Introduction to Pathology

Definitions of pathology

- The word **'pathology'** is derived from two Greek words:
    - ***Pathos*** meaning suffering,
    - ***Logos*** meaning study.
- The study of the essential nature of disease, including symptoms/signs, pathogens, complications and morphological consequences including structural and functional alterations in cells, tissues and organs.
- The study of the *gross* and *microscopic* patterns of disease.
- Pathology is, thus, scientific study of structure and function of the body in disease; or in other words, pathology consists of the abnormalities that occur in normal anatomy (including histology) and physiology owing to disease.
- **Pathophysiology:**
    - ***Patho***- suffering
    - ***Physiology***- study of normal function.
- Pathophysiology, thus, includes study of disordered function or breakdown of homeostasis in diseases.
- Pathologists are the diagnosticians of disease.

Terminology in pathology

- **Patient** is the person affected by disease.
- **Disease** is a condition in which the presence of an abnormality of the body causes a loss of normal health.
    - **Idiopathic** – no identifiable causes.
    - **Iatrogenic** – occur as a result from medical treatment.
    - **Congenital** – disease existing at birth or before birth, involves in the development of fetus.
    - **Acquired** – develops post–fetally.
    - **Nosocomial** – due to being in a hospital environments.
    - **Lesions** are the characteristics changes in tissues and cells produced by disease in an individual or environmental animal.
- **Pathological changes** or **morphology** consists of examination of diseased tissues.
- Pathologic changes can be recognized with the naked eye (**gross or macroscopic changes**) or studied by **microscopic** examination of tissues.
- Causal factors responsible for the lesions (or disease) are included in **etiology** of disease (i.e. 'why' of disease).
- Mechanisms by which the lesions are produced is termed **pathogenesis** of disease (i.e. 'how' of disease).
- Functional implications of the lesions felt by the patients are **symptoms** (pain, nausea, vomiting, etc.) and those discovered by the clinician are the physical **signs** (pulse rate, blood pressure, temperature, etc.).
- Clinical significance of the morphologic and functional changes together with results of other investigations help to arrive at an answer to what is wrong **(diagnosis),** what is going to happen **(prognosis),** what can be done about it **(treatment),** and finally what should be done to avoid complications and spread **(prevention)** (i.e. 'what' of disease).
- **Epidemiology** is the study of tracking patters of disease occurrence and transmission among populations and by geographic areas.
    - *Epi*= among
    - *Demos*= People
    - *Logy*= study
        - **Incidence** of a disease – is the number of new cases occurring in specific time of period.

- **Prevalence** of a disease – is the number of existing cases within a populations during the specific time of period.

Pathology Basis of Disease (disease process)

- The four aspects of a disease process that form the core of pathology are:
    1. its cause ***(etiology)***,
    2. *the mechanisms of its development (**pathogenesis**),*
    3. *the structural alterations induced in the cells and* organs of the body *(**morphologic changes**),*
    4. *the functional consequences of the morphologic changes (**clinical significance**).*

1. **Etiology (cause)**
    a. Genetic
    b. Acquired (e.g., infectious, nutritional, chemical, physical).
2. **Pathogenesis**: sequence of events in the response of cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the disease
3. **Morphologic changes**
    a. Gross changes
    b. Microscopic changes
4. **Clinical significance**
    a. Signs and symptoms
    b. Disease course- complications
    c. Prognosis

Methods Used in Pathology

1. **Gross examination of organs**

a. Gross examination of organs has two major components

i. Identifying the organ (what organ)
ii. Identifying the pathology (what's wrong)

b. Useful gross features

i. Size
ii. Shape
iii. Consistency
iv. Color

2. Microscopic examination of tissue

a. Light microscopy

i. *Hematoxylin and Eosin (H&E) - Gold Standard Stain*

- Most **widely used histological stain**.
- Comparatively **simple** and has ability to **demonstrate clearly** an enormous number of different tissue structures.
- Hematoxylin (*basic dye; stains acidic components*) stains the cell nuclei **blue/black**, with good intranuclear detail,
- while the eosin *(acidic dye; stains basic components)* stains cell cytoplasm and most connective tissue fibres in varying shades and intensities of **pink, orange and red**.

Table: Structure stained by *Hematoxylin and Eosin (H&E)*

Hematoxylin	Eosin
Stains blue to purple	**Stains pink to red**
• Neuclei	• Cytoplasm
• Neucleoli	• Collagen
• Bacteria	• Fibrin
• Calcium	• RBCs
• Many others…	• Thyroid colloid
	• Many others…

b. Other histochemical stains (chemical reactions)

i. Prussian blue – iron
ii. Congo red – amyloid
iii. Acid fast (Ziehl-Neelson, Fite) – acid-fast bacilli
iv. Periodic Acid-Schiff (PAS) – with high carbohydrate content molecules
v. Gram's stain – bacteria
vi. Trichrome – cells and connective tissue
vii. Reticulin – collagen type III molecules

c. Immunohistochemical (antibody) stains

i. Cytokeratin – epithelial cells
ii. Vimentin – cells of mesenchymal origin
iii. Desmin – smooth, cardiac and skeletal myosin
iv. Prostate specific antigen (PSA)
v. Many others

3. Ancillary techniques

1. **Immunofluorescence microscopy (IFM)**
    1. Renal diseases
    2. Autoimmune diseases
2. **Transmission electron microscopy (EM)**
    1. Renal disease
    2. Neoplasms
    3. Infections
    4. Genetic disorders
3. **Molecular techniques**
    1. Protein electrophoresis
    2. Southern and Western blots
    3. Polymerase chain reaction (PCR)

Cell injury

Definition of Cell

- A cell is the smallest unit that is capable of performing life functions.
  (***Structural and functional unit of life***)
- Cells forms organs and systems in the human body

Definition of Cell injury

Cell injury is defined as *a variety of stresses a cell encounters as a result of changes in its internal and external environment.*

Cellular response to stress

May vary and depends upon the following variables:

1. The type of cell and tissue involved.
2. Extent and type of cell injury.

Cellular response to cell injury

1. When there is increased functional demand, the cell may adopt to the changes which are expressed morphologically and then revert back to normal after the stress is removed (***cellular adaption***).
2. When the stress is mild to moderate, the injured cell may recover (***reversible cell injury***), while when the injury is persistent cell death may occur (***irreversible cell injury***).
3. The residual effects to reversible cell injury may persist in the cell as evidence of cell injury at subcellular level (***subcellular changes***), or metabolites may accumulate within the cell (***intracellular accumulations***).

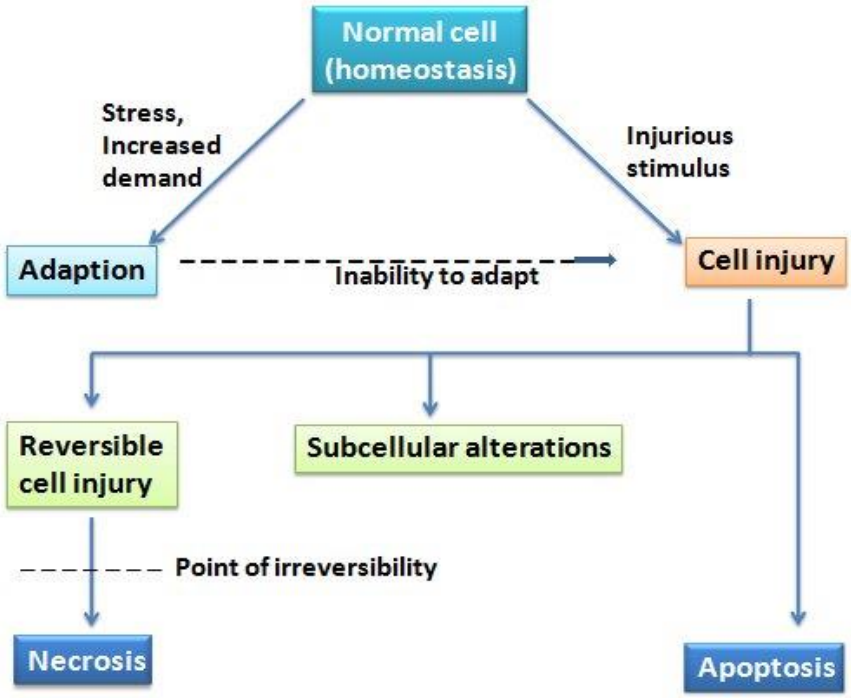


Fig: Stages in the cellular response to stress and injurious stimuli.

<u>Terminologies</u>

<u>Atrophy</u>: *decrease in cell size and functional ability*

Causes of atrophy:

i. Deceased workload/disuse (immobilization)

ii. Ischemia (atherosclerosis)
iii. Lack of hormonal or neural stimulation
iv. Malnutrition
v. Aging

Hypertrophy: *an increase in cell size and functional ability due to increased synthesis of intracellular components*

Causes of hypertrophy:

i. Increased mechanical demand
   - Physiologic ---striated muscle of weight lifters
   - Pathologic ---cardiac muscle in hypertension

ii. Increased endocrine stimulation
   - Puberty (growth hormone, androgens/estrogens, etc.)
   - Gravid uterus (estrogen)
   - Lactating breast (prolactin and estrogen)

Hyperplasia: *an increase in the number of cells in a tissue or organ.* Some cell types are unable to exhibit hyperplasia (e.g. nerve, cardiac, skeletal muscle cells)

1. *Physiologic causes of hyperplasia*
   i. Compensatory (e.g., after partial hepatectomy)
   ii. Hormonal stimulation (e.g., breast development at puberty)
   iii. Antigenic stimulation (e.g. lymphoid hyperplasia)
2. *Pathologic causes of hyperplasia*
   i. Endometrial hyperplasia
   ii. Prostatic hyperplasia of aging

Metaplasia: *a reversible change of one cell type to another, usually in response to irritation*.

- It has been suggested that the replacement cell is better able to tolerate the environmental stresses. For example, *bronchial columnar epithelium undergoes squamous metaplasia* in response to the chronic irritation of tobacco smoke.

Dysplasia: *an abnormal proliferation of cells that is characterized by changes in cell size, shape, and loss of cellular organization*

Dysplasia is not cancer but may progress to cancer (preneoplastic lesion)
Example: cervical dysplasia

Ischemia: *deficient blood supply to part of tissue*. The cessation of blood supply may be complete (complete ischemia) or partial (partial ischemia).

Causes of cell injury

1. **Hypoxia**
   - *Most common cause of injury*
   - Definition: *lack of oxygen leads to the inability of the cell to synthesize sufficient ATP by aerobic oxidation*

- Major causes of hypoxia
    i. *Ischemia:* loss of blood supply
    Most common cause of hypoxia
    Decreased arterial flow or decrease venous outflow
    e.g., arteriosclerosis, thrombus
    ii. *Cardiopulmonary failure*
    iii. *Decreased oxygen-carrying capacity of the blood* (example: anemia)

2. **Infections**
    - Viruses, bacteria, parasites, and fungi (and probably prions)
    - Mechanism of injury
        i. Direct infection of cells
        ii. Production of toxins
        iii. Host inflammatory response
3. **Immunologic reactions**
    a. Hypersensitivity reactions
    b. Autoimmune diseases
4. **Congenital disorders**
    - *Inborn errors of metabolism (i.e., inherited disorders)*
5. **Chemical injury**
    a. Drugs
    b. Poisons (cyanide, arsenic, mercury, etc.)
    c. Pollution
    d. Occupational exposure (CCI4 asbestosis, carbon monoxide, etc.)
    e. Social/lifestyle choices (alcohol, cigarette smoking, intravenous drug abuse [IVDA], etc.)
6. **Physical forms of injury**
    a. Trauma (blunt/penetrating/crush injuries, gunshot wounds, etc.)
    b. Burns
    c. Frostbite
    d. Radiation
    e. Pressure changes
7. **Nutritional or vitamin imbalance**
    a. **Inadequate calorie/protein intake**
        i. Marasmus and kwashiorkor
        ii. Anorexia nervosa
    b. **Excess caloric intake**
        i. Obesity
        ii. Atherosclerosis
    c. **Vitamin deficiency**
        i. Vitamin A – night blindness, squamous metaplasia, immune deficiency
        ii. Vitamin C – scurvy
        iii. Vitamin D – rickets and osteomalacia
        iv. Vitamin K – bleeding diathesis
        v. Vitamin B12 – megaloblastic anemia, neuropathy and spinal cord degeneration
        vi. Folate – megaloblastic anemia and neural tube defects
        vii. Niacin – pellagra (diarrhea, dermatitis, and dementia)
    d. **Hypervitaminosis**

Cellular changes during injury

1. **General**
2. **Reversible cell injury**
3. **Irreversible cell injury**

1. General

a. **Cellular responses to injury**
   i. Adaptation
   ii. Reversible injury
   iii. Irreversible injury and cell death (necrosis/apoptosis)

b. **Cellular response to injury depends on several important factors**
   i. The *type of injury*
   ii. The *duration of injury*
   iii. The *severity and intensity of injury*
   iv. The *type of cell injured*
   v. The cell's *metabolic state*
   vi. The cell's *ability to adapt*

c. **The critical intracellular systems that are susceptible to injury**
   i. DNA
   ii. Production of ATP via aerobic respiration
   iii. Cell membranes
   iv. Protein synthesis

d. **Important mechanisms of cell injury**
   i. Damage to DNA, proteins, lipid membranes, and circulating lipids (LDL) caused by oxygen-derived free radicals
      - Superoxide anion ($O2^-$)
      - Hydroxyl radical (OH^-)
      - Hydrogen peroxide (H2O2)
   ii. ATP depletion
   iii. Increased cell membrane permeability
   iv. Influx of calcium
      - Second messenger
      - Activates a wide spectrum of enzymes
      - Proteases – protein breakdown
      - ATPases – contributes of ATP depletion
      - Phospholipases – cell membrane injury
      - Endonucleases – DNA damage
   v. Mitochondrial dysfunction
      - Decreased oxidative phosphorylation and ATP production
      - Formation of mitochondrial permeability transition *(MPT)* channels
      - Release of *cytochrome c* is a trigger for apoptosis

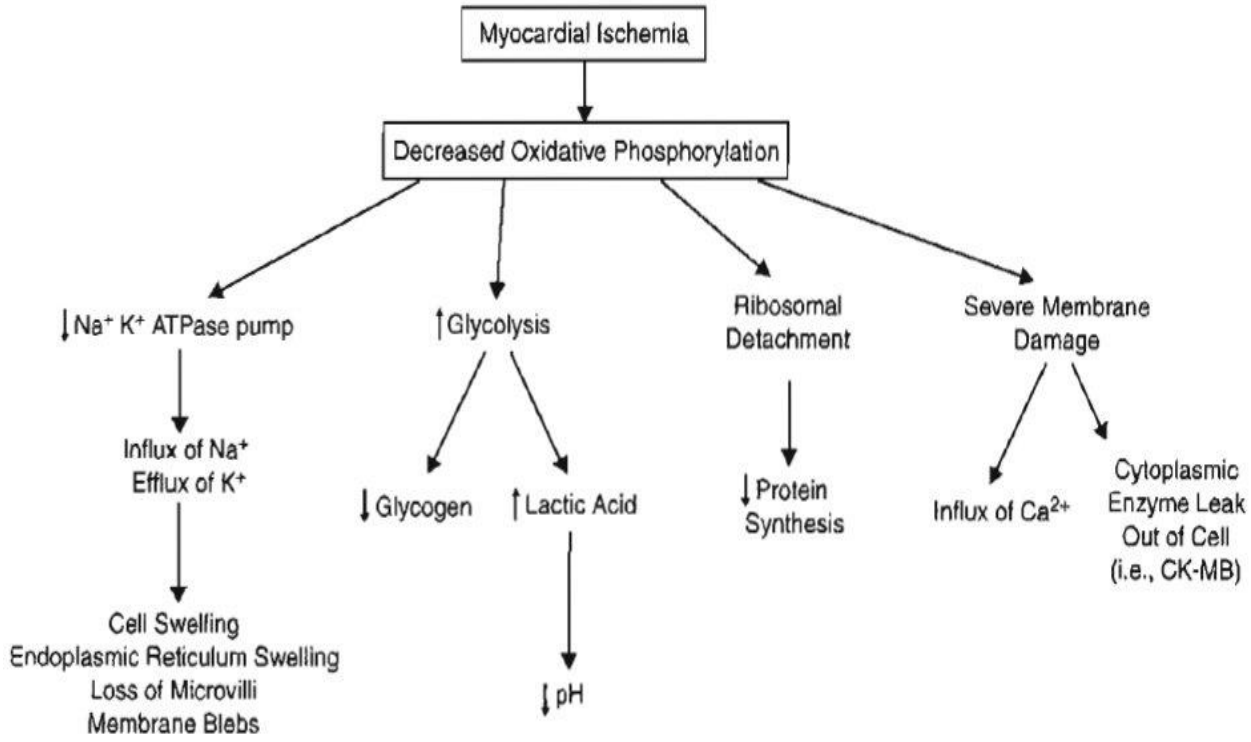


Figure 2-1. Classic Example of Cellular Injury Caused by Hypoxia

2. **Reversible cell injury**

a. Decreased synthesis of ATP by oxidative phosphorylation
b. Decreased function of Na^+K^+ ATPase membrane pumps
    i. Influx of Na^+ and water
    ii. Efflux of K^+
    iii. Cellular swelling (hydropic swelling)
    iv. Swelling of the endoplasmic reticulum
c. Switch to glycolysis
    i. Depletion of cytoplasmic glycogen
    ii. Increased lactic acid production
    iii. Decreased intracellular pH
d. Decreased protein synthesis
    i. Detachment of ribosomes from the rough endoplasmic reticulum
e. Plasma-membrane blebs and myelin figures may be seen

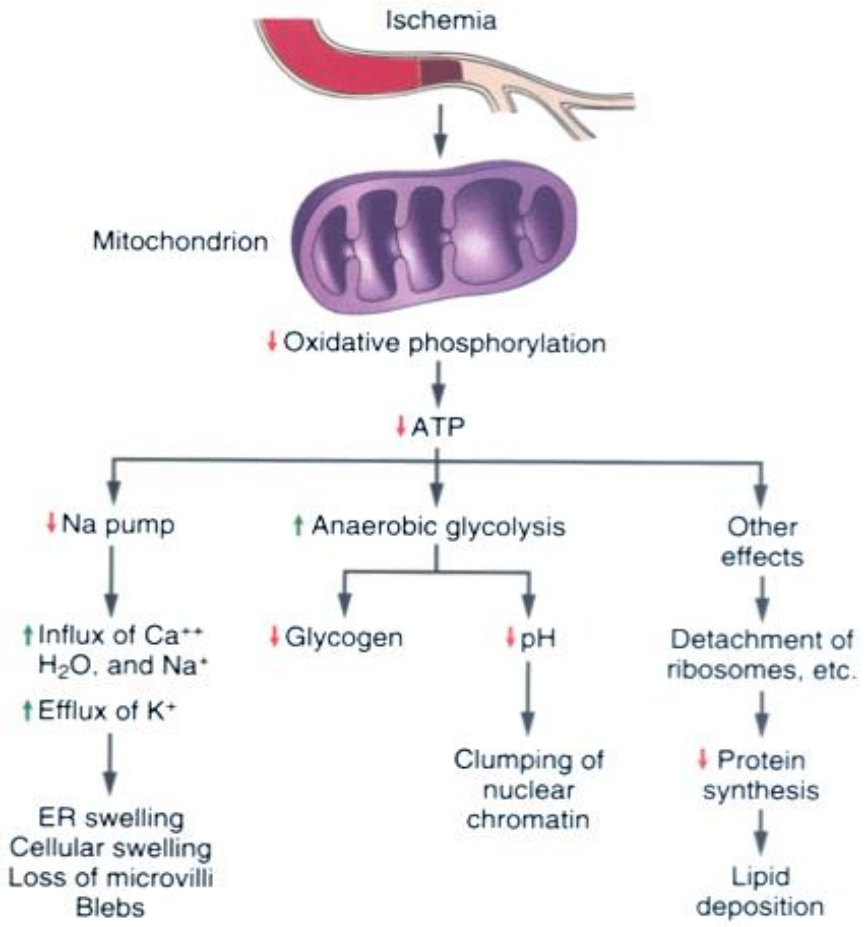


Figure: Mitochondrial dysfunction in cell injury.

3. **Irreversible cell injury**

a. Severe membrane damage
   i. Membrane damage plays a critical role in irreversible injury
   ii. Massive influx of calcium
   iii. Efflux of intracellular enzymes and proteins into the circulation

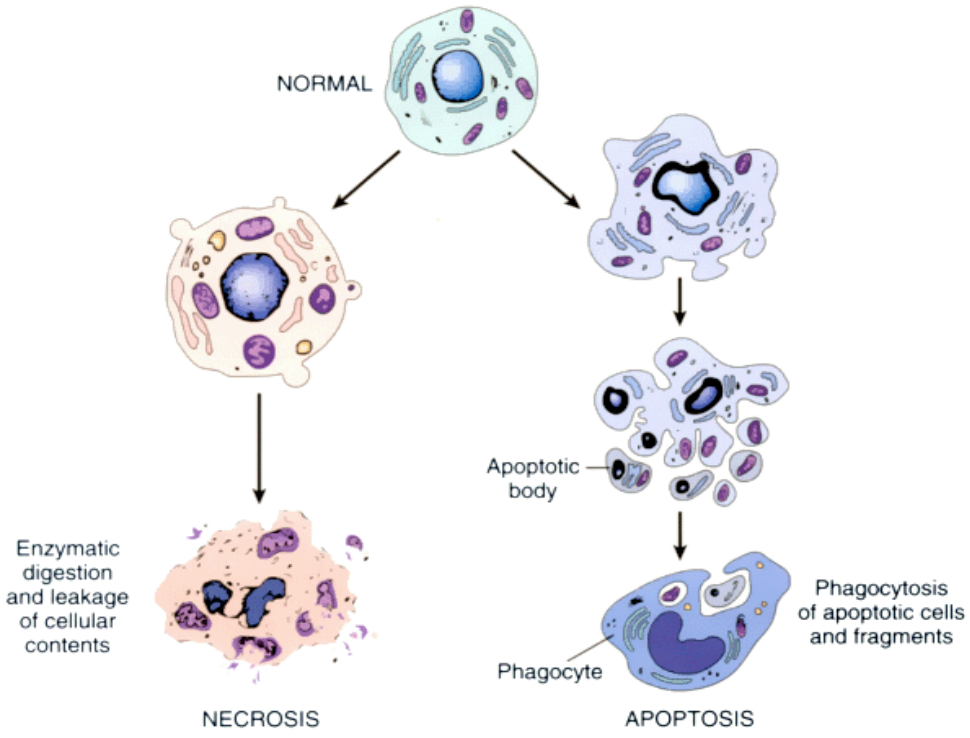
b. Marked mitochondrial dysfunction
   i. Mitochondrial swelling
   ii. Large densities are seen within the mitochondrial matrix
   iii. Irreparable damage of the oxidative phosphorylation pathway
   iv. Inability to produce ATP

c. Rupture of the lysosomes
   i. Release of lysosomal digestive enzymes into the cytosol
   ii. Activation of acid hydrolases followed by autolysis

d. Nuclear changes
   i. *Pyknosis:* degeneration and condensation of nuclear chromatin
   ii. *Karyorrhexis:* nuclear fragmentation
   iii. *Karyolysis:* dissolution of the nucleus

Features of Necrosis and Apoptosis

Features	Necrosis	Apoptosis
Definition	Cell death along with degradation of tissue by hydrolytic enzymes	Programmed and coordinated cell death
Causative agents	Hypoxia, toxins	Physiological and pathological process
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis – karyorrhexis – karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage



Figur : The sequential ultrastructural changes seen in necrosis *(left) and apoptosis (right)*

Inflammation

Introduction

- Inflammation is a **protective response intended to eliminate the initial cause of cell injury as well as necrotic cells and tissues resulting from original insult**.
- It is defined as the **reaction of vascularized connective tissue to sub-lethal injury**. It is fundamentally a **protective response to get rid of offensive injury**.
- **Exogenous and endogenous stimuli that cause cell injury can provoke a complex reaction in vascularized connective tissue which is known as inflammation**.
- In human, **inflammation is characterized by reaction of blood vessels leading to accumulation of fluid and leukocytes in extravascular tissue**.
- Inflammation **helps to destroy, dilute or neutralizing harmful agents (e.g., microbes and toxins)** but in turn sets into motion a series of events that **heal and reconstitute the damaged tissue**.
- Hence, without inflammation, infections would go unchecked, wounds would never heal and injured organs might remain as permanent stress/ulcers.
- **Inflammatory reaction may be potentially harmful** as for e.g., during life threatening hypersensitivity by insect bites, drugs and toxins or rheumatoid arthritis, arthrosclerosis and lung fibrosis.
- Hence, **anti-inflammatory drugs** are used to control the harmful effects of inflammation.

Causing agents of inflammation

1. ***Infective agents*** like bacteria, viruses and their toxins, fungi, parasites.
2. ***Immunological agents*** like cell-mediated and antigen-antibody reactions.
3. ***Physical agents*** like heat, cold, radiation, mechanical trauma.
4. ***Chemical agents*** like organic and inorganic poisons.
5. ***Inert materials*** such as foreign bodies.

Cardinal features of inflammation

1. *Rubor* (**redness**)
2. *Tumor* (**swelling**)
3. *Calor* (**heat**)
4. *Dolor* (**pain**)
5. *Functio laesa* (**loss of function**)

Types of inflammation

Depending upon the defense capacity of the host and duration of response, inflammation can be classified a acute and chronic.

1. **Acute inflammation**
   - It is a **rapid response to injury or microbes and other foreign substances that is designed to deliver leukocytes and plasma proteins to sites of injury**.
   - It is **short duration** (lasting less than 2 weeks) and represents the early body reaction, resolves quickly and usually followed by healing.

     Main features:

     1. Accumulation of fluid and plasma at the affected site
     2. Intravascular activation of platelets
     3. Polymorphonuclear neutrophils as inflammatory cells

Two major components:

1. ***Vascular changes***: increased blood flow (***vasodilation***) and permit plasma proteins to leave the circulation (***increased vascular permeability***).

2. ***Cellular events***: emigration of the leukocytes from the microcirculation and accumulation in the focus of injury (***cellular recruitment and activation***). Principle leukocytes are neutrophils (polymorphonuclear leukocytes).

Exudation:

Escape of fluid, proteins and blood cells from the vascular system into interstitial tissue and body cavities.

a. An ***exudate*** is a fluid which has high protein concentration, cellular debris and specific gravity >1.020.
b. A ***transudate*** is a fluid with low protein concentration and specific gravity <1.020.
c. **Edema**: It denotes an excess of fluid in the interstitial or serous cavities which can be an exudates or transudates.
d. **Pus**: It is an exudate rich in neutrophils and cell debris.

Stimuli for acute inflammation:

1. *Infections* (bacterial, viral, fungal and parasitic)
2. *Trauma* and *physical and chemical agents* (e.g., penetration, radiation, burns, frostbite)
3. *Tissue necrosis* (e.g., MI)
4. *Foreign bodies* (e.g., dirt, sutures)
5. *Immune reactions* (e.g., reaction to bee sting)

Hemodynamic changes

i. Initial transient vasoconstriction
ii. **Massive vasodilation** mediated by **histamine, bradykinin and prostaglandins**.
iii. **Increased vascular permeability**
   a. Chemical mediators of increased permeability
      - Vasoactive amines, histamine and serotonin
      - Bradykinin, an end-product of kinin cascade
      - Leukotrienes
   b. Mechanism of increased vascular permeability
      - Endothelial and pericyte contraction
      - Direct endothelial cell injury
      - Leukocyte of cell injury
      - **Blood flows slows (stasis)** due to **increased viscosity**, allows **neutrophils to marginate**.

Cellular changes

1. ***Neutrophils margination and adhesion***
   - Adhesion is mediated by complementary molecules on the surface of neutrophils and endothelium
   - Adhesion molecules are selectins and integrins
2. ***Emigration***
   - Leukocyte emigrate from the vasculature by extending pseudopods between the endothelial cells
   - They then move between the endothelial cells, migrating through the basement membrane towards the inflammatory stimulus
3. ***Chemotaxis***
   - It is the attraction of cells towards a chemical mediator that is released in the area of inflammation.
   - Important chemotactic factors of neutrophils
      1. Bacteria products

2. Leukotrine B4
3. Complement system C5a

4. ***Phagocytosis and degranulation***
    - Opsonins enhance recognition and phagocytosis of bacteria.
    - Important opsonins are
        1. Fc portion of IgG,
        2. complement system product C3b,
        3. plasma protein collection
    - Engulfment
        - Neutrophils sends out cytoplasmic processes that surrounds the bacteria
        - The bacteria are internalized within a phagosome
        - The phagosome fuse with lysosomes (degranulation)
5. ***Intracellular killing***
    - **Oxygen dependent killing**
        1. **Respiratory brust**
            1. Requires oxygen and NADPH oxidase
            2. Produces **superoxide**, **hydroxyl radicals** and **hydrogen peroxide**
        2. **Myeloperoxide**
            1. Requires **hydrogen peroxide** and **halide** (Cl^-)
            2. Produces **HOCL** (hypochlorous acid)
    - **Oxygen independent killing**
        - Lysozyme
        - Lactoferrin
        - Acid hydrolases
        - Defensins
        - Bacterial permeability increasing protein (BPI)

Chemicals mediators of inflammation

1. ***Vasoactive amines***
    a. **Histamine**
        i. Produced by basophils, platelets, and mast cells
        ii. Effect: vasodilation and increased vascular permeability
    b. **Serotonin**
        - Produced by platelets
        - Effect: vasodilation and increased vascular permeability
2. ***Kinin system***
    - Activated Hageman factor (factor XII) converts **prekallerian – kallikerin**
    - Kallikerin cleaves high mol. wt. kininogen (HMWK) – **bradykinin**
    - Effects of **bradykinin**
        1. Increased vascular permeability
        2. Vasodilation
        3. Pain
        4. Bronchoconstriction
3. ***Arachidonic acid products***
    1. Cyclooxygenase pathway
        - **Thromboxane A2**
            1. Produced by platelets and vascular epithelium
            2. Vasoconstriction and platelet aggregation
        - **Prostacyclin (PGI2)**

1. Produced by vascular epithelium
2. Vasodilation and inhibit platelet aggregation

- **Prostaglandin E2**: pain

2. Lipoxygenase pathway
    - Leucotrine B4 (LTB4): neutrophil chemotaxis
    - Leucotrine C4,D4,E4: vasoconstriction

4. ***The complement cascade***
    1. Important products
        - C5b, C9: MAC (membrane attack complex)
        - C3a, C5a: anaphylotoxins stimulate release of histamine
        - C5a: leucocyte chemotactic factor
        - C3b: opsonin for phagocytosis
5. ***Cytokines***
    - IL-1 and TNF

Outcomes of Acute inflammation

- Complete resolution with regeneration
- Complete resolution with scarring
- Abscess formation
- Transition to chronic inflammation

2. **Chronic inflammation**

➢ **It is the inflammation of prolonged duration (weeks to months to years) in which active inflammation, tissue injury and healing proceed simultaneously.**

Chronic inflammation is characterized by:

- ***Infiltration with mononuclear cells***, including macrophages, lymphocytes and plasma cells.
- ***Tissue destruction***, largely induced by the products of the inflammatory cells.
- ***Repair, involving new vessel proliferation (angiogenesis) and fibrosis***.

Causes

1. **Following a bout of acute inflammation**
2. **Persistent infection**
3. **Infection with certain organisms**
    - Viral infection
    - Mycobacteria
    - Parasitic infections
    - Fungal infections
    - **Autoimmune diseases**
4. **Response to foreign material**
5. **Response to malignant tumors**

Important cells in chronic inflammation

1. **Macrophages**
    - Derived from blood monocytes
    - Life span (60 – 120 days)
    - Histocytes – connective tissue

- Kuffer cells – liver
- Osteoclasts – bone
- Microglia – brain
- Alveolar macrophages – lungs

2. **Lymphocytes**
    - B cells and plasma cells
    - T cells
3. **Eosinophils**
    - Play role in IgE mediated allergic reaction and parasitic infestation
    - Granules contains MBP (major basic protein) which is toxic to parasites
4. **Basophils**
    - Present mostly in lungs and skin
    - Important role in IgE mediated reactions (allergies and anaphylaxis)
    - Release histamine

Histologic features

- ***Infiltration with mononuclear cells*****,** which include macrophages, lymphocytes and plasma cells, a reflection of persistent reaction to injury.
- ***Tissue destruction***, largely induced by inflammatory cells
- Attempts at ***healing by connective tissue replacement of damaged tissue***, accompanied by proliferation of small blood vessels (***angiogenesis***) and ***fibrosis and scar***.

Chronic granulomatous inflammation

Definition: Specialized form of chronic inflammation characterised by *small aggregation of modified macrophages* (*epithelioid cells and multinucleated giant cells*) usually *surrounded by a rim of lymphocytes*.

Composition of granuloma

- Epithelioid cells
- Multinucleated giant cells
- Lymphocytes and plasma cells
- Central caseous necrosis

Granulomatous diseases

- Tuberculosis
- Cat-scratch fever (small gm -ve bacillus (*Bartonella henselae).* cat – reservoir – enlarged lymph node, pus formation, fever, headache, malaise)
- Leprosy
- Fungal infection (e.g., coccidioidomycosis)
- Parasitic infections (e.g., schistosomiasis)
- Foreign bodies
- Berylliosis (lung disease – inhalation of beryllium oxide)
- Sarcoidosis (uncommon chronic inflammatory disease of unknown origin – skin and lungs)

Systemic effects of chronic inflammation

1. **Fever**: mild fever with weight loss and weakness
2. **Anemia**: anemia of varying degree
3. **Leucocytosis**: relative leucocytosis
4. **ESR**: elevated ESR
5. **Amyloidosis**: secondary systemic amyloidosis (deposits of complex protein, known as amyloid)

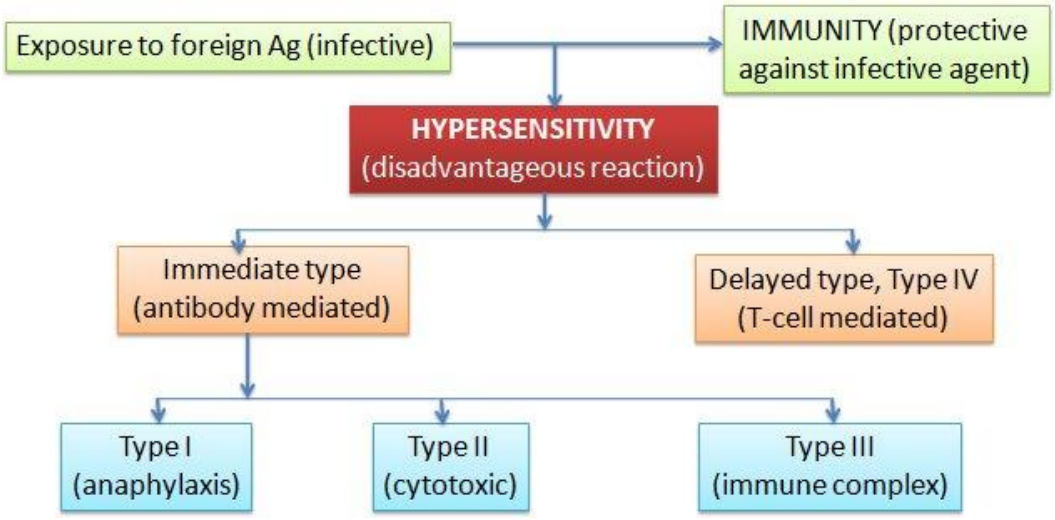
Hypersensitivity reactions

Introduction

- Hypersensitivity refers to **excessive undesirable (damaging, discomfort producing and sometimes fatal) reactions** produced by the normal immune system.
- It denotes an immune response resulting in **exaggerated or inappropriate reaction harmful to host**.
- It is a harmful immune response in which tissue damage is induced by exaggerated or inappropriate immune responses in a sensitized individual on re-exposure to the same antigen.
- Hypersensitivity essentially has two components.
    - First primary dose (first dose) of antigen is essential, which is required to prime the immune system,
    - followed by a shocking dose (second dose) of the same antigen that results in the injurious consequences.

Classification

- Two main types: **immediate** and **delayed type**.
- Immediate form is mediated by humoral antibody and manifests in few minutes to few hours while delayed form appears more slowly, usually after 24 hours which reaches a peak after 48-72 hours and is mediated by sensitised CD4 T cells.



Classified into 4 groups:

1. **Type I**: IgE mediated – allergy – mast cells and basophils
2. **Type II**: IgG and IgM based – activates complement and destroys cells
3. **Type III**: Immune complexes accumulate (IgM and IgG)
4. **Type IV**: T-cell based (slow) – delayed type hypersensitivity (DTH)

Types of hypersensitivity reactions

Type I (anaphylactic) reaction:

- Anaphylaxis (*ana*: against; *phylaxis*: protection) is a type of IgE mediated hypersensitivity reactions, which develops quickly after introduction of a large shocking dose of antigen following one or more small sensitising doses.
- The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis).
- The reaction takes 15-30 minutes from the time of exposure to the antigen.

Pathogenesis:

Type I reaction includes participation by B lymphocytes and plasma cells, **mast cells** and basophils, neutrophils and eosinophils.

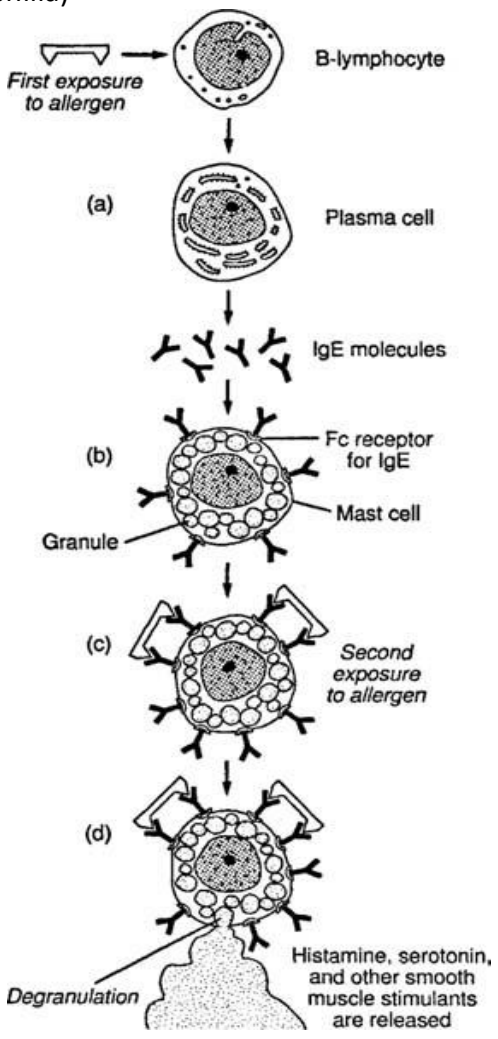
i. *First contact* of host with antigen, *sensitisation* takes place; circulating B lymphocytes get activated; differentiate to form IgE-secreting plasma cells; IgE Abs bind to Fc receptors in mast cells and basophils.

ii. *Second contact* with same Ag; IgE Abs on surface of mast cells-basophils are so firmly bound to Fc receptor that it sets in cell damage – membrane lysis, influx of sodium and water and *degranulation* of mast cells-basophils.

iii. Released granules contain important chemical and enzymes with *proinflammatory properties* – histamine, serotonin, vasoactive intestinal peptides, leukotrienes B4 and D4, prostaglandins and platelet activating factors.

The effects of these agents are:

- Increased vascular permeability
- Smooth muscle contraction
- Vasodilation
- Shock
- Increased gastric secretion
- Increased nasal and lacrimal secretion
- Increased migration of eosinophils and neutrophils at site of injury as well as in blood (eosinophilia, neutrophilia)



TYPE I Hypersensitivity Reaction

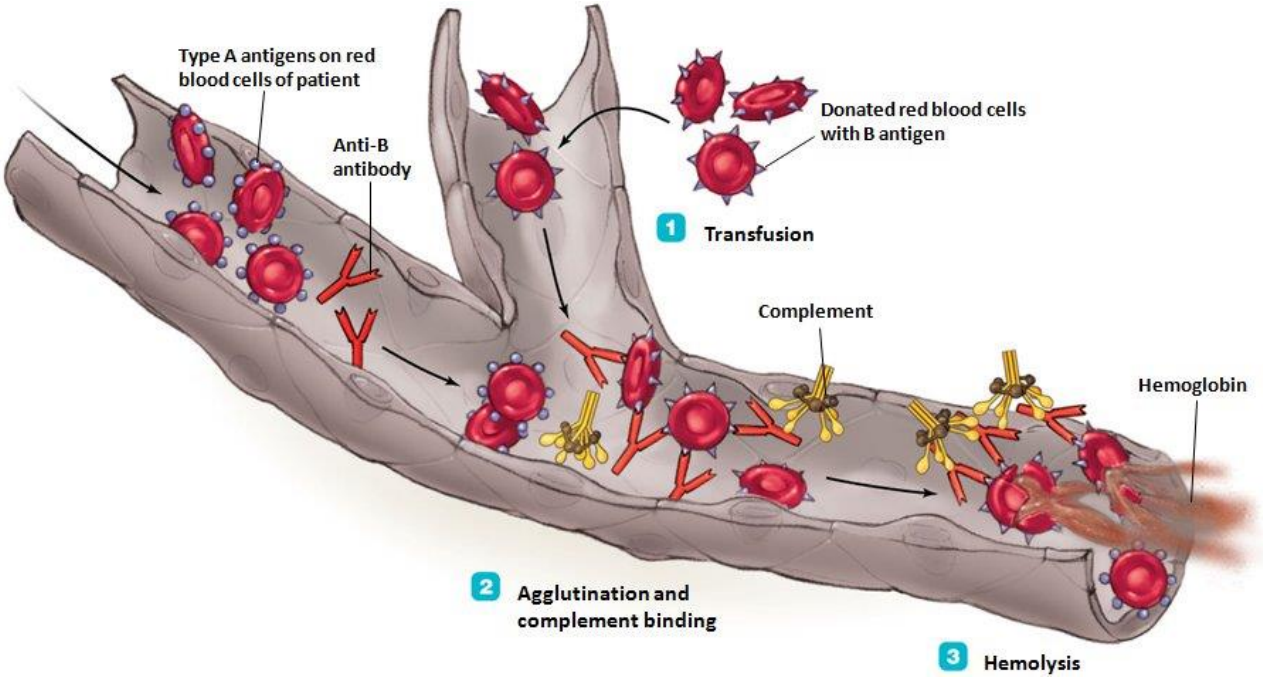
Type II (cytotoxic) reaction:

- It is defined as reactions by humoral antibodies that attack cell surface antigens on the specific cells and tissues and cause lysis of target cells.
- The reaction also takes 15-30 minutes from the time of exposure to the antigen.
- **Examples:** autoimmune haemolytic anaemia, transfusion reactions, erythroblastosis foetalis (haemolytic disease of newborn), drug induced cytotoxic reaction (penicillin, methyl dopa, rifampicin, etc.)

Pathogenesis:

It has participation by IgG & IgM Abs, tissue macrophages, platelets, NK cells, neutrophils, eosinophils and complement system. It is tissue specific and reaction occurs after antibodies bind to tissue specific antigens, most often on blood cells.

i. Ag on the surface of target cell (foreign cell) attracts and binds Fab portion of the Ab (IgG or IgM) forms *Ag-Ab complex.*
ii. The unattached Fc fragment of Abs forms a link between the *antigen and complement*.
iii. These causes *activation* of classical pathway of serum *complement* which generates activated complement components, C3b.
iv. Activated *C3b bound to target cell*, acts as opsonin and attracts phagocytes to the site of cell injury and initiates *phagocytosis*.
v. Ag-Ab complex also activates complement system and exposes *membrane attack complex (MAC) that attcks and destroy the target cell*.



Events in hemolysis

Type III (immune complex) reaction:

- Type III reactions result from deposition of Ag-Ab complexes on tissues, which is followed by activation of the complement system and inflammatory reaction, resulting in cell injury.
- The onset of type III reaction takes about 6 hours after exposure to the antigen.
- **Examples**: immune complex glomerulonephritis, rheumatoid arthritis, SLE, etc.

Serum Sickness

It is a disease caused by the injection of large doses of a protein antigen into the blood and characterized by the deposition of antigen-antibody complexes in blood vessel walls, especially in the kidneys and joints.

Route	Resulting disease	Site of immune-complex deposition
Intravenous (high dose)	Vasculitis	Blood vessel walls
	Nephritis	Renal glomeruli
	Arthritis	Joint spaces
Subcutaneous	Arthus reaction	Perivascular area
Inhaled	Farmer's lung	Alveolar/capillary interface

Pathogenesis:

Deposition of Ag-Ab complex on tissues and subsequent sequence of cell injury takes place. It has participation by IgG & IgM Abs, neutrophils, mast cells and complement.

i. Immune complex are formed by interaction of soluble Ab and soluble or insoluble Ag.
ii. Immune complex which fails to get removed from body fluid get deposited into tissues.
iii. Fc portion of Ab links with complement resulting in formation of C3a, C5a & MAC.
iv. C3a stimulates histamines, effects on increased vascular permeability and edema.
v. C5a releases proinflammatory mediators and chemotactic agents for neutrophils.
vi. Accumulated neutrophils and macrophages in the tissue release cytokines and results in tissue destruction.

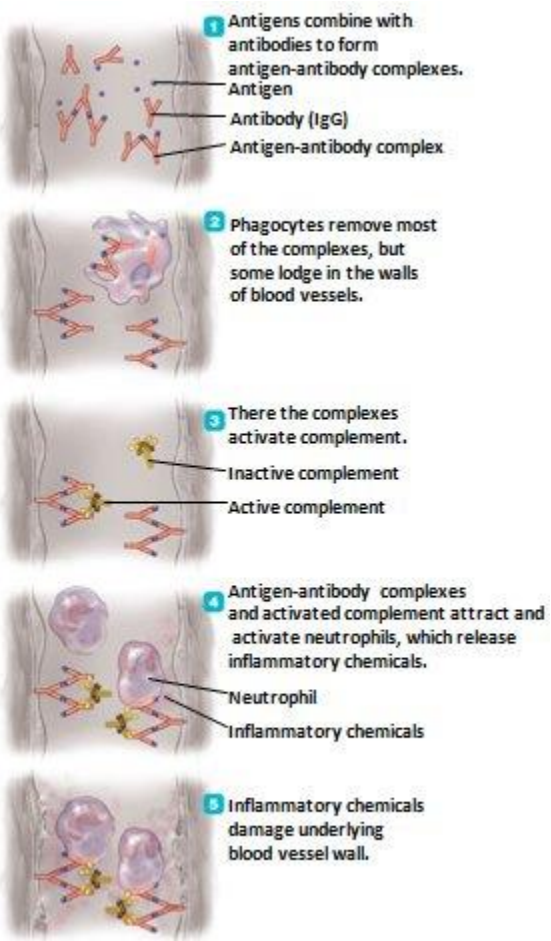


Fig: The mechanism of type III (immune-complex mediated) hypersensitivity-overview

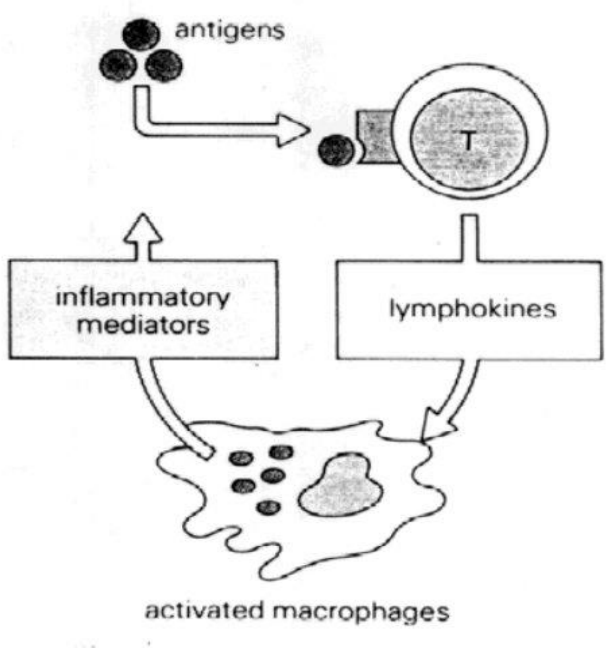
Type IV (delayed type) reaction:

- Type IV or delayed hypersensitivity reaction is tissue injury by cell mediated immune response without formation of antibodies but is instead a slow and prolonged response of specifically-sensitised T lymphocytes.
- The reaction occurs about 24 hours after exposure to antigen and the effects is prolonged which may last up to 14 days.
- **Examples**: reaction against MTB infection e.g., tuberculin reaction, reaction against virally infected cells, reaction against organ transplantation e.g., transplant rejection, graft versus host reaction.

Pathogenesis:

Type IV reaction involves role of mast cells and basophils, macrophages and CD8+ T-cells.

i. Ag is recognized by CD8+ T-cells (cytotoxic T-cells) and is processed by antigen presenting cells (APCs).
ii. APCs migrate to lymph node where Ag is presented to helper T-cells (CD4+ T-cells).
iii. Helper T cells release cytokines that stimulate T cell proliferation and activate macrophages.
iv. Activated T cells and macrophages release proinflammatory mediators and cause cell destruction.



Autoimmune disease

- **Autoimmunity** is a state in which the body's immune system fails to distinguish between '**self**' and '**non-self**' and reacts by formation of autoantibodies against one's own tissue antigen.
- In other words, there is loss of tolerance to one's own tissues; autoimmunity is the opposite of immune tolerance.
- **Immune tolerance** is a normal phenomenon present since foetal life and is defined as the ability of an individual to recognise self tissue and antigens.
- Normally, the immune system of the body is able to distinguish self from non-self antigens.
- The mechanisms by which the immune tolerance of the body is broken causes autoimmunity.
- These mechanisms or theories of autoimmunity may be immunological, genetic and microbial, all of which may be interacting.

Types:

1. **Organ specific diseases:**
    - The autoantibodies formed react specifically **against an organ or target tissue component** and causes its chronic inflammatory destruction.
    - The tissues affected are endocrine glands (thyroid, pancreatic islets of Langerhans, adrenal cortex), alimentary tract, blood cells, etc.
2. **Organ non-specific (systemic) disease:**
    - These are diseases in which a number or autoantibodies are formed which react with antigen **in many tissues and thus cause systemic lesions**.
    - These include Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, etc.

Systemic Lupus Erythematosus (SLE)

- It is the systemic autoimmune collagen disease, '*lupus*' Latin word meaning 'wolf', believed to affect skin only and eat always skin like a wolf.
- Connective tissue disease that mainly affects the skin, blood, joints and kidneys.
- Occurs predominantly in women of childbearing age.
- The disease is characterized by the presence of autoantibodies, which form immune complexes with autoantigens and are deposited within the kidney glomeruli.
- The resulting type III hypersensitivity is responsible for the glomerulonephritis (Inflammation of blood capillary vessels in the glomeruli).

1. **Systemic or disseminated form:**
   It is characterized by acute and chronic inflammatory lesions widely scattered in the body and there is presence of various nuclear and cytoplasmic autoantibodies in the plasma.
2. **Discoid form:**
   It is characterized by chronic and localised skin lesions involving the bridge of nose and adjacent cheeks without any systemic manifestation.

Etiology: Exact etiology is unknown, however autoantibodies against nuclear and cytoplasmic components of the cells are demonstrable in plasma by Immunofluorescence tests in almost all cases of SLE.

- Antinuclear antibodies (ANAs)
- Antibodies to double-stranded (anti-dsDNA)
- Anti-Smith antibodies (anti-Sm)
- Anti-ribonucleoprtoeins (anti-RNP)
- Anti-histone antibody
- Others

Pathogenesis:

The autoantibodies formed are the mediators of tissue injury in SLE.

Two types of immunologic tissue injury:

a) ***Type II hypersensitivity*** is characterized by formation of autoantibodies against blood cells (red blood cells, platelets, leucocytes) and results in haematologic derangement in SLE.

b) ***Type III hypersensitivity*** is characterized by antigen-antibody complex (commonly DNA-anti-DNA antibody) which is deposited at sites such as renal glomeruli, wall of small blood vessels, etc.

LE cell phenomenon:

- First diagnostic laboratory test described for SLE.

- The test is based on the principle that ANAs cannot penetrate the intact cells and thus cell nuclei should be exposed to bind them with the ANAs.
- The binding of exposed nucleus with ANAs results in homogenous mass of nuclear chromatin material which is called LE body.
- LE cell is a phagocytic leucocyte, commonly polymorphonuclear neutrophils, and sometimes monocytes, which engulf the homogenous nuclear material of the injured cell.

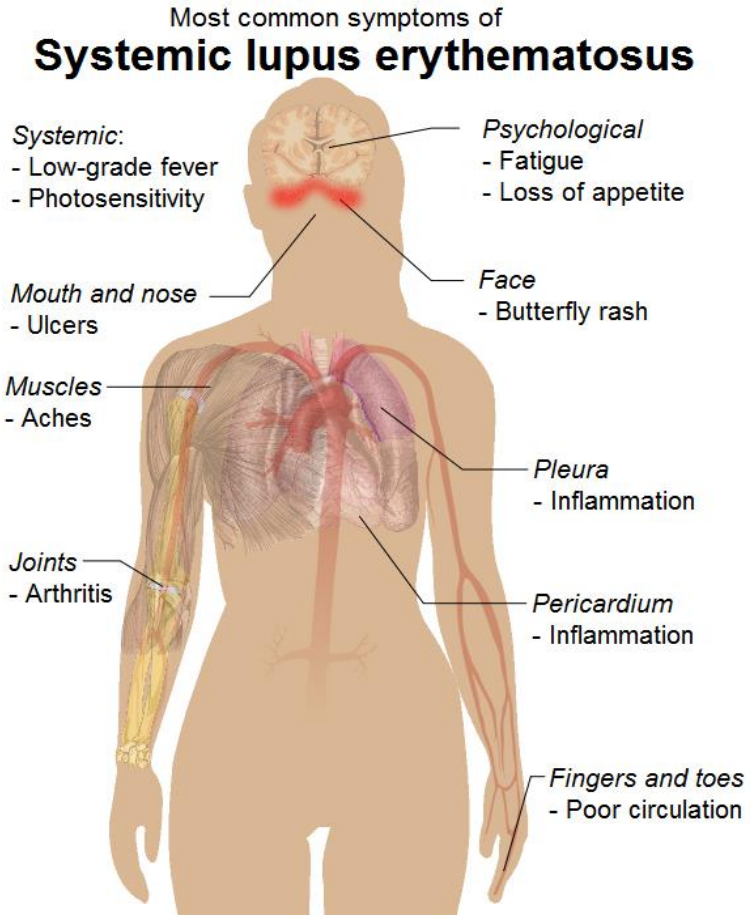
Clinical features:

- Targeted organs are musculoskeletal system, skin, kidneys, nervous system, lungs, heart and blood vessels, GI system, haematopoietic system.
- Fatigue and myalgia (pain in a muscle) are present.
- Severe illness with fever, weight loss, anaemia and organ related manifestations.

Diagnosis:

Four or more diagnostic criteria must be fulfill:

1. *Malar rash* (erythema, flat or raised over malar eminences (butterfly rash)
2. *Discoid rash* (erythematous circular raised patches)
3. *Photosensitivit*y (rash on exposure to sunlight)
4. *Oral ulcers*
5. *Non-erosive arthritis* (affecting two or more joints, swelling, tenderness, effusion)
6. *Serositis* (as pleuritis or pericarditis)
7. *Renal manifestation*
8. *Neurological manifestation*
9. *Haematologic derangements* (hemolytic anaemia, thrombocytopenia, leucopenia)
10. *Immunological derangements* (positive test for anti-dsDNA, etc.)
11. *Antinuclear antibodies* (by Immunofluorescence)



HIV and AIDS

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immunodeficiency Syndrome

- AIDS is caused by an RNA retrovirus called human immunodeficiency virus (HIV) which is a type of human T cell leukemia-lymphoma virus (HTLV).
- It is **characterized by infection and depletion of CD4+ T lymphocytes**, and by profound immunosupression leading to opportunistic infections, secondary neoplasms, and neurological manifestations.
- AIDS is end-stage disease of HIV infection which denotes irreversible breakdown of immune system of the host.

Epidemiology

- First described in United States in 1981; but now been reported in every country in the world.
- Worldwide, more than 22 million people have died of AIDS; about 42 million people are living with the disease and about 5 million infections each year.
- Worldwide, 95% of HIV infections are in developing countries, with Africa alone carrying more than 50% of the HIV burden.
- Although largest number of infection is in Africa, the most rapid increase in HIV infection in the past decades are in Southeast Asian countries, including Thailand, India and Indonesia.

Structure

- HIV-I virus particles is spherical in shape and 100-140 nm in size.
- It contains a core having core particles, p24 and p18, two strands of genomic RNA and the enzyme, reverse transcriptase.
- The core is covered by a double layer of lipid membrane derived from the outer membrane of infected host cell during budding process of virus.
- The membrane studded with 2 envelope glycoproteins, gp120 and gp41.
- Three important genes codes for the respective components of virion:
    - gag (group antigen) for core proteins
    - pol (polymerase) for reverse transcriptase, and
    - env (envelope) for the envelope proteins.

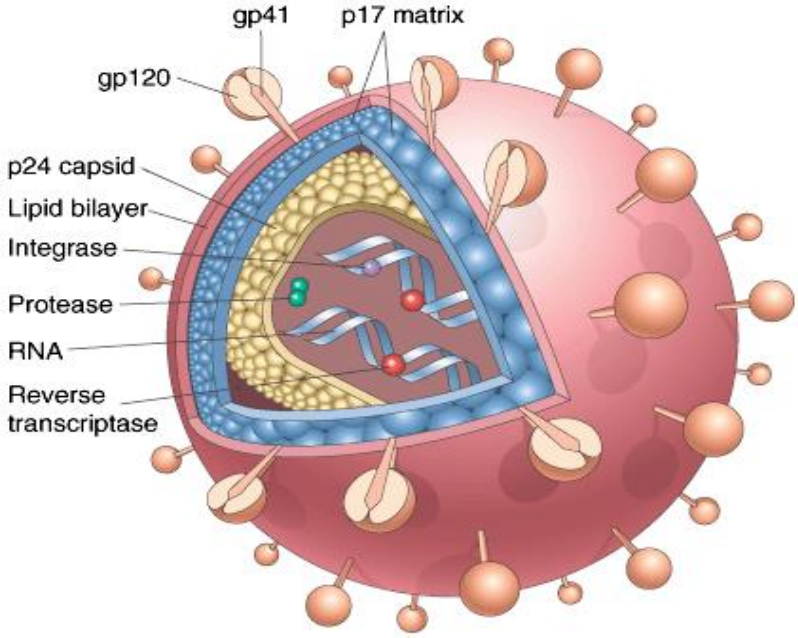


Fig: Schematic illustration of an HIV-1 virion. The viral particle is covered by a lipid bilayer that is derived from the host cell.

Route of Transmission

1. Sexual transmission
2. Transmission via blood and blood products
3. Perinatal transmission
4. Occupational transmission
5. Transmission by other body fluids (saliva, tears, sweat, urine, semen, vaginal and cervical secretions, breast milk, CSF, etc.

- *AIDS cannot be transmitted by casual non-sexual contact like shaking hands, hugging, sharing household facilities like beds, toilets, utensils, etc.*
- *Sterilization and disinfection: by the use of sodium hypochlorite, formaldehyde (5%), ethanol (70%), glutaraldehyde (2%), heating at 56 ^{o}C for 30 mins.*

Pathogenesis:

The pathogenesis of HIV infection is largely related to the depletion of CD4+ T cells (helper T cells) resulting in profound immunosupression.

1. **Selective tropism for CD4 molecule receptor:** (gp120 env protien)
2. **Internalisation:** (entry of virus in CD4 cell)
3. **Uncoating and viral DNA formation:** (viral RNA ssDNA (*reverse transcriptase*) dsDNA (*DNA polymerase*))
4. **Viral integration:** (Viral DNA integrates into host cell DNA)
5. **Viral replication:** (many virus particles are produces)
6. **Latent period and immune attack:** (overpowers the host immune system)
7. **CD4+ T cell destruction:** (destruction of CD4 cells)
8. **Viral dissemination:** (and finally releases and attacks other CD4 cells, immune cells and other body cells; produces viraemia).

Opportunistic Infections Associated with AIDS

Disease	Causative Agent	Organ Primarily Affected (Cha
Coccidioidomycosis	*Coccidioides* (fungus)	Lung (22)
Cytomegalovirus disease	*Cytomegalovirus*	Brain (20), liver (23)
Diarrhea (severe and prolonged)	Various bacteria, *Cryptosporidium* (protozoan)	Intestines (23)
Herpes	*Herpesvirus*	Skin (19)
Histoplasmosis	*Histoplasma* (fungus)	Lung (22)
Kaposi's sarcoma	Human herpesvirus 8	Blood vessels (21)
Meningitis	*Cryptococcus* (yeast), *Listeria* (bacterium)	Brain and meninges (20)
Oral hairy leukoplakia	*Lymphocryptovirus* (Epstein-Barr virus)	Tongue (23)
Pneumonia	*Pneumocystis* (fungus)	Lung (22)
Shingles	*Varicellovirus*	Skin (19)
Thrush	*Candida* (yeast)	Mouth and tongue (23), vagina (24)
Toxoplasmosis	*Toxoplasma* (protozoan)	Brain (20)
Tuberculosis	*Mycobacterium*	Lung (22)

Shock

Definition

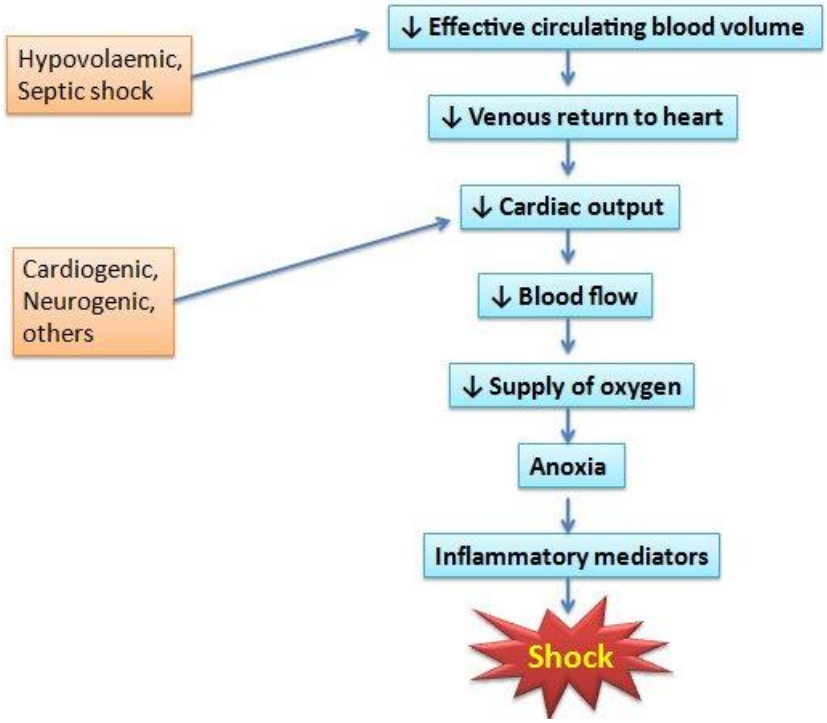
- It is a clinical syndrome characterized by decreased blood supply to body tissue.
- Shock or cardiovascular collapse constitute systemic hypoperfusion due to reduction either in cardiac output or in the effective circulating blood volume whose end results are hypotension followed by impaired tissue perfusion and cellular hypoxia.

Types of shock

1. Cardiogenic shock (pump failure)
2. Hypovolaemic shock (reduced blood volume)
3. Septic shock (bacterial infection)
4. Neurogenic shock
5. Anaphylactic shock

1. **Cardiogenic shock (pump failure)**
    - Myocardial infarction
    - Cardiac arrhythmias
    - Pulmonary embolism
    - Rupture of heart, ventricles or papillary muscles
    - Cardiomyopathies
    - ➢ Failure of myocardial pump due to intrinsic myocardial damage, extrinsic pressure or obstruct to outflow.
2. **Hypovolaemic shock (reduced blood volume)**
    - Acute haemorrhage
    - Dehydration from vomiting, diarrhoea
    - Burns or trauma
    - Excessive use of diuretics
    - Acute pancreatitis
3. **Septic shock**
    - Gram-negative septicaemia (endotoxic shock) e.g., infection with *E. coli, Proteus, Klebsiella, Pseudomonas*, etc.
    - Gram-positive septicaemia (exotoxic shock) e.g., infection with *streptococci, pneumococci*
4. **Neurogenic shock**
    - High cervical spinal cord injury
    - Accidental high spinal anaesthesia
    - Severe head injury
    - Hypotension
    - Bradycardia
5. **Anaphylactic shock**
    - Caused by type I hypersensitivity
    - IgE mediated
    - Reaction to the drugs and other allergens
      e.g., bronchospasm, hypotension

Pathogenesis of Shock:



Pathophysiology (Stages of shock)

1. Compensated shock:

- Non- progressive, initial, reversible shock
- Maintain adequate cerebral and coronary blood supply by redistribution of blood so that the vital organs (brain and heart) are adequately perfused and oxygenated.
- It is achieved by:
  - i. **Widespread vasoconstriction**
    - Activation of neural and humoral factors (baroreceptors, chemoreceptors, catecholamines, renin and angiotensin-II)
    - Effects: tachycardia, increased blood pressure and peripheral resistance, cool clammy skin
  - ii. **Fluid conservation by kidney**
    - Activation of renin-angiotensin-aldosterone mechanism, release ADH, reduced glomerular filtration rate (GFR), shifting of tissue fluids into plasma
  - iii. **Stimulation of adrenal medulla**
    - Release of catecholamines (epinephrine and non-epinephrine) which increase heart rate and cardiac output.

2. **Progressive decompensated shock**

- During which there is widespread tissue hypoxia.
- Patients suffers from some other stresses or risk factors (e.g., pre-existing cardiovascular or lung disease), progressive deterioration.
- Effects:
  - i. Pulmonary hypoperfusion and increased vascular permeability.
  - ii. Tissue ischemia; aerobic response is replaced by anaerobic glycolysis with production of lactic acid, lowers pH, vasodilation and peripheral pooling of blood occurs; leads to decrease cardiac output and urinary output, mental confusion.

3. **Irreversible decompensated shock**

- Irreversible tissue injury and organ failure ultimately resulting in death.
- Lysozymal enzyme leakage causes widespread cell injury.
- Myocardial contractility worsens and septic shock may superimpose.

- At this point there is complete renal shut down due to active tubular necrosis.
- Despite various measures, the clinical condition deteriorates which may end to death.
- Largely affects heart, brain, lungs, kidney, liver, GI, blood, etc.

Edema

- Approximately 60% of lean body weight is water; two thirds of this water is intracellular, and the remainder is found in the extracellular space, mostly as interstitial fluid (only about 5% of total body water is in blood plasma).
- The term *edema signifies increased fluid in the interstitial tissue spaces.*
- In addition, depending on the site, fluid collections in the different body cavities are variously designated *hydrothorax, hydropericardium, and hydroperitoneum (ascites).*
- ***Anasarca*** is a severe and generalized edema with profound subcutaneous tissue swelling.

It is a extravasation of fluid from vessels into interstitial spaces; the fluid may be protein poor (transudate) or may be protein rich (exudate).

Edema results from any of the following conditions:

i. **Increased hydrostatic pressure**, caused by a reduction in venous return (as in heart failure)
ii. **Decreased plasma/colloid osmotic pressure**, caused by reduced concentration of plasma albumin (due to decreased synthesis, as in liver disease, or increased loss, as in kidney disease)
iii. **Lymphatic obstruction** that impairs interstitial fluid clearance (as in scarring, tumors, or certain infections)
iv. **Primary renal sodium and water retention** (in renal failure)
v. **Increased vascular permeability** (in inflammation)

Thrombosis

- **Thrombosis** is the process of formation of solid mass in circulation from the constituents of flowing blood; the mass itself is called a **thrombus**.
- In contrast, a ***blood clot*** is the mass of coagulated blood formed *in vitro* e.g., in a test tube.
- **Haematoma** is the extravascular accumulation of blood clot e.g., into the tissues.
- **Haemostatic plugs** are the blood clots formed in healthy individuals at the site of bleeding e.g., in injury to the blood vessel.
- Normally, blood flowing through blood vessels do not clot because of smooth endothelial wall of vessels, normal blood flow and anticoagulants flowing in the blood.
- When derangements in above mentioned factors occurs then blood may coagulate in blood vessels which is known as thrombosis.

Pathogenesis

Factors involved in thrombus formation (**Virchow's Triad**)

i. *Endothelial injury*
    - Atherosclerosis
    - Vasculitis
    - Many others
ii. *Alterations in laminar blood flow*
    - Stasis of blood (e.g., immobilization)
    - Turbulence (e.g., aneurysms)
    - Hyperviscosity of blood (e.g., polycythemia vera)
iii. *Hypercoaguability of blood*
    - Clotting disorders (deficiency of antithrombin III, protein C, or protein S)
    - Tissue injury (post-operative and trauma)
    - Neoplasia

- Nephrotic syndrome
- Advanced age
- Pregnancy
- Oral contraceptives

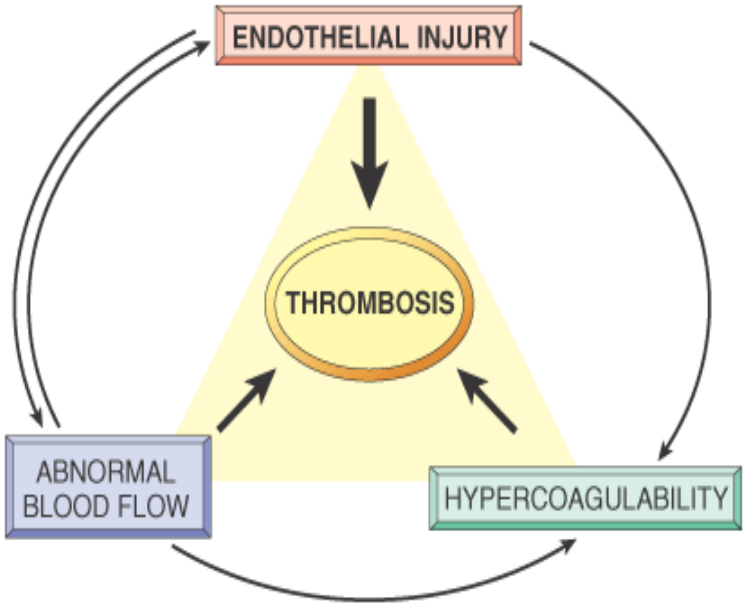


Fig: Virchow triad in thrombosis. Endothelial integrity is the single most important factor. Note that injury to endothelial cells can affect local blood flow and/or coagulability; abnormal blood flow (stasis or turbulence) can, in turn, cause endothelial injury. The elements of the triad may act independently or may combine to cause thrombus formation.

Table : Comparison of a Thrombus with a Blood Clot

	Thrombus	Blood Clot
Location	Intravascular	Extravascular or intravascular (postmortem)
Composition	Platelets Fibrin RBCs and WBCs	Lacks platelets Fibrin RBCs and WBCs
Lines of Zahn	Present	Absent
Shape	Has shape	Lacks shape

Common locations of thrombus formation

i. Coronary and cerebral arteries
ii. Heart chambers atrial fibrillation or post-MI
iii. Aortic aneurysms (swelling / dilatation of an artery due to weakening of its wall)
iv. Heart valves
v. Deep leg veins (deep vein thrombosis-DVTs)

Outcomes of thrombosis

i. Vascular occlusion and infarction
ii. Embolism
iii. Thrombolysis
iv. Organization and recanalization (reopen)

Embolism

- Any intravascular mass that has been carried down the bloodstream from its site of origin, resulting in the occlusion of a vessel is known as embolism.
- Embolus: an embolus is a detached intravascular solid, liquid or gaseous mass that is carried by blood to a distant site from its site of origin.
- Most usual forms of emboli (90%) are thromboemboli i.e. originating from thrombi or their parts detached from the vessel wall.

Types:

a. *Thromboemboli – most common (98%)*
b. Atheromatous emboli – severe atherosclerosis
c. Fat emboli – bone fractures and soft-tissue trauma
d. Bone marrow emboli – bone fractures
e. Gas emboli – decompression sickness
f. Amniotic fluid emboli – complication of labor
g. Tumor emboli – metastasis
h. Talc emboli – intravenous drug abuse (IVDA)
i. Bacterial/septic emboli – Infectious endocarditis

1. Pulmonary emboli (PE)

- Often clinically silent
- Most commonly missed diagnosis in hospitalized patients
- Found in almost half of all hospital autopsies

Morphology:

- It involves the lower lobes of the lung.
- Produces wedge shaped infarct which is grayish brown and hemorrhagic.
- The overlying pleura is thick and fibrinous.
- The infracted are later undergo fibrosis and forms a scar tissue.

Pathology

- Most (95%) arise in *deep leg veins thrombosis (DVT)*
- Pelvic venous plexuses of the prostate and uterus
- Right side of the heart

Clinical features:

- Chest pain
- Difficulty in breathing
- Shock
- Cough
- Tachycardia
- Hemoptysis
- Pleural pain

Potential outcomes of PEs

i. No sequela (75%) (i.e., not any condition or disorder subsequent to disease)
   - No infarction (dual blood supply)
   - Complete resolution
ii. Infarction (15%)
   - More common in patients with cardiopulmonary compromise
   - Shortness of breath (SOB), hemoptysis, pleuritic chest pain, pleural effusion
   - Regeneration or scar formation
iii. Sudden death (5%) (Large emboli may lodge)

iv. Chronic pulmonary hypertension (3%) (Caused by recurrent PEs)

Pulmonary emboli Prevention

- Pulmonary embolism is preventable condition
- It can be avoided by:
    - Giving isometric leg exercise
    - Prophylactic therapeutics measures *(e.g. use of anticoagulant therapy with heparin, warfarin)*
    - Embolectomy or thrombolysis (*streptokinase*)

Diagnosis

i. Doppler ultrasound of the leg veins to detect a DVT
ii. Plasma-D-dimer ELISA test is elevated *(a protein measured in a blood to diagnose thrombosis).*

2. Systemic arterial emboli

- Refers to the emboli travelling within arterial circulation
- Most arise in the heart
- Most cause infarction

Common sites of infarction

i. Lower extremities
ii. Brain
iii. Intestine
iv. Kidney
v. Spleen

Infarction

Definition: localized area of necrosis secondary to ischemia

Pathogenesis

i. Most infarcts (99%) result from *thrombotic or embolic occlusion of an artery or vein*
ii. Vasospasm
iii. Torsion (twisting) of arteries and veins (e.g., volvulus, ovarian torsion)

Factors that predict the development of an infarct:

i. Vulnerability of the tissue to hypoxia
ii. Degree of occlusion
iii. Rate of occlusion
iv. Presence of a dual blood supply or collateral circulation
v. Oxygen-carrying capacity of the blood

Common sites of infarction:

i. Heart
ii. Brain
iii. Lungs
iv. Intestines

Gross pathology of infarction

a. Often has a wedge shape
b. Apex of the wedge tends to point to the occlusion
c. Anemic infarcts (pale or white color)
    - Occur in solid organs with a single blood supply such as the spleen, kidney, and Heart
d. Hemorrhagic infarcts (red color)

- Occur in organs with a dual blood supply or collateral circulation, such as the lung and intestines
- Also occur with venous occlusion (e.g., testicular torsion)

Microscopic pathology of infarction

a. Coagulative necrosis – most organs
b. Liquifactive necrosis – brain
c. General sequence of tissue changes after infarction:

Ischemia → coagulative necrosis → inflammation → granulation tissue → fibrosis → infarction

Neoplasia

- The term 'neoplasia' literally means new growth; the new growth produced is called 'neoplasm' or 'tumor'.
- All new growth are not neoplasms e.g., embryogenesis, regeneration, repair.
  - Proliferate throughout life (labile cells)
  - Limited proliferation (stable cells)
  - Do not replicate (permanent cells)
- Neoplasm or tumor is *a mass of tissue formed as a result of abnormal, excessive, uncontrolled, autonomous and purposeless proliferation of cells even after cessation of stimulus for growth which caused it*.
- The study of tumors is called oncology (from oncos, "tumor", and logos, "study of").

Terminologies:

- **Differentiation**: refers to the extent to which parenchymal cells resemble comparable normal cells, both morphologically and functionally. In general, benign tumors are well differentiated.
- **Dysplasia**: means disordered growth. Mainly seen in epithelium and include a loss in uniformity of individual cells as well as loss in their architectural orientation.
- **Metastasis**: the distant spread of malignant tumor from the site of origin. This occurs through blood stream, lymphatic system and across body cavities.
- **Anaplasia**: lack of differentiation/normal cell characteristics which may to such a degree that is impossible to define origin of the cell. A typical malignant tumor.
- **Pleomorphism**: variation in shape and size of cell. The condition in which an individual assumes a number of different forms during its life cycle. The malarial parasites (plasmodium) displays pleomorphism. Nuclear cytoplasmic ratio 1:1 instead of normal 1:4 or 1:6.
- **Carcinoma**: malignant tumors of epithelial origin
- **Sarcoma**: malignant mesenchymal tumors
- **Melanoma**: carcinoma of melanocytes
- **Hepatoma**: carcinoma of hepatocytes
- **Lymphoma**: malignant tumors of the lymphoid tissue
- **Seminoma**: malignant tumors of the testis
- **Leukaemia**: cancer of the blood forming cells
- **Fibroma**: benign tumor of fibrous tissue
- **Chondroma**: benign cartilaginous tumor
- **Adenoma**: benign epithelial neoplasms producing gland pattern
- **Adenocarcinoma**: carcinoma that grows in glandular pattern

Pathways of cancer spread

1. **Directly through the body cavities:**
    - Most involved is in peritoneal cavity. Other are pleural cavity, pericardial cavity, subarachnoid and joint space may be affected. It is characteristics of cancer arising in ovaries.
2. **Lymphatic spread:**
    - Most essential and common for initial dissemination of cancer and sarcomas. The pattern lymph node involvement follows the natural route of damage.
3. **Haematogenous spread:**
    - Spread through blood.

Differences between Benign and Malignant tumors

Benign tumors	Malignant tumors
Well differentiated	Lack of differentiation
Less cellular pleomorphism	High cellular pleomorphism
Absence of mitosis	Presence of mitosis
Nuclear cytoplasmic ratio 1:4/1:6	Nuclear cytoplasmic ratio 1:1
Normochromatic nucleus	Hyperchromatic nucleus
Cellular dysplasia absent	Cellular dysplasia present
Soft to firm in consistency	Stony hard in consistency
Doesn't bleed on touch	Bleeds profusely on touch
Well encapsulated	Non-capsulated
Slow growth of rate	High and uncontrolled rate of growth
Not ulcerated and isn't bleeding	Ulcerated with bleeding
Cells provide bipolar spindles	Cells are atypical and show bizarre mitotic figure producing tripolar, bipolar or multipolar spindles
Grows as cohesive expansile masses that are localized to their site of origin and do not have capacity to infiltrate inside or metastasize. E.g., oesteoma, chondroma, adenoma, fibroma	Grows as progressive mass that can infiltrate, invade or destruct the surrounding tissue. E.g., carcinoma, sarcoma, melanoma

Wound Healing, Repair and Regeneration of Tissue

Healing is the body response to injury in an attempt to restore normal structure and function.

Wound healing involves regeneration of the damaged tissue by cells of the same type and tissue repair with replacement by connective tissue.

Hence, healing involves 2 distinct processes:

1. **Regeneration** when healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.
2. **Repair** when healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

1. **Tissue repair**

- Regeneration and healing of damaged cells and tissues starts almost as soon as the inflammatory process begins.
- Tissue repair involves five overlapping processes:
  - i. Hemostasis – coagulation, platelets
  - ii. Inflammation – neutrophils, macrophages, lymphocytes, mast cells
  - iii. Regeneration – stem cells and differentiated cells
  - iv. Fibrosis – macrophages, granulation tissue (fibroblasts, angiogenesis), type III collagen
  - v. Remodeling – macrophages, fibroblasts, converting collagen III to I.

2. **Regeneration**

Different tissues have different regenerative capacities

a. Labile cells
   - i. Regenerate throughout life
   - ii. Examples: surface epithelial cells (skin and mucosal lining cells),hematopoietic cells, stem cells, etc.

b. Stable cells
   - i. Replicate at a low level throughout life
   - ii. Have the capacity to divide if stimulated by some initiating event
   - iii. Examples: hepatocytes, proximal tubule cells, endothelium, etc.

c. Permanent cells
   - i. Very low level of replicative capacity.
   - ii. Examples: neurons and cardiac muscle

3. **Fibrosis and remodeling phases**

a. Replacement of a damaged area by a connective tissue scar

b. Tissue repair is mediated by various growth factors and cytokines
   - i. Transforming growth factor (TGF-P)
   - ii. Platelet derived growth factor (PDGF)
   - iii. Fibroblast growth factor (FGF)
   - iv. Vascular endothelial growth factor (VEGF)
   - v. Epidermal growth factor (EDF)
   - vi. Tumor necrosis factor (TNF-a) and IL-l

c. Granulation tissue
   - i. Synthetically active fibroblasts
   - ii. Capillary proliferation

d. Wound contraction is mediated by myofibroblasts

e. Scar formation

Conditions required for wound healing

1. **Systemic factors:**

These include good nutritional status and general health. Infection, impaired immunity, poor blood supply and systemic conditions, e.g. diabetes mellitus and cancer, reduce the rate of wound healing.

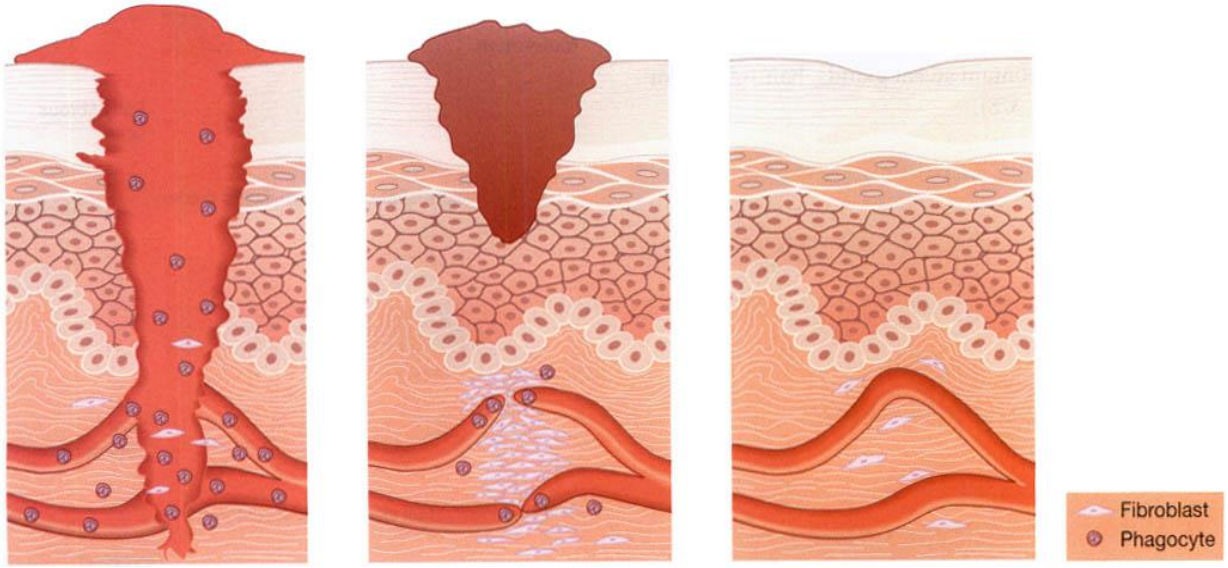
1. **Local factors:**

Local factors that facilitate wound healing include:

- Good blood supply providing oxygen and nutrients and removing waste products
- Freedom from contamination by, e.g., microbes, foreign bodies, toxic chemicals.

a. **Primary union (healing by first intention)**

- **Definition:** occurs with clean wounds when there has been little tissue damage and the wound edges are closely approximated.
- The classic example is a surgical incision



Inflammation **Proliferation** **Maturation**

Fig: Stages in primary wound healing.

b. Secondary union (healing by secondary intention)

- Definition: occurs in wounds that have large tissue defects and when the two skin edges are not in contact.
- It requires larger amounts of granulation tissue to fill in the defect.
- Often accompanied by significant wound contraction.
- Often results in larger residual scars

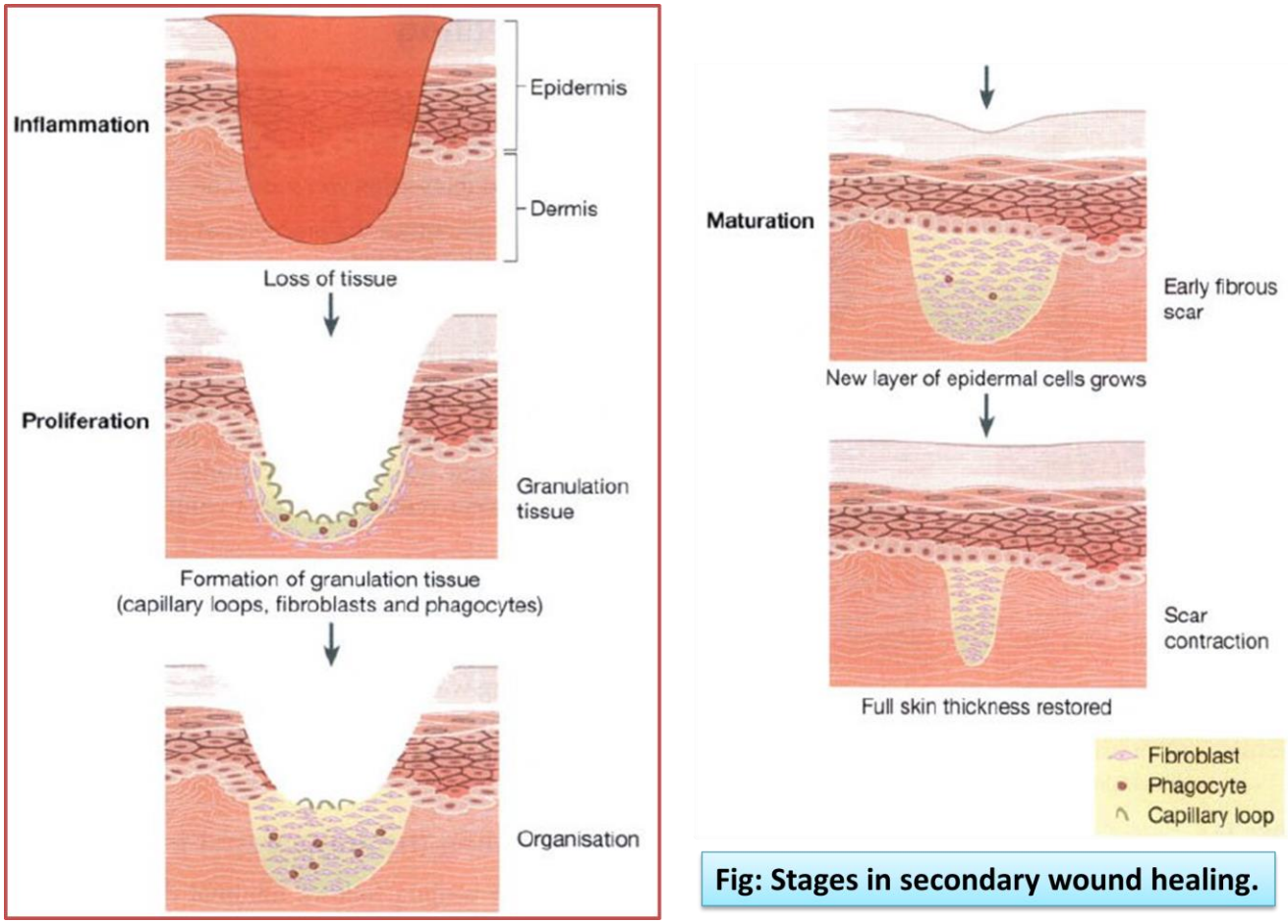


Fig: Stages in secondary wound healing.