PATHOPHYSIOLOGY

UNIT 1 NOTES

- BASIC PRINCIPLE OF CELL INJURY
- INFLAMMATION

Rx Pharma Education

PATHOPHYSIOLOGY

- The word Pathophysiology is derived or made from 3 words :-
  - Pathos - Disease
  - Physio - Nature / Biological function
  - Logy - Study

- Pathophysiology can be simply defined as changes that occurs in biological functions caused by a disease.

Some Other Common Definitions

Etiology

It is simply the study of causes / reasons of disease.

Pathogenesis

It is the study of mode / manner / mechanism of disease formation.

HOMEOSTASIS

It is made up of two words 'Homeo' and 'stasis'

Homeo	+	Stasis
(Same)		(State)

Homeostasis is defined as the ability of human body to maintain a constant internal environment by maintaining and balancing a pH, temperature, acid- base level etc.

The regulation / maintainance of the homeostasis is govern by the feedback systems of the body.

FEEDBACK SYSTEM

When there are some changes takes place in the internal environment of body then body's feedback system works to take it back into the normal / equillibrium condition.
A feedback system includes three basic components

- Receptor
- Control Centre
- Effector

Receptor

A receptor is a body structure that monitors / detects changes in the internal environment of body.

Control Centre

A control centre in the body is receive the input from the receptors and generates output in the form of nerve impulse, harmones or other chemical signals.

Effector

Effector is a body structure that receives output from the control centre and respond to the commands of control centre.

Types of Feedback Systems

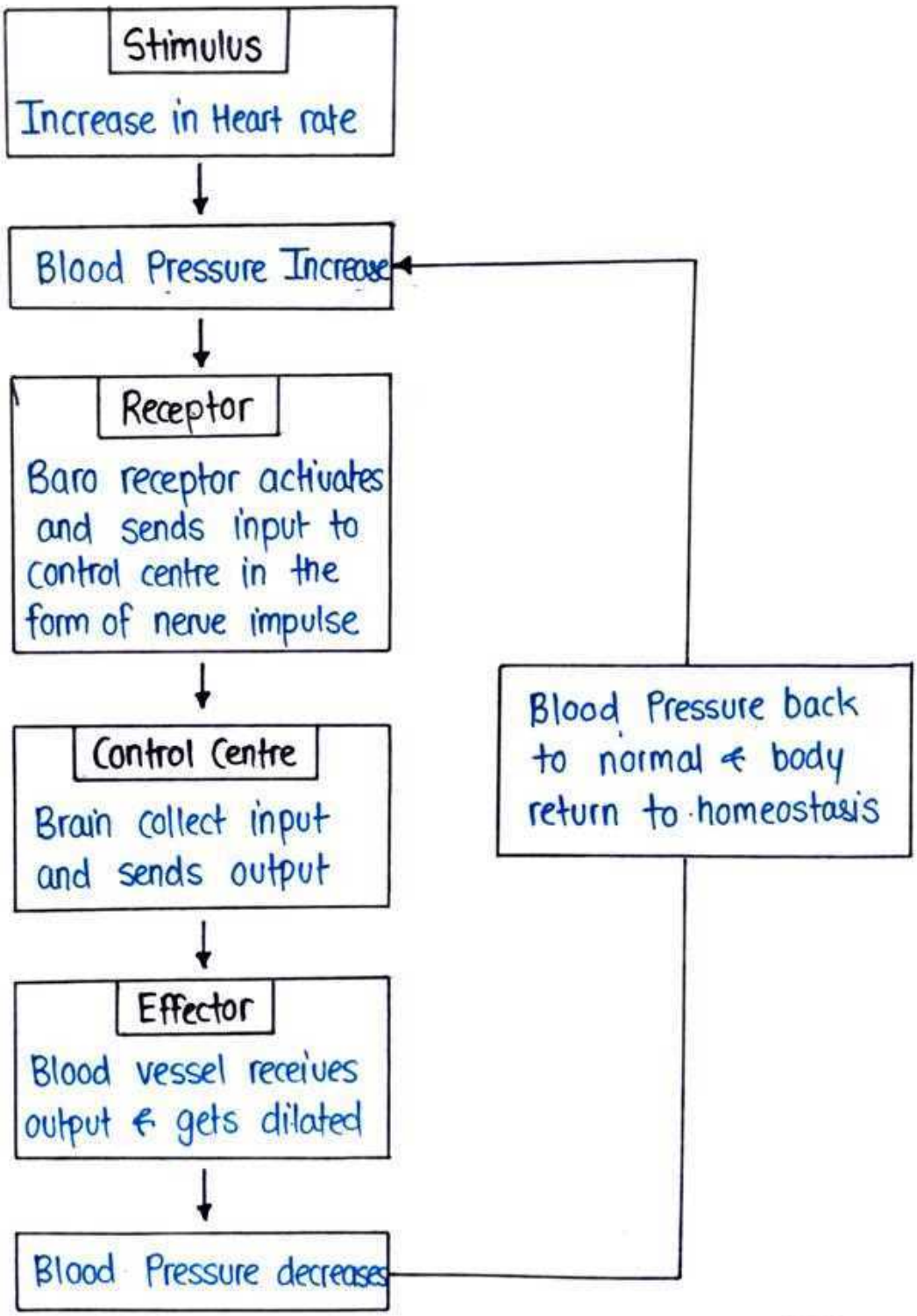
There are basically two types of feedback system

① Positive Feedback System
② Negative Feedback System

NEGATIVE FEEDBACK SYSTEM

A negative feedback system responses to reverse / decrease the changes in internal environment.

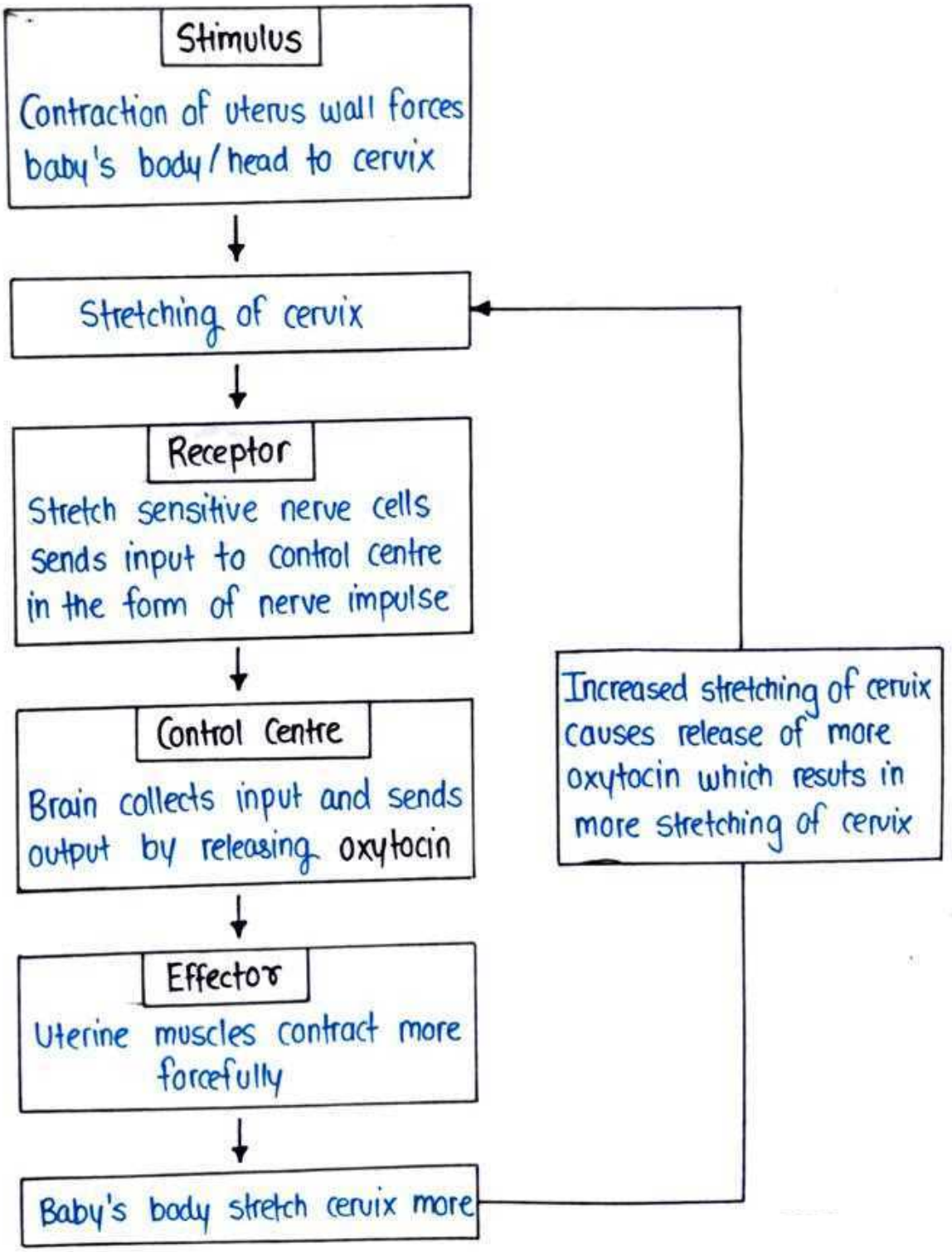
example : Regulation of blood pressure



POSITIVE FEEDBACK SYSTEM

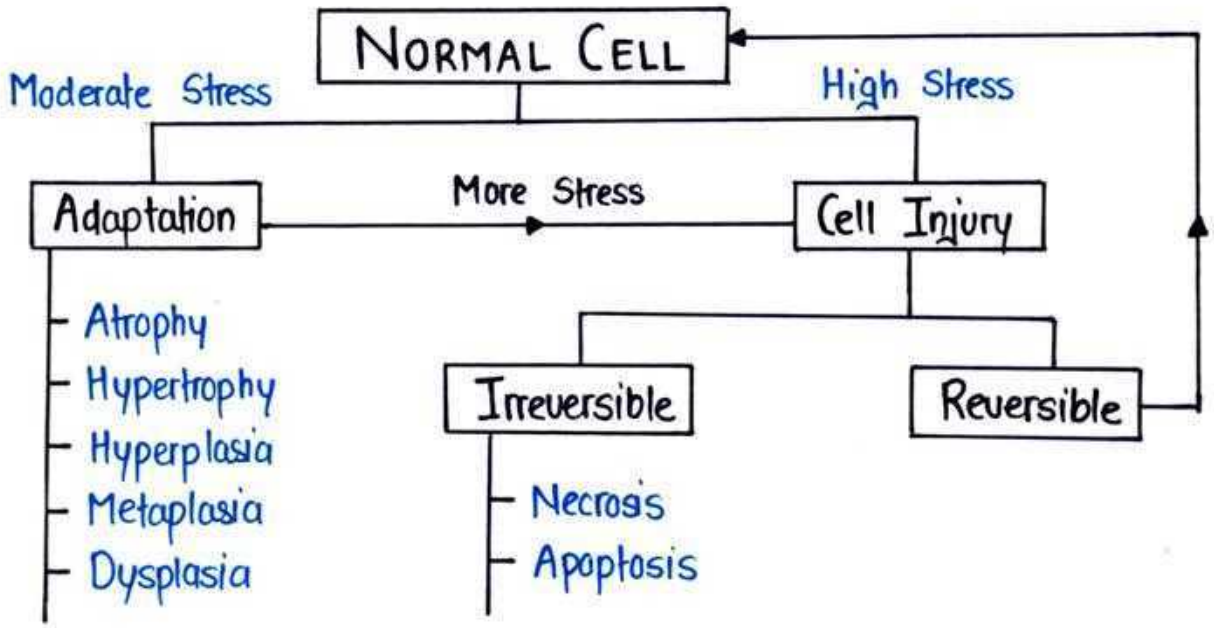
A positive feedback system responses to increases the change in internal environment

example : Normal Child Birth.



CELL INJURY

- Cells are the basic unit of tissues, which forms organ & ti systems in human body.
- Cell Injury is defined as effect of variety of stresses that cause changes in cell's internal as well as external environment.
- The cellular responses to stress depends on variety of factors and also the cell injury can be either reversible or irreversible.



Cellular Adaptation

Cellular adaptation is a process of any cell to survive in any opposite or adverse situation. These are the temporary or permanent changes in the shape, size or type of cell.

example : Atrophy, Hypertrophy, Hyperplasia etc.

Reversible Cell Injury

If the stress applied on the cell is mild to moderate level then after sometime when applied stress is removed cells recovered back to its normal state and this phenomenon is known as Revesible cell Injury

Irreversible Cell Injury

If the stress applied on the cell is very severe level then it may leads to cell death and cells never recovered back, then this type of phenomenon is known as Irreversible cell injury.

Etiology / Causes of Cell Injury

There are variety of causes / stress which can cause cell injury, they can be mainly classified into two classes :

(A) Genetic Causes
(B) Acquired Causes

Genetic Causes

- When cell injury occurs due to defect in genes or chromosomes, then these type of causes are known as genetic causes.
- They are of following types

① Developmental Defect
② Cytogenic Defect
③ Single Gene Defect
④ Multifunctional Inheritance Disorder

Developmental Defect : These are the defects that occurs in the starting of development of fetal life.

Cytogenic Defect : These are the defects that occurs or related with abnormalities of chromosomes. it can be either structural or ~~functional~~ numerical.

Single Gene Defects : It is also known as Mendelian Disorder and occurs due to disorder in single specific gene.

Multifunctional Inheritance Disorder : These are the disorders that occurs due to multifunctional gene defect.

Acquired Causes

- Other than genetic there are many other acquired causes that are responsible for cell injury :
- They are as follows -

① Hypoxia / Ischemia
② Physical Agents
③ Chemical Agents
④ Microbial Agents
⑤ Immunological Agents
⑥ Nutritional Dearrangements
⑦ Psychogenic

Hypoxia & Ischemia : Cells of different tissues require oxygen & blood to generate energy & perform different functions. Hypoxia is defined as loss of oxygen supply while Ischemia is defined as loss of blood supply & both are one of the major causes for cell injury.

Physical Agents : There are many physical defects that can cause cell injury :

- Mechanical Trauma : Accidents
- Thermal Trauma : Heat / Cold
- Electricity : Current
- Radiation : UV rays
- Rapid Change in Atmosphere

Chemical Agents : Following chemical defects can cause cell injury

- Chemical Poisoning : Cyanide, As etc.
- Strong Acid / Base : H_2SO_4, NaOH, HCl etc.
- Environmental Pollutants
- Pesticides & Insectisides
- Hypertonic Salt
- Alcohol, Nicotine, Drugs

Microbial Agents : Various microbial agents like bacteria, Fungi, Virus Protozoa, Paracites etc can also cause defect in cellular functions & responsible for cellular injury.

Immunological Agents : The immune system works in the defence against foreign agents but sometime immune response reactions such as Hypersensitivity reactions, Autoimmune Disorders can cause cell injury.

Nutritional Dearrangements : Dificiency or excess of nutrients may lead to Nutritional Imbalance which ultimately can cause cell injury

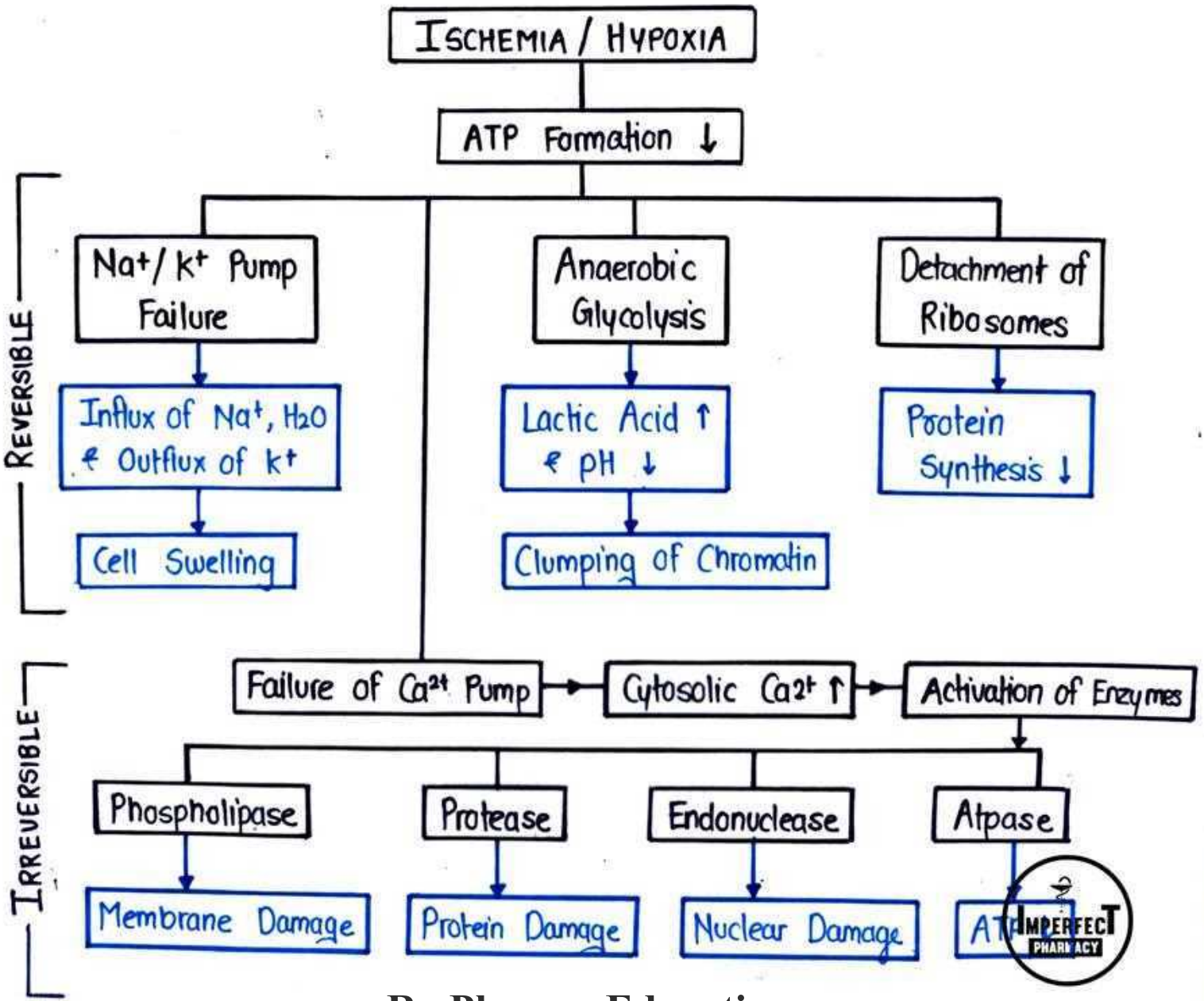
- Dificiency : Anaemia
- Excess : Obesity

Psychogenic Defects : Psychogenic defects like Anxiety, Depression & Drug Addictness like alcohol, smoking leads to cell injury.

Mechanism / Pathogenesis of Cell Injury

- Injury to cell may have many causes that can be either known or unknown but in most of the cases oxygen plays a central role in cell injury.
- Pathogenesis of cell injury mainly include :

① Cell Membrane Damage
② Mitochondrial Damage
③ Ribosome Damage
④ Nuclear Damage



Pathogenesis of Reversible Cell Injury

- Hypoxia / Ischemia leads to decreased generation of cellular ATP.
- Sodium - potassium pump damage leads to accumulation of sodium & water inside the cell which ultimately cause cell swelling.
- Increased anaerobic glycolysis leads to increased formation of lactic acid which cause clumping of chromatin.
- Detachment of ribosomes from endoplasmic reticulum leads to decreased formation of proteins.

Pathogenesis of Irreversible cell injury

- Increased calcium influx : Mitochondrial Damage
- Phospholipase Activation : Membrane Damage
- Protease Activation : Protein Damage
- Endonuclease Activation : Nuclear Damage
- Atpase Activation : ATP Damge
- Bursting of Lysosomal Enzymes : Cell Death

General Steps / Pathogenesis of Cell Injury

Cell Membrane Damage

- Membrane of cell can be easily damaged by any type of destructive physical agents like heat or radiation.
- Loss of oxygen supply caused by hypoxia decreases the ATP formation & due to this supply of essential material that cell needs to survive gets reduced.
- Also the membrane damage increases the influx of Ca^{2+} ions inside the cell which ultimately plays major role in cell injury.

Mitochondrial Damage

- Increased in cytosolic calcium leads to increase in inorganic phosphate and certain fatty acids.
- Inorganic phosphate and fatty acids alone can not damage the mitochondria but along with Ca^{2+} they can extremely damaged the mitochondria.
- Even Calcium can alone damage the mitochondria.

Ribosome Damage

- Decreased ATP formation leads to detachment of ribosomes from rough endoplasmic reticulum which ultimately leads to decreased protein synthesis
- Decrease in the protein synthesis ultimately leads to major cell injury.

Nuclear Damage

- The decrease in ATP formation & loss of oxygen supply leads to increased anaerobic glycolysis which results in the increased formation of Lactic Acid.
- This lactic acid leads to clumping of chromatin & fall in pH.
- The fall in pH leads to bursting to lysosomal enzymes which ultimately cause cell death.

Free Radicle Mediation of Cell Injury

- Free radicals are chemical species that have single unpaired electron in their outer orbit.
- In biological system the term free radicals mainly refer to reactive oxygen species (ROS).
- Free radicles are exteremely unstable and reacts with cell membrane & nucleic acid in the cell.
- There are some radicals like superoxide radicals, peroxide ions etc that are very destructive to cells that cause lipid damage oxidation of protein, DNA damage etc.

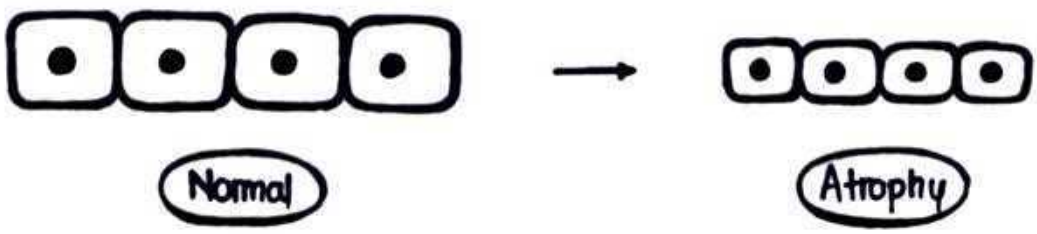
Morphology Of Cell Injury - Adaptive Changes

- Adaptive changes are the adjustments which the cell make in response to stresses.
- These changes can be physiological as well as pathological. Adaptive changes are generally related to change in size, shape or type of cell.
- These are the following adoptations a cell make in response to various type of stresses.

① Atrophy
② Hypertrophy
③ Hyperplasia
④ Metaplasia
⑤ Dysplasia

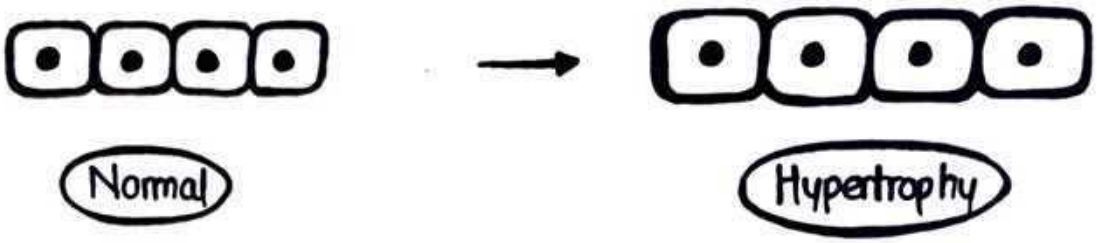
Atrophy

Atrophy is defined as decrease in size of the cell.
If atrophy takes place in enough number of an organ's cell the complete organ gets smaller.
Atrophy is mainly found in heart, skeletal muscles, brain etc.
It can be either physiological or pathological.



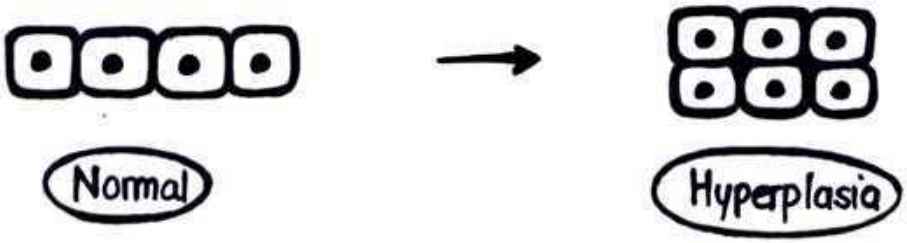
Hypertrophy

- Hypertrophy is defined as increase in size of the cell.
- If hypertrophy occured in enough number of cells of a particular organ then it leads to increase in complete organ size.
- It generally occured due to increased functional demand.
- Hypertrophy can be either physiological or pathological.



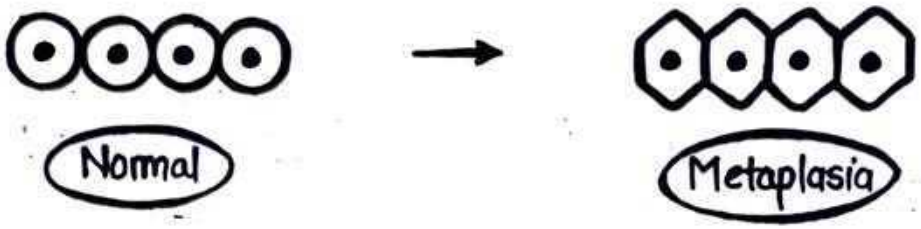
Hyperplasia

- Hyperplasia is defined as an increase in number of cells.
- If hyperplasia continues then finally it results in the enlargement of organs.
- It can be either physiological or pathological



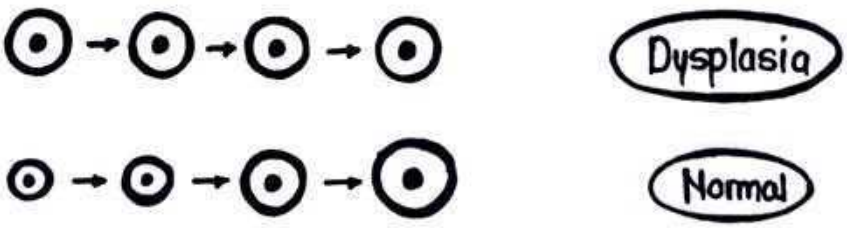
Metaplasia

- Metaplasia is simply defined as directly change in type of the cell.
- In metaplasia function of one cell is completely change into function of another cell.
- It can be either physiological or pathological.



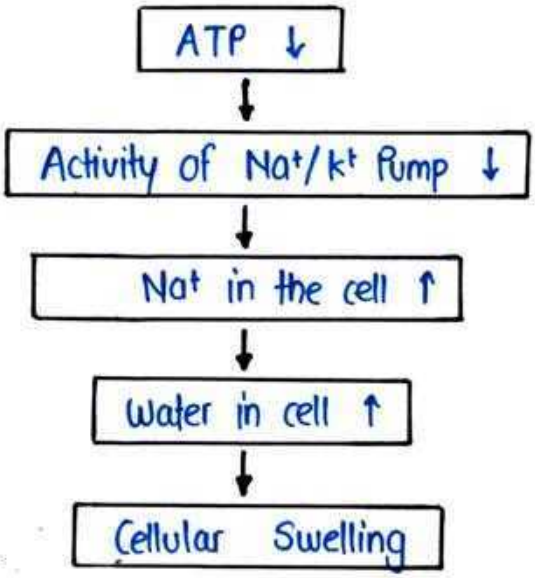
Dysplasia

- Dysplasia is defined as abnormal or stoppage of growth.
- When the growth of cell is stop and its shape & size remain constant as per germ cell then it is called dysplasia.
- It can be either physiological or pathological.



CELLULAR SWELLING

- Cell Swelling is simply defined as accumulation of water.
- Cell Swelling is generally occured due to disbalance in the function of Na^+/K^+ pump.
- Cell swelling is generally caused by high fever, Burns or due to any chemical or bacterial agent
- Generally cell swelling results in the increase of size & weight of the organ.
- The swelling of cell is reversible.



Intracellular Accumulation

- Intracellular accumulation is simply defined as accumulation of abnormal substances that can temporarily or permanently damage a cell.
- It can be occur due to overproduction, abnormal metabolism or disbalance in normal physiology.
- It can be either reversible or irreversible.

Calcification

- Calcification is defined as accumulation of calcium in body tissues.
- It normally occurs in the formation of bone but abnormal deposition or buildup of calcium can disrupt body's natural process.
- Calcification can be occur almost in every part of body & eventually leads to health problems.
- It can be occur due to hypercalcemia, calcium metabollic disorders, calcium rich diets etc.

Enzyme Leakage & Cell Death

- The lysosomes inside the cell is fulfilled with hydrolytic enzymes.
- These enzymes are so much destructive that it can instantly destroy the whole cell hence they are safely packed inside lysosomal membranes.
- Disbalance in normal body function & acid- base balance can leads to breakage of lysosomal membranes and leakage of these enzymes that eventually leads to cell death.

Acidosis & Alkalosis

- Most of the body's organs functions at a certain pH range.
- Disbalance in thes pH range can cause disturbance in functioning. Ideally pH of blood is 7.4.
- If this pH goes below 7.4 then it is defined as acidosis.
- If the pH goes above 7.4 then it is defined as alkalosis.
- Now this acidosis / alkalosis are of generally two types

① Respiratory (Increases or decreases rate of CO_2 elimination)
② Metabolic (Other than respiratory)

Electrolyte Imbalance

- Bloodstream contains many chemicals that are very essential for normal body functions. Electrolytes are one of them.
- Calcium, Magnesium, Sodium, Potassium are some examples of electrolytes.
- Now Disbalance in these electrolytes can cause variety of disturbances.
- Electrolyte Imbalance can become result into Vomiting, Diarrhoea, sweating, High fever etc.

INFLAMMATION

- Inflammation can be simply defined as a protective response of body's immune system against injury.
- It can also be defined as a process by which our body's white blood cells protect us from infection with foreign particles.
- Inflammation is body's natural reaction against injury & infection.

Causes Of Inflammation

There are various causes of inflammation as follows :

- Physical Agents : Heat, Cold, Radiation, Mechanical Trauma
- Chemical Agents : Acid, Base, Toxic Gases.
- Biological Agents : Viral bacteria, fungal Infections.
- Metabolic Products : Uric Acid, Urea.
- Circulation Disorders : Thrombosis, Infarction.

Clinical Signs Of Inflammation

- Redness (Rubor)
- Swelling (Tumor)
- Heat (Calor)
- Pain (Dolor)
- Loss of Function (Functio Laesa)

Types of Inflammation

Depending on the time of duration, inflammation are of two types :

① Acute Inflammation
② Chronic Inflammation

Acute Inflammation

- It occurs for a short time period and on rapid onset.
- The characteristics of acute inflammations are :
  - Accumulation of fluid & plasma proteins on affected side.
  - Activation of platelets & neutrophills.

Chronic Inflammation

- It occurs for a long time period & remain for longer duration.
- The characteristics of chronic inflammations are :
  - Mononuclear Infiltration
  - Activation of Lymphocytes & Macrophages.

MECHANISM OF INFLAMMATION

- Inflammation is a process by which body's white blood cells protect the body from foreign substances. such as bacteria & viruses.
- The mechanism of inflammation can be understand in two major steps :

① Vascular Events
② Cellular Events

VASCULAR EVENTS

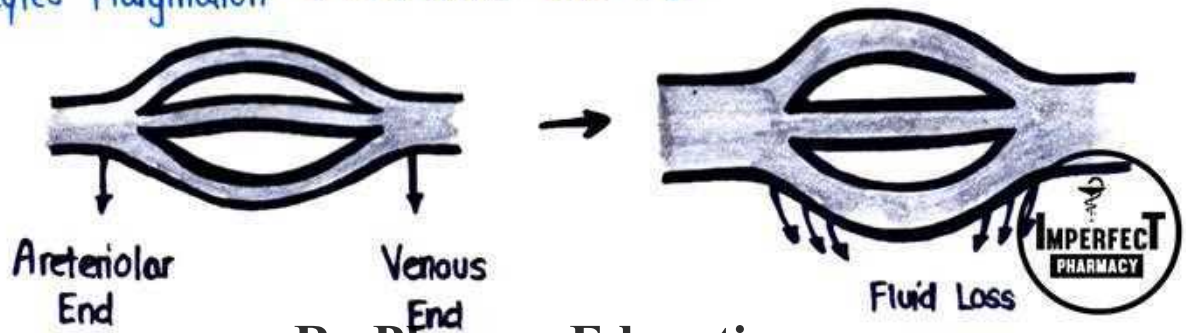
- It is the earliest response towards tissue injury.
- It is further divided into two steps.

(1) Haemodynamic Changes
(2) Alteration in vascular permeability

Haemodynamic Changes

The following haemodynamic changes occurs during an inflammatory response :

- Transient vasoconstriction (3-5 second)
- Persistent Progressive Vasodilation (Occurs in half an hour; Blood Flow ↑ → Redness & Warmth)
- Increased Hydrostatic Pressure (transudation of fluid → Swelling)
- Slowing / Stasis (Fluid Volume ↓; Red Blood Cells ↑)
- Leukocytes Margination



Alteration in Vascular Permeability

- Due to increase in hydrostatic pressure there is a excessive fluid escape or fluid loss seen in the vessels.
- Now if this fluid loss is without increased vascular permeability then it is called **Transudation**.
- But in case of inflammation vascular permeability get increased & due to this there is large amount of proteins also comes out with this fluid & this process is called **Exudation**.
- And this protein rich fluid that is lost from vessels is known as **Fluid Exudate**

- Loss of fluid from blood vessels and accumulation in interstitial space is known as **Edema**, it can be either transudate or exudate.

CELLULAR EVENTS

After the completion of vascular events there is a quick start of cellular events :

- Migration of WBCs / Exudation of Leukocytes
- Phagocytosis

Migration of WBCs / Exudation of Leukocytes

- Migration of WBCs or Exudation of leukocytes is defined as escape of white blood cells from blood vessel to injured tissue.
- Now this migration is further divided into some steps :

① Changes in formed elements of blood
② Rolling & Adhesion
③ Emigration
④ Chemotaxis

Changes in formed Elements : As we already see in vascular events that due to increased blood flow, loss of fluid increased which leads to slowing of blood stream.

Now due to this :

- Central Stream } → Margination
- Peripheral Zone
- WBCs comes close to vessels wall → Pavementing

Rolling & Adhesion : The leukocytes (mainly neutrophills) starts rolling & adheres on endothelial wall of blood vessels. Selectins responsible for rolling & Integrins responsible for adhesion.

Rolling

- Weak Attachment
- Mediated by Selectins

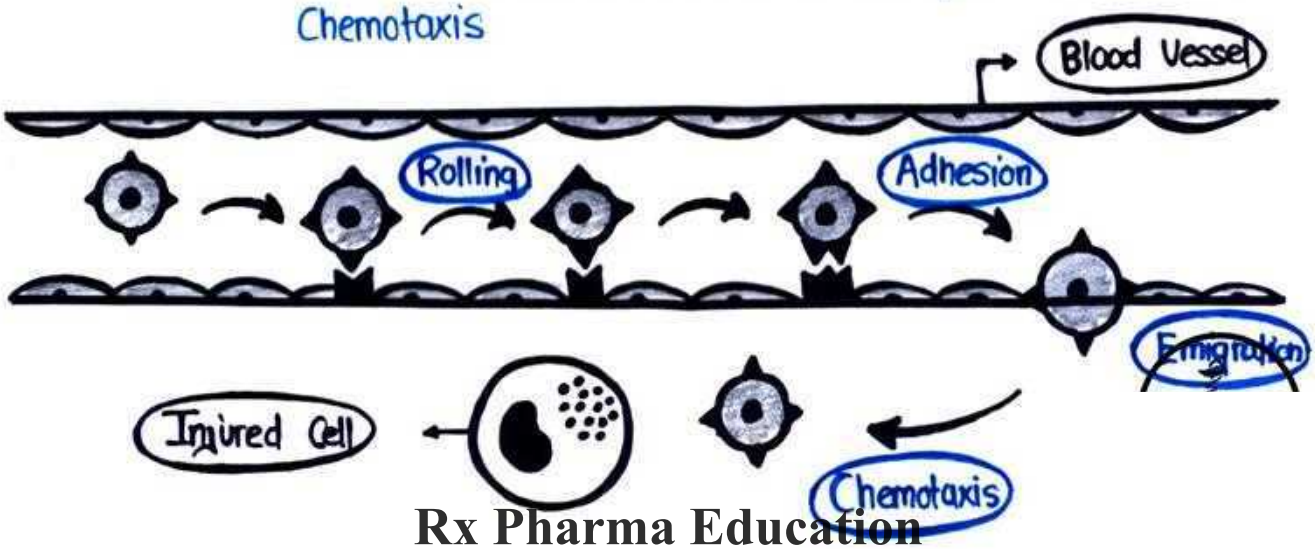
Selectins
- E Selectin } Endothelium
- P Selectin } Endothelium
- L Selectin } Neutrophills

Adhesion

- Strong Attachment
- Mediated by Integrins.
- They are of two types
  1. B_1 Integrins
  2. B_2 Integrins

Emigration : Once the leukocytes reaches on endothelium surface it starts secreting collagenases which destroy the basement membrane and after that leukocytes started moving towards injured cell / tissue & this process is known as Emigration

Chemotaxis : The transmigration of leukocytes after crossing several barrier to reach the site of injury is known as Chemotaxis



Phagocytosis

- The process of killing or engulfment of foreign particles (bacteria, virus etc) by WBCs (leukocytes) is known as Phagocytosis.
- It is further divided into three steps :

① Recognition & Attachment
② Engulfment
③ killing & Degradation

Recognition & Attachment : The release of chemotactic factors by bacterial products helps the phagocytic cells (WBCs) to recognise bacteria & attach with them

Engulfment : The psudopods present on the surface of leukocytes wrap the foreign particles & engulf them & the new structure formed is known as **Phagosome**.

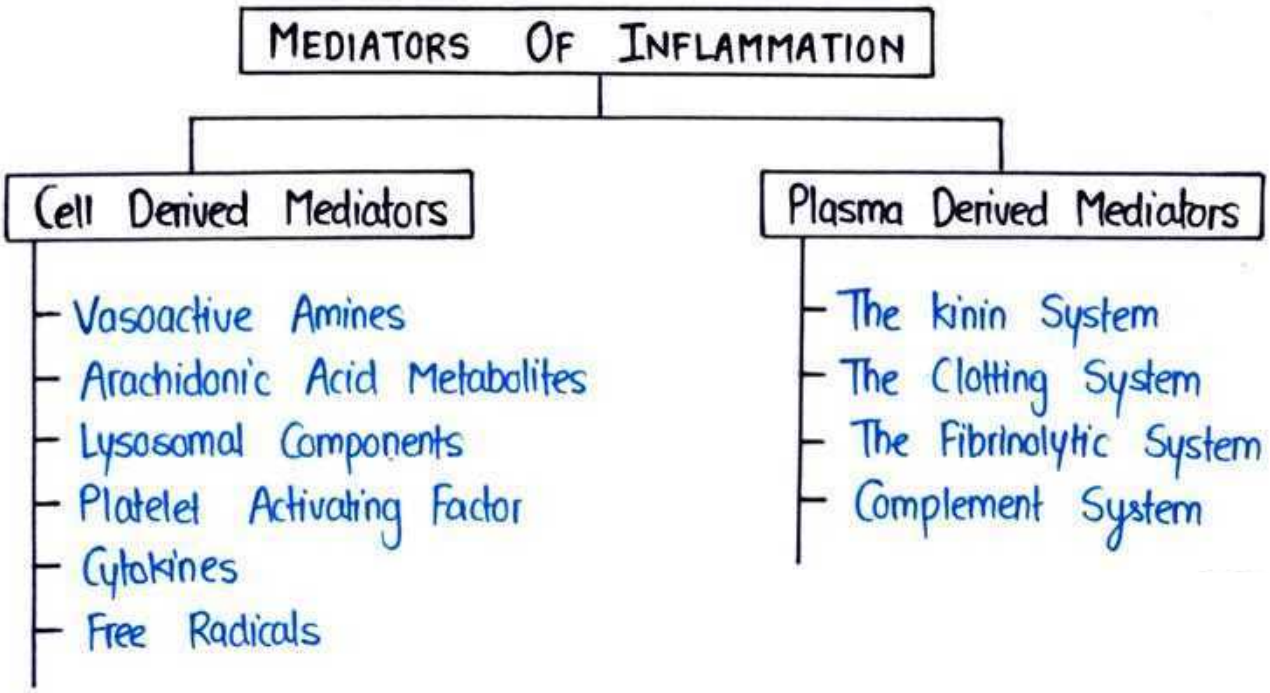
killing & Degradation : The phagosome fuses with lysosome & forms **Phagolysosome**. & after that lysosomal enzymes released inside phagolysosome which kills & digest the bacteria

MEDIATORS OF INFLLAMMATION

- Factors or chemicals that mediate the process of inflammation by vascular and cellular events are known as Mediators of Inflammation.
- These mediators can be either cell derived or plasma derived.

Properties of Mediators of Inflammation

- These mediators are released either from cells or from plasma proteins.
- Mediators are released in response to certain stimuli.
- Mediators act on different targets. They may have similar action on different target cells or different action on different target cells.
- They may act on cells which itself produced them or on other body cells.
- The common actions of mediators are : Increased vascular permeability, vasodilation, fever, pain etc.
- Mediators have short life span.



CELL DERIVED MEDIATORS

The various cell derived mediators are given as follows :

① Vasoactive Amines

- They give earliest inflammatory response
- They are of mainly 3 types

1. Histamine
2. Serotonine (5- Hydroxytryptamine)
3. Neuropeptides

	HISTAMINE	SEROTONIN	NEUROPEPTIDES
•	It is stored in granules of mast cells, basophills and platelets.	It is present in cells of GIT, spleen, mast cells etc.	It is another class of vasoactive amines but rarely activates or rarely seen.
•	Released due to heat, cold, irritation etc.	Release due to injury.	
•	Action : Vasodilation Vascular Permeability ↑ Itching, Pain etc.	Action : Same as histamine but less potent	

② Arachidonic Acid Metabolites (Eicosanoids)

- Arachidonic acid is a fatty acid.
- It is a constituent of phospholipid cell membrane.
- It is release from cell membrane by phospholipases.
- Prostaglandin is major arachidonic acid metabolite.

③ Lysosomal Components

- The inflammatory cells - neutrophills and monocytes contains lysosomal granules which acts as inflammatory mediators.
- They are responsible for chemotaxis, degradation of bacteria, release of collagenase etc.

④ Platelet Activating Factor

- It is released from basophills, mast cells, endothelium & platelets.
- It shows following actions :
  - Increased vascular permeability
  - Vasodilation
  - Adhesion
  - Chemotaxis

⑤ Cytokines

- Cytokines are polypeptide substances produced by activated lymphocytes and activated monocytes
- Its major functions are adhesion & vasodilation.

⑥ Oxygen Metabolites and Nitric Oxide

- Oxygen derived metabolites are released from activated neutrophills and macrophages & plays major role in increasing vascular permeability.
- Nitric acid is responsible for vasodilation.

PLASMA DERIVE MEDIATORS

These mediators are derived from activation and interaction of 4 interlinked system (kinin , Clotting , Fibrinolytic & Complement) as follows :

The kinin System

- The system is activated by XIIa factor that generates bradykinin
- Bradykinin shows following actions :
  - Smooth muscle contraction
  - Vasodilation
  - Increased Vascular Permeability

The clotting System

- This system is also activated by factor XIIa that generates fibrinogen which further forms Fibrin .
- They shows following actions :
  - Increased vascular permeability
  - Chemotaxis

The Fibrinolytic System

- This system is activated by plasminogen activator .
- It shows following actions :
  - Activates factor XII
  - Increased vascular permeability

Complement System

- The complement system gets activated either by :

(i) The classic pathway of forming antigen - antibody complex or

(ii) The alternate pathway involve non - immunologic agents.

- After activation it shows following actions :

- Release Histamine
- Increase vascular permeability
- Increase Phagocytosis

BASIC PRINCIPLE OF WOUND HEALING

- Wound healing is a complex and dynamic process.
- Wound is defined as any type of cut or injury which breaks the continuity of tissue.
- Wound healing is defined as repair and regeneration of damaged tissues due to any type of injury.

Phases of Wound Healing

There are basically 4 phases of wound healing :

① Hemostasis
② Inflammation
③ Proliferation / Granulation
④ Remodeling / Maturation

Hemostasis

- Hemostasis is the first step of healing.
- It begins just after the injury to stop the bleeding.
- In this step body activates the blood clotting system that blocks the blood loss.
- Blood clotting occurs by vasoconstriction & accumulation of platelets on the site of injury.

Inflammation

- It is the second phase of wound healing.
- It is the defensive phase focuses on destroying bacteria & other foreign particles.
- This inflammatory phase is further divided into two subphases : Early inflammatory phase and late inflammatory phase.
- During early inflammatory phase WBCs (specially neutrophills) destroys bacteria & phase is last for 24 - 48 hours.
- During late inflammatory phase WBCs (specially macrophages) continue destroying bacteria & clearing debris.
- The cells also secreting growth factors that helps in tissue repair. The late inflammatory phase often last for 4 - 6 days.

Proliferation / Granulation

- It is the 3rd phase of wound healing.
- This stage is mainly focuses on :
  - Filling the wound
  - Contraction of wound margins
  - Covering the wound
- In this first granulated tissue fills the wound, then wound margins contracts and after that finally epithelial tissue started to covering the wound.
- The proliferation phase often last for 20 - 25 days.

Remodelling / Maturation Phase

- During the maturation phase, newly formed tissues gains strength and flexibility.
- It is the last phase of wound healing.
- In this phase, collagen fibres reorganize, tissue remodels & matures & overall strength increased.
- The maturation phase last from 21 days - 2 years depending on type of wound.

Factors affecting wound healing

The following factors can affect the time duration of wound healing :

- Infection
- Blood supply
- Hypoxia
- Age
- Diabetes
- Alcohol, Tobacco etc.