2

The Hematopoietic System

A. TRANSITION GRID

Information concerning Chapter 4, "Structure and Function of Hematopoietic Organs"; Chapter 5, "The Erythrocyte"; Chapter 6, "Hemoglobin"; and Chapter 7, "The Leukocyte" may also be referenced in the following hematology textbooks.

Clinical Laboratory Hematology	*Chapter 4*	*Chapter 5*	*Chapter 6*	*Chapter 7*
McKenzie, 1st edition	Chapter 3	Chapter 4	Chapter 5	Chapter 6
Harmening, 5th edition	Chapter 1	Chapter 3	Chapter 3	Chapter 15
Rodak, 3rd edition	Chapter 7	Chapters 8, 9	Chapter 10	Chapter 12
Turgeon, 4th edition	Chapter 4	Chapter 5	Chapter 5	Chapters 14, 16

B. OBJECTIVES

Chapter 4 – Structure and Function of Hematopoietic Organs

Level I

1. Identify the sites of hematopoiesis during embryonic and fetal development as well as in childhood and adulthood.
2. Identify organ/tissue sites in which each hematopoietic cell type differentiates.
3. Explain the difference between primary and secondary lymphoid tissue.
4. Describe the function of bone marrow, spleen, lymph nodes, and thymus.

Level II

1. Associate physical findings (hypersplenism, lymphadenopathy) with the presence of hematologic disease.

2. Describe the pathophysiologic changes that lead to bone marrow hyperplasia or extramedullary hematopoiesis.
3. Identify sites of extramedullary hematopoiesis.
4. Describe the structure of bone marrow, spleen, lymph nodes, and thymus.

Chapter 5 – The Erythrocyte

Level I

1. List and describe the stages of erythrocyte maturation in the marrow from youngest to most mature cells.
2. Explain the maturation process of reticulocytes and the cellular changes that take place.
3. Identify the normal range for reticulocytes.
4. Explain the function of erythropoietin; include the origin of production, bone marrow effects, and normal values.
5. Describe the function of the erythrocyte membrane.
6. Name the energy substrate of the erythrocyte.
7. Diagram the mechanism of extravascular erythrocyte destruction and hemoglobin catabolism.
8. Diagram the mechanism of intravascular erythrocyte destruction and hemoglobin catabolism.
9. State the average dimensions and life span of the normal erythrocyte.
10. Describe the function of 2,3-BPG and its relationship to the erythrocyte.

Level II

1. Summarize the mechanisms involved in the regulation of erythrocyte production.
2. Describe the structure of the erythrocyte membrane, including general dimensions and features; assess the function of the major membrane components.
3. Explain the mechanisms used by the erythrocyte to regulate permeability to cations, anions, glucose, and water.
4. Compare and contrast three pathways of erythrocyte metabolism and identify key intermediates as well as the relationship of each to erythrocyte survival and longevity.
5. Generalize the metabolic and catabolic changes within the erythrocyte that occur with time that "label" the erythrocyte for removal by the spleen.
6. Compare and contrast erythrocyte extravascular destruction with intravascular destruction and identify which process is dominant given laboratory results.
7. Predict the effects of increased and decreased erythropoietin levels in the blood.

Chapter 6 – Hemoglobin

Level I

1. Diagram the quaternary structure of a molecule of hemoglobin identifying the heme ring, globin chains, and iron.
2. Assemble fetal and adult hemoglobin molecules with appropriate globin chains.
3. Explain how pH, temperature, 2,3-BPG, and PO_2 affect the oxygen dissociation curve (ODC).

4. List the types of hemoglobin normally found in adults and newborns and give their approximate concentration.
5. Summarize hemoglobin's function in gaseous transport.
6. Define *normal hemoglobin values.*
7. Explain how the fine balance of hemoglobin concentration is maintained.
8. Compare HbA with HbA1c and explain what an increased concentration of HbA1c means.

Level II

1. Construct a diagram to show the synthesis of a hemoglobin molecule.
2. Describe the ontogeny of hemoglobin types; contrast differences in oxygen affinity of HbF and HbA, and relate them to the structure of the molecule.
3. Explain the molecular control of heme synthesis.
4. Given information on pH, 2,3-BPG, temperature, and HbF concentration, interpret the ODC and translate it into the physiologic effect on oxygen delivery.
5. Contrast the structures and functions of relaxed and tense hemoglobin and propose how these structures affect gaseous transport.
6. Describe how abnormal hemoglobins are acquired, and select a method by which they can be detected in the laboratory.
7. Assess the oxygen affinity of abnormal acquired hemoglobins and reason as to how this affects oxygen transport.
8. Compare and contrast the exchange of O_2, CO_2, H^+ and Cl^- at the level of capillaries and the lungs.

Chapter 7 – The Leukocyte

Level I

1. Identify terms associated with increases and decreases in leukocytes.
2. Differentiate morphologically the leukocyte precursors found in the proliferative compartment of the bone marrow.
3. Compare and contrast the development including distinguishing maturation and cell features of the granulocytic, monocytic-macrophage, and lymphocytic cell lineages.
4. Compare and contrast the morphologic and other distinguishing cell features of each of the leukocytes found in the peripheral blood.
5. Compare and contrast the function of each of the leukocytes found in the peripheral blood.
6. Summarize the process of neutrophil migration and phagocytosis.
7. List the adult reference ranges for the leukocytes found in the peripheral blood.
8. Calculate absolute cell counts from data provided.
9. Differentiate absolute values and relative values of cell count data.
10. List causes/conditions that increase or decrease absolute numbers of individual leukocytes found in the peripheral blood.
11. Compare and contrast pediatric and newborn reference ranges and adult reference ranges.
12. Explain immunoglobulin diversity.

Level II

1. Summarize the kinetics of the granulocytic, monocytic-macrophage, and lymphocytic cell lineages.
2. Describe the processes that permit neutrophils to leave the peripheral blood circulation and move to a site of infection and propose how defects in these processes affect the body's defense mechanism.
3. Compare and contrast the immunologic features and functions of each of the leukocytes found in the peripheral blood.
4. Summarize lymphocyte membrane characteristics and molecular changes used to differentiate subtypes.
5. Differentiate between polyclonal and monoclonal antibodies and discuss each type in relationship to a patient's clinical condition.
6. Compare and discriminate morphological features of Russell bodies, Mott cells, and flame cells.
7. Design systems to evaluate laboratory data of leukocytes for error detection.
8. Formulate pathways to correlate laboratory data of leukocytes with clinical knowledge of the patient.

Note: *Statements in parts C, D, & E identified with asterisks suggest Level II competencies*

C. ACTIVE LEARNING SUGGESTED ACTIVITIES

{Background information on each suggested activity is provided in the ***Introduction/Teaching Tips*** *section at the beginning of this Instructor's Resource Manual.}*

1. **Clear the Mud** At the end of class, pass out index cards to all students and ask each of them to write down any topic, current or past, that is still unclear. Have students place their respective index cards into a container on the instructor's desk. As students leave, they should randomly pick an index card from the container, research the topic, and prepare an answer or explanation to the "muddy point" written on the card. The instructor may choose to ask a few students to present their explanation during the next class period.
2. **Diagram**
   a. The mechanism of extravascular hemoglobin catabolism
   b. The mechanism of intravascular hemoglobin catabolism
   c. The quaternary structure of a molecule of hemoglobin
   d. **Graphically design all erythroid precursors.
3. **Extra, Extra, Read All About It**
   a. Have each learner write a newspaper or magazine article about the celebrity group, ***"Erythropoietin,"*** they interviewed. Include in this article where "our stars" are from, what influences them, what affect they have on their environment, and describe "their" most important contribution.
   b. **You are a traveller through the bone marrow. Describe what you see when you come upon the ***Erythroblastic Island.*** Tell the story of the erythroblast inhabitant.
   c. **Have the student ceate a travel log for a **neutrophil's** experience after it leaves the bone marrow. Instruct the learner to include the adventures during adherence, migration, and phagocytosis.

4. **Mapping** Create a Map for:
   a. The development of hematopoiesis from fetus to adult
   b. **The chemical synthesis of heme and globin chains
   c. **Lymphocytes, including function, development, and markers
   d. **Metabolic pathways in the erythrocyte

5. **Match-Up Game** Create a Concentration Game with:
   a. The names of different types of hemoglobin and their corresponding globin chain pairs. May also include in this activity the definitions and names of hemoglobin when combined with different substances (e.g., oxyhemoglobin, sulfhemoglobin, etc.).
   b. Divide the learners into small groups. Have each group "create" their own concentration game for the following. When completed have each group play the other groups' game.
      - The list of leukocytes and their reference ranges
      - The list of leukocytes and their morphology
      - The list of leukocytes and conditions in which each would be increased or decreased
        - **This same exercise can be adjusted to a Level II activity if cells such as promonocytes, prolymphocytes, immunoblasts, and so on are included.
      - **The following cells and their functions
        - Megakaryocytes
        - Mast cells
        - Osteoblasts
        - Osteoclasts
        - Macrophages
        - Reticular cells
        - Adipocytes

6. **Mystery Box**
   a. Provide information on hematopoiesis
      - Time of gestation (e.g., third month of fetal life)
      - Type of cell produced (e.g., primitive erythroblast, T cell, etc.)
      - Organ or location (e.g., yolk sac, thymus, etc.)
      - Have the learners pull each piece of paper and match the time of gestation, type of cell produced, and organ to solve the hematopoiesis mystery.
   b. Provide pieces of paper that have a basic disease condition listed on them, that is, bacterial infection, flu, and so on.
      - Have the learners select a disease condition and create correlating CBC and manual differential results.
   c. Provide the total WBC counts and differential percents for the normal leukocytes.
      - Have the learners calculate the absolute values for each set of results provided.
      - Also have learners evaluate the absolute values using the appropriate medical terms, that is, lymphocytosis, neutropenia, and so on.
        - An alternate Mystery Box is to provide the medical terms, that is, agranulocytosis and basophilia, and ask the learners to create corresponding differential and CBC results.
   d. **On separate pieces of paper write the:
      - Size and N:C ratio
      - Cytoplasmic characteristics
      - Nuclear characteristics

Have students combine the appropriate characteristics and identify the correct name of the erythroid precursor. To extend this exercise, the instructor may consider asking students to draw, or graphically design, each erythroid precursor and then match each with the appropriate characteristic.

7. **One-Minute Paragraph**
   a. **Without prior learning or lecture, have the learners read the appropriate sections and ask them to write a one-minute paragraph on the following topics.
      - Discuss the negative consequences of hyperplasia.
      - Explain why blood cells must have the ability to "deform."
      - Explain the reason for a hypoxic, acidic, and hypoglycemic environment in the spleen.
   b. Describe the function of bone marrow, spleen, thymus and lymph nodes. Give one minute for each site.
   c. After the appropriate lecture, give the learners one minute to explain the structure of the hemoglobin molecule.
   d. ** Explain the *Bohr effect.*
   e. ** Describe the relationship between lymphocytes and macrophages in the immune system.
8. **Mnemonic Device** Have each learner develop and share a mnemonic device to learn the:
   a. Erythrocyte maturation stages, e.g., Princess Brown's Pet Ox Ran Everywhere
   b. Neutrophilic maturation stages
9. **Small Group Teaching** Assign a small group of learners the following topics. They should be instructed to present and teach these concepts to the rest of the class.
   a. Erythrocyte destruction (extravascular and intravascular)
   b. Oxygen dissociation curve and how pH, temperature, 2,3-BPG, and PO_2 affect the curve
   c. **The role of the iron responsive element-binding protein (IRE_BP)
   d. **Differentiate the marginating and circulating pools of neutrophils. Explain how the two pools freely exchange neutrophils.
10. **Think-Pair-Share**
    a. Distinguish between primary and secondary lymphoid tissues.
    b. Describe the morphology that differentiates a band from a segmented neutrophil.
    c. **In detail, explain the hemoglobin-2,3 BPG interaction.
    d. **Discuss the relationship between neutrophils and coagulation.
    e. **Differentiate between polyclonal and monoclonal antibodies and describe clinical conditions where each is found.
11. **Thumbs Up/Thumbs Down**

    Remember to get immediate feedback on any topic during the class period, call for a quick "Thumbs Up or Thumbs Down." Ask students to indicate if they comprehend the information presented by showing either a thumbs up, indicating they understand the information, or thumbs down, meaning more explanation or clarification is needed.
12. **Web Search**
    a. Have each learner conduct a Web search on the following topics and write two to three paragraphs on the information they collected.
       - Glycolytic pathway (Embden-Meyerhoff pathway)
       - Hexose monophosphate shunt
       - Methemoglobin reductase pathway
       - Rapoport-Leubering shunt
    b. Have each learner find and share a Web site that provides leukocyte morphology.

D. LABORATORY ACTIVITIES

1. Discuss specimen requirements, preparation, and handling for WBC, RBC, and Hgb.
2. Discuss pre-analytical, analytical, and post-analytical causes for unexpected results.
3. Perform manual cell counts for
   - WBC
   - RBC
4. Perform automated procedures on learner/patient or quality control samples to evaluate:
   - WBC
   - RBC
   - Hgb
5. Discuss interfering substances for WBC, RBC, and Hgb analysis.
6. **Morphologically identify RBC stages of maturation using prepared peripheral smears, Kodachrome, or CD-ROM programs.
7. Morphologically identify normal WBC using prepared peripheral smears, Kodachrome, or CD-ROM programs.

E. PRACTICE QUESTIONS

1. The role of the macrophage in the *erythroblastic island* is to [Taxonomy 1]
   a. Insulate the maturing erythrocytes
   b. Protect the erythroblast from other invading cells
   c. Provide nutrients to the erythroblast
   d. Regulate erythropoiesis by secreting various cytokines
2. **What is the rate limiting enzyme in heme synthesis? [Taxonomy 1]
   a. ALAS
   b. Ferrochelatase
   c. Glucose-6-phosphatase
   d. Peptidase
3. **Describe how oxygen diffuses from the blood into the tissues. [Taxonomy 1]
4. **List two sites of extramedullary hematopoiesis and describe the structure of each. [Taxonomy 1]
5. Distinguish between the "hematopoietic compartment" and the "vascular compartment." [Taxonomy 2]
6. Tommy moved from a location at sea level where his red count $= 4.90 \times 10^{12}$/L to a mountain home at 10,000 feet. Select the red blood cell count that might reflect his living in the mountains for 12 months. [Taxonomy 2]
   a. 3.70×10^{12}/L
   b. 4.80×10^{12}/L
   c. 5.70×10^{12}/L
   d. 6.90×10^{12}/L

7. **Explain the "high mortality" of neutrophils during a sustained inflammatory response. [Taxonomy 2]
8. **Compare and contrast the content and structure of the red and white pulp in the spleen. [Taxonomy 3]
9. **Estimate the change in the factors that affect oxygen affinity of an individual at rest and one that has completed 20 minutes of strenuous exercise. [Taxonomy 3]
10. Compare and contrast the nucleus and cytoplasmic morphology in mature and immature neutrophils. [Taxonomy 3]
11. A 15-year-old female patient was seen at a city medical clinic. For the past three days, she has complained of an "upset stomach" and excessive vomiting. Her guardian gave her a drink of sodium bicarbonate and water each day to calm her stomach. Laboratory results revealed a condition of metabolic alkalosis. How would this patient's acid-base condition affect her oxygen affinity and the oxygen dissociation curve? [Taxonomy 3]

The Hematopoietic System—Level I

Figure out what words the clues represent. Then find the words in the grid. Words can go horizontally, vertically, and diagonally in all eight directions.

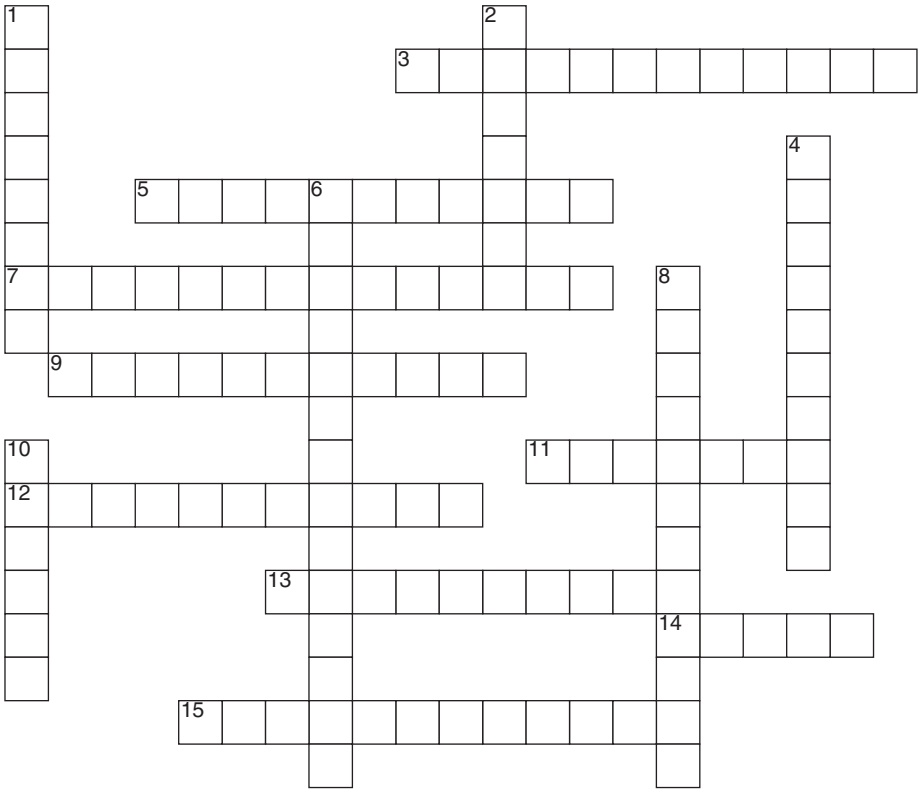
B Z T N W D T Y N H B Q T W T S J J D
X H Y P E R P L A S I A T K L T N T E
H J H V S Y L P L C F Z L I K S T B O
Y J B T I L K E Y C M K H Q M A J T X
P F L T S P I B U K T P D Q J L X P Y
E D N X O Q D H W K O X C K E B R R H
R N K C T T M W P N O V K X L O R L E
S W F V Y T N H I O F P T Y N E R D M
E C R M C G Q S P N R R E O J T M D O
G G L X O R O Z M B A T R N L S H G G
M R C T G E C C D M R M U L I O B J L
E N D G A P X L E K O D E E H A K X O
N R N Z H H M D M B R C K Z N K V Q B
T Y Z M P D U Q L L T R W I P R V W I
E L R C Y L W A P S R N N B D P X L N
D L D D L T S Z A J E T Y C O N O M C
T L N A N T G M K M M T K B D L E B T
P X R M E T A M Y E L O C Y T E K Y Y
Q Y D P C V N I B O L G O M E H T E M

- cell process in which cell engulfs foreign substances
- cell that is increased in parasitic infections
- excessive proliferation of normal cells within an organ
- hemoglobin without oxygen
- decrease in leukocytes
- earliest morphologically recognizable erythrocyte precursor
- largest mature cell in peripheral blood
- neutrophil with >5 lobes
- type of hematopoiesis outside the bone marrow
- most numerous WBC in adult peripheral blood
- cells involved in the formation of calcified bone
- precursor granulocytic cell with kidney bean shaped nucleus
- tissue basophil (2 words)
- organ that produces EPO
- Hb with Fe+++

The Hematopoietic System—Level I

- cell process in which cell engulfs foreign substances (phagocytosis)
- cell that is increased in parasitic infections (eosinophil)
- excessive proliferation of normal cells within an organ (hyperplasia)
- hemoglobin without oxygen (deoxyhemoglobin)
- decrease in leukocytes (leucopenia)
- earliest morphologically recognizable erythrocyte precursor (pronormoblast)
- largest mature cell in peripheral blood (monocyte)
- neutrophil with >5 lobes (hypersegmented)
- type of hematopoiesis outside the bone marrow (extramedullary)
- most numerous WBC in adult peripheral blood (neutrophil)
- cells involved in the formation of calcified bone (osteoblasts)
- precursor granulocytic cell with kidney bean shaped nucleus (metamyelocyte)
- tissue basophil (2 words) (mast cell)
- organ that produces EPO (kidney)
- Hb with Fe+++ (methemoglobin)

The Hematopoietic System—Level I



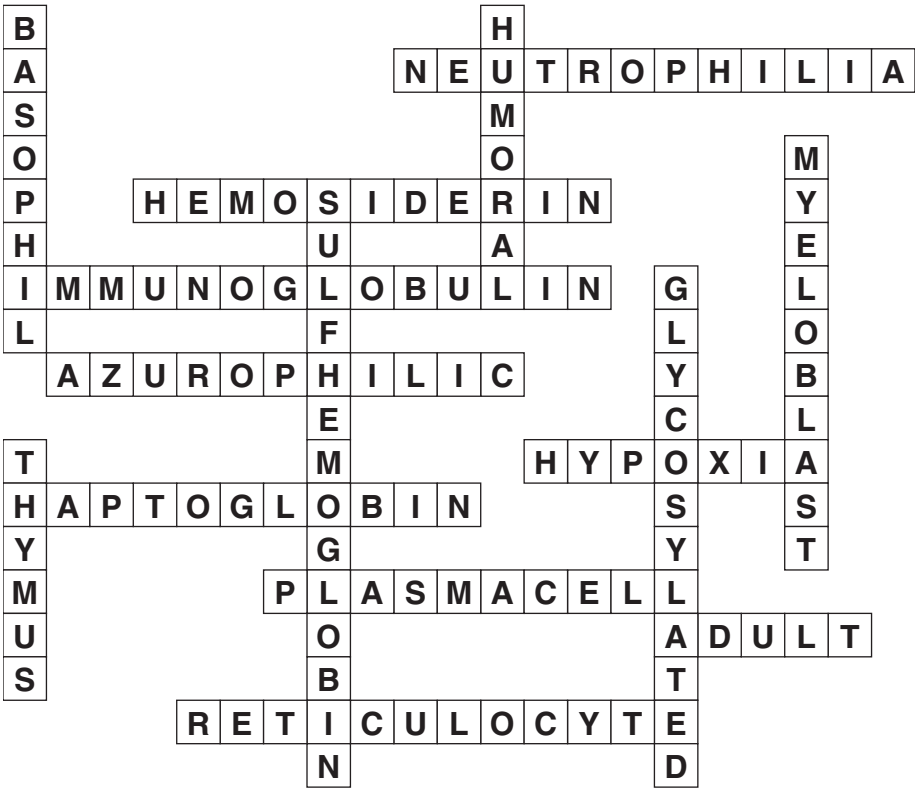
ACROSS

3 Increase in neutrophils
5 Iron-protein complex visualized with Prussian-blue stain
7 Unique molecule produced by B lymphocytes and plasma cells
9 Reddish-purple primary granules
11 Inadequate oxygen at the tissue level
12 Plasma glycoprotein that transports free hemoglobin
13 Type of lymphocyte with nucleus eccentrically placed (2 words)
14 Type of hemoglobin with two alpha and two beta globin chains is the major Hb of _____
15 Non-nucleated RBC with residual RNA

DOWN

1 Mature granulocyte with presence of large basophilic granules
2 Type of immunity produced by antibodies by B lymphocytes
4 Earliest morphologically recognizable granulocyte precursor
6 Sulfur atom combined with hemoglobin
8 Type of Hb with glucose irreversibly attached
10 During fetal development, major site of T cell production

The Hematopoietic System—Level I



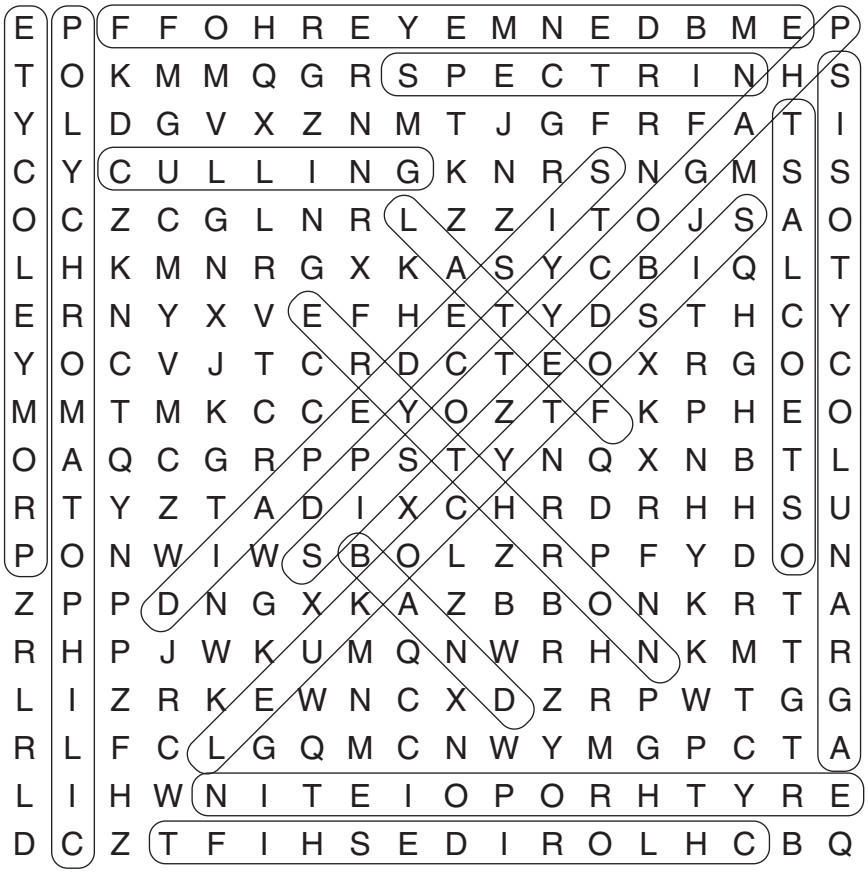
The Hematopoietic System—Level II

Figure out what words the clues represent. Then find the words in the grid. Words can go horizontally, vertically, and diagonally in all eight directions.

E P F F O H R E Y E M N E D B M E P
T O K M M Q G R S P E C T R I N H S
Y L D G V X Z N M T J G F R F A T I
C Y C U L L I N G K N R S N G M S S
O C Z C G L N R L Z Z I T O J S A O
L H K M N R G X K A S Y C B I Q L T
E R N Y X V E F H E T Y D S T H C Y
Y O C V J T C R D C T E O X R G O C
M M T M K C C E Y O Z T F K P H E O
O A Q C G R P P S T Y N Q X N B T L
R T Y Z T A D I X C H R D R H H S U
P O N W I W S B O L Z R P F Y D O N
Z P P D N G X K A Z B B O N K R T A
R H P J W K U M Q N W R H N K M T R
L I Z R K E W N C X D Z R P W T G G
R L F C L G Q M C N W Y M G P C T A
L I H W N I T E I O P O R H T Y R E
D C Z T F I H S E D I R O L H C B Q

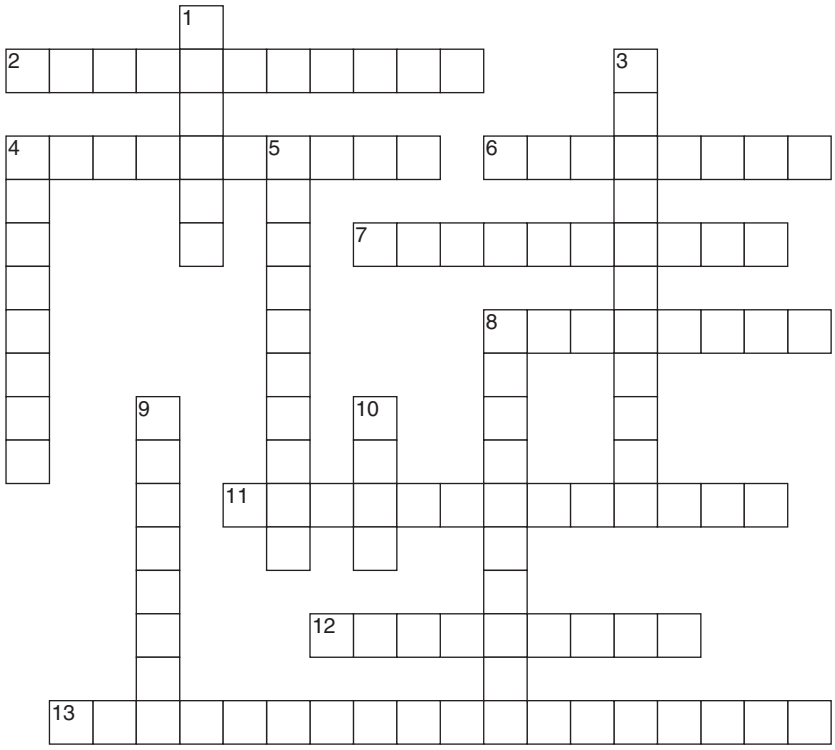
- first granulocytic precursor with presence of azurophilic granules
- last normoblast stage capable of mitosis
- increase in leukocytes
- filtering and destruction of damaged red cells by the spleen
- granulocyte with a horseshoe shaped nucleus
- cell process in which cell engulfs foreign substances
- pathway for metabolism of glucose in RBC (2 words)
- hormone that stimulates production of RBC
- type of hemoglobin that constitutes <2% of total Hb in adults
- cell involved in resorption and remodeling of calcified bone
- Cl—diffuses into the cell from the plasma (2 words)
- passage of blood cells through the unruptured capillary wall
- predominant skeletal protein
- totality of all stages of erythrocytes
- absence of granulocytes

The Hematopoietic System—Level II



- first granulocytic precursor with presence of azurophilic granules (promyelocyte)
- last normoblast stage capable of mitosis (polychromatophilic)
- increase in leukocytes (leukocytosis)
- filtering and destruction of damaged red cells by the spleen (culling)
- granulocyte with a horseshoe shaped nucleus (band)
- cell process in which cell engulfs foreign substances (phagocytosis)
- pathway for metabolism of glucose in RBC (2 words) (Embden Meyerhoff)
- hormone that stimulates production of RBC (erythropoietin)
- type of hemoglobin that constitutes <2% of total Hb in adults (fetal)
- cell involved in resorption and remodeling of calcified bone (osteoclast)
- Cl—diffuses into the cell from the plasma (2 words) (chloride shift)
- passage of blood cells through the unruptured capillary wall (diapedesis)
- predominant skeletal protein (spectrin)
- totality of all stages of erythrocytes (erythron)
- absence of granulocytes (agranulocytosis)

The Hematopoietic System—Level II



ACROSS

2 Abnormal RBC shape due to an alteration in membrane lipids
4 Neutrophil migration guided by chemoattractant gradients
6 Syndrome; lack of thymus development in the fetus
7 Form by which most CO_2 is transported by the blood
8 Inactive X chromosome appears as an appendage of the neutrophil nucleus (2 words)
11 Neutrophilic precursor; kidney-bean shaped nucleus
12 Projection of calcified bone extending from cortical bone into the marrow space
13 Normoblast with abundant gray-blue cytoplasm and low N:C ratio

DOWN

1 Microenvironment that supports hematopoietic cell proliferation in the bone marrow
3 Characteristics of most growth factors in which they act on more than one cell type
4 Result of excess deoxygenated hemoglobin in the blood
5 Type of cell in which the cytoplasm is replaced with a single fat vacuole
8 The effects of pH on hemoglobin-oxygen affinity (2 words)
9 Plasma cell filled with globules containing immunoglobulins
10 First enzyme in the heme synthetic pathway (abrv)

The Hematopoietic System—Level II