Blood

Blood (about 5.5 L in a man) consists of the cells and fluid that flow in a regular unidirectional movement within the closed circulatory system. Blood is made up of two parts:***blood cells***, *and* ***plasma***. The ***blood cells***are **erythrocytes** (red blood cells), **platelets,** and **leukocytes** (white blood cells).

Blood that is collected and kept from coagulating by the addition of anticoagulants (eg, heparin, citrate) separates, when centrifuged, into layers that reflect its heterogeneity. The **hematocrit** is an estimate of the volume of packed erythrocytes per unit volume of blood. The normal value is 40–50% in men and 35–45% in women.

The translucent, yellowish, somewhat viscous supernatant obtained when whole blood is centrifuged is the **plasma**. The formed elements of the blood separate into two easily distinguishable layers. The lower layer represents 42–47% of the entire volume of blood in the hematocrit tube. It is red and is made up of erythrocytes. The layer immediately above (1% of the blood volume), which is white or grayish in color, is called the **buffy coat** and consists of leukocytes. These elements separate because the leukocytes are less dense than the erythrocytes. Covering the leukocytes is a fine layer of platelets not distinguishable by the naked eye.

Leukocytes, which have diversified functions, are one of the body's chief defenses against infection. They circulate throughout the body via the blood vascular system, but while suspended in the blood they are round and inactive. Crossing the wall of venules and capillaries, these cells penetrate the tissues, where they display their defensive capabilities. The blood is a distributing vehicle, transporting oxygen, carbon dioxide (CO_2), metabolites, and hormones, among other substances. O_2 is bound mainly to the hemoglobin of the erythrocytes, whereas CO_2, in addition to being bound to the proteins of the erythrocytes (mainly hemoglobin), is carried in solution in the plasma as CO_2 or HCO_3^-.

The plasma transports nutrients from their site of absorption or synthesis, distributing them to various areas of the organism. It also transports metabolic residues, which are removed from the blood by the excretory organs. Blood, as the distributing vehicle for the hormones, permits the exchange of chemical messages between distant organs for normal cellular function. It further participates in the regulation of body temperature and in acid–base and osmotic balance.

Composition of Plasma

Plasma is an aqueous solution containing substances of low or high molecular weight that make up 10% of its volume. The plasma proteins account for 7% of the volume and the inorganic salts for 0.9%; the remainder of the 10% consists of several organic compounds ,eg, amino acids, vitamins, hormones, lipoproteins of various origins.

The composition of plasma is usually an indicator of the mean composition of the extracellular fluids in general.

The main plasma proteins are **albumin** and **globulins; lipoproteins,** and proteins that participate in blood coagulation, such as **prothrombin** and **fibrinogen.** Albumin, the most abundant component, has a fundamental role in maintaining the osmotic pressure of the blood.

Products and Functions of the Blood Cells.		
Cell Type	***Main Products***	***Main Functions***
Erythrocyte	Hemoglobin	CO_2 and O_2 transport
Leukocytes	Specific granules and modified lysosomes(azurophilic granules)	Phagocytosis of bacteria
Neutrophil (terminal cell)		
Eosinophil (terminal cell)	Specific granules, pharmacologically active substances	Defense against parasitic helminths; modulation of inflammatory processes
Basophil (terminal cell)	Specific granules containing histamine and heparin	Release of histamine and other inflammation mediators
Monocyte (not terminal cell)	Granules with lysosomal enzymes	Generation of mononuclear-phagocyte system cells in tissues; phagocytosis and digestion of protozoa and virus and senescent cells
B lymphocyte	Immunoglobulins	Generation of antibody-producing terminal cells (plasma cells)
T lymphocyte	Substances that kill cells. Substances that control the activity of other leukocytes (interleukins)	Killing of virus-infected cells
Natural killer cell (lacks T and B cell markers)	Attacks virus-infected cells and cancer cells without previous stimulation	Killing of some tumor and virus-infected cells
Platelet	Blood-clotting factors	Clotting of blood

Staining of Blood Cells

Blood cells are generally studied in ***smears or films*** prepared by spreading a drop of blood in a thin layer on a microscope slide. The blood should be evenly distributed over the slide and allowed to dry rapidly in air. In such films the cells are clearly visible and distinct from one another. Their cytoplasm is spread out, facilitating observation of their nuclei and cytoplasmic organization.

Blood smears are routinely stained with special mixtures of red (acidic) and blue (basic) dyes. These mixtures also contain **azures,** dyes that are useful in staining some structures of blood cells known as **azurophilics** (azure + Gr. *philein,* to love). Some of these special mixtures ***(eg, Giemsa, Wright's, Leishman's)*** are named for the investigators who introduced their own modifications into the original mixture.

Erythrocytes

Erythrocytes (red blood cells), which are anucleate, are packed with the O_2-carrying protein hemoglobin. Under normal conditions, these corpuscles never leave the circulatory system.

Most mammalian erythrocytes are biconcave disks without nuclei. When suspended in an isotonic medium, human erythrocytes are 7.5 mμ in diameter, 2.6 mμ thick at the rim, and 0.8 mμ thick in the center. *The biconcave shape provides erythrocytes with a large surface-to-volume ratio, thus facilitating gas exchange.*

The normal concentration of erythrocytes in blood is approximately 3.9–5.5 million per microliter in women and 4.1–6 million per microliter in men.

Leukocytes

Leukocytes (white blood cells) migrate to the tissues, where they perform multiple functions and most die by apoptosis. According to the type of granules in their cytoplasm and the shape of their nuclei, leukocytes are divided into two groups: **granulocytes** (polymorphonuclear leukocytes) and **agranulocytes** (mononuclear leukocytes). Both granulocytes and agranulocytes are spherical while suspended in blood plasma, but some become ameboid after leaving the blood vessels and invading the tissues. Their estimated sizes mentioned below refer to blood smears, in which the cells are spread and appear larger than they actually are in the blood.

Granulocytes possess two types of granules: 1-the **specific** granules that bind neutral, basic, or acidic components of the dye mixture and have specific functions and 2-the **azurophilic granules.**Azurophilic granules stain purple and are lysosomes. Granulocytes have nuclei with two or more lobes and include the **neutrophils, eosinophils,** and **basophils**. All granulocytes are nondividing terminal cells with a life span of a few days, dying by apoptosis in the connective tissue. The resulting cellular debris is removed by macrophages and does not elicit an inflammatory response. Being nondividing terminal cells, granulocytes do not synthesize much protein. Their Golgi complex and rough endoplasmic reticulum are poorly developed. They have few mitochondria (low energy metabolism) and depend more on glycolysis; they contain glycogen and can function in regions scarce in oxygen, such as inflamed areas.

Agranulocytes do not have specific granules, but they do contain azurophilic granules (lysosomes) that bind the azure dyes of the stain. The nucleus is round or indented. This group includes **lymphocytes** and **monocytes**.

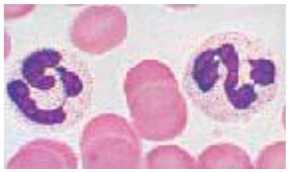
Number and Percentage of Blood Corpuscles (Blood Count).		
Corpuscle Type	**Approximate Number per μL[a]**	**Approximate Percentage**
Erythrocyte	Female: 3.9–5.5 x 10^6/μL	
	Male: 4.1–6 x 10^6/μL	
Reticulocyte		1% of the erythrocyte count
Leukocyte	6000–10,000	
Neutrophil	5000	60–70%
Eosinophil	150	2–4%
Basophil	30	0.5%
Lymphocyte	2400	28%
Monocyte	350	5%
Platelet	300,000	

Leukocytes are involved in the cellular and humoral defense of the organism against foreign material. In suspension in the circulating blood, they are spherical, nonmotile cells, but they are capable of becoming flattened and motile on encountering a solid substrate. Leukocytes leave the venules and capillaries by passing between endothelial cells and penetrating the connective tissue by **diapedesis**, a process that accounts for the unidirectional flow of granulocytes and monocytes from the blood to the tissues. Diapedesis is increased in individuals infected by microorganisms. Inflamed areas release chemicals originating mainly from cells and microorganisms, which increase diapedesis. The attraction of specific cells by chemical mediators is called **chemotaxis,** a significant event in inflammation through which leukocytes rapidly concentrate in places where their defensive properties are needed.

The number of leukocytes in the blood varies according to age, sex, and physiological conditions. In normal adults, there are roughly 6000–10,000 leukocytes per microliter of blood.

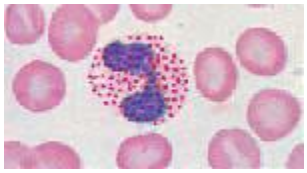
Neutrophils (Polymorphonuclear Leukocytes)

Neutrophils constitute 60–70% of circulating leukocytes. They are 12–15 mμ in diameter (in blood smears), with a nucleus consisting of two to five (usually three) lobes linked by fine threads of chromatin.



Eosinophils

Eosinophils are far less numerous than neutrophils, constituting only 2–4% of leukocytes in normal blood. In blood smears, this cell is about the same size as a neutrophil and contains a characteristic bilobednucleus. The main identifying characteristic is the presence of many large and elongated refractile specific granules (about 200 per cell) that are stained by eosin.It contains a protein—called the **major basic protein**—with a large number of arginine residues. This protein constitutes 50% of the total granule protein and accounts for the eosinophilia of these granules. *The major basic protein also seems to function in the killing of parasitic worms such as schistosomes.*

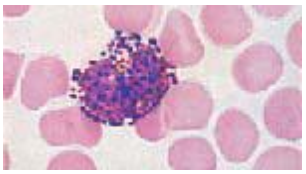


Basophils

Basophils make up less than 1% of blood leukocytes and are therefore difficult to find in smears of normal blood. They are about 12–15 mμ in diameter. The nucleus is divided into irregular lobes, but the overlying specific granules usually obscure the division.

The specific granules (0.5 mμ in diameter) stain metachromatically (change the color of the stain used) with the basic dye of the usual blood stains. This metachromasia is due to the presence of heparin. Specific granules in basophils are fewer and more irregular in size and shape than the granules of the other granulocytes. Basophilic specific granules contain heparin and histamine. Basophils may supplement the functions of mast cells in immediate hypersensitivity reactions by migrating into connective tissues.

There is some similarity between granules of basophils and those of mast cells. Both are metachromatic and contain heparin and histamine. Despite the similarities they present, mast cells and basophils are not the same, for even in the same species they have different structures, and they originate from different stem cells in the bone marrow.



Lymphocytes

Lymphocytes constitute a family of spherical cells with similar morphological characteristics. They can be classified into several groups according to distinctive surface molecules (markers), which can be distinguished by immunocytochemical methods. They also have diverse functional roles, all related to immune reactions in defending against invading microorganisms, foreign macromolecules, and cancer cells.

Lymphocytes with diameters of 6–8 mμ are known as **small lymphocytes.** A small number of **medium-sized lymphocytes** and **large lymphocytes** with diameters up to 18 mμ are present in the circulating blood. This difference has functional significance in that some larger lymphocytes are believed to be cells activated by specific antigens. The small lymphocyte, which is predominant in the blood, has a spherical nucleus, sometimes with an indentation. Its chromatin is condensed and appears as coarse clumps, so that the nucleus is intensely stained in the usual preparations, a characteristic that facilitates identification of the lymphocyte. In blood smears, the nucleolus of the lymphocyte is not visible, but it can be demonstrated by special staining techniques and with the electron microscope. The cytoplasm of the small lymphocyte is scanty, and in blood smears it appears as a thin rim around the nucleus. It is slightly basophilic, assuming a light blue color in stained smears. It may contain a few azurophilic granules. The cytoplasm of the small lymphocyte has a few mitochondria and a small Golgi complex; it contains free polyribosomes.

Lymphocytes vary in life span; some live only a few days, and others survive in the circulating blood for

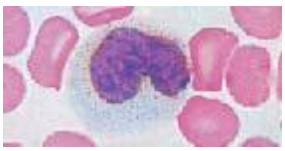
many years. Lymphocytes are the only type of leukocytes that return from the tissues back to the blood, after diapedesis.

Monocytes

Monocytes are bone marrow-derived agranulocytes with diameters varying from 12 to 20 mμ. The nucleus is oval, horseshoe, or kidney shaped and is generally eccentrically placed. The chromatin is less condensed than that in lymphocytes. Because of their delicate chromatin distribution, the nuclei of monocytes stain lighter than do those of large lymphocytes.

The cytoplasm of the monocyte is basophilic and frequently contains very fine azurophilic granules (lysosomes), some of which are at the limit of the light microscope's resolution. These granules are distributed through the cytoplasm, giving it a bluish-gray color in stained smears. In the electron microscope, one or two nucleoli are seen in the nucleus, and a small quantity of rough endoplasmic reticulum, polyribosomes, and many small mitochondria is observed. A Golgi complex involved in the formation of the lysosomal granules is present in the cytoplasm. Many microvilli and pinocytotic vesicles are found at the cell surface.

Blood monocytes are not terminal cells; rather, they are precursor cells of the mononuclear phagocyte system. After crossing venule or capillary walls and entering connective tissues, monocytes differentiate into macrophages.



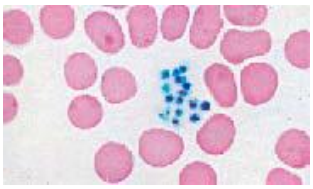
Platelets

Blood platelets (**thrombocytes**) are nonnucleated, disklike cell fragments 2–4 mμ in diameter. Platelets originate from the fragmentation of giant polyploid**megakaryocytes** that reside in the bone marrow. Platelets promote blood clotting and help repair gaps in the walls of blood vessels, preventing loss of blood. Normal platelet counts range from 200,000 to 400,000 per microliter of blood. Platelets have a life span of about 10 days.

In stained blood smears, platelets often appear in clumps. Each platelet has a peripheral light blue-stained transparent zone, the **hyalomere,** and a central zone containing purple granules, called the

granulomere.

Platelets contain a system of channels, the **open canalicularsystem,** that connects to invaginations of the platelet plasma membrane. This arrangement is probably of functional significance in facilitating the liberation of active molecules stored in platelets. Around the periphery of the platelet lies a **marginal bundle** of microtubules; this bundle helps to maintain the platelet's ovoid shape. In the hyalomere, there are also a number of electron-dense irregular tubes known as the **dense tubular system.** Actin and myosin molecules in the hyalomere can assemble to form a contractile system that functions in platelet movement and aggregation. A cell coat rich in glycosaminoglycans and glycoproteins, 15–20 nm thick, lies outside the plasmalemma and is involved in platelet adhesion.The central granulomere possesses a variety of membrane-bound granules and a sparse population of mitochondria and glycogen particles.



Platelet Functions

The role of platelets in controlling hemorrhage can be summarized as follows.

1-Primary aggregation—Discontinuities in the endothelium, produced by injuries, are followed by platelet aggregation to the exposed collagen, via collagen-binding protein in platelet membrane. Thus, a **platelet plug** is formed as a first step to stop bleeding.
2-Secondary aggregation—Platelets in the plug release an adhesive glycoprotein and ADP. Both are potent inducers of platelet aggregation, increasing the size of the platelet plug.
3-Blood coagulation—During platelet aggregation, factors from the blood plasma, damaged blood vessels, **fibrin,** that forms a three-dimensional network of fibers trapping red cells, leukocytes, and platelets to form a **blood clot,** or **thrombus.**
4-Clot retraction—The clot that initially bulges into the blood vessel lumen contracts because of the interaction of platelet actin, myosin, and ATP.
5-Clot removal—Protected by the clot, the vessel wall is restored by new tissue formation. The clot is then removed, mainly by the proteolytic enzyme.

Hematopoiesis

Mature blood cells have a relatively short life span (Gr. *haima,* blood, + *poiesis,* a making) organs. In the earliest stages of embryogenesis, blood cells arise from the *yolk*

sac mesoderm. Sometime later, the *liver and spleen* serve as temporary hematopoietic tissues, but by the second month the clavicle has begun to ossify and begins to develop bone marrow in its core. As the prenatal ossification of the rest of the skeleton accelerates, the *bone marrow* becomes an increasingly important hematopoietic tissue.

At last 1/3 of intrauterine life, after birth and on into childhood, erythrocytes, granular leukocytes, monocytes, and platelets are derived from stem cells located in bone marrow. The origin and maturation of these cells are termed, respectively, erythropoiesis (Gr. *erythros,* red, + *poiesis*), granulopoiesis, monocytopoiesis, and megakaryocytopoiesis. The bone marrow also produces cells that migrate to the lymphoid organs, producing the various types of lymphocytes.

Before attaining maturity and being released into the circulation, blood cells go through specific stages of differentiation and maturation. Because these processes are continuous, cells with characteristics that lie between the various stages are frequently encountered in smears of blood or bone marrow.

Pluripotential Hematopoietic Stem Cells

It is believed that all blood cells arise from a single type of stem cell in the bone marrow. Because this cell can produce all blood cell types, it is called a *pluripotential stem cell*. These cells proliferate and form one cell lineage that will become *lymphocytes* (lymphoid cells) and another lineage that will form the *myeloid cells* that develop in bone marrow (granulocytes, monocytes, erythrocytes, and megakaryocytes). Early in their development, lymphoid cells migrate from the bone marrow to the thymus, lymph nodes, spleen, and other lymphoid structures, where they proliferate.

Progenitor & Precursor Cells

Hematopoiesis is therefore the result of simultaneous, continuous proliferation and differentiation of cells derived from stem cells whose potentiality is reduced as differentiation progresses. This process can be observed in both *in vivo* and *in vitro* studies, in which colonies of cells derived from stem cells with various potentialities appear. Colonies derived from a myeloid stem cell can produce erythrocytes, granulocytes, monocytes, and megakaryocytes, all in the same colony.

In these experiments, however, some colonies produce only red blood cells (erythrocytes). Other colonies produce granulocytes and monocytes. Cells forming colonies are called colony-forming cells (CFC) or colony-forming units (CFU). The convention in naming these various cell colonies is to use the initial letter of the cell each colony produces. Thus, MCFC denotes a monocyte-forming colony, ECFC forms erythrocytes, MGCFC forms monocytes and granulocytes, and so on.

Once the necessary environmental conditions are present, the development of blood cells depends on factors that affect cell proliferation and differentiation. These substances are called growth factors, colony-stimulating factors (CSF).

Under normal conditions, the production of blood cells by the bone marrow is adjusted to the body's needs, increasing its activity several-fold in a very short time. Bone marrow is found in the medullary canals of long bones and in the cavities of cancellous bones. Two types of bone marrow have been described based on their appearance on gross examination: *red, or hematogenous*, bone marrow, whose color is produced by the presence of blood and blood-forming cells; and *yellow bone marrow*, whose color is produced by the presence of a great number of adipose cells. In newborns, all bone marrow is red and is therefore active in the production of blood cells. As the child grows, most of the bone marrow changes gradually into the yellow variety. *Under certain conditions, such as severe bleeding or hypoxia, yellow bone marrow is replaced by red bone marrow.*

Red Bone Marrow

Red bone marrow is composed of a **1-*stroma*,2- *hematopoietic cords*, and 3-*sinusoidal capillaries*.** The stroma is a three-dimensional meshwork of reticular cells and a delicate web of reticular fibers containing hematopoietic cells and macrophages. The stroma of bone marrow contains collagen types I and III, fibronectin, laminin, and proteoglycans. The sinusoids are formed by a discontinuous layer of endothelial cells.

An external discontinuous layer of reticular cells and a loose net of reticular fibers reinforce the sinusoidal capillaries.

The main functions of red bone marrow are the production of blood cells, destruction of worn-out red blood cells, and storage (in macrophages) of iron derived from the breakdown of hemoglobin.

Maturation of Erythrocytes

A mature cell is one that has differentiated to the stage at which it has the capability of carrying out all its specific functions. The basic process in maturation is *the synthesis of hemoglobin* and *the formation of an enucleated*, biconcave, small corpuscle, the erythrocyte. During maturation of the erythrocyte, several major changes. Cell volume decreases, and the nucleoli diminish in size until they become invisible in the light microscope. The nuclear diameter decreases, and the chromatin becomes increasingly more dense until the nucleus presents a pyknotic appearance and is finally extruded from the cell. There is a gradual decrease in the number of polyribosomes (basophilia decreases), with a simultaneous increase in the amount of hemoglobin (an

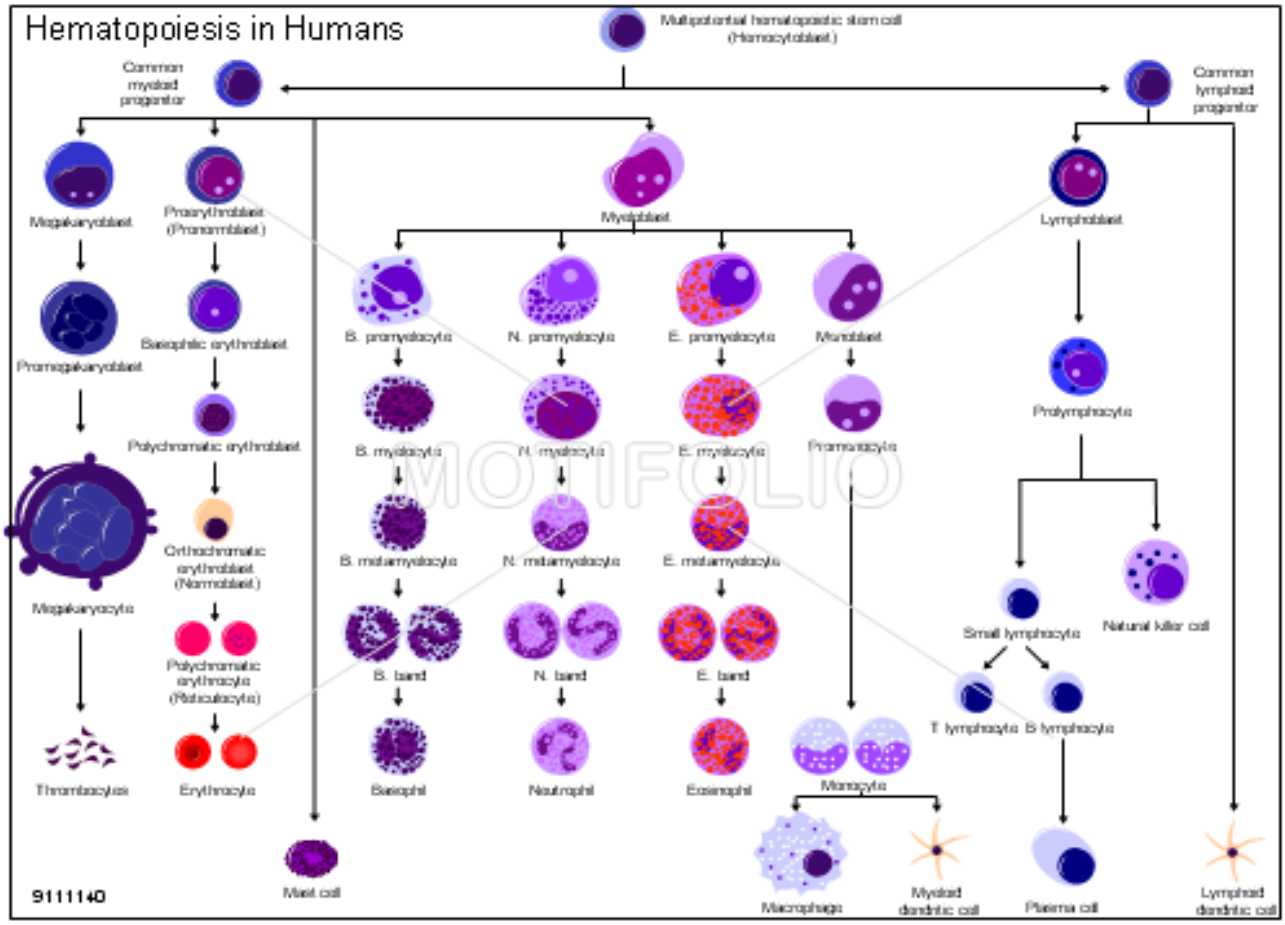
acidophilic protein) within the cytoplasm. Mitochondria and other organelles gradually disappear.

There are three to five intervening cell divisions between the proerythroblast and the mature erythrocyte. The development of an erythrocyte from the first recognizable cell of the series to the release of reticulocytes into the blood takes approximately 7 days. ***The hormone erythropoietin and substances such as iron, folic acid, and cyanocobalamin (vitamin B_{12}) are essential for the production of erythrocytes*.** Erythropoietin is a glycoprotein produced mainly in the kidneys that stimulates the production of mRNA for globin, the protein component of the hemoglobin molecule.

Differentiation

The differentiation and maturation of erythrocytes involve the formation (in order) of proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, orthochromatophilic erythroblasts (normoblasts), reticulocytes, and erythrocytes.

The first recognizable cell in the erythroid series is the *proerythroblast*. It is a large cell with loose, lacy chromatin and clearly visible nucleoli; its cytoplasm is basophilic. The next stage is represented by *the basophilic erythroblast*, with a strongly basophilic cytoplasm and a condensed nucleus that has no visible nucleolus. The basophilia of these two cell types is caused by the large number of polyribosomes involved in the synthesis of hemoglobin. During the next stage, polyribosomes decrease, and areas of the cytoplasm begin to be filled with hemoglobin. At this stage, staining causes several colors to appear in the cell *the polychromatophilic erythroblast*. In the next stage, the nucleus continues to condense and no cytoplasmic basophilia is evident, resulting in a uniformly acidophilic cytoplasm *the orthochromatophilic erythroblast*. At a given moment, this cell puts forth a series of cytoplasmic protrusions and expels its nucleus, encased in a thin layer of cytoplasm. The expelled nucleus is engulfed by macrophages. The remaining cell still has a small number of polyribosomes that, when treated with the dye brilliant cresyl blue, aggregate to form a stained network. This cell is *the reticulocyte*, which soon loses its polyribosomes and becomes a *mature erythrocyte.*



Granulopoiesis.

The maturation process of granulocytes takes place with cytoplasmic changes characterized by the synthesis of a number of proteins that are packed in two organelles: the azurophilic and specific granules. These proteins are produced in the rough endoplasmic reticulum and the Golgi complex in two successive stages. The first stage results in the production of the azurophilic granules, which stain with basic dyes in the Wright or Giemsa methods and contain enzymes of the lysosomal system. In the second stage, a change in synthetic activity takes place with the production of several proteins that are packed in the specific granules. These granules contain different proteins in each of the three types of granulocytes and are utilized for the various activities of each type of granulocyte. Evidently, a shift in gene expression occurs in this process, permitting neutrophils to specialize in bacterial destruction and eosinophils and basophils to become involved in the regulation of inflammation.

Maturation of Granulocytes

The *myeloblast* is the most immature recognizable cell in the myeloid series. It has a finely dispersed chromatin, and nucleoli can be seen. In the next stage, the *promyelocyte*(*pro,* before, + Gr. *myelos,* marrow, + *kytos,* cell) is characterized by its

basophilic cytoplasm and azurophilic granules. These granules contain lysosomal enzymes and myeloperoxidase. The promyelocyte gives rise to the three known types of granulocyte. The first sign of differentiation appears in the *myelocytes*, in which specific granules gradually increase in quantity and eventually occupy most of the cytoplasm. These *neutrophilic, basophilic, and eosinophilicmyelocytes* mature with further condensation of the nucleus and a considerable increase in their specific granule content. Before its complete maturation, the neutrophilic granulocyte passes through an intermediate stage in which its nucleus has the form of a curved rod (band cell). This cell appears in quantity in the blood after strong stimulation of hematopoiesis.

Maturation of Lymphocytes & Monocytes

Study of the precursor cells of lymphocytes and monocytes is difficult, because these cells do not contain specific cytoplasmic granules or nuclear lobulation, both of which facilitate the distinction between young and mature forms of granulocytes. Lymphocytes and monocytes are distinguished mainly on the basis of size, chromatin structure, and the presence of nucleoli in smear preparations. As lymphocyte cells mature, their chromatin becomes more compact, nucleoli become less visible, and the cells decrease in size. In addition, subsets of the lymphocyte series acquire distinctive cell-surface receptors during differentiation that can be detected by immunocytochemical techniques.

Lymphocytes

Circulating lymphocytes originate mainly in the thymus and the peripheral lymphoid organs (eg, spleen, lymph nodes, tonsils). However, all lymphocyte progenitor cells originate in the bone marrow. Some of these lymphocytes migrate to the thymus, where they acquire the full attributes of T lymphocytes. Subsequently, T lymphocytes populate specific regions of peripheral lymphoid organs.

Other bone marrow lymphocytes differentiate into B lymphocytes in the bone marrow and then migrate to peripheral lymphoid organs, where they inhabit and multiply in their own special compartments.

The first identifiable progenitor of lymphoid cells is the *lymphoblast*, a large cell capable of incorporating and dividing two or three times to form *prolymphocytes*. Prolymphocytes are smaller and have relatively more condensed chromatin but none of the cell-surface antigens that mark prolymphocytes as *T or B lymphocytes*. In the bone marrow and in the thymus, these cells synthesize cell-surface receptors characteristic of their lineage, but they are not recognizable as distinct B or T lymphocytes in routine histological procedures. Using immunocytochemical techniques makes the distinction.

Monocytes

The *monoblast* is a committed progenitor cell that is almost identical to the myeloblast in its morphological characteristics. Further differentiation leads to *the promonocyte*, a large cell (up to 18 mμ in diameter) with a basophilic cytoplasm and a large, slightly indented nucleus. The chromatin is lacy, and nucleoli are evident. Promonocytes divide twice in the course of their development into *monocytes*. A large amount of rough endoplasmic reticulum is present, as is an extensive Golgi complex in which granule condensation can be seen to be taking place. These granules are primary lysosomes, which are observed as fine azurophilic granules in blood monocytes. Mature monocytes enter the blood stream, circulate for about 8 h, and then enter the connective tissues, where they mature into macrophages and function for several months.

Origin of Platelets

In adults, platelets originate in the red bone marrow by fragmentation of the cytoplasm of mature megakaryocytes (Gr. megas, big, + karyon, nucleus, + kytos), which, in turn, arise by differentiation of megakaryoblasts.

*Megakaryoblasts :*The megakaryoblast is 15–50 μm in diameter and has a large ovoid or kidney-shaped nucleus with numerous nucleoli. The nucleus becomes highly polyploid (ie, it contains up to 30 times as much DNA as a normal cell) before platelets begin to form. The cytoplasm of this cell is homogeneous and intensely basophilic.

Megakaryocytes :The megakaryocyte is a giant cell (35–150μm in diameter) with an irregularly lobulated nucleus, coarse chromatin, and no visible nucleoli. The cytoplasm contains numerous mitochondria, a well-developed rough endoplasmic reticulum, and an extensive Golgi complex. Platelets have conspicuous granules, originating from the Golgi complex, that contain biologically active substances, such as platelet-derived growth factor, fibroblast growth factor, von Willebrand's factor (which promotes adhesion of platelets to endothelial cells), and platelet factor IV (which stimulates blood coagulation). With maturation of the megakaryocyte, numerous invaginations of the plasma membrane ramify throughout the cytoplasm, forming the demarcation membranes. This system defines areas of a megakaryocyte's cytoplasm that shed platelets, extruding them into the circulation.