

Plasma Proteins

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Normal Values: Total protein = $6.4 - 8.3 \text{ g/dL}$

Serum albumin = 4.7 g/dL (3-5)

Serum globulin = 2.3 g/dL (2-3)

Fibrinogen = 0.3 g/dL

Albumin/Globulin Ratio: A/G ratio

Normal A/G ratio = 2:1 (1.7:1)

Indicator of some diseases of the liver & kidney.

This ratio is reversed in liver diseases or during increased globulin levels associated with hyperproteinemia.

(Plasma proteins are synthesized in the liver.)

Types:

Albumin: it determines the colloidal osmotic pressure (oncotic pressure) of plasma.

→ formed in the liver

→ in kidney diseases with glomerular injury it appears early in urine due to its small diameter (albuminuria).

Globulin: → formed in the liver, reticuloendothelial system & plasma cells

→ categories: α , β , γ

→ Antibodies are γ -globulins (Ig) formed by plasma cells.

→ Transport proteins having globulins: transferrin ceruloplasmin, etc.

Fibrinogen: produced in the liver.

→ plays an important role in blood coagulation

→ contributes to viscosity of plasma & determination of ESR.

Functions: Osmotic Pressure (OP): OP due to plasma proteins is called oncotic pressure

→ Normal value = 25 mm Hg

→ prevents loss of fluid from capillaries into the interstitial tissue space.

→ Decrease in OP due to hypoproteinemia leads to edema.

Viscosity: Plasma proteins contribute to 50% of blood viscosity.

Fibrinogen > albumin (because of the elongated shape of fibrinogen)

Immunity: Antibodies (immunoglobulins) are gamma globulins

→ they mediate humoral immunity

Coagulation: fibrinogen forms fibrin thread which is the final step of blood coagulation.

→ clotting factors like prothrombin are plasma proteins.

Transport: they serve as carrier molecules for substances like hormones, drugs, metals, etc.

Buffering: plasma proteins form an important buffering system and thus, maintain acid-base balance of the body.

Determination of ESR: ESR depends on fibrinogen concentration in plasma

→ Fibrinogen facilitates rouleaux formation which increases sedimentation of red cells.

Transport Function: → Cortisol is transported by transcortin

→ Vit. B₁₂ is transported by transcobalamin.

→ Copper is transported by ceruloplasmin.

→ Free Hb in the vessels is bound by haptoglobin & carried to reticuloendothelial system.

Reserve Proteins: Plasma proteins serve as reserve proteins which are utilised during fasting, inadequate protein intake

Hypoproteinaemia: generalised decrease in level of plasma proteins

Causes: (i) dietary deficiency & starvation

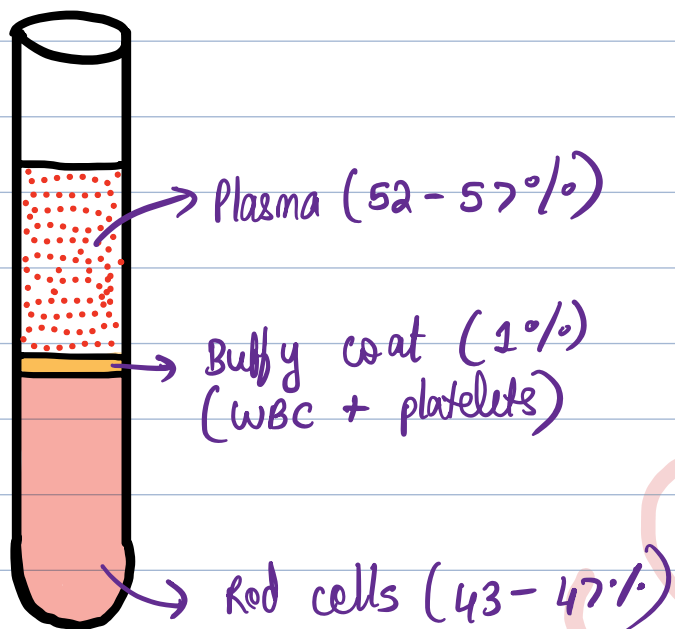
(ii) malabsorption syndrome due to intestinal diseases

(iii) liver diseases like hepatitis & cirrhosis (due to reduced protein synthesis)

(iv) renal diseases like nephrotic syndrome

(v) haemorrhage & extensive burns

(vi) hereditary anaalbuminaemia.



centrifuged blood

normal blood volume = 5-6 L

⇒ 8% of body weight.

Erythropoiesis

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It is the process of formation & development of RBCs.

Sites:

In first 2 months of gestation: yolk sac (mesoblastic stage)

From 3rd month: Liver & spleen (hepatic stage)
↳ till birth

From 20th week: begins in the bone marrow also

By 7th or 8th month: bone marrow is the main site (myeloid stage)

→ active haemopoietic bone marrow is red in colour due to marked cellularity
∴ called red bone marrow (RBM)

→ however, there is progressive fatty replacement throughout the long bones converting RBM to yellow bone marrow (YBM).

In adults: haemopoietic RBM is confined to axial skeleton & proximal ends of long bones.

Process/Stages: According to the monophyletic theory of haemopoiesis, all blood cells originate from pluripotent or multipotent stem cells (stem cells are capable of cell division & can differentiate into specialized cells called progenitor cells).

Progenitor cells:

- (i) CFU - GEMM (colony forming unit - granulocyte, erythrocyte, megakaryocyte, macrophage)
- (ii) BFU-E (burst forming unit - erythrocyte) ⇒ erythrocyte series
- (iii) CFU-E (colony forming unit - erythrocyte) ⇒ erythrocytes.
- (iv) Ba-CFU ⇒ basophil
- (v) Eo-CFU ⇒ eosinophil
- (vi) M-CFU ⇒ monocyte
- (vii) G-CFU ⇒ neutrophil

Pluripotent Stem Cell

Myeloid Stem Cell

Lymphoid Stem Cell

CFU - GEMM

T Lymphocyte

B Lymphocyte

BFU-E

Ba-CFU

Eo-CFU

M-CFU

G-CFU

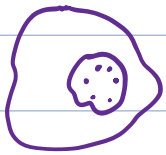
Erythrocyte

Basophil

Eosinophil

Monocyte

Neutrophil



BFU-E



Proerythroblast



Early normoblast



Intermediate normoblast



Late normoblast



Reticulocyte

Erythrocyte.



progressive decrease in size (20.0 μ m $\rightarrow$ 7.5 μ m)

Stage	Nucleus	Hb	Staining	Mitoses
Homocytoblast (stem cell)	Very large	Absent	Deep basophilic	Present ++
Pronormoblast	Large	Absent	Deep basophilic	++
Early normoblast	Large (nucleoli disappear)	Absent	Basophilic	++
Intermediate normoblast (polychromatic)	Nucleus becomes dense	Appears	Acidophilic + Basophilic (polychromatic)	+
Late normoblast (orthochromatic)	Small nucleus	Increased Hb	Acidophilic	Absent
Reticulocyte	Absent	Increased Hb	Acidophilic	Absent

Regulation:

by erythropoietin: → hormone mainly produced by the juxta-glomerular apparatus of kidney.
→ release of erythropoietin is stimulated by hypoxia or decrease in number of RBCs.

Erythropoietinogen
(α globulin)

renal
erythropoietic
factor

erythropoietin → increases erythropoiesis by acting at the site of erythropoiesis
→ promotes every stage of maturation from pronormoblast to mature red cells.
→ promotes Hb synthesis by promoting globin synthesis & potentiating ALA synthase
→ promotes release of RBCs from bone marrow into peripheral circulation.

Factors:

Factors Increasing Erythropoietin Secretion: (i) Hormones (androgens, thyroxine, ACTH, prolactin)
(ii) Haemolysates (products released following RBC destruction)
(iii) Nucleotides (NAD, NADP, cAMP)
(iv) Vasoconstriction drugs

Factors Decreasing Erythropoietin Secretion: (i) adenosine antagonists like theophylline
→ aka extrinsic factor (ii) oestrogen

Vitamin B12: essential for red cells maturation

→ required for synthesis of DNA & maturation of nucleus

→ deficiency causes failure of maturation of nucleus & cells remain large (megaloblasts)

Folic acid: Required for DNA synthesis

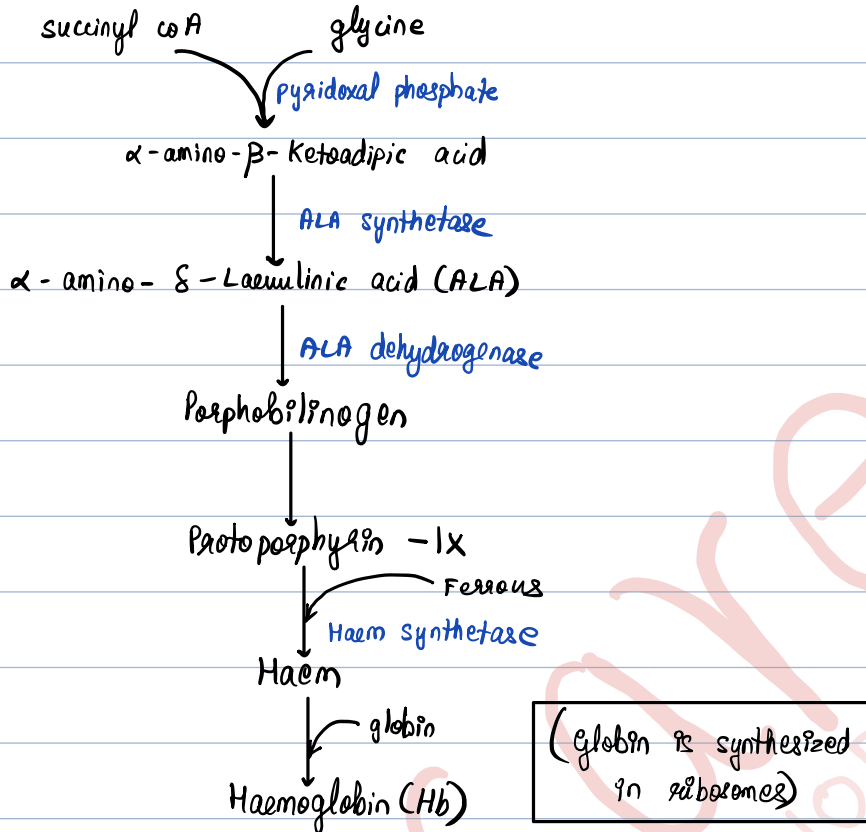
→ deficiency causes megaloblastic anaemia

Hb Synthesis & Fate:

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Synthesis: synthesized in the cytoplasm of intermediate normoblasts

Steps:



Fate of RBCs: destroyed after about 120 days due to increased fragility of old RBC cell membrane

→ spleen = graveyard of RBCs.

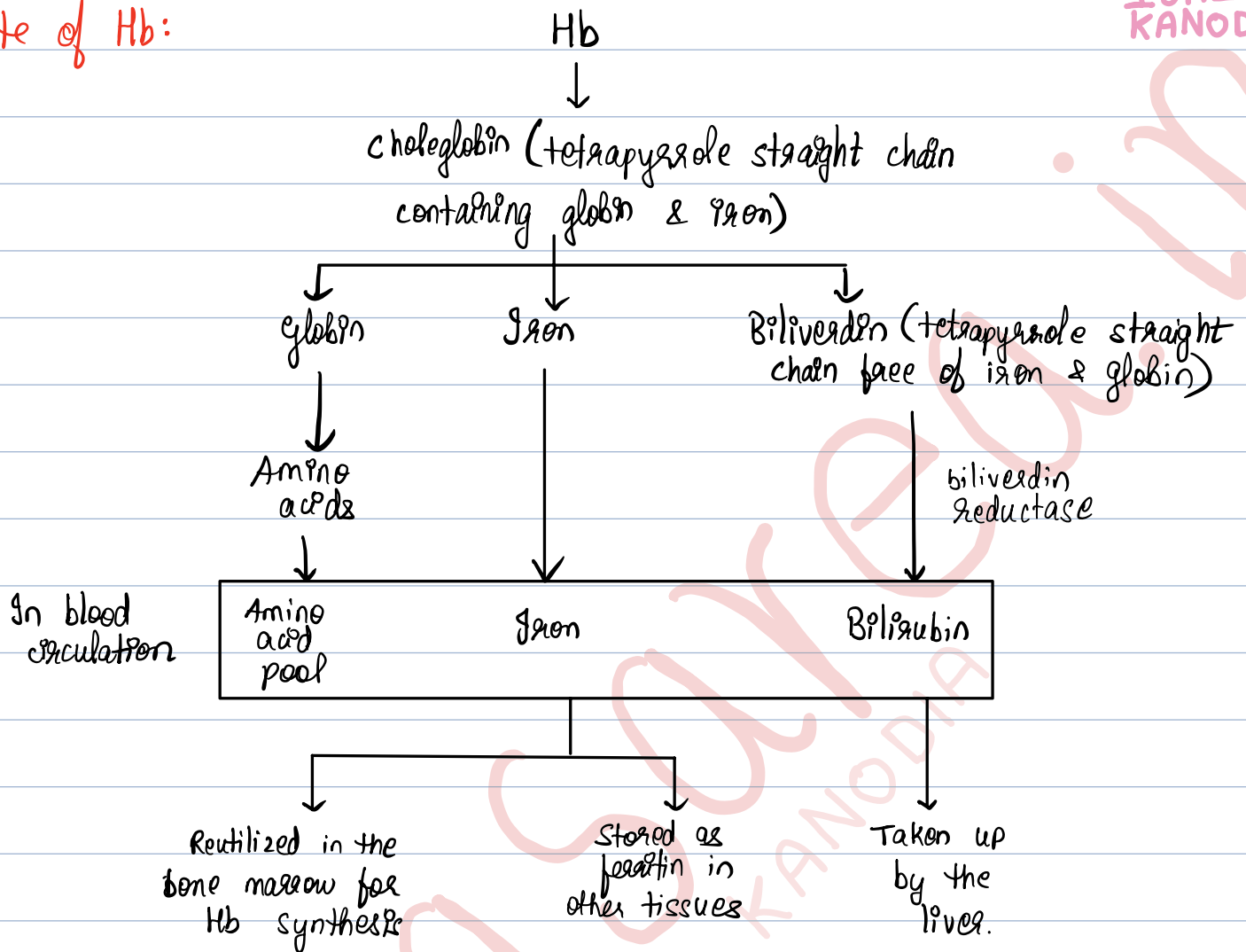
→ Hb released after haemolysis of red cells is taken up by tissue macrophages.

Tissue Macrophage System / Reticuloendothelial system: consists of:

- (i) in the bone marrow - part of lining of blood sinuses (littoral cells)
- (ii) in the liver - Kupffer cells
- (iii) in the spleen - found in the pulp
- (iv) in the lymph nodes - line the lymphatic paths

Fate of Hb:

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Anemia

Definition: A group of disorders with Hb concentration of blood below normal range:

In adult males: $< 13 \text{ g/dL}$

In adult females: < 11.5

In newborns: < 15

At 3 months of age: < 9.5

→ Low RBC count ($< 4 \text{ million}/\mu\text{L}$) is usually associated with low Hb in anemia.

Grading of Anemia: Mild: $8-10 \text{ g/dL}$

Moderate: $6-8$

Severe: < 6

Classification: etiological (Whitty's) classification: (Based on causes)

Type	Example
Deficiency Anaemias	(i) Iron deficiency anaemia (ii) Megaloblastic anaemia (pernicious anaemia) due to vit. B12 deficiency (iii) Megaloblastic anaemia due to folic acid deficiency (iv) Protein & vit. C deficiency
Blood loss anaemia (Haemorrhagic anaemia)	(i) Acute post-haemorrhagic anaemia in accidents (ii) Chronic post-haemorrhagic anaemia
Haemolytic anaemias	<u>Hereditary:</u> (i) Thalassemia (ii) Sickle cell anaemia (iii) Hereditary spherocytosis (iv) G6PD deficiency <u>Acquired:</u> (i) due to direct toxic effects (malaria, snake venom) (ii) splenomegaly (iii) paroxysmal nocturnal haemoglobinuria
Aplastic Anaemia	due to failure of bone marrow to produce RBCs.
Anaemia due to chronic diseases	tuberculosis, malignancies, chronic infections, chronic lung diseases, etc.

Morphological (Wintrobe's) Classification: (Based on MCV & MCHC)

Type	MCV	MCHC	Example
Normocytic Normochromic	normal (78 - 94 μm^3)	normal (30 - 38%)	• acute post-haemorrhagic anaemia • chronic post-haemorrhagic anaemia • thalassemia
Microcytic Hypochromic	reduced (< 78 μm^3)	reduced (< 30%)	• Iron deficiency anaemia • chronic post-haemorrhagic anaemia • thalassemia
Macrocytic normochromic	increased (> 94 μm^3)	normal (30 - 38%)	• megaloblastic (pernicious) anaemia (vit. B12 deficiency) • megaloblastic anaemia (folic acid deficiency)

General Clinical Features of Anaemia: anaemic hypoxia

(due to decreased O_2 carrying capacity of blood due to reduced Hb)

- generalised muscular weakness (due to muscle hypoxia)
- pallor of skin & mucous membrane (due to deficiency of red coloured Hb in blood)
- respiratory symptoms - breathlessness, increased rate & force of respiration
(due to compensatory stimulation of respiratory centre)
- cardiovascular manifestations - tachycardia, palpitation (compensatory mechanism to increase cardiac output).
- increased basal metabolic rate
- lethargy, headache, faintness, drowsiness (CNS manifestations)

Daily iron requirement: Adult males: 5-10 mg/day

Adult females: 20 mg/day

Pregnant & lactating women: 40 mg/day

Characteristic features of iron deficiency anaemia:

- Koilonychia (nails become dry, soft & spoon-shaped)
- Atrophic glossitis (tongue becomes angry red)
- Angular stomatitis (mouth)
- Plummer - Vinson Syndrome - oesophagus may develop membranous webs at postcricoid area leading to dysphagia
- RBCs are microcytic, hypochromic
- anisocytosis, poikilocytosis
- serum iron ($< 50 \text{ mg \%}$) [Normal = $60 - 160 \text{ mg \%}$]
- low serum ferritin

Characteristic features of megaloblastic anaemia:

- RBCs are macrocytic
- $\text{MCV} > 94 \text{ fL}$ → MCH increases = 50 pg (normal = $28 - 32 \text{ pg}$).
- MCHC usually normal ($30 - 38 \text{ g \%}$) [because both MCV & MCH increase]
- increased serum bilirubin = $> 1 \text{ mg/dL}$ (normal = $0.2 - 0.8 \text{ mg/dL}$)

Blood Grouping & Transfusion

Landsteiner Law: It states that:

- If an agglutinin is present on RBC membrane of an individual, the corresponding agglutinin must be absent in plasma
- If an agglutinin is absent on RBC membrane of an individual, the corresponding agglutinin must be present in plasma.

(Applicable only to ABO blood group system).

Rh factor: Rh antigen (D antigen) first in Rhesus monkeys

- 85% population: Rh +ve
- 15% population: Rh -ve
- There are no natural antibodies of Rh antigens in our body (unlike ABO system).
- Rh antibodies (IgG can cross the placenta) are produced in response to introduction of Rh antigen (Rh +ve blood) in an Rh -ve individual; these antibodies persist in blood for years & produce serious reactions during 2nd transfusion.

Haemolytic Disease of Newborn:

Mechanism: → Entrance of Rh +ve fetal RBCs into Rh -ve mother's circulation during first pregnancy (at the time of delivery, due to severance of umbilical cord)

- Production of Rh antibodies (anti-D) in mother during post-partum period
- Rh incompatibility reaction during second pregnancy (if the second pregnancy also bears a Rh +ve child)
 - the Rh antibodies (IgG) cross the placenta & enter fetal circulation
 - agglutination of fetal RBCs causing haemolytic disease of newborn.

Manifestations:

- (i) Erythroblastosis foetalis — appearance of large number of erythroblasts in peripheral blood
 - anaemia due to excessive haemolysis
- (ii) Icterus gravis neonatorum — jaundice within 24h of birth due to excessive bilirubin formation.
 - enlarged liver & spleen
- (iii) Kernicterus — neurological syndrome since excessive bilirubin formed crosses the not well-developed blood-brain-barrier of infants
 - affects the basal ganglia producing disturbance of motor activities
 - develops when serum bilirubin $> 18 \text{ mg/dL}$.
- (iv) Hydrops foetalis — fetus is grossly oedematous

Prevention: Injecting single dose of Rh antibodies (anti-D) to mother soon after 1st delivery.

Blood Transfusion:

Common situations: → blood loss

- for quick restoration of Hb in case of severe anaemia during pregnancy or emergency surgery
- exchange transfusion in case of haemolytic disease of newborn.
- blood diseases like aplastic anaemia, leukaemia, purpura
- acute CO poisoning

Donor criteria: Age = 18-60 years

- screened for diseases which spread through body fluids (HIV, syphilis, malaria)
- Hb & PCV should be within normal range (female Hb $\geq 12 \text{ g\%}$; male Hb $\geq 13 \text{ g\%}$)

Universal Donor: O (O^{-ve})

Universal Recipient: AB (AB⁺)

Cross-matching $\begin{cases} \text{major} \\ \text{minor} \end{cases}$

Major: cells of the donor are directly matched against the recipient:

- to ensure that antibodies present in the recipient's plasma do not harm donor's red cells
- though donor's red cells are less in quantity than the recipient, they cause agglutination due to high antigenic activity of ABO agglutinogens.
- ABO agglutinins do not react highly, as they are cold antibodies.
- $\therefore$ important to match donor's agglutinogens against recipient's plasma (agglutinin).

Minor: donor's plasma is checked against red cells of recipient

→ not very important

Mismatched Transfusion: incompatible blood transfusion causing agglutination reaction of donor's red cells followed by their hemolysis

→ called acute hemolytic transfusion reaction.

Complications: (i) shivering & fever (febrile reactions)

(ii) Hemoglobinemia & hemoglobinuria

(iii) hemolytic jaundice

(iv) acute renal failure due to - Hb casts block & damage the renal tubules
- release of toxic substances from lysed red cells cause renal vasoconstriction

(v) hyperkalemia (due to release of K^+ from red cells)

→ may cause cardiac arrest in diastole.

Functions:

Leucocyte	Functions
Neutrophil	(i) phagocytosis (ii) febrile response through endogenous pyrogen (iii) cause reactions of inflammation like vasodilation, edema.
Eosinophils	(i) mild phagocytosis (ii) defense mechanism of body in parasitic infestations (iii) role in allergic reaction - detoxifying inflammation inducing substances, inhibit mast cell division
Basophils	(i) mild phagocytosis (ii) they release eosinophil chemotactic factor that causes eosinophils to migrate to the inflamed allergic tissue (iii) release histamine, serotonin, bradykinin which cause vascular & tissue reactions that cause allergic manifestations (iv) release heparin which prevents clotting of blood
Lymphocytes	(i) B-lymphocytes & their derivatives (plasma cells) are responsible for humoral immunity (ii) T-lymphocytes are responsible for cell-mediated immunity.
Monocytes	(i) phagocytosis (ii) kill tumour cells after sensitization by lymphocytes (iii) synthesize complements & other biological substances.

Phagocytosis (cell eating)

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→ refers to process of engulfment & destruction of solid particulate material by the cells

Steps:

I Chemotaxis: process of migration of neutrophils to the site of infection

→ chemical factors that are released from the site of infection/inflammation attracts the neutrophils & are called chemotaxins (eg- complement proteins)

→ neutrophils change their shape to become highly amoeboid.

→ bone marrow is stimulated to produce more neutrophils.

II Diapedesis: process of neutrophils passing through the capillary endothelial cells to reach the site of invasion in tissue

→ neutrophils first marginate (margination & pavementing) & adhere tightly to endothelial lining (rolling & adhesion) with the help of L-selectins

III Opsonization & Adherence: process by which bacteria are made tasty to the phagocyte

→ chemicals that promote opsonisation (opsonins) - IgG antibody, complement proteins (C3a, C3b)

→ opsonized bacteria bind to the receptor on the neutrophil membrane by a process called adherence.

IV Ingestion (Endocytosis): membrane of phagocyte extends projections (pseudopodia) from both sides to engulf the microbe.

→ The pseudopodia unite to form phagocytic vesicle around the microbe

(pseudopodia formation $\Rightarrow$ actin polymerization)

→ phagocytic vesicle fuses with lysosome to form phagolysosome.

V Killing:

non-oxidative
oxidative

→ Non-oxidative - Lysosome hydrolyzes the cell wall of bacteria & lactoferrin sequesters iron which is required for bacterial growth.

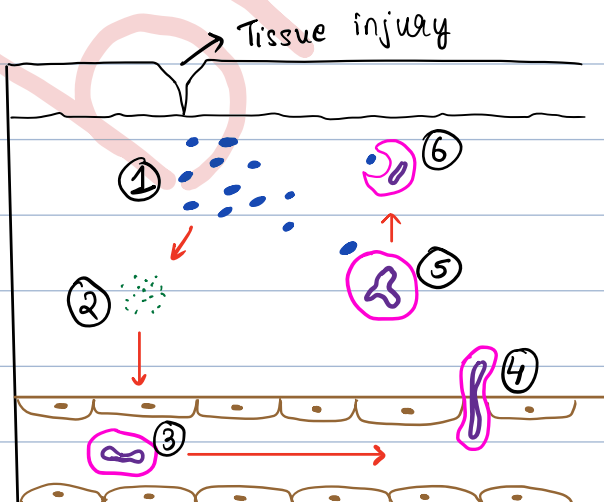
- Defensins released from azurophilic granules have unusual cyclic structure

& kill bacteria by disrupting their outer membrane & breaking single-strand DNA

→ Oxidative - by oxygen metabolites like $\text{OH}\cdot$, O_2^- , H_2O_2

- these metabolites are generated by NADPH oxidase

- Activation of NADPH oxidase is associated with increased oxygen intake of neutrophil called respiratory burst.



① = Invasion

② = Release of chemotaxins

③ = Chemotaxis

④ = Diapedesis

⑤ = Opsonization

⑥ = Ingestion & Killing.

Non-Specific / Innate Immunity

→ present from birth

- Defense mechanisms are -
- Mechanical defense
 - Chemical defense
 - Defense by NK cells
 - Defense by phagocyte cells
 - Defense by inflammation & fever.

Mechanical Defense: → skin forms the partition between external environment & the body

- Mucous membrane covers the body cavities & mechanically traps the organisms & secrete inhibitory chemicals
- Mucous traps organisms especially in the respiratory & GI systems.
- Hair guards almost all openings of the body & filter all organisms & prevent their entry.
- Cilia also filter microorganisms, remove dust & microbes.
- Tear (secreted from lacrimal apparatus) washes the microbes & dilutes chemical substances produced by them.
- Saliva washes microbes from the oral cavity & also contains anti-microbial chemicals.
- Urine flow washes microbes from urinary tract.
- Defecation washes away microbes from lower GI tract.

Chemical Defense: Acidic pH of skin inhibits microbial growth.

- Sebum (from sebaceous glands of skin) contain bactericidal substances like unsaturated fatty acids.
- Chemicals in body secretions like lysozyme (in tear, saliva, sweat) inhibit growth of microbes.
- Acidic pH of Stomach & Vagina kills microbes & destroys toxins
- Complement proteins in plasma (activated in response to entry of microbes) help in destroying microbes by facilitating opsonization & phagocytosis
- Interferons are antiviral substances secreted by activated lymphocytes.

Defense by NK Cells: Natural Killer (NK) cells are third category of lymphocytes (after B & T)

- they have the ability to kill a wide variety of microbes & tumour cells.
- these are large granular lymphocytes
- lack surface antigen receptors
- recognize antibody-coated target cells & kill them by antibody-dependent cell-mediated cytotoxicity (ADCC).

Mechanisms of Lysis — osmotic lysis by incorporating perforins into surface of microbes

- release interferons
- possess F_c receptors that allow them to kill antibody-coated viruses.
- Kill by ADCC

Defense by Phagocytic Cells: Granulocytes, monocytes & macrophages kill microbes by phagocytosis

- Two types of macrophages — wandering macrophages (mobile in the tissues)
 - are mononuclear
 - fixed macrophages (present in specific tissue sites in the body)
- ∴ called as mononuclear phagocyte system (MPS)
 - ↳ previously known as reticuloendothelial system.

MPS includes — Kupffer cells of liver

- Alveolar macrophages in lungs
- Microglia of brain
- Osteoclasts in bone
- Mesengial cells in kidney
- Langerhans cells in skin
- Histiocytes in connective tissue.

Defense by Inflammation & Fever: chemicals released by inflammatory cells kill microbes.

→ Inflammation is the response of a tissue to injury

→ Characteristics of inflammation at the site of injury

- Rubor (redness)
- Dolor (pain)
- Calor (increased temperature)
- Tumor (swelling)
- Functio laesa (loss of function of injured part of body)

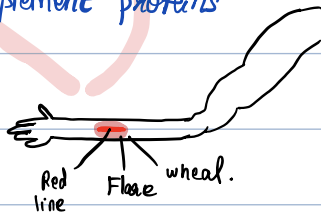
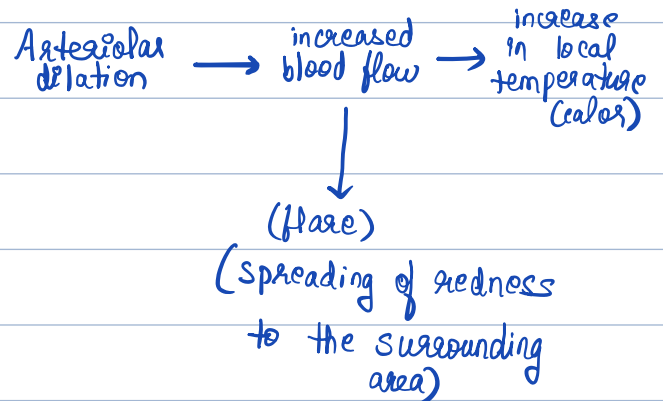
Stages of Inflammation:

① Vasodilation & Increased permeability:



Vasodilation & Increased permeability are caused by:

- histamine (from mast cells, basophils)
- bradykinin (blood, tissues)
- prostaglandins (from damaged cells)
- complement proteins



∴ Triple response = Red line, Wheal, flare.

II Phagocyte Migration & Phagocytosis:

- first to appear is neutrophil; followed by monocyte & macrophage.
- phagocytes reach the site of injury by chemotaxis & diapedesis
- phagocytes die in the process of killing microbes.
- within few days, dead phagocytes & damaged tissue cells form viscous fluid called pus.
- usually pus is absorbed; but there could be abscess formation sometimes (localised accumulation of pus).

III Tissue Repair: healing stage

- facilitated by migration of fibroblasts, macrophage, epithelial cells to the site of injury.
- tissue plasmin promotes migration of keratinocytes that aid healing
- proliferation of collagen produces scar.

Fever: protective phenomenon of the body against infections

- increased temperature prevents microbial growth
- fever facilitates action of interferons & different body enzymes that inhibit microbial growth.
- Thus, (unless very high & deleterious) fever should not be brought down immediately by anti-pyretics.

Acquired / Specific Immunity:
 $\left\{ \begin{array}{l} \text{cell-mediated} \\ \text{humoral/antibody-mediated} \end{array} \right.$

HUMORAL IMMUNITY: mediated by antibodies produced by plasma cells in turn produced by B lymphocytes

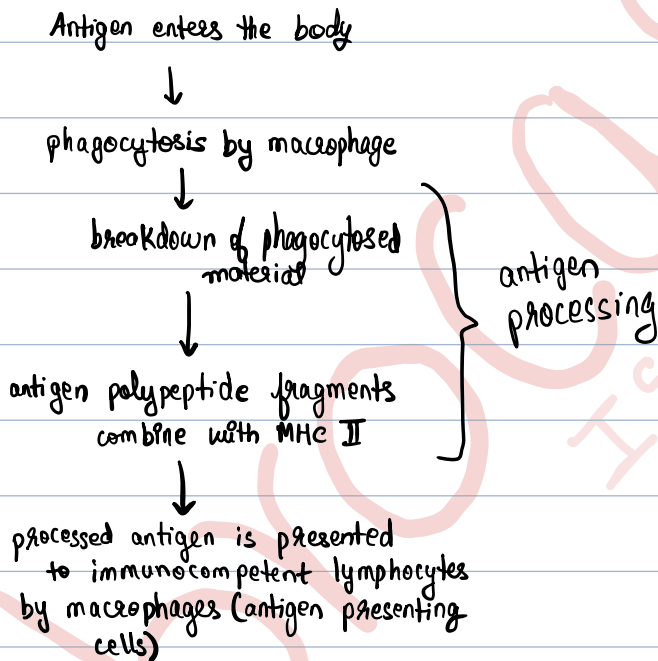
- Role: - defence against **extracellular bacterial & viral pathogens**
- **immediate hypersensitivity reactions** type I, II, III.
- associated with certain **autoimmune diseases**.

Types:

- **Primary:** response of the body on its first encounter with a specific antigen (latency period = 4 days - 4 weeks).
- **Secondary:** response of the body on subsequent encounter with the antigen (quicker & more abundant due to immunological memory).

Stages / Mechanism:

① **Antigen Processing & Presentation:**

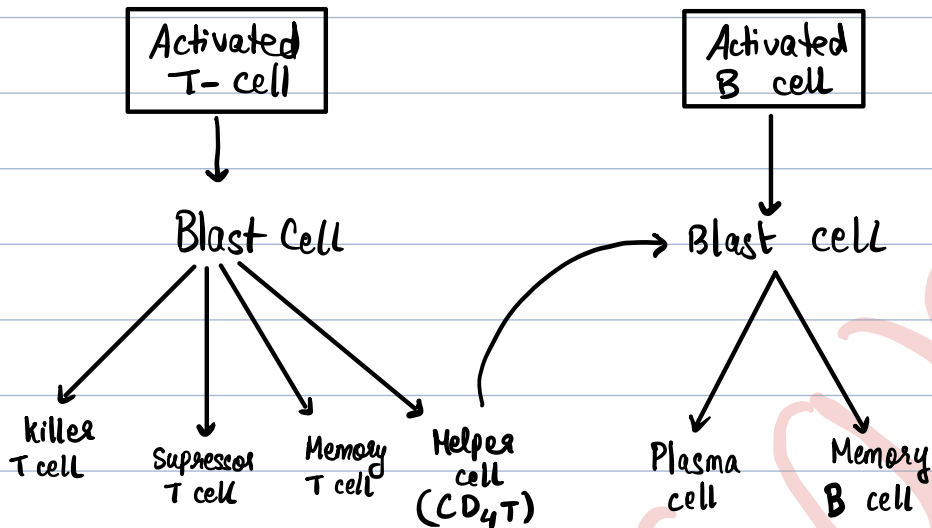


② **Recognition of Antigen by Lymphocytes:**

- lymphocytes have antigen recognition receptors (immunoglobulins in B-lymphocytes & T-cell receptors in T-lymphocytes)
- receptors are specific
- processed antigen, on recognition, binds to specific receptors on the lymphocyte surface

③ Lymphocyte Activation:

- lymphocytes bind with antigens & become activated (become larger) called Blast transformation.



Memory B cells provide immunological memory for subsequent encounter with the specific antigen.

④ Production of Antibodies:

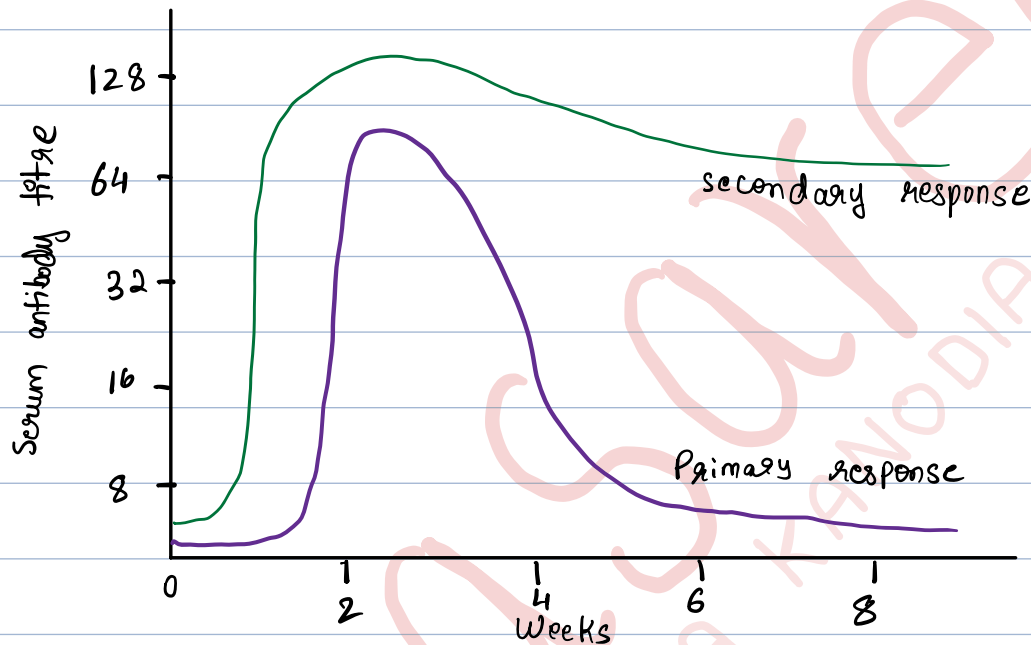
- Plasma cells secrete antibodies (immunoglobulins) at the rate of 2000 molecules/s
- In primary response, IgM is produced initially & later switched to IgG.

⑤ Inactivation of Antigen / Attack Phase / Effector Phase:

- Inactivation of antigen by antibodies by 2 methods
- (i) Direct attack
- Agglutination & clumping
 - Ag-Ab precipitate formation
 - Neutralization of Ag by ab.
 - Ab cause rupture of Ag cells.

(ii) Attack through Complement System

- Classical Pathway (activated by antigen-antibody rxn)
- Alternative/Properdin Pathway (activated by binding of properdin with cell wall of invading microbe)

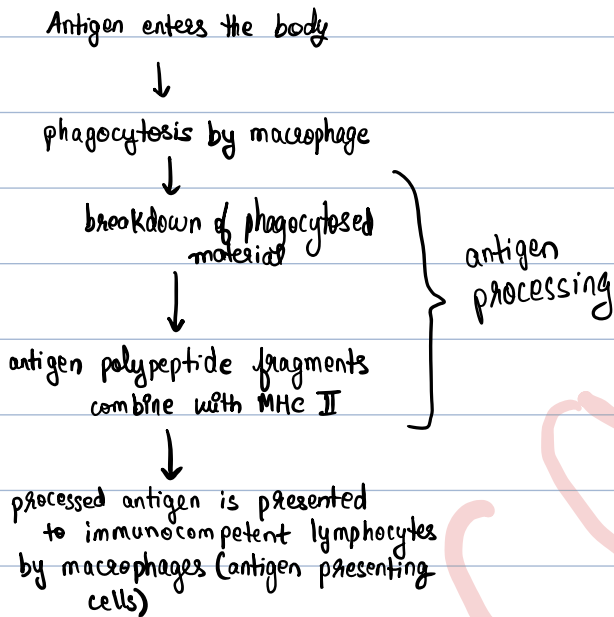


CELL-MEDIATED IMMUNITY:

- Role:
- protects the host against viruses, fungi, intracellular pathogens
 - participates in allograft rejection
 - participates in delayed hypersensitivity reaction.
 - associated with certain autoimmune diseases
 - immunity against cancer (tumour immunity).

Stages:

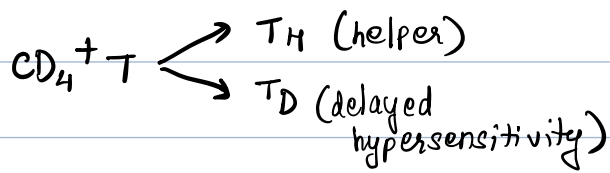
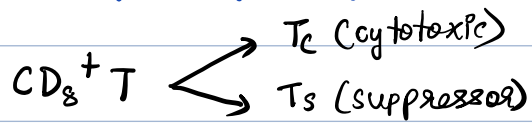
① Antigen processing & presentation



② Recognition of Antigen by Lymphocytes:

- lymphocytes have antigen recognition receptors (immunoglobulins in B-lymphocytes & T-cell receptors in T-lymphocytes)
- receptors are specific
- processed antigen, on recognition, binds to specific receptors on the lymphocyte surface
- mature lymphocytes
 - CD_4^+ $\Rightarrow$ recognise class I MHC
 - CD_8^+ $\Rightarrow$ recognise class II MHC

③ T-lymphocytes differentiation



T-T co-operation - differentiation of T lymphocytes into T_H , T_s , T_c , T_D is interdependent.

T-lymphocyte memory cells are also formed which spread throughout the lymphoid tissue of the body & cause more powerful secondary response on subsequent exposure.

④ Attack phase

→ T_c cells bind antigen bearing cells & destroy them by following mechanisms:

- Perforin mediated killing - perforins punch holes in the membrane of target cells in the presence of extracellular Calcium which cause cell death
- Lysis through cytotoxic substances
- Induction of apoptosis - by secreting tumor necrosis factor β (TNF- β) which increases Ca^{2+} permeability in target cell; increased intracellular calcium activates enzymes that cause degradation of nucleus producing apoptosis

→ T_H cells $\begin{cases} \rightarrow T_{H1} \Rightarrow \text{secrete cytokines (IL 2, gamma interferon (INF-}\gamma\text{), TNF-}\beta\text{)} \\ \rightarrow T_{H2} \Rightarrow \text{secrete IL-4, 5, 6, 10, 13} \end{cases}$

$\Rightarrow$ involved in activation of B-lymphocytes to produce Ab (T-B cooperation)

- T_s cells - regulate activity of T_c cells
- prevent T_c cells from destroying body's own tissue
 - suppress the activities of T_H cells.

Platelets

Functions:

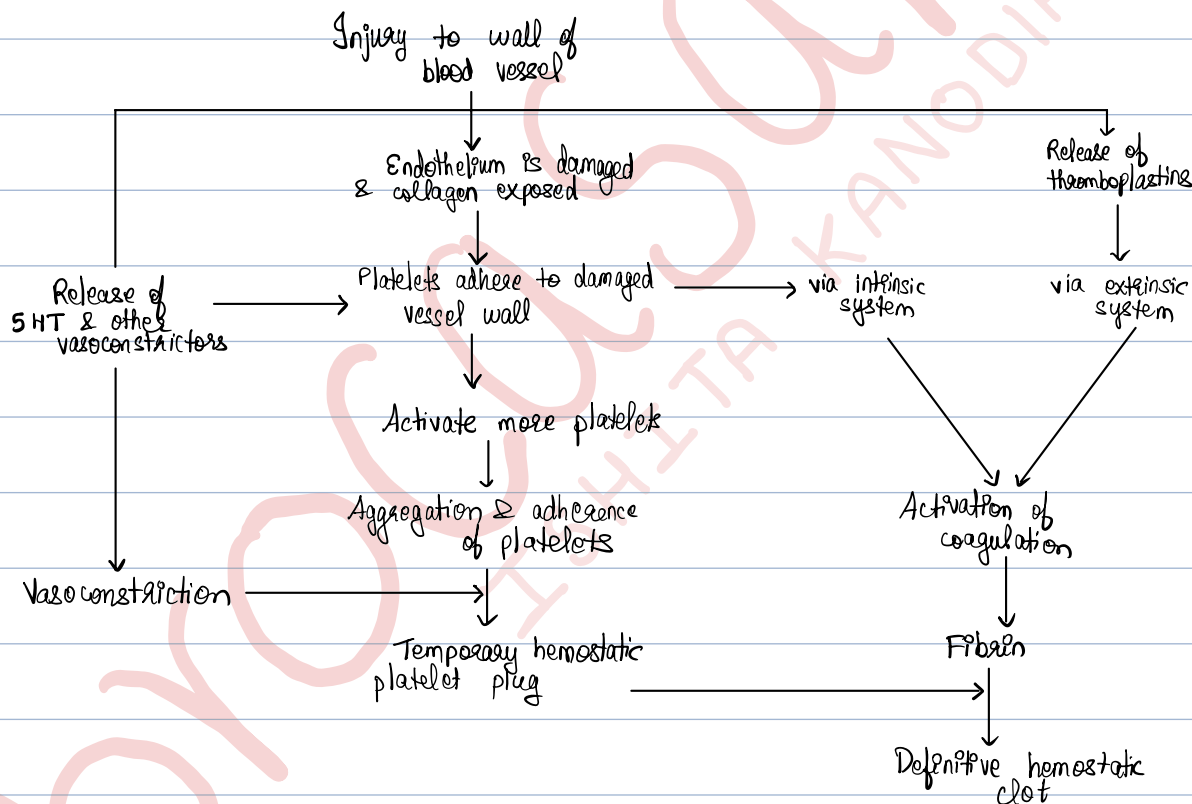
- (i) Role in hemostasis: hemostasis is the spontaneous arrest of bleeding from an injured blood vessel.
- (ii) Role in clot formation: important role in the formation of intrinsic prothrombin activator which is responsible for onset of blood clotting
- (iii) Clot retraction: due to contraction of contractile proteins (actin, myosin, thrombostenin) present in platelets
- (iv) Repair of injured blood vessels: PDGF in cytoplasm of platelets helps in endothelium repair
- (v) Defense Mechanism: due to their property of agglutination, platelets are capable of phagocytosis.
- (vi) Transport & Storage: 5HT (serotonin) is stored in platelets & transported to the site of injury where it is released

Normal Count: 150,000 - 450,000/ μ L

Hemostasis: spontaneous arrest or prevention of bleeding from injured/damaged vessels by physiological process.

→ 3 steps - vasoconstriction

- formation of temporary hemostatic plug
- formation of definitive hemostatic clot.



Clotting/coagulation - loss of fluidity of blood to a jelly-like mass called clot

Steps of coagulation:

- formation of prothrombin activator
 - conversion of prothrombin to thrombin
 - conversion of fibrinogen into fibrin
- extrinsic pathway
intrinsic pathway

Clotting factors: I - Fibrinogen

II - Prothrombin

III - Thromboplastin

IV - Calcium

V - Labile factor, proaccelerin

VI - Stable factor / proconvertin

VIII - Antihaemophilic globulin (AHG)

IX - Christmas factor, Plasma thromboplastin component (PTC)

X - Stuart - Prower factor

XI - Plasma thromboplastin antecedent

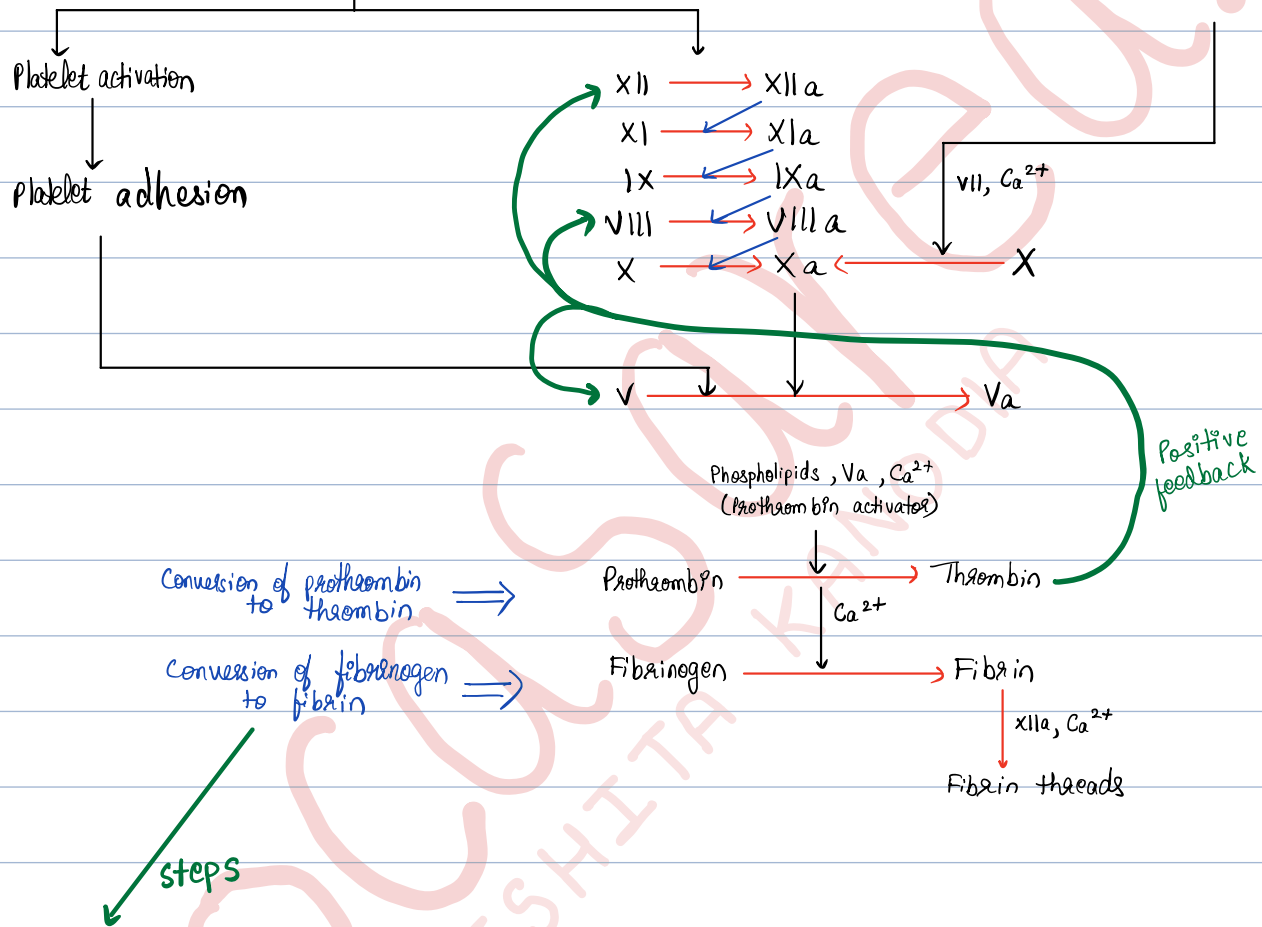
XII - Hageman factor

XIII - Fibrin stabilizing factor.

(VI - X)

Mechanism: Intrinsic Pathway

- Blood trauma or
- Exposure of blood to collagen underlying damaged endothelium or
- exposure of blood to electronegatively charged wettable surface such as glass



Conversion of prothrombin to thrombin $\Rightarrow$

Conversion of fibrinogen to fibrin $\Rightarrow$

steps

soluble fibrinogen

Fibrin monomer + peptides

fibrin polymer (soluble fibrin clot)

insoluble fibrin clot

Proteolysis

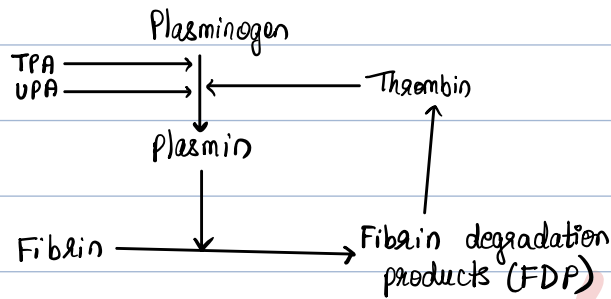
Polymerization

Stabilization of fibrin polymer

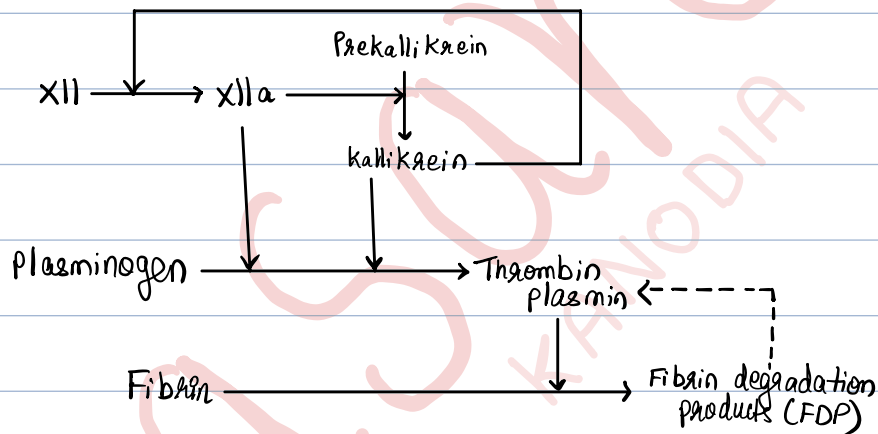
Fibrinolysis: process that brings about dissolution of fibrin by plasmin/fibrinolysin which is present in blood in inactive form called plasminogen/pro-fibrinolysin.

Plasminogen activator systems (PAS) $\begin{cases} \text{extrinsic} \\ \text{intrinsic} \end{cases}$ (TPA = Tissue plasminogen activator
UPA = Urokinase-type plasminogen activator)

Extrinsic PAS:



Intrinsic PAS:



Anticoagulants: substances which delay or prevent the process of coagulation of blood.

Anticoagulants $\begin{cases} \rightarrow \text{endogenous} \Rightarrow \text{heparin, protein C, antithrombin III} \\ \rightarrow \text{exogenous} \Rightarrow \text{heparin, EDTA, Dicumarol, Warfarin} \end{cases}$

EDTA (Ethylenediamine Tetra-acetic Acid):

$\rightarrow$ acts by its chelating effect on blood calcium

$\rightarrow$ inactivates calcium by forming insoluble complex with it & thus, Ca is unavailable for clot formation.

Sodium Citrate: $\rightarrow$ prevents coagulation by inactivating Ca ions

Double oxalate: (ammonium & potassium oxalate)

$\rightarrow$ oxalates form an insoluble complex with calcium in blood & thus, prevent coagulation.

Sodium fluoride: not a strong anticoagulant; mixed with oxalate & used for collecting blood sample for plasma glucose estimation.

Heparin: prevents coagulation for approx. 24 hours by neutralizing thrombin

$\rightarrow$ facilitates action of anti-thrombin III & thus, prevents formation of fibrin from fibrinogen

Haemophilia A: Classic hemophilia

- bleeding disorder due to deficiency of factor VIII
- X-linked recessive disease

Clinical features: bleeding tendency which appears in infancy (may appear in adult life)

- (i) Soft tissue hematomas & hemarthroses (bleeding into joints) leading to severe crippling hemarthropathy
- (ii) Bleeding usually persists from days to weeks inspite of clot formation.

Diagnosis: prolonged APTT (activated partial thromboplastin time)

- prothrombin time & bleeding time are normal.

Treatment: transfusion of fresh blood (as on storage, factor VIII is rapidly lost)
or transfusion of factor VIII - concentrate.

Hemophilia B (Christmas Disease):

- deficiency of factor IX
- sex-linked recessive hemorrhagic disease

Features: clinically indistinguishable from Hemophilia A

Diagnosis: prolonged PTT (partial thromboplastin time)
(normal PT)

Treatment: replacement of factor IX

von Willebrand Disease: most common inherited bleeding disorder

- due to deficiency of von Willebrand factor (vWF)
- vWF plays an important role in hemostasis as it serves as a carrier for factor VIII & essential for adhesion of platelets to the injured vessel wall.

- deficiency of vWF leads to defects in formation of temporary & definitive hemostatic plugs.

Clinical Features: mucocutaneous bleeding

- epistaxis, easy bruising, hematoma, menorrhagia, GI bleeding

Diagnosis: prolonged bleeding time

- assays of plasma vWF.

Treatment: Desmopressin (DDAVP) ⇒ analogue of ADH; increases factor VIII activity

$$\text{ECF} = \frac{\text{Dye injected} - \text{Dye excreted}}{\text{Final plasma conc. of dye}} \times 100$$

(ml or L)

O₂ carrying capacity: (ml)

1 g% of Hb carries 1.34 ml of O₂ → 100% saturated

$$\text{MCV} = \frac{\text{PCV (per 100ml normal blood)} \times 10}{\text{RBC count}}$$

μm³ → %
78-94 → million/mm³

$$\text{MCH} = \frac{\text{Hb (in g/dL)} \times 10}{\text{RBC count}}$$

pg → million/mm³
28-32

$$\text{MCHC} = \frac{\text{Hb (in g/dL)} \times 100}{\text{PCV (per 100mL)}}$$

g/dL → %
30-38 %

$$\text{CI} = \frac{\text{Hb \%}}{\text{Rbc \%}} \left[\frac{2/15}{4/5} \right]$$

→ no units

$$\text{BMR} = \frac{\text{calories consumed per hour}}{\text{Body surface area}}$$

cal/hr/m² → kcal/hr
→ m²

$$V_D = TV \left[1 - \frac{PE_{CO_2}}{PA_{CO_2}} \right]$$

(ml)

$$RMV = V_T \times RR \text{ (ml or L)}$$

$$\text{Dyspnoea index \%} = \frac{MVV - RMV}{MVV} \times 100$$

$$\text{Cardiac output (CO)} = \frac{O_2 \text{ consumption}}{\text{Atrio-venous oxygen difference}}$$

ml/min

$$\text{Stroke volume (SV)} = \frac{\text{Cardiac output}}{\text{heart rate}}$$

ml

$$GFR = \frac{UV}{P}$$

cc/min

$$\text{Normal urea clearance} = \frac{UV}{P}$$

cc/min

$$\text{Standard urea clearance} = \frac{U \sqrt{V}}{P}$$

cc/min

$$\text{Filtration fraction} = \frac{GFR}{RPF} \quad \left\{ GFR = \frac{UV}{P} \right\}$$

(no units)