Blood (5600 ml "8%" of B.W.)

**Plasma** (55%)
- Water
- Inorganic S. (ions)
- Organic S. (plasma proteins + others)

**Cells** (45%)
- RBCs (erythrocytes)
- WBCs (leucocytes)
- Platelets (thrombocytes)

**Plasma proteins** (conc. 7.2 – 7.4 gm/dl)

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Globulins (α, β, γ)</th>
<th>Fibrinogen</th>
<th>Prothrombin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc. 3.5 – 5 (highest)</td>
<td>2.5</td>
<td>0.4</td>
<td>0.01</td>
</tr>
<tr>
<td>M. W 69,000</td>
<td>90,000 – 156,000</td>
<td>340,000 (highest)</td>
<td>68,700</td>
</tr>
</tbody>
</table>

**Formation site**
Liver + (50% of globulins) in lymphoid tissue (RES)

**Functions**
- **Osmotic function**
- **Defensive function (γ)**
- **Transport function** (albumin + α, β globulins)
- **Blood viscosity**
- **Blood clotting**
- **Capillary function** – **Buffering function** – **Source of a.a. for tissues**

**Albumin / globulin (A/G) ratio**: (N. 1.2 – 1.6)
↓↓ A/G ratio: ↓↓ albumin (↓↓ production "liver disease" – ↑↑ loss "kidney diseases") or ↑↑ globulin (infections)

**RBCs (Erythrocytes)**
- **Count**: ♂: 5.5 million/mm^3 ♂: 4.8 million/mm^3
- **Shape**: biconcave non nucleated discs
- **Size**: 7.2 µ in diameter
- **Volume**: 90 µ^3.
- **Life span**: 120 ± 7 days
- **Fate**: old RBCs are destroyed in (R.E.S) mainly in the spleen

**Structure**
- (1) **Erythrocyte membrane**: semipermeable, plastic
- (2) **Cytoplasm**: Hb: (34% of RBCs wt.) – K+ – **Carbonic anhydrase** (for CO_2 transport)
  \(\text{NO}^+\) nucleus, \(\text{NO}^+\) ribosomes, \(\text{NO}^+\) mitochondria.
### Hemoglobin (Hb)

**Molecular weight** 64,000  
**Concentration in RBCs** 34%

<table>
<thead>
<tr>
<th>Hb content</th>
<th>Adult ♂: 15-16 gm/dl</th>
<th>Adult ♀: 13-14 gm/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Newly born infants: 19 gm/dl (due to relative hypoxia during IUL)</td>
<td></td>
</tr>
</tbody>
</table>

**Structure**  
Hb molecule is composed of 4 subunits. 4 (heme + polypeptide chain)

<table>
<thead>
<tr>
<th>Types of Hb</th>
<th>1- Adult Hb (HbA)</th>
<th>2- Fetal Hb (HbF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contains 2α &amp; 2 β polypeptide chains</td>
<td>Contain 2 α &amp; 2 γ polypeptide chains</td>
</tr>
<tr>
<td></td>
<td>the main Hb in adults</td>
<td>the main Hb during fetal life &amp; at birth</td>
</tr>
</tbody>
</table>

**Abnormal Hb**

1. **Thalassemia**  
   - (↓↓) or absent α or β chains  
   - (due to defects in the globin gene)

2. **Sickle cell anaemia**  
   - Abnormal production of α or β chains  
   - (due to gene mutation) ⇒ abnormal Hb (HbS)

**Chemical reactions of Hb** (binds with)

- O$_2$ ⇒ oxyhemoglobin (Fe$^{++}$)
- CO$_2$ ⇒ carbaminohaemoglobin (amino group)
- CO ⇒ carboxyHb (Fe$^{++}$)
- Oxidizing agents ⇒ methaemoglobin (Fe$^{+++}$)

**Functions of Hb**

1. **Carriage** of O$_2$ & CO$_2$.
2. **Strong buffer** system (6 times that of plasma proteins).

**Function of RBCs**

1. **Function of the cell membrane**: it encloses Hb.  
   - If Hb gets out to the plasma, it will:
     1- Filtered in the kidney ⇒ block renal tubules ⇒ renal failure
     2- ↑↑ viscosity of blood ⇒ ↑↑ B.P. ⇒ ↑↑ Heart work
     3- ↑↑ Colloidal osmotic pr. of plasma ⇒ ↑↑ Heart work.

2. **Function of the cell contents**:
   1. Hb. (mentioned before).
   2. Carbonic anhydrase for CO$_2$ transport as HCO$_3$⁻
   3. NADPH methemoglobin reductase (reduce Fe$^{3+}$ to Fe$^{2+}$)

Each gm of Hb can unite with 1.33 ml O$_2$  
*The affinity of Hb to O$_2$ is (↓↓) in:*
- ↑↑ H$^+$, ↑↑ temperature, ↑↑ CO$_2$, ↑↑ 2,3 DPG

(2)
Erythropoiesis

**Definition**: Formation of new erythrocytes.

**Site of erythropoiesis**
- Bone marrow of ends of long bones
- Membranous bones in persons > 20 years
- Liver & spleen in fetus and all bones in children.
- In adults.

**Factors affecting erythropoiesis**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia ⇒ stimulation of kidney &amp; liver ⇒ ↑↑ erythropoietin production ⇒ B.M. stimulation ⇒ ↑↑ RBCs production</td>
<td>It is the site of formation of RBCs</td>
<td>It is the site of formation of globin &amp; 15% of erythropoietin</td>
<td>It is the site of formation of 85% of erythropoietin.</td>
<td>Specific: erythropoietin acts locally on BM. Non-specific: thyroid hormones, androgens, estrogens &amp; glucocorticoids stimulate erythropoiesis</td>
<td>Vitamins: B₁₂, folic acid &amp; vit. C Minerals: iron, copper, cobalt. Proteins: of high biological value for globin synthesis</td>
</tr>
</tbody>
</table>

**Erythropoietin**

**Sources**: (glycoprotein hormone) - In adults: 85% formed by kidney & 15% formed by liver.
- In fetus: almost formed by liver.

**Mechanism of action**: Erythropoietin combines with specific receptors on erythropoietin-sensitive stem cells ⇒ ↑↑ number & development of these stem cells in B.M.

**Regulation of secretion**: (1) Hypoxia (the main stimulant) (2) Alkalosis (at high altitudes) (3) Androgen & estrogen (4) Adenosine (5) Catecholamines (6) Cobalt.
**Blood**

**Iron**

**Functions**
- formation of Hb, myoglobin
- cytochrome
- cytochrome- oxidase, peroxidase & catalase

**Absorption**
From upper small intestine (duodenum)
Iron is absorbed in the ferrous state by an active process: reduced by HCL & vitamin C
Dietary iron $\text{Fe}^{3+}$ (ferric) $\rightarrow$ ferrous ($\text{Fe}^{2+}$) in the stomach

**Distribution**
- 70% in Hb
- 3% in myoglobin
- 27% in ferritin (in liver & intestine)

Transferrin saturation with iron is 35%

**Storage of iron**
in liver, spleen & bone marrow.

**Haemosiderosis:** (excess ferritin deposits in tissues due to iron overload)
Leads to $\Rightarrow$ skin hyperpigmentation, pancreatic damage $\Rightarrow$ diabetes(bronzed diabetes), liver cirrhosis & carcinoma

**Deficiency of iron** $\Rightarrow$ iron deficiency anemia

**Vitamin B12 = cyanocobalamine**
Extrinsic factor = Maturation factor

**Sources**
animal origin (liver & meat)  Daily requirement  5 µg

**Absorption**
from lower ileum
Vitamin $\text{B}_{12}$ + intrinsic factor $\Rightarrow$ complex $\Rightarrow$ carried on plasma protein (Transcobalamin II) $\Rightarrow$ liver (stored)

Intrinsic factor is: a glycoprotein, secreted from parietal cells of the stomach important for absorption of vitamin $\text{B}_{12}$:
1- protects $\text{B}_{12}$ from digestion by HCL.
2- complexes with $\text{B}_{12}$ & binds it to special receptors in the lower ileum mucosa.
3- stimulates endocytosis of $\text{B}_{12}$.

**Functions**
1- Essential for DNA synthesis, cell division & maturation of RBCs
2- Formation of myelin sheath of nerves.

**Deficiency**
1- Macrocytic anaemia.
2- Neurological manifestations

**Vitamin $\text{B}_{12}$ & folic acid** are essential for DNA synthesis, cell division & maturation

Deficiency of any of them $\Rightarrow$ DNA synthesis $\Rightarrow$ cell division $\Rightarrow$ failure of nuclear maturation. erythroblasts fail to proliferate $\Rightarrow$ megaloblasts in B.M $\Rightarrow$ megalocytes pass to peripheral blood $\Rightarrow$ macrocytic (megaloblastic) anaemia

---

**Blood**

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Anaemia

Anaemia

↓↓ RBCs count: < 4.5 million / mm³ in ♂ & < 3.9 million / mm³ in ♀

↓↓ Hb. content: < 13.5 gm / dl in ♂ & < 11.5 gm / dl in ♀

Blood indices

MCH = Hemoglobin content \times 10 \quad (N. 80 – 95 μ³)

RBCs count

MCHC = Hemoglobin content \times 100 \quad (N. 32-38 gm%)

Hematocrite value

Classification of anaemia

I- According to size & Hb content of RBCs

1. Normocytic normochromic anaemia
2. Microcytic hypochromic anaemia
3. Macrocytic anaemia

II- According to the cause: e.g. hemolytic, iron deficiency, aplastic, ……

1. Normocytic normochromic anaemia

Causes

1. Acute blood loss: (hemorrhage)
2. Aplastic anaemia: ↓↓ RBCs synthesis due to BM destruction by (drugs – malignancy – irradiation)
3. Hemolytic anaemia: ↑↑ hemolysis of RBCs due to:

<table>
<thead>
<tr>
<th>1. Intrinsic disorders of RBCs</th>
<th>2. Extrinsic disorders of RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Membrane disorders: e.g. hereditary spherocytosis</td>
<td>1) Antibody causing hemolysis: e.g. erythrobastosis foetalis or incompatible blood transfusion.</td>
</tr>
<tr>
<td>2) Hb. disorders: e.g. sickle cell anaemia.</td>
<td>2) Bacterial toxins</td>
</tr>
<tr>
<td>3) Enzyme disorders: e.g. ↓↓ G6PD</td>
<td>3) Chemicals: e.g. anticonvulsant &amp; antimalarial drugs.</td>
</tr>
</tbody>
</table>

Causes

2. Microcytic hypochromic anaemia (iron deficiency anaemia)

↓↓ iron intake

| Absolute e.g. starvation |
| Relative e.g. in children & in pregnancy(↑↑ iron demand) |

Partial gastrectomy: ↓↓ HCL or vitamin C deficiency

Small intestine diseases (e.g. malabsorption)

↑↑ phosphate, phytate & oxalate intake \Rightarrow insoluble salts with iron

<table>
<thead>
<tr>
<th>Chronic blood loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylostoma &amp; Bilharziases infestation.</td>
</tr>
<tr>
<td>Bleeding from G.I.T (piles &amp; peptic ulcer)</td>
</tr>
</tbody>
</table>

3. Macrocytic anaemia (megaloblastic anaemia)

↓↓ absorption as in small intestinal diseases & after gastrectomy due to absence of intrinsic factor (pernicious anaemia)

It is an autoimmune disease (antibodies against gastric parietal cells) \Rightarrow achlorhydria & absence of intrinsic factor.

Causes

Vitamin B₁₂ deficiency

↓↓ intake, ↓↓ absorption, ↓↓ demands, antifolate drugs

Folic acid deficiency

↑↑ intake, ↑↑ absorption, ↑↑ demands, antifolate drugs
**Platelets**

**Count**  (250,000 - 400,000 / mm³)

**Half life**  4 days

**Formation**  multipotent uncommitted stem cells → committed stem cells for platelets

**Distribution**  70% in blood & 30% in spleen

**Structure**  Platelets are small, granular, non-nucleated round or oval bodies

1. **Platelet membrane:**
   1. A glycoprotein coat.
   2. Receptors for collagen, Von Willebrand factor & fibrinogen.
   3. Platelet factor 3 (PF₃): important in blood clotting.
   4. Platelet membrane invaginated to form canalicular system

2. **Platelet cytoplasm:** contains contractile proteins & skeleton of microtubules

   - 2 types of granules
     1. **Dense granules:** contain serotonin, ADP & Ca²⁺.
     2. **Alpha granules:** contain:
        1. Clotting factors: factor (XIII) & Von-Willebrand factor
        2. Platelet derived growth factor (PDGF)
        3. Platelet activated factor (PAF)
        4. Prostaglandins – forming enzymes

**Diameter**  2 - 4 micrometer

**Origin**  in B.M. (from megakaryocytes)

**GM-CSF**  Megakaryocytes

**Hemostasis**

**Definition**  it is the prevention of blood loss after injury (stoppage of bleeding)

**Mechanism**

1. **Vascular spasm**  (vasoconstriction)
2. **Temporary** hemostatic plug formation  (platelet reaction)
3. **Definitive** hemostatic plug formation  (blood coagulation)
Blood clot is a network of insoluble fibrin entrapping blood cells, platelets, and plasma proteins. Formation of fibrin clot needs:

- **Clotting factors**:
  - **Nature**: B-globulins.
  - **Site of formation**: Liver (except factor VIII related antigen "VW factor" formed in platelets & endothelial cells).
  - **Functions**: Proteolytic enzymes (activate each other).

**Hemostasis**

1. **Vascular spasm** (local VC)
   - Nervous reflexes
   - Myogenic spasm of vessels
   - Local VC factors (serotonin & thromboxane A2)

2. **Temporary hemostatic plug formation** (platelet reaction)
   - PLT adhesion
   - PLT activation
   - PLT release reaction
   - PLT aggregation
   - PLT procoagulant activity
   - PLT fusion

   - To subendothelial collagen, PLT swell, put out pseudopodia.
   - PLT release their contents.
   - PLT adhere to each other.
   - PLT membrane phospholipid

   - Irreversible aggregation is caused by ADP, thromboxane A2 & PAF.

3. **Definitive hemostatic plug formation** (blood coagulation)

**Classification of Coagulation factors**

<table>
<thead>
<tr>
<th>(1) Fibrinogen group</th>
<th>(2) Prothrombin group</th>
<th>(3) Contact group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen &quot;factor I&quot;, F. V, VIII, XIII</td>
<td>Prothrombin &quot;factor II&quot;, F. VII, IX, X</td>
<td>factors XI &amp; XII</td>
</tr>
<tr>
<td>F. V &amp; VIII Not present in serum</td>
<td>All (except prothrombin) are present in serum</td>
<td>Present in serum</td>
</tr>
<tr>
<td>F. V &amp; VIII lose their activity on storage</td>
<td>Stable on storage.</td>
<td>Stable on storage.</td>
</tr>
<tr>
<td>Formed in liver (factor XIII is also formed in platelets)</td>
<td>Formed in the liver &amp; need vitamin K for their formation</td>
<td></td>
</tr>
<tr>
<td>Activated by thrombin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The clotting mechanism

**Intrinsic system**
- Activated *in vivo* by: exposure to subendothelial collagen
- & *in vitro* by: exposure to –ve charged wettable surfaces

1. XII → XIIa
2. XI → Xla
3. IX → IXa
4. X → Xa
5. Prothrombin → Thrombin
6. Fibrinogen → Fibrin

**Extrinsic system**
- Traumatized tissue releases tissue thromboplastin

**Important notes**
- An important reaction in blood clotting is the conversion of soluble protein fibrinogen to insoluble fibrin (fibrin thread formation)
- Loose fibrin (fibrin monomer) → tight fibrin (fibrin polymer)
- Contraction of actin & myosin of the platelets → clot retraction of the tight strands → closes & adheres to the injured vessel wall.
- Ca++ is required for all the reactions of blood clotting except the 1st 2 steps of intrinsic system
- Thrombin activates factor V → acceleration of prothrombin activation → thrombin
- When a critical amount of thrombin is formed → vicious circle develops → more blood clotting
- Blood clotting continues until limiting reactions stop (clot growth)
- Clot is dissolved (by plasmin) to resume normal blood flow after tissue repair
Anticlotting mechanisms

1. **General reactions**: 3
   - Smooth endothelium & rapid blood flow prevent activation of factor XII or platelets.
   - Heparin (a natural anticoagulant).

2. **Specific reactions**: 3
   - Interaction between thromboxane A₂ & prostacyclin
   - Antithrombin III: (a protease inhibitor) inhibits F IXa, Xa, Xla & XIIa (activated serine proteases).
     Its action is facilitated by heparin.

### (1) Plasmin (fibrinolysin)
- **Inactive** plasminogen → **active** plasmin (fibrinolysin)
- Fibrin & fibrinogen → fibrin degradation products (FDPs) → inhibit thrombin

### (2) Protein C
- Endothelial cells ⇒ thrombomodulin + thrombin ⇒ thrombomodulin–thrombin complex ⇒ activates protein C
- **Active protein C + protein S**: inactivate factors V & VIII.
  - inactivate an inhibitor of tissue plasminogen activator ⇒ ↑↑ plasmin formation.

### (3) Fibrinolytic system
- Plasminogen activator (TPA)
- TPA (tissue plasminogen activator)

### Anticoagulants

#### (1) In vitro anticoagulants outside the body
- Citrate: binding Ca²⁺
- Oxalate: precipitating Ca²⁺.
- Silicone coated tubes: (prevent activation of factors XII & platelets)
- Heparin.

#### (2) In vivo anticoagulants inside the body

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Heparin</th>
<th>Dicumarol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Origin</strong></td>
<td>Liver, mast cells &amp; basophiles</td>
<td>Plant origin</td>
</tr>
<tr>
<td><strong>Onset &amp; duration</strong></td>
<td>Rapid onset &amp; short duration</td>
<td>Slow onset &amp; long duration</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td>Sulphated mucopolysaccharide</td>
<td>Similar to vitamin K</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Protamine sulphate 1%</td>
<td>Blood transfusion</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Injection (I.V. &amp; I.M.)</td>
<td>Oral (by mouth)</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Facilitates the action of antithrombin III (inactivates factors IXa, Xa, Xla, XIIa)</td>
<td>Competitive inhibition with vitamin K in the liver ⇒ inhibits synthesis of factors II, VII, IX, X.</td>
</tr>
<tr>
<td><strong>Site of Action</strong></td>
<td>In vivo &amp; in vitro</td>
<td>Only in vivo</td>
</tr>
</tbody>
</table>
Abnormalities of hemostasis

(1) Excessive bleeding

(1) Vitamin K deficiency

Causes of deficiency:
- Sterility of intestine, as in newborn infants & long-term treatment with antibiotics.
- Absorption as in fat malabsorption because vitamin K is a fat-soluble vitamin.
- Liver diseases.
- Anticoagulants: dicumarol.

(2) Excessive clot formation inside blood vessels

Causes:
- Roughness of atherosclerotic plaques & after operations (slow blood flow)

(3) Both excessive bleeding & intravascular clotting

Causes:
- Retention of dead fetus in the uterus for weeks.
- Septic shock.

Mechanism:
DIC (traumatized tissue)
- Massive production of thromboplastin
- Wide spread clotting (DIC)

Bleeding (due to consumption of coagulation factors)

(3) Thrombocytopenic purpura

Due to ↓ platelet count (< 50,000/mm³ ⇒ symptoms appear)

Characterized by subcutaneous hemorrhages (petechiae) & prolonged bleeding time.

White blood cells (leucocytes)

Count: 4,000 – 11,000 / mm³

Functions of WBCs

<table>
<thead>
<tr>
<th>(1) Neutrophils</th>
<th>(2) Eosinophils</th>
<th>(3) Basophils</th>
<th>(4) Lymphocytes</th>
<th>(5) Monocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Neutrophils: (60 – 70%) of WBCs</td>
<td>1. Attack &amp; kill parasites</td>
<td>1. Contain histamine, heparin &amp; leukotrienes.</td>
<td>1. Formed in B.M., lymph nodes, thymus &amp; spleen</td>
<td>1. Monocytes pass to areas of inflammation soon after neutrophils ⇒ phagocytose &amp; digest bacteria, dead neutrophils &amp; dead tissue.</td>
</tr>
<tr>
<td>2. Eosinophils: (2 – 6%) of WBCs</td>
<td>2. Produce chemical mediators in allergic conditions.</td>
<td>2. Responsible for immediate type hypersensitivity reactions (as urticaria)</td>
<td>2. The key cells of specific immunity (play an important role in defending the body)</td>
<td>2. Precursors of tissue macrophages &amp; together form the monocyte–macrophage system (have high defense &amp; phagocytic function)</td>
</tr>
<tr>
<td>3. Basophils: (0 – 1%) of WBCs</td>
<td>3. Weak phagocytes &amp; show chemotaxis.</td>
<td>3. Have receptors that bind IgE-coated antigens ⇒ degranulation of basophils</td>
<td>3. The key cells of specific immunity (play an important role in defending the body)</td>
<td>3. Precursors of tissue macrophages &amp; together form the monocyte–macrophage system (have high defense &amp; phagocytic function)</td>
</tr>
</tbody>
</table>

(10)