Blood is a specialized fluid connective tissue. It consists of **formed elements** (living "cells") suspended in a non-living liquid matrix, known as **plasma**. The formed elements consist of **erythrocytes** (red blood cells), **leukocytes** (white blood cells), and **platelets**.

Blood's color depends on oxygen content. It can range from scarlet (oxygen-rich) to dark red (oxygen-poor). Blood is 5x more viscous (in other words, 5x stickier, and more resistant to flow) than water. This is primarily due to the presence of the formed elements. Blood is slightly alkaline (basic) with a normal pH range between 7.35 and 7.45. Blood's temperature is slightly higher than body temperature. 100.4°F vs. 98.6°F. The average blood volume is 5-6L in male and 4-5L in females.

The main functions of blood can be described as distributory, regulatory, and protective.

Blood transports: nutrients from the digestive tract and body reserves to all cells; oxygen from lungs to all cells; wastes from all cells to elimination sites (CO_2 to the lungs, nitrogenous wastes to the kidneys); hormones from endocrine glands to target tissues.

Blood regulates body temperature by controlling the degree of blood flow to the skin's surface and thus regulating how much heat radiates away from the body. Blood is responsible for maintaining: normal pH of body fluids; adequate fluid volume in the body; electrolyte balance in the body.

Blood's protective functions include: preventing blood loss by initiating clotting mechanisms in response to blood vessel damage; preventing infection by transporting immune cells (leukocytes) and immune proteins.

Keeping blood "homeostatically okay" keeps interstitial fluid "homeostatically okay," which in turn keeps cells "homeostatically okay," and therefore alive.

Blood plasma is about 55% of blood volume. 90% of plasma is water. Water acts as a solvent and suspending medium. Solutes dissolved in plasma include: proteins, nutrients, electrolytes, respiratory gases, and wastes.

Albumin is the most abundant plasma protein (60%). The liver produces it and its primary function is to maintain plasma osmotic pressure. It also acts as a buffer and is involved in the transport of steroids and bilirubin.

Globulins are type of plasma protein. Many are produced in the liver and act as transport proteins for lipids, metal ions, and fat-soluble vitamins. Other globulins, known as **antibodies**, are produced by **plasma cells** (a type of leukocyte) during the immune response.

Plasma also contains clotting proteins. Most are produced in the liver. Two important examples are **prothrombin** and **fibrinogen**.

Additional plasma proteins include enzymes, hormones, and other immune proteins.

Plasma contains nutrients – materials absorbed from the GI tract or body reserves and distributed throughout the body. Includes amino acids, glucose, fatty acids, triglycerides, vitamins, and cholesterol.

Plasma also contains electrolytes (ions, such as Ca^{2+}, Na^{+}, and K^{+}, etc.), respiratory gases (dissolved CO_2, O_2, and N_2), wastes (byproducts of cell metabolism, e.g., urea, uric acid, ammonia, creatinine, and lactic acid), and buffers (chemicals that function to prevent fluctuations in plasma pH).

Red blood cells are small (7.5μm diam.), biconcave discs. The biconcave shape gives them a lot of surface area (good for O_2 entry/exit) and increased flexibility (good for squeezing thru tight capillaries). They are anucleate and lack organelles. Basically, they are membranous bags stuffed with **hemoglobin** proteins. There are normally 4-6 million RBCs per μL of blood. Their primary function is O_2 transport. They also play a minor role in CO_2 transport.

Hemoglobin is the protein that is contained in abundance within RBCs. A small amount of Hb is also found within the plasma. It reversibly binds and releases O_2. Hb is made up of the protein **globin**, bound to red **heme** pigments. Globin consists of four polypeptide chains, each with their own associated heme group. Each heme group contains one **iron** atom that can reversibly combine with one molecule of O_2. Thus, each Hb molecule can transport four O_2 molecules. In lungs, Hb binds O_2 and is referred to as **oxyhemoglobin**. In tissues, Hb releases O_2 and is referred to as **deoxyhemoglobin** or **reduced hemoglobin**. About 20% of blood's CO_2 is transported by combining with the amino acids in the globin portion of Hb.

Blood cell formation is known as **hemopoiesis** or **hematopoiesis**. All blood cells are made w/i red bone marrow. (Adult red marrow is primarily found in ribs, vertebrae, sternum, pelvis, and proximal humeri and femurs). RBC formation is known as **erythropoiesis**. All blood cells arise from the **hemopoietic stem cell** or **hemocytoblast**. In the process of erythropoiesis, a hemocytoblast divides and differentiates. Its nucleus and organelles are discarded while Hb stores are built up to tremendous levels.

The # of RBCs in the blood stream is remarkably constant and maintained by a negative feedback loop. Too few RBCs compromises O_2 transport, while too many RBCs causes a detrimental ↑ in blood viscosity. A kidney hormone, **erythropoietin (EPO)**, controls the rate of erythropoiesis. If blood O_2 content ↓, the kidneys release EPO. EPO stimulates RBC synthesis to ↑. RBC # ↑ and this ↑ blood O_2 content. O_2 delivery to the kidney could change due to RBC count, altitude, increased aerobic activity, lung disease, or cardiovascular disease.

A typical RBC is formed in the red bone marrow from hemocytoblasts. It travels thru the circulatory system (arteries, capillaries, and veins) and after about 120d, it will have become old and/or damaged. The lack of a nucleus and organelles precludes replication or self-repair. Old/damaged RBCs are engulfed by scavenger cells, known as **macrophages**, in the spleen, liver, and red bone marrow. The Hb within the phagocytosed RBC will be broken down and partially recycled and partially excreted. Hb is broken down into its globin and heme portions. The globin is reduced to its constituent amino acids and released from the macrophage into the blood stream for reuse elsewhere. The iron is removed from the heme and is then transported to the liver by the plasma protein **transferrin**. In the liver, the iron is stored. The remainder of the heme is converted into a pigment called **bilirubin**. Bilirubin is released from the macrophage and transported to the liver by albumin. The liver then modifies bilirubin and secretes it into the small intestine as part of **bile**. In the intestine, bilirubin is metabolized by resident bacteria producing metabolites that are ultimately excreted in the feces and urine.

Leukocytes are the only formed elements with nuclei and normal organelles. They account for far less than 1% of total blood volume. They help protect the body from pathogens, toxins, and cancerous cells. Leukocytes are formed in red bone marrow. Like RBCs, they also begin as hemocytoblasts. Their normal range is 5000-10,000 WBCs per μL of blood. Only a small fraction of the body's total WBCs are found in the blood at any one time. Most are in lymphatic organs (e.g., lymph nodes, spleen, tonsils, and appendix) and within the loose connective tissue that underlies the reproductive, respiratory, digestive, and urinary tracts. They use the blood as a highway to travel from place to place. They have the ability to leave the blood stream (this is known as **diapedesis**) and enter connective or lymphatic tissue where they mount an immune response. They are capable of flowing thru the tissue spaces with an **amoeboid-like motion**. They're also capable of following chemical cues released by pathogens, damaged cells, or activated WBCs. This is known as **positive chemotaxis**.

There are 5 types of leukocytes: **neutrophils, lymphocytes, monocytes, eosinophils,** and **basophil**s. The mnemonic *"never let monkeys eat bananas"* specifies the 5 types in order of abundance. WBCs are divided into 2 large classes: **granulocytes** and **agranulocytes**. Granulocytes contain membrane-bound granules that are stained with a dye known as **Wright's stain**. Agranulocytes do not contain stainable granules.

Granulocytes include neutrophils, eosinophils, and basophils. All are spherical, larger than RBCs, have lobed nuclei, and stain specifically with Wright's stain. Neutrophils are the most numerous circulating WBC. They constitute 50-70% of the circulating WBC population. They are 2x the size of RBCs and have a lifespan of 6hrs to a few days. They contain fine lilac colored granules that take up both acidic and basic dyes, and a nucleus can consist of 3-6 lobes - b/c of this, they are often said to be **polymorphonuclear**. Neutrophil count increases during acute bacterial infections.

Eosinophils make up 2-4% of the circ. WBC pop. They are the same size as neutrophils and have bilobed nuclei. They take up acidic dyes, which cause granules to turn reddish orange. Their function is attacking parasitic worms. They'll gather around an invading worm and release enzymes stored w/i their granules onto its surface, effectively killing it. They also act to lessen the severity of allergies by phagocytosing the immune complexes involved in allergy attacks. They have a typical lifespan of 8-12d.

Basophils make up <1% of the circ. WBC pop. They take up basic dyes, which cause their granules to turn a dark purple. Their granules contain the vasodilator **histamine** as well as the anticoagulant **heparin**. Both are released during inflammation. They have an unknown lifespan.

The agranulocytes lack any visible granules that take up Wright's stain. They are the lymphocytes and monocytes. Lymphocytes comprise 30% of the circ. WBC pop. They have large, round, purple nuclei taking up most of the cell volume. They are 1-2x the size of an RBC and have a lifespan of hrs to yrs. There are trillions of lymphocytes in the body, but only a relatively small # in the blood. Most are found w/i lymphatic tissues (e.g., lymph nodes, spleen). There are 2 main types of lymphocytes. **T lymphocytes** defend against virus-infected and tumor cells, and control and manage the immune response. **B lymphocytes** differentiate into **plasma cells**, which produce **antibodies**.

Monocytes comprise 3-8% of the circ. WBC pop. They are the largest leukocyte – they can be more than 3x the size of an RBC. They have a lifespan of several months. They contain pale blue cytoplasm and a dark U or kidney-shaped nucleus. Monocytes leave the bloodstream to become **macrophages** – cells specialized in phagocytosis of foreign particles and debris.

WBC synthesis is known as **leukopoiesis**. It primarily occurs within the red bone marrow. The stem cell for all WBCs is the hemocytoblast. Lymphocytes can also be produced w/i lymphatic tissues.

Platelets are fragments (2-4μm diameter) of extremely large bone marrow cells that are derived from hemocytoblasts. Platelets contain membrane-bound granules filled with chemicals important to the blood clotting process. There are typically 150,000-400,000 platelets per μL of blood. Platelets are sometimes referred to as **thrombocytes**. Platelet formation (**thrombopoiesis**) occurs in the bone marrow. They remain in the bloodstream for about 10-12d.

Hemostasis is the set of processes that stop bleeding and help heal damaged blood vessel walls. It consists of 3 events: **vascular spasm**, **platelet plug formation**, and **coagulation**.

Damaged vessels release chemicals that cause the smooth muscle in their walls to contract. This ↓ BV diameter, which will ↓ blood loss and (by ↓ local blood pressure) facilitate patching and repair. This event is vascular spasm.

Platelets are activated by the exposure of the collagen that underlies the simple squamous epithelium of the wall of an intact blood vessel. Activated platelets begin to aggregate at the site of injury. These aggregated, activated platelets will release chemicals that: enhance vascular spasm; are involved in coagulation; and facilitate the activation and aggregation of more platelets at the injury site (a +feedback process). The pile of aggregated platelets is known as a **platelet plug** and provides a temporary seal to the break in the BV wall. The platelet plug is restricted to the injury site b/c intact endothelial cells release the chemical **prostacyclin**, which strongly inhibits platelet aggregation.

Coagulation is a complicated multi-step process that results in the formation of a sturdy clot that seals the tear until repairs are complete. We'll concentrate on the final steps:

A. In response to vessel damage, **prothrombin activator** (PTA) is formed.
B. PTA converts the inactive protein **prothrombin** into the active **thrombin**.
C. Thrombin converts the soluble protein **fibrinogen** into the insoluble **fibrin**.
D. Fibrin molecules then link to one another and form a meshwork of strands on the platelet plug. RBCs, WBCs, and plasma are trapped w/i the fibrin mesh. This results in a **blood clot**.

There are 2 pathways by which prothrombin activator is formed: **extrinsic** and **intrinsic**. The extrinsic path begins when blood is exposed to a chemical released by *damaged tissue cells outside the blood vessel*. The extrinsic path has few steps and, thus, prothrombin activator can be formed <u>quickly</u>. The intrinsic path begins in response to the release of certain chemicals by *damaged blood vessel cells*. The intrinsic path has many steps. This makes it slower than the extrinsic path, but it allows for <u>amplification</u>, which yields tremendous amounts of prothrombin activator. In the body, both pathways typically occur in response to the same event. Having 2 pathways allows for prothrombin activator to be formed quickly (extrinsic) as well as in large amounts (intrinsic). Once the fibrin mesh has been created and the clot has formed, **clot retraction** will occur. Platelets contain actin and myosin. They contract. This compacts the clot and pulls the edges of the torn vessel together (facilitating repair).

Multiple clotting factors are involved in the coagulation process. Many of these are formed in the liver. **Vitamin K** is required for their synthesis. **Calcium** is also required for coagulation.

Another plasma protein, **plasminogen**, is involved in **fibrinolysis –** the breakdown of the clot. Plasminogen is converted to **plasmin**, which begins to digest fibrin once repairs have taken place.

Coagulation can be promoted by roughened vessel lining, which can attract and activate platelets. Also, pooling of blood w/i blood vessels can result in the activation of clotting factors and the initiation of the coagulation process.

Coagulation can be inhibited by **aspirin**, which inhibits platelet aggregation. Coagulation is also impaired by vitamin K abnormalities. This includes chemicals that block the use of vitamin K and lack of absorption of dietary vitamin K (can be due to fat malabsorption). **Broad-spectrum antibiotics** can impair coagulation because they can kill the resident intestinal bacteria that provide us with much of our vitamin K. Liver disease impairs coagulation b/c the liver makes the majority of the clotting factors. Chemicals known as **calcium chelators** impair blood clotting b/c they bind calcium and prevent its involvement in coagulation. A low platelet count will also impair coagulation.