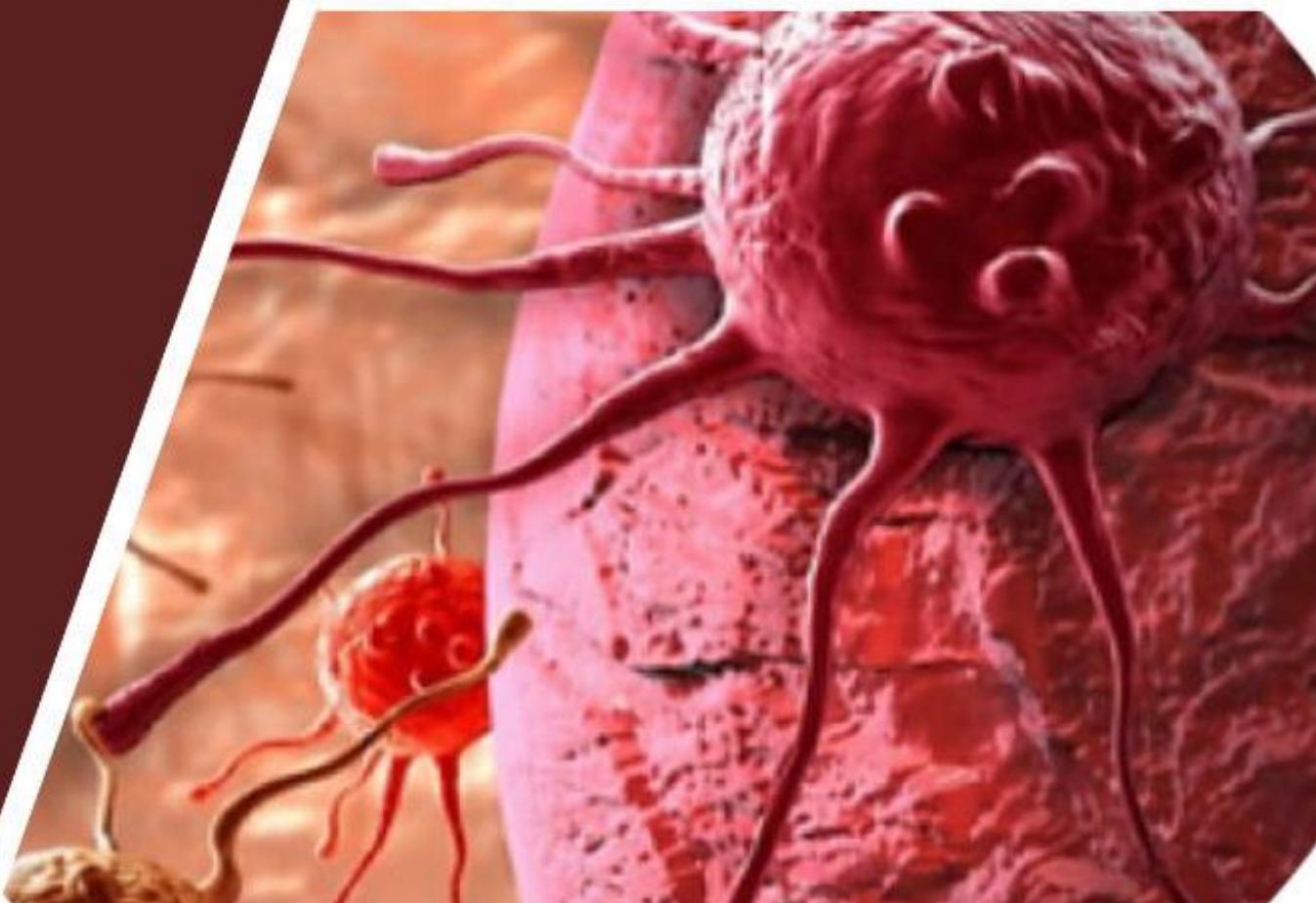




PART 1



2023
SWG



GENERAL PATHOLOGY
FIRST YEAR

BY
PATHO TEAM

N.B: Lesion is the structural changes in the tissue as a result of a disease.

5- Fate & Prognosis:

- The end result of the disease either cure or death of the patient.
- **Complications:** are the pathological changes which may occur during or after the usual course of the disease affecting the prognosis.

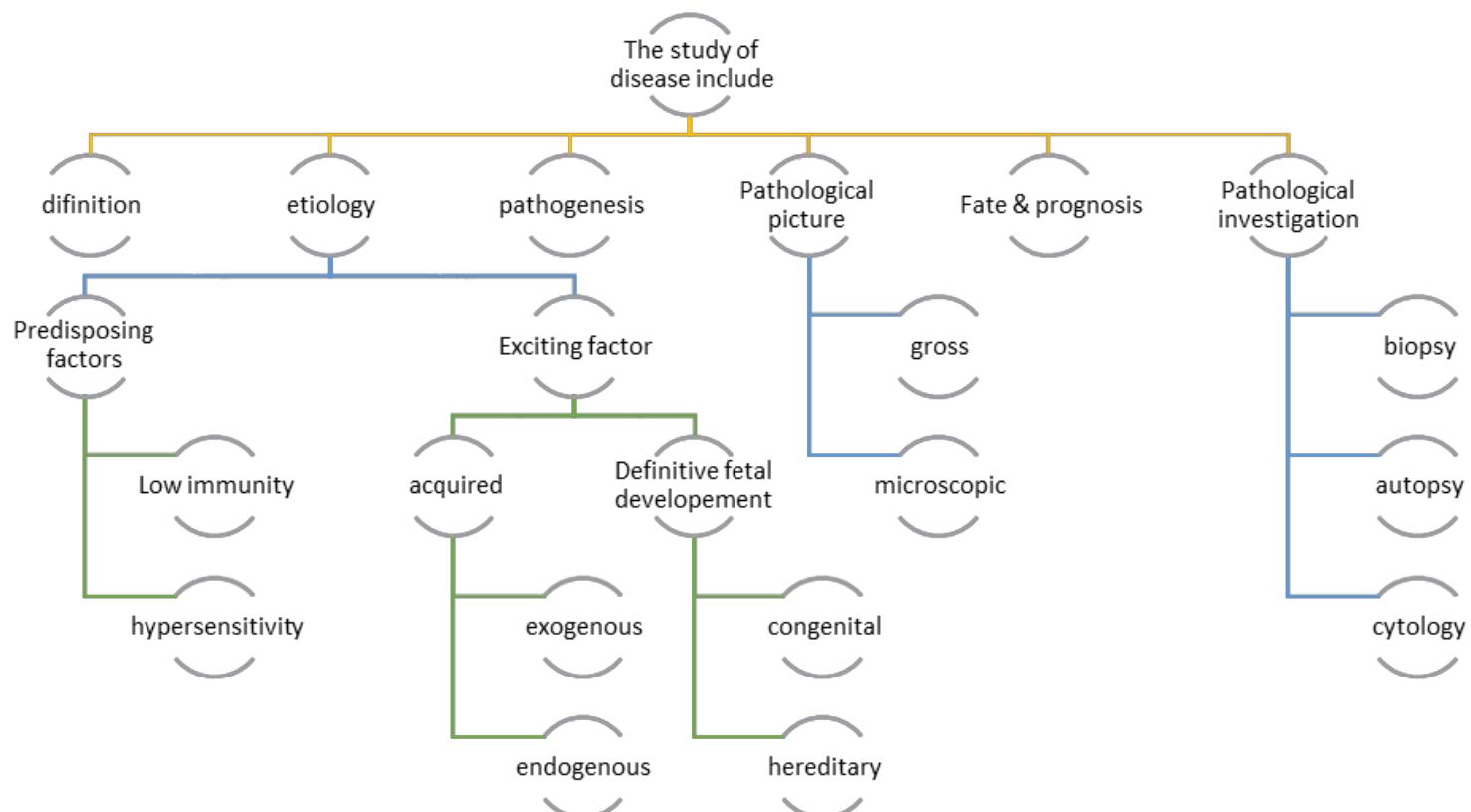
6- Pathological investigation:

a- **Biopsy:** Tissue specimen during life.

- Surgical.
- Endoscopic.
- Biopsy guided by radiological procedures (e.g. Ultrasound-guided Biopsy).
- Paraffin sections or frozen sections Stained by H&E then examined.

b- **Autopsy:** Post-mortem tissue examination

c- **Cytology:** Examination of cell.



INTRODUCTION

Pathology: Is the study of diseases.

The study includes the following Points:

1- Definition of the disease.

2- Etiology: Is the cause or causes of the disease which includes:

a- Predisposing Factors: Factors which help disease development as:

- **Low immunity:** favors infection.
- **Hypersensitivity:** (may be hereditary as bronchial asthma).

b- Exciting factor: Is the direct cause of the disease. It may be:

- **Acquired:**

1- Exogenous as microbes.

2- Endogenous as endocrinal diseases, hypertension or peptic ulcer.

- **Defective fetal development:**

1- Congenital: In-utero affection of normal fertilized ovum by microbes, X-ray or drugs.

2- Hereditary: Genetic diseases (inherited from Parents.).

3- Pathogenesis: Is the mechanism of disease development (The mechanism through which the cause operates to produce the pathological and clinical manifestations)

4- Pathological pictures: include:

a- Gross Picture (macroscopic picture): Include the changes in tissues and organs that can be detected on naked-eye examination.

b- Microscopic picture (histopathology): Representing the changes in tissues and organs detected on microscopic examination by:

1- Light microscope.

2- Electron microscope.

3- Immunohistochemical methods.

SWG

CELL INJURY

CHAPTER 1

PATHO TEAM

CELL RESPONSE TO INJURY

Causes of cell injury:

1- Hypoxia (Decreased oxygen supply): Is the main cause of cell injury.

Caused by:

a- **ischemia (decrease of blood supply)** e.g. arterial occlusion and atherosclerosis.

b- **Inadequate oxygenation** e.g. heart and lung diseases.

c- **Decreased oxygen carrying capacity of the red blood corpuscles** e.g. anemia and carbon monoxide poisoning.

2- Infectious agents: Bacteria, viruses, rickettsia, fungi and parasites.

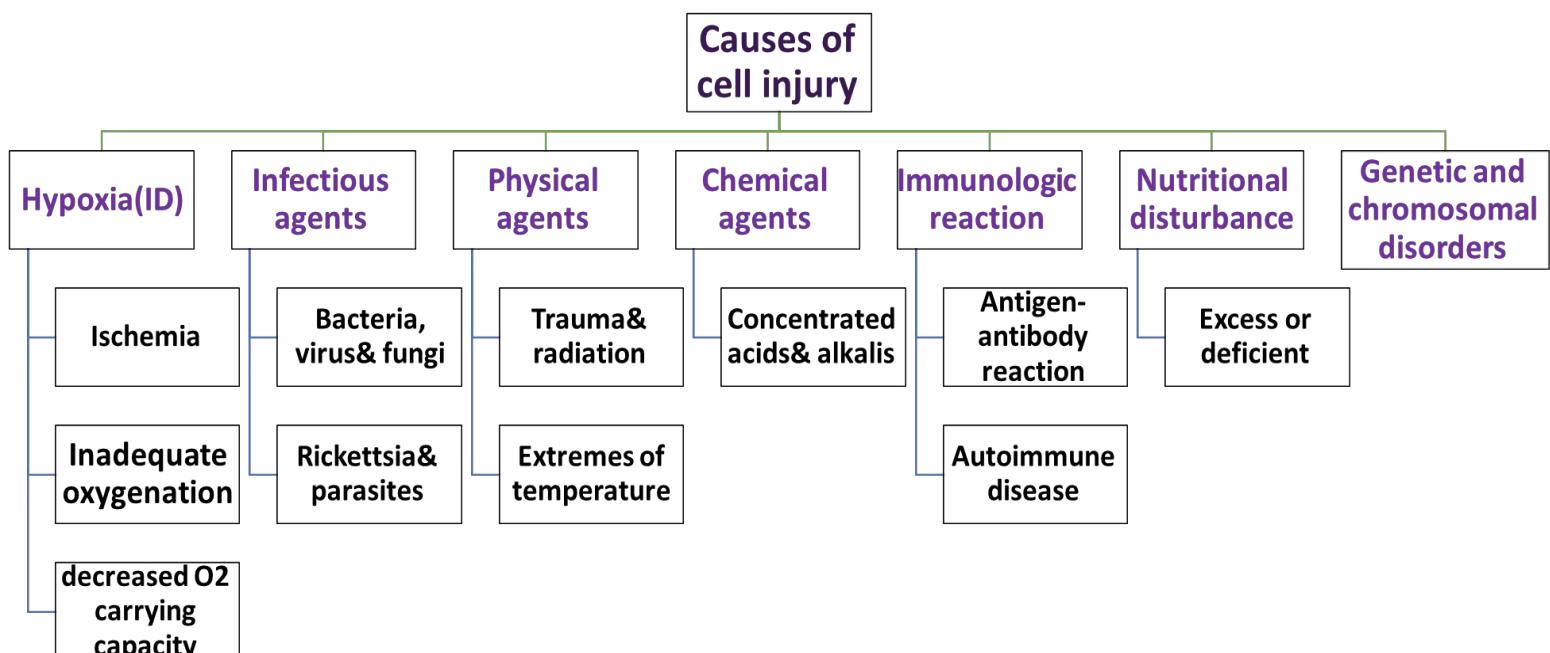
3- Physical agents: Trauma, extremes of temperature, radiation.

4- Chemical agents: Concentrated acids, alkalis.

5- Immunologic reactions: Antigen-Antibody reaction& autoimmune disease.

6-Nutritional disturbance: Excess or deficient.

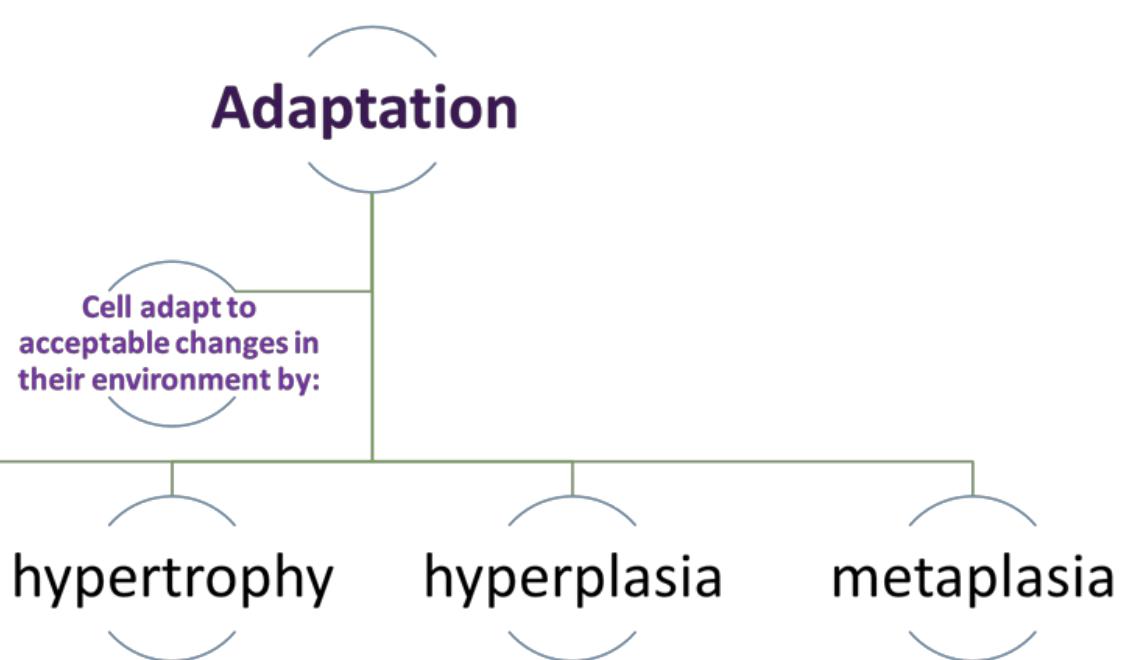
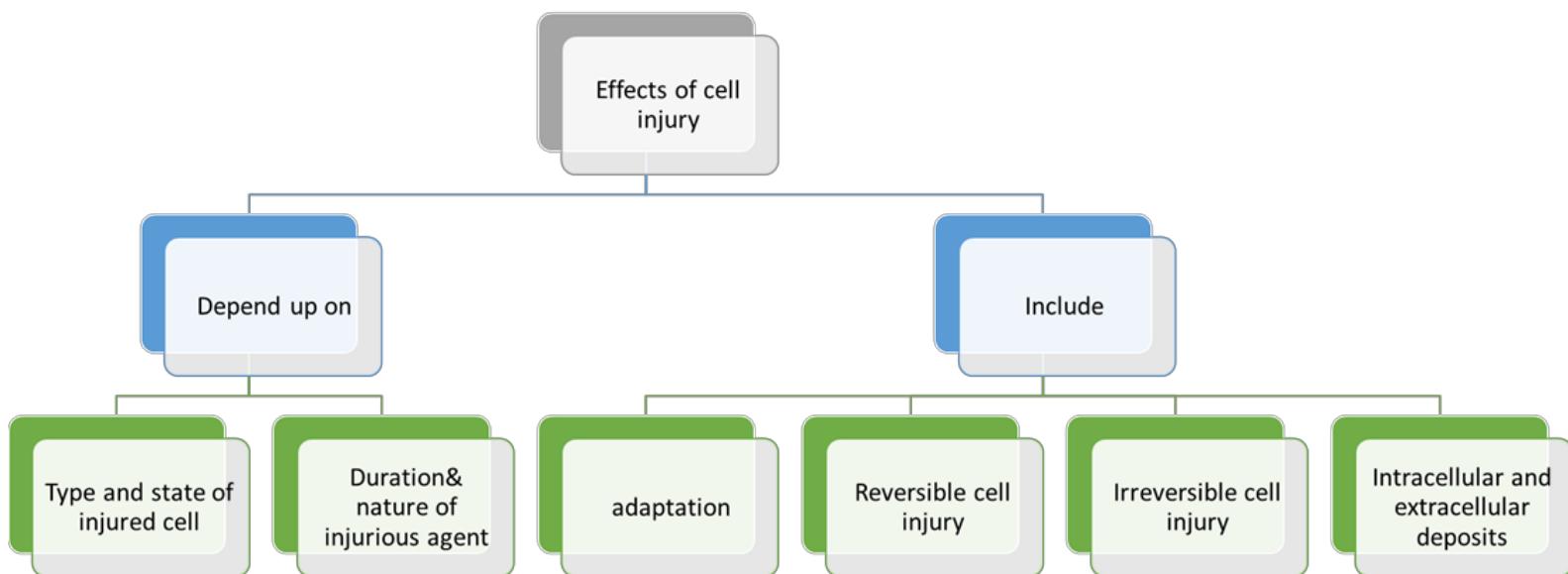
7- Genetic and chromosomal defects.

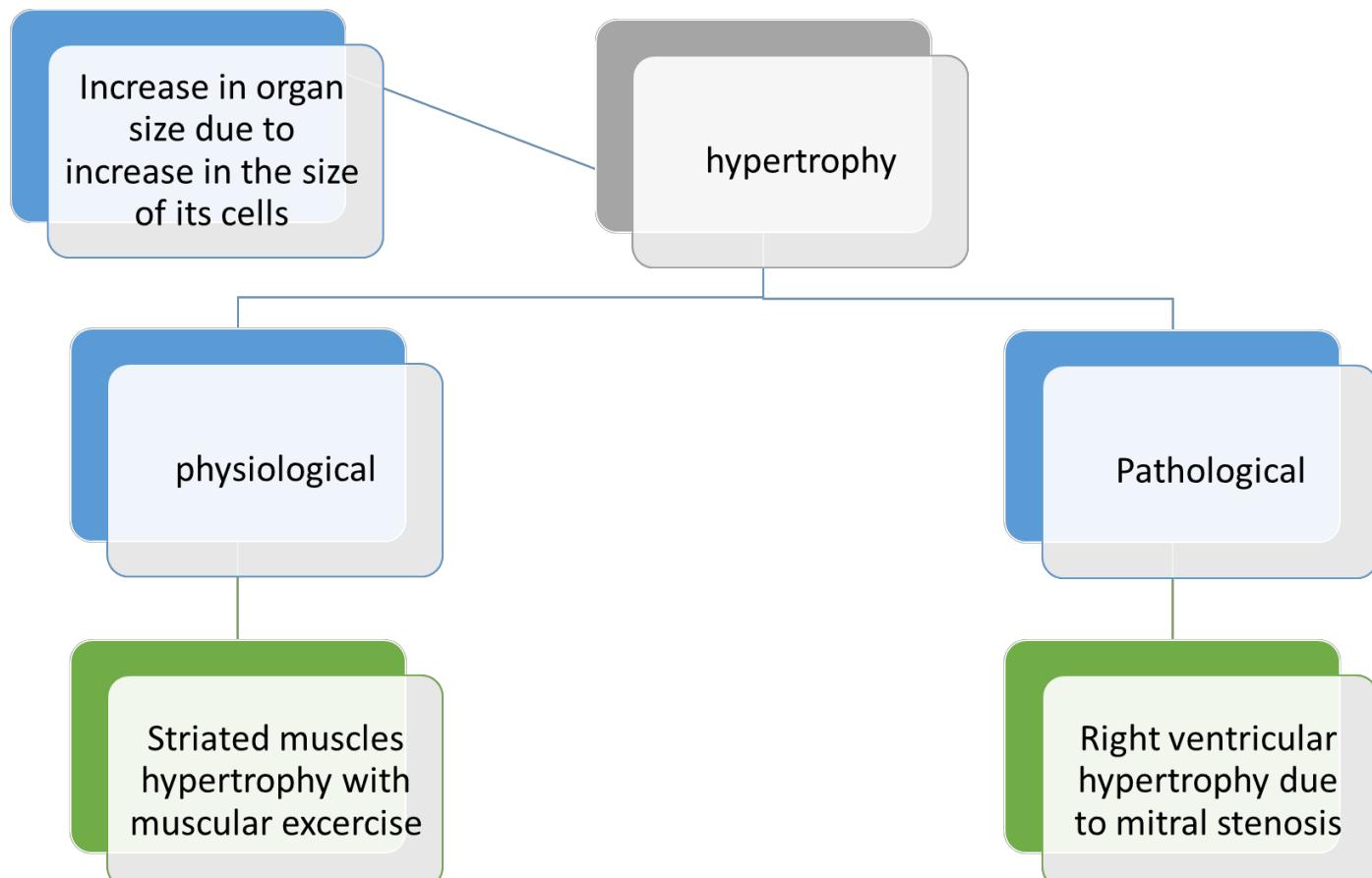
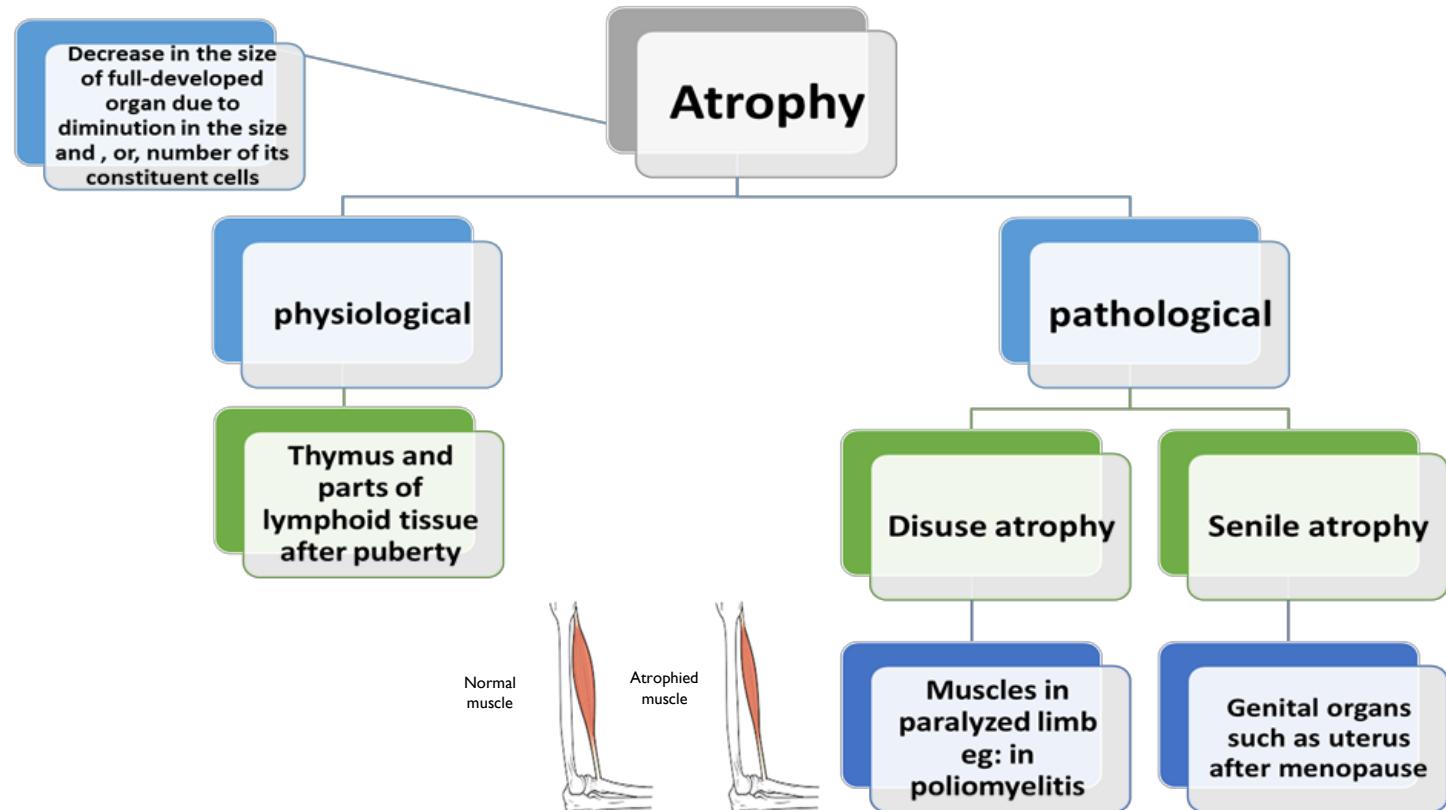


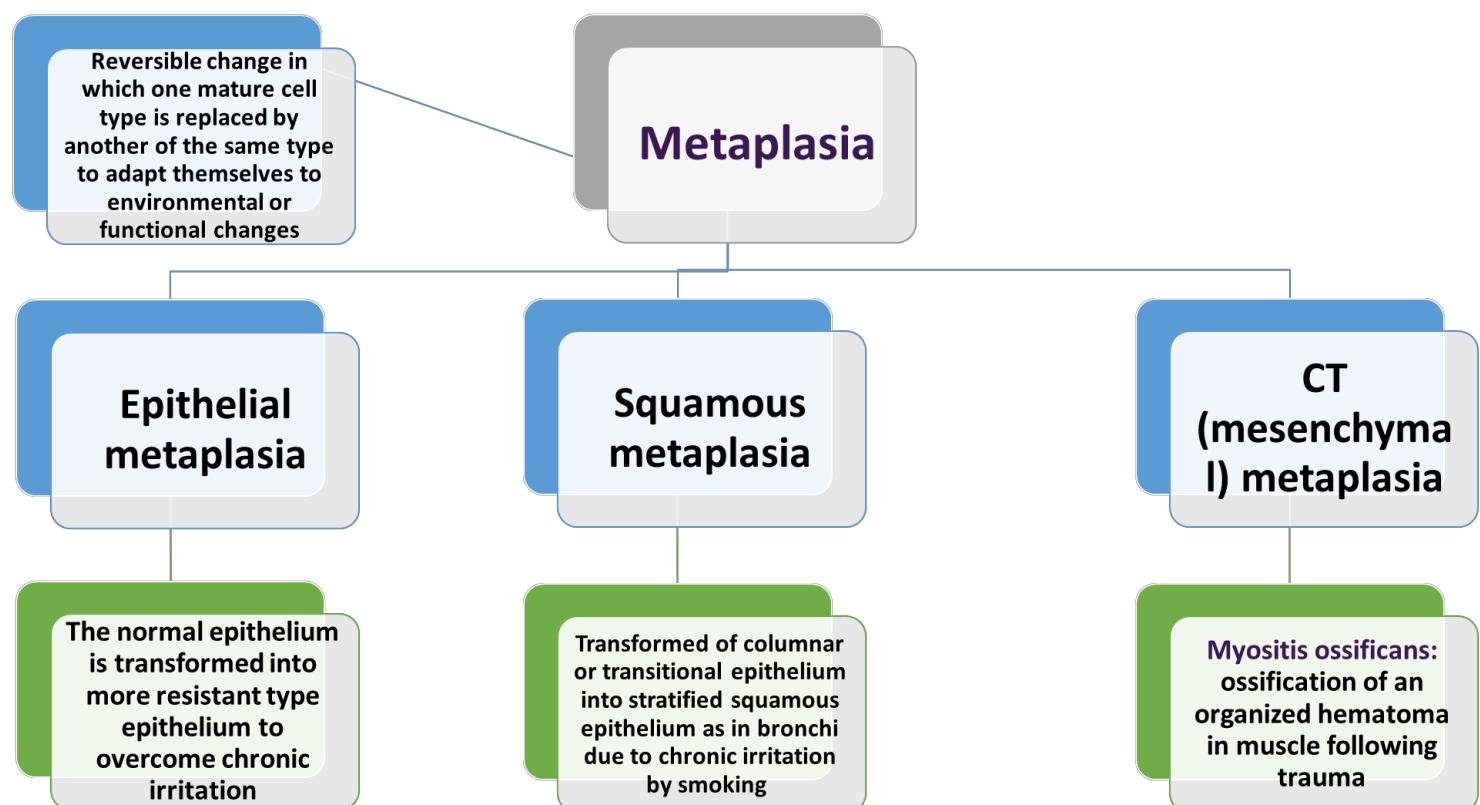
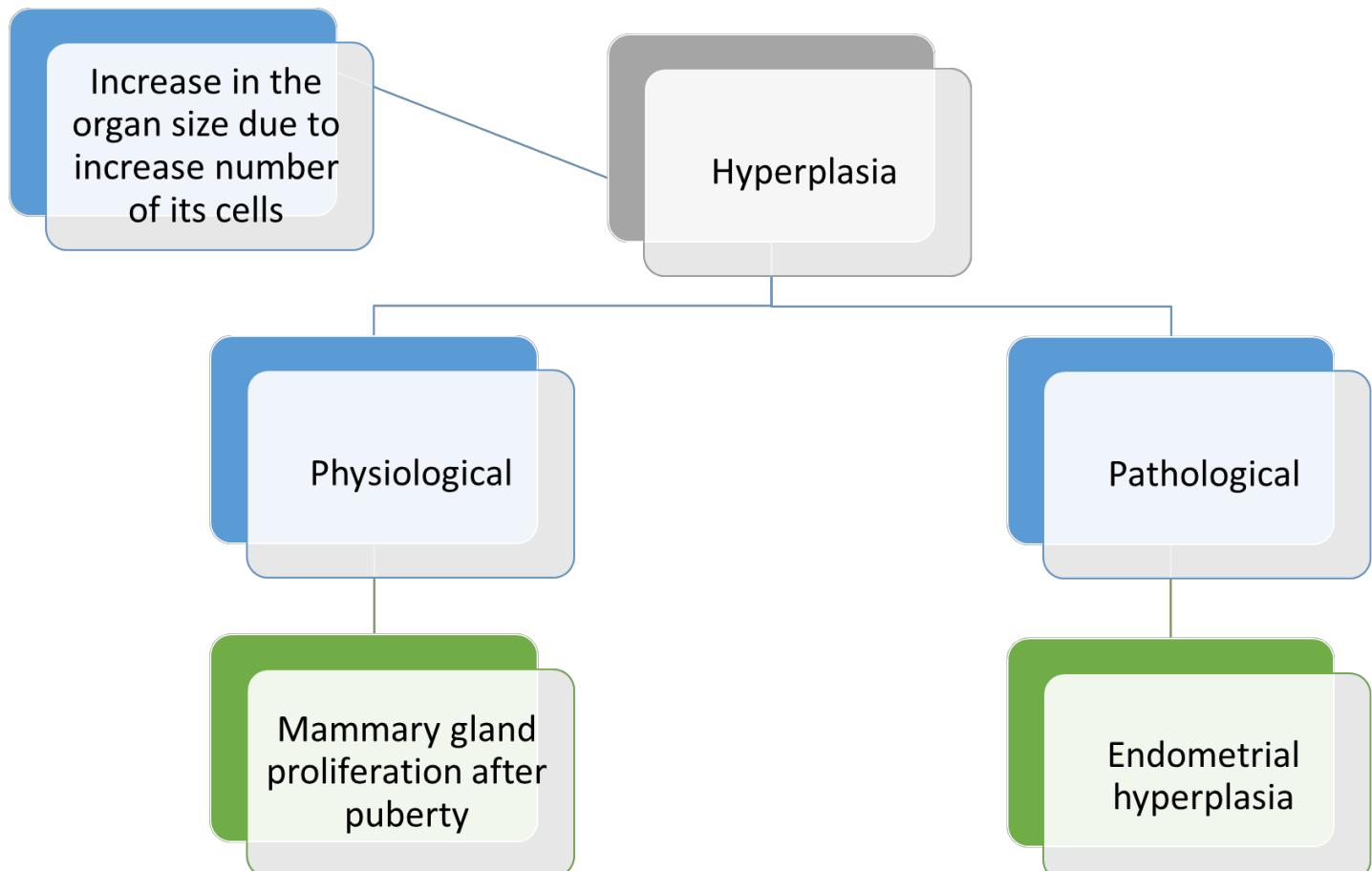
Mechanisms of cell injury:

❖ Biochemical disturbance of:

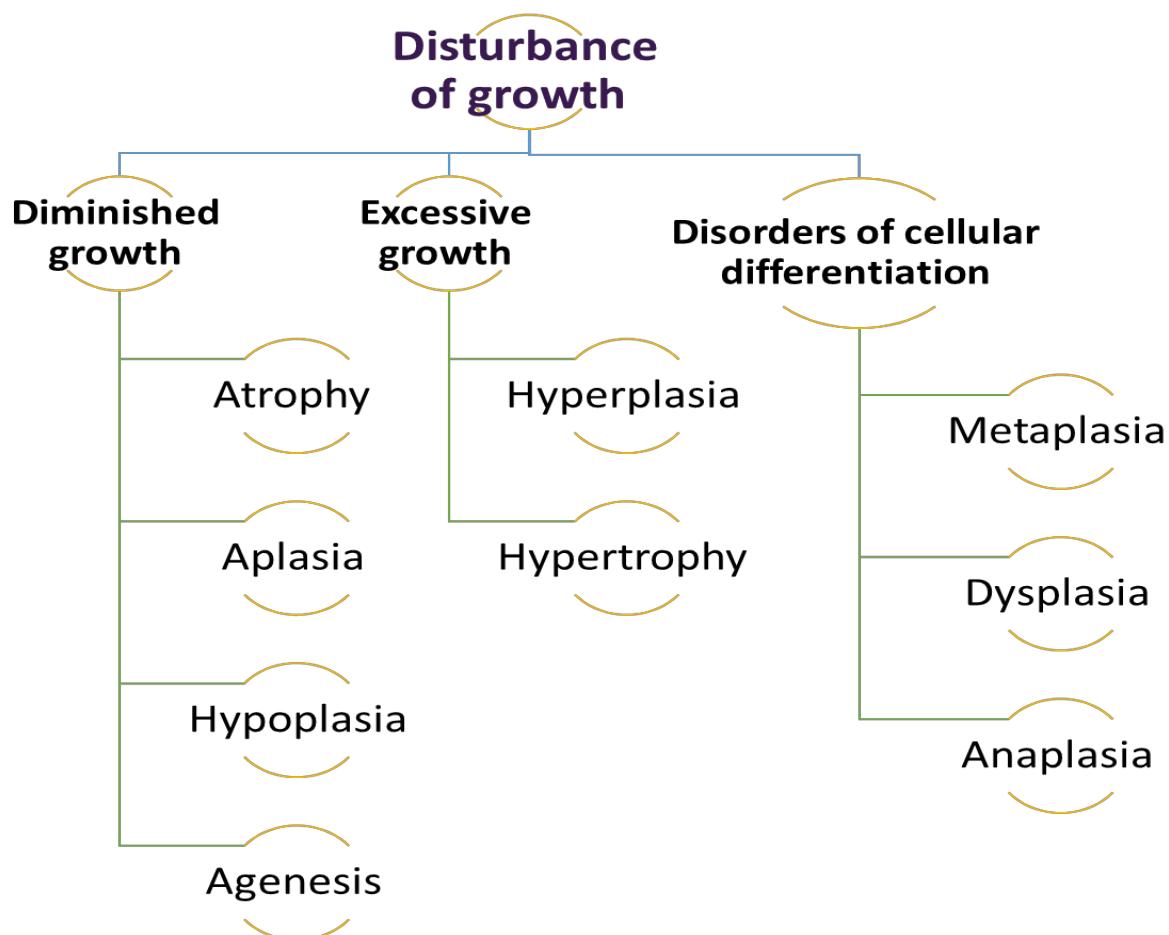
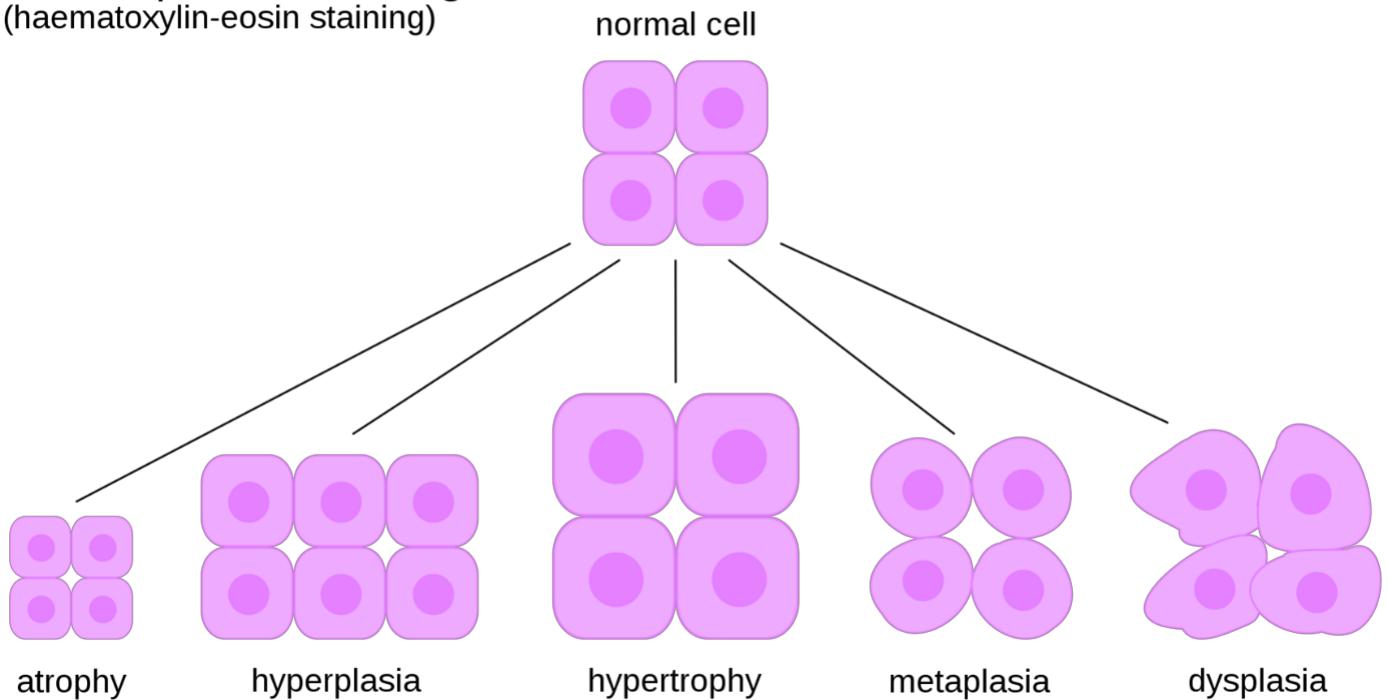
- 1- Cell membrane integrity which preserve cellular homeostasis.
- 2- oxidative phosphorylation by mitochondria and ATP Production.
- 3- Synthesis of the enzymatic and structural protein.
- 4- The integrity of the cellular genetic apparatus (DNA-RNA).
- 5- Reactive oxygen metabolites.







Non-neoplastic cell changes
(haematoxylin-eosin staining)



❖ Hypoplasia:

It is a malformation in which there is failure of the organ to develop into the full adult size, leading to a small underdeveloped organ.

e.g: an infantile uterus, hypoplastic testis & hypoplastic kidney.

❖ Aplasia:

It is a complete failure of cell growth and multiplication.

e.g: bone marrow hypoplasia (aplastic anemia).

❖ Agenesis:

It is the congenital malformation in which there is complete absence of an organ.

e.g: congenital absence of one kidney.

❖ Dysplasia:

It is non neoplastic atypical cellular changes usually caused by chronic irritation.

- **Dysplastic cells are atypical cells characterized by:**

- Cellular pleomorphism(the cells are different in size and shape)
- Loss of polarity(loss of their architectural orientation).
- Enlarged dark (Hyperchromatic) nuclei.
- Increased mitotic activity.

- **Degree of dysplasia:**

- **Mild:** affects the lower third of the epithelium.
- **Moderate:** lower two third.
- **Sever:** the whole thickness.

- **Fate of dysplasia:**

- Mild is commonly reversible.
- Sever is a precancerous lesion.

❖ Anaplasia:

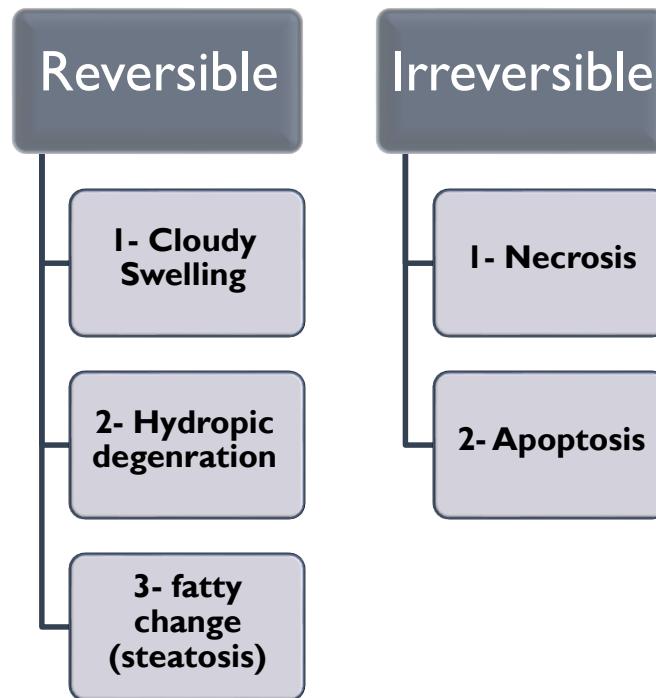
It is lack of differentiation and it is the characteristic feature of malignant cells.

- **Cytologic features:**

- Nuclear and Cellular pleomorphism.
- Loss of polarity.
- Hyperchromasia.
- Increased N\C ratio.
- Increased mitotic activity.



RESULT OF CELL INJURY



Reversible cell injury

1- Cloudy Swelling:

- **Definition:** Reversible cell injury characterized by mild intracellular water accumulation.
- **Cause:** Mild injury or injury of short duration.
- **Pathogenesis:**

Injurious agents mainly hypoxia inhibit oxidative phosphorylation and ATP formation by the mitochondria lead to:

- a- Failure of the active cell membrane transport (sodium pump). Sodium enters the cell (followed by water entry) and potassium diffuses out of the cell.
- b- Anaerobic ATP synthesis occurs and catabolites as lactate and inorganic phosphates accumulate increasing the intracellular osmotic load resulting in water entry.

- **Pathological Features:**

- **Organs affected:** Highly specialized **parenchymatous cells** e.g. liver cells, renal cells and heart muscles
- **Gross Picture:** The affected organ appears:

Organ: swollen.

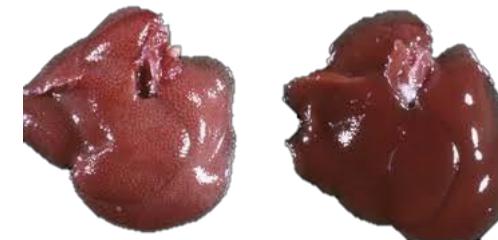
Consistency: soft.

Color: pale.

Outer surface: smooth.

Border: rounded.

Cut surface: appears cloudy and bulging.



- **Microscopic picture:**

1- The **cells** are swollen.

2- The **cytoplasm** is granular.

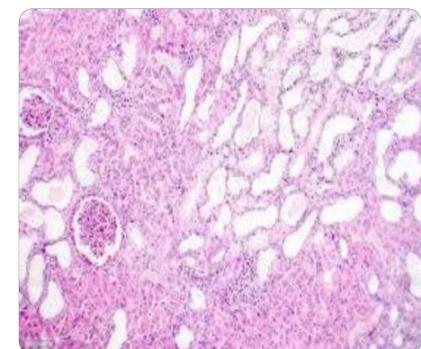
3- The **nucleus** is normal.

4- The **capillaries** between the cells are compressed.

- **Fate:**

a- Cloudy swelling is reversible if the injury stops.

b- If the injury continues, proceeds to hydropic swelling, or complete necrosis.



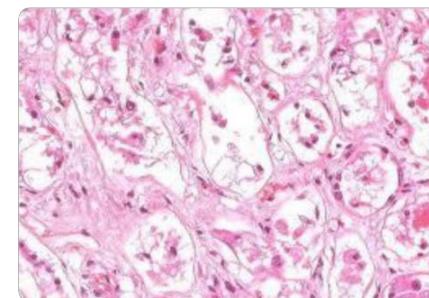
2- Hydropic swelling (Hydropic Degeneration):

- **Definition:** Reversible cell injury characterized by excess intracellular water accumulation which may replace the whole cytoplasm.
- **Causes and pathogenesis:** Similar to cloudy swelling.
- **Gross:** Similar to cloudy swelling.
- **Microscopic Picture:**

Cells are swollen.

The **cytoplasm** is: pale and shows multiple vacuoles.

The **nucleus** is: normal.



- **Examples of hydropic degeneration are:**
- Epidermal cells in burns, urticaria and viral infections
- Ballooning degeneration of liver cells in viral hepatitis
- Beta cells of islets of Langerhans in early stages of diabetes mellitus.

3- Fatty Change (steatosis):

- **Definition:** Reversible cell injury characterized by accumulation of neutral fat in parenchymatous cells.

- **Causes:**

1- Hypoxia.

2- Bacterial toxins of acute and chronic infections.

3- Chemical agents as alcohol, phosphorous and carbon tetrachloride.

4- Because of the importance of the liver in fat metabolism, fatty changes in the liver cells are also caused by:

a- Excess fat brought to the liver cells as in:

- Excess intake of fats and carbohydrates.
- Starvation.

b- Diseases of the liver cells as in viral hepatitis C.

c- Deficiency of lipotropic factors as choline and methionine.

d- **Alcoholism:** alcohols **increase** fatty acid synthesis, **decrease** fatty oxidation, **increase** lipolysis and fat mobilization to liver.

- **Pathogenesis:** Hypoxic or toxic cell injury **Diminished enzyme activity** → Fail to metabolize fat produced in (or carried to) injured cells → Intracellular fat accumulation.

- **Gross Picture:** The affected organ is:

Size: enlarged.

Consistency: soft.

The outer surface: smooth.

Color: pale yellow.

Borders: rounded.



capsule: tense.

cut surface: bulges and is greasy to touch.

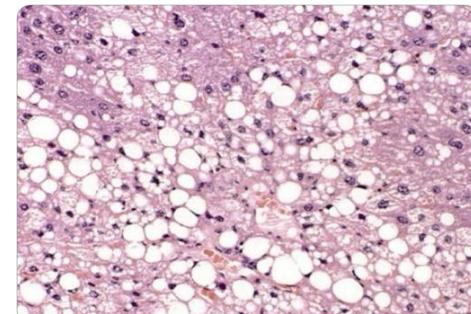
- **Microscopic Picture:**

- The cells appear **swollen** and show multiple tiny cytoplasmic vacuoles (**fat globules dissolve in xylol**) around the nucleus.

- The fat globules **fuse together** forming a **big globule** that pushes and flattens the nucleus against the cell membrane **giving the cell a signet ring appearance.**

- Fat can be stained **by fat stains**. It stains **orange** with **sudan III** and **black** with **osmic acid**.

- **Organs Affected:** Liver, heart, kidney "either diffuse or patchy".



Irreversible cell injury

1- Necrosis:

- **Definition:** Morphological changes that follow death of group of cells within the living body which occur either directly or follow reversible.
- **Causes:** Severe injury or injury of long duration causing damage of the nucleus and cell death.

- **Pathogenesis:**

- 1- Destruction of cell membranes with release of **proteolytic enzymes**.

- 2- Increased intracellular calcium which caused by **ca++ influx**.

- 3- Calcium activates the following **cellular enzymes**:

- a- Phospholipases.

- b- Protease.

- c- ATPases.

- d- Endonucleases which fragment chromatin.

- **Gross Picture:**

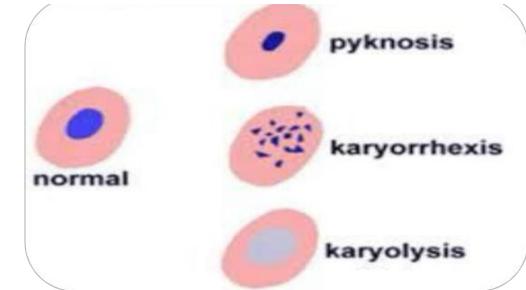
- 1- Necrotic tissue appears opaque and **whitish or yellowish** in color.

- 2- Surrounding tissue appears **red** due to inflammatory hyperemia.

- Microscopic Picture:

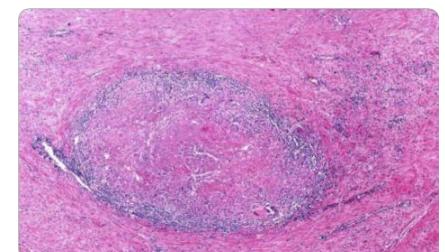
1- Nuclear changes:

- a- **Pyknosis:** The nucleus shrinks and stains darkly with dense chromatin
- b- **Karyorrhexis:** The nucleus is fragmented
- c- **Karyolysis:** Nucleus dissolves and fails to be stained due to chromatin hydrolysis.



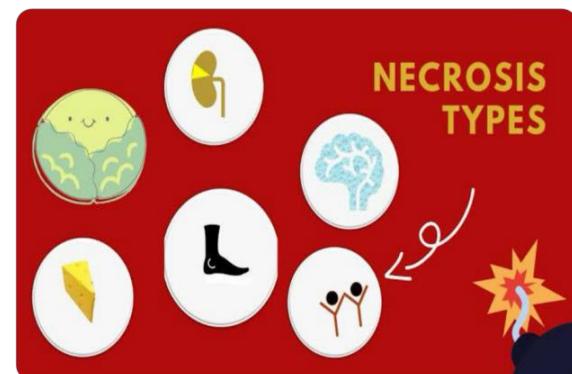
2- Cytoplasmic changes:

- a- **Cytomegaly (cells are swollen).**
- b- **Cytoplasmic eosinophilia.**
- c- The cell membrane becomes indistinct



■ Types of necrosis:

- 1- Coagulative necrosis.
- 2- Liquefactive necrosis.
- 3- Caseation necrosis.
- 4- Fat necrosis.
- 5- Hemorrhagic necrosis.
- 6- Fibrinoid necrosis.



1- Coagulative Necrosis: Commonly caused by sudden cut of the blood as in supply sin infarction except brain infarction.

- **Microscopically:** dead tissue appears homogenous, structureless and pink.

2- Liquefactive Necrosis:

- a- **Infarctions of the brain and spinal cord:** The softening and liquefaction is due to the high lipid and fluid content of the nervous tissue.
- b- **Pyogenic abscess:** The central necrotic core is liquefied by the proteolytic enzymes released from the pus cells.

3- Caseation Necrosis:

- a- Necrosis followed by slow partial liquefaction.
- b- Caseous necrosis is caused by an antigen antibody reaction. Caseation occurs in **tuberculous** lesions and in gumma of **syphilis**.
- **Grossly:** the caseating material is **dry, pale yellow** and resembles cream cheese or casein.
- **Microscopically:** all cellular details are lost and the tissues appear structureless, granular or homogenous.

4- Fat Necrosis:

- a- **Enzymatic fat necrosis:** It occurs in acute haemorrhagic pancreatitis.
 - The enzyme lipase escapes from the ruptured pancreatic ducts and digests surrounding fat into glycerol and fatty acids.
 - Glycerol is absorbed in the blood and fatty acids deposit with calcium as small dull opaque white patches.
 - **Microscopically:** the affected fat cells appear cloudy and surrounded by foreign body giant cell reaction and fibrosis.
- b- **Traumatic fat necrosis:**

It occurs as a result of trauma to the adipose tissue of the breast and subcutaneous fat.

5- Hemorrhagic Necrosis:

This occurs when cell death is due to blockage of venous drainage.

6- Fibrinoid Necrosis:

- In arteries in cases of vasculitis and hypertension.
- When fibrin is deposited in the damaged necrotic vessel wall.

■ **Fate of Necrotic Tissue:**

1- Small area of necrosis:

- Part of the necrotic tissue is removed by the macrophages. The rest drained by the lymphatics and veins. Healing occurs by regeneration or by granulation tissue formation followed by fibrosis.

2- Large area of necrosis:

- Surrounded by fibrous capsule and may show dystrophic calcification later on.

3- Gangrene: Massive necrosis of tissue with superadded putrefaction.



2- Apoptosis:

- Definition:** Distinctive morphologic pattern of cell death affecting a single cell or small group of cells. Apoptosis is energy-dependent programmed cell death for removal of unwanted individual cells.
- Apoptosis occurs in the following settings:**

1- Physiologic:

- During embryogenesis, to remove web between fingers.
- Hormone dependent involution: Endometrial cells break down in females.

2- Pathological events:

Some stimuli may induce either necrosis or apoptosis **depending on the severity and duration** e.g.

- Cell death by injurious stimuli in low doses (**Radiation – Cytotoxic drugs**).
- Viral diseases:** e.g. in viral hepatitis, the apoptotic liver cells are called Councilman Bodies.
- Reduction of cell number** in pathological atrophy.

■ **Mechanisms of apoptosis:**

- Stimulation of apoptotic process: physiological or pathologic stimuli.
- Control and regulation of apoptosis: **bcl-2 family gene**.

3- Execution phase.

■ Morphological Changes:

1- Shrinkage of the cell.

2- Condensation and fragmentation of chromatin.

3- Rapid break down of the cell to form apoptotic bodies.

Apoptotic bodies are phagocytosed by neighboring cells or by macrophages.

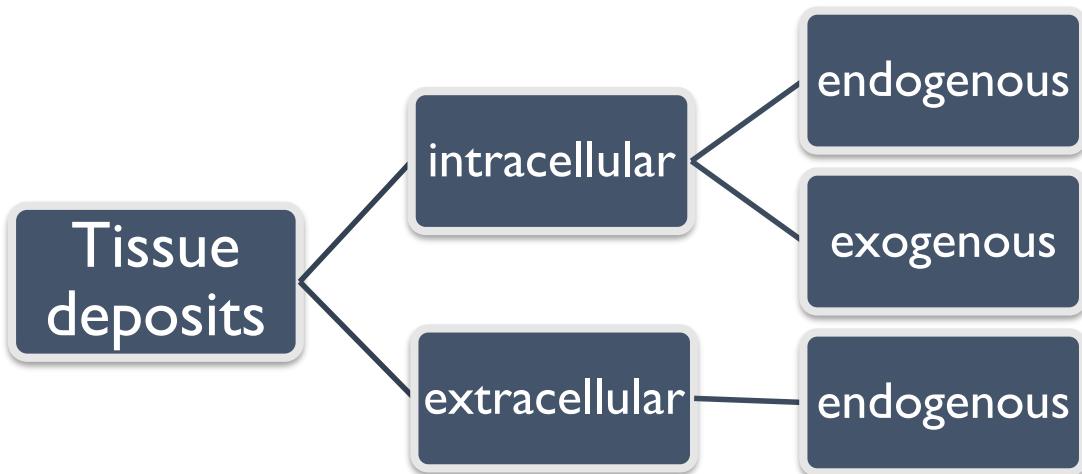
4- Lack of inflammation in surrounding tissue.



	Necrosis	Apoptosis
Stimuli	Injury (Ischemia and chemical injury)	Injury or physiologic
Cells	Severe swelling and rupture	Shrinkage
Cell membrane	Indistinct	Form blebs then membrane bound cytoplasmic bodies
Nucleus	Undergoes pyknosis, karyorrhexis and karyolysis	Chromatin condensation and fragmentation
Organelles	Breakdown	Aggregation
Inflammatory reaction	Present	Absent

TISSUE DEPOSITS (TISSUE ACCUMULATION)

DEF: Tissues may accumulate abnormal amounts of various substances.



1- Intracellular accumulation:

CHO

- Glycogen Ex: glycogen storage diseases.
- Mucin Ex: - catarrhal inflammation.
- mucid carcinoma.

Lipids

- Neutral lipid (TAG) Ex: fatty change.
- Cholesterol Ex: atherosclerosis.

Proteins (Intracellular Hyalinosis)

- Russell bodies Ex: rhinoscleroma.

Protein: It is alterations of intracellular proteins to appear as cytoplasmic homogenous rounded eosinophilic.

■ **Pigments:**

- **Definition:** An abnormal intracytoplasmic accumulation of colored substance.

- **Types:**

1) Exogenous

2) Endogenous

3) Parasitic (eg Bilharzial pigments)

Exogenous	Endogenous
Inhalation: <ul style="list-style-type: none"> ● Anthracosis: carbon particles accumulation causing black pigments in lung due to smoking or to air pollution. ● Silicosis: silica cause grayish pigment in lung in coal miners. 	Melanin
Injection <ul style="list-style-type: none"> ● Tattooing: colored dye (Indian ink) inoculated “injected” through the skin. 	Lipofuscin
Ingestion <ul style="list-style-type: none"> ● Plumbism (lead poisoning): lead may be absorbed through GIT, respiratory tract, skin which is precipitated as a blue line on gums. 	Hemoglobin Pigments

Endogenous pigments:

1- Melanin:

	Hyperpigmentation	Hypopigmentation
Generalized or Whole the body	<ul style="list-style-type: none"> Exposure to sun light. Addison disease: increase melanocyte stimulating hormone. 	<ul style="list-style-type: none"> Albinism: congenital absence of melanin
Localized or Small part of the body	<ul style="list-style-type: none"> Melanocytes tumors: <ul style="list-style-type: none"> - benign: nevus. - malignant: melanoma. Café au lait spots: due to multiple neurofibromatosis Melanosis coli: due to constipation. Chloasma: brownish coloration of face, nipple and genitalia during pregnancy 	<ul style="list-style-type: none"> Leukoderma: White skin patches due to melanin loss. Vitiligo: Acquired sharply defined depigmented skin patches

2- Lipofuscin (lipochrome) pigment:

Definition: brown or yellow pigments represent undigested intracellular materials (phospholipid with protein).

It normally exists as intracellular residual bodies in different sites of the body.

■ Mechanism:

It is formed of phospholipids complexed with proteins and it is increased due to tear and wear ~ Tissue breakdown ~ Release of phospholipids ~ Phagocytosed by the healthy neighboring cells ~ Intracellular accumulation of lipofuscin pigment ~ Brownish coloration.

Ex: Brown atrophy of the heart: Excessive intracellular lipofuscin pigment accumulation in myocardial fibers

3- Hemoglobin derived pigment:

- RBCs contain a lot of hemoglobin.
- Hemoglobin is composed of: (amino acids, bile, porphyrin, iron).

- RBCs are synthesized in bone marrow. Its life span is **120 days** then be **hemolysed** forming four "actually two" types of pigments.
- **Four pigments** may be formed from hemoglobin breakdown:

1- Hemosiderin: Iron-containing brown insoluble granules.

Hemolysed RBCs → Liberated iron → Stored in cells in association with apoferritin protein → Forming ferritin molecules → Aggregated to form hemosiderin.

2- Bilirubin: Iron-free pigment. Excess bilirubin leads to jaundice.

3- Porphyrin: Disturbance of porphyrin metabolism leads to porphyria

4- Hematin: A brown pigment formed by the action of acids and alkalis on hemoglobin.

NB: It's **not** found normally in the body.

Pigment	Hemosiderin	Bilirubin		hematin
Disease	hemochromatosis	Jaundice	Porphyria	
Accumulated substance	Iron	Protein + porphyrin	Not porphyrin	

4- Hemosiderosis:

- **Definition:** increase haemosiderin production which appear in macrophage of (liver, spleen, lymph node, bone marrow, and other).



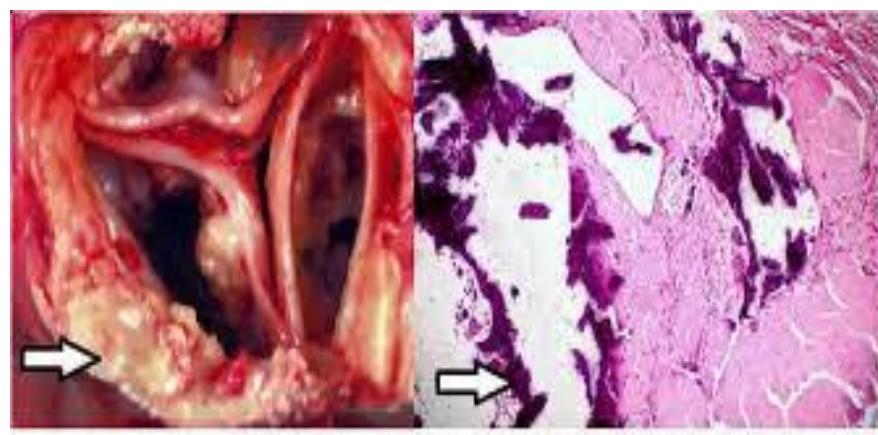
Generalized	Localized
<ul style="list-style-type: none"> ● Primary: Genetic error due to abnormality in ferritin-transferrin system controlling iron absorption from the duodenum leading to increased iron absorption and deposition in parenchymatous cells of: <ul style="list-style-type: none"> - liver: pigmentary cirrhosis. - Pancrease: DM. - Skin: bronzed coloration. - Skin & Pancrease: bronzed diabetes. 	<ul style="list-style-type: none"> ● In any tissue: <p>Mechanism:</p> <ol style="list-style-type: none"> 1/Hemorrhage or hematoma 2/RBCs hemolysis liberating iron 3/Hemosiderin deposition 4/Phagocytoased by macrophages 5/Yellow or brown coloration
<ul style="list-style-type: none"> ● Secondary: increased iron due to: <ul style="list-style-type: none"> - repeated blood transfusion. - hemolytic anemia. - increased iron intake. 	<ul style="list-style-type: none"> ● In lung: <p>Mechanism:</p> <ol style="list-style-type: none"> 1/Chronic venous congestion 2/Increase capillary blood pressure 3/RBCs extravasation 4/Iron release forming Hemosiderin 5/Phagocytosed by alveolar macrophages forming heart failure cells .

❖ Pathological calcification:

- **Definition:** deposition of calcium salts in sites other than bone and teeth.
- **Gross picture:**
 - Colour: opaque white.
 - Consistency: hard.
- **Microscopic:** Calcium appear dark blue with hematoxylin.

- Types:

Dystrophicic	<ul style="list-style-type: none"> ● Def: calcification of injured and necrotic tissue. N.B: blood calcium is normal. ● Examples: In injured tissues as : Atheroma In necrotic tissues as: Old thrombi.
Metastatic	<ul style="list-style-type: none"> ● Def: calcification normal living tissue ● Causes: elevated blood calcium level is due to : <ul style="list-style-type: none"> A-Increase calcium absorption from intestine as in hypervitaminosis D B-increase calcium mobilization from the bone ● Examples: Renal tubules (nephrocalcinosis).
Calcinosis	Rare type of unknown cause.
Stone Formation	Ca deposition in cavities of hollow organ as urinary and biliary tracts



2- Extracellular deposits:

■ May be:

- CHO: myxomatous change.
- Protein: connective tissue hyalinosis.
- Amyloid: amyloidosis.

● Amyloidosis (Fibrillosis / Amyloid deposit):

- Definition: extracellular deposition of homogeneous hyaline eosinophilic amyloid (**abnormal protein**).

- Classification:

1- Systemic (generalized):

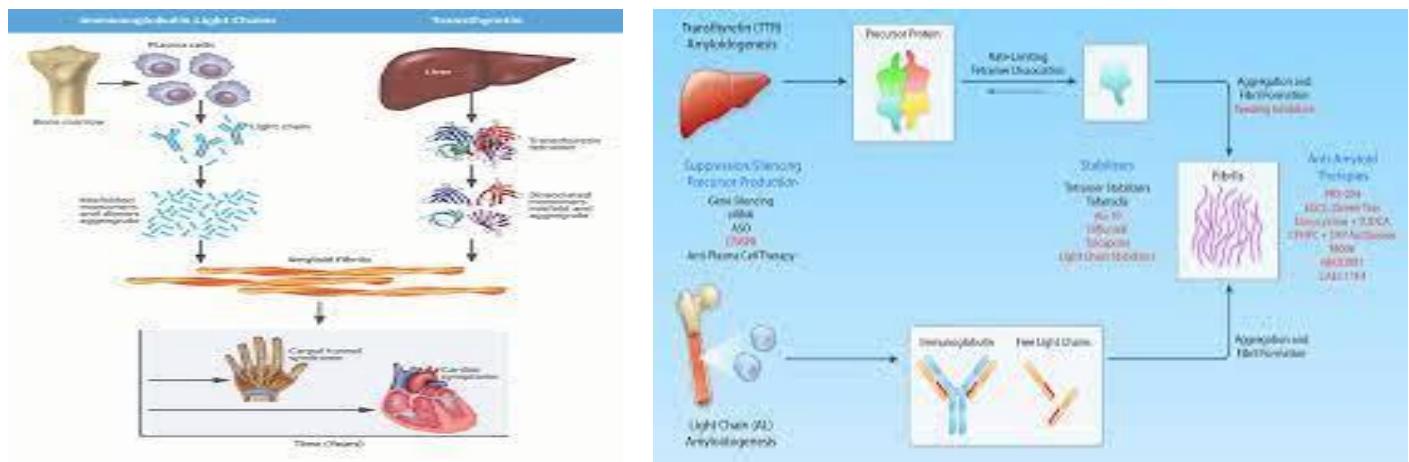
- a- Primary Amyloidosis.. Immunocytic Derived AL type
- b- Secondary Amyloidosis.. Reactive Amyloid (AA)
- c- Haemodialysis (70% of chronic renal failure patients).
- d- Heredofamilial.

2- Localized:

A) Systemic Amyloidosis

	Primary	Secondary
Etiology	<p>Primary disease of unknown etiology which may be due to :</p> <ul style="list-style-type: none"> -Colonial expansion of immunocyte proliferation -Neoplastic proliferation of immunocytes as in multiple myeloma (mm) 	<p>1-Chronic suppurative inflammation:</p> <ul style="list-style-type: none"> -Chronic osteomyelitis -Chronic lung abcess <p>2-Chronic specific inflammation as tuberculosis</p> <p>3-Autoimmune disease</p> <p>4-Malignant tumors as renal cell carcinoma</p> <p>5-Others; Crohn's disease and ulcerative colitis (UC) .</p>
Mechanism	<p>1) Immunocyte proliferation</p> <p>2) Increase abnormal Ig secretion</p>	<p>All causes are chronic diseases characterized by</p> <p>1) persistent tissue breakdown</p>

	<p>3) Degradation of immunoglobulins into heavy and light chains</p> <p>4) Increase light chains</p> <p>5) AL type Amyloid</p> <p>6) Deposition extracellular</p> <p>7) Primary Amyloidosis</p>	<p>2) Secretion of proteolytic enzymes and cytokines</p> <p>3) Stimulation of liver to secret SAA (Serum Amyloid Associated Protein)</p> <p>4) Deposition extracellular in many organs (secondary Amyloidosis)</p>
Organ affected	<p>-Myocardium - Intestine - Esophagus - skin - Peripheral nerves -</p> <p>-May be also in solid organs as Kidney</p>	<p>- Widely distributed but particularly affect parenchymatous organs:</p> <p>Kidneys _ liver</p> <p>Spleen _ lump nodes</p> <p>- May be intestine and heart</p>



3- Haemodialysis associated amyloidosis:
occur in **70% of patients with chronic renal failure subjected to chronic haemodialysis.**

B) Localized Amyloidosis

1- Endocrine associated amyloidosis.

- Ex: in medullary carcinoma of thyroid.

2- Senile amyloid heart.

- In old age amyloid material (**transthyretin**) may be deposited extracellularly in heart.
- **Pathological picture of amyloidosis:**
 - **Gross:** **enlarged** size, **smooth** outer surface, **firm** consistency, the cut section is **waxy** in colour with **sharp borders**.
 - **Microscopic:** homogenous, eosinophilic, glassy material deposits in the **walls of arteries** of the organ then leads to **atrophy**.

C) Amyloidosis in different organs

- **Spleen:** may be localized or diffuse.

	Localized	Diffuse
Amyloid deposition	<ul style="list-style-type: none"> -Walls of central arterioles of lymph follicles -Interstitial tissue of the splenic follicles white pulp. 	Reticulum of red pulp and walls of sinusoids Pressure atrophy of the splenic follicles.
Gross PIC	Moderately enlarged. C/S: scattered waxy colored nodules in a red brownish background (Sego spleen).	<ul style="list-style-type: none"> - Markedly enlarged. - C/S: diffusely replaced by waxy colored Amyloid material
Mic PIC	<ul style="list-style-type: none"> - Narrowing of arteriolar lumen that leads to Atrophy of the follicle then completely replaced by waxy material 	Amyloid deposits in walls of sinusoids replacing red pulp. Follicles undergo atrophy

■ Amyloidosis in liver:

- Gross: brown streaks on yellow background.

- Microscopic:

- Amyloid deposits in:

- a) Walls of blood vessels

- b) Hepatic sinusoids

- Liver cells degenerate

■ Amyloidosis in kidney:

- Gross: pale grey streaks on yellow background.

- Microscopic: deposition in:

- a- walls of arterioles and venules leads to ischemia and fatty degeneration in convoluted tubules leads to atrophy and fibrosis.
- b- Basement membrane of glomeruli & collecting tubules.
- c- Interstitial tissue between renal tubules.

■ Staining of amyloid:**- Gross staining:**

* Lugol's iodine: stain mahogany brownish into violet blue on adding 1 % sulfuric acid.

- Microscopic staining:

- a. Hematoxin and eosin → Pink (homogenous glass).

- b. Congo red turns to Orange color.

- C. Methyl violet → Rose pink in frozen sections.

- D. Immunostaining: By antibodies against the type of amyloid to detect:

- a. AL type “By AL antibodies”.

- b. AA type “By AA antibodies”

S W G



INFLAMMATION

CHAPTER 2

Patho Team

INFLAMMATION

- **Definition:** it is the vascular, lymphatic & cellular reactions of the living tissue against an irritant by which the defense mechanisms of the body can attack the cause to prevent tissue damage. Aiming at localization, destruction of the irritant and preparing for repair.
- **Nomenclature:** suffix + itis e.g. tonsillitis – appendicitis.
- **Types of inflammation:** 1- Acute. 2- Subacute. 3- Chronic.

ACUTE INFLAMMATION

- **Definition:** It is a type of inflammation caused by mild or severe irritant. It is characterized by short duration and rapid tissue response.
- **Mechanism of acute inflammation:**

I- Local changes:

1. Local tissue destruction.
2. Local vascular phenomenon.
3. Local reaction of tissue histiocytes.

II- General Changes:

1. Changes in blood cells.
2. Fever.
3. Loss of appetite.
4. Liver secretes proteins.
5. Hyperplasia of the draining lymph nodes.
6. Degenerative changes in parenchymatous organs.
7. Septicemia.
8. Pyaemia.

I- Local Changes of Acute Inflammation:

1. Local tissue destruction: Due to the injurious agents together with inflammatory mediators.

2. Local vascular phenomenon:

a- Transient vasoconstriction:

- Due to direct action of irritant.
- It lasts for few seconds.
- It is a protective process.

b- Vasodilatation of arterioles, capillaries & venules:

- Causing redness and hotness due to increased blood flow
- Caused by:
 - Chemical mediators.
 - Local axon reflex.
- Persists to the end of inflammation.

c- Slowing of blood flow (stasis):

■ Caused by:

1- Swelling of endothelial cells of capillaries.

2- vasodilatation and opening of capillary bed (100%) so blood distributes in wider area (stasis).

3- Viscosity due to escape of fluid exudates.

d- Formation of inflammatory exudates:

Inflammatory exudate is composed of fluid part and cellular part.

■ **Fluid exudate:** Escape of plasma to the zone of inflammation causing inflammatory edema.

■ It occurs due to:

1- Increased capillaries permeability due to:

- a. Formation of endothelial gaps by chemical mediators.
- b. Direct endothelial injury by the causative agent.
- c. Leucocytes mediated endothelial injury.

d. Transcytosis across endothelial cytoplasm.

e. Leaky newly formed capillaries.

2- Increase in hydrostatic pressure in the capillaries due to increased blood flow.

3- Increase in the osmotic pressure of the interstitial tissue fluid due to break down of large tissue protein into smaller ones.

4- Increase in the fluidity of the cement ground substances helping diffusion of the exudate in the interstitial tissue.

■ **Composition:**

1- Increased Protein (4-8gm%).

2- Increased Specific gravity (> 1018).

3- Increased fibrinogen fibrin network & clot on standing.

4- Turbid (leucocytes).

■ **Function:**

1- Formation of fibrin network to localize irritant and facilitate movement of leucocytes.

2- Dilute bacterial toxins.

3- Brings antibodies to kill bacteria.

 **Cellular exudates:**

Mechanism

1- Margination and pavementation of leukocytes.

2- Migration of leucocytes.

3- Leucocytes activation.

4- Diapedesis: Escape of RBC through wide pore.

NBs:

- ❖ PNLs Escape early (**6:24h**).
- ❖ Monocytes escape late (**1-2 days**) and become phagocytic known as macrophage.
- ❖ Eosinophils increase in allergic inflammation.
- **Function of cellular exudate:**
 - Polymorphnuclear cells attack, phagocytose and kill the organism by the action of their enzymes i.e microphage.
 - Later on phagocytosis by macrophage takes place.

▪ Chemotaxis:

Attraction of leukocytes towards the irritant by chemotactic e.g: bacterial toxins, C5, leukotriens & IL8.

▪ Phagocytosis:

it is the ingestion and destruction of foreign body and bacteria by phagocytic cells.

Steps:

- a) **opsonization:** Coating bacteria with certain proteins (opsonin) to target it for phagocytosis
 - b) **Recognition and attachment:** Opsonized bacteria bind to leucocytes receptors.
 - c) **Engulfment** by pseudopodia.
 - d) **Killing and degradation:** kill bacteria and help repair.
 - e) **Dilatation of lymphatic vessels:** to drain fluid exudate to lymph nodes, thoracic duct then to circulation to end inflammation.
- NB:** If exudate contains bacteria, lymphangitis and lymphadenitis occur.

3- Local reaction of tissue histiocytes:

Chemical mediators stimulate tissue histiocytes (macrophages) to proliferate and chemotact blood monocytes to the inflamed tissue to kill bacteria.

II- General Changes of Acute Inflammation:

1- Changes of blood cells:

a- **WBC's:** (normal leucocytic count:5000-10000/mm³)

1. **Leucocytosis:** Increase number of WBC more than 10.000/mm³.

- Neutrophils increase in pyogenic or suppurative inflammation.
- Eosinphils increase in parasitic infection and allergic reactions.
- Lymphocytes increase in viral infection and chronic inflammation.
- Monocytes increase in malaria.

2. **Leucopenia:** Decrease number of leucocytes e.g. typhoid fever.

B- **RBCS:** Some degree of anemia.

2- **Fever:** Due to affection of heat regulatory centers in hypothalamus by circulating pyrogens.

3- **Loss of appetite.**

4- **Liver secrete** c- reactive proteins and amyloid material A.

5- **Hyperplasia of the draining lymph nodes** and may occur in the reticuloendothelial system e.g. liver, spleen and bone marrow as a generalized defense mechanisms of the body.

6- **Degenerative changes** in parenchymatous organs due to toxic effects e.g. cloudy swelling and fatty changes.

7- **Septicemia.**

8- **Pyaemia.**

- **Cells of acute inflammation:**

1- P.N.L. (neutrophils).

2- Pus cells: killed P.N.L.

3 -Macrophage (histiocytes).

4- RBCs.

- **Cardinal signs of acute inflammation:**

1- Redness: Due to vasodilatation and increased blood Flow. Hotness:
Due to increased blood Flow.

2- Hotness: due to increased blood flow

3- Swelling: Due to fluid exudates.

4- Pain: Due to stimulation of nerve endings by bradykinin and PGE2 or its pressure by inflammatory edema.

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

- **Chemical mediators of acute inflammation:**

- **Vasodilation** is caused by Prostaglandins & Nitric oxide.

- **Increased Vascular Permeability** is caused by Vasoactive amines (histamine, serotonin), Bradykinin, Leukotrienes C4, D4, E4& Platelet-activating factor.

- **Chemotaxis, Leukocyte Activation** is caused by C5a, Leukotriene B4& Chemokines (e.g., interleukin 8).

- **Fever** is caused by: IL-1, IL-6, tumor necrosis factor & Prostaglandins.

- **Pain** is by: Prostaglandins & Bradykinin.

- **Tissue Damage** is caused by: Neutrophil and macrophage lysosomal enzymes, Oxygen metabolites & Nitric oxide.

- **Fate of acute inflammation:**

1- Resolution: When the cause of inflammation overcome by defensive mechanisms

2- Spread:

a) Local by breaking through fibrin barrier.

b) By natural passages

c) Lymphatic: Causing lymphangitis and lymphadenitis.

d) Blood: Bacteremia, septicaemia or pyaemia.

3- Chronicity: if the cause cannot be completely destroyed by the defensive mechanisms.

TYPES OF ACUTE INFLAMMATION

❖ **Suppurative inflammation (diffuse or localized).**

❖ **Non-suppurative inflammation.**

1- Acute Suppurative inflammation:

- **Definition:** It is an acute inflammation characterized by pus formation.

- **Cause:** pyogenic organism e.g staphylococci, streptococci

- **Composition of pus:**

1- The causative bacteria & their toxins.

2- Necrotic tissue.

3- Inflammatory fluid exudate.

4- Inflammatory cellular exudates with dead polymorphs i.e. pus.

- **Types s of suppurative inflammation:**

1- Localized suppurative inflammation:

a- **Abscess:**

- **Definition:** A localized suppurative inflammation characterized formation of a cavity containing pus.

- **Cause:** Staphylococci

- **Site: Any organ in the body**
- **Pathogenesis & pathological picture of abscess:**
 - a) Pyogenic bacteria & toxins cause central area of necrosis.
 - b) Necrosis surrounded by acute inflammatory cells mainly polymorphs and dilated congested blood vessels. So, abscess is now formed of **2 zones:**
 - 1- Central necrosis.
 - 2- Peripheral acute inflammation (pyogenic membrane).
 - c) Many PNL die and transformed to pus cells that secrete liquefying enzymes to liquefy the necrotic tissue. Now, abscess is formed of **3 zones:**
 - 1- Central necrosis.
 - 2- Mid zone of pus.
 - 3- Peripheral zone of acute inflammation (pyogenic membrane)Abscess enlarges by further necrosis & liquefaction.
- **Complications of abscess:**
 1. Chronic abscess.
 2. Spread of infection.
- 3. **Complications of healing:**
 - a) **Ulcer:** Persistent loss of continuity of surface epithelium
 - b) **Sinus:** A blind ended tract formed of infected granulation tissue between abscess cavity and the skin surface.
 - c) **Fistula:** A tract of infected granulation tissue between the abscess cavity and a hollow organ or between two hollow organs.
 - d) **Keloid:** large scar projecting on the surface. It is due to overdone repair.

b- Furuncle (boil):

- **Definition:** Small abscess in relation to hair follicle or sebaceous gland.
- **Site:** Face, neck and axilla.

c- Carbuncle:

- **Definition:** It is a localized suppurative inflammation characterized by multiple communicating deep abscesses, open on the surface by multiple sinuses.
- **Site:** Thick skin (back of neck, scalp, buttocks).

2- Diffuse suppurative inflammation (cellulitis):

- **Definition:** It is an acute diffuse suppurative inflammation.
- **Site:** loose subcutaneous tissue e.g. areolar tissue of orbit & scrotum.
- **Cause:** streptococcus hemolyticus.

❖ Cellulitis differs from abscess in:

- 1- Pus is thin and slowly.
- 2- Increased necrosis (slough).
- 3- Sanguineous.
- 4- Rapid spread.

II- Non-suppurative inflammation:

There's no pus formation. It's classified according to features of exudate

- | | |
|---------------|------------------|
| - Catarrhal. | - Fibrinous. |
| - Serous. | - Serofibrinous. |
| - Membranous. | - Necrotizing. |
| - Allergic. | - Haemorrhagic. |

1- Catarrhal Inflammation:

- **Definition:** It is a mild acute non suppurative **inflammation of mucous membranes** characterized by exudates rich in mucin.
- **Sites:** Mucosa of G.I.T & upper respiratory system e.g. Rhinitis (common cold)

2- Serous Inflammation:

- **Definition:** It is an acute non suppurative inflammation characterized by an exudate rich in serous fluid (i.e. watery fluid)
- **Examples:**

a- Burn blisters.

b- Inflammation of serous membranes (pleura, pericardium, peritoneum).

3- Fibrinous Inflammation:

- **Definition:** It is an acute non suppurative, inflammation characterized by exudates rich in fibrin.
- **Sites:**

a- Serous membranes (pleura, pericardium & peritoneum).

b- Alveoli of the lung (lobar Pneumonia).

4- Serofibrinous Inflammation:

- **Definition:** It is an acute non suppurative inflammation characterized by an exudate rich in serous fluid and fibrin.
- **Site:** Serous membranes.
- **Gross:** Visceral and parietal layers are thick, opaque, grey white, rough with loss of luster. Then increased serous fluid (= effusion).
- **Microscopic examination:**
- a- **Serosal cells** are swollen at first then become necrosed and desquamate (ulceration). Other cells appear degenerated and swollen.

b- Subserosal tissue: show dilated, congested blood vessels, acute inflammatory cells and edema.

c- Cavity: exudates rich in fibrin network together with inflammatory cells collect in the cavity. Then clear yellow serous fluid accumulate (effusion).

CHRONIC INFLAMMATION

▪ **Definition:** it slow, **long-term** inflammation lasting for prolonged periods of several months to years. It is characterized by the simultaneous tissue destruction and attempts of healing.

▪ **Causes:**

1- **After** acute inflammation which fail to cure.

2- **After** repeated acute attacks.

3- Or **chronic from the start** due to low virulent organism (when it is caused by a mild infection with a prolonged action such as tuberculosis)

▪ **Mechanism:**

1- **Persistent infections:** By certain microorganisms of low virulent type.

2- **Prolonged exposure to potentially toxic agents, either exogenous or endogenous:**

- **Exogenous:** as prolonged exposure to silica particles which causes inflammatory lung disease (silicosis)

- **Endogenous:** as atherosclerosis

3- **Autoimmunity:** autoantigens evoke immune reaction that results in chronic tissue damage and inflammation.

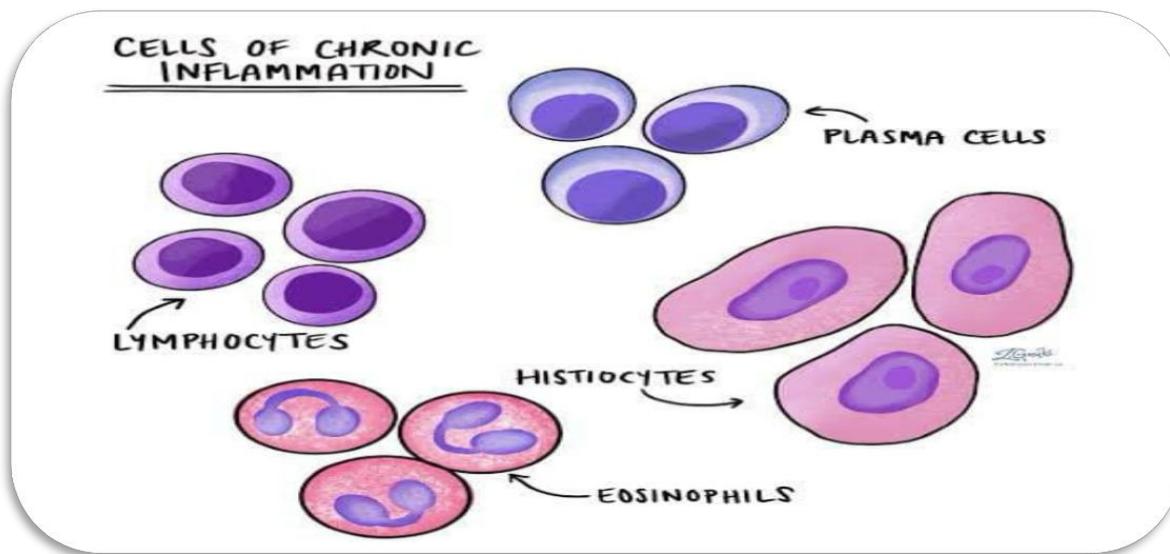
▪ **Morphological features:**

1- Minimal tissue destruction.

2- Scantly fluid exudates.

3- Blood vessels show endarteritis obliterans (EAO) (thick wall & narrow lumen).

4- Cells of chronic inflammation (diffuse or perivascular): lymphocytes, eosinophils, plasma cells, macrophages, fibroblasts and foreign body giant cells.



Types

Specific

- Caused by **specific organisms** which produces characteristic histologic appearance.
- The chronic inflammatory cells may form **tumor like mass called granuloma as TB.**

Non-specific

- Caused by **different types of organism** which **do not produce characteristic histologic appearance.**

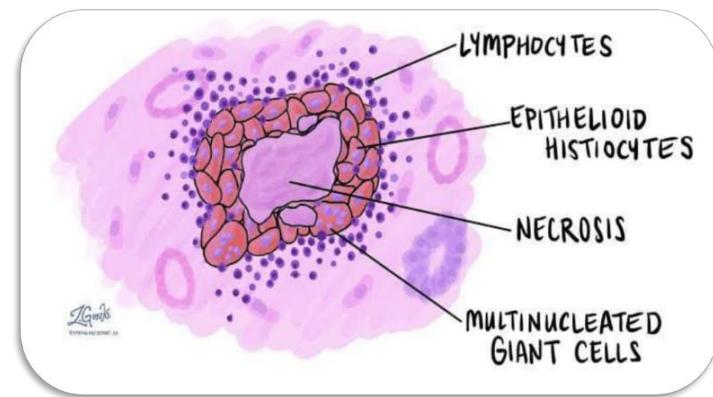
	Acute Inflammation	Chronic Inflammation
Onset	Sudden	Gradual
Duration	Short	Prolonged
Vascular Phenomena	Present	Slight or absent
Fluid Exudate	Abundant	Scanty(little)
Cardinal signs of Inflammation	Present	Slight or absent
Toxemia	Acute Type	Chronic Type
Cells	Mainly Neutrophils, Histiocytes(appears later on)	Lymphocytes, Plasma cells, Eosinophils, Giant cells, Fibroblast
Blood Vessels	Thin walled, dilated and congested	Endarteritis Obliterans

Granulomatous Inflammation

■ Definition of granuloma:

A **specific** pattern of chronic inflammation having characteristic histological appearance.

- It consists of a microscopic aggregation of **macrophages** that are transformed into **epithelium-like** cells (**Epithelioid cells**) surrounded by a collar of mononuclear leukocytes, principally **lymphocytes** and occasionally **plasma cells**.
- Immune reactions (**type IV hypersensitivity**) are usually involved in the development of granulomas.



■ Pathogenesis of granuloma:

Two types of granulomas, differ in their pathogenesis

1- Foreign body granulomas:

- Caused by **inert foreign bodies** as sutures, silica
- Macrophages engulf the foreign material and present some of it to appropriate **T-lymphocytes** resulting in their activation to produce **cytokines** and **IFN-γ**
- These mediators activate **macrophages** and transform them into **epithelioid cells** and **multinucleate giant cells**.

2- Immune granulomas: by agent's poorly degradable **delayed type hypersensitivity (DTH, type IV)**:

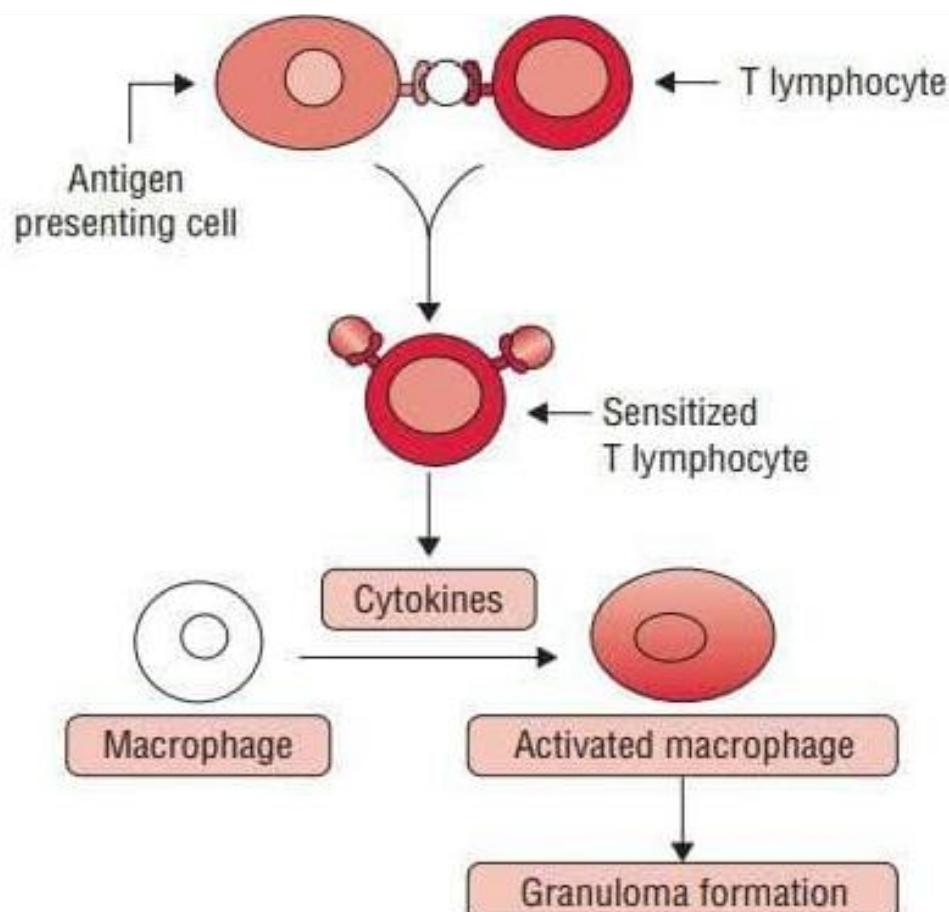
(A) Proliferation and Differentiation of CD4+ T Cells.

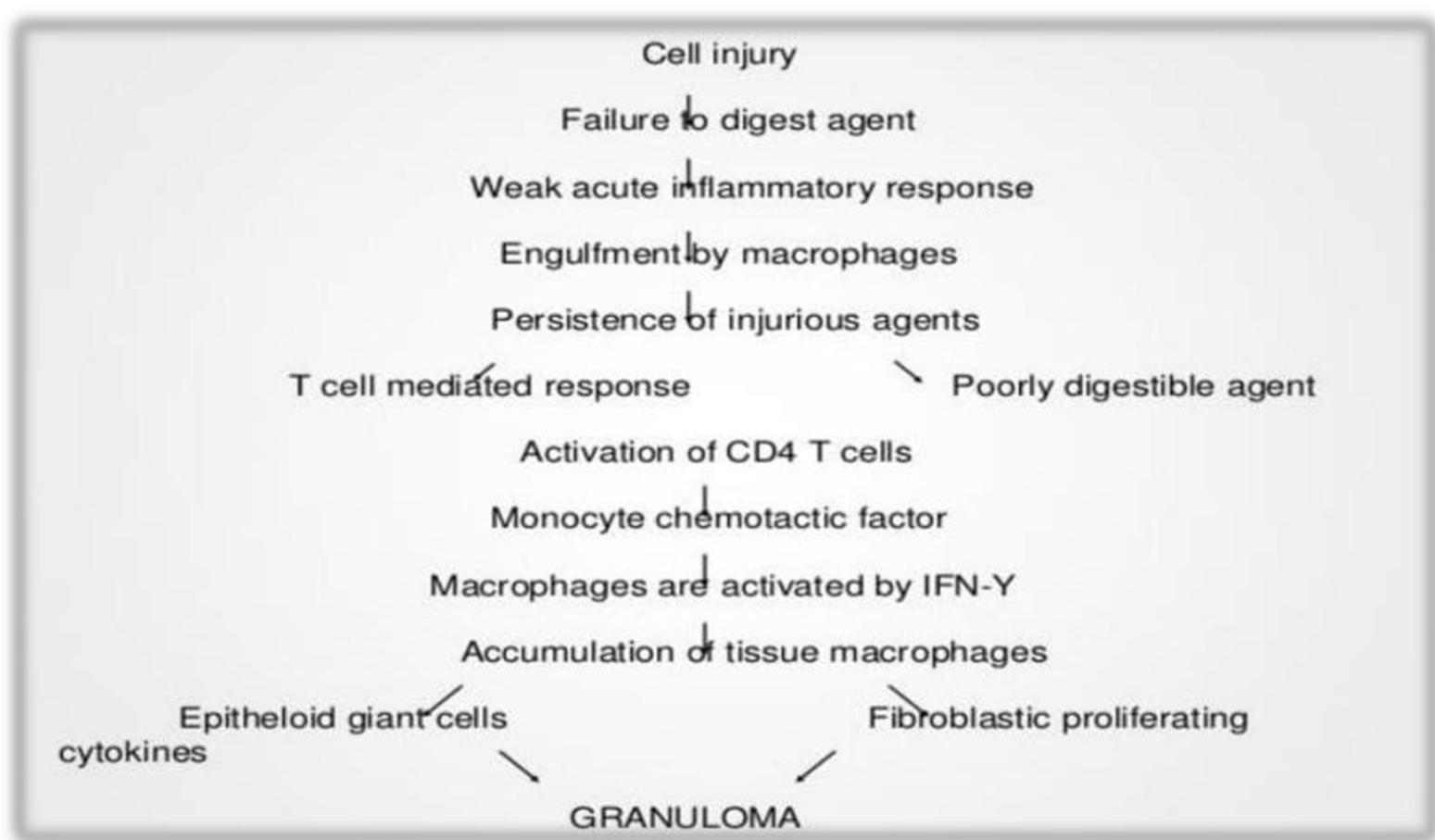
1] Macrophages engulf foreign protein antigen, process it, and present peptides to AG-specific Naive CD4+ T cells, and produce IL-12, which induces differentiation of CD4+ T cells to the TH1 subset

2] Some of the differentiated activated TH1 cells enter the circulation and may remain in the memory pool of T cells for long periods, sometimes years.

(B) Responses of Differentiated Effector T Cells.

- Repeated exposure to an antigen → activated TH1 secrete cytokines:
- The released cytokines (lymphokines) have the following actions:
 1. Attract leucocytes to the area of inflammation.
 2. Inhibit macrophages migration.
 3. Stimulate lymphocytes proliferation.
 4. Trigger inflammation and Causes tissue necrosis.





▪ Types of granulomatous inflammation:

1) Bacterial:

- a) Tuberculosis (*Mycobacterium tuberculosis*)
- b) Leprosy (*Mycobacterium leprae*)
- c) Syphilitic gumma (*Treponema pallidum*)
- d) Cat-scratch disease (*Bartonella henselae*)

2) Parasitic:

- a) Schistosomiasis (*Schistosoma mansoni*, *S. hematobium*, *S. japonicum*)

3) Fungal infection:

- a) *Histoplasma capsulatum* Blastomycosis
- b) *Cryptococcus neoformans*
- c) *Coccidioides immitis*

4) Inorganic Metals or Dusts:

- a) Silicosis
- b) Berylliosis

5) Foreign Body: Suture, breast prosthesis, vascular graft.

6) Unknown:

a) Sarcoidosis.

b) Crohn's disease.

Tuberculosis

- **Definition:** Chronic infective **granuloma** caused by **mycobacterium tuberculosis**; tubercle bacilli (human and bovine).
- In tuberculosis the granuloma is referred to as a **tubercle**.
- **Etiology:**



The disease is caused by **Mycobacterium tuberculosis** (human & bovine)

Types

Primary TB

- Infection for first time.
- Occur in Tonsils, Lung, Intestine, Skin.

Secondary TB

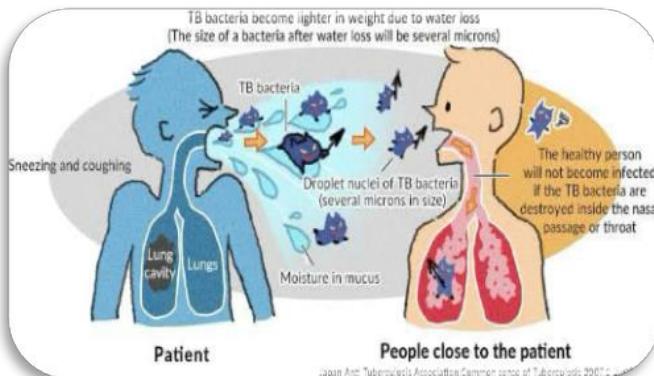
- Reinfection (2nd time).
- Occur Anywhere.

- **Route of infection:**

1. Inhalation: is **the commonest** method. The inhaled bacilli infect the tonsils or lungs.

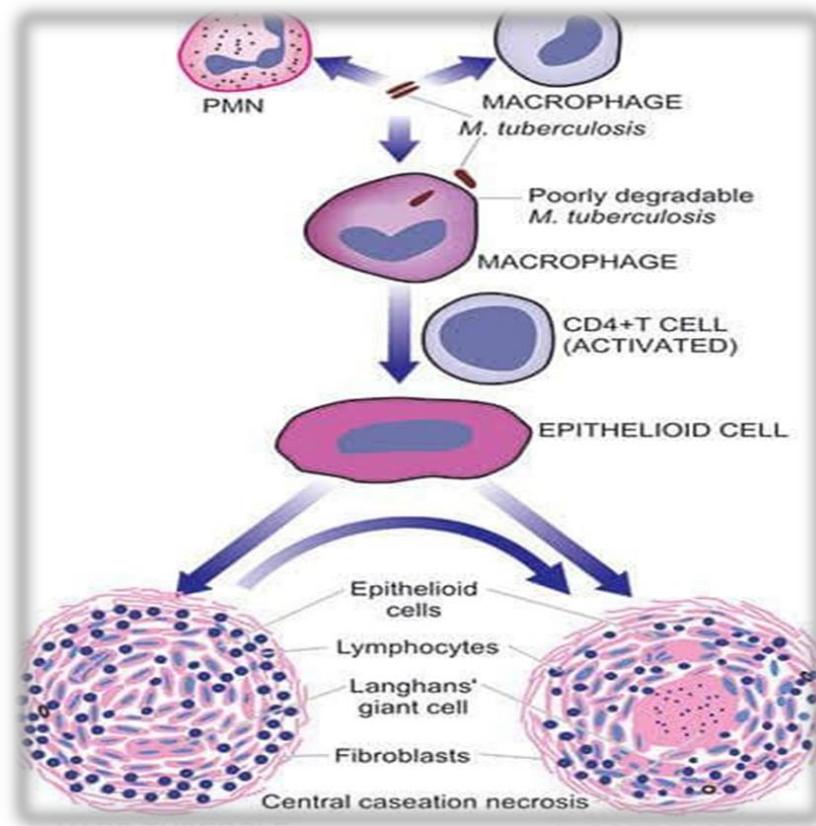
2. Ingestion: of **raw milk contaminated with bovine** (**mycobacterium bovis**) or human bacilli, infect the tonsils or the intestine.

3. Skin inoculation: by handling infected materials as **infected meat**. This method is not common.



■ Pathogenesis:

- **Mycobacterium tuberculosis does not produce any exotoxin, endotoxin or any histolytic enzyme but the pathogenesis depends on its ability to escape killing by macrophages and induce delayed type hypersensitivity.**
- **Hypersensitivity to tubercle bacilli plays the dominant role in tissue reaction and tubercle formation.**
- **Tubercle formation occur in the following steps:**
 - 1. Polysaccharide fraction of the tubercle bacilli attracts the neutrophil leucocytes within few hours.**
 - 2. They phagocytose the bacteria but are unable to destroy them as the bacteria are protected by the lipid capsule and the neutrophils do not contain the enzyme lipase.**
 - 3. The lipid fraction of the capsule attracts the macrophages (tissue histiocytes & blood monocytes) after the first day.**
 - 4. They collect and phagocytose the free bacilli and those inside the neutrophils and are now called epithelioid cells.**
 - 5. The bacilli are partially digested with the release of tuberculoprotein.**
 - 6. The tuberculoprotein stimulates a cell mediated immune response (delayed hypersensitivity) within a period of about 10 days.**
 - 7. Sensitized T-lymphocytes appear and surround the epithelioid cells.**
 - 8. The sensitized lymphocytes release various cytokines that increase accumulation of more macrophages and Sensitized T- lymphocytes and tubercle formation.**



■ Morphology:

❖ Macroscopic picture:

- The tubercle is of microscopic size.
- Numbers of tubercles exist side by side and may **fuse** forming small rounded grossly visible **gray follicles** 1-2 millimeters in diameter.
- When caseation occurs, the lesion appears **pale yellow** and **cheesy** in consistency.

Microscopically:

The tubercle appears as a rounded or oval compact collection of many **epithelioid cells**, **langhan's giant cells** and **lymphocytes**.

a) Epithelioid cells:

- Form **the center** of the tubercle.
- They are derived from blood **monocytes** and tissue **histiocytes**.
- They have an **epithelial** like shape and arrangement.
- The cytoplasm is **abundant** and **pale red**.
- The pale color is caused by **the lipids** of the tubercle bacilli.

- The cell borders are **indistinct**.
- The nuclei are **large, round or oval** and **vesicular**.

b) Langhan's giant cells:

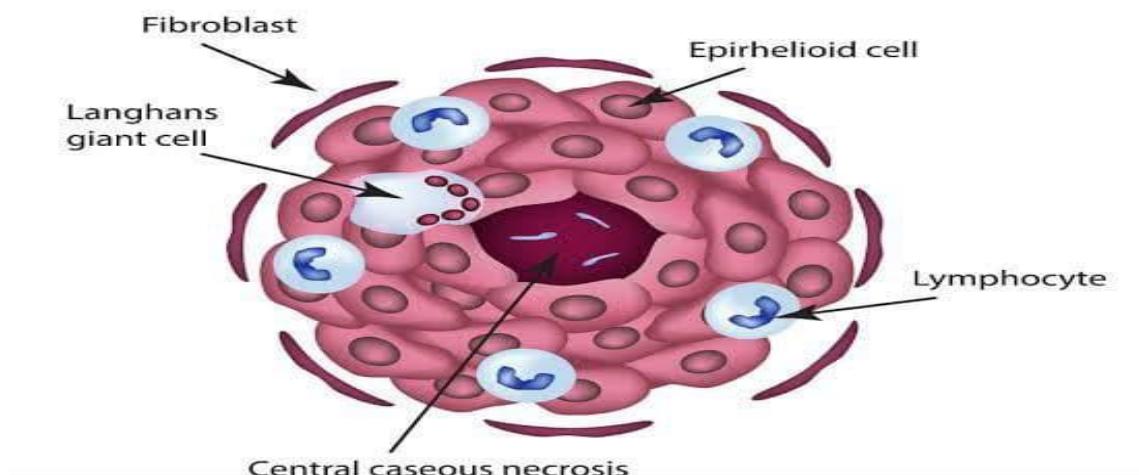
- Appear among the epithelioid cells.
- They are formed by **fusion** of a number of epithelioid cells.
- They have **large bodies**, **abundant red cytoplasm** and **multiple round or oval nuclei** arranged in a **circle or arch of a circle in the periphery**
- They remove caseating material and bacteria.

c) Lymphocytes:

- Form a ring around the epithelioid cells and extend in between them.

d) Older tubercles are surrounded by fibroblasts.

Structure tuberculous granulomas



■ **Fate of tubercle:**

1- High immunity:

a. Small foci are completely fibrosed.

b. Large foci are capsulated by fibrous tissue and its central caseating part shows dystrophic calcification.

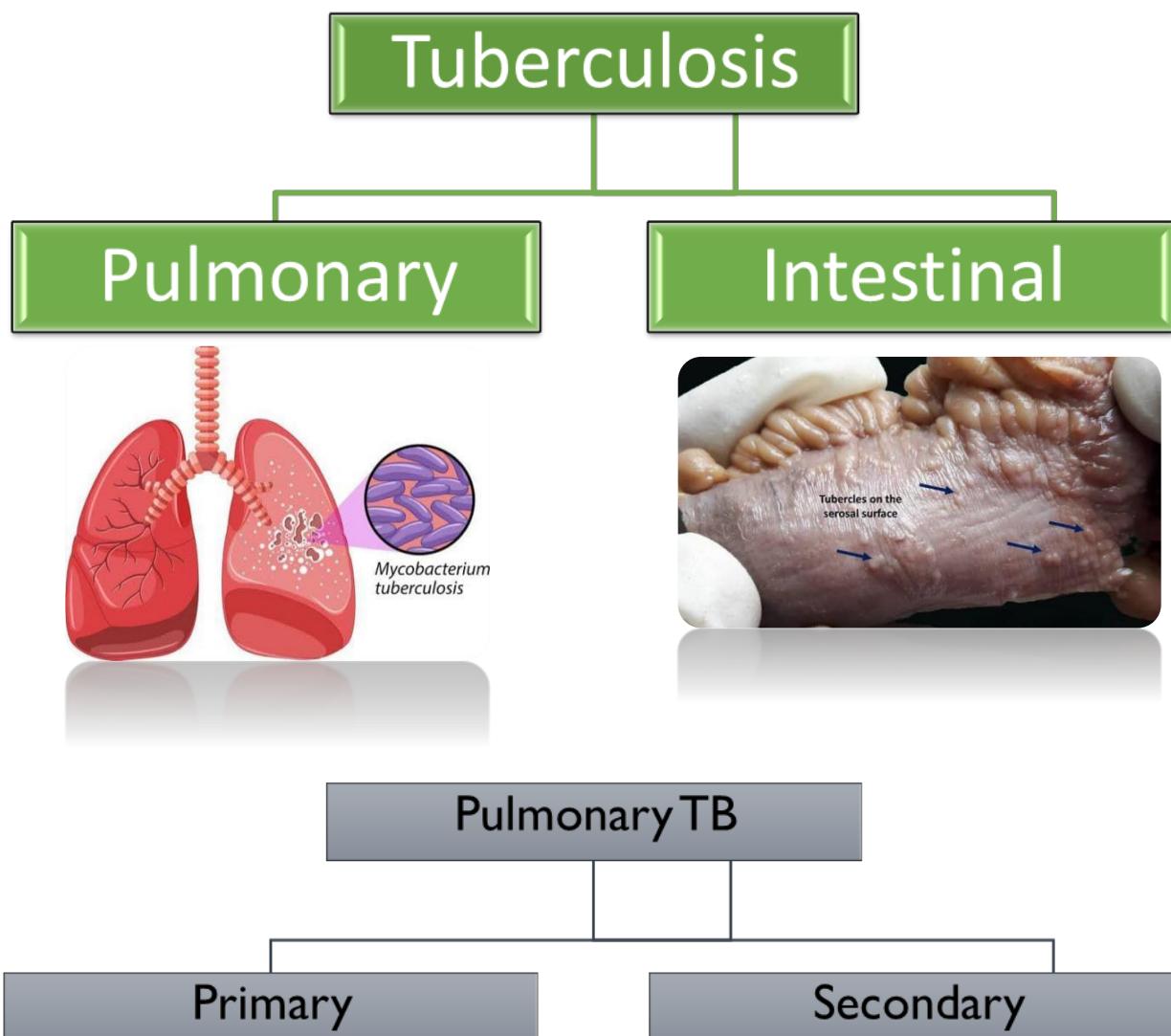
2- Low immunity:

a. **Direct spread:** to the surrounding tissues.

b. **Lymphatic spread:** pass via lymphatic vessels to the regional lymph nodes, causing tuberculous lymphadenitis.

c. **Blood spread:** A caseous focus may involve a blood vessel and the bacilli pass to the blood stream.

d. **Intracanicular spread:** spread through the lumen of a natural tube, e.g. spread through the bronchi or the ureter.



1- Primary Pulmonary Tuberculosis:

- **Definition:** Type of tuberculosis which follows the first infection of the lung with tubercle bacilli.
- **Pathology of primary pulmonary tuberculosis:** (Primary Pulmonary Complex)
- • **Triad formed of:**
 - 1) Ghon's focus.
 - 2) Tuberculous lymphangitis.
 - 3) Tuberculous lymphadenitis of the regional lymph nodes.

1) Ghon's focus:

Grossly:

- a) It is a **yellowish lesion**.
- b) 1-1.5 cm in diameter.
- c) It is commonly **subpleural**.
- d) It occurs anywhere in the lung, but the most frequently involved sites are the **lower aspect of the upper lobes** or **upper aspect of lower lobes**.

Microscopically:

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**.
- Caseation may be marked and the nodes may become matted forming a "**cold abscess**"

❖ **Fate of primary pulmonary complex:**

- 1) Healing.
- 2) Spread.

2- Secondary pulmonary tuberculosis: (re-infection)

- **Definition:** Secondary tuberculosis is that phase of tuberculous infection that arises in a **previously sensitized** individual whether the tubercle bacilli are derived from **endogenous** or **exogenous** sources "whenever defenses are lowered".
- **Infection is either:**
 - a. **Exogenous:** **inhalation** of human bacilli.
 - b. **Endogenous:**
 - **Reactivation** of a capsulated primary focus.
 - The lesion usually starts at **the apex of the lung** (less blood supply and more aeration)
 - Commonly **the right** (right bronchus is more in line with the trachea than the left bronchus).

- **Course:**

1- Regression:

- Occurs with **small number** of bacilli and **high immunity**.
- The lesion heals **by fibrosis** and is called fibrotic tuberculosis.

2- Progression: to

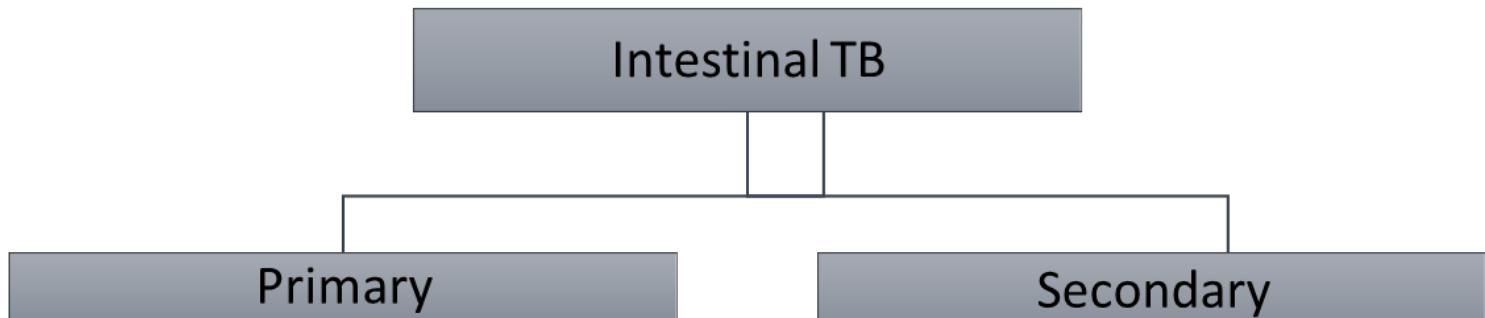
- **Chronic fibrocaseous pulmonary tuberculosis**
- **Bronchopneumonia** (Acute caseous pneumonia)

A. Chronic fibrocaseous pulmonary tuberculosis:

- In patients with **moderate levels of immunity** and **hypersensitivity**.
- **Slow chronic course.**

B. Acute caseous pneumonia (Bronchopneumonia):

- It is a **rare fatal condition** which develops as a complication of primary or secondary pulmonary tuberculosis.
- The lesion is caused by a **large dose of bacteria** in a patient with **high hypersensitivity and low immunity**.



1- Primary intestinal tuberculosis:

■ Etiology:

Due to **ingestion** of bovine bacilli in milk, forming a **primary complex** usually at the terminal ileum.

■ Pathology:

A primary intestinal complex occurs composed of:

1- Intestinal lesions:

- **Tubercles in the payer's patches** at the terminal ileum.
- The covering mucosa is intact or showing **tiny ulcers**.

2- Tuberculous lymphangitis.

3- Tuberculous lymphadenitis: (**tabes mesentericis**). The mesenteric lymph nodes become **enlarged, caseous and adherent**.

■ Fate:

1- Localization.

2- Spread:

- a) **Direct** and lymphatic: this leads to **tuberculous peritonitis**.
- b) **Hematogenous spread** leading to **isolated organ** or **miliary tuberculosis**.

2- Secondary intestinal tuberculosis:

■ Etiology:

Due to **swallowing infected sputum** in patients with chronic fibrocaseous tuberculosis.

■ Pathological features:

1- The lesions develop mainly in the **terminal ileum** and adjacent caecum.

2- The bacilli reach the **payer's patches**

3- **Caseous necrosis** and **erosion** of the covering mucosa results in **tuberculous ulcers**.

● These tuberculous ulcers are characterized by:

- a. **Multiple**.
- b. Their edges are **ragged** and **undermined**.
- c. Their floors are **yellowish, caseous** and **soft**.

d- The mesenteric lymph nodes show minimal lesions.

■ Complications: **FIFA hp**

1- Intestinal **Fistula**.

2- Spread of **Infection**.

3- **Fibrosis** leads to **intestinal obstruction**.

4- Secondary **Amyloidosis**.

5- Intestinal **hemorrhage**.

6- **Perforation** of the ulcers leads to **septic peritonitis**.



Bilharziasis (schistosomiasis)

- **Shistosoma is the most important helminthic disease.**
- The disease is endemic in Egypt and caused by two species:
 - **Shistosoma hematobium:** infect urogenital system.
 - **Shistosoma mansoni:** infect digestive system.
- **Pathogenesis of granuloma formation:**
 - Bilharzial lesions represent hypersensitivity reactions (**type I and IV**) against antigens produced by cercaria, adult worm and ova.
 - The miracidium inside the trapped ova secretes antigens and proteolytic enzymes → sensitization of T-lymphocytes → secrete lymphokines → attract macrophages, eosinophils and plasma cells → granulomatous reaction.

1. Bilharziasis of the Urinary System (bilharzial cystitis)

Lesion	Pathological picture	
	Gross	Microscopic
1- Hyperemia and petechial hemorrhage in bladder mucosa		
2- Sandy patches	Irregular grayish, gritty, granular patches covered by thin, atrophic mucosa.	1-Atrophic mucosa 2-Submucosa show large number of calcified ova surrounded by fibrosis
3- Polyps	1- 2:20 mm in diameter. 2- Reddish with granular, ulcerated surface. 3- Single or multiple. 4- Sessile or pedunculated.	Consist of: 1- Core of connective tissue showing ova surrounded by granulomatous reaction.

	5- Simple or complex.	2- Covered by hyperplastic mucosa.
4- Ulcers	<p>1- Show sharp border, granular floor, firm base.</p> <p>2- Single or multiple.</p> <p>3- Small or large.</p> <p>4- Superficial (shallow), deep (excavating) or very deep (fissured).</p>	<p>1- Loss of mucosal covering.</p> <p>2- Edge, floor and base of the ulcer show ova surrounded by granulomatous reaction with fibrosis.</p>
5- Dense fibrosis		
6- Urothelial changes *very common*		
a- Hyperplasia		
b- Brunn's nest (focal dipping of hyperplastic mucosa)		Solid buds- of Urothelial epithelium in the submucosa.
c- Cystitis cystica (central degenerative changes of Brunn's nests)		Cysts (small or large) lined by transitional epithelium
d- Cystitis glandularis (metaplastic changes in cystitis cystica)		Cysts lined by mucin-secreting columnar cells
e- Squamous metaplasia		
f- Leucoplakia	g- Dysplasia	

■ **Complications:**

1- Anemia due to recurrent hematuria.

2- Bladder neck obstruction by fibrosis leading to:

- Hypertrophy, dilatation and trabeculations of the bladder.
- Bladder diverticulum.
- Bilateral hydroureter and hydronephrosis.
- Chronic renal failure.
- Urine retention.

3- Bacterial infection → alkaline urine → stone formation, fistula and fibrosis

4- Carcinoma of urinary bladder as **cystitis glandularis**, **squamous metaplasia** and **leucoplakia** are precancerous lesions.

2. Bilharziasis of Digestive System (Intestinal Bilharziasis)

■ **Etiology:**

- It is caused by **schistosoma mansoni**.
- The oviposition is heavy in the rectum and decreases gradually towards the small intestine.

■ **Pathological lesions:**

- Hyperemia, edema and petechial hemorrhage in the mucosa and submucosa.
- **Polyps:** numerous, the covering epithelium shows glandular hyperplasia.
- **Ulcers:** usually small and superficial.
- **Sandy patches:** due to healing of lesions containing large number of ova by fibrosis.
- **Closed bilharzial lesions:** extensive fibrosis may affect musculosa and ova deposited outside the intestinal wall - indurated peritoneal

nodules or bilharzial pericolic mass. The affected segment is usually narrowed due to fibrosis. Ova may be not detected in the stool (closed lesion).

■ **Complications:**

- Anemia due to recurrent intestinal hemorrhage.
 - Secondary infection leading to dysentery.
 - Fibrosis and stenosis.
 - Hepatic bilharziasis.
-



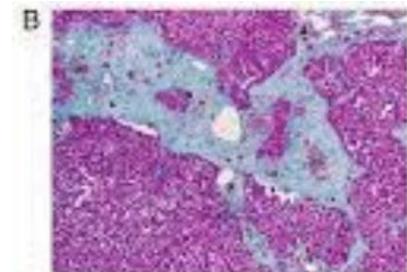
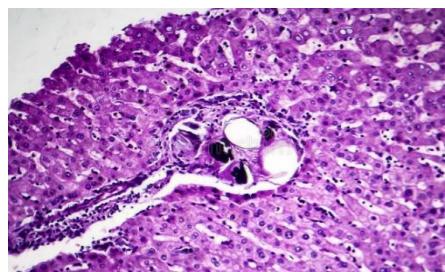
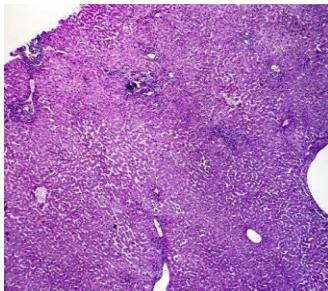
❖ Pathology of hepatic fibrosis

There are two types:

- 1- Fine periportal fibrosis.
- 2- Coarse periportal fibrosis.

what is the differences? gross:3s+4c+b microscopic:- architecture

	coarse	fine
cause	Deposition of large number of ova in large portal tracts.	Deposition of small number of ova in fine portal tracts.
size	decreased	normal
surface	irregular(elevations&depressions)	granular
Consistency	Firm	
color	Dark brown (B pigments)	
capsule	thick&fibrosed	
Border	Sharp	
cut section	Show thickened grayish white bands of fibrous tissue forming white collar around portal vein branches similar to patent pipes (pipe stem fibrosis)	Show fine grayish white strands of fibrous tissue inside portal tract
Architecture		preserved
hepatocytes	fatty change	
Kupffer cells	bilharzial pigments	
Portal tracts	Proliferating bile ducts. -Angiomatoids(new vessels formation). - Bilharzial pigments	
bilharzial granuloma	Large number of ova & dead worms deposited in coarse portal tracts forming granuloma	Small number of ova deposited in fine portal tracts forming granuloma.
Intravascular thrombosis & inflammation	Present (due to impaction of dead worms in portal vein branches in coarse portal tracts)	absent



❖ Complications:

1. Portal hypertension: Pathogenesis:

- a- Portal fibrosis → compression of portal veins.
- b- Angiomatoids transmit high pressure of hepatic artery to portal veins

Effects:

- a- Splenomegaly.
- b- Ascites.
- c- Porto-systemic shunt → esophageal varices → hematemesis.
- Piles → Bleeding per rectum.
- Caput medusae.

2. Portal and splenic vein thrombosis due to stasis.

3. Impaired hepatic function → lower plasma proteins & gynecomastia in male.

4. Ammonia encephalopathy:

Normally ammonia produced in the colon by the action of bacteria is converted to urea in the liver and does not reach the systemic circulation. In bilharzial periportal fibrosis with portosystemic shunt, ammonia can reach the systemic circulation and then the brain causing encephalopathy leading to coma.

QUESTIONS

■ Which one of the following is not an acceptable characteristic of bilharzial granuloma:

- a. It predominantly consists of a nodular collection of macrophages.
- b. Giant cells may develop.
- c. Neutrophils are always present. Eosinophilis are always present.

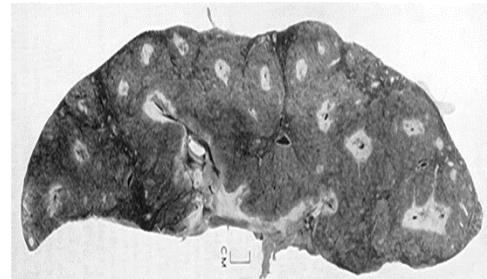
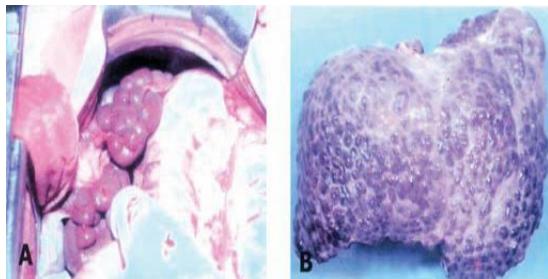
■ What is the most common bilharzial • cystitis lesion grossly?

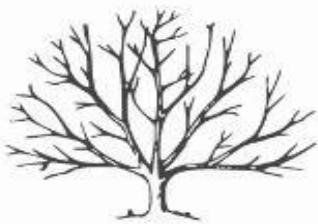
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|-----------|------------------|
| 1-ulcer. | 2-fibrosis. |
| 3-polyps. | 4-sandy patches. |

■ true or false

- intestinal bilharzial cause carcinoma .
- intestinal or bilharzial cystitis cause pulmonary bilharziasis.

■ which type is this?





CHAPTER 3

HEALING & REPAIR

PATHO TEAM

HEALING & REPAIR

- **STEM CELLS:** Mother of all cells. They are **unspecialized immature** retain the ability to renew themselves through mitotic cell division and differentiate into a diverse range of specialized cell types.
- **Healing and repair:** Repair is the replacement of damaged tissue by new healthy one.
- **Types of Repair:**

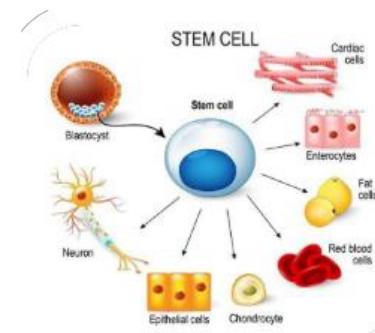
1- Regeneration:

Replacement of the injured tissue by cells of the same tissue type.

2- Replacement by connective tissue (Fibrosis):

Occur with sever local damage and if cells cannot regrow leading to replacement of damaged tissue by connective tissue (**scar formation**).

- **Types of Repair Depends on:**
 - a- Type of damaged cells.
 - b- Severity of tissue damage.

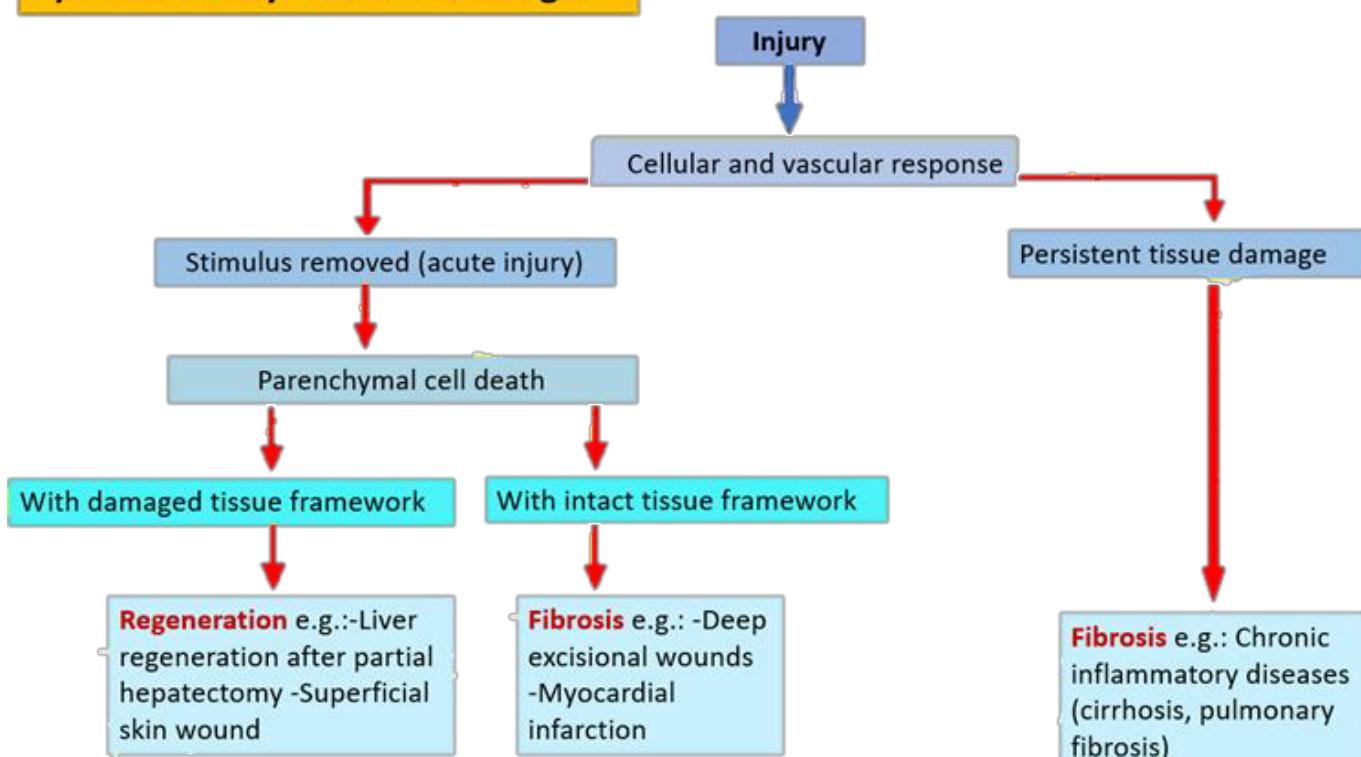


A) Type of damaged cells and their capacity to divide or proliferate

	Labile cells	Stable cells	Permanent cells
Character	Continuously dividing cells	Can undergo division in response to stimuli	Not dividing cells in postnatal life
Examples	- Surface epithelium - Hematopoietic and lymphoid tissue	- Parenchymal cells of glandular organs (liver, kidney). - Mesenchymal cells as (fibroblast, smooth muscle cells).	- Nerve cells. - Skeletal and cardiac ms cells.
Repair by	Complete regeneration	- small damage»» regeneration - large damage»» fibrosis	Fibrosis

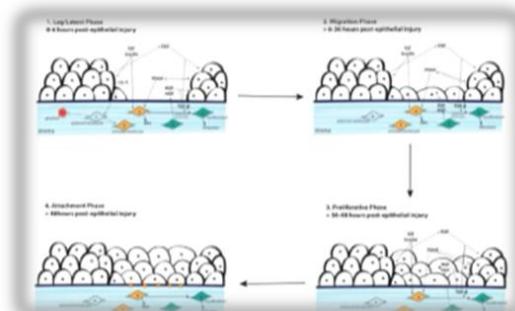


B) The severity of tissue damage:



1- Healing by regeneration

- **Definition:** Replacement of the injured tissue by cells of the same tissue type.
- **Mechanism:**
 - The neutrophils (**PNLs**) phagocytose and destroy all causative bacteria.
 - PNLs release enzymes which break up fibrin and remnant of dead cells, naming it into liquid re-absorbed through lymphatics.
 - **Macrophages** phagocytose any residual undigested debris which passes to lymphatics then to regional lymph nodes.
 - Remnant epithelial stem cells divide and replace the injured area



- **Examples of Repair by Regeneration:**

a- Regeneration of skin:

- The epidermis is **labile cells** which regenerate easily.
- The damaged dermis heals by granulation tissue and fibrosis(scar).

b- Regeneration of liver cells:

- **Acute** liver injury not disturbing hepatic framework → Regeneration e.g: Acute viral hepatitis.
- **Chronic** liver injury disturbing hepatic framework → fibrosis → regeneration nodules →→ Cirrhosis (e.g: Chronic viral hepatitis).

c- Repair of bone fracture.

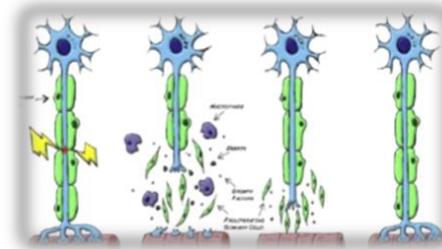
d- Peripheral nerve injury:

- **Healing of a peripheral nerve injury:**

* recover within **3 weeks**:

- Nerve injury → nerve cells **degeneration** (swell, Nissel granules disappear and nuclei become eccentric).

- Within 48 hours, the myelin and axis cylinder "axon" of the nerve become disintegrated.



- Schwann cells and macrophages engulf products of degeneration.

- Schwann cells proliferate from both **distal** and **proximal** stumps to form continuous **nurilemmal tube** in which a new myelin and axis cylinder grow.

2- Healing by fibrosis

- **Definition:** Replacement of the damaged tissue by granulation tissue which mature to fibrous tissue "**scar**".
- **Granulation tissue:** **Pink**, soft, granular tissue formed of proliferated fibroblasts and new thin-walled, delicate capillaries in loose extracellular matrix (ECM).
- **Mechanism:**

1- Migration and infiltration of the site of injury by macrophages, fibroblasts and myofibroblasts.

2- Angiogenesis: Formation of new blood vessels from pre-existing vessels.

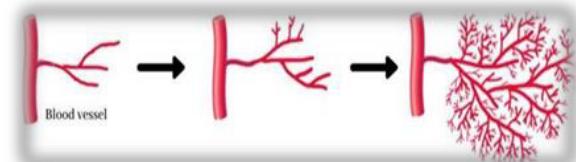
- **Steps:**

a- Basement membrane degradation of parent vessels.

b- Migration of endothelial cells.

c- Proliferation of endothelial cells giving solid buds

d- Maturation and organization into capillary tubes.



The new capillaries is leaky for proteins and red cells to the extravascular spaces giving edematous new granulation tissue.

3- Fibrogenesis:

a- Fibroblasts proliferation.

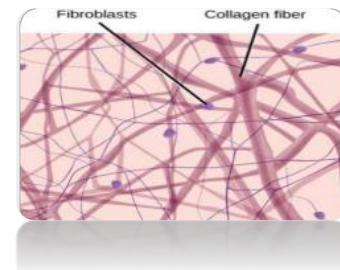
b- **Extracellular matrix deposition:** Fibroblasts secretes extracellular matrix proteins and collagen.

4- Remodeling:

- Maturation and reorganization of connective tissue to form a scar:

a- Newly-formed capillaries **regress gradually.**

b- Fibroblasts deposit sufficient amount of extracellular collagen forming fibrous granulation tissue then become inactive.



c- Contraction of granulation tissue through the contractile effect of myofibroblasts.

d- Dense collagen form collagenous scar, then macrophages secrete collagenase enzyme to modify the scar size.

e- The mature scar consists of:

- ✓ Dense collagen [type 1].
- ✓ Few capillaries.
- ✓ Extra cellular matrix.
- ✓ Inactive fibroblasts.

Wound Healing

- Wound healing is a good example of both **epithelial regeneration** (healing of epidermis) and **repair by granulation tissue** (healing of the dermis).
- The process is complex and controlled by growth factors.

■ **Mechanism:**

- It includes a number of processes:

1- Regeneration of epithelial cells.

2- Migration and proliferation of both fibroblasts and connective tissue cells (fibrogenesis and angiogenesis).

3- Synthesis of extracellular matrix protein.

4- Remodeling of granulation tissue and parenchymal components.

5- Collagenization and wound strength.

■ **Types of wound healing:**

Depending on **the type of wound**, there are:

a- Primary union (first intension): In clean, incised wound with minimal tissue loss (surgical incision).

b- Secondary union (second intension): In infected, large wound with extensive tissue loss (abscess, ulcers, gaping, wounds).

(A) Healing by primary union

Day	Events
Day 1	<ul style="list-style-type: none"> - Blood clot formation. - Neutrophils appear. - Mitosis of epithelial basal cells begins.
Day 3	<ul style="list-style-type: none"> - Macrophages replace PNL and start phagocytosis. - Granulation tissue invades the wound gap. - Collagen fibers start to appear.
Day 5	<ul style="list-style-type: none"> - The incision space filled by granulation tissue. - Normal thickness of epidermis with normal keratinization.
Second week	<ul style="list-style-type: none"> - Collagen accumulates with proliferated fibroblast. - Progressive disappearance of capillaries. - Scab separates.

At the end of first month	The mature scar consists of: <ul style="list-style-type: none"> - Cellular granulation tissue devoid of inflammatory infiltrate. - Covered by regenerated epidermis. - Tensile strength of scar take months to get its maximal strength.
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(B) Healing by secondary union

- **Similar to first intension but differs in:**

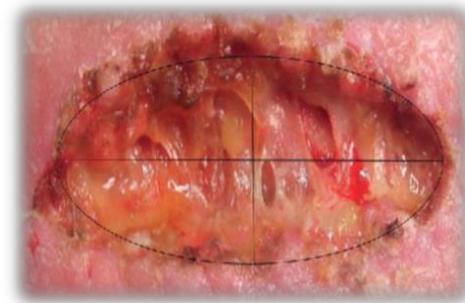
1- More loss of tissue, excess inflammation, healing takes longer time.

2- **Epithelial proliferation cannot fill the gap** so granulation tissues grow in from the margin to fill the gap. Then epidermal cells grow over the surface of granulation tissue to complete epithelial regeneration.

3- The amount of **granulation tissue is large** so the formed scar is big.

4- **Dermal adenexa** do not regenerate.

5- Tensile strength increases gradually.



❖ Factors affecting the healing process

Systemic factors	Local factors
1) Nutrition:	#Impair healing:
a- Vitamins C and D deficiency.	1- Infection.
b- Zinc deficiency.	2- Impaired blood supply.
c- Low protein diet.	3- Type of injured cells Perfect in labile& stable cell, Scar in permanent cell.
2) Diabetes mellitus.	4- Radiation Delay wound healing.
3) Steroid therapy.	5- Denervation.
	#Promote healing:
	1- Removal of dead tissues.
	2- Antibiotic administration.

❖ Complications of wound healing:

More in secondary union:

1- Cosmetic deformity (contraction) due to extensive shortening of collagen.



2- Functional troubles due to contracture of scar:

- Fibrosis of inflamed joint produce joint ankylosis.

- Fibrosis of serous membranes produces adhesion (fibrosis between visceral and parietal layers).

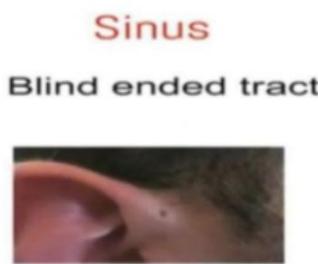
3- Keloid formation: Swelling at site of wound due to excessive collagen formation projecting on the surface covered by thin stretched epidermis, **Common in black**, Recurs after surgical incision, but **shrinks by irradiation**.

4- Chronic ulcer: is a loss of continuity of the surface epithelium, or mucous membrane.

5- Chronic sinus: a **blind ended tract** between the depth of the wound and the skin surface due to persistent infection which destroy granulation tissue forming a tract lined by infected granulation tissue.

6- Fistula: a **tract** between two hollow organs due to damage to granulation tissue.

7- Squamous cell carcinoma: very rare from epithelium of the scar.



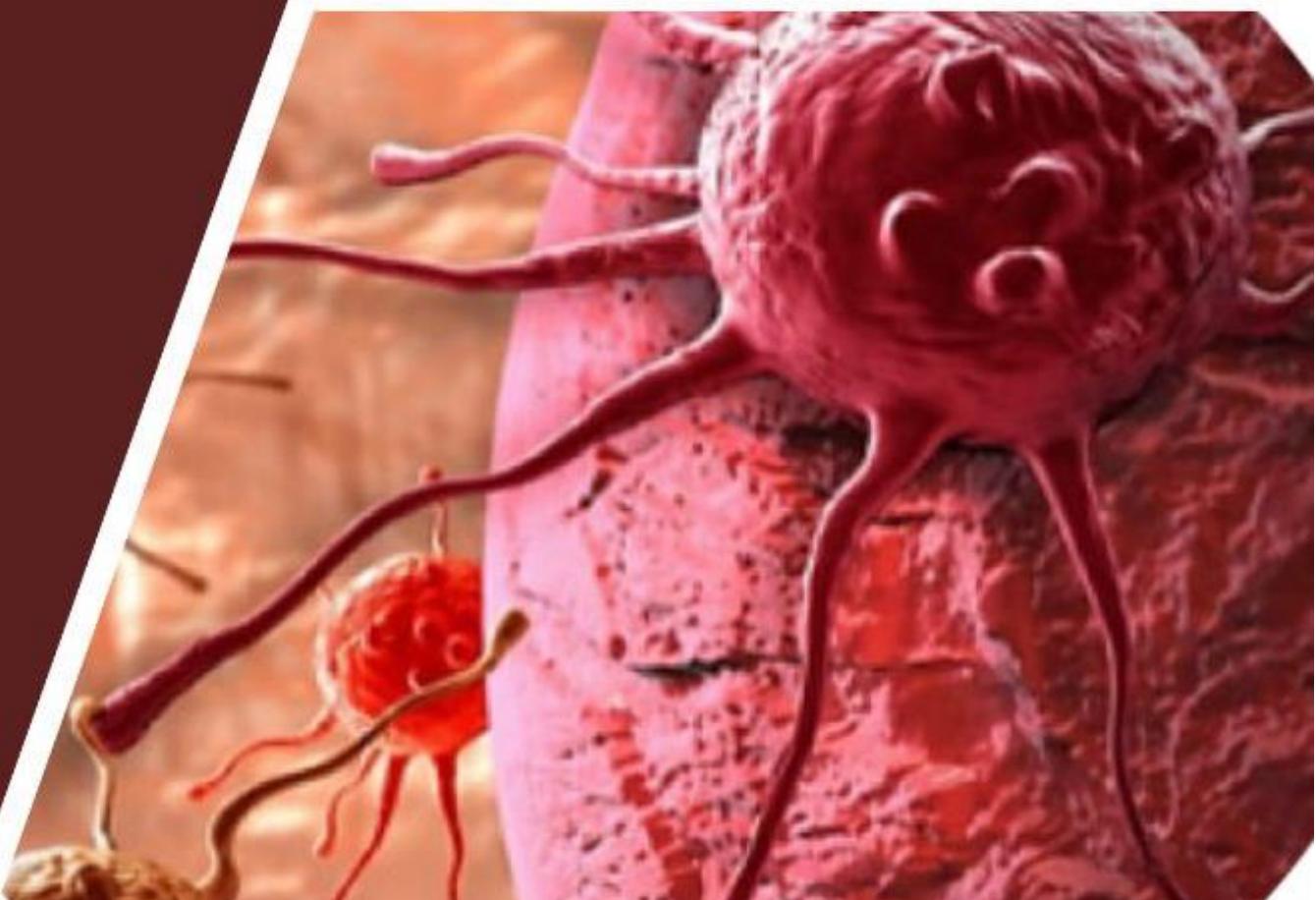
Wait for part 2

GOOD LUCK

PART 2



2023
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GENERAL PATHOLOGY
FIRST YEAR

BY
PATHO TEAM

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Chapter 4

Bacterial Infection

BACTERIAL INFECTION

- **Definition:** Invasion of the body by pathogenic organism.

- **Types:**

- 1- Toxemia.
- 2- Bacteremia.
- 3- Pyaemia.
- 4- Septicemia.



- **Routes of Infection:**

- 1- **Exogenous organisms:** enter the body by:

- a- Direct contact.
- b- Inhalation.
- c- Ingestion.

- 2- **Endogenous:** they present normally in the body, cause pathogenesis if there is any deficit in "Immune system".

- **Degree of infection (depends on 2 factors):**

- a- Virulence & Dose of organism.
- b- Resistance (Immunity) of the body.

Toxemia

- **Definition:** is a circulation of bacterial “**Toxins**” in the blood with production of pathological & clinical manifestation.

- **Bacterial Toxin may be:**

- **Exotoxin:** Diphtheria & Tetanus bacilli.
- **Endotoxin:** Pneumococci.

- **Types of toxemia:**

a- Acute.

b- Chronic.

- **Manifestations of toxemia:**

a- **Acute toxemia:**

1- general signs: fever, rigors, sweating, headache and pain all over the body.

2- degeneration such as:

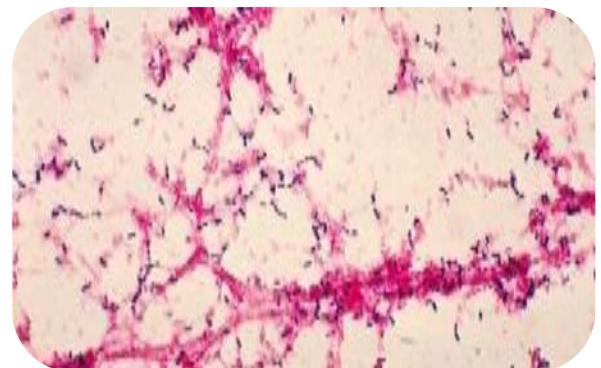
- **Cloudy swelling** in the heart, liver and kidney.
- **Hemorrhage** and **necrosis** in adrenal cortex may cause death.
- **Tubular necrosis** of the kidney and **peripheral neuritis** are specific effects of toxemia on certain organs according to the type of infection.

b- **Chronic toxemia:**

1- Amyloidosis eg: TB.

2- Depression of bone marrow cause “**anemia**”.

3- Low grade fever.



Bacteremia

- **Definition:** it is a “**transient**” presence of bacteria in blood from septic focus or after tooth extraction e.g: Tonsillitis.
- **Effects:**

1- Small numbers of organisms:

Rapidly phagocytosed by (R.E.S) “liver, spleen and lymph node”.



2- Large numbers of organisms: may result:

- a- Rigors.
- b- Kidney may filter the organism and may be affected causing ***Renal infection***.
- c- Subacute endocarditis in patient with congenital deficit in heart caused by streptococcal viridans bacteremia.

Pyaemia

- **Definition:** it is a condition in which multiple small “**abscesses**” form in different organs as a result of impaction of septic emboli or due to arrest of pyogenic organisms circulating in blood in various organs.
- **Pathogenesis:**
 - Septic thrombophlebitis (**specific focus involves a vein**).
 - Break down of the septic thrombus into fragments **by proteolytic enzymes**.
 - These fragments circulate in the blood stream as: **septic emboli**.
 - Next the septic emboli get impacted in small vessels of different organs, producing multiple small pyemic abscesses.

■ Types of pyaemia:

1- Systemic pyaemia: occur when the septic emboli are carried by the systemic veins as occurs in:

- a- acute hematogenous osteomyelitis.
 - b- septic sinus thrombosis.
 - c- puerperal sepsis.
 - d- acute bacterial endocarditis.
- **Sites of systemic pyaemia:** kidney, liver and brain.
 - **The abscesses form primarily in lungs.**

2- Portal pyaemia:

The septic emboli are carried by “**portal veins**”.

- **Occur in:**

a- acute suppurative appendicitis.

b- infected piles.

c- suppuration of the gall bladder, colon and rectum.

- **Sites:** mainly in “**liver**”.

- **Pathological picture of pyemic abscesses:**

a- The affected organs show multiple small abscesses.

b- The abscesses are the same in size, peripheral in position, rounded in shape, **yellow** in color, surrounded by dark “**red**” zone of congestion.

Septicemia

■ **Definition:** Circulation and multiplication of pathogenic **virulent organisms** and their “**toxins**” in the blood.

■ **Causes:** any pyogenic organism can complicate the following conditions:

a- Puerperal sepsis or suppurative endometritis.

b- Acute hematogenous osteomyelitis.

c- Septic wounds in foot & hands.

■ **Pathological features of septicemia:**

- 1- **Petechial haemorrhage** all over the body e.g: skin, mucous membrane.
- 2- The blood become “**fluid**” and the post-mortem clotting will not form.
- 3- **Degeneration** in heart, kidney and liver.
- 4- Acute bacterial endocarditis.
- 5- Acute splenic swelling “**pathognomonic**”.

Toxemia	Bacteremia	Pyaemia	Septicemia
Caused by bacterial toxins	Small amount of bacteria	Cause septic emboli	Large amount of bacteria
There are 2 types: a- Acute b- Chronic	Good Immunity	There are 2 types: a- Systemic b- Portal	Bad Immunity
Chronic toxemia cause anemia	No toxin	The abscesses are yellow, peripheral, rounded, surrounded by dark red zone of congestion.	Toxin

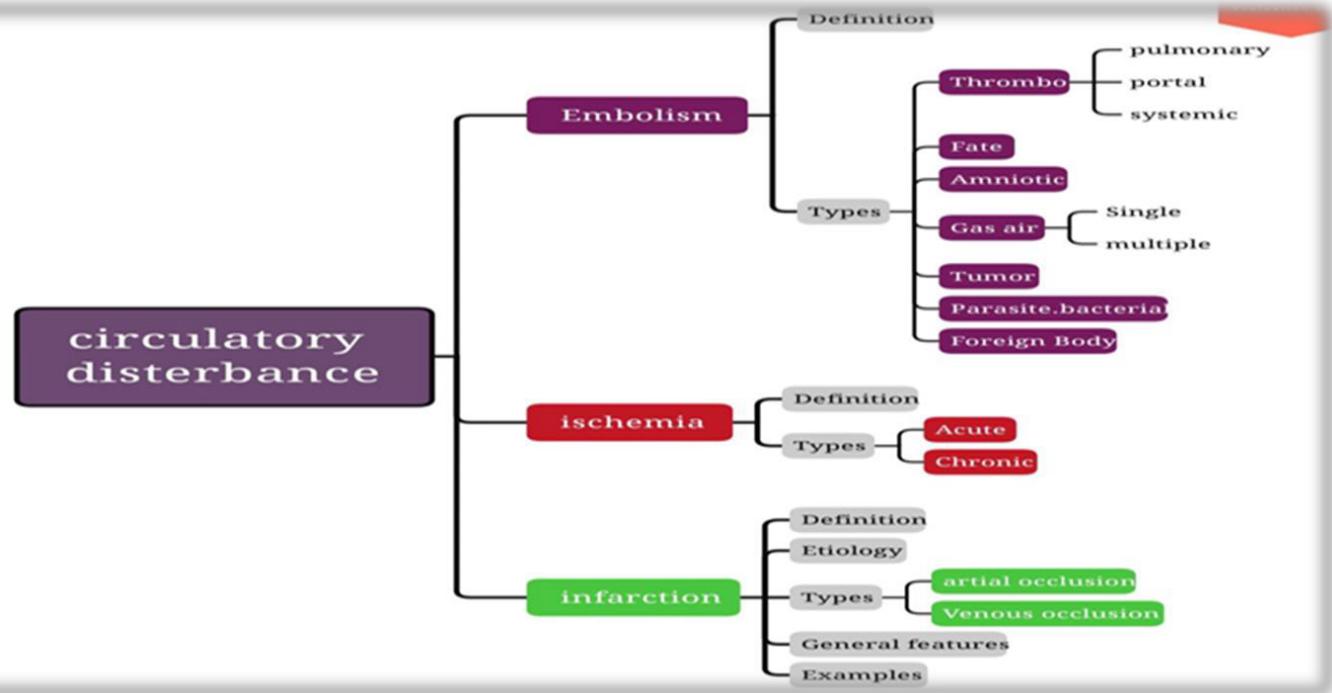
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CIRCULATORY DISTURBANCE

Chapter 5

Patho Team

CIRCULATORY DISTURBANCE



Ischemia

- **Definition:** Reduction of arterial blood supply to a tissue.

Types	Acute ischemia	Chronic ischemia
Definition	Sudden complete arterial occlusion.	Gradual Incomplete arterial occlusion.
Causes	1- Thrombosis. 2- Embolism. - Thrombosis and embolism are the most common cause. 3- Severe arterial spasm a- Raynaud's disease: rare disease characterized by <u>Spasmodic attacks</u> of small arteries and	1- Atherosclerosis 2- Endarteritis: Syphilis . 3- Arterial compression: Tumor . - Effects: The gradual occlusion give chance for the collaterals to open up:

	<p>arterioles in response to cold.</p> <p>B. Buerger's disease: inflammatory occlusion of vessels in <u>heavy smoking middle aged males.</u></p> <p>4- Surgical ligation of an artery.</p> <p>5- Strangulation of vessels as those of intestine in case of Strangulated intestinal obstruction (hernia Strangulated).</p> <p>6- Twisting of vessel as those of ovary and testis.</p> <p>7- Severe arterial compression, as in tight tourniquet.</p> <p>- Effect:</p> <p>Depend on the efficiency of collaterals:</p> <p>a- Occlusion of an end artery or artery with poor collateral results in ischemic necrosis (Infarction or gangrene)</p> <p>b- Occlusion of an artery with good collaterals may cause no significant effect.</p>	<p>a- With efficient collaterals: no effects.</p> <p>b- With poor collaterals, the following effects occur: Pain on exercise e.g. angina pectoris (cardiac pain) and intermittent claudications (lower limb muscle pain).</p>  <p>TORNIQUETE TOURNIQUET COMPLICATIONS © Study.com</p>
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Infarction

- **Infarct:** is an area of ischemic necrosis due to acute ischemia.
 - **Etiology:**
 - 1- **Arterial occlusion** by thrombus or embolus represents about 99% of cases.
 - 2- **Extensive venous obstruction** may rarely lead to ischemia.
 - The parenchymatous cells undergo necrosis earlier than fibrous stroma (**Coagulative necrosis**) except in **CNS infarction**, which is (**liquefactive**).
 - **Types of infarction:**
 - Infarction may be pale anemic or red hemorrhagic.
- 1- Infarction Due to Arterial Occlusion:**
- The occluded artery has poor collateral (end artery), therefore immediately after occlusion **no blood reaches the area which appears pale**.
 - After 24 hours blood collects in the area following **dilatation of the poor arterial collaterals**. Thus the infarction appears red.
 - After 36 hours, the necrotic cells within the infarction become swollen. This results in:
 - a- **Solid organs** as heart, kidney, spleen and brain, the blood cells within the ischemic area are squeezed outside the area; thus the infarct appears pale and is called **Pale or anemic infarction**.
 - b- **Loose richly vascularized tissues** as lung, much blood is trapped inside the ischemic area and will not be squeezed out, so the infarct appears red and is called **red hemorrhagic infarction**.

2- Infarctions Due to Venous Occlusion:

- Occur with or without arterial occlusion.
- Are **red hemorrhagic infarction**.
- These include infarction of intestine, ovary and testis due to twisting of their vessels.

■ General pathological features of infarction:

1- Gross features:

a- The infarction is usually **pyramidal** or **wedge-shaped** with its apex at the site of vascular occlusion and its base at surface of the organ. This is due to the fan distribution of end arteries.

b- When the infarction base is a serosal surface (pleura, pericardium, or peritoneum) it shows fibrinous exudates (**due to fibrinous inflammation**).

c- Margins of the infarction are hyperemic due to inflammation.

d- Infarction may be pale or hemorrhagic.

2- Microscopic picture:

a- The infarction is an area of **coagulative necrosis**. The necrotic cells exhibit pyknosis, karyorrhexis or karyolysis and appear swollen. They retain their structural outlines for sometimes but later becomes structureless.

b- In case of **CNS infarction** in which necrosis is of **liquefactive type**, the area is structureless from the start.

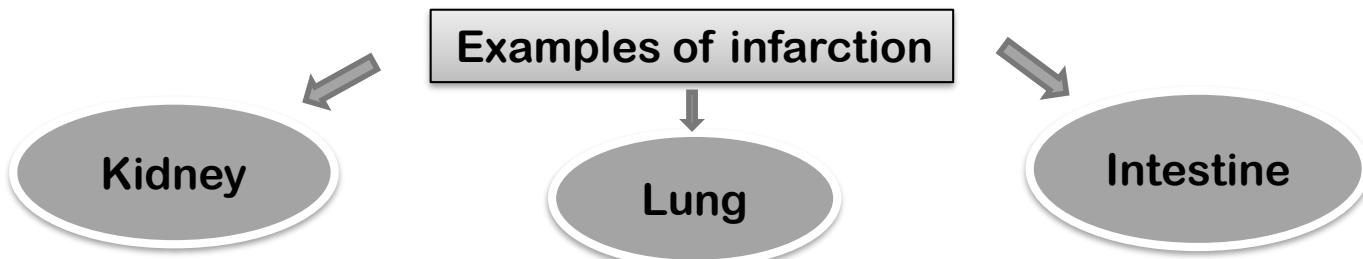
c- The margins of the infarction show **dilated capillaries** and some **inflammatory cells**.

d- The rest of the organ appears normal except in case of lung infarction where the **lung** shows **picture of chronic venous congestion**.

■ Fate:

Small infarction	Large infarction
Necrotic tissues are removed by macrophages, then granulation tissue fills the defect followed by fibrosis.	Gets surrounded by a fibrous capsule and its substance may show dystrophic calcification.





Gross picture: Pale infarct appears on the **convex border** of the kidney as a pale red cuboidal area.

Microscopic picture:

- a- Early the cells show various **post-necrotic changes**.
- b- Later on all structural details are lost, but appear as **homogenous pink shadows (coagulative necrosis)**.
- c- Lastly the necrotic tissue appears as granular red debris (**liquefactive necrosis**).
- d- The margin of the infarction is hyperemic and infiltrated by **neutrophils and macrophage**.

Clinically: Hematuria. No pain as kidney capsule is not affected.

Causes: The lung has a **double blood supply** therefore infarction does not occur unless both pulmonary and bronchial arteries are affected.

Gross picture: A Pyramidal **subpleural** red infarct. The pleural covering shows **fibrinous exudates**. Early infarct is swollen. Later healing occurs.

Microscopic picture:

- a- The infarct shows necrotic alveolar walls. The alveolar lumens are filled with blood (**intact and hemolysed RBCs**)
- b- The **margin of the infarct is inflamed**.

- c- The **adjacent lung tissue shows picture of chronic venous congestion**.

Clinically: Chest pain and hemoptysis.

Gross picture: The affected loop appears dark red, thick, and edematous.

The serosal coat is covered by fibrinous exudates. The intestinal wall, lumen and peritoneal cavity show hemorrhages.

Microscopic picture: Ischemic **coagulative necrosis** of mucosa (or transmural) with **hemorrhage and edema**.

Clinically: Functional acute **intestinal obstruction**.

Hyperemia

- **Active hyperemia:**

- **Definition:** an increase in the blood flow to an organ as a result of active dilation of its arterioles and capillaries.

- **Active means:** change in the muscle tone of the vessel.

- **Types:**

- **Physiological:** e.g. in muscular exercise.

- **Pathological:** e.g. in acute inflammation.

Congestion

(Passive hyperemia)

- **Definition:** Increase venous blood in an organ as a result of **Obstruction** to the venous outflow.

- The veins, venules and capillaries in the organ **become passively dilated**.

- **Types:**

1- **General:** which may be acute or chronic.

2- **Local:** which may be acute or chronic.

GENERAL VENOUS CONGESTION

a- Acute general venous congestion:

- Terminal condition in **acute heart failure**.
- **All viscera show acute congestion.**

b- Chronic general venous congestion:

- **Definition:** Gradual venous congestion affecting the whole venous system.
- **Causes:** It is caused by right sided heart failure due to chronic obstructive lesions affecting:

1- **The heart:** As **mitral stenosis**.

2- The pulmonary vessels: As **congenital pulmonary stenosis** and **bilharziasis** of the lung which cause narrowing of the pulmonary arterioles.

3- The lung: As **emphysema** and **extensive fibrosis**.

- **General effects:**

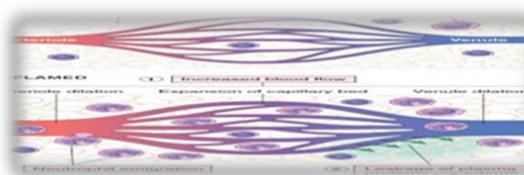
1- Dyspnea: shortness of breath.

2- Cyanosis: bluish or purplish discolouration of skin or mucous membrane as the tissues near the skin surface having low oxygen saturation.

3- Cardiac edema:

Physiological

Pathological



LOCAL VENOUS CONGESTION

- **It is localized congestion in any part of the body whose venous outflow becomes obstructed.**

a- Acute Local Venous Congestion:

- **Causes:** Sudden complete venous obstruction due to thrombosis, ligature or twisting of the pedicle of a movable organ or strangulated hernia.
- **Pathology:** Rapid severe distention of the veins and capillaries which may rupture, oedema occurs rapidly in the tissue.

b- Chronic Local venous congestion:

- **Causes:**

1- Gradual incomplete venous obstruction.

2- It results from venous compression by a tumor, enlarged lymph node or pregnant uterus.

3- Also it results from liver cirrhosis and bilharzial hepatic fibrosis.

- **Pathology:**

1- The veins, venules and capillaries proximal to the obstruction become dilated and congested resulting in oedema.

2- Gradual opening of the collateral and anastomotic veins.

Thrombosis

- **Definition:** Formation of a **compact mass** composed of the elements of the circulating blood inside **a vessel** or a **heart cavity** during life.

- **Causes:**

Three primary factors predispose to thrombosis (**Virchow Triad**).

1- Endothelial injury.

2- Hypercoagulability.

3- Alteration of normal blood flow.

Endothelial injury

- **Etiology:**

a- **Mechanical:** e.g. trauma, pressure and ligature.

b- **Inflammatory:** e.g. phlebitis, arteritis and endocarditis.

c- **Degenerative:** e.g. ulcerated atheroma and myocardial infarction.

- **Effect:** Physical loss of endothelium leads to exposure of underlying Collagen, followed by platelet adhesion.

Alteration of normal blood flow

- **Etiology:**
 - a- **Stasis:** in leg veins, in heart failure.
 - b- **Turbulence:** Atheroma.
- **Effects:** In normal blood stream, **blood cells** occupy **the central part** while **plasma** occupies **the peripheral part**. Alteration in blood flow:
 - a- Disrupts laminar blood flow bringing platelet in contact with endothelium.
 - b- Prevents dilution of activated clotting factors by fresh blood flow.
 - c- Retards inflow of clotting factors inhibitors.
 - d- Promotes endothelial cell activation.

Hypercoagulability

- Any alteration in coagulation pathway. It may be
 - a- **Primary (genetic):** e.g. mutation in prothrombin gene.
 - b- **Secondary (acquired):** High risk for thrombosis:
 - Prolonged immobilization.
 - Atrial fibrillation.
- **Mechanism of thrombus formation:**
 - 1- The initial thrombus is composed of platelets only as follow:**
 - a- **Platelet adhesion:** Following endothelial injury, platelets adhere to the exposed subendothelial collagen by the help of (**factor VIII**)
 - b- **Platelet activation and secretion:** The adherent adenosine diphosphate (**ADP**) and that promote platelet aggregation and adhesion forming a **small white mass**.

2- Stasis allows clotting factors to accumulate in the area leading to:

- a- Activation of **coagulation cascade**, either extrinsic or intrinsic pathways.
- b- Both pathways converge ending in **formation of thrombin**.
- c- Thrombin, binds to platelet surface receptors, **along with ADP**, causing **further platelet aggregation** followed by platelets contraction.
- d- At the same time, **thrombin converts fibrinogen to fibrin** which stabilizes further platelets accumulation.
- e- Between laminae, fibrin deposits entangling red and white blood cells (**blood clot**).
- f- Now thrombus is formed of platelet masses and blood clots.

■ Morphology:**a- Gross examination:**

- 1- **Pale thrombus:** Small, grayish white, firmly adherent mass.
- 2- **Red thrombus:** Dark red, soft loosely attached mass (rare).
- 3- **Mixed:** Most thrombi have red and pale components.

b- Microscopic examination:

- 1- **Pale thrombus:** Mainly composed of platelets and fibrin.
- 2- **Red thrombus:** Mainly composed of red cells and fibrin.
- 3- **Mixed thrombus:** Alternate layers of fused platelets, and fibrin with blood cells.

N.B: in mixed thrombus, fused platelets appear as **homogenous reddish violet streaks** called lines of zahn.

■ Classification of thrombi:**a- According to color:**

- 1- Red.
- 2- Pale.
- 3- Mixed.

b- According to the presence or absence of bacteria:

- 1- Infected thrombus (septic).
- 2- None infected thrombus (aseptic).

■ **Sites of thrombus formation:**

1- Thrombosis in veins:

a- Thrombophlebitis (thrombosis initiated **by inflammation** of the venous wall).

b- Phlebothrombosis (thrombosis caused by factors **other than inflammation** e.g. thrombosis in leg and calf veins in cardiac patient, confined to bed)

2- Thrombosis in arteries: Less common than venous due to:

a- rapid blood flow.

b- thick elastic wall which resist injury.

3- Thrombosis in the heart: More common in the **left side**.

The following types occur:

a- Mural thrombi: occur over infarction.

b- Vegetations: pale thrombi **over the valves** as in rheumatic fever and bacterial endocarditis.

d- Thrombosis in capillaries: Rarely occurs in acute inflammation, sever cold and **frost bite**. It is **due to stasis**, endothelial damage and Hemoconcentration.

■ **Clinical effects:**

1- Arterial thrombus: Is more serious causing ischemia and infarction.

2- Venous thrombosis: Causes congestion, edema, stasis, infection and ulceration.

■ Fate of thrombus:

1- Septic thrombus: Fragmented by proteolytic enzymes into septic emboli causing pyemic abscesses.

2- Aseptic thrombus:

- If small: Removed by fibrinolytic activity (**dissolution**).
- If large: It undergoes 5 processes:

a- Organization: The thrombus is invaded by capillaries and fibroblasts from the vascular wall and changes to a fibrous mass causing permanent vascular occlusion.

b- Organization and recanalization: Occasionally, some of the capillaries allowing passage of blood through thrombus or the fibrosed thrombus shrink from the vascular wall leaving a space which gets lined by endothelium.

c- Dystrophic calcification (phlebolith).

d- Detachment: Forming **aseptic emboli** causing infarction.

e- Propagation: Arterial thrombus may grow in **retrograde direction**.

While **venous thrombus** grows in the **direction of blood flow** i.e. towards the heart.

* **Blood clot:** A mass of blood elements formed in stagnant blood.

Differences between:	
Thrombosis	Blood clotting
Antimortem	Antimortem or postmortem
It occurs inside the cardiovascular system (in vivo)	In vivo: ● inside the CVS: during life (as a tail of thrombus) and after death. ● outside CVS as in hematoma. In vitro (in test tube outside the body)
It is formed while the blood is circulating	It is formed while the blood is stagnant
It is composed of alternating layers of aggregated platelets & fibrin (line of zahn)	It is composed of randomly oriented fibrin with entrapped platelets & blood cells (no lines of zahn)
It is firmly attached to the endothelium	It is loosely attached to the endothelium
It is firm & friable	It is jelly like

Embolism

- **Definition:**

Embolus	Embolism
An Insoluble, solid, liquid or gaseous mass circulating in the blood carrying it away from its original site.	The process of impaction of the embolus in a blood vessel.

- **Origin and Types of Emboli:**

1- Thromboembolism:

- **Source:** Fragmented or detached thrombi.
- **Sites of impaction:** Pulmonary, Portal, Systemic.

a- Pulmonary embolism:	b- Portal Embolism:	c- Systemic Embolism:
<p>Source: Emboli are derived from thrombi of systemic veins and become impacted in pulmonary arteries.</p> <p><u>May lead to pulmonary hypertension and right sided heart failure.</u></p>	<p>Emboli are derived from the mesenteric or splenic veins and are impacted in the portal radicles.</p>	<p>Emboli are derived from :</p> <ol style="list-style-type: none"> 1- Thrombi of pulmonary veins. 2- Thrombi of the heart. 3- Aortic thrombi. <p>These emboli pass to the systemic arterial circulation and become impacted in different sites as <u>cerebral, renal, splenic and hepatic</u> arteries.</p>

- Effects of thromboembolism: It depends on

1- Size of the embolus

2- State of the collaterals circulation in the affected organ.

3- Nature of embolus, Septic or aseptic:

a- **Septic Emboli:** cause **pyemia**, which is characterized by **multiple small abscesses**, usually peripherally located within the affected organ (fatal).

b- **Aseptic Emboli:**

1- Occlusion of arteries with **poor collaterals** leads to ischemic damage of the tissue (**infarction or gangrene**)

2- Occlusion of arteries with **efficient collateral circulation**: insignificant effects.

2- Fat embolism:

- Etiology: Minute **fat** globules may reach the pulmonary circulation (pulmonary fat embolism) following:

a- **Fracture of long bones (derived from bone marrow fat).**

b- **Severe fatty liver.**

c- **Skin burns.**

d- **Severe inflammation of fatty tissues.**

3- Amniotic Fluid Embolism:

Infusion of **amniotic fluid** into the **maternal circulation** may be induced by **vigorous uterine contractions.**

4- Gas (Air) Embolism:

Single embolism	Multiple embolism
<ul style="list-style-type: none"> • Injury of a neck vein leads to suction of atmospheric air during inspiration. • Air bubbles are carried through the superior vena cava to the right ventricle causing serious impairment of cardiac action. 	<ul style="list-style-type: none"> • It occurs in Caisson disease or decompression sickness. • In divers the high atmospheric pressure leads to dissolution of high concentration 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

5- Tumor Emboli:

Cells from **malignant tumor** deposits in distant organ forming **secondary tumors or metastases**.

6- Parasitic and Bacterial Emboli:

Examples include **bilharzia ova** and **clumps of bacteria**.

7- Foreign Body Emboli:

These are rare e.g. **Crushed tablets injected intravenously in drug addicts.**

Edema

- **Definition:** accumulation of abnormal amounts of fluid in the intercellular tissue spaces and/or body cavities.
- Edema fluid may be transudate, exudate or lymph.

- **Causes and pathogenesis of edema:**
 - 1- Increased Capillary Hydrostatic pressure.
 - 2- Increased Capillary Permeability.
 - 3- Increased Tissue Osmotic Pressure.
 - 4- Decreased Colloid Osmotic Pressure of plasma.
 - 5- Sodium and water retention.
 - 6- Lymphatic obstruction as in cases of filariasis, lymphatic permeation by malignant cells.

- **Class According to fluids:**

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

- **Class According to cause of edema:**

a- Generalized or localized:

Generalized (anasarca)	Localized
1- Cardiac edema: due to right sided heart failure.	1- Inflammatory edema: due to acute inflammation.
2- Nutritional edema: due to hypoproteinemia in cases of Malnutrition.	2- Obstructive edema; venous & lymphatic subtypes.
3- Renal edema: <u>Nephrotic type</u> due to nephrotic syndrome or <u>nephritic type</u> due to nephritic syndrome.	

b- Pitting or non pitting: depends on protein content in fluids:

Pitting	Non pitting
<ul style="list-style-type: none"> • In all types of generalized edema and in the congestive type of localized edema, the fluid is transudate (low protein) 	<ul style="list-style-type: none"> • It occurs in cases of lymphatic edema and sometimes in inflammatory edema.

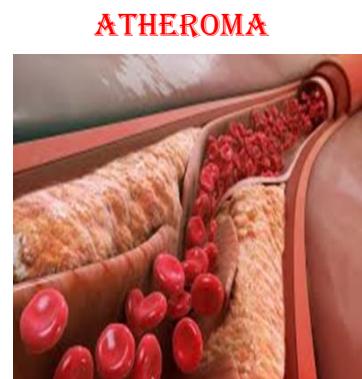
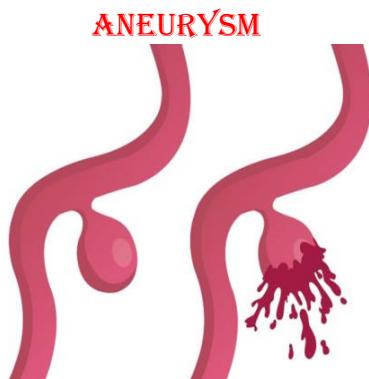
- **Pathological aspects of oedema:**
- **Gross Features:** Edema causes swelling, heaviness and pallor of the affected tissue.
- **Microscopic features:** Edema appears as homogenous pale eosinophilic substance.
- **Clinical effects:** depend on the site e.g. dyspnea in cases of pulmonary edema, Neurological manifestation in case of brain edema due to increased intracranial tension.

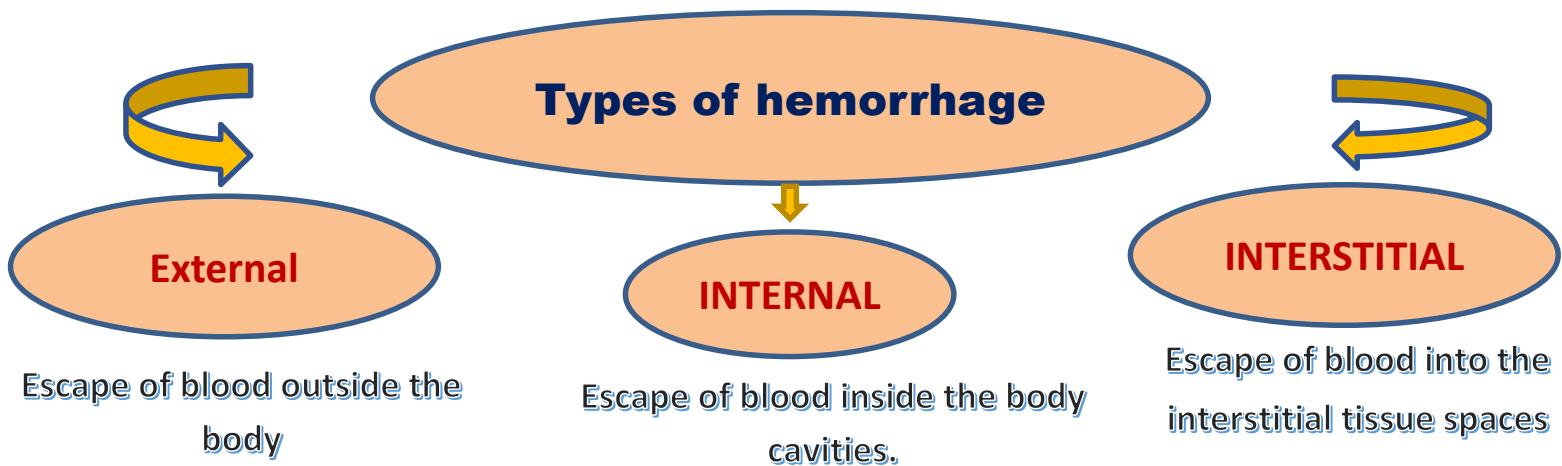
Hemorrhage

- **Definition:** Hemorrhage is extravasation of blood from vessels or cardiac chambers into the extravascular space.

- **Causes of hemorrhage:**

- 1- Traumatic: caused by mechanical injury to the vascular wall.
- 2- Spontaneous: due to:
 - a- Diseases of the vascular wall e.g. atheroma and aneurysm.
 - b- Inflammatory injury to the vascular wall as in phlebitis.
 - c- Destruction of the vascular wall by tuberculosis, malignancy or peptic ulceration.
 - d- Increased intravascular tension e.g. chronic venous congestion and hypertension.
 - e- Hemorrhagic blood diseases as hemophilia and purpura.
 - f- Vitamin C and K deficiency.





1- Epistaxis: bleeding from the nose.

2- Hematemesis: **vomiting** of blood. The source of bleeding is the **esophagus**, **stomach** and **duodenum**. The blood is digested, **brown** and mixed with food particles.

3-Hemoptysis: **coughing** of blood. The source of blood is the **lung** or the **bronchi**. The blood is **red** and **frothy**.

4- Melena: dark digested blood in stool.

5- Hematuria: blood in urine.

1- Hemothorax: into the pleura.

2- Hemoperitoneum: into the peritoneum.

3- Hemopericardium: into the pericardium

4- Hematocele: into the tunica vaginalis.

5- Hemoatherosis: into the joint cavity.

1- Petechial hemorrhage: small amount of blood of capillary origin.

2- Echymosis: Moderate amount of blood.

3- Hematoma: Large amount of blood causing a swelling.



Shock

- **Definition:** a widespread **hypoperfusion** of the cells and the tissues occurring due to **inadequate effective circulating blood volume**.
- **Types:**
 - 1- Hypovolemic shock.
 - 2- Cardiogenic shock.
 - 3- Septic shock.
 - 4- Rare types (neurogenic and anaphylactic shock).

Hypovolemic Shock

- **Causes:** Loss of blood or plasma volume. This may be caused by:
 - a- Severe hemorrhage.
 - b- Severe burns: hypovolemia results from inflammatory exudation of plasma fluid from the damaged blood vessels in extensive burns.
 - c- Severe acute dehydration: due to vomiting and diarrhea in gastroenteritis and cholera.
- **Pathogenesis:**

Reduction in the effective circulating blood volume and decreased venous return to the heart, decreased cardiac output, reduced blood flow and reduced blood supply to the tissue (**anoxia**).

Cardiogenic Shock

- It results from **failure of the cardiac pump** and **marked reduction in the cardiac output**.

Septic Shock

■ Causes:

1- Most cases of septic shock (approximately 70%) are caused by **endotoxin** producing **gram-negative bacilli** as E. coli (hence the term endotoxic shock) or **gram positive bacteria** as streptococci.

2- These bacterial infections are aggravated in:

a- Septicemia.

b- Infected burns.

c- Infected surgical procedures.

d- Immunodeficiency states as leukemia and lymphoma.

■ Stages of shock: !!!!

- Shock is a progressive disorder that if **uncorrected** leads to **death**.

- Shock tends to evolve through **three general stages**.

- These stages have been documented most clearly in **hypovolemic shock** as well:

1- An initial non-progressive stage:

- During which **reflex compensatory mechanisms** are activated and **perfusion** of vital organs is maintained.

2- A progressive stage:

- Characterized by **tissue hypoperfusion** and onset of worsening circulatory and metabolic imbalances.

- This is a **reversible stage** in which, hemodynamic defects **can be Corrected**.

3- An irreversible stage:

- Cellular and tissue injury become so **severe** and **irreversible**.

- **Survival is not possible.**

The background of the entire image is a dense, dark forest scene. Sunlight filters through the canopy of tall trees, creating bright highlights on the leaves and branches. The overall atmosphere is mysterious and natural.

Neoplasia

Chapter 6

NEOPLASIA 1

- **Definition:** an abnormal tissue whose growth exceeds and is **uncoordinated** with that of adjacent normal tissue and persists after cessation of the stimuli that provoked it.

- **Characters of tumors:**

1- Neoplasms are composed of:

a- Neoplastic (transformed) cells.

b- Supporting stroma and blood vessels.

2- Tumor form mass with no useful function.

- **Classification of tumors:**

1- According to tumor behaviour:

a- Benign. b- Locally malignant tumors. c- Malignant.

2- According to tissue of origin:

a- Epithelial

b- Mesenchymal (connective tissue, muscle, blood vessels tumors, etc)

▪ **Difference between benign and malignant tumors:**

		Benign tumor	Malignant tumor
Growth rate	Usually slow	Usually rapid	
Invasiveness	Well-circumscribed. No invasion of surrounding tissue.	Invasive (infiltrating the surrounding normal tissue)	
Metastases	No	Often present	
Recurrence	Don't recur after surgical removal	Usually recur after removal	
Prognosis	Good	Fatal	
Gross picture			
Capsule	Usually encapsulated	Not capsulated	
Margins	Well defined	Irregular or ill defined	
Ulceration, hemorrhage and necrosis	Rare or absent	Very common	
Shape: 1- inside solid organ 2- surface epithelial tumor	- Ovoid and capsulated. - Non capsulated	Irregular and non capsulated - Fungating: bulging over the surface. - Ulcerative: irregular ulcer. - Infiltrative: especially in tubular organs as intestine.	
Microscopic picture			

Differentiation	Differentiated	Some loss of differentiation
Cell arrangement	Uniform- regular spacing- cohesive cells	- Loss of polarity of cells (nuclei are oriented in different directions and irregularly spaced) - Loss of cohesiveness (cells falling apart from each other)
Cell uniformity	Uniform	Pleomorphic: variation in size, shape and numbers of nuclei
Nuclei		
Nucleocytoplasmic ratio(N/C) ratio	Usually not increased	Increased
Nuclear size	Usually not increased	Increased
Hyperchromasia	Not hyperchromatic	hyperchromatic
Nucleoli	Small, round	Often prominent Sometimes numerous
Mitosis	Few or absent	Numerous, may be with abnormal forms.
Effect on host	- Doesn't destroy the surrounding tissue. - Doesn't kill the host except if compressing vital structures (brain& trachea).	Usually kills the patient

	<ul style="list-style-type: none"> - May cause obstruction in a tubular organ (ureter). - May have endocrine function as thyroid. 	
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ORIGIN	Benign	Malignant
1- Epithelial		
a- Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
b- Urinary Epithelium (transitional)	Transitional cell papilloma	Transitional cell carcinoma
c- Melanocytes	Nevus	Melanoma
d- Glandular or ductal epithelium	Adenoma (e.g of colon)	Adenocarcinoma (e.g of colon)
2- Mesenchymal Origin		
a- Connective tissue		
Bone	Osteoma	Osteosarcoma
Cartilage	Chondroma	Chondrosarcoma
Fibroblast	Fibroma	Fibrosarcoma
b- Muscle		
Smooth muscle	Leiomyoma	Leiomyosarcoma
Striated(skeletal) muscle	Rhabdomyoma	Rhabdomyosarcoma
c- Vascular		
Blood vessels	Haemangioma	Hemangiosarcoma
Lymphocytic vessels	Lymphangioma	Lymphangiosarcoma
d- Hematopoietic		
Erythroid		Erythroid leukemia
Myeloid		Myelogenous leukemia
Lymphoid		Malignant lymphoma

Etiology of tumors and carcinogenesis

- **Carcinogenesis:** Mechanism of transformation of normal cells to tumor cells. It is **gradual, multistep process**.
- **The etiology of cancer is multifactorial.** (Interaction of multiple factors occurs).
- **Possible causes of tumors:**

1- Molecular genetics carcinogens (cancer related genes):

- a- Growth promoting proto-oncogenes.
- b- Growth inhibiting tumor suppressor genes.
- c- Genes regulating apoptosis.
- d- Genes regulating DNA repair.

2- Environmental factors:

- a- Chemical carcinogens.
- b- Physical carcinogens and radiation.
- c- Biologic carcinogens (Bacterium and viral oncogenesis)
- d- Hormonal causes.
- e- Immunological.
- f- Chronic diseases.

■ Carcinogenesis multistep process: include

- 1- Initiation:** It caused **Irreversible DNA damage (mutation)** in a target gene by which the cell is transformed into latent tumor cell (**initiated cell**).
- 2- Promotion:** it is characterized by proliferation of an initiated cell by promoting agent e.g. **hormones** and **oncogenic viruses**.

3- Progression: It is characterized by Persistent irreversible proliferation of the cells acquired the genetic abnormalities leading to **tumor growth, infiltration, invasion** and **metastasis**.

I- Genetic basis of tumors

■ The role of cancer related genes:

1- Proto-Oncogenes and Oncogenes:

- Proto-oncogenes are the normal cellular genes encode proteins that regulate **cell division and growth**.
- Mutation of Proto-oncogenes lead to loss of their regulation and **transformed into oncogenes**.
- Oncogenes encode oncoproteins which may act as:
 - a- **Growth Factors:** as PDGF, which causes **stimulation of neoplastic cells growth**.
 - b- **Growth-Factor Receptors:**
 - They have strong signal-transduction role in promoting cell growth.
 - e.g. **Tyrosine-kinase receptors**.
 - c- **Signal-Transducing Proteins:**
 - Ras is the **most common signal transducing protein**.
 - Ras gene mutation results in its persistent signal transducing activity and uncontrolled cell growth and proliferation.
 - d- **Nuclear Transcription Proteins:** As c-myc which is involved in progression of the cell from G0 to complete the cell cycle.

2- Tumor-Suppressor Genes (TSG):

- They are genes that normally **suppress cell proliferation**.
- dysregulation of TSG results in **sustained cell proliferation**.
- Examples for tumor suppressor genes:
 - a- **P53 gene** (the most common genetic defect found in cancers).
 - b- **Retinoblastoma gene** (Rb gene result in retinoblastoma).

c- Wilm's Tumor Gene (Childhood form of renal cancer).

d- BRCA1 (Breast Cancer).

3- Abnormal Apoptosis-Regulatory Genes:

- Apoptosis-Regulatory Genes normally control the programmed cell death.
- Their mutation results in **escaping cell death**.

4- Failure of DNA Repair Genes:

- DNA Repair Genes are responsible for repair of DNA damage.
- Their mutation results in **Inability to repair DNA damage**.

II- Environmental Causes of Cancer (Carcinogenic Agents)

- **Chemical Carcinogens.**
- **Physical Carcinogens:** Radiation injury: has role in **thyroid cancer**.
- **Biological Carcinogens:**

1- Viruses: as

a- Human papilloma virus (HPV) (**subtypes 16 & 18**) which cause **cancer cervix**.

b- Hepatitis-B virus (HBV) which cause **Hepatocellular carcinoma**.

c- Epstein-Barr virus (EBV) which cause **nasopharyngeal carcinoma** and **Burkitt's lymphoma**.

2- Bacterial: as Helicobacter pylori which cause **gastric carcinoma**.

3- Protozoal: as Bilharziasis which cause **urinary bladder carcinoma**.

Staging of Malignant Neoplasms

- **Definition:** the anatomic extent of malignant disease as evaluated by **Clinical and pathological examination**, to determine the treatment and the prognosis.
- **The main staging is TNM system:**
 - T:** extent of primary tumor.
 - N:** Absence or presence and extent of **regional lymph node** metastases.
 - M:** Absence or presence of **distant metastases**.
- **TNM staging:**

T0	No detectable tumor
Tx	Could not be assessed as it was removed before or regressed by radiotherapy or chemotherapy
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

Grading of Neoplasms

- **Definition:** The histologic estimate of the degree of malignancy.
- Grading is based on **microscopic estimation** of cellular differentiation, anaplasia and mitotic activity.
- **Grading of Neoplasms:**

Grade I	Well differentiated
Grade II	Moderately differentiated
Grade III	Poorly differentiated.
Grade IV	Undifferentiated

- A **well-differentiated neoplasm** is composed of cells that closely resemble the cell of origin.
- **Undifferentiated neoplasms** have cells that are difficult to recognize as to their cell of origin.
- **Clinical effects of neoplasms:**

1- Anemia: caused by:

a- Metastasis in bone marrow.

b- Ulceration and bleeding of tumor.

c- Folic acid deficiency as it is utilized by the tumor cells.

2- Malnutrition: alimentary tract tumors interfere with food intake, digestion and absorption.

3- Renal failure: caused by tumors of the genito-urinary system and the rectum due to **urinary tract obstruction**.

4- Obstructive jaundice and hepatic failure: caused by tumors of the liver, biliary tract and pancreas.

5- Increased intra-cranial and pressure on vital centres: caused by **intracranial tumors**.

6- Chronic toxemia: due to **secondary bacterial infection** in ulcerated tumors.

7- Malignant cachexia: state of **general weakness** and **wasting**.

8- Paraneoplastic Syndromes.

9- Death: due to combination of the previous factors.

Prognosis of malignant tumors

■ **The prognosis of a malignant tumor depends on:**

1- **Type of the tumor:** certain malignant tumors are more aggressive than others e.g. Skin malignant melanoma has **poor prognosis** than skin squamous cell carcinoma.

2- **Tumor stage:** the **extent of spread** and the presence or absences of metastasis are the most important factors in prognosis.

3- **Tumor grade:** **histological grading**; well differentiated tumors are usually of better prognosis.

4- **Host immune response:** cellular immunity is believed to play a role in the defense mechanism against tumors.

5- **Mitotic index.**

6- **Vascular invasion.**

7- **Tumor radiosensitivity.**

8- **Other factors:** **age** of the patient, **anatomical site** and **duration** are Factors in the prognosis. Tumors of young age are worse in prognosis because of the rapid growth, spread and recurrence.

Spread of malignant tumors

■ Pathways of Spread and Metastasis:

I- Local infiltration or spread.

II- Distant spread (metastasis):

1- Lymphatic spread:

a- Lymphatic embolism.

b- Lymphatic permeation

2- Hematogenous spread.

3- Transcoelomic spread.

4- Implantation:

a- Direct implantation.

b- Implantation via the natural passages.

I- Local infiltration or spread

- Spread into the surrounding normal structures.
- Occurs in all the malignant and locally malignant tumors.
- Spread to the skin and mucous membranes result in malignant ulcer.

II- Distant spread (metastasis)

1- Lymphatic spread:

- This is the most common pathway for spread of carcinomas.
- Follows the natural routes of drainage.
- It occurs by two ways:

a- Lymphatic embolism:

- Malignant cells invade the wall of a lymph vessel, detach and are carried as emboli by lymph flow.

- Progressive lymphatic spread may reach the main lymphatic ducts (thoracic duct), from which malignant cells may enter the general circulation resulting in hematogenous spread.

b- Lymphatic permeation:

- Malignant cells grow along lymph vessel wall forming **solid mass**.
- The lymph vessel is **obliterated** resulting in **lymphatic edema**.
- For example, in **breast carcinoma**, lymphatic permeation leads to **skin edema** producing "**peau d'orange**" appearance.

2- Hematogenous spread:

- Occurs when malignant cells **infiltrate small veins** (thin-walled).
- Arteries are **more difficult** for tumor to penetrate than veins.
- With venous invasion, the blood-borne cells follow the venous flow draining the site of the tumor.
- Tumor emboli reach **distant organs** by blood, get adherent to capillary endothelium, proliferate and form secondary growths (**metastases**).
- **Liver, lungs, bones, brain** are frequently involved.
- This pathway of spread is typical **for sarcomas**.
- **Morphology:**

a- **Grossly:** Metastases appear as **multiple scattered round nodules** slightly variable in size.

b- **Microscopically:** Metastases resemble **the primary tumor** from which they are derived.

3- Transcelomic spread:

- This is spread through the **serous cavities**.
- It occurs in tumors of organs covered by **serous membranes**.
- When the serosal covering is infiltrated by the malignant cells, tumor cells **separate and falls in the related sac**.
- They get implanted on the surface of another organ, proliferate and form **metastases**.

- Example:

a- **Abdominal tumors:** specially gastric and colic carcinomas form deposits on the surface of the ovary.

b- **The ovarian metastases:** are known as "**krukrnberg's tumor**".

4- Implantation:

a- Direct implantation:

- **Surgical implantation:** during surgical removal of malignant tumor, some malignant cells may **contaminate the instrument** to be implanted directly into the surgical wound resulting in **metastatic nodule in the scar**.
- In the carcinoma of the lower lip: metastatic nodule may appear in the **upper lip by direct implantation**.

b- Implantation via the natural passages:

- As in **transitional cell carcinoma of renal pelvis**, a metastatic growth may appear in **urinary bladder mucosa** by implantation.



Locally Malignant Tumors

- **Definition:** Group of malignant tumors characterized by:
 - 1- **Slow rate of growth** than frank malignant tumors.
 - 2- **Local spread** by infiltration only, no distant metastasis.
 - 3- Histologically The cells **show malignant characters.**

- **This group includes: (A,B,C)**

1- Admantinoma.	2- Astryctoma (grade II).
3- Bronchial adenoma.	4- Basal cell carcinoma.
5- Carcinoid tumor of the appendix.	6- Craniopharyngioma.

Teratoma

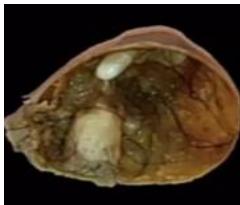
- **Definition:** A composite tumor containing structures derived from **totipotent embryonic** cells giving rise to the three germinal layers; **ectoderm, mesoderm and endoderm.**
 - a- The ectoderm: skin, teeth, nerve cells and fibers.
 - b- The mesoderm: fibrous tissue, muscle fibers, blood vessels, bone, cartilage, fatty tissue.
 - c- The endoderm: intestinal epithelium, glands as thyroid.

- **Site:** The commonest site is the **ovary** less common is **testis.**

■ Types:

Benign teratoma (Mature teratoma)	Malignant teratoma (Immature teratoma)	Monodermal teratoma (specialized)
<p>a- Solid Teratoma: Less common.</p>	<p>It is rare</p>	<p>These are teratomas that differentiate along the line of a single abnormal tissue.</p>
<p>B- Cystic Teratoma (dermoid cyst): <ul style="list-style-type: none"> - More common. - Lined by <u>stratified squamous epithelium</u> and is filled with <u>thick creamy sebaceous material</u> and contains hairs, bone, Cartilage and teeth. </p>	<p>Consist of a mixture of mature and malignant immature tissue.</p>	<p>EX Strauma ovarii: a benign teratoma composed of thyroid tissue.</p>

CYSTIC TERATOMA



SOLID TERATOMA



Embryonic Tumors

- Are usually malignant tumors which arise from **embryonic tissues** in early life (infants and young children).
- **Examples:**
 - 1- Wilms' tumor (**kidney**).
 - 2- Retinoblastoma (**eye**).
 - 3- Medulloblastoma (**brain**).
 - 4- Neuroblastoma (**adrenal medulla**).

Hamartoma

- **Definition:** is a **tumor-like mass** formed due to **developmental error** and consists of normal tissues of the part from which it arises, but are **irregularly arranged**.
- Hamartoma is present **at birth** but become **manifest during post-natal life**.
- **Examples:**
 - a- Hamartoma of **lung** and **kidney** (left).
 - b- Capillary and cavernous hemangioma, cavernous lymphangioma.



Benign Tumors

I- Benign Epithelial Tumor:

1- Surface Epithelial (**Papilloma**). 2- Glandular Epithelial (**Adenoma**).

1- Papilloma:

- It is the benign tumor arising from **surface epithelium**.
- Sessile or pedunculated.
- Formed of a **central core of vascular connective tissue** covered by the epithelium.
- According to the **covering epithelium**, papilloma is classified into:

a- **Squamous cell papilloma:**

- Arises from the **stratified squamous epithelium** of skin, lip, tongue, larynx and anal canal.

b- **Columnar cell papilloma:** such as:

- **Duct papilloma:** arises from the epithelium of the **large ducts of the breast**.

c- **Transitional cell papilloma:** arising mainly from urinary bladder, ureter and pelvis of the kidney.



2- Adenoma:

- It is a simple tumor arising from **secretory epithelium** or **glands**.

• **Sites:**

a- The commonest site is the endocrine glands as **thyroid** and **ovary**.

b- It may arise from other glands such as **mucus membrane of Gut**.

• **Gross picture:**

Appear as **solid rounded well capsulated mass** showing the **same microscopic appearance** as that of the gland from which it arises.

• **Microscopic picture:**

a- **Simple adenoma:**

The tumor consists of **proliferated glands** lined by cuboidal columnar epithelium separated by **delicate fibrovascular core** e.g. pancreatic adenoma, colorectal adenoma.

b- Mixed adenoma:

It consists of **glandular** as well as stroma proliferations, e.g. breast Fibroadenoma.

c- Cyst adenoma:

In some types of adenomas, secretions are **retained leading to cystic dilatation** of the proliferated acini, e.g. ovarian cystadenoma.

d- Papillary cyst adenoma:

It is a cystadenoma in which the **epithelial lining** of the **cyst** proliferate forming **papillae** e.g. Papillary cystadenoma of the ovary.

- **Effect of adenoma:**

1- Adenoma may be functioning: e.g. **Hormonal secretion** as in ovarian adenoma secreting estrogen lead to endometrial hyperplasia.

2- Adenoma may change to adenocarcinoma.

Fibroadenoma

- The **commonest benign tumor of the breast**.
- It is an **estrogen dependent tumor**.
- **Gross picture:**

a- The tumor is usually solitary, occasionally multiple, well circumscribed rounded or oval, firm in consistency.

b- The cut surface is greyish-white, bulging with whorl-like pattern.

c- Vary in size from less than 1 cm to giant forms 10-15 cm in diameter.

- **Microscopic picture:**

a- Pericanalicular fibroadenoma:

Acini is patent, small round Fibrous tissue around acini is **less**.

b- Intracanalicular fibroadenoma:

Acini is compressed due to fibrous tissue around acini is **more** & Acini are star shape.

II- Benign Mesenchymal Tumors:

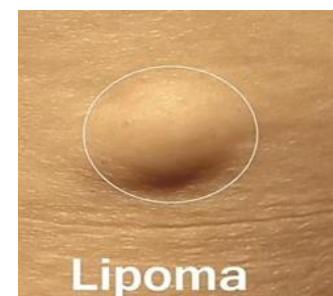
1- FT Fibroma. 2- Adipose Tissue Lipoma. 3- Cartilage Chondroma.

1- Fibroma:

- It is **uncommon benign tumor of fibrous tissue.**
- **Sites:** It may arise in **dermis, subcutaneous tissue, and fibrous stroma** of organs as **breast, ovary, and kidney.**
- The tumor consists of variable amount of **collagenous bundles** with large number of **fusiform fibroblasts.**

2- Lipoma:

- It is tumor of **adipose tissue.**
- It is the **most common soft tissue tumor.**
- **Site:** It may arise in several tissues as **subcutaneous tissue** especially in the back of the **neck, buttocks, thigh** and retroperitoneal fatty tissue.
- **Gross picture:**
 - a- A **well capsulated, lobulated, soft, greasy, yellow tumor.**
 - b- Cut section is **pale yellow bulging and greasy.**
- **Microscopic picture:**
 - a- The tumor consists of **lobules composed of mature fat cells (adipocytes)** which are large vacuolated cells with flattened **eccentric nuclei (signet ring).**
 - b- The lobules are separated by **fibrovascular septa.**



3- Osteoma:

- It is a **benign tumor** arises from **the bone.**
- It is of two types:
 - a- **Compact osteoma:** arises from **membranous bone of the skull.**
 - b- **Osteoid osteoma:** arises in **cancellous part of long bones, vertebral arches and short bones.**

4- Chondroma:

- A **benign tumor composed of hyaline cartilage**.
- **Sites:**
 - a- Short bones of hands and feet are the commonest site.
 - b- Flat bones of pelvis, ribs, and sternum.
 - c- It may arise from any cartilagenous tissue as larynx and bronchi.
- Consist of islets of **cartilage** separated by **fibrous septa**.

5- Leiomyoma:

- It is the **benign tumor of smooth muscles**.
- The commonest site is the **uterus**.
- Leiomyoma is the **commonest tumor in females**.
- It is **estrogen dependent** and occurs during the reproductive period of life.
- **Gross picture:**
 - **Multiple, or single.**
 - Firm, rounded, **uncapsulated but surrounded by a false capsule of compressed surrounding muscles.**
 - The cut section is grayish and shows a **whorly appearance** as **fibroadenoma**.
- **Microscopic picture:**
 - It consists of interlacing bundles of **smooth muscle fibers** and dense fibrous tissue.
 - The **muscle fibers have elongated rod shaped with rounded ends nuclei**, while those of fibroblasts have large fusiform nuclei.

6- Hemangiomas:

- They are **benign tumors of blood vessels**.
- They appear since birth and are considered as congenital tumor-like malformations (**Hamartomas**) rather than true neoplasms.
- They are **non-capsulated** and **do not change malignant**.

- They are of two types:

a- Capillary Haemangioma:

- It usually appears in the **skin of face**.
- Consist of multiple **small capillary-like blood spaces** by endothelial cells and **contain blood**. The spaces are separated by **fibrous tissue**.
- The tumor is **non capsulated**.

b- Cavernous Haemangioma:

- Common sites are the **skin of the face, lips and tongue**, internal Organs as **liver, spleen, and bones**.
- It is formed of **large blood spaces**, lined by endothelial cells and filled with blood.
- The spaces are separated by **fibrous tissue**.

7- Lymphangioma:

- It is a **benign tumor of lymph vessels**.
- Is also considered as **hamartomatous malformation**.
- It is **more common in children**.
- Consist of small **thin-walled lymphatic channels** in **capillary lymphangioma** and **larger thin-walled channels** in **cavernous lymphangioma**, separated by **fibrous stroma**.

Malignant Tumor

I- Carcinoma.

II- Sarcoma.

I- Carcinoma:

They are malignant tumors of epithelial origin & the **commonest type** of all malignant tumors.

- **Types of carcinoma:**

- a- **Carcinoma from surface epithelium:**

- 1- **Squamous cell carcinoma.**

- 2- **Basal cell carcinoma.**

- 3- **Transitional cell carcinoma.**

- b- **Carcinoma arising from glandular epithelium:**

- 1- **Adenocarcinoma.**

- 2- **Mucoid carcinoma.**

Squamous Cell Carcinoma (Epidermoid Carcinoma)

- It is a **very common malignant tumor.**
- It arises from the **prickle cell layer** of the stratified squamous epithelium all over the body such as the skin, lips, tongue, larynx, esophagus, cervix, vagina and anal canal.
- The tumor may arise **de novo** or on top of **squamous cell papilloma**.
- It may also arise after **squamous metaplasia** especially in urinary bladder, bronchial mucosa and gall bladder.

- **Gross picture:**

- It starts as a **small hard nodule** in the epithelium.

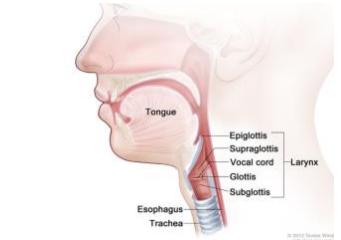
- later:

- a- **Polypoid = fungating carcinoma.**

- b- **Infiltrating carcinoma.**

- c- **Ulcerative carcinoma: The commonest type.**

Characterized by raised everted edges, fixed indurated base and a necrotic floor.



C, NODULAR TYPE

- **Microscopic picture:**

- There is infiltration of sub epithelial tissue by large polygonal cell arranged in solid masses of variable size and shape which are separated by **dense fibrous stroma**.
- The malignant cell have **abundant eosinophil cytoplasm** and **large Rounded darkly stained nuclei** having one or more prominent nucleoli.
- Cell nest, in some masses the cells in the central area are **replaced by structureless lamellae of keratin** (stained bright red). This occur in **differentiated groups**.

Basal Cell Carcinoma (Rodent Ulcer)

- It is a common **locally malignant tumor** arising from **basal cell of the skin** of areas exposed to sunshine, particularly the face and the neck.
- In the face it usually arises from the skin above a line drawn from **the angle of the mouth** and **above the lobule of ear**.

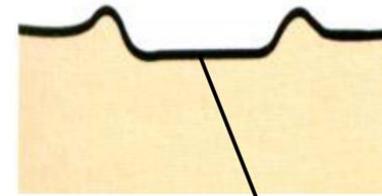
- **Gross picture:**
- It arises as a **small firm nodule**, gradually **increases in size** and **ulcerates** forming an irregular ulcer with **rolled-in beaded edges**, **fixed indurated base** and **necrotic floor**.
- It **does not metastasize** but it may infiltrate deeply into underlying structures. (**a locally malignant tumor**)

2. Basal cell carcinoma
Rodent ulcer



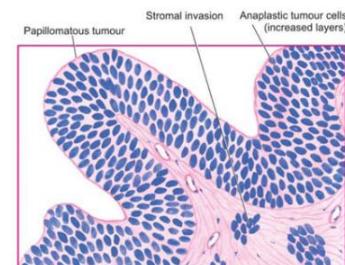
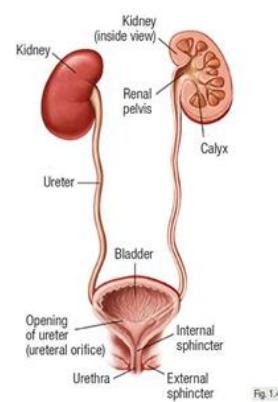
▪ Microscopic picture:

- The dermis is infiltrated by masses of malignant epithelial cells variable in size and shape.
- The cells appear **blue**.
- The outer cell layer is **columnar** and **parallel** "palisade arrangement". The inner cells are **polyhedral** and **rounded**.



Transitional Cell Carcinoma

- It is **malignant tumor of transitional epithelium**.
- It occurs mainly in the **urinary bladder**.
- **Gross picture:**
 - Commonly the tumor appears in a **papillary form**.
 - **Non-papillary tumors** are **less common**, and usually are **funicating**, **ulcerating** or **infiltrating**.
- **Microscopic picture:**
 - Formed of sheets of **malignant transitional epithelium** with **indefinite outline** separated by **fibrous stroma**.



Adenocarcinoma

- Adenocarcinoma is a **malignant tumor** of Glandular epithelium.

- **Sites:**

a- The commonest site is the **gastrointestinal tract** as the stomach, colon, and rectum.

b- Other sites are thyroid, ovary, endometrium and prostate.

- **Gross picture:**

1- Ulcerative carcinoma (**the commonest**).

2- Polypoid or fungating carcinoma.

3- Infiltrative carcinoma.

- **Microscopic picture:**

- Infiltrating malignant acini which are variable in size and shape.

- They are lined by **one or more layers of malignant columnar or rounded cells** having large rounded **darkly-stained nuclei** with many mitotic figures.
- Acini may be distended with the secretion forming cysts which may show papillae, e.g. cyst adenocarcinoma in the ovary.

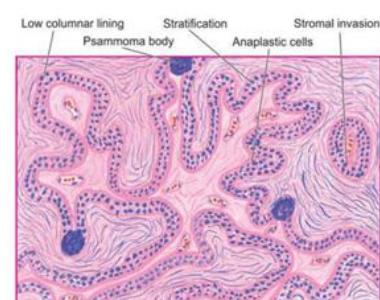
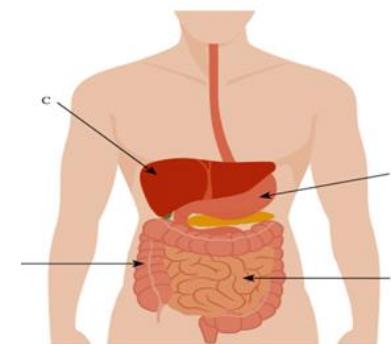
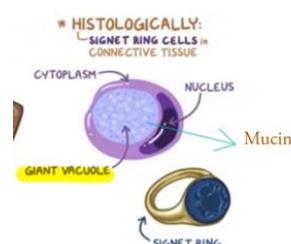


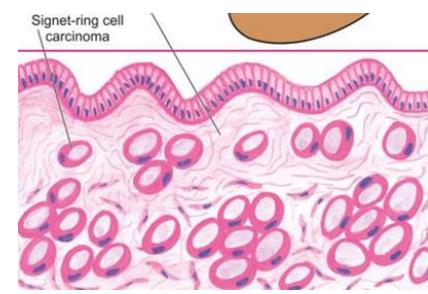
Figure 22.22 Papillary serous cystadenocarcinoma of the ovary. Microscopic

Mucoid (Mucinous) Carcinoma

- it is a **malignant tumor** of glandular epithelium, in which the malignant cells secrete excess mucin.
- Common sites are Stomach and large intestine.
- **Gross picture:** it appears **soft, large, gelatinous mass**.



- **Microscopic Picture:**
- Malignant cells arranged in **acinar or alveolar pattern**.
- The malignant cells are **distended with pale blue homogenous mucoid material** and the **nucleus is eccentric and flattened (signet-ring cells)**.
- Rupture of cell form **lakes of mucin** with scattered malignant cells.



II- Sarcoma:

Malignant tumor arising from mesenchymal tissue.

- **Microscopically:**
- It is usually a **highly cellular tumor** with increased number of small malignant cells, showing **darkly stained nuclei** and **many mitotic figures**.
- **Multinucleated tumor giant cells** may be present.
- The stroma is usually **scanty, separated non-cohesive individual cells** and is very vascular.
- **Necrosis, hemorrhage** and **myxomatous degeneration** are common findings.
- Other histological features are added depending on the **type of sarcoma** and the **degree of differentiation**.

- **Classification of sarcoma:**

a- Differentiated sarcomas:

The Tumor cells form an **intracellular substance** which points to the **type of tissue of origin** e.g. collagen fibers in fibrosarcoma, osteoid and osseous tissue in osteosarcoma....etc.

b- Undifferentiated sarcoma:

The **intercellular substance** is **scanty** or **absent** and the tumor is named according to the morphology of the cells e.g. spindle, round, mixed or giant cell sarcoma.

- **Type of sarcoma:**

I- Differentiated sarcomas	II- Undifferentiated Sarcoma
1- Liposarcoma	1- Spindle cell sarcoma
2- Myxosarcoma	2- Giant cells sarcoma
3- Osteosarcoma	3- Round cell sarcoma
4- Chondrosarcoma	4- Mixed cell sarcoma
5- Leiomyosarcoma	
6- Rhabdomyosarcoma.	
7- Hemangiosarcoma.	

		Carcinoma	Sarcoma
Tumor origin		Malignant tumor of epithelium	Malignant tumor of the mesenchyme
Age of onset		Usually at the age of 40 years	Usually younger age
Growth rate		Slower than sarcoma	Faster than carcinoma
Tumor margins		More infiltrative	More expansile
Gross features	Size	Less bulky than sarcoma	Form bulky masses
	Hemorrhage and necrosis	Usually less	Usually prominent
	Consistency	Usually hard	Usually soft
	Color	Usually grayish	Red due to <u>richer vascularity</u>
Microscopic features	Anaplasia	Less marked	More marked
	Cell cohesion	Variable	Often absent
	Blood vessels	Less & better formed	More and thin walled
	Hemorrhage, necrosis	Less	Common
Distant spread		Slower than in sarcoma Mostly, occurs early by lymphatics then later by blood	Faster than in carcinoma Occurs early by blood and rarely by lymphatics

Pigmented Neoplasms

- Pigmented Tumors are those arising **from melanin pigmented cells**.

1- Pigmented Nevus (Mole):

- It is a **benign tumor of melanocyte of the skin of the face, neck, chest and back**.
- It is present nearly in every individual and usually dates since birth and so it is now considered as a hamartomatous malformation.

Pathological features:

- Variable in size but usually small.
- The color ranges from light brown to black.
- The surface is **flat**, slightly **elevated** or **papillary**.
- Nevi are usually **hairless**, but sometimes fine hairs are present.

Types:

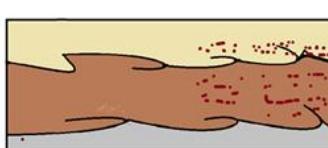
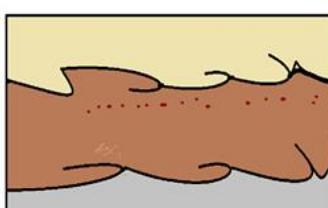
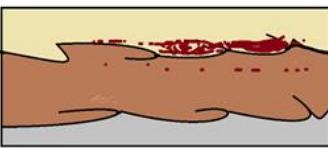
a- **Junctional nevus:** Pigmented cells are present **deep in the epidermis** (at the dermoepidermal junction) and in the **upper dermis**.



b- **Intradermal nevus:** Pigmented cells are in the **upper dermis only**.

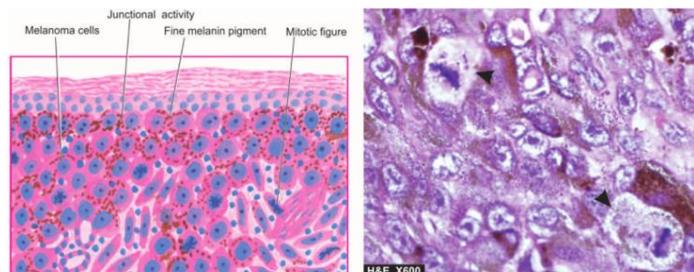
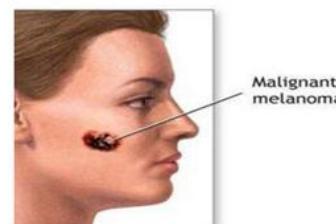


c- **Compound nevus:** The microscopic picture of both types described above.



2- Malignant Melanoma:

- It is a **highly malignant tumor** which arise from the following sites:
 - 1- Skin: Either in **pre-existing nevus** or **commonly directly from the melanocytes (de novo)**.
 - 2- Pigmented cells of the eye.
 - 3- Mucus membrane of the **rectum**, **mouth cavity**, and **vagina** occur due to prolonged exposure to ultraviolet rays of the sun.
- **Gross picture:** it forms a **rapidly growing, ulcerated, deep brown tumor**, which infiltrate the surrounding.
- **Microscopic picture:**
 - **Proliferation of atypical anaplastic melanocyte invading the surrounding tissue.**
 - **Melanin pigment is found both intracellular and extracellular.**



بالتوفيق يا اذطال، مستشفي شرق عولنا معاً كوا

GOOD LUCK