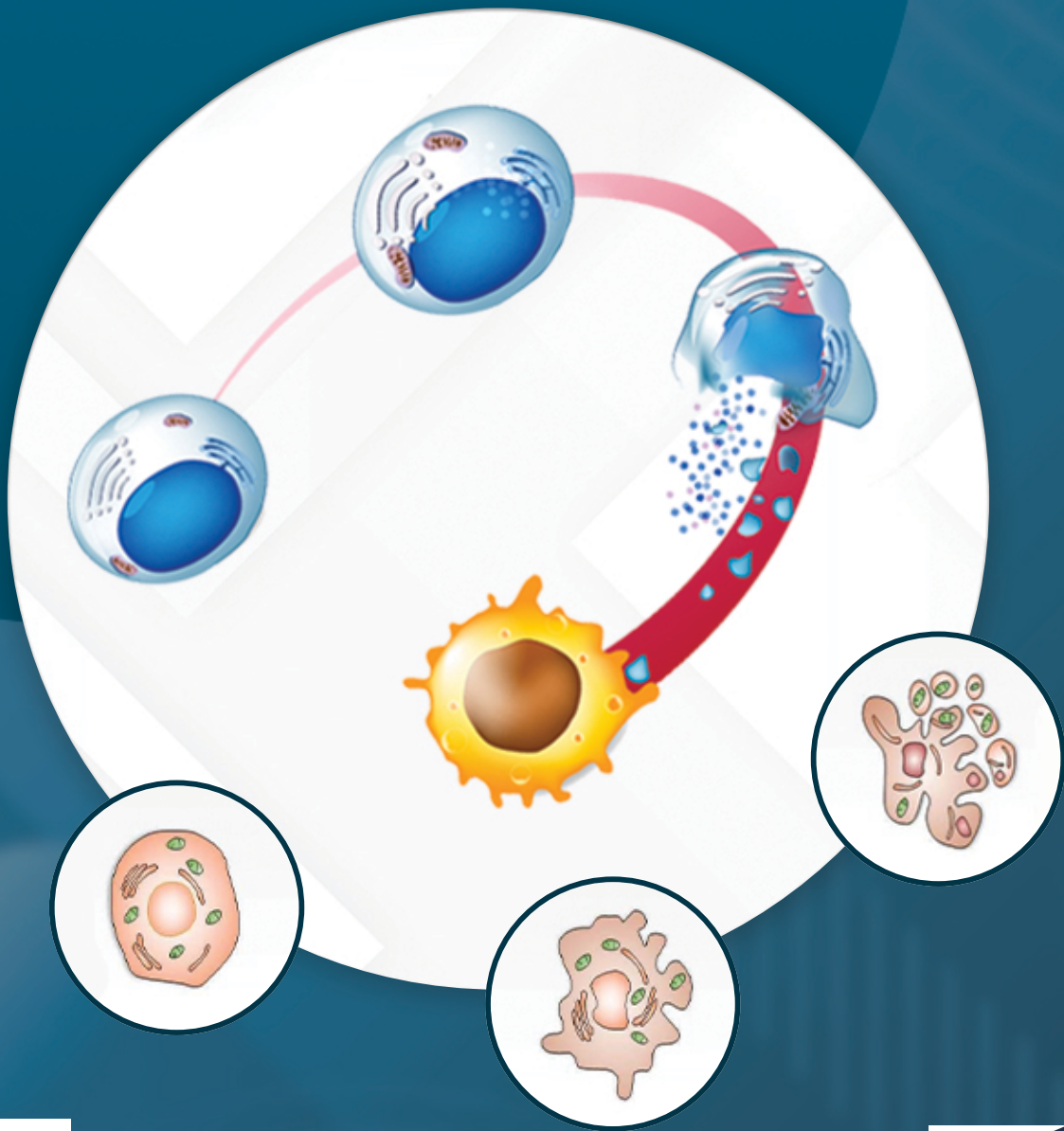


PATHOLOGY

CHAPTER 1

1ST YEAR - MODULE 108



KASR ALAINY UNIVERSITY

DR AHMED ELNEMR

مكتبة سكاى الحديثة



Cellular Response to Injury

Normal cell function requires a **balance between physiologic demands and the limitations** of cell structure and metabolic capacity; the result is a **steady state, or homeostasis**.

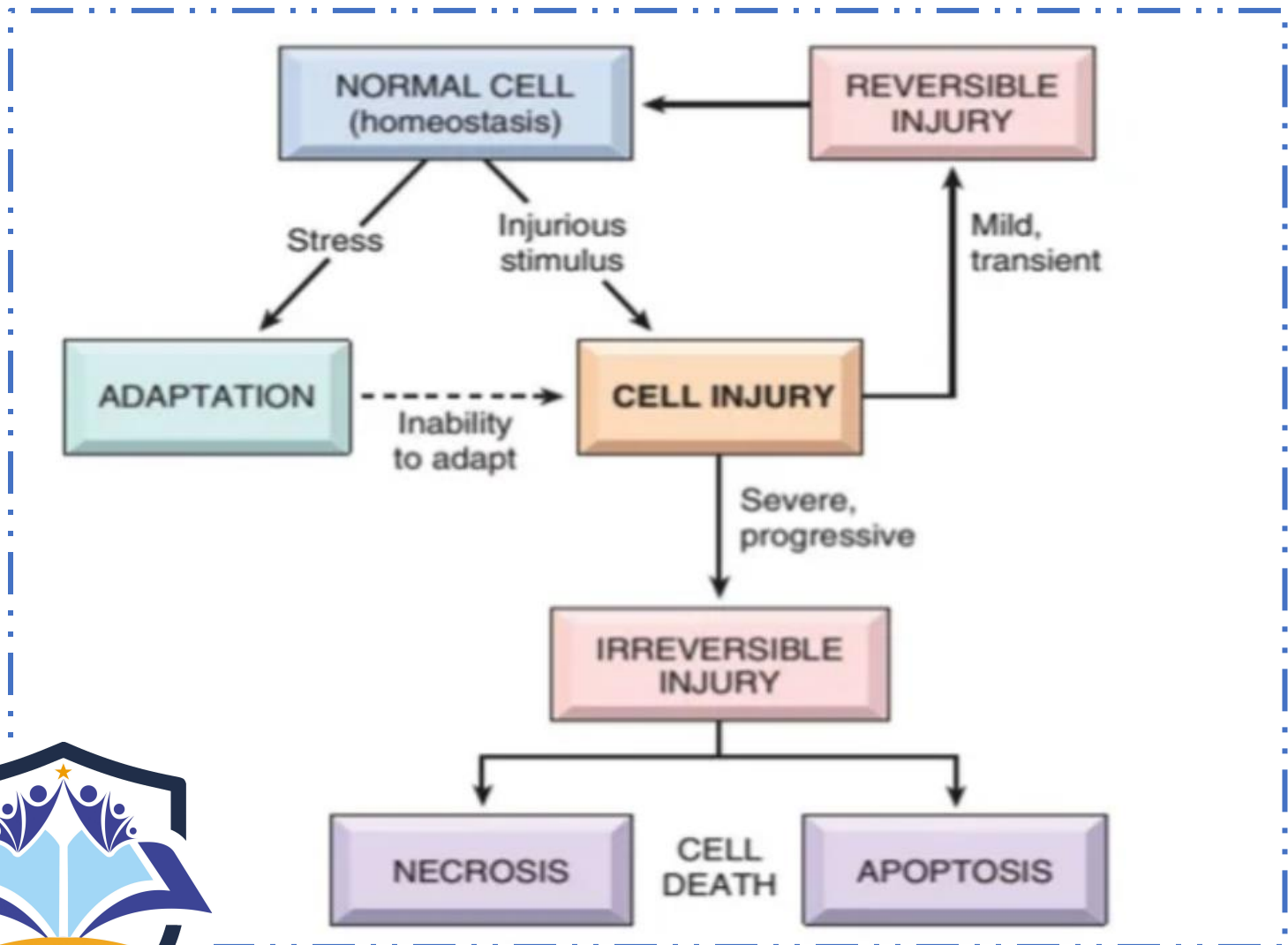
Cells can **alter their functional state** in response to modest stress to maintain the steady state.

More excessive physiologic stresses, or adverse pathologic stimuli (injury), result in:

1) **Adaptation.**

2) **Reversible Injury**, or **Irreversible Injury** and cell death.

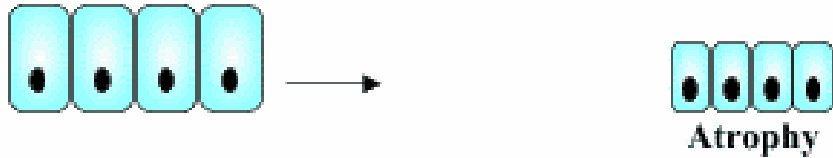
NB: These responses may be considered a continuum of progressive impairment of cell structure and function.



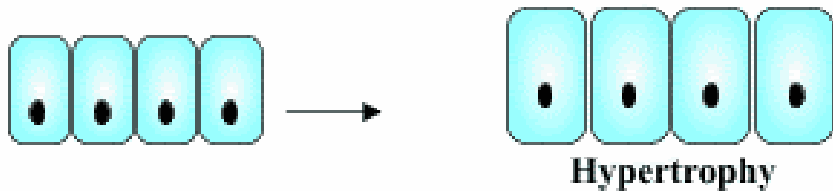
1. Adaptation

- It occurs when **physiologic or pathologic** stressors induce a **new state that changes** the cell but **otherwise preserves its viability in the face of the exogenous stimuli**.
- These changes include:

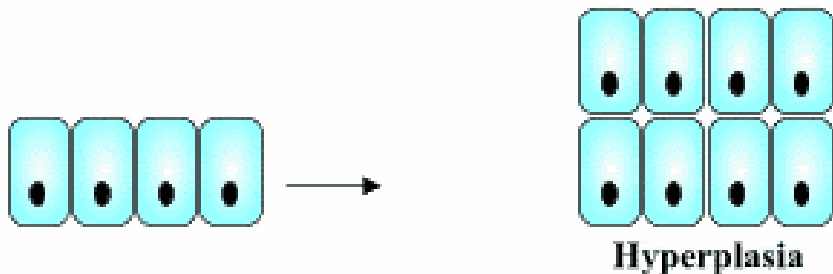
A. Atrophy.



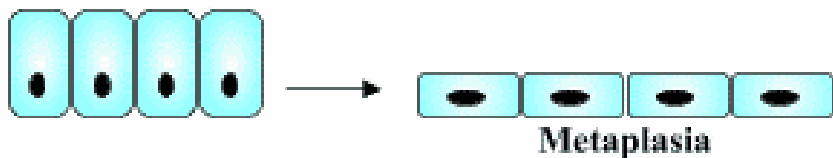
B. Hypertrophy.



C. Hyperplasia.



D. Metaplasia.



2. Reversible Injury

- It denotes **pathologic cell changes**
- It can be **restored to normal** if the stimulus is **removed or if the cause of injury is mild**.

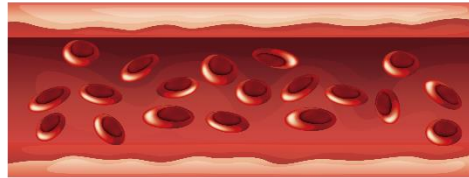
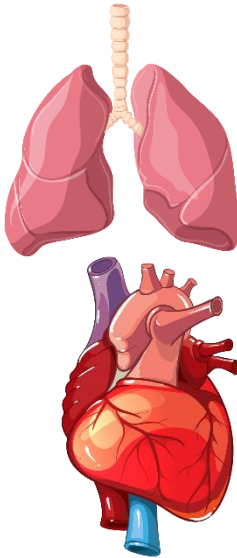
3. Irreversible Injury

- It denotes permanent pathologic changes that cause cell death.
- It occurs when **stressors exceed the capacity of the cell to adapt**
(Beyond a point of no return) **نقطة اللاعودة**

Causes Of Cell Injury:

1) Oxygen deprivation (hypoxia)

- It affects **aerobic respiration** and therefore the ability to generate adenosine triphosphate (**ATP**).
- This extremely **important and common cause of cell injury and death**.
- **Hypoxia occurs as a result of:**
 - **Ischemia** (deficient blood supply).
 - **Inadequate oxygenation** (e.g., cardiorespiratory failure).
 - **Loss of oxygen-carrying capacity of the blood**
(e.g., anemia, carbon monoxide poisoning).



2) **Physical agents** including trauma, heat, cold, radiation, and electric shock.

3) **Chemical agents** and **drugs**, including therapeutic drugs, poisons, environmental pollutants, alcohol and narcotics.

4) **Infectious agents**, including viruses, bacteria, fungi, and parasites.

5) **Immunologic reactions**, including autoimmune diseases, and cell injury following responses to infection.

6) **Genetic derangements**, such as chromosomal alterations and specific gene mutations.

7) **Nutritional imbalances**, including protein-calorie deficiency or lack of specific vitamins, as well as nutritional excesses.

Mechanisms Of Cell Injury

✚ The degree of injury depends on

- 1) Duration and persistence of injury,
- 2) Nature of injurious agent
- 3) Type of cells affected.

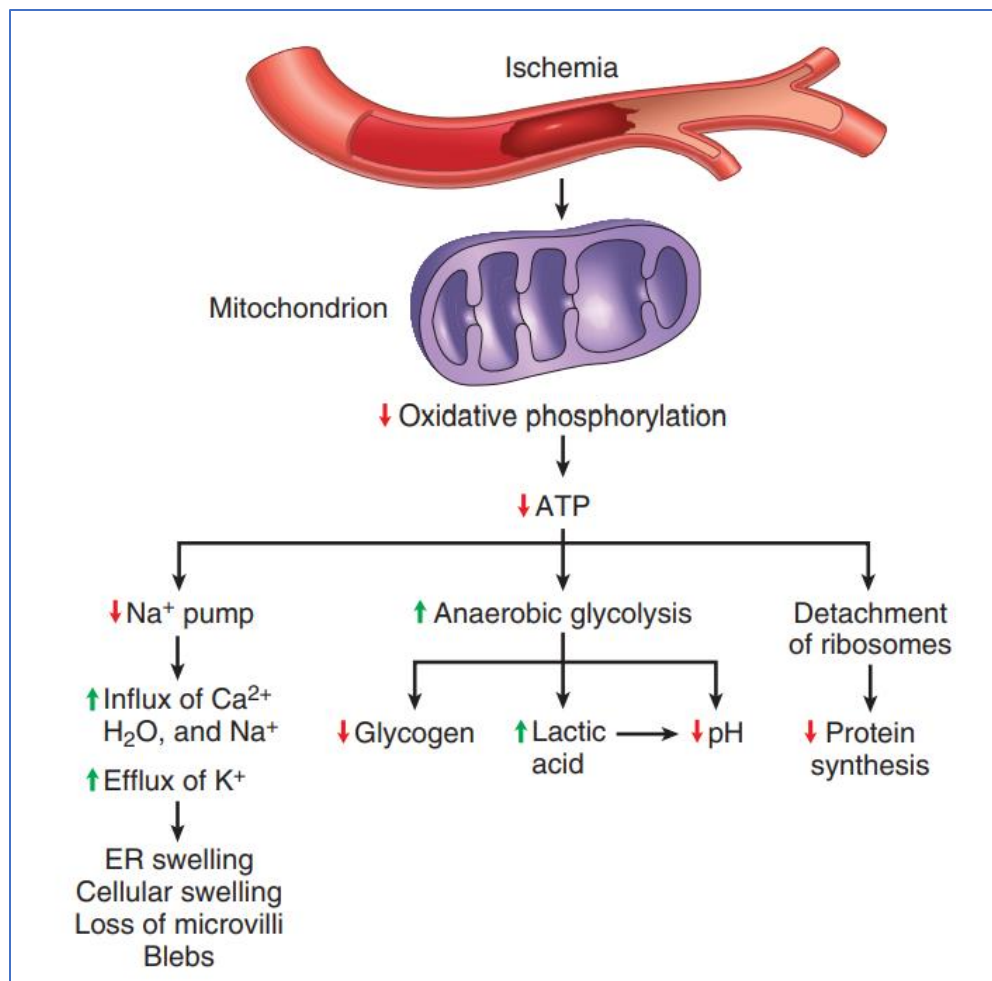
✚ Cell injury occurs by the following mechanisms:

1. Interference with aerobic respiration in mitochondria (oxidative phosphorylation)

➤ This leads to reduction of ATP and therefore impairs biochemical processes in the cell, with the following effects:

- i. **Reduction of activity of sodium pump**,
leading to accumulation of **sodium inside the cell**
with **influx of water** into the cell causing it to swell (**cytomegaly**)
- ii. **Interferes with protein synthesis.**
- iii. **Increase of intracellular calcium**

(The calcium levels are kept in check by ATP-dependent enzymes).



2. Accumulation of reactive oxygen species (oxidative stress) (حاول تقسم الجزء)

Definition:

- Free radicals, including reactive oxygen species are chemical species that **have a single unpaired electron in an outer orbit.**
- They **are highly reactive** thus interact and alter adjacent molecules.

The source:

They are produced normally in small amounts

- During The Reduction-Oxidation Reactions
- During Mitochondrial Respiration
- Energy Generation.

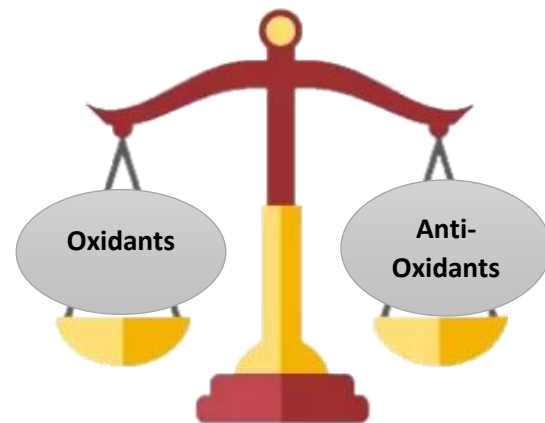
Examples of oxidants:

Reactive oxygen species include:

- superoxide (O_2^-)
- hydroxyl radical ($OH^\cdot$)
- hydrogen peroxide (H_2O_2).

Examples of Anti-oxidants:

- vitamin E
- enzymes such as superoxide dismutase



Normally:

- there is a balance between free radicals and defense mechanisms which includes antioxidants as vitamin E and enzymes such as superoxide dismutase.

In some situations:

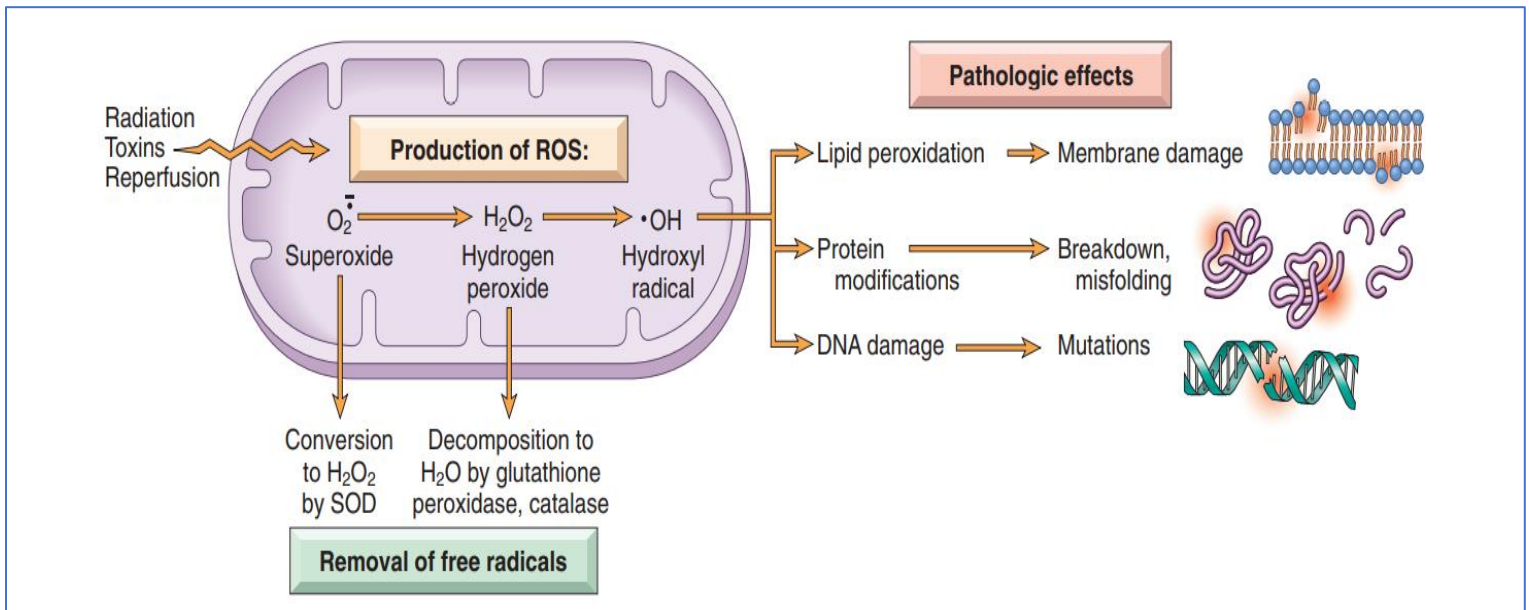
- The defense mechanisms are overcome and free radicals interact with
 - Lipids In Cell Membranes (Peroxidation),
 - Cellular Proteins
 - DNA,

(This Is Referred to As Oxidative Stress)

Free radicals play a major role in

- i. **Reperfusion Injury** (following restoration of blood flow in ischemic tissue),
- ii. **Cellular Aging,**
- iii. **Chemical Injury**
- iv. **Radiation Damage.**





3. Disruption of membranes:

A common result of the above mechanisms is disturbance of the function of membranes.

- **ATP depletion affects the Na pump of plasma membrane.**
 - ✓ Increase intracellular calcium causes activation of **phospholipases** which break down membranes.
- **Free radical peroxidation of lipids** in membranes further damages the structure.
- **Disruption of lysosomal membranes**
 - ✓ leads to release of various enzymes including **DNases, and proteases**, into the cytosol leading to **death of the cell**.

NOTES:

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Morphologic Alternations in Cell Injury

1. Reversible Injury (Degeneration):

A- Cloudy Swelling:

Definition: One of the **earliest changes** seen in injury

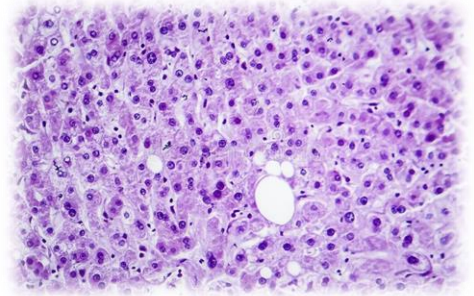
causes:

- loss of Na pump
- accumulation of sodium and water inside the cell.

Morphology:

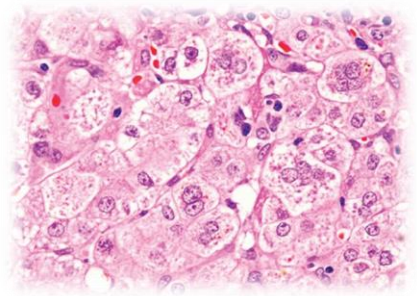
- The cell is swollen and the cytoplasm appears granular.

Site: It is seen in liver cells, myocardial cells and renal tubular cells.



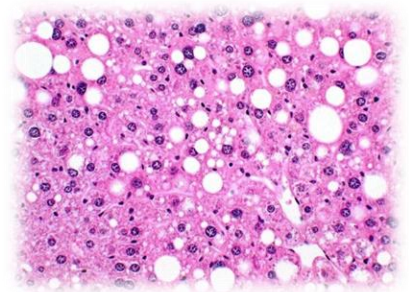
B- Hydropic, Ballooning or Vacuolar Change:

- Same mechanism as cloudy swelling but more advanced.
- The cells are swollen due to excess water accumulation.
- The cytoplasm is pale and shows **multiple vacuoles**.



C- Fatty Change:

- Fatty change occurs in **hypoxic and toxic injury**.
- Lipid appears as **empty vacuoles** in the cytoplasm.
- It is seen in cells involved in or dependent on fat metabolism, such as hepatocytes and myocardial cells.
- Fatty change in myocardium can be
 - **Spotty** (in case of **ischemia**) or
 - **Diffuse** (in case of **toxemia** e.g., in diphtheria).



(See fatty change of the liver in chapter 2)

2- Irreversible Injury:

- Cell death occurs primarily through two morphologic patterns and mechanisms:
Necrosis And Apoptosis.

NECROSIS

Definition: Necrosis is death of a group of cells within a living body.

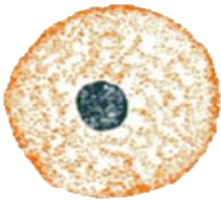
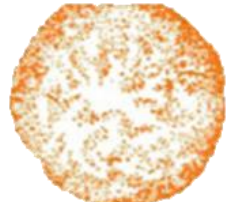
- ♥ With **severe or prolonged moderate** injury, there is **loss of membrane integrity** and release of lysosomal enzymes in the cytosol leading to **destruction of the cellular constituents**.
- ♥ There is also **leakage of cell constituents into the surrounding tissue**, resulting in **an inflammatory response**.
- ♥ **Necrotic area** is **removed by macrophages** and **repaired by fibrosis**.
- ♥ **Dystrophic calcification** may occur.

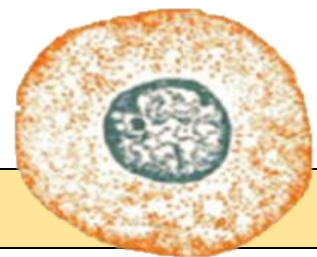
Mechanism:

- Two processes underlie the basic morphologic changes:
- 1) **Denaturation of proteins**.
 - 2) **Enzymatic digestion of organelles** and other cytosolic components.

Morphology:

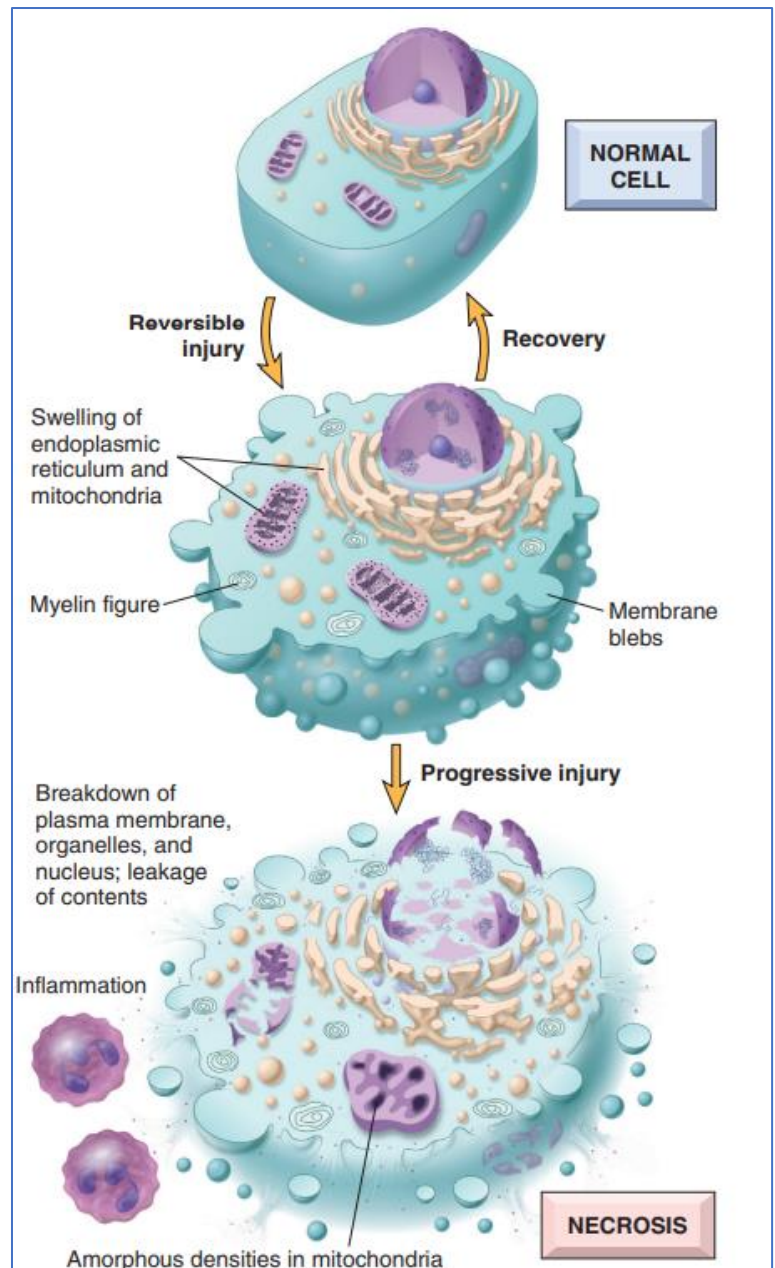
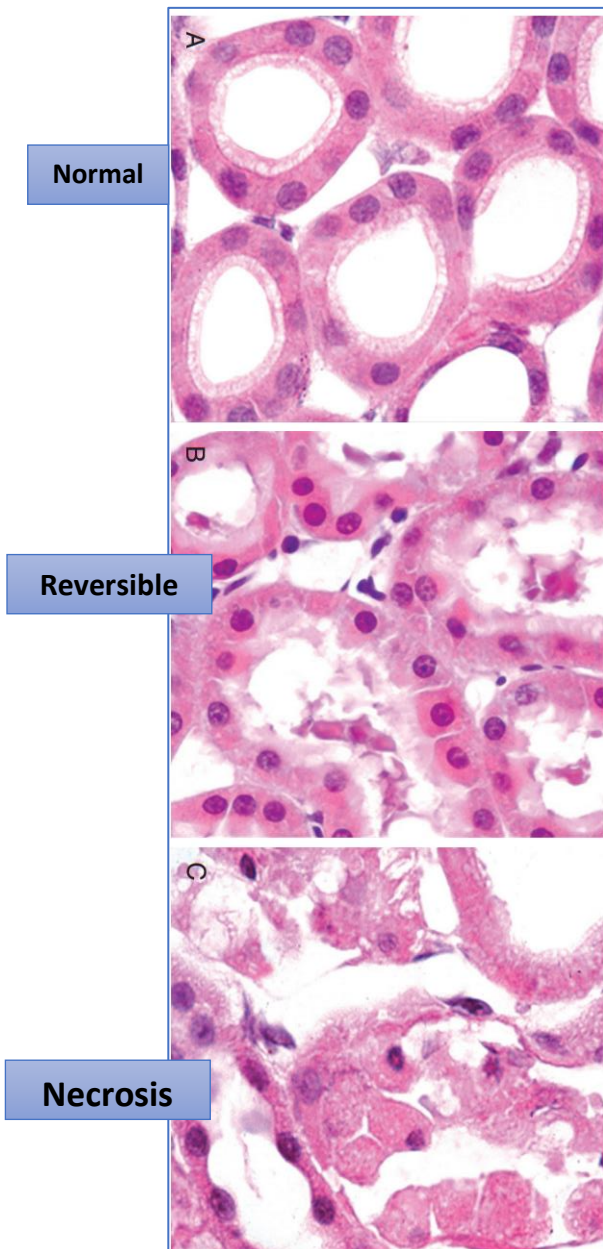
- There are several distinctive features:

1- Nuclear Changes:	
➤ Pyknosis: Nuclear shrinkage.	
➤ Karyorrhexis: Destructive nuclear fragmentation.	
➤ Karyolysis: Fading of nuclear basophilia. ♥ Eventually the nucleus disappears completely.	



2- Cytoplasmic Changes:

- **Necrotic cells are more eosinophilic**
(Stain more pink) with hematoxylin and eosin **Due To**
 - 1) **loss of cytoplasmic RNA** which binds the blue dye (hematoxylin)
 - 2) **presence of denatured cytoplasmic proteins** which bind the red dye (eosin).
- **There is loss of cell border definition.**
- **Later the necrotic tissue appears structureless pink**
due to autolysis by lysosomal enzymes.



Types of necrosis:

1. Coagulative necrosis (ischemic necrosis):

Etiology:

- ♥ It occurs as a result of **acute ischemia** (sudden decrease in blood supply).

Pathogenesis:

- It is due to **protein denaturation**.
- Presumably, the injury denatures structural proteins, as well as the enzymes that cause proteolysis (autolysis) so the cellular outlines are maintained for some time.

(Ghost Cell)

SITE:

- ♥ Any Organs except Brain
e.g.: infarction of kidney, spleen and heart.

Morphology:

Gross picture:

- The necrotic area is initially white/yellow but of normal consistency ,

Microscopic picture:

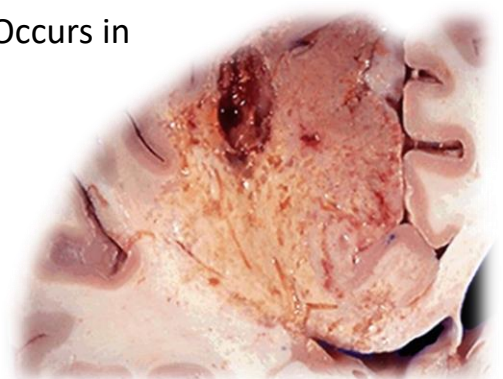
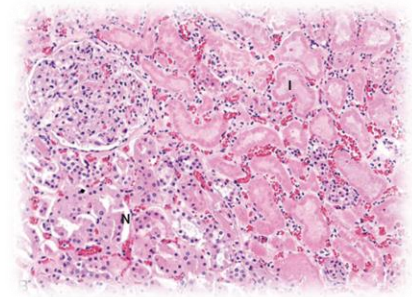
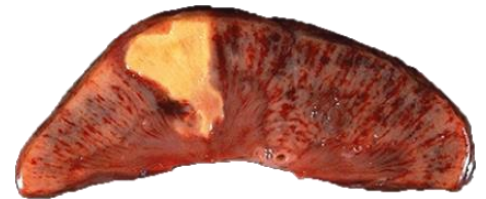
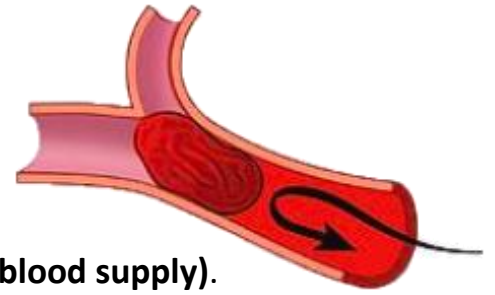
- **loss of nuclei**.
- **increased eosinophilia** of the cytoplasm with retention of the general cellular outline (Appearing as ghost of the original tissue).
- Eventually, **this cellular outline is lost and tissues break down** and appear structureless pink.
- **Inflammatory cells infiltrate** the necrotic tissue and **macrophages remove** the dead tissue.

2. Liquefactive or colliquative necrosis: Occurs in

A. CNS infarctions, where the tissues are **Rich in lipid**, **Soft** and **Lack supporting stroma**.

- Necrotic area becomes **surrounded by glial tissue** and is changed into a cyst.

B. Pus in suppurative inflammation.



3. Caseation Necrosis:

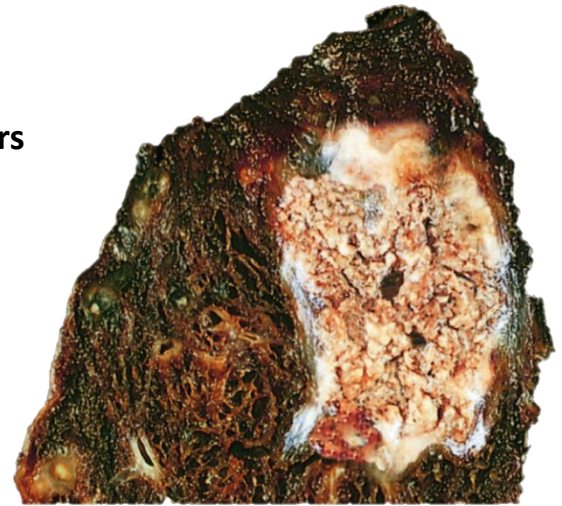
- ✚ It is a type of necrosis where the necrotic tissue appears
 - ♥ semi-solid,
 - ♥ yellowish and cheese-like (casein).

Microscopic Picture:

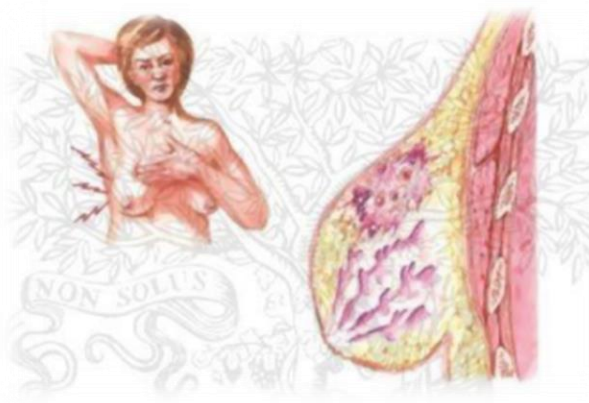
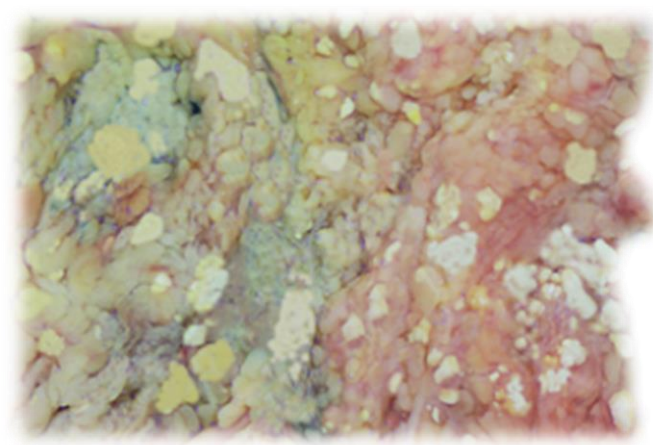
- appears as granular structureless pink material.

Pathogenesis:

- This occurs mainly in **Tuberculosis** due to tissue digestion by activated macrophages.
- Also, **liberation of lipids from the tubercle bacilli** capsule adds to the cheese-like appearance.



4. Fat Necrosis is of two types:

A- Traumatic Fat Necrosis:	B- Enzymatic Fat Necrosis:
Site: ♥ A common site is the breast where it results in a palpable mass. Pathogenesis: ➤ Trauma to adipose tissue leads to the release of intracellular fat which provokes an inflammatory response. ➤ Macrophages engulf the fat and eventually lead to fibrosis. 	Site: ♥ Pancreas Pathogenesis: ➤ In acute pancreatitis, there is leakage of pancreatic lipase, which acts on mesenteric fat cells splitting fat into fatty acids, which combine with calcium to form white calcium soaps. 

5. Fibrinoid necrosis:

Definition:

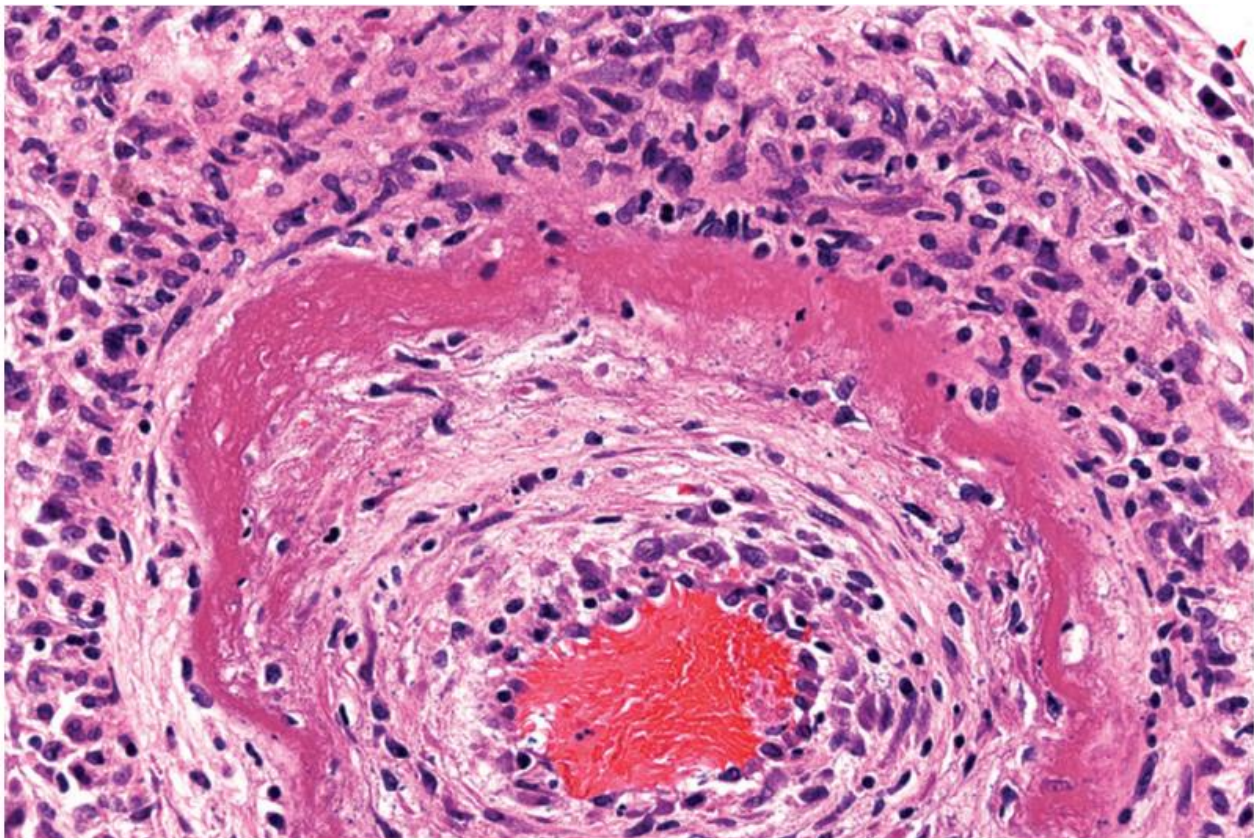
- ♥ Fibrinoid necrosis is a **special form of necrosis**,
- ♥ where the necrotic material has some **staining reactions resembling fibrin**.

Morphology:

- The material is **Deep Red and Homogenous** with Hematoxylin and eosin stain.

Causes:

- It is seen with collagen damage in
 - some **autoimmune diseases** as **rheumatoid arthritis** and
 - in **immune reactions involving blood vessels**, e.g., **polyarteritis nodosa**.



APOPTOSIS

Definition: Apoptosis means falling away in Greek.

- ♥ It is a **programmed cell death** which is **energy dependent**.
- ♥ It is a form of cell death which leads to the deletion of individual cells.
- ♥ **Their membranes remain intact** and thus **do not provoke an inflammatory response**.

Causes of apoptosis:

- It can occur in physiologic and pathological conditions.

1. Apoptosis in physiological conditions:

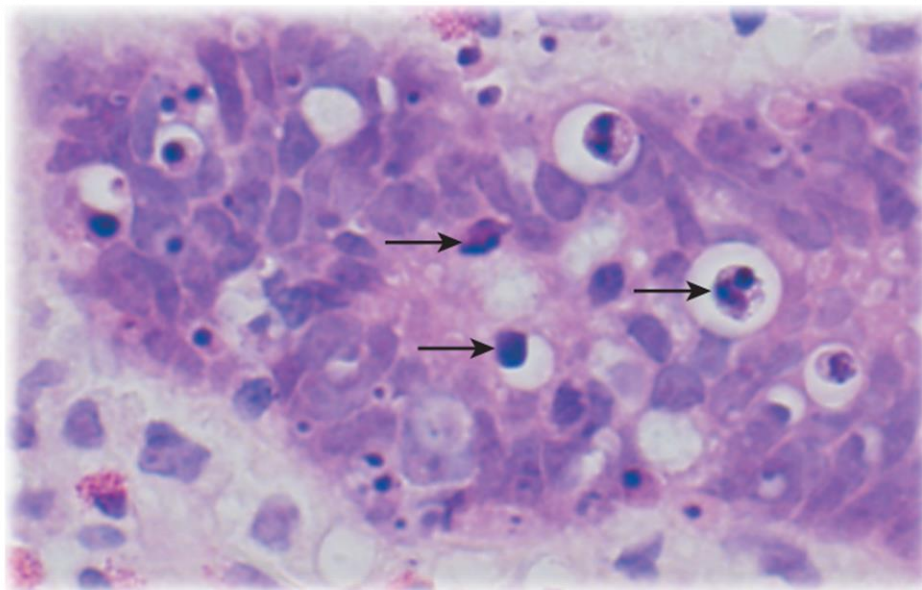
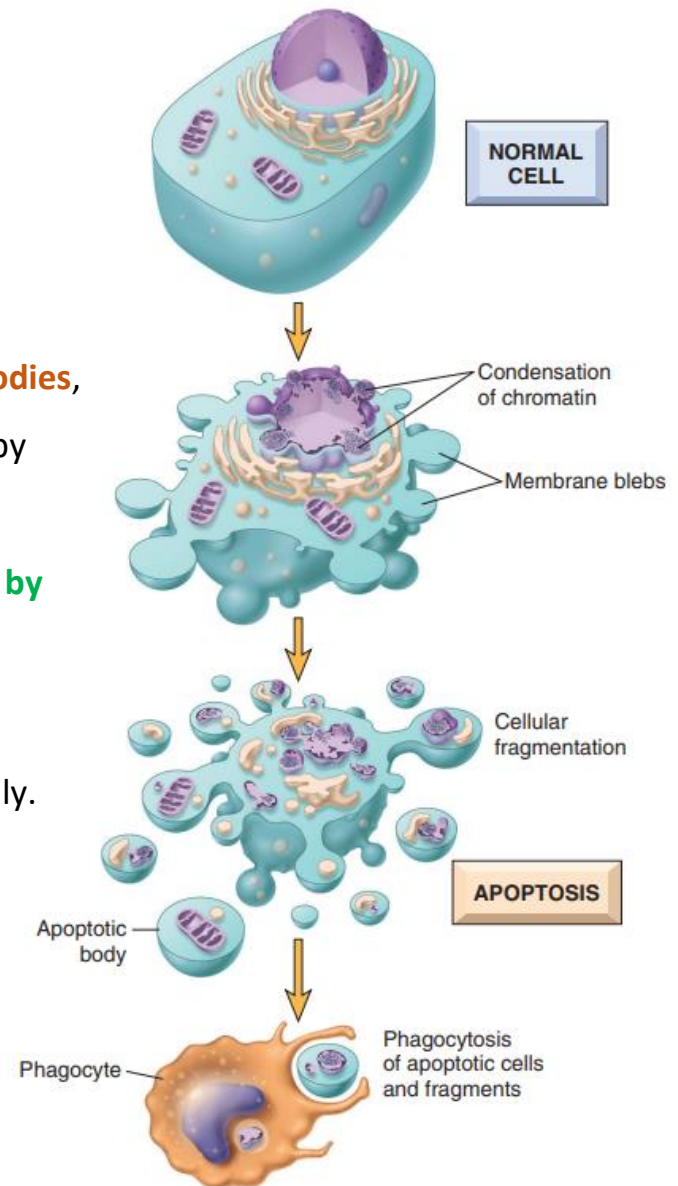
- A. Programmed destruction of cells **during embryogenesis**.
- B. **Hormone dependent involution** of tissues e.g., **in the endometrium during menstruation**.
- C. Cell deletion **in proliferating cell populations** (e.g., **intestinal epithelium**) to maintain a constant cell number.
- D. Defective cells which acquire significant DNA damage are removed by apoptosis, to get rid of **cells with unwanted mutations**.

2. Apoptosis in pathological conditions:

- A. **Cell death in virus infected cells**, which may be induced by the virus as in HIV infection or by the host immune response e.g., viral hepatitis.
- B. **Irradiation damage** (DNA damage).
- C. **Elimination of cancer cells** (including action of anticancer drugs).
- D. Cytotoxicity induced by T lymphocytes as in **organ transplant rejection**.
- E. **Accumulation of misfolded proteins**
 - (e.g., due to inherited defects or due to free radical damage).
 - This may be the basis of cell loss in a number of neurodegenerative disorders.
- F. **Pathologic atrophy** in parenchymal organs **after duct obstruction** (e.g., pancreas).

Morphological Changes:

- The **cytoplasm condenses** and the cell shrinks, retaining an **intact plasma membrane**.
- **The nucleus shrinks and fragments**.
- Apoptotic cells show **surface blebs** which **later fragment into** membrane bound **apoptotic bodies**, consisting of a **dark nuclear fragment** surrounded by **eosinophilic cytoplasm**.
- Apoptotic cells and apoptotic bodies are **removed by adjacent cells or macrophages**.
- **Control of Apoptosis:**
 - ♥ Apoptosis is controlled by the **Bcl2** protein family.
 - ♥ Apoptosis is brought about **by activation** of a group of **enzymes** called **caspases**.
 - ♥ These enzymes result in **destroying the nuclear membrane** and **activate DNases which degrade nuclear DNA**.



MCQ On Chapter 1

- 1) The mildest and commonest type of degeneration is:
- a) Hyaline degeneration
 - b) Cloudy swelling.
 - c) Amyloid degeneration
 - d) Fatty degeneration.
- 2) Cell response to injurious stimuli depends on
- a) Type of injury
 - b) Duration of exposure to injury
 - c) Cell type
 - d) All of the above
- 3) Changes associated with water metabolism are EXCEPT
- a) Irreversible cell injury
 - b) Cellular edema
 - c) Normal nucle.
 - d) Energy defect
- 4) Cloudy swelling occurs in:
- a) Parenchymatous cells.
 - b) Muscle cells.
 - c) Connective tissue fibroblasts
 - d) Non of the above.
- 5) Which of the following is a reversible damage?
- a) Karyorrhexis .
 - b) Pyknosis.
 - c) Karyolysis
 - d) Swelling of endoplasmic reticulum.

1- B	2- D	3- A	4- A	5- D
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6) Which of the following is a reversible change?

- a) Karyorrhexis.
- b) Pyknosis.
- c) Karyolysis.
- d) Swelling of endoplasmic reticulum.
- e) Gangrenous necrosis.

7) Enzymatic digestion is the predominant event in the following type of necrosis:

- a) Coagulative necrosis.
- b) Liquefactive necrosis
- c) Caseous necrosis.
- d) Fat necrosis

8) In hypoxic cell injury swelling of the cell occurs because intracytoplasmic accumulation of:

- a) Lipids.
- b) Proteins.
- c) Glycogen.
- d) Lipofuscin
- e) Water.

9) Fibrinoid necrosis is found in the following EXCEPT:

- a) Rheumatoid arthritis
- b) Necrotizing arteriolitis in malignant hypertension
- c) acute hemorrhagic pancreatic necrosis
- d) Systemic lupus erythematosus

10) Fat necrosis is usually due to

- a) Autoimmune reaction
- b) Traumatic
- c) Ischemia
- d) None of the above.

6- D	7- B	8- E	9- C	10- B
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11) All are correct about Necrosis EXCEPT:

- a) Local death of small or large group of cells in living tissue.
- b) opaque white with hyperemia in the surrounding tissues.
- c) Nuclei of the cells are not affected .
- d) It often occurs due to ischemia.

12) Necrosis of the following lesions is liquefactive type EXCEPT:

- a) An abscess.
- b) Brain infarction.
- c) Renal infarction
- d) Amoebic liver abscess.

13) All the following are signs of necrosis EXCEPT:

- a) Lipofuscin
- b) Pyknosis.
- c) Karyolysis.
- d) Karyorrhexis.

14) Coagulation necrosis occurs in all EXCEPT:

- a) Kidney.
- b) Heart.
- c) Spleen.
- d) Central nervous system.

15) Liquefactive ischemic necrosis is especially seen in:

- a) Heart.
- b) Brain.
- c) Spleen.
- d) Kidney.

11- C	12- C	13- A	14- D	15- B
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- 16) A 76-year-old develops signs and symptoms suggestive of Myocardial infarction. Microscopic examination of the heart is most Likely to reveal:
- A. Caseous necrosis.
 - B. Coagulative necrosis.
 - C. Enzymatic fat necrosis.
 - D. Gangrenous necrosis.
 - E. Liquefactive necrosis.
- 17) In the process of necrosis, a reduction in the size of the nucleus and a condensation of nuclear material is known as:
- a) Pyknosis
 - b) Karyolysis.
 - c) Karyorrhexis
 - d) Metachromasia.
 - e) Hypochromasia
- 18) The underlying tissue damage in most cases of hemorrhagic Infarction of the lung is:
- a) Caseous necrosis.
 - b) coagulation necrosis.
 - c) Fibrinoid necrosis.
 - d) Gangrenous necrosis.
 - e) Liquefactive necrosis.
- 19) of the following, caseous necrosis would most likely be Associated with:
- a) Pulmonary tuberculosis
 - b) Soft tissue abscesses.
 - a) Sore throat.
 - b) Thrombophlebitis.
 - c) Viral bronchitis.

16- B	17- A	18- B	19- A
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20) Which type of the following types of necrosis is grossly opaque and chalky white

- a) Coagulative.
- b) Liquefactive.
- c) Caseous necrosis
- d) Fat necrosis.

21) Cell or tissue death within the living body is termed:

- a) Lysis.
- b) phagocytosis.
- c) pyknosis
- d) necrosis
- e) Karyolysis.

22) Caseous necrosis is most commonly in which of the Following disease processes?

- a) Tuberculosis
- b) Pneumonia.
- c) Syphilis.
- d) Scarlet fever.
- e) Chickenpox.

23) A type of necrosis present in tuberculosis:

- a. Coagulative necrosis.
- b. Caseation necrosis.
- c. Liquefactive necrosis.
- d. Enzymatic fat necrosis.
- e. Traumatic fat necrosis.

24) Acute pancreatitis is characterized by:

- a) Coagulative necrosis.
- b) Caseous necrosis
- c) Fat necrosis,
- d) Fibrinoid necrosis.
- e) Liquefactive necrosis.

20- D	21- D	22- A	23- B	24- C
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25) Localized area of ischemic necrosis is mostly associated with:

- a) Ascites.
- b) Petechiae
- c) infarction.
- d) Emboli formation.
- e) Hematoma.

26) Apoptosis has the following features EXCEPT:

- a. There is cell shrinkage in apoptosis.
- b. There are no acute inflammatory cells surrounding apoptosis.
- c. There may be single cell loss or affect clusters of cells.
- d. Apoptosis is seen in pathologic processes only.

27) Apoptosis occurs in all EXCEPT:

- a) During embryogenesis
- b) Viral hepatitis.
- c) Menstruation
- d) Tuberculosis.

28) Apoptosis is characterized by the following Except

- a) Cell shrinkage.
- b) Cytoplasmic blebs.
- c) Cell membrane rupture
- d) Formation of apoptotic bodies.

29) Apoptosis ends by:

- a- Fibrosis.
- b- Phagocytosis of apoptotic bodies.
- c- Giant cell reaction.
- d- All of the above.

25- C	26- D	27- D	28- C	29- B
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30) Active programmed cell death is called

- a) Coagulative necrosis.
- b) Fat necrosis.
- c) Autolysis.
- d) Apoptosis

31) Apoptosis causes EXCEPT:

- a) Activation of caspases.
- b) Local inflammatory response.
- c) Phagocytosis of cell fragment by local macrophages.
- d) Condensation of chromatin.

32) Features of apoptosis include all the following except:

- a. Shrinkage of cell size.
- b. Nuclear chromatin condensation.
- c. Formation of membrane blebs.
- d. Inflammation.
- e. DNA fragmentation.

33) Apoptosis is brought about by a group of enzymes called

- a) Lipases.
- b) Proteases.
- c) Caspases.
- d) Catalases.

30) D	31) B	32) D	33) C
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SMART VISION INSTITUTE PATHOLOGY



TISSUE DEPOSITION

DR AHMED ELNEMR

INTRACELLULAR ACCUMULATION AND EXTRACELLULAR DEPOSITIONS

⇒ Cells may accumulate abnormal amounts of various substances:

a) **A normal endogenous substance:-** [Water protein, carbohydrate, & lipid]

⇒ **Causes:** { if the metabolic rate is inadequate to remove it.
E.g. fat accumulation in liver cells.
due to genetic or acquired defects in its metabolism
E.g. lysosomal storage diseases).

b) **An abnormal endogenous substance:-**

⇒ **Causes:** (product of a mutated gene) accumulates due to defective folding or transport, and inadequate degradation

⇒ E.g. α1 antitrypsin disease).

c) **An abnormal exogenous substance:-**

⇒ **Causes:** accumulate when normal cells are unable to degrade such substances

⇒ E.g. macrophages laden with environmental carbon.

INTRACELLULAR ACCUMULATIONS

♣ Examples:

A) Lipids intracellular accumulations

⦿ Triglycerides (the most common).

⦿ Cholesterol

⦿ Phospholipids.

} can accumulate in cells.

1- Steatosis (Fatty Change)

❖ Definition:

- ∂ An abnormal accumulation of **triglycerides** within parenchymal cells either due to excessive entry or defective metabolism.
- ∂ Fatty change is typically reversible, but it can lead to inflammation and fibrosis.

❖ Sites:

- ∂ The most common site is in the liver.
- ∂ However, it can occur in heart, muscle, & kidney.

❖ Causes of hepatic steatosis:

- ∂ include alcohol abuse (most common cause in USA).
- ∂ protein malnutrition.
- ∂ diabetes mellitus.
- ∂ obesity , hypoxia, & toxins.



Healthy Liver

❖ Pathogenesis:

⇒ Excessive entry or defective metabolism of lipids:

Effect	Due to:-
Increased fatty acids entering the liver	Starvation, Corticosteroids
Decreased fatty acid oxidation	Hypoxia
Increased triglyceride formation	Alcohol
Impaired lipoprotein secretion from liver	Alcohol

❖ Gross picture:

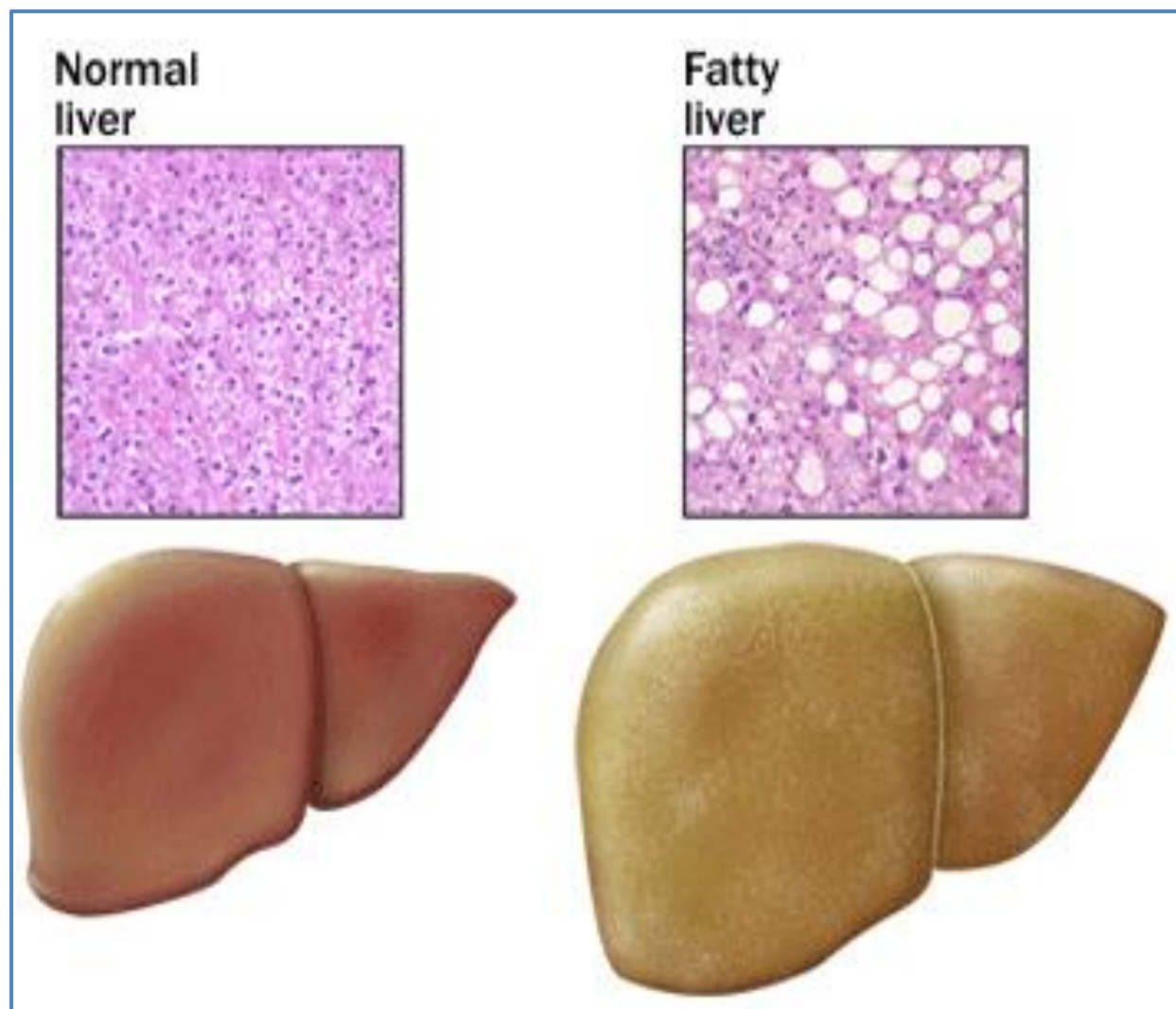
- ∂ **Fatty livers** :- enlarged, and soft.
- ∂ **The borders**:- are rounded
- ∂ **The cut section**:- is yellow and greasy.



Fatty Liver

❖ Microscopic picture:

- ∂ Small, **intracytoplasmic** droplets or large vacuoles of fat accumulate in the liver cells.
- ∂ **The nucleus**:- becomes flattened and pushed to one side giving the cell a signet ring appearance.



2-Cholesterol & Cholesterol Esters

✚ Normally:

Cholesterol is required for cell membrane or lipid-soluble hormone synthesis; production is tightly regulated,

✚ Pathologically:

accumulation can be present in:

1) Atherosclerosis:

- Cholesterol & cholesterol esters accumulate in:
arterial wall smooth muscle cells & macrophages.
- Extracellular accumulations appear microscopically as cleft-like spaces.

(due to dissolved cholesterol crystals during normal histologic processing).



2) Xanthomas:

In acquired & hereditary hyperlipidemias, lipids accumulate in "foamy" macrophages forming clusters in subcutaneous tissues and tendons producing masses called xanthomas.

B) Hyaline Change

✚ Definition:-

- an alteration within cells or in the extracellular space that gives a homogeneous, glassy, pink appearance in routine histologic sections stained with H & E.
- It is widely used as a descriptive histologic term rather than a specific marker for cell injury.

1) Examples of intracellular hyaline change:-

⌚ Russell bodies:

This is hyaline change in plasma cells in chronic inflammation due to distension with immunoglobulins.

⌚ Mallory alcoholic hyaline change:

in hepatocytes due to chronic alcoholism.

2) Examples of extracellular hyaline change:-

- ∂ Collagenous fibrous tissue in **old scars** may appear hyalinized, but the biochemical basis of this change is not clear
- ∂ **Mesenchymal soft tissue tumors particularly leiomyoma (Smooth muscle tumor).**
- ∂ **Vascular hyalinosis:**

In long-standing hypertension and diabetes mellitus, the walls of arterioles, especially in the kidney, become hyalinized, resulting from extravasated plasma protein and deposition of basement membrane material.

C) Glycogen

- ∂ Glycogen is commonly stored within cells as a ready energy source.
- ∂ Excessive intracellular deposits (**seen as clear vacuoles**) are seen in **glycogen storage diseases (so-called glycogenosis) & in diabetes mellitus.**

D) Pigments

➤ Pigments can be exogenous, coming from outside the body, or endogenous, synthesized within the body itself.

1) Exogenous Pigments:

1) Carbon particles:-

➤ Cause:

When inhaled In air polluted by factory and car exhaust.

➤ Pathogenesis:

- it is picked up by **macrophages** within the alveoli and is then transported through lymphatic channels to the regional lymph nodes in the tracheobronchial region.
- Accumulations of this pigment blacken the tissues of the lungs (**anthracosis**) and the involved lymph nodes.

➤ In coal miners:

the aggregates of carbon dust may induce a fibroblastic reaction and thus cause a serious lung disease known as coal worker's pneumoconiosis.

2) Tattooing:-

The pigments inoculated in the skin are phagocytosed by dermal macrophages, resulting in permanent localized pigmentation.



2) Endogenous Pigments:

1) Lipofuscin

➤ Lipofuscin is an insoluble pigment, also known as lipochrome or wear-and-tear pigment.

➤ Formation & pathogenesis:

- It is derived through lipid peroxidation of cellular membranes.
- It is not injurious to the cell or its functions.
- It is a sign of free radical injury and lipid peroxidation throughout the cell life.

➤ Sites:

- It is seen in the liver and heart cells of aging patients.
- patients with severe malnutrition and cancer.

➤ Micro:

- It appears as a yellow-brown, finely granular cytoplasmic, often perinuclear, pigment.

Brown atrophy of the heart

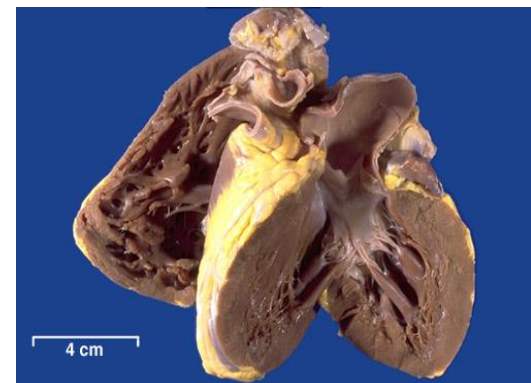
❖ **Definition:-** This is senile atrophy of the heart with excess lipofuscin pigment.

❖ **Gross appearance:**

- The heart is reduced in size and brown in color.
- The coronaries appear more tortuous due to decreased size of the heart with normal length arteries.
- The pericardial fat is replaced by edematous jelly-like tissue (serous atrophy of the fat).

❖ **Microscopic picture:**

- The muscle fibers are thin and atrophic.
- Excess fine yellowish brown lipofuscin pigments are seen on both sides of the nucleus in sections stained with hematoxylin only.



2) Melanin

↪ Melanin is an endogenous, non-hemoglobin-derived, brown-black pigment

↪ **Formation:**

enzyme tyrosinase catalyzes the oxidation of tyrosine to di-hydroxy- phenylalanine in melanocytes.

↪ **Causes of melanin hyperpigmentation:-**

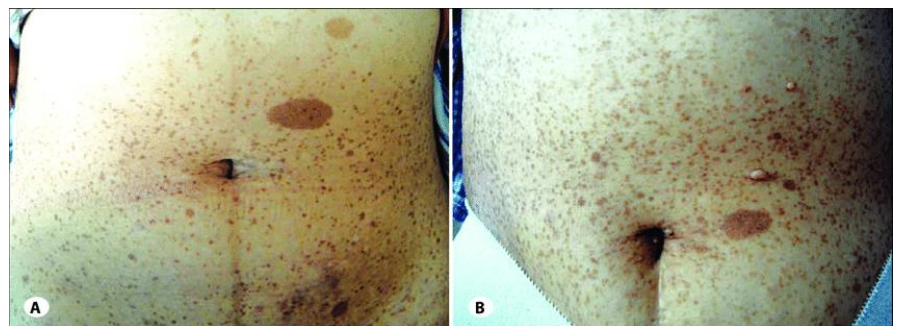
- 1) Prolonged exposure to the sun.
- 2) Melanocytic nevi and melanomas.
- 3) Cafe au lait patches in neurofibromatosis.
- 4) Chloasma of pregnancy:
 - Brown patches in the skin of :- face, nipple and genitalia
 - due to:- hormonal changes.



5) Addison's disease:

- In individuals with primary adrenal disease,:-
hyperpigmentation of the skin, particularly of sun-exposed areas and at pressure points, such as the neck, elbows, knees, and knuckles.
- Cause:-

This is caused by elevated levels of pro-opio-melanocortin (POMC) which is derived from the anterior pituitary and is a precursor of both ACTH and melanocyte stimulating hormone (MSH).



3) Hemoglobin-derived pigments

A) Haemosiderin

➤ It is a hemoglobin-derived, **golden yellow-to-brown**, granular pigment.

➤ Pathology :-

- Iron is normally carried by specific transport proteins, **transferrins**.
- In cells, it is stored in association with a protein, **apoferritin**, to form **ferritin micelles**.
- Ferritin is a constituent of most cell types.
- When there is a local or systemic excess of iron, ferritin forms hemosiderin granules, which are easily seen with the light microscope.
- Hemosiderin pigment represents aggregates of ferritin micelles.

➤ Increased hemosiderin in tissues can be **localized or generalized**.

1) Localized hemosiderosis

➤ Aetiology:-

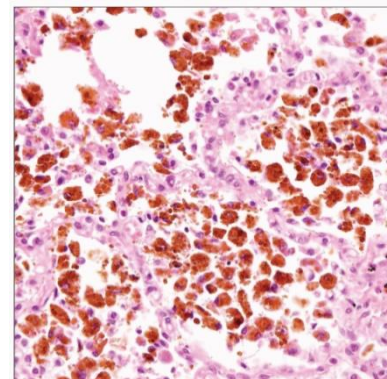
Local excess of hemosiderin result from hemorrhages in tissues.

➤ Pathogenesis:-

Extravasated red blood cells at the site of injury are **phagocytosed** over several days by macrophages, which break down the hemoglobin; the iron released from heme is incorporated into ferritin and eventually hemosiderin

➤ E.g:-

chronic venous congestion of lung.



2) Generalized (systemic) hemosiderosis:

A) Secondary Generalized hemosiderosis

↳ Definition:-

It is a deposition of hemosiderin in many organs and tissues. When there is systemic overload of iron,

↳ The main causes are :

- Increased absorption of dietary iron.
- Hemolytic anemia.

[in which abnormal quantities of iron are released from erythrocytes.]

- Repeated blood transfusions.

[because the transfused red cells constitute an exogenous load of iron.]

↳ Pathology:-

- Site:

- Early:

hemosiderin is deposited at **first** in the mononuclear phagocytes of the liver, bone marrow, spleen, and lymph nodes and in scattered macrophages throughout other organs such as the skin, pancreas, and kidneys.

- Later:

With **progressive accumulation**, parenchymal cells throughout the body (principally in the liver, pancreas, heart, and endocrine organs) become pigmented.

- Micro:

- Iron pigment appears as a coarse, golden, granular pigment lying within the cell's cytoplasm. It can be visualized in tissues by the Prussian blue reaction.

↳ Effect:-

In most instances , the pigment does not damage the parenchymal cells or impair organ function.

B) Primary Haemochromatosis

✚ It is the most common form of iron overload.

✚ The main causes are:

- It is a congenital disorder due to a gene defect on chromosome 6.
- Heterozygotes have increased absorption of iron,
- But only in homozygotes does this reach dangerous levels.
- The defect causes increased absorption of iron in small intestine even while transferrin is fully saturated.

✚ Pathology:

- In the liver:
 - Micro:
- Hemosiderin appears as golden-yellow granules in the cytoplasm of periportal hepatocytes, which stain blue with the Prussian blue stain.
- With increasing iron load, there is progressive involvement of the rest of the lobule, along with bile duct epithelium and Kupffer cell pigmentation.
- Fibrous septa develop slowly, leading ultimately to a micronodular pattern of cirrhosis in an intensely pigmented liver.
 - Gross:

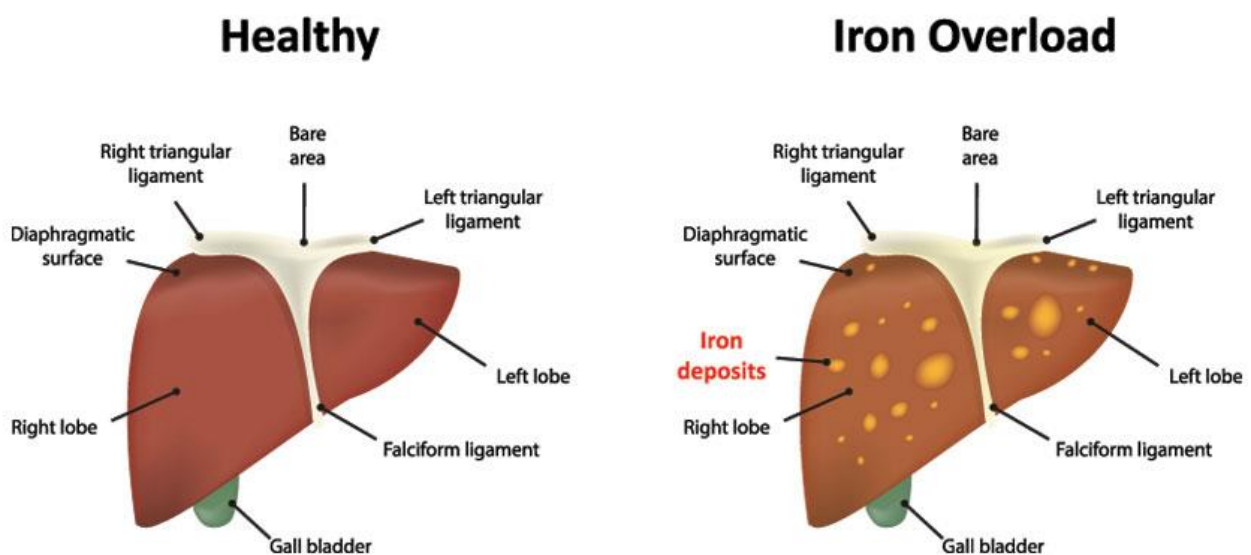
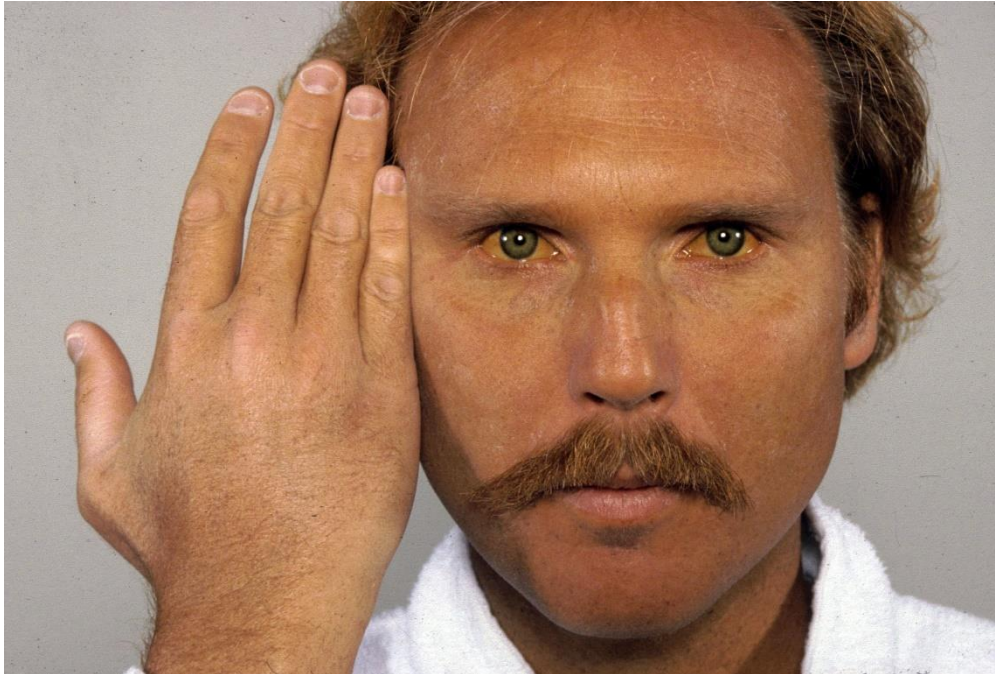
At this stage, the liver is typically slightly larger than normal, dense, and chocolate brown.

- In advanced disease:
 - hemosiderin is deposited in many tissues, notably endocrine glands as pancreas, adrenal, pituitary and thyroid.
 - Bronze diabetes is due to iron-induced damage of pancreatic islets and increased melanotropin secretion by pituitary leading to excess melanin production in skin, in addition to hemosiderin deposition in the skin.
- In the heart

Deposition of hemosiderin can lead to heart failure.

B) Hemozoin

- Hemozoin is a brownish iron containing pigment that is produced by parasites feeding on blood cells as **malaria and bilharziasis**.
- It is not reactive with Prussian blue.
- The pigments are released in blood and taken by macrophages of liver, spleen and other organs.



EXTRACELLULAR DEPOSITIONS

1) Pathological calcification

- This is abnormal deposition of calcium salts in tissue other than teeth or bone.
- Calcification may be dystrophic or metastatic.

a) Dystrophic calcification

- It occurs in tissues already affected by disease. Serum calcium is normal.
- The calcification is due to local precipitation of insoluble calcium salts.

➤ Examples:

- 1) Atheromatous plaques.
- 2) Congenital bicuspid aortic valves.
- 3) Areas of necrosis as in old tuberculous lesions.
- 4) Old thrombi.
- 5) Lithopedion (dead fetus).
- 6) Fat necrosis.



b) Metastatic calcification

- Calcification which occurs in viable tissues in cases of hypercalcemia.

➤ Causes:

- 1) Elevated parathyroid hormone e.g. hyperparathyroidism due to parathyroid tumors or ectopic parathyroid hormone secreted by other neoplasms.
- 2) Secondary hyperparathyroidism in chronic renal failure.
- 3) Bone destruction as in primary marrow malignancies (e.g. multiple myeloma) diffuse skeletal metastasis (e.g., breast cancer) or by accelerated bone turnover (Paget's disease), or immobilization.
- 4) Hypervitaminosis D.
- 5) Less common cause, milk alkali syndrome due to excessive ingestion of calcium and absorbable antacids such as milk and calcium carbonate.

✎ Main sites of calcium deposition in metastatic calcification:

- The interstitial tissue in:
 - 1) The gastric mucosa.
 - 2) Kidney.
 - 3) Lungs.
 - 4) Systemic arteries and pulmonary veins.
- Usually deposits cause no clinical dysfunction.
- Massive deposits in the kidney (**nephrocalcinosis**) may in time cause renal failure.

✎ Morphology of calcification:

- Both dystrophic and metastatic show
- **Grossly:**
Chalky white granular material.
- **Microscopic:**
Calcium salts have a basophilic amorphous granular appearance.



2) AMYLOIDOSIS

↳ Definition:

- Amyloidosis is extracellular deposition of abnormal protein having beta pleated configuration with a glycoprotein (amyloid P protein).
- It is deposited on basement membrane, reticulin fibers, and walls of small blood vessels.
- The affected tissue becomes hard & waxy.

↳ Pathogenesis of amyloidosis:

- Amyloidosis results from:-
[abnormal folding of proteins] which become:
insoluble, aggregate, and deposit as fibrils in extracellular tissues.
- Degradation of misfolded proteins:-
intracellular → in proteasomes
extracellular → by macrophages.
- It appears that in amyloidosis, these quality control mechanisms fail leading to :
accumulation of a misfolded protein outside cells.

N.B:-

The proteins that form amyloid fall into two general categories:

1) Normal proteins:-

that have an inherent tendency to fold improperly, associate and form fibrils when they are produced in increased amounts.

2) Mutant proteins:-

that are prone to misfolding and subsequent aggregation.

↳ Types of amyloid protein:

Of more than 20 distinct forms, The most common are:

- Amyloid light chain (AL) protein:
Immunoglobulin light chains derived from plasma cells.
- Amyloid-associated (AA) protein:
A non-immunoglobulin protein derived from a larger serum precursor called serum amyloid-associated (SAA) protein synthesized by hepatocytes as part of the "acute phase response"

↳ Classification:

Amyloidosis is classified into systemic or localized types.

A) Systemic amyloidosis:

- The material is deposited in many organs:-
liver, spleen, tongue, heart, and kidney.
- This results in organomegaly :-
e.g. hepatomegaly, splenomegaly, macroglossia
- can lead to organ dysfunction:-
e.g. heart failure and proteinuria.
- Systemic amyloidosis is further classified according to its etiology into:-

1) Primary amyloidosis (Myeloma-associated amyloidosis):

∂ The amyloid material is AL (amyloid light chain) protein.

∂ This is associated with:-

Myeloma, a plasma cell tumor, often multiple, arising in bone marrow and causing extensive bone erosion.

∂ It produces:-

extensive amount of immunoglobulin of a single class (e.g, IgG) with one type of light chain (e.g, Kappa).

∂ The amyloid deposits in:-

liver, kidneys, heart spleen etc.

N.B:-

- In some cases, this type of amyloidosis is **not** associated with a clinically apparent myeloma tumor.
- But there are **increased levels of light chain immunoglobulins** as detected by serum electrophoresis.
- Such conditions are referred to as **monoclonal gammopathy**.

2) Secondary (reactive) amyloidosis:

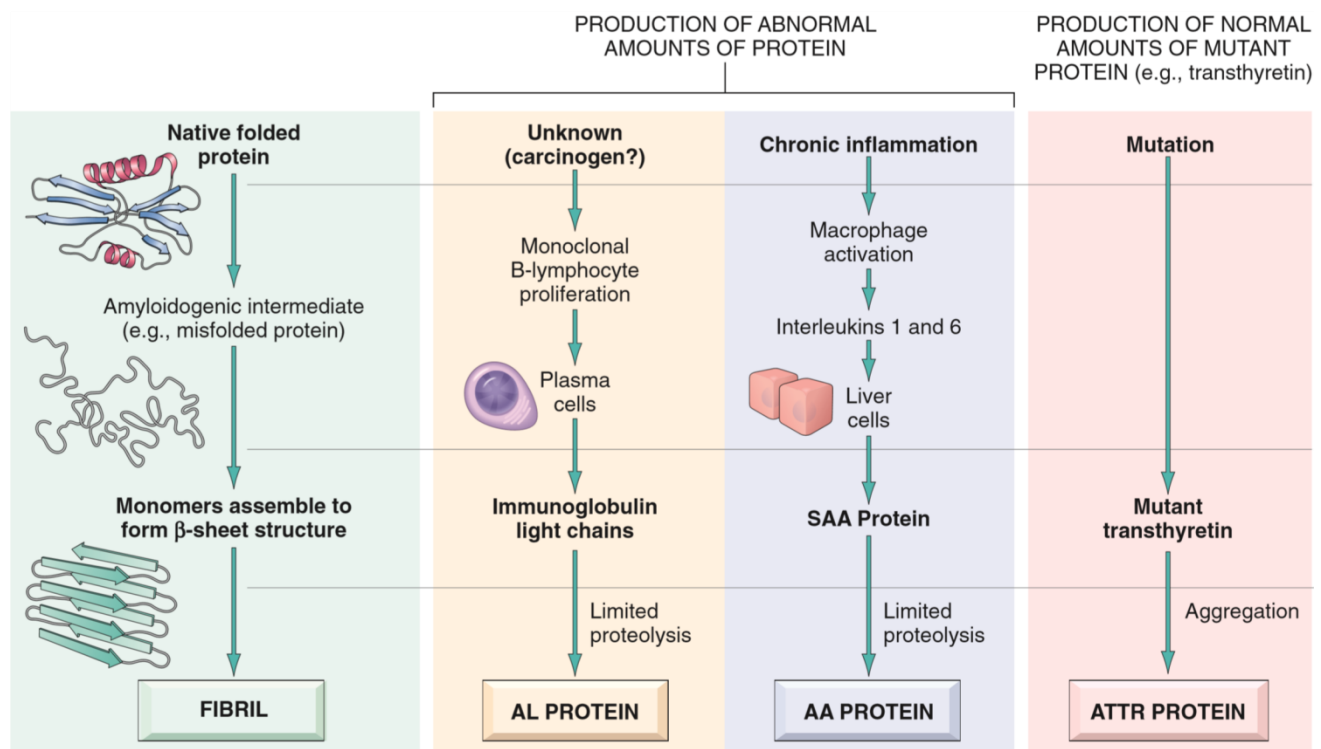
- The amyloid substance is **AA protein** derived from serum amyloid associated (SAA) protein.
- SAA protein is an acute phase reactant protein secreted by the liver**, when stimulated by cytokines produced by inflammatory cells.
- So reactive amyloidosis is **secondary to long-lasting chronic inflammatory disorders** such as:
 - ∅ Bronchiectasis.
 - ∅ Chronic osteomyelitis.
 - ∅ Rheumatoid disease.
 - ∅ Tuberculosis.
 - ∅ Crohn's disease & ulcerative colitis.

N.B:-

Secondary amyloidosis is also **widespread** but has a predilection for the liver, spleen and kidneys.

3) Senile amyloidosis:

- Minute deposits of **amyloid, transthyretin**,
- May be found in the **heart and in the wall of blood vessels**.
- Only in a few cases do they result in significant clinical disease.



B) Localized amyloidosis:

Amyloid deposits are limited to a single tissue or organ.

Examples are:

1) In medullary carcinoma :-

- a tumor from calcitonin secreting **C cells in the thyroid.**
- amyloid material is seen in the **stroma surrounding the tumor cells.**
- The amyloid material is **calcitonin precursor** molecules arranged in beta pleated sheets configuration.
- It has no clinical effect but **helps in identification of the tumor.**

2) Cerebral amyloid is found in Alzheimer disease.

They are seen in **neuritic plaques** and in the wall of **blood vessels (A β 2 protein).**

3) Localized deposits of amyloid :

are rarely seen without any obvious cause, e g. in the skin, laryngeal wall, lung, ureter and urinary system.

4) In the islets of Langerhans in individuals with type 2 diabetes mellitus.

↪ Staining characteristics of amyloid:

A) Gross staining:

1) If a slice of tissue is Immersed in Lugol's iodine:

- amyloid stains dark brown.
- while the rest of the tissue stains yellow
(hence the name amyloid, starchlike).

2) If a slice of tissue is immersed in iodine [followed by 1% sulphuric acid]:

- the amyloid stains blue.

B) Microscopic staining:**1) With Hematoxylin and Eosin stain:**

Amyloid stains **pink**.

2) With Congo red Stain:

Amyloid stains **orange red**

3) When examined by polarized light :

(using two filters in the path of light of a microscope, one fixed and one rotating)

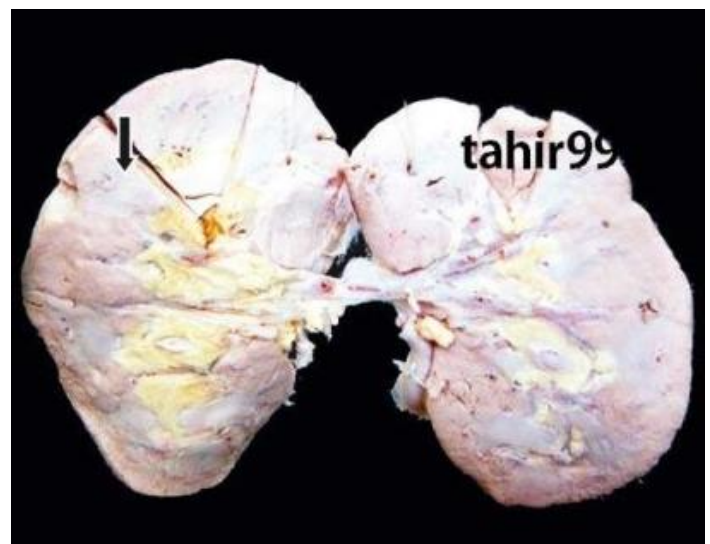
the amyloid appears as an **apple- green light** against a dark background
(apple green birefringence)

4) With metachromatic stains [e g. methyl violet and crystal violet] :

Amyloid stains rose red while the rest of the tissues **stain violet**.

↪ Pathological changes in different organs in amyloidosis:**1) The liver****2) The spleen } (see later in hematopoietic module).****3) Amyloidosis of the kidney: results in:**

- ✓ loss of proteins in urine (proteinuria),
- ✓ hypoproteinemia,
- ✓ generalized edema.



4) The gastrointestinal tract:

- ✓ Any part of GIT can be affected.
- ✓ Amyloid deposits in the tongue causes macroglossia.
- ✓ Amyloid deposits in the intestine:

The early lesions mainly affect blood vessels but eventually extend to involve the adjacent areas of the submucosa, muscularis, and subserosa resulting in mucosal atrophy.

- ✓ The effect is malabsorption and protein loss.

5) The heart:

- ✓ Amyloid is deposited in the walls of small blood vessels and in the interstitial tissue surrounding and replacing muscle fibers.
- ✓ The heart is enlarged and the myocardium is thickened and firm.
- ✓ The effects are cardiac arrhythmias and heart failure.

6) Other organs:

Adrenals, thyroid and pituitary.

🔑 Diagnosis of amyloidosis:

- ✓ The diagnosis of amyloidosis depends on the histologic demonstration of amyloid deposits in tissues.
- ✓ The most common sites biopsied are the kidney.
- ✓ when renal manifestations are present, or rectal or gingival biopsy in patients suspected of having systemic amyloidosis



Techniques Used in Pathologic Diagnosis

Tissue Sampling

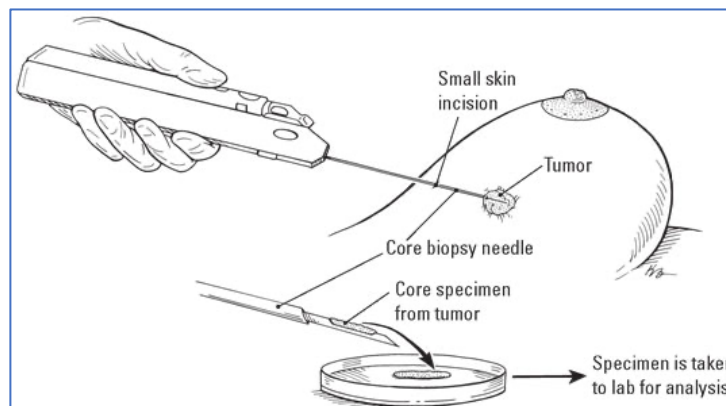
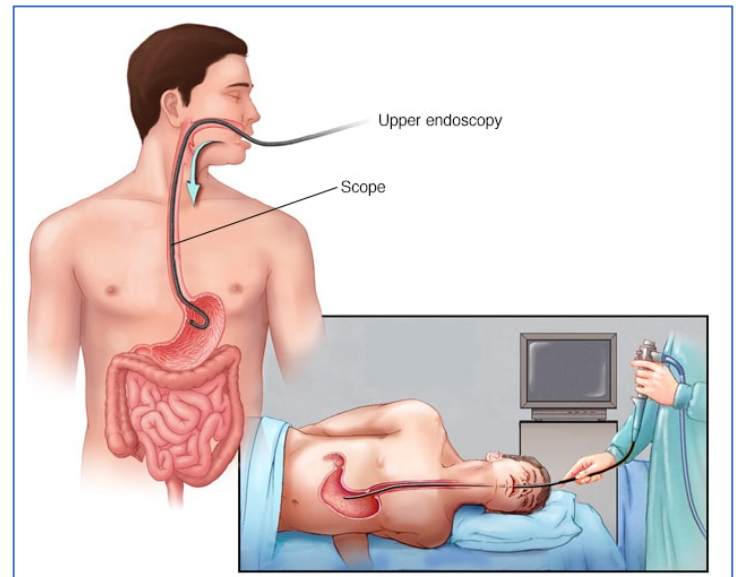
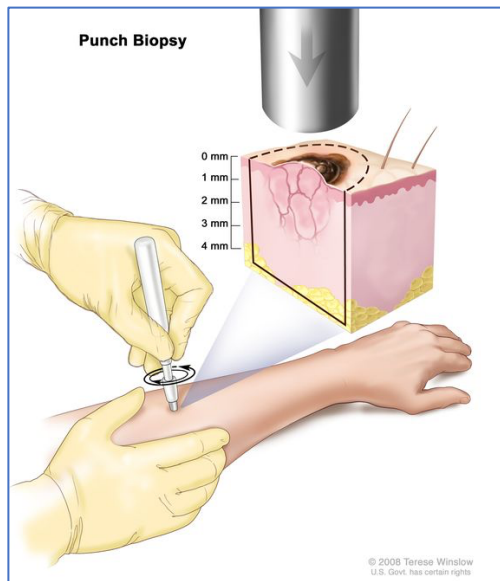
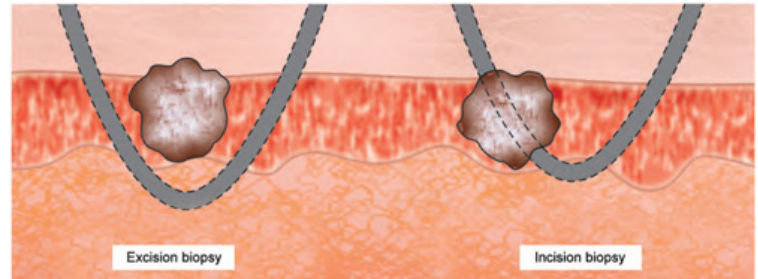
The value of tissue sample in variable lesions:

- 1) Determine a tissue diagnosis where clinical diagnosis is doubtful e.g. liver core biopsy in cases of cirrhosis of unknown etiology.
- 2) Ascertain whether benign or malignant e.g. gastric ulcer biopsy.
- 3) Ascertain extent of spread of disease.
- 4) In itself, the biopsy with excision of the lesion may be a form of local treatment e.g. excision biopsy of rodent ulcer.



Methods for tissue sampling:

1. **Excision biopsy:** The whole lesion removal.
2. **Incision biopsy:** Part of the lesion is sampled.
3. **Core needle biopsy.**
4. **Endoscopic biopsy.**
5. **Punch biopsy.**
6. **Frozen section:**
 - Examination of fresh samples for rapid intra-operative diagnosis.



The Routine Specimen manipulation:

1. Labeling:

Each specimen must be labeled with the patient's name, hospital number, source of the tissue and site and side of the body.



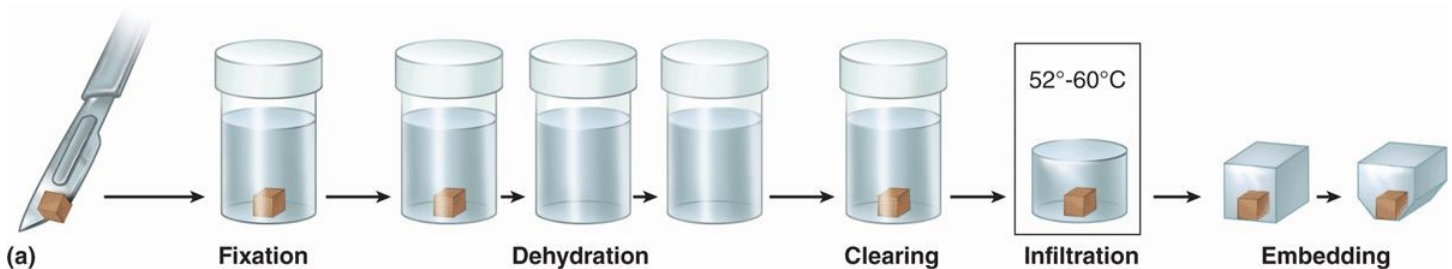
2. Specimen Fixation:

Proper and timely fixation is a critical step in tissue preparation for diagnosis.

The fixative of choice is **10% buffered formalin**.

3. Tissue Processing:

- Once the tissue has been fixed, it must be processed into a form in which it can be made into thin microscopic sections.
- The usual way this is done is with paraffin.
- Tissues embedded in paraffin, which is similar in density to tissue, can be sectioned at 3 to 10 microns using a microtome.
- The technique of getting fixed tissue into paraffin is called tissue processing.
- The main steps in this process are dehydration and clearing.



Drive wheel
Block holder
Paraffin block
Tissue
Steel knife



CYTOPATHOLOGY

Definition: a rapid, inexpensive and non invasive method of patient evaluation.

Uses:

1. Screening: Early detection of premalignant & early invasive neoplasia:

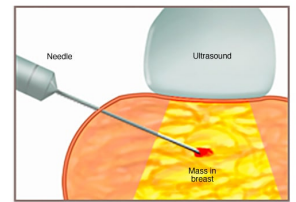
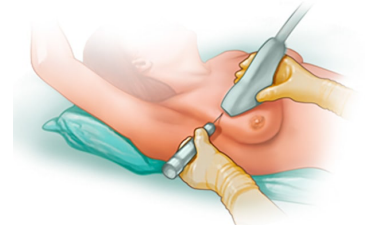
- Cervico-vaginal (PAP) smears for detection of premalignant lesions of the cervix
- Urine screening for cancer in those exposed to certain industrial carcinogens

2. Initial diagnosis.

3. Follow up and monitoring of treatment e.g. examination of urine for cancer cells after transurethral removal of malignant tumors of the bladder.

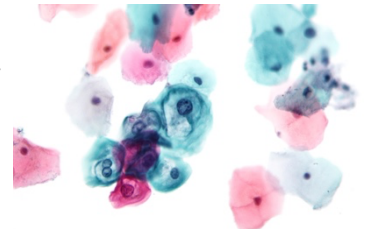
Cytology samples:

- Fluids** such as effusions, ascitic fluid, urine, CSF
- Smears** e.g. Cervico-vaginal PAP smears\
- Sputum.**
- FNAC:** fine needle aspiration cytology
- Needle aspirates from accessible organs e.g.** lymph nodes, thyroid.
- Discharge** e.g. Nipple discharge.



Technical aspects:

- Fluids are centrifuged and the sediment is smeared on a slide like a blood film.
- Smears are then fixed in 95% ethanol.
- The perfect stain for cytology is the Papnicolaou stain (PAP).



Clinically Diagnostic Techniques

A. Cytohistochemistry:

These are special stains used to identify substances in issue with specific chemical structure:

1) Mucin stains:

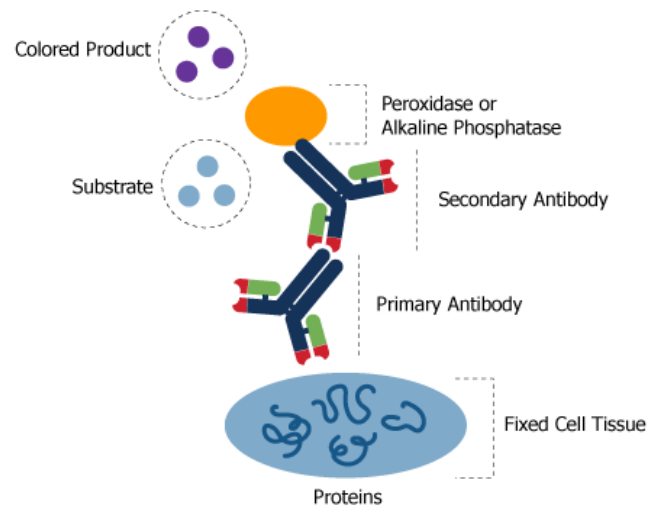
- Alcian blue
- PAS (periodic acid-Schiff)
- Mucicarmine

2) Fat stains: Sudan Black

3) Trichrome stains for collagen e.g. Masson trichrome

B. Immunohistochemistry:

- Immunohistochemistry is the localization of **PROTEINS (antigens) in tissue sections**.
- Immunohistochemistry involves **specific antigen-antibody reaction**.
- Tagging such an antibody with **a fluorescent, radioactive or enzymatic label** allows specific substances to be identified and localized in tissue sections or cytological preparations.
- This is particularly useful in the **diagnosis of tumors**, in which it is important to classify the tumor on the basis of the differentiation it shows (according to the protein it expresses) to allow **the most appropriate treatment to be given**.



C. Molecular pathology & Cytogenetics:

- In molecular pathology, rather than attempt to identify proteins within a cell, expression of the genes (the biochemical composition of single nucleotides) responsible could be identified through **polymerase chain reaction (PCR) or insitu hybridization**.
- Cytogenetics: Involves the study of abnormal chromosomes and genes responsible for certain diseases by a process of karyotyping.





GENERAL PATHOLOGY

MODULE 208



DR. AHMED ELNEMR
مكتبة سكاى الحديثة





Welcome to a new journey,

Yesterday is history... Tomorrow is a mystery, but today is a gift that's why it's called present. So, we will do our best to exploit this gift to achieve the desired excellence.

Always learn that success is the sum of your efforts, so just believe in yourself and show me what you can do.

DR. Ahmed EL-Nemr

Subject	Page
Inflammation	1
Healing & Repair	28
Disorders of growth and Neoplasia	43
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INFLAMMATION

Definition:

Inflammation is the **response** of living **vascularized tissue** to **injury**. It is a **protective** mechanism intended **to eliminate** the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, **and to initiate** the process of repair.

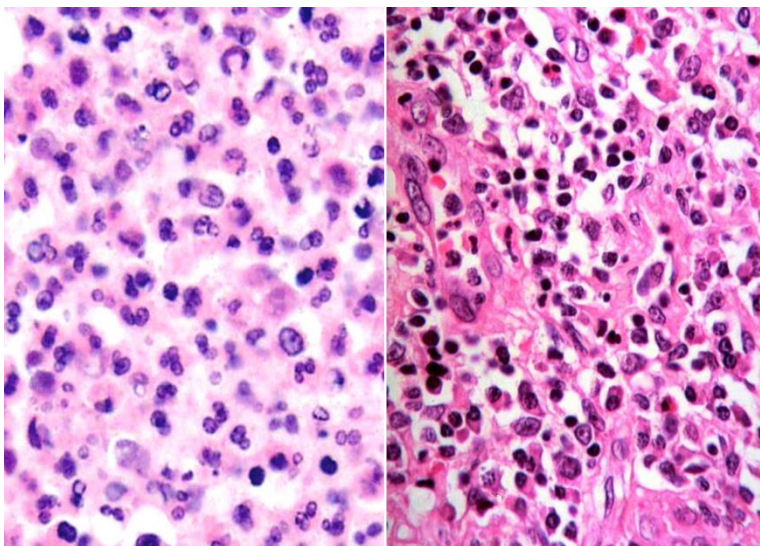
Classification:

Inflammation can be **acute** or **chronic**, differences between which depend on onset and duration as summarized in the following table.

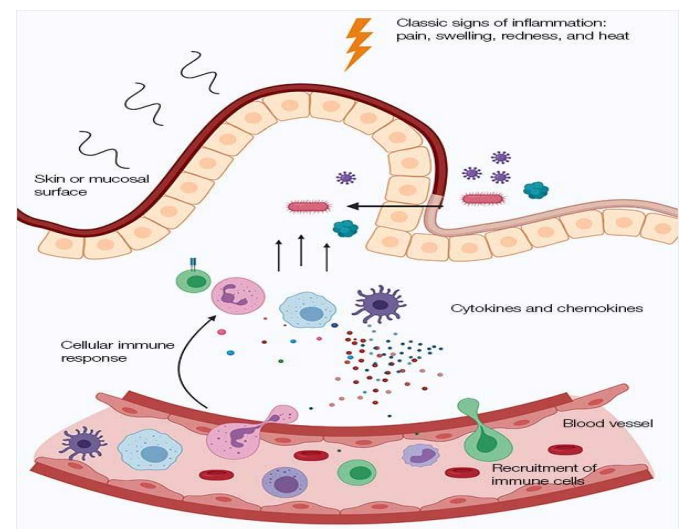
➤ **Subacute inflammation is a grade of inflammation between acute and chronic.**

Table (3-1): Differences between acute and chronic inflammations:

	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Duration	Short (days or weeks)	Long (months or years)
Tissue injury	Usually mild and self- limited	Often severe and progressive.
Local and systemic signs	Prominent	Less prominent; may be subtle



Acute (neutrophils) vs chronic (mononuclear cells) inflammation





Acute Inflammation

Causes of acute inflammation:

1. **Infections** (bacterial, viral, fungal, parasitic) are among the most common and medically important causes of inflammation.
2. **Trauma and various physical and chemical agents** (e.g., thermal injury, such as burns or frostbite; irradiation; toxicity from certain environmental chemicals) injure host cells and elicit inflammatory reactions.
3. **Tissue necrosis** (from any cause), including ischemia (as in a myocardial infarct) and physical and chemical injury.
4. **Foreign bodies** (splinters, dirt, sutures, crystal deposits).
5. **Immune reactions** (also called hypersensitivity reactions) against environmental substances or against “self” tissues (auto-immune diseases).

The acute inflammatory response:

The acute inflammatory response involves **vascular** and **cellular events** that are mediated by various chemical substances (**chemical mediators**).

1- Vascular changes:

Include two phases:

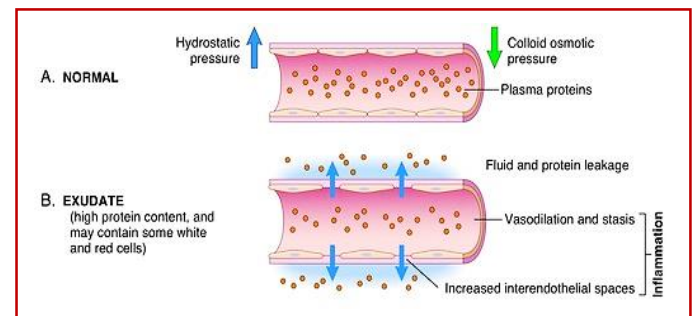
A. Changes in vascular caliber and flow:

- i. **Transient vasoconstriction** (lasting only for seconds), followed by
- ii. **Arteriolar vasodilation**, mainly under the effect of histamine leading to active increase of blood flow in capillaries (**hyperemia**).
- iii. This leads to **increase intra-capillary hydrostatic pressure** leading to movement of fluids outside the vessel.
- iv. This **hyperemia is the cause of the redness (erythema)** and **warmth** characteristic of acute inflammation.



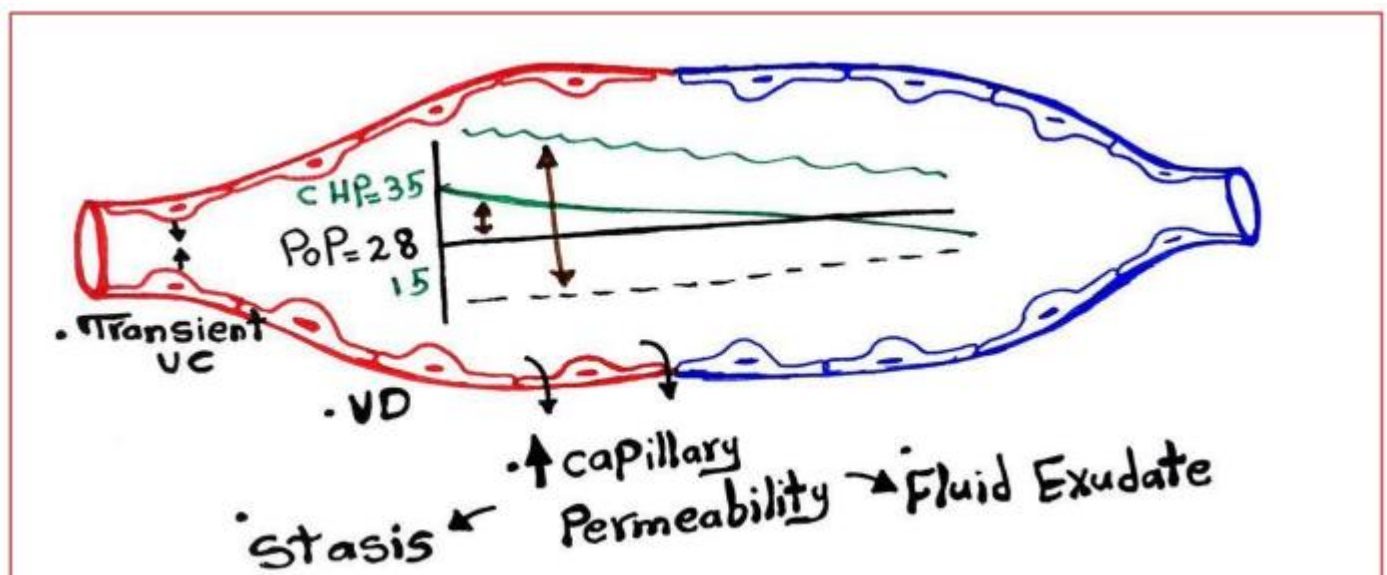
B. Increased vascular permeability:

- i. **Increasing vascular permeability** leads to the **movement of protein-rich fluid into the extravascular tissues**.
- ii. This in turn **increases the osmotic pressure of the interstitial fluid**, leading to **more outflow of water from the blood into the tissues by osmosis**.
- iii. The resulting **protein rich fluid accumulation** is called an **exudate**.
- iv. **Increased vascular permeability occurs as a result of:**
 - **Endothelial cell contraction** leading to **intercellular gaps**. Endothelial cell contraction occurs due to effect of the chemical mediators **histamine** and **bradykinin**
 - **Endothelial injury**: Endothelial cells are damaged after **severe injury such as** with burns and some infections.



Beneficial effects of fluid exudate:

- 1) **Dilution of toxins** produced **by bacteria**.
- 2) **Entry of antibodies**, where they can **lyse microorganisms** or **help in phagocytosis** through **opsonization**.
- 3) **Transport of antibiotics**.
- 4) **Fibrin formation from exuded fibrinogen may impede** the movement of microorganisms, trapping them **facilitating phagocytosis**, and serves as a **matrix for the formation of granulation tissue (healing)**.
- 5) **Delivery of oxygen and nutrients** for active cells **such as neutrophils**.





2- Cellular events:

Leukocyte recruitment and activation:

A. Leukocyte recruitment:

- In this phase **leukocytes; neutrophils then monocytes** accumulate within the **extravascular space**. **This occurs through the following steps:**

- i. **Margination and rolling of leukocytes:** in the **normal** circulation, **cells are confined to the central (axial) stream** and do not flow in the **peripheral (plasmatic zone)** near to the endothelium.

However, **loss of intravascular fluid and increase in plasma viscosity** with **slowing of flow** at the **site of acute inflammation** allows **neutrophils to flow in this plasmatic zone (Margination)**.

When endothelial cells are **activated by mediators**, they **express** adhesion molecules **to which the leukocytes attach loosely**. These cells **bind, detach**, and thus **begin to tumble on the endothelial surface**, **a process called rolling**. The selectin family of adhesion molecules mediates rolling.

Selectins are receptors expressed on leukocytes and endothelium.

- ii. **Pavementing of leukocytes:** The **adhesion of** neutrophils to the vascular endothelium **at the sites of acute inflammation is called 'pavementing'**. This **adhesion is mediated by integrins** expressed on **leukocyte cell surfaces** interacting with **their ligands** on endothelial cells.

- iii. **Emigration of Leukocytes:** After adhering to the endothelial surface, leukocytes migrate **through the vessel wall** primarily **by squeezing between cells at intercellular junctions**. This occurs **mainly in the venules**. Migration of leukocytes is **driven by chemokines** produced in **extravascular tissues**, which stimulate movement of the leukocytes toward their chemical gradient. After passing through the endothelium, **leukocytes secrete collagenases** that **enable them to pass through the vascular basement membrane**.

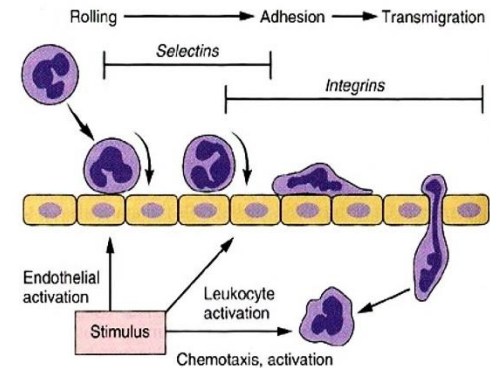
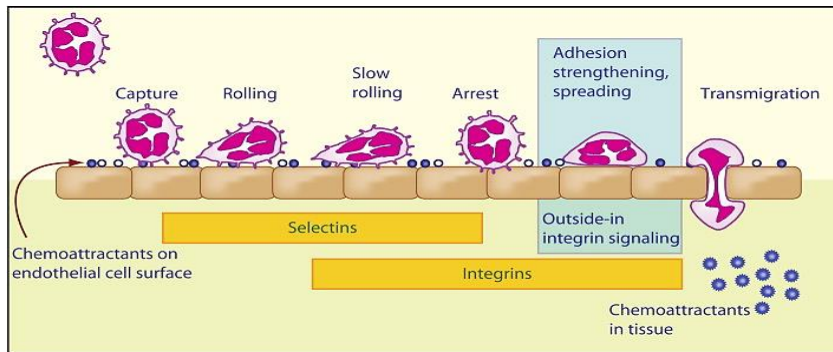
- iv. **Chemotaxis:** After **extravasating from the blood**, leukocytes move toward sites of infection or injury **along a chemical gradient by a process called chemotaxis**.



Chemotactic factors include the following:

1. **Bacterial products.**
2. **Cytokines**, especially those of the **chemokine family**.
3. **Components of the complement system**, particularly **C5**.
4. **Products of arachidonic acid (AA) metabolism**, particularly **leukotriene B4 (LTB4)**.

Chemotactic molecules bind to specific cell **surface receptors**, which triggers the assembly of **cytoskeletal contractile elements** necessary for **movement**. **Leukocytes move by extending pseudopods** that anchor to the extracellular matrix (**ECM**) and then pull the cell in the direction of the extension.



B. Leukocyte Activation:

Leukocyte activation results in the enhancement of the following functions:

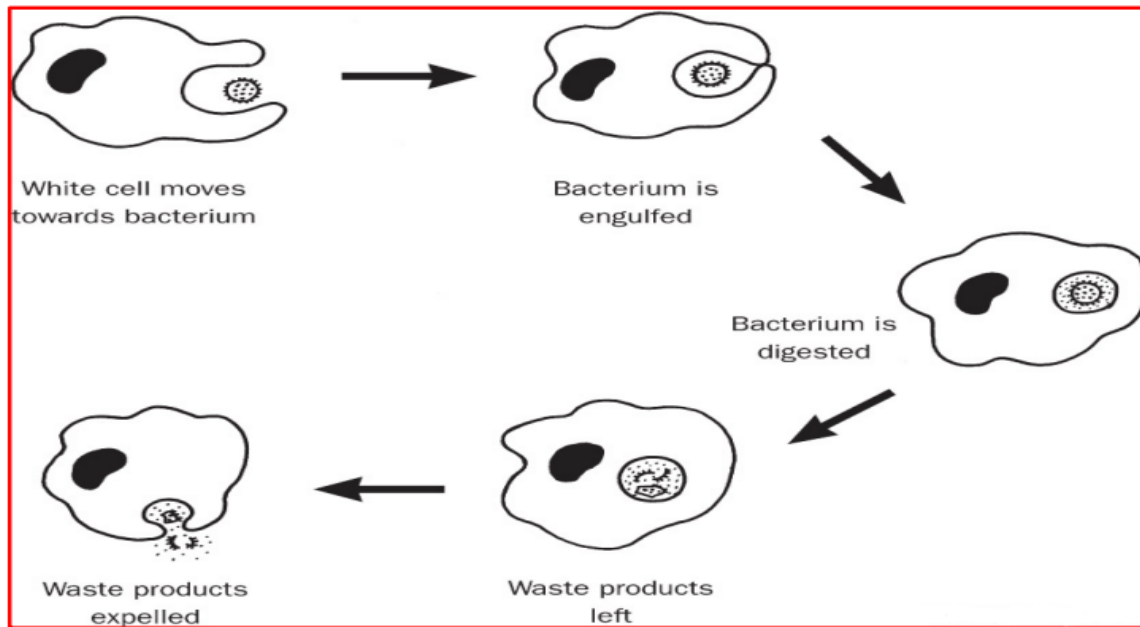
i. Phagocytosis of particles:

Definition:

Recognition and attachment of the particle to the **ingesting leukocyte**; then **engulfment**, with **subsequent killing** and **degradation** of the ingested material.

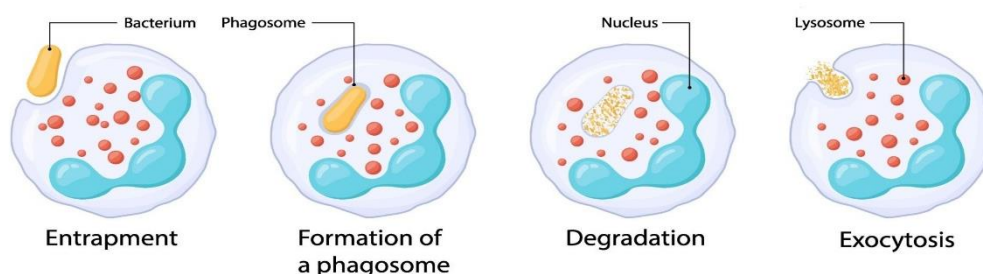
Steps of phagocytosis:

- Leukocytes bind and ingest** most microorganisms and dead cells by **means of specific surface receptors**.
- Some** of these receptors **recognize components** of the **microbes and dead cells**.
- Other** receptors recognize host proteins, **called opsonins** that **coat microbes and target them for phagocytosis (the process called opsonization)**. The most important opsonins **are antibodies of the immunoglobulin G (IgG) class** that bind to **microbial surface antigens**.
- Killing and degradation** of the **ingested particles**. The key steps in this reaction **are fusion of the lysosomes with phagosomes**, thus **exposing the ingested particles to lysosomal enzymes and reactive oxygen species (ROS)**.



Steps of Phagocytosis

- i. **Liberation of substances** that **destroy extracellular microbes** and **dead tissues**, which are **largely the same** as the substances produced **within phagocytic vesicles**.
- ii. **Production of mediators**, including **arachidonic acid metabolites** and **cytokines** that **amplify the inflammatory reaction**, **by recruiting and activating more leukocytes**
- iii. **The role of macrophages**: **Blood monocytes** also **arrive at the site**, and on leaving the blood vessels, **transform into macrophages**, becoming **active, motile and phagocytic**.
 - In most acute inflammations, **macrophages play a lesser role in phagocytosis compared with neutrophils**. They do not predominate until the **later stages** when the neutrophils have diminished in number and the macrophages have increased in number **by local proliferation**. They are **responsible for clearing away tissue debris and damaged cells**.
 - **Both macrophages and neutrophils** may discharge their **lysosomal enzymes** in the extracellular fluid **by exocytosis**, or when the cells die. Release of these enzymes **assist in the digestion of inflammatory exudate**, and it is finally **drained by the lymphatics**. (**Final fate of exudate**).
 - In addition, macrophages **secrete various growth factors**, which are important in the **process of repair** (see later).





Local signs & symptoms of acute inflammation:

- 1 **Redness** due to vasodilatation & opening of capillary bed leading to increased blood flow.
- 2 **Hotness** due to increased blood flow.
 - Redness & hotness are called flare.
- 3 **Swelling** (the wheal) due to accumulation of exudate (inflammatory edema).
- 4 **Pain:** due to:
 - ✓ Nerve compression by exudate
 - ✓ Irritation by mediators as bradykinin and prostaglandin E2
- 5 **Loss of function:** due to pain and tissue damage.

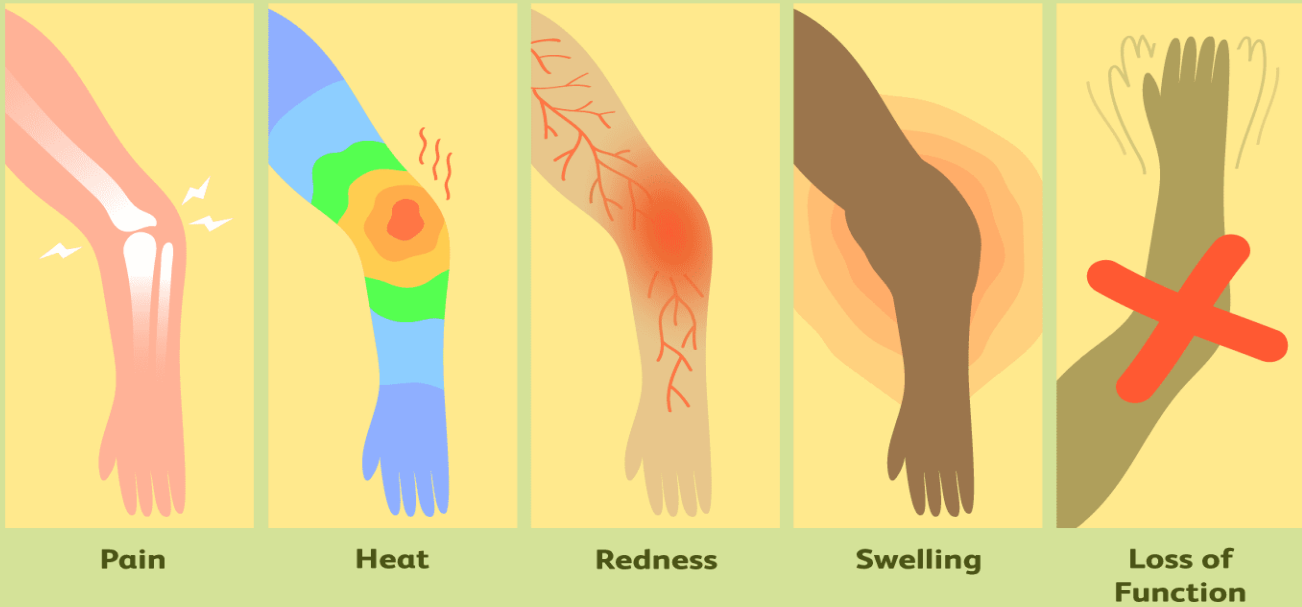
Systemic effects of acute inflammation:

- 1 **Fever:**
 - Cytokines (TNF, IL-1) stimulate production of prostaglandins in hypothalamus.
 - In the hypothalamus the prostaglandins, stimulate the production of neurotransmitters, which function to reset the temperature set point at a higher level.
- 2 **Production of acute-phase proteins:**
 - ❖ Acute phase proteins such as C-reactive protein, fibrinogen, serum amyloid A (SAA), are secreted in excess by the liver cells under the effect of cytokines (IL-6, others).
 - ❖ Many acute-phase proteins, such as CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement, thus promoting the elimination of the microbes.
 - ❖ Fibrinogen binds to erythrocytes and causes them to form stacks (Rouleau) that sediment more rapidly at unit gravity than individual erythrocytes. This is the basis for measuring the erythrocyte sedimentation rate (ESR) as a simple test for the systemic inflammatory response.
- 3 **Leukocytosis:**

cytokines (Colony stimulating factors: CSFs) stimulate production of leukocytes from precursors in the bone marrow.



5 Cardinal Signs of Inflammation



Outcomes of acute inflammation:

- 1. Resolution:** There is **complete restoration of tissue to normal**. When there is **rapid destruction of the causative agent**, then the necrotic debris, edema fluid, and inflammatory cells are **cleared by phagocytes and lymphatic drainage**.
- 2. Progression and spread:** **With weak immunity, bacteria may spread:**
 - Direct spread** causing extension and widening of the inflammatory field.
 - Lymphatic spread** causing lymphangitis and lymphadenitis.
 - Blood spread** which may lead to serious effects as septicemia.
- 3. Chronic inflammation may follow acute inflammation** if the offending agent is **not removed** (e.g., in viral infections or immune responses to self- antigens).
- 4. Fibrosis and scarring** is a **type of repair after substantial tissue destruction** (as in abscess formation) or **when inflammation occurs in tissues that do not regenerate**. The outcome is **fibrosis**, a process that can significantly compromise function.



Types of acute inflammation:

Although acute inflammation is characterized by **vascular changes and leucocytic infiltration**, distinctive features may be present **according to tissues affected and causative agents**. There are **two major groups** of inflammation: **suppurative and non –suppurative**.

1. Suppurative inflammation:

Definition:

Acute inflammation **manifested by the collection of large amounts of purulent exudate (pus) consisting of neutrophils, pus cells, necrotic cells, and edema fluid**.

Etiology:

Certain organisms (e.g., **staphylococci, gonococci, pneumococci and others**) are more likely to induce such suppuration and are therefore **referred to as pyogenic (pus-forming) organisms**.

Mechanism (pathogenesis) of pus formation:

A. Pyogenic organisms cause:

- a) **Remarkable necrosis.**
- b) **Attraction of** a huge number of **neutrophils**.
- c) **Death of many neutrophils** due to high virulence of the bacteria.

B. **Dead neutrophils (pus cells) release** their proteolytic enzymes leading to liquefaction of necrotic tissue & fibrin.

- ✓ The liquefied material **mixed with pus cells & fluid exudate** form a turbid creamy fluid **called pus**, which does not coagulate on standing (fibrin is liquefied).
- It is **yellow** in case of staphylococcal infection due to bacterial pigments.
- Pus is **sanguineous (blood-stained)** in case of streptococcal infections
- **Green** in pyocyanous infections.



Types of suppurative inflammation:

Localized and diffuse suppurative inflammation.

A. Localized suppurative inflammation:

Commonly **caused by *Staphylococcus aureus***, which secrete **coagulase enzyme**. Coagulase enzyme **changes fibrinogen into fibrin**, thus walling off the area of pus. **The most common forms of localized suppurative inflammation are:**

- i) Abscess.
- ii) Boil (furuncle).
- iii) Carbuncle.

Abscess:

Definition:

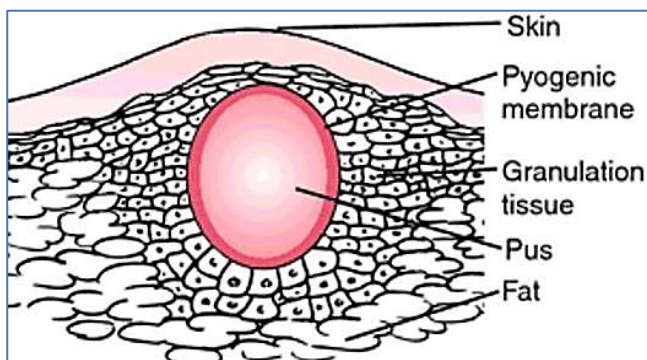
An abscess is a **collection of pus** (or a **cavity containing pus**) that may be **caused by seeding of pyogenic organisms into a tissue** or by **secondary infections of necrotic foci**.

Morphology:

Abscesses typically have a **central, largely necrotic region** rimmed by **a layer of preserved neutrophils** with a **surrounding zone of** dilated vessels and fibroblast proliferation indicative of attempted repair.

➔ **As time passes**, the abscess may become **completely replaced by connective tissue**.

Because of the underlying tissue destruction, **the usual outcome with abscess formation is scarring**.





Fate of an abscess:

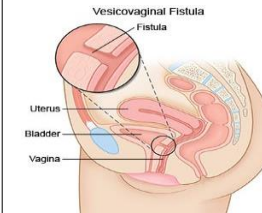
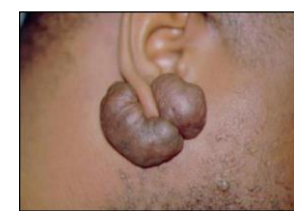
Small abscess	Large abscess
Pus may be absorbed, followed by healing	Since absorption of pus occurs at a very slow rate , a big abscess (if not surgically incised) pointing and rupture (spontaneous evacuation) will occur followed by healing.

Complications of an abscess:

1 Spread of infection:

- **Direct spread** leads to **abscess enlargement**.
- **Lymphatic spread** leads to **lymphangitis and lymphadenitis**.
- **Blood spread** may lead to: **Toxemia or septicemia or pyemia**.

2 Complications of evacuation and healing:

Ulcer	Sinus	Fistula	Hemorrhage	Rupture	Keloid
It is a local defect within a surface (skin, mucosa...). It is due to separation of inflammatory necrotic tissue. ➤ If infection persists ➔ Defective healing ➔ Chronic ulcer	It is a blind-ended tract between a deep abscess and the surface, e.g. peritoneal abscess may cause sinuses on the abdominal wall. ➤ If infection persists, it remains as a chronic sinus	Evacuation of a deep abscess may result in a tract communicating between two surfaces or hollow organs. This double-ended tract is called fistula. Ano-rectal fistula complicating e.g. perianal abscess ➤ If infection persists, it changes into a chronic fistula	e.g. hemoptysis when a lunge abscess opens into a bronchus.	e.g. brain abscess into ventricles & right hepatic lobe abscess into base of right lung	
			 Vesicovaginal Fistula Fistula Uterus Bladder Vagina Fistula	 Keloid	



3 Chronicity:

- ✓ If the abscess is evacuated **neither spontaneously nor surgically**, it gets **surrounded by fibrosis** and **becomes a chronic abscess**.
- ✓ **Pus dries and dystrophic calcification may occur.**

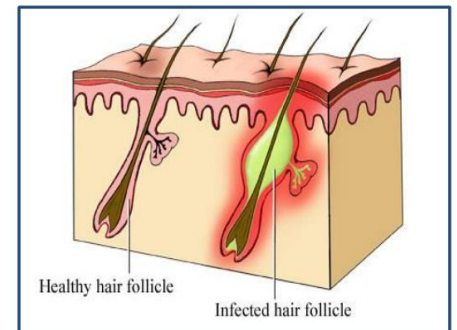
Examples: Chronic breast abscess: may be clinically mistaken for a tumor and Chronic lung abscess.

4 Other complications:

- **Putrefaction and gangrene** (e.g. putrefaction of a lung abscess **by saprophytic bacteria**).
- **Compression effects:** e.g. in case of brain abscess **resulting in increased intracranial tension** and liver abscess **resulting in obstructive jaundice**.

Furuncle

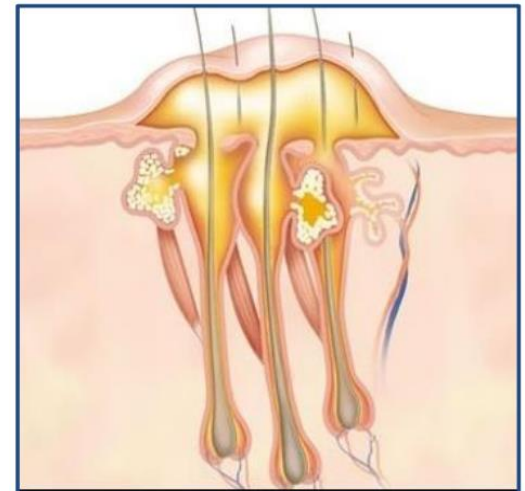
Staphylococcal infection of the hair follicles (**folliculitis**)



Carbuncle:

- ✓ **Multiple communicating deep subcutaneous abscesses**, opening on skin by **multiple sinuses**, commonly **on the back of the neck**.
- ✓ **More common in diabetics (low immunity)**.

Folliculitis	Furuncle (Boil)	Carbuncle
Epidermis Follicle Dermis WBCs		
1mm perifollicular red papule or pustule	About 1cm tender red papule or fluctuant nodule	Several cm diam red plaque
Areas of sweat & abrasion	Areas of sweat & abrasion	Nape of neck
Rx: Tetracycline or erythromycin 500 mg 2x/day	1. Incise & curettage. 2. Dicloxacillin 250mg 4x/d for 10 days, or Augmentin 500mg 2x/day for 10+ days	1. Incise and curettage or excise 2. Dicloxacillin 250mg 4x/day for 10+ days or rampin 300mg 2x/day for 10+ days (Orange body fluids)





A. Diffuse suppurative inflammation:

- It is commonly caused by *streptococcus hemolyticus* (*streptococcus pyogenes*).
- Streptococci secrete **fibrinolysin (virulence factor)** which breaks down fibrin and help spreading of infection in the tissues. It also secretes **hyaluronidase (spreading factor)**.
- Pus produced by streptococci is **thin and sanguineous** because its toxins cause hemolysis of RBCs.

Examples of diffuse suppurative inflammation

i. Cellulitis:

Diffuse suppurative inflammation, which occurs in loose tissues as **subcutaneous tissues, loose areolar tissues of the orbit and scrotum**.

ii. Acute diffuse suppurative appendicitis.

iii. Septic peritonitis.

2- Non suppurative inflammation

a) **Serous inflammation** characterized by moderate **increase of** vascular permeability with **accumulation of** a watery, relatively protein poor thin fluid.

➤ It occurs in:

- Pleural, pericardial, peritoneal and synovial cavities and are **called effusions**.
- **Burn blisters**.

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b) Fibrinous inflammation

Occurs as a consequence of more severe injuries, **resulting in greater vascular permeability** that allows large molecules (**such as fibrinogen**) to pass **the endothelial barrier**.

➤ **It occurs in serous cavities:** pleura, pericardium and peritoneum.

The visceral and parietal layers are **coated by a layer of fibrin** giving them a **“bread and butter” appearance**. **It also occurs in** the lung in lobar pneumonia.

➤ **Histologically**, the accumulated **extravascular fibrin** appears as an eosinophilic meshwork of threads. Such exudates may be **degraded by fibrinolysis**, and then **removed by macrophages**, resulting in **resolution**. However, extensive fibrin-rich exudates may be replaced by an ingrowth of fibroblasts **leading ultimately to scarring**.

c) Catarrhal inflammation:

Characteristics:

A **mild form of acute inflammation of mucous membranes** characterized by an exudate mixed with mucus secreted by **the irritated mucous membrane**.

Examples:

Catarrhal rhinitis (**common cold**) and catarrhal appendicitis.

d) Pseudomembranous (membranous) inflammation:

A **severe form of acute inflammation of mucous membranes due to** infection with bacteria, which produce a powerful necrotizing toxin.

The toxin causes necrosis of surface epithelial cells.

The mucosa becomes covered by a false membrane **composed of precipitated fibrin, necrotic epithelium, and leukocytes** **e.g.** infection of throat and larynx Diphtheria bacilli, and infection of the large intestine by shigella bacilli causing bacillary dysentery.



e) **Allergic inflammation**: The underlying cause of inflammation is hypersensitivity e.g. **Urticaria and allergic rhinitis** characterized by **edema, infiltration by lymphocytes, plasma cells and eosinophils**.

f) **Hemorrhagic inflammation** occurs when there is **vascular damage** e.g.

- **Small pox.**
- **Acute hemorrhagic pancreatitis:**
 - Where the vessels are damaged by proteolytic enzymes released from damaged pancreatic cells.

Cells of acute inflammation:

1. **Neutrophils** (microphages, polymorphnuclear neutrophils).
 - They are **most numerous in pyogenic infections**.
 - Dead neutrophils are **called pus cells**.
2. **Macrophages**: They are derived from **blood monocytes**.
3. **Other cells** e.g.:
 - **Eosinophils** in allergic inflammation.
 - **Lymphocytes & plasma** cells in viral infections.

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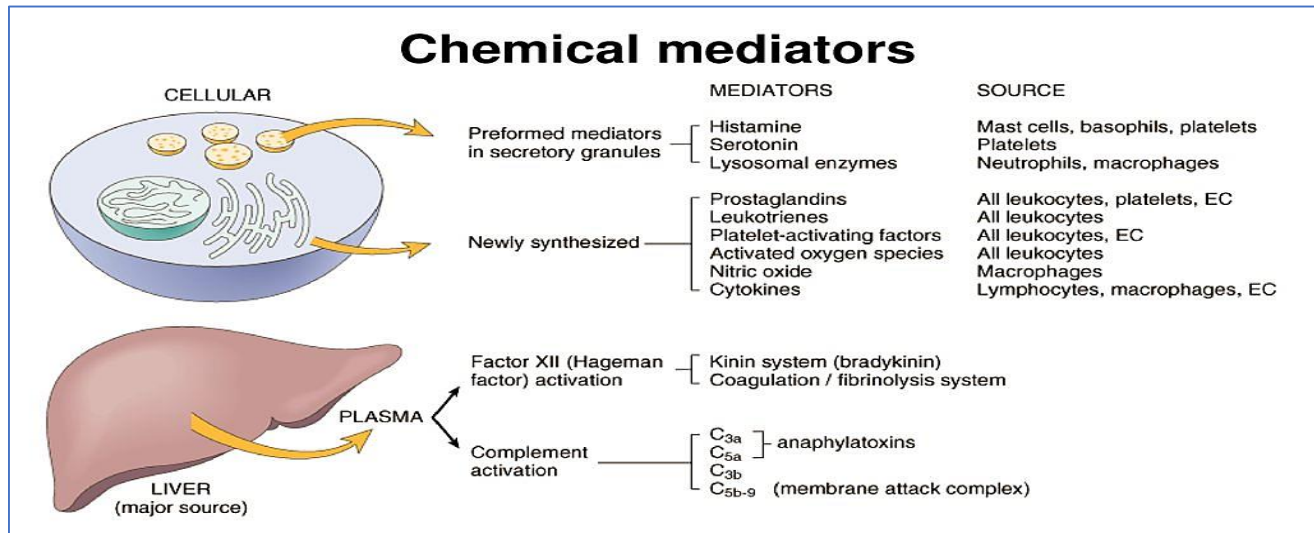
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Chemical Mediators and Regulators of Inflammation.

Having described the vascular and cellular events in acute inflammation, we next discuss the chemical mediators that are responsible for these events.



I- Cell-derived mediators:

Tissue macrophages, mast cells, and endothelial cells at the site of inflammation, as well as leukocytes that are recruited to the site from the blood, are all capable of producing different mediators of inflammation. These include:

Vasoactive Amines:

➤ Are among the first mediators to be released in acute inflammatory reactions.

✓ Histamine

- It is produced by many cell types, particularly mast cells, as well as circulating basophils and platelets.
- Histamine causes arteriolar dilation and rapidly increases vascular permeability.
- Soon after its release, histamine is inactivated by histaminase.

✓ Serotonin (5-hydroxytryptamine)

- It is a **preformed vasoactive mediator** found **within platelet granules** that is released **during platelet aggregation**.
- It **induces vasoconstriction during clotting**.



Arachidonic Acid Metabolites:

Prostaglandins, Leukotrienes, and Lipoxins, are products **derived from the metabolism of arachidonic acid** and **affect a variety of biologic processes**, including inflammation and hemostasis.

➤ Prostaglandins:

- Prostaglandins **potentiate the effect of histamine**.
- The prostaglandins also **contribute to the pain and fever that accompany inflammation**.

➤ Leukotrienes:

- Leukotrienes are **produced by neutrophils and some macrophages** and is a **potent chemotactic agent for neutrophils and monocytes**.
- It **increases vascular permeability**.

➤ Lipoxins:

- Once leukocytes enter tissues, they **gradually** change their products from leukotrienes to anti-inflammatory mediators **called lipoxins**, which **inhibit neutrophil chemotaxis and adhesion to endothelium** and **thus serve as endogenous antagonists of leukotrienes**.
- Platelets that are activated and adherent to leukocytes also are **important sources of lipoxins**.

Cytokines:

- Cytokines are **proteins** produced **principally** by **activated lymphocytes and macrophages** that **modulate the function of other cell types**.
- **Chemokines are cytokines** that **stimulate** leukocyte movement (**Chemotaxis**)
- Two of the most important cytokines mediating inflammation and produced by macrophages are: **Tumor necrosis factor and interleukin-1**
 - ✓ Which **enhance the expression of adhesion molecules on endothelium and inflammatory cells, activate fibroblasts** for later healing and **induce systemic response** such as fever, lethargy, neutrophilia.



Reactive Oxygen Species (ROS):

- ROS are released from **neutrophils and macrophages** that are activated **by inflammatory stimuli**.
- When the ROS are produced **within lysosomes**, they function to **destroy phagocytosed microbes and necrotic cells**.
- When secreted **at low levels**, ROS can **increase chemokine, cytokine, and adhesion molecule expression**.
- **At higher levels**, these mediators are **responsible for tissue injury by several mechanisms**, including
 - 1 Endothelial damage
 - 2 Protease activation a net increase in breakdown of the ECM; and
 - 3 Direct injury to other cell types.
- Fortunately, **various antioxidant protective mechanisms** (e.g. superoxide dismutase, and glutathione) present in tissues and blood **minimize the toxicity of the oxygen metabolites**.

Nitric Oxide:

Nitric oxide is a **short-lived, soluble, free radical gas** produced by many cell types.

NO plays roles in inflammation, including **vasodilation**, and **reduction of leukocyte recruitment at inflammatory sites**.

Lysosomal Enzymes of Leukocytes:

- The lysosomal granules of neutrophils and monocytes **contain many enzymes that destroy phagocytosed substances** and are capable of causing tissue damage **as collagenase, and cathepsin**.
- **The potentially damaging effects of lysosomal enzymes** are **limited by antiproteases** present in the plasma and tissue fluids.



II- Plasma derived mediators:

1. Complement proteins:

Complement components, numbered C1 to C9, are present in plasma in inactive forms, and many of them are activated by proteolysis leading to the generation of multiple breakdown products, **which are responsible for:**

- i. **Vascular effects:** C3a and C5a increase vascular permeability and cause vasodilation by inducing mast cells to release histamine.
- ii. **Leukocyte activation, adhesion, and chemotaxis:** C5a.
- iii. **Phagocytosis:** When fixed to a microbial surface, C3b acts as opsonins, augmenting phagocytosis.
- iv. **C9 kills some bacteria.**

2. Coagulation system:

Responsible for the conversion of fibrinogen to fibrin, and produces plasmin, which lyses fibrin.

3. Kinins:

Bradykinin causes increased vascular permeability, arteriolar dilation, mediates pain.

Table (3.2) Role of Mediators in Different Reactions of Inflammation.

Reactions of inflammation	Principal mediator
Vasodilation	Histamine and Prostaglandins
Increased vascular permeability	Histamine C3a, C5a and Leukotrienes
Chemotaxis , leukocyte recruitment & activation	TNF, IL-1 Chemokines C3a, C5a and Leukotrienes
Fever	IL-1, TNF and Prostaglandins
Pain	Prostaglandins & Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes & Reactive oxygen species



Chronic Inflammation

Definition:

Chronic inflammation **is inflammation of prolonged duration (weeks to years)** in which continuing inflammation, tissue injury, and healing, often by fibrosis, proceed simultaneously.

Chronic inflammation may arise in the following settings:

1. **Persistent infections by microbes that are difficult to eradicate.**
 - These include *Mycobacterium tuberculosis* and *Treponema Pallidum*.
2. **Immune-mediated inflammatory diseases** (hypersensitivity diseases) and **autoimmune diseases.**
3. **Prolonged exposure to potentially toxic agents.**
 - Examples are non- degradable exogenous materials such as inhaled particulate silica.

Pathologic features of chronic inflammation:

- ① **Minimal edema fluid.**
- ② **Infiltration by blood monocytes and lymphocytes.**

Blood monocytes change to macrophages and B lymphocytes change into plasma cells (mononuclear inflammatory cells).
- ③ **Ongoing tissue destruction by inflammatory response.**
- ④ **Attempts at healing by fibrosis.**

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Role of macrophages in chronic inflammation:

The macrophage is a key cell in chronic inflammation.

- ① They **derive from blood monocytes**, which migrate from blood into the tissues **under the effect of chemokines**, and are **capable of phagocytosis**.
- ② They may be **activated by microbial products** such as endotoxins, **or by T- cell derived cytokines**.
 - Activation **causes macrophages to proliferate**, stay **longer** at site of inflammation (immobilization), and **increase their intracellular killing and degradation**.
- ③ Macrophages **produce a variety of proteolytic enzymes**: proteases, elastase, collagenase, lipase...
 - This **leads to degradation of extracellular matrix and tissue damage**.
- ④ Macrophages **produce a variety of growth factors**:
 - ✓ **epidermal growth factor (EGF)**
 - ✓ **fibroblast growth factor (FGF)**
 - ✓ **and transforming growth factor beta**
 - Which **influence the process of repair**.
- ⑤ **Fate:**
 - After the initiating stimulus is **eliminated** and the inflammatory reaction **ends**, **macrophages eventually die** or **wander off into lymphatics**.
 - In chronic inflammatory sites, however, macrophage accumulation persists, because of continued recruitment from the blood and local proliferation.
 - **IFN-γ** can also **induce macrophages to fuse into large, multinucleate giant cells**.



Role of Lymphocytes:

Origin:

Both classes of lymphocytes **migrate into inflammatory sites** using some of the adhesion molecule pairs and chemokines that recruit other leukocytes.

Role in the inflammatory response.

1. In the tissues, **B lymphocytes** may develop into **plasma cells**, which **secrete antibodies**.
2. **CD4+ T lymphocytes** are activated to **secrete cytokines**.

Other Cells of Chronic Inflammation:

• **Eosinophils:**

- Are characteristically **found in inflammatory sites around parasitic infections** and as part of immune reactions **mediated by IgE**, typically associated with allergies.
- Their recruitment is **driven by adhesion molecules** similar to those used by neutrophils, and by specific chemokines.
- Eosinophil **granules contain major basic protein that is toxic to parasites**.

• **Mast cells:**

- In **atopic persons** (those prone to allergic reactions), mast cells are “**armed**” with **IgE antibody specific for certain environmental antigens**.
- When these antigens are subsequently encountered, the **IgE-coated mast cells are triggered to release histamines and AA metabolites** that elicit the early vascular changes of acute inflammation.

• **Neutrophils:**

- Though is **the hallmark of acute inflammation**, many forms of chronic inflammation may continue to show extensive neutrophilic infiltrates, **as a result of** either persistent microbes or necrotic cells, or mediators elaborated by macrophages.
- Such inflammatory lesions are sometimes **called “acute on top of chronic”**.



Types of chronic inflammation:

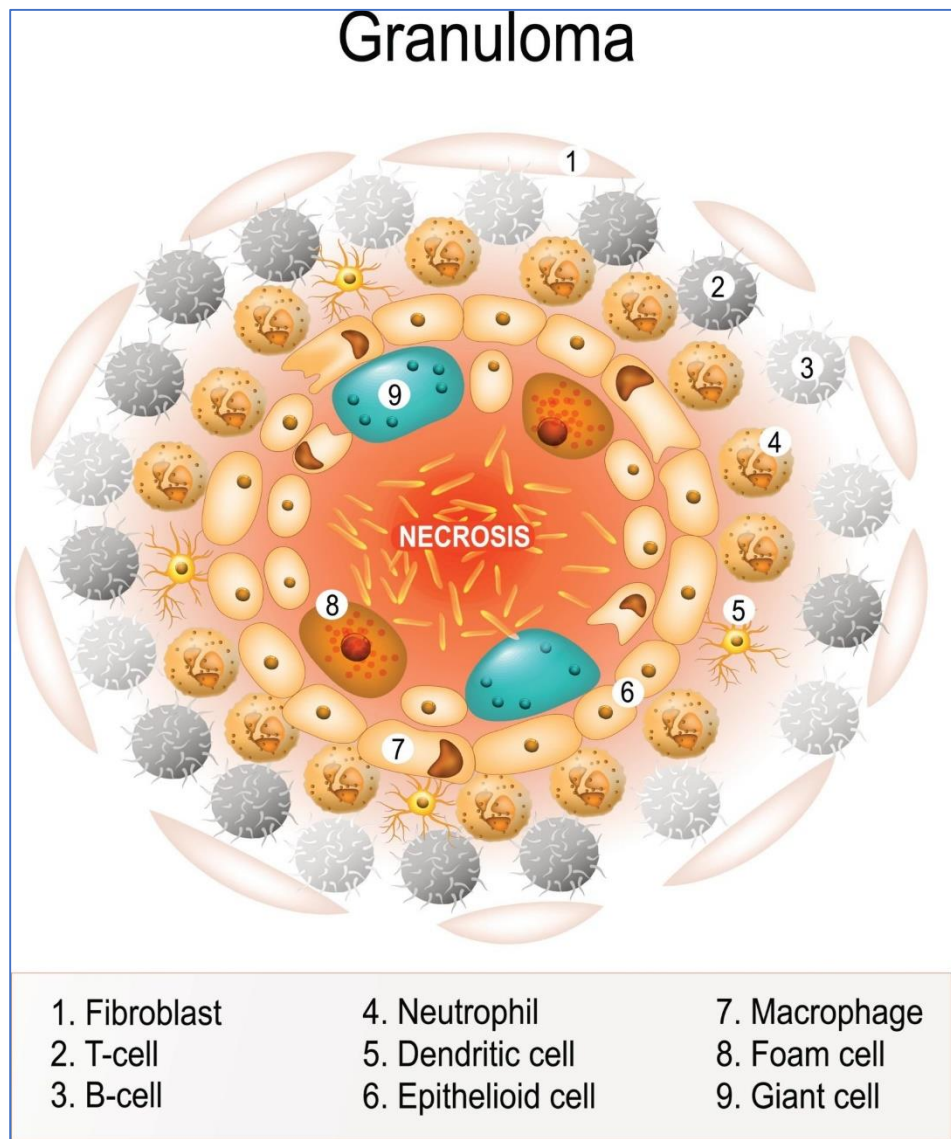
1. Chronic non-specific inflammation:

Usually **follows acute inflammation** and whatever the cause **they all show the same picture**. Thickening of the arterioles may occur, a change called **endarteritis obliterans**, with perivascular accumulation of lymphocytes, plasma cells and macrophages.

2. Granulomatous inflammation (granuloma):

Definition:

Granulomatous inflammation is a specific pattern of chronic inflammation **characterized by** the localized aggregation of activated macrophages (granuloma).

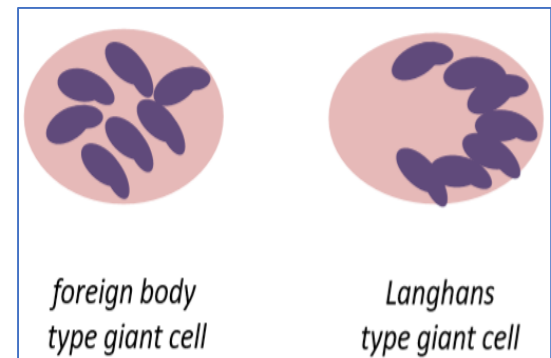




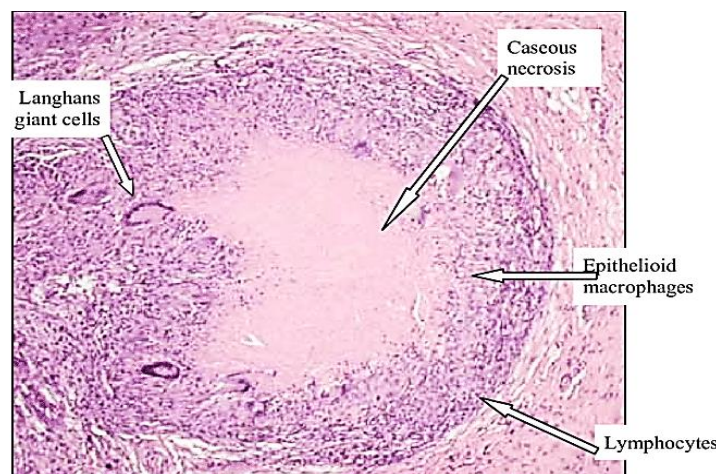
Morphology of granuloma:

- These aggregates form tiny granules which fuse to form a tumor like mass hence the suffix *-oma*. 😊
- It is formed of a localized aggregate of macrophages, which are activated and transformed into so-called epithelioid cells surrounded by a cuff of lymphocytes.
 - ✓ With hematoxylin and eosin stain, epithelioid cells have abundant pale eosinophilic granular cytoplasm (similar to an epithelial cell) with indistinct cell boundaries.
 - ✓ Multiple macrophages may fuse together to form a multinucleated giant cell.
- Examples of giant cells:

Langhans' giant cells where nuclei are arranged in peripheral horse-shoe pattern seen in tuberculous granuloma, and **foreign body type giant cells**, where the cell has many nuclei arranged in the center of the cell.



- In granulomas associated with certain infectious organisms (most classically the tubercle bacillus), a combination of hypoxia and free radical injury leads to a central zone of necrosis.
 - On gross examination, this has a granular, cheesy appearance and is therefore called caseous necrosis.



- Healing of granulomas is accompanied by fibrosis that may be quite extensive.



Mechanism of granuloma formation:

1. Immune-mediated granuloma (Type IV hypersensitivity):

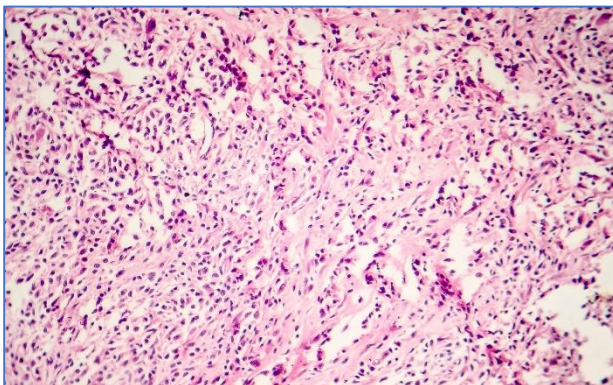
Immune granulomas are formed by immune T cell-mediated responses to persistent, poorly degradable antigens.

IFN- γ from activated T cells causes:

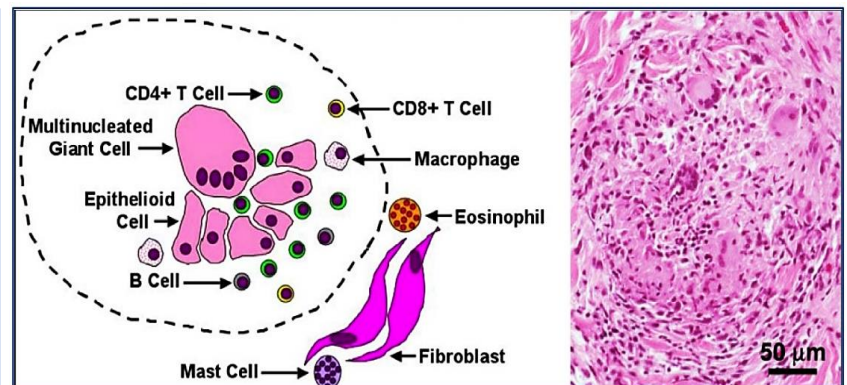
- ✓ the **macrophage transformation to epithelioid cells**
- ✓ and the **formation of multinucleate giant cells.**
- **Granulomas form** after macrophages have initially digested the pathogenic organism. During the killing and partial digestion of the organism, antigenic peptides are **expressed on the macrophage surface.**
- They pass through the lymphatics to the draining lymph nodes, **where they stimulate antigen – recognizing T lymphocytes.**
- The activated T lymphocytes proliferate and migrate to the inflammatory focus and **secrete cytokines** which **activate and immobilize macrophages.**
- **Macrophage activation release proteases and lysosomal enzymes** which **result in the pale granular cytoplasm.**
- **Extracellular release of these digestive enzymes may result in tissue necrosis.**

Foreign body granuloma:

It elicited by inert foreign particles that are **difficult for the macrophage to clear** but **do not elicit a specific immune response** (e.g., suture or talc).



Foreign body granuloma





Types of granulomas:

1. Infectious granuloma:

- **Bacterial** e.g. Tuberculosis & Leprosy.
- **Parasitic** e.g. Bilharziasis.
- **Fungal** e.g. Cryptococcosis.

2. Foreign body granuloma:

- **Silicosis** (inhalation of silica dust causes granuloma in the lung).
- Foreign body granuloma **around surgical sutures, glass, wood etc...**

3. Granulomas of unknown etiology:

- **Sarcoidosis** (a disease characterized by granulomas in multiple organs mainly lung and hilar lymph nodes).

It may represent **abnormal response** to some **external agent** as **bacteria or chemicals**)

- **Crohn's disease** (chronic granulomatous inflammation of the intestines).

The exact trigger for the granuloma is unknown.

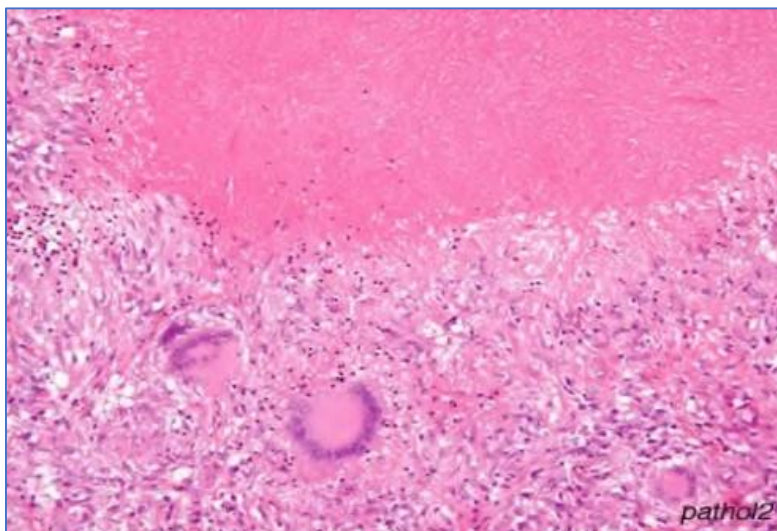


Figure (3.4) tuberculous granuloma with central necrosis, epithelioid macrophages and Langhans type giant cells.
(Photo-library of Pathology).



Formative Assessment

SAQ

1. List cell types seen in acute inflammation.
2. List cell types seen in chronic inflammation.
3. List cells in granulomatous inflammation.

MCQ

- 1) Chemotactic substances for neutrophils include all of the following except
 - a) Leukotrienes
 - b) Bacterial products
 - c) C3a, and C5a
 - d) Histamine
- 2) An abscess is
 - a) Diffuse suppurative inflammation
 - b) Localized suppurative inflammation
 - c) Non suppurative inflammation
 - d) An initially chronic type of inflammation.



HEALING AND REPAIR

Definition:

Healing or repair is the **replacement of injured tissue by new healthy one**.

It occurs by two types: Regeneration or Fibrosis (scar formation).

1-Regeneration

- **It is the replacement of the damaged cells by same cell type** (either from proliferating uninjured cells or from stem cells) **and restoration of normal tissue status**.
- It occurs following damage to **rapidly dividing labile cells** such as surface epithelium of skin or following minimal damage in parenchymal organs as liver which affects the cells only.

2-Fibrosis (Scar Formation)

- **It is the replacement of the damaged cells by fibrous tissue (scar)**.

It occurs following damage to **permanent non dividing cells** as cardiac and skeletal muscle. It also occurs following severe damage in parenchymal organs as liver which affects the cells and tissue framework.

Tissue Proliferative Activity

The tissues of the body are divided into **three groups** based on **their intrinsic proliferative capacity** into:

1. Labile tissues:

- Cells of these tissues have **continuous replicating activity**.
- These cells have **short G0 resting phase** and are in continuous mitotic division.
- **e.g.:** Hematopoietic cells and the majority of surface epithelia, **such as the stratified squamous surfaces of the skin and, mucus membranes**.



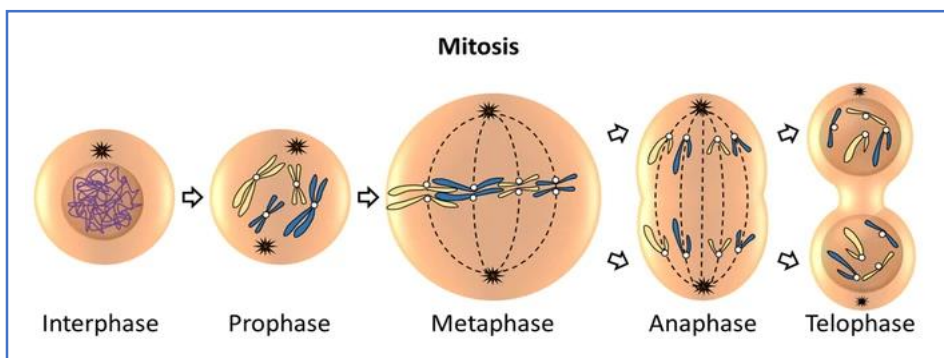
2. Stable tissues:

- Cells of these tissues are quiescent and have only minimal replicative activity in their **normal state and limited capacity to regenerate** after injury (except for the liver).
- These cells have **long G0 resting phase** but can enter in mitotic division when stimulated.
- e.g.:** Parenchymal cells of most solid tissues, such as liver, kidney, and pancreas. Other cells such as fibroblasts, smooth muscle cells and, endothelial cells; these cells are particularly important in wound healing.

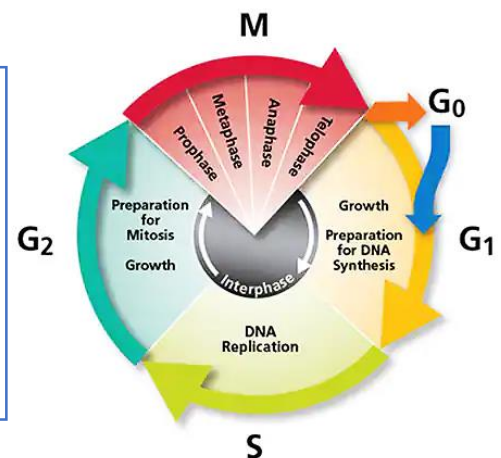
3. Permanent tissues:

- Cells of these tissues are considered to be **terminally differentiated** and **non-proliferative** in **postnatal life**.
- These cells are irreversibly post-mitotic and can't divide.
- e.g.:** neurons and cardiac muscle cells. Thus, injury to brain or heart is irreversible and results in a scar.

The Cell Cycle:



Cell cycle phases.



- The principal difference between **rapidly dividing cells** and **those which divide slowly** is the **time spent in the G1 phase of the cell cycle**.
✓ Some cells remain in the G1 phase for **days or even years**.
- Some cells** (e.g. some of stable cells) may **escape from the G1 phase of the cell cycle** by temporarily entering the G0 “resting” phase (**growth arrest**).
Cells in the G0 phase, **under the influence of growth factors** may re-enter the cell cycle at **G1**, thereby **regaining the proliferative state**.
- Permanent cells** are terminally **differentiated cells** that are confined to **G0 state**.
✓ If they die they cannot be replaced, as there are no stem cells.



Healing by fibrosis (Scar Formation)

Definition:

- **Replacement of damaged tissue** by granulation tissue which matures into fibrous tissue (**scar tissue**).
- **The term organization** is used when **granulation tissue is formed on the basis of fibrin** as the case of organization of an inflammatory exudate in serous sacs or organization of a thrombus.

Granulation tissue:

- **Granulation tissue formation is the early stage of repair.**
- It is formed of proliferated capillaries and fibroblasts (**some are myofibroblasts**).
- The term **derives from the appearance of the base of a healing skin ulcer**, where the formed capillaries have a granular appearance.
- **Granulation tissue is moist, red and bleeds easily.**

The following are the steps of healing by fibrosis (scar formation):

1- Angiogenesis:

Angiogenesis is the process of new blood vessel development from existing vessels, primarily venules which occurs under the influence of **growth factors mainly**; vascular endothelial growth factor (**VEGF**) and fibroblast growth factor (**FGF**).

Steps of angiogenesis:

- Proteolytic degradation** of the parent vessel basement membrane **by metalloproteinases**.
- Migration and proliferation** of endothelial cells toward the area of tissue injury and **producing solid buds**.
- Remodeling** into capillary tubes.
- Recruitment of periendothelial cells** (pericytes for small capillaries and smooth muscle cells for larger vessels) to form **the mature vessel**.



2- Activation of Fibroblasts and Deposition of Connective Tissue:

The laying down of connective tissue in the scar **occurs in two steps:**

- a) **Migration and proliferation of fibroblasts into the site of injury** under the influence of **growth factors mainly**; platelet derived growth factor (**PDGF**), fibroblast growth factor (**FGF-2**) and transforming growth factor beta (**TGF- β**).
 - ✓ **The major source of these factors is inflammatory cells, particularly macrophages.**
- b) **Deposition of ECM proteins** (laminin, fibronectin and, proteoglycans) **and collagen type III synthesis** produced by proliferating fibroblasts.
 - ✓ Ultimately, the granulation tissue is formed from the new capillaries and proliferating fibroblasts.

3- Remodeling of Connective Tissue and Scar:

As repair continues:

- a) The number of proliferating endothelial cells and fibroblasts **decreases**.
- b) **Collagen type I deposition increases** which is important in tensile strength of healing wounds.
- c) **Collagenase secreted by macrophage** modifies the size of the scar.
 - ✓ **Myofibroblasts contraction also helps to reduce the size of the scar.**
- d) **Finally the scar is pale, nearly avascular, and composed of inactive fibroblasts (fibrocytes) and dense collagen.**

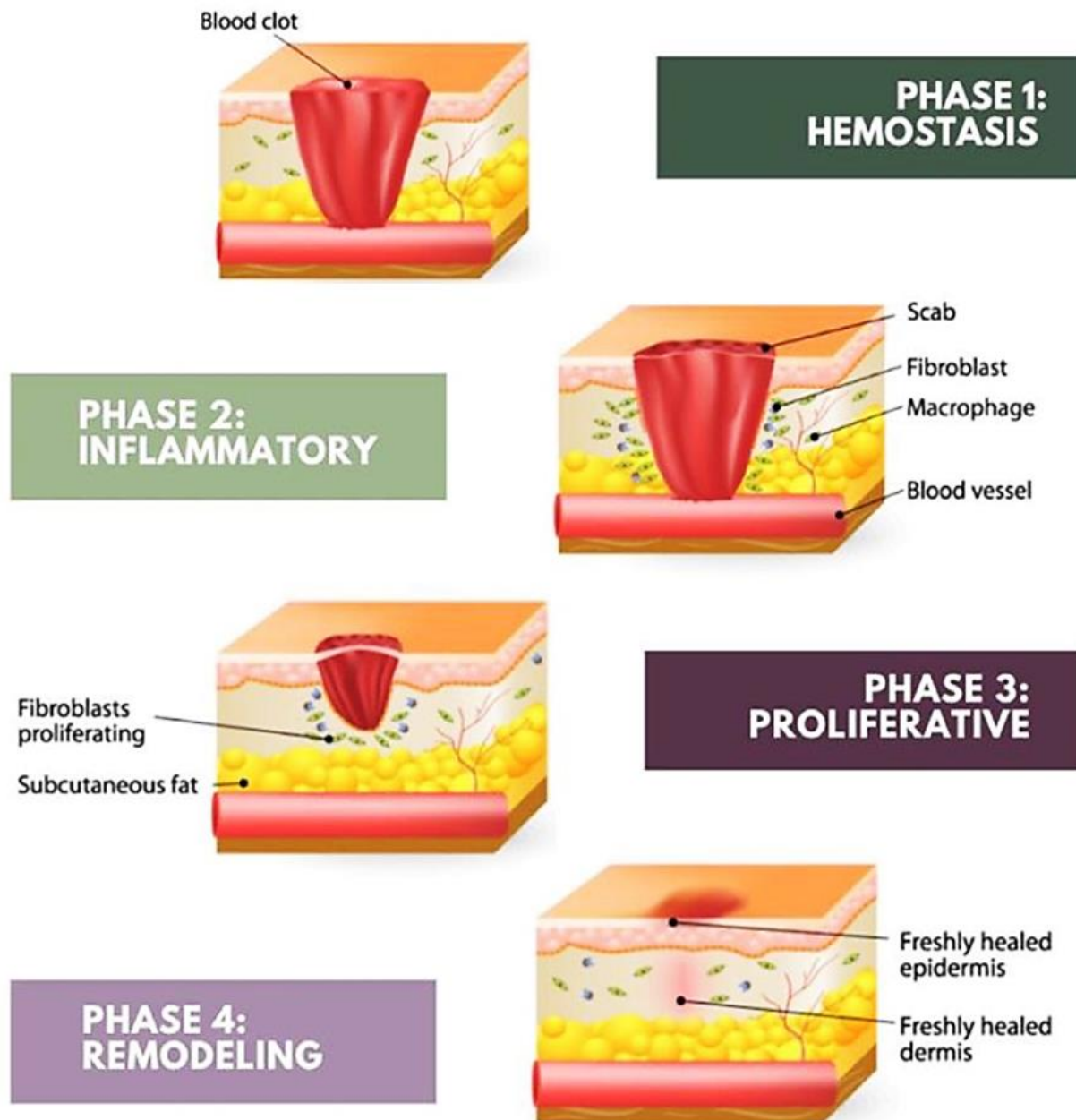
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Steps of scar formation

Factors controlling regeneration and repair by connective tissue:

The mechanisms which control regeneration and the repair by fibrous tissue involve **growth factors**, **cell-cell** and **cell-matrix interaction**.

✓ They can be divided into stimulatory & inhibitory factors



1. Stimulatory factors:

a) Growth factors:

➤ Variable growth factors are known.

- They are mainly **produced by** macrophages, platelets and fibroblasts.
- Epithelium, endothelial cells, mast cells and T cells can also contribute.

➤ Extracellular growth factors bind to specific receptors on the cell surface, inducing expression of genes which promote entry in the cell cycle.

Besides stimulating proliferation, growth factors can influence **cell movement, contractility, differentiation, and angiogenesis**.

➤ Major growth factors are:

- Epidermal growth factor (**EGF**).
- Transforming growth factor alpha.
- Fibroblast growth factor (**FGF**).
- Platelet derived growth factors.
- Vascular endothelial growth factor (**VEGF**).
- Cytokines as interleukin 1 (**IL1**) & tumor necrosis factor alpha (**TNFα**).

➤ Transforming growth factor beta (TGF-β)

- It is **the main fibrogenic factor**.
- Although it is an inhibitor of cell proliferation (see later), **it switches on the fibroblast to produce collagen**.

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➤ **Three types of signals can produce proliferation:**

a) Autocrine signaling:

where the growth factors are **secreted by the cells themselves** and therefore **control their own proliferation**. This occurs in epithelial proliferation **in wounds, in liver** regeneration and **in some tumors**.

b) Paracrine signaling:

the growth factors are **secreted by cells nearby**, **e.g. growth factors** secreted by **macrophages** can **stimulate proliferation** of endothelial and mesenchymal cells.

c) Endocrine signaling:

substances **produced at a distant site**, can control cell proliferation.

b) Cell-matrix interaction:

- Cells are attached to surrounding extracellular matrix, by cell surface receptors **called integrin**.
Integrins binds to fibronectin (a glycoprotein component of extracellular matrix).
- Tissue repair and regeneration **depend not only on the activity of growth factors, but also on interactions between cells and the components of** the extracellular matrix (ECM).
- ECM components can regulate **cell proliferation, migration and differentiation by signaling through integrins**.
- **ECM acts as scaffolding** on which the cells can adhere and migrate.
- Although labile and stable cells are capable of regeneration, there is **failure of restitution** of the normal structure if the ECM is damaged.
 - ❖ Disruption of these structures **leads to collagen deposition and scar**.

2. Inhibitory factors:

- ✓ When repair is completed, cell proliferation is inhibited.
- ✓ These inhibitory factors are not yet completely understood.



a) Some Growth Factors: Some Growth factors have inhibitory activity as:

- **TGF alpha:** Stimulates collagen degradation.
- **TGF beta:** Inhibits cell growth.

b) Cell- Cell Interaction and contact inhibition:

After injury, **healthy nearby cells proliferate to fill the gap**, when they come in contact with each other, **they stimulate inhibitory receptors** on cell surface which **inhibit further cell growth**; **this is referred to as contact inhibition**, and controls both growth and movement.

Factors that influence tissue repair

1 General Factors:

Nutrition:	Protein and vitamin C deficiency inhibit collagen synthesis and retard healing.
Metabolic status:	Diabetes mellitus is associated with delayed healing , as a consequence of microangiopathy .
Circulatory status:	Poor blood supply due to arteriosclerosis or obstructed venous drainage (e.g., in varicose veins) also impairs healing.
Hormones:	Glucocorticoids (steroids) have well-documented anti-inflammatory effects , and inhibit TGF-β production thus reduce fibrosis.

2 Local Factors:

Infection:	Is clinically the most important cause of delay as it results in persistent tissue injury .
Mechanical:	Such as increased local pressure or torsion can compress blood supply .
Foreign bodies	Such as fragments of steel, glass, or even bone impede healing.
The type and severity of tissue injury:	as described before



EXAMPLES OF TISSUE REPAIR AND FIBROSIS

Healing of wounds:

1. Healing by first intention:

- This occurs in **incised wounds e.g.** surgical wounds, where there is **little damage** to the tissues on either side of the cut.
- Blood escaping from blood vessels **clots on the wound surface and fills the gap between the wound edges**, and as the gap is small, **fibrin acts as glue** which holds the cut surfaces together. **(Also helped by sutures or adhesive plasters).**
- ✓ **The dry blood on the surface forms a scab which seals the wound.**

After 24 hours	There is a mild inflammatory reaction , with fluid exudate and neutrophils, which start digestion of the clot
Within 24-48 hours	Basal cells start to proliferate (regeneration) and migrate to bridge the gap, and afterwards continue to proliferate to restore the full thickness of the epidermis.
From day 3	Macrophages appear in the inflammatory exudate, and complete digestion of fibrin and cellular debris. Small amount of granulation tissue (capillaries and fibroblasts) form from the edges of the wound to repair the dermis.
by day seven	Fibroblasts lay down collagen which unites the edges of the wound.
From the second week onwards	The capillaries disappear, remodeling occurs and the scar becomes stronger.

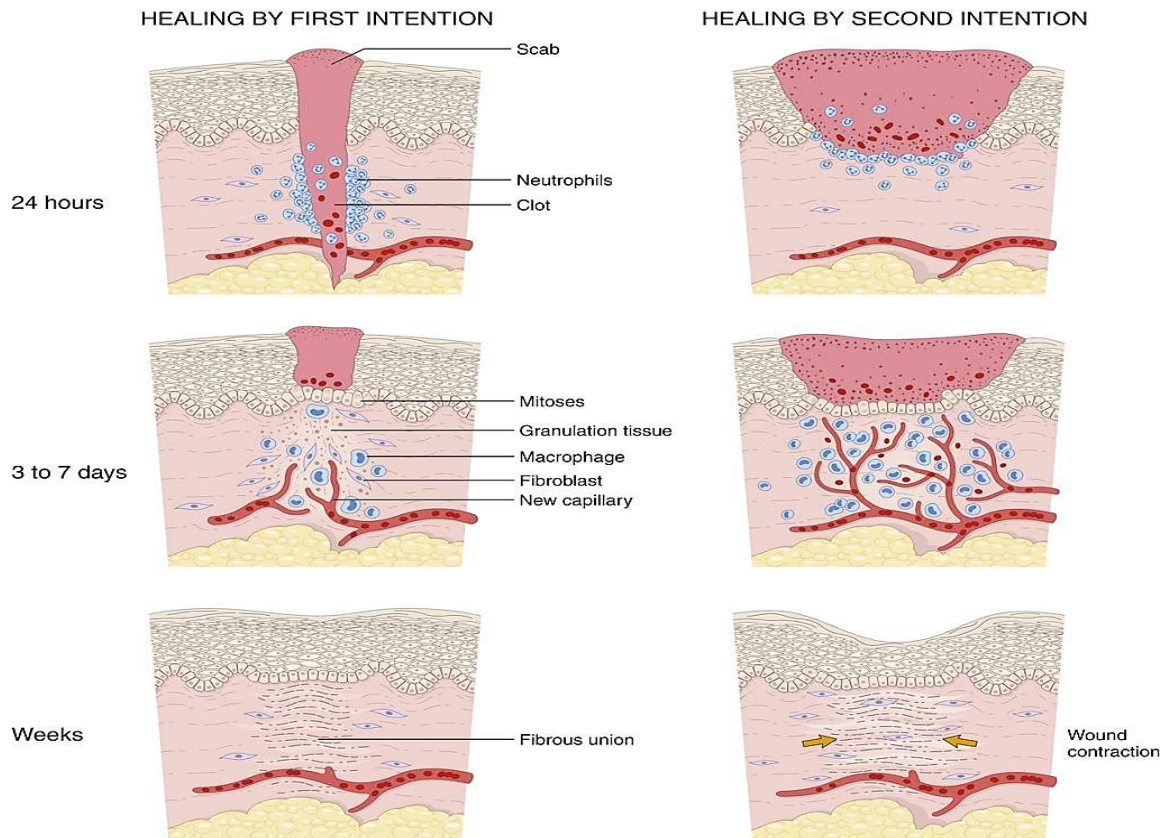
- Some sensory nerves may regenerate **but specialized sensory organs as Pacinian corpuscles do not regenerate.**
- The **end result** of healing by **first** intention is **a fine pale linear scar.**



2. Healing by second intention:

- This type of healing **occurs in open gaping wounds** with tissue loss, **or infected wounds**.
 - ✓ It is also the type of healing **for an abscess, or an ulcer**.
 - ✓ In this type of healing there is **abundant granulation tissue**, which grows from the base of the wound to fill the defect.
 - ✓ Healing takes **longer time than first intention**.
- **Initially there is hemorrhage and exudation of fibrin** on the surface of the wound.
- There is **infiltration** by large number of **neutrophils** and **later, macrophages**.
 - ✓ These remove fibrin and cellular debris.
- At the margin of the defect basal cells start to proliferate **but cannot bridge the gap**, until the granulation tissue from the base of the wound starts to fill the wound space.
- Granulation tissue forms from the base and when it reaches the surface, the basal cells grow on its surface **to close the gap, and then restore the full thickness of the epidermis**.
- Collagen is **laid down** and **maturation of scar tissue occurs**.
- **Wound contraction occurs by myofibroblasts**.
- **Skin adnexa do not regenerate**.





wound healing by primary and secondary union.

Healing by First Intention	Healing by Second Intention
Type of wound: clean, non- gaping e.g. surgical incision.	Type of wound: gaping, infected e.g. abscess.
Minimal tissue damage.	Extensive tissue damage.
Steps of healing: - The epithelial gap is closed first by epithelial regeneration followed by formation of granulation tissue in the dermis The scar is small, fine pale and linear	Steps of healing: - Because the gap is wide granulation tissue fills the wound from below upwards until it reaches the epidermis, forming a base upon which the epithelial cells can grow. - Formation of a large scar, followed by wound contraction mediated by the action of myofibroblasts
The dermal appendages destroyed in the line of the incision are permanently lost.	The dermal appendages destroyed in the line of the incision are permanently lost.
Complications are less common.	Complications are more common

Comparison between the two types of wound healing.



Complications of wound healing:

1 Cosmetic deformities	Due to extensive scarring.
2 contracture	Excessive scar contraction may lead to contracture which is distortion or limitation of movement across joints .
3 Keloid formation	This is excessive fibroblast proliferation and collagen production after dermal injury (overdone repair). This phenomena is genetically determined, and is more common in blacks. A firm mass covered by stretched skin may follow surgery or burns.
4 Implantation epidermal cyst	During regeneration of the epidermis some epidermal cells may grow down the cut edges of the dermis. These are later resorbed; if they remain they may grow into a keratin-filled cyst in the epidermis.
5 Chronic ulcer, sinus or fistula	Due to defective repair in case of persistent infection or foreign body. It may be due to deposition of collagen at the edges of the wound without filling the whole wound with granulation tissue.
6 Carcinoma	Carcinoma may develop from the edges of chronic ulcers and scar tissue especially related to burns. It is known as Marjolin ulcer .





Healing of neural tissue:

In Central nervous system:

- **Neurons** don't effectively regenerate.
- **Glial cells**, however, may proliferate in response to injury, a process referred to as **gliosis**.

In Peripheral nerves:

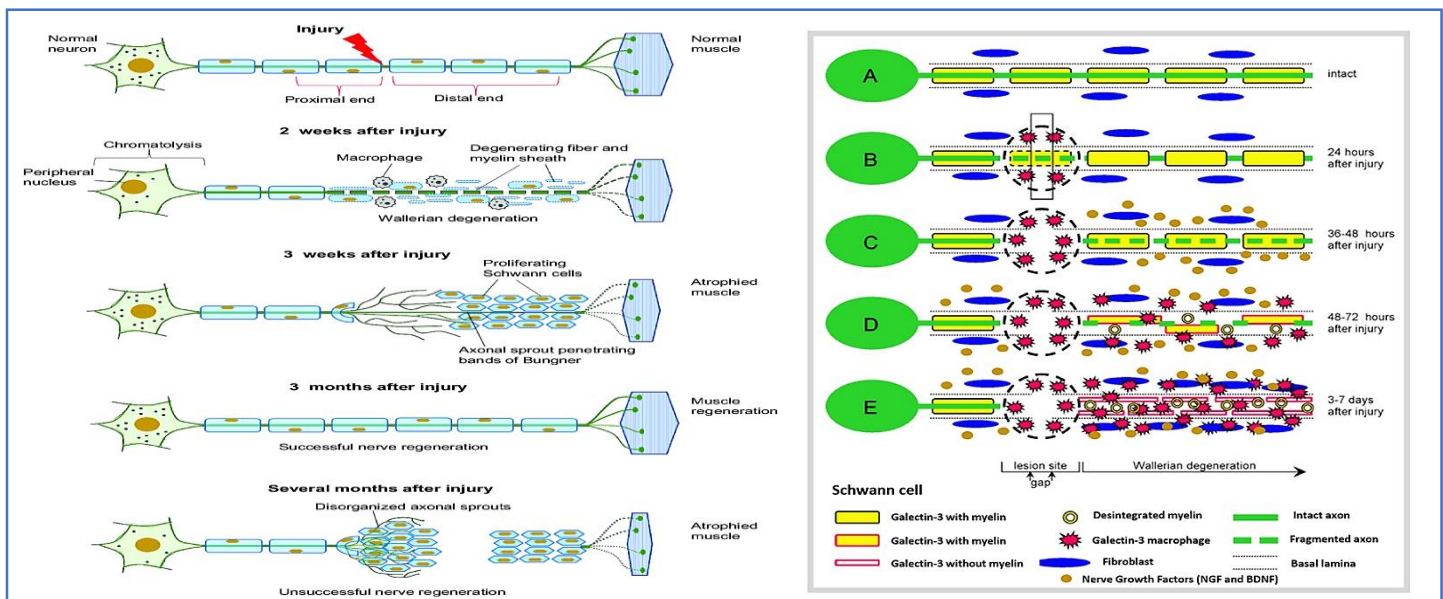
Peripheral nerves heal by regeneration

- If a nerve is transected, axons degenerate **proximally** until the first node of Ranvier, and **distally** by **Wallerian degeneration**.
 - The axon and myelin disintegrates and only Schwann cells survive.
- **Retrograde degeneration** of the neuron occurs; it loses its nissl granules (**chromatolysis**).
 - This is reversible.
- **Regeneration starts by Schwann cell proliferation** to restore the neurilemmal tube.

If there is good alignment of the cut ends the axon **regrows into the neurilemmal tube**, however **full functional recovery does not always occur**.

When there is **poor alignment or amputation** of the distal end of the nerve, the regrowth of axons will form a tangled mass of axons and stroma called **amputation neuroma**.

✓ Sometimes this is painful and has to be removed.



Peripheral nerve repair.



Repair in parenchymal organs:

Healing in the liver:

Hepatocytes have excellent regenerative capacity, although they are a **stable population** and replicate only **slowly**.

- 1) **Conditions** that simply result in hepatocytes loss may be followed by **regeneration and complete restitution**.
- 2) **Conditions** destroying both the hepatocytes and architecture **e.g. chronic hepatitis** the hepatocytes **regenerate but fail to reconstruct** the architecture , **the result is regeneration of liver cells** forming nodules surrounded by fibrous scarring, a condition called cirrhosis .

Healing in the kidney:

- The kidney is similar to the liver.
 - **The epithelium can regenerate but the architecture cannot.**
- **Loss of tubular epithelium e.g.** due to toxins, can be replaced by epithelial regeneration.
- **Injury to the interstitium by inflammation or necrosis** of part of the renal parenchyma **e.g. infarction**, is going to be repaired by fibrous scarring

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Formative Assessment

MCQ

1-While skipping rope, a 7 year old girl falls and scrapes her knee on the pavement. Four days later, she picks at a hard, reddish-brown raised formation at the site of the injury which reveals soft, moist pink tissue. Which is the predominant cell type found in this underlying tissue?

- a) Epithelioid macrophage.
- b) Fibroblast.
- c) Mast cell.
- d) Neutrophil.

2-Which of the following is the correct sequential order of the phases of healing?

- a) Remodeling, inflammation, hemostasis, and repair
- b) Inflammation, hemostasis, proliferation, and maturation
- c) Hemostasis, inflammation, repair, and remodeling
- d) Inflammation, maturation, proliferation, and hemostasis



DISORDERS OF GROWTH AND NEOPLASIA

Growth:

It is the process of increase in size resulting from the synthesis of specific tissue components that may occur through:

- Increase in numbers of cells (as in embryogenesis),
- Increased size of individual cells (as in skeletal muscle),
- Increase in intercellular tissue components, as in bone and cartilage.
- Combined patterns of all (as in embryological development).

Differentiation:

It is the process whereby a cell develops a distinct specialized function and morphology (phenotype) that was not present in the parent cell.

DISORDERS OF GROWTH AND DIFFERENTIATION

Cells adapt to acceptable changes in their environment by modification of their metabolism and growth pattern (increased or decreased cell activity or altered structure).

I- Increased growth:

1. Hypertrophy: Increasing cell size without cell replication.
2. Hyperplasia: Increasing cell numbers by cell division.
3. A combination of both.

II- Decreased growth:

Atrophy.

III- Altered growth & differentiation:

1. Metaplasia.
2. Dysplasia.



Hypertrophy

Definition:

Increased size and weight of organ due to increase in size of its cells. The increased size of the cells is due to the synthesis and assembly of additional intracellular structural components which are necessary for increasing the metabolism.

Types:

It may be physiological or pathological.

1. **Physiological:** Pregnant uterus due to hormone stimulation & muscle hypertrophy in athletes.
2. **Pathological:**
 - a) **Adaptive type:** It affects the muscle coat of hollow organs due to increased intraluminal pressure e.g.
 - Left ventricular hypertrophy due to hypertension or aortic valve stenosis.
 - Urinary bladder hypertrophy due to obstruction of the bladder neck.
 - b) **Compensatory type:** If one of a paired organ is out of function or surgically removed, the other organ undergoes compensatory hypertrophy e.g. kidney enlargement when the other kidney is surgically removed.



Figure (5.1) Left ventricular hypertrophy.



Hyperplasia

Definition:

Increased size & weight of organ due to Increase in number of its cells (**Increased cell division**). Hyperplasia can occur in any cell type capable of division.

Types:

It may be physiological or pathological.

1. Physiological:

- a) Hormonal hyperplasia e.g. mammary glands & genitalia at puberty due to estrogen stimulation.
- b) Compensatory e.g. bone marrow hyperplasia after hemorrhage.

2. Pathological:

- a) Hormonal hyperplasia e.g. endometrial hyperplasia in repeated anovulatory cycles
- b) Lymphoid hyperplasia in response to antigenic stimulation

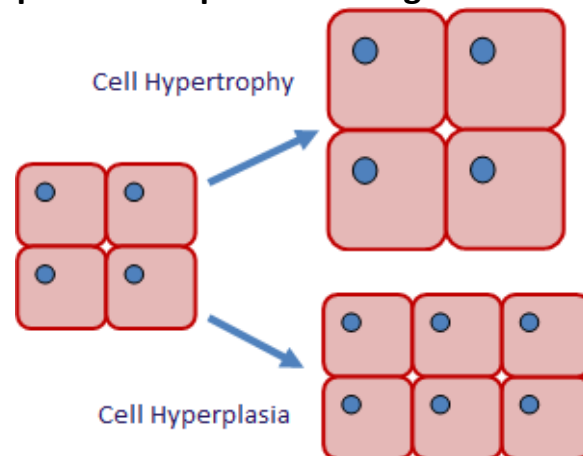


Figure 5.2 Cell hyperplasia and cell hypertrophy.

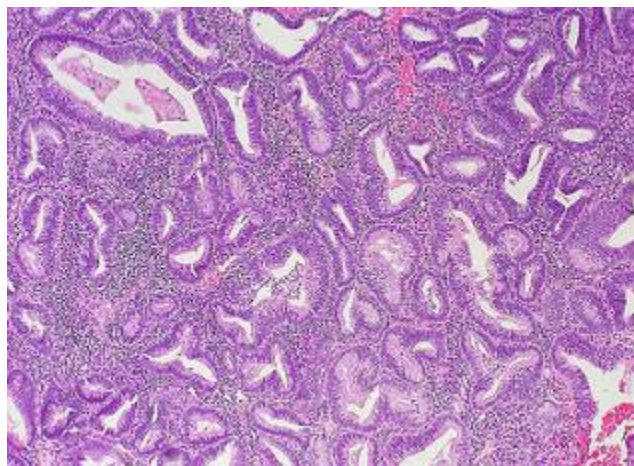


Figure 5.3 Endometrial hyperplasia.



Atrophy

Definition:

It is decrease in size and weight of organ, after organ had reached its adult size. It is due to decrease in the cell size.

Types:

It may be physiological or pathological.

1. Physiological:

- a) Localized atrophy as thymus after puberty and breasts after menopause.
- b) Generalized atrophy in case of senility. Aging results in diminution in organ size & function e.g. brown atrophy of the heart.

2. Pathological:

a) Localized atrophy:

- i. Hormonal atrophy due to loss of hormonal stimulation e.g. breast atrophy following bilateral excision of ovaries.
- ii. Vascular atrophy e.g. renal atrophy due to atherosclerosis of renal artery.
- iii. Pressure atrophy: Atrophy of the vertebral bodies due to pressure atrophy by aneurysm (likely due to ischemia, and compromise of blood supply)
- iv. Neuropathic atrophy: Atrophy of limb muscles due to loss of innervation as in poliomyelitis.
- v. Disuse atrophy: e.g. muscles after prolonged immobilization after a fracture of bone.

b) Generalized atrophy: It affects all organs. Heart is small, skin is wrinkled due to loss of elastic fibers, bones and muscle are weak, and teeth fall. e.g.

- Decreased anabolism in cases of chronic malnutrition and starvation.
- Increased catabolism as in advanced stages of malignancy (cachexia) and thyrotoxicosis.



Metaplasia

Definition:

Replacement of one mature differentiated cell type to another type. It is usually an adaptive response to injury, where the new type of cell is more resistant to chronic injury.

It is often associated with an increased risk of malignancy (e.g. squamous cell carcinoma associated with squamous metaplasia in bronchi).

Mechanism of metaplasia:

Metaplasia does not result from a change in the phenotype of an already differentiated cell type; instead it is the result of a reprogramming of stem cells that are known to exist in normal tissues, or of undifferentiated mesenchymal cells present in connective tissue. In a metaplastic change, these precursor cells differentiate along a new pathway.

Types of metaplasia:

i. Epithelial Metaplasia:

1) **Squamous Metaplasia:** Transformation of columnar or transitional cells to squamous epithelium e.g.

- Respiratory epithelium of the trachea and bronchi in smokers.
- Columnar epithelium of bile duct, gall bladder due to gall stones
- Transitional bladder epithelium in the presence of stones, and in the presence of ova of the Schistosoma haematobium

Leukoplakia:

- **Leukoplakia** is a white patch that may develop in the oral cavity, tongue or vulva due to chronic irritation.
- **It may also develop in** the urinary bladder or bronchus after squamous metaplasia.

Morphology:

Gross: Thick irregular white patches

Microscopic: Thickened squamous epithelium with keratinization and subepithelial chronic inflammation.



- 2) **Intestinal Metaplasia:** Transformation of columnar cells to mucus secreting cells like those of intestine e.g. gastritis and at the edges of peptic ulcers. Or the replacement of the normal squamous epithelium of the oesophagus by columnar epithelium (**glandular metaplasia**) e.g. Barrett's oesophagus.

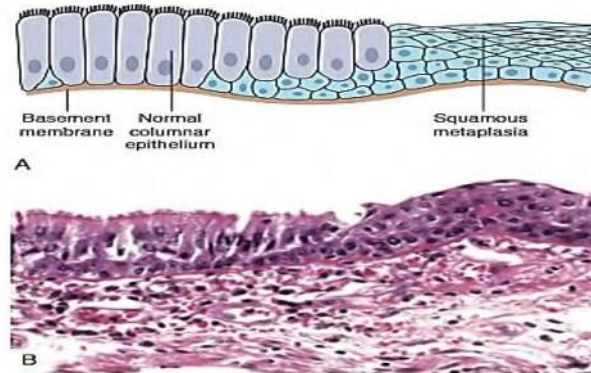


Figure (5.5) Metaplasia of columnar epithelium to squamous epithelium in bronchus.

ii. Mesenchymal Metaplasia:

Connective tissue metaplasia is the formation of cartilage, bone, or adipose tissue (**mesenchymal tissues**) in tissues that normally do not contain these elements. For example, bone formation in muscle, designated myositis ossificans, occasionally occurs after intramuscular hemorrhage.

Dysplasia

Definition:

It is non-neoplastic disordered proliferation of cells, usually induced by prolonged cell irritation.

Sites:

1. **Mucous membranes** of the cervix uteri, bronchi, oral cavity, urinary bladder, colon and gall bladder.
2. Epidermis.

Gross:

Nonspecific gross appearance.



Microscopic: is characterized by:

1. Loss of normal orderly arrangement (**polarity**)
2. Cellular pleomorphism (**different shapes & sizes**) and nuclear hyperchromasia (**increased nuclear color**).
3. Increased mitosis.
4. **Grading of dysplasia:** Dysplasia may be low grade or high grade depending on the degree of cellular atypia.

In squamous epithelium:

- Low grade dysplasia affects the lower third of the epithelium.
- High grade dysplasia affects the lower two-thirds and may extend to the upper third

Prognosis & Clinical significance:

- **Low grade dysplasia** is commonly reversible when the irritating cause is removed.
- **High grade dysplasia** passes to carcinoma in situ.

Carcinoma In Situ (CIS)

Definition:

Carcinoma in situ (CIS) represents a pre-invasive stage of carcinoma involving full thickness of the epithelium, and is characterized by severe epithelial atypia (**severe dysplasia**) without invasion of the basement membrane (**separating it from potential routes of metastases i.e. blood vessels and lymphatics**).

Once the basement membrane is invaded the CIS phase ends and actual malignant tumor starts.

Microscopic features: CIS is essentially a microscopic change characterized by:

- Diffuse cellular atypia involving the whole thickness of the affected epithelium. The cells are pleomorphic with dark nuclei and numerous mitoses. Their architectural orientation (**polarity**) is disturbed.
- No invasion of basement membrane.

Fate:

Progression into invasive carcinoma occurs after a variable time (**usually years**).



Examples of common sites of CIS:

- 1) Bladder.
- 2) Cervix.
- 3) GIT.
- 4) Mammary gland.
- 5) Skin.

Cancer ← Dysplasia ← Hyperplasia ← Normal

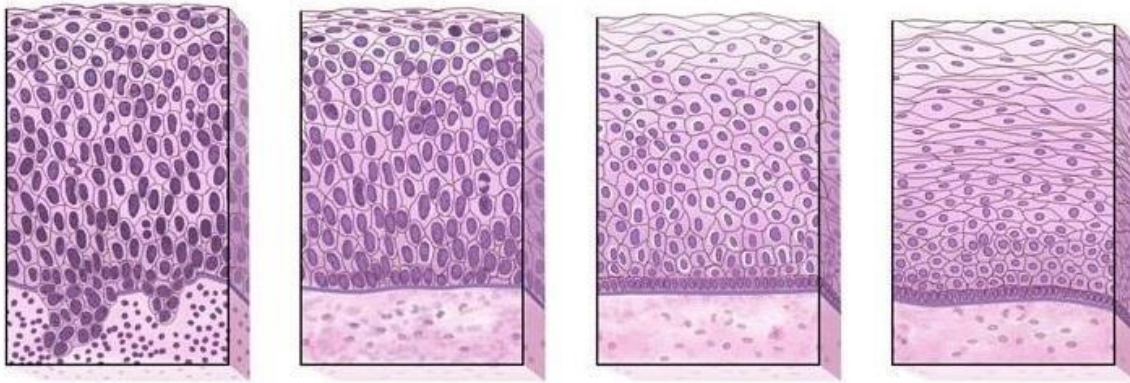


Figure (5.6) Change of normal cells to cancer.



NEOPLASIA

Definition:

Neoplasia means “new growth”. A neoplasm (tumor) is a new growth forming an abnormal mass, caused by autonomous self-controlling proliferation of cells.

Neoplasia is irreversible, uncontrolled, unlimited, progressive & purposeless.

Table (5.1) Difference between hyperplasia and neoplasia.

HYPERPLASIA	NEOPLASIA
- Excited by a stimulus - Reversible, i.e. pathological hyperplasia stops and disappears if the stimulus subsides. - Proliferated cells are normal-shaped. - May be useful (e.g. compensatory hyperplasia).	- A stimulus is not always detected. - Irreversible, i.e. cell proliferation is unlimited and progresses independent of any stimuli. - Proliferated cells in case of malignant neoplasia are abnormal-shaped. - Harmful.

Any Tumor has Two Basic Components:

1. The transformed (neoplastic) cells: Cells which have undergone genetic damage.
2. The supporting stroma & vessels: Non-transformed elements derived from the host in response to factors released from the tumor, e.g. angiogenesis factor.

Classification of Tumors

A. According to their behavior:

- 1) Benign Tumors.
- 2) Malignant Tumors.
- 3) Intermediate Tumors.

B. According to cell of origin (Histogenetic Classification):

- 1) Epithelial tumors.
- 2) Mesenchymal tumors.
- 3) Others.



Characteristics of Benign Tumors

In general benign tumors appear to be genetically simple, harboring fewer mutations than cancer cells and genetically stable, changing little in their genotype over time.

A. Morphology:

Gross Features: Benign tumors appear as:

- Well circumscribed globular or ovoid masses.
- Most are capsulated. This capsule probably is derived from the stroma of the host tissue as the parenchymal cells undergo atrophy under the pressure of the expanding tumor. Some benign tumors do not have a capsule e.g. a leiomyoma.
- Cut section of the tumor is commonly uniform with no hemorrhage or necrosis.

Microscopic Features:

1- Cell Differentiation:

- Cellular differentiation is the extent to which tumor cells resemble comparable normal cells.
- In benign tumors, the cells are perfectly differentiated i.e. closely mimic the corresponding normal cells, e.g. fat cells in lipoma resembles normal fat cells in subcutaneous tissue. Mitosis is rare or absent.

2- Histologic Differentiation:

- This is the degree of resemblance of the structural pattern of the tumor to that of the normal tissue.
- In benign tumors, the tumor cells exhibit structural patterns similar to the normal tissue. Thus adenoma of thyroid consists of acini almost similar to those of normal thyroid gland.

3- Other Features: Hemorrhage and necrosis are extremely rare.

B. Rate of Growth: It is often slow.



C. Local Invasion & Metastases (Distant Spread):

- Benign tumors do not have the capacity to infiltrate, invade or metastasize to different sites.
- Most benign tumors do not recur if well excised.

D. **Prognosis:** Benign tumors have good prognosis, but in certain locations can have serious effects (see later).

Characteristics of Malignant Tumors

A. Morphology:

Gross Features: Benign tumors appear as:

- A malignant tumor appear as irregular non-capsulated mass, with ill- defined infiltrating margin.
- Cut section of the tumor: often shows areas of hemorrhage and necrosis.

Microscopic Features:

I. **Cellular Anaplasia (lack of differentiation):** Malignant cells show grades of cellular atypia, referred to as anaplasia, ranging between mild to marked. anaplasia is characterized by:

- 1) **Cellular pleomorphism:** Malignant cells vary in size & shape. However some tumors are monomorphic.
- 2) **Nuclear pleomorphism:** Nuclei may be irregular or bizarre shaped.
- 3) **Nuclear enlargement & hyperchromatism:** Due to increased synthesis of DNA, the nuclei appear dark (**hyperchromatic**) & the nucleo-cytoplasmic (**N/C**) ratio is increased approaching 1:1 (**normally N/C ratio is approximately 1:5**).
- 4) **Nucleoli may be prominent.**
- 5) **Abundant mitoses & frequently abnormal mitotic figures (e.g. tripolar spindles).**
- 6) **Tumor giant cells containing a single large polypoid nucleus or multiple nuclei.**



II. Histological differentiation:

- **In addition to** cytologic abnormalities, anaplastic cells usually fail to develop recognizable patterns of orientation to one another (**i.e., they lose normal polarity**). They may grow in sheets, with total loss of common structures, such as glands or stratified squamous architecture.
- **Carcinoma may be** graded as well differentiated (**grade I**), moderately differentiated (**grade II**), poorly differentiated (**grade III**) & undifferentiated (**grade IV**).
- **Better differentiated tumors tend to** show less marked cellular anaplasia & grow slower. On the other hand undifferentiated tumors show great cellular anaplasia & grow faster. Undifferentiated (**grade IV**) carcinoma is sometimes termed anaplastic carcinoma.

B. Rate of growth: It is often rapid.

C. Local Invasion & Metastases (Distant Spread):

- **Cancers grow by** progressive infiltration, invasion and destruction of the surrounding tissue. They do not develop well-defined capsules. **The infiltrative mode of** growth makes it necessary to remove a wide margin of surrounding normal tissue during surgical excision. **These margins have to** be examined carefully by surgical pathologists for presence of cancer cells.
- **Metastases:** Metastases are secondary implants of a tumor that are discontinuous with the primary tumor and located in remote tissues. More than any other feature, the property of metastases identifies a neoplasm as malignant.

D. Prognosis:

- Malignant tumors spread (**see later**).
- **Recurrence after surgical excision is** very common either from tumor cell remnants (**not removed with the excised tissue**) or from a new neoplastic transformation.
- **Malignant tumors are** serious & cause death. (**see later**)



Benign Neoplasms	Malignant Neoplasms
- Resemble tissue of origin and are well differentiated. - Generally slow growing. - Expansile growth, well circumscribed and have a capsule. - Benign tumors remain localized to the site of origin.	- Poorly or completely undifferentiated. - Generally grow faster. - Poorly circumscribed and invade the surrounding normal tissue. - Malignant tumors metastasize to different sites.



Figure (5.7) Benign tumor on the left: well defined and encapsulated; malignant tumor, on the right: irregular infiltrating the fat.

Routes (Pathways) of Spread of Malignant Tumors

1. **Local (Direct) Spread:** Tumor cells invade adjacent structures in direct continuity e.g. cancer tongue can directly spread to the floor of mouth.

2. **Distant Spread (Metastasis):**

A. **Lymphatic Spread:** Occurs more commonly with carcinomas than sarcomas. Lymphatic spread occurs in two ways: lymphatic embolism and lymphatic permeation

• **Lymphatic Embolism:**

Malignant cells invade the wall of lymphatic vessels forming tumor emboli and reach the lymph node. Spread from one node to another may occur by efferent lymphatics.

Grossly: The affected nodes are enlarged & hard. They may become fused & fixed. **Microscopically** the metastatic deposit resembles the primary tumor from which it is derived.



Progressive spread by the lymphatic route may ultimately lead to tumor emboli within the main lymphatic ducts (thoracic duct), from which tumor emboli reach the venous circulation causing hematogenous spread.

- **Lymphatic Permeation:**

The tumor cells grow as solid columns inside lymphatics leading to lymphatic obstruction and lymphatic oedema.

Example: breast carcinoma spread by permeation of axillary lymphatics leads to edema of the whole arm

N.B. Enlargement of nodes near a primary neoplasm does not always imply cancerous involvement. **The necrotic products of** the neoplasm and tumor antigens often evoke immunologic responses in the nodes, such as hyperplasia of the follicles (**lymphadenitis**) and proliferation of macrophages in the subcapsular sinuses (**sinus histiocytosis**). **Thus, histopathologic verification of** tumor within an enlarged lymph node is required.

Sentinel Lymph Node:

A “**sentinel lymph node**” is the first regional lymph node that receives lymph flow from a primary tumor. **It can be identified by injection of** blue dyes or radiolabeled tracers near the primary tumor. **Biopsy of** sentinel lymph node, during surgery and examination by frozen section allows determination of the extent of spread of tumor and can be used to plan treatment.

B. Hematogenous (Blood) Spread:

- **Emboli derived from primary tumors of** organs drained by systemic veins e.g. breast, and kidney reach the right side of the heart via the vena cava, and then, through the pulmonary arteries reach the lungs causing lung metastases.
- **Emboli derived from tumors of** lungs (**whether primary or metastatic**) are carried through pulmonary veins to left side of heart and systemic arterial circulation causing metastases in different organs as liver, bones, brain ... etc.
- **Emboli derived from tumors of** organs drained by the portal vein (**tumors of gastrointestinal tract**) give rise to liver metastases. Further spread from liver gives rise to emboli that reach the hepatic veins and then through inferior vena cava to lungs etc.
- **Tumors arising from** organs near the vertebral column can embolize through the paravertebral plexus, this pathway is probably involved in the frequent vertebral metastases of carcinomas of thyroid and prostate.



Pathology of Organ Metastases:

Gross picture: Metastases appear as scattered round nodules of variable sizes. The most common sites of metastases include the liver, lungs, bones & brain.

Metastases are rare in muscles, spleen, pancreas & intestine.

Microscopic picture: Metastases resemble the primary tumor from which they are derived.

Bone metastases: are commonly osteolytic but in case of cancer prostate it may be osteosclerotic (**new bone formation is stimulated around the metastatic deposit, since malignant cells of prostatic origin secrete phosphatase**).

C. Seeding of Body Cavities (Transcoelomic Spread):

When the serosal covering of an organ is infiltrated by malignant cells of a tumor within this organ, some of these cells may detach and become implanted on the serosal surface on other sites. This may be associated with hemorrhagic effusion.

Transcoelomic spread includes:

1. **Transperitoneal spread from carcinoma of stomach, colon, pancreas etc...** cause metastatic peritoneal/omental nodules accompanied by hemorrhagic ascites. In females, carcinoma of stomach (**or colon**) may be associated with bilateral ovarian metastases, termed "Krukenberg tumors" which were considered to represent transcoelomic spread. They are now believed to be due to retrograde lymphatic or blood spread, since Krukenberg tumors can also occur in case of cancers of breast, urinary bladder & biliary tract.
2. **Transpleural and transpericardial spread from lung or breast cancer** resulting in metastases on the diaphragm accompanied by hemorrhagic pleural or pericardial effusion.
3. **CSF:** Malignant tumors of brain may give rise to tumor cells within the CSF leading to metastases within the lining of the ventricles, base of skull and spinal cord.

D. Other methods of spread:

Transluminal spread: malignant cells detached from transitional carcinoma of the renal pelvis may become implanted in the mucosa of urinary bladder forming secondary deposits.



Figure (5.8) Liver metastases.

Mechanism of Spread of malignant tumors:

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

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

1. **Loss of cellular cohesion**: Normal cells are glued together by molecules called cadherins. Tumor cells lose the normal cadherin expression, allowing them to detach (**loosening up**).
2. **Attachment of tumor cells (through receptors) to matrix components**; mainly to laminin of basement membrane and fibronectin of the interstitial tissue. Attachment to ECM promotes the next steps.
3. **Degradation of the ECM** by proteolytic enzymes secreted by the tumor cells or by stimulated host cells (**fibroblasts & macrophages**). Several enzymes are released as type IV collagenase (**causing lysis of basement membranes of epithelia and of vessels**) and cathepsin D (**causing degradation of interstitium**). Degradation of ECM is very important for the tumor cells to create passage ways for their migration.
4. **Migration (mobility) of tumor cells (by pseudopodia)**. This is mediated by tumor-derived cytokines (**mobility factors**) such as “**autocrine mobility factor**”. The process may be helped by acquiring negative charges on surface of tumor cells causing their repulsion and loss of contact inhibition.



b) Vascular Dissemination and Homing of Tumor Cells:

1. Tumor cell mobility allows cells to come in contact with blood vessels.
2. Tumor cells can penetrate lymphatics, capillaries & venules, but rarely arterioles (**thick-walled**).
3. Once the tumor cells cross the vascular basement membranes, they reach circulation as tumor emboli.

Fate of tumor emboli:

- a) Most tumor emboli are destroyed by immune mechanisms.
- b) The surviving tumor cells adhere to platelets. This affords them some protection from antitumor host immune cells.
- c) Finally the surviving tumor cell emboli get impacted in small vessels, where they adhere to the endothelium, cross the basement membrane (**by mechanisms similar to those described above**) & settle in the new site (**homing**). In their new sites, tumor cells proliferate forming metastatic deposits (**metastasis, secondary tumors**).

Some tumors show **organ tropism**. For example, prostatic carcinoma preferentially spreads to bone, bronchogenic carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver and bones. Such organ tropism may be related to expression of adhesion molecules

whose ligands are expressed by endothelial cells and the metastatic site or chemokine receptors on tumor cell surface.

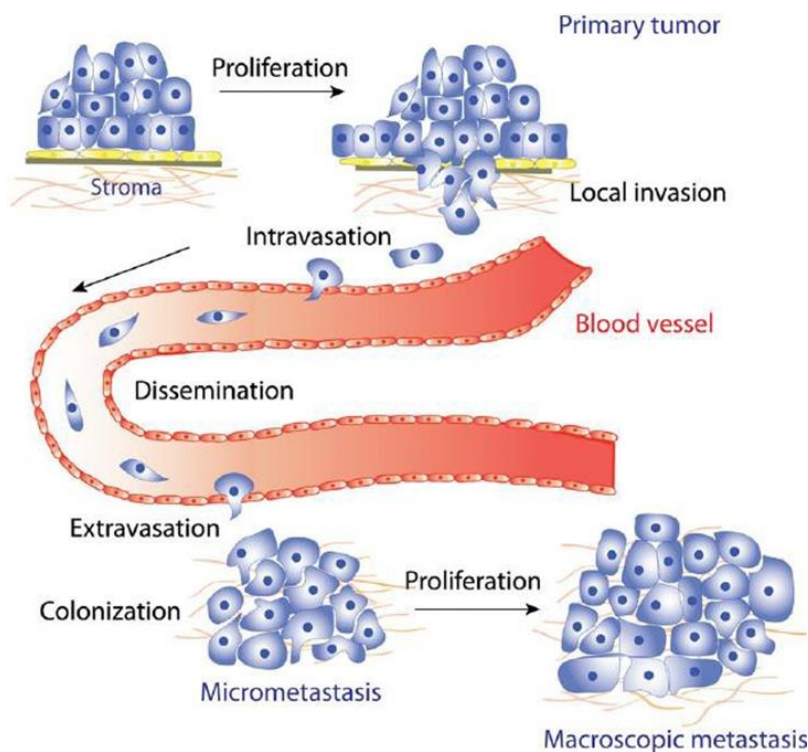


Figure (5.9) Vascular dissemination of malignant tumors.



Intermediate Tumors (Locally Malignant Tumors)

Some malignant tumors are locally invasive and destructive but rarely give rise to metastases (previously termed locally malignant tumors). Such tumors usually grow slowly, can recur after surgical excision, but have a better prognosis than malignant tumors that metastasize.

Examples:

1. Basal cell carcinoma of the skin.
2. Giant cell tumor of bone (osteoclastoma).
3. Adamantinoma.
4. Some neuroendocrine tumors as carcinoid tumor.
5. Chordoma
6. Some tumors of CNS as craniopharyngioma.

Histogenetic Classification of Tumors and their Nomenclature

The major categories are:

- A. Tumors arising from epithelial cells
- B. Tumors arising from mesenchyme
- C. Tumors arising from lymphoid and hematopoietic organs
- D. Miscellaneous tumors

Table (5.3) Histological Classification of Tumors

Tissue of Origin	Benign	Malignant
A. Epithelium		
1. Surface epithelium.		
a. Stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
b. Transitional	Transitional cell papilloma	Transitional cell carcinoma
c. Ducts of glands	Duct papilloma	Duct carcinoma
2. Glandular epithelium		
Endocrine & Exocrine glands	Adenoma	Adenocarcinoma
Mucosa of GIT	Adenomatous polyp	Adenocarcinoma
B. MESENCHYME		
1. Connective tissue		
a. Fibrous	Fibroma	Fibrosarcoma
b. Adipose	Lipoma	Liposarcoma
a. Primitive mesenchyme	Myxoma	



b. Bone	Osteoma &osteoblastoma	Osteosarcoma.
c. Cartilage	Chondroma, osteochondroma	Chondrosarcoma
2. Smooth muscle 3. Striated muscle 4. Endothelium 5. Mesothelium 6. Synovium	Leiomyoma Rhabdomyoma Angioma Rare	Leiomyosarcoma Rhabdomyosarcoma Angiosarcoma Mesothelioma Synovial sarcoma
C. LYMPHOID & HEMOPOEITIC	Lymphoma & leukemia	
D. OTHER TUMORS		
1. Pigmented cells	Nevus (benign melanoma)	Malignant melanoma
2. Trophoblast	Vesicular mole	Choriocarcinoma
3. Totipotent cells	Teratoma, mature (benign)	Teratoma, immalure (malignant)
4. Embryonic cells		Embryonic tumors
5. Schwann cells	Schwannoma	Malignant peripheral sheath tumor

A. Tumors arising from Epithelial cells:

1- Benign epithelial tumors:

Benign epithelial tumors comprise papilloma and adenoma.

a. Papilloma:

Definition: A papilloma is a benign surface epithelial tumor that produces microscopic or macroscopic finger-like fronds.

Microscopic Picture:

- They have a branching fibrovascular core covered by proliferated epithelium.
- Papillomas are rarely endophytic pushing the basement membrane and grow inwards, compressing the subepithelial tissues without invasion, thus called inverted papilloma e.g. inverted papillomas of urinary bladder & nose.

Papillomas are classified according to type of epithelium into:

i. Squamous Cell Papilloma:

Definition & origin: A benign tumor of stratified squamous epithelium.

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

Gross Picture: A small sessile or pedunculated projection. With progressive tumor growth, its surface becomes thrown into branching folds → complex papillary pattern.



Microscopic Picture: Connective tissue cores covered by thick proliferated stratified squamous epithelium exhibiting acanthosis (**increased prickle cell layers**) and hyperkeratosis.

Complications: May rarely change into squamous cell carcinoma.

ii. Transitional Cell Papilloma (Villous Papilloma):

Definition & origin: A benign tumor arising from urothelium (**transitional mucosa of urinary tract**). It is strongly pre-malignant. (**see systemic pathology**)

iii. Columnar Cell Papilloma: These are papillomas arising from columnar epithelium e.g. duct papilloma arising from the epithelium of major ducts, e.g. of breast or pancreas (**systemic pathology**)

b. Adenoma:

Definition and origin: A benign tumor arising from glandular epithelium (**acini and /or small ducts**).

Sites:

- i- **Exocrine or endocrine glands** (**breast, ovary, salivary glands, pancreas, thyroid, pituitary, adrenal glands... etc**)
- ii- **Mucosal glands:** e.g. GIT & endometrium (**mucosal adenoma, adenomatous polyp**). (**see below**)

i- Adenomas of Endocrine or Exocrine Glands:

Gross Picture: In solid organs, an adenoma appears as a capsulated globular or ovoid mass. Cut section may be solid, cystic or cystic with small projecting papillae.

Microscopic Picture: **Several Patterns:**

- **Simple adenoma (tubular adenoma):** Consists of proliferated glands lined by cuboidal or columnar epithelium, separated by fibrovascular stroma. **Example:** pancreatic adenoma.
- **Fibroadenoma:** Consists of glandular & wide stromal proliferations. Breast is the main site.
- **Cystadenoma:** In some types of adenoma, secretions are retained leading to cystic dilatation of the proliferated acini. **Example:** ovarian cystadenoma.
- **Papillary Cystadenoma:** It is a cystadenoma in which the epithelial lining of the cyst proliferates forming papillae. **Example:** papillary cystadenoma of the ovary.



Complications:

1. Adenoma of endocrine glands may function e.g. thyroid adenoma may cause thyrotoxicosis.
2. Malignant change (**adenocarcinoma**).

ii. Adenomas of Mucosal Glands:

Gross Picture: Adenomas of mucosal glands such as the colon may project on the surface of mucosa into the colonic lumen and is called a polyp. A polyp may be sessile or pedunculated.

Microscopic Picture: It is covered by columnar epithelium and the core contains proliferated glands, so it is called adenomatous polyp. Some adenomas of the colon may acquire a papillary architecture and are called villous adenomas.

2- Malignant Epithelial Tumors:

Malignant epithelial tumors are called carcinomas. **These comprise:** carcinomas of surface epithelium and carcinomas of glandular epithelium.

- **Carcinomas of** surface epithelium include squamous cell carcinoma, basal cell carcinoma and transitional cell carcinoma.
- **Carcinomas of** glandular epithelium are called adenocarcinoma

General features of carcinomas

1. If arising from surface epithelium they take one of the following patterns:
 - Fungating polypoid mass
 - **Ulcerative pattern:** an irregular ulcer with raised everted edges, rough necrotic floor and indurated base.
 - Infiltrative pattern which can cause annular stricture in hollow organs
2. In solid organs, carcinoma presents as an irregular infiltrating, hard mass. (**carcinos** = crab in Greek)
3. Carcinomas spread locally, by lymphatics and late by blood.



Examples of carcinoma

• Squamous Cell Carcinoma:

Definition & Origin: A malignant tumor of stratified squamous epithelium.

Sites:

- a. Skin.
- b. Squamous mucous membranes as lip, tongue, mouth, pharynx, larynx, oesophagus, cervix, vagina & anal canal.
- c. Other mucous membranes on top of squamous metaplasia e.g. squamous cell carcinoma of urinary bladder on top of squamous metaplasia due to bilharziasis.

Predisposing factors:

1. Prolonged exposure of skin to the sun
2. Chemical carcinogens as arsenic and tar
3. Squamous metaplasia & leukoplakia.

Gross Picture: (See general characteristics of carcinoma)

Microscopic Picture:

- The dermis or submucosa is infiltrated by malignant epithelial cells which in well differentiated neoplasms form "cell nests".
- These cell nests consist of malignant cells that replicate the organization of the normal epidermis i.e. the periphery of these nests shows basal cell differentiation, followed by prickle cells then granular cells with the center of the nests showing whorly keratin (keratin pearls).
- In less differentiated neoplasms, fewer cell nests are formed & in anaplastic carcinoma, no cell nests may be detected.

Broder's Grading of Squamous Cell Carcinoma:

Grade I: 75-100% of the tumor consists of cell nests.

Grade II: 50-75% cell nests.

Grade III: 25-50% cell nests.

Grade IV: 0-25% cell nests.

Spread: Local, lymphatic and late by blood.

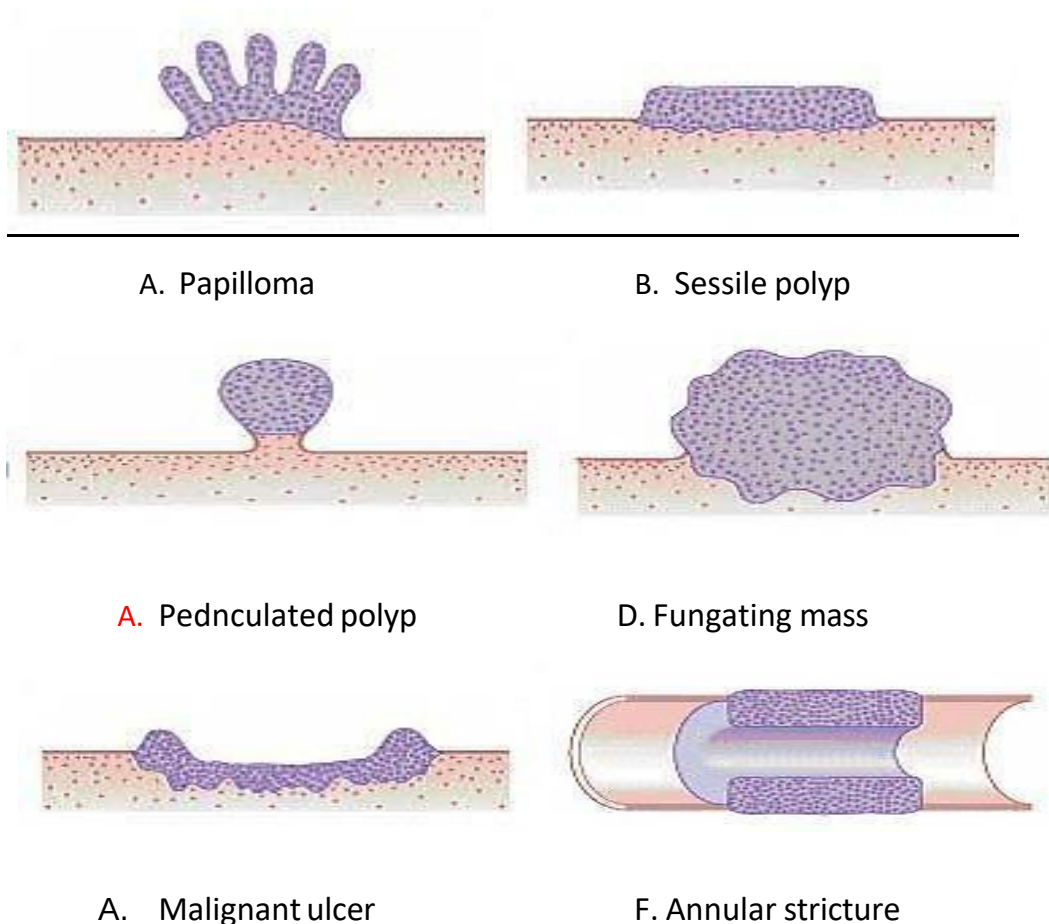


Figure (5.10) Gross appearance of surface epithelial tumors: A,B,C benign; D,E,F:malignant

• Adenocarcinoma:

Definition and origin: These are malignant tumors arising from glandular epithelium either of:

1. The mucosal surfaces (as gastrointestinal mucosa, endometrium or endocervix).
2. Glandular organs (endocrine or exocrine glands as prostate, ovary, mammary gland, salivary glands... etc).

Gross Picture: (see general characteristics of carcinoma) Spread: Local, lymphatic and late by blood

Microscopic Types:

1. Well differentiated Adenocarcinoma:

- In well differentiated adenocarcinoma, the malignant cells show acinar arrangement. These malignant acini differ from the normal acini in several respects:
 - They are irregular with no definite basement membranes.
 - Their lumens are irregular.
 - The cells show malignant features (describe).



- They exist in abnormal sites (as **submucosa, muscularis or serosa**) due to infiltration.
- They may be cystically dilated (**cystadenocarcinoma**) if the malignant cell secretions are retained. Some malignant cells in these tumors may show papillary proliferations (**papillary adenocarcinoma or papillary cystadenocarcinoma**).
- Less differentiated adenocarcinomas show less degrees of acinar differentiation.

2. Mucin secreting carcinomas: Two types:

- Mucinous adenocarcinoma (muroid or colloid Carcinoma)**: This is an adenocarcinoma with abundant extracellular mucin secretion
- Signet ring cell carcinoma**: The malignant cells show intracytoplasmic mucin that pushes the nuclei eccentrically. No acinar differentiation.

3. Carcinoma simplex (undifferentiated carcinoma, spheroidal cell carcinoma). These are malignant tumors of glandular origin that neither exhibit acinar differentiation nor secrete mucin. Malignant cells form solid groups

Sites:

- Most common in breast
- Less common in other glandular sites mainly GIT.

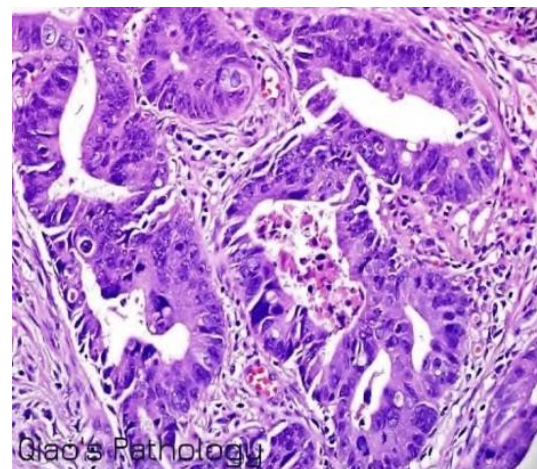
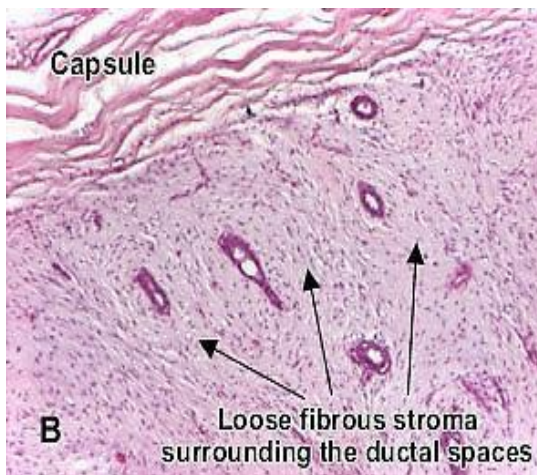


Figure (5.11) Left: Fibroadenoma showing regular glands separated by stroma, and surrounded by CT capsule. Right: Adenocarcinoma showing irregular glands lined by multiple layers of pleomorphic cells with hyperchromatic nuclei

**B. Mesenchymal Tumors (connective tissue and other mesenchymal tissue):**

These are either benign or malignant.

1. Benign Mesenchymal Tumors:

These are named according to the cell or tissue of origin with a suffix “oma” e.g.

- **Fibroma:** benign tumor of fibroblasts.
- **Lipoma:** benign tumor from fat cells (**lipocytes**) of adipose tissue

2. Malignant Mesenchymal Tumors:

These are called sarcomas.

General features of sarcoma

- Sarcomas are more common in adolescents and young adults.
- They form large bulky fleshy masses (**sarc= Flesh in Greek**).
- They are more expansile than carcinomas, with infiltration at the edges.
- They spread early by blood. (**see table 5.4**)

C. Tumors arising from Lymphoid and Hemopoietic Organs:

- **Tumors arising from** lymphoid tissue are called lymphoma.
- **Tumors arising from** leukocyte forming cells in the bone marrow are called leukemia.



Table (5.4) Major Differences between Carcinoma and Sarcoma.

Carcinoma	Sarcoma
Definition: Malignant tumor of epithelium Most common form of malignancy. Age: Usually (but not always) above age of 40 years. Growth rate: Rapid Mode of growth: Infiltrative & expansile. Gross Features: 1. Size is usually less bulky than sarcoma. 2. Consistency: Usually hard. 3. Color is usually grayish. 4. Appearance: Irregular infiltrating growth. Microscopic Features: 1. Cellular anaplasia: Usually less marked than sarcoma. 2. Cell cohesion: Neoplastic cells exhibit variable grades of cohesion. This is however poor in anaplastic carcinomas. Connective tissue surrounds groups of cells and not individual cells. 3. Blood vessels are less and better formed than in sarcoma. 4. Hemorrhage, necrosis and secondary changes are usually less profound than in sarcoma. Distant spread 1) Usually slower than sarcoma 2) Occurs early by lymphatics then later by blood.	Definition: Malignant tumor of mesenchyme. Much less common than carcinoma. Age: Usually (but not always below age of 20 years). Growth rate: Faster than carcinoma. Mode of growth: as carcinoma, but its rapid rate of growth gives it a more expansile appearance. Gross Features: 1. Most sarcomas form bulky masses. 2. Consistency: Usually soft and fleshy. 3. Color is tinged pink due to richer vascularity. 4. Large, bulky, expansile Microscopic Features: 1. Cellular anaplasia is generally greater than carcinoma. 2. Cell cohesion is absent and the tumor cells occur singly. CT and extracellular matrix surrounds individual cells. 3. Blood vessels are more numerous and thin-walled. 4. Hemorrhage, necrosis and secondary changes as hyaline and myxomatous changes are common. Distant spread 1) Usually faster than carcinoma 2) Occurs early by blood & rarely (10%) by lymphatics.



D. Other Tumors:

I. Teratomas:

Definition, origin & sites:

Teratomas are germ cell tumors. They likely arise from neoplastic transformation of totipotent germ cells (**an ovum after the first meiotic division**) capable of differentiating into the three germ cell layers. They may exist in post-natal life in some sites as ovary, testis, sacrococcygeal region & mediastinum. The structure of teratoma is foreign to the site from which it arises.

Age: Any age; children, young adults or elderly.

Types:

A. Mature teratoma (**Benign Teratoma**):

Grossly: Mature teratomas are commonly cystic (**DERMOID CYST**) Commonest in ovary, usually large. It consists of a dermoid ridge which is a solid part covered by skin, and contains different tissue and structures (**e.g. teeth**). The rest of the tumor is cystic and contains sebaceous material and tufts of hair.

Microscopically: These tumors consist of a haphazard mixture of mature ectodermal structures such as skin, neuroglial cells & teeth, mature endodermal structures such as thyroid tissue & other types of glandular epithelium & mature mesodermal structures such as cartilage, bone, adipose tissue, fibrous tissue, muscle ... etc. It maybe cystic & consist predominantly of skin & hairs (**dermoid cyst**).

Malignant transformation occurs in 1 % of mature teratomas (**any type of malignancy, but squamous cell carcinoma is the most common**).

B. Monodermal teratomas (**Specialized Teratomas**):

Monodermal or specialized teratomas differentiate along the line of a single abnormal tissue.

Example:

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



C. Immature teratoma (Malignant Teratoma):

- They are rare tumors composed of embryonic (**rather than adult**) elements resembling immature fetal tissues (**typically primitive neuroectodermal**).
- These occur chiefly in adolescents and young women.
- Grading is performed based on the amount of immature neuroepithelium.
- Although they grow rapidly and frequently penetrate the capsule, low- grade tumors have an excellent prognosis, and even high-grade malignancies can respond well to chemotherapy.



Figure (5.12) Ovarian teratoma (Dermoid cyst) showing hair and teeth.

II. EMBRYONIC TUMORS:

Definition, origin and age:

Embryonic tumors are malignant tumors derived from embryonic cell remnants in infants and young children. Occasionally, the cells may show some differentiation towards the tissues which normally arise from their related cell type.

Structure: They consist of primitive embryonic (**undifferentiated**) malignant small round cells.

Examples:

1. Neuroblastoma of adrenal medulla & sympathetic ganglia.
2. Retinoblastoma of eye.
3. Nephroblastoma of kidney.
4. Hepatoblastoma of liver.
5. Medulloblastoma of brain.



TUMOR-LIKE LESIONS

HAMARTOMA

This is a tumor-like developmental malformation formed of noncapsulated mature tissues of the affected organ (**not foreign to them**), but arranged haphazardly. It **usually stops** growing after puberty. Some hamartomas are precancerous.

Examples of hamartomas:

- 1- Lung hamartoma (a mixture of cartilage, smooth muscle and bronchial mucosal tissue).
- 2- Kidney hamartoma.
- 3- Angiomas are now considered as hamartomas rather than true neoplasms.
- 4- Pigmented nevi.
- 5- Exostosis (osteochondromas) & neurofibromatosis are regarded as hamartomatous malformations.

CHORISTOMA

Choristoma is a congenital anomaly consisting of a heterotropic rest of cells. For example: a small nodule of well-developed and normally organized pancreatic tissue may be found in the mucosa of the stomach, duodenum or small intestine.

EPIDEMIOLOGY OF CANCER

Study of cancer patterns in population:

The incidence of cancer varies with geography, age, race, and genetic background.

1. Cancer incidence and mortality by site and sex:

In men, cancers of prostate, lung and colon are leading causes of cancer death. In women, cancers of breast, lung and colon are leading causes of cancer death.



2. Geographic and environmental Factors:

Environmental factors significantly affect occurrence of specific forms of cancer in different parts of the world.

Examples of environmental factors:

- Cigarette smoking causes cancer lung.
- Prolonged exposure to sun (**UV rays**) leads to skin cancer as in farmers.
- Occupational exposure to carcinogens as asbestos, arsenic, nickel,...
- Chronic alcohol consumption leads to alcoholic cirrhosis and hepatocellular carcinoma.

3. Age:

In general the frequency of cancer increases with age this may be explained by:

- Accumulation of successive mutations with prolonged exposure to carcinogens.
- The decline in immune competence with aging.

Most carcinomas occur after the age of 55 years. Prostatic cancer is almost present in every male above the age of 100 years.

Certain malignant tumors are common in infants and children, e.g. acute leukemia, retinoblastoma, neuroblastoma and Wilm's tumor.

4. Genetic Predisposition to cancer: divided into 3 categories:

A. Autosomal dominant inherited cancer syndromes:

Inheritance of a single mutant gene, usually a point mutation in one allele of cancer suppressor gene.

Transmission: Autosomal dominant.

Only specific sites or tissues are affected.

Examples:

- Retinoblastoma: 40% are familial; one defective allele of RB gene is inherited in germ line, Retinoblastoma develops when the normal RB allele is mutated in retinoblasts



(**inevitable somatic mutation in some retinoblasts**). Persons with inherited RB gene mutation also show increased risk of developing other certain malignancies.

- Those born with one mutant allele of adenomatous polyposis coli (**APC**) tumor suppressor gene develop innumerable adenomatous polyps in the colon (familial adenomatous polypi). When the other allele is lost by somatic mutation, one or more polyps develop cancer (**100% of cases will develop colon carcinoma by the age of 50**).

B. Defective DNA repair syndromes: A group of cancer predisposing conditions characterized by defects in DNA repair and resultant genomic instability → increased predisposition to environmental carcinogens. Examples: xeroderma pigmentosum. Also BRCA1 and BRCA2 account for 80% of cases of familial breast cancer.

C. Familial cancers: Familial clustering of specific forms of cancer, but role of inherited predisposition may not be clear in an individual case. Examples: breast cancer, ovarian cancer, colon cancer other than familial adenomatous polypi.

5. Non hereditary predisposing conditions (Acquired preneoplastic disorders): Some chronic diseases may lead to precancerous lesions. **Examples include:**

A. Chronic inflammatory diseases as:

- Bilharziasis of the urinary bladder.
- Ulcerative colitis.
- Atrophic gastritis
- Radiodermatitis
- Tertiary syphilis of tongue
- Lupus vulgaris (**cutaneous T.B**)

B. Gall stones and urinary stones

C. Hyperplastic, metaplastic and dysplastic lesions as leukoplakia, endometrial hyperplasia, mammary hyperplasia and cervical dysplasia.

D. Some Benign Tumors e.g. villous bladder papilloma & GIT adenomatous polyps.

E. Others as liver cirrhosis, varicose ulcers, Paget's disease of bone, undescended testis.



MOLECULAR BASIS OF CANCER

- Cancer is a genetic disorder caused by DNA mutations that are mostly acquired spontaneously or induced by environmental insults (**initiating mutation**).
- These genetic mutations are passed to daughter cells upon cell division.
- Most tumors are monoclonal.
- It is thought that these mutations provide the cells with survival advantages over the neighboring cells and allow them to dominate the population (**Darwinian selection**).

Carcinogenesis (tumorigenesis):

Tumor results from the accumulation of complementary mutations in a stepwise fashion over time (**multistep process**). Once established, tumors evolve genetically during their outgrowth and progress under the pressure of Darwinian selection (**survival of the fittest**).

Carcinogenesis is a multistep process:

- 1- **Initiation:** Induction of certain irreversible changes in the genome of the cells. These initiated cells are not transformed cells and do not have growth autonomy. They just have altered DNA (**gene mutation**) and are called latent tumor cells.
- 2- **Promotion:** Promoters enhance the proliferation of initiated cells, an effect that may contribute to the acquisition of additional mutation.
- 3- **Neoplastic transformation:** Abnormal differentiation occurs and the cells undergo continuous purposeless uncontrolled irreversible proliferation.

During this process, there is competition among tumor cells for access nutrients, and subclones with the capacity to overgrow their predecessors tend to “**win**” this Darwinian contest and dominate the tumor mass, only to be replaced by other, still malignant subclones. This pernicious tendency of tumors to become more aggressive over time is referred to as tumor progression. As a result, even though malignant tumors are clonal in origin, by the time they become clinically evident their constituent cells are often extremely heterogeneous genetically.

The principal targets of cancer-causing mutations are:

- The growth promoting proto-oncogenes.
- The growth-inhibiting tumor suppressor genes.
- Genes that regulate programmed cell death (**apoptosis**).

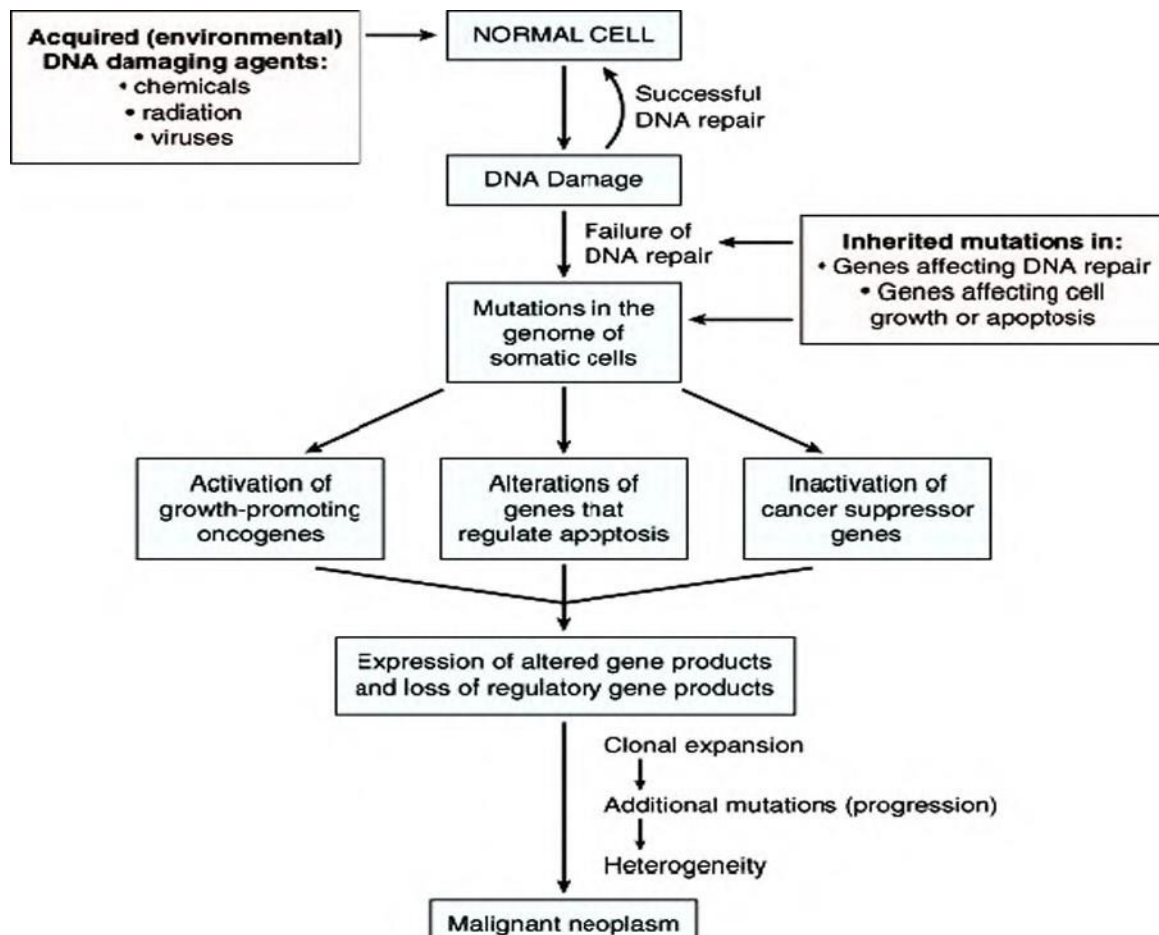


Figure (5.12) Carcinogenesis process.

A- Oncogenes:

Proto-oncogenes: These are normal cellular genes that encode proteins that drive cell proliferation.

The transformation of proto-oncogenes into cancer-causing oncogenes occurs by one of three mechanisms:

- Point mutations, possibly due to exposure to cancer-causing chemicals.
- Chromosomal translocations, where during cell divisions, a part of a certain chromosome (**with its genes**) is relocated into another chromosome leading to gene fusion or change in the sequence of genes, finally resulting in activation and transformation of proto-oncogenes.
- Gene amplification: this is reduplication of proto-oncogenes.

Oncogenes encode synthesis of proteins called oncoproteins. These oncoproteins are produced in transformed (**neoplastic**) cells and cause cell to divide regardless of the normal control mechanisms for cell division.



The numerous oncogenes fall into at least four main categories:

- **Genes Which** produce growth factors
- **Genes which** produce the growth factor receptors e.g. erbB2 encodes a growth factor receptor, HER2. The erbB2 gene is amplified in certain breast carcinomas, leading to overexpression of the HER2 receptor. A high level of HER2 protein in breast cancer is an indication of poor prognosis and generally respond to target therapy with anti-HER2 antibodies (**Herceptin**).
- **Genes which** encode signal transduction i.e proteins which transmit the growth signal to the nucleus. E.g. Mutations of ras gene is common in colon and thyroid cancers.
- **Genes which** encode DNA transcription e.g. MYC gene amplification in breast, colon and lung carcinoma. Also in neuroblastoma

B- Tumor Suppressor Genes:

Tumor suppressor genes are usefully placed into two general groups, “governors” and “guardians.”

- “**Governors**” are classic tumor suppressor genes, whose products normally stop cell proliferation such as retinoblastoma gene (**RB**). Mutation of this gene leads to uncontrolled cellular proliferation.
- “**Guardian**” genes are responsible for sensing genomic damage. The response of these genes is to arrest proliferation to allow for DNA repair or, if the damage is too great to be repaired, the induction of apoptosis.

TP53, the so-called “**guardian of the genome**,” is a prototypic tumor suppressor gene of this type. Mutation of TP53 does not directly transform cells, as loss of guardian function has no direct effect on cellular proliferation or apoptosis.

Instead, loss of the guardian genes permits and accelerates the acquisition of mutations in oncogenes and tumor suppressor genes that can lead to the development of cancer.

C- Genes that control apoptosis

- **Cell number depends on** cell proliferation as well as rate of cell loss.
- **Apoptosis, or programmed cell death is** controlled by a number of genes.
- **Aberrant expression of these genes is** a cause of some cancers e.g. Bcl 2 (**anti apoptotic**) gene overexpression in follicular lymphoma



Telomerases and cancer

- **Most normal human cells have a** capacity of 60 to 70 doublings. After this the cells lose the capacity to divide and enter a non-replicative senescence. **This phenomenon is** related to progressive shortening of telomeres at the ends of chromosomes. With each cell division, telomeres are shortened, and beyond a certain point, loss of telomeres leads to massive chromosomal abnormalities and death.
- **Tumor cells must develop ways to** avoid cellular senescence; this is acquired by activation of the enzyme telomerase, which can maintain normal telomere length. **In 85% to 95% of cancers,** there is up-regulation of the enzyme telomerase. Telomerase is active in normal stem cells but is absent from most somatic cells.

CARCINOGENIC AGENTS

Types of Carcinogens:

1) Chemical Carcinogens:

Most chemical carcinogens are mutagenic causing malignant transformation from mutations that affect proto-oncogene and tumor suppressor genes.

Examples:

1. Aromatic hydrocarbons as 3,4 benzpyrene (**exist in cigarette smoke**) cause cancer lung.
2. Aromatic amines as B naphthylamine: cause cancer bladder.
3. **Asbestos:** cause mesothelioma.
4. Aflatoxins (**produced by Aspergillus flavus fungus**) cause hepatic carcinoma.
5. Vinyl chloride cause hepatic angiosarcoma.
6. Arsenic causes skin cancer.

2) Physical carcinogens:

1. **Prolonged exposure to** ultraviolet rays (**sun**) can cause skin malignancy (**basal cell carcinoma, Squamous cell carcinoma, and melanoma**).
2. **Ionizing radiation:** Ionizing radiation causes chromosome breakage, translocations, and less frequently point mutations, leading to genetic damage and carcinogenesis e.g. leukemia, osteosarcoma, skin malignancy and lung cancer.



3) Viruses:

Viruses may lead to development of cancer by:

1. Integrating viral oncogenes into host DNA thus altering DNA.
2. Producing proteins that inactivate products made by tumor suppressor genes.

Some viruses that have been implicated in causing neoplasms include:

1. **Epstein-Barr virus e.g.**
 - a. Burkitt's lymphoma
 - b. Nasopharyngeal carcinoma
 - c. other B cell lymphomas and some cases of Hodgkin's disease
 2. **Hepatitis B virus causes** hepatocellular carcinoma
 3. **Human papilloma virus causes** cervical carcinoma and some forms of carcinoma of skin cancers
 4. **HTLV-1 (Human T lymphotropic virus I) causes** T cell leukaemia/lymphoma.
- 4) **Hormones:** They cannot cause tumor initiation but may act as promoters. Examples:
1. **Estrogen:** High levels of oestrogen (**as in anovulation in adults & in cases of granulosa cell tumor of the ovary**) can promote endometrial & mammary carcinoma.
 2. **Diethyl stilbesterol (DES):** Administration of DES in a pregnant lady can promote vaginal adenocarcinoma (**clear cell type**) in her baby (**if female**) later on in life.
 3. **Androgens:** Androgen in high levels can promote prostatic carcinoma.
 4. **Role of contraceptive pills in cancer breast** is questionable. However they can lead to benign tumors of liver (**hepatic adenoma**).

CLINICAL ASPECTS OF NEOPLASIA

Benign tumors are not dangerous unless:

1. They arise in vital organs as brain e.g. a small pituitary adenoma can destroy the whole pituitary gland.
2. They arise in hollow organs (**as intestine**) causing obstruction.



3. They produce hormones as in tumors of endocrine glands e.g. adenomas from beta cells of pancreas can cause hyperinsulinism, sometimes fatal.
4. Some benign tumors may change malignant.

Malignant tumors are serious & cause death.

Causes of Death include:

1. Local organ destruction by direct spread.
2. Distant organ destruction by metastases.
3. Destruction of vital centers (**brain tumors**).
4. Obstruction of the lumen of hollow organs e.g. intestinal tumors.
5. Organ failure e.g.
 - Renal failure due to urinary obstruction (**or bilateral renal tumors**).
 - Liver failure & jaundice in case of primary or metastatic liver tumors.
6. **Malnutrition due to:**
 - Loss of appetite.
 - Interference with food intake (**in cancer of GIT**).
 - Chronic toxemia due to secondary bacterial infection.
 - **Anaemia is common due to :**
 - a. Recurrent hemorrhages from the tumor.
 - b. Bone marrow destruction by metastases.
 - c. High tumor cell metabolism may lead to folic acid deficiency. Iron deficiency may also occur.
 - d. Autoimmune hemolysis in some cases.
 - **Cachexia:**
 - a) This is marked decrease of body fat and lean body mass, weakness, anorexia and anemia.
 - b) There is some correlation between the size and extent of tumor spread and cachexia.
 - c) Cachexia does not result due to nutritional demands of the tumor.
 - d) Evidence indicates that cachexia result from the action of soluble factors such as cytokines produced by the tumor and the host (**TNF secreted by macrophages or the tumor**).



7. Some malignant tumors may secrete hormones:

- Functioning endocrine tumor.
- Para-neoplastic syndromes occur in 10% of cases. They are caused by abnormal products of the tumor e.g. lung carcinoma may produce ACTH causing Cushing's syndrome.

8. Hypercoagulability (migratory thrombophlebitis, disseminated intravascular coagulation, nonbacterial thrombotic endocarditis)

GRADING AND STAGING OF TUMORS

Grading:

- **Grading of** a cancer is based on the degree of differentiation of the tumor cells and, in some cancers, the number of mitoses or architectural features.
- **Grading schemes differ for** each type of malignancy, and generally range from two categories (**low grade and high grade**) to four categories.
- **Although histologic grading is** useful, the correlation between histologic appearance and biologic behavior is less than perfect.

Staging:

- **The staging of** solid cancers, determined by imaging or surgical exploration, is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases.
- **The major staging system currently in** use is the American Joint Committee on Cancer Staging.
- **This system uses** a classification called the TNM system—T for primary tumor, N for regional lymph node involvement, and M for metastases.
- **TNM staging varies for** specific forms of cancer, but there are general principles:
 - **The primary lesion is** characterized as T1 to T4 based on increasing size. T0 is used to indicate an in situ lesion.
 - **N0 would mean no** nodal involvement, whereas N1 to N3 would denote involvement of an increasing number and range of nodes.



- **M0 signifies no** distant metastases, whereas M1 or sometimes M2 indicates the presence of metastases and some judgment as to their number.

Staging is of greater value than grading, e.g. as regards choice of treatment and prognosis.

LABORATORY DIAGNOSIS OF CANCER

Morphologic Methods:

Several histologic and cytologic sampling of tumors are available e.g. Excision biopsy, fine needle aspiration and cytologic smears.

Immunohistochemistry:

Immunohistochemistry is a powerful tool in determining the histogenesis of poorly differentiated tumors.

1- Identification of different tumor types is by using antibodies against different specific proteins expressed by tumor cells e.g.:

- Leucocyte common antigen (**LCA**) is detected in lymphomas.
- Cytokeratins (**CK**) are present in carcinomas.
- Vimentin is detected in sarcomas,
- S100 protein is detected in tumors of schwann cells and malignant melanoma.

2- Immunohistochemistry may be applied for identification of prognostic indicators e.g.:

- Ki 67 is a proliferation marker. Highly proliferative tumors are more aggressive.
- Detection of estrogen & progesterone receptor expression in cancer breast.
- Detection of HER 2 (**growth factor receptor**) expression in cancer breast. Tumors with increased Her 2 receptors are more aggressive and are treated with anti Her 2 antibodies (**Herceptin**).

Tumor Markers:

Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood cannot be used for definitive diagnosis of cancer; **however**, they contribute to the detection of cancer and in some instances are useful in determining the effectiveness of therapy or the appearance of a recurrence.



Table (5.5) The most common tumor markers used in diagnosis and follow up.

Tumor marker	Tumor type
Hormones	
Human Chorionic Gonadotrophin	Trophoblastic tumors
Calcitonin	Medullary carcinoma, thyroid
Oncofetal antigens	
Alpha feto-protein	Hepatocellular carcinoma
Carcino-embryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
Antigens	
Prostatic specific antigens	Cancer prostate
Immunoglobulins	Multiple myeloma
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer

Formative Assessment

MCQ

- Which of the following is characteristic of hypertrophy
 - Disordered atypical non-neoplastic cellular proliferation.
 - Increase in the size of the cells.
 - Uncontrolled autonomous cell growth.
 - Increase in the number of the cells
- After leg immobilization in plaster due to fracture, decrease in size of calf muscle is due to
 - Atrophy.
 - Aplasia.
 - Hypoplasia.
 - Dystrophy.



3) The following is true about adenoma except

- a) Benign mesenchymal tumor.
- b) Are capsulated.
- c) May secrete hormone.
- d) May turn malignant.

4) Serum tumor markers that can be used in diagnosis of neoplasia include all of the following except

- a) PSA.
- b) Alpha feto protein.
- c) Carcinoembryonic antigen.
- d) P53.
- e) CA125.

EMQ

Match each of the following tumors or masses in column A with their corresponding name in column B. Each choice in column B may be used once, more than once or not at all.

- | | |
|--|-----------------|
| 1) Benign tumor of adipose tissue. | a. Choristoma. |
| 2) Tumor of three germ cell layers foreign to the organ in which they arise | b. Embryoma. |
| 3) Non capsulated tissue mass not foreign the organ from to which they arise | c. Lipoma. |
| | d. Rhabdomyoma. |
| | e. Teratoma. |
| | f. Hamartoma. |

SAQ

- 4) List routes of spread of malignant tumors
- 5) Name the 2 classes of tumor suppressor genes, describe how they work and give one example for each



DISORDERS OF BLOOD FLOW

Hyperemia and congestion:

Terms mean **increased blood volume** in tissues.

Hyperemia

Definition:

- It increased **blood flow** to an organ, resulting in increased **blood content**.
- It is due to **active vasodilatation** of its arterioles and capillaries

Types:

- **Physiological:** skeletal muscle during exercise.
- **Pathological:** at sites of inflammation.

Morphology:

The affected tissues appear red (**erythema**) owing to engorgement with **oxygenated blood**.

CONGESTION

Definition:

It is a **passive process** caused by impaired blood outflow from the tissue **resulting in** increased its blood contents.

Types:

Systemic (generalized) congestion	Localized congestion
occurs in heart failure	In occlusion or external pressure on a vein .
Both types may be acute or chronic	



Effects of congestion:

Acute Congestion	Chronic Congestion
The vessels are distended and organs are grossly red in color	Gradual congestion is associated with edema , focal hemorrhages , with RBC breakdown leading to accumulation of hemosiderin-laden macrophages
Usually associated with interstitial edema .	The associated chronic hypoxia may result in ischemic tissue injury and scarring .

Examples of congestion:

Chronic venous congestion of the lung:

Causes:

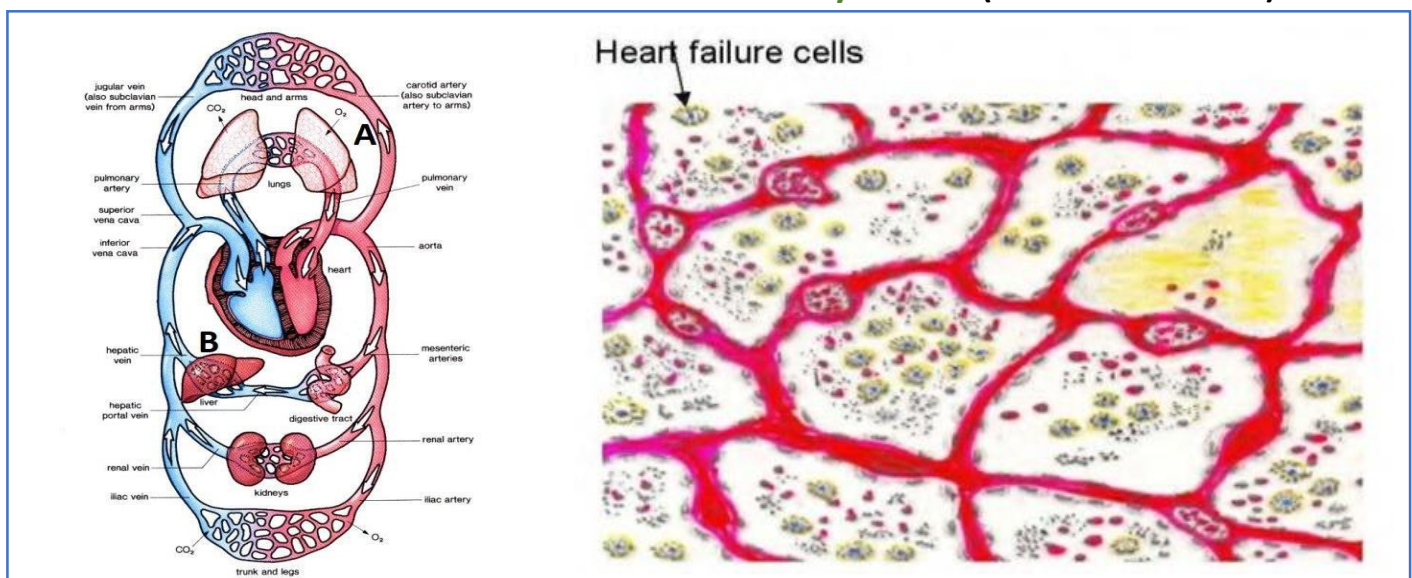
It occurs in **mitral stenosis** or **left sided heart failure**

Gross:

Early the lungs are **dark red**, moist and heavy, later **they appear brown** and indurated

Microscopic:

- Early the **alveolar walls** showed congested capillaries, edema and hemorrhage.
- Intra-alveolar heart failure cells (**macrophages engulfing hemosiderin**) which may **migrate to** the draining lymph nodes.
- **Later** the released hemosiderin are **surrounded by fibrosis** (brown induration).





Chronic venous congestion of the liver:

Causes:

It occurs in chronic generalized **venous congestion**, as heart failure

Gross:

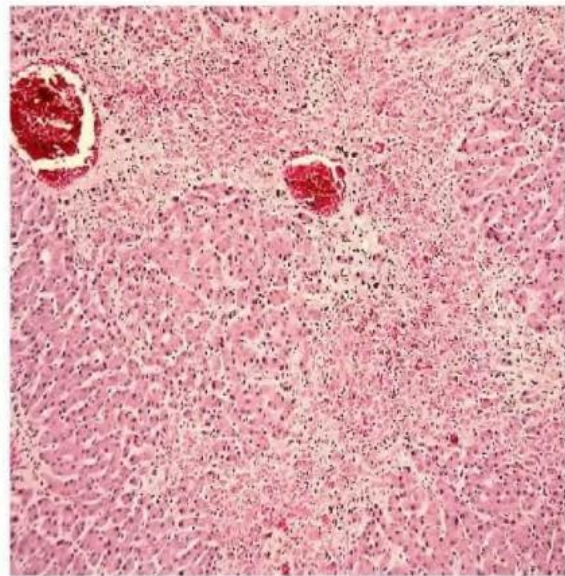
Early the liver is enlarged and heavy, **cut section** showed **dark red** spots of congested centrilobular areas against a **yellow background** of fatty change (**Nutmeg appearance**)

Later, the liver become **shrunk** with **irregular surface** due to fibrosis.

Microscopic:

- Early congestion of the central veins and central parts of the sinusoids.
- There is pressure atrophy and death of the **centrilobular** hepatocytes due to severe **hypoxia**, and steatosis of the **peripheral** hepatocytes due to less hypoxia.
- Later, fibrosis around the **central** areas occurs.

The following pictures show Nutmeg liver: **Left** gross and **Right** microscopic



Spleen Congestion:

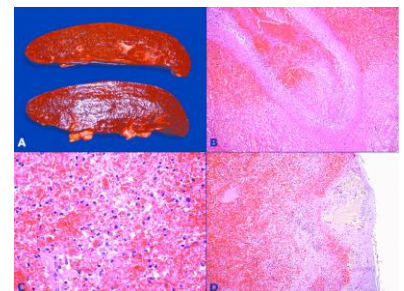
Gross

Enlarged heavy spleen with **dark** congested cut section

Microscopic

Early congested sinusoids and atrophic lymph follicles.

Later hemosiderin with surrounding fibrosis forms **fibrosiderotic nodules**.





Edema

Background

The movement of water & solutes between intravascular & interstitial spaces is balanced **by two opposing forces**:

- 1) **vascular hydrostatic pressure**
- 2) **Plasma colloid osmotic pressure.**

Increased capillary pressure or **diminished** colloid osmotic pressure leads to increased interstitial fluid.

If the **net** movement of water into tissues exceeds lymphatic drainage, **fluid** will accumulate.

Definition:

Pathological accumulation of excess fluids (**transudate or exudate**) in **the interstitial tissue** spaces and **serous sacs**.

Difference between Exudate and transudate:

Exudate	Transudate
High protein content > 3 gm% .	Low protein content < 3 gm% .
High specific gravity > 1015	Low specific gravity < 1015
High fibrinogen content [clots]	No fibrinogen [does not clot].
Rich in inflammatory cells	Low cellularity
Cloudy due to the presence of white cells	Straw colored
May be due either to inflammation or to mild vascular injury	due either to inflammation or to mild vascular injury

NOTES:



Causes of edema:

1-Increased Hydrostatic Pressure:

- a) Impaired venous return, as in congestive heart failure
- b) Venous obstruction or compression, may be due to external pressure
(e.g., thrombus, pregnancy)

2- Reduced Plasma Osmotic Pressure (Hypoproteinemia):

- a) Protein-losing glomerulopathies (nephrotic syndrome).
- b) Liver cirrhosis (ascites).
- c) Malnutrition.

3-Lymphatic Obstruction:

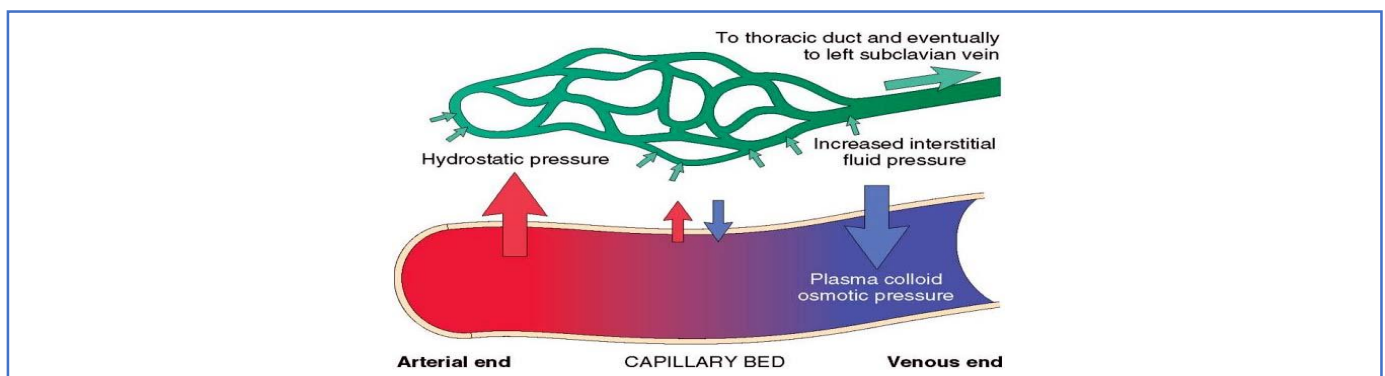
- a) **Congenital:** hypoplasia of lymphatics Milroy disease-
- b) **Inflammatory:** lymphadenitis , filariasis-
- c) **Neoplastic:** Lymphatic permeation by malignant cells-
- d) **Postsurgical:** edema of upper limb due to surgical excision of lymph nodes in radical mastectomy for treatment of cancer breast
- e) **Post irradiation:** due to lymphatic obstruction by fibrosis.

4-Sodium Retention:

- a) Excessive salt intake with renal insufficiency
- b) Renal hypoperfusion.

5-Inflammation

In **acute inflammation**, there is formation of acute inflammatory **exudate**.





Classification of edema:-

1- Generalized edema is usually due to:

Cardiac	Nutritional	Renal
Due to heart failure	Due to hypoproteinaemia	Nephrotic syndrome due to loss of proteins in urine (proteinuria) e.g. in renal amyloidosis
Increase systemic venous congestion.	- Malnutrition - Malabsorption, protein losing enteropathies - Cirrhosis of the liver	Nephritic syndrome: e.g. in some glomerulonephritis due to salt retention

2- Localized edema :

Caused by obstruction of **veins** or **lymphatics** and inflammation

Examples of localized edema:

- **Pulmonary veins in left-sided heart failure.**

Lungs can reach two to three times their normal weight.

Sectioning reveals a frothy, blood-tinged mixture of air, edema fluid, & RBCs.

- **Leg veins:**

Due to thrombosis or pregnancy ("**pressure of the uterus**")

Morphology of edema:

- Edema is easily recognized **grossly**;
- **Microscopically**, it appears as clearing and separation of the extracellular matrix and cell swelling.
- **Subcutaneous edema is often influenced by gravity**

E.g. it appears in the legs when standing and the sacrum when recumbent, a feature termed **dependant edema**.

Finger pressure over markedly edematous subcutaneous tissue displaces the interstitial fluid and leaves a depression, a sign called **pitting edema**.



N.B.

➤ **Non pitting edema occurs in:**

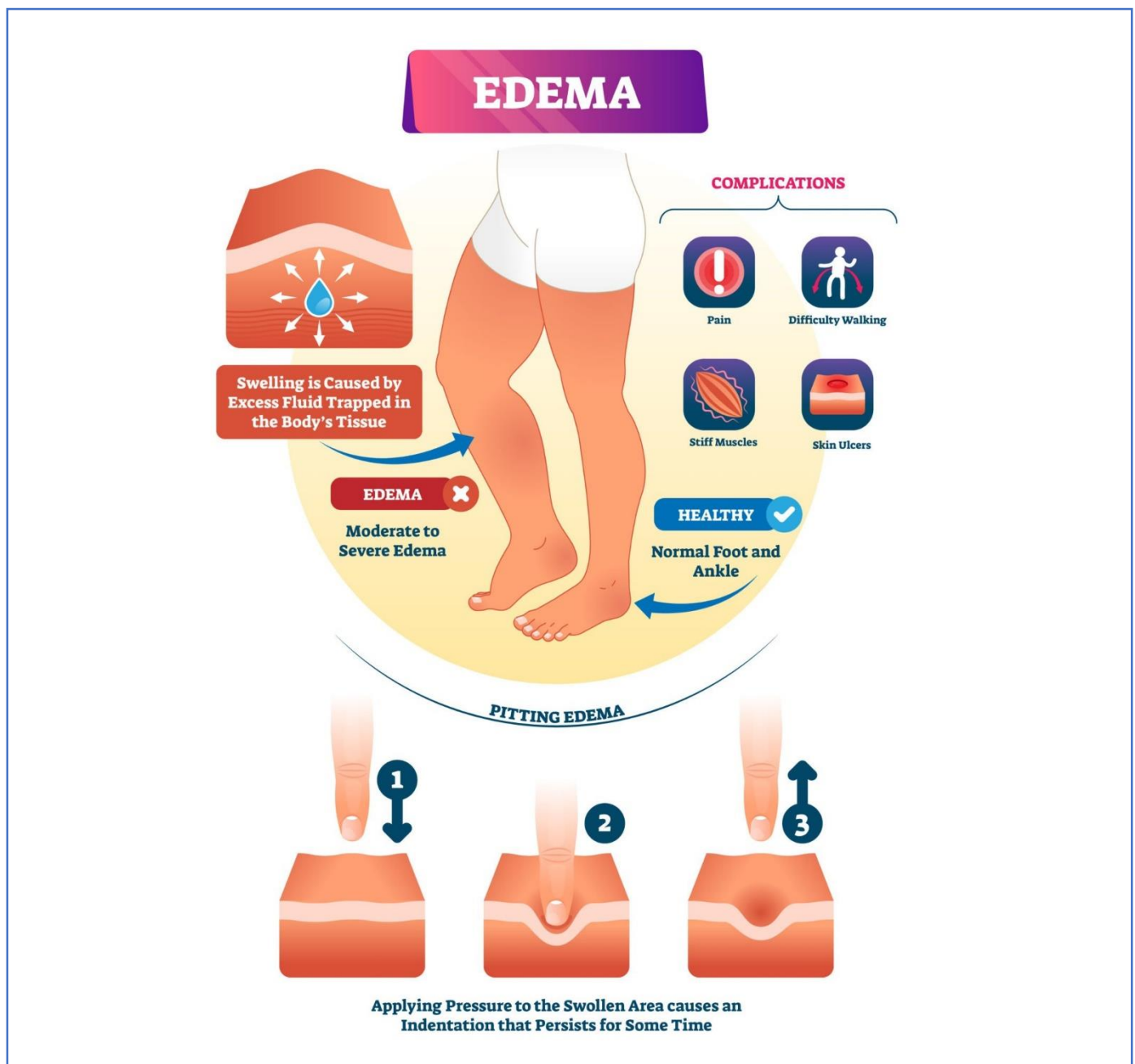
Inflammatory edema and **edema due to lymphatic obstruction**, because the fluid is rich in protein.

➤ **Edema resulting from renal dysfunction:**

Often appears initially in parts of the body containing loose connective tissue, **such as the eyelids**; **periorbital edema** is thus a characteristic finding in severe renal disease.

➤ **Chylous effusion:**

Are milky due to the presence of lipids absorbed from the gut.





HEMOSTASIS AND THROMBOSIS

Hemostasis:

It is the process by which blood clots form at sites of vascular injury

Thrombosis

It is a pathologic state, resulting in formation of a solid compact mass inside uninjured cardiovascular system or after minor injury during life due to inappropriate activation of hemostatic mechanisms.

➤ Hemostasis & thrombosis are closely related processes that depend upon three components:

- 1 Endothelium.
- 2 Platelets.
- 3 Coagulation cascade.

Aetiology of thrombosis:

There are three primary factors in thrombus formation, called Virchow's triad:

1- Endothelial injury: is a dominant cause of thrombosis.

Causes:

- Endocarditis.
- Ulcerated atherosclerotic plaque.
- Injury can be due to hemodynamic stresses (e.g. hypertension or turbulent blood flow)
- Endotoxin, radiation, or noxious agents (e.g. hypercholesterolemia, or cigarette smoke).

2- Alterations in normal blood flow:

Normal blood flow is laminar (i.e., cellular elements flow centrally in the vessel lumen, separated from endothelium by a plasma clear zone).

Stasis & turbulence lead to:

- Disrupt laminar flow & bring platelets into contact with the endothelium.
- Prevent dilution of activated clotting factors by flowing blood.
- Retard the inflow of clotting inhibitors.
- Promote endothelial cell activation.



3- Hypercoagulability:

Any **alteration of the coagulation pathways** that predisposes to **thrombosis**.

- **Heritable hypercoagulable states:**

E.g. Deficiencies of **antithrombin III**, **protein C**, or **protein S** also typically present with venous thrombosis & recurrent thromboembolism.

- **Acquired hypercoagulable states:**

Oral contraceptives or the hyperestrogenic state of pregnancy may **cause hypercoagulability** by **increasing hepatic synthesis of** coagulation factors & **reduced synthesis of** antithrombin III. Increase in number of platelets postoperative.

✓ Certain malignancies can release procoagulant tumor products.

Mechanism of thrombosis:

Endothelial injury leading to:

① **Exposure of subendothelial collagen.**

② **Adhesion of the platelets to the exposed collagen** which is mediated by factor VIII.

- ✓ This factor is **produced by** the endothelial cells.
- ✓ The initial thrombus is formed of **platelets only**.
- ✓ They adhere to exposed collagen **at site of endothelial injury**.
- ✓ The platelets **release ADP** which promotes further aggregation of more platelets.
- ✓ This thrombus is **pale, fragile** and can be **washed out**.

③ **The platelets derived thromboxane A₂** causes platelet contraction

and platelet factor 3 is involved in **formation of thrombin from prothrombin**.

④ **Thrombin leads to transformation of fibrinogen into fibrin.**

- ✓ These fibrin threads deposit on the platelet thrombus (**blood clot**) and **encourage further** deposit of platelets.
- ✓ Platelets **deposit in layers at right angles** to the blood stream

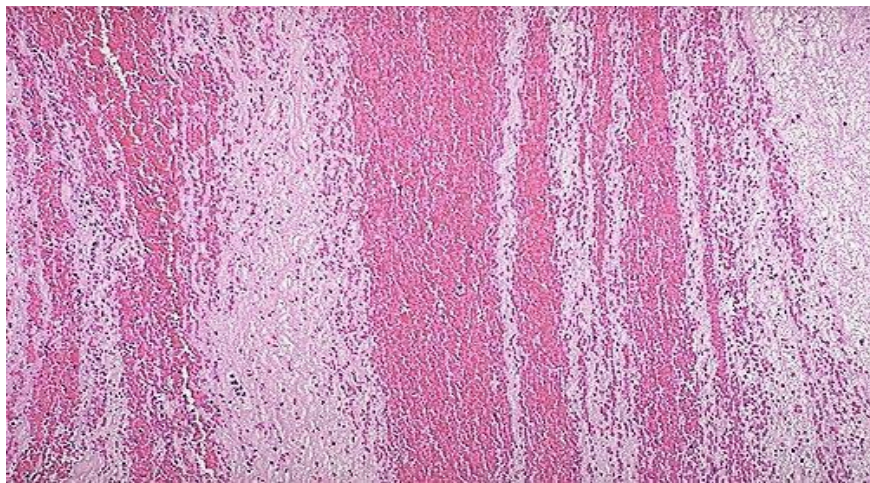


Morphology of the thrombus:

The **thrombus** is formed of platelets arranged in **homogenous pink lines** known as **lines of Zahn**. In between these lines there is a network of fibrin entangling **red and white blood cells**.

According to relative amount of platelets, fibrin and blood cells, thrombi may be:

Pale thrombi	Red thrombi
Made predominantly of platelets. These form in fast-moving blood (heart, arteries)	When thrombi form in slow-moving blood (veins, sites of turbulence and stasis), they are more rich in fibrin and blood cells than platelets.



Lines of Zahn in a recent thrombus.

Sites & types of thrombi:

- Mural thrombi form on the walls** of the cardiac chambers and aorta.
 - ✓ **As a rule**, they do not occlude the lumen.
- Arterial thrombi usually occur** over ruptured atherosclerotic plaques, Less often **at sites of other vascular disease or old surgery**.
 - ✓ Except in the aorta, arterial thrombi **generally occlude the artery**, adhering tightly to the wall, and seldom embolize.
 - ✓ **Thrombi that form in the aorta are embolizing**.
- Vegetations are thrombi which occur on cardiac valves**.
- Venous thrombi** almost always occlude the vein & **easily embolize**.

Thrombosis in veins is **more common** because veins are **thin-walled, superficial** [easily injured) and **blood flow is slow**.

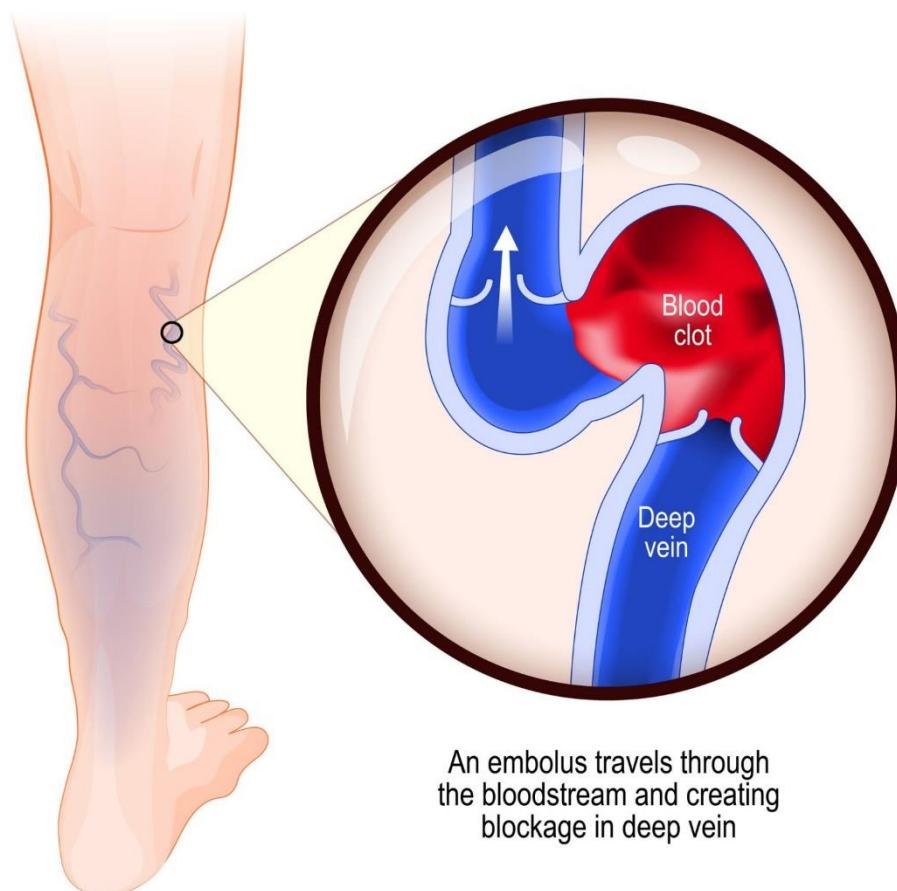


They are of 2 types of venous emboli:

a) Thrombophlebitis:	b) Phlebothrombosis:
Thrombosis occurs in inflamed veins. It may be: a- Septic (in veins draining areas of acute suppuration) b- Aseptic (in veins exposed to trauma or radiation).	Thrombosis initiated by factors other than inflammation. It occurs in veins calf in cardiac patients due to stasis and compression of veins against mattress; Or in femoral and pelvic veins after labor or operations due to increase in number of platelets, stasis and mild inflammation.

Deep venous thromboses are asymptomatic in approximately **50% of patients**, being recognized only after embolization.

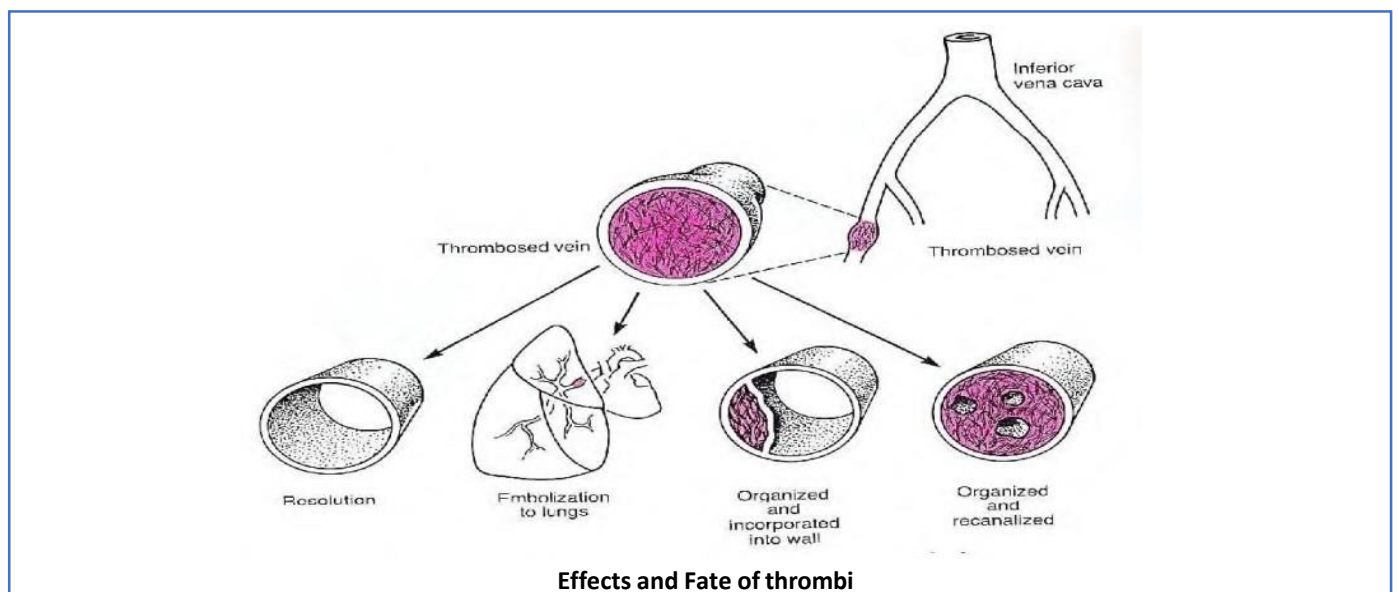
Deep vein thrombosis





Effects and Fate of thrombi:

1- Fragmentation	Thrombi may fragment, producing thrombo-emboli. ✓ If the thrombus is from septic thrombophlebitis it causes pyaemia and multiple pyemic abscesses.
2- Occlusion	Of an artery will result in ischemia and of a vein will lead to congestion and edema.
3- Organization	They are invaded by granulation tissue which converts into scar (organization). Mural thrombi generally take a long time to organize, incorporate into the lumen and they even calcify.
4- Organization and canalization	As the thrombus turns, over a few weeks, into vascular granulation tissue, it recanalizes. Ultimately, an occluded vessel ends up with many tiny lumens.
5- Propagation	When a thrombus occludes a vein completely, the proximal column of blood clots till the next tributary. Opposite the tributary another thrombus is formed (the blood is moving) and when it occludes the lumen completely it results in the formation of another clot proximal to it. The process may be repeated several times (resulting in alternating thrombi and clots) and may even reach the heart [fatal].





EMBOLISM

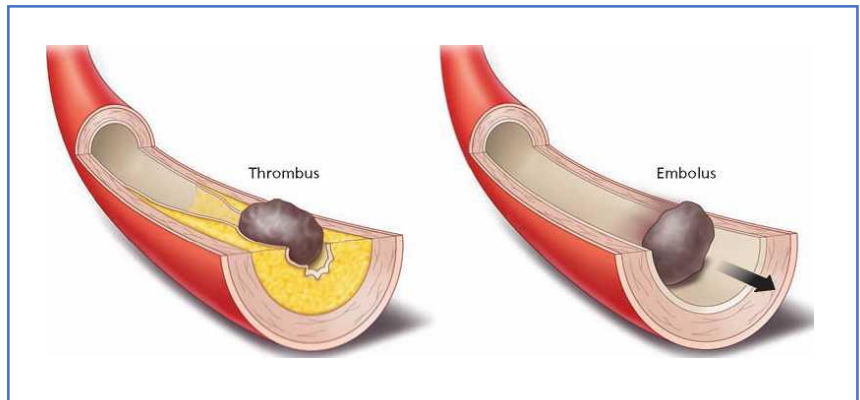
Embolus & Embolism

Embolus is an insoluble mass circulating in the blood stream.

Embolism is the process of impaction of embolus in a narrow vessel.

Types of emboli:

1. **Most** emboli are dislodged or fragmented thrombi (**thromboemboli**).
2. **Amniotic fluid** emboli.
3. **Air** emboli.
4. **Fat** emboli.
5. **Tumor** emboli.
6. **Parasitic** emboli.



Sites of embolism:

Systemic arteries, pulmonary arteries, portal vein

1- Thromboembolism:

Dislodged or fragmented thrombi.

- ✓ Size of the embolus.
- ✓ Nature (septic or aseptic).
- ✓ The state of collateral circulation.

Aseptic embolus:	Septic embolus:
Produces transient ischemia if the collateral circulation is good and infarction when poor .	Produce pyaemic abscess at the site of its impaction.

Course of emboli of thrombotic origin:

- Emboli from **systemic vein** or right side of heart impact in lungs (**pulmonary embolism**)
- Emboli from **aorta** or **left side** of heart impact in any organ (**systemic embolism**).
- Emboli from **portal vein** impact in liver.
- Emboli from **systemic vein** may by-pass the lungs through **septal defect** in the heart & impact in any organ. **This is called paradoxical embolism.**



Pulmonary embolism:

Source:

The large majority of pulmonary emboli **come from the deep leg veins** and may be from thrombi **in iliac and pelvic veins** or **right side of the heart**.

Effects:

Depending on size of the embolus

Small-sized embolus	Has no effect. 60-80% of pulmonary emboli are clinically silent
Medium-sized embolus in healthy lung:	No effect because the lung has double blood supply (bronchial and pulmonary).
Medium-sized embolus in a patient with chronic venous congestion of the lung:	Hemorrhagic infarction results.
Big embolus:	Occluding the pulmonary trunk or one of its main branches result in release of excessive amounts of serotonin from the platelets leading to bilateral pulmonary artery vasoconstriction and sudden death due to acute right sided heart failure.
Patients may have several episodes of embolization	Leading to permanent high pulmonary vascular resistance (pulmonary hypertension)



Pulmonary thromboembolism showing an embolus in a large pulmonary artery.



Systemic embolization:

It is an embolization down a systemic artery.

Source:

- Most come from the heart (80%)

E.g. mural thrombi from myocardial infarcts or left atrial thrombosis.

- The remaining originate from aortic aneurysms, thrombi overlying ulcerated atherosclerotic plaques, fragmented valvular vegetations.
- Or the venous system (*paradoxical emboli*).

Sites:

- Common arterial embolization sites include the lower extremities and CNS
- Intestines, kidneys, and spleen are less common targets.

Effect:

Systemic arterial emboli often lodge in end arteries and cause infarction or limb gangrene.

2- Amniotic fluid embolism:

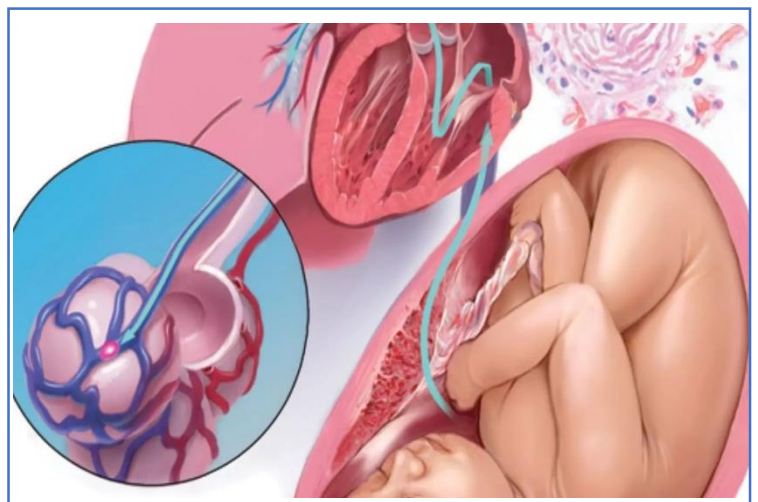
This very lethal event occurs in 1 out of 50,000 deliveries.

Cause:

Amniotic fluid, which is full of baby's debris, enters the maternal circulation

Effects:

Respiratory difficulty and shock are followed by DIC (Disseminated intravascular coagulopathy).



The mechanism:

The amniotic fluid vasoactive substances cause pulmonary vasoconstriction and its thrombogenic factors cause intravascular coagulation.



3- Air Embolism:

Causes:

- ① Injury to large neck veins.
- ② Ruptured chest veins due to chest trauma.
- ③ Decompression sickness:

Scuba divers are exposed to **high atmospheric pressure**, so increased amounts of gas particularly **nitrogen** are dissolved in blood.

If the diver ascends **too rapidly**, the dissolved gases in the tissue **escapes into the circulation** as **bubbles**.

The acute form **causes pain within skeletal muscles** and **around joints**, **neurological** and **breathing** problems.

Effects of air embolism:

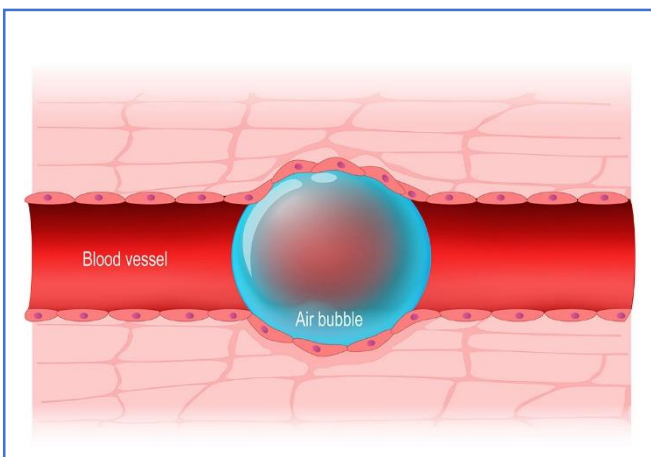
- ✓ The gas lodges in the vessels and it interferes with blood flow.
- ✓ Large amounts of gas in the heart render pumping ineffective.

N.B.

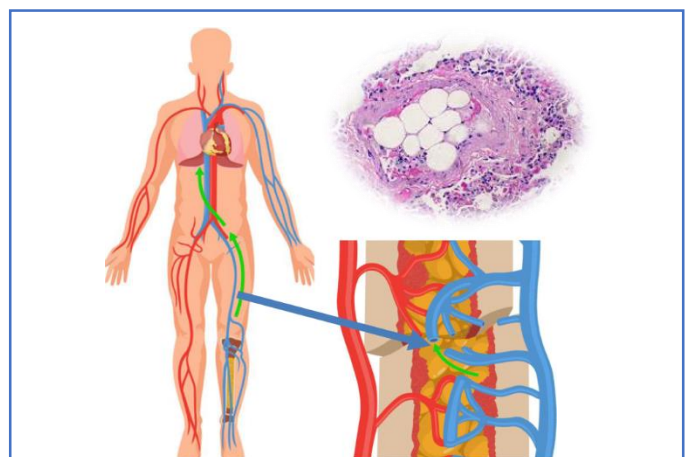
- ❖ The **few bubbles introduced into the blood** during intravenous therapy seem to be harmless.
- ❖ It takes **maybe 100 mL** of gas to harm a grown-up.

4- Fat Embolism:

Fat embolism usually **arises following some severe trauma** with **fracture to long bones**, extensive soft tissue **injury** or **severe burns**.



Air embolism



Fat embolism

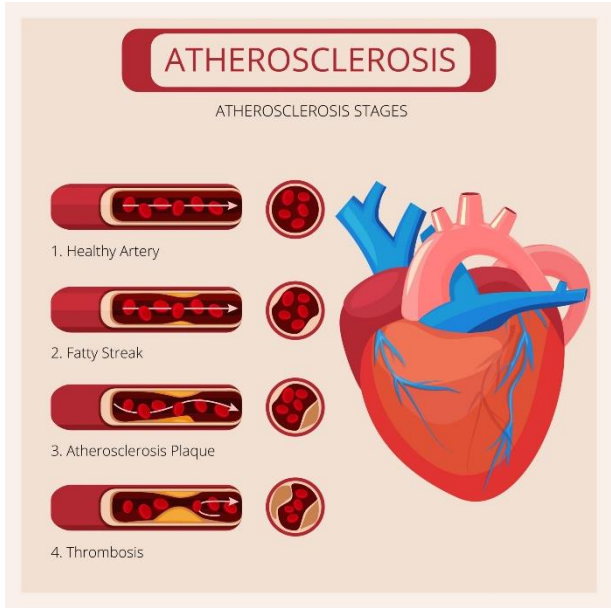


ISCHEMIA

Definition:

Decrease of arterial blood supply to organ or tissue **due to** occlusion of its artery.

Types of ischemia:

A. Acute Ischemia.	B. Chronic ischemia.
Sudden complete arterial occlusion.	Gradual incomplete arterial occlusion.
Causes	
1) Thrombus or embolus. 2) Strangulation of vessels as occlusion of intestinal vessels in strangulated hernia, intussusception and volvulus. 3) Twisting of pedicle of movable organ, e.g. ovary 4) Surgical ligature of artery. 5) Severe arterial spasm as in ergot poisoning. 6) Extensive venous obstruction as in case of mesenteric venous thrombosis (marked venous engorgement, this impedes the arterial blood flow leading to ischemia).	1) Atherosclerosis. 2) Arteritis as in marked endarteritis obliterans in syphilis. 3) Artery compression as by tumour.
	
Effects	
○ Sudden occlusion of arteries with poor collaterals [end arteries] causes infarction or gangrene. ○ Sudden occlusion of arteries with good collaterals has no effect	With poor collaterals: Ischaemic atrophy and fibrous replacement as in myocardial fibrosis due to coronary atherosclerosis. With good collaterals: No effect.



INFARCTION

Definition:

An **infarct** is an area of ischemic necrosis caused by occlusion of the vascular supply to the affected tissue.

Aetiology:

1- Arterial thrombosis or arterial embolism (underlies the vast majority of infarctions).

2- Less common causes include:

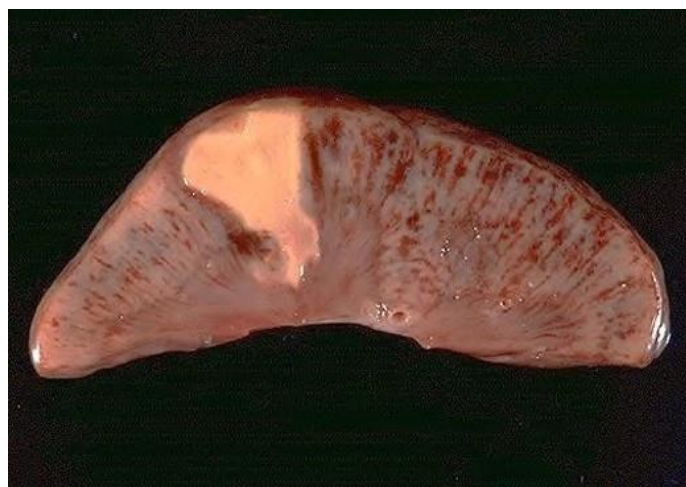
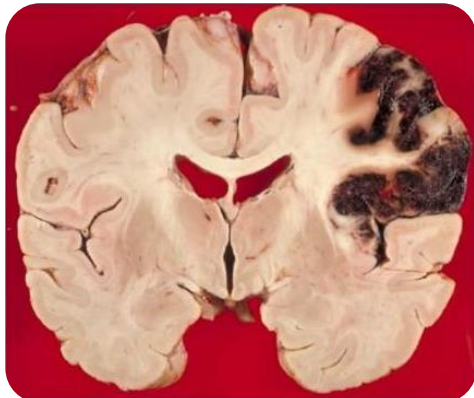
- Vasospasm.
- Extrinsic compression of a vessel, such as by tumor.

Types of infarctions

	1- Red infarcts:	2- Pale infarcts:
Causes:	• Venous occlusions (such as in ovarian torsion). • In loose tissues (e.g., lung) where blood can collect in infarcted zones. • In tissues with dual circulations such as lung and small intestine, that allow blood to flow from an unobstructed parallel supply into a necrotic zone • In previously congested tissues (as a consequence of sluggish venous outflow).	Arterial occlusions in solid organs with end-arterial circulations (e.g., heart, spleen, and kidney).



Gross picture:	• Infarcts tend to be wedge-shaped, with the occluded vessel at the apex and the organ periphery forming the base. • Its base is raised when recent (edema), covered by fibrinous exudate. • Latera • I margins: A narrow rim of hyperemia due to inflammation.
Microscopic picture:	• Ischemic coagulative necrosis. • Liquefactive necrosis (in CNS). • The margins of necrosis show inflammation which begins within few hours followed by repair.
Fate of infarcts	Healing by fibrosis may followed by dystrophic calcification . The infarct becomes depressed below the surface of the organ.



A white wedge shaped white infarction of the kidney.



GANGRENE

Definition:

Massive tissue necrosis followed by putrefaction.

Aetiology:

- Necrosis is mainly caused by ischaemia e.g. in gangrene of limb or bowel.
- Another cause of necrosis is a result of severe inflammation caused by virulent bacteria (infective gangrene. See later)
- Putrefaction is caused by:
Saprophytic bacteria which break down proteins and produce hydrogen sulphide (bad odour).
The latter reacts with iron of haemoglobin forming iron sulphide (black in color).

Types:

Gangrene is classified according to the amount of blood and tissue fluids in the affected part at the time of its death.

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

1- Dry Gangrene:

- The typical example is the dry gangrene of the toes and feet of an old patient due to ischemia caused by severe atherosclerosis (senile gangrene)
- The gangrene usually starts in one of the toes farthest away from blood supply, and extends slowly upwards until it reaches a point where the blood supply is adequate.



Shows dry gangrene of the big toe.



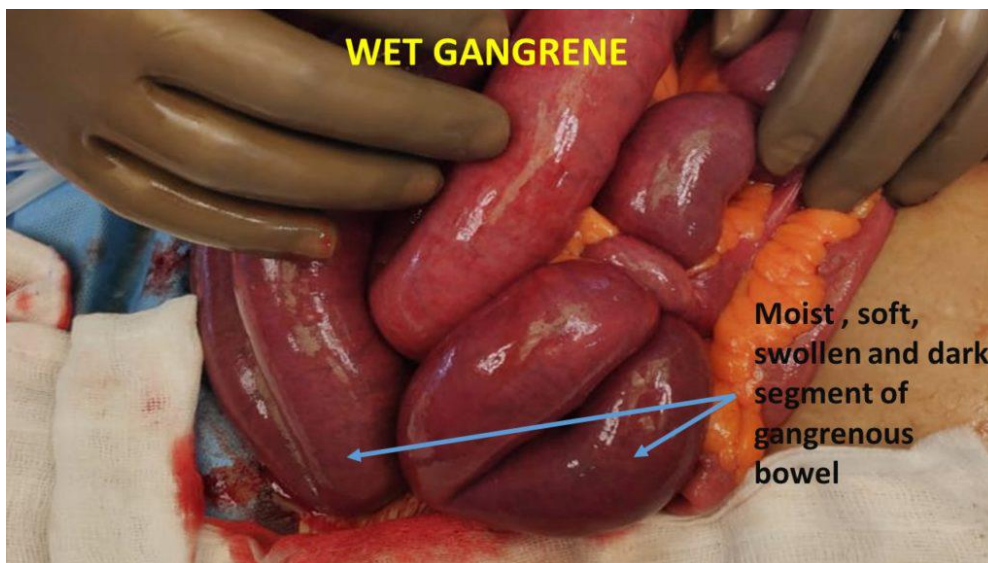
Pathology:

- The affected part is dry, shrunken, mummified and black in color.
- A red line of demarcation develops between the gangrene and healthy tissue .
This is a zone of inflammation due to irritation of the viable tissue by the necrotic tissue.
- Later a line of separation (a groove) develops, due to healing by granulation tissue and fibrosis and may lead to complete separation of the dead gangrenous tissue, leaving a conical stump.
The conical shape is because the deeper tissues have a better blood supply than the superficial tissues.
- There is minimal growth of bacteria due to dryness.

2- Moist (wet) Gangrene:

Causes:

- Moist gangrene is caused by occlusion of both arterial and venous blood supply and usually affects internal organs e.g. strangulated hernia, volvulus, or intussusception of the intestines.
- The affected part is stuffed with blood which favors the rapid growth of putrefactive bacteria.
- The toxic products of bacteria are absorbed causing severe toxemia and finally death.
- The line of demarcation is poorly developed and spontaneous separation doesn't occur.



Moist Gangrene



Major differences between dry and moist gangrene.

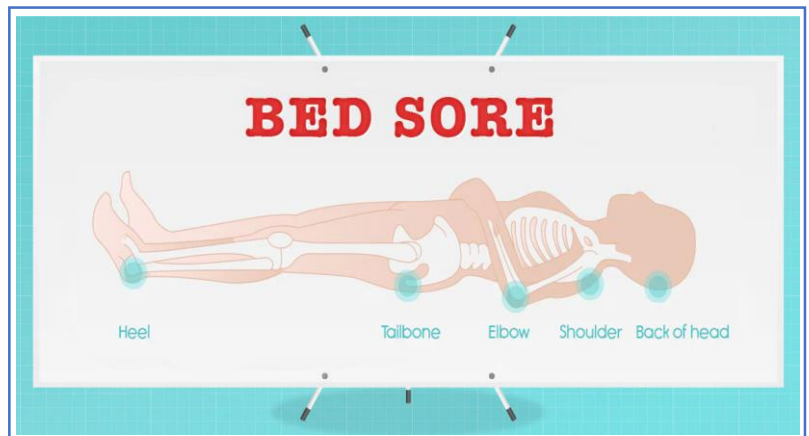
Dry Gangrene	Moist Gangrene
1- Caused by occlusion of arterial blood supply alone.	1- Caused by occlusion of both arterial and venous blood supply.
2- Usually affects exposed limbs.	2- Usually affects internal organs.
3- Putrefaction is slow.	3- Putrefaction is rapid.
4- Spread is slow.	4- Spread is rapid.
5- Toxemia is mild (not fatal).	5- Toxemia is Severe (fatal).
6- Line of demarcation is well developed	6- Line of demarcation is poorly developed
7- Line of separation is well developed.	7- Line of separation is absent.
8- Natural amputation can occur.	8- Natural amputation cannot occur.
9- Affected part is shrunken & black.	9- Affected part is swollen and brown.

Other examples of moist gangrene:

a) **Bed sores:**

Skin ulcer **over bony prominence** due to **prolonged recumbence**.

They are due to blood stagnation & thrombosis of the vessels followed by bacterial infections.

b) **Diabetic gangrene:**

More common in diabetic females after the age of 45 years.

- ✓ **Uncontrolled diabetes** results in **hyperlipidemia** which leads to **atherosclerosis** at an earlier age.
- ✓ It **begins in the tip of the big toe** or in **the sole of the foot**.
- ✓ The **gangrene is moist** because **low body resistance** and **excess sugars** in the tissues help putrefaction and **lead to rapid occlusion of the venous drainage**.
- ✓ It is **characterized by rapid** putrefaction, **rapid spread**, **excess toxins**, **severe toxaemia**, **poorly developed line of demarcation**, **no line of separation** and **no natural amputation**.



3- Infective Gangrene:

It is a **subtype of moist gangrene** in which bacteria cause both tissue necrosis and putrefaction.

Examples:

- **Lung gangrene:** e.g. putrefaction of lung abscess.
- **Cancrum oris:** Oral gangrene caused by **treponema vincenti** & **Bacillus fusiform** in debilitated children.

4- Gas Gangrene:

It is a **subtype of infective gangrene** characterized by **elaboration of several gases** which is very serious and commonly fatal due to toxemia.

Causes and pathogenesis:

- It is a special form of infective gangrene caused by gas forming Clostridia (**gram positive anerobic bacteria**), which **contaminate deep open wounds**, especially in the muscles.
- It produces powerful toxins which **cause tissue necrosis, and putrefaction**.
- The gangrenous part is swollen edematous, painful and crepitant due to accumulation of carbon dioxide gas (**fermentation of carbohydrates**).
- The gangrenous part has a foul odour due to hydrogen sulphide gas



Gas Gangrene



Infective Gangrene



Formative Assessment

SAQ

1. Define Gangrene. Explain the differences between dry and moist gangrene
2. Discuss fate of a thrombus in deep leg veins

MCQ

- 1) Concerning lung infarcts, all are true except
 - a) May be multiple.
 - b) Are a complication of deep venous thrombosis.
 - c) May heal by fibrosis.
 - d) Commonly are of the pale type.
- 2) The following is not true about sudden occlusion of an artery
 - a) May be due to embolism.
 - b) May not cause tissue damage.
 - c) Usually causes oedema.
 - d) May lead to gangrene.

