Review of Blood Cells

Course Outline

- Course Objectives
- Introduction: Historical background of phlebotomy and hematology
- Blood composition
    - Blood: The Fluid Tissue
    - Plasma and Cellular Elements
- Blood Cell Formation and Development
- Red Blood Cells
    - RBC formation
    - RBC morphology and function
        - Role of Hemoglobin in Gas Exchange
    - Normal RBC Count and Associated Abnormalities
- White Blood Cells
    - WBC formation
    - Cell types and appearance
    - Granulocytes
        - Neutrophils
        - Eosinophils
        - Basophils
        -
    - Normal WBC count and Associated Abnormalities
- Platelets
    - Platelet formation and structure
    - Hemostasis
        - Primary Hemostasis
        - Secondary Hemostasis
        - Fibrinolysis
    - Normal Platelet Count and Associated Abnormalities
- Summary
- Quiz

Course Objectives

1. Review role of blood (as a liquid tissue) and its components
2. Discuss the process of hematopoiesis, including the role of bone marrow progenitor cells in blood cell development
3. Discuss the morphology and function of red blood cells, including the role of hemoglobin in oxygen transport and gas exchange
4. Discuss the morphology of white blood cells, the different WBC types, and their roles in the immune response
5. Discuss the development of platelets and their role in hemostasis
6. Review normal adult cell counts and the terminology associated with abnormal levels,
7. Discuss some conditions related to the abnormal blood cell counts

Introduction: Historical Background of Phlebotomy and Hematology

Throughout history and across different cultures, man has regarded blood as something essential for life. The Greek physician Hippocrates, commonly referred to as the Father of Medicine, considered blood to be one of four body fluids that, when kept in balance, maintained proper health. Up to the Middle Ages, the practice of bloodletting was routinely performed as a therapeutic measure for various ailments. Other practices such as the application of leeches also involved the removal of blood from the body as a curative measure. Thus phlebotomy, the practice of drawing blood from the body by cutting into a vein, has been a part of the evolution of the field of medicine since early times. Hematology, the study of blood, had a significant breakthrough in the early 1600s with the development of the microscope: for the first time, researchers could view objects and processes previously invisible to the naked eye. This eventually led to the observation of cells within the blood by Antonie van Leeuwenhoek in 1674, and the description of different types of cells by William Hewson in 1770. These discoveries proved that blood is not simply a dark-red liquid flowing within our veins; it actually contains microscopic components with unique characteristics. Further

understanding of the structure and functions of these components would gradually emerge within the field of hematology. Currently, tests involving blood and the blood cells continue to serve as fundamental tools in the diagnosis, evaluation, and treatment of various conditions. As technological capabilities continue to advance, research in this field remains an important part of ongoing scientific exploration and innovation.

Blood Composition

Blood is composed of two main portions. The first portion is a liquid called *plasma*. Plasma makes up the majority (55%) of blood and is referred to as the *fluid portion* of the blood. Plasma itself consists of approximately 90% water. The remaining 10% are dissolved substances (such as gases, nutrients, minerals, and hormones) which are transported by the bloodstream. When isolated from whole blood, plasma normally has a pale-yellow color.

The second portion of the blood are the *formed (cellular) elements*. These are the different cells (red blood cells, white blood cells and platelets) which float within the plasma and make up 45% of the blood. Unlike plasma, which is a liquid, the cells are solid elements of the blood. The majority of the formed elements are the red blood cells (also known as RBCs, or *erythrocytes*). The primary function of RBCs is to carry oxygen within the bloodstream. Oxygenated (oxygen-rich) blood is essential for the nourishment of cells within the various body organ systems. The second type of blood cells are white blood cells (also called WBCs or *leukocytes*). WBCs play a role in the body's immune system, which mainly defends against invasion by foreign bodies such as bacteria and viruses. The third type of blood cells are platelets (also called *thrombocytes*) which are involved in the process of clotting, in which blood turns from a liquid to solid form.

Within the bloodstream, plasma and the cells remain mixed. Although plasma by itself has a pale-yellow color, blood as a whole appears dark-red due to all the red blood cells flowing within the plasma. The fact that blood has two portions becomes more evident when blood is collected into a tube, after which plasma can be separated from the cells via centrifugation. (Insert picture of separated plasma and cells in collection tube)

Blood: The Fluid Tissue

Blood is a fluid substance that continuously flows within the body. The bloodstream is carried within the blood vessels, which are found throughout the body and allow blood to flow through all the organs. As a result, the bloodstream is able to perform many functions. It is an important means of transporting and distributing various substances within the body. Blood carries nutrients and oxygen, which need to be delivered to all the cells to sustain them. Blood also carries away waste products and carbon dioxide from the cells, preventing the buildup of harmful substances within the tissues. Since glands secrete hormones into the bloodstream to deliver messages to target organs, blood serves as a means of communication between different parts of the body. Blood also contains elements of the body's immune system, which constantly look out for foreign bodies and defend against infections. Blood helps maintain the natural fluid balance of the body, which is important for normal physiological functions to take place. Blood is also considered to be liquid connective tissue due to its composition and functions, similar to the way bone and cartilage serve to keep the body connected as a whole.

Blood Cell Formation and Development

The process of creating new blood cells is known as *hematopoiesis* or *hemopoiesis*. Constant blood cell formation is important in replacing older, damaged, and dying cells, as well as replacing cells that are lost due to bleeding. Hematopoiesis is integral to maintaining the normal population of cells circulating in the bloodstream.

Blood cell formation begins early during the embryonic stage of development, within a primitive structure called the yolk sac. It continues through the fetal stage where the liver, spleen and bone marrow become involved in hematopoiesis. In adults, blood cells are formed primarily in the bone marrow. Other organs such as the liver, spleen, thymus, and lymph nodes are also involved, specifically in the production of white blood cells.

In the adult circulatory system, all mature blood cells (erythrocytes, leukocytes, and thrombocytes) originate from the *hemopoietic stem cells* that are found in the

bone marrow. Stem cells, which are present since embryonic development and have the ability to differentiate to other cell types, give rise to the progenitor cells (cells of different lineages) which in turn will produce the three blood cell groups. Each line of cells undergoes several stages of development until eventually mature cells emerge and are released into the bloodstream. Although the rate of hematopoiesis varies per individual, the typical number of blood cells produced per day is in the tens to hundreds of billions. (Britannica) (Insert diagram of hematopoiesis in bone marrow)

Red Blood Cells

RBC Formation

In adults, all RBCs originate from the bone marrow, which constantly produces new erythrocytes to replace older or damaged cells. The rate of erythrocyte generation can restore almost one percent of the body's erythrocytes daily. (Britannica) Stem cells in the marrow differentiate into *proerythroblasts*, the progenitor cells which undergo further stages of maturation. Part of this process involves each cell losing its nucleus as it becomes a mature RBC. Towards the end of cell development, *reticulocytes* are immature RBCs which still have remnants of their nucleus present.

RBC Morphology and Function

Mature RBCs released into the circulation have a *biconcave* shape, meaning the RBC has the form of a flattened disc with an indentation on both sides at the center. (Insert picture of RBC structure) As they are carried within the bloodstream, RBCs can deform in order to pass through smaller blood vessels, particularly as they squeeze through tiny capillaries. (Hartman's)

Role of Hemoglobin in Gas Exchange

RBCs contain an iron-based protein called *hemoglobin*, which as a pigment is responsible for giving these cells (and the blood itself) their typical red color. Hemoglobin has the ability to bind oxygen as the bloodstream passes through the lungs. This allows the RBCs to transport oxygen throughout the body, delivering it to the cells of the various organ systems (primarily via the

arteries of the systemic circulation). As the cells in the organs obtain oxygen from the blood, they in turn release carbon dioxide into the blood. Hemoglobin can also bind carbon dioxide to some extent. As oxygenated blood passes through a capillary, the RBCs release oxygen to the cells. Blood then becomes deoxygenated, as RBCs pick up carbon dioxide coming from the cells. This process of *gas exchange* is made possible by in part by the presence of hemoglobin in the RBCs, and the constant flow of blood through the organs and tissues provides a continuous means of oxygen supply and carbon dioxide removal for the cells. (Insert diagram of gas exchange)

Erythrocytes are the most numerous blood cells and make up about 40% of the total blood volume. (Hartman's) RBCs have an average lifespan of 120 days. As aging and damaged cells are cleared from the circulation by the liver and spleen, production of new RBCs takes place continuously in the bone marrow in order to maintain the normal cell population.

Normal RBC Count and Associated Abnormalities

In adults the normal number of RBCs in the blood is between 4.5 to 5 million erythrocytes per mm^3. * Production of RBCs by the bone marrow is influenced by *erythropoietin*, a hormone secreted by the kidneys. *Erythrocytosis* is the term for abnormally elevated levels of RBCs. *Polycythemia vera* is a disease where the bone marrow produces excessive amounts of erythrocytes and is caused by a genetic mutation. Polycythemia creates problems with blood flow and clotting within the blood vessels, leading to stroke or a heart attack. *Erythrocytopenia* or *erythropenia* is an abnormally decreased number of RBCs, as seen in different types of anemia. Iron deficiency anemia is the most common, associated with dietary causes, menstrual or gastrointestinal bleeding, and pregnancy. Patients can develop pallor, fatigue, or weakness. Another type is *dyserythropoietic anemia,* caused by a genetic mutation which also affects platelet production. Patients can develop abnormal bleeding and may require blood transfusions.

*The unit of measurement for cell counts is the *number of cells per cubic millimeter*. As a measure of volume, a cubic millimeter (mm^3) or *microliter*, describes a cube whose sides are each 1mm long. A simplified description of

this measurement would be the number of cells in a blood drop roughly the size of a pin head. Cell counts are routinely included in blood testing.

White Blood Cells

WBCs make up only about 1 percent of the total blood volume (Hartman's), but they play a critical role in the body's defense against infection. 60 to 70 percent of WBCs come from the bone marrow. Lymphatic tissues in the lymph nodes, thymus, liver, and spleen are also involved in WBC production. (Britannica) Hematopoietic stem cells differentiate into progenitor cells (myeloblasts and lymphoblasts), which in turn give rise to 5 different cell lineages.

When microscopic examination of blood samples is performed, staining of the blood smear with specific dyes helps to differentiate the types of WBCs. Once stained, the cells' structural properties (such as cell size and appearance of the nucleus) become more observable, which helps in their identification. A significant finding from early microscopic studies was that certain leukocytes contain distinct granules in their cytoplasm while others do not. Based on this observation, WBCs were classified into 2 general types: *granulocytes* are WBCs which contain granules, while *agranulocytes* are WBCs which do not contain granules. (Insert picture of 5 types of WBC)

Granulocytes

Granulocytes are comprised of 3 types of cells: neutrophils, eosinophils, and basophils. Granulocytes come from progenitor cells called myeloblasts. Their names are derived from the staining properties of the cells' granules: neutrophils are more fully stained by neutral dye, eosinophils by acidic dye, and basophils by basic (alkaline) dye.

Neutrophils are the most numerous among WBC types, making up 1/2 to 2/3 of the entire leukocyte population. Neutrophils have a multi-lobed or segmented nucleus, which is why they are also referred to as *segmenters* or *polymorphonuclear* (PMN) leukocytes. They have very fine purple-staining

granules. Neutrophils serve as the body's first line of defense against infection. As they pass through the circulation, they migrate towards areas of inflammation or infection. Upon encountering a foreign body such as bacteria, neutrophils perform *phagocytosis*, a process in which the cell surrounds, engulfs, and digests the bacteria. In this way, neutrophils (and other phagocytic cells) are able to destroy foreign substances and damaged tissues. They are most involved in fighting against bacterial and fungal infections. (Insert diagram of phagocytosis)

Eosinophils have a bilobed nucleus and their spherical granules stain with a pinkish color. From the bloodstream, they enter tissues with ongoing inflammation. Eosinophils can perform phagocytosis on microbes and foreign protein complexes, though they are not as effective as eosinophils in destroying intracellular bacteria (Merck). They can also release substances from their granules which are toxic to parasites, particularly intestinal worms. Eosinophil numbers increase particularly during allergic reactions and parasitic infections.

Basophils are the rarest type of WBC, making up less than 1 percent of the total number of leukocytes. They have a bilobed or S-shaped nucleus, and their large granules stain dark blue. In response to inflammation, basophils release chemicals from their granules, including histamine, heparin, and cytokines. Histamine is a chemical which enlarges the size of blood vessels, increasing blood flow and allowing more immune cells to migrate to the area. Histamine also mediates a variety of responses throughout the body, mainly related to inflammation and allergic reaction. (Insert table of histamineeffects/allergic symptoms) Heparin is a natural anticoagulant which prevents blood from clotting. Cytokines are proteins released by certain types of WBCs, which stimulate the growth and activity of cells in the immune system. They aid in the body's immune and inflammatory response, and also have cancer-fighting properties. Basophil numbers are elevated in asthma and allergic reactions. (Insert table of cytokine types and functions)

Agranulocytes

There are 2 types of agranulocytes: lymphocytes and monocytes. Lymphocytes come from progenitor cells called lymphoblasts. Their lifespan varies greatly from a few hours to years. Monocytes come from myeloblasts, similar to the granulocytic leukocytes, and live for several months.

Lymphocytes are the second most numerous type of WBC, making up 20 to 30 percent of the total WBC population. There are 2 subtypes: T-lymphocytes (T cells) and B-lymphocytes (B cells). T cells perform cellular (cell-mediated) immunity, while B cells are involved in humoral (antibody-mediated) immunity.

After being produced in the bone marrow, T cells undergo further maturation in the thymus gland and then differentiate into subtypes. (Insert diagram of T cell differentiation/functions) Helper T cells can detect *antigens* (foreign substances that indicate infection) on other cells. In response, they produce cytokines, alert other leukocytes, and stimulate B cells to release *antibodies* (see below). Cytotoxic T cells attack virus-infected cells, as well as cancerous or foreign cells (i.e., organ transplants). They release chemicals which destroy the target cells. Regulatory T cells send chemical signals which lower the activity of the immune system, preventing prolonged or hyperreactive immune reactions which would harm the normal body tissues. After an infection, Memory T cells retain the ability to recognize specific antigens for a prolonged period. They can mount a rapid immune response to reinfection should the body be exposed again to the same antigen.

B cells are produced in the bone marrow and undergo further stages of development in the lymphoid tissues such as the spleen, lymph nodes, and tonsils. When the immune system detects the presence of antigens (such as bacteria, viruses, toxins, or foreign cells) in the body, B cells transform into *plasma cells*, which in turn release antibodies (also called immunoglobulins) into the bloodstream. Antibodies are proteins which are designed to recognize, bind to, and neutralize specific antigens. This specificity allows an antibody to quickly inactivate its target antigen (such as a measles virus) but will not let it recognize other antigens (such as chickenpox or mumps viruses). Binding allows antibodies to isolate and directly inactivate antigens. Antibody-antigen complexes also become targets for phagocytosis. Furthermore, the presence of antibodies stimulates other elements of the immune system into action. Certain antibodies are involved in allergic reactions. After exposure to an antigen, certain B cells can remain active for a long time, multiplying and producing more antibodies. This acts as a type of memory for the immune system, providing extended protection against future exposure to the antigen. (Insert diagram of antibody production and activity)

Monocytes are the largest WBCs. They are roughly twice the size of red blood cells and have a bilobed, kidney-shaped nucleus. Monocytes are released into the bloodstream by the bone marrow, but upon detecting infection or inflammation they can enter the tissues, releasing cytokines to stimulate further immune response at the affected site. They can also transform into dendritic cells (DCs) and macrophages, which have been found to have overlapping functions. (CJASN) (Insert pictures of Monocyte, Dendritic Cell as APC, and Macrophage performing phagocytosis)

When antigens are encountered, *dendritic cells* process the foreign substance, then express the antigen on the cell's surface. By acting as antigen-presenting cells (APCs), dendritic cells alert T cells to the presence of infection and precipitate an immune response. *Macrophages* can perform phagocytosis, engulfing then destroying foreign bodies and dead tissue. They become specialized phagocytic cells within various organs (i.e., kidney mesangial cells, bone osteoclasts). (NIH) Both DCs and macrophages can also activate T cells by releasing cytokines.

Normal WBC Count and Associated Abnormalities

The normal number of WBCs in the blood is between 5,000 to 10,000 leukocytes per mm^3. *Leukocytosis* is the term for an abnormal increase in number of WBCs in the blood. WBCs can become elevated in response to general stresses to the body, including fever, inflammation, and injury. Certain cell types increase prominently in reaction to specific disease conditions (i.e., eosinophils increase in allergic reactions, lymphocytes increase with viral infection).

Leukocytopenia or *leukopenia* is an abnormal decrease in the number of WBCs, which can be caused by disorders of the bone marrow or spleen, cancers of the blood and bone marrow, chemotherapy, infections such as HIV, or autoimmune disorders like lupus. Specific subtypes of WBCs may become abnormally low, such as *neutropenia*, where the body has low numbers of neutrophils. Severe neutropenia makes the body more susceptible to infections.

Platelets

In adults, all platelets come from the bone marrow (Britannica). They are produced by the fragmentation of giant precursor cells called megakaryocytes and are not considered true cells. Platelets are the smallest of the formed elements and have a lifespan of 10 days. Platelets are the first responders to blood vessel injury, forming a plug to seal up the vessel wall and preventing further bleeding. (Insert picture of platelets)

Hemostasis

For the circulation to function properly, continuous flow of the bloodstream must be maintained. Even during times of injury and inflammation, the body needs to preserve this normal flow. When blood vessels are damaged, *hemostasis* is the body's way of stopping blood loss at the site of injury, while ensuring normal blood flow continues in other parts of the circulation. Several components of the vascular system are involved in hemostasis, including the blood vessels, chemical factors in the plasma, and the blood cells. These components maintain a balance wherein clotting can rapidly seal a damaged vessel to minimize blood loss, at the same time excessive clotting activity (which may adversely affect blood flow) is avoided.

Primary Hemostasis

The inner lining of blood vessels (called the endothelium) is in direct contact with the bloodstream and promotes normal blood flow, so long as the lining is intact. The endothelium produces heparan sulfate, which is an anticoagulant (a substance that prevents clotting). The presence of this anticoagulant on the inner surface of blood vessels inhibits the clotting process and supports normal blood flow.

When the endothelium is damaged (such as by trauma, infection, or a blood draw procedure), a substance called von Willebrand factor (vWF) is exposed to the bloodstream. vWF is one of the clotting factors (chemicals which promote

clotting) and causes platelets to adhere to the site of injury. Only platelets that are exposed to the damaged endothelium undergo *adhesion*; other platelets in the bloodstream remain inactive. This confines the extent of clotting activity to the injured site. Upon adhesion, platelets undergo *activation*, producing more clotting factors. Through a series of chemical reactions, the clotting factors convert prothrombin in the blood to *thrombin*, which has simultaneous effects on platelets and the plasma. The presence of thrombin causes platelets to change shape and become stuck to each other (called *aggregation*), recruiting even more platelets, and propagating the aggregating process. Thrombin also converts fibrinogen in the plasma into *fibrin*, a protein with a fiber-like structure that binds with the platelets. Together, the platelets and fibrin form what is called a *primary platelet plug* over the damaged endothelium. When injury to the vessel is minimal, this plug is sufficient to quickly stop bleeding. In primary hemostasis, the small amount of thrombin produced limits the clotting process to the affected area, while clot-inhibiting factors from the plasma and endothelium ensure that this process ends quickly. (Phlebotomy Essentials) (Insert diagram of platelet plug formation)

Secondary Hemostasis

When there is greater damage to a blood vessel, higher amounts of thrombin need to be produced. The thrombin already present from primary hemostasis stimulates the production of even more thrombin by further recruiting and activating platelets and clotting factors. This is leads to clotting activity beyond just the formation of a primary platelet plug. The greater number of activated platelets increases thrombin levels to the point where insoluble fibrin is formed at the site. This fibrin creates a meshwork which traps not only platelets but other blood cells. The mesh then stabilizes the clot, forming a secondary *hemostatic plug*. It also confines the activated clotting factors within the clot and restricts their activity to the injured site. Once a stable clot is formed, fibrin production stops, thus halting the process. (Insert diagram of secondary hemostasis/clot formation)

Fibrinolysis

Within the stable hemostatic plug, platelets produce a growth factor which stimulates repair of the endothelium. Once the blood vessel is repaired, the clot is no longer needed and must be removed. *Fibrinolysis*, the process of dissolving a clot after vessel injury is resolved, begins even as clotting itself is taking place. When clotting factors are activated, the endothelium and WBCs simultaneously produce another set of factors which transform plasminogen in the blood to plasmin. *Plasmin* is an enzyme which breaks down fibrin, effectively dismantling the clot. Fibrin fragments are then cleared from the circulation by phagocytic cells. Fibrinolysis is important in returning the blood vessel to its original state (one in which there was neither damage nor clot present). This process also prevents clotting activity from going on unchecked, which would interfere with normal blood flow within the vessel. (Insert diagram of fibrinolysis)

Normal Platelet Count and Associated Abnormalities

Platelets normally number between 150,000 to 400,000 thrombocytes per mm^3. *Thrombocytosis* or *thrombocythemia* is the medical term for an abnormal increase in the number of platelets, typically in reaction to an ongoing disease process such as infection, inflammation, iron deficiency, blood loss, or cancer. Less commonly, it could be caused by a bone marrow disorder. The most severe complications from thrombocytosis come from exaggerated clotting activity, such as clots developing within the arteries supplying the heart or brain, leading to a heart attack or stroke.

Thrombocytopenia is an abnormally low number of platelets. Possible causes include bone marrow disorders, infections, cancer, aplastic anemia, autoimmune diseases, or disorders of the spleen. Low platelets puts the body at risk for abnormal, prolonged bleeding. Signs include *purpura* and *petechiae*, red and purple dots in the skin caused by bleeding vessels. (Insert picture of purpura and petechiae)

Summary

Far from being a simple red liquid in our veins, blood is a complex liquid tissue. Its formed elements have common origins in the bone marrow but develop into unique cell types which serve diverse functions including metabolism, physiologic balance, defense, and hemostasis. Normal blood cell production, development and function is crucial to overall health, as any abnormality in these either cell numbers or activity could lead to disease.

Quiz

1. The medical term for red blood cells (RBCs) is:
    a. Leukocytes
    b. Thrombocytes
    c. Erythrocytes
    d. Monocytes

2. All of the following WBCs are granulocytes, except:
    a. Basophils
    b. Neutrophils
    c. Lymphocytes
    d. Eosinophils

3. What are reticulocytes?
    a. cells involved in the clotting process
    b. granulocytic white blood cells
    c. cells which perform phagocytosis
    d. immature red blood cells

4. Leukocytosis is defined as:
    a. elevated number of red blood cells
    b. decreased number of white blood cells
    c. elevated number of white blood cells
    d. decreased number of platelets

5. Megakaryocytes are the precursor cells for:
    a. White blood cells
    b. Platelets
    c. Red blood cells
    d. Plasma cells

6. Which of the following cells is capable of producing antibodies?
    a. Plasma cells
    b. Monocytes
    c. Cytotoxic T cells
    d. Helper T cells

7. Which of the following cells become macrophages in the tissues?
    a. Plasma cells
    b. Monocytes
    c. Cytotoxic T cells
    d. Helper T cells

8. Which of the following cells is primarily involved in hemostasis?
    a. T lymphocytes
    b. Thrombocytes
    c. Macrophages
    d. B lymphocytes

9. Which of the following cells is involved in humoral immunity?
    a. Monocytes
    b. T lymphocytes
    c. Erythrocytes

d. B lymphocytes

10. Polycythemia is a disease primarily associated with:
    a. Leukocytosis
    b. Erythrocytosis
    c. Thrombocytopenia
    d. Leukopenia

References

Hartman's Complete Guide for the Phlebotomy Technician (2020) pp. 95 - 96

Phlebotomy Essentials Enhanced 7th Edition (2021). Ruth E. McCall.

NEJM Resident 360. History of Hematology. April 20, 2022.

https://resident360.nejm.org/content-items/history-of-hematology

Hindawi. Understanding the Journey of Human Hematopoietic Stem Cell Development. Akhilesh Kumar, Saritha S. D'Souza, Abir S. Thakur. *Stem Cells International*, vol. 2019, Article ID 2141475, 13 pages, 2019.https://www.hindawi.com/journals/sci/2019/2141475/

ScienceDirect. Development of the Hematopoietic System. Robert M. Kliegman MD, in Nelson Textbook of Pediatrics, 2020 https://www.sciencedirect.com/topics/medicine-and-dentistry/hematopoiesis#:~:text=Hematopoiesis%20in%20the%20Human%20Embryo,mesoblastic%2C%20hepatic%2C%20and%20myeloid.

Medical News Today. What to know about hematopoiesis. Zawn Villines. September 27, 2017.

https://www.medicalnewstoday.com/articles/319544

Cleveland Clinic. Lymphatic System. Updated on February 23, 2020 from:

https://my.clevelandclinic.org/health/articles/21199-lymphatic-system

Cleveland Clinic. Basophils. Updated June 14, 2022 from:

https://my.clevelandclinic.org/health/body/23256-basophils#:~:text=Basophils%20also%20release%20an%20enzyme,response%20to%20destroy%20the%20organism.

Cleveland Clinic. High White Blood Cell Count. Updated January 19, 2022 from:

https://my.clevelandclinic.org/health/diagnostics/17704-high-white-blood-cell-count

Cleveland Clinic. Neutropenia. Updated May 27, 2022 from:

https://my.clevelandclinic.org/health/diseases/21058-neutropenia

NIH National Library of Medicine. Red Blood Cell Production. Updated January 9, 2022 from https://medlineplus.gov/ency/anatomyvideos/000104.htm#:~:text=Red%20blood%20cells%20are%20formed,a%20new%20red%20blood%20cell.

NIH National Library of Medicine. How Neutrophils Kill Microbes.

Anthony W. Segal. Annu Rev Immunol. 2005; 23: 197–223.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2092448/#:~:text=Neutrophils%20provide%20the%20first%20line,and%20digesting%20bacteria%20and%20fungi

NIH National Library of Medicine. Dyserythropoietic anemia and thrombocytopenia. Updated October 1, 2014 from:

https://medlineplus.gov/genetics/condition/dyserythropoietic-anemia-and-thrombocytopenia/#synonyms

NIH National Heart, Lung, and Blood Institute. Platelet disorders: Thrombocytopenia. Updated March 24, 2022 from:

https://www.nhlbi.nih.gov/health/thrombocytopenia#:~:text=Thrombocytopenia%20is%20a%20condition%20that,is%20called%20a%20blood%20clot.

British Society for Immunology. Eosinophils. Karen Buckland.

https://www.immunology.org/public-information/bitesized-immunology/cells/eosinophils

Merck Manual Professional Version. Eosinophil Production and function. Jane Liesveld, MD. Updated September 2022 from:

https://www.merckmanuals.com/professional/hematology-and-oncology/eosinophilic-disorders/eosinophil-production-and-function

ScienceDirect. Eosinophils. David S. Silberstein, in Encyclopedia of Immunology (Second Edition), 1998.

https://www.sciencedirect.com/topics/immunology-and-microbiology/eosinophil-granulocyte

American Cancer Society. Cytokines and their Side Effects. Updated December 27, 2019 from:

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/cytokines.html

Clinical Journal of the American Society of Nephrology. Dendritic Cells and Macrophages: Sentinels in the Kidney. Christina K. Weisheit, Daniel R. Engel and Christian Kurts. CJASN October 2015, 10 (10) 1841-1851

https://cjasn.asnjournals.org/content/10/10/1841#:~:text=The%20mononuclear%20phagocytes%20(dendritic%20cells,cells%20and%20microbes%20by%20phagocytosis.

Mayo Clinic. Thrombocytosis. October 27, 2020.

https://www.mayoclinic.org/diseases-conditions/thrombocytosis/symptoms-causes/syc-20378315

Johns Hopkins Medicine. Polycythemia Vera. 2022.

https://www.hopkinsmedicine.org/health/conditions-and-diseases/polycythemia-vera

Johns Hopkins Medicine. Iron-deficiency anemia. 2022.
https://www.hopkinsmedicine.org/health/conditions-and-diseases/irondeficiency-anemia