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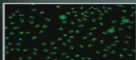
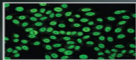
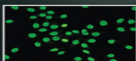
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Clinical Immunology & Serology FIFTH EDITION

A Laboratory Perspective

Linda E. Miller
Christine Dorresteyn Stevens



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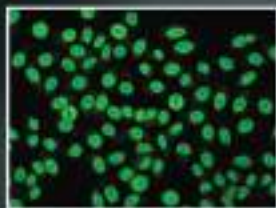
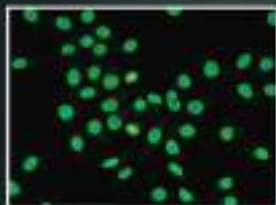
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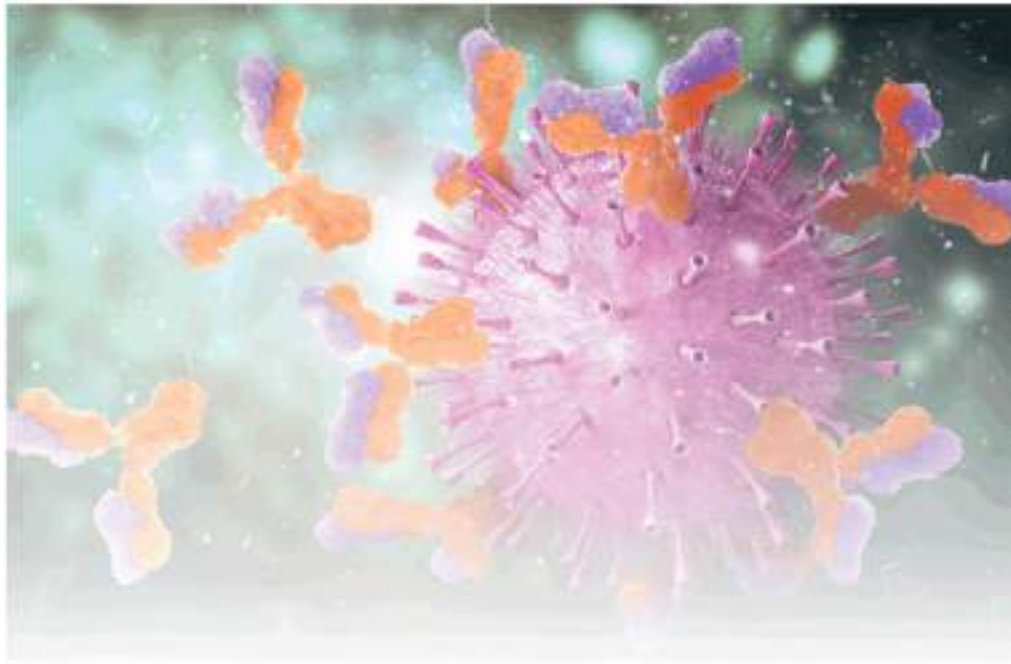


 F.A. DAVIS

Clinical Immunology and Serology

A Laboratory Perspective

FIFTH EDITION





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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

SECTION I

Nature of the Immune System

1 Introduction to Immunity and the Immune System

Christine Dorresteyn Stevens, EdD, MT(ASCP)

Immunity and Immunization

Innate Versus Adaptive Immunity

Cells of the Innate Immune System

Leukocytes in Peripheral Blood

Tissue Cells

Cells of the Adaptive Immune System

B Cells and Plasma Cells

T Cells

Innate Lymphoid Cells and Natural Killer Cells

Organs of the Immune System

Primary Lymphoid Organs

Secondary Lymphoid Organs

2 Innate Immunity

Christine Dorresteyn Stevens, EdD, MT(ASCP) and Nadine Lerret, PhD, MLS^{CM}(ASCP)

External Defense System

Internal Defense System

Pattern Recognition Receptors

Pattern Recognition Receptors and Disease

Acute-Phase Reactants

Inflammation

Phagocytosis

Action of Natural Killer Cells

Innate Lymphoid Cells

3 Nature of Antigens and the Major Histocompatibility Complex

Aaron Glass, PhD, MB^{CM}(ASCP)

Factors Influencing the Immune Response

Traits of Antigens and Immunogens

Epitopes

Haptens

Adjuvants

Relationship of Antigens to the Host

Major Histocompatibility Complex

Genes Coding for MHC Molecules (HLA Antigens)

Expression of Class I and II MHC Molecules

Structure of Class I MHC Molecules

Structure of Class II MHC Molecules

Role of Class I and II Molecules in the Immune Response

The Class I MHC–Peptide Presentation Pathway

The Class II MHC–Peptide Presentation Pathway

Clinical Significance of MHC

4 Adaptive Immunity

Aaron Glass, PhD, MB^{CM}(ASCP)

T-Cell Differentiation

Double-Negative Stage

Double-Positive Stage

Single-Positive Stage

Mature T Cells

Stages in B-Cell Differentiation

Pro-B Cells

Pre-B Cells

Immature B Cells

Mature B Cells

Plasma Cells

The Role of T Cells in the Adaptive Immune Response

Antigen Presentation

Actions of T Helper and T Regulatory Cells

Action of Cytotoxic T Cells

The Role of B Cells in the Adaptive Immune Response

Immune Response to T-Dependent Antigens

Immune Response to T-Independent Antigens

5 Antibody Structure and Function

Linda E. Miller, PhD, MB^{CM}(ASCP)SI

General Structure of Immunoglobulins

Two-Dimensional Structure

Treatment With Proteolytic Enzymes

- Hinge Region
- Isotypes, Allotypes, and Idiotypes
- Three-Dimensional Structure of Antibodies

Antibody Classes

- Immunoglobulin G (IgG)
- Immunoglobulin M (IgM)
- Immunoglobulin A (IgA)
- Immunoglobulin D (IgD)
- Immunoglobulin E (IgE)

Immunologic Memory: Primary and Secondary Antibody Responses

Antibody Specificity and Diversity

- Clonal Selection
- Immunoglobulin Genes
- Rearrangement of Heavy-Chain Genes
- Light-Chain Rearrangement
- Additional Sources of Diversity
- Immunoglobulin Class Switching

Monoclonal Antibodies

- Hybridomas
- Clinical and Research Applications

6 Cytokines

Aaron Glass, PhD, MB(ASCP)^{CM}

Introduction to Cytokines

Cytokines in the Innate Immune Response

- Cytokines and the Innate Response to Extracellular Microbes
- The Interleukin-1 (IL-1) Cytokine Family
- Tumor Necrosis Factors
- Interleukin-6
- Chemokines
- Transforming Growth Factor- β
- Interferon- α and Interferon- β (Type I Interferons)

Cytokines in the Adaptive Immune Response

- Cytokines Produced by Th1 Cells
- Cytokines Produced by Th2 Cells
- Cytokines Associated With T-Regulatory Cells

Th17 Cytokines in Innate and Adaptive Immune Responses

Hematopoietic Growth Factors

Cytokine and Anti-Cytokine Therapies

Clinical Assays for Cytokines

7 The Complement System

Bradley Dixon, MD and Ashley Frazer-Abel, PhD, D(ABMLI)

Pathways of the Complement System

- The Classical Pathway

- The Lectin Pathway

- The Alternative Pathway

System Controls

- Regulation of the Classical and Lectin Pathways

- Regulation of the Alternative Pathway

- Regulation of Terminal Components

Complement Receptors and Their Biological Roles

Biological Manifestations of Complement Activation

Complement and Disease States

Abnormalities of Major Pathway Complement Components

Abnormalities of Regulatory Complement Components

Laboratory Detection of Complement Abnormalities

- Immunologic Assays of Individual Components

- Assays for the Classical Pathway

- Alternative and Lectin Pathway Assays

- Testing Levels of Complement Activation

- Interpretation of Laboratory Findings

Complement Therapeutics

SECTION II

Basic Immunologic Procedures

8 Safety and Quality Management

Marjorie Schaub Di Lorenzo, MT(ASCP)SH

Laboratory Hazards

- Biological Hazards

- Sharps Hazards

- Chemical Hazards

- Safety Data Sheets (SDS)

- Chemical Hygiene Plan

- Radioactive Hazards

- Electrical Hazards

- Fire and Explosive Hazards

- Physical Hazards

Quality Management

- Procedure Manual

- Preexamination Variables
- Examination Variables
- Postexamination Variables

Regulatory Issues

- Clinical Laboratory Improvement Amendments (CLIA)
- Clinical and Laboratory Standards Institute (CLSI)
- The Joint Commission (TJC)
- College of American Pathologists (CAP)

Quality Management Systems

- Quality System Essentials
- The Lean System
- Six Sigma
- Root Cause Analysis

9 Principles of Serological Testing

Linda E. Miller, PhD, MB^{CM} (ASCP) SI and Christine Dorresteyn Stevens, EdD, MT(ASCP)

Blood Specimen Preparation and Measuring

Dilutions

- Simple Dilutions
- Compound Dilutions
- Serial Dilutions
- Test Parameters

10 Precipitation and Agglutination Reactions

Christine Dorresteyn Stevens, EdD, MT(ASCP) and Linda E. Miller, PhD, MB^{CM}(ASCP)SI

Antigen–Antibody Binding

- Affinity
- Avidity
- Law of Mass Action

Precipitation Curve

- Three Zones of the Precipitation Reaction
- Prozone and Postzone

Immunoturbidimetry and Nephelometry

Passive Immunodiffusion Techniques

- Radial Immunodiffusion
- Ouchterlony Double Diffusion

Electrophoretic Techniques

Comparison of Precipitation Techniques

- Principles of Agglutination Reactions
- Types of Agglutination Reactions
 - Direct Agglutination
 - Passive Agglutination
 - Reverse Passive Agglutination
 - Agglutination Inhibition
- Instrumentation
- Quality Control and Result Interpretation

11 Labeled Immunoassays

Paul R. Johnson, PhD, MBA, MT(ASCP), DABCC

- Immunoassay Labels
- General Immunoassay Formats
 - Heterogeneous Versus Homogeneous Immunoassays
 - Competitive Versus Noncompetitive Immunoassays
- Radioimmunoassay (RIA)
- Enzyme Immunoassays (EIAs)
- Heterogeneous Enzyme Immunoassays
 - Competitive Enzyme Immunoassays
 - Noncompetitive Enzyme Immunoassays
 - Capture (Sandwich) Immunoassays
 - Biotin-Avidin Labeling
- Interferences in Immunoassays
 - Antigen Interference
 - Antibody Interference
 - Biotin Interference
 - Other Technical Concerns
- Homogeneous Enzyme Immunoassays
- Chemiluminescent Immunoassays
 - Chemiluminescent Microparticle Immunoassay
 - Electrochemiluminescence Immunoassay
- Fluorescent Immunoassays
 - Direct Immunofluorescence Assays
 - Indirect Immunofluorescence Assays
 - Multiplex Immunoassay (MIA)
 - Fluorescence Polarization Immunoassays
- Rapid Immunoassays

12 Molecular Diagnostic Techniques

Lela Buckingham, PhD, MB(ASCP), DLM(ASCP)

- DNA and RNA

- Substituted Nucleotides
- The Nucleic Acid Polymer
- DNA Replication
- RNA Synthesis
- Protein Synthesis
- DNA Sequence Changes
- Polymorphisms
- Electrophoresis
 - Gel Electrophoresis
 - Capillary Electrophoresis
- Molecular Analysis
- Strand Cleavage Methods
 - Specific Procedures
- Hybridization Methods
 - Specific Procedures
- Amplification Methods
 - Specific Procedures
- DNA Sequencing
 - Specific Procedures
 - Chain Termination (Sanger) Sequencing
 - Pyrosequencing
 - Next-Generation Sequencing
 - Bioinformatics

13 Flow Cytometry and Laboratory Automation

Jeannie Guglielmo, MS, MAT, MLS^{CM}(ASCP) and Songkai Hu, MA, MLS^{CM}(ASCP)

- Flow Cytometry
 - Instrumentation
 - Sample Preparation
 - Data Acquisition and Analysis
 - Clinical Applications
- Immunoassay Automation
 - Validation

SECTION III

Immune Disorders

14 Hypersensitivity

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- Type I Hypersensitivity

- Immunologic Mechanism
- Genetic and Environmental Influences on Type I Hypersensitivity
- Clinical Manifestations of Type I Hypersensitivity
- Treatment of Type I Hypersensitivity
- Testing for Type I Hypersensitivity
- Type II Hypersensitivity
 - Immunologic Mechanism
 - Clinical Examples of Type II Hypersensitivity
 - Testing for Type II Hypersensitivity
- Type III Hypersensitivity
 - Immunologic Mechanism
 - Clinical Examples of Type III Hypersensitivity
 - Testing for Type III Hypersensitivity
- Type IV Hypersensitivity
 - Immunologic Mechanism
 - Clinical Manifestations of Type IV Hypersensitivity
 - Skin Testing for Delayed Hypersensitivity
 - Interferon Gamma Release Assays (IGRAs)

15 Autoimmunity

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- Etiology of Autoimmune Disease
 - Self-Tolerance
 - Genetics
 - Other Endogenous and Environmental Factors
- Systemic Autoimmune Diseases
 - Systemic Lupus Erythematosus (SLE)
 - Anti-Nuclear Antibodies (ANAs)
 - Anti-Phospholipid Antibodies
 - Rheumatoid Arthritis (RA)
 - Other Systemic Autoimmune Rheumatic Diseases (SARDs)
 - Granulomatosis With Polyangiitis (Wegener's Granulomatosis)
 - Anti-Neutrophil Cytoplasmic Antibodies (ANCA)
- Organ-Specific Autoimmune Diseases
 - Autoimmune Thyroid Diseases (AITDs)
 - Type 1 Diabetes Mellitus (T1D)
 - Celiac Disease
 - Autoimmune Liver Diseases
 - Multiple Sclerosis (MS)
 - Myasthenia Gravis (MG)

Anti-Glomerular Basement Membrane Disease (Goodpasture's Syndrome)

16 Transplantation Immunology

John L. Schmitz, PhD, D(ABMLI, ABHI)

Histocompatibility Systems

Major Histocompatibility Complex (MHC) Antigens

Minor Histocompatibility Antigens (mHAs)

MHC Class I-Related Chain A (MICA) Antigens

ABO Blood Group Antigens

Killer Immunoglobulin-Like Receptors (KIRs)

Self-Antigens

Allorecognition

Transplant Rejection

Hyperacute Rejection

Acute Rejection

Chronic Rejection

Graft-Versus-Host Disease (GVHD)

Immunosuppressive Agents

Clinical Histocompatibility Testing

HLA Typing

HLA Phenotyping

HLA Genotyping

HLA Antibody Screening, Identification, and Crossmatching

Post-Transplant Testing

17 Tumor Immunology

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Introduction to Tumor Biology

Tumor Antigens

Clinically Relevant Tumor Markers

Clinical Uses of Tumor Markers: Benefits and Limitations

Serum Tumor Markers

Laboratory Detection of Tumors

Tumor Morphology

Immunohistochemistry

Immunoassays for Circulating Tumor Markers

Molecular Methods in Cancer Diagnosis

Interactions Between the Immune System and Tumors

Immune Defenses Against Tumor Cells

Innate Immune Responses

- Adaptive Immune Responses
- Immunoediting and Tumor Escape
 - Elimination
 - Equilibrium
 - Escape
- Immunotherapy
 - Active Immunotherapy and Cancer Vaccines
 - Passive Immunotherapy
 - Adoptive Immunotherapy

18 Immunoproliferative Diseases

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Malignant Transformation of Hematologic Cells

- Cell Properties
- Genetic Changes

Classification of Hematologic Malignancies

Leukemias

- Acute Lymphoblastic Leukemias (ALLs)
- Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
- Hairy-Cell Leukemia

Lymphomas

- Hodgkin Lymphomas (HLs)
- Non-Hodgkin Lymphomas (NHLs)

Plasma-Cell Dyscrasias

- Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)
- Multiple Myeloma
- Waldenström Macroglobulinemia
- Heavy-Chain Diseases

Role of the Laboratory in Evaluating Immunoproliferative Diseases

- Immunophenotyping by Flow Cytometry
- Evaluation of Immunoglobulins
- Serum Protein Electrophoresis (SPE)
- Immunofixation Electrophoresis (IFE)
- Serum Free Light-Chain (sFLC) Analysis
- Evaluation of Genetic and Chromosomal Abnormalities

19 Immunodeficiency Diseases

Thomas S. Alexander, PhD, D(ABMLI)

Clinical Effects of Primary Immunodeficiency Diseases

The Nine Categories of Primary Immunodeficiency Diseases

Category 3: Predominantly Antibody Deficiencies

Category 1: Immunodeficiencies Affecting Cellular and Humoral Immunity

Category 2: Combined Immunodeficiencies With Associated or Syndromic Features

Category 4: Diseases of Immune Dysregulation

Category 5: Congenital Defects of Phagocyte Number, Function, or Both

Category 6: Defects in Intrinsic and Innate Immunity

Category 7: Autoinflammatory Disorders

Category 8: Complement Deficiencies

Category 9: Phenocopies of Primary Immunodeficiencies

Laboratory Evaluation of Immune Dysfunction

Screening Tests

Confirmatory Tests

Newborn Screening for Immunodeficiencies

Evaluation of Immunoglobulins

Bone Marrow Biopsy

Family History

Primary Immune Deficiencies in a Computer App

SECTION IV

Serological and Molecular Diagnosis of Infectious Disease

20 Serological and Molecular Detection of Bacterial Infections

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Human–Microbe Relationships

Bacterial Virulence Factors

Structural Virulence Features

Extracellular Virulence Factors

Endotoxin and Exotoxins

Immune Defenses Against Bacterial Infections and Mechanisms of Evasion

Immune Defense Mechanisms

Bacterial Evasion Mechanisms

Laboratory Detection and Diagnosis of Bacterial Infections

Bacterial Culture

Microscopic Visualization

Antigen Detection

Molecular Detection

Serological Diagnosis

Proteomics

Group A Streptococci (*Streptococcus pyogenes*)

- Classification and Structure
- Virulence Factors
- Clinical Manifestations of Group A Streptococcal Infection
- Group A Streptococcal Sequelae
- Laboratory Diagnosis

Helicobacter pylori

- Helicobacter pylori* Virulence Factors
- Pathology and Pathogenesis
- Diagnosis of *H. pylori* Infection

Mycoplasma pneumoniae

- Mycoplasma pneumoniae* Pathogenesis
- Dermatological Manifestations
- Immunology of *Mycoplasma pneumoniae* Infection
- Laboratory Diagnosis of *Mycoplasma pneumoniae* Infection

Rickettsial Infections

- Agents of *Rickettsia*-Related Disease
- Rocky Mountain Spotted Fever

21 Spirochete Diseases

Hamida Nusrat, PhD, PHM

Syphilis

- Characteristics of *Treponema pallidum*
- Mode of Transmission
- Stages of the Disease
- Congenital Syphilis
- Nature of the Immune Response
- Laboratory Diagnosis
- Direct Detection
- Treatment

Lyme Disease

- Characteristics of *Borrelia* Species
- Mode of Transmission
- Stages of the Disease
- Nature of the Immune Response
- Laboratory Diagnosis
- Treatment

Leptospirosis

- Characteristics of *Leptospira* Species
- Mode of Transmission
- Stages of the Disease

Laboratory Diagnosis
Treatment

22 Serological and Molecular Diagnosis of Parasitic and Fungal Infections

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Parasitic Immunology

Immune Responses to Parasites
Parasite Survival Strategies
Serodiagnosis of Parasitic Diseases
Molecular-Based Diagnosis of Parasitic Disease

Fungal Immunology

Characteristics of Fungi
Classification of Mycotic Infections (Mycoses)
Immune Responses to Fungi
Laboratory Diagnosis of Fungal Infections
Fungal Pathogens

23 Serological and Molecular Detection of Viral Infections

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Immune Defenses Against Viral Infections

Viral Escape Mechanisms

Laboratory Testing for Viral Infections

Hepatitis Viruses

Hepatitis A
Hepatitis E
Hepatitis B
Hepatitis D
Hepatitis C

Herpes Virus Infections

Epstein-Barr Virus (EBV)
Cytomegalovirus (CMV)
Varicella-Zoster Virus (VZV)

Other Viral Infections

Rubella
Rubeola
Mumps
Human T-Cell Lymphotropic Viruses

24 Laboratory Diagnosis of HIV Infection

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HIV Transmission

Characteristics of HIV

Composition of the Virus

Structural Genes

Viral Replication

Immunologic Manifestations

Immune Responses to HIV

Effects of HIV Infection on the Immune System

Clinical Symptoms of HIV Infection

Treatment and Prevention

Laboratory Testing for HIV Infection

Screening and Diagnosis

Testing Algorithms

Serological Test Principles

Qualitative Nucleic Acid Tests (NATs)

Disease Monitoring

CD4 T-Cell Enumeration

Quantitative Viral Load Assays

Drug-Resistance and Tropism Testing

Testing of Infants Younger Than 18 Months

25 Immunization and Vaccines

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Vaccines

Historical Evolution of Vaccines

Types of Vaccines

Factors Influencing Immunogenicity

Challenges and Future Directions in Vaccine Development

Benefits and Adverse Effects of Vaccines

Passive Immunization

Passive Immunization as Therapy for Infectious Diseases

Advantages and Limitations of Passive Immunization

Immunosuppressive Effects of Passive Immunization

Monoclonal Antibodies

Adoptive Immunotherapy

Adoptive Immunotherapy for Cancer

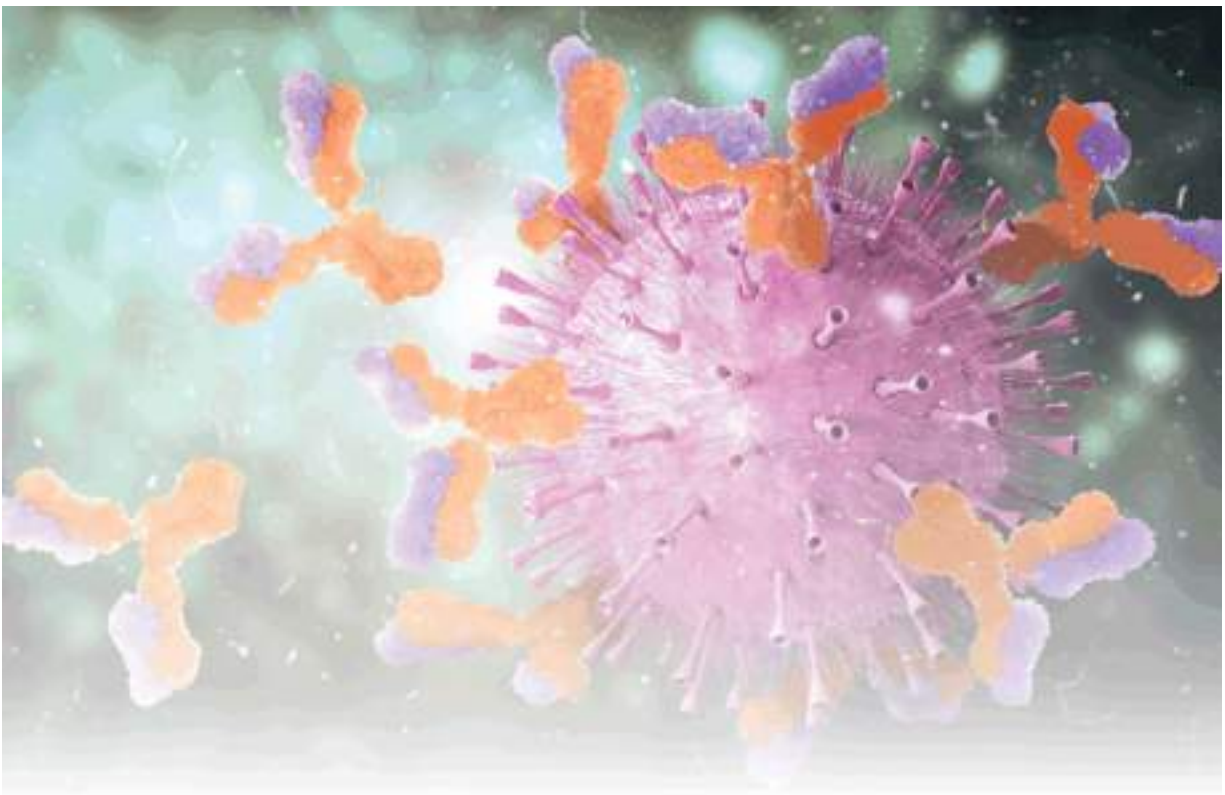
CAR-T-Cell Therapy

Other Applications of Adoptive Immunotherapy

Glossary

References
Answer Key
Index

Nature of the Immune System



1

Introduction to Immunity and the Immune System

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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

IMMUNITY AND IMMUNIZATION

INNATE VERSUS ADAPTIVE IMMUNITY

CELLS OF THE INNATE IMMUNE SYSTEM

Leukocytes in Peripheral Blood

Tissue Cells

CELLS OF THE ADAPTIVE IMMUNE SYSTEM

B Cells and Plasma Cells

T Cells

Innate Lymphoid Cells and Natural Killer Cells

ORGANS OF THE IMMUNE SYSTEM

Primary Lymphoid Organs

Secondary Lymphoid Organs

SUMMARY

CASE STUDIES

REVIEW QUESTIONS

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.

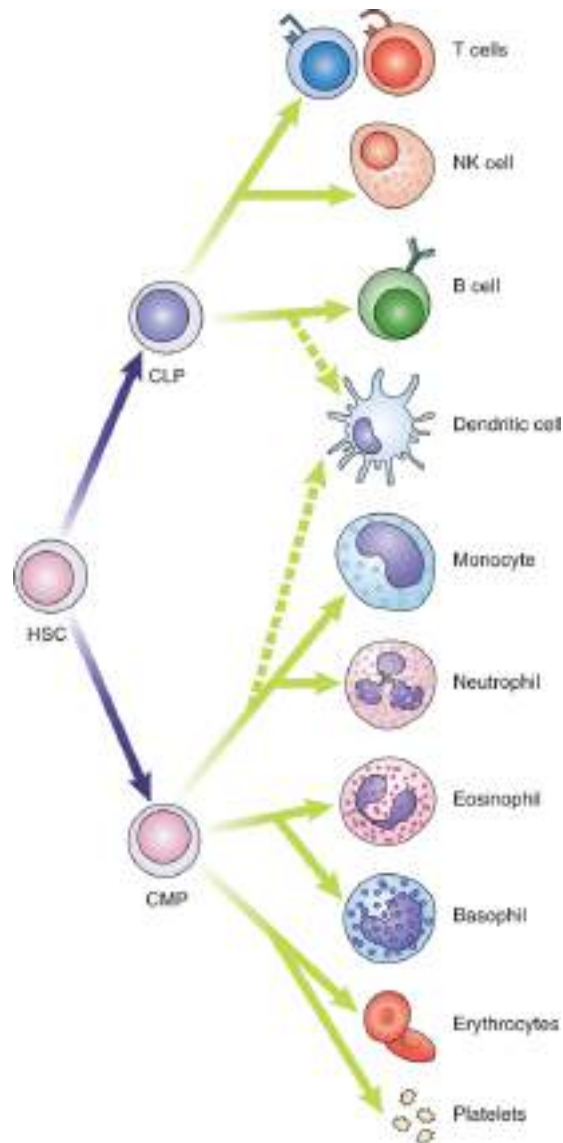


FIGURE 1-2 Simplified scheme of hematopoiesis. In the marrow, HSCs give rise to two different lines—a CLP and a CMP. CLPs give rise to T/NK progenitors, which differentiate into T and NK cells, and to B-cell progenitors, which become B cells and dendritic cells. The CMP differentiates into another type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

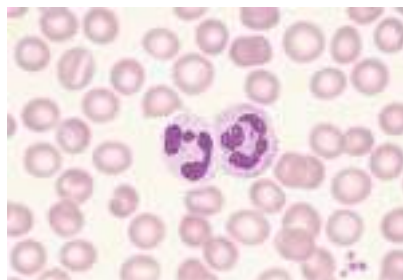


FIGURE 1-3 Neutrophils. (From *Harmening D. Clinical Hematology and Fundamentals of Hemostasis. 5th ed. Philadelphia, PA: F.A. Davis; 2009: Fig. 1-4.*)

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.

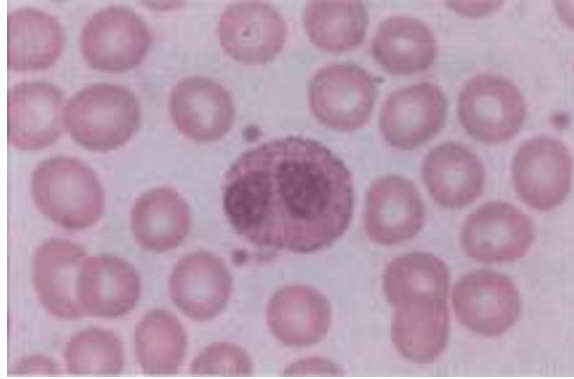


FIGURE 1-4 Eosinophil. (From Harmening D. *Clinical Hematology and Fundamentals of Hemostasis*. 5th ed. Philadelphia, PA: F.A. Davis; 2009: Fig. 1–6.)

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

Index

A

abusive relationships

blaming themselves, abused as [ref1](#)

children [ref1](#), [ref2](#), [ref3](#), [ref4](#), [ref5](#), [ref6](#), [ref7](#), [ref8](#), [ref9](#), [ref10](#)

conspiracy theories [ref1](#)

domestic abuse [ref1](#), [ref2](#)

economic abuse and dependency [ref1](#)

isolation [ref1](#)

physical abuse [ref1](#)

psychological abuse [ref1](#)

signs of abuse [ref1](#)

addiction

alcoholism [ref1](#)

frequencies [ref1](#)

substance abuse [ref1](#), [ref2](#)

technology [ref1](#), [ref2](#), [ref3](#)

Adelson, Sheldon [ref1](#), [ref2](#), [ref3](#)

Agenda 21/Agenda 2030 (UN) [ref1](#), [ref2](#), [ref3](#), [ref4](#)

AIDs/HIV [ref1](#)

causal link between HIV and AIDs [ref1](#), [ref2](#)

retroviruses [ref1](#)

testing [ref1](#), [ref2](#)

trial-run for Covid-19, as [ref1](#), [ref2](#)

aliens/extraterrestrials [ref1](#), [ref2](#)

aluminium [ref1](#)

Amazon [ref1](#), [ref2](#), [ref3](#)