Blood Physiology

Part 2

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Platelets (Thrombocytes)

- Develop by fragmentation of giant cells in the bone marrow known as megakaryocyte.
- Platelets are anucleated cells with granular cytoplasm.
- Their differentiation takes 10 days.
- Their life-span is also 10 days.
- They are present in the bone marrow in a quantity only sufficient for about one day. Therefore, human beings are susceptible to develop thrombocytopenia more quickly than leukopenia or anemia.
- Their count normally ranges from 200,000 to 400,000cells/µL. A platelets count higher than or lower than this range is termed thrombocytosis or thrombocytopenia, respectively.
- Their production rate is mainly regulated by thrombopoietin; a hormone produced by the kidneys and in little amounts by the liver.
- Platelets contain many substances such as K^+, Mg^{2+}, prostaglandins, thromboxanes, epinephrine, histamine, antiplasmin and lipoproteins. These substances are not found in granules.
- They also contain many types of granules; **α**, **δ, γ and λ.**
- **α** granules contain platelet factor 4, fibrinogen, coagulation factors V and XIII, fibronectin, B-thromboglobulin, acid hydrolases, von Willebrand (vW) factor, P-selectin, growth factors (transforming growth factor-β1 and platelet-derived growth factor).
- **δ** (or dense) granules contain ATP, ADP, Ca^{2+}, catecholamines and serotonin.
- Platelets and their granules are important to maintain the integrity of blood vessels and thus, prevent RBCs from leaving the vascular system.

Hemostasis

- It means the prevention of blood loss especially in cases of vessels rupture. It's a complex process involving many tissues type and chemicals.
- Immediately following blood vessel injury, many events take place in order to prevent further blood loss and to repair the damaged blood vessel. However, bleeding form large vessels can't be prevented by the physiological mechanisms discussed later.

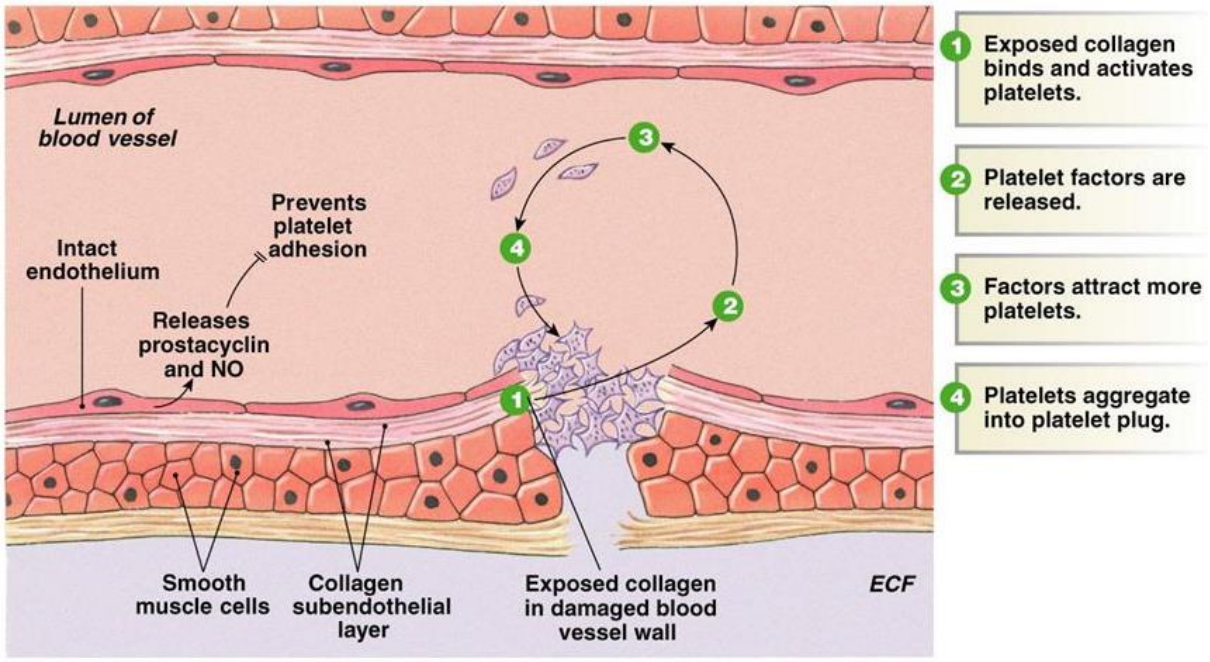
- These events can be divided into 3 stages. First, vascular constriction; second, formation of platelet plug and third, formation of a clot rich in fibrous tissue.

Vascular constriction

- An important event to reduce blood flow and thus, blood loss.
- It's due to both mechanical and chemical factors.
- The mechanical part is by the contraction of the vascular smooth muscle cells in response to a trauma. The degree of this local myogenic spasm increases with the severity of the injury.
- The chemical part is by local autacoid factors released by either the damaged cells (e.g., endothelin) or the platelets (e.g., serotonin, epinephrine and TxA_2). All these chemicals are vasoconstrictors.

Formation of platelets plug

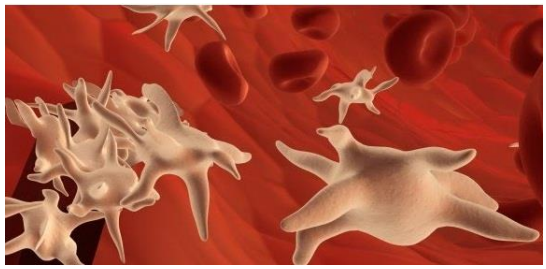
- Small vessels are ruptured many thousands of times daily. Also, many small holes through the endothelial cells occur. The platelet-plugging mechanism is extremely important for closing these ruptures and holes.
- A person who has few blood platelets develops each day thousands of small hemorrhagic areas under the skin and throughout the internal tissues.



- Normally, platelets circulate in the blood and don't adhere to the endothelial cells

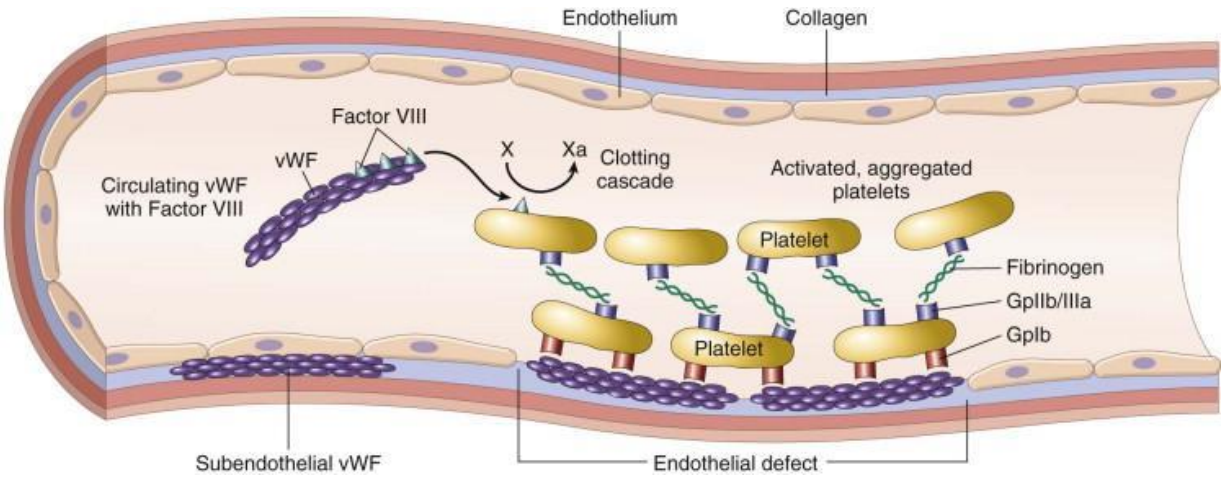
Explained later: this is because endothelial cells release NO and PGI_2 which inhibit platelets aggregation. Also, on the membranes of platelets is a coat of glycoproteins that repulses adherence to the intact endothelial cells and yet causes adherence to injured areas.

- Once circulating platelets come in contact with a damaged vascular surface, especially with the exposed collagen fibers, they:
  - Swell and pseudopods appear on their surfaces.
  - Release granules with the contained factors by contraction of the contractile proteins (actin and myosin)
  - Become sticky and adhere to collagen and to a protein called von Willebrand factor (vWF) which leaks from the plasma to the injured tissue.
  - Secrete ADP and thromboxane A_2 (TxA_2).
    - These two act on nearby platelets which become activated and adhere to the first activated platelets rather than collagen.
    - More and more platelets aggregate to eventually from the plug.
    - This plug, however, is loose but later, fibrin attaches tightly.
  - Secrete serotonin which causes vasoconstriction as mentioned earlier.



Platelets adhesion

- Glycoprotein 1b (GPIb) is found on the surfaces of platelets.
- vWF is normally bound to factor 8 to protect it from degradation. It's released by the action of thrombin during the coagulation process.
- Free vWF binds to GPIb to connect platelets with collagen fibrils and cause their adherence.
- GPIb is deficient in Bernard-Soulier syndrome.



Factors release and platelets aggregation

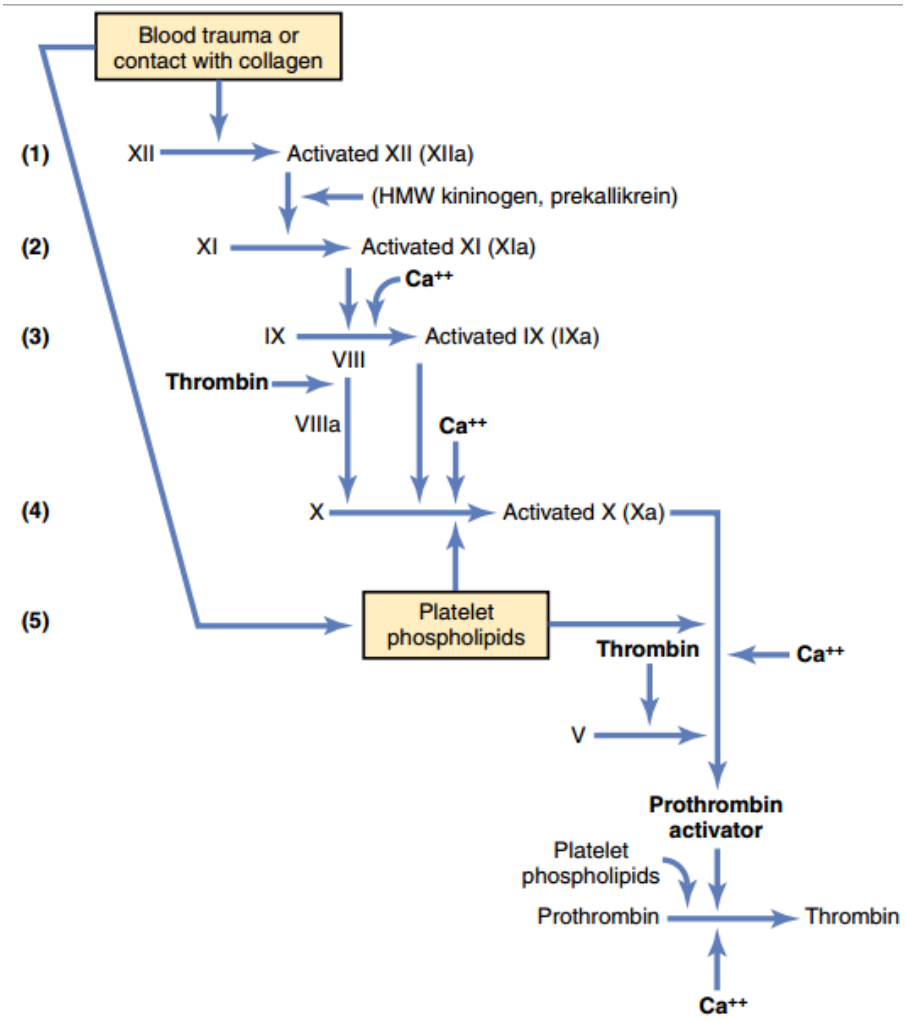
- As a result of exposure to collagen, platelets release ADP, serotonin, fibrinogen, lysosomal enzymes, heparin neutralizing factor (platelet factor 4 or PF4) and TxA_2.
- TxA_2 and ADP cause platelet aggregation. TxA_2 also has a vasoconstrictive activity as mentioned earlier.
- PGI_2 (prostacyclin) inhibits platelets aggregation by increasing cAMP level in platelets. It's synthesized by the vascular endothelial cells.
- TxA_2 is necessary to cause platelets aggregation; PGI_2 is necessary to inhibit platelets aggregation.
- Aspirin inhibits TxA_2 synthesis which accounts for its ability to reduce platelets aggregation and thus, stroke and thrombosis.

Coagulation

- Most of these factors are produced by the liver.
- Factors II, VII, IX and X are vitamin K-dependent.
- The coagulation cascade is divided into 2 pathways which both lead to the activation of factor X and end by the formation of fibrin.
- The 2 pathways are initiated simultaneously after tissue injury.
- The intrinsic pathway which takes minutes to occur is slower than the extrinsic which takes only seconds. However, the intrinsic is longer-lasting and more important.
- "a" letter is added to the factor number to designate the active form of it.

Clotting Factor	Synonyms
Fibrinogen	Factor I
Prothrombin	Factor II
Tissue factor	Factor III; tissue thromboplastin
Calcium	Factor IV
Factor V	Proaccelerin; labile factor; Ac-globulin (Ac-G)
Factor VII	Serum prothrombin conversion accelerator (SPCA); proconvertin; stable factor
Factor VIII	Antihemophilic factor (AHF); antihemophilic globulin (AHG); antihemophilic factor A
Factor IX	Plasma thromboplastin component (PTC); Christmas factor; antihemophilic factor B
Factor X	Stuart factor; Stuart-Prower factor
Factor XI	Plasma thromboplastin antecedent (PTA); antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight kininogen	Fitzgerald factor; HMWK (high-molecular-weight kininogen)
Platelets	

Intrinsic pathway



- Initiated by the contact of Factor XII and platelets with the negatively charged collagen in the vascular wall or by blood trauma.

1) Factor XII is activated and phospholipids are released from platelets.

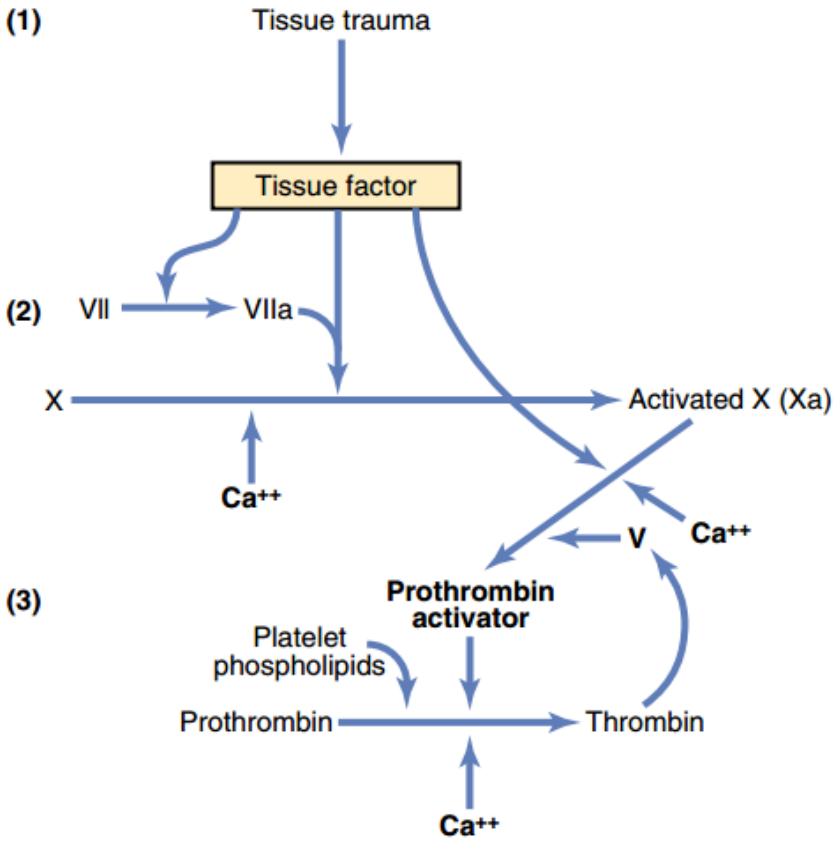
2) Factor XIIa is a proteolytic enzyme which activates factor XI
  - This reaction requires HMWK (high molecular weight kininogen) which binds prekallikerin and factor XI and keep them close to factor XII.
  - Prekallikerin only accelerates the process and is not required for factor XI activation.
  - Factor XII, HMWK and prekallikerin are not necessary for the activation of factor XI because platelets can directly activate it. A deficiency in any one of these three, therefore, doesn't cause serious problems.

- Unlike the all upcoming steps, these 2 steps don't require Ca^{2+}.

3) Factor XIa enzymatically activate factor IX.

4) Factor IXa, factor VIIIa, Ca^{2+}, platelets phospholipids form a complex which activate factor X.
  - Factor VIII is called antihemophilic factor because its deficiency causes classic hemophilia. Note that factor VIII is activated by thrombin.
  - Note that platelets are necessary in this step.

Extrinsic pathway



- Initiated by a traumatized vascular wall or traumatized extravascular tissues that come in contact with the blood.

1) Traumatized tissues release tissue factor (thromboplastin or thrombokinase).
  - This factor is what gives the pathway its name since it's normally not circulating in the blood.
  - It's composed of membrane phospholipids and a lipoprotein with enzymatic activity.

2) Thromboplastin, Factor VII and Ca^{2+} act enzymatically on factor X activating it.

Common pathway

- By activation of factor X to form the proteolytic enzyme Xa, the two pathways converge.

1) Factor Xa combines with phospholipids, Ca^{2+} and factor Va to form prothrombin activator.
  - The phospholipids are either part of tissue factors or released from platelets.
  - The formation of this complex is the rate limiting step in the blood coagulation process.
  - **In prothrombin activator complex:**
    - Factor X and Ca^{2+} are required for its activity.
    - Factor X is the actual proteolytic enzyme that splits prothrombin to form thrombin.
    - Phospholipids act as a vehicle that accelerates the process.

- The proteolytic action of thrombin itself activates factor V which then becomes a part of thrombin activator complex to strongly accelerate thrombin formation
- Note the positive feedback effect of thrombin, acting through Factor V, to accelerate the entire process once it begins.

2) Thrombin acts proteolytically on fibrinogen which has leaked from the plasma in high amounts to form fibrin monomers.

3) Fibrin monomers spontaneously polymerize to from the long insoluble fibrin fibers. These fibers are stabilized by Ca^{2+}, thrombin and factor XIII (which is activated by thrombin).

Role of Ca^{2+}

- Ca^{2+} is required in all the previously mentioned steps except for the first two in the intrinsic pathway, as noted earlier.
- In platelets, it's also needed to:
  - Cause the release of the platelets granules.
  - Cause the contraction of actin and myosin.
  - Activate phospholipase enzymes.

Prevention of blood clotting

- Normally, blood flows in the intact vascular system and does not clot. This is achieved by:

1. The smoothness of the endothelial cell surface, which prevents contact activation of the intrinsic clotting system
2. A layer of negatively charged glycocalyx on the endothelium which repels clotting factors and platelets.
3. A protein bound with the endothelial membrane, thrombomodulin, which:
   - Binds thrombin removing it thereby, slowing the clotting process.
   - Binds thrombin to form thrombomodulin-thrombin complex. This complex activates a plasma protein, protein C, that acts as an anticoagulant by inactivating factors Va and VIIIa in the presence of Ca^{2+}. Protein C requires a cofactor, protein S. Both proteins are vitamin K-dependent.
4. The action of plasma anticoagulants in removing thrombin from the blood such as:
   - Fibrin fibers formed during the clotting process.

        - These fibers adsorb most of the formed thrombin. This prevents the spread of thrombin and the clot.
    - Antithrombin III (antithrombin-heparin cofactor).
        - Combines with the rest of thrombin formed. It first blocks its action and later, inactivates it.
    - Heparin.
        - Produced by mast cells and basophils.
        - Physiological concentrations in blood do not cause anticoagulation except under some condition.
        - However it's widely used in pharmacological concentrations to prevent clotting.
        - It does not cause anticoagulation itself; it binds to antithrombin III to dramatically increase its activity in removing thrombin. This complex, also, removes other activated coagulation factors (XII, XI, X and IX)
5. The many minor clots which form daily, as mentioned earlier.
    - Their formation prevents the formation of one bigger clot.
6. α2-macroglobulin and α1-antitrypsin.
7. Fibrinolytic system discussed next

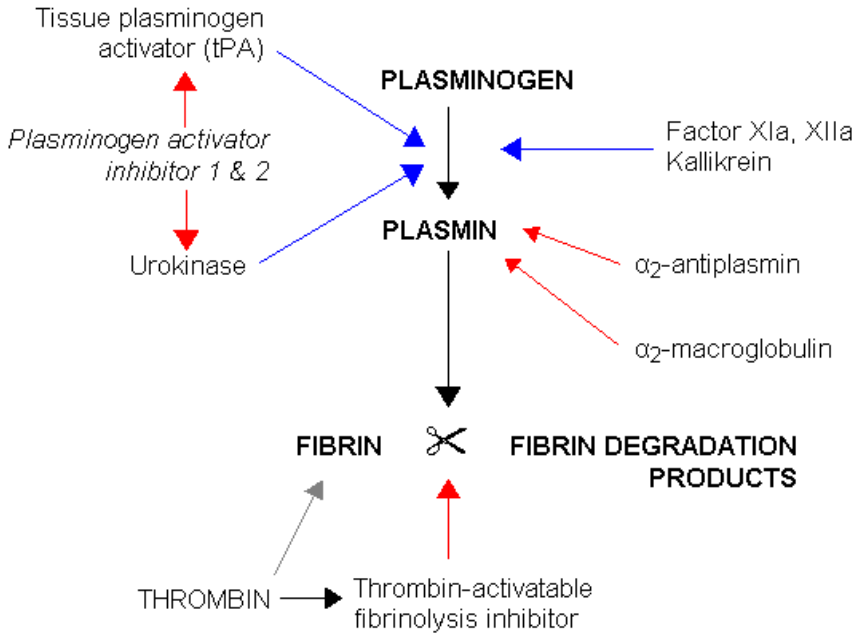
Summary of thrombin actions:

Activates factors V, VIII, XIII**;** cleaves fibrinogen**;** activates platelets**;** activates protein C.

Fibrinolytic system – clot lysis

- The liver synthesizes a globulin called plasminogen (or profibrinolysin) and secretes it into the plasma.
- When a clot is formed, a large amount of inactive plasminogen is trapped in the clot along with other plasma proteins.
- The same injured tissue and vascular endothelium that initiated coagulation very slowly release a powerful activator called tissue plasminogen activator (t-PA).
- A few days later, after the clot has stopped the bleeding, t-PA converts inactive plasminogen to active plasmin (or fibrinolysin).
- Plasmin digests fibrin, fibrinogen and some coagulation factors (V, VIII, XII and prothrombin)
- Fibrin degradation produces soluble fibrin degradation products (FDPs) which compete with thrombin and slow fibrin formation.

- Plasminogen activators are either endogenous or exogenous.
- Endogenous activators are t-PA and the intrinsic pathway of coagulation.
- Exoenous activators are urokinase in the plasma, and streptokinase which is secreted by streptococci, and when injected, immediately dissolves the thrombus (called the life injection).
- Plasmin is inactivated by α2-macroglobulin and α2-antiplasmin.



Clot retraction

- It's the shrinkage of blood clot to reconstruct the injured vessel. This is mainly accomplished by the contraction of platelets causing their shrinkage; a Ca^{2+} dependent process.
- Clot retraction time is the time needed for a clot to retract. Partial retraction takes 1-2 hours while complete retraction takes 24 hours.

Thrombus and embolus

- Thrombus is an abnormal fixed clot in a blood vessel.
- Continued blood flow breaks it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as emboli.
- The embolus may cause serious problems if it reaches narrow vessels, especially in the heart or the brain.

- Thromboembolism occurs when blood flows:
  - Through a vessel with a roughened endothelial surface as in arteriosclerosis, infection, or trauma
  - Very slowly through blood vessels, where small quantities of thrombin and other procoagulants are always being formed.
- Arteriosclerosis is a thickening of the arterial vascular wall which results in loss of elasticity. Mild arteriosclerosis is common and normal among elderly.
- Atherosclerosis is a form of arteriosclerosis in which an artery's wall thickens as a result of accumulation of WBCs and proliferation of vascular smooth muscle cells.
- Causes of thrombosis in humans:
  - Injury to blood. The inflammation attracts monocyte and initiates the extrinsic pathway.
  - Infections such as cellulitis and blood vessels infections.
  - Slowing of the blood stream after childbirth which results in platelet deposition.
    - The mother is advised to walk or receive heparin injection.
  - Changes in the blood composition.

Bleeding disorders

- **Vascular disorders**
  - Defect in the blood vessel or in the surrounding connective tissue.
  - The skin displays many small, purplish blotches, giving the disease the name purpura.
  - The vessel is easily bruised and bleeds spontaneously.
  - Could be inherited or acquired.
  - The inherited form is mild in childhood but is progressive and becomes severe in older ages.
  - The acquired form has many types; senile purpura (of old age), infectious purpura, steroid purpura and purpura associated with scurvy in which normal vitamin C (necessary for collagen synthesis) is deficient.

- **Thrombocytopenia**
  - The most common cause for excessive bleeding.
  - It's a decrease in platelets count as in:
    - General bone marrow failure. (RBCs and WBCs synthesis is also affected).
    - Leukemia (the cells that form the malignant WBCs would have, otherwise, formed RBCs and platelets).
    - Blood dilution by transfusing massive amounts of blood.
    - Abnormal distribution of platelets as in splenomegaly where the spleen stores a large proportion of the platelets (splenectomy could be curative).
    - Failure of platelets production as in drug administration or viral infections.
    - Increased destruction of platelets as in heparin administration.
  - It's characterized by skin purpura, hemorrhage and prolonged bleeding especially after a trauma. The purpura is termed thrombocytopenic purpura.
- **Abnormal platelets function**
  - Could be inherited or acquired.
  - The inherited form can be a deficiency in the synthesis or release of platelets substances or its glycoproteins such as TxA_2, factor VIII, GP1 and GP4. Platelets aggregation is also affected especially if the synthesis of the vWF is deficient.
  - The acquired form is more common and is attributable to aspirin administration which decreases TxA_2 production.
- **Coagulation factors defects**
  - The second most common cause for excessive bleeding.
  - Hemophilia A, Hemophilia B, von Willebrand diseases are the most common.
  - In most diseases, the inheritance is somatic. However, some are X-linked.
  - These patients should avoid dental extractions and circumcisions unless under proper medical care because they have a high tendency for bleeding.
  - There's usually a correlation between the symptoms and the severity of the disease.
  - Factor XII deficiency doesn't seriously affect coagulation.
  - Factor XI can be activated directly by platelets; its deficiency causes mild symptoms.
  - Factor XIII is important in stabilizing the fibrin fibers along with thrombin and Ca^{2+}. Therefore, Its deficiency results in severe bleeding.

Hemophilia A (classic hemophilia)

- The most common hereditary cause of serious bleeding; its incidence is 1/10,000.
- X-linked recessive disorder caused by reduced factor VIII activity. However, 30% of the patients don't have a family history; that is, caused by new mutations.
- Primarily affects males. Females can only be carriers because homozygous females don't survive.

Hemophilia B

- Less common than hemophilia A but clinically indistinguishable from hemophilia A.
- X-linked recessive disorder in which factor IX is mutated and severely deficient.

von Willibrand disease

- Autosomal dominant disorder in which vWF is reduced or abnormal.
- Results in rapid destruction of factor VIII.
- Platelets adhesion or coagulation may be affected.

Remember:

- Factor VIII is an essential cofactor for factor IX, which activates factor X in the intrinsic coagulation pathway.
- Circulating factor VIII binds to vWF.
- Factor VIII is therefore, composed of 2 parts; large vWF (or VIII:Ag) and VIII:C.
- vWF prevents the factor degradation. The C part is the one involoved in clotting
- Endothelial cells are the major source of plasma vWF, whereas most factor VIII is synthesized in the liver.
- vWF is found in the plasma (in association with factor VIII), in platelet granules, in endothelial cells, and in the subendothelium, where it binds to collagen.

Excessive fibrolytic activity

- Abnormal increase in fibrin degradation once formed. This weakens the already formed clot and thus, increase bleeding tendency.

Anti-coagulant substances

- **Heparin**
  - Extracted from several animal tissues.
  - Increases blood clotting time.
  - Given as IV or IM injection and has rapid onset of action.
  - Its mechanism of action has already been discussed.
  - Heparinase in the blood destroys it.

- **Coumarins such as warfarin**
  - Extracted from plant tissues.
  - Given orally and have a slow onset of action.
  - Decrease the production of vitamin K-dependent factor by decreasing the active vitamin K level.
  - Decrease production of thromboplastin (thrombokinase) which is important in the activation of factor X in the extrinsic pathway.
- **Hirudin**
  - Extracted from leech.
  - Acts on thrombin and fibrinogen to reduce coagulation.
- **Stirring**
  - Mechanically removes the thrombus.

Additional info:

- Vitamin K is an essential factor to a liver carboxylase that adds a carboxyl group to glutamic acid residues on five of the important clotting factors: prothrombin, Factor VII, Factor IX, Factor X, and protein C.
- In adding the carboxyl group to glutamic acid residues on the immature clotting factors, vitamin K is oxidized and becomes inactive.
- Another enzyme, vitamin K epoxide reductase complex 1 (VKOR c1), reduces vitamin K back to its active form. This is the enzyme inhibited by warfarin.
- Vitamin K is synthesized in the intestinal tract by bacteria.

Blood Groups

- Several systems are used for grouping blood. The most important two of which are the classic O-A-B system and the Rh system.
- Hundreds of antigens on RBCs' surfaces were defined. Most of these antigens are weak and of no importance in blood transfusion.

O-A-B system

- Two antigens, A and B are found in large proportion in human beings. These are called agglutinogens because they can cause blood agglutination.
- Agglutinins are antibodies produced against the agglutinogens not normally found on RBCs.
- They are formed 2 to 8 months after birth because small amounts of type A and B antigens enter the body in food, in bacteria, and in other ways, and these substances initiate the development of the anti-A and anti-B agglutinins.

Genotypes	Blood Types	Agglutinogens	Agglutinins
OO	O	–	Anti-A and Anti-B
OA or AA	A	A	Anti-B
OB or BB	B	B	Anti-A
AB	AB	A and B	–

- One can determine the phenotype (blood type) if given the genotype. The opposite is not true. For example, a person with blood type A may have the genotypes OA (heterozygous) or AA (homozygous).
- B antigen is relatively rarely found on RBCs. Therefore, the prevalence of blood types B and AB are much less common than A or O.

Rh system

- There are six common types of the Rh antigen; C, c, D, d, E and e.
- Each person must have only one antigen of each of these 3 pairs. For example, cDe.
- The type D antigen is widely prevalent in the population and considerably more antigenic than the other Rh antigens.
- Anyone who has this type of antigen is said to be Rh positive, whereas a person who does not have type D antigen is said to be Rh negative.
- Note, however, that even in Rh-negative people, some of the other Rh antigens can still cause transfusion reactions, although the reactions are usually much milder.

- Unlike in the O-A-B system, in which agglutinins form spontaneously, in the Rh system, agglutinins don't form unless the person has been massively exposed to Rh antigen.

Blood transfusion

- **Indications:**
  - Blood loss (hemorrhage).
  - Decreased blood cells count of any type.
  - Eryhtroblastosis fetalis; a condition in which the mother agglutinins pass to the fetus and attack its RBCs causing their hemolysis.
  - Decreased proteins level (hypoproteinemia) such as antibodies.
- **Risks:**
  - **Early:**
  - Agglutination and hemolysis which can be immediate or delayed.
    - Note: Autoagllutination is condition in which antibodies attack the person's own RBCs. This is not associated with blood transfusion.
  - Infection at the site of injection.
  - Allergic reaction due to the transfused blood cells or plasma protein.
  - Circulatory overload.
  - Air embolism.
  - Citrate toxicity.
  - Hyperkalemia.
  - Clotting abnormalities (in massive transfusion).
  - Late:
  - Transmission of infectious diseases.
  - Iron overload.
  - Immunologic sensitization.
- Blood is stored at 4^{o} C in the blood bank using anticoagulants such as citrate dextrose, and can be stored up to 2 weeks.
- After 2 weeks, RBCs hemolyze. This is because Na^{+}/K^{+} pumps in old RBCs beome less active allowing Na^{+} level to increase inside the cell and K^{+} level to increase in the plasma with a net increase in the osmolarity in these RBCs. This cause water to enter the cells in great amounts casuing cells rupture.

Cross matching test

- Performed to determine whether the donator blood is compatible with the recipient blood.
- First, free plasma from the donator and RBCs from the recipient are mixed. Second, free plasma from the recipient ant RBCs from the donator are mixed. If any clumping is observed under the microscope then the transfusion is not safe. Otherwise, the blood of the donator is compatible with that of the recipient.
- If enough blood of the same type of the recipient one is not available, blood of the O- type is injected; if this is also not available, blood of the O+ type is injected.

Body fluids

- In a 70-Kg person, on average, intracellular fluids constitute 28L of all body fluids while extracellular fluids constitute 14L.
- 5L of the total water is in the blood; 22L are in the muscles; 9L are in the skin. Bone also contains water. Adipose tissues contain the least amount of water.
- The percentage and distribution of water is somewhat different in males from females. This is mainly because of the difference in the percentage and distribution of fat. Therefore, these differences are negligible at childhood and after menopause but are evident at the productive age (18-40) because of the higher estrogens levels in females than males. At this age, on average, the percentage of water in males is 61% while in males it's 51%.
- Extracellular fluids can be divided into interstitial fluid (fluids between cells) and blood plasma. The difference in composition between these two is limited to proteins which are present in the plasma bot not the interstitial fluid.
- The difference in composition between intracellular fluid and extracellular fluid is very big and physiologically important. The difference is mainly in the concentrations of K^+, Na^+, SO_4^{2-}, PO_4^{3-}, and proteins.
- The osmolality of blood is 290 mOsm/Kg. The main contributors (280 mOsm/Kg) are Na^+, K^+ and Cl^-. The rest 10 mOsm/Kg is caused by proteins, glucose and other nonionic substances.
- Water intake (from fluids intake, from food, from metabolism or others) must be equal to water output (in urine, by lungs, by skin or in feces).

Water homeostasis

- In hypervolemia, ADH secretion is inhibited; ANF (atrial natriuretic factor) is secreted. ANF increases Na^+ excretion thus, water excretion.
- In hypovolemia, renin is secreted to catalyze the eventual formation of angiotensin 2 which in turn:
  - Stimulates thirst.
  - Constricts blood vessels.
  - Promotes ADH and aldosterone actions.

Dehydration

- **Has many causes such as:**
  - Drinking too little amounts of water.
  - Defective physiological response to hypovolemia.
  - Decreased absorption of water from the GI tract.
  - Loss of water from skin as in wounds or burns.
  - Excessive sweating.
  - Diarrhea or prolonged vomiting.
  - Massive renal diuresis as in DM.
- **Dehydration can be:**
  - Isotonic: the concentrations of electrolytes in fluids lost are the same as in body fluids.
  - Hypertonic: the concentrations of electrolytes in fluids lost are much less than in body fluids.
  - Hypotonic: the concentrations of electrolytes in fluids lost are much higher than in body fluids.
- **Clinical features:**
  - Shrunken body and face.
  - Loss of skin elasticity.
  - Loss of weight.
  - Cerebral disturbances, excitement, delirium and coma.
  - Acidosis.
  - Anuria (no excretion of urine).
  - Circulatory failure.
  - Fever duo to loss of an important cooling metabolism, sweating.

Water intoxication

- Has many causes such as excessive water intake and impaired loss of water mechanism.
- The dilution of cellular component and flooding of the cells result in:
  - Cells disorientation.
  - Convulsions.
  - Coma.
  - GI dysfunction.
  - Muscular weakness.
  - Arrhythmia.

Lymphatic system

- Consists of lymphatic vessels, lymphatic ducts, lymph nodes and related organs (spleen, tonsils, thymus and appendix).
- Some tissues don't contain lymphatic vessels; avascular tissues (e.g., epithelial tissues), CNS, bone marrow and a portion of the spleen.

Remember:

- A blood capillary has an arterial end and a venous end.
- In the capillary, two forces govern the movements of fluids; the hydrostatic pressure (as a result of heart pumping) which favors fluids movement from the capillary to the interstitial fluid, and the oncotic (osmotic) pressure (caused by the nondiffusible plasma proteins, especially albumin) which favors fluids movement from the interstitial fluid to the capillary.
- At the arterial end, the hydrostatic pressure is 32 mmHg while the oncotic pressure is 28 mmHg. This causes a net diffuse of fluids from the capillary to the interstitial fluids.
- At the venous end, the hydrostatic pressure decreases to 16 mmHg while the oncotic pressure remains 28 mmHg. This causes a net diffuse of fluids from the interstitial fluids to the capillary.

- At the arterial end of a blood capillary, some of the plasma proteins pass to the interstitial fluids and don't reenter the capillary at the venous end. These are transferred in lymph through lymph vessels to drain into the venous blood via the thoracic duct and the right lymphatic duct.
- **The functions of the lymphatic system:**
  - Return of the excess fluids and proteins filtered at the arterial ends of the capillaries.
  - Lymphocytes defend against microorganisms and are mainly transferred to the blood vessels via the lymphatic vessels.
  - Lymphatic vessels transport the absorbed fat from the GI tract.
- **Forces that cause lymph to flow in the vessels:**
  - Contraction of skeletal muscles including those that contract while breathing.
  - Contraction of the smooth muscles in the walls of the large lymphatic vessels.

Edema

- Accumulation of excess fluids in the interstitial fluids. This may be a result of any of the following:
  - High hydrostatic pressure in the arterial or venous ends of the blood capillaries.
  - Low oncotic pressure that causes excess fluids to be filtered at the arterial end and decreased fluid reuptake at the venous end.
  - Increased capillaries' permeability.
  - Lymphatic vessels blockage.