Al muthanna University **Pharmacy college**
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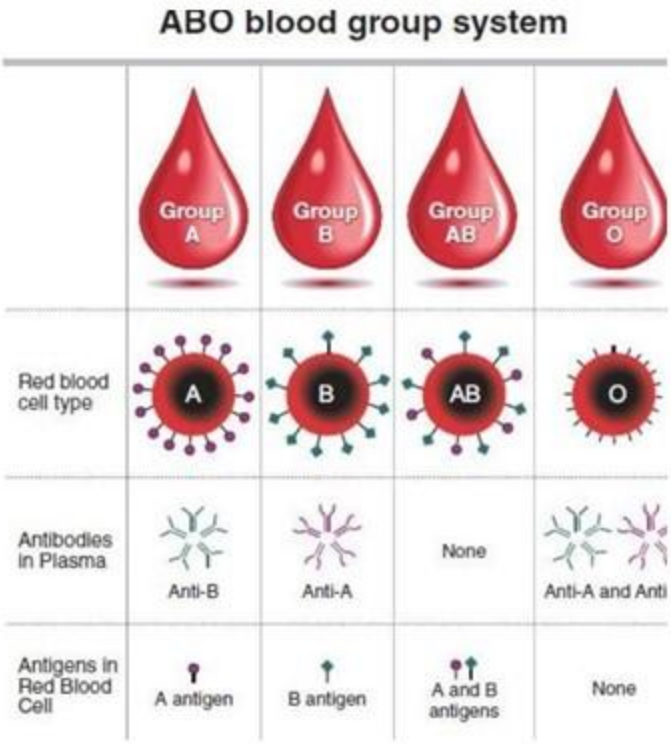
Blood physiology

BLOOD TYPES



The membranes of human red cells contain a variety of blood group antigens, which are also called agglutinogens. The most important and best known of these are the A and B antigens, there are define four major blood types.

Type A individuals have the A antigen,

Type B have the B antigen,

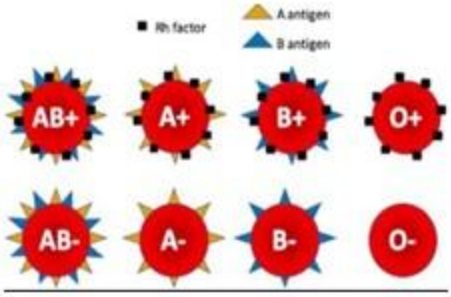
Type AB have both antigen,

Type O have neither antigen,.

Antibodies against red cell agglutinogens are called agglutinins. Antigens very similar to A and B are common. The infants rapidly develop antibodies against the antigens not present in their own cells. Thus, type A individuals develop anti-B antibodies, type B individuals develop anti-A antibodies, type O individuals develop both, and type AB individuals develop neither. When the plasma of a type A individual is mixed with type B red cells, the anti-B antibodies cause the type B red cells to clump (agglutinate). ABO blood typing is performed by mixing an individual's red blood cells with antisera containing the various agglutinins and checking for agglutination.

TRANSFUSION REACTIONS

Dangerous hemolytic transfusion reactions occur when blood is transfused into an individual who has agglutinins against the red cells in the transfusion. The severity of the resulting transfusion reaction may vary from an asymptomatic minor rise in plasma bilirubin to severe jaundice and renal tubular damage leading to anuria and death.



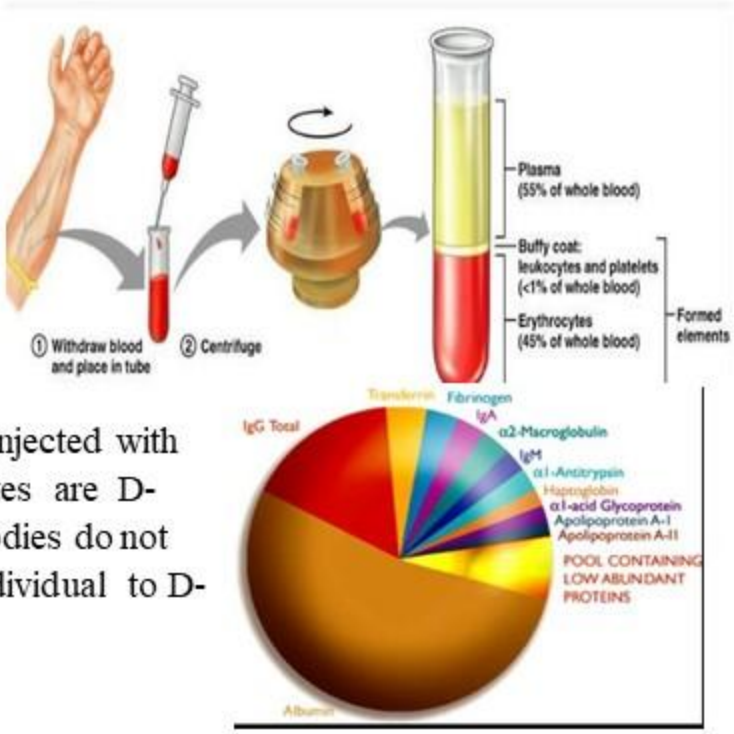
Persons with type AB blood are —universal recipients‖ because they have no circulating agglutinins and can be given blood of any type. Type O individuals are —universal donors‖ because they lack A and B antigens, and type O blood can be given to anyone without producing a transfusion reaction due to ABO incompatibility.

However, the possibility of reactions due to incompatibilities

in systems other than ABO always exists. In cross matching, donor red cells are mixed with recipient plasma on a slide and checked for agglutination.

THE RH GROUP

The Rh system is of the greatest clinical importance. The Rh factor is composed primarily of the C, D, and E antigens, although it actually contains many more. D is by far the most antigenic component, and the term Rh-positive as it is generally used means that the individual has agglutinogen D. The Rh-negative individual has no D antigen and forms the anti-D agglutinin when injected with D-positive cells. Eighty-five percent of whites are D-positive and 15% are D-negative. anti-D antibodies do not develop without exposure of a D-negative individual to D-positive red cells.



PLASMA

The fluid portion of the blood, is a solution containing ions, inorganic molecules, and organic molecules that are in transit to various parts of the body. Plasma clots on standing, remaining fluid only if an anticoagulant is added. If whole blood is allowed to clot and the clot is removed, the remaining fluid is called serum.

Serum has the same composition as plasma, except that its fibrinogen and clotting factors II, V, and VIII have been removed and it has a higher serotonin content because of the breakdown of platelets during clotting.

Plasma proteins functions

The plasma proteins consist of albumin, globulin, and fibrinogen fractions.

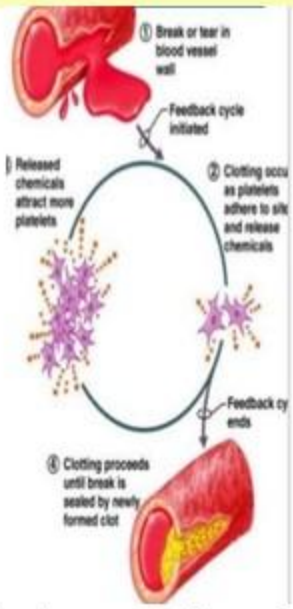
1. Osmotic force: Most capillary walls are relatively impermeable to these, so they exert an osmotic force of about 25 mm Hg across the capillary wall (oncotic pressure) that pulls
2. water into the blood.
   The buffering capacity of plasma proteins are also responsible for 15% of the buffering capacity of proteins in the blood (hemoglobin) because of the weak ionization of their
3. substituent COOH and NH2 groups.
4. The plasma contain antibodies
5. The plasma contain clotting factors
   Nonspecific carriers for various solutes.

ORIGIN OF PLASMA PROTEINS

Circulating antibodies are manufactured by lymphocytes. Most of the other plasma proteins are synthesized in the liver. Synthesis plays an important role in the maintenance of albumin levels. In normal adult humans, the plasma albumin level is 3.5–5.0 g/dL, the degraded albumin is replaced by hepatic synthesis. Albumin synthesis is carefully regulated. It is decreased (hypoproteinemia) during fasting, malabsorption syndromes, liver disease, and in nephrosis, because large amounts of albumin are lost in the urine. But increased in conditions where there is excessive albumin

FACTORS INVOLVED IN BLOOD CLO

- Factor I: Fibrinogen
- Factor II: Prothrombin
- Factor III: Thromboplastin
- Factor IV: Calcium
- Factor V: Labile factor
- Factor VI: Prescence has not been proved
- Factor VII: Stable Factor
- Factor VIII: Antihemophilic
- Factor IX: Christmas factor
- Factor X: Stuart factor
- Factor XI: Plasma Thromboplastin antecedent
- Factor XII: Hagan factor
- Factor XIII: Fibrin stabilizing factor



HEMOSTASIS

Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. A collection of complex mechanisms operates to balance coagulation and anticoagulation.

THE CLOTTING MECHANISM

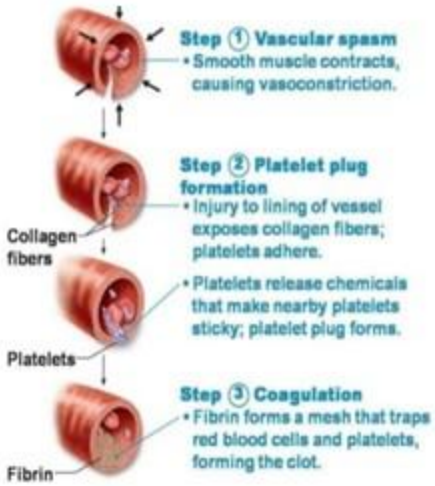
When a small blood vessel is damaged, the injury initiates a series of events that lead to the formation of a clot. This seals off the damaged region and prevents further blood loss.

1- The initial event is constriction of the vessel .Vasoconstriction is due to serotonin and other vasoconstrictors liberated from platelets that adhere to the walls of the damaged vessels.

2- Formation of a temporary hemostatic plug of platelets that is triggered when platelets bind to collagen and aggregate.

3- The temporary plug is bound together and converted into the definitive clot by fibrin. Fibrin formation involves a cascade of enzymatic reactions and a series of numbered clotting factors. The fundamental reaction is conversion of the soluble plasma protein fibrinogen to insoluble fibrin through:

a- The initial reaction in the intrinsic system is conversion of inactive factor XII to active factor XII (XIIa). This activation, which is catalyzed by high-molecular-weight kininogen and kallikrein, can be brought about by collagen fibers underlying the endothelium.



b- Active factor XII then activates factor XI, and active factor XI activates factor IX.
c- Activated factor IX forms a complex with active factor VIII, which is activated when it is separated from von Willebrand factor.
d- Factor X can be activated by either the intrinsic and extrinsic systems.
1- The intrinsic systems. The complex of IXa and VIIIa activate factor X. Phospholipids (PL) from aggregated platelets and Ca^2 are necessary for full activation of factor X.
2- The extrinsic system is triggered by the release of tissue thromboplastin (TPL), a protein–phospholipid mixture that activates factor VII. TPL and factor VII activate factors IX and X.
In the presence of PL, Ca 2 , and factor V, activated factor X. The extrinsic pathway is inhibited by a tissue factor pathway inhibitor that forms a quaternary structure with TPL, factor VIIa, and factor Xa.
e- Thrombin is a serine 2 protease that is formed from its circulating precursor, prothrombin, by the action of activated factor X.
It has additional actions, including activation of platelets, endothelial cells, and leukocytes via the so called proteinase-activated receptors, which are G-protein–coupled.
f- The fibrin is initially a loose mesh of interlacing strands. It is converted by the formation of covalent cross linkages to a dense, tight aggregate (stabilization). This latter reaction is catalyzed by activated factor XIII and requires Ca. The conversion of fibrinogen to fibrin is catalyzed by thrombin.

Anticlotting mechanisms

The tendency of blood to clot is balanced in vivo by reactions that prevent clotting, break down any clots that do form, or both. These reactions include:
1- The interaction between the platelet-aggregating effect of thromboxane A2 and the antiaggregating effect of prostacyclin.
2- Antithrombin III is a circulating protease inhibitor that binds to serine proteases in the coagulation system. This binding is facilitated by heparin, a naturally occurring anticoagulant. The clotting factors that are inhibited are the active forms of factors IX, X, XI, and XII.
3- The endothelium of the blood vessels also plays an active role in preventing the extension of clots. All endothelial cells except those in the cerebral microcirculation produce thrombomodulin, a thrombin-binding protein, on their surfaces. In circulating blood, thrombin is a procoagulant that activates factors V and VIII, but when it binds to thrombomodulin, it becomes an anticoagulant that activates protein.
4- Activated protein C (APC), along with its cofactor protein S, inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin. Plasmin (fibrinolysin) is the active component of the plasminogen (fibrinolytic)

system. This enzyme lyses fibrin and fibrinogen, with the production of fibrinogen degradation products (FDPs) that inhibit thrombin. Plasminogen receptors are located on the surfaces of many different types of cells and are plentiful on endothelial cells. When plasminogen binds to its receptor, it is activated, so intact blood vessel walls are provided with a mechanism that discourages clot formation.

Anticoagulants

- Heparin is Low-molecular-weight fragments of heparin have a longer half-life and produce a more predictable anticoagulant response than unfractionated heparin.
- In vivo, a Ca^2 level low enough to interfere with blood clotting is incompatible with life, but clotting can be prevented in vitro if Ca^2 is removed from the blood.
- Coumarin derivatives such as dicumarol and warfarin are also effective anticoagulants. They inhibit vitamin K, a necessary cofactor for the six of the proteins involved in clotting (factors II (prothrombin), VII, IX, and X, protein C, and protein S) require before being released into the circulation.

LYMPH

Lymph is tissue fluid that enters the lymphatic vessels. It drains into the venous blood via the thoracic and right lymphatic ducts. The lymph vessels contain valves and regularly traverse lymph nodes.

- collect plasma and its constituents that have exuded from the capillaries into the interstitial space
- It contains clotting factors and clots on standing.
- In most locations, it also contains proteins that have traversed capillary walls and can then return to the blood via the lymph. Nevertheless, its protein content is generally lower than that of plasma.
- Lipids are absorbed from the intestine into the lymphatics, and the lymph in the thoracic duct after a meal is milky because of its high fat content.
- Lymphocytes also enter the circulation principally through the lymphatics.

White blood cell

Granulocytes: All granulocytes have cytoplasmic granules that contain biologically active substances involved in inflammatory and allergic reactions.

Neutrophil

The average half-life of a neutrophil in the circulation is only 6 h. Many neutrophils enter the tissues. They are attracted to the endothelial surface by cell adhesion molecules known

as selectins, and they roll along it. They then bind firmly to integrins and insinuate themselves through the walls of the capillaries by diapedesis. Many of those that leave the circulation enter the gastrointestinal tract and are eventually lost from the body. Invasion of the body by bacteria triggers the inflammatory response.

Phagocytes (opsonization):

1- Bacterial products trigger production of agents (chemotaxis) that attract at first neutrophils to the area. Chemotactic agents include a component of the complement system (C5a); leukotrienes; and chemokine polypeptides from lymphocytes, mast cells, and basophils.

Other plasma factors coat the bacteria to make them —tasty‖ to the phagocytes (opsonization). The principal opsonins are immunoglobulin G and complement proteins.

2- The coated bacteria then bind to G-protein–coupled receptors on the neutrophil membrane.

3- This triggers increased motor activity of the cell,

4- Exocytosis, neutrophil granules discharge their contents into phagocytic vacuoles containing bacteria and also into the interstitial space (degranulation). The granules contain various proteases plus antimicrobial proteins called defensins.

5- In addition, the cell membrane-bound enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is activated, with the production of toxic oxygen metabolites.

6- Neutrophils also discharge the enzyme myeloperoxidase, which catalyzes conversion of $Cl+O^{2-}$ to the corresponding acids (HOCl, HOBr, etc) that are also potent oxidants.

7- The combination of the toxic oxygen metabolites and the proteolytic enzymes from the granules makes the neutrophil a very effective killing machine for bacteria, but may also cause local destruction of host tissue.

Eosinophils

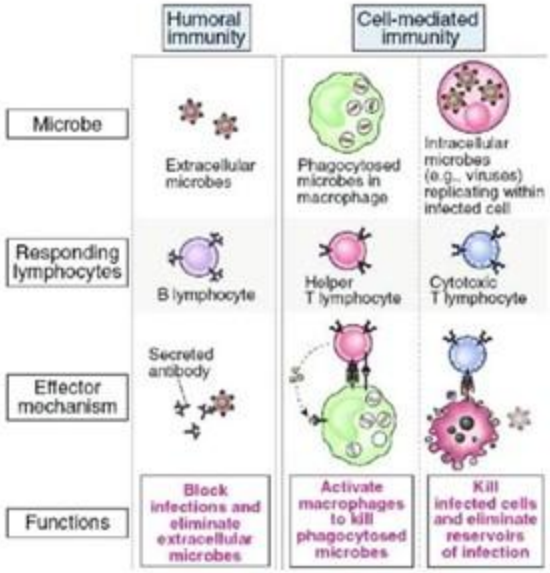
It has a short half-life in the circulation, are attracted to surface of endothelial cells by selectins, bind to integrins, and enter the tissues by diapedesis. Like neutrophils, they release proteins, cytokines, and chemokines that produce inflammation but are capable of killing invading organisms. However, eosinophils have some selectivity in the way in which they respond and in the killing molecules they secrete. Their maturation and activation in tissues is particularly stimulated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). They are especially abundant in the mucosa of the gastrointestinal, respiratory and urinary tracts, and are increased in allergic diseases such as asthma.

Basophils

Also enter tissues and release proteins and cytokines. They resemble mast cells, and like mast cells they release histamine and other inflammatory mediators when activated by binding of antigens to cell fixed IgE molecules, and participate in immediate-type hypersensitivity (allergic) reactions. The antigens that trigger IgE formation to as allergens.

MAST CELLS

are heavily granulated connective tissue cells that are abundant beneath epithelial surfaces. Their granules contain proteoglycans, histamine, and many proteases. They are involved in inflammatory responses initiated by immunoglobulins IgE and IgG and release TNF-α in response to bacterial products by an antibody independent mechanism, thus participating in innate immunity.



Non Granulocytes

MONOCYTES

Monocytes enter the blood from the bone marrow and circulate for about 72 h. They then enter the tissues and become tissue macrophages. These persist in tissues for about 3 months. Some may end up as the multinucleated giant cells seen in chronic inflammatory diseases such as tuberculosis. Tissue macrophages include: Kupffer cells of the liver, pulmonary alveolar macrophages, and microglia in the brain. Macrophages are activated by cytokines released from T lymphocytes, among others. Activated macrophages migrate in response to chemotactic stimuli and engulf and kill bacteria by processes generally similar to those occurring in neutrophils. They play a key role in innate immunity. They also secrete factors that affect lymphocytes and other cells, prostaglandins of the E series, and clot-promoting factors.

Lymphocytes

Lymphocytes are key elements in acquired immunity. After birth, most are formed in the lymph nodes, thymus, and spleen from bone marrow precursor cells that were processed in the thymus (T cells) or bone marrow (B cells). Lymphocytes enter the bloodstream for the most part via the lymphatics. Another lymphoid subset that forms in the thymus is the NKT cell, so-called because it shares features of both T lymphocytes and natural killer (NK) cells. After residence in the thymus, liver, or bone marrow, many T and B lymphocytes

migrate to the lymph nodes. T and B lymphocytes are morphologically indistinguishable but can be identified by markers on their cell membranes.

- **B cells** differentiate sequentially into cells capable of production of the various classes of immunoglobulins and thereafter into plasma cells.
- **T cells:** There are two major types of T cells:

1- **Cytotoxic T cells** destroy transplanted cells and those expressing foreign antigens (eg, virally infected targets),it display the glycoprotein cluster of differentiation (CD) 8, These proteins are closely associated with T cell receptors and may function as coreceptors. with their development aided and directed by helper T cells.

2- Helper T cells, there are at least four subtypes of helper T cells:

A- T helper 1 (TH1) cells secrete IL-2 and γ-interferon and are concerned primarily with stimulating cellular immunity;

B- TH2 cells secrete IL-4 and IL-5 and interact primarily with B cells in relation to humoral immunity.

C- TH17 cells are induced in response to bacterial infections, produce IL-6 and IL-17, and help recruit neutrophils. They are also implicated in inflammatory responses.

D- Treg cells produce IL-10 to dampen T-cell-driven responses.

Most helper T cells display the glycoprotein CD4. These proteins are closely associated with T cell receptors and may function as coreceptors.