White Blood Cells

Chapter 16

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INTRODUCTION

White blood cells (WBCs) or leukocytes are the colorless and nucleated formed elements of blood (leuko is derived from Greek word leukos = white). Alternate spelling for leukocytes is leucocytes.

Compared to RBCs, the WBCs are larger in size and lesser in number. Yet functionally, these cells are important like RBCs because of their role in defense mechanism of body and protect the body from invading organisms by acting like soldiers.

WBCs Vs RBCs

WBCs differ from RBCs in many aspects. The differences between WBCs and RBCs are given in Table 16.1.

1. Larger in size.
2. Irregular in shape.
3. Nucleated.
4. Many types.
5. Granules are present in some type of WBCs.
6. Lifespan is shorter.

CLASSIFICATION

Some of the WBCs have granules in the cytoplasm. Based on the presence or absence of granules in the cytoplasm, the leukocytes are classified into two groups:

1. Granulocytes which have granules.
2. Agranulocytes which do not have granules.

1. Granulocytes

Depending upon the staining property of granules, the granulocytes are classified into three types:

i. Neutrophils with granules taking both acidic and basic stains.
ii. Eosinophils with granules taking acidic stain.
iii. Basophils with granules taking basic stain.

2. Agranulocytes

Agranulocytes have plain cytoplasm without granules. Agranulocytes are of two types:

i. Monocytes.
ii. Lymphocytes.

MORPHOLOGY OF WHITE BLOOD CELLS

NEUTROPHILS

Neutrophils which are also known as polymorphs have fine or small granules in the cytoplasm. The granules take acidic and basic stains. When stained with **Leishman's stain** (which contains acidic eosin and basic methylene blue) the granules appear violet in color.

Nucleus is multilobed (Fig. 16.1). The number of lobes in the nucleus depends upon the age of cell. In younger cells, the nucleus is not lobed. And in older neutrophils, the nucleus has 2 to 5 lobes. The diameter

TABLE 16.1: Differences between WBCs and RBCs

Feature	WBCs	RBCs
Color	Colorless	Red
Number	Less: 4,000 to 11,000/cu mm	More: 4.5 to 5.5 million/cu mm
Size	Larger Maximum diameter = 18 μ	Smaller Maximum diameter = 7.4 μ
Shape	Irregular	Disk-shaped and biconcave
Nucleus	Present	Absent
Granules	Present in some types	Absent
Types	Many types	Only one type
Lifespan	Shorter ½ to 15 days	Longer 120 days

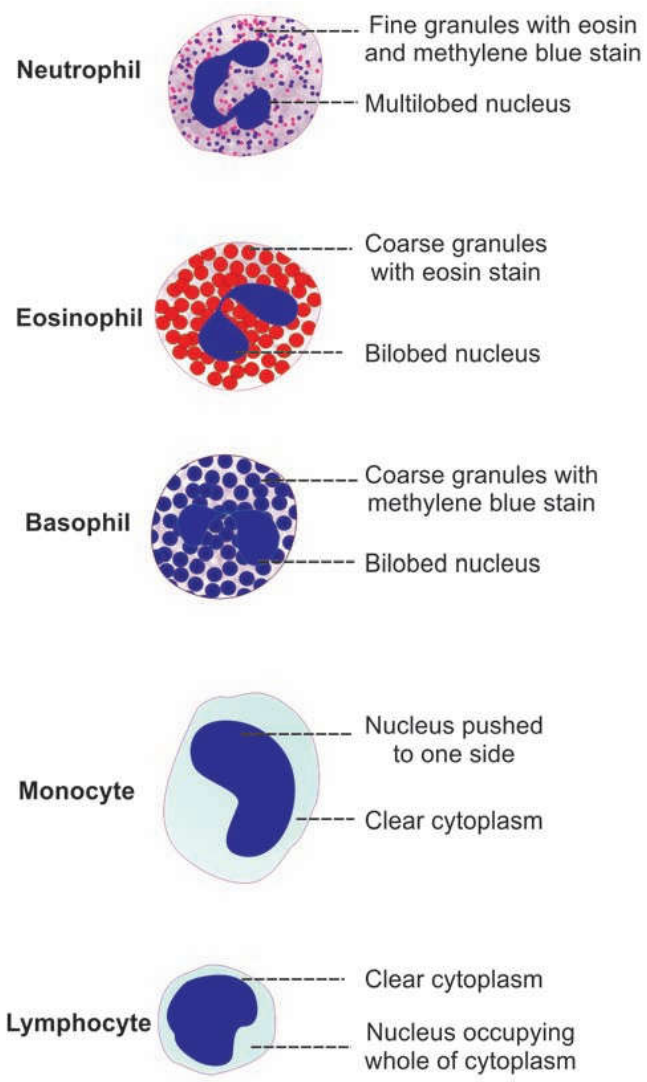

FIGURE 16.1: Different white blood cells

of cell is 10 to 12 μ (Table 16.2). The neutrophils are ameboid in nature.

■ EOSINOPHILS

Eosinophils have coarse (larger) granules in the cytoplasm, which stain pink or red with eosin. Nucleus is bilobed and spectacle-shaped. Diameter of the cell varies between 10 and 14 μ.

■ BASOPHILS

Basophils also have coarse granules in the cytoplasm. The granules stain purple blue with methylene blue. Nucleus is bilobed. Diameter of the cell is 8 to 10 μ.

■ MONOCYTES

Monocytes are the largest leukocytes with diameter of 14 to 18 μ. The cytoplasm is clear without granules. Nucleus is round, oval and horseshoe shaped, bean shaped or kidney shaped. Nucleus is placed either in the center of the cell or pushed to one side and a large amount of cytoplasm is seen.

■ LYMPHOCYTES

Like monocytes, the lymphocytes also do not have granules in the cytoplasm. Nucleus is oval, bean-shaped or kidney-shaped. Nucleus occupies the whole of the cytoplasm. A rim of cytoplasm may or may not be seen.

Types of Lymphocytes

Depending upon the size, lymphocytes are divided into two groups:

1. *Large lymphocytes:* Younger cells with a diameter of 10 to 12 μ.
2. *Small lymphocytes:* Older cells with a diameter of 7 to 10 μ.

Depending upon the function, lymphocytes are divided into two types:

1. *T lymphocytes:* Cells concerned with cellular immunity.
2. *B lymphocytes:* Cells concerned with humoral immunity.

TABLE 16.2: Diameter and lifespan of WBCs

WBC	Diameter (μ)	Lifespan (days)
Neutrophils	10 to 12	2 to 5
Eosinophils	10 to 14	7 to 12
Basophils	8 to 10	12 to 15
Monocytes	14 to 18	2 to 5
Lymphocytes	7 to 12	½ to 1

NORMAL WHITE BLOOD CELL COUNT

1. Total WBC count (TC): 4,000 to 11,000/cu mm of blood.
2. Differential WBC count (DC): Given in Table 16.3.

VARIATIONS IN WHITE BLOOD CELL COUNT

Leukocytosis

Leukocytosis is the increase in total WBC count. Leukocytosis occurs in both physiological and pathological conditions.

Leukopenia

Leukopenia is the decrease in total WBC count. The term leukopenia is generally used for pathological conditions only.

Granulocytosis

Granulocytosis is the abnormal increase in the number of granulocytes.

Granulocytopenia

Granulocytopenia is the abnormal reduction in the number of granulocytes.

Agranulocytosis

Agranulocytosis is the acute pathological condition characterized by absolute lack of granulocytes.

PHYSIOLOGICAL VARIATIONS

1. *Age:* WBC count is about 20,000 per cu mm in infants and about 10,000 to 15,000 per cu mm of blood in children. In adults, it ranges between 4,000 and 11,000 per cu mm of blood.
2. *Sex:* Slightly more in males than in females.
3. *Diurnal variation:* Minimum in early morning and maximum in the afternoon.
4. *Exercise:* Increases slightly.
5. *Sleep:* Decreases.
6. *Emotional conditions like anxiety:* Increases.
7. *Pregnancy:* Increases.
8. *Menstruation:* Increases.
9. *Parturition:* Increases.

TABLE 16.3: Normal values of different WBCs

WBC	Percentage	Absolute value per cu mm
Neutrophils	50 to 70	3,000 to 6,000
Eosinophils	2 to 4	150 to 450
Basophils	0 to 1	0 to 100
Monocytes	2 to 6	200 to 600
Lymphocytes	20 to 30	1,500 to 2,700

PATHOLOGICAL VARIATIONS

All types of leukocytes do not share equally in the increase or decrease of total leukocyte count. In general, the neutrophils and lymphocytes vary in opposite directions.

Leukocytosis

Leukocytosis is the increase in total leukocyte (WBC) count. It occurs in conditions such as:

1. Infections
2. Allergy
3. Common cold
4. Tuberculosis
5. Glandular fever.

Leukemia

Leukemia is the condition which is characterized by abnormal and uncontrolled increase in leukocyte count more than 1,000,000/cu mm. It is also called blood cancer.

Leukopenia

Leukopenia is the decrease in the total WBC count. It occurs in the following pathological conditions:

1. Anaphylactic shock
2. Cirrhosis of liver
3. Disorders of spleen
4. Pernicious anemia
5. Typhoid and paratyphoid
6. Viral infections.

Variation in Differential Leukocyte Count

Differential leukocyte count varies in specific diseases. Details are given in Table 16.4.

Neutrophilia

Neutrophilia or neutrophilic leukocytosis is the increase in neutrophil count. It occurs in the following conditions:

1. Acute infections
2. Metabolic disorders
3. Injection of foreign proteins

4. Injection of vaccines
5. Poisoning by chemicals and drugs like lead, mercury, camphor, benzene derivatives, etc.
6. Poisoning by insect venom
7. After acute hemorrhage.

Eosinophilia

Eosinophilia is the increase in eosinophil count and it occurs in:

1. Asthma and other allergic conditions
2. Blood parasitism (malaria, filariasis)

TABLE 16.4: Pathological variations in different types of WBCs

Disorder	Variation	Conditions
Neutrophilia or neutrophilic leukocytosis	Increase in neutrophil count	1. Acute infections 2. Metabolic disorders 3. Injection of foreign proteins 4. Injection of vaccines 5. Poisoning by chemicals and drugs like lead, mercury, camphor, benzene derivatives, etc. 6. Poisoning by insect venom 7. After acute hemorrhage
Neutropenia	Decrease in neutrophil count	1. Bone marrow disorders 2. Tuberculosis 3. Typhoid 4. Autoimmune diseases
Eosinophilia	Increase in eosinophil count	1. Allergic conditions like asthma 2. Blood parasitism (malaria, filariasis) 3. Intestinal parasitism 4. Scarlet fever
Eosinopenia	Decrease in eosinophil count	1. Cushing's syndrome 2. Bacterial infections 3. Stress 4. Prolonged administration of drugs like steroids, ACTH and epinephrine
Basophilia	Increase in basophil count	1. Smallpox 2. Chickenpox 3. Polycythemia vera
Basopenia	Decrease in basophil count	1. Urticaria (skin disorder) 2. Stress 3. Prolonged exposure to chemotherapy or radiation therapy
Monocytosis	Increase in monocyte count	1. Tuberculosis 2. Syphilis 3. Malaria 4. Kala-azar
Monocytopenia	Decrease in monocyte count	Prolonged use of prednisone (immunosuppressant steroid)
Lymphocytosis	Increase in lymphocyte count	1. Diphtheria 2. Infectious hepatitis 3. Mumps 4. Malnutrition 5. Rickets 6. Syphilis 7. Thyrotoxicosis 8. Tuberculosis
Lymphocytopenia	Decrease in lymphocyte count	1. AIDS 2. Hodgkin's disease (cancer of lymphatic system) 3. Malnutrition 4. Radiation therapy 5. Steroid administration

3. Intestinal parasitism
4. Scarlet fever.

Basophilia

Basophilia is the increase in basophil count and it occurs in:

1. Smallpox
2. Chickenpox
3. Polycythemia vera.

Monocytosis

Monocytosis is the increase in monocyte count and it occurs in:

1. Tuberculosis
2. Syphilis
3. Malaria
4. Kala-azar
5. Glandular fever.

Lymphocytosis

Lymphocytosis is the increase in lymphocyte count and it occurs in:

1. Diphtheria
2. Infectious hepatitis
3. Mumps
4. Malnutrition
5. Rickets
6. Syphilis
7. Thyrotoxicosis
8. Tuberculosis.

Neutropenia

Neutropenia is the decrease in neutrophil count. It occurs in:

1. Bone marrow disorders
2. Tuberculosis
3. Typhoid
4. Vitamin deficiencies
5. Autoimmune diseases.

Eosinopenia

Decrease in eosinophil count is called eosinopenia. It occurs in:

1. Cushing's syndrome
2. Bacterial infections
3. Stress
4. Prolonged administration of drugs such as steroids, ACTH, epinephrine.

Basopenia

Basopenia or basophilic leukopenia is the decrease in basophil count. It occurs in:

1. Urticaria (skin disorder)
2. Stress
3. Prolonged exposure to chemotherapy or radiation therapy.

Monocytopenia

Monocytopenia is the decrease in monocyte count. It occurs in:

1. Prolonged use of prednisone (immunosuppressant steroid)
2. AIDS
3. Chronic lymphoid leukemia.

Lymphocytopenia

Lymphocytopenia is the decrease in lymphocytes. It occurs in:

1. AIDS
2. Hodgkin's disease (cancer of the lymphatic system)
3. Malnutrition
4. Radiation therapy
5. Steroid administration.

LIFESPAN OF WHITE BLOOD CELLS

Lifespan of WBCs is not constant. It depends upon the demand in the body and their function. Lifespan of these cells may be as short as half a day or it may be as long as 3 to 6 months. Lifespan of WBCs is given in Table 16.2.

PROPERTIES OF WHITE BLOOD CELLS

1. *Diapedesis*

Diapedesis is the process by which the leukocytes squeeze through the narrow blood vessels.

2. *Ameboid Movement*

Neutrophils, monocytes and lymphocytes show amebic movement, characterized by protrusion of the cytoplasm and change in the shape.

3. *Chemotaxis*

Chemotaxis is the attraction of WBCs towards the injured tissues by the chemical substances released at the site of injury.

4. Phagocytosis

Neutrophils and monocytes engulf the foreign bodies by means of phagocytosis (Chapter 3).

FUNCTIONS OF WHITE BLOOD CELLS

Generally, WBCs play an important role in defense mechanism. These cells protect the body from invading organisms or foreign bodies, either by destroying or inactivating them. However, in defense mechanism, each type of WBCs acts in a different way.

NEUTROPHILS

Neutrophils play an important role in the defense mechanism of the body. Along with monocytes, the neutrophils provide the first line of defense against the invading microorganisms. The neutrophils are the free cells in the body and wander freely through the tissue and practically, no part of the body is spared by these leukocytes.

Substances Present in Granules and Cytoplasm of Neutrophils

Granules of neutrophils contain enzymes like proteases, myeloperoxidases, elastases and metalloproteinases (Table 16.5). These enzymes destroy the microorganisms. The granules also contain antibody like peptides called **cathelicidins** and **defensins,** which are antimicrobial peptides and are active against bacteria and fungi.

Membrane of neutrophils contains an enzyme called **NADPH oxidase** (dihydronicotinamide adenine dinucleotide phosphate oxidase). It is activated by the toxic metabolites released from infected tissues. The activated NADPH oxidase is responsible for bactericidal action of neutrophils (see below).

All these substances present in the granules and cell membrane make the neutrophil a powerful and effective killer machine.

Neutrophils also secrete **platelet-activating factor (PAF),** which is a cytokine. It accelerates the aggregation of platelets during injury to the blood vessel, resulting in prevention of excess loss of blood.

Mechanism of Action of Neutrophils

Neutrophils are released in large number at the site of infection from the blood. At the same time, new neutrophils are produced from the progenitor cells. All the neutrophils move by diapedesis towards the site of infection due to chemotaxis.

Chemotaxis occurs due to the attraction by some chemical substances called **chemoattractants,** which are released from the infected area. After reaching the area, the neutrophils surround the area and get adhered to the infected tissues. Chemoattractants increase the adhesive nature of neutrophils so that all the neutrophils become sticky and get attached firmly to the infected area. Each neutrophil can hold about 15 to 20 microorganisms at a time. Now, the neutrophils start destroying the invaders. First, these cells engulf the bacteria and then destroy them by means of phagocytosis (Chapter 3).

Respiratory Burst

Respiratory burst is a rapid increase in oxygen consumption during the process of phagocytosis by neutrophils and other phagocytic cells. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is responsible for this phenomenon. During respiratory burst, the free radical O_2^- is formed. $2O_2^-$ combine with $2H^+$ to form H_2O_2 (hydrogen peroxide). Both O_2^- and H_2O_2 are the oxidants having potent bactericidal action.

Pus and Pus Cells

Pus is the whitish yellow fluid formed in the infected tissue by the dead WBCs, bacteria or foreign bodies and cellular debris. It consists of white blood cells, bacteria or other foreign bodies and cellular debris. The dead WBCs are called pus cells.

During the battle against the bacteria, many WBCs are killed by the toxins released from the bacteria. The dead cells are collected in the center of infected area. The dead cells together with plasma leaked from the blood vessel, liquefied tissue cells and RBCs escaped from damaged blood vessel (capillaries) constitute the pus.

EOSINOPHILS

Eosinophils play an important role in the defense mechanism of the body against the parasites. During parasitic infections, there is a production of a large number of eosinophils which move towards the tissues affected by parasites. Eosinophil count increases also during allergic diseases like asthma.

Eosinophils are responsible for detoxification, disintegration and removal of foreign proteins.

Mechanism of Action of Eosinophils

Eosinophils are neither markedly motile nor phagocytic like the neutrophils. Some of the parasites are larger in size. Still eosinophils attack them by some special type of cytotoxic substances present in their granules. When

TABLE 16.5: Substances secreted by WBCs

WBC	Substance secreted	Action
Neutrophil	Proteases	Destruction of microorganisms
	Myeloperoxidases	
	Elastases	
	Metalloproteinases	
	Defensins	Antimicrobial action Anti-inflammatory action Wound healing Chemotaxis
	Cathelicidins	Antimicrobial action
	NADPH oxidase	Bactericidal action
	Platelet-activating factor	Aggregation of platelets
Eosinophil	Eosinophil peroxidase	Destruction of worms, bacteria and tumor cells
	Major basic protein	Destruction of worms
	Eosinophil cationic protein	Destruction of worms Neurotoxic action
	Eosinophil-derived neurotoxin	Neurotoxic action
	Interleukin-4 and 5	Acceleration of inflammatory response Destruction of invading organisms
Basophil	Heparin	Prevention of intravascular blood clotting
	Histamine	Production of acute hypersensitivity reactions
	Bradykinin	
	Serotonin	
	Proteases	Destruction of microorganisms
	Myeloperoxidases	
	Interleukin-4	Acceleration of inflammatory response Destruction of invading organisms
Monocyte	Interleukin-1	Acceleration of inflammatory response Destruction of invading organisms
	Colony stimulation factor	Formation of colony forming blastocytes
	Platelet-activating factor	Aggregation of platelets
	Chemokines	Chemotaxis
T lymphocytes	Interleukin-2, 4 and 5	Acceleration of inflammatory response Destruction of invading organisms Activation of T cells
	Gamma interferon	Stimulation of phagocytic actions of cytotoxic cells, macrophages and natural killer cells
	Lysosomal enzymes	Destruction of invading organisms
	Tumor necrosis factor	Necrosis of tumor Activation of immune system Promotion of inflammation
	Chemokines	Chemotaxis

Contd...

B lymphocytes	Immunoglobulins	Destruction of invading organisms
	Tumor necrosis factor	Necrosis of tumor Activation of immune system Acceleration of inflammatory response
	Chemokines	Chemotaxis

released over the invading parasites from the granules, these substances become lethal and destroy the parasites. The lethal substances present in the granules of eosinophils and released at the time of exposure to parasites or foreign proteins are:

1. *Eosinophil peroxidase*: This enzyme is capable of destroying helminths (parasitic worms), bacteria and tumor cells.
2. *Major basic protein (MBP):* It is very active against helminths. It destroys the parasitic worms by causing distension (ballooning) and detachment of the tegumental sheath (skin-like covering) of these organisms.
3. *Eosinophil cationic protein (ECP):* This substance is the major destroyer of helminths and it is about 10 times more toxic than MBP. It destroys the parasites by means of complete disintegration. It is also a neurotoxin.
4. *Eosinophil-derived neurotoxin:* It destroys the nerve fibers particularly, the myelinated nerve fibers.
5. *Cytokines:* Cytokines such as interleukin-4 and interleukin-5 accelerate inflammatory responses by activating eosinophils. These cytokines also kill the invading organisms.

■ BASOPHILS

Basophils play an important role in healing processes. So their number increases during healing process.

Basophils also play an important role in allergy or acute hypersensitivity reactions (allergy). This is because of the presence of receptors for IgE in basophil membrane.

Mechanism of Action of Basophils

Functions of basophils are executed by the release of some important substances from their granules such as:

1. *Heparin:* Heparin is essential to prevent the intravascular blood clotting.
2. *Histamine, slow-reacting substances of anaphylaxis, bradykinin and serotonin:* Theses substances produce the acute hypersensitivity reactions by causing vascular and tissue responses.
3. *Proteases and myeloperoxidase:* These enzymes destroy the microorganisms.
4. *Cytokine:* Cytokine such as interleukin-4 accelerates inflammatory responses and kill the invading organisms.

Mast Cell

Mast cell is a large tissue cell resembling the basophil. Generally, mast cells are found along with the blood vessels and are prominently seen in the areas such as skin, mucosa of the lungs and digestive tract, mouth, conjunctiva and nose. These cells usually do not enter the bloodstream.

Origin

Mast cells are developed in the bone marrow, but their precursor cells are different. After differentiation, the immature mast cells enter the tissues. Maturation of mast cells takes place only after entering the tissue.

Functions

Mast cell plays an important role in producing the hypersensitivity reactions like allergy and anaphylaxis (Chapter 17). When activated, the mast cell immediately releases various chemical mediators from its granules into the interstitium. Two types of substances are secreted by mast cell:

1. *Preformed mediators:* These substances are already formed and stored in secretory granules. These substances are histamine, heparin, serotonin, hydrolytic enzymes, proteoglycans and chondroitin sulfates.
2. *Newly generated mediators:* These substances are absent in the mast cell during resting conditions and are produced only during activation. These substances are **arachidonic acid** derivatives such as leukotriene C (LTC), prostaglandin and cytokines.

■ MONOCYTES

Monocytes are the largest cells among the leukocytes. Like neutrophils, monocytes also are motile and phagocytic in nature. These cells wander freely through all tissues of the body.

Monocytes play an important role in defense of the body. Along with neutrophils, these leukocytes provide the first line of defense.

Monocytes secrete:

1. Interleukin-1 (IL-1).
2. Colony stimulating factor (M-CSF).
3. Platelet-activating factor (PAF).

Monocytes are the precursors of the tissue macrophages. Matured monocytes stay in the blood only for few hours. Afterwards, these cells enter the tissues from the blood and become tissue macrophages. Examples of tissue macrophages are Kupffer cells in liver, alveolar macrophages in lungs and macrophages in spleen. Functions of macrophages are discussed in Chapter 24.

LYMPHOCYTES

Lymphocytes play an important role in immunity. Functionally, the lymphocytes are classified into two categories, namely T lymphocytes and B lymphocytes. T lymphocytes are responsible for the development of cellular immunity and B lymphocytes are responsible for the development of humoral immunity. The functions of these two types of lymphocytes are explained in detail in Chapter 17.

LEUKOPOIESIS

Leukopoiesis is the development and maturation of leukocytes (Fig. 16.2).

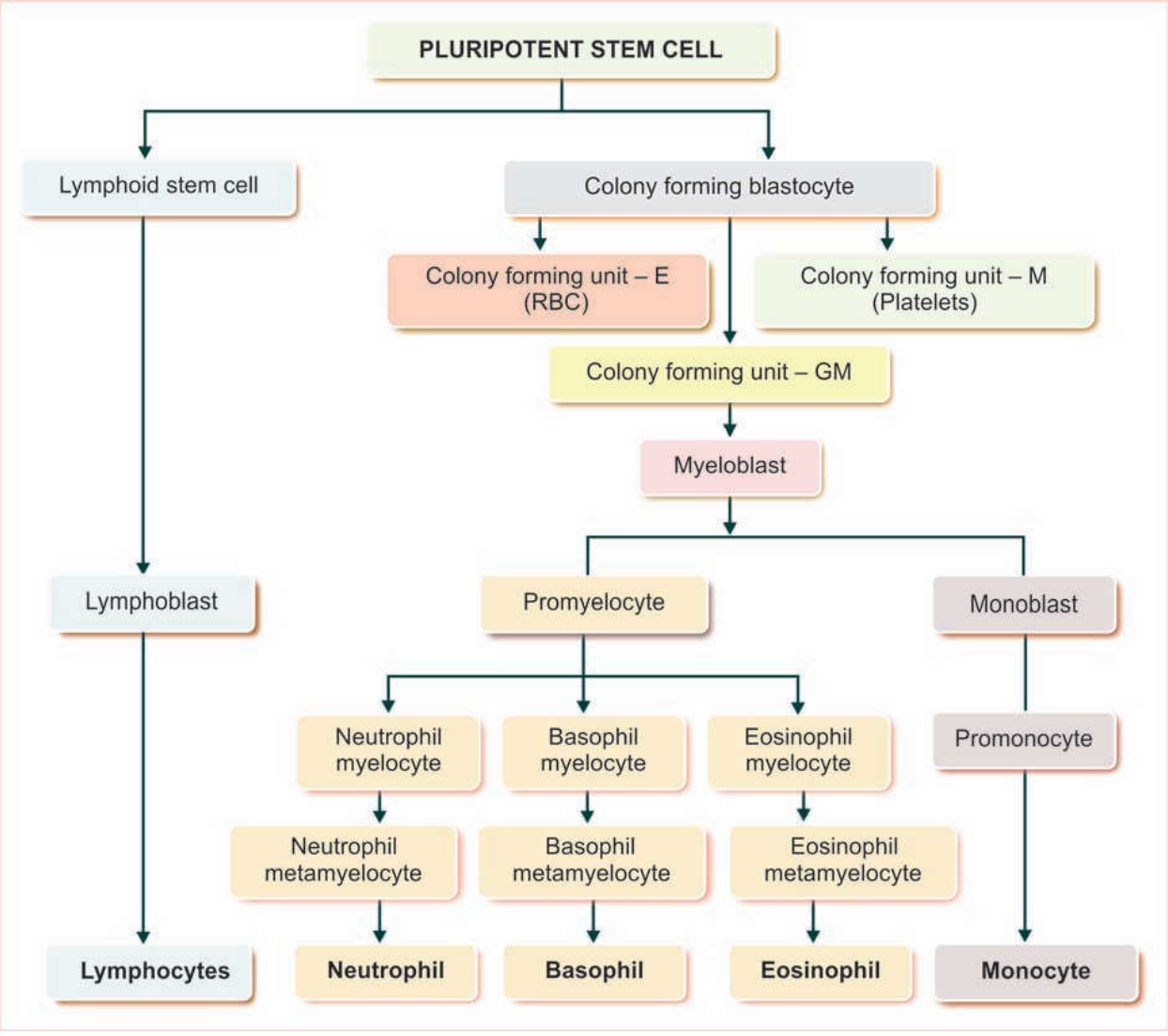

FIGURE 16.2: Leukopoiesis

STEM CELLS

Committed pluripotent stem cell gives rise to leukocytes through various stages. Details are given in Chapter 10.

FACTORS NECESSARY FOR LEUKOPOIESIS

Leukopoiesis is influenced by hemopoietic growth factors and colony stimulating factors. Hemopoietic growth factors are discussed in Chapter 10.

Colony stimulating Factors

Colony stimulating factors (CSF) are proteins which cause the formation of colony forming blastocytes. Colony stimulating factors are of three types:

1. Granulocyte-CSF (G-CSF) secreted by monocytes and endothelial cells
2. Granulocyte-monocyte-CSF (GM-CSF) secreted by monocytes, endothelial cells and T lymphocytes
3. Monocyte-CSF (M-CSF) secreted by monocytes and endothelial cells.