

Introduction to Hematology

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I. Introduction

Hematology is the study of the normal and pathologic aspects of blood and blood elements. Blood is a unique fluid comprised of many cellular elements as well as a liquid portion consisting of proteins, amino acids, carbohydrates, lipids and elements. The hematopoietic system is characterized by turnover and replenishment throughout life. The pluripotent hematopoietic stem cell (HSC) is the progenitor of the cells in blood. The cellular elements that arise from this stem cell that circulates in blood include red blood cells, white blood cells, and platelets. Normal white blood cells in the peripheral circulation include neutrophils, monocytes, eosinophils, basophils and lymphocytes. Since the HSC also gives rise to cells of the lymphoid system, the study of hematology also includes the lymph nodes and lymph tissue. There is no specific organ for hematologic disorders and its diseases arise within the bone marrow, lymph nodes, or the intravascular compartment. The intravascular compartment where these cells circulate includes the endothelial cell lining of blood vessels and the proteins in the blood plasma. The circulating cell–endothelial cell interface and the rheologic aspects of blood coursing through the intravascular compartment also influence “hematology” and its many parts.

This text has been structured to introduce the trainee to the area of hematology. Since the vast majority of medical students and residents do not become hematologists, there are certain essential items that all trainees must learn about this area of medicine. The trainee will learn the physician’s approach to anemia and red blood cell disorders and be able to fully evaluate a complete blood count (CBC). Screening tests for bleeding disorders for the diagnosis of an individual who has a defect in the proteins or cellular elements that prevent bleeding will be addressed. The trainee also will be exposed to the clinical, biologic, and genetic risk factors that contribute to thrombosis. Finally,

the student will be introduced to those white cell disorders that are diagnosed and treated by non-hematologists and the uncommon but serious white blood cell disorders where a hematology consultation is needed.

II. Origins of hematopoietic cells

Hematopoiesis begins early in embryonic development. The HSC and the blood vessel lining cells or endothelial cells are thought to be derived from the same precursor cell in the aorto-gonad mesonephros (AGM) system. The common precursor to the HSC and the endothelial cell is the hematoblast. It has been proposed that this cell has the capacity to differentiate into both cell classes. The HSC is present in small numbers and retains its ability to differentiate into all blood cells as well as proliferate. In the earliest stages of embryogenesis, these cells circulate through the embryo to supply oxygen and deliver nutrients. The stem cells that arise from the AGM later in embryogenesis give rise to the blood system that seeds the liver and then the bone marrow. These cells demonstrate the ability to “travel” from the time they leave the yolk sac to populate tissues and still circulate in small numbers even in adults, a property exploited in clinical hematopoietic cell transplantation. These cells regress in the liver, kidney, and spleen, but in times of stress, they can resume blood product production as seen in myeloproliferative disorders and myelofibrosis. Under the influence of specific growth and transcription factors, cells become committed to specific lineages.

A. The myeloid system

Cells of this group arise in the central marrow cavity (called the “medullary” cavity). Myeloid lineage blood cells arising elsewhere in the body are designated as “extramedullary” in origin. The myeloid system consists of the following cells: red blood cells (erythrocytes), white blood cells (neutrophils, monocytes, eosinophils, basophils) and platelets (thrombocytes). Neutrophils, eosinophils and basophils have been collectively called “granulocytes” because the presence and nature of their cytoplasmic granules define their function; however, when physicians use the term “granulocytes”, they are often referring just to neutrophils.

1. Erythrocytes (red blood cell, RBC)

An erythrocyte is a specialized anucleated cell that packages hemoglobin, the protein that is a respiratory gas transport vehicle that carries oxygen from the lungs to and carbon dioxide from tissues and back to the lungs to dispel. Erythrocytes undergo erythropoiesis whereby they mature from an early progenitor cell to the non-nucleated, biconcave disk, the erythrocyte, that with the absence of its nucleus and the flexibility of its membrane is able to bend to traverse 2–3 micron capillaries. It is regulated by the growth factor, erythropoietin. The process of erythropoiesis takes 4 days to produce a non-nucleated biconcave disk that enters the circulation with residual RNA in its cytoplasm. A new RBC in the circulation is slightly bigger than older cells.

The reticulocyte count as identified by a special stain represents the percentage of early RBC of the total number of RBC in the circulation. Red blood cell RNA remains in the erythrocyte about 1 day, so a normal “reticulocyte count” is <2%. The red cell life span is 120 days, and normally there are about 5 million RBC/ μ L in whole blood in adult males and 4.5 million RBC/ μ L in adult females. Old RBCs lose their energy-producing (ATP) capacity, develop stiff membranes, and are removed from circulation by the macrophages of the mononuclear–phagocytic system of the spleen. Their hemoglobin is normally retained in the reticuloendothelial (RE) system but can be lost when there is brisk shortened red blood cell survival, i.e., hemolysis.

2. Neutrophils

Neutrophils are also referred to as polymorphonuclear neutrophils, PMN or polys, segmented neutrophils, or segs (Atlas Figure 2; see also Chapter 3). The neutrophil contains a nucleus that is usually a 3–4 lobed or “segmented” structure that stains a bluish color with Wright–Giemsa stain. An early form of a neutrophil is a “band” that shows an unsegmented nucleus. A neutrophil normally takes 12–13 days to be produced in bone marrow. Its life span in the circulation is about 12 hours and they can live in tissues for several days. The marrow pool of mature neutrophils is 30–40 times that seen in the circulation. In the circulation, half are “marginated” or adherent to the endothelial cells and half flow of the blood stream. Margination of neutrophils allows them to serve as a “reserve” to be released in time of stress such as infection. Only one half of the neutrophils that circulate are reflected in the “white blood cell count” (WBC). In the adult, neutrophils constitute 50–80% of the total WBC analyzed (4000–10,000/ μ L). Neutrophils exit the circulation via diapedesis into tissue through the capillary junctions in response to chemotactic stimuli. Their functions are to phagocytize and digest bacteria, cellular debris, and dead tissue. Both neutrophils and monocytes are part of the body’s innate immunity in contrast to adaptive or learned immunity of lymphocytes (see below; see also Chapter 16).

3. Monocytes

Monocytes are large, mononuclear cells with an indented (kidney-shaped) nucleus that form the circulating component of the mononuclear phagocyte system (Atlas Figure 3). The nucleolus in mature monocytes circulating in the peripheral circulation is usually not identified on blood by light microscopy. Monocytes spend 1–3 days in bone marrow and 8–72 hours in the peripheral blood. They have a similar functional role to neutrophils in host defense against organisms. Once they traverse into tissues, they can differentiate into *macrophages* that can survive in tissues for long periods (up to 80 days). Macrophages are tissue-resident as opposed to circulating monocytes. Macrophages are characterized and named for their tissue origin: alveolar macrophages in lung, Kupffer cells in liver, splenic macrophages, and oligodendrocytes/glia cells in brain. They function to phagocytize pathogens, cellular debris and dead tissue.

4. Eosinophils

Eosinophils are characterized by their prominent orange-reddish (refractile) granules seen on Wright–Giemsa stain (Atlas Figure 6). Eosinophils usually have bilobed nuclei. Eosinophils increase in reaction to foreign protein and thus are seen in parasitic infection (especially larva of roundworms, helminths), allergic conditions, cancer and certain drugs. Granules contain several proteins, most notably major basic protein (MBP). Normally eosinophils constitute 0–2% of WBC differential cell count.

5. Basophils

Basophils are equally colorful with very dark, bluish prominent granules following Wright–Giemsa stain (Atlas Figure 7). Granules contain: histamine, heparin, and hyaluronic acid. Histamine release (basophil degranulation) is part of the allergic reaction. Normally basophils are 0–1% of WBC differential blood count. They are often increased in patients with chronic myelogenous leukemia and other myeloproliferative disorders. Mast cells which are tissue basophils also have prominent granules and play a role in host defenses against parasites.

6. Platelets (thrombocytes)

Platelets bud off from the cytoplasm of the bone marrow megakaryocytes. The “mega” karyocyte in the bone marrow is recognized by its large size. Uniquely, the cell doubles its nuclear and cytoplasmic material but does not divide. Megakaryocyte growth and platelet segmentation is regulated by thrombopoietin. Platelets are anucleated cell fragments that contain remnant mRNA. They have a 7–10 day half-life and their first 1–2 days are spent in the spleen. Platelets can be entrapped by an enlarged spleen as seen in congestive and inflammatory disorders. They play a central role in hemostasis as they contain many hemostatic cofactors and inhibitors in their granules. They also have a role in inflammation since they contain many growth factors. At the megakaryocyte level, plasma proteins can be adsorbed and packaged into platelet granules (see Chapter 13).

B. Mononuclear phagocytic system

The mononuclear phagocyte system consists of circulating monocytes derived from the myeloid progenitor cell in the bone marrow that migrate from the circulation into tissues and differentiate into macrophages. The mononuclear phagocytic system is also called the reticuloendothelial (RE) system. These cells are found in bone marrow, thymus, lymph nodes, spleen, serosal surfaces, adrenal cortex, Peyer’s patches, and Waldeyer’s ring. They function as a “clean-up system” for circulating debris, microorganisms and aged, defective or antibody-coated RBC.

C. Lymphocyte system

Lymphocytes are mostly in lymph nodes, but are also a large blood and bone marrow component. As already mentioned above, they are part of our

adaptive immunity system. The major lymphocyte subsets are B and T cells. NK (natural killer) cells are a specialized lymphoid population. All cells arise in the bone marrow, but T cells mature in the thymus and B cells mature in the lymph nodes, spleen or other lymphoid tissue, e.g., Peyer's patches in the gut and Waldeyer's ring in the throat. Immunosurface markers are used to classify lymphocytes. B cells are identified by CD19 and CD20. T cells are identified by CD3, CD4 or CD8. NK cells comprise 10% of circulating lymphocytes and are identified by the CD3–CD56+ phenotype.

III. The physical states of blood

- (i) Blood is a *suspension* of cells in a solute of water, water-soluble proteins, and electrolytes.
- (ii) The *viscosity* of blood = 1.1–1.2 centipoise. The viscosity of blood is highly influenced by red blood cell and protein concentration. Increased viscosity can occur from an elevation in the cellular components as is seen in polycythemia (increased numbers of red blood cells) and protein as seen in disorders such as multiple myeloma (elevated IgG levels) and Waldenström's macroglobulinemia (elevated IgM levels)]. Red cell size (smaller size increases viscosity) and the speed of blood flow in a given vessel also influence viscosity (viscosity in the aorta is much less than in a small arteriole).
- (iii) Blood volume averages 70 mL/kg of body weight; thus the 70 kg adult has roughly 5 liters of blood. The blood volume of an individual (man, dog, etc.) is approximately 7% of the total body weight. Children may have a slightly higher % (~10%) blood volume to total body weight.
- (iv) Cellular composition of blood averages 38–42% in women, 40–44% in men; the percent volume contributed by red blood cells is called the "*hematocrit*" or packed cell volume.
- (v) *Plasma* is anticoagulated blood (i.e., blood where the calcium chloride has been chelated [i.e., bound] and not available for interaction with proteins) from which the cellular components (red cells, white cells, and platelets) have been removed by centrifugation. It contains the blood coagulation proteins. *Serum* is the liquid in blood that has been collected without an anticoagulant. Many of the proteins have "clotted" and form a precipitate along with the cellular components of the blood. It is usually yellow in color unless the red blood cells lyse (hemolyze) releasing free hemoglobin that gives a red color in visible light. Plasma coagulation studies can only be performed on blood that has been obtained with a proper anticoagulant (usually sodium citrate in clinical medicine) and the plasma separated from the blood cells.