Histology

Blood and Hemopoiesis

Blood is a unique form of connective tissue that consists of three major cell types: erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (thrombocytes). These cells, also called the formed elements of blood, are suspended in a liquid medium called plasma. Blood cells transport gases, nutrients, waste products, hormones, antibodies, various chemicals, ions, and other substances in the plasma to and from different cells in the body.

Plasma

The plasma accounts for 55% of the blood volume. It consists of a solution of water (92%), proteins, lipids, inorganic ions (salts) and glucose. The proteins include hormones. The salts include urea, that are waste products of cells.

The proteins make up 6-7% of blood and are made up mostly of serum albumin, and serum globulins. Serum albumin is made in the liver, and helps to maintain the osmotic pressure of blood. There are three types of serum globulins; alpha, beta and gamma. Alpha is involved in transporting vitamin A, beta in transporting transferrin, and most antibodies are gamma globulins.

Hemopoiesis

Blood cells have a limited life span, and, as a result, they are continuously replaced in the body by a process called hemopoiesis. In this process, all blood cells are derived from a common stem cell in red bone marrow. Because the stem cell can produce all blood cell types, it is called the pluripotential hemopoietic stem cell. Pluripotential stem cells, in turn, produce two descendants that form pluripotential myeloid stem cells and pluripotential lymphoid stem cells. Before maturation and release into the bloodstream, the stem cells from each line undergo numerous divisions and intermediate stages of.

Myeloid stem cells develop in red bone marrow and give rise to erythrocytes, eosinophils, neutrophils, basophils, monocytes, and megakaryocytes. Lymphoid stem cells also develop in red bone marrow. Some lymphoid cells remain in the bone
marrow, proliferate, mature, and become B lymphocytes. Others leave the bone marrow and migrate via the bloodstream to lymph nodes and the spleen, where they proliferate and differentiate into B lymphocytes.

Other undifferentiated lymphoid cells migrate to the thymus gland, where they proliferate and differentiate into immunocompetent T lymphocytes. Afterward, T lymphocytes enter the bloodstream and migrate to specific regions of peripheral lymphoid organs. Both B and T lymphocytes reside in numerous peripheral lymphoid tissues, lymph nodes, and spleen. Here, they initiate immune responses when exposed to antigens.

Because all blood cells have a limited life span, the pluripotential hemopoietic stem cells continually divide and differentiate to produce new progeny. When the blood cells become worn out and die, they are destroyed in different lymphoid organs, such as the spleen.

Sites of Hemopoiesis

Hemopoiesis occurs in different organs of the body, depending on the stage of development:

- In the embryo, hemopoiesis initially occurs in the yolk sac
- later in the liver, spleen, and lymph nodes.
- After birth, hemopoiesis continues almost exclusively in the red marrow of different bones (in the newborn, all bone marrow is red).

The red bone marrow is highly cellular and consists of hemopoietic stem cells and precursors of different blood cells. Red marrow also contains a loose arrangement of fine reticular fibers. In adults, red marrow is found primarily in the flat bones of the skull, sternum and ribs, vertebrae, and pelvic bones. The remaining bones, normally the long bones, gradually accumulate fat, their marrow becomes yellow, and they lose hemopoietic functions.

Major Blood Cell Types

Microscopic examination of a stained blood smear reveals the major blood cell types. Erythrocytes or red blood cells are nonnucleated cells and are the most numerous blood cells.

During the maturation process, the erythrocytes extrude their nuclei, and the mature blood cells enter the blood vessels without their nuclei. Erythrocytes remain in the blood and perform their major functions within the blood vessels.
In contrast, leukocytes, or white blood cells, are nucleated and subdivided into granulocytes and agranulocytes, depending on the presence or absence of granules in their cytoplasm. Granulocytes are the neutrophils, eosinophils, and basophils. Agranulocytes are the monocytes and lymphocytes. Leukocytes perform their major functions outside of the blood vessels. They migrate out of the blood vessels through capillary walls and enter the connective tissue, lymphatic tissue, and bone marrow.

The primary function of leukocytes is to defend the body against bacterial invasion or the presence of foreign material. Consequently, most leukocytes are concentrated in the connective tissue.

**Platelets**

Platelets or thrombocytes are not blood cells. Instead, they are the smallest, nonnucleated formed elements in the blood and appear in the blood of all mammals. Platelets are cytoplasmic fragments or remnants of megakaryocytes, the largest cells in the bone marrow. Platelets are produced when small, uneven portions of the cytoplasm separate or fragment from the peripheries of the megakaryocytes and are extruded into the bloodstream. Like the erythrocytes, platelets perform their major functions within the blood vessels. Their main function is to continually monitor the vascular system and to detect any damage to the endothelial lining of the vessels. If the endothelial lining breaks, the platelets adhere to the damaged site and initiate a highly complex chemical process that produces a blood clot.

**ERYTHROCYTE**

The background cells in this micrograph are erythrocytes (red blood cells). These cells are non-nucleated, biconcave discs that are filled with hemoglobin. The primary function of these cells is to carry oxygen from the lungs to the body cells.

Woman usually have 4-5 million erythrocytes per cubic millimeter of blood, men have 5-6 million. If this number is considerably higher, polycythemia may be the cause. If the number is considerably less, the person has anemia.
Anemia

Definition: A significant reduction in the total body erythrocyte mass, measured as a reduction in the RBC count, the hemoglobin, and the hematocrit. Anemia exists when the hemoglobin is less than 12 g/dL or the hematocrit is less than 37%.

Classification

Anemias can be classified by cytometric schemes (microcytic, macrocytic, or normocytic), erythrokinetic schemes (those that take into account the rates of RBC production and destruction), and biochemical/molecular schemes (those that consider the etiology of the anemia at the molecular level).

Sickle cell anemia is an inherited condition which results in some erythrocytes being malformed. The gene for this condition causes the hemoglobin to be incorrectly formed, which in turn causes some erythrocytes to take on a crescent shape. These cells are not able to carry adequate amounts of oxygen to cells.

THROMBOCYTES - PLATELETS

Platelets, which are cell fragments, are seen next to the “t's” above. (Many of the other micrographs on this page contain them as well.) Platelets are important for proper blood clotting.

Each cubic millimeter of blood should contain 250,000 to 500,000 of these. If the number is too high, spontaneous clotting may occur. If the number is
too low, clotting may not occur when necessary.

**NEUTROPHIL**

This granulocyte has very tiny light staining granules (the granules are very difficult to see): The nucleus is frequently multi-lobed with lobes connected by thin strands of nuclear material. These cells are capable of phagocytizing foreign cells, toxins, and viruses.

When taking a Differential WBC Count of normal blood, this type of cell would be the most numerous. Normally, neutrophils account for 50-70% of all leukocytes. If the count exceeds this amount, the cause is usually due to an acute infection such as appendicitis, smallpox or rheumatic fever. If the count is considerably less, it may be due to a viral infection such as influenza, hepatitis, or rubella.

**EOSINOPHIL**

This granulocyte has large granules (A) which are acidophilic and appear pink (or red) in a stained preparation. This micrograph was color enhanced to illustrate this feature. The nucleus often has two lobes connected by a band of nuclear material. (Does it looks like a telephone receiver?) The granules contain digestive enzymes that are particularly effective against parasitic worms in their larval form.
These cells also phagocytize antigen-antibody complexes.

These cells account for less than 5% of the WBC's. Increases beyond this amount may be due to parasitic diseases, bronchial asthma or hay fever. Eosinopenia may occur when the body is severely stressed.

BASOPHIL

The basophilic granules in this cell are large, stain deep blue to purple, and are often so numerous they mask the nucleus. These granules contain histamines (cause vasodilation) and heparin (anticoagulant).

In a Differential WBC Count we rarely see these as they represent less than 1% of all leukocytes. If the count showed an abnormally high number of these cells, hemolytic anemia or chicken pox may be the cause.

MONOCYTE

This cell is the largest of the leukocytes and is agranular. The nucleus is most often “U” or kidney bean shaped; the cytoplasm is abundant and light blue (more blue than this micrograph illustrates). These cells leave the blood stream
(diapedesis) to become macrophages. As a monocyte or macrophage, these cells are phagocytic and defend the body against viruses and bacteria.

These cells account for 3-9% of all leukocytes. In people with malaria, endocarditis, typhoid fever, and Rocky Mountain spotted fever, monocytes increase in number.

LYMPHOCYTE

The lymphocyte is an agranular cell with very clear cytoplasm which stains pale blue. Its nucleus is very large for the size of the cell and stains dark purple. (Notice that the nucleus almost fills the cell leaving a very thin rim of cytoplasm.) This cell is much smaller than the three granulocytes (which are all about the same size). These cells play an important role in our immune response. The T-lymphocytes act against virus infected cells and tumor cells. The B-lymphocytes produce antibodies.

This is the second most numerous leukocyte, accounting for 25-35% of the cells counted in a Differential WBC Count. When the number of these cells exceeds the normal amount, one would suspect infectious mononucleosis or a chronic infection. Patients with AIDS keep a careful watch on their T-cell level, an indicator of the AIDS virus' activity.
Function of Erythrocytes

Mature erythrocytes are specialized to transport oxygen and carbon dioxide. This specialization is attributable to the presence of the protein hemoglobin in their cytoplasm. Iron molecules in hemoglobin bind with oxygen molecules. As a result, most of the oxygen in the blood is carried in the combined form of oxyhemoglobin, which is responsible for the bright red color of arterial blood. Carbon dioxide diffuses from the cells and tissues into the blood vessels. It is carried to the lungs partly dissolved in the blood and partly in combination with hemoglobin in the erythrocytes as carbaminohemoglobin, which gives venous blood its bluish color.

During differentiation and maturation in the bone marrow, erythrocytes synthesize large amounts of hemoglobin. Before an erythrocyte is released into the systemic circulation, the nucleus is extruded from the cytoplasm, and the mature erythrocyte assumes a biconcave shape. This shape provides more surface area for carrying respiratory gases. Thus, mature mammalian erythrocytes in the circulation are nonnucleated biconcave disks that are surrounded by a membrane and filled with hemoglobin and some enzymes.

The life span of erythrocytes is approximately 120 days, after which the worn-out cells are removed from the blood and phagocytosed by macrophages in the spleen, liver, and bone marrow.

Function of Platelets

The main function of platelets is to promote blood clotting. When the wall and the endothelium of the blood vessel are damaged, platelets aggregate at the site and adhere to the damaged wall. The platelets are activated and form a plug to occlude the site of damage. The platelets in the plug release adhesive glycoproteins that increase the plug size, which is then reinforced by a polymer fibrin formed from numerous plasma proteins. Fibrin forms a mesh around the plug, trapping other platelets and blood cells to form a blood clot. After blood clot formation and cessation of bleeding, the aggregated platelets contribute to clot retraction, which is later removed through enzymatic action.

Function of Leukocytes

Neutrophils have a short life span. They circulate in blood for about 10 hours and then enter the connective tissue, where they survive for another 2 or 3 days. Neutrophils are active phagocytes. They are attracted by chemotactic factors.
(chemicals) released by damaged or dead cells, tissues, or microorganisms, especially bacterial, which they phagocytose (ingest) and quickly destroy with their lysosomal enzymes.

Eosinophils also have a short life span. They remain in blood for up to 10 hours and then migrate into the connective tissue, where they remain for up to 10 days. Eosinophils are also phagocytic cells with a particular affinity for antigen-antibody complexes that are formed in the tissues in allergic conditions. The cells also release chemicals that neutralize histamine and other mediators related to inflammatory allergic reactions. Eosinophils also increase in number during parasitic infestation and defend the organism against helminthic parasites by destroying them.

Lymphocytes have a variable life span, from days to months, and show size variability. The difference between small and large lymphocytes has a functional significance. Large lymphocytes represent the cells that were activated by specific antigens. Lymphocytes are essential for immunologic defense of the organism. Some lymphocytes (B lymphocytes), when stimulated by specific antigens, differentiate into plasma cells in the connective tissue and produce antibodies to counteract or destroy the invading organisms.

Monocytes can live in the blood for 2 to 3 days, after which they move into the connective tissue, where they may remain for a few months or longer. Blood monocytes are precursors of the mononuclear phagocyte system. After entering the connective tissue, monocytes become powerful phagocytes. At the site of infection, monocytes differentiate into tissue macrophages and then destroy bacteria, foreign matter, and cellular debris.

Basophils have a short life span and their function is similar to that of mast cells. Their granules contain histamine and heparin. Exposure to allergens results in release of histamine and other chemicals that mediate and intensify inflammatory responses. These reactions cause severe allergic reactions, vascular changes that lead to increased fluid leakage from blood vessels, and hypersensitivity responses and anaphylaxis.
OVERVIEW FIGURE * Differentiation of myeloid and lymphoid stem cells into their mature forms and their distribution in the blood and connective tissue. (Important figure)