YO! Physiologer dudes

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Many of my friends have found these notes useful in their study for Physiology 1A.

But before you take a look at them and start cramming as if your life depends on it, take a moment to meet the God that created a universe that is so complex and worthy of study, yet knows you and I personally:

Psalm 139:13-14 - "For you created my inmost being; you knit me together in my mother's womb. I praise you because I am fearfully and wonderfully made; your works are wonderful, I know that full well."

Check it out sonnnnnn!: http://www.matthiasmedia.com.au/2wtl/

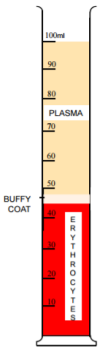
1 Lecture 1

1.1 Describe the main functions of blood

1. **Transport of:**
   - **Nutrients**: Absorbed in digestive tract/from liver adipose energy stores to tissues.
   - **Metabolites**: Lactic acid in muscles to liver for breakdown/urea to kidney for excretion.
   - **Gases**: O_2/CO_2 between respiratory organs and tissues.
   - **Hormones**: Adrenaline (rapid response), growth hormone (slow response)
   - **Cells of non-respiratory function**: Leukocytes, platelets.
   - **Heat**: Blood rushes to surface of skin to dissipate deeper heat.
2. **Force transmission**
3. **Coagulation**
4. **Cell homeostasis**

1.2 Identify the major components of blood

- Blood constitutes 8% of total body weight.
- Men have $\approx$ 5.5L, Women have $\approx$ 5L.
- It consists of:
  1. **Erythrocytes (45%)**
     - 30% Haemoglobin (also called the haematocrit)
     - 1% Lipids
     - H_2O
     - Electrolytes (mostly K^+, Cl^-, HCO_3^-, but also Na^+, Mg^{2+}, Ca^{2+}).
  2. **Buffy Coat (<1%)**
     - Leukocytes
     - Platelets
  3. **Plasma (55%)**
     - $>$ 90% H_2O
     - Electrolytes (mostly Na^+, Cl^-, HCO_3^-, but also K^+, Mg^{2+}, Ca^{2+}.
     - Plasma proteins (7g% (or 7g/L))
       * Albumins (4.5g%)
       * Globulins (2.5g%)
       * Fibrinogens (0.3g%)



1.3 Identify the types of leukocytes (white blood cells) and describe their roles in defence

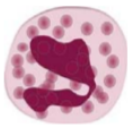
- Originate from undifferentiated pluripotential stem cells which reproduced to produce committed myeloid stem cells.

1.3.1 Granulocytes

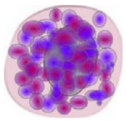
- Named based on their **affinities** for **certain dyes** and thus the colour of their granules.
- Contain **multi-lobed nuclei (polymorphonuclear)** and many **cytoplasmic granules**.

1. **Neutrophils (50-80%)**
    - No preference for any dye (**neutral**)
    - Very **effective phagocytic** cells which engulf/digest microorganisms, abnormal cells and foreign particles.
    - Live 7-10 hours in circulating blood, then 4-5 days in tissues.
    - **Chemotaxic**: Chemicals produced by inflamed/infected tissue travel to the bone marrow, triggering the release of neutrophils which travel to the area.
    - If the increase in the number of neutrophils at the area is more or equal to fivefold it is termed **neutrophilia**.

2. **Eosinophil (1-4%)**
    - Show preference for the acidic dye **eosin**.
    - **Weak** defence and may be harmful to normal tissues/trigger allergic reactions.
    - Also phagocytic but it is **not** their main function. Their main function is destroying parasites too big to be phagocytosed, by attaching to the parasite and releasing toxic substances from their granules,



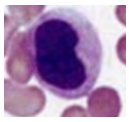
3. **Basophils (<1%)**
    - Show preference for **basic** dyes.
    - **Non-phagocytic**
    - Release toxic molecules that damage invaders.
    - Release histamine (contributes to allergic reaction), heparin (inhibits blood clotting and accelerates removal of fat particles from blood following a fatty meal) and other chemicals.



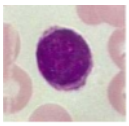
1.3.2 Agranulocytes

- Single, large non-segmented nucleus.
- Very few granules.

1. **Monocytes & macrophages**
   - Kidney shaped nucleus.
   - Leave the bone marrow as immature cells and spend 10-20 hours in transit via the bloodstream to a target tissue.
   - Once in the tissue, they mature and become large macrophages which are very phagocytic.
   - Wandering macrophages migrate through body tissues whilst fixed macrophages remain at particular sites.
   - Form a first line of defence in the skin, and are also present in the lymphatic system, the alveoli, liver, spleen and bone marrow.
   - A collection of dead neutrophils, macrophages, necrotic tissue and tissue fluid is called **pus**.



2. **Lymphocytes**
   - Originate from undifferentiated pluripotential stem cells that reproduced to form lymphoid stem cells, however most new lymphocytes are produced by existing lymphocytes in lymphoid tissue.
   - Their lifespan is approximately 100-300 days.
   - There are 3 types:
     - **B lymphocytes** produce antibodies in response to exposure to target antigens.
     - **T lymphocytes** do not produce antibodies but directly destroy target cells by secreting molecules that create pores in the target cell membrane allowing fluid influx which causes the target cell to burst. This is called **cell mediated immune response**.
     - **Null cells** or **natural killer cells** are large granular lymphocytes which function in non-specific defence in a fashion similar to T-cells.



1.4 Describe the characteristics of erythrocytes (red blood cells)

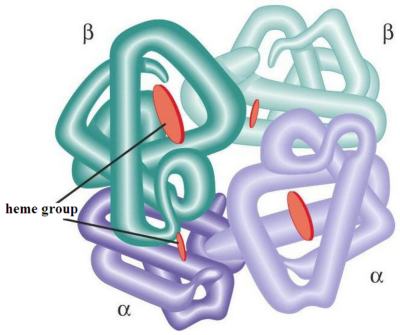
- There are on average 5 billion erythrocytes per mL of blood. They live $\approx$ 120 days.
  - 5.2 million/mm^3 (males)
  - 4.7 million/mm^3 (females)

  They are:
- **Biconcave** discs (8 μm diameter) because they lack a nucleus, providing a larger surface area for O_2 diffusion. They also lack ribosomes and organelles.
- **Thin**, facilitating rapid diffusion (1 μm at thinnest point, 2.5μm at outer edges).
- **Flexible** due to the protein **spectrin** which allows the cell to deform without rupturing through narrow capillaries.

1.5 Understand the structure and functions of haemoglobin

1.5.1 Structure

- Erythrocytes contain a respiratory pigment called **haemoglobin (Hb)**
- Appears red when bound to O_2, blue when bound to CO_2.
- Hb consists of,
  1. The **globin portion**; a protein consisting of 4 folded polypeptide chains.
  2. 4 ferrous ion (Fe^{2+}) containing haem groups. Each haem group is bound to a polypeptide chain of the globin portion.



1.5.2 Functions

1. **Increases the gaseous carrying capacity of blood**
   - CO_2 and O_2 are both dissolved in the plasma albeit in small concentrations (<1 mL O_2/100 mL blood). In the absence of Hb, the carrying capacity of the plasma would be insufficient for regular function.
   - 1g of Hb carries 1.34 mL of O_2. $[Hb]_{male}$ = 16g/100 mL blood, and $[Hb]_{female}$ = 14g/100 mL blood. Thus the average Hb concentration is ≈ 15g/100 mL blood. Hence, Hb increases the carrying capacity of O_2 by approximately 20 fold!

     $$1.34\text{mL/g} \times 15\text{g}/100\text{ mL} = 20\text{mL}/100\text{ mL}$$

   - This facilitates function 2.
2. **Transport of O_2/CO_2/Buffering**
   - The main function of haemoglobin is the transport of O_2 from the lungs to the tissues/CO_2 from the tissues to the lungs as well as serving as an acid-base buffer.
   - O_2 and CO_2 are continuously binding and unbinding to Hb in a dynamic and competitive process. At the alveoli, the concentration of O_2 is very high compared to the CO_2. Thus when CO_2 unbinds, O_2 molecules replace the CO_2 and bind reversibly to the 4 haem groups. The CO_2 diffuses into the alveoli and is expired.

     $$Hb + 4O_2 \rightleftharpoons Hb.4O_2$$

   - As the blood travels towards the tissues, the concentration of CO_2 is now higher than that of O_2. Thus when O_2 unbinds, CO_2 molecules replace the O_2 and bind reversibly to the 4 haem groups. The O_2 diffuses into the tissue.

     $$CO_2 + HbO_2 \rightleftharpoons Hb.COO^- + H^+ + O_2$$

   - CO_2 can also react with H_2O in the RBC per the reaction below.

     $$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

- Note that both reactions produce H^+ which has the potential to make the venous blood very acidic (7.35 compared to the arterial pH, 7.4).
- To prevent this, Hb serves as an acid-base buffer:

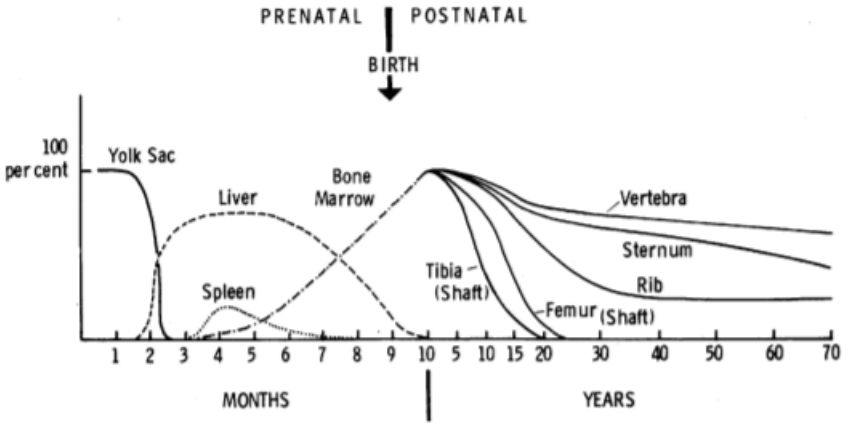
$$H^+ + HbO_2 \rightleftharpoons H^+Hb + O_2$$

1.6 Describe the changes in haemoglobin concentration with age

- **At birth** $[Hb] = 17$g/100 mL blood. RBCs are larger and more variable in size.
- **7-9 weeks** $[Hb] = 11$g/100 mL. It is much easier for the baby to get O_2 through its lungs once born rather than via the maternal blood crossing the placenta. Hb levels decline as they do not need to be as high.
- **6 months - 2 years** $[Hb] \approx 12$g/100 mL.
- **2 years to puberty**
  - Girls: $[Hb] = 14$g/100 mL
  - Boys: $[Hb] = 16$g/100 mL

1.7 Identify the sites of red blood cell formation at different ages

1. **Yolk sac**: 0 to 2.5 months
2. **Liver**: 1.5 to 10 months
3. **Spleen**: 3 to 7 months.
4. **Bone marrow**: In children (starting at 4 months) haematopoiesis occurs in the marrow of long bones such as the femur, humerus and tibia. At 20 years old, the red marrow is confined to the upper ends of these long bones and after this, most red cells are produced in the flat bones of the sternum, ribs, vertebrae, cranium and pelvis.

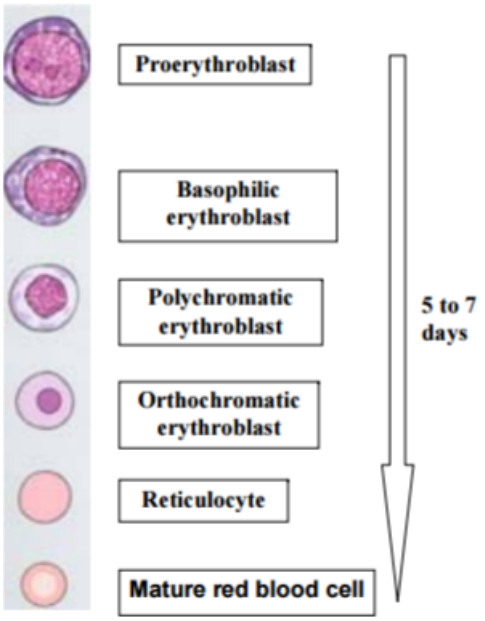


from: "Blood and Its Disorders", R.M. Hardisty and D.J. Weatherall Eds. Second Edition. 1982. Blackwell Scientific Publications: Oxford.

2 Lecture 2

2.1 Describe the developmental stages of the red blood cell

- The lifespan of erythrocytes is limited to $\approx$ 120 days and must be replaced on a daily basis. The body must also respond to situations of greater demand including accidents and increased altitude.
- The **proerythroblast** is the earliest recognisable erythroid cell in the marrow. It is a **large cell** with a dark blue cytoplasm and a primitive nuclear pattern of chromatin or DNA.
- As the cells become more differentiated, they become progressively **smaller** and contain **increasing amounts** of **Hb**. This causes the **cytoplasm** to become **pinker** and pinker. The **nuclear chromatin** also becomes **more condensed** until it reaches the stage of the late **orthochromatic erythroblast**. After this line, the nucleus is completely extruded, and the next line of cells, the **reticulocytes** have **no nucleus** albeit still contains some ribosomal RNA capable of synthesising Hb.
- The reticulocyte will spend 1-2 days in the bone marrow and a further 1-2 days in the peripheral blood within the spleen where the RNA is completely lost and a **mature red blood cell results**.
- Each proerythroblast can give rise to 32 RBCs through multiple divisions.



2.2 Describe the control of erythropoiesis and the role of erythropoietin

2.2.1 Control of erythropoiesis

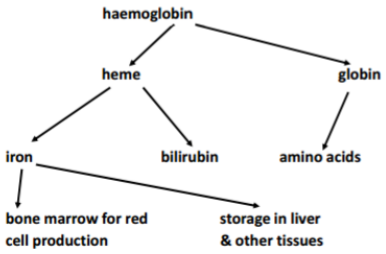
- The basic regulator of erythropoiesis is the **state of tissue oxygenation**.
- **Any condition causing the quantity of oxygen transported to the tissues to decrease, stimulates increased erythropoiesis**.
- This may include:
  - Haemorrhage
  - Bone marrow destruction
  - Lower O_2 at high altitudes
  - Circulatory/pulmonary diseases

2.2.2 Role of EPO

- **Erythropoietin (EPO) is a hormone that stimluates erythropoiesis** via the production of proerythroblasts from myeloid committed stem cells in marrow due to **hypoxia**. EPO also causes these cells to pass more rapidly through the developmental stages.
- Erythropoeisis continues as long as hypoxia is maintained or until enough erythrocytes have been produced.
- **Testosterone** increases EPO secretion which stimulates an increased basal rate of erythropoiesis. In males this contributes to larger haematocrits to service higher muscle mass.
- 90% of EPO is formed in the kidneys, the rest in the liver.

2.3 Understand the nutritional requirements for red cell production

1. **Vitamin B_{12} (colbalamin)**
   - Vitamin B_{12} is essential for DNA production in red cells.
   - It is water soluble and only found in animal products. The minimum amount required each day is 1-3μg.
   - It can only be absorbed from the intestine if it is bound to **intrinsic factor**; a glycoprotein released by cells in the stomach. Once absorbed, it is stored in large quantities in the liver and slowly released as needed to bone marrow and other tissues.
2. **Folic acid**
   - Folic acid is also essential for DNA production in red cells.
   - It is found in leafy plants, yeast and liver but is easily destroyed by cooking.
3. **Iron**
   - Iron is essential for haemoglobin synthesis. The total quantity of iron in the body is 4-5 grams: 65% Hb, 4% myoglobin, 15-30% stored mainly in liver. 10% of ingested iron is absorbed into blood.
   - Fe^{2+} (ferrous) ions are absorbed much more easily than Fe^{3+} (ferric) ions. Vitamin C increases iron absorption by reducing ferric ions to ferrous ions. Phosphate and oxalate can form insoluble compounds with ingested iron that can't be absorbed.
   - In order for iron to be absorbed, the liver must secrete apotransferrin which binds free iron and iron-containing compounds to form transferrin.
   - Because the iron is loosely bound, it is easily released into any tissue. Transferrin is absorbed into epithelial cells and released into blood capillaries.
   - Excess iron in blood is deposited into all cells but mainly the liver and bone marrow.
   - In the receiving cell cytoplasm, iron combines mainly with the protein apoferritin to form ferritin; the storage form of iron. If the supply of iron from diet drops, stored iron is released from ferritin, binds to transferrin and is carried in plasma to wherever it is required.
   - Aged erythrocytes are destroyed in the spleen via macrophages which catabolise Hb and eventually release iron.



2.4 Describe some of the different types of anaemias

Anaemia is a deficiency of Hb $\rightarrow$ decreased O_2 carrying capacity.

1. **Nutritional anaemia**
   - Fe **deficiency** leads to decreased Hb synthesis. The number of erythrocytes is normal but there isn't enough Hb inside the cells resulting in very small red cells. This is called **microcytic anaemia**.
   - **Folic acid deficiency** leads to slowed red cell reproduction. Those that are produced are called **megaloblasts** because they are large, oddly shaped, and have fragile membranes. This is called **megaloblastic anaemia**.
2. **Pernicious anaemia**
   - The gastric mucosa of the stomach fails to produce intrinsic factor. This reuslts in an inability of vitamin B_{12} to be adequately absorbed resulting in **megaloblastic anaemia**.
3. **Haemorrhagic anaemia**
   - After rapid haemorrhage, the **plasma** volume is **replaced faster** than the red cells leading to a **lower concentration of red cells**.
4. **Aplastic anaemia**
   - Deficiency of all blood cells due to a lack of functional bone marrow due to damaging exposure to radiation, x-rays, chemicals and drugs.
5. **Haemolytic anaemia**
   - Hereditary **abnormality** of the red cells that make them **fragile**.
     - **Spherocytosis**: Results in small, spherical cells that cannot be compressed like normal blood cells and therefore rupture resulting in anaemia.
     - **Sickle cell**: Caused by an abnormal type of Hb which crystallises when it is exposed to low O_2 concentration. These crystals damage the cell membrane causing it to rupture resulting in anaemia.
     - **Thalassaemia**: Absent or abnormal globin chains resulting in immature or non-functional erythrocytes and thus anaemia.

2.5 Understand the basis of ABO blood groups and the reasons for incompatibilities

- Erythrocytes have plasma membrane proteins and carbohydrates that function as antigens when exposed to another person's blood. The most important antigen blood group for transfusion reactions is **ABO**.
- Two genes, one of each of 2 paired chromosomes determine the ABO blood group.
  - The O gene is practically functionless and causes no significant O antigen. It is recessive.
  - A and B genes cause strong antigens and are co-dominant.

Genetic possibilities

Homozygous	Heterozygous	Antigen	Blood Group	Antibody in Plasma	Frequency (%)
AA	AO	A	A	Anti-B	38
BB	BO	B	B	Anti-A	10
-	AB	A and B	AB	Neither	3
OO	-	Neither	O	Both	49

Incompatibility

- If an individual does not have an X antigen, then they will have the X antibody.
- Only the **recipients antibodies** are **important**. The **donor's antibodies** are **diluted** in the **recipients plasma**.
- **AB** is the **universal recipient**, because the **recipient's blood** has **no antibodies**.
- **O** is the **universal donor** because the **donor's blood** has **no antigens**.

Note: Newborn babies do not have any Anti-A or B in their plasma. These develop after birth in response to A and B antigens that enter the body via food, bacteria and other avenues.

2.6 Understand the basis of Rhesus blood groups and the repercussions of incompatibilities

- We also need to consider the **Rhesus (Rh)** blood type during transfusion.

Homozygous	Heterozygous	Antigen	Blood Group	Antibody in Plasma	Frequency (%)
DD	Dd	Rh	Rh+	None	81
dd	-	None	Rh-	Anti-Rh	19

- An Rh- person does not develop anti-Rh until there is a massive exposure to the Rh antigen, usually via the transfusion of blood. The first transfusion usually causes no reaction, but the recipient becomes sensitised to the antigen and subsequent transfusions can cause severe reactions.
- When an Rh- mother gives birth to an Rh+ baby, the blood cells containing the Rh antigen will enter the maternal circulation, triggering the production of Rh antibodies and can diffuse through the placenta into the foetus.
- This can result in **erythroblastosis fetalis** or **haemolytic disease of the newborn**. It is characterised by agglutination and phagocytosis of the baby's red blood cells.
- Affected babies usually die from severe anaemia and are jaundiced (due to bilirubin from red cell destruction). Those that survive the anaemia may have permanent brain damage due to the precipitation of bilirubin in neuronal cells that causes their destruction.
- The liver and spleen are also enlarged in an attempt to replace damaged red blood cells.
- Fortunately, the mother doesn't become sensitised until the time of labour/birth when there is mixing of maternal and foetal blood. This means the first baby generally escapes unharmed, but the incidence with subsequent births increases.
- **Prevention** involves flooding of the mother's blood with anti-Rh just after each child is delivered in order to destroy any fetal cells that may have entered the mother's blood before they can initiate the production of anti-Rh that would affect the subsequent Rh+ babies.

3 Lecture 3

3.1 Understand the term haemostasis

- Blood vessels are frequently damaged and can lead to internal or external bleeding. This bleeding is usually **minor** and can be stopped by the body's own defence mechanism, **haemostasis**.
- Lower pressure venous bleeding is much less rapid and can be controlled by lifting the site above heart level or by the pressure of accumulated blood in the interstitial tissue of the affected organ.
- A **collection of blood** in the tissues from any vessel type is called a **haematoma**.
- **Haemostasis** consists of a 5 step process:
  1. **Vascular spasm**
  2. **Formation of platelet plug**
  3. **Formation of blood clot through coagulation**
  4. **Clot retraction**
  5. **Replacement of clot with fibrous tissue**

3.2 Describe the role of vascular spasm in haemostasis

- Immediately after a vessel is cut or ruptured, the trauma to the vessel wall itself is sufficient to stimulate vessel wall contraction.
- This contraction can result from:
  - Nervous reflexes initiated by pain
  - Local smooth muscle spasm
  - Local chemical factors produced by traumatised tissues
- The greater the damage, the greater the degree of spasm. The local spasm lasts from minutes to hours during which the wound is sealed by the **formation of a clot**.

3.3 Describe how a platelet plug is formed

Platelet pre-knowledge

- **Platelets** are formed in bone marrow from megakaryocytes. They are round, 2-4 μm in diameter and there are 200,000-500,000 platelets/mm^3. They contain mitochondria, smooth ER and cytoplasmic granules but no nuclei and they cannot reproduce. They live for 8 days before being eliminated by macrophages. A special glycoprotein coat on the cell membrane allows platelets to attach to injured areas but slide past normal walls.

Formation

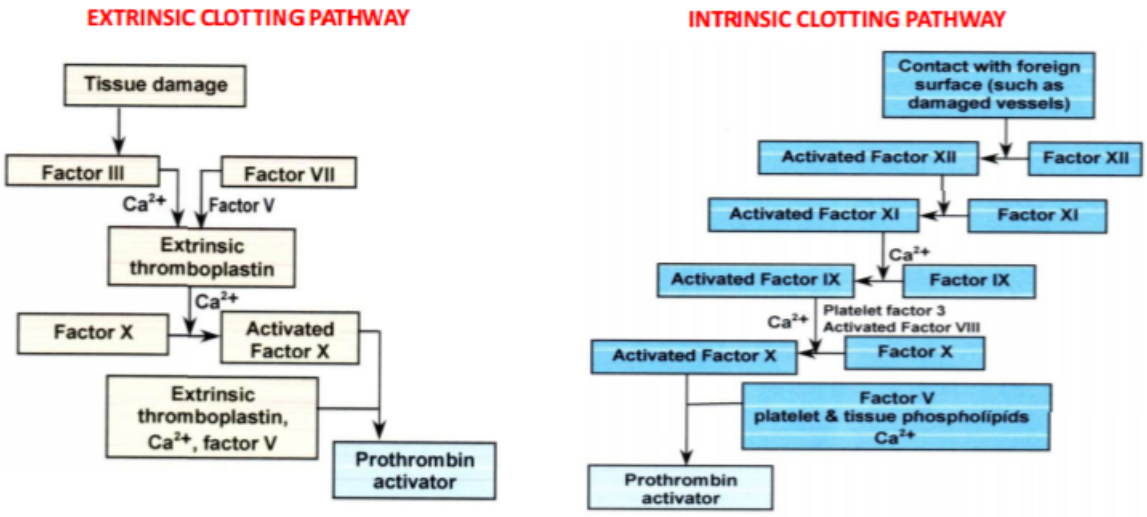
1. Damaged vessel disrupts endothelium and exposes CT and collagen.
2. Platelets swell, forming irregular shapes with numerous psuedopods and attach to the exposed collagen (**platelet adhesion**).
3. Contractile proteins in platelets contract forcefully releasing multiple active factors including the potent vasoconstrictors adrenaline and serotonin, as well as ADP and thromboxane A_2.
4. ADP causes the surface of nearby platelets to become sticky and adhere to the first layer of platelets. These platelets also release ADP, which causes cyclic platelet aggregation.
5. Thromboxane A_2 directly promotes platelet aggregation and triggers the release of more ADP from platelet granules.
6. The normal endothelium releases prostacyclin limits the plug to the site of vessel injury by strongly inhibiting platelet aggregation.
7. If the hole is small, a platelet plug can itself stop blood loss. If the hole is large, a blood clot in addition to the platelet plug is required to stop the bleeding.

3.4 Describe the 3 major stages of blood coagulation including the intrinsic and extrinsic pathways

1. Injury to vessel triggers cascade of chemical reactions that results in the formation of the prothrombin activator.
2. Prothrombin is converted to thrombin, catalysed by prothrombin activator.
3. Thrombin acts an enzyme, converting fibrinogen to fibrin fibres that trap platelets, blood cells and plasma to form a clot.

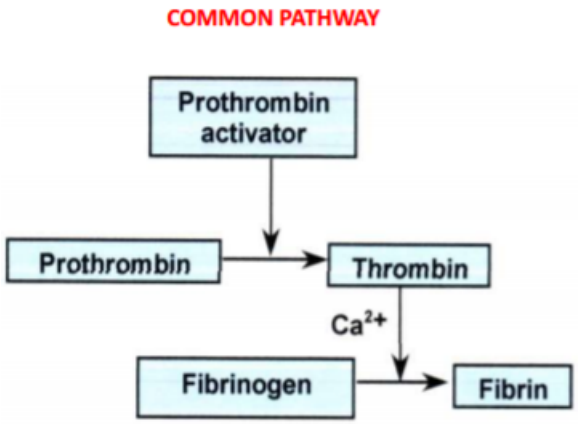
3.4.1 Prothrombin activator, intrinsic and extrinsic clotting pathway [Expanding on step 2]

- Formation of the prothrombin activator is the rate limiting step in blood coagulation, and is achieved via:
  1. The **extrinsic** pathway involving factors present in the damaged tissue.
  2. The **intrinsic** pathway involving factors already present in plasma.
- In both pathways, a series of plasma proteins called clotting or coagulation factors play a major role. Most of these are inactive forms of proteolytic enzymes that when activated cause the next cascading reaction of the clotting process.



3.4.2 Conversion of fibrinogen [Expanding on step 3]

- Fibrinogen is a high molecular weight protein formed in the liver that is present in the plasma in concentrations of 100-700mg/100 mL plasma.
- Thrombin converts fibrinogen into smaller fibrin monomers with polymerise with other fibrin monomers to form a loose network of strands held together by weak hydrogen bonds.
- The meshwork is stabilised and strengthened by the formation of covalent linkages between strands. This reaction is catalysed by fibrin stabilising factor.
- The meshwork of fibrin fibres entrap blood cells, platelets and plasma, creating the final clot.
- The fibrin fibres adhere to the damaged blood vessels, preventing further blood loss.



3.5 Understand clot retraction

- Actin and myosin in the platelets pull the edges of the vessel together.
- Serum (plasma without fibrinogen) is exuded.

3.6 Understand how a clot is replaced with fibrous tissue

- The platelets secrete a basic protein which stimulates the growth of arterial smooth muscle and skin fibroblasts.
- Serotonin may play a role, stimulating the secretion of collagen by fibroblasts.
- The clot is then converted into fibrous tissue within 1-2 weeks.

3.7 Describe some clotting abnormalities

Bleeding disorders

1. **Vitamin K deficiency**
   - Since vitamin K is required for the production of several important clotting factors required in coagulation, its deficiency results in serious bleeding disorders.
   - Vitamin K is bacterially synthesised in the GI tract. For vitamin K to be absorbed from the gut, it requires bile because it is fat soluble. A frequent cause of vitamin K deficiency is an inability of the liver to secrete sufficient bile into the small intestine, or the bile duct is blocked.
2. **Haemophilia**
   - Haemophilia is a hereditary disease characterised by uncontrolled bleeding of varying severity due to a lack of factor VIII in 80% of cases.
   - Haemophilia is a recessive sex-linked disease and is carried by the mother on the X chromosone. Males only require one altered copy of the gene, but females require two to develop haemophilia.
3. **Thrombocytopenia**
   - Thromocytopenia is low platelet numbers due to the formation of antibodies which destroy platelets.
   - This results in a tendency to bleed usually from the small venules/capillaries, causing characteristic purplish skin patches.
   - This may be caused by transfusion or autoimmunity (cause is unknown).

Excess clotting disorders

1. **Thrombus**
   - Abnormal clot in vessel.
   - Commonly due to endothelial walls roughened by atherosclerosis or infection.
2. **Embolus**
   - Free flowing clot that causes damage when it causes blockage.
   - An embolus originating in the left side of the heart or a large artery can be transported to and damage any organ. Embolism can result in renal obstruction, a blockage of a cerebral vessel resulting in a stroke, or a blockage in the eye resulting in blindness.
   - Emboli originating in the right side of the heart or large vein block the pulmonary arteries. If the clot is large enough to block both pulmonary arteries simultaneously, instant death results.

3.8 Understand the mechanism of action of some anticlotting drugs and other agents

Oral

- **Aspirin**: Inhibits formation of thromboxane A_2, decreasing platelet aggregation and platelet plug formation.
- **Warfarin**: Competitive inhibitor for vitamin K, lowering the level of prothrombin and other clotting factors.

Intravenous

- **Heparin**: Naturally produced by the basophils and mast cells. Heparin inhibits formation of thrombin and reduces platelet function.
- **Tissue plasminogen activator(t-PA)**: When delivered directly to the area of thrombosis, it activates plasminogen to plasmin which can dissolve clots (thrombolytic).
- **Streptokinase**: Same action as t-PA, produced by streptococci bacteria.

In vitro

- **Silicon**
- **Heparin**
- Ca^{2+} **binding substances (oxalate, citrate, EDTA)**