Chapter -1

Pathophysiology

An understanding of pathophysiology requires a review of normal physiology — how the body functions day to day, minute to minute, at the levels of cells, tissues, organs, and organisms.

Pathophysiology : **deals with the changes or processes that occur in the human body in response to the presence of disease or injury**

- **Etiology (aetiology)** : is the study of causation, or origination.
- **Pathogenesis** : is the mechanism by which the disease is caused.

HOMEOSTASIS
Its maintaining a dynamic equilibrium and steady state of internal balance.

Any change or damage at the cellular level can affect the entire body.
When homeostasis is disrupted by an external stressor -such as injury, lack of nutrients, or invasion by parasites or other organisms — illness may occur.

Homeostasis reflects the ability of the body to maintain a relatively stable metabolism and to function normally despite many changes.

Many external stressors affect the body's internal equilibrium throughout the course of a person's lifetime.

MAINTAINING BALANCE
The structures in the brain which are responsible for maintaining homeostasis of the entire body:
a. Medulla oblongata, which is the part of the brain stem associated with vital functions such as respiration and circulation.
b. **Pituitary gland**, which regulates the function of other glands and, thereby, a person's growth, maturation, and reproduction

These mechanisms have three components:

- a **sensor** that detects disruptions in homeostasis
- a **control center** that regulates the body's response to those disruptions
- an **effector** mechanism that acts to restore homeostasis.

An endocrine or hormone-secreting gland usually serves as the **sensor**.
It signals the **control center** in the central nervous system to initiate the **effector** mechanism.

DISEASE AND ILLNESS
Although disease and illness are often used interchangeably, they aren't synonyms.
Disease occurs when homeostasis isn't maintained.
Illness occurs when a person is no longer in a state of perceived "normal" health.

For example, a person may have coronary artery disease, diabetes, or asthma but not be ill all the time because his body has adapted to the disease. In such a situation, a person can perform necessary activities of daily living.
Illness usually refers to subjective symptoms, that may or may not indicate the presence of disease.

Cell injury

Normal cells are in a state of equilibrium with their environment .

- **Cell Injury** : is defined as a set of biological and /or morphological changes that occur when the state of equilibrium is changed by adverse influences.

Cell injury may be
- Reversible
- Irreversible

The differences are mostly ***quantitative***
- Reversible injury is usually mild and following the removal of adverse influences ,the cell reverts to its normal state .
- If the cell cannot return to its normal state ,then the injury considered to be irreversible.

The causes of cell injury :- cell injury can occur due to :-

excessive prolonged normal stimuli

The causes of cell injury are classified as exogenous or endogenous

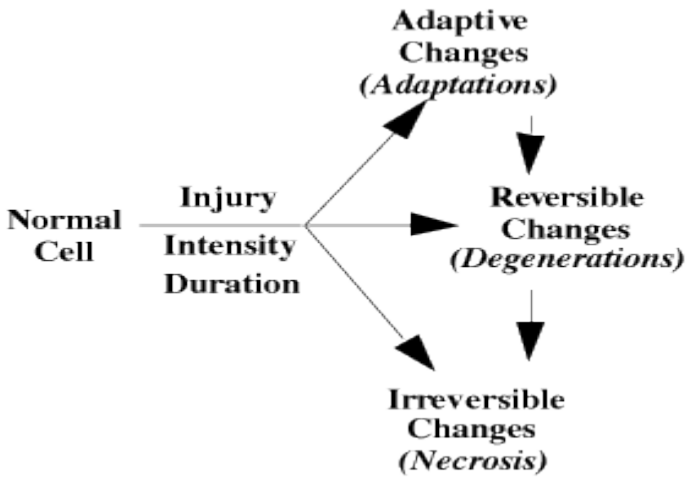
- **Exogenous causes :**
  1. Physical causes : -heat ,cold , radiation ,burn , trauma .
  2. Chemical causes : -drugs ,strong acid ,toxins, , alcohol, narcotics, tobacco.
  3. Biological causes: -viruses, bacteria, fungi, parasites .
  4. Oxygen deprivation : - hypoxia.
  5. Nutritional Imbalances: protein-calorie deficiencies, vitamin deficiencies; excess food intake (obesity, atherosclerosis).
- **Endogenous causes** : include

a. Genetic defects ----genetic defects like Down syndrome , Sickle cell anemia.
b. Metabolites (diabetes mellitus)

- ***How the body responds to these conditions :***

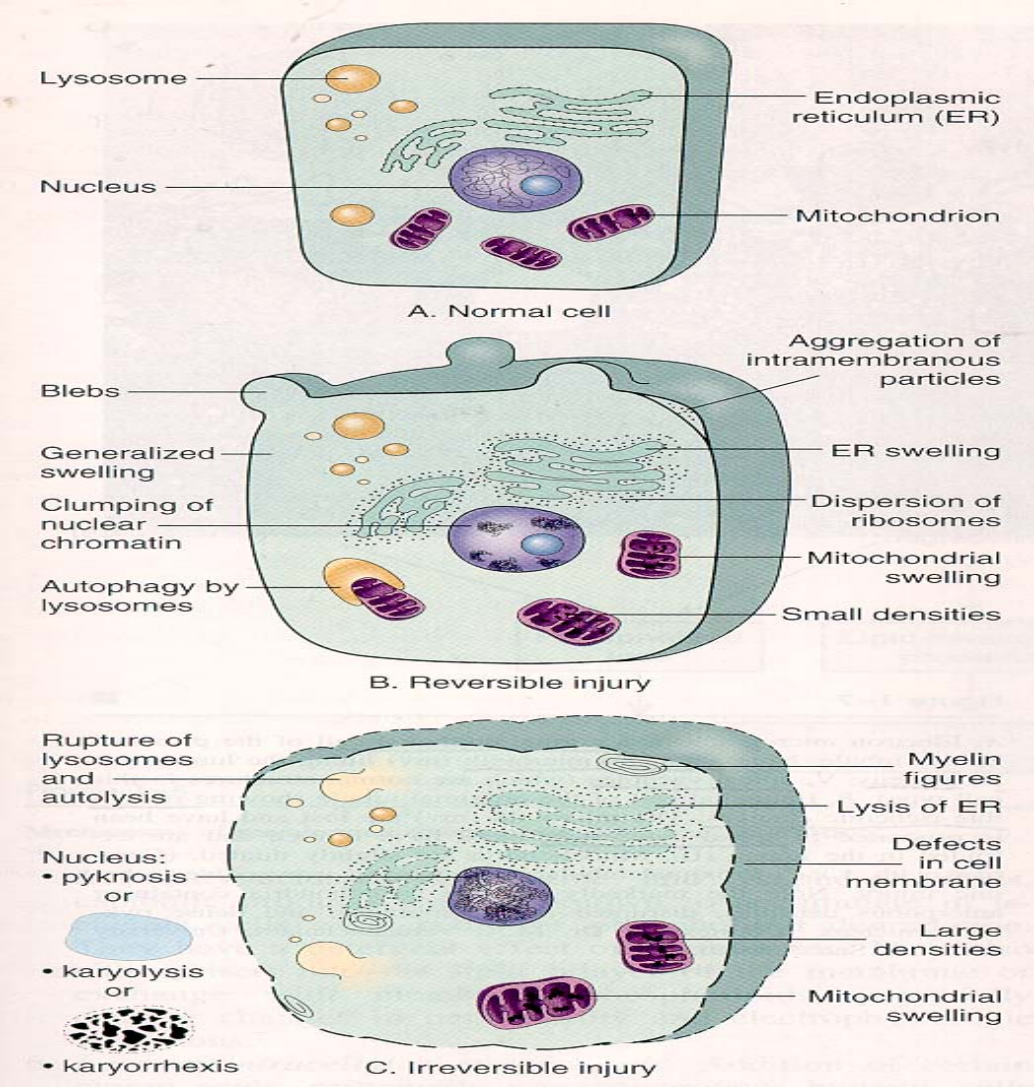
So in response to these conditions,the cell may undergo :-

1. **Reversible cell injury** : which include
   a. Cell adaptation
   b. Sick cell (degeneration)
2. **Irreversible cell injury** (cell death): which include
   a. Necrosis (cell death caused by external injury)
   b. Apoptosis (cell death caused by intracellular process result in cell suicide)



Cellular features of reversible cell injury:

1. *Mitochondrial swelling .*
2. *Endoplasmic reticulum swelling and dispersion of ribosomes.*
3. *Cytoplasmic blebs*
4. *Clumping of nuclear chromatin*



1. Reversible cell injury which include:

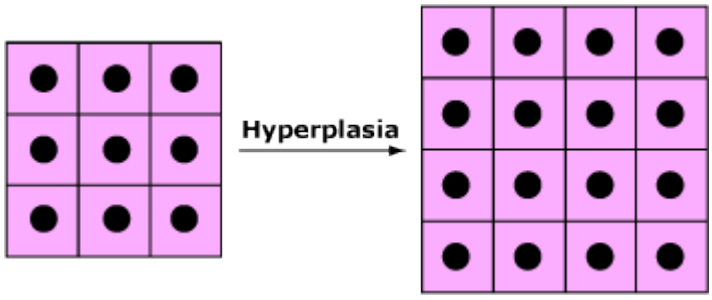
A. Cell Adaptation :

it is the changes that occur in cell and tissues in response to prolonged stimulation or chronic injury and it includes the following :

a. Hyperplasia
b. Hypertrophy
c. Atrophy
d. Metaplasia

a) Hyperplasia ;(increase in cell number)

It is an increase in the size of a tissue or organ due to an increase number of constituent cells.



Is hyperplasia always pathological ?

No, hyperplasia can also be ***physiological*** .

For example :-

Physiological hyperplasia ;

- The enlargement of uterus in pregnancy is a physiological event .
- Bone marrow hyperplasia in high altitudes.

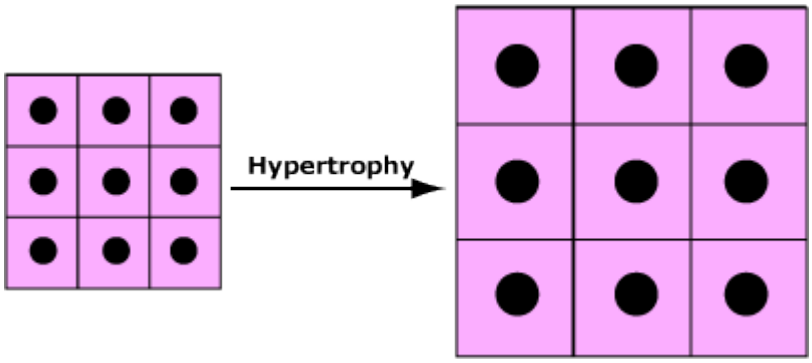
Pathological hyperplasia ;

Occur in most instances due to excessive hormonal stimulation

Example 1: excessive estrogen hormone stimulation in female lead to uterine endometrial hyperplasia and if not stopped , it may lead to uterine endometrial carcinoma.

b) . Hypertrophy : (increase in cell size)

it is an increase in the size of organs due to an increased size of constituent cells without an increase in the cell number.



Hypertrophy can be :

- Pure (only hypertrophy)
- Mixed(hypertrophy +hyperplasia)

a. **Pure hypertrophy :**occur in
   - ✓ Heart muscles :hypertension and heart failure
   - ✓ Skeletal muscle :in exercise

NOTE **:**Hyperplasia cannot occur in the heart muscle because cardiac muscle fibers cannot divide

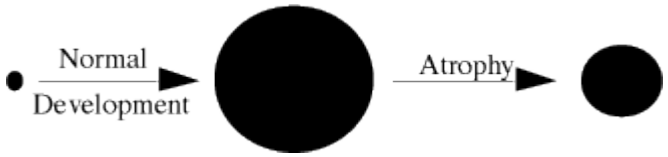
b. **Mixed hypertrophy and hyperplasia :** can be happened together at the same time . examples :

- ✓ Thickening of an obstructed urinary bladder muscle cells are increased not only in number but also in size

c). Atrophy (decrease in cell size)

It is the reduction in the size of the cells ,tissues or organs.

Atrophic cells are smaller than normal because their nucleus and cytoplasm have shrunken in size .



Types of atrophy :

1. Physiological
2. Pathological

Example of *physiological atrophy* :

- ✓ Atrophy of uterus after delivery.
- ✓ Atrophy of the thymus gland.

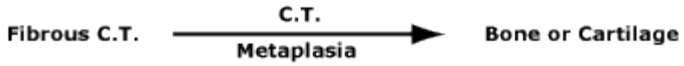
- ***Pathophysiology of pathological atrophy* :**
  - **1)** Decreased work load (disuse atrophy)
  - **2)** Denervation skeletal muscle
  - **3)** Loss of the hormonal stimulation.
  - **4)** Ischemia :reduced blood supply to kidney which will lead to renal atrophy
  - **5)** Malnutrition

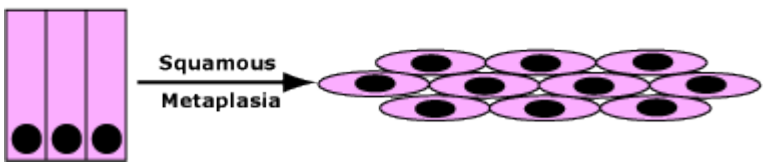
d.) Metaplasia :

It is the replacement of one type of mature cell type by another one .

Example 1:

Replacement of bronchial stratified columnar epithelium by squamous epithelium ,this is an example of squamous metaplasia that occur in smokers



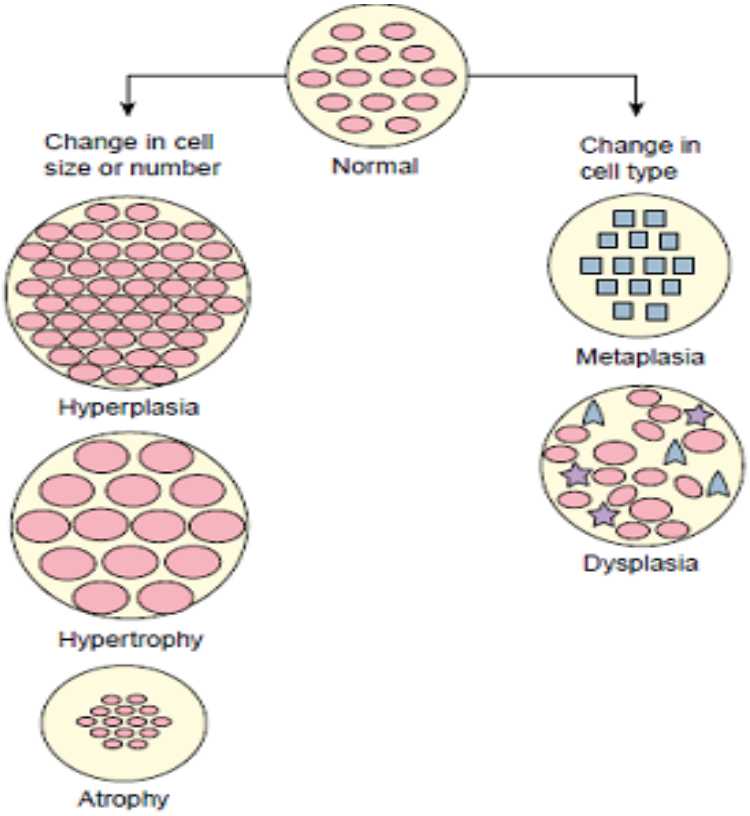


Example 2:

In most cases ,metaplasia is reversible and the tissues reverts to its normal state once the stimulus or irritant has been removed .

If the abnormal stimulus persist ,metaplasia may progress to dysplasia and then frank neoplasia which is irreversible.

Smoking → squamous metaplasia → dysplasia → cancer of the bronchial epithelium .



■ FIGURE 2-1 ■ Adaptive tissue cell responses (large circles) involving a change in number (hyperplasia), cell size (hypertrophy and atrophy), cell type (metaplasia), or size, shape, and organization (dysplasia).

B . Sick cell (Degeneration): (reversible cell injury) .

Under some circumstances, cell may accumulate abnormal amounts of various substances .then may cause varied degree of injury .The location of the substances may either in the cytoplasm or in the nucleus.

Example: fatty changes :

abnormal accumulation of triglycerides(fat) within the liver cells .

it is most often seen in the liver but it may occur also in the heart ,skeletal muscles, kidney .

it may be caused by :

1) toxin
2) protein malnutrition
3) obesity

4) diabetes mellitus
5) anoxia
6) alcohol abuse

Pathological highlights:

1. *Hypertrophy and hyperplasia generally result from increased functional demand .*
2. *Atrophy result from decreased functional demand or chronic ischemia.*
3. *Metaplasia result from persistent injury*

Chapter -2

Pathophysiology

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2. Irreversible cell injury (necrosis)

- **Necrosis** = death of cell or tissues in a living organism

Cellular features of irreversible cell injury

1. **Cell membrane** → rupture
2. **Nuclear changes** :- which include →
   - Pyknosis → chromatin condensation
   - karyolysis → chromatin lysis
   - karyorrhexis → nuclear fragmentation

3.Mitochondrial changes :

1. Rupture of double membrane of mitochondria
2. Fragmentation
3. Calcification

4. Endoplasmic reticulum (ER) :

Rupture and lysis of lysosome and autolysis

- What are laboratory signs of severe cell injury ???

Severe cell injury is associated with a release of cytoplasmic enzymes into the blood .for example :-

1. Creatine kinase → cardiac or skeletal muscle injury
2. Aspartate aminotransferase (AST) and alanine amino transferase (ALT)→ liver cell injury

3. Prostatic acid phosphatase → prostate cell injury
4. High amylase level → ex. pancriatitis

Histological types of necrosis :

1. Coagulative necrosis
2. Liquefactive necrosis
3. Caseous necrosis
4. Fat necrosis
5. Fibrinoid necrosis

1. Coagulative necrosis :

it is the most common form of necrosis , which occurs in almost all internal organ. occurs when the blood supply to any organ(except the brain) is interrupted.

It characterized by sudden cessation of basic cell function due to blockage of action of most its lysosomal enzymes ,it characterized by :-

1. Cellular outline of dead tissue remains preserved
2. Necrotic tissue appears paler than normal tissues.
3. It typically affects the kidneys, heart, and adrenal glands.

examples :-

- ✓ Myocardial infarction ,caused by occlusion of coronary artery which lead to ischemia.
- ✓ Infarction of solid organ like kidney , spleen

Release of cardiac enzymes and proteins

When the heart muscle is damaged (by coagulative necrosis), the integrity of the cell membrane is impaired, and intracellular contents — including cardiac enzymes and proteins — are released and can be measured in the blood stream by laboratory test .

The released enzymes include :

1. Creatine kinase(**CKMB**),
2. **Troponin T, troponin I**
3. Lactate dehydrogenase (**LDL**) ,
4. Aspartate aminotransferase **(AST)**
5. Myoglobin.

2. Liquefactive necrosis

It is characterized by softening of the necrotic tissue to the point where it transforms into a paste like or watery debris.

Liquefaction of tissues occurs due to the actions of hydrolytic enzymes released from dead cells .

-Examples of liquefactive necrosis : -

A .Brain infarction :

TNhe necrotic area soften and the necrotic tissue debris is phagotized by macrophage . The remaining cavity filled by diffusion of fluid from the surrounding interstitial spaces of the brain

b .Abscess :

It presents as cavity filled with pus , i.e., liquefactive tissue of the affected organ is permeated with dead and dying neutrophile

3. Caseous necrosis :

It is typically found in the tuberculous and fungal infection.

- on gross examination it is soft and greasy resemble cheese

4. Fat necrosis :

This mainly due to acute pancreatitis .It is found in and around pancreas . In fat necrosis, enzymes called lipases (released from damaged pancreatic cells) break down intracellular triglycerides into free fatty acids. These free fatty acids combine with sodium, magnesium, or calcium ions to form soaps.

5. Fibrinoid necrosis :

It is limited to small blood vessels ,typically it involves small arteries ,arterioles and glomeruli affected by autoimmune diseases or malignant hypertension

6. Gangrenous necrosis :

- a form of coagulative necrosis, typically results from a lack of blood flow and is complicated by an overgrowth and invasion of bacteria.
- It commonly occurs in the lower legs as a result of arteriosclerosis

Gangrene can occur in one of three forms:

a. Dry gangrene
b. Moist (wet) gangrene
c. Gas gangrene

a. Dry gangrene :

- occurs when bacterial invasion is minimal.
- It's marked by dry, wrinkled, dark brown or blackened tissue on an extremity.

b. Moist gangrene :

- develops with liquifactive necrosis that includes extensive lytic activity from bacteria and white blood cells to produce a liquid center in an area of tissue.
- It can occur in the internal organs as well as the extremities.

c. Gas gangrene :

- develops when anaerobic bacteria of the genus ***Clostridium*** infect tissue.

- It's more likely to occur with severe trauma and may be fatal.
- The bacteria release toxins that kill nearby cells
- Release of gas bubbles from affected muscle cells indicates that gas gangrene is present.

Outcome of necrosis

1. Complete resolution → repair by regeneration .this occur mainly in liver and kidney .
2. Repair by fibrous scarring :
   In the heart the dead myocardium are removed by phagocytes and replaced by fibrous scar
3. Calcification : in some cases ,deposition of calcium salts in the necrotic area and lead to calcification .
4. Resorption of necrotic tissues : in the brain ,the necrotic tissues is removed by macrophages and the infarct transformed into a fluid filled cyst (pseudo cyst).

CHAPTER 3

Inflammation"

It is a local response of living tissue to cell injury and occurs in vascularized tissues and designed to deliver leukocytes to the site of injury .

- **The aims of inflammation .**

The aim is to eliminate or neutralize the cause of injury and repair its consequences .

-Types of inflammation :

1. Acute inflammation
2. Chronic inflammation

-Acute inflammation characterized by:

1. It is an early and immediate response to injury
2. Short duration (few minutes – few days)
3. Formation of fluid exudate rich in cells and protein .

NOTE :

The causes of acute inflammation are the same causes of cell injury

-Cells of acute inflammation :

1. Neutrophil
2. Eosinophil
3. Basophil
4. Monocytes

Acute inflammatory response

The main component of acute inflammation are *:*

Every inflammatory response is based on a coordinated activation and interaction of many components which are :

1. Vascular phase (hemodynamic) : during which

a. blood flow increased : There is vasodilation of the vessels that supply the area , As a result, the area becomes congested, causing the ***redness (erythema)*** *and* ***hotness*** associated with acute inflammation.

b. Capillary permeability are increased : fluid is moving into the tissues and cause ***swelling, pain, and impaired function.***
The exudation or movement of the fluid out of the capillaries into the tissue spaces dilutes the causative agent.

2. Cellular phase : during which phagocytic white blood cells move into the area of injury to engulf and degrade the causative agent.
Two types of leukocytes participate in the acute inflammatory response—***the granulocytes and monocytes***.

- ***Clinical features of inflammation are*** :
  1. Generalize malaise
  2. Fever
  3. Pain often localized to the inflamed area
  4. Tachycardia (rapid pulse rate) .

- ***Laboratory investigations of acute inflammation :***

  1. Increased neutrophil count (↑ WBC count)
  2. Increased Erythrocyte sedimentation rate (↑ESR)
  3 Increased ***acute phase proteins*** in the blood

Acute phase proteins

Acute-phase proteins are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli

Acute-phase response

It is a systemic effects which usually begins within hours or days of the onset of inflammation or infection, includes changes in the concentrations of plasma proteins, increased erythrocyte sedimentation rate (ESR), fever, increased numbers of leukocytes(WBC) , skeletal muscle catabolism and lethargy.
The metabolic changes including skeletal muscle catabolism, provide amino acids that can be used in the immune response and for tissue repair

The most important acute phase proteins are :

1. C- reactive protein(CRP)
2. Fibrinogen
3. Serum amyloid

- **CRP & Serum amyloid** binds to phospholipids on the bacterial cell wall membrane and act to facilitate phagocytosis .
- **Fibrinogen** : When the liver releases acute phase proteins , the level of fibrinogen in the serum is increased .
  Fibrinogen coats the surface of RBC which make its aggregation more easy and sediment more rapidly than do individual red cells .

A blood test called erythrocyte sedimentation rate (ESR)
provides a simple measure of the level of inflammation .
Thus an elevated ESR indicates the presence of inflammation in the body .

The greater the inflammation ,
The faster the RBC settle to bottom of a test tube
The higher the ESR .

- The ESR is a nonspecific but clinically useful indicator of inflammation .
- Serum CRP activity is also used a nonspecific indicator of inflammation in a manner similar to the ESR .
- Elevated serum levels of CRP have been proposed as a marker for increased risk of myocardial infarction in patients with coronary artery disease .
- It is postulated that inflammation involving atherosclerotic plaques in the coronary arteries may predispose to thrombosis and subsequent infarction, and CRP is produced during inflammation.

Another protein whose production is increased in the acute-phase response is the iron-regulating protein ***hepcidin.***
Chronically elevated plasma concentrations of hepcidin reduce the availability of iron and are responsible for the *anemia* associated with chronic inflammation

Outcome of acute inflammation :

1. **Resolution** :in most of cases of acute inflammation all signs disappear without any consequences and occur when the injury is limited and of short duration.
2. **Suppuration** : with destruction of localized tissues which occur mainly in infection with pyogenic organism. (abscess).
3. **Change to chronic inflammation**
4. **Healing and repair by fibrosis**

❖ ***Systemic signs and symptoms of acute inflammation*** :

1. Fever ,sweating and shivering
2. Tachycardia (> 90 beat per minute **)**
3. Tachypnea (>20 per minute)
4. Constitutional symptoms like loss of appetite ,tiredness ,weakness

Chronic inflammation

Any inflammation that does not heal on its own can be called chronic

❖ **Chronic inflam. Characterized by :-**

1. Long duration (weeks – months)
2. Infiltration with mononuclear chronic inflammatory cells which include (macrophage ,lymphocyte, plasma cell)
3. Tissue destruction largely by inflammatory cells
4. Repair involving new vessels proliferation (angiogenesis)and fibrosis

- **Etiology of chronic inflammation :**

1. 1..Non healing or persistent acute inflammation for ex. non healing bacterial pneumonia .

2. Persistent infections caused by pathogens that cannot eliminate like T. B.

3. . Continuous exposure to toxic exogenous influences (tobacco smoke)

4. Foreign materials like surgical material left in the wound

Chapter -4

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Microbial Mechanisms of Disease

Microbial Mechanisms of Disease

Normal Flora of Human Body

- Normal flora: population of microorganisms routinely found growing on the body of healthy individuals
- Many different species of microorganisms make up normal flora and they occur in large numbers
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Importance of normal flora :

1. Protection against potentially harmful microorganisms
2. Stimulate the immune system
3. Flora of intestine stays stable- beneficial to both human and bacteria

Establishment of Disease

To cause disease microorganisms must pass through many steps :

1. Transmit disease to host
2. Enter the body
3. Adhere to host tissues
4. Penetrate or evade host defenses
5. Damage the host tissues

1 . Transmission of disease :

- Microorganisms can be transmitted from the reservoir of infection to a susceptible host by three principle routes
    a. Contact (direct ,indirect, droplet)
    b. Vehicles (waterborne ,food borne, airborne)

c. Vectors (Mechanical- Biological transmission)
- Mechanical - passive (insects feet or other body parts)
- Biological - active process

a. Contact transmission

- **Direct** contact transmission- physical contact between microorganisms source and susceptible host
- **Indirect** contact transmission- when microorganism transmitted from reservoir to susceptible host by means of nonliving object
- **Droplet** transmission- microorganisms spread by droplets that travel only short distance

2 Portals of Entry:

- Mucous membranes: often respiratory tract
- Skin: must enter through openings(wound)
- Parenteral route: deposited directly into tissues beneath the skin or mucous membranes
- Binding or adhesions of microbe to receptors on host cells
- Adhesions may be located on glycocallyx or other microbial surfaces such as pili, or flagella

How bacterial pathogens penetrate host defenses

Bacterial pathogens can penetrate host defenses by several ways:

1. Capsules
2. Enzymes
3. Antigenic variation
4. Penetration into host cell cytoskeleton (Microbes attach by adhesions & produce invasions to the host cells)

Capsule

Some bacteria make a glycocallyx that is outside of the cell wall

- Glycocallyx impairs phagocytosis
- Immune system can overcome this glycocallyx

Enzymes

- **Coagulates:** form blood clot
- **Kinases**: break down fibrin and dissolve blood clots formed by the body to isolate infection
- **Hyaluronidase**: breaks down polysaccharide that holds together connective tissue
- **Collagenase**: breaks down collagen

Antigenic Variation

- Some pathogens can alter surface antigens, makes it more difficult for immune system to fight against it

How Bacterial Pathogens Damage Host Cells

If pathogen overcomes host defenses then microorganism can damage host cells by:

1. **Using host cell nutrients** (bacteria take iron from host cell)
2. **Causing direct damage** (pathogens metabolize and multiply in cells, then cells usually rupture.
3. **Inducing hypersensitivity reactions**
   - Occurs in people who have been sensitized by a previous exposure with an antigen
   - When exposed to again, their immune system reacts to it in a damaging manner
4. **Producing toxins**

   Produce fever, cardiovascular disturbances, diarrhea, and shock
   inhibit protein synthesis, destroy red blood cells, disrupt nervous system

   Two types: Endotoxins and Exotoxins

Infectious diseases :

The main human infectious agents are :-

1. Viruses
2. Chlamydia
3. Mycoplasma
4. Bacteria
5. Rickettsia
6. Fungi
7. Protozoa

☻ **Infectivity:--**

It is the minimum number of infective particles required to induce a recognizable infection.

❖ It is depend on :-

1. properties of the pathogens

2. Factors related to the host , which include
   a) route of infection (I.V. ,oral , respiratory
   b) physiologic conditions of the host (nutritional status)
   c) immune status of the host (decrease body immunity → more susceptible to infection).

☻Natural body defenses to infection (innate immunity):--

1. Mechanical barrier
   - ❖ Keratin on the surface of the skin
   - ❖ Mucous on the surface **of** bronchial mucosa
2. Physical forces :-

the movement of cilia ,move the mucous and facilitates the expectoration of bacteria that entered the respiratory tract

3. Chemical forces :-
   HCl acid in the stomach is strongly bactericidal

4. Neutrophil and macrophage :-
   They can eliminate bacteria by phagocytozing them .

►BACTERIAL TOXINS ARE OF TWO TYPES: --

1. Exotoxins (are secreted from living bacteria)
2. Endotoxins (it is apart of bacterial wall ,so it is only released after death of the bacteria)

► BACTERIAL INFECTION OF BLOOD :-

Bacteria can present in the blood in sufficient numbers and this presence can be classify into :

1. Bacteremia
2. Septicemia
3. Pyemia

1. BACTEREMIA:

It means the presence of bacteria in the blood .
Small number of bacteria of low virulence are present from time to time in the blood of normal human being ,bacteria when they enter the blood ,it may settle in parts of the body specially abnormal heart valves and leading to infective endocarditis

2. SEPTICEMIA :

Presence of multiplying bacteria in the blood
(rapid multiplication of highly pathogenic bacteria)

3. PYEMIA :

Presence of pus in the blood

In localized pyogenic infection ,toxic injury to the endothelium of vessel may result in thrombosis . bacteria may invade the thrombus and multiply inside it and changed to septic thrombus

- small fragment of thin septic thrombus may then break away and carried out by the blood and when they become impacted in small vessel and causing local injury by obstructing the vessels and release toxins from their contained bacteria

► What are the common signs of infection???

They may be classified into :

1. systemic (non specific)
2. organ-specific

Chapter - 5

Cancer Pathology(Neoplasia)

Definition:

Neoplasia means "new growth," and a new growth is called a *neoplasm*

Neoplasm : it is an abnormal mass of tissue in which abnormal cells divide without control and persists in the same excessive manner after cessation of the stimuli which evoked the change and are able to invade other tissues and spread to other parts of the body .

Oncology (Greek *oncos* = tumor) is the study of tumors or neoplasms.

The growth of body cells is usually controlled and organized by regulatory genes that regulate their growth and proliferation, so any genetic mutation for these genes lead to excessive and unregulated proliferation that becomes autonomous (independent of physiologic growth stimuli), although tumors generally remain dependent on the host for their nutrition and blood supply.

The entire population of neoplastic cells within an individual tumor arises from a single cell that has genetic change, and hence tumors are said to be ***clonal***.

The cancer characterize by :

- The growth of this cancer is uncoordinated with that of normal tissue.
- Neoplastic cells are continue to replicate and not controlled by regulatory mechanisms
- Neoplasm behaves as parasites and competes with normal cells for their metabolic needs.

The healthy body is well equipped to defend itself against cancer. Only when the immune system and other defenses fail , does cancer prevail.

Current evidence suggests that cancer develops from a complex interaction of exposure to carcinogens and accumulated mutations in several genes.

Four classes of normal regulatory genes are the principal targets of genetic damage :

1. ***Proto-oncogenes***: are genes found in all cells and have essential roles in regulating the growth and proliferation of normal cells.
   - when activated, stimulate a cell to go through the cell cycle.
   - when this gene is damaged, cellular proliferation can occur without control.
   - Any mutation in these genes cause uncontrolled cell division, at that time they are called oncogenes, or cancer-causing genes

2. ***Tumor suppressor genes (TSG)*** : prevent or suppress the growth of tumors , it remain dormant unless it lose its function by genetic or acquired mutation resulting in uncontrolled neoplastic cell growth .

TSG can lose their normal function by a variety of mechanisms :

a. Mutations (hereditary or acquired)
b. Binding of normal TSG to viral genes.

3. ***Genes that regulate programmed cell death (apoptosis***), and
4. ***Genes involved in DNA repair***

Pathogenesis of tumor formation :(How does cancer happen ?)

The main concepts of carcinogenesis involves three steps:

a. Initiation
b. Promotion
c. Progression.

a. Initiation

Initiation refers to the **irreversible DNA damage** that occurs when the cell is exposed to a carcinogenic agent during DNA transcription that makes them susceptible to malignant transformation.

The carcinogenic agents can be **chemical**, **physical**, or **biologic**, and produce irreversible changes in the genome of a previously normal cell .

Normally, enzymes detect errors in transcription and remove or repair them.

But sometimes an error is missed ----then we two possibilities:

a. If regulatory proteins **recognize** the error and block further division, then the error may be repaired or the cell may self-destruct.

b. If regulatory proteins **miss the error again**, it becomes a permanent mutation that is passed on to future generations of cells.

b. Promotion

It involves the exposure of the already initiated cells to factors (promoters) that enhances its unregulated growth. This exposure may occur either shortly after initiation or years later The latency period varies with the type of agent, and its dosage.

Promotion is ***reversible*** if the promoter substance is removed

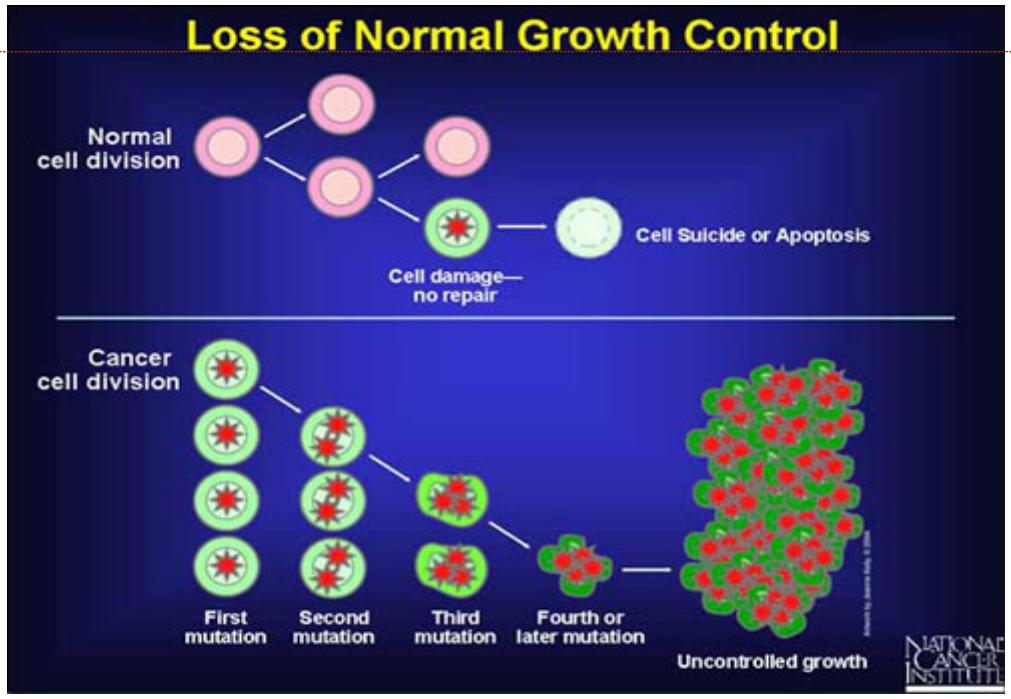
Promoters may be --hormones, such as estrogen;
---food additives, such as nitrates;
---drugs, such as nicotine.

Promoters can affect the mutated cell by altering function of genes that control cell growth.

Many chemical carcinogens are called **complete carcinogens** because they can **initiate** and **promote** neoplastic transformation.

c. Progression

The progression is actually a late promotion phase in which the cancer invades, metastasizes, and becomes resistant to drugs and have a tendency for autonomous growth. This step is irreversible.



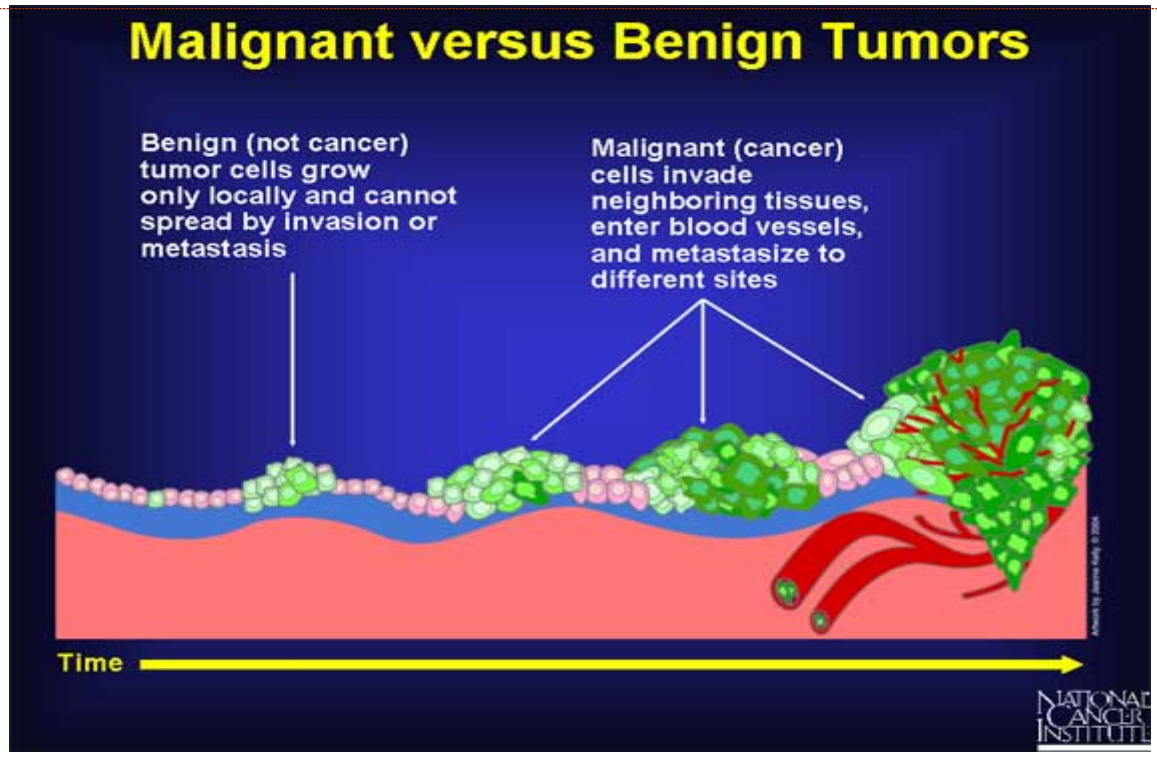
The main categories of cancer include:

1. **Carcinoma** - cancer that begins in the skin or in tissues that line or cover internal organs.
2. **Sarcoma** - cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective tissue.
3. **Leukemia**: cancer that starts in the bone marrow(blood-forming tissue) and tend to accumulate in large numbers in the blood stream
4. **Lymphoma** - cancers that begin in the cells of the immune system.

Tumor are divided according to their behavior into 2 main groups

- Benign
- Malignant

Feature	Benign tumor	Malignant tumor
Mode of growth	Remain local	Infiltration and metastasis
Rate of growth	Slow	Rapid
Histological feature	Similar to the tissue of origin	Differ from tissue of origin
Clinical effect	Local (pressure effect)	Local and destructive effect



Tumors are classified by **cell of origin into**:

- Epithelial in origin
- Messynchymal in origin.

Epithelial	Benign	Malignant
Surface epithelium	Papilloma	Carcinoma
Glandular	Adenoma	Adenocarcinoma

Mesenchymal	Benign	Malignant
Adipose tissue	Lipoma	Liposarcoma
Fibrous tissue	Fibroma	Fibrosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma

Epithelial tumor → carcinoma
Mesenchymal tumor → sarcoma

Causes of tumor:-

1. **Persistent irritation** :bladder carcinoma may result from bladder stone
2. **Radiation:** radiation in the form of ultraviolet or ionization radiation can cause cancer:-
    - ultraviolet rays :natural UV radiation is derived from the sun can cause skin cancer specially those people with fair skin, the exposed skin to sun light is more liable to tumor

    - Ionization radiation (electromagnetic radiation) is carcinogenic.
      ex. like what occur in Hiroshima and Nagasaki(Japan) , which result in increase in the incidence of certain types of leukemia

3. **Chemical substances** :
    - Aromatic amines (present in tobacco smoking) → bladder carcinoma
    - Inorganic substances → lung carcinoma.

4. **Viruses :**
    - DNA viruses :like human Papilloma virus which cause cervical carcinoma in females
    - RNA viruses: which associated with some types of leukemia and lymphoma?

5. **Hormonal**
    - Estrogen excess → uterine carcinoma

CHAPTER SIX

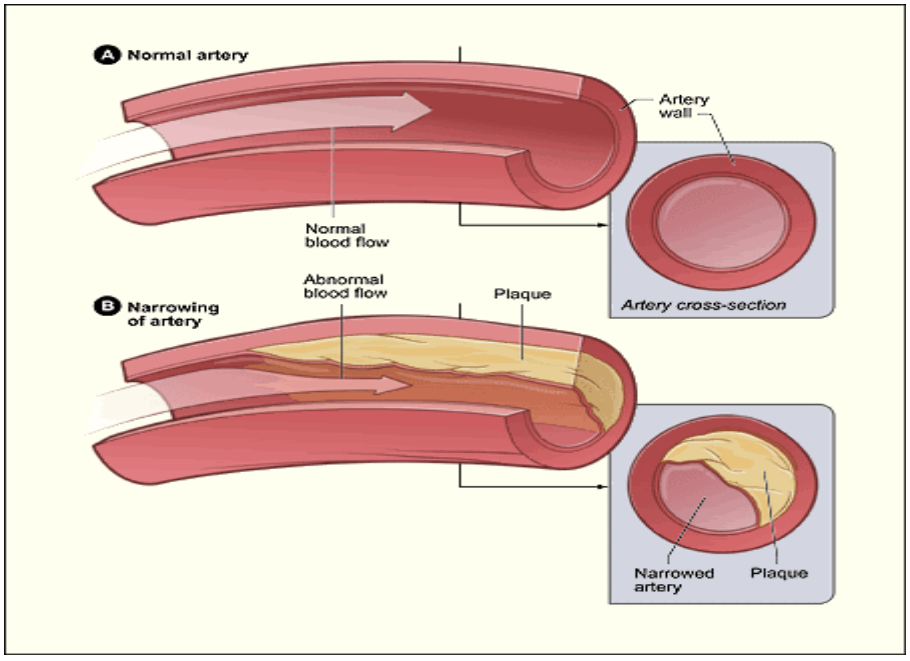
Atherosclerosis

Atherosclerosis : It is originated from Greek word (ather—paste , sclerosis – hardening)

It is defined as **hardening of the arteries. It is a term used for thickening and loss of elasticity of the arterial wall**.

It means degenerative disease of arteries (large and medium sized but not the vein) , characterize by accumulation of lipid rich materials in the internal layer of the arteries

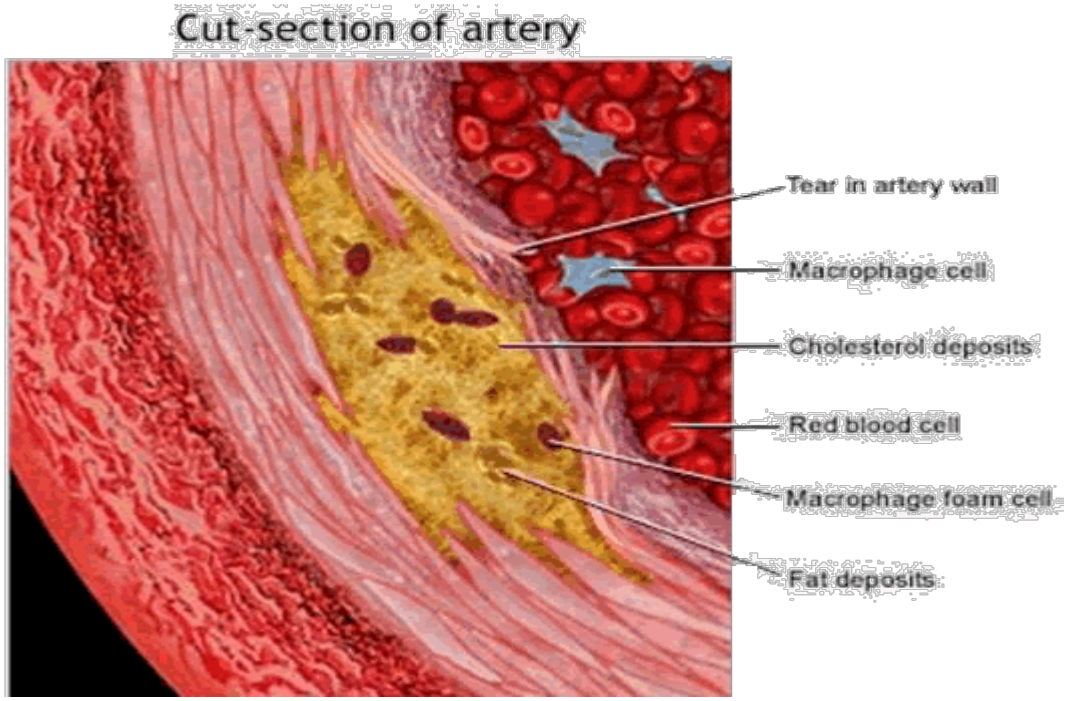
The internal mass (plaque) is called atheroma which is protruded into the lumen and weakening the underlying layer by a bud of fat.

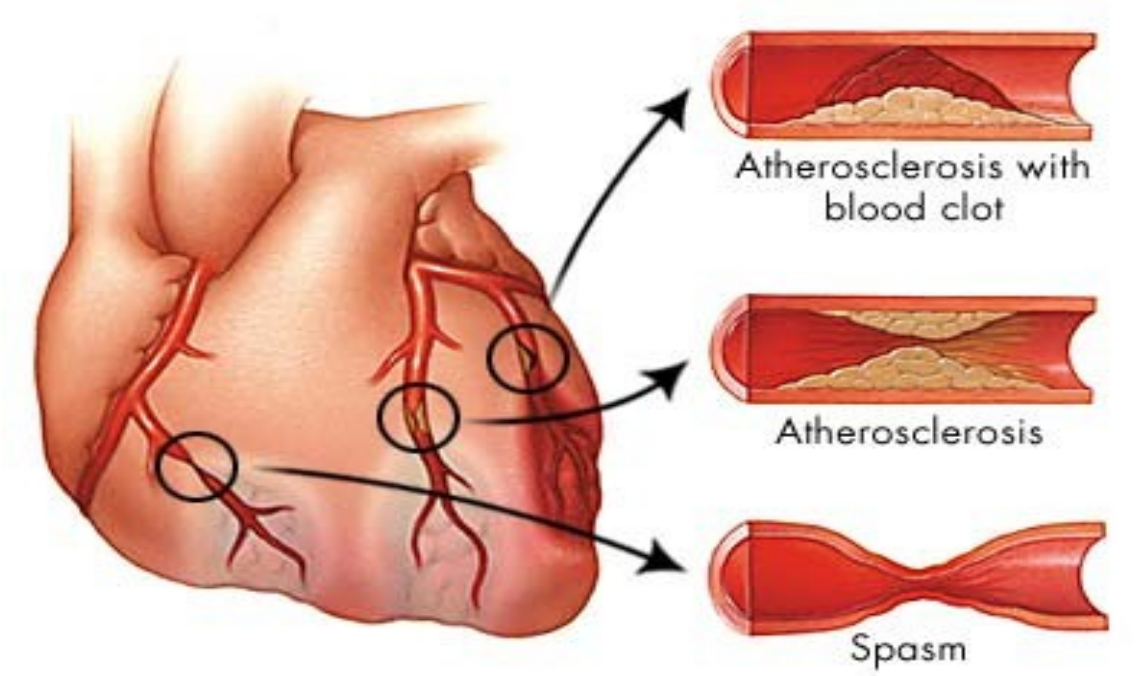


Pathophysiology of atherosclerosis

The most common mechanism of coronary ischemia is the development of **coronary atherosclerotic plaque** : which is a raised white – yellow lesion protruding into the vessel lumen , resulting in reduced myocardial oxygen supply. Atherosclerotic plaques most likely develop at sites of fatty streaks, in areas where there are accumulations of "foam cells" which are filled with lipid-laden macrophages.

Plaques may be either "soft" or "hard", depending on the ratio of lipid-laden foam cells to fibrous tissue within the plaque .





The most common affected arteries are:

1- Aorta especially abdominal aorta and aortic aneurysm.
2- Coronary arteries lead to ischemic heart disease (angina pectoris and myocardial infarction
3- Cerebral arteries lead to ischemic brain disease and CVA(cerebrovascular accident)

RISK FACTORS FOR ATHEROSCLEROSIS

1- Nonpreventable factors:

A- **Age**: risk increase with age

b- **Sex**: up to the age of 55y males more than females (2:1)due to the protective effect of estrogen in females.
But after the55y M=F

c- **Family history**: some families with risk factors such as: hypertension, DM and hyperlipidemia

d- **Genetic defects** in the metabolism of lipid

2- Preventable factors:

a- Hyperlipidemia (high serum cholesterol) associated with increase IHD especially LDL but HDL decrease the incidences of IHD.

b- Hypertension: accelerate atherosclerosis by direct damage to the vessel wall especially after the age of 45y.

c- Diabetes mellitus: induce hypercholesterolemia. Myocardial infarction is two times more common in diabetics patient

d- Obesity

e- Oral contraceptive pills

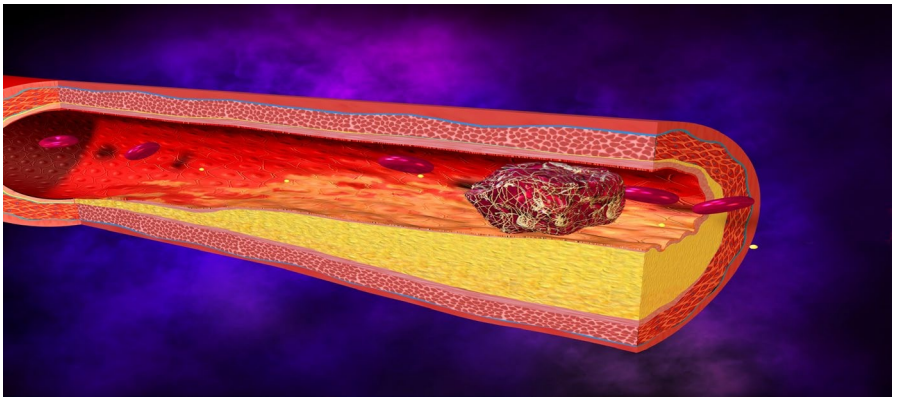
f- Cigarette smoking: more than 20 cigarette per day increase the risk of myocardial infarction

g-Physical activity: protect against M.I

- ***Thrombosis :***

Thrombosis is defined as intravascular formation of a solid or semisolid mass from constituents of the blood during life .

Clots formed in circulating blood inside the blood or cardiac chambers are called thrombi



- ***Causes of thrombosis :***

1. changes in the vessel wall (endothelial damage) for e.g. myocardial infarction

2. changes in blood flow:
   Two main changes in the blood flow that predispose to thrombosis

   - Stasis ,typically found in dilated veins
   - Turbulent flow, typically in abnormally dilated cardiac chambers that are not contracting regularly, and aneurysm

3. Increased coagulability of the blood which occur mainly in:
   - after trauma
   - surgical operation
   - metastatic cancer:
4. smoking
5. obesity

☻ Fate of thrombus

1. Resolution:
Thrombi may be removed by fibrinolytic activity **.** venous thrombi are lyzed more readily than cardiac or arterial thrombi

2. Embolization :
Thrombi may dislodge and transported to the other sites in the vasculature

3. Propagation :
The thrombus may accumulate more platelets and fibrin, lastly obstructing some important vessels

4. Recanalization :
Thrombi may induce inflammation and fibrosis and may lastly recanalized

- **Complications of thrombosis:**

1. **infarction :** occlusive thrombi may completely interrupt blood flow through an artery causing ischemic necrosis of the tissue supplied by that vessel. This is a typical complication of arterial thrombosis (coronary artery thrombosis)

2. **Edema and obstruction venous outflow** : this is typically seen in venous thrombosis.

3. **Emboli :** embolization is a common complication of thrombosis regardless of whether the thrombi venous ,arterial or cardiac.

4. **infection :** thrombi are a good media for the growth of bacteria, so they are easily infected.

5. **inflammation of the vessel wall :** organization of the infected venous thrombi induces an inflammatory response in the vessel wall ,this is called **thrombophlebitis** ,and it is associated with redness, swelling , and pain of the tissue around the thrombosed vein (become cord-like) .

CHAPTER SEVEN

RESPIRETORY DISEASES

ASTHMA

- **Definition**

Asthma is : a chronic inflammatory disorder of the airways which leads to recurrent episodes of airway obstruction, characterized by:

1. Wheezing.
2. Breathlessness
3. chest tightness
4. cough that often is worse at night and in the early morning.
5. Many cells and cellular elements play a role, in particular, mast cells, eosinophil, T lymphocytes, and epithelial cells .
6. These episodes, which usually are reversible either spontaneously or with treatment

- **Classification**

Asthma can be divided into:

1. **Extrinsic** - implying a definite external cause
2. **Intrinsic or cryptogenic** - when no causative agent can be identified.

- **Extrinsic asthma : (early onset asthma)**

a. Occurs most frequently in the first two decades of life
b. Commonly associated with other allergic diseases (eczema is) in the patient and in other family members .
c. There is elevated blood eosinophil count .
d. It is episodic and tends to improves in many patients .
e. Have elevated circulating antibody (IgE) in their serum

- **Intrinsic asthma**: **(late onset asthma**).

a. Often starts in middle age .
b. Usually no allergic or family history and no demonstrable skin sensitivities .
c. Normal or nearly normal blood eosinophil count
d. Aggravating factors includes aspirin , pulmonary infections , cold, exercise .
e. Have normal circulating antibody (IgE) in their serum

- **Precipitating factors**

1. **Occupational sensitizers**

2. **Non-specific factors**

   a. **Cold air** : The inhalation of cold, dry air will precipitate an attack
   b. **Exercise** : Most asthmatics wheeze after prolonged exercise. the attack does not occur , while exercising but afterwards.

   c. **Atmospheric pollution and irritant dusts, and fumes**
      1. cigarette smoke,
      2. car exhaust fumes,
      3. strong perfumes
      4. high concentrations of dust in the atmosphere.

   d. **Diet**: Increased intakes of fresh fruit and vegetables have been shown to be , protective possibly owing to the increased intake of antioxidants.
   e. **Drugs**
   Non-steroid anti-inflammatory drugs (NSAIDs) particularly aspirin and propionic acid derivatives, e.g. indomethacin, have a major role in the development and precipitation of attacks in approximately 5% of patients with asthma.

Pneumonia

Definition : its an inflammation of lung tissue.

General causes of pneumonia :

A. Bacterial causes:

1. The most common pathogen is **Streptococcus pneumonia** and usually the patients is previously healthy

2. Legionella → Institutional outbreaks (hospitals and hotels)
3. Haemophilus influenzae → Pre-existing lung disease
4. Staphylococcus aureus → Children, intravenous drug abusers, associated with influenza virus infections
5. Mycobacterium tuberculosis →tuberculous pneumonia
6. Chlamydia → Contact with birds

B. Viral causes : Influenza A virus .→ usually with a bacterial component

C. Chemical causes, such as in the aspiration of vomit.

D. Radiotherapy

E. Allergic mechanisms → allergic pneumonia

Streptococcus Pneumoniae

Causes :

- often follows viral infection with influenza or parainfluenza
- Cigarette smoking (the strongest independent risk factor for invasive pneumococcal disease).
- Bronchiectasis (e.g. in cystic fibrosis).
- Bronchial obstruction (e.g. carcinoma)
- Immunosuppression (e.g. AIDS or treatment with cytotoxic agents) - rganisms include Pneumocystis carinii, , cytomegalovirus. Inhalation from oesophageal obstruction - often associated with infection with anaerobes