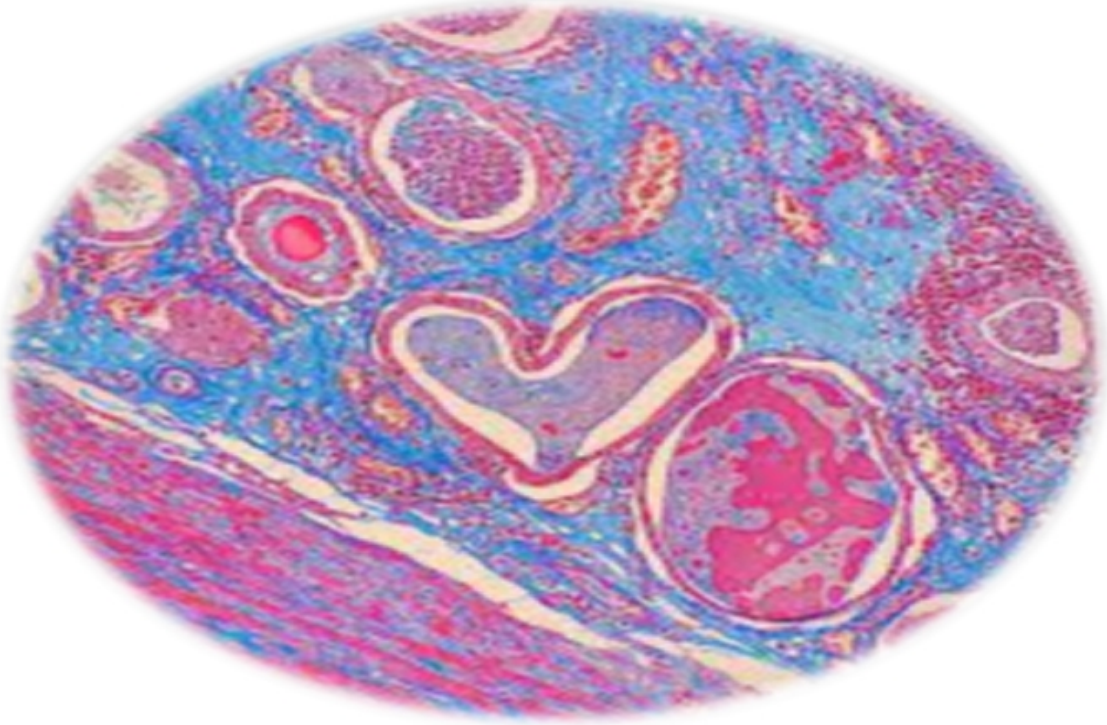
SYNOPSIS OF

GENERAL PATHOLOGY



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INTRODUCTION

WHAT IS PATHOLOGY?

Pathology is the study of disease

THE MAIN ASPECTS OF ANY DISEASE INCLUDE

DEFINITION

AETIOLOGY: This includes:

- **Predisposing factors** what makes a person at risk of developing a disease.
- **Exciting cause:** what triggers the disease
- **Pathogenesis:** how the disease happens

MORPHOLOGIC CHANGES (PATHOLOGICAL FEATURES): These are divided into:

- **Gross Features:** They are also called naked eye features or macroscopic features. They include all changes that can be detected by the naked eye e.g. change in size, color & consistency of the diseased organ. **Microscopic Features** (by ordinary light microscopy): These are cellular and/or extracellular changes that characterize each disease.
- **Special Microscopic Studies:** Electron microscopy & immunohistochemistry.

FATE, PROGNOSIS AND COMPLICATIONS:

- **Fate** is the disease outcome. It may be:
  - ❖ Good fate e.g. regressive disease course in mild inflammations
  - ❖ Bad fate: Complications (including death).
- **Prognosis** is prediction of the disease course. It may be
  - ❖ Good prognosis as mild inflammations & benign tumors
  - ❖ Poor prognosis as in malignant tumors (cancer) and septicemia.

TYPES OF SPECIMENS REFERRED FOR PATHOLOGICAL DIAGNOSIS

1-Biopsy: this means examination of a tissue specimen which may be**:**

- **Punch biopsy** e.g. from GIT, lung & bladder lesions through endoscopy (endoscopic biopsy)

- **Core biopsy** e.g. from liver ,kidney, lung, mediastinum …etc; usually guided by ultrasonography (US) or computerized tomography (CT guided biopsies)
- **Incisional biopsy**: This is a surgically obtained part of a lesion e.g. part of a breast mass
- **Excisional biopsy**: This is surgical excision of the whole lesion e.g. whole breast mass
- **Partial organ excision** e.g. partial nephrectomy, or subtotal thyroidectomy
- **Whole organ excision** as mastectomy splenectomy, total thyroidectomy, hysterectomy… etc

2-Autopsy: This is examination of tissue obtained from dead bodies

3- Frozen section examination:

Frozen section (FS) examination is used for rapid diagnosis during surgery The biopsy is immediately transferred into a cryostat chamber, where it is frozen (within minutes) without fixation for rapid intra-operative diagnosis, e.g. a breast or thyroid mass needs to be evaluated whether benign or malignant to determine the type of surgery.

4- Cytology: Examination of body fluids or smears to detect any abnormal cells such as malignant cells & inflammatory cells. Examples:

- **Body fluids** as urine, CSF, effusions (pleural, pericardial & synovial), ascites, synovial & cystic fluid e.g. ovarian cysts, mammary cysts
- **Sputum**
- **Discharge** e.g. nipple discharge, conjunctival discharge.
- **Lavage fluid** e.g. bronchial lavage, bladder and/or pelviureteric wash.
- **Brush cytology** e.g. brush of common bile duct, bronchial and gastric brush.
- **Touch imprint cytology** e.g. imprint of the cut surface of an excised lymph node or excised breast tumor, testicular imprint…
- **Fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB)**
- **Cervicovaginal smears** (PAP-smears): These smears are stained with Papanicolau stain

FIXATION OF SPECIMENS FOR MICROSCOPIC EXAMINATION:

1- Preservation (fixation):

- **Tissue specimens (biopsy or autopsy**):
  a) **For frozen sections: No fixation** is required and has to be avoided.
  b) **To obtain paraffin sections**, the tissue is pre-fixed in 10% buffered **formalin.** Some tissues need special fixatives e.g. Bouin's solution for testicular biopsies.
- **Cytology specimens** may not need fixation or get fixed e.g. in ethyl alcohol

CHAPTER 1 RESPONSE OF CELL TO INJURY

Causes of cell injury:

- **Hypoxia** (decreased oxygen supply).
- **Biological**: viruses, bacteria, fungi and parasites.
- **Physical agents**: heat, cold, radiation and electric shock.
- **Chemical agents** as acids, alkalies, alcohol, metals, drugs.
- **Mechanical:** trauma
- **Immunologic reactions** (hypersensitivity).
- **Nutritional deficiencies.**
- **Genetic diseases.**

Mechanism of cell injury:

- **Targets of cell injury:**
  1. Cell membranes.
  2. ATP production.
  3. The genetic apparatus
- **Steps of cell injury:**
  1. **ATP depletion** (mainly in cases of hypoxia e.g. due to ischemia).
  2. **Altered cell membrane permeability** due to stoppage of cell membrane pumps with resultant influx of calcium and sodium inside the cell.
  3. **Intracellular influx of sodium and calcium** across damaged cell membrane.
     - Increase of intracellular calcium activates:

     a) Phospholipases that degrade membrane phospholipids.

b) ATP-ase cause more ATP depletion.
c) Endonucleases cause DNA injury.
d) Proteases that break cellular proteins.

❖ Increase of intracellular sodium:

Water accumulation inside cells

Effects of cell injury:

I) ADAPTATION **II DAMAGE**

I) ADAPTATION

ATROPHY

Definition: acquired reduction of cell size leading to reduction in organ weight and size.

Atrophy may be:

1) Physiological:

a) Atrophy of thymus after puberty.

b) Atrophy of female breasts and ovaries after menopause due to diminished hormone stimulation.

2) Pathological:

a) Disuse atrophy: atrophy of limb muscles following prolonged immobilization after bone fracture.

b) Neuropathic atrophy atrophy of muscles of affected limb in case of poliomyelitis.

HYPERTROPHY

Definition: acquired increase in the size of the cell; consequently leading to increase in the size and weight of the affected tissue or organ.

Hypertrophy may be:

1- Physiological: The best examples include:

a) Pregnant uterus due to hormone stimulation.

b) Hypertrophy of muscles in muscle builders.

2- Pathological:

a) Left ventricular hypertrophy due to systemic hypertension.

b) Urinary bladder hypertrophy due to bladder neck obstruction.

c) Kidney hypertrophy when the other kidney is surgically removed (Compensatory hypertrophy).

HYPERPLASIA

Definition: acquired increase in the number of cells, leading to increase in the size and weight of the affected tissue or organ. It is usually accompanied by hypertrophy. Hyperplasia is a precancerous condition.

Hyperplasia may be:

1-Physiological:

a) Mammary glands & genitalia at puberty (hormonal hyperplasia).

b) Pregnant uterus.

2-Pathological:

a) Hormonal hyperplasia e.g. endometrial hyperplasia due to excessive estrogen stimulation.

b) Bone marrow hyperplasia following hemorrhage or hemolysis.

METAPLASIA

Definition: Replacement of one mature differentiated cell type by another of the same category. It is a reversible process aiming at transforming cells that are more sensitive to stress by another which is more resistant, therefore can better withstand the adverse environment conditions. It is precancerous.

Aetiology and Types:

1- Epithelial Metaplasia: The most common examples include:

a) Squamous metaplasia:

- Urinary bladder mucosa in case of bilharzial cystitis.
- Tracheal and bronchial mucosa in smokers.

b) Columnar Metaplasia: of the squamous epithelium in lower part of esophagus into columnar in case of reflux esophagitis ***(Barrett's esophagus)***.

2- Mesenchymal Metaplasia: in case of muscle injury, fibroblasts may transform into chondroblasts or osteoblasts; thus producing bone or cartilage in abnormal sites. Therefore, causing soft tissue ossification ***(Myositis Ossificans).***

II) DAMAGE

A) REVERSIBLE DAMAGE (DEGENERATION):

Degenerations are either due to intracellular accumulation of water or fat.

1. Cell swelling due to accumulation of water: It is a mild form of cell injury. Two subtypes:

a) **Cloudy Swelling:** Small amount of water → cell swelling with granular cytoplasm.

b) **Hydropic Swelling** (also called vacuolar degeneration or hydropic degeneration or ballooning degeneration). Accumulation of larger amounts of water → the cytoplasm appears pale with clear cytoplasmic vacuoles.

2. Cell swelling due to accumulation of fat (Fatty change or steatosis)

Definition: Intracytoplasmic accumulation of fat inside parenchymal cells. It can affect any organ, but is most common in the liver (hepatic steatosis).

Etiology:

1- **Fatty change of liver**: **Causes include:**

a) Obesity (excess dietary fat).

b) Starvation & diabetes mellitus: → excessive mobilization of fat from fat stores to liver.

c) Deficiency of lipotropic factors as choline & methionine.

d) Hepatotoxins as alcohol.

e) Some liver cell diseases as viral hepatitis C.

Pathology:

Gross Picture:

The organ appears enlarged, with stretched capsule. Consistency is soft greasy. Cut surface is bulging with round borders. Color is yellow.

Microscopic Picture:

Enlarged hepatocytes with clear cytoplasm and eccentric flattened nucleus giving signet ring appearance.

Fat can be stained orange (Sudan III) or black (osmic acid).

B) IRREVERSIBLE DAMAGE (CELL DEATH):

1- NECROSIS

Definition: premature death of a group of cells within a living body.

Gross features:

- The necrotic tissue appears swollen and yellowish white.
- The surrounding tissues appear hyperemic due to inflammation.

Microscopic features:

1- Cellular Changes:

a) Nuclear Changes:

- Pyknosis: The nucleus becomes small and dark.
- Karyorrhexis: Nuclear fragmentation.
- Karyolysis: nuclear disappearnace.

b) Cytoplasmic Changes:

- Cytomegaly
- Cell membrane blebs.

2- Architectural Changes: Two main possibilities:

a) Necrotic tissue may rapidly appear **structureless** due to cell lysis by lysosomal enzymes.

b) Protein denaturation (coagulation) which preserves the architectural outlines of the original tissue → **ghosts.** However lysis occurs later and the necrotic tissue finally appears structureless.

Fate of necrotic tissue:

1-Inflammation surrounds the necrotic area.

2-Healing: Regeneration or fibrosis.

3- Dystrophic calcification may occur.

Types of necrosis:

1- Coagulative Necrosis:

- It is the most common type.
- The structural outline is preserved due to protein denaturation.
- It occurs due to ischemic necrosis of all organs except CNS.

2- Liquefactive Necrosis:

- Structureless material.
- Occurs in CNS and in pus.

3- Caseous Necrosis:

- **This type of necrosis is typical of tuberculosis**. It combines features of both coagulative and liquefactive.
- The necrotic tissue appears yellowish white & "cheesy" resembling casein (caseous).

4- Fat Necrosis: Two subtypes:

a) Enzymatic Fat Necrosis:

It occurs in cases of acute hemorrhagic pancreatitis. Ruptured pancreatic ducts allows escape of lipase and protease enzymes leading to necrosis of the surrounding peritoneal fat cells. Liberated free fatty acids combine with calcium forming calcium soap. The affected areas show chalky white hard calcific patches.

b) Traumatic Fat Necrosis:

It is common in the female breast usually caused by trauma. The hard mass may be clinically mistaken for a tumor.

5- Fibrinoid Necrosis: It develops in autoimmune collagen diseases due to autoantibodies against collagen forming fibrin like material.

APOPTOSIS

Definition: it is cell suicide or programmed cell death aiming at removal of un-necessary or diseased cells. It can occur in physiological and pathological conditions.

Morphological features of apoptosis:

- Shrinkage of cell size.
- Nuclear chromatin condensation, followed by fragmentation of DNA.
- Formation of membrane blebs, followed by their separation forming apoptotic bodies.
- The apoptotic bodies consist of a dark nuclear fragment surrounded by eosinophilic cytoplasm. They become engulfed by phagocytic cells.
- Apoptosis does not excite inflammation

Types

1-Physiological:

- During embryogenesis.
- Hormone dependent involution of tissues e.g. endometrium during menstrual cycle
- Cells after achieving their purpose e.g. neutrophils in acute inflammation

2-Pathological:

- Apoptosis of malignant tumor cells.
- In some cases of atrophy.

CHAPTER 2 INTRACELLULR ACCUMULATIONS AND EXTRACELLULAR DEPOSITIONS

I- INTRACELLULAR ACCUMULATIONS

1- MUCIN

A- MUCOID DEGENERATION

This is intracellular accumulation of mucin inside epithelial cells showing vacuolated cytoplasm, with eccentric nuclei (signet ring cells).

Cells may rupture leading to extracellular pools of mucin. E.g. catarrhal inflammation.

B- MYXOMATOUS DEGENERATION

This is extracellular accumulation of mucin e.g. myxedema in hypothyroidism.

2- PROTEINS

HYALINE CHANGE (HYALINOSIS)

Either intracellular or extracellular accumulation of homogenous, glassy-pink protein with no specific gross features.

Examples:

- Russel bodies: Hyaline change of plasma cells due to overproduction of immunoglobulins in some prolonged chronic inflammations.
- Mallory bodies: seen in liver cells in alcoholic hepatitis.

3- PIGMENTS

Intracellular accumulation of pigments includes two major forms:

A) EXOGENOUS PIGMENTATION

1-By inhalation: The most common example is **ANTHRACOSIS** which is black pigmentation of lungs caused by inhalation of carbon due to smoking or air pollution which is engulfed by macrophages and is partly carried to the draining lymph nodes.

2-By skin inoculation (tattooing)

B) ENDOGENOUS PIGMENTATION

i-MELANIN

Causes:

- Prolonged exposure to sun.
- Pigmented tumors: Benign melanoma (nevi) and malignant melanoma.

ii- LIPOFUSCIN (LIPOCHROME)

This yellowish brown lipid-derived pigment normally exists in small amounts in different cells of the body. Pigment is produced from peroxidation of lipids in cell membranes.

Brown Atrophy Of the Heart:

It is caused by aging (senility). Heart is reduced in size (atrophic) and has dark brown myocardium. Coronaries appear tortuous & pericardial fat disappears.

iii- HAEMOGLOBIN -DERIVED PIGMENTS

HAEMOSIDERIN

A brownish iron containing pigment. It gives positive Prussian blue reaction i.e. it gives a blue coloration when treated with potassium ferrocyanide & hydrochloric acid. The pigment occurs in localized or systemic forms:

-LOCALIZED HAEMOSIDEROSIS

In areas of hemorrhage, as in cases of lung congestion.

-GENERALIZED HAEMOSIDEROSIS (HEMOCHROMATOSIS)

If there is abnormal iron overload, excess ferritin aggregates forming hemosiderin causing abnormal brown pigmentation of both parenchymal and phagocytic cells. Types:

a- **Primary Haemochromatosis (Bronze Diabetes):** hereditary genetic error leading to excess absorption of dietary iron leading to hemosiderin deposits in various organs. Mostly affect **Skin:** Bronze discoloration and **Pancreas** causing Diabetes mellitus.

b- **Secondary Hemochromatosis** as in cases of repeated blood transfusions.

II- EXTRACELLULAR DEPOSITIONS

1- CALCIUM

PATHOLOGICAL CALCIFICATION

Definition: Deposition of calcium salts in sites other than bones and teeth.
Grossly: the calcified tissue appears chalky white, coarse and hard.
Microscopically: calcification appears as blue granules (with hematoxylin & eosin)

Types:

A- DYSTROPHIC CALCIFICATION

Definition: This is calcification of dead or degenerated tissues in spite of a normal blood calcium level. It is due to breakdown of organic phosphates→ change of pH (alkalinity) of dead tissues which has great affinity to calcium.

Examples:

- Atherosclerosis
- Thrombi
- Intrauterine dead fetus.

B- METASTATIC CALCIFICATION

Definition This is calcification of normal tissues due to hypercalcemia.

Causes of hypercalcemia

1-Hyperparathyroidism due to parathyroid hyperplasia or tumors.

2- Bone destruction by malignant tumors.

2- AMYLOIDOSIS

Definition:

- Amyloidosis is extracellular deposition of abnormal protein, mainly in walls of blood vessels, basement membranes & along reticulin fibers.
- Although protein in nature, it was termed amyloid i.e. starch-like because it reacts with iodine and sulphuric acid giving a blue color.

Staining of amyloid:

- **Gross Staining**

  1) Lugol's iodine stains amyloid dark brown and the rest of tissue pale yellow.

  2) Iodine and 1% sulphuric acid stain the amyloid blue.

- **Microscopic staining:**

  1) Hematoxylin & eosin stain: Amyloid appears homogenous & eosinophilic

  2) Congo red stain: Amyloid is stained orange red. If the same sections are examined under polarizing light, amyloid exhibits characteristic apple-green bipolar refringence.

  3) Metachromatic stains as crystal violet or methyl violet stain the amyloid deposits rose red, while the rest of tissues are stained violet.

Types of amyloidosis:

A- Systemic amyloidosis, the amyloid fibril proteins may be:

1) AL (amyloid light chain protein of immunoglobulins). It is secreted by plasma cells in case of plasma cell neoplasms (known as plasmacytoma or multiple myeloma)

2) AA (amyloid-associated protein). It is a non-immunoglobulin protein secreted by the liver in response to chronic destructive disease anywhere in the body as tuberculosis.

3) Less common proteins as B2 microglobulin & transthyretin

B- Localized amyloidosis, amyloid is locally formed in the affected tissue, as in Alzaheimer.

C) Hereditary Amyloidosis: as in familial Mediterranean fever.

D- Hemodialysis-associated Amyloidosis affects patients with chronic renal failure subjected to chronic hemodialysis.

Pathology of the affected organs:

Gross Picture:

- The affected organ is enlarged.
- Cut section: Pale gray waxy amyloid deposits are seen. The cut surface is flat and the borders are sharp.
- Firm in consistency.

Microscopic Picture:

- Amyloid appears homogenous pink material.
- Special stains are applied.

3- URIC ACID & URATES

GOUT

Definition: Disturbance in purine metabolism, leading to increase of serum uric acid & deposition of urate crystals in tissues.

Etiology:

1) Primary gout: caused by deficiency in enzymes responsible for purine metabolism.

2) Secondary gout due to excess nucleoprotein destruction as in chronic myeloid leukemia.

Effects:

a) Acute arthritis. Joints (particularly the big toe) are severely inflamed

b) Tophi:

Subcutaneous small nodular lesions formed of granulomas.

c) Gouty nephropathy: It is characterized by

- Tophi in interstitial tissue of kidneys.
- Uric acid/ urate stones in renal pelvis and calyces.
- Renal failure may occur.

CHAPTER 3 NFLAMMATION

Definition: Inflammation is a reaction of living vascularized tissues to injury.

Types of inflammation:

1-Acute inflammation: Rapid onset & short duration (days or weeks)

2-Chronic inflammation: Gradual onset & longer duration (several months or years).

3-Subacute inflammation: Type of inflammation between acute and chronic.

I- ACUTE INFLAMMATION

Pathogenesis:

A) RELEASE OF CHEMICAL MEDIATORS

Definition: Chemical mediators are chemical substances that control the inflammatory process. They are derived from cells, plasma and bacterial products.

Effects:

- **Vasodilatation** (e.g. by histamine & prostaglandins).
- **Increased vascular permeability** (e.g. by histamine & prostaglandins)
- **Fever**, **leukocytosis and pain** (e.g. by prostaglandins, tumor necrosis factor and interleukens).

B) VASCULAR PHASE

1- **Transient Vasoconstriction** due to irritation of the vessel wall leading to stimulation of the vasoconstrictor nerves. It lasts for seconds or minutes, followed by vasodilatation.

2- **Vasodilatation:**

- Caused by action of chemical mediators as histamine on vessel walls.

- It affects arterioles, capillaries and venules.
- There is increased blood flow (hyperemia) → redness & hotness of the inflamed area (*flare* phenomenon)

3- Increased Vascular Permeability & Formation of Exudate:

Under the effect of chemical mediators, endothelial cell contract and retract causing widening of the intercellular junctions creating gaps between the endothelial cells, leading to vascular leakage which results in:

i) FLUID EXUDATE The inflammatory fluid exudate has the following important functions:

- **Dilutes bacterial toxins** and chemical irritants; thus minimizing their effects.
- **Brings antibodies**
- **Brings chemical mediators**
- **Brings nutrients** for the inflammatory cells.
- **Contains fibrinogen which changes to fibrin**
  - Helps localizing infection by surrounding the inflamed area
  - Forms a network upon which phagocytic cells can move towards their target.
  - Fibrin also allows movement of proliferating fibroblasts during the process of repair.

ii) VASCULAR STASIS which is an important step allowing for leukocyte migration since leukocytes cannot leave the blood vessels if the blood flow is rapid. However, it has an adverse effect leading to thrombosis.

C) CELLULAR PHASE

The cellular phase only follows the vascular phase, it comprises the FOLLOWING STEPS:

1- Margination and Pavementing of Leucocytes:

- In normal flowing blood, erythrocytes and leucocytes are confined to the central (axial) column surrounded by plasma.
- When blood slows down, some leukocytes (mainly neutrophils & monocytes) fall out of the central column and begin to line themselves along the endothelium (*margination*).

- Adhesion of the marginating leukocytes to the endothelial surface occurs like a key and lock via receptors include selectins, immunoglobulins and integrins (*pavementing*).

2- Emigration of leucocytes

- Once the leukocytes adhere to the endothelium, they insert pseudopods into the junctions between the endothelial cells, eventually traversing the basement membrane (*diapedesis*) and escape into the extravascular space (*emigration*).
- Neutrophils (also called polymorphnuclear neutrophils, PMNs or microphages) emigrate first, therefore considered first line of defense, followed 24 hours later by macrophages.

3- Chemotaxis:

- It is defined as the directional movement of emigrating leukocytes to the site of injury.
- Chemotactic agents include complement components particularly C5a & C3a, neutrophil components, lymphokines & bacterial products.

4 - Phagocytosis:

Phagocytosis is defined as the process by which the phagocytic cells recognize then engulf abnormal particles such as bacteria, dead cells, fibrin and foreign bodies, followed by their degradation. Steps include:

a) Recognition & attachment of bacteria: Bacteria are coated by an opsonin which is an immunoglobulin or complement factor to be attractive to leucocytes (*opsonization*).

b) Engulfment: Phagocytic leukocytes surround the opsonised bacteria & send cytoplasmic extensions (pseudopods) around the bacteria or the object to be engulfed forming phagocytic vacuole (phagosome). Phagosome fuses with the limiting membrane of the lysosomal granules →discharge of granule contents → phagolysosome→ bacterial degradation.

c) Degradation: Killing bacteria may be done through:

i) Oxygen dependent mechanisms: Formation of hydrogen peroxide or superoxide which are bactericidal.

ii) Oxygen-independent mechanisms: Lysosome hydrolyzes bacterial wall glycoproteins → a powerful bactericidal activity.

Clinical picture:

SYSTEMIC (GENERAL)

1- Leukocytosis: Increased blood leukocytes above normal (> 10,000 per mm^3).

2- Fever (pyrexia): Pyrogenic factors, principally IL-1 & TNF→ disturbance of the thermoregulatory center in the hypothalamus → vasoconstriction of skin vessels → fever (reduced heat loss).

LOCAL

1- Redness due to increased blood flow.

2-Hotness due to increased blood flow. Redness & hotness are called flare phenomenon

3- Swelling (the wheal) due to accumulation of exudate

4-Pain: due to:

- Nerve compression by exudate
- Irritation by mediators as bradykinin and prostaglandin E2

5- Loss of function: due to pain and tissue damage.

Fate of acute inflammation

1- **Resolution:** This is return of the tissue to its normal state. It occurs when inflammation is limited and tissue damage is minimal.
2- **Healing:** there is tissue damage which is gradually repaired.
3- **Progression and spread:** With weak immunity, bacteria may spread:
   - Direct spread causing extension and widening of the inflammatory field.
   - Lymphatic spread causing lymphangitis and lymphadenitis.
   - Blood spread which may lead to serious effects as septicaemia.
4- **Chronicity:** This occurs if the injurious agent could not be eliminated completely.

TYPES OF ACUTE INFLAMMATION

1- Suppurative (purulent, septic or pyogenic) inflammation: defined as type of acute inflammation characterized by pus formation. Suppurative inflammation may be:

a) Localized as abscess, boil and carbuncle.
b) Diffuse as cellulitis and suppurative appendicitis.

2- Non suppurative types:

A) Serous B) Fibrinous
C) Serofibrinous D) Catarrhal
E) Pseudomembranous F) Hemorrhagic
G) Necrotizing H) Allergic

A. SUPPURATIVE INFLAMMATION

Definition: Acute inflammation characterized by pus formation

Caused by pyogenic organisms as Staphylococcus aureus, Streptococcus hemolyticus

Mechanism (pathogenesis) of pus formation:

- Pyogenic organisms cause:
  a) Remarkable necrosis.
  b) Attraction of a huge number of neutrophils.
  c) Death of many neutrophils due to high virulence of the bacteria.
  d) Dead neutrophils (pus cells) release their proteolytic enzymes cause liquefaction of necrotic tissue. The liquefied material mixed with pus cells & fluid exudate forming a creamy fluid called pus.

Composition of pus:

- Fluid exudate.
- Cells: A large number of pus cells, neutrophils, some macrophages & some RBCs
- Necrotic tissue.
- Bacteria

Types of suppurative inflammation:

1- Localized: Commonly caused by Staphylococcus aureus which produce coagulase enzyme → fibrin deposition → localization. The most common forms of localized suppurative inflammation are: a) **Abscess.** b**) Boil (furuncle**). c) **Carbuncle.**

2- Diffuse: Caused by Streptococcus haemolyticus which produce hyaluronidase (spreading factor) & streptokinase (fibrinolysin) which dissolves fibrin. The most common examples are: a) **Cellulitis**
b) **Suppurative appendicitis**

LOCALIZED ABSCESS

Definition:
A type of localized suppurative inflammation characterized by a cavity containing pus.

Aetiology: It is commonly caused by Staphylococcus aureus infection.

Sites: It is most common in the subcutaneous tissues, but can occur in any organ (lung, liver, brain, bone, kidney, testis, ovary …etc)

Pathological Features:

1- **Early,** two zones can be recognized:
   a) A central zone of necrosis.
   b) A peripheral zone of inflammation showing many neutrophils, pus cells, macrophages, dilated capillaries and fibrin.

2- **Later,** progressive liquefaction starts at the margin of necrotic tissue→ three zones:
   a) A central necrotic core.
   b) A mid zone of pus.
   c) The peripheral zone of inflammation

Fate of abscess:
a) Small abscess: Pus is absorbed, followed by resolution.
b) Large abscess: A big abscess (if not surgically removed) → pointing & rupture (spontaneous evacuation) followed by healing.

Complications of abscess:

1-Spread of infection:
a) Direct spread leads to abscess enlargement.
b) Lymphatic spread leads to lymphangitis and lymphadenitis.
c) Blood spread may lead to:

- Toxaemia: Bacterial toxins circulating in the blood.
- Septicaemia: large numbers of virulent bacteria & their toxins circulating in blood. Commonly fatal.
- Pyaemia: Septic venous thrombi (septic thrombophlebitis) may develop close to the abscess. If these thrombi become fragmented → circulating septic emboli → multiple small abscesses in distant organs. These small abscesses are called pyemic abscesses and the whole process is called pyemia

2- Complications of evacuation and healing:

a) Ulcer: An area of lost surface.

b) Sinus: It is a single ended tract between a deep abscess and the surface.

c) Fistula: A double ended tract communicating between two surfaces or hollow organs.

d) Keloid: overdone repair.

e) Hemorrhage

f) Rupture.

3-Chronicity: If the abscess is neither evacuated spontaneously nor surgically, it becomes surrounded by fibrosis and changes into a chronic abscess.

FURUNCLE (BOIL)

Abscess related to the hair follicles is common in the face of males and axilla of females.

CARBUNCLE

- A special type of localized suppurative inflammation characterized by multiple communicating deep subcutaneous abscesses, opening on skin by multiple sinuses.
- It only occurs in special sites where the skin and subcutaneous tissues are thick and tough due to dense fibrous septa that extend between the deep fascia and the dermis; thus dividing the subcutaneous fat into compartments. Sites of carbuncle include back of neck, scalp & buttocks.
- More common in diabetics (low immunity).

DIFFUSE CELLULITIS

Definition: Cellulitis is an acute diffuse suppurative inflammation, more common in diabetics. The differences between cellulitis and abscess are listed in the following table:

ABSCESS	CELLULITIS
• Localized suppurative inflammation. • Caused by Staphylococcus aureus. • Bacteria → coagulase→ localization. • Occurs in any organ or tissue, but is most common in subcutaneous tissue. • Pus is characterized by: a) Thick due to the presence of large amount of fibrin. b) Contains few erythrocytes. c) Contains few sloughs. • Spread of infection is less common.	• Diffuse suppurative inflammation. • Streptococcus haemolyticus. • Bacteria → fibrinolysin & hyaluronidase → diffusion. • Occurs in loose connective tissues as subcutaneous tissues, areolar tissue of orbit, scrotum. • Pus is characterized by: a) Thin, due to less amount of fibrin (fibrinolysin antagonizes fibrin deposition). b)Sanguineous (contains many RBCs) c) Contains many sloughs due to extensive necrosis • Spread of infection is more common

B- NON SUPPURATIVE INFLAMMATION

SEROUS INFLAMMATION

Characterized by an exudate with excessive serous fluid poor in fibrin.

Examples:

- Skin blisters due to skin burns.
- Epidermal vesicles due to herpes simplex viral infection.
- Inflammation of serous membranes (pleura, pericardium and peritoneum).

FIBRINOUS INFLAMMATION

Characterized by an exudate rich in fibrin, with a little fluid component.

Examples:

- Lobar pneumonia:
- Inflammation of serous membranes.

SEROFIBRINOUS INFLAMMATION

Definition: This is inflammation of serous membranes rich in both fluid exudate & fibrin.

- Inflammation of serous membranes.

CATARRHAL INFLAMMATION

Characteristics: A mild form of acute inflammation of mucous membranes characterized by an exudate mixed with mucus.

Examples: Catarrhal rhinitis (common cold)

PSEUDOMEMBRANOUS (MEMBRANOUS) INFLAMMATION

Characteristics: A severe form of acute inflammation of mucous membranes characterized by replacement of the normal mucous membrane by a false membrane composed of necrotic tissue & fibrin

Examples: Diphtheria and Bacillary dysentery.

HAEMORRHAGIC INFLAMMATION

Characterized by excess RBCs within the exudate due to associated vascular damage.

Example: Small pox & hemorrhagic cystitis

NECROTIZING INFLAMMATION

Characterized by: extensive necrosis in association with inflammation.

Example: Cancrum oris.

ALLERGIC INFLAMMATION

Characterized by many eosinophils.

Examples: Urticaria, allergic rhinitis and bronchial asthma.

II- CHRONIC INFLAMMATION

PATHOLOGICAL FEATURES OF CHRONIC INFLAMMATION

- Chronic inflammation has a delayed onset and lasts for a long duration.
- It may follow acute inflammation due to failure of defense mechanisms.
- It may start chronic by gradual onset (not preceded by an acute phase)
- The main differences between acute &chronic inflammation are listed in the table:

ACUTE INFLAMMATION	CHRONIC INFLAMMATION
• Rapid onset and short duration. • Marked vasodilatation • Main inflammatory cells: Neutrophils & macrophages • Edema	• Gradual onset & long duration • Endarteritis obliterans occurs (thickening & narrowing of small blood vessels) • Main inflammatory cells: Macrophages, lymphocytes, plasma cells and giant cells • Fibrosis.

TYPES OF CHRONIC INFLAMMATION

1- CHRONIC NONSPECIFIC INFLAMMATIONS:

- They usually follow acute inflammation, e.g. chronic abscess.
- They are termed "nonspecific" since they all show the same microscopic features (chronic inflammatory cells, fibrosis, and vascular thickening .etc.) irrespective of the cause.

2- CHRONIC SPECIFIC INFLAMMATIONS:

- They usually start chronic without a pre-existing acute phase.
- They exhibit the conventional microscopic features of chronic inflammation in addition to features specific for the cause as the presence of bilharzia ova in cases of bilharziasis.
- The majority of chronic specific inflammations occur in the form of **granulomas.**

GRANULOMAS

Definition: A specific form of chronic inflammation characterized by nodular collections of macrophages, epithelioid cells (main cells forming granulomas), with a variable mixture of lymphocytes, plasma cells, giant cells & sometimes neutrophils.

Pathological characteristics:

- The macrophages commonly change into larger eosinophilic cells called epithelioid cells.
- Some granulomas may exhibit central necrosis.

- Granulomas often represent type IV hypersensitivity, where stimulated T lymphocytes release lymphokines that attract large numbers of macrophages.

Types of granulomas:

1- Infectious granulomas: Most of these granulomas are necrotizing. Examples:

- Bacterial as tuberculosis, syphilis, leprosy.
- Parasitic as schistosomiasis (bilharziasis).
- Fungal as coccidiomycosis, cryptococcosis and histoplasmosis.

2- Foreign body granulomas: Mostly non-necrotizing granulomas. Examples:

- Silicosis.
- Foreign body granulomas around surgical sutures.

3-Idiopathic granulomas: Examples:
Sarcoidosis

CHAPTER 4 REPAIR (HEALING)

REPAIR (HEALING)

Definition:
Repair is the replacement of a damaged tissue by a new healthy one.

Types of repair:

1- Regeneration: Replacement of the damaged tissue by tissue of the same type.

2- Fibrosis/Gliosis: Replacement of the damaged tissue by fibrous/glial tissue

- Fibrosis in any part of the body except CNS
- Gliosis (in CNS).

Factors determining the type of repair

A-Type of damaged cells

1- Labile cells:

These cells continuously divide through life even without a stimulus. They have short G0 phase. Labile cells include:

- Surface epithelia of skin and mucous membranes.
- Hematopoietic and lymphoid tissue.

2-Stable cells (quiescent cells):

These cells divide only in presence of a stimulus. They remain in the G0 phase for long periods but retain the capacity to enter the mitotic cell cycle if in need i.e. following injury. Stable cells include:

- Parenchymal cells (liver, kidney, pancreas...etc).
- Mesenchymal cells as fibroblasts, osteoblasts, chondroblasts, smooth muscle and endothelial cells.

3- Permanent (non-dividing) cells:

These cells have no capacity for division in postnatal life. Injury to these cells is repaired by connective tissue deposition. Permanent cells include:

- Cardiac muscle cells.
- CNS.

B-Severity of injury

Factors affecting quality of repair:

a) Local Factors:

- Local ischemia delays repair.
- Persistent infection delays repair.
- Presence of foreign bodies delays repair.

b) General (Systemic) Factors:

- Age: Repair is better in younger ages.
- Nutritional deficiencies including proteins, vitamin C and some minerals as zinc (zinc is important for collagen synthesis).
- Cytotoxic drug therapy delays repair
- Endocrine diseases as diabetes mellitus & Cushing syndrome leads to defective repair.

I- REPAIR BY REGENERATION

Definition:

Replacement of the damaged tissue by new healthy tissue of the same type.

CELLS CAPABLE OF REGENERATION:

1-Labile cells

2-Stable cells

EXAMPLES OF REGENERATION:

1- REGENERATION OF SKIN AND MUCOUS MEMBRANE:

a) Abrasion: Superficial injury → complete regeneration.

b) Skin wound: which includes injury of epidermis and dermis. The epidermis regenerates and the dermis undergoes healing by fibrosis

2- REGENERATION OF LIVER CELLS:

Mild parenchymal liver injury not disturbing the extracellular hepatic framework (e.g. in acute viral hepatitis) leads to complete regeneration restoring the normal liver structure.

3- HEALING OF BONE FRACTURE:

Mechanism of Healing: The following steps occur between the fracture ends of bone

1) Transient vasoconstriction
2) Hematoma formation
3) Procallus formation: granulation tissue invades the area within one week. It consists of capillaries, fibroblasts, few collagen bundles and inflammatory cells.
4) Provisional callus: some mesenchymal cells differentiate into chondroblasts → cartilage islands & other mesenchymal cells differentiate into osteoblasts → osteoid tissue (woven bone) without calcification.
5) Permanent callus: the woven (nonlamellar) bone is gradually removed by osteoclasts and replaced by lamellar bone which undergoes calcification.
6) Remodeling: through the action of osteoblasts and osteoclasts.

Causes of Defective (Imperfect) Bone Healing & failure of bony union:

Some conditions may lead to nonunion, weak union or fibrous union (pseudoarthrosis):

A) Local factors:

a) Inadequate immobilization or malalignment.
b) Pathological fracture e.g. due to bone tumor.
c) Soft tissue interposition between the fracture ends.
d) Ischemia.
e) Infection.

B) General factors:

a) Old age
b) Nutritional deficiency
c) Diabetes mellitus.

II- HEALING BY FIBROSIS

Definition:

Replacement of damaged tissue by **granulation tissue** which matures into fibrous tissue then finally scar.

Mechanism of fibrosis:

- The process starts by formation of granulation tissue (fibroblasts & capillaries), which matures into fibrous tissue by deposition of collagen bundles followed by remodeling.
- Granulation tissue is painful and appears moist, red (richly vascularized) and granular, while fibrous tissue is firm & grayish (hypovascular) and finally the scar is avascular.
- The process of granulation tissue followed by fibrosis runs along the following steps:

  1- Angiogenesis (neovascularization): Formation of new capillaries occurs as follows:

  a) Proteolytic degradation of the basement membrane of the parent vessel to allow for migration of endothelial cells, which proliferate forming solid endothelial buds.

  b) Canalization (maturation) of endothelial buds to form capillary tubes which anastomose with each other.

  2) Fibrogenesis:

  a) Migration of fibroblasts to the site of injury followed by fibroblast proliferation.

  b) Fibroblasts secrete ECM proteins (fibronectin & proteoglycan) followed by type III collagen (thin fibrils) which later becomes replaced by stronger type I collagen (thick fibrils).

  3) Remodeling to form the permanent scar. Some fibroblasts acquire smooth muscle contractile function called myofibroblasts to minimize the scar size.

EXAMPLES OF HEALING BY FIBROSIS

1- HEALING OF WOUNDS

Types Of Wound Healing

A) Healing by Primary Union(First Intention)	B) Healing by Secondary Union(Secondary Intention)
• Type of wound: clean, non-gaping e.g. surgical incision • Mechanism of healing: a)Day 1: The narrow wound gap is filled with clotted blood and covered by a scab b)Day2: Epidermal regeneration occurs at both edges. The process is complete within 1-2 days. Exudation of neutrophils appears in the wound gap. c)Day3: Macrophages replace neutrophils and start phagocytosis & secretion of growth factors. d)Day4,5: Granulation tissue arises from the wound edges & fills the gap. Collagen fibrils start to appear. e)Second to fourth week: -The surface scab separates (by the end of the 2nd week) -Maturation of granulation tissue into fibrous tissue. Finally the wound consists of a small mature scar covered by regenerated epidermis. • Complications: Less common	• Type of wound: gaping, infected • Mechanism of healing: Healing is basically similar to first intention, but differs in: a) Necrotic debris, clots & inflammatory cells (neutrophils & macrophages) are more extensive. Phagocytosis takes longer time & therefore the process of healing takes a longer period. b) Epidermal proliferation starts early, but fails to reconstitute the epidermal covering, except after filling the gap with granulation tissue. By this time the epidermal cells can grow over the surface of granulation tissue to complete the process of epidermal regeneration. c) The amount of granulation tissue is much larger, and consequently the scar is big. d) Wound contraction is a major difference; an action done by myofibroblasts. • Complications: More common.

Complications of Wound Healing : More common in secondary union.

1) Cosmetic deformities due to extensive scarring.

2) Functional problems e.g. due to contracture of scars across joints.

3) Keloid:

- It is a claw like scar whose boundaries go beyond the wound margins. (DD. Hypertrophic scar)

- It is due to overdone repair, which occurs, in some susceptible persons. It recurs after surgical excision but shrinks by irradiation.

4) Epidermoid cyst (implantation cyst): It is a cyst filled with keratin. It is due to proliferation of epithelial cells that become entrapped within the depth of the wound during epithelial regeneration.

5) Chronic ulcer, chronic fistula or chronic sinus

6) Carcinoma may rarely develop from scar; particularly squamous cell carcinoma on top of scars of burns known as **Marjolin's ulcer**.

2- HEALING OF LIVER

- Healing of liver by fibrosis is called liver cirrhosis.
- Cirrhosis is **defined** as Progressive diffuse necrosis of liver cells, associated with framework destruction, followed by healing by both regeneration of hepatocytes (in the form of hepatic regeneration nodules) and fibrosis, i.e. the normal hepatic architecture and lobular pattern cannot be restored.

GROSS:

- **Size:** Commonly reduced (shrunken).
- **Consistency** is firm due to fibrosis.
- **Surface & cut section** are nodular. According to size of regeneration nodules, cirrhosis is classified into:

a) Micro-nodular cirrhosis: Regeneration nodules are 2-3 mm in diameter.

b) Macro-nodular cirrhosis: Regeneration nodules are more than 3 mm in diameter and may reach up to 6 cm. The prognosis is worse than micronodular type.

c) Mixed micro and macro nodular cirrhosis

MICROSCOPY: Loss of normal architecture and replacement by:

- **Regeneration nodules**: These consist of proliferating liver cell plates with an irregular sinusoidal pattern. Central veins are absent or eccentric.
- **Fibrous septa** around the regeneration nodules showing chronic inflammatory cells and proliferating bile ducts.

CHAPTER 5 DISORDERS OF BLOOD FLOW

HYPEREMIA

HYPEREMIA: This is active process of arterial vasodilatation increasing arterial blood flow to an organ.

Physiologic: during exercise
Pathologic: in inflammation

CONGESTION

CONGESTION: This is passive dilatation of veins due to venous outflow obstruction. It may be local or general congestion and each may be acute or chronic.

1-ACUTE LOCAL VENOUS CONGESTION

Etiology: Sudden occlusion of a vein by thrombus, ligature or strangulation...etc.

Effects:

- Edema
- Hemorrhage.
- Rarely infarction

2-CHRONIC LOCAL VENOUS CONGESTION

Etiology: Gradual incomplete venous occlusion as in cases of:

- **Pregnancy:** Uterine enlargement → gradual compression of iliac veins → congestion and edema of leg veins.
- **Mitral stenosis and Left ventricular failure:** → chronic pulmonary congestion.

Effects:

- Oedema
- Hemorrhage
- Stasis predisposes to thrombosis
- Gradual opening of collaterals
- Development of varicosity (thickening, dilatation, elongation and tortuosity of the chronically congested veins).

Example: Chronic Venous Congestion of The Lungs:

Etiology: Mitral stenosis and left ventricular failure.

Gross:

- Early the lungs are dark red, moist and heavy.
- Later lungs appear brownish (hemosiderin) & indurated (firm) due to fibrosis.

Microscopy:

- Early the inter-alveolar capillaries are congested, accompanied by edema & hemorrhage. Heart failure cells (macrophages engulfing hemosiderin) are seen.
- Later, hemosiderin is liberated from dead macrophages associated with some fibrosis

3-ACUTE GENERAL VENOUS CONGESTION

Etiology: Acute heart failure.

4-CHRONIC GENERAL VENOUS CONGESTION

Etiology: Right ventricular failure.

THROMBOSIS

Definition:

A thrombus is a solid insoluble mass formed inside the cardiovascular system during life from circulating blood elememts. It primarily consists of platelets, fibrin entangling blood cells.

Etiology: VIRCOW'S TRIAD

1) ENDOTHELIAL INJURY:

Causes of endothelial injury include:

- Atherosclerosis.
- Traumatic injury of arteries and veins.
- Inflammations (phlebitis, arteritis, endocarditis).

Endothelial injury is an important cause of thrombosis due to exposure of subendothelial collagen, to which platelets adhere firmly.

2) ALTERATION IN THE BLOOD FLOW (STASIS AND TURBULENCE):

STASIS (SLOWING): As in varicose veins. Stasis → deviation of platelets from the axial blood stream → contact with the exposed collagen →aggregation.

TURBULENCE OF BLOOD: As in aneurysm. Turbulence is distortion of the blood stream (eddy current)→the blood stream abnormally hits the vascular or cardiac lining→ deviation of platelets + endothelial damage.

3) HYPERCOAGULABILITY OF BLOOD:

- **Congenital:** lack of natural anticoagulants: antithrombin III, protein S or protein C.
- **Acquired:** in cases of oral contraceptives, hyperlipidemia, disseminated cancer, late in pregnancy, & severe burns.

MECHANISM OF THROMBOSIS:

1) Exposure of subendothelial collagen & release of endothelial thrombotic factors.

2) Adhesion of the platelets to the exposed collagen. This is mediated by von Willebrand factor (factor VIII), which acts as a bridge between platelet surface receptors & collagen.

3) Platelet aggregation (which may be reversible). However, with progressive increases of ADP + the secretion of thromboxane A2 (TXA2) from the platelets → platelet contraction → irreversible mass of aggregated platelets

4) Platelet Factor 3 is activated and converts prothrombin into thrombin.

5) Thrombin leads to transformation of fibrinogen into fibrin. The end result is a platelet/ fibrin plug (thrombus).

COMPOSITION OF THROMBI:

Alternating lamellae of platelets (called lines of Zahn) and fibrin entangling RBCs.

CLASSIFICATION OF THROMBI:

1) According To Color:

a) Pale: They predominantly consist of platelets with little fibrin.

b) Red: They consist predominantly of fibrin with many RBCs.

c) Mixed

2) According To Presence Or Absence Of Bacteria:

a) Aseptic: containing no bacteria.

b) Septic: as in cases of septic thrombophlebitis

3) According To The Site Of Thrombosis:

a) Arterial Thrombi

b) Cardiac Thrombi:

- **Valvular** thrombi (Vegetations): These are small thrombi developing on inflamed valves as in rheumatic endocarditis or bacterial endocarditis.
- **Atrial** thrombi in case of atrial fibrillation
- **Ventricular** mural thrombi develop opposite myocardial infarction.

c) Venous Thrombi: more common than arterial due to slower venous circulation & because veins are thin walled more liable to injury. Two main types of venous thrombosis:

- **Phlebothrombosis:** This is thrombosis in noninflamed veins.
- **Thrombophlebitis:** This is thrombosis in inflamed veins.

FATE AND COMPLICATION OF THROMBI:

1) SEPTIC THROMBI: →Fragmentation by proteolytic enzymes released due to infection →septic emboli that circulate in the blood → pyemic abscesses (**pyemia)**

2) ASEPTIC THROMBI:

a) Lysis of early small thrombi may occur by fibrinolysins.

b) Organization (fibrosis) due to invasion of the thrombus by granulation tissue.

c) Recanalization: The granulation tissue that invades the thrombus consists of fibroblasts and capillaries. Capillaries may form wide anastomosing channels that cross between the two ends of the thrombus to establish some vascular continuity.

d) Dystrophic calcification

e) Embolization: The effects of aseptic emboli depend on the efficiency of collaterals:

- **With poor collaterals →** ischemic necrosis (infarction).
- **With good collaterals →** no major effects.

iii) Propagating thrombi may lead to:

- **Ischemia** (if arterial)
- **Congestion** & edema (if venous)

EMBOLISM

Definition: An embolus is an insoluble mass circulating in the blood. It becomes impacted in a blood vessel. Origin & types of emboli include:

A) THROMBOEMBOLISM

Etiology: Fragmented thrombi.

Sites of impaction of the emboli may be pulmonary, portal, systemic or paradoxical

-Pulmonary Embolism:

Source & course: Emboli are derived from thrombi of systemic veins, reach the venae cava and finally become impacted in pulmonary arteries. Most common source is DVT.

Effects:

1-Large emboli are impacted in the main pulmonary trunk or the main pulmonary branches (massive pulmonary embolism) → sudden death from acute heart failure.

2-Medium-sized emboli are impacted in the medium-sized & small branches:

- With good collateral flow (bronchial artery), no effects.
- With poor collateral flow (inadequate bronchial artery flow) infarction develops.

3-Very small emboli pass unnoticed.

-Portal Embolism: Emboli are derived from the mesenteric or splenic veins and are impacted in the portal circulation.

-Systemic Embolism: Emboli are derived from thrombi of pulmonary veins and left side of heart → systemic arterial circulation & become impacted in different sites as cerebral, renal, splenic & hepatic arteries.

-Paradoxical Embolism: Emboli circulating in the systemic veins may not cause pulmonary embolism and instead lead to systemic embolism by one of two mechanisms:

1-Very small emboli may by-pass the pulmonary capillaries & reach left side of heart

2-Emboli pass from right to left side of the heart in some cases of congenital septal defects (ASD and VSD).

B) FAT EMBOLISM

Aetiology: Minute fat globules reach the circulation in cases of:

- Fracture of long bones: Bone marrow fat may reach circulation through injured vessels
- Skin burns.

C) AMNIOTIC FLUID EMBOLISM

- A rare condition occurring in one every 50.000 to 80.000 deliveries. It is a major cause of maternal mortality
- Infusion of amniotic fluid into the maternal circulation may be induced by vigorous uterine contractions.

D) GAS (AIR) EMBOLISM

a) Single embolism: as in case of injury of a neck vein → suction of atmospheric air → air bubbles reach the superior vena cava → right ventricle frothing → acute heart failure.

b) Multiple embolism: It occurs in Caisson disease or decompression sickness: In divers the high atmospheric pressure leads to dissolution of high concentrations of atmospheric gases in their blood. If divers are decompressed too quickly; these gases come out in the circulation in the form of bubbles. Occlusion of several vessels including the cerebral vessels leads to serious ischemic effects.

ISCHAEMIA

Definition: This is reduction of arterial blood supply to a tissue.

Types:

A) ACUTE ISCHEMIA (Sudden Complete Arterial Occlusion):

Causes:

1) Thrombosis
2) Embolism } the most 2 common causes of acute ischemia

3) Surgical ligature of an artery

4) Strangulation of vessels as those of intestine in case of strangulated intestinal obstruction (strangulated hernia, intussusception and volvulus).

5) Twisting of vessels as those of ovary and testis.

Effects: Effects of arterial occlusion depend on the efficiency of collaterals:

1) Good collaterals → no effects.

2) Poor collaterals →infarction

B) CHRONIC ISCHEMIA (Gradual Incomplete Arterial Occlusion):

Causes:

1) Atherosclerosis

2) Endarteritis obliterans; as in chronic inflammation

3) Arterial compression e.g. by tumors.

Effects:

1) With good collaterals → no effects.

2) With poor collaterals → infarction.

INFARCTION

Definition:

An area of ischemic necrosis due to sudden ischemia. The type of necrosis is coagulative except in CNS infarction, which is liquefactive.

Aetiology:

1) Arterial occlusion by thrombus or embolus represents about 99% of cases.

2) Extensive venous congestion may rarely lead to ischemia

Types of infarcts:

1) **Pale anemic infarction:**
   - **In case of arterial occlusion.**
   - **In organs supplied by a single blood supply.**
   - **In solid organs** as heart & kidney, the blood within the ischemic area are squeezed outside the area; thus the infarct appears pale.

2) **Red hemorrhagic infarction:**
   - **In case of venous occlusion** (with or without arterial occlusion).
   - **In organs with double blood supply like lung.**
   - **In loose tissues like lung.**

General pathological features of infarcts:

Gross Features:

- The infarct is usually pyramidal or wedge- shaped with its apex pointing at the occluded vessel and its base at surface of the organ. This is due to the fan-shaped distribution of end arteries.
- When the infarct base is a serosal surface (pleura, pericardium or peritoneum), it shows fibrinous inflammation.
- Margins of the infarct are hyperemic due to inflammation.
- Early the infarct is swollen, but later it becomes contracted due to healing.
- Infarcts may be pale or hemorrhagic

Microscopic Features:

- Infarcts of all organs except CNS consist of coagulative necrosis. The necrotic cells retain their structural outlines for sometime but later become structureless. CNS infarcts are structureless from the start (liquefactive necrosis).
- The margins of the infarct show acute inflammation.

GANGRENE

Definition: Gangrene is infarction followed by putrefaction.

Aetiology:

1) **Causes of Necrosis:**

- Acute Ischemia
- Bacterial infections

2) **Putrefaction:** It is caused by action of certain bacteria (saprophytes), which normally exist in the human body but cannot act except on dead tissues. These bacteria decompose the dead tissue leading to liberation of hydrogen sulphide gas (foul odor). Reaction between hydrogen sulphide and iron of blood leads to formation of iron sulphide, which gives the gangrenous tissue its black discoloration.

Types of gangrene:

1-Dry gangrene 2-Moist gangrene 3-Infective gangrene 4- Gas gangrene.

1-DRY GANGRENE

Pathogenesis:

Dry gangrene is due to arterial occlusion, while veins are patent. Usually occurs in limbs. Toxemia is mild.

Pathological Features:

1) The affected limb appears dry, shrunken, black and mummified.
2) Line of demarcation: This is a prominent red zone of acute inflammation seen at the margin of the black gangrenous area. It is due to irritant products released from the dead gangrenous tissues.
3) Line of separation: This is a groove that appears in the vicinity of the line of demarcation. It gradually deepens until the dead gangrenous part separates from the viable (living) tissues (autoamputation).

Examples:

- Senile gangrene (commonest example)

SENILE GANGRENE

Predisposing factors:

- At old age there is gradual narrowing of arteries due to atherosclerosis.
- At old age, weak cardiac action leads to low blood supply.
- Because of the above factors ischemia is common aggravated by wearing tight shoes. Gangrene usually starts at the big toe

2- MOIST GANGRENE (WET GANGRENE)

Moist gangrene occurs when both artery and vein are occluded (as limb tight tourniquet) and in organs rich in fluids like intestine. Toxemia is marked. Line of demarcation is poor & self-separation (auto-amputation) does not occur as in dry gangrene. The main differences between dry & moist gangrene are listed in this table:

DRY GANGRENE	MOIST GANGRENE
1) Due to arterial occlusion with patent vein. 2) Occurs in limbs in cases of: • Senile gangrene. 4) Does not occur in internal organs. 4) Mild toxemia. 5) Gangrenous part is dry and mummified. 6) Prominent line of demarcation. 7) Line of separation.	1) Due to occlusion of both artery and vein. 2)Occurs in limbs in cases of: • Tight tourniquet. 3) 4) Occurs in internal organs (intestine). 4) Severe toxemia. 5) Gangrenous part is edematous & swollen . 6) Poor line of demarcation. 7) No line of separation.

DIABETIC GANGRENE

Diabetics are very prone to gangrene because:

1-Diabetes leads to atherosclerosis, which may be complicated by thrombosis and ischemia.

2-Trophic changes (due to sensory loss) make slight injuries pass unnoticed.

3-Sugar in tissues and low immunity favor infection → fluid exudation & vascular thrombosis.

Pathology:

Diabetic gangrene may start dry then becomes moist. The exudative changes due to infection make the area edematous and moist. The gangrenous process is accompanied by severe toxemia and limb amputation may be lifesaving. In most of cases it starts in the big toe and then progresses with no tendency towards demarcation or self-separation.

3-INFECTIVE GANGRENE

It is considered a subtype of moist gangrene. It is called infective gangrene because necrosis is caused by bacteria followed by putrefaction by saprophytes. Examples of infective gangrene:

1) **Lung gangrene** due to putrefaction of lung abscess.
2) **Bed Sores:** These are skin ulcers that develop over bony prominences (sacrum and greater trochanters) in cases of prolonged recumbence due to paralysis, bone fractures or coma. They are due to ischemic necrosis and secondary bacterial infection.
3) **Cancrum oris:** This is oral gangrene affecting debilitated children caused by spirochete called Borrelia Vincenti.

4- GAS GANGRENE

Definition: A subtype of infective gangrene characterized by production of several **gases** (hydrogen, carbon dioxide, hydrogen sulphide…) It is commonly fatal due to severe **toxemia.**

Etiology: It is due to contamination of **deep wounds (**with certain **clostridia spores,** which are anaerobic organisms that normally exist in the intestines of man and animals and can therefore contaminate the soil (through fecal material). Common examples of gas gangrene are seen in battle casualties and agricultural accidents.

EDEMA

Definition:

Edema is accumulation of abnormal amounts of fluid in the intercellular tissue spaces and/or body cavities. Edema fluid may be transudate or exudate or lymph.

TRANSUDATE	EXUDATE
• Low protein content below 3g/dl	High protein content above 3g/ dl
• Protein content mainly albumin	Protein content mainly fibrinogen
• Does not clot (no fibrinogen)	Undergoes clotting
• Low specific gravity below 1015	High specific gravity above 1015
• Poor cellularity.	Rich in inflammatory cells
• Ex. Obstruction	Ex. Inflammation

Causes & pathogenesis of edema:

1) Increased Capillary Hydrostatic Pressure as in cases of venous congestion

2) Decreased plasma Osmotic Pressure due to hypoproteinemia

3) Increased Tissue Osmotic Pressure

4) Increased Capillary Permeability as in inflammation

5) Sodium and water retention

6) Lymphatic Obstruction as in cases of:

- **Filariasis** (the adult parasites live inside lymphatics). Edema affects limbs & genitalia. The affected limb may be massively swollen (elephantiasis).
- **Lymphatic permeation by malignant cells** as in breast cancer → breast edema.
- **Surgical removal of lymphatics** (as in cases of radical mastectomy which is surgical removal of breast & axillary lymphatics for treatment of breast cancer)→ Lymphatic edema (affects arms in case of radical mastectomy).
- **Post-irradiation** (for treatment of cancer): Irradiation may lead to severe fibrosis ending in lymphatic obstruction.
- **Lymphangitis and lymphadenitis**.
- **Congenital hypoplasia of lymphatics** (Milroy's Disease).

Classification: types of edema:

1-Localized edema:

a) Inflammatory edema (due to acute inflammation).

b) Obstructive edema: venous & lymphatic subtypes:

- **Venous obstruction**:
  - Edema of leg due to venous thrombosis or late in pregnancy.
  - Lung edema due to left sided heart failure
- **Lymphatic edema** due to lymphatic obstruction.

2-Generalized edema (anasarca):

a) Cardiac edema due to right sided heart failure.

b) Nutritional edema due to hypoproteinemia in cases of:

- Malnutrition.
- Malabsorption.
- Liver cell failure

c) Renal edema:

Nephrotic syndrome.

HEMORRHAGE

Definition: Escape of blood outside the cardiovascular system.

Aetiology:

1- Local causes of bleeding as:

- Traumatic injury of vessels: accidents, surgery.
- Erosion of vessels e.g. in case of malignant tumors, tuberculosis & peptic ulcers.
- Rupture of aneurysm
- Local venous congestion.

2- General Causes of bleeding:

- Hypertension and general venous congestion.
- Blood diseases as hemophilia, purpura and leukemia.
- Vitamin C or K deficiency

Types of hemorrhage:

1) External Hemorrhage:

- Epistaxis: bleeding from the nose.
- Hemoptysis: coughing blood.
- Hematemesis: vomiting of blood
- Hematuria: blood in urine

2) Internal Hemorrhage: This is bleeding into body cavities

a) Hemothorax: hemorrhage in the pleural sac

b) Hemopericardium: hemorrhage in the pericardial sac.

c) Hemoperitoneum: hemorrhage in the peritoneal sac.

d) Hematocele: hemorrhage inside tunica vaginalis sac

e) Hemarthrosis: hemorrhage inside joint cavities.

3) Interstitial Hemorrhage: This is hemorrhage in the interstitial tissue spaces.

Effects of hemorrhage:

a- **Chronic (repeated) blood loss:** as in cases of bilharziasis → iron deficiency anemia.

b- **Rapid blood loss:** The effects depend on the amount of hemorrhage:

- **Very small amount**: → No effect.
- **Moderate amounts** less than 750-1000 ml of blood: Compensation from bone marrow.
- **Massive amounts** more than 1 liter lead to shock

SHOCK

Definition: Shock is sudden acute widespread tissue hypoperfusion.

Clinical picture:

- Hypotension.
- Weak rapid pulse.
- Shallow rapid respiration
- Oliguria or anuria.
- Patient is restless and anxious.
- Skin is pale, cool and sweaty (except in septic shock the skin is warm and flushed).

Types , causes & pathogenesis of shock:

1) Hypovolemic Shock:

Pathogenesis: It is due to sudden reduction of blood volume & hence fall of blood pressure & reduction of cardiac output. Causes:

a- Severe hemorrhage (post hemorrhagic shock), due to trauma, surgery, blood diseases... etc.

b- Severe fluid loss (dehydration) in cases of

- Severe diarrhea or vomiting.
- Severe burns due to loss of fluid from damaged blood vessels

2) Cardiogenic shock:

Pathogenesis: It is due to failure of myocardial pump and hence low cardiac output & fall of blood pressure.

Causes:

1-Myocardial infarction.

2-Rupture of a valve.

3-Severe arrhythmias.

4-Cardiac tamponade.

3) Shock Due to Peripheral Pooling of the Blood:

It is due to peripheral vasodilatation leading to peripheral pooling of blood at the expense of vital organs. Causes:

a) **Septic shock (Endotoxic shock)**
   It is due to gram negative bacterial infections (and less commonly gram positive bacteria), as in cases of septicemia caused by E coli, streptococci, meningococci.
b) **Neurogenic shock** due spinal cord injury or anesthesia resulting in neurogenic mediated vasodilatation.
c) **Anaphylactic shock:** type I hypersensitivity.

CHAPTER 6 INFECTIONS

HYPERSENSITIVITY

Definition: A harmful immune response against irritants leading totissue destruction.

I- ANTIBODY MEDIATED IMMUNE RESPONSE

1-TYPE I HYPERSENSITIVITY (Immediate Hypersensitivity)

Mechanism:

Introduction of the antigen for the first time stimulates IgE formation, which becomes fixed to the surface of mast cells. Re-exposure to the same antigen elicits reaction with IgE fixed on the mast cell surface resulting in their burst and liberation of histamine and other chemical mediators leading to:

- Vasodilatation and peripheral pooling of blood
- Allergic inflammation characterized by excess fluid exudate (edema) and eosinophils
- Bronchospasm
- Increased mucus secretion by mucous glands

Examples:

1-Anaphylactic Shock
2-Bronchial asthma
3-Urticaria

2-TYPE II HYPERSENSITIVITY (Cytotoxic Hypersensitivity)

Mechanism:

The antibodies (IgG and IgM) combine with the antigen producing immune complex leads to target cells lysis.

Examples:

1-Incompatible blood transfusion.

2-**Rh incompatibility** (erythroblastosis foetalis).

3-**Autoimmune hemolytic anemias**.

3-TYPE III HYPERSENSITIVITY (Immune Complex Reaction)

Mechanism:

- The antibodies (IgG and IgM) combine with the antigen producing immune complex
- The immune complexes become deposited in the vascular basement membranes.
- Complement activation leads to lysis and destruction of the basement membrane.

Examples:

1-Acute proliferative post-streptococcal glomerulonephritis.

2-Some autoimmune diseases as SLE.

II-CELL MEDIATED IMMUNE RESPONSE

TYPE IV HYPERSENSITIVITY (Delayed Hypersensitivity)

Mechanism:

- The antigen stimulates T lymphocytes→Sensitized T lymphocytes produce cytotoxic lymphokines causing tissue necrosis.

Examples:

1) **Caseous necrosis in tuberculosis.**
2) **Cell-mediated graft rejection**.

BACTERIAL INFECTIONS

INTRODUCTION

Effects of bacterial infection on blood:

a) Bacteremia. b) Toxemia c) Septicemia d) Pyemia

BACTERAEMIA

Definition: This is blood invasion with bacteria only.
Pathogenesis: Bacteremia can occur in the following conditions:
1-After tooth extraction (Streptococcus viridans bacteria).
2-Blood spread of a small number of bacteria derived from a septic focus as tonsillitis & sinusitis.
3-During the incubation period of some bacterial diseases as typhoid.
Effects:
1-**In normal individuals**: no harmful effects.
2-**In susceptible individuals**: the bacteria localize in tissue causing lesions. e.g.Streptococcus viridans that reach the blood after tooth extraction can cause subacute infective endocarditis on top of rheumatic valvulitis.

TOXAEMIA

Definition:
This is the circulation of bacterial toxins in the blood. These toxins may be endotoxins (released only from dead bacteria like E coli and typhoid) or exotoxins (released from alive bacteria like cholera)

Effects:
a) General: Fever, weakness, pallor, headache, rigors.
b) Local: Degenerations and **Tissue necrosis** mostly affect parenchymal cells as liver, kidney & heart → multiple system organ failure.

SEPTICAEMIA

Definition:
A very serious commonly fatal condition in which bacteremia is accompanied by severe toxemia.
Aetiology:
1-**Causative bacteria:**
a)**Cocci** as Strept hemolyticus (most common cause of septicemia), staphylococci & gonococci.
b)**Bacilli** as Bacillus anthrax & Bacillus proteus.
2-**Predisposing factor:** Low immunity as diabetics, terminal cancer & immunosuppressive therapy

Effects:

1-Effects of Toxemia

2-Vascular & Hematological Disorders:

a)Blood: Hemolysis of RBCs .

b)Capillary hemorrhages (due to capillary destruction by bacterial toxins & enzymes).

PYAEMIA

Definition:

It is the development of multiple small abscesses (pyaemic abscesses) within one or more organs caused by the circulation of septic emboli derived from septic thrombi. Commonly fatal

Mechanism (pathogenesis):

- The condition starts by development of septic thrombi, most commonly in veins in cases of septic thrombophlebitis and less commonly in heart from septic vegetations in case of acute infective endocarditis. The causative bacteria are usually Staphylococcus aureus.
- Proteolytic enzymes derived from inflammatory cells will cause fragmentation of the septic thrombus → septic emboli.
- Septic emboli (multiple) will circulate in the blood, until they get impacted in the small blood vessels of organs.
- Multiple small abscesses (pyemic abscesses) will develop in the vicinity of impacted emboli i.e adjacent to small vessels in the peripheral parts of organs.

Pathological Features:

1-Grossly:

Pyemic abscesses are multiple, small & superficially located within the affected organ.

2-Microscopically: Describe abscess.

EXAMPLES OF BACTERIAL INFECTIONS

TUBERCULOSIS

Definition: Tuberculosis is a chronic infectious granulomatous disease caused by Mycobacterium tuberculosis.

Aetiology:

- **Predisposing factors:** Tuberculosis is common in low socio-economic standards with poor housing conditions (leading to low natural resistance).The disease is common in Egypt.
- **The causative bacteria:**
  - The disease is caused by Mycobacterium tuberculosis (tubercle bacilli).
  - There are several types of these tubercle bacilli, but only two types can cause disease in man: 1) Human tubercle bacilli and 2) Bovine tubercle bacilli.
  - Tubercle bacilli are Gram-positive, acid-fast bacilli, best stained with Ziehl-Neelsen stain.
  - The bacteria consists of an outer lipid capsule covering a body composed of a polysaccharide and a protein component (tuberculoprotein).
  - The bacteria do not produce toxins, but their tuberculoprotein is strongly antigenic and the destructive lesions of tuberculosis are mainly attributed to **hypersensitivity type IV** reaction.
- **Mode of infection:** Tubercle bacilli reach the body either by inhalation or swallowing. Rarely the organisms are inoculated through skin abrasions.

1-Human Tubercle Bacilli: These bacteria are expectorated in sputum of patients having pulmonary tuberculosis. Bacteria can contaminate dust & survive for long periods in dust since they are resistant to drying. They infect other persons by:

a) Inhalation of contaminated dust leads to lung tuberculosis.

b) Swallowing of contaminated dust leads to tuberculosis of tonsils or intestine.

c) Inoculation through skin is extremely rare.

2-Bovine Tubercle Bacilli: These bacteria exist in milk of tuberculous cows and are transmitted to man by swallowing of infected milk causing tuberculosis of tonsils or intestine.

TISSUE REACTION IN TUBERCULOSIS:

Infected tissues show granuloma called **(TUBERCLE):**

It is the basic lesion of tuberculosis. It develops around the tubercle bacilli. Several tubercles are formed and as they enlarge, they fuse together.

Mode of Formation of Tubercles:

1-Neutrophils are attracted within few hours to the polysaccharide fraction of the bacilli. They may engulf the bacilli but cannot digest them since the bacilli are protected by their lipid capsules, while neutrophils lack the enzyme lipase. Neutrophils die rapidly.

2-Macrophages are attracted to the lipid part of the bacilli & accumulate gradually. They engulf the bacteria & since macrophages contain lipase enzyme, they digest the lipid capsule of these bacteria→ liberation of tuberculoprotein in the cytoplasm of macrophages→ alteration of macrophages which become swollen and pink resembling epithelial cells and are therefore termed **epithelioid cells.**

3-Some epithelioid cells fuse together forming giant cells called **Langhan's giant cells**

4-T-lymphocytes Sensitized T lymphocytes accumulate around the epithelioid cells in 10-14 days and release cytotoxic lymphokines which are responsible for development of **tissue caseous necrosis**.

Gross Features:

Tubercles are of microscopic size, but when they fuse they give rise to grossly visible small yellowish white nodules; that appear soft and cheesy due to caseation.

Microscopic Features: Each tubercle consists of:

1-Caseous necrosis caused by hypersensitivity reaction type IV (cytotoxic lymphokines). It appears in the center of the tubercle as pink structureless material. It is surrounded by epithelioid cells, giant cells and lymphocytes.

2-Epithelioid cells: Large altered macrophages with abundant pink cytoplasm (resembling epithelial cells) and large vesicular nuclei.

3-Langhan's giant cells: These are large cells with pink cytoplasm and many peripherally located nuclei forming a circle or U-shaped arch (horse shoe pattern).

4-Lymphocytes (mainly T cells) form a peripheral zone.

Fate of Tubercles:

1-Localization: With adequate immunity the lesions heal by fibrosis

a) Small lesions are totally replaced by fibrosis.

b) Larger lesions may be only surrounded by fibrosis (encapsulation), where some bacilli may remain alive and dormant within the healed lesions. If later on the body resistance is lowered, these dormant bacilli lead to reactivation of tuberculosis.

2-Spread of tuberculosis due to failure of localization.

Routes of Spread: The main routes of spread are:

1-Direct spread to the surroundings. Tubercle bacilli are non-motile. Macrophages carry the bacilli to different sites.

2-Lymphatic spread to the draining lymph nodes.

3-Blood spread: Effects depend on number of bacteria:

a) No effects may be produced if a small number of organisms reach the blood, since these bacteria are destroyed by the phagocytic cells of the different organs.

b) Isolated organ tuberculosis: The organisms settle in one or few organs causing lesions.

c) Miliary tuberculosis: A large number of bacteria reach the blood. The lungs, liver, kidneys, adrenals, serous membranes and other organs will show huge numbers of small adjacent tuberculous lesions; 1-2 mm each. The condition is rapidly fatal.

4-Intracanalicular spread: e.g. coughed sputum may spread the bacteria to larynx, tonsils, tongue....etc.

TYPES OF TUBERCULOSIS:

Primary Tuberculosis Childhood type	**Secondary Tuberculosis adult type**
• This is tuberculous infection for the first time.	• This is tuberculous infection for the second time (reinfection)
• In Egypt it mainly affects children.	• In Egypt it mainly affects adults.
• Spread of infection is more common.	• Spread of infection is less common (due to the presence of acquired immunity).
• Tissue destruction is less marked.	• Tissue destruction is more marked (due to hypersensitivity).
• Course of infection is mainly affected by innate immunity.	• Course of infection is determined by degrees of innate immunity and acquired immunity.

COMPLICATIONS OF TUBERCULOSIS: Common complications (regardless of the site):
1-Spread (see above)
2-Hemorrhage (necrotic erosion of a blood vessel)
3-Organ destruction and severe fibrosis
4-Amyloidosis (in chronic cases)
5-Recurrence (re-activation)
6- Dystrophic calcification

PRIMARY TUBERCULOSIS (CHILDHOOD TYPE)
I) PRIMARY PULMONARY TUBERCULOSIS

Etiology: Inhalation of human tubercle bacilli.
Pathology: Primary Complex:
1-Ghon's Focus: It is the initial tuberculous lung lesion:
Gross: A yellowish white lesion; 1-2 cm in diameter, commonly subpleural. It occurs anywhere in the lung, but most frequent sites are the lower aspect of the upper lobe or the upper aspect of the lower lobe.
Microscopy: It consists of several adjacent caseating tubercles
2-Tuberculous Lymphangitis: A chain of tubercles along the course of lymphatic vessels.
3-Tuberculous Lymphadenitis: The hilar lymph nodes are enlarged and show caseating tubercles.
Fate of primary pulmonary tuberculosis:
1-Localization and healing (fibrous replacement or capsulation), but living bacilli may persist within healed lesions.
2-Spread:
a)**Direct** spread to:
- Adjacent lung tissue → tuberculous pneumonia.
- Pleura → tuberculous pleurisy

b)**Lymphatic spread**.
c)**Hematogenous** : As previously described, the effects depend on number of bacteria:
- Small number→ No effect (bacteria are destroyed by organs' phagocytic cells)
- Moderate number → Isolated organ tuberculosis (one or few organs are affected)

- Large number (usually after caseous destruction of vessels) → Miliary tuberculosis.

d)**Bronchial spread:** Caseous erosion of a bronchus from Ghon's focus or hilar lymph nodes → bronchial spread → distal bronchi and adjacent lung tissue → tuberculous bronchopneumonia). Coughing of infected sputum → affection of larynx, tonsils...etc.

3-Reactivation

II) PRIMARY TUBERCULOSIS OF INTESTINE

Etiology: Swallowing of human or bovine tubercle bacilli with dust or infected milk.

Pathology: Primary complex:

1-The initial lesion usually appears in the terminal ileum and consists of a group of tubercles in the region of the Peyer's patches (where macrophages carry the bacilli to this area). The covering mucosa may undergo minimal ulceration.

2-Tuberculous Lymphangitis.

3-Tuberculous Lymphadenitis (tabes mesenterica): The mesenteric lymph nodes are enlarged and show caseating tubercles.

Fate:

1-Localization.

2-Spread:

a) Direct and lymphatic: This leads to tuberculous peritonitis.

b) Hematogenous spread leading to isolated organ or miliary tuberculosis.

III) PRIMARY TUBERCULOSIS OF TONSILS

Etiology:

Swallowing of human or bovine tubercle bacilli.

Pathology: Primary complex.

1-The initial lesion is a small focus composed of tubercles. The covering mucosa of tonsil may ulcerate.

2-Tuberculous lymphangitis.

3-Tuberculous lymphadenitis of the cervical lymph nodes which become enlarged & show caseating tubercles.

Fate: 1-Localization. 2-Spread.

IV) PRIMARY TUBERCULOSIS OF SKIN (rare)

Tubercle bacilli inoculated through a skin abrasion lead to a primary complex, which may localize or spread.

TUBERCULOUS LYMPHADENITIS

Tuberculous lymphadenitis occurs as a part of primary complex. The hilar lymph nodes are affected in case of primary pulmonary T.B, the cervical nodes in case of primary T.B of tonsils & the mesenteric nodes in case of primary intestinal T.B.

Gross Features: The affected nodes are enlarged, first discrete, then may become fused together with soft yellowish white C/S due to marked caseation forming **a Cold Abscess** (a misnomer).

Microscopy: Tubercles

Fate & Complications:

1-Localization

2-Spread:

a) Direct: from cervical lymph nodes → cervical skin sinus formation, from hilar nodes→ tuberculous pericarditis and from mesenteric nodes → tuberculous peritonitis.

b) Lymphatic spread to other lymph nodes.

c) Blood spread causing isolated organ or miliary tuberculosis.

d) Bronchial spread due to bronchial erosion from hilar nodes in case of pulmonary tuberculosis.

3-Reactivation (if immunity is lowered)

SECONDARY (REINFECTION) TUBERCULOSIS (ADULTHOOD TYPE)

This is tuberculosis in persons that have had a previous primary exposure to tuberculosis.

It may be due to one of two possibilities:

1-New exogenous infection (inhalation, ingestion).

2-Reactivation of dormant living tubercle bacilli within a healed primary tuberculous lesion.

I) SECONDARY PULMONARY TUBERCULOSIS

Aetiology:

1- Re-inhalation of human tubercle bacilli (exogenous route)

2-Reactivation of healed or capsulated Ghon's focus containing living tubercle bacilli.

Chronic Fibrocaseous Pulmonary Tuberculosis	Acute Caseous Bronchopneumonia
Occurs in patients with moderate levels of immunity and hypersensitivity.	One or more of the following factors: 1)Large dose of virulent bacteria 2)High hypersensitivity 3)Low immunity
Slow chronic course.	Acute fatal course.

A) CHRONIC FIBROCASEOUS TUBERCULOSISB (CAVITARY TUBERCULOSIS)

Gross Features:

This type of tuberculosis is essentially characterized by a cavity (or sometimes more than one cavity), most commonly in lung apex, associated with secondary lesions (acinar lesions) due to transbronchial spread. Lymph node lesions are minimal:

1-Apical Lesion:

In most cases, the lesions start in the apex of one or both lungs (more common in right lung which has a wider bronchus).

2-Basal Lesions (acinar lesions): Small caseous foci occurring in the base of lung due to transbronchial spread following caseous bronchial erosion from the apical lesion.

3-Hilar lymph nodes: insignificant. Lymphatic spread is uncommon

Microscopic Features:

1-Large areas of caseous necrosis.

2- Fibrosis & scattered tubercles (epithelioid cells, Langhan's giant cells & lymphocytes).

3-Adjacent vessels show endarteritis. Hemorrhage is common.

Complications:

1-Hemoptysis, due to erosion of vessels.

2-Rupture of the cavity into the pleural sac results in pneumothorax.

3-Spread of infection (relatively less common than primary T.B):

a) Direct leading to:

i) Tuberculous pleurisy

ii) Tuberculous pericarditis and mediastinitis.

b) Blood spread leading to isolated organ tuberculosis or miliary tuberculosis.

c) Bronchial spread:

i) Coughing of infected sputum may lead to tuberculosis of larynx, tonsils, tongue.

ii) Swallowing of this sputum causes secondary intestinal tuberculosis.

d) Lymphatic spread : Uncommon.

4-Right-sided heart failure may develop due to bilateral lung fibrosis (in bilateral cases).

5-Secondary amyloidosis (reactive systemic amyloidosis).

B) ACUTE TUBERCULOUS BRONCHOPNEUMONIA

This rare type occurs when one or usually more than one of three factors exist (large dose of virulent bacteria, low immunity or high hypersensitivity).

Gross Features:

1-The affected lung shows multiple caseous foci around the bronchioles (bronchopneumonia) that rapidly progress leading to caseous consolidation of almost the whole lung (tuberculous pneumonia). Focal liquefaction of the caseous material leads to small irregular cavities. The pleura shows tuberculous empyema.

2-The hilar lymph nodes are enlarged and caseous.

Microscopic Features:

Extensive caseation, few epithelioid cells, few Langhan's giant cells and no fibrosis.

Fate: Rapidly fatal. Miliary tuberculosis is common.

II) SECONDARY TUBERCULOSIS OF INTESTINE

Etiology: Usually due to re-ingestion of infected sputum in patients with chronic fibrocaseous pulmonary tuberculosis.

Pathological Features:

1-The lesions develop mainly in the terminal ileum and adjacent caecum. The bacilli reach the Peyer's patches (and solitary follicles of caecum) → caseous necrosis and erosion of the covering mucosa → tuberculous ulcers which are characterize by:

- Multiple.
- Edges are ragged and undermined.

- Ulcer floor is yellowish white due to caseation.
- In the terminal ileum they are transversely arranged (girdle ulcers) since the affected Peyer's patches are anatomically arranged in the form of transverse arcs.
- They heal by fibrosis.

2-The **mesenteric lymph nodes** show minimal lesions.

Complications:
1-Intestinal Hemorrhage.
2-Intestinal fistulae.
3-Perforation of the ulcers leads to septic peritonitis.
4-Spread of infection:
a) Direct and Lymphatic → tuberculous peritonitis.
b)Blood spread → isolated organ or miliary tuberculosis.
5-Fibrosis → intestinal obstruction.
6-Secondary amyloidosis.

III) SECONDARY TUBERCULOSIS OF TONSILS

It is usually caused by spread of tubercle bacilli through infected sputum. A tuberculous ulcer with undermined edges develops.

IV) SECONDARY TUBERCULOSIS OF SKIN

There are several patterns but the most common type is Lupus Vulgaris.

LUPUS VULGARIS:
- Due to blood spread (e.g. from pulmonary tuberculosis) but it may also be due to exogenous infection of previously sensitized individuals.
- The skin of face and neck is the most commonly affected site (more than 90% of cases).
- The skin shows nodules and ulcers with undermined edges.
- The lesions are precancerous.

TUBERCULOSIS OF VERTEBRAE (POTT'S DISEASE)

Aetiology:

Blood borne infection.

Pathological Features:

- Two or more adjacent vertebrae as well as the intervening discs are destroyed. Destruction of the discs is an important radiological sign that distinguishes Pott's disease from metastases. In case of metastases the vertebrae are destroyed, while the discs are spared.

D.D. SARCOIDOSIS

DEFINITION: *This is a systemic disorder, characterized by small multiple non-caseating granulomas. Commonly mistaken for tuberculosis.*

AETIOLOGY: *Uncertain, possibly an immunological disorder. Women are more commonly affected between 20-30 years.*

PATHOLOGICAL FEATURES:

Sites: *The disease is systemic affecting lungs, lymph nodes, skin, liver, spleen & other organs.*

Grossly, *the lesions appear as small multiple nodules.*

Microscopically *it is characterized by small noncaseating epithelioid cell granulomas containing Langhan's type giant cells & associated with fibrosis. The cytoplasm of giant cells may show inclusion bodies in the form of Schaumman bodies (which are round, calcified laminated bodies) and Asteroid bodies (which are pink star-shaped inclusions).*

COURSE (FATE):

1-About 65% of patients undergo spontaneous remission. Steroids are helpful in treatment.

2-Death may occur due to pulmonary fibrosis or secondary infection.

LEPROSY

Definition: Chronic infective granulomatous disease caused by Mycobacterium leprae.

Etiology: The mode of transmission of Mycobacterium leprae (lepra bacilli) is thought to be through nasal mucosa (inhalation) or through skin abrasions, after prolonged contact with a patient. Incubation period is very long, up to several years.

Types: The mildest form of leprosy is called **tuberculoid** leprosy (in patients with high resistance). The severest form is called **lepromatous** leprosy (low resistance).

SYPHILIS

Definition: Syphilis is a chronic infective disease caused by spirochaetes called Treponema pallidum.

Aetiology: The spirochaetes can be transmitted in one of 2 ways:

I) Acquired Syphilis:

a) Venereal Type (most common). Bacteria are transmitted by sexual contact.

b) Non-venereal type: 1)Touching syphilitic lesions. 2)Blood transfusion from syphilitic donor.

II) Congenital Syphilis: Transplacental transmission from syphilitic mother to her fetus.

Syphilitic Tissue Reaction :Syphilis is characterized by:

- Progressive endarteritis obliterans causing necrosis in tertiary stage.
- Chronic proliferative inflammatory reaction rich in plasma cells
- Granulation tissue and fibrosis.
- Considerable necrosis caused by endarteritis obliterans, mainly in tertiary stage.

I) ACQUIRED SYPHILIS

1-PRIMARY SYPHILIS (CHANCRE)

Onset: Lesion appears at site of infection, 2 weeks after infection. It is called chancre or hard sore. It is infective.

Sites of chancre:

a) Genitalia: penis, vulva, vagina, cervix.

b)Extragenital: lips, tongue, nipple and anus (in homosexuals).

Gross:

1-A hard painless small papule, which ulcerates. The lesion is infective. The ulcer heals by minimal fibrosis → thin scar

2-The regional lymph nodes are enlarged and discrete.

Microscopy: Syphilitic reaction.

2-SECONDARY SYPHILIS

Onset: Two months after the primary stage. It is the most infective stage.
Gross Features: The following lesions develop:
1-Skin lesions:
a) Skin rash: A generalized painless skin rash all over the body, in the form of red macules, red papules & yellowish pustules (secondary infected papules).
b) Condyloma latum: A large raised cutaneous swelling occurring in moist areas as vulva & axilla.
c) Other lesions as alopecia areata (focal loss of scalp hair).
2-Mucus patches develop in oropharyngeal, anal or vaginal mucosa. These patches may ulcerate.
3-Generalized lymph node enlargement
Microscopic picture: Syphilitic reaction.

3- TERTIARY SYPHILIS

Onset: 2-10 years after healing of the lesions of the secondary stage.
Pathology: Any organ may be affected. Lesions are destructive & include two types:
1-Gumma (Localized Affection):
Gross Picture: Single or multiple. It can occur in several sites. It is variable sized circumscribed pale yellowish gray rubbery mass.
Microscopic Picture: Gumma consists of central necrosis surrounded by syphilitic inflammatory reaction and fibrosis.
2-Diffuse Syphilitic Inflammation:
Grossly: The affected organ or tissue appears firm grayish and fibrotic.
Microscopically: Minimal scattered foci of necrosis, associated with diffuse syphilitic reaction and fibrosis.

II) CONGENITAL SYPHILIS

Etiology: It is due to transplacental infection from a syphilitic mother to her fetus.
a)Early Manifestations: These develop during the first 2 years of life.
1-Skin rash and condyloma latum.
2-Mucus patches.
3-Generalized lymph node enlargement.

4-Rhagades: Radiating scars at the angles of mouth and anus.
5-Syphilitic inflammation of organs, resulting in:
- Pneumonia alba: pale lungs showing syphilitic inflammation.
-Syphilitic cirrhosis.
6-Syphilitic osteochondritis → retardation of bone growth.

b)Late Manifestations (2-30 years):

1-Hutchinson's Teeth: The permanent central incisors are short, notched & widely separated.
2-Deafness due to affection of 8th cranial nerves.
3-Eye: Keratitis, iritis, retinitis
4-Sabre tibia (Sword tibia): The tibia is thickened and bent.
5- Palate perforation and saddle nose.
6-Neurosyphilis .

ACTINOMYCOSIS

Definition:

Actinomycosis is chronic suppurative granulomatous disease caused by gram-positive anaerobic bacteria "Actinomyces israeli", normally present in the oral cavity and intestine as harmless commensals.

Pathology:

Gross Features: Multiple abscesses open onto skin by multiple sinuses that discharge pus and bacterial colonies, the later grossly resemble sulphur granules.

Microscopy:

1-Bacterial colonies: consist of peripherally arranged red-stained clubs and central blue hyphae.
2-Inflammatory cells (neutrophils, pus cells, macrophages, lymphocytes, plasma cells) surround the colonies.
3-Granulation tissue and fibrosis are seen at the periphery.

TYPES:

1-Cervicofacial Actinomycosis: This is the most common type (60%):
2-Intestinal Actinomycosis (20%):
3-Pulmonary Actinomycosis (15%):
4-Actinomycosis of skin (5%).

FUNGAL INFECTIONS
(Mycotic Infections)

MYCETOMA PEDIS (MADURA FOOT, NOCARDIASIS)

Definition:
Fungal mycetoma is chronic suppurative granulomatous disease caused by a group of mycetoma fungi (also called Nocardia fungi).

Etiology: the fungus lives in soil & can be inoculated in the skin of the bare-footed individuals, through skin abrasions. The disease is famous in India (in Madura district) and hence the name "Madura Foot'. It also occurs in Egypt.

Gross picture:
Foot is swollen, indurated and there is widespread destruction of tissues resulting in multiple abscesses that open onto the skin by multiple sinuses discharging pus and fungal colonies which often appear as black granules.

Microscopy:
1-Fungal colonies: Grow as hyphae and largely resemble the bacterial colonies of actinomycosis.
2-Inflammatory cells: Neutrophils, pus cells, macrophages, lymphocytes and plasma cells.
3-Granulation tissue and fibrosis.

CANDIDIASIS (MONILIASIS)

Definition: This is disease caused by fungus known as "Candida albicans"

Etiology:
This fungus is a normal commensal of oral cavity, GIT, vagina and skin. It becomes pathogenic in the following conditions:
1-Prolonged broad spectrum antibiotic therapy.
2-Low immunity as in cases of
a) Immunosuppressive therapy.
b) Immunocompromization as diabetes and AIDS.

Pathology: There are several patterns:

1-Superficial Candidiasis: Most common. Usually due to prolonged antibiotic use. Manifestations:

a) Oral Thrush: White oral mucosal patches composed of fungal colonies, necrotic debris & inflammatory cells.

b) Vaginal lesions: cottage cheese like vaginal discharge.
c) Paronychia (lesions under the nails) and macerations of interdigital skin.

2-GIT Candidiasis: Most common in oesophagus; particularly in AIDS.
3-Invasive (disseminated) Candidiasis: It is due to blood spread. It is often fatal.

VIRAL INFECTIONS

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Definition: AIDS is a chronic disease caused by HIV that leads to marked immunosuppression.

Pathogenesis:

- The causative virus is an RNA virus called HIV (human immunodeficiency virus).
- The modes of transmission of HIV include:
  1-Sexual transmission:
  a) Homosexual or bisexual males (70%) b)Heterosexual partners
  2-Intravenous drug abusers.
  3-Recipients of blood or blood.
  4-Organ transplantation from a diseased donor.
  5-Maternal transmission: a) Transplacental b) Through breast milk.

Pathology:

Progressive loss of CD4 T helper cells (which have a high affinity for HIV) → marked immunosuppression. The major pathological features of AIDS include:

1-Opportunistic Infections: These are very common and include:

a)Bacterial infections as tuberculosis, atypical mycobacteriosis, salmonella & shigella infections.

b)Fungal infections: as Candidiasis (commonly disseminated) & cryptococcosis (involving CNS).

c)Viral infections: as CMV and Herpes simplex virus infections.

2-Malignant Neoplasms:

a)Lymphomas (Non-Hodgkin's B cell lymphomas).

b)Kaposi's Sarcoma: This is a malignant vascular neoplasm characterized by cutaneous & visceral lesions which grossly appear as purple patches or nodules and microscopically consist of endothelium-lined vascular channels associated with sheets of plumb spindle cells

showing slit-like vascular spaces filled with erythrocytes. Kaposi's sarcoma occurs in about 25% of AIDS patients.

3-Generalized lymph node enlargement: There is Initial B Cell (follicular) hyperplasia, followed by generalized lymphocyte depletion.

HUMAN PAPILLOMA VIRUS (HPV) INFECTION

There are many types of HPV which can cause many diseases;

1. Benign as skin warts and genital warts (types 6 and 11)
2. Malignant as squamous cell carcinoma of tongue and female cervix (types 16 and 18)

MEASLES

Etiology:

Measles is the most infectious viral disease, transmitted by droplet infection. Incubation period is 1-2 weeks.

Pathology:

1-Catarrhal inflammation of respiratory mucosa.
2-Generalized skin rash composed of macules and papules.
3-Koplik's spots: these are tiny hyperemic spots in the buccal mucosa.
4-Cervical lymph node enlargement.

PARASITIC INFECTIONS

SCHISTOSOMIASIS (BILHARZIASIS)

Definition: Bilharziasis is a chronic granulomatous disease caused by Schistosoma infection.

Etiology: The disease is endemic in Egypt and is caused by one of the following two species: 1-Schistosoma hematobium: It affects the genitourinary system. 2-Schistosoma mansoni: It affects the digestive system.

General pathological features:

Bilharzial lesions represent hypersensitivity reactions (types I and IV). The lesions include:

1-**LESIONS PRODUCED BY CERCARIA**: Acute allergic dermatitis develops at sites of skin penetration by the cercaria.

Grossly: Maculopapular skin rash.

Microscopically: Dilated capillaries, neutrophils, eosinophils and macrophages.

2-**LESIONS PRODUCED BY ADULT WORMS**: Adult worms live inside veins around bladder (S hematobium) or colon (S mansoni).

a)Dead worms → severe venous wall necrosis & inflammation causing thrombophlebitis.

b)Living worms produce:

i) Brown bilharzial pigment which is engulfed by phagocytic cells

ii)Ova.

3-**LESIONS PRODUCED BY OVA**:

a) Recurrent bleeding (due to injury by the spines of ova) leads to anemia. Bleeding is in the form of hematuria or blood passing with stools.

b) Some ova may be trapped in the wall forming **granulomas (bilharziomas)**

4-**BILHARZIAL ANTIGENS** from worms or ova → hyperplasia of lymphoid & reticuloendothelial cells.

Pathological lesions:

1-Sandy Patches:

Pathogenesis: Large numbers of ova get trapped in the submucosa, associated with dystrophic calcification→ pressure atrophy of the overlying mucosa.

Gross: Irregular grayish gritty patches covered by thin atrophic mucosa.

Microscopy: The submucosa shows a large number of calcified ova surrounded by dense fibrosis. The mucosa is atrophic.

2-Bilharzial Polyps:

Pathogenesis: A small number of ova is trapped in the submucosa surrounded by inflammation. Repetition of the process leads to mucosal elevation associated with mucosal hyperplasia and polyp formation.

Gross: Single or multiple polyps which may be sessile, pedunculated or complex branching polyps. The polyps are reddish and show granular cut surface.

Microscopy: Polyp consists of:

a) A core of connective tissue derived from the submucosa showing ova surrounded by macrophages, lymphocytes, eosinophils & fibroblasts.

b) A covering hyperplastic mucosa.

3-Bilharzial Ulcers:

Pathogenesis:

a) Shedding of the atrophic mucosa of sandy patches.

b) Ulceration of a polyp.

Gross:

Single or multiple ulcers; small or large, but usually less than 1 cm in diameter with sharp edges, granular floor and firm base.

Microscopy: Edges, floor and base of ulcers show ova surrounded by inflammatory cells and fibrosis.

4-Dense Fibrosis: In long standing severe cases, fibrosis may be extensive.

COMPLICATIONS:

1-Recurrent hemorrhages → anemia.
2-Secondary infection
3- Obstruction
4-Spread → bilharziasis of liver and sometimes lungs.
5- Carcinoma.

BILHARZIASIS OF THE URINARY BLADDER
(Bilharzial Cystitis)

1-Most common lesion is **sandy patches** followed by **ulcers.**

2- Epithelial (Urothelial) Changes (very common): The transitional mucosa has a great capability to undergo hyperplastic, metaplastic & dysplastic changes in response to chronic irritation. May be precancerous.

a) Hyperplasia.

b) Brunn's nests: These are solid buds of transitional cells present in the submucosa due to focal dipping of the hyperplastic urothelium

c) Cystitis cytica: These are cysts lined by transitional epithelium.

d) Cystitis Glandularis: These are cysts lined by mucin-secreting columnar cells. The lesion is precancerous and causes adenocarcinoma of the bladder.

e) Squamous metaplasia & Leukoplakia: Squamous metaplasia is very common. These lesions are precancerous

f) Dysplasia & carcinoma in situ. These lesions are precancerous.

BILHARZIASIS OF LARGE INTESTINE
(Bilharzial Colitis)

Most common lesion is **bilharzial polyp** formation followed by **ulcers.**

BILHARZIASIS OF LIVER
(Bilharzial Hepatic (periportal) Fibrosis)

Pathogenesis & microscopy:

1-The Portal Tracts show

1-Granulomas around the ova.

2-The venules show thrombophlebitis.

3-Angiomatoids*:* These are dilated capillaries seen in the fibrotic tracts. They represent dilated collateral channels between branches of the hepatic artery & portal veins.

4-Fibrosis

2-The Hepatic Lobules show minimal insignificant lesions. The framework (architecture) is preserved. Therefore cirrhosis does not develop

Gross features:

1-Early the liver is enlarged. Later with progressive portal fibrosis the liver becomes shrunken.

2-The fibrotic fine portal tracts appear as delicate grayish bands & the fibrotic coarse tracts appear as thick grayish collars resembling patent pipes (pipe stem fibrosis).

EFFECTS AND COMPLICATIONS:

1-Portal Hypertension:

2-Portal Vein Thrombosis

CHAPTER 7 NEOPLASIA

GROWTH DISTURBANCES

CONGENITAL:

1-Agenesis: Failure of formation of an organ e.g. absent kidney.

2-Hypoplasia: undersized organ e.g. hypoplastic kidney and infantile uterus.

3-Aplasia: failure of organ development from its premordium. The affected organ is rudimentary (e.g. rudimentary kidney, rudimentary tooth.

ACQUIRED:

1- Atrophy
2- Hypertrophy
3- Hyperplasia
4- Metaplasia
5- Dysplasia

DYSPLASIA

Definition:

Dysplasia is a non-neoplastic disordered proliferation of epithelial cells; usually induced by prolonged cell irritation. It is a precancerous condition.

Microscopic Characteristics:

- It is characterized by loss of polarity (architectural orientation of cells). Dysplastic cells are atypical looking. They show features of anaplasia like pleomorphism (variation in size and shape), enlarged dark (hyperchromatic) nuclei and increased mitotic activity.
- Degree of dysplasia: According to degree of cell atypia and extent of involvement, dysplasia is graded into:
  A- Mild (affecting lower third), reversible
  B- Moderate(affecting lower two thirds) reversible
  C- Severe. Involves the entire epithelial thickness and corresponds to carcinoma in situ. Irreversible.

CARCINOMA IN SITU

(Intraepithelial Neoplasia Intraepithelial Carcinoma, Pre-invasive Carcinoma)

Definition:

Carcinoma in situ (CIS) represents a preinvasive cancer & is characterized by severe epithelial dysplasia involving full epithelial thickness, without invasion of the basement membrane.

CIS is a microscopic change. Once the basement membrane is invaded the CIS changes into invasive malignant tumor.

Fate: Progression into invasive carcinoma occurs after some time (usually years).

NEOPLASIA (TUMORS)

Definition:

An irreversible, unlimited, autonomous self-controlled cell proliferation forming an abnormal mass. Tumors can be derived from any cells, even from permanent cells.

Microscopically any neoplasm has two basic components:

1. **The transformed (neoplastic) cells:**
   The vast majority of tumors arise from a single transformed cell i.e. monoclonal. These transformed cells are anaplastic.
2. **The supporting stroma** consist of non-transformed elements like blood vessels, connective tissue derived from the host

CLASSIFICATION OF TUMORS

A) ACCORDING TO THEIR BEHAVIOR

1) Benign neoplasms (similar to normal, have good prognosis).
2) Malignant neoplasms (dissimilar to normal, have poor prognosis).
3) Intermediate tumors (locally malignant neoplasms locally aggressive tumors).

B) ACCORDING TO TISSUE OF ORIGIN (HISTOLOGICAL CLASSIFICATION)

1) Epithelial tumors
2) Mesenchymal tumors
3) Others

CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS

BENIGN NEOPLASMS	MALIGNANT NEOPLASMS
A) TUMOR BEHAVIOR	**A) TUMOR BEHAVIOR**
1-**Rate of Growth:** Often slow.	1-**Rate of Growth:** Often rapid.
2-**Mode of Growth**: Expansile, i.e. compressing the surrounding tissues without invasion.	2-**Mode of growth**: Invasive, i.e. infiltrating and destroying the surrounding normal tissues.
3- Prognosis: a)Benign tumors do not spread	**3- Prognosis:** a)Malignant tumors spread

b)Benign tumors do not recur if well excised. c)Benign tumors are not dangerous unless: • They arise in vital organs as brain. • They arise in hollow organs (as intestine) causing obstruction. • They produce hormones as in tumors of endocrine glands. • Some benign tumors may change malignant.	b)Recurrence after surgical excision is very common either from tumor cell remnants (not removed with the excised tissue) or from a new neoplastic transformation. c)Malignant tumors are serious & cause death. **Causes of Death include**: • Local organ destruction by direct spread. • Distant organ destruction by metastases • Destruction of vital centers (brain tumors) • Obstruction of the lumen of hollow organs e.g. intestinal tumors • Organ failure
B) TUMOR STRUCTURE 1-**GROSS FEATURES:** • Tumor margins are well defined. • Cut section of the tumor is commonly homogenous with no hemorrhage or necrosis. • A tumor arising inside a solid organ appears as a well-defined capsulated mass (capsule composed of a rim of connective tissue). • A tumor arising from surface epithelia form a non-capsulated polyp (papilloma).	**B) TUMOR STRUCTURE** 1-**GROSS FEATURES:** • Tumor margins are irregular or ill-defined. • Cut section of the tumor often shows areas of hemorrhage and necrosis (heterogenous) • A tumor inside a solid organ appears as an irregular noncapsulated mass. • Tumors arising from surface epithelia appears as non-capsulated masses assuming different patterns: - Polypoid fungating cauliflower-like

	- Ulcer: raised everted edge, rough necrotic floor, and indurated base. - Diffuse infiltrating (endophytic)
2-**MICROSCOPIC FEATURES:** **a)Cell:** Cells closely mimic the corresponding normal cells. Rare mitoses. **b)architecture:** In benign tumors the tumor cells exhibit structural patterns similar to the normal tissue.	2-**MICROSCOPIC FEATURES:** **a)Cell:** **Anaplasia** characterized by: • Cellular pleomorphism: malignant cells vary in size & shape. • Nuclear pleomorphism: Nuclei may be irregular or bizarre shaped. • Nuclear enlargement & hyperchromatism: Due to increased synthesis of DNA, the nuclei appear dark (hyperchromatic) & the nucleo-cytoplasmic (N/C) ratio is increased approaching 1:1 • Nucleoli may be prominent. • Abundant mitoses & frequently abnormal mitotic figures. • Tumor giant cells containing a single large polypoid nucleus or multiple nuclei. **b) architecture**: • Malignant tumors are graded according to the degree of

	resemblance of the structural pattern of the tumor to that of the normal tissue.

SPREAD OF MALIGNANT TUMORS

MECHANISM OF SPREAD

Malignant tumors spread locally to surrounding tissues and distantly to remote sites (metastases). Mechanism of spread includes:

1) Invasion of Extracellular Matrix (ECM): The following steps are included:

- Loss of cellular cohesion: Normal cells are glued together by molecules called cadherins. Tumor cells lose the normal cadherin expression, allowing them to detach (loosen up).
- Attachment of tumor cells (through receptors) to matrix components; mainly to laminin of basement membrane and fibronectin.
- Degradation of the ECM by proteolytic enzymes secreted by the tumor cells to create passages for their migration.
- Migration (mobility) of tumor cells by pseudopods.

2) Vascular Dissemination and Homing of Tumor Cells:

- Tumor cell move freely
- Tumor cell penetrate lymphatics, capillaries & venules, but rarely arterioles (thick-walled).
- Once the tumor cells cross the vascular basement membranes, they reach circulation as tumor emboli.
- Finally tumor cell emboli get impacted in small vessels→ adherence to the endothelium → crossing the basement membrane (by mechanisms similar to those described above) → settlement in the new site (homing)→ proliferation of tumor cells →metastatic deposits (metastasis, secondary tumors).

ROUTES OF SPREAD

1- LOCAL (DIRECT) SPREAD

- Malignant cells spread in all directions.

2- DISTANT SPREAD (METASTASIS)

Definition: Metastasis is the development of secondary malignant implants, discontinuous with the primary tumor. It can occur by many routes; the most common of which is lymphatic & vascular spread.

A) LYMPHATIC SPREAD: Occurs more commonly with carcinomas than sarcomas.

B) HEMATOGENOUS (BLOOD) SPREAD: more common in sarcomas than carcinomas. It occurs early in sarcomas and late in carcinomas. Most affected organs are: LUNG-LIVER-BRAIN-BONE.

C) SPREAD THROUGH BODY CAVITIES (TRANSCOELOMIC SPREAD):

When the serosal covering of an organ is infiltrated by malignant cells of a tumor, some of these cells may detach and become implanted in other sites.

GRADING OF MALIGNANT TUMORS:

Depends on the degree of resemblance of tumor to normal (differentiation). It consists of 4 grades according to Brooder's classification:

1- Grade I: >75% of tumor is differentiated.
2- Grade II: 50-75% of tumor is differentiated.
3- Grade III: 25-50% of tumor is differentiated.
4- Grade IV: <25% of tumor is differentiated.

STAGING OF MALIGNANT TUMORS

Depends on the extent of tumor progression. The most applied is TNM staging system:

T: tumor
N: lymph node involvement
M: distant metastasis

CHARACTERISTICS OF CARCINOMA AND SARCOMA

CARCINOMA	SARCOMA
Definition: Malignant tumor of epithelium **Most common**. **Age:** Usually above 40 years. **Growth rate**: rapid but slower than sarcoma. **Gross Features:** • Size is usually less bulky than sarcoma • Haemorrhage & necrosis are usually less. • Consistency: Usually firm. • Colour is usually grayish. • Carcinoma in a solid organ forms an irregular growth. • Carcinoma arising from a surface forms a fungating cauliflower mass, an ulcerative growth or an infiltrative pattern. **Microscopic Features:** • Cellular anaplasia: Usually less marked than sarcoma. • Blood vessels are less and better formed than in sarcoma. • Hemorrhage, necrosis & secondary changes are usually less profound than in sarcoma. **Distant spread** • Usually slower than sarcoma • Occurs early by lymphatics then later by blood.	**Definition:** Malignant tumor of mesenchyme. **Less common**. **Age:** Usually below 20 years. **Growth rate:** generally faster than carcinoma. **Gross Features**: • Most sarcomas form bulky masses. • Haemorrhage & necrosis: Usually prominent. • Consistency: Usually soft & fleshy. • Colour is pinkish. • Sarcomas arising in a solid organ forms a fairly defined bulky growth. • Sarcomas do not arise from surface. **Microscopic Features:** • Cellular anaplasia is generally greater than carcinoma • Blood vessels are more numerous and thin- walled. • Hemorrhage, necrosis & secondary changes as hyaline and myxomatous changes are common. **Distant spread** • Usually faster than carcinoma • Occurs early by blood & rarely (10%) by lymphatics.

CHARACTERISTICS OF INTERMEDIATE TUMORS (LOCALLY MALIGNANT TUMORS)

- **These tumors are characterized by:**

1- A slower rate of growth than malignant tumors, but faster than benign tumors.

2- Local invasion only **without distant spread** (no metastases)

3- Proliferating tumor cells usually show low grade atypia.

- **Prognosis:** Much better than malignant tumors. However:

1-Local recurrence after surgical excision is common.

2-They may rarely change into malignant tumors that metastasize.

Examples:

1- Basal cell carcinoma.

2- Giant cell tumor of bone (osteoclastoma).

EXAMPLES OF TUMORS

BENIGN EPITHELIAL TUMORS

1- PAPILLOMA

- **Definition**: A benign tumor of surface epithelium, composed of connective tissue cores containing blood vessels covered by proliferated epithelial cells resting on intact basement membranes.
- Papillomas are classified according to type of epithelium into:

A) SQUAMOUS CELL PAPILLOMA

Definition: A benign tumor of stratified squamous epithelium.

Sites: Skin, lip, tongue, oral mucosa, pharynx, larynx, esophagus, cervix, vagina & anal canal.

Gross Picture: A small finger like projection, with progressive tumor growth, its surface becomes thrown into branching folds → complex papillary pattern.

Microscopic Picture: The tumor consists of connective tissue cores covered by thick proliferated stratified squamous epithelium, acanthosis (increased prickle cell layers) and hyperkeratosis.

Complications: May rarely change into squamous cell carcinoma.

B) TRANSITIONAL CELL PAPILLOMA (VILLOUS PAPILLOMA)

Definition: A benign tumor arising from urothelium. It is strongly pre-malignant.

Sites: Urinary bladder, urethra, ureter or renal pelvis.

Gross Picture: The tumor appears as a noncapsulated velvety friable mass of delicate papillary processes.

Microscopic Picture: Delicate vascularized connective tissue cores covered by usually not more than six layers of regular transitional cells.

Complications:

- Bleeding (hematuria).
- Malignant change into transitional cell carcinoma is not uncommon.
- Bladder neck, urethral or ureteric obstruction

C) COLUMNAR CELL PAPILLOMAS

Definition: These are papillomas arising from columnar epithelium. Two subtypes:

1- DUCT PAPILLOMA

Definition: A benign tumor arising from the epithelium of major ducts.

Sites: Major ducts, as those of breast (most common) or pancreas.

Gross Picture: Appears as a small complex papillary projection inside the duct lumen.

Microscopic Picture: Delicate vascular connective tissue cores covered by regular ductal epithelial cells.

Complications:

- Bleeding per nipple
- Malignant transformation into duct carcinoma.

2- MUCOUS CELL PAPILLOMA (Adenomatous polyp)

Definition: A common benign tumor of surface glandular mucosa. It grossly appears as papilloma (being projecting from the mucosal surface) and structurally appears as adenoma (being composed of proliferated mucosal glands) and therefore it is commonly known as adenomatous polyp, or mucosal adenoma).

Sites: Gastrointestinal tract is the commonest site.

Gross Picture: It appears as a sessile, pedunculated or complex papillary projection.

Microscopic Picture: a polyp formed of proliferated mucosal glands lined by regular columnar epithelium, supported by fibrovascular stroma.

Complications:

- Gastrointestinal bleeding is common.
- Malignant transformation → adenocarcinoma.
- Obstruction (e.g. pyloric obstruction)

2- ADENOMA

Definition: A benign tumor arising from solid glandular epithelium.

Sites: Exocrine or endocrine glands (breast, ovary, salivary glands, pancreas, thyroid, pituitary, adrenal glands… etc)

Gross Picture: A well-defined capsulated globular or ovoid mass. Cut section may be solid, cystic or cystic with small projecting papillae.

Microscopic Picture: Several Patterns:

- **Simple adenoma (tubular adenoma):** Consists of proliferated glands lined by cuboidal or columnar epithelium, separated by fibrovascular stroma. Example: Pancreatic adenoma.
- **Fibroadenoma:** adenoma with excess stromal proliferations. Breast is the main site.
- **Cystadenoma:** In some types of adenoma, secretions are retained leading to cystic dilatation. Example: ovarian cystadenoma.
- **Papillary Cystadenoma:** It is a cystadenoma in which the epithelial lining of the cyst proliferates forming papillae. Example: papillary cystadenoma of the ovary.
- **Special types** e.g.:
  a)**Pleomorphic adenoma** of major or minor salivary glands in which the adenomatous elements are associated with proliferation of myoepithelial cells, together with proliferated mesenchymal elements in the form of excess stromal mucin and metaplastic cartilaginous islands.
  b)**Papillary cystadenoma lymphomatosum (Warthin's tumor)** which also occurs in salivary glands and differs from ordinary papillary cystadenoma in two features; eosinophilic (oncocytic) epithelium & lymphocyte rich stroma forming lymphoid aggregates.

Complications:

- Adenoma of endocrine glands may function e.g. thyroid adenoma may cause thyrotoxicosis.
- Malignant change →adenocarcinoma.

BENIGN MESENCHYMAL TUMORS

1- CONNECTIVE TISSUE TUMORS

A) LIPOMA

Definition: A benign tumor of adipose tissue. It is the most common soft tissue tumor.

Sites: It can develop almost anywhere in the human body, except brain. Common examples include subcutaneous tissue, particularly at the region of shoulders, neck, back and buttocks.

Gross Picture: A well-defined capsulated globular or ovoid mass, with lobulated yellowish soft greasy C/S. It is commonly single, but may be multiple (lipomatosis).

Microscopic Picture:

Classic lipoma consists of lobules of mature fat cells (adipocytes) which are large vacuolated cells with flattened eccentric nuclei. The lobules are separated by fibrovascular septa.

Malignant transformation into liposarcoma is extremely rare.

B) FIBROMA

Definition: An uncommon benign tumor of fibrous tissue.

Sites:

- Dermis and subcutaneous tissue.
- Organs as ovary, wall of GIT.

Gross Picture:

A well-defined capsulated mass with grayish firm C/S.

Microscopic Picture:

The tumor consists of variable proportions of fibroblasts, collagen and blood vessels. Fibroblasts appear as spindle shaped cells with elongated nuclei showing tapering ends. Secondary changes as hyalinosis, myxomatous change & calcification may occur

Malignant transformation into fibrosarcoma is extremely rare.

C) CHONDROMA

Definition: A benign tumor of cartilage

Sites:
Most commonly short bones of hands & feet, less commonly at ends of long bones or in flat bones as pelvis, ribs, sternum & scapula.

Gross Picture:
A firm globular well defined capsulated mass, with firm, bluish gray and translucent C/S.

Microscopic Picture:
Lobules of cartilage composed of hyaline matrix and cartilage cells residing inside their lacunae. Cartilage cells (chondrocytes) are rounded with vacuolated cytoplasm. Secondary changes particularly myxoid change & calcification are common

Complications: Malignant transformation into chondrosarcoma is rare in solitary chondroma.

D) OSTEOMA

1- OSTEOID OSTEOMA

Definition: Benign bone tumor arising in bone composed of osteoid bone.

Sites Any bone, the commonest bones are femur and tibia.

Gross Picture:
The tumor is solitary, less than 2 cm in diameter (commonly < 1 cm). It appears pink, gritty and friable.

Microscopic Picture:
Trabeculae of osteoid and poorly mineralized woven bone prominently rimmed by osteoblasts. The intervening stroma is loose and richly vascularized.

Complications: Osteoid osteoma causes a characteristic nocturnal pain which is dramatically improved by aspirin. Pain is due to excess production of prostaglandin E2.

D.D.: Osteoblastoma is microscopically similar to osteoid osteoma. It differs in the following:

a) Larger in size <2 cm b) painless c) More common in the spine.

2- COMPACT OSTEOMA: (Ivory Osteoma):

Definition: Benign tumor arising in bones composed of compact bone.

Sites: skull.

Gross Picture: A well-defined hemispherical, non-capsulated mass with hard ivory white C/S.
Microscopic Picture: concentrically arranged compact bone lamellae with Haversian canal formation.
Complications: Disfigurement and pressure symptoms e.g. proptosis.

2- BENIGN TUMORS OF MUSCLES (MYOMAS)

LEIOMYOMA

Definition: A benign tumor of smooth muscle.
Sites: It is a common tumor. Sites include:

- Uterus is the most common site. Leiomyoma is the commonest tumor in females. It occurs during the reproductive period of life and is estrogen-dependent.
- Wall of esophagus, stomach, intestine, urinary bladder, blood vessels and skin.

Gross Picture:

- Single or multiple.
- Sharply circumscribed, round and firm.
- Uncapsulated but may acquire false capsule from compressed surrounding muscles.
- The cut section is firm, grayish white with whorly appearance.

Microscopic Picture:

- Interlacing bundles of smooth muscle cells and fibroblasts.
- Secondary changes as hyaline, myxoid and cystic changes, ischemic necrosis and calcification are common.

Complications:

- Malignant change into leiomyosarcoma is extremely rare.
- Uterine myoma may lead to uterine bleeding and infertility.

3- BENIGN TUMORS OF VESSELS

ANGIOMAS

Benign uncapsulated lesions composed of vascular spaces filled with blood (hemangioma) or lymph (lymphangioma). They are usually detected in early

life & represent congenital tumor-like malformations (hamartomas) rather than true neoplasms. They do not change malignant.

HEMANGIOMA: Benign tumor /hamartomatous of blood vessels. Two main types:

CAPILLARY HEMANGIOMA	CAVERNOUS HEMANGIOMA
Sites: • Mostly Skin, particularly of face; often since birth (birth mark). • Mucus membranes of lip and tongue. • Rarely organs as brain & kidney	**Sites:** • Less common, skin, particularly of the face. • Mucus membranes of lip & tongue. Enlargement of lip (macrochelia) or tongue (macroglossia) may occur. • Common in organs as liver, spleen, muscles & bones
Gross: A deep red well defined patch.	**Gross:** A purple well defined soft swelling.
Microscopy: Small vascular spaces lined by endothelium, mostly empty or contain little blood & separated by stroma.	**Microscopy:** Wide vascular spaces lined by endothelium, filled with excess blood, some clotted, & separated by stroma.

4-BENIGN TUMORS OF PERIPHERAL NERVES

A) SCHWANNOMA

It arises from schwann cells of peripheral nerve as a well-defined capsulated firm mass located at one side of the nerve. It consists of proliferated schwann cells which have thin palisading nuclei.

B) NEUROFIBROMA

It arises from all elements of the nerves. It appears as a non capsulated fusiform swelling in the center of nerve trunk composed of haphazardly arranged nerve fibers and Schwann cells. It may be solitary or multiple (neurofibromatosis syndromes).

INTERMEDIATE (LOCALLY MALIGNANT) TUMORS

1- BASAL CELL CARCINOMA
RODENT ULCER

Definition: A locally malignant tumor arising from basal cell layer of epidermis of skin.

Sites:

The tumor occurs in skin exposed to sun, commonly that of face, particularly above an imaginary line drawn from the angle of the mouth to the lobule of ear, particularly at the inner and outer angles of eyes, side of nose and angle of mouth.

Predisposing factors:

Prolonged exposure to sun.

Gross Picture: The tumor starts as a red papule that gradually enlarges & ulcerates. The ulcer is irregular and shows the following features:

- Raised, rolled in, beaded edges.
- Rough necrotic floor.
- Firm base.

Microscopic Picture:

The dermis is infiltrated by masses of malignant blue epithelial cells, the peripheral cells are columnar basal cells with **palisade** (parallel) arrangement, while the central cells are polyhedral.

Spread:

Local spread only. No distant spread.

2- GIANT CELL TUMOR (OSTEOCLASTOMA)

Definition: it is a locally malignant tumor of bone.

Site: They can arise from any bone but the most common sites are around the knee joint (distal femur and proximal tibia).

Grossly: An eccentric mass that erodes the bone. The covering cortical bone becomes markedly thinned (egg shell-like). Cut section is partly solid, partly cystic with areas of hemorrhage and necrosis.

Microscopic picture: The tumor consists of a mixture of non neoplastic multinucleated osteoclastic giant cells and neoplastic mononuclear stromal cells of unsettled origin (? osteoblastic or fibroblastic).

MALIGNANT EPITHELIAL TUMORS (CARCINOMA)

1- SQUAMOUS CELL CARCINOMA

Definition: A malignant tumor of stratified squamous epithelium.

Sites:

- Skin
- Mucous membranes lined by stratified squamous epithelium: lip, tongue, oral mucosa, pharynx, larynx, oesophagus, cervix, vagina and anal canal
- On top of squamous metaplasia.

Predisposing factors:

a) Prolonged exposure to sun.
b) Squamous metaplasia & leukoplakia.
c) Malignant transformation of papilloma.

Gross Picture:

- Fungating cauliflower, polypoid pattern.
- Ulcerative pattern:
  - Irregular ulcer with raised everted edges.
  - Rough necrotic floor.
  - Indurated base.
- Infiltrative pattern.

Microscopic Picture:

Groups of malignant pinkish epithelial cells which in well differentiated neoplasms form "**cell nests**". The center of the nests showing keratin (keratin pearls).

Spread:

- Local spread
- Distant spread (early by lymphatics then by blood)

2- CARCINOMAS OF GLANDULAR ORIGIN

A) ADENOCARCINOMA

Definition: A malignant tumor of glandular epithelium.

Sites:

- Endocrine and exocrine glands as pancreas, prostate, salivary glands, breast, ovaries.
- Mucous surfaces as GIT, gall bladder, endometrium, cervix, bronchi...

Gross Picture:

- In endocrine and exocrine glands, the tumor forms an irregular infiltrative growth.
- In mucous surfaces the tumor pattern may be:
  - Fungating cauliflower, polypoid pattern.
  - Malignant ulcer type.
  - Infiltrative pattern (annular and diffuse subtypes).

Microscopic Picture:

In well differentiated adenocarcinoma, the malignant cells show irregular variable sized acini with no definite basement membranes, lined by malignant cells.

Spread:

- Local
- Distant spread a) By lymphatics (early) b) By blood (late) c) Transcoelomic in case of carcinoma of GIT.

B) MUCIN SECRETING ADENOCARCINOMAS

Definition: These are malignant tumors of glandular epithelium characterized by mucin production.

Sites:

1-Mucosal surfaces e.g. GIT , gall bladder & bronchi

2-Glands e.g. breast, ovaries & pancreas

Gross Picture: Soft gelatinous tumors, which in endocrine & exocrine glands form infiltrative masses while in mucosal surfaces may form fungating polypoid mass, ulcerative growth or deeply infiltrative growth.

Microscopic Picture: Two types:

1-Mucinous Carcinoma (mucoid or colloid Carcinoma): This is an adenocarcinoma with abundant extracellular mucin secretion, which appears as pale mucinous pools around the malignant acini.

2-Signet Ring Cell Carcinoma: The malignant cells show intracytoplasmic mucin that pushes the nuclei eccentrically giving signet ring appearance. No acinar differentiation. The prognosis of this neoplasm is very poor.

Spread: As adenocarcinoma (local spread & distant spread).

3- UROTHELIAL CARCINOMA

Definition: A malignant tumor of transitional epithelium. It arises de novo or on top of villous papilloma.
Sites: Urinary bladder, urethra, ureter and renal pelvis.
Gross Picture:

- Papillary Type: A villous papilliferous growth.
- Flat Types:
  a)Fungating polypoid mass.
  b)Malignant ulcer.
  c)Infiltrative pattern.

Microscopic Picture:

- Papillary: Complex, branching vascular connective tissue cores, covered by usually more than 6 layers of anaplastic transitional cells. Papillary tumors tend to invade less deeply than flat ones and therefore has a better prognosis.
- Flat: The malignant transitional cells form invasive solid groups.

Spread:

- Local
- Distant: mainly by lymphatics & late by blood.
- Transluminal implantation may occur.

MALIGNANT MESENCHYMAL TUMORS (SARCOMAS)

1- LIPOSARCOMA

Definition: A malignant tumor of adipose tissue.
Sites: Retroperitoneal, subcutaneous tissue.
Gross Picture: Large soft yellowish greasy mass with foci of necrosis and hemorrhage.
Microscopic Picture: In well differentiated liposarcoma, the malignant cells contain abundant intracytoplasmic fat (lipoblastic differentiation).
Spread: Direct & blood routes.

2- FIBROSARCOMA

Definition: A malignant tumor of fibrous tissue.
Sites: Subcutaneous, periosteal, intermuscular.

Gross: An ill-defined non capsulated large grayish mass with areas of necrosis and hemorrhage.
Microscopy: In well differentiated fibrosarcoma the malignant spindle cells are separated by abundant collagenous stroma. In less differentiated forms there is little collagen and more marked cellular anaplasia.
Spread: Direct & blood routes.

3- CHONDROSARCOMA

DEFINITION: Malignant mesenchymal tumor of cartilage.

SITE: Usually axial skeleton.
GROSS: Ill-defined infiltrating mass with areas of hemorrhage and necrosis. Calcification and myxoid changes are common.

MICROSCOPE: Malignant chondrocytes showing criteria of malignancy lying within a hyaline matrix.

SPREAD:

1) Direct. 2) Blood.

4- OSTEOSARCOMA

DEFINITION: Malignant mesenchymal tumor of bone.
SITE: Any bone especially long bones around knee joint (lower end of femur and upper end of tibia).
GROSS: Ill-defined infiltrating mass with areas of hemorrhage and necrosis showing fleshy pinkish cut section.
MICROSCOPIC: Sheets of malignant spindle cells with scattered irregular osteoid or osseous tissue.

SPREAD:

1) Direct. 2) Blood.

MISCELLANEOUS BENIGN & MALIGNANT TUMORS

1- PIGMENTED (MELANOCYTIC) TUMORS

Definition: These are benign & malignant tumors arising from melanocytes.

Sites:

- Skin
- Mucous membranes & mucocutaneous junctions (as conjunctiva, rectum, mouth & vagina)
- Eye as choroid and iris.
- Leptomeninges.

Classification:

1-Benign: Pigmented nevus (mole).

A) Congenital types: i) Giant nevus ii) Blue nevus

B) Acquired types: i) junctional ii) intradermal iii) combined types.

2-Malignant: Melanoma.

A) Vertical Type: Nodular melanoma.

B) Radial Types:

- Lentigo maligna
- Superficial spreading melanoma
- Acral lentiginous melanoma

2- TERATOMA

Definition: Teratoma is a composite tumor containing mixture of structures derived from ectoderm, mesoderm & endoderm.

Sites:

1-Ovary and testis are the most common sites.

2-Other sites as anterior mediastinum, retroperitoneum, base of skull, sacrococcygeal region.

Origin: Totipotent cells.

Age: Any age; mostly children, young adults.

Types:

1-MATURE TERATOMA (Benign Teratoma):

These tumors consist of a haphazard mixture of mature ectodermal structures such as skin, neuroglial cells & teeth, mature endodermal structures such as thyroid tissue & other types of glandular epithelium and mature mesodermal structures such as cartilage, bone, adipose tissue,

fibrous tissue, muscle …etc.. Malignant transformation of mature teratoma is rare (≤ 1%) → any type of malignancy, but squamous cell carcinoma is the most common. There are two main types of mature teratoma:

a)Cystic Teratoma (dermoid cyst): Most common in ovary. The tumor is large. It consists of a dermoid ridge which is a solid part covered by skin and contains most of the tissues. The rest of the tumor is cystic and contains sebaceous material, tufts of hair, teeth and other structures.

b)Solid Teratoma: Less common.

2-IMMATURE TERATOMA (Malignant Teratoma):

Grossly: A bulky, predominantly solid mass with areas of necrosis and hemorrhage.

Microscopically: A varied amount of immature tissues (immature cartilage, neuroepithelium, glands...etc). The degree of malignancy is proportionate to the degree of immaturity. According to the proportion of immature to mature structures, they are given grade I, grade II & grade III.

3-MONODERMAL TERATOMAS (Specialized Teratomas):

These are teratomas that differentiate along the line of a single abnormal tissue.

Examples:

a) Struma ovarii: A benign ovarian teratoma composed of thyroid tissue.

b) Ovarian or testicular choriocarcinoma: A malignant placental epithelial tumor.

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