



Hematology



WHAT IS HEMATOLOGY?

The study (morphology, physiology, and pathology) of blood and blood-forming organs and the diseases thereof

- Uses:
 - As part of a routine medical exam to assess overall health
 - Diagnosis (e.g., an infection, anemia, leukemia)
 - Monitoring of a condition and its treatment

HEMATOPOIESIS/HEMOPOIESIS

The formation of blood cells and platelets. In a fetus, formation starts in the yolk sac, moves to the liver and spleen, and then moves to the bone marrow. In an infant, formation occurs in bone marrow, which is present in almost all bones. In an adult, formation of blood cells (red and most white) and platelets occurs in the marrow of the proximal ends of the femur, pelvis, sacrum, vertebrae, ribs, sternum, and skull.

- **Hemopoietic growth factors:** Erythropoietin (EPO), FLT3 ligand (FLT3-L), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage-CSF (GM-CSF), interleukin-1 (IL-1), IL-3, IL-5, IL-6, macrophage-CSF (M-CSF), stem cell factor (SCF), thrombopoietin (TPO), tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF). Effects are mediated by binding receptors on cell surfaces.
- **Hemopoietic stem cell:** Pluripotent, rare (frequency is 1 per 20 million nucleated cells in bone marrow) CD34⁺CD38⁻Lin⁻ phenotype. Gives rise to more than 10⁶ mature cells after 20 cell divisions and can self-renew by asymmetric cell division.
- **Hemopoietic progenitor cell:** Multipotent.
- **Erythropoiesis:** Formation of red blood cells (RBCs); regulated by EPO, which is secreted by the kidneys in response to hypoxia (oxygen tension, the partial pressure of oxygen).
 - Stem cell → progenitor cell → colony-forming unit (CFU) granulocyte, erythroid, monocyte, and megakaryocyte (GEMM) (CFU_{GEMM}) → burst-forming unit (BFU) erythroid (BFU-E) (CFU_E) → proerythroblast → series of normoblasts in marrow that decrease in size, increase in hemoglobin (Hb) content, lose RNA; protein synthesis apparatus, and increase chromatin condensation → reticulocyte (nucleus extruded; nuclear DNA lost), which contains some ribosomal RNA (rRNA) and synthesizes Hb → mature erythrocyte (RBC) (red), which is a non-nucleated, bi-concave disc (i.e., cell-like).
 - Assays by Hb level, reticulocyte count, and bone marrow exam.
 - **Total erythropoiesis** assessed by the cellularity of marrow and myeloid/erythroid ratio.
 - **Effective erythropoiesis** assessed by reticulocyte count.
 - **Ineffective erythropoiesis:** 50–15% of erythroblasts die in bone marrow; increases in some chronic anemias; associated with increased unconjugated bilirubin (derived from the breakdown of Hb) and lactate dehydrogenase LDH (derived from breakdown of cells) in serum.
- **Extramedullary hematopoiesis (EH):** Formation and development of blood cells outside bone marrow in response to the failure of erythropoiesis in bone marrow.
- **Granulopoiesis:** Formation of granulocytes.
 - Stem cell → CFU → CFU granulocyte progenitor (CFU_G) → basophil
 - Stem cell → CFU → CFU granulocyte monocyte neutrophil (CFU_{GMN}) → CFU eosinophil progenitor (CFU_E) → eosinophil (acidophil)
 - Mast cell (mastocyte or basophil)
 - Stem cell → CFU → CFU → CFU granulocyte monocyte progenitor (CFU_{GMP}) → CFU-G → neutrophil
- **Lymphopoiesis:** Formation of lymphocytes and natural killer (NK) cells.
 - Stem cell → common lymphoid progenitor → B-lymphocyte (B cell)
 - Stem cell → common lymphoid progenitor → thymus → T lymphocyte (T cell)
 - Stem cell → common lymphoid progenitor → natural killer cell (NK cell)
- **Myelopoiesis:** Formation of blood marrow and all blood cells in marrow.
 - Monocyte formation
 - Stem cell → CFU → CFU → CFU → CFU-M → monocyte
- **Thrombopoiesis:** Formation of thrombocytes, or platelets, in about 10 days; regulated by TPO (95% from the liver; 50% constitutively produced and 50% produced in response to platelet destruction). As the platelet ages, it loses cell-surface sialic acid, exposing galactose residues that attach to the Achewell-Morell receptor in the liver, signaling for TPO production.
 - Stem cell → CFU → CFU megakaryocyte progenitor (CFU_{MK}) → platelet (fragment of cytoplasm of megakaryocyte)
 - TPO binds to the c-MPL receptor on megakaryocytes and platelets, so plasma TPO is low in patients with excess platelets and high in patients with thrombocytopenia.

ORGANS OF THE LYMPHATIC SYSTEM

- **Bone marrow:** Modified connective tissue in bone cavities that is soft, fatty, and vascular.
 - **Red marrow:** Where blood cells are formed.
 - **Yellow marrow:** Mostly fat.
- **Lymph nodes:** Small, widespread organs of the lymphatic system, connected by lymphatic vessels. They filter lymph, form lymphocytes, become inflamed/enlarged with infection, disease, and injury, and are used to stage cancer.
- **Thymus gland:** Lymphoid organ behind the sternum where T cells are produced and mature; mature T cells migrate to lymph nodes throughout the body. This gland decreases in size with the onset of puberty and is replaced with fat.
 - **Thymosin:** Hormone produced by the thymus gland; stimulates T cell development.
- **Tonsils:** Pair of masses of lymphoid tissue located at the root of the tongue in the throat; M cells on the surface take up antigens (Ag) produced by pathogens and stimulate B cells and T cells; they also produce T cells.
- **Spleen:** Largest organ of the lymphatic system, located in the upper left quadrant of the abdomen. It filters blood, including old and damaged red blood cells, and produces lymphocytes.

BLOOD

Delivers oxygen, nutrients, and hormones to tissues; delivers carbon dioxide to lungs and other waste products to kidneys for removal; blood that leaves the heart returns in 20–30 seconds; there are 5–6 quarts of blood in the human body.

COMPONENTS

Red Blood Cells (RBCs)

- Also called **erythrocytes**, they are non-nucleated, bi-concave discs when mature. They contain Hb, have a 120-day lifespan, and are 6–8 µm diameter (avg).
- **Hemoglobin (Hb):** 4 polypeptide (globin) chains: 96–98% Hb-A (α₂β₂), 1.5–3.2% Hb-A₂ (α₂β₂), and 0.5–0.8% Hb-F (α₂γ₂), wherein each polypeptide chain (α, β, γ, and δ) contains an iron atom bound to protoporphyrin to form a heme; it transports oxygen from lungs to body tissues and carbon dioxide from body tissues to lungs.

White Blood Cells (WBCs)

Also called **leukocytes**, they defend the body against infection. There is ~1 WBC for every 500–700 RBCs.

GRANULOCYTES

- Also called **myelocytes**, they are immune cells containing granules that release enzymes.
- **Basophil:** Cell's granules release enzymes during an allergic reaction, asthma, and infection. It can be stained by basic dye, is phagocytic, and has a lifespan of a few hours to a few days.
- **Eosinophil (acidophil):** Cell's granules release enzymes during an allergic reaction, asthma, and an infection with parasites. It can be stained by acidic dye, is phagocytic, and has a lifespan of 8 to 12 days.
- **Neutrophil (polymorph):** Most numerous WBC; characterized by a dense, multi-lobed nucleus (2–5 lobes) and a pale cytoplasm with an irregular outline and fine azurophilic granules, which are predominantly secondary (specific) granules (see **myelocyte** below). Has a 6–50 hour lifespan.
 - These precursors, located in bone marrow, rarely occur in normal peripheral blood other than the band, stab, and juvenile forms.
- **Myeloblast:** Also called **myelomonoblast**, it is the earliest recognizable precursor; characterized by a large nucleus with fine chromatin and 2–5 nucleoli, and a cytoplasm with no granules. It varies in size, is capable of cell division, and it gives rise to promyelocytes. Bone marrow comprises less than 5% myeloblasts and it is difficult to distinguish from monoblasts, promonocytes, and monocytes (see **monocyte** below).
- **Promyelocyte:** Slightly larger than myeloblasts, can distinguish commitment to basophilic, eosinophilic, and neutrophilic lineages using electron microscopy (EM). Cytoplasm contains primary granules (of lysosomal origin) containing myeloperoxidase (MPO) and other acid hydrolases. It is capable of cell division, and gives rise to myelocytes.
- **Myelocyte:** Can distinguish morphological commitment to basophilic, eosinophilic, and neutrophilic lineages. The nuclear chromatin is more condensed, nucleoli are not visible, and the cytoplasm contains secondary (specific) granules of lysosomal origin containing lactoferrin, lysozyme, and other enzymes. It is capable of cell division and gives rise to metamyelocyte.
- **Metamyelocyte:** Non-dividing cell. The nucleus is indented or band-shaped and the cytoplasm contains primary and secondary granules.
- **Band, stab, or juvenile:** Forms of neutrophil between metamyelocyte and mature neutrophil. They are distinguishable from mature neutrophil by the absence of clear, fine filaments between nuclear lobes.
- **Functions:**
 - **Chemotaxis:** Cell is mobilized and migrates to a foreign material (e.g., bacterium, fungus, debris) or a site of inflammation by chemotactic substances released by damaged tissue, cytokines, and by the interaction of leukocyte adhesion molecules with ligands on damaged tissue.
 - **Phagocytosis:** Ingestion of bacteria, fungi, foreign debris, and dead or damaged host cells.
 - **Cling and digestion:**
 - **Oxygen-dependent:** Superoxide, hydrogen peroxide, and other activated oxygen species are generated from oxygen and reduced nicotinamide adenine dinucleotide phosphate (NADPH). Bacteria are killed when hydrogen peroxide reacts with halide and myeloperoxidase; process may also involve activated oxygen species.
 - **Oxygen-independent:** Proteins, such as cathelicin C, lysozyme (with hydrogen peroxide), or elastase (with hydrogen peroxide) kill bacteria; may also act with a decrease in pH inside a phagocytic vacuole containing lysosomal enzymes. Lactoferrin binds iron, thereby depriving bacteria of iron and generating free radicals (bacteriostatic).

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Table of Contents Hematology Study Guide For Specialty Test

1. Understanding the eBook Hematology Study Guide For Specialty Test
 - The Rise of Digital Reading Hematology Study Guide For Specialty Test
 - Advantages of eBooks Over Traditional Books
2. Identifying Hematology Study Guide For Specialty Test
 - Exploring Different Genres
 - Considering Fiction vs. Non-Fiction
 - Determining Your Reading Goals
3. Choosing the Right eBook Platform
 - Popular eBook Platforms
 - Features to Look for in an Hematology Study Guide For Specialty Test
 - User-Friendly Interface
4. Exploring eBook Recommendations from Hematology Study Guide For Specialty Test
 - Personalized Recommendations
 - Hematology Study Guide For Specialty Test User Reviews and Ratings
 - Hematology Study Guide For Specialty Test and Bestseller Lists
5. Accessing Hematology Study Guide For Specialty Test Free and Paid eBooks

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 - Adjustable Fonts and Text Sizes of Hematology Study Guide For Specialty Test
 - Highlighting and Note-Taking Hematology Study Guide For Specialty Test
 - Interactive Elements Hematology Study Guide For Specialty Test
- 8. Staying Engaged with Hematology Study Guide For Specialty Test
 - Joining Online Reading Communities
 - Participating in Virtual Book Clubs
 - Following Authors and Publishers Hematology Study Guide For Specialty Test
- 9. Balancing eBooks and Physical Books Hematology Study Guide For Specialty Test
 - Benefits of a Digital Library
 - Creating a Diverse Reading Collection Hematology Study Guide For Specialty Test
- 10. Overcoming Reading Challenges
 - Dealing with Digital Eye Strain
 - Minimizing Distractions
 - Managing Screen Time
- 11. Cultivating a Reading Routine Hematology Study Guide For Specialty Test
 - Setting Reading Goals Hematology Study Guide For Specialty Test
 - Carving Out Dedicated Reading Time
- 12. Sourcing Reliable Information of Hematology Study Guide For Specialty Test
 - Fact-Checking eBook Content of Hematology Study Guide For Specialty Test
 - Distinguishing Credible Sources
- 13. Promoting Lifelong Learning
 - Utilizing eBooks for Skill Development

- Exploring Educational eBooks

14. Embracing eBook Trends

- Integration of Multimedia Elements
- Interactive and Gamified eBooks

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