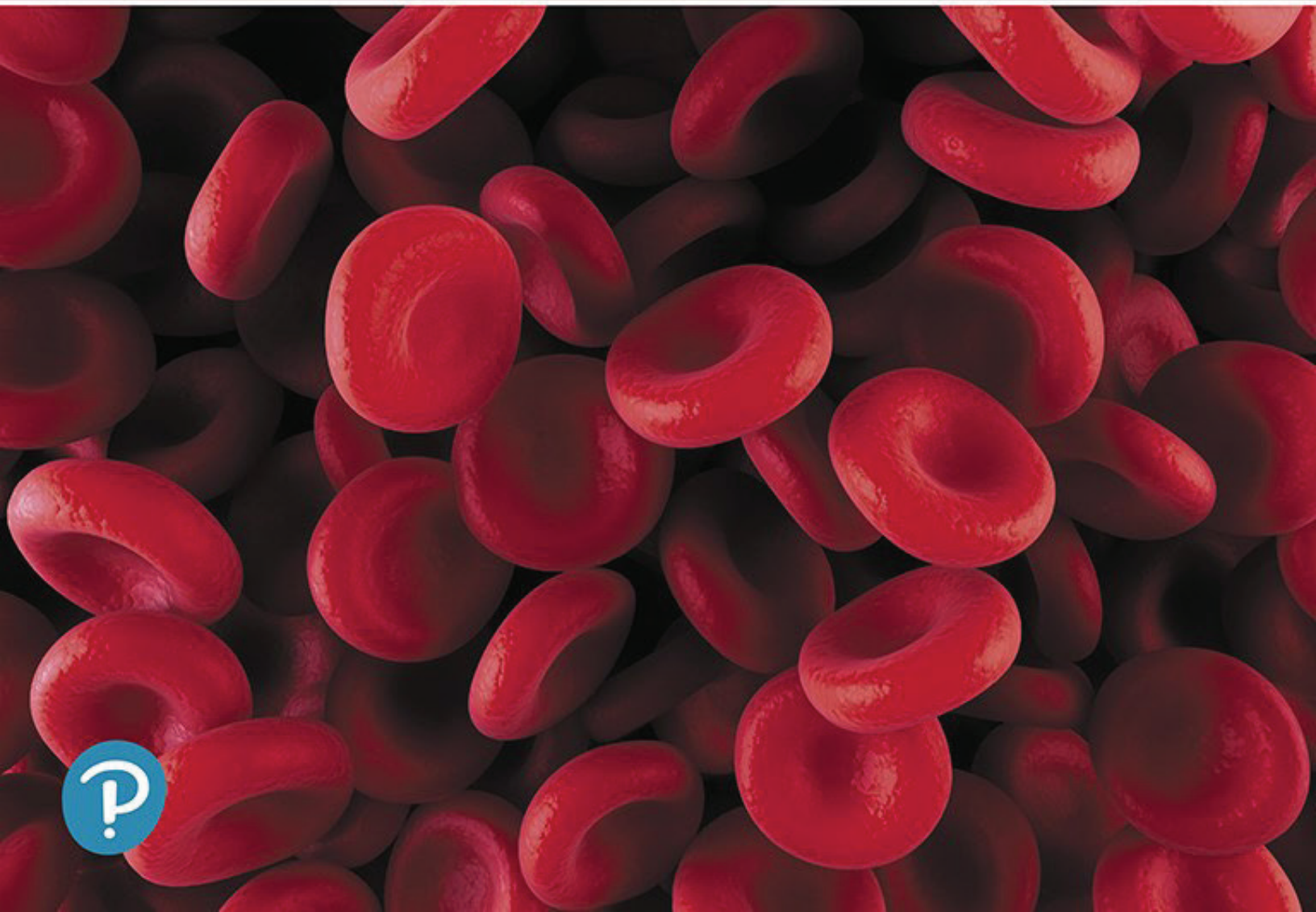
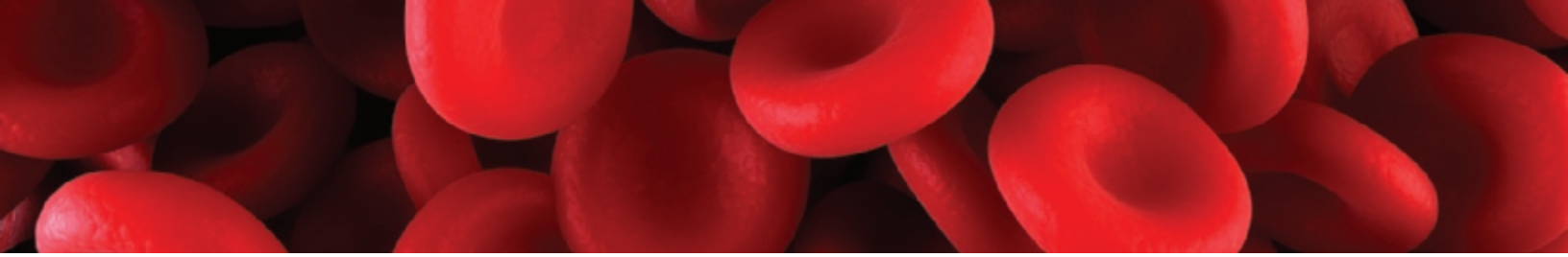
Clinical Laboratory HEMATOLOGY

Fourth Edition

Shirlyn McKenzie | Kristin Landis-Piwowar | Lynne Williams





Fourth Edition

Clinical Laboratory Hematology

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Manufacturing Buyer: Maura Zaldivar-Garcia, LSC Communications, Inc.
Cover Designer: Pearson CSC

Library of Congress Cataloging-in-Publication Data

Names: McKenzie, Shirlyn B., author. | Landis-Piwowar, Kristin, author. | Williams, Joanne Lynne, 1949- author.
Title: Clinical laboratory hematology / Shirlyn B. McKenzie, Kristin Landis-Piwowar, J. Lynne Williams.
Other titles: Pearson clinical laboratory science series.
Description: Fourth edition. | Hoboken : Pearson, [2020] | Series: Pearson's clinical laboratory science series | Includes bibliographical references and index.
Identifiers: LCCN 2019010608| ISBN 9780134709390 | ISBN 013470939X
Subjects: | MESH: Clinical Laboratory Techniques | Hematology—methods | Hematologic Diseases—diagnosis | Hematopoietic System—physiology
Classification: LCC RB45 | NLM WH 25 | DDC 616.1/5075—dc23 LC record available at https://lccn.loc.gov/2019010608

ISBN-13: 978-0-134-70939-0
ISBN-10: 0-134-70939-X

To my family, the wind beneath my wings, Gary, Scott, Shawn, Belynda, and Dora; my special grandchildren Lauren, Kristen, Weston, Waylon, and Wyatt; to the memory of my parents, George and Helen Olson.

—Shirlyn B. McKenzie

To Theron and Kaia, you sustain my every breath and to Todd, you are my rock.

—Kristin R. Landis-Piwowar

For my mother, Mary Williams, who gave her children roots as well as wings; for Lee, Laurie, Roger, and Richard, who sustain my roots; for Dulaney, Corie, Chris, Ava, and Holden, whom I love as my own; and to the memory of my father, David Williams.

—J. Lynne Williams

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Foreword

Clinical Laboratory Hematology is part of Pearson's Clinical Laboratory Science (CLS) series of products, which is designed to balance theory and practical applications in a way that is engaging and useful to students. The authors of and contributors to *Clinical Laboratory Hematology* present highly detailed technical information and real-life case studies that will help learners envision themselves as members of the health care team, providing the laboratory services specific to hematology that assist in patient care. The mixture of theoretical and practical information relating to hematology provided in this text allows learners to analyze and synthesize this information and, ultimately, to answer questions and solve problems and cases. Additional instructional resources are available at www.pearson.com

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Preface

Revel ™ for *Clinical Laboratory Hematology* takes on a new face as a digital textbook. Revel is Pearson's newest way of delivering our respected content. Fully digital and highly engaging, Revel offers an immersive learning experience designed for the way today's students read, think, and learn. Enlivening course content with media interactives and assessments, Revel empowers educators to increase engagement with the course, and to better connect with students. To our knowledge this is the first book written for medical laboratory technician (MLT) and medical laboratory science (MLS) students in this format. Pearson performed in-depth analysis to determine the learning preferences of our students and teaching methods of instructors. The results indicated that many students prefer to read and study using digital resources. Furthermore, on-line instruction is now commonplace. Based on this knowledge, the decision was made to update to the fourth edition using the Revel platform. The focus of the book remains the same; it is a comprehensive resource that MLT and MLS students can use in all their hematology courses. Laboratory practitioners will find the book a welcome resource to help them keep up with advances in the field. Although the book is primarily written for clinical laboratory students and practitioners, it also is suited for use by students and practitioners in other health care professions including pathology, medicine, physician assistant, and nursing. Great effort has been put in by our authors to ensure this edition is thoroughly updated to include the latest in advances in laboratory medicine. Each chapter has a similar format that makes it easy for readers to find information on each topic. The digital format makes it convenient to instantly find word definitions, cell images, and other information as needed. An image atlas, test bank, powerpoint presentation and instructor's manual are available for instructors who adopt the book for their classes. In summary, the book is not just a book but a package of learning tools.

You will note that we have added a new editor, Dr. Kristin Piwowar-Landis. Kristin was a consulting editor on the previous edition. Based on her outstanding writing and editing skills as well as thorough knowledge of hematology with a focus on hematopoietic genetics, she was invited to serve as an editor in this edition with Dr. McKenzie as her mentor. The ultimate goal is for Kristin to replace Dr. McKenzie who wants to retire from the responsibilities of primary editor in future editions. It has been a pleasure to mentor her through the book writing process. Dr. Lynne Williams continues as an editor in this edition. Lynne's in-depth knowledge in hemostasis as well as cellular biology shines through in the chapters she authors.

Organization

We believe that students must have a thorough knowledge of normal hematopoiesis and cell processes to understand the pathophysiology of hematologic/hemostatic diseases, evaluate and correlate laboratory test results, and ensure the appropriate utilization of the laboratory in diagnosis and patient follow-up. Thus, this book is organized so that the first nine chapters give the students a comprehensive base of knowledge about blood cell proliferation, maturation, and differentiation and the processes that control hematopoiesis. Section One (Chapters 1–2) includes an introduction to hematology and hematopoiesis, including cell morphology and the cell cycle and its regulation. This introduction includes a description of cellular processes at the molecular level, which could be new material for some students and a basic review for others. The reader might want to review these chapters before beginning a study of neoplastic disorders (Chapters 23–28). Section Two (Chapters 3–10) includes chapters on normal hematopoiesis, including a description of the structure and function of hematopoietic tissue and organs, erythropoiesis, leukopoiesis, thrombopoiesis, and hemoglobin. Hemoglobin synthesis, function, and breakdown are discussed in Chapter 6. The chapter on leukocytes is divided into two separate chapters: granulocytes/monocytes (Chapter 7) and lymphocytes (Chapter 8). An introductory chapter on platelets (Chapter 9) completes the discussion of normal blood cells. Details of platelet function and physiology are found in Section Seven, Chapter 31. Rounding out this section, "The Complete Blood Count and Peripheral Blood Smear Examination" (Chapter 10) describes the information that can be gained about blood cells from these frequently ordered laboratory tests. Most of the remaining chapters refer to the tests that are described in this chapter.

The next three sections include discussions of hematologic disorders. Section Three (Chapters 11–20) begins with an introduction to anemia (Chapter 11). We combined the introduction to anemia and the introduction to hemolytic anemia into one chapter because many anemias have a hemolytic component. This chapter is followed by chapters on the various anemias. Each anemia is discussed in the following manner: introduction, etiology, pathophysiology, clinical presentation, laboratory presentation, and therapy. This format helps readers understand what laboratory tests can help in diagnosis and how to interpret the results of these tests. Section Four (Chapters 21 and 22) covers the nonmalignant disorders of leukocytes. Section Five (Chapters 23–29) is a study of hematopoietic neoplasms. This section begins with

an overview of these disorders to help students understand the classification, terminology, and pathophysiology of neoplasms and the laboratory's role in diagnosis and therapy. As a part of this section, we included a chapter on stem cell transplantation (Chapter 29) because it is a frequently used therapy for these neoplasms and the laboratory plays a critical role in harvesting the stem cells and preparing them for transplant. Molecular studies are becoming a major diagnostic tool for neoplastic disorders and are discussed within each chapter as well as in the chapter devoted to molecular diagnostics (Chapter 42). Some instructors might prefer to cover Section Eight, the study of bone marrow (Chapter 38), flow cytometry (Chapter 40), cytogenetics (Chapter 41), and molecular diagnostics (Chapter 42) before teaching Section Five or integrate this material with Section Five. Some hematology courses do not include these topics, or instructors might not want to cover them in the depth presented in this book.

Section Six (Chapter 30) is a study of body fluids from a hematologic perspective and thus includes a large number of photographs of cells found in body fluids. Discussions of semen analysis and amniotic fluid lamellar body counts are included. Not all hematology courses include this topic, but the chapter is written in such a way that it can be used separately in a body fluid course.

Section Seven (Chapters 31–36) is a study of hemostasis. Chapters on normal hemostasis include primary and secondary hemostasis and fibrinolysis. They are followed by three chapters on disorders of hemostasis. Chapter 36 describes the testing procedures for hemostasis, including information on automation. This chapter describes an extensive collection of coagulation procedures.

Section Eight (Chapters 37–42) includes chapters on test procedures that help in the diagnosis of hematologic disorders. Automation in hematology is included in Chapter 39. Chapter 42 is designed to introduce molecular procedures and their use in detecting various hematologic and hemostatic disorders. A background in genetics is suggested before students begin this chapter.

Section Nine (Chapter 43) is a thorough discussion of quality assessment in the hematology laboratory. Problems discussed include common abnormal results, errors, and alert flags. Corrective action to take to resolve these problems is described. Several excellent tables help to quickly find needed information. We suggest that these tables be read early in the course of study because they can be used periodically when attempting to interpret and correlate laboratory test results. Chapter 10 refers the reader to these tables because it discusses interpretation of test results and abnormalities in the CBC.

Appendices collect additional information including step-by-step procedures for some hematology testing, and reference tables.

The text emphasizes the effective, efficient, and ethical use of laboratory tests. The clinical laboratory professional is in an ideal position to assist physicians in interpreting laboratory test results and choosing the best reflex tests to arrive at a diagnosis or evaluate therapy. Many laboratories develop algorithms to assist in these tasks. This text includes several algorithms that some laboratories use.

Suitable for all Levels of Learning

The book is designed for both MLT and MLS students. Using only one textbook for both levels is beneficial and economic for laboratory science programs that offer both levels of instruction. It also is helpful for programs that have developed articulated MLT to MLS curricula. The MLS program can be confident of the MLT's knowledge in hematology without doing a time-consuming analysis of the MLT course. In addition, this book is expected to be a great resource for students in on-line courses and for instructors who teach using this format.

Objectives are divided into two levels: Level I (basic) and Level II (advanced). MLT instructors who reviewed the objectives for this text generally agreed that most Level I objectives are appropriate for the MLT body of knowledge. They also indicated that some Level II objectives are appropriate for MLTs. MLS students should be able to meet both Level I and Level II objectives in most cases. If the MLS program has two levels of hematology courses—Level I and Level II—this book can be used for both.

All instructors, regardless of discipline or level, need to communicate to their students what is expected of them. They might want their students to find the information in the text that allows them to satisfy selected objectives, or they might assign particular sections to read. If not assigned specific sections to read, the MLT students may read more than expected, which is not a bad thing!

The design of the text is such that each chapter is divided into modules and each objective is identified with the module that addresses it. These objectives are divided into Level 1 and Level 2. There are two levels of review questions at the end of each module and chapter that are matched to the two levels of objectives. Case Study questions and the Checkpoints are included within each module and are appropriate for the information in that module or another previous module. Checkpoints and case study questions are not delineated by level. Students should use these valuable resources to assess their understanding of the material.

We recognize that there are many approaches to organizing a hematology course and that not all instructors teach in the same topic sequence or at the same depth. Thus, we encourage instructors to use the book by selecting appropriate chapters and objectives for their students based on their course goals. Each program should assess what content fits its particular curriculum. The layout of the book is such that instructors can select the sequence of chapters

in an order that fits their course design, which might not necessarily be the sequence in the book. However, we recommend that the course begin with Sections One and Two and that the chapters "Introduction to Anemia" and "Introduction to Hematopoietic Neoplasms" be studied before the individual chapters that follow on these topics. The Background Basics sections help the instructor determine which concepts students should master before beginning each chapter. This feature helps instructors customize their courses. Some hematology courses might not include some chapters on subjects such as molecular techniques, cytogenetics, flow cytometry, and body fluids but they might be helpful in other courses.

As a note, this text uses "mc" as an abbreviation for "micro", which replaces μ. Thus, abbreviations of mcg, mcL, mcM replace those that use the Greek letter "mu" (μg, μL, μM).

Unique Pedagogical Features

As in the past, the text has a number of unique pedagogical features to help the students assimilate, organize, and understand the information. Each chapter begins with a group of components intended to set the stage for the content to follow.

- The **Objectives** comprise two levels: Level I for basic or essential information and Level II for more advanced information. Each instructor should guide students to the appropriate level to meet course expectations.
- The **Key Terms** feature alerts students to important terms used in the chapter and found in the glossary. With this digital version, these terms are provided as links within the chapter, giving the student the definition within the glossary.
- The **Background Basics** component alerts students to material that they should have learned or reviewed before starting the chapter. In most cases, this feature links readers to previous chapters to help them find the material if they want to review it.
- The **Case Study** is a running scenario that first appears at the beginning of a chapter, giving a patient's clinical and laboratory information that is related to the chapter content. It is meant to focus the students' attention on the chapter subject matter. At appropriate places throughout the chapter additional information on the case is provided, such as additional laboratory test results, followed by questions that relate to the material presented in preceding sections. The answers are provided after the student submits the answers.
- The **Overview** gives readers an idea of the chapter content and organization.
- **Checkpoints** are integrated throughout the chapter to help the student determine if they understand what they just read. They are questions that require students to pause along the way to recall or apply information covered in preceding sections. The answers are provided after the student submits their answer.
- A **Summary** concludes the text portion of each chapter to help students bring all the material together.
- **Review Questions** appear at the end of each chapter. The two sets of questions, Level I and Level II, are referenced and organized to correspond to the Level I and Level II objectives. Answers are provided in the Appendix.
- Image Atlas

The page design features a number of enhancements intended to aid the learning process.

- **Figures and tables** are used liberally to help students organize and conceptualize information. This is especially important for visual learners.
- **Microphotographs** are displayed liberally in the book and are typical of those found in a particular disease or disorder. Students should be aware that cell variations occur and that blood and bone marrow findings do not always mimic those found in textbooks. Because there is so much variation in the morphology of normal and abnormal cells, we added a Flash Card review of additional cells at the end of many chapters. The legend for each microphotograph gives the original magnification but sometimes the image was zoomed to enhance detail.

Appendices

- Appendix A contains tables of reference intervals for common hematology test results.
- The table in Appendix B was extensively revised and updated consistent with the WHO 2017 classification of hematopoietic and lymphoid tissue through a collaborative effort of several authors (Drs. Kathleen Wilson, Katalan Keleman, Sara Taylor, and Tim Randolph). It lists hematopoietic neoplasms with the following information on each: immunophenotype using CD markers, cytogenetic abnormalities, and genotypic findings. This table provides a ready reference for information from the chapters in Section Five (Neoplastic Hematologic Disorders) and Section 8 (Hematology Procedures).
- Appendix C is a comprehensive classification of hematopoietic, lymphopoietic, and histiocytic/dendritic neoplasms using the updated 2017 WHO classification.
- Appendix D is a collection of common laboratory procedures that are linked from Chapter 37 where the procedure is discussed. These can be printed and used in hematology laboratory courses.

- Appendix E provides the answers to the multiple choice questions that appear at the end of each chapter.
- Appendix F provides the answers to the Checkpoint questions that appear throughout each chapter.
- Appendix G provides the answers to the Case Study questions that appear throughout each chapter.

A Complete Teaching and Learning Package

A variety of ancillary materials designed to help instructors be more efficient and effective and students more successful complements this book.

An **Instructor's Resource Center** is available upon adoption of the text and gives the instructor access to a number of powerful tools in an electronic format. The following materials are downloadable:

- The **TestGen** feature includes questions to allow instructors to design customized quizzes and exams. Download the TestGen desktop application and test bank, choose questions that align to your textbook, and generate your test — it's that easy!
- The **PowerPoint Lectures** tool contains key discussion points and color images for each chapter. This feature provides dynamic, fully designed, integrated lectures that are ready to use, allowing instructors to customize the materials to meet their specific course needs. These ready-made lectures will save instructors time and allow an easy transition into using *Clinical Laboratory Hematology*.
- The **Image Library** feature contains all of the images from the text. Instructors have permission to copy and paste these images into PowerPoint lectures, printed documents, or website as long as they are using *Clinical Laboratory Hematology* as their course textbook.
- The **Instructor's Resource Manual** tool in Word formats can be accessed.

Acknowledgments

Writing a textbook is a complicated task that requires a team of dedicated authors, editors, copy editors, artists, permission researchers, educators, practitioners, content reviewers, project and program managers, and many other individuals behind the scenes. The team that Pearson and the editors put together to make the fourth edition of this book an excellent hematology and hemostasis resource for students and health care practitioners worked tirelessly over several years to bring the project to completion. Dr. Kristin Landis-Piwowar envisioned how the mechanics of this new digital "book" could lend to a pioneering form of medical laboratory science education. The new and returning authors ensured that their chapters were up to date and accurate. Content reviewers and users of the previous editions provided helpful suggestions that were incorporated into the chapters. Dave Falleur, Diana Cochran-Black, Muneez Esani, Sara Wagner, Holly Weinberg, and Linda Whaley had important roles in reviewing select chapters. We offer our thanks to this group who ensured a quality textbook for a wide audience.

Mark Cohen from Pearson was responsible for the creation of the first edition of this text. His keen insights into developing a unique textbook design with pedagogical enhancements helped *Clinical Laboratory Hematology* become a leading textbook in the field of clinical laboratory science. Thank you, Mark. Thank you, Pearson, for having faith in us to publish a fourth edition in digital format. Thank you for creating and providing the special team of experts to help us accomplish this task. We recognize that the job is not over but will require the efforts of sales and marketing to ensure widespread use and adoption. John Goucher had the foresight to develop the fourth edition and for the background work that identified and justified the need for a digital version. He had faith in us and provided support and encouragement for another edition of *Clinical Laboratory Hematology*.

Michael Giacobbe was the Pearson man behind the scenes who kept the entire process moving forward. He also on-boarded authors for support materials including PowerPoints, test questions, and the instructor's manual. This group of author educators, Elizabeth Warning, MS, MLS(ASCP)^{CM}, University of Cincinnati; Joshua J. Cannon, MS, MLS(ASCP)^{CM}, Thomas Jefferson University; and Holly Weinberg, BS, MLS(ASCP)^{CM}, contributed behind the scenes to enhance the instructors' use of this book. Thank you all for your timely assistance. Ellen Viganola, Digital Project Manager for Pearson did a great job transferring the manuscript from print to digital.

Development editor, Barbara Price was our daily contact who kept us on track even though it meant multiple deadline revisions. This was especially challenging as we moved from a paper copy to a digital version of the book. Her gentle prodding was evident and appreciated. Her editing was superb. Dan Knott, Editorial Project Manager, and Prathiba Rajagopal, Senior Project Manager, both from SPI Global, kept track of the many people, files and technical elements involved in bringing the book to the digital realm.

Sara Wagner and John Landis contributed countless hours of scanning slides and taking pictures to produce an incredible image atlas that accompanies this fourth edition. John Landis lead the compiling, organizing, and editing of the atlas images and as well as other microphotographs in the book.

Maggie Sera carefully reviewed and edited the references in this edition. Her attention to detail and sleuthing skills were imperative to ensuring that we presented our citations properly.

SBM, KLP, JLW

I have enjoyed the unique opportunity to edit four editions of Clinical Laboratory Hematology with Pearson. As our knowledge in hematology has expanded, many new tests have been developed to help diagnose hematologic diseases. Likewise, the number of authors and editors needed to cover this material has increased. My thanks go out to all hematologists who have contributed over the years to make this text a leader for MLS/MLT education and practice. I am privileged to work with my brilliant coeditors, Lynne and Kristin. Thank you to Kristin for the superb job you have done in creating, editing, and authoring, especially the image atlas. I couldn't have found a better replacement. Thank you to my colleague and friend Dr. J. Lynne Williams for her dedication to this process in the last several editions. Her sharp eyes, superb writing talent and keen mind are essential traits for an editor. We have similar philosophies about teaching hematology and often discussed how to best present the information in this book and make it better.

During the time this book was under development, my professional life took over many hours of my personal life. Many thanks to my husband and best friend Gary for his support, sacrifices, and understanding during some very stressful times so this edition could become a reality. My sincerest gratitude to my parents, George and Helen Olson, who instilled in me the confidence that I could accomplish anything I set my heart to. This mind-set has stuck with me through life, especially in this task. I hope that through example I have provided the same to my children and grandchildren.

SBM

I am thankful to those who helped to build my fire. My father, John Landis, guided me into medical laboratory science and became my hematology professor. My fascination with blood cells was sparked by my dad. Lynne Williams provided me the opportunity of an academic position and encouraged me to participate in the third edition of this book; Lynne has kindled my professional work. As digital natives, my students have taught me how they learn in the technology era. They inspired my vision and pursuit of a novel means to teach hematology through technology; these past students are my energizing air. The foundation of this book is the ingenuity of Shirlyn McKenzie who has dedicated her life to educating generations of budding hematologists. Because she entrusted me as editor, Shirlyn is my flame.

I am also thankful to those who sustained my fire. My husband, Todd, and my children, Theron and Kaia, are the glowing embers that supported my fire when my professional endeavors intersected with my personal life. And my mother, whose empowering spirit, eternal energy, and helping hands keep my blaze roaring. I wouldn't be half of who I am without my family.

My gratitude is endless to you all.

KLP

I extend a special thank you to my colleagues in the Clinical and Diagnostic Sciences program at Oakland University—Dr. Sumit Dinda, Dr. Bekah Martin, Lisa DeCeuninck, Terese Trost, and Bill Van Dyke, and our many part-time instructors—who kept the programs moving forward while we were working on this new edition and to the CDS students of the past 2 years who tolerated a distracted and often absent-minded professor. To all my former students: You have been my inspiration to try to create a meaningful and useful book to support your educational endeavors. But special thank you to my co-editors, Dr. Shirlyn McKenzie, for the privilege of accompanying you on this wonderful journey through these three editions together, and Dr. Kristin Landis-Piwowar, who has been a major guiding force and visionary for this new e-edition book.

JLW

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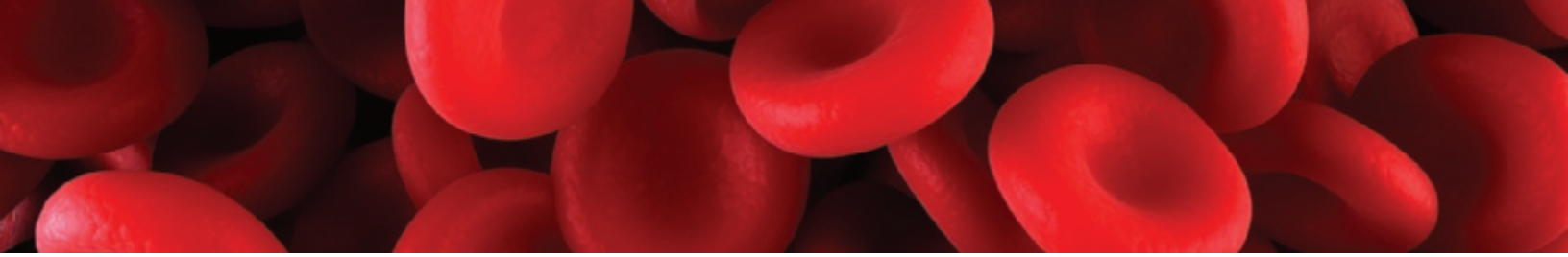
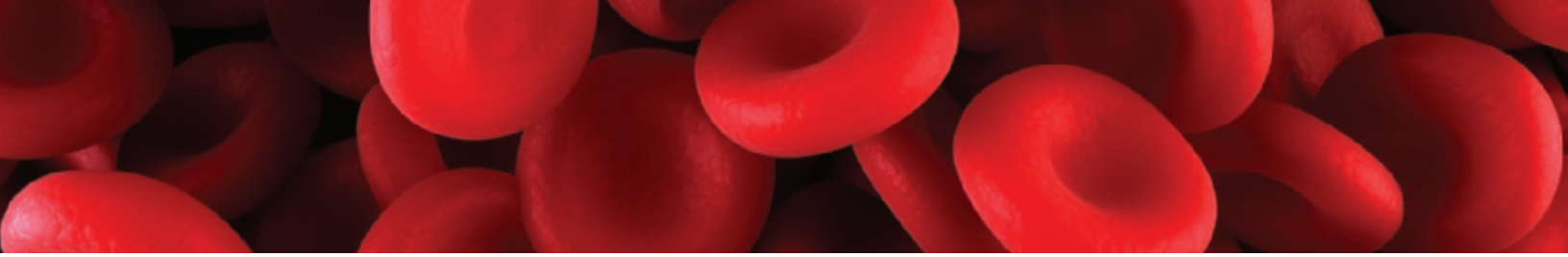


Section One

Introduction to Hematology



Chapter 1
Introduction

Shirlyn B. McKenzie, PhD

Objectives—Level I and Level II

At the end of this unit of study, the student should be able to:

1. Compare the reference intervals for hemoglobin, hematocrit, erythrocytes, and leukocytes in infants, children, and adults.
2. Identify the function of erythrocytes, leukocytes, and platelets.
3. Describe the composition of blood.
4. Explain the causes of change in the steady state of blood components.
5. Describe reflex testing, and identify the laboratory's role in designing reflex testing protocols.
6. Define hemostasis and describe the result of an upset in the hemostatic process.
7. Identify hematology and hemostasis screening tests.
8. List the three components of laboratory testing and correlate errors with each component.
9. Define value-based health care and give an example of how the laboratory can assist in building the value agenda.

Chapter Outline

Key Terms

Activated partial thromboplastin time (APTT)
Complete blood count (CBC)
Diapedese
Erythrocyte
Hematocrit
Hematology
Hematopoiesis
Hemoglobin
Hemostasis
Leukocyte
Plasma
Platelet
Prothrombin time (PT)
RBC indices
Red blood cell (RBC)
Reflex test
Serum
Thrombocyte
White blood cell (WBC)

Background Basics

Students should complete courses in biology and physiology before beginning this study of hematology.

CASE STUDY

We refer to this case study throughout the chapter.

Aaron, a 2-year-old male, was seen by his pediatrician because he had a fever of 102–104 °F over the past 24 hours. Aaron was lethargic. Before this, he had been in good health except for two episodes of otitis.

Consider why the pediatrician might order laboratory tests and how this child's condition might affect the composition of his blood.

Overview

Hematology is the study of blood and blood-forming organs. The hematology laboratory is one of the busiest areas of the clinical laboratory. Even small, limited-service laboratories usually offer hematology tests. This chapter is an introduction to the composition of blood and the testing performed in the hematology laboratory to identify the presence and cause of disease.

Introduction

Blood has been considered the essence of life for centuries. One of the Hippocratic writings from about 400 B.C. describes the body as being a composite of four humors: black bile, blood, phlegm, and yellow bile. It is thought that the theory of the four humors came from the observation that four distinct layers form as blood clots in vitro: a dark-red, almost black, jellylike clot (black bile); a thin layer of oxygenated red cells (blood); a layer of white cells and platelets (phlegm); and a layer of yellowish serum (yellow bile).[1] Health and disease were thought to occur as a result of an upset in the equilibrium of these humors.

The cellular composition of blood was not recognized until the invention of the microscope. With the help of a crude magnifying device that consisted of a biconvex lens, Antonie van Leeuwenhoek (1632–1723) accurately described and measured the **red blood cells** (also known as **RBCs** or **erythrocytes**). The discovery of **white blood cells** (also known as **WBCs** or **leukocytes**) and **platelets** (also known as **thrombocytes**) followed after microscope lenses were improved.

As a supplement to these categorical observations of blood cells, Karl Vierordt, in 1852, published the first quantitative results of blood cell analysis.[2] His procedures for quantification were tedious and time consuming. After several years, many others attempted to correlate blood cell counts with various disease states.

Improved methods of blood examination in the 1920s and the increased knowledge of blood physiology and blood-forming organs in the 1930s allowed anemias and other blood disorders to be studied on a rational basis. In some cases, the pathophysiology of hematopoietic disorders was realized only after the patient responded to experimental therapy.

Contrary to early hematologists, modern hematologists recognize that alterations in the components of blood are the *result* of disease, not a *primary cause* of it. Under normal conditions, the production of blood cells in the bone marrow, their release to the peripheral blood, and their survival are highly regulated to maintain a steady state of morphologically normal cells. Quantitative and qualitative hematologic abnormalities can result when an imbalance occurs in this steady state.

Composition of Blood

Blood is composed of a liquid called **plasma** and of cellular elements, including leukocytes, platelets, and erythrocytes. After blood coagulates, the resulting liquid component is called **serum**. The normal adult has about 6 liters of this vital fluid, which composes from 7% to 8% of the total body weight. Plasma makes up about 55% of the blood volume; about 45% of the volume is composed of erythrocytes, and 1% of the volume is composed of leukocytes and platelets. Variations in the quantity of these blood elements are often the first sign of disease occurring in body tissues. Changes in diseased tissue may be detected by laboratory tests that measure deviations from normal in blood constituents. Hematology is primarily the study of the formed cellular elements of the blood.

The principal component of plasma is water, which contains dissolved ions, proteins, carbohydrates, fats, hormones, vitamins, and enzymes. The principal ions necessary for normal cell function include calcium, sodium, potassium, chloride, magnesium, and hydrogen. The main protein constituent of plasma is albumin, which is the most important component in maintaining osmotic pressure. Albumin also acts as a carrier molecule, transporting compounds such as bilirubin and heme. Other blood proteins carry vitamins, minerals, and lipids. Immunoglobulins, synthesized by lymphocytes, and complement are specialized blood proteins involved in immune defense. The coagulation proteins responsible for **hemostasis** (arrest of bleeding) circulate in the blood as inactive enzymes until they are needed for the coagulation process. An upset in the balance of these dissolved plasma constituents can indicate a disease in other body tissues.

Blood plasma also acts as a transport medium for cell nutrients and metabolites; for example, the blood transports hormones manufactured in one tissue to target tissue in other parts of the body. Albumin transports bilirubin, the main catabolic residue of hemoglobin, from the spleen to the liver for excretion. Blood urea nitrogen, a nitrogenous waste product, is carried to the kidneys for filtration and excretion. Increased concentration of these normal catabolites can indicate either increased cellular metabolism or a defect in the organ responsible for their excretion. For example, in liver disease, the bilirubin level in blood increases because the liver is unable to function normally and clear the bilirubin. In hemolytic anemia, however, the bilirubin concentration can rise because of the increased metabolism of hemoglobin that exceeds the ability of a normal liver to clear bilirubin.

When body cells die, they release their cellular constituents into surrounding tissue. Eventually, some of these constituents reach the blood. Many constituents of body cells are specific for the cell's particular function; thus, increased concentration of these constituents in the blood, especially enzymes, can indicate an abnormal increase in cell destruction in a specific organ.

Blood cells are produced and develop in the bone marrow. This process is known as **hematopoiesis**. Undifferentiated hematopoietic stem cells (precursor cells) proliferate and differentiate under the influence of proteins that affect their function (cytokines). When the cell reaches maturity, it is released into the peripheral blood.

Each of the three cellular constituents of blood has specific functions. Erythrocytes contain the vital protein **hemoglobin**, which is responsible for transport of oxygen from the lungs to the body tissues. Erythrocytes also facilitate the transport of carbon dioxide from the tissues back to the lungs. The five major types of leukocytes are neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Each type of leukocyte has a role in defending the body against foreign pathogens such as bacteria and viruses. Platelets are necessary for maintaining hemostasis. Blood cells circulate through blood vessels, which are distributed throughout every body tissue. Erythrocytes and platelets generally carry out their functions without leaving the vessels, but leukocytes **diapedese** (pass through intact vessel walls) to tissues where they defend against invading foreign pathogens.

CASE STUDY *(continued from page 3)*

1. If Aaron was diagnosed with otitis media, what cellular component(s) in his blood would be playing a central role in fighting this infection?

Reference Intervals for Blood Cell Concentration

Physiologic differences in the concentration of cellular elements can occur according to race, age, sex, and geographic location; pathologic changes in specific blood cell concentrations can occur as the result of disease or injury. The greatest differences in reference intervals occur between newborns and adults. In general, newborns have a higher erythrocyte concentration than any other age group. The erythrocytes are also larger than those of adults. In the 6 months after birth, erythrocytes gradually decrease in number and then slowly increase. Hemoglobin and erythrocyte counts increase in children between the ages of 5 and 17. The leukocyte concentration is high at birth but decreases after the first year of life. A common finding in young children is an absolute and relative lymphocytosis (increase in lymphocytes). After puberty, males have higher hemoglobin, **hematocrit** (packed red blood

cell volume in whole blood), and erythrocyte levels than females. The hemoglobin level decreases slightly after age 70 in males. This is thought to be due to the decrease in testosterone. Appendix D, Tables A through J give hematologic reference intervals for various age groups and by sex if appropriate.

Each individual laboratory must determine reference intervals of hematologic values to account for the physiologic differences of a population in a specific geographical area. Reference intervals for a hematologic parameter are determined by calculating the mean ±2 standard deviations for a group of healthy individuals. This interval represents the reference interval for 95% of normal individuals. A value just below or just above this interval is not necessarily abnormal; normal and abnormal overlap. Statistical probability indicates that about 5% of normal individuals will fall outside the ±2 standard deviation range. The further a value falls from the reference interval, however, the more likely the value is to be abnormal.

CASE STUDY *(continued from page 4)*

Aaron's physician ordered a complete blood count (CBC). The results are Hb 11.5 g/dL; Hct 34%.

2. What parameters, if any, are outside the reference intervals? Why do you have to take Aaron's age into account when evaluating these results?

Hemostasis

Hemostasis is the property of the circulation that maintains blood as a fluid within the blood vessels and the system's ability to form a barrier (blood clot or thrombus) to prevent excessive blood loss when the vessel is traumatized, limit the barrier to the site of injury, and dissolve the thrombus to ensure normal blood flow when the vessel is repaired. Hemostasis occurs in stages called *primary* and *secondary hemostasis* and *fibrinolysis* (breakdown of fibrin). These stages are the result of interaction of platelets, blood vessels, and proteins circulating in the blood. An upset in any of the stages can result in bleeding or abnormal blood clotting (thrombosis). Laboratory testing for abnormalities in hemostasis is usually performed in the hematology section of the laboratory; occasionally, hemostasis testing is performed in a separate specialized section of the laboratory.

Checkpoint 1.1

What cellular component of blood can be involved in disorders of hemostasis?

Blood Component Therapy

Blood components can be used in therapy for various hematologic and nonhematologic disorders. Whole blood collected from donors can be separated into various cellular and fluid components. Only the specific blood component (i.e., platelets for thrombocytopenia or erythrocytes for anemia) needed by the patient will be administered. In addition, the components can be specially prepared for the patient's specific needs (i.e., washed erythrocytes for patients with IgA deficiency to reduce the risk of anaphylactic reactions). Table 1-1 lists the various components that can be prepared for specific uses.

Table 1.1 Blood Components and Their Uses

Component Name	Composition	Primary Use
Whole blood	Red blood cells and plasma	Not used routinely; can be used in selected trauma, autologous transfusions, and neonatal situations; increases oxygen-carrying capacity and volume
Packed red blood cells (PRBCs)	PRBCs	Used in individuals with symptomatic anemia to increase oxygen-carrying capability
PRBCs, washed	PRBCs; plasma with most leukocytes and platelets removed	Used for individuals with repeated allergic reactions to components containing plasma and for IgA-deficient individuals with anaphylactic reactions to products containing plasma
PRBCs, leukoreduced	PRBCs; WBC removed	Used to decrease the risk of febrile nonhemolytic transfusion reaction, HLA sensitization, and cytomegalovirus (CMV) transmission
PRBCs, frozen, deglycerolized	PRBCs frozen in cryroprotective agent, thawed, washed	Used for individuals with rare blood groups (autologous donation)
PRBCs, irradiated	PRBCs with lymphocytes inactivated	Used to reduce the risk of graft-versus-host disease
Platelets, pooled[a]	4–6 units of random donor platelets	Used to increase platelet count and decrease bleeding when there is a deficiency or abnormal function of platelets
Platelets, single[a] donor (pheresis)	Equivalent of 4–6 donor platelets collected from single donor	Used to treat patients refractory to random platelet transfusion or to increase platelet count due to a deficiency or abnormal function of platelets

(*Continued*)

Table 1.1 Blood Components and Their Uses (*Continued*)

Component Name	Composition	Primary Use
Fresh frozen plasma (FFP)	Plasma with all stable and labile coagulation factors; frozen within 8 hours of collection of unit of blood	Used to treat patients with multiple coagulation factor deficiencies; disseminated intravascular coagulation (DIC); used with packed RBC in multiple transfusions
Cryoprecipitated AHF[b]	Concentrated FVIII, fibrinogen, FXIII, von Willebrand factor	Used to treat patients with hypofibrinogenemia, hemophilia A, von Willebrand's disease, FXIII deficiency
Plasma, cryo-poor	Plasma remaining after cryo removed	Used to treat thrombotic thrombocytopenic purpura (TTP)
Liquid plasma	Plasma not frozen within 8 hours of collection	Used in patients with deficiency of stable coagulation factor(s) and for volume replacement
Granulocytes	Granulocytes	Used to treat the neutropenic patient who is septic and unresponsive to antimicrobials and who has chance of marrow recovery

[a] Platelets can also be leukoreduced or irradiated. See PRBC for reasons.

[b] Cryoprecipitated antihemophilic factor.

Courtesy of Linda Smith, Ph.D., MLS(ASCP)^{CM}; adapted from the *circular of information for the use of human blood and blood components*. Prepared jointly by the American Association of Blood Banks, America's Blood Centers, and the American Red Cross (2002).

Investigation of a Hematologic Problem

Laboratory testing is divided into three components: preexamination, examination, and post-examination (formerly known as preanalytical, analytical, postanalytical). The *preexamination* component includes all aspects that occur prior to the testing procedure that affect the test outcome such as phlebotomy technique and transport and storage of the specimen after it is drawn but before the test is run. The *examination phase* refers to all aspects affecting the test procedure. The *post-examination* component includes all aspects after the testing is completed such as reporting of results and execution of appropriate clinical responses. These three aspects of testing are the backbone of a quality assessment program. See Chapters 10 and 43 for a detailed description of these three phases.

A physician's investigation of a hematologic problem includes taking a medical history and performing a physical examination. Clues provided by this preliminary investigation help guide the physician's choice of laboratory tests to help confirm the diagnosis. The challenge is to select appropriate tests that contribute to a cost-effective and efficient diagnosis. Laboratory testing usually begins with screening tests; based on results of these tests, more specific tests are ordered. The same tests can be ordered again on follow-up to track disease progression, evaluate treatment, identify side effects and complications, or assist in prognosis.

Hematology screening tests include the **complete blood count (CBC)**, which quantifies the WBCs, RBCs, hemoglobin, hematocrit, and platelets, and the **RBC indices** (Chapter 10). The indices are calculated from the results of the hemoglobin, RBC count, and hematocrit to define the size and hemoglobin content of RBCs. The indices are important parameters used to differentiate causes of anemia and help direct further testing. The CBC can also include a WBC differential. This procedure enumerates the five types of WBCs and reports each as a percentage of the total WBC count. A differential is especially helpful if the WBC count is abnormal. When the count is abnormal, the differential identifies which cell type is abnormally increased or decreased and determines whether immature and/or abnormal forms are present, thus providing a clue to diagnosis. The morphology of RBCs and platelets is also studied as a routine part of the differential and reported if abnormal. The assessment of RBC morphology can provide key information to a differential diagnosis and help guide the selection of additional tests for a definitive diagnosis.[3]

If a hemostasis problem is suspected, the screening tests include the platelet count, **prothrombin time (PT)**, and **activated partial thromboplastin time (APTT)** (Chapter 36). The PT and APTT tests involve adding calcium and thromboplastin or partial thromboplastin to a sample of citrated plasma and determining the time it takes to form a clot. These tests provide clues that guide the choice of follow-up tests to help identify the problem.

The Value of Laboratory Testing

The "value agenda" of health care advocates is achieving the best outcomes at minimal cost without sacrificing quality.[4] In 2011, the Centers for Medicare and Medicaid Services (CMS) announced a reimbursement model intended to increase the accountability for achieving the best patient outcomes at minimal cost without sacrificing quality of care.[5] The focus is on population health management versus a fee for service based on volume. By 2014, 20% of Medicare reimbursement shifted to value-based payment models that

directly link reimbursement to the health and well-being of patients. The goal is to have 50% of Medicare payments in these value-based payment models by 2018. The laboratory can play a major role in creating and advancing the value agenda by improving clinical outcomes through the use of appropriate laboratory testing while helping payers hold down costs (economic outcomes).

Follow-up testing that is done based on results of screening tests is referred to as **reflex testing**. These testing protocols are sometimes referred to as *algorithms*. Follow-up tests can include not only hematologic tests but also chemical, immunologic, microbiologic, and/or molecular analysis. As scientists learn more about the pathophysiology and treatment of hematologic disease and hemostasis, the number of tests designed to assist in diagnosis expands and, without testing guidelines, the cost can increase due to inappropriate and unnecessary test selection. Errors in selection of the most appropriate laboratory tests and interpretation of results can result in misdiagnosis or treatment errors and is a major source of poor patient outcomes. Laboratory professionals can assist in promoting good patient outcomes by assisting physicians and patient care teams in selecting the most efficient and effective testing strategies[6,7,8] through development of test ordering protocols and assisting in interpretation of test results.[9] Furthermore, validation studies of algorithms may help determine if a particular testing protocol is better than others in helping diagnose or follow effectiveness of treatment. Readers are urged to use the reflex testing and algorithm concepts in their thought processes when studying the laboratory investigation of a disease.

In an effort to help the student gain the knowledge to perform these functions, in this text each hematologic disorder is discussed in the following order: etiology, if known, pathophysiology, clinical presentation, laboratory evaluation, and therapy. The reader should consider which laboratory tests provide the information necessary to identify the cause of the disorder based on the suspected disorder's pathophysiology. Although it is unusual for the physician to provide a patient history or diagnosis to the laboratory when ordering tests, this information is often crucial to direct investigation and assist in interpretation of the test results. In any case, if laboratory professionals need more patient information to appropriately perform testing, they should obtain the patient's chart or call the physician.

Checkpoint 1.2

A 13-year-old female saw her physician for complaints of a sore throat, lethargy, and swollen lymph nodes. A CBC was performed with the following results: Hb 9.0 g/dL; Hct 30%; WBC 15 $\times$ 10^3/mcL. On the basis of these results, should reflex testing be performed?

Summary

Hematology is the study of the cellular components of blood: erythrocytes, leukocytes, and platelets. Physiological changes in the concentrations of these cells occur from infancy until adulthood. Diseases can upset the steady state concentration of these parameters. A CBC is usually performed as a screening test to determine whether there are quantitative abnormalities in blood cells. The physician can order reflex tests if one or more of the CBC parameters are outside the reference interval. Platelet count, PT, and APTT are screening tests for disorders of hemostasis.

Changes in the health care system focus on containing costs while maintaining quality of care. The laboratory's role in this system is to work with physicians to optimize utilization of laboratory testing.

Review Questions

Level I and Level II

1. In which group of individuals would you expect to find the highest reference intervals for hemoglobin, hematocrit, and erythrocyte count? (Objective 1)

- **a.** Newborns
- **b.** Males older than 12 years of age
- **c.** Females older than 17 years of age
- **d.** Children between 1 and 5 years of age

2. Which cells are important in transporting oxygen and carbon dioxide between the lungs and body tissues? (Objective 2)

- **a.** Platelets
- **b.** Leukocytes
- **c.** Thrombocytes
- **d.** Erythrocytes

3. Forty-five percent of the volume of blood is normally composed of: (Objective 3)
   - **a.** erythrocytes
   - **b.** leukocytes
   - **c.** platelets
   - **d.** plasma

4. Alterations in the concentration of blood cells generally are the result of: (Objective 4)
   - **a.** laboratory error
   - **b.** amount of exercise before blood draw
   - **c.** a disease process
   - **d.** variations in analytical equipment

5. Leukocytes are necessary for: (Objective 2)
   - **a.** hemostasis
   - **b.** defense against foreign pathogens
   - **c.** oxygen transport
   - **d.** excretion of cellular metabolites

6. Laboratories can use which type of testing to help direct the physician's selection of appropriate testing after screening tests are performed? (Objective 5)
   - **a.** Reflexive based on results of screening tests
   - **b.** Manual repeat of abnormal results
   - **c.** Second test by a different instrument
   - **d.** Standing orders for all inpatients

7. Screening tests used to evaluate the hemostasis system include: (Objective 6)
   - **a.** PT and APTT
   - **b.** CBC
   - **c.** hemoglobin
   - **d.** WBC count

8. A patient blood specimen is stored in a car for 2 hours with the outside temperature of 95 °F. This is an example of error in which component of testing? (Objective 8)
   - **a.** Pre-examination
   - **b.** Examination
   - **c.** Post-examination

9. The value of laboratory medicine can be increased by: (Objective 9)
   - **a.** providing raw data to payers when asked
   - **b.** prompting physicians to use a testing algorithm for anemia diagnosis
   - **c.** focusing on fee for service based on increasing testing volume.
   - **d.** not interfering with physician test ordering

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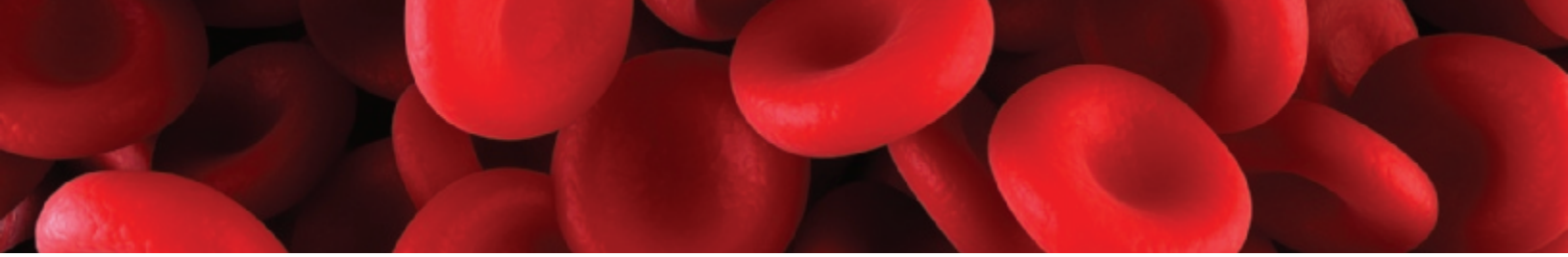

Chapter 2
Cellular Homeostasis

Kristin Landis-Piwowar, PhD

Objectives—Level I

At the end of this unit of study, the student should be able to:

1. Describe the location, morphology, and function of subcellular organelles of a cell.
2. Describe the lipid asymmetry found in the plasma membrane of most hematopoietic cells.
3. Differentiate DNA replication, transcription, translation, and DNA repair.
4. Differentiate the parts of the mammalian cell cycle.
5. Define R (*restriction point*) and its role in cell-cycle regulation.
6. Define *apoptosis* and explain its role in normal human physiology.
7. Classify and give examples of the major categories of initiators and inhibitors of apoptosis.
8. List the major events regulated by apoptosis in hematopoiesis.

Objectives—Level II

At the end of this unit of study, the student should be able to:

1. Explain the significance of SNPs, introns, exons, UTRs, and post-translational protein modifications.
2. List the components and explain the function of the ubiquitin-proteasome system.
3. Define *cyclins* and *Cdks* and their role in cell-cycle regulation; describe the associated Cdk partners and function of cyclins D, E, A, and B.
4. Define the two major classes of CKIs (cyclin-dependent kinase inhibitors) and describe their function.
5. Compare the function of cell-cycle checkpoints in cell-cycle regulation.
6. Describe/illustrate the roles of p53 and pRb in cell-cycle regulation.
7. Propose how abnormalities of cell-cycle regulatory mechanisms can lead to malignancy.