MBBS Pathology Notes: Cell Injury and Adaptation

1. Introduction to Cell Injury

Definition

The cell is the basic functional unit of the body, existing in a state of **homeostasis**, a dynamic steady state maintained by regulating its internal environment. When cells encounter physiologic stresses or pathologic stimuli, they can undergo **adaptation** to achieve a new steady state. However, if the adaptive capability is exceeded or if the stress is inherently harmful, **cell injury** results.

Cell injury is defined as a sequence of events that occur when the stress or injurious stimulus is too severe or prolonged for the cell to adapt.

- **Reversible Cell Injury**: If the stimulus is mild or transient, the injury is reversible. The cell can return to its normal state once the stress is removed.
- **Irreversible Cell Injury**: If the stimulus is severe and persistent, the injury becomes irreversible, leading to **cell death**.

2. Etiology (Causes) of Cell Injury

Cell injury can be caused by a wide variety of agents:

1. **Hypoxia and Ischemia**:
    - **Hypoxia** refers to oxygen deficiency, which impairs aerobic respiration.
    - **Ischemia** is the loss of blood supply to a tissue due to impeded arterial flow or reduced venous drainage. It is the most common cause of hypoxia and also results in a loss of substrate delivery and waste removal.
2. **Physical Agents**: Mechanical trauma, extremes of temperature (burns, frostbite), sudden changes in atmospheric pressure, radiation, and electric shock.
3. **Chemical Agents and Drugs**:
    - Simple chemicals (e.g., glucose, salt) in hypertonic concentrations.
    - Poisons (e.g., arsenic, cyanide).

- Industrial pollutants, insecticides, alcohol, and illicit drugs.
- Therapeutic drugs (e.g., paracetamol) in toxic doses.

4. **Infectious Agents**: Viruses, bacteria, fungi, and parasites.
5. **Immunologic Reactions**: Autoimmune reactions against one's own tissues, allergic reactions, and excessive or chronic inflammatory responses.
6. **Genetic Derangements**: Genetic abnormalities such as chromosomal malformations (e.g., Down syndrome), single gene mutations (e.g., sickle cell anemia), or multifactorial genetic changes.
7. **Nutritional Imbalances**:
   - **Deficiencies**: Protein-calorie malnutrition, vitamin deficiencies.
   - **Excesses**: Obesity, which increases the risk of diabetes mellitus and atherosclerosis.

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3. Reversible vs. Irreversible Cell Injury

A. Reversible Cell Injury

This is the early stage of cell injury where the functional and morphological changes are reversible if the stimulus is withdrawn.

Mechanisms:

The primary mechanism involves reduced energy production and membrane dysfunction:

1. **ATP Depletion**: The first event, typically in hypoxic injury.
2. **Ion Imbalance**: Failure of the ATP-dependent **Na+/K+ pump**. This causes sodium to accumulate *inside* the cell and potassium to leak *out*.
3. **Water Influx**: To maintain osmotic balance, water follows sodium into the cell, leading to **cellular swelling**.
4. **Altered Metabolism**: A switch to anaerobic glycolysis occurs, which depletes glycogen stores and increases lactic acid, lowering the intracellular pH. This further clumps nuclear chromatin.

Morphology of Reversible Injury:

Two main features are observed:

1. **Cellular Swelling (Hydropic Change):**
    - **Gross:** The organ may appear pale and turgid, with an increase in weight.
    - **Microscopy:** Cells appear swollen with a pale, granular, or vacuolated cytoplasm (small, clear vacuoles). This is also known as **hydropic change** or **vacuolar degeneration**. The swelling is due to distension of the endoplasmic reticulum and mitochondria.
2. **Fatty Change (Steatosis):**
    - This is the appearance of lipid vacuoles in the cytoplasm.
    - It is a common manifestation of reversible injury in cells involved in fat metabolism, such as hepatocytes (liver) and myocardial cells.
    - **Microscopy:** Clear, sharply demarcated lipid vacuoles are seen in the cytoplasm.

B. Irreversible Cell Injury (Leading to Cell Death)

This occurs when the persistent or severe injury pushes the cell past a "point of no return."

Mechanisms:

Two key events characterize the transition to irreversible injury:

1. **Severe Mitochondrial Damage**:
    - Persistent ATP depletion becomes profound.
    - The mitochondria themselves are damaged, often by increased intracellular Ca++.
    - They develop large, amorphous densities and lose the ability to perform oxidative phosphorylation.
    - Leakage of **cytochrome c** from the mitochondria into the cytoplasm occurs, which is a potent trigger for **apoptosis**.
2. **Profound Membrane Damage**:
    - **Plasma Membrane Damage:** The cell can no longer maintain its osmotic or biochemical balance.

- **Lysosomal Membrane Damage:** Leakage of lysosomal enzymes (hydrolases) into the cytoplasm occurs. These enzymes, now active in the low intracellular pH, digest the cell's own components (an act called **autolysis**).
- **Mitochondrial Membrane Damage** (as above).

Morphology of Irreversible Injury (Necrosis):

- **Microscopy:** The cell shows increased **eosinophilia** (pinkness) of the cytoplasm, as it binds more eosin dye due to denatured proteins.
- **Nuclear Changes** (the hallmark of cell death):
  - **Pyknosis:** Nuclear shrinkage and increased basophilia (darkening); the chromatin condenses.
  - **Karyorrhexis:** The pyknotic nucleus fragments.
  - **Karyolysis:** The fragmented nucleus dissolves and disappears, often due to DNase activity.

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4. Cell Death

Cell death is the end result of irreversible cell injury. There are two main types: Necrosis and Apoptosis.

A. Necrosis

Necrosis is a form of cell death characterized by the enzymatic digestion of the lethally injured cell and a subsequent **inflammatory response** in the surrounding living tissue. It is *always* a pathologic process.

Morphological Types of Necrosis:

Type of Necrosis	Key Features & Mechanism	Gross Appearance	Microscopic Appearance	Clinical Examples
Coagulative	**Most common type.** Denaturation of	The tissue is pale, firm, and slightly swollen. (e.g., a "wedge-	"Ghost-like" anucleated cells. Cell outlines are retained,	Infarcts (ischemic necrosis) in all solid organs

Type of Necrosis	Key Features & Mechanism	Gross Appearance	Microscopic Appearance	Clinical Examples
	structural and enzymatic proteins. **Cellular architecture is preserved** for several days.	shaped" infarct)	but cytoplasmic and nuclear detail is lost. Increased eosinophilia.	*except* the brain (e.g., Myocardial Infarction, kidney infarct).
Liquefactive	**Enzymatic digestion** of the dead cells. The tissue is liquefied. This occurs in two main settings: (1) Ischemic injury in the CNS, (2) Bacterial or fungal infections.	The tissue becomes a soft, viscous liquid mass. If initiated by inflammation, this is **pus**.	Complete loss of tissue architecture. The area is replaced by necrotic debris and (in infections) masses of neutrophils.	Cerebral infarction (stroke), abscesses.
Caseous	A combination of coagulative and	Friable, white-yellow, "cheesy"	Necrotic area is composed of **amorphous,**	**Tuberculosis** (the classic example). Can also be

Type of Necrosis	Key Features & Mechanism	Gross Appearance	Microscopic Appearance	Clinical Examples
	liquefactive necrosis. The term means "cheese-like."	material. Soft and granular.	**granular, eosinophilic debris** (the "caseous material"). **Loss of all cellular detail.** Often surrounded by a **granuloma** (macrophages and giant cells).	seen in some fungal infections.
Fat	Necrosis of adipose tissue, resulting from the release of activated **lipases**.	"Chalky-white" areas. This is **fat saponification**—the released fatty acids combine with calcium ions to form soaps.	Shadowy outlines of necrotic fat cells (adipocytes). The cytoplasm is replaced by a basophilic (blue) deposit of calcium. An inflammatory infiltrate is present.	**Acute pancreatitis** (pancreatic enzymes leak into surrounding fat), trauma to fatty tissue (e.g., breast).

Type of Necrosis	Key Features & Mechanism	Gross Appearance	Microscopic Appearance	Clinical Examples
Fibrinoid	A special type seen in immune reactions involving blood vessels.	Not visible grossly.	Vascular walls are infiltrated with a bright pink, amorphous, "fibrin-like" deposit. This is composed of immune complexes and plasma proteins.	Polyarteritis nodosa, malignant hypertension, autoimmune vasculitis.

Autolysis: This refers to the post-mortem degradation of tissues by their own lysosomal enzymes, *without* an inflammatory response. It is different from necrosis, which is a vital process (occurs in a living organism).

B. Apoptosis

Apoptosis is a "programmed" or "regulated" form of cell death ("cell suicide") designed to eliminate unwanted or irreparably damaged cells with minimal local disturbance. It **does not** elicit an inflammatory response.

Causes of Apoptosis:

- **Physiologic Apoptosis**:
    - **Embryogenesis:** Removal of unneeded structures (e.t., webbing between fingers).
    - **Hormone-dependent involution:** Endometrial shedding during the menstrual cycle, regression of the lactating breast after weaning.
    - **Elimination of self-reactive lymphocytes:** Preventing autoimmunity.
    - **Cell turnover:** Eliminating old cells in intestinal epithelia.

- **Pathologic Apoptosis**:
    - **DNA damage:** Radiation, chemotherapy, or free radicals cause damage that is beyond repair.
    - **Viral infections:** Elimination of virus-infected cells (e.g., in viral hepatitis).
    - **Duct obstruction:** Leading to atrophy in glands (e.g., pancreas, parotid).
    - **Neurodegenerative diseases:** Cell death in conditions like Alzheimer's or Parkinson's.

Mechanisms of Apoptosis:

Apoptosis is driven by a family of enzymes called Caspases. There are two main pathways that converge to activate "executioner" caspases:

1. **The Intrinsic (Mitochondrial) Pathway**:
    - This is the major pathway in most mammalian cells.
    - It is triggered by cellular stress (e.g., DNA damage, loss of growth factors).
    - The balance of pro-apoptotic (BAX, BAK) and anti-apoptotic (BCL-2, BCL-XL) proteins on the mitochondrial membrane is tipped.
    - Pro-apoptotic proteins create pores in the mitochondria, allowing **Cytochrome c** to leak into the cytoplasm.
    - Cytochrome c binds to a protein (Apaf-1) to form the **apoptosome**, which activates the initiator caspase, **Caspase-9**.
2. **The Extrinsic (Death Receptor) Pathway**:
    - This pathway is initiated by signals from *outside* the cell.
    - Cells have "death receptors" on their surface, such as **Fas (CD95)** and the **TNF receptor**.
    - When a ligand (e.g., FasL) binds to the receptor, it triggers the activation of the initiator caspase, **Caspase-8**.

Execution Phase:

Both pathways converge to activate the executioner caspases (e.g., Caspase-3, Caspase-6). These enzymes:

- Activate DNAses to cleave nuclear DNA into "ladder" fragments.
- Degrade the nuclear and cytoskeletal proteins.

Morphology of Apoptosis:

- **Cell Shrinkage:** The cell becomes smaller and denser.
- **Chromatin Condensation:** The most characteristic feature. Chromatin aggregates peripherally under the nuclear membrane.
- **Formation of Apoptotic Bodies:** The cell membrane "blebs" and fragments into membrane-bound vesicles called apoptotic bodies, which contain fragments of cytoplasm and nucleus.
- **Phagocytosis:** These apoptotic bodies are rapidly engulfed by macrophages *without* triggering inflammation.

Comparison of Necrosis and Apoptosis:

Feature	Necrosis	Apoptosis
Stimulus	Hypoxia, toxins, trauma (Pathologic)	Physiologic or Pathologic
Cell Size	Enlarged (swelling)	Reduced (shrinkage)
Cellular Content	Enzymatic digestion; leaks out	Intact; released in apoptotic bodies
Plasma Membrane	Disrupted	Intact; altered for recognition
Inflammation	**Present** (Significant)	**Absent**
Nuclear Change	Pyknosis, Karyorrhexis, Karyolysis	Chromatin condensation, fragmentation
Mechanism	ATP depletion, membrane damage	Gene activation, caspases

Feature	Necrosis	Apoptosis
Outcome	Pathologic, uncontrolled	Regulated, controlled

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5. Other Topics in Cell Injury

A. Pathologic Calcification

This is the abnormal deposition of calcium salts in tissues.

1. **Dystrophic Calcification:**
    - **Definition:** Deposition of calcium in **dead, dying, or abnormal** tissues.
    - **Serum Calcium: Normal.**
    - **Mechanism:** Occurs despite normal calcium levels. The necrotic or degenerating tissue provides a nidus for calcification.
    - **Examples:**
        - In areas of caseous necrosis (Tuberculosis).
        - In damaged heart valves (e.g., rheumatic fever).
        - In atherosclerotic plaques.
2. **Metastatic Calcification:**
    - **Definition:** Deposition of calcium in **normal, living** tissues.
    - **Serum Calcium: High (Hypercalcemia).**
    - **Mechanism:** Caused by elevated serum calcium levels, which "force" calcium into normal tissues (like lung, kidney, stomach).
    - **Causes of Hypercalcemia:**
        - Hyperparathyroidism.
        - Bone destruction (e.g., multiple myeloma, bone metastases).
        - Vitamin D-related disorders.
        - Renal failure.

B. Gangrene

Gangrene is a clinical term, not a specific type of cell death. It refers to the necrosis of a large area of tissue, often a limb, modified by superimposed factors.

1. **Dry Gangrene**:
    - **Mechanism**: Caused by **ischemia** (e.g., peripheral artery disease in diabetics).
    - **Pathology**: Dominated by **coagulative necrosis**.
    - **Appearance**: The tissue becomes dry, shrunken, and "mummified." It is dark black due to iron sulfides. There is a clear line of demarcation. Bacterial infection is minimal.
2. **Wet Gangrene**:
    - **Mechanism**: Occurs when the ischemic area becomes **superinfected** with saprophytic bacteria.
    - **Pathology**: Dominated by **liquefactive necrosis** due to the action of bacterial and leukocytic enzymes.
    - **Appearance**: The tissue is moist, swollen, soft, and foul-smelling. There is no clear line of demarcation, and it spreads rapidly. This is a medical emergency.
3. **Gas Gangrene**:
    - **Mechanism**: A specific type of wet gangrene caused by gas-forming bacteria, typically **Clostridium perfringens**, in deep, contaminated wounds.
    - **Appearance**: The tissue is swollen and edematous. Gas bubbles can be felt under the skin (**crepitus**). This is also a rapidly spreading, life-threatening emergency.

6. Cellular Adaptations

These are reversible changes in the size, number, phenotype, or arrangement of cells in response to changes in their environment.

1. **Atrophy**:
    - **Definition**: A decrease in the **size** and **number** of cells in an organ, resulting in a decrease in the size of the organ.
    - **Causes**:
        - **Disuse atrophy**: (e.g., skeletal muscle in a casted limb).
        - **Denervation atrophy**: (e.g., muscle after nerve damage).
        - **Diminished blood supply (Ischemia)**: (e.g., senile atrophy of the brain).
        - **Inadequate nutrition**: (e.g., cachexia).
        - **Loss of endocrine stimulation**: (e.g., atrophy of the endometrium after menopause).
2. **Hypertrophy**:
    - **Definition**: An increase in the **size** of cells, resulting in an increase in the size of the organ.
    - **Mechanism**: Occurs in cells that cannot divide (e.g., muscle). It is caused by increased production of cellular proteins.
    - **Examples**:
        - **Physiologic**: Skeletal muscle enlargement in bodybuilders; uterine enlargement during pregnancy.
        - **Pathologic**: Cardiac hypertrophy (enlargement of the heart) due to chronic hypertension or valvular disease.
3. **Hyperplasia**:
    - **Definition**: An increase in the **number** of cells, resulting in an increase in the size of the organ.
    - **Mechanism**: Occurs in cells capable of division.

- **Types**:
  - **Physiologic Hyperplasia**:
    - *Hormonal:* Proliferation of breast glandular epithelium during puberty and pregnancy.
    - *Compensatory:* Proliferation of the remaining liver after partial resection (liver regeneration).
  - **Pathologic Hyperplasia**:
    - Caused by excessive hormonal or growth factor stimulation.
    - *Example:* **Endometrial hyperplasia** due to excess estrogen; **Benign Prostatic Hyperplasia (BPH)**.
    - *Significance:* Provides a fertile soil for the development of cancer.

4. **Metaplasia**:
   - **Definition**: A reversible change in which one mature cell type (epithelial or mesenchymal) is **replaced** by another mature cell type.
   - **Mechanism**: It is a cellular "reprogramming" in response to chronic irritation, allowing the tissue to better withstand the stress.
   - **Examples**:
     - **Squamous Metaplasia**: The most common type. Ciliated columnar epithelium of the bronchus in a chronic smoker is replaced by more-resistant stratified squamous epithelium.
     - **Intestinal (Barrett's) Metaplasia**: Stratified squamous epithelium of the lower esophagus in chronic GERD is replaced by intestinal-type columnar epithelium (with goblet cells).
   - **Significance**: It is an adaptive change, but if the stimulus persists, it can predispose to malignant transformation (e.g., squamous metaplasia -> squamous carcinoma; Barrett's metaplasia -> adenocarcinoma).

5. **Dysplasia**:
    - **Definition**: Literally means "disordered growth." It is a precancerous (but still potentially reversible) alteration in adult cells characterized by variations in cell size, shape, and organization.
    - **Features**: Loss of uniformity, loss of architectural orientation, increased nuclear size, and increased mitotic figures.
    - **Significance**: It is considered a pre-neoplastic lesion. If the stimulus is removed, it may regress. If it persists, it can progress from mild to moderate to severe dysplasia, and finally to **carcinoma in situ** (a pre-invasive cancer).

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7. Mechanisms of Cellular Aging

Cellular aging, or senescence, is the progressive decline in the life span and functional capacity of cells.

Key Mechanisms:

1. **DNA Damage**: Accumulation of mutations and DNA damage (e.g., from oxidative stress) over time. The cell's repair mechanisms become less efficient with age.
2. **Telomere Shortening (Replicative Senescence):**
    - Telomeres are the protective caps at the ends of chromosomes.
    - With each cell division, the telomeres become progressively shorter.
    - Once they reach a critically short length, the cell can no longer divide and enters a state of **senescence**.
    - The enzyme **telomerase** can add back telomere repeats but is inactive in most somatic cells.
3. **Defective Protein Homeostasis (Proteostasis):**
    - With age, the cellular systems responsible for folding, repairing, and degrading proteins (chaperones, proteasomes) become less effective.

- This leads to the accumulation of misfolded proteins, which can be toxic (e.g., in Alzheimer's disease).

4. **Oxidative Stress:** The long-term accumulation of damage from **Reactive Oxygen Species (ROS)**, or free radicals, which damage lipids, proteins, and DNA.

Important University Questions

Question 1: Define necrosis. Describe the different morphological types of necrosis with examples.

Answer:

Definition: Necrosis is a form of cell death in a living organism characterized by the denaturation of intracellular proteins and enzymatic digestion of the lethally injured cell. It is *always* a pathologic process and is typically accompanied by an **inflammatory response** in the surrounding tissues.

The morphologic appearance of necrosis is the result of these two processes (denaturation and digestion) and is characterized by cytoplasmic changes (increased eosinophilia) and nuclear changes (pyknosis, karyorrhexis, karyolysis).

There are five main morphological types of necrosis:

1. **Coagulative Necrosis:**
    - This is the most common pattern of necrosis, characteristic of ischemic injury (infarction) in all solid organs except the brain.
    - **Mechanism:** The injury causes denaturation of both structural and enzymatic proteins, which blocks the cell's own autolytic enzymes.
    - **Gross Appearance:** The affected tissue appears pale, firm, and swollen.
    - **Microscopic Appearance:** The hallmark is the **preservation of the basic cellular architecture** for several days. The cells are "ghost-like" outlines, lacking a nucleus and cytoplasmic detail, and are strongly eosinophilic.
2. **Liquefactive Necrosis:**
    - This pattern is characterized by the complete enzymatic digestion of the dead cells, resulting in a liquid, viscous mass.

- **Mechanism:** It occurs in two main settings: (1) Ischemic injury (infarction) in the **central nervous system (CNS)**, where the brain tissue liquefies; and (2) **Bacterial or fungal infections**, where the enzymes from the microbes and the host's own neutrophils (in pus) cause rapid liquefaction.
- **Gross Appearance:** The tissue is transformed into a soft, liquid, or "gooey" mass. If it is an abscess, it will contain pus.
- **Microscopic Appearance:** There is a complete loss of tissue architecture. The area is filled with necrotic debris and, in infections, a large number of neutrophils.

3. **Caseous Necrosis:**
    - This type is a combination of coagulative and liquefactive necrosis and is "cheese-like" in appearance. It is classically associated with **Tuberculosis**.
    - **Gross Appearance:** The necrotic area is soft, friable, yellowish-white, and granular, resembling cottage cheese.
    - **Microscopic Appearance:** There is a complete loss of cellular detail. The necrotic focus is composed of **amorphous, granular, eosinophilic debris**. This is typically surrounded by a characteristic inflammatory border known as a **granuloma** (composed of epithelioid macrophages and giant cells).
4. **Fat Necrosis:**
    - This refers to the specific necrosis of adipose tissue.
    - **Mechanism:** It is most commonly seen in **acute pancreatitis**, where pancreatic lipases leak out and digest the fat in the pancreas and surrounding peritoneal cavity. These enzymes split fat into fatty acids, which then combine with calcium to form **saponification** (soap formation).
    - **Gross Appearance:** Visible as firm, "chalky-white" deposits or nodules.
    - **Microscopic Appearance:** Shadowy outlines of necrotic adipocytes are seen, often with a surrounding inflammatory reaction. The key feature is the basophilic (blue) deposits of calcium soaps in the necrotic fat.

5. **Fibrinoid Necrosis:**
    - This is a special type of necrosis, visible only microscopically, that occurs in the walls of blood vessels.
    - **Mechanism:** It is characteristic of immune-mediated reactions (e.g., vasculitis) or severe hypertension.
    - **Microscopic Appearance:** The vessel wall is replaced by a bright pink, amorphous, and "fibrin-like" deposit (hence "fibrinoid"), which is composed of immune complexes and plasma proteins that have leaked into the vessel wall.

Question 2: Define apoptosis. Discuss its mechanisms and differentiate it from necrosis.

Answer:

Definition: Apoptosis is a highly regulated, energy-dependent pathway of "programmed cell death" or "cell suicide." Its purpose is to eliminate unwanted, senescent, or irreparably damaged cells without causing damage or inflammation to the surrounding tissue. It can be a physiologic or pathologic process.

Mechanisms of Apoptosis:

Apoptosis is mediated by a family of enzymes called Caspases. The process is divided into two main pathways that activate these enzymes:

1. **The Intrinsic (Mitochondrial) Pathway:** This is the major pathway, triggered by cellular stress such as DNA damage or loss of growth factors.
    - This stress activates pro-apoptotic proteins (like BAX and BAK) and inactivates anti-apoptotic proteins (like BCL-2).
    - BAX and BAK form pores in the mitochondrial membrane, allowing **Cytochrome c** to leak into the cytoplasm.
    - Cytochrome c binds to other factors to form the **apoptosome**, which activates the initiator **Caspase-9**.
2. **The Extrinsic (Death Receptor) Pathway:** This pathway is triggered by signals from other cells.
    - Cells have "death receptors" on their surface (e.g., **Fas/CD95**).

- When a ligand (e.g., FasL) binds to this receptor, it causes the activation of the initiator **Caspase-8**.

Both pathways converge to activate the **Executioner Caspases** (e.g., Caspase-3), which then systematically dismantle the cell by digesting the cytoskeleton and activating DNAses to cleave DNA.

Differences between Apoptosis and Necrosis:

The most effective way to answer this is with a table:

Feature	**Necrosis**	**Apoptosis**
Definition	Pathologic cell death by "murder" (injury)	Programmed cell death by "suicide"
Stimulus	Hypoxia, toxins, trauma	Physiologic (e.g., embryogenesis) or Pathologic (e.g., DNA damage)
Cell Size	**Enlarged** (Cellular swelling)	**Reduced** (Cell shrinkage)
Nucleus	Pyknosis -> Karyorrhexis -> Karyolysis	Chromatin condensation and fragmentation
Plasma Membrane	**Disrupted** (leaks contents)	**Intact**; "blebs" to form apoptotic bodies
Inflammation	**Present** (due to leakage of cell contents)	**Absent** (apoptotic bodies are phagocytosed)
Mechanism	ATP depletion, membrane damage, enzyme leakage	Regulated caspase cascade (energy-dependent)

Feature	Necrosis	Apoptosis
Outcome	Always pathologic, affects groups of cells	Affects single, scattered cells

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Question 3: Write short notes on: (a) Cellular Adaptations and (b) Pathologic Calcification.

Answer:

(a) Cellular Adaptations

Cellular adaptations are reversible changes in the size, number, phenotype, or arrangement of cells in response to persistent stress or changes in their environment. These adaptations allow the cell to survive and function. The main types are:

1. **Hypertrophy:** An increase in the **size** of cells, leading to an increase in organ size. This occurs in non-dividing cells. *Example:* Left ventricular hypertrophy in chronic hypertension.
2. **Hyperplasia:** An increase in the **number** of cells, leading to an increase in organ size. This occurs in cells capable of division. *Example:* Benign prostatic hyperplasia (BPH) or endometrial hyperplasia due to hormonal stimulation.
3. **Atrophy:** A decrease in the **size** and **number** of cells, leading to a decrease in organ size. *Example:* Disuse atrophy of a muscle in a limb immobilize in a cast.
4. **Metaplasia:** A reversible change where one mature cell type is **replaced** by another mature cell type that is better able to withstand the stress. *Example:* Squamous metaplasia in the bronchus of a smoker, where ciliated columnar epithelium is replaced by stratified squamous epithelium.
5. **Dysplasia:** Disordered cell growth characterized by a loss of uniformity (pleomorphism) and architectural orientation. It is a precancerous condition. *Example:* Cervical dysplasia (Cervical Intraepithelial Neoplasia) following HPV infection.

(b) Pathologic Calcification

This is the abnormal deposition of calcium salts in tissues. There are two types:

1. **Dystrophic Calcification:**
    - This is the deposition of calcium in **dead, dying, or abnormal** tissues.
    - It occurs even when **serum calcium levels are normal**.
    - The necrotic or degenerating tissue provides a nidus (initiation site) for calcium deposition.
    - **Examples:** Calcification in atherosclerotic plaques, damaged heart valves (e.g., following rheumatic fever), and in areas of caseous necrosis in tuberculosis.
2. **Metastatic Calcification:**
    - This is the deposition of calcium in **normal, living** tissues.
    - It is *always* caused by **hypercalcemia** (elevated serum calcium).
    - The high serum calcium "forces" the salts into normal tissues, particularly those that are alkaline, such as the lungs, kidneys, and gastric mucosa.
    - **Examples:** Occurs in conditions like hyperparathyroidism, renal failure, or widespread bone metastases, which all lead to hypercalcemia.

1. Definition

Amyloid is a pathologic, extracellular deposit of a misfolded fibrillar protein. It is not a single chemical entity but a term for a group of different proteins that share a common physical structure.

Amyloidosis is a group of diseases characterized by the extracellular deposition of this misfolded amyloid protein in various tissues and organs, leading to tissue damage and organ dysfunction.

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2. Physical and Chemical Nature of Amyloid

All forms of amyloid, regardless of their biochemical makeup, share distinct characteristics:

Physical Nature:

1. **Fibrillar Structure:** On electron microscopy, amyloid is composed of continuous, non-branching fibrils. These fibrils have a diameter of approximately 7.5 to 10 nm.
2. **Beta-Pleated Sheet Configuration:** This is the key physical property. The polypeptide chains of the amyloid protein are folded into **beta-pleated sheets** that are arranged perpendicular (cross-beta) to the axis of the fibril. This specific conformation is responsible for its unique staining properties and its resistance to degradation.

Chemical Nature:

Amyloid deposits consist of two main components:

1. **Fibril Proteins (95%):** This is the major component and varies depending on the type of amyloidosis. It is this protein that is misfolded.
2. **Non-Fibrillar Components (5%):**
    - **Amyloid P Component (AP):** A universal component found in *all* types of amyloid. It is a normal serum glycoprotein (derived from Serum Amyloid P - SAP).
    - **Other components:** Proteoglycans, heparin sulfate, and glycosaminoglycans (GAGs).

3. Classification of Amyloidosis

Amyloidosis is classified based on the biochemical nature of the fibril protein and its clinical distribution.

Clinical Type	Fibril Protein	Precursor Protein	Associated Conditions
Systemic (Generalized)			
Primary Amyloidosis (Immunocyte Dyscrasia)	**AL**	Immunoglobulin **L**ight Chain	Multiple myeloma, plasma cell dyscrasias
Secondary (Reactive) Amyloidosis	**AA**	Serum **A**myloid-**A**ssociated (SAA)	Chronic inflammation (e.g., TB, Rheumatoid Arthritis), chronic infections
Hemodialysis-Associated	**Aβ$_2$m**	**β2**-Microglobulin	Long-term chronic hemodialysis (β2m is not filtered by dialysis membranes)
Hereditary (Familial)			
Familial Mediterranean Fever (FMF)	**AA**	Serum Amyloid-Associated (SAA)	Autosomal recessive disorder with recurrent inflammation
Familial Amyloidotic Polyneuropathy	**ATTR**	Mutant **T**ransthyretin (TTR)	Autosomal dominant; mutant TTR produced by the liver
Systemic Senile Amyloidosis	**ATTR**	**Normal T**ransthyretin (TTR)	Seen in the elderly, primarily affects the heart (senile cardiac amyloidosis)
Localized Amyloidosis			

Clinical Type	Fibril Protein	Precursor Protein	Associated Conditions
Senile Cerebral	**Aβ**	**A**myloid **β**-Precursor Protein (APP)	**Alzheimer's disease**
Endocrine Amyloid	**ACal**	**Cal**citonin	**Medullary carcinoma of the thyroid**
	AIAPP	**I**slet **A**myloid **P**olypeptide (Amylin)	**Type 2 Diabetes Mellitus** (in islets of Langerhans)

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4. Pathogenesis of Amyloidosis

The central event in amyloidosis is the **misfolding of a protein**. This misfolded protein becomes insoluble, resistant to breakdown (proteolysis), and aggregates into extracellular fibrils.

The pathogenesis involves three main steps:

1. **Abnormal Protein Production**:
    - **Production of an abnormal protein**: This occurs in hereditary forms, where a **mutation** leads to the synthesis of a mutant protein (e.g., mutant **Transthyretin - ATTR**) that is inherently unstable and prone to misfolding.
    - **Production of excessive amounts of a normal protein**: This occurs in systemic amyloidosis. These normal proteins have an intrinsic tendency to misfold when produced in large amounts.
        - **Example 1 (AL Amyloid):** In plasma cell tumors (like multiple myeloma), a monoclonal population of B-cells produces vast quantities of abnormal immunoglobulin **light chains (AL)**.
        - **Example 2 (AA Amyloid):** In chronic inflammatory states, the liver is stimulated by cytokines (IL-1, IL-6) to produce large amounts of an acute-phase reactant protein called **Serum Amyloid-Associated (SAA)**.

2. **Aggregation and Fibril Formation**:
    - The abnormal or excess proteins misfold and form insoluble aggregates.
    - These aggregates are not degraded by the body's normal clearance mechanisms (macrophages, proteasomes).
    - They self-assemble into the characteristic beta-pleated sheet fibrils.
3. **Deposition in Tissues**:
    - These insoluble, resistant fibrils are deposited in the extracellular matrix of various tissues.
    - The deposit physically compresses and damages adjacent cells, leading to pressure atrophy and organ dysfunction.
    - The amyloid deposit itself can also be directly toxic to cells.

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5. Pathology (Morphology) of Amyloidosis

A. Staining and Diagnosis (Pathognomonic Features)

The diagnosis of amyloidosis is made by **tissue biopsy** and specific staining.

1. **H&E Stain**:
    - Amyloid appears as an **extracellular, amorphous, eosinophilic (pink), hyaline** material.
    - This appearance is non-specific, as other materials (like collagen or fibrin) can also look similar.
2. **Congo Red Stain**:
    - This is the **principal diagnostic stain** for amyloid.
    - Under **ordinary light**, amyloid deposits stain **pink or red**.
    - When the Congo Red-stained slide is viewed under **polarized light**, the amyloid fibrils show a pathognomonic **apple-green birefringence**. This is the definitive diagnostic feature.

3. **Electron Microscopy**:
    - Confirms the presence of non-branching fibrils, each 7.5–10 nm in diameter.

B. Gross Morphology

The affected organ is typically **enlarged, firm, and waxy**. The cut surface has a pale, gray, and "lardaceous" (resembling lard) appearance.

- **Iodine Test (Historical):** Applying iodine followed by sulfuric acid to the cut surface of an organ with amyloid causes the deposits to turn blue-violet (a starch-like reaction, which is the origin of the name "amyloid").

C. Organ Involvement (Microscopic Features)

Amyloid deposition is always **extracellular**, beginning between cells and in the walls of blood vessels. It progressively encroaches on and compresses the surrounding parenchymal cells, causing them to undergo **pressure atrophy**.

- **Kidney**:
    - This is the **most common and most serious** organ involved in systemic amyloidosis.
    - Deposits are found primarily in the **glomeruli**, leading to massive protein leakage. Deposits also occur in the walls of arterioles and the peritubular (interstitial) tissue.
    - **Clinical Correlation:** This damage is the primary cause of **nephrotic syndrome** in amyloidosis, which often progresses to renal failure.
- **Spleen**:
    - Deposition follows two main patterns:
        1. **"Sago Spleen":** Deposits are limited to the splenic follicles, appearing as tapioca-like granules on the cut surface.
        2. **"Lardaceous Spleen":** Deposits involve the walls of the splenic sinuses in the red pulp, creating large, map-like areas of amyloid.
    - The spleen is often enlarged and firm.
- **Liver**:
    - The liver is often enlarged and firm.

- Deposits begin in the **Space of Disse** (the space between hepatocytes and sinusoids) and progressively compress the hepatocyte plates, causing pressure atrophy.
- Liver function is usually well-preserved until the disease is very advanced.

- **Heart**:
  - Amyloid deposits occur between the myocardial fibers.
  - This infiltration causes the heart wall to become stiff and non-compliant, leading to **restrictive cardiomyopathy** and heart failure.
  - This is the most common cause of death in **systemic senile amyloidosis (ATTR)**.

- **Other Sites**:
  - **Gastrointestinal Tract**: Can cause malabsorption or diarrhea.
  - **Tongue**: Deposits can cause enlargement (**macroglossia**).
  - **Blood Vessels**: Amyloid in vessel walls makes them rigid and fragile, leading to an increased bleeding tendency (e.g., "pinch purpura").

Part 1: Acute Inflammation

1.1. Definition and General Features

Definition: Inflammation is a rapid, non-specific, and protective response of **living, vascularized tissue** to injury. It is a fundamental component of the body's innate immunity.

The primary purpose of inflammation is to:

- Deliver defensive cells (leukocytes) and molecules (plasma proteins, e.g., antibodies, complement) from the circulation to the site of injury.
- Eliminate the injurious agent (e.g., microbes, toxins).
- Remove the consequences of the injury (e.g., necrotic cells and debris).
- Initiate the process of repair.

Although inflammation is a protective response, it can also be harmful if it is misdirected (e.g., in autoimmune diseases), occurs against a harmless substance (e.g., in allergies), or is inadequately controlled.

1.2. Stimuli (Causes) for Acute Inflammation

Acute inflammation can be triggered by various stimuli:

- **Infections**: Bacterial, viral, fungal, or parasitic. This is the most common and medically important cause.
- **Tissue Necrosis**: Cell death from any cause, including **ischemia** (e.g., myocardial infarction), physical trauma, thermal injury (burns, frostbite), or chemical injury.
- **Foreign Bodies**: Splinters, sutures, dirt, or urate crystals (in gout).
- **Immune Reactions (Hypersensitivity):** When the immune system damages the body's own tissues (e.g., autoimmune diseases, allergic reactions).

1.3. The Cardinal Signs of Inflammation

The five classical (cardinal) signs of acute inflammation are:

1. **Rubor** (Redness): Caused by vasodilation and increased blood flow.
2. **Tumor** (Swelling): Caused by the accumulation of protein-rich fluid (exudate) due to increased vascular permeability.

3. **Calor** (Heat): Caused by increased blood flow (vasodilation) in peripheral parts.
4. **Dolor** (Pain): Caused by the direct action of mediators (like bradykinin and prostaglandins) on nerve endings, and by the tension of tissue swelling.
5. **Functio laesa** (Loss of function): Added by Virchow, this is a consequence of pain, swelling, and tissue damage.

1.4. Key Events in Acute Inflammation

The acute inflammatory response consists of two main components: vascular events and cellular events.

A. Vascular Events (Hemodynamic Changes)

These changes begin rapidly after injury:

1. **Transient Vasoconstriction:** A brief, neurogenic constriction of arterioles, lasting only seconds.
2. **Vasodilation:** The first major event. It involves the arterioles and leads to the opening of new capillary beds. This is mediated by **histamine** and **nitric oxide (NO)**. This is the cause of **rubor** (redness) and **calor** (heat).
3. **Increased Vascular Permeability:** This is the **hallmark** of acute inflammation. It allows protein-rich fluid (exudate) and leukocytes to escape into the extravascular tissue.
    - **Mechanism:** Primarily due to the contraction of endothelial cells in post-capillary venules, creating gaps. This is a rapid and short-lived response (15-30 minutes) mediated by **histamine** and **bradykinin**.
    - **Result:** This leakage of fluid leads to **tumor** (swelling) and **stasis**.
4. **Stasis:** The loss of fluid makes the blood more viscous and slows its flow. This slowing allows leukocytes to accumulate along the endothelial surface, a process called **margination**.

Exudate vs. Transudate

The increased permeability leads to the formation of an exudate. This must be distinguished from a transudate.

Feature	Transudate	Exudate
Cause	Increased hydrostatic pressure or decreased osmotic pressure (non-inflammatory)	**Inflammation** (Increased vascular permeability)
Protein Content	**Low** (< 3 g/dL)	**High** (> 3 g/dL), contains fibrinogen
Specific Gravity	Low (< 1.015)	High (> 1.020)
Cells	Few (mesothelial cells, lymphocytes)	**Many** (Neutrophils, macrophages)
Appearance	Clear, straw-colored	Cloudy, purulent, or fibrinous (clots)
Example	Edema in heart failure, cirrhosis	Pus in an abscess, fluid in pneumonia

B. Cellular Events (Leukocyte Extravasation)

This is the journey of the leukocyte (primarily the neutrophil in acute inflammation) from the vessel lumen to the site of injury.

1. **Margination and Rolling:** Due to blood stasis, leukocytes move from the central flow to the periphery (margination). They then tumble and transiently stick to the endothelium.
    - **Mediators:** This process is mediated by **Selectins** (P-selectin and E-selectin on the endothelium) which bind loosely to carbohydrates on the leukocyte.
2. **Adhesion (Pavementing):** The leukocytes stick firmly to the endothelium.
    - **Mediators:** This firm adhesion is mediated by **Integrins** (on the leukocyte) binding to their ligands (like **ICAM-1** and **VCAM-1** on the endothelium). Cytokines (TNF, IL-1) stimulate the expression of these ligands.
3. **Transmigration (Diapedesis):** The leukocyte squeezes *between* the endothelial cells at their junctions.

- **Mediator**: This process is mediated by a molecule called **PECAM-1 (CD31)**.

4. **Chemotaxis**: After exiting the vessel, the leukocyte migrates toward the site of injury along a chemical gradient.
    - **Chemoattractants (Chemotactic agents):**
        - **Exogenous:** Bacterial products (e.g., N-formylmethionine).
        - **Endogenous:** Complement components (**C5a**), AA metabolites (**Leukotriene B4 - LTB4**), and cytokines (**IL-8**).

C. Leukocyte Activation and Phagocytosis

Once at the site, leukocytes must eliminate the offending agent.

1. **Recognition and Attachment**: Leukocytes recognize microbes through receptors. This process is greatly enhanced by **opsonins**—host proteins that "coat" the microbe.
    - **Major Opsonins**: **IgG** antibodies and **C3b** (a complement product).
2. **Engulfment**: The leukocyte extends pseudopods around the opsonized particle, forming a phagocytic vesicle (phagosome).
3. **Killing and Degradation**: The phagosome fuses with a lysosome (forming a phagolysosome). Killing is accomplished by two mechanisms:
    - **Oxygen-Dependent (Respiratory Burst):** This is the most potent mechanism.
        - It involves the enzyme **NADPH oxidase**, which generates **superoxide free radicals (O_2^-)**.
        - Superoxide is converted to **hydrogen peroxide (H_2O_2)**
        - In neutrophils, the enzyme **Myeloperoxidase (MPO)** combines (H_2O_2) with Cl^- to create **HOCl** (hypochlorous acid, or bleach), a powerful microbicidal agent.
    - **Oxygen-Independent**: Involves pre-formed enzymes from leukocyte granules, such as lysozyme and major basic protein (in eosinophils).

1.5. Chemical Mediators of Acute Inflammation

These are the substances that initiate and regulate the inflammatory response. They can be cell-derived or plasma-derived.

Mediator Group	**Specific Mediator**	**Source**	**Primary Action(s)**
Cell-Derived			
1. Vasoactive Amines	**Histamine**	**Mast cells**, Basophils, Platelets	**Vasodilation**, **Increased vascular permeability** (early transient response)
2. Arachidonic Acid (AA) Metabolites	**Prostaglandins** (PGE2, PGI2, PGD2)	Mast cells, Leukocytes (via Cyclooxygenase pathway)	Vasodilation, Edema. **PGE2** also mediates **Fever** and **Pain**.
	Leukotrienes (LTC4, LTD4, LTE4)	Mast cells, Leukocytes (via Lipoxygenase pathway)	**Bronchoconstriction**, Increased vascular permeability
	Leukotriene B4 (LTB4)	Leukocytes	Powerful **Chemotaxis**
3. Cytokines (Polypeptides)	**TNF, IL-1**	Macrophages, Mast cells	Endothelial activation (adhesion molecules), **Systemic effects (Fever)**, Fibroblast activation
	IL-8 (Chemokine)	Macrophages	**Chemotaxis** for neutrophils
4. Others	**Nitric Oxide (NO)**	Endothelium, Macrophages	**Vasodilation**, Bactericidal
	Platelet-Activating Factor (PAF)	Leukocytes, Endothelium	Vasodilation, Bronchoconstriction, Chemotaxis

Mediator Group	Specific Mediator	Source	Primary Action(s)
Plasma-Derived (Liver)			
1. Complement System	**C3a, C5a** (Anaphylatoxins)	Plasma (via complement cascade)	Histamine release (vasodilation, increased permeability)
	C5a	Plasma (via complement cascade)	**Chemotaxis** (leukocyte recruitment)
	C3b	Plasma (via complement cascade)	**Opsonization** (enhances phagocytosis)
2. Kinin System	**Bradykinin**	Plasma (from HMWK via Kallikrein)	**Pain**, Vasodilation, Increased vascular permeability

1.6. Morphological Patterns of Acute Inflammation

- **Serous Inflammation**: Marked by the exudation of thin, cell-poor fluid. *Example:* Skin blister (e.g., from a burn), pleural effusion.
- **Fibrinous Inflammation**: Occurs with more severe injury, allowing large molecules like fibrinogen to pass out. The fibrin forms a thick, shaggy exudate. *Example:* Fibrinous pericarditis ("bread-and-butter" appearance).
- **Suppurative (Purulent) Inflammation**: Characterized by the production of **pus**, which is an exudate rich in neutrophils, liquefied necrotic debris, and edema fluid. *Example:* **Abscess** (a localized collection of pus in a tissue).
- **Ulcer**: A local defect or excavation of the surface of an organ or tissue that is produced by the shedding (sloughing) of inflamed, necrotic tissue.

1.7. Outcomes of Acute Inflammation

Acute inflammation can have one of four outcomes:

1. **Complete Resolution**: The ideal outcome. The injurious agent is eliminated, the tissue is cleared of debris, and the injured tissue is replaced by native cells, restoring normal function.
2. **Healing by Scarring (Fibrosis):** Occurs after substantial tissue destruction, when the tissue is not capable of regeneration, or when there is abundant fibrin. The tissue is replaced by connective tissue, resulting in a scar.
3. **Abscess Formation**: May occur in the context of suppurative inflammation.
4. **Progression to Chronic Inflammation**: This occurs when the acute response cannot be resolved, either because the injurious agent persists or because of interference with the normal healing process.

Part 2: Chronic Inflammation

2.1. Definition and General Features

Definition: Chronic inflammation is an inflammation of **prolonged duration** (weeks to months) in which active inflammation, tissue destruction, and attempts at healing (fibrosis and angiogenesis) are proceeding **simultaneously**.

Unlike acute inflammation, which is dominated by vascular changes, edema, and neutrophils, chronic inflammation is characterized by:

- Infiltration with **mononuclear cells** (macrophages, lymphocytes, plasma cells).
- **Tissue destruction**, largely mediated by the inflammatory cells.
- **Attempts at healing** through fibrosis (scarring) and angiogenesis (new blood vessel formation).

2.2. Causes (Stimuli) of Chronic Inflammation

- **Persistent Infections**: By microorganisms that are difficult to eradicate, such as *Mycobacterium tuberculosis*, *Treponema pallidum* (syphilis), certain fungi, and parasites.
- **Hypersensitivity Diseases (Immune-Mediated):**

    - **Autoimmune diseases**: The injurious agent is self-antigen (e.g., rheumatoid arthritis, multiple sclerosis).
    - **Allergic diseases**: An excessive immune response to a common environmental substance (e.g., bronchial asthma).
- **Prolonged Exposure to Toxic Agents:**
    - **Exogenous**: Inhaled particulate matter like **silica** (silicosis), which is non-degradable.
    - **Endogenous**: Persistent metabolic toxins (e.g., lipid components in **atherosclerosis**).

2.3. Cells and Mediators of Chronic Inflammation

- **Macrophages**: These are the **dominant cells** in chronic inflammation. They are derived from circulating blood monocytes. Macrophages are activated by cytokines (especially **IFN-γ**) from T-cells.
    - **Destructive Role**: Secrete proteases and Reactive Oxygen Species (ROS) that destroy tissue.
    - **Healing Role**: Secrete growth factors (e.g., PDGF, FGF) that stimulate fibroblast proliferation and collagen deposition (fibrosis).
- **Lymphocytes (T and B cells):** These cells are mobilized by an adaptive immune response.
    - **T-cells** (especially CD4+ TH1 cells) are critical. They produce **IFN-γ**, which is the single most important cytokine for activating macrophages (the "macrophage-activating" cytokine).
    - **B-cells** differentiate into **Plasma Cells**, which secrete antibodies.

2.4. Types of Chronic Inflammation

1. Non-specific Chronic Inflammation

This is the most common form. It consists of a diffuse, non-organized accumulation of macrophages, lymphocytes, and plasma cells in the affected tissue, accompanied by variable degrees of fibrosis.

Example: Chronic cholecystitis, chronic gastritis, chronic pyelonephritis.

2. Granulomatous Inflammation

This is a distinctive, organized pattern of chronic inflammation.

- **Definition**: A **granuloma** is a focal, microscopic aggregate of activated macrophages (called **epithelioid cells**), often surrounded by a "cuff" of lymphocytes.
- **Formation**: It is a cellular attempt to contain an offending agent that is difficult to eradicate.
    1. An indigestible agent (e.g., *M. tuberculosis*) is phagocytosed by a macrophage, which then presents the antigen to a **CD4+ T-cell**.
    2. The T-cell differentiates into a **TH1 cell** and releases **IFN-γ**.
    3. IFN-γ activates the macrophages, transforming them into **Epithelioid cells** (large cells with abundant pink cytoplasm and indistinct borders) and **Multinucleated Giant Cells** (formed by the fusion of epithelioid cells).
- **Key Types of Granulomas**:
    - **Caseating Granuloma**: The center of the granuloma undergoes necrosis, appearing as amorphous, pink, "cheesy" debris (caseous necrosis). This is the hallmark of **Tuberculosis**.
    - **Non-Caseating Granuloma**: Lacks central necrosis. It is a tight, organized cluster of epithelioid cells and giant cells. This is seen in **Sarcoidosis** and **Crohn's disease**.
    - **Foreign Body Granuloma**: Forms in response to inert materials like sutures, talc, or a splinter. The giant cells (foreign body type) engulf the material.

Part 3: Comparison of Acute and Chronic Inflammation

Feature	Acute Inflammation	Chronic Inflammation
Onset	Rapid: Minutes to hours	Slow: Days to weeks
Duration	Short (days)	Long (weeks to months/years)
Dominant Cells	**Neutrophils**	**Macrophages, Lymphocytes, Plasma cells**
Vascular Events	Prominent: Vasodilation, Increased Permeability, Edema	Less prominent; Angiogenesis (new vessel formation)

Feature	Acute Inflammation	Chronic Inflammation
Tissue Injury	Usually mild and self-limited	Often severe and progressive
Healing	Resolution or Abscess formation	**Fibrosis (scarring)** is a key feature
Systemic Signs	Prominent (Fever, leukocytosis)	Less prominent (Low-grade fever, weight loss, anemia)

Important University Questions

Question 1: Define acute inflammation. Describe the vascular and cellular events that occur.

Answer:

Definition: Acute inflammation is the rapid, immediate, and non-specific response of living, vascularized tissue to an injurious stimulus. Its primary function is to deliver leukocytes (mainly neutrophils) and plasma proteins to the site of injury to eliminate the offending agent and remove necrotic debris. It is characterized clinically by the five cardinal signs: redness (rubor), swelling (tumor), heat (calor), pain (dolor), and loss of function (functio laesa).

The response is divided into two main components:

1. Vascular Events:

These events involve changes in blood vessel caliber and permeability:

- **Vasodilation:** Following a brief moment of vasoconstriction, the arterioles dilate. This is one of the earliest signs, mediated by histamine and nitric oxide. It increases blood flow to the area, causing redness and heat.
- **Increased Vascular Permeability:** This is the hallmark of acute inflammation. The endothelial cells of post-capillary venules contract, creating gaps. This is mediated by histamine, bradykinin, and leukotrienes. This permeability allows protein-rich fluid, or **exudate**, to leak into the extravascular space, causing swelling (edema).

- **Stasis:** The loss of fluid from the vessel causes the blood to become more viscous and flow more slowly. This leads to the "margination" of leukocytes, as they move from the center of blood flow to the periphery, along the vessel wall.

2. Cellular Events (Leukocyte Extravasation):

This is the process of recruiting neutrophils (and later, monocytes) to the site of injury:

- **Margination and Rolling:** As blood flow slows (stasis), leukocytes tumble and stick loosely to the endothelium. This "rolling" is mediated by **Selectin** molecules (P-selectin, E-selectin) on the endothelium.
- **Adhesion (Pavementing):** Cytokines (TNF, IL-1) from local macrophages activate the endothelium to express adhesion ligands (ICAM-1, VCAM-1). Leukocytes express **Integrins**, which bind tightly to these ligands, causing the cells to adhere firmly to the vessel wall.
- **Transmigration (Diapedesis):** The leukocytes then squeeze through the junctions between endothelial cells to enter the interstitial tissue. This process is mediated by **PECAM-1 (CD31)**.
- **Chemotaxis:** Once in the tissue, the leukocytes migrate toward the site of injury by following a chemical gradient of **chemoattractants**. Key chemoattractants include complement component **C5a**, leukotriene **LTB4**, and bacterial products.
- **Phagocytosis:** At the site, the leukocytes are activated to recognize, engulf, and kill the injurious agent. This process is enhanced by opsonins (IgG, C3b). Killing is achieved primarily via the **respiratory burst**, using NADPH oxidase and myeloperoxidase (MPO) to generate hypochlorous acid (HOCl).

Question 2: Classify and describe the key chemical mediators of acute inflammation.

Answer:

Chemical mediators are substances that initiate and regulate the inflammatory response. They are derived from either plasma or cells and are generally short-lived.

Classification and Description:

1. **Cell-Derived Mediators:**
    - **Vasoactive Amines:**
        - **Histamine:** The principal mediator of the immediate, transient phase. It is stored pre-formed in mast cells and basophils. It causes vasodilation and increased vascular permeability.
    - **Arachidonic Acid (AA) Metabolites:** These are synthesized de novo during inflammation.
        - **Prostaglandins (via Cyclooxygenase):** Mediate vasodilation and edema. **PGE2** is responsible for **fever** and **pain**. (Aspirin/NSAIDs work by inhibiting this pathway).
        - **Leukotrienes (via Lipoxygenase): LTC4, LTD4, and LTE4** cause intense bronchoconstriction and increased permeability. **LTB4** is a potent **chemotactic agent**.
    - **Cytokines (TNF and IL-1):** These are polypeptides produced by activated macrophages and mast cells.
        - They are the primary drivers of the **systemic effects** of inflammation, such as **fever**, lethargy, and the acute-phase response.
        - They are essential for "activating" the endothelium to express adhesion molecules (E-selectin, ICAM-1) required for leukocyte binding.
    - **Nitric Oxide (NO):** A short-acting gas produced by endothelial cells (eNOS) and macrophages (iNOS). It is a potent **vasodilator** and is also microbicidal.
2. **Plasma-Derived Mediators (from the Liver):**
    - **The Complement System:** A cascade of plasma proteins that are critical for defense. When activated, its key products are:
        - **C3a and C5a (Anaphylatoxins):** Cause histamine release from mast cells (leading to vasodilation and permeability).
        - **C5a:** A powerful **chemotactic agent** for neutrophils and macrophages.

        - **C3b:** The primary **opsonin** in inflammation, coating microbes for phagocytosis.
    - **The Kinin System:**
        - **Bradykinin:** This mediator is activated by Factor XII (Hageman factor). Its actions are similar to histamine (vasodilation, permeability) but it is most notable as the primary mediator of **pain**.

Question 3: Define chronic inflammation. What is a granuloma? Describe its formation and types, with examples.

Answer:

Definition: Chronic inflammation is a prolonged inflammatory response (weeks to months) where the processes of active inflammation, tissue destruction, and attempts at healing (fibrosis) occur simultaneously. It is characterized by an infiltrate of **mononuclear cells**, primarily **macrophages, lymphocytes, and plasma cells**.

Granulomatous Inflammation and the Granuloma:

Granulomatous inflammation is a distinctive, specialized pattern of chronic inflammation. A granuloma is a focal, microscopic aggregate of activated macrophages, which are often transformed into epithelioid cells (cells with abundant pink cytoplasm and indistinct borders), and are typically surrounded by a collar of lymphocytes.

Formation of a Granuloma (Pathogenesis):

A granuloma is formed as a T-cell-mediated attempt to contain an offending agent that is difficult to eradicate.

1. An indigestible agent (e.g., *M. tuberculosis*) is ingested by a macrophage.
2. The macrophage fails to kill the agent and presents its antigen to a **CD4+ T-cell**.
3. The T-cell differentiates into a **TH1 cell** and secretes the key cytokine, **Interferon-gamma (IFN-γ)**.
4. IFN-γ "activates" the macrophage, transforming it into an epithelioid cell.
5. Activated epithelioid cells may fuse, forming **multinucleated giant cells** (e.g., Langhans giant cell, foreign body giant cell).

6. This collection of activated macrophages, giant cells, and surrounding lymphocytes forms the granuloma.

Types of Granulomas and Examples:

Granulomas are broadly classified based on the presence or absence of central necrosis.

- **Caseating Granuloma:** This granuloma features a central core of **caseous necrosis**, which appears as amorphous, eosinophilic, granular debris. This pattern is the hallmark of **Tuberculosis**.
- **Non-Caseating Granuloma:** This type lacks central necrosis. It is composed of a tight, organized cluster of epithelioid cells and giant cells. This pattern is characteristic of:
    - **Sarcoidosis**
    - **Crohn's disease**
    - **Foreign body reactions** (e.g., to a suture or talc particle).