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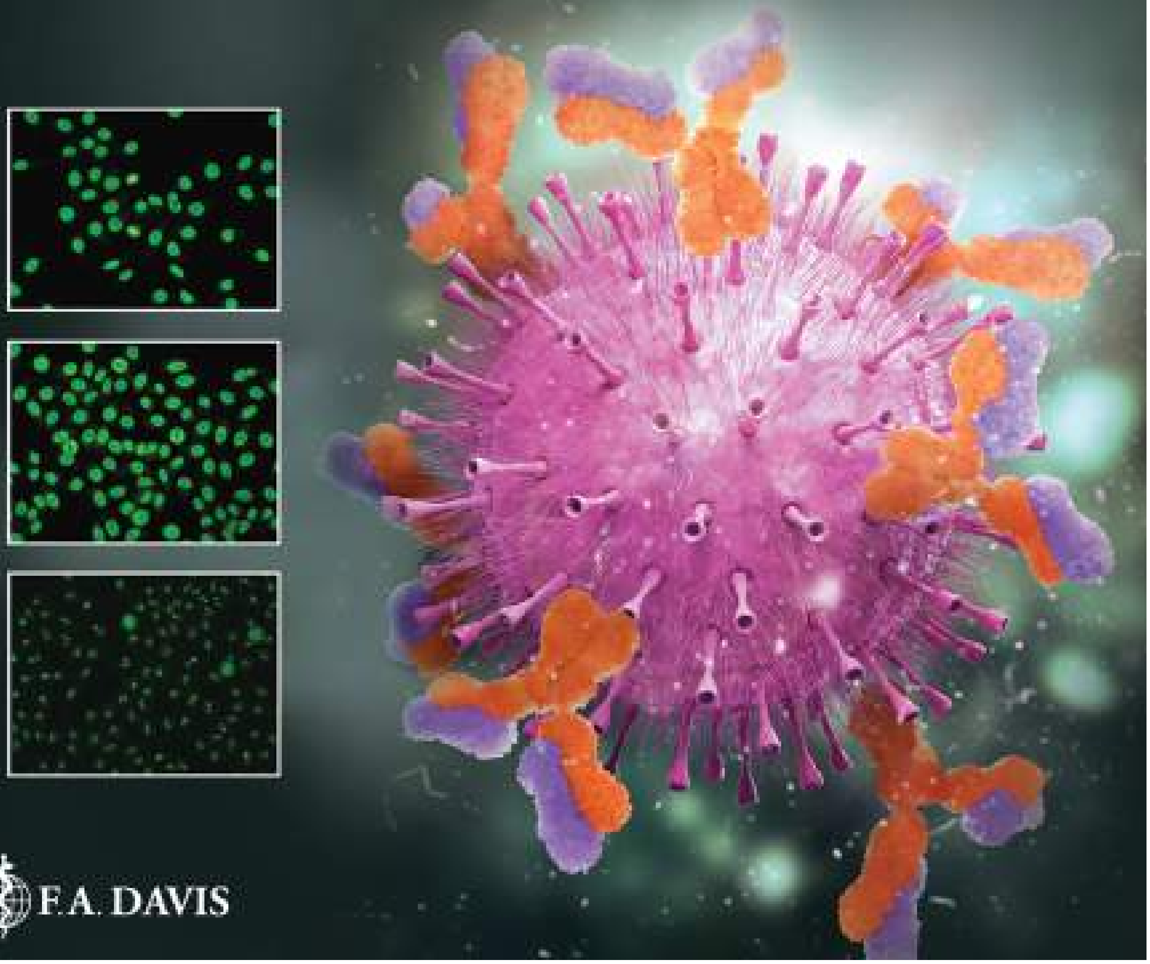
FIFTH EDITION

A Laboratory Perspective

Linda E. Miller
Christine Dorresteyn Stevens



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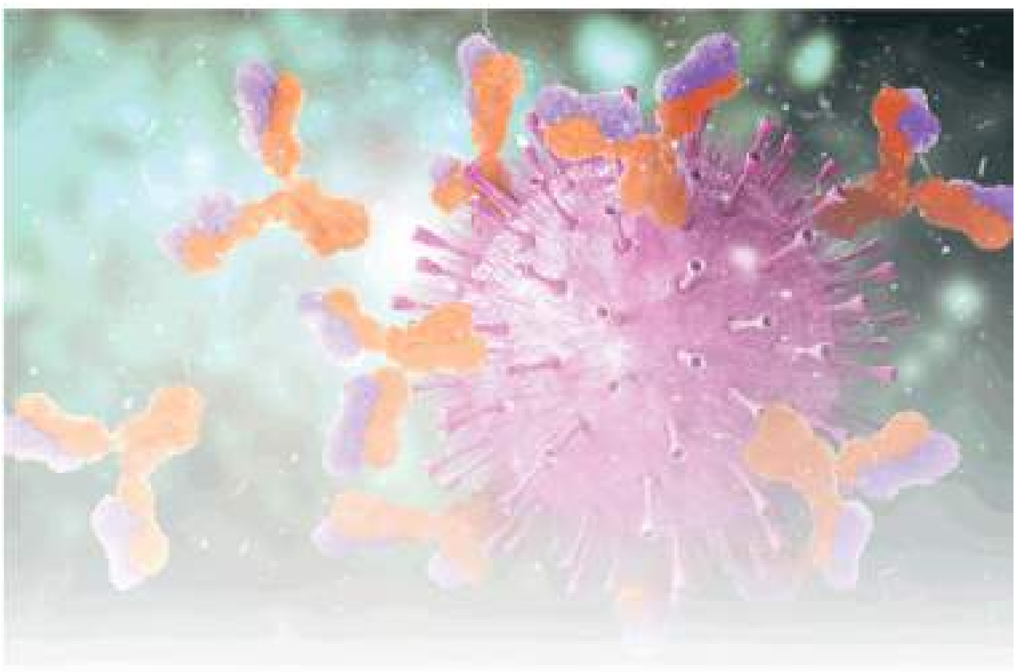

Clinical Immunology and Serology

A Laboratory Perspective

FIFTH EDITION

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To my wonderful family, for their love and support; to the Clinical Laboratory Science faculty at SUNY Upstate Medical University, in appreciation of their expertise and collegiality; and especially to my students, who have inspired me to share my passion for immunology over the years.

— L.E.M.

To my wonderful family: Eric, Kathy, Hannah, and Matthew, and Kevin, Melissa, Turner, and Avery for their love and encouragement and to Bayard for his love and faith in me.

— C.D.S.

Preface

Clinical Immunology and Serology: A Laboratory Perspective is designed to meet the needs of medical laboratory science students on both the 2- and 4-year levels. It uniquely combines practical information about laboratory testing with a discussion of the theory behind the testing and the diseases for which the tests are used. For practicing laboratorians and other health professionals, the book may serve as a valuable reference about new developments in the field of immunology.

The fifth edition of *Clinical Immunology and Serology: A Laboratory Perspective* is built on the success of the first four editions. The organization of the chapters is based on the experience of many years of teaching immunology to medical laboratory science students. The book is divided into four major sections: I. Nature of the Immune System; II. Basic Immunologic Procedures; III. Immune Disorders; and IV. Serological and Molecular Diagnosis of Infectious Disease. The sections build upon one another, and the chapters relate previous material to new material by means of boxes titled Connections and Clinical Correlations. These features help the students recall information from previous chapters and bridge theory with actual clinical diagnosis and testing. Information in the chapters is related to real-world events to make it more interesting for the student and to show the important role that immunology plays in people's daily lives. The Study Guide Tables at the end of most of the chapters can be used as study tools by the students.

Section I of this edition has been revised to provide a more in-depth discussion on basic immune mechanisms, building a strong foundation for understanding the pathogenesis of diseases related to abnormalities of the immune system. All the chapters in Sections II, III, and IV have been updated to include new information about laboratory testing and treatments for immunologic diseases. For example, information on the Globally Harmonized System and root cause analysis has been added to Chapter 8—Safety and Quality Management. Chapter 9—Principles of Serological Testing—has been revised to include additional examples to help students perform the types of dilutions commonly used in serology. The chapters on

Labeled Immunoassays (Chapter 11) and Molecular Diagnostic Techniques (Chapter 12) have been revised to include principles and illustrations for newer technologies that have been incorporated into the clinical laboratory. Additional autoimmune diseases have been added to the chapter on Autoimmunity (Chapter 15). Chapter 18—Immunoproliferative Diseases—has been revised to include updated information on the immunophenotype and cytogenetic abnormalities associated with selected hematologic malignancies. New information on testing for Lyme disease and leptospirosis is presented in Chapter 21—Spirochete Diseases.

The book remains a practical introduction to the field of clinical immunology that combines essential theoretical principles with serological and molecular techniques commonly used in the clinical laboratory. The theory is comprehensive but concise, and the emphasis is on direct application to the clinical laboratory. The text is readable and user-friendly, with learning outcomes, chapter outlines, and a glossary of all key terms. Each chapter is a complete learning module that contains theoretical principles, illustrations, definitions of relevant terminology, and review questions and case studies that help to evaluate learning.

For the instructor, there are many online resources at FADavis.com to assist in course development. Part of this edition was written in the early phases of the COVID-19 pandemic, when many course instructors were forced to convert teaching materials that would normally be presented in the classroom to an online or remote-learning format. The resources provided with this edition can serve as valuable tools to the instructor in developing course materials that can be used not only in in-person teaching but also in online or hybrid learning environments. They include updated PowerPoint slides, suggested learning activities and laboratory exercises, additional case studies, and an expanded bank of test questions that can be used for review or test preparation.

Because the field of immunology continues to grow so rapidly, the challenge in writing this book has been to ensure adequate coverage but to keep it on an introductory level. Every chapter has been revised to include current practices as of the time of writing. It is hoped that this book will kindle an interest in both students and laboratory professionals in this exciting and dynamic field.

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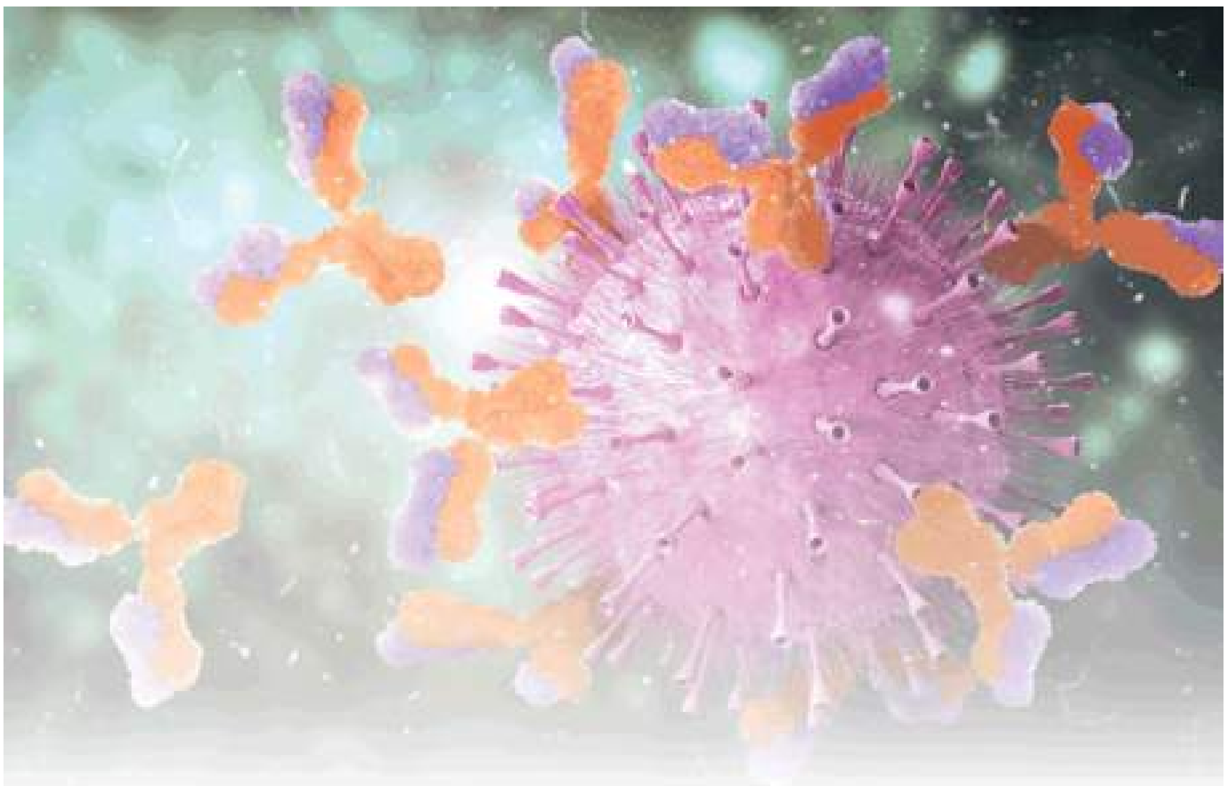
Our immunology students—past, present, and future—are the reason for writing this book. We hope that this text will inspire interest in the field of immunology and help to make a very complex subject easier to understand.

Finally, a big thank-you goes to our families, whose support, encouragement, and patience made it possible for us to engage in this labor of love.

Contents

I

Nature of the Immune System



1

Introduction to Immunity and the Immune System

Christine Dorresteyn Stevens, EdD, MT(ASCP)

LEARNING OUTCOMES

After finishing this chapter, you should be able to:

1. Discuss how immunology as a science began with the study of immunity.
2. Describe what is meant by an attenuated vaccine.
3. Explain how the controversy over humoral versus cellular immunity contributed to expanding knowledge in the field of immunology.
4. Contrast innate and adaptive immunity.
5. Describe the types of white blood cells (WBCs) capable of phagocytosis.
6. Discuss the roles of macrophages, mast cells, and dendritic cells in the immune system.
7. Identify the two primary lymphoid organs and discuss the main functions of each.
8. List four secondary lymphoid organs and discuss their overall importance to immunity.
9. Describe the function and architecture of a lymph node.
10. Compare a primary and a secondary follicle.
11. Define "cluster of differentiation" (CD).
12. Differentiate the roles of T cells and B cells in the immune response.
13. Discuss how natural killer (NK) cells differ from T lymphocytes.

CHAPTER OUTLINE

Go to FADavis.com for the laboratory exercises that accompany this text.

KEY TERMS

Adaptive immunity
Antibodies
Antigens
Attenuation
B lymphocytes
Basophils
Bone marrow
Cell-mediated immunity
Chemotaxins
Clusters of differentiation (CD)
Cytokines
Dendritic cells
Diapedesis
Eosinophils
Germinal center
Hematopoiesis
Humoral immunity
Immunity
Immunology
Innate (natural) immunity
Leukocytes
Lymph nodes
Lymphocyte
Macrophages
Mast cells
Memory cells
Monocytes
Natural killer (NK) cells
Neutrophil
Periarteriolar lymphoid sheath (PALS)

Phagocytosis
Plasma cells
Primary follicles
Primary lymphoid organs
Secondary follicles
Secondary lymphoid organs
Spleen
T lymphocytes
Thymocytes
Thymus

Although humans have been trying for centuries to unravel the secrets of preventing disease, the field of immunology is a relatively new science. **Immunology** can be defined as the study of a host's reactions to foreign substances that are introduced into the body. Such foreign substances that induce a host response are called **antigens.** Antigens are all around us in nature. They vary from substances, such as pollen, that may make us sneeze to serious bacterial pathogens, such as *Staphylococcus aureus* or Group A *Streptococcus,* that can cause life-threatening illnesses. The study of immunology has given us the ability to prevent diseases such as smallpox, polio, diphtheria, and measles through the development of vaccines. In addition, understanding how the immune system works has made successful organ transplantation possible and has given us new tools to treat diseases such as cancer and autoimmune diseases. Immunological techniques have affected testing in many areas of the clinical laboratory and allowed for such testing to be more precise and automated. Thus, the study of immunology is important to many areas of medicine. We begin this chapter by providing a brief look at the history of immunology. An introduction to the cells and tissues of the immune system follows to help the student form a basis for understanding how the immune response works. In later chapters, we will apply this knowledge to principles of testing for specific diseases.

Immunity and Immunization

Immunology as a science has its roots in the study of **immunity:** the condition of being resistant to infection. The first recorded attempts to deliberately induce immunity date back to the 15th century when people living in China and Turkey inhaled powder made from smallpox scabs in order to produce protection against this dreaded disease. The hypothesis was that if a healthy individual was exposed as a child or a young adult, the effects of the disease would be minimized. However, rather than providing protection, the early exposure had a fatality rate of 30%. Further refinements did not occur until the late 1700s when an English country doctor by the name of Edward Jenner was able to successfully prevent infection with smallpox by injecting a less harmful substance—cowpox—from a disease affecting cows. Details of the development of this first vaccine can be found in Chapter 25.

The next major development in disease prevention did not occur until almost a hundred years later when Louis Pasteur, often called the "father of immunology," observed by chance that older bacterial cultures accidentally left out on a laboratory bench for the summer would not cause disease when injected into chickens **(Fig. 1–1).** Subsequent injections of more virulent organisms had no effect on the birds that had been previously exposed to the older cultures. In contrast, chickens that were not exposed to the older cultures died after being injected with the new fresh cultures. In this manner, the first attenuated vaccine was discovered; this event can be considered the birth of immunology. **Attenuation,** or change, means to make a pathogen less virulent; it takes place through heat, aging, or chemical means. Attenuation remains the basis for many of the immunizations that are used today. Pasteur applied this same principle of attenuation to the prevention of rabies in exposed individuals. He was thus the first scientist to introduce the concept that vaccination could be applied to any microbial disease.

Innate Versus Adaptive Immunity

In the late 1800s, scientists began to identify the actual mechanisms that produce immunity in a host. Élie Metchnikoff, a Russian scientist, observed under a microscope that foreign objects introduced into transparent starfish larvae became surrounded by motile amoeboid-like cells that attempted to destroy the penetrating objects. This process was later termed **phagocytosis,** meaning “cells that eat cells.” He hypothesized that immunity to disease was based on the action of these scavenger cells and was a natural, or innate, host defense. He was eventually awarded a Nobel Prize for his pioneering work.

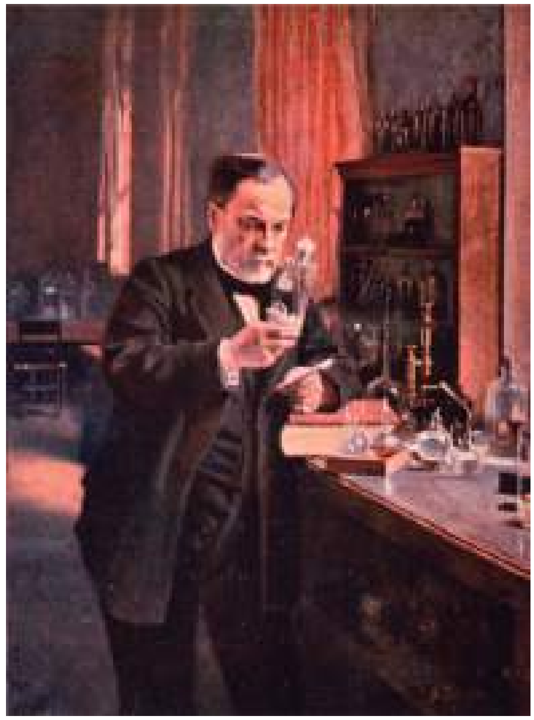


FIGURE 1-1 Louis Pasteur. *(Courtesy of the National Library of Medicine.)*

Other researchers contended that noncellular elements in the blood were responsible for protection from microorganisms. Emil von Behring demonstrated that diphtheria and tetanus toxins, which are produced by specific microorganisms as they grow, could be neutralized by the noncellular portion of the blood, or serum, of animals previously exposed to the microorganisms. Von Behring was awarded the first Nobel Prize in Physiology for his work with serum therapy. The theory of **humoral immunity** was thus born and sparked a long-lasting dispute over the relative importance of cellular immunity versus humoral immunity.

In 1903, an English physician named Almroth Wright linked the two theories by showing that the immune response involved both cellular and humoral elements. He observed that certain humoral, or circulating, factors called *opsonins* acted to coat bacteria so that they became more susceptible to ingestion by phagocytic cells. These serum factors include specific proteins known as *antibodies,* as well as other factors called *acute-phase reactants* that increase nonspecifically in any infection. **Antibodies** are serum proteins produced by certain lymphocytes when exposed to a foreign substance, and they react specifically with that foreign substance (see Chapter 5).

These discoveries showed that there were two major branches of immunity, currently referred to as innate immunity and adaptive immunity. **Innate,** or **natural immunity,** is the individual's ability to resist infection by means of normally present body functions. Innate defenses are considered nonadaptive or nonspecific and are the same for all pathogens or foreign substances to which one is exposed. No prior exposure is required and the response lacks memory and specificity, but the effect is immediate. Many of these mechanisms are subject to influence by such factors as nutrition, age, fatigue, stress, and genetic determinants.

Adaptive immunity, in contrast, is a type of resistance that is characterized by specificity for each individual pathogen, or microbial agent, and the ability to remember a prior exposure. Memory and specificity result in an increased response to that pathogen upon repeated exposure, something that does not occur in innate immunity. Both systems are necessary to maintain good health. In fact, they operate in combination and depend on one another for maximal effectiveness. Certain key cells are considered essential to both systems, and they will be discussed next.

Cells of the Innate Immune System

Leukocytes in Peripheral Blood

White blood cells (WBCs), or **leukocytes,** in the peripheral blood play a key role in both innate and adaptive immunity. Leukocytes defend against invasion by bacteria, viruses, fungi, and other foreign substances. There are five principal types of leukocytes in peripheral blood: neutrophils, eosinophils, basophils, monocytes, and lymphocytes. The first four types are all part of innate immunity. Because lymphocytes are considered part of adaptive immunity, they will be considered in a separate section. Several cell lines that are found in the tissues, namely, mast cells, macrophages, and dendritic cells, will also be discussed in this chapter because they all contribute to the process of immunity.

All blood cells arise from a type of cell called a *hematopoietic stem cell* (HSC). Approximately one and one-half billion WBCs are produced in the bone marrow daily. To form WBCs, the HSC gives rise to two distinct types of precursor cells: common myeloid precursors (CMPs) and common lymphoid precursors (CLPs). CMPs give rise to the WBCs that participate in phagocytosis, which are known as the *myeloid line.* Phagocytic cells are key to innate immunity, but they are also important in processing antigens for the adaptive response. Lymphocytes arise from CLPs and form the basis of the adaptive immune response. Mature lymphocytes are found in the tissues as well as in peripheral blood. Refer to **Figure 1–2** for a simplified scheme of blood cell development, known as **hematopoiesis.**

Neutrophils

The **neutrophil,** or polymorphonuclear neutrophilic (PMN) leukocyte, represents approximately 50% to 70% of the total peripheral WBCs in adults. These cells are around 10 to 15 µm in diameter with a nucleus that has between two and five lobes, which are connected by thin, threadlike filaments **(Fig. 1–3).** Hence, they are often called *segmented neutrophils,* or "segs." They contain a large number of neutral staining granules when stained with Wright stain, two-thirds of which are specific granules; the remaining one-third are called *azurophilic granules.* Azurophilic or primary granules contain antimicrobial products such as myeloperoxidase, lysozyme, elastase, proteinase-3, cathepsin G, and defensins, which are small proteins that have antibacterial activity. Specific granules, also known as *secondary granules,* contain lysozyme, lactoferrin, collagenase, gelatinase, and components essential for the oxidative burst. See Chapter 2 for a discussion of the oxidative burst, which takes place during phagocytosis. The main function of neutrophils is phagocytosis, resulting in the destruction of foreign particles.

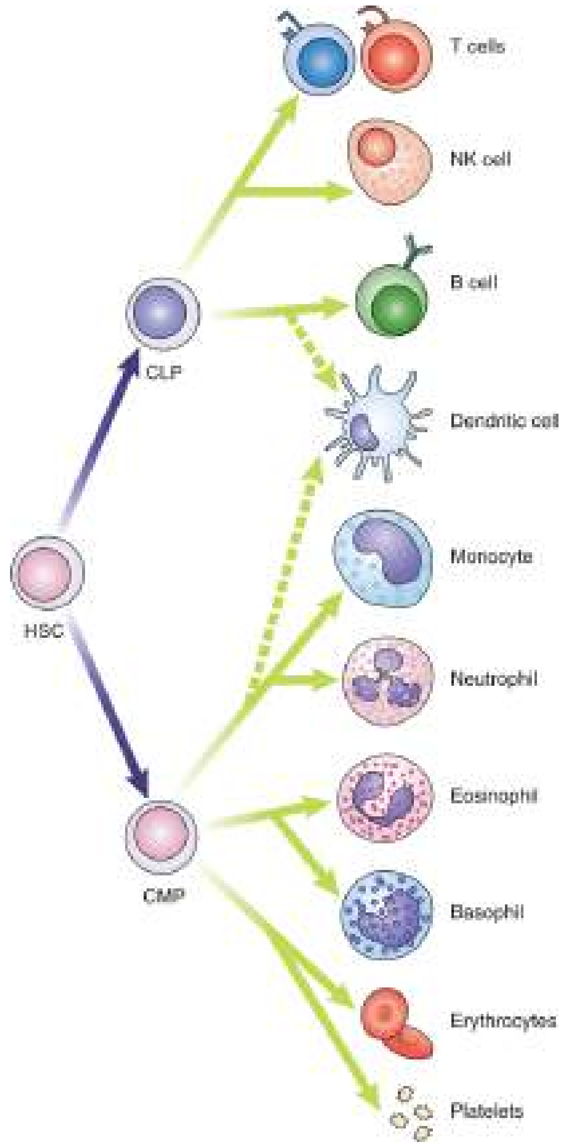


FIGURE 1-2 Simplified scheme of hematopoiesis. In the marrow, HSCs give rise to two different lines—a CLP and a CMP. CLPs give rise to T/NK progenitors, which differentiate into T and NK cells, and to B-cell progenitors, which become B cells and dendritic cells. The CMP differentiates into another type of dendritic cell, monocytes/macrophages, neutrophils, eosinophils, basophils, erythrocytes, and platelets.

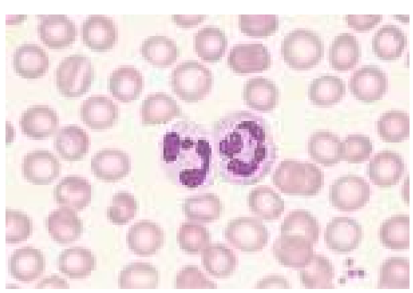


FIGURE 1-3 Neutrophils. (*From Harmening D.* Clinical Hematology and Fundamentals of Hemostasis. *5th ed. Philadelphia, PA: F.A. Davis; 2009: Fig. 1–4.*)

Normally, half of the total neutrophil population in peripheral blood is found in a marginating pool adhering to blood vessel walls, whereas the rest of the neutrophils circulate freely for approximately 6 to 8 hours. There is a continuous interchange, however, between the marginating and the circulating pools. Margination occurs to allow neutrophils to move from the circulating blood to the tissues through a process known as **diapedesis,** or movement through blood vessel walls. They are attracted to a specific area by chemotactic factors. **Chemotaxins** are chemical messengers that cause cells to migrate in a particular direction. Once in the tissues, neutrophils have a life span of up to several days. Normally, the influx of neutrophils from the bone marrow equals the output from the blood to the tissues to maintain a steady state. However, in the case of acute infection, an increase of neutrophils in the circulating blood can occur almost immediately. These cells are then driven rapidly to the site of an infection.

Eosinophils

Eosinophils are approximately 10 to 15 μm in diameter and normally make up between 1% and 4% of the circulating WBCs in a nonallergic person. Their number increases in an allergic reaction or in response to certain parasitic infections. The nucleus is usually bilobed or ellipsoidal and is often eccentrically located **(Fig. 1–4).** Eosinophils take up the acid eosin dye, and the cytoplasm is filled with large orange to reddish-orange granules. Granules in eosinophils, which are spherical and evenly distributed throughout the cell, contain a large number of previously synthesized proteins, including eosinophil-derived neurotoxin, peroxidase, histamine, proteases, **cytokines** (chemical messengers), growth factors, and cationic proteins.

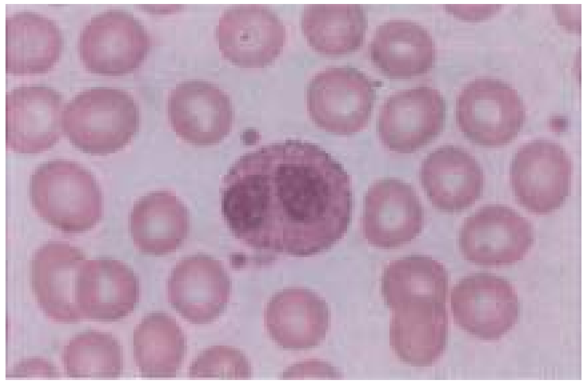


FIGURE 1-4 Eosinophil. (*From Harmening D.* Clinical Hematology and Fundamentals of Hemostasis. *5th ed. Philadelphia, PA: F.A. Davis; 2009: Fig. 1–6.*)

Eosinophils are capable of phagocytosis but are much less efficient than neutrophils because they are present in smaller numbers and they lack digestive enzymes. Eosinophils are able to neutralize basophil and mast cell products. In addition, they can use cationic proteins released during degranulation to damage cell membranes and kill larger parasites, such as helminth worms, that cannot be phagocytized. (See Chapter 22 for details.) However, the most important role of eosinophils is regulation of the adaptive immune response through cytokine release.

Basophils

Basophils are the least numerous of the WBCs found in peripheral blood, representing less than 1% of all circulating WBCs. The smallest of the granulocytes, basophils are slightly larger than red blood cells (RBCs) (between 10 to 15 μm in diameter) and contain coarse, densely staining deep-bluish-purple granules that often obscure the bilobed nucleus **(Fig. 1–5).** Constituents of these granules include histamine, cytokines, growth factors, and a small amount of heparin, all of which have an important function in inducing and maintaining allergic reactions. Histamine contracts smooth muscle, and heparin is an anticoagulant. In addition, basophils regulate some T-helper (Th) cell responses and stimulate B cells to produce the antibody immunoglobulin E (IgE). Basophils have a short life span of only a few hours in the bloodstream; they are then removed and destroyed by macrophages in the spleen.

Monocytes

Monocytes are the largest cells in the peripheral blood, with a diameter that can vary from 12 to 20 μm (the average is 18 μm). One distinguishing

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