMATOID ARTHRITIS 🦴
- ➤ OSTEOPOROSIS 💀
- ➤ GOUT 💎
- ➤ PRINCIPLE OF CANCER ⚕️
- ➤ CLASSIFICATION OF CANCER 📊
- ➤ ETIOLOGY AND PATHOGENESIS OF CANCER 🧬

🦠 INFLAMMATORY BOWEL DISEASES

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory conditions affecting the gastrointestinal tract. These disorders are characterized by periods of remission and exacerbation, involving abnormal immune responses to intestinal microflora in genetically susceptible individuals.

TYPES OF INFLAMMATORY BOWEL DISEASES

The two major forms of IBD include:

- **Crohn's Disease**
- **Ulcerative Colitis**

CROHN'S DISEASE

Crohn's disease is a chronic inflammatory condition that can affect any part of the gastrointestinal tract from mouth to anus. The inflammation is transmural, meaning it extends through all layers of the bowel wall.

Pathophysiology:

- The disease involves dysregulated immune response to normal intestinal bacteria
- T-helper 1 (Th1) and Th17 cells produce excessive inflammatory cytokines
- Transmural inflammation leads to tissue damage and scarring
- Granuloma formation is characteristic but not always present

Clinical Features:

- Abdominal pain, typically in the right lower quadrant
- Chronic diarrhea, often without blood
- Weight loss and malnutrition
- Fatigue and fever during active phases
- Perianal complications including fissures and fistulas

ULCERATIVE COLITIS

Ulcerative colitis is a chronic inflammatory disease limited to the colon and rectum. The inflammation is superficial, affecting only the mucosa and submucosa.

Pathophysiology:

- Abnormal immune response primarily involving Th2 cells
- Inflammation is continuous and limited to the mucosa
- Loss of epithelial barrier function
- Increased production of inflammatory mediators

Clinical Features:

- Bloody diarrhea with mucus
- Lower abdominal cramping
- Urgency and tenesmus
- Systemic symptoms during flares including fever and weight loss

Feature	Crohn's Disease	Ulcerative Colitis
Location	Any part of GI tract	Colon and rectum only
Pattern	Skip lesions	Continuous
Depth	Transmural	Mucosal/submucosal
Complications	Strictures, fistulas	Toxic megacolon

JAUNDICE

DEFINITION

Jaundice is a clinical manifestation characterized by yellow discoloration of the skin, sclera, and mucous membranes due to elevated levels of bilirubin in the blood (hyperbilirubinemia).

BILIRUBIN METABOLISM

Normal bilirubin metabolism involves several steps:

- Red blood cell breakdown releases hemoglobin
- Hemoglobin is converted to unconjugated bilirubin
- Unconjugated bilirubin travels to the liver bound to albumin
- Hepatic conjugation converts it to conjugated bilirubin
- Conjugated bilirubin is excreted in bile

CLASSIFICATION OF JAUNDICE

1. PRE-HEPATIC JAUNDICE

Results from excessive breakdown of red blood cells or impaired bilirubin transport to the liver.

Causes:

- Hemolytic anemia
- Ineffective erythropoiesis
- Reabsorption of large hematomas
- Gilbert's syndrome

Characteristics:

- Elevated unconjugated bilirubin
- Normal liver function tests
- Increased urobilinogen in urine

2. HEPATIC JAUNDICE

Results from hepatocyte dysfunction affecting bilirubin uptake, conjugation, or excretion.

Causes:

- Viral hepatitis
- Drug-induced hepatotoxicity
- Alcoholic liver disease
- Cirrhosis
- Hereditary disorders (Dubin-Johnson syndrome)

Characteristics:

- Both conjugated and unconjugated bilirubin elevated
- Abnormal liver function tests
- Presence of urobilinogen and bilirubin in urine

3. POST-HEPATIC JAUNDICE

Results from obstruction of bile flow from the liver to the duodenum.

Causes:

- Gallstones
- Pancreatic cancer
- Cholangiocarcinoma
- Strictures of bile ducts
- Sclerosing cholangitis

Characteristics:

- Elevated conjugated bilirubin
- Absent urobilinogen in urine
- Dark urine and pale stools
- Elevated alkaline phosphatase

HEPATITIS (A, B, C, D, E, F)

INTRODUCTION

Hepatitis refers to inflammation of the liver, most commonly caused by viral infections. Different hepatitis viruses have distinct modes of transmission, clinical courses, and long-term outcomes.

HEPATITIS A (HAV)

Hepatitis A is an acute viral infection caused by the hepatitis A virus.

Transmission:

- Fecal-oral route
- Contaminated food and water

- Close personal contact

Pathophysiology:

- RNA virus that replicates in hepatocytes
- Immune-mediated liver damage
- Self-limiting infection with complete recovery

Clinical Course:

- Incubation period: 15-50 days
- Acute illness with jaundice, fatigue, nausea
- No chronic form exists
- Lifelong immunity after infection

HEPATITIS B (HBV)

Hepatitis B is caused by a DNA virus and can cause both acute and chronic liver disease.

Transmission:

- Blood and body fluids
- Sexual contact
- Mother-to-child transmission
- Needle sharing

Pathophysiology:

- DNA virus that integrates into host genome

- Immune response determines disease outcome
- Can progress to chronic hepatitis, cirrhosis, and hepatocellular carcinoma

Clinical Manifestations:

- Acute phase: jaundice, fatigue, abdominal pain
- Chronic phase: often asymptomatic
- Long-term complications: cirrhosis, liver cancer

HEPATITIS C (HCV)

Hepatitis C is an RNA virus that commonly causes chronic liver disease.

Transmission:

- Primarily through blood contact
- Injection drug use
- Healthcare exposures
- Less commonly through sexual contact

Pathophysiology:

- RNA virus with high mutation rate
- Chronic infection in 70-85% of cases
- Progressive liver fibrosis and cirrhosis
- Increased risk of hepatocellular carcinoma

HEPATITIS D (HDV)

Hepatitis D is a defective RNA virus that requires hepatitis B virus for replication.

Characteristics:

- Co-infection or superinfection with HBV
- More severe disease course than HBV alone
- Similar transmission routes as HBV
- Prevention through HBV vaccination

HEPATITIS E (HEV)

Hepatitis E is an RNA virus causing acute hepatitis, similar to hepatitis A.

Features:

- Fecal-oral transmission
- Waterborne outbreaks common
- Usually self-limiting
- Severe disease in pregnant women
- Chronic infection in immunocompromised patients

HEPATITIS F

Hepatitis F was initially proposed as a separate viral entity but its existence as a distinct virus remains controversial and unconfirmed.

Virus	Type	Transmission	Chronic Form	Vaccine Available
HAV	RNA	Fecal-oral	No	Yes
HBV	DNA	Blood, sexual	Yes	Yes
HCV	RNA	Blood	Yes	No
HDV	RNA	Blood (with HBV)	Yes	No (HBV vaccine)
HEV	RNA	Fecal-oral	Rare	Limited

🍺 ALCOHOLIC LIVER DISEASE

INTRODUCTION

Alcoholic liver disease (ALD) represents a spectrum of liver pathology resulting from chronic alcohol consumption. The disease progresses through several stages, from fatty infiltration to cirrhosis.

STAGES OF ALCOHOLIC LIVER DISEASE

1. ALCOHOLIC FATTY LIVER (STEATOSIS)

The earliest and most common manifestation of alcohol-induced liver injury.

Pathophysiology:

- Alcohol metabolism alters hepatic lipid metabolism
- Increased fatty acid synthesis and decreased oxidation
- Accumulation of triglycerides in hepatocytes
- Reversible with alcohol cessation

Clinical Features:

- Often asymptomatic
- Hepatomegaly may be present
- Elevated liver enzymes
- Complete reversibility with abstinence

2. ALCOHOLIC HEPATITIS

An acute inflammatory condition that can occur at any stage of ALD.

Pathophysiology:

- Direct toxic effects of alcohol and its metabolites
- Oxidative stress and lipid peroxidation
- Inflammatory cell infiltration
- Hepatocyte necrosis and ballooning

Clinical Manifestations:

- Jaundice
- Fever
- Abdominal pain
- Anorexia and weight loss
- May progress to liver failure

3. ALCOHOLIC CIRRHOSIS

The end-stage of alcoholic liver disease characterized by irreversible scarring.

Pathophysiology:

- Progressive fibrosis and regenerative nodules
- Distortion of liver architecture
- Portal hypertension development
- Hepatocellular dysfunction

Complications:

- Portal hypertension
- Esophageal varices
- Ascites
- Hepatic encephalopathy
- Increased risk of hepatocellular carcinoma

RISK FACTORS

- Duration and quantity of alcohol consumption
- Gender (women more susceptible)
- Genetic factors
- Concurrent viral hepatitis
- Malnutrition
- Iron overload

🦴 DISEASES OF BONES & JOINTS

INTRODUCTION

Bone and joint diseases encompass a wide range of conditions affecting the musculoskeletal system. These diseases can result from inflammatory processes, metabolic disorders, or degenerative changes.

🦴 RHEUMATOID ARTHRITIS

DEFINITION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease primarily affecting synovial joints, characterized by persistent inflammation leading to joint destruction and deformity.

PATHOPHYSIOLOGY

The pathogenesis of RA involves complex interactions between genetic susceptibility and environmental factors.

Molecular Mechanisms:

- Activation of T-helper cells and B lymphocytes
- Production of autoantibodies (rheumatoid factor, anti-CCP)
- Synovial membrane inflammation and hyperplasia
- Release of inflammatory mediators (TNF-α, IL-1, IL-6)
- Cartilage degradation by metalloproteinases
- Bone erosion through osteoclast activation

Synovial Changes:

- Synovial hyperplasia and increased vascularity
- Inflammatory cell infiltration (T cells, B cells, macrophages)
- Pannus formation (inflammatory granulation tissue)
- Release of proteolytic enzymes

CLINICAL MANIFESTATIONS

Joint Symptoms:

- Symmetric polyarthritis affecting small joints initially
- Morning stiffness lasting more than one hour
- Joint swelling, warmth, and tenderness
- Progressive joint deformity and loss of function

Systemic Features:

- Fatigue and malaise
- Low-grade fever
- Subcutaneous nodules
- Cardiovascular complications
- Pulmonary manifestations
- Ocular complications (dry eyes)

Laboratory Findings:

- Elevated erythrocyte sedimentation rate (ESR)
- Increased C-reactive protein (CRP)

- Positive rheumatoid factor (70-80% of patients)
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies

💀 OSTEOPOROSIS

DEFINITION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and susceptibility to fractures.

PATHOPHYSIOLOGY

Bone remodeling is a continuous process involving bone resorption and formation. In osteoporosis, this balance is disrupted.

Normal Bone Remodeling:

- Osteoclasts resorb old bone tissue
- Osteoblasts form new bone matrix
- Balanced process maintains bone mass and strength

Osteoporotic Changes:

- Increased osteoclast activity
- Decreased osteoblast function
- Net loss of bone tissue
- Deterioration of bone microarchitecture
- Reduced mechanical strength

Hormonal Influences:

- Estrogen deficiency (postmenopausal)
- Parathyroid hormone regulation
- Vitamin D metabolism
- Calcitonin effects

TYPES OF OSTEOPOROSIS

PRIMARY OSTEOPOROSIS

- **Type I (Postmenopausal):** Estrogen deficiency-related
- **Type II (Senile):** Age-related bone loss in elderly

SECONDARY OSTEOPOROSIS

Results from underlying medical conditions or medications:

- Endocrine disorders (hyperthyroidism, hyperparathyroidism)
- Malabsorption syndromes
- Chronic kidney disease
- Medications (corticosteroids, anticonvulsants)

RISK FACTORS

- Age and gender (postmenopausal women)
- Family history
- Low body weight
- Smoking and excessive alcohol consumption

- Physical inactivity
- Nutritional deficiencies (calcium, vitamin D)

CLINICAL CONSEQUENCES

- Fragility fractures (hip, vertebrae, wrist)
- Loss of height due to vertebral compression fractures
- Chronic pain
- Decreased mobility and independence
- Increased mortality risk

💎 GOUT

DEFINITION

Gout is a metabolic arthritis caused by the deposition of monosodium urate crystals in joints and surrounding tissues, resulting from hyperuricemia (elevated serum uric acid levels).

PATHOPHYSIOLOGY

Uric Acid Metabolism:

- Uric acid is the end product of purine metabolism
- Produced endogenously and from dietary purines
- Excreted primarily by the kidneys (70%) and intestines (30%)

Hyperuricemia Development:

- Overproduction of uric acid

- Underexcretion of uric acid
- Combined overproduction and underexcretion

Crystal Formation and Deposition:

- Supersaturation of body fluids with uric acid
- Formation of monosodium urate crystals
- Deposition in joints, tendons, and soft tissues
- Preferential deposition in cooler, peripheral joints

Inflammatory Response:

- Crystal phagocytosis by neutrophils
- Release of inflammatory mediators
- Complement activation
- Acute inflammatory reaction

CLINICAL PHASES OF GOUT

1. ASYMPTOMATIC HYPERURICEMIA

- Elevated serum uric acid without symptoms
- May persist for years before first attack
- Not all individuals develop clinical gout

2. ACUTE GOUTY ARTHRITIS

- Sudden onset of severe joint pain and swelling
- Often affects the first metatarsophalangeal joint (podagra)

- Associated with erythema and warmth
- Self-limiting episodes lasting days to weeks

3. INTERCRITICAL GOUT

- Asymptomatic periods between acute attacks
- Progressive shortening of symptom-free intervals
- Continued crystal deposition

4. CHRONIC TOPHACEOUS GOUT

- Development of tophi (urate crystal deposits)
- Joint deformity and chronic arthritis
- Kidney involvement and stone formation

COMPLICATIONS

- Joint destruction and deformity
- Chronic kidney disease
- Uric acid nephrolithiasis
- Cardiovascular disease association

Phase	Duration	Symptoms	Serum Uric Acid
Asymptomatic	Years	None	Elevated
Acute	Days-weeks	Severe pain, swelling	Variable
Intercritical	Months-years	None	Usually elevated
Chronic	Persistent	Chronic pain, tophi	Elevated

⚕ PRINCIPLE OF CANCER

INTRODUCTION

Cancer represents a group of diseases characterized by uncontrolled growth and spread of abnormal cells. Understanding cancer principles involves examining the fundamental biological processes that lead to malignant transformation.

DEFINITION

Cancer is defined as a disease caused by an uncontrolled division of abnormal cells in a part of the body. These cells have the ability to invade other tissues and spread to distant sites through the processes of invasion and metastasis.

FUNDAMENTAL CHARACTERISTICS OF CANCER

Cancer cells exhibit several distinctive properties that differentiate them from normal cells:

Hallmarks of Cancer:

- Self-sufficiency in growth signals
- Insensitivity to growth inhibitory signals
- Evasion of programmed cell death (apoptosis)
- Limitless replicative potential
- Sustained angiogenesis
- Tissue invasion and metastasis
- Reprogramming of energy metabolism

- Evading immune surveillance

Cellular Changes:

- Loss of normal growth control mechanisms
- Resistance to cell death signals
- Independence from external growth factors
- Acquisition of invasive properties
- Ability to stimulate blood vessel formation
- Capacity for unlimited cell division

📊 CLASSIFICATION OF CANCER

HISTOLOGICAL CLASSIFICATION

Cancer classification is primarily based on the tissue of origin and cellular characteristics.

1. CARCINOMAS

Tumors arising from epithelial tissues.

Subtypes:

- **Adenocarcinoma:** From glandular epithelium
- **Squamous cell carcinoma:** From squamous epithelium
- **Transitional cell carcinoma:** From transitional epithelium
- **Basal cell carcinoma:** From basal cells of the skin

Common Sites:

- Lung, breast, prostate, colon, stomach
- Skin, cervix, bladder
- Account for approximately 85% of all cancers

2. SARCOMAS

Tumors arising from mesenchymal tissues (connective tissue).

Types:

- **Osteosarcoma:** Bone tissue
- **Chondrosarcoma:** Cartilage tissue
- **Liposarcoma:** Fat tissue
- **Leiomyosarcoma:** Smooth muscle
- **Rhabdomyosarcoma:** Skeletal muscle

Characteristics:

- Less common than carcinomas
- Often more aggressive
- Can occur at any age

3. HEMATOPOIETIC MALIGNANCIES

Cancers of blood-forming tissues.

Categories:

- **Leukemias:** Cancers of blood cells

- **Lymphomas:** Cancers of lymphatic system
- **Multiple myeloma:** Cancer of plasma cells

Classification:

- Acute vs. chronic
- Lymphocytic vs. myelocytic
- Hodgkin vs. non-Hodgkin lymphoma

4. NEUROECTODERMAL TUMORS

Tumors arising from neural tissue.

Examples:

- Gliomas (brain tumors)
- Neuroblastoma
- Retinoblastoma
- Melanoma

STAGING AND GRADING

TNM STAGING SYSTEM

- **T (Tumor):** Size and extent of primary tumor
- **N (Nodes):** Regional lymph node involvement
- **M (Metastasis):** Presence of distant metastases

HISTOLOGICAL GRADING

- **Grade I:** Well-differentiated, low-grade

- **Grade II:** Moderately differentiated
- **Grade III:** Poorly differentiated
- **Grade IV:** Undifferentiated, high-grade

🧬 ETIOLOGY AND PATHOGENESIS OF CANCER

ETIOLOGY (CAUSES OF CANCER)

1. GENETIC FACTORS

Inherited genetic alterations contribute to cancer susceptibility.

Mechanisms:

- Inherited tumor suppressor gene mutations
- Oncogene amplifications
- DNA repair gene defects
- Familial cancer syndromes

Examples:

- BRCA1/BRCA2 mutations (breast/ovarian cancer)
- p53 mutations (Li-Fraumeni syndrome)
- APC gene mutations (familial adenomatous polyposis)
- Lynch syndrome genes (colorectal cancer)

2. ENVIRONMENTAL CARCINOGENS

Chemical Carcinogens:

- Tobacco smoke (lung, bladder, cervical cancers)
- Asbestos (mesothelioma, lung cancer)
- Benzene (leukemia)
- Aflatoxin (liver cancer)
- Occupational chemicals

Physical Carcinogens:

- Ultraviolet radiation (skin cancer)
- Ionizing radiation (leukemia, thyroid cancer)
- Chronic mechanical irritation

Biological Carcinogens:

- Human papillomavirus (cervical cancer)
- Hepatitis B and C viruses (liver cancer)
- Helicobacter pylori (gastric cancer)
- Epstein-Barr virus (lymphomas)

3. LIFESTYLE FACTORS

- Diet and nutrition
- Alcohol consumption
- Physical inactivity
- Obesity
- Reproductive factors

PATHOGENESIS (CANCER DEVELOPMENT)

MULTI-STEP CARCINOGENESIS

Cancer development is a multi-step process involving accumulation of genetic alterations.

Steps in Carcinogenesis:

1. **Initiation:** Initial genetic damage to DNA
2. **Promotion:** Clonal expansion of initiated cells
3. **Progression:** Additional genetic changes leading to malignancy

Molecular Events:

- Activation of oncogenes
- Inactivation of tumor suppressor genes
- Defects in DNA repair mechanisms
- Alterations in apoptosis pathways
- Changes in cell cycle control

ONCOGENES AND TUMOR SUPPRESSOR GENES

Oncogenes:

- Normal genes (proto-oncogenes) that promote cell growth
- When mutated or overexpressed, drive cancer development
- Examples: RAS, MYC, HER2, BCL2

Tumor Suppressor Genes:

- Normal genes that prevent uncontrolled cell growth

- Loss of function contributes to cancer
- Examples: p53, RB, APC, BRCA1/BRCA2

GENOMIC INSTABILITY

- Accumulation of mutations over time
- Defective DNA repair mechanisms
- Chromosomal instability
- Microsatellite instability

CANCER PROGRESSION MODEL

Benign to Malignant Transformation:

- Normal epithelium → Hyperplasia → Dysplasia → Carcinoma in situ → Invasive carcinoma → Metastatic carcinoma

Key Features of Progression:

- Loss of growth control
- Invasion of surrounding tissues
- Angiogenesis (blood vessel formation)
- Metastasis to distant sites

Metastatic Cascade:

- Local invasion
- Intravasation into blood vessels
- Survival in circulation
- Extravasation at distant sites

- Colonization and growth

Factor Type	Examples	Associated Cancers
Genetic	BRCA1/2, p53, APC	Breast, ovarian, colorectal
Chemical	Tobacco, asbestos, benzene	Lung, mesothelioma, leukemia
Biological	HPV, HBV, H. pylori	Cervical, liver, gastric
Physical	UV radiation, ionizing radiation	Skin, thyroid, leukemia

Topper Nest