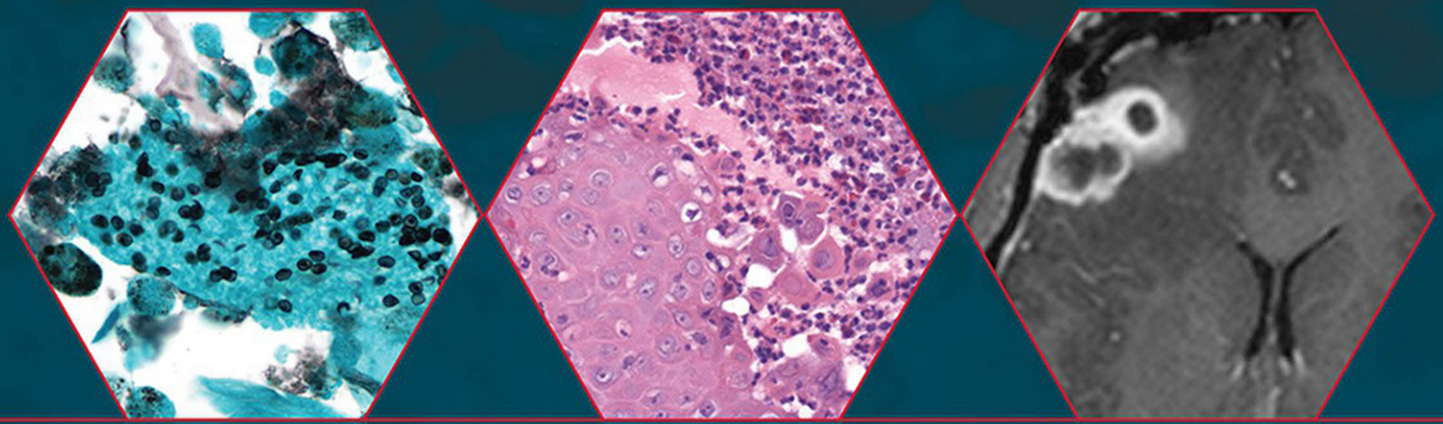
THIRD EDITION

FIRST AID FOR THE® BASIC SCIENCES

General Principles



TAO LE • WILLIAM HWANG
LUKE PIKE

Mc Graw Hill Education

FIRST AID FOR THE® BASIC SCIENCES

General Principles

Third Edition

SENIOR EDITORS

TAO LE, MD, MHS
Associate Clinical Professor
Chief, Section of Allergy and Immunology
Department of Medicine
University of Louisville

WILLIAM L. HWANG, MD, PhD
Resident, Harvard Radiation Oncology Program
Massachusetts General Hospital
Brigham & Women's Hospital

EDITORS

LUKE R.G. PIKE, MD, DPhil
Resident, Harvard Radiation Oncology Program
Massachusetts General Hospital
Brigham & Women's Hospital

M. SCOTT MOORE, DO
Clinical Research Fellow
Affiliated Laboratories, Scottsdale

Mc Graw Hill Education

New York / Chicago / San Francisco / Athens / London / Madrid / Mexico City
Milan / New Delhi / Singapore / Sydney / Toronto

ISBN: 978-1-25-958702-3

MHID: 1-25-958702-9.

The material in this eBook also appears in the print version of this title: ISBN: 978-1-25-958701-6,
MHID: 1-25-958701-0.

eBook conversion by codeMantra
Version 1.0

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors and the publisher of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

DEDICATION

To the contributors to this and future editions, who took time to share their knowledge, insight, and humor for the benefit of students and physicians everywhere.

and

To our families, friends, and loved ones, who supported us in the task of assembling this guide.

This page intentionally left blank

Contents

CONTRIBUTING AUTHORS

Ezra Baraban, MD
Yale School of Medicine
Class of 2016

Nashid H. Chaudhury
Medical Scientist Training Program
Yale School of Medicine
Class of 2020

Richard Giovane, MD
Resident, Department of Family Medicine
University of Alabama

Jessica F. Johnston, MSc
Medical Scientist Training Program
Yale School of Medicine
Class of 2020

Young H. Lim
Medical Scientist Training Program
Yale School of Medicine
Class of 2020

Margaret MacGibeny, MS
Rutgers Robert Wood Johnson Medical School and
Princeton University MD/PhD program
Class of 2020

Benjamin B. Massenburg
Icahn School of Medicine at Mount Sinai
Class of 2017

Jake Prigoff, M
Resident, Department of Surgery
New York Presbyterian Hospital

Ritchell van Dams, MD, MHS
Intern, Department of Medicine
Norwalk Hospital

Zachary Schwam, MD
Yale School of Medicine
Class of 2016

FACULTY REVIEWERS

Susan Baserga, MD, PhD
Professor, Molecular Biophysics & Biochemistry Genetics and Therapeutic Radiology
Yale School of Medicine

Sheldon Campbell, MD, PhD
Associate Professor of Laboratory Medicine
Co-director, Attacks and Defenses Master Course
Director, Laboratories at VA CT Healthcare System
Director, Microbiology Fellowship
Yale School of Medicine

Conrad Fischer, MD
Residency Program Director, Brookdale University Hospital Brooklyn, New York
Associate Professor, Medicine, Physiology, and Pharmacology
Touro College of Medicine

Matthew Grant, MD
Assistant Professor of Medicine (Infectious Disease)
Director, Yale Health Travel Medicine
Yale School of Medicine

Marcel Green, MD
Resident Physician, Department of Psychiatry
Mount Sinai Health System, St. Luke's–Roosevelt Hospital

Peter Heeger, MD
Irene and Arthur Fishberg Professor of Medicine
Translational Transplant Research Center
Department of Medicine
Icahn School of Medicine at Mount Sinai

Jeffrey W. Hofmann, MD, Ph
Resident, Department of Pathology
University of California, San Francisco

Gerald Lee, MD
Assistant Professor, Department of Pediatrics
University of Louisville School of Medicine

Alexandros D. Polydorides, MD, PhD
Associate Professor of Pathology and Medicine (Gastroenterology)
Icahn School of Medicine at Mount Sinai

Sylvia Wassertheil-Smoller, PhD
Distinguished University Professor and Molly Rosen and Maneoloff Chair in Social Medicine, Emerita
Department of Epidemiology and Population Health
Albert Einstein College of Medicine

Howard M. Steinman, PhD
Professor, Department of Biochemistry
Assistant Dean for Biomedical Science Education
Albert Einstein College of Medicine

Peter Takizawa, PhD
Assistant Professor, Department of Cell Biology
Director, Medical Studies
Yale School of Medicine

George J. Trachte, PhD
Professor, Department of Biomedical Sciences
University of Minnesota

Prashant Vaishnava, MD
Assistant Professor, Department of Medicine
Mount Sinai Hospital and Icahn School of Medicine at Mount Sinai

Ana A. Weil, MD
Instructor in Medicine
Massachusetts General Hospital

This page intentionally left blank

Preface

With this third edition of *First Aid for the Basic Sciences: General Principles,* we continue our commitment to providing students with the most useful and up-to-date preparation guides for the USMLE Step 1. For the past year, a team of authors and editors have worked to update and further improve this third edition. This edition represents a major revision in many ways.

- Brand new Public Health and Patient Safety sections have been added.
- Every page has been carefully reviewed and updated to reflect the most high-yield material for the Step 1 exam.
- New high-yield figures, tables, and mnemonics have been incorporated.
- Margin elements, including flash cards, have been added to assist in optimizing the studying process.
- Hundreds of user comments and suggestions have been incorporated
- Emphasis on integration and linkage of concepts was increased.

This book would not have been possible without the help of the hundreds of students and faculty members who contributed their feedback and suggestions. We invite students and faculty to please share their thoughts and ideas to help us improve *First Aid for the Basic Sciences: General Principles.* (See How to Contribute, p. xiii.)

Louisville Tao Le
Boston William Hwang

How to Use This Book

Both this text and its companion, *First Aid for the Basic Sciences: Organ Systems*, are designed to fill the need for a high-quality, in-depth, conceptually driven study guide for the USMLE Step 1. They can be used alone or in conjunction with the original *First Aid for the USMLE Step 1*. In this way, students can tailor their own studying experience, calling on either series, according to their mastery of each subject.

Medical students who have used the previous editions of this guide have given us feedback on how best to make use of the book.

- **It is recommended that you begin using this book as early as possible** when learning the basic medical sciences. We advise that you use this book as a companion to your preclinical medical school courses to provide a guide for the concepts that are most important for the USMLE Step 1.
- As you study each discipline, **use the corresponding section in *First Aid for the Basic Sciences: General Principles*** to consolidate the material, deepen your understanding, or clarify concepts.
- As you approach the test, use both *First Aid for the Basic Sciences: General Principles* and *First Aid for the Basic Sciences: Organ Systems* to review challenging concepts.
- Use the margin elements (ie, Flash Forward, Flash Back, Key Fact, Clinical Correlation, Mnemonic, Flash Cards) to test yourself throughout your studies.

To **broaden** your learning strategy, you can **integrate** your *First Aid for the Basic Sciences: General Principles* study with *First Aid for the USMLE Step 1*, *First Aid Cases for the USMLE Step 1*, and *First Aid Q&A for the USMLE Step 1* on a chapter-by-chapter basis.

Acknowledgments

This has been a collaborative project from the start. We gratefully acknowledge the thoughtful comments and advice of the residents, international medical graduates, medical students, and faculty who have supported the editors and authors in the development of *First Aid for the Basic Sciences: General Principles*.

For support and encouragement throughout the process, we are grateful to Thao Pham and Louise Petersen.

Furthermore, we wish to give credit to our amazing editors and authors, who worked tirelessly on the manuscript. We never cease to be amazed by their dedication, thoughtfulness, and creativity.

Thanks to our publisher, McGraw-Hill Education, for their assistance and guidance. For outstanding editorial work, we thank Allison Battista, Christine Diedrich, Ruth Kaufman, Isabel Nogueira, Emma Underdown, Catherine Johnson, and Hannah Warnshuis. A special thanks to Rainbow Graphics, especially David Hommel, for remarkable production work.

We are also very grateful to the faculty at Uniformed Services University of the Health Sciences (USUHS) for use of their images and Dr. Richard Usatine for his outstanding dermatologic and clinical image contributions.

For contributions and corrections, we thank Abraham Abdul-Hak, Mohamed Abdulla, Zachary Aberman, Andranik Agazaryan, Zain Ahmed, Anas Alabkaa, Allen Avedian, Syed Ayaz, Andrew Beck, Michael Bellew, Konstantinos Belogiannis, Candace Benoit, Brandon Bodie, Aaron Bush, Robert Case, Jr., Anup Chalise, Rajdeep Chana, Sheng-chieh Chang, Yu Chiu, Renee Cholyway, Alice Chuang, Diana Dean, Douglas Dembinski, Kathryn Demitruk, Regina DePietro, Nolan Derr, Vikram Eddy, Alejandra Ellison-Barnes, Leonel Estofan, Tim Evans, Matt Fishman, Emerson Franke, Margaret Funk, Alejandro Garcia, William Gentry, Richard Godby, Shawn Gogia, Marisol Gonzalez, William Graves, Jessie Hanna, Clare Herickhoff, Joyce Ho, Jeff Hodges, David Huang, Andrew Iskandar, Anicia Ivey, Jeffrey James, Angela Jiang, Bradford Jones, Caroline Jones, Charissa Kahue, Sophie Kerszberg, Michael Kertzner, Mani Khorsand Askari, Peeraphol La-orkanchanakun, Juhye Lee, Jessica Liu, Jinyu Lu, James McClurg, Gregory McWhir, Rahul Mehta, Kristen Mengwasser, Aleksandra Miucin, Morgan Moon, Jan Neander, Michael Nguyen, Jay Patel, Nehal Patel, Iqra Patoli, Matthew Peters, Yelyzaveta Plechysta, Qiong Qui, Peter Francis Raguindin, Kenny Rivera, Luis Rivera, Benjamin Robbins, Jorge Roman, Julietta Rubin, Kaivan Salehpour, Abdullah Sarkar, Hoda Shabpiray, Neal Shah, Chris Shoff, Rachael Snow, Gregory Steinberg, Ryan Town, Michael Turgeon, Hunter Upton, Zack Vanderlaan, Christopher Vetter, Liliana Villamil Nunez, Sukanthi Viruthagiri, David Marcus Wang, and Andy Zureick.

Louisville Tao Le
Boston William Hwang

This page intentionally left blank

How to Contribute

To continue to produce a high-yield review source for the USMLE Step 1, you are invited to submit any suggestions or corrections. We also offer paid internships in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for:

- New facts, mnemonics, diagrams, and illustrations
- High-yield topics that may reappear on future Step 1 examinations
- Corrections and other suggestions

For each new entry incorporated into the next edition, you will receive an **Amazon gift card** with a value of up to $20, as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the change improves readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the *AMA Manual of Style* recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc).

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: **www.firstaidteam com.**

Alternatively, you can email us at: **firstaidteam@yahoo.com**

NOTE TO CONTRIBUTORS

All contributions become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

AUTHOR OPPORTUNITIES

The *First Aid* author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series.

English writing/editing experience, familiarity with Microsoft Word, and Internet access are required. For more information, email us at **firstaidteam@yahoo.co** with a résumé and summary of your interest or samples of your work.

This page intentionally left blank

CHAPTER 1

Anatomy and Histology

Cellular Anatomy and Histology

THE CELL

The cell is the most basic structural and functional unit of life. Living organisms are composed of cells, which may exist as independent units or form more complex organisms. Each cell is a collection of integral, diverse components, required for the biochemical processes that sustain the life of the organism. The most important eukaryotic cellular components will be covered in the following sections.

Plasma Membrane

Every eukaryotic cell is enveloped by an asymmetric lipid bilayer membrane. This membrane consists primarily of two sheets of **phospholipids,** each one-molecule thick (Figure 1-1B). Phospholipids are amphipathic molecules, containing both a water-soluble hydrophilic region and a fat-soluble hydrophobic region (Figure 1-1).

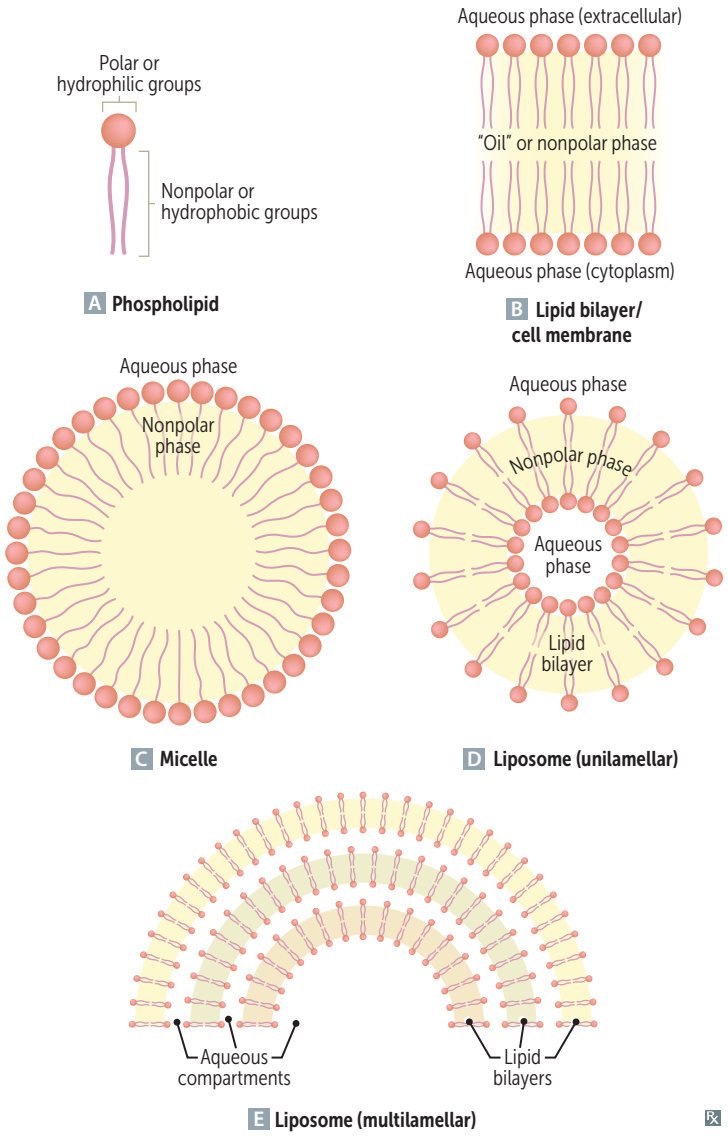


FIGURE 1-1. Amphipathic lipids. A Phospholipid, with a phosphate head group and a lipid tail; B lipid bilayer with both aqueous and nonpolar phases; C micelle in aqueous solution surrounding a nonpolar core; D unilamellar; and E multilamellar liposomes.

- The **hydrophilic** portions (ie, phosphate groups) of each phospholipid layer face both the aqueous extracellular environment as well as the aqueous cytoplasm.
- The **hydrophobic** portions of each phospholipid layer (ie, fatty acid chains) make up the fat-soluble center of the phospholipid membrane.

This bilayer membrane also contains **steroid** molecules (derived from **cholesterol**), glycolipids (fatty acids with sugar moieties), sphingolipids, proteins, and glycoproteins (proteins with sugar moieties). The cholesterol and glycolipid molecules alter the physical properties of the membrane (eg, increase the melting point) in relative proportion to their quantity. The proteins serve important and specific roles in the transport and trafficking of nutrients across the membrane, signal transduction, and interactions between the cell and its environment.

KEY FACT

Biologically important proteins include transmembrane transporters, ligand-receptor complexes, and ion channels. Protein dysfunction underlies many diseases.

The cell membrane performs the following functions:

- Enhances cellular structural stability.
- Protects internal organelles from the external environment.
- Regulates the internal environment (chemical and electrical potential).
- Enables interactions with the external environment (eg, signal transduction and cellular adhesion).

Nucleus and Nucleolus

The nucleus is the control center of the cell. The nucleus contains genetically encoded information in the form of DNA, which directs the life processes of the cell. It is surrounded by the nuclear membrane, which is composed of two lipid bilayers: The inner membrane defines the boundaries of the nucleus, and the outer membrane is continuous with the **rough endoplasmic reticulum (RER)** (Figure 1-2). In addition to DNA, the nucleus houses a number of important proteins that enable the maintenance (protection, repair, and replication), expression (transcription), and transportation of genetic material (capping, transport).

FLASH FORWARD

Genetic mutations may cause dysfunction of regulatory proteins, often leading to debilitating diseases. For example, xeroderma pigmentosum is an autosomal recessive disorder of nucleotide excision repair that leads to increased sensitivity to UV light and increased rates of skin cancer.

Most of the cell's **ribosomal RNA (rRNA)** is produced within the nucleus by the **nucleolus.** The rRNA then passes through the **nuclear pores** (transmembrane protein complexes that regulate trafficking across the nuclear membrane) to the cytosol, where it associates with the RER.

Rough Endoplasmic Reticulum and Ribosomes

As previously described, the RER is home to the majority of the cell's ribosomes. The *rough* in rough endoplasmic reticulum comes from the many ribosomes that stud the membrane of the RER. Ribosomes associate with **transfer RNA (tRNA)** to translate **messenger RNA (mRNA)** into amino acid sequences and, eventually, into proteins (Figure 1-3). The RER functions primarily as the location for membrane and secretory protein production as well as protein modification (Figure 1-2). The RER is highly developed in cell types that produce secretory proteins (eg, pancreatic acinar cells or plasma cells).

KEY FACT

The RER in neurons is referred to as Nissl body when viewed under a microscope.

Smooth Endoplasmic Reticulum

The smooth endoplasmic reticulum (SER) is the site of fatty acid and phospholipid production and therefore is highly developed in cells of the adrenal cortex and steroid-secreting cells of the ovaries and testes. Hepatocytes also have a highly developed SER, as they are constantly detoxifying hydrophobic compounds through conjugation and excretion.

FLASH FORWARD

The cytochrome P-450 system is a family of enzymes located in the SER or mitochondria that metabolize millions of endogenous and exogenous compounds.

Golgi Apparatus

Shortly after being synthesized, proteins from the RER are packaged into transport vesicles and secreted from the RER. These vesicles travel to and fuse with the **Golgi apparatus.** Within the lumen of the Golgi apparatus, secretory and membrane-bound

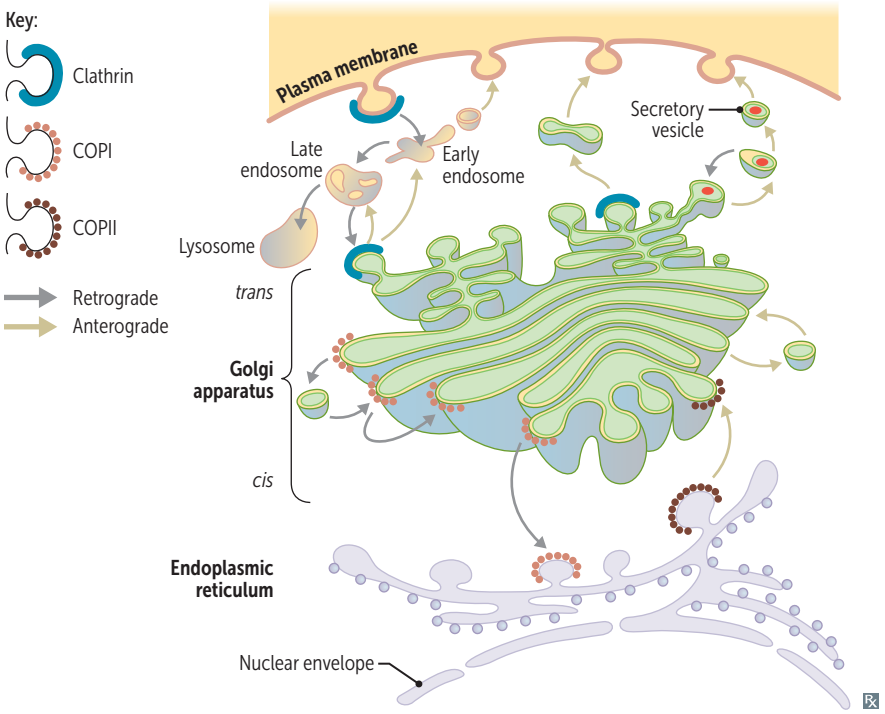


FIGURE 1-2. Representation of the rough endoplasmic reticular branch of protein sorting. Newly synthesized proteins are inserted into the endoplasmic reticulum membrane, or enter the lumen from membrane-bound polyribosomes, depicted as light blue spheres studding the endoplasmic reticulum. Those proteins are then transported out of the endoplasmic reticulum to the Golgi apparatus. Transport to the Golgi apparatus (anterograde transport) is mediated by COPII membrane proteins. Transport from the Golgi apparatus back to the endoplasmic reticulum (retrograde transport) is mediated by COPI membrane proteins. The proteins can be modified in the various subcompartments of the Golgi apparatus and are then segregated and sorted in the trans-Golgi network. Secretory proteins accumulate in secretory storage granules, from which they may be expelled. Proteins destined for the plasma membrane, or those that are secreted in a constitutive manner, are carried out to the cell surface in transport vesicles. This transport is mediated by clathrin membrane proteins. Some proteins enter prelysosomes (late endosomes) and fuse with endosomes to form lysosomes.

CLINICAL CORRELATION

Inclusion-cell (I-cell) disease, also known as mucolipidosis type II, results from a defect in *N*-acetylglucosaminyl-1-phosphotransferase, leading to a failure of the Golgi apparatus to phosphorylate mannose residues (ie, mannose-6-phosphate) on N-linked glycoproteins. Thus, hydrolytic enzymes are secreted extracellularly, rather than delivered to lysosomes, hindering the digestion of intracellular waste. Coarse facial features and restricted joint movements result (refer to Biochemistry chapter for discussion of lysosomal storage disorders).

CLINICAL CORRELATION

A number of lysosomal storage diseases, such as Tay-Sachs disease, result from lysosomal dysfunction and the accumulation of protein metabolites targeted for destruction or further modification.

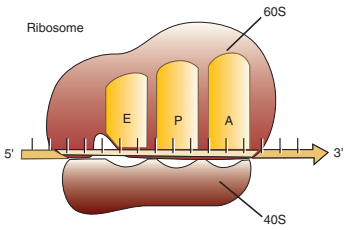


FIGURE 1-3. Schematic representation of translation. Here, the 40S and 60S subunits of rRNA are shown, translating a portion of mRNA in the 5′ to 3′ direction. Many of these ribosomes are located within the membrane of the RER so that their initial protein product ends up within the lumen of the RER, where it undergoes further modification. **E** site, holds **E**mpty tRNA as it **E**xits; **P** site, accommodates growing **P**eptide; **A** site, **A**rriving **A**minoacyl tRNA.

proteins undergo modification. Depending on their final destination, these proteins may be modified in one of the three major regions of Golgi networks: **cis (CGN), medial (MGN)**, or **trans (TGN)**. These proteins are then packaged in a second set of transport vesicles, which bud from the trans side and are delivered to their target locations (eg, organelle membranes, plasma membrane, and lysosomes; Figure 1-2).

Functions of the Golgi Apparatus

- Distributes proteins and lipids from the endoplasmic reticulum to the plasma membrane, lysosomes, and secretory vesicles.
- Modifies *N*-oligosaccharides on asparagines.
- Adds *O*-oligosaccharides to serine and threonine residues.
- Assembles proteoglycans from core proteins.
- Adds sulfate to sugars in proteoglycans and tyrosine residues on proteins.
- Adds mannose-6-phosphate to specific proteins (targets the proteins to the lysosome).

Lysosomes

The lysosome is the **trash collector** of the cell. Bound by a single lipid bilayer, the lysosome is responsible for hydrolytic degradation of obsolete cellular components. Extra-

cellular materials, ingested via endocytosis or phagocytosis, are enveloped in an endosome (temporary vesicle), which fuses with the lysosome, leading to enzymatic degradation of endosomal contents. Lysosomal enzymes (nucleases, proteases, and phosphatases) are activated at a pH below 4.8. To maintain this pH, the membrane of the lysosome contains a hydrogen ion pump, which uses adenosine triphosphate (ATP) to pump protons into the lysosome, against the concentration gradient.

Mitochondria

The mitochondria are the primary site of **ATP** production in aerobic respiration. The proteins of the **outer membrane** enable the transport of large molecules (molecular weight ~10,000 daltons) for oxidative respiration. The **inner membrane** is separated from the outer by the intermembranous space and is more selectively permeable (Figure 1-4). The inner membrane has a large surface area due to its numerous folds, known as **cristae,** and it maintains its selectivity with transmembrane proteins. These transmembrane proteins constitute the electron transport chain, and maintain a proton gradient between the intermembranous space and the lumen of the inner membrane. The role of the electron transport chain is to generate energy for storage in the bonds of ATP.

Microtubules and Cilia

Microtubules are aggregate intracellular protein structures important for cellular **support, rigidity,** and **locomotion.** They consist of α- and **β-tubulin** dimers, each bound to two guanosine triphosphate (GTP) molecules, giving them a positive and negative polarity. They combine to form cylindrical polymers of of 24 nm in diameter and variable lengths (Figure 1-5A). Polymerization occurs slowly at the positive end of the microtubule, but depolymerization occurs rapidly unless a GTP cap is in place.

Microtubules are incorporated into both flagella and **cilia.** Within cilia, the microtubules occur in pairs, known as **doublets.** A single cilium contains nine doublets around its circumference, each linked by an ATPase, **dynein** (Figure 1-5B). Dynein, anchored to one doublet, moves toward the negative end of the microtubule along the length of a neighboring doublet in a coordinated fashion, resulting in ciliary motion. Kinesin is another intracellular transport ATPase that moves toward the positive end of a microtubule, opposite of dynein.

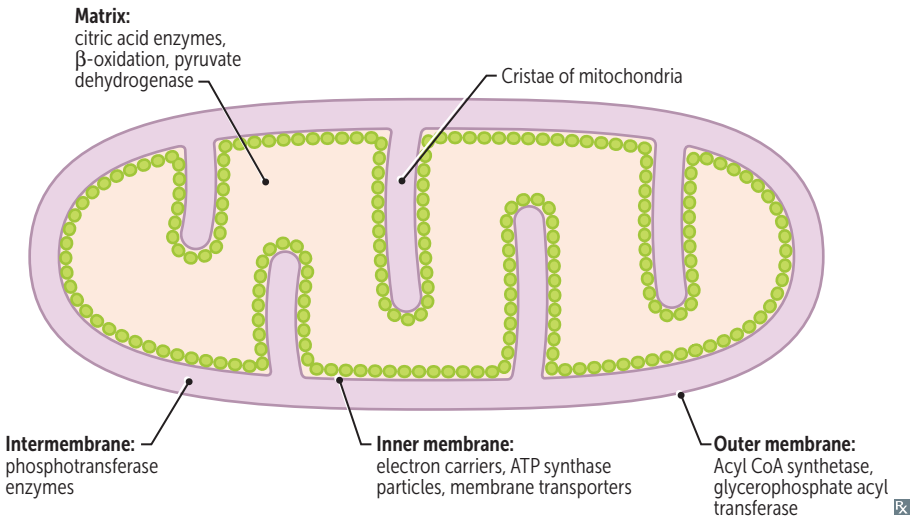


FIGURE 1-4. Structure of the mitochondrial membranes. The inner membrane contains many folds, or cristae, and the enzymes for the electron transport chain, used in aerobic cellular respiration, are located here.

CLINICAL CORRELATION

Chédiak-Higashi disease, resulting from abnormal microtubular assembly, leads to impaired polymorphonuclear leukocytes (PMNs) phagocytosis and frequent infections.

CLINICAL CORRELATION

Various inherited disorders can be maternally transmitted via mitochondrial chromosomes. These can show a variable expression in a population due to heteroplasmy, or the presence of heterogenous mitochondrial DNA in an individual. These diseases primarily affect the muscles, cerebrum, or the nerves, where energy is needed the most. For example, myoclonic epilepsy with ragged-red fibers is a mitochondrial disorder characterized by progressive myoclonic epilepsy, short stature, hearing loss, and "ragged-red fibers" on biopsy.

KEY FACT

Drugs that act on microtubules:

Drug	Disease
Mebendazole/ albendazole	Parasitic infections
Taxanes	Cancers
Griseofulvin	Fungal infections
Vincristine/ vinblastine	Cancers
Colchicine	Gout

CLINICAL CORRELATION

A number of diseases arise from ineffective or insufficient ciliary motion.

Kartagener syndrome: A dynein arm defect that impairs ciliary motion and mucus clearance that results in recurrent lung infections, hearing loss, infertility, and dextrocardia situs inversus.

Dextrocardia/situs inversus: Proper directional development does not occur during embryogenesis, causing all internal organs to be located on the opposite side of the body.

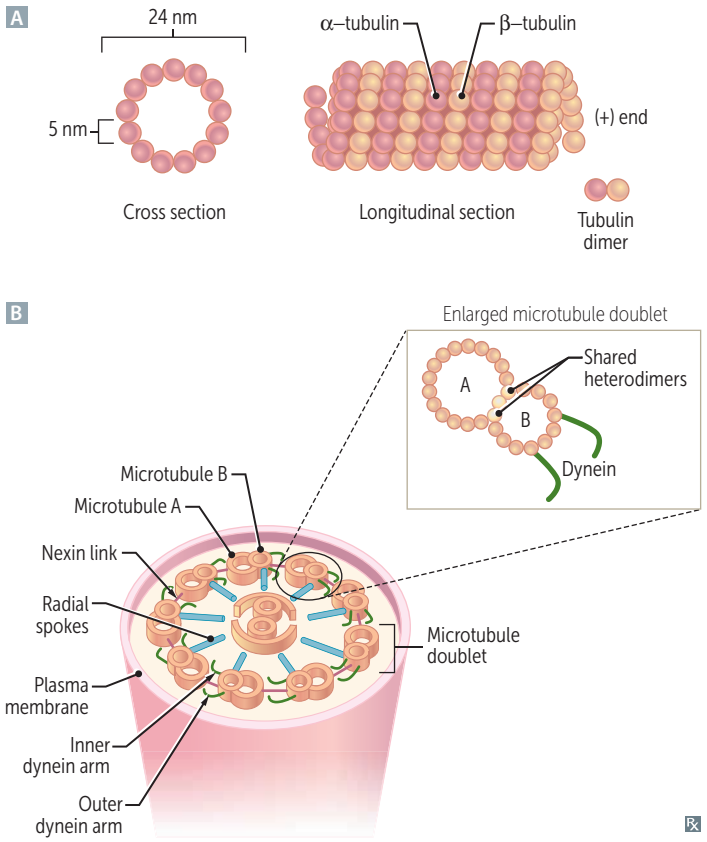


FIGURE 1-5. Microtubules. A Structure. The cylindrical structure of a microtubule is depicted as a circumferential array of 13 dimers of α- and β-tubulin. The tubulin dimers are being added to the positive end of the microtubule. B Ciliary structure. Nine microtubule doublets, circumferentially arranged, create motion via coordinated dynein ATP cleavage.

Epithelial Cell Junctions

Transmembrane proteins mediate intercellular interaction by providing cellular adhesion and cell signaling. Cellular adhesion and communication are vitally important to both the integrity and the function of an organ.

Organs and tissues exposed to the external environment are the most resilient. These tissues are referred to as **epithelial,** primarily due to their embryologic origin. The epithelial cells of these external tissues contain an array of **cell junctions** that mediate cellular adhesion and communication processes. There are five principal types of cell junctions: **zonula occludens (tight junctions), zonula adherens (intermediate junctions), macula adherens (desmosomes), hemidesmosomes,** and **gap junctions (communicating junctions)** (Figure 1-6).

Zonula Occludens

Tight junctions, also referred to as occluding junctions, have the following two primary functions:

- Determine epithelial cell polarity, separating the apical pole from the basolateral pole.
- Regulate passage of substances across the epithelial barrier **(paracellular transport).**

In a typical epithelial tissue, the membranes of adjacent cells meet at regular intervals to seal the paracellular space, preventing the paracellular movement of solutes. These connections occur during the interaction of the junctional protein complex with neighboring cells, composed of **claudins** and **occludins.**

CLINICAL CORRELATION

Malignant epithelial cells contained by the basal membrane are termed **carcinoma in situ.** Loss of cell junctions allows penetration through the basement membrane as **invasive carcinoma.** When cells enter the bloodstream or lymphatics and establish new tumors at distant sites, they are considered **metastatic.**

MNEMONIC

CADHErins are **C**alcium-dependent **ADHE**sion proteins.

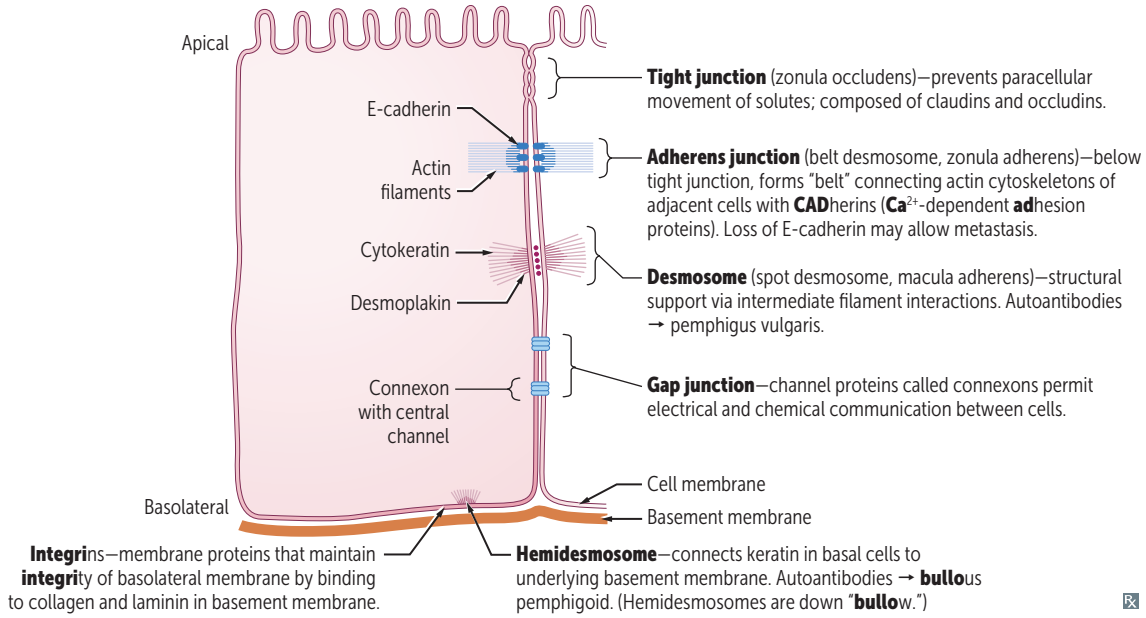


FIGURE 1-6. Epithelial cell junctions. Five types of epithelial cell junctions are depicted along with their supporting and component proteins.

Zonula Adherens

Intermediate junctions are located just below tight junctions, near the apical surface of an epithelial layer. Like the zonula occludens, the zonula adherens are located in a beltlike distribution. Inside the cell, these transmembrane protein complexes are associated with actin microfilaments. Outside the cell, **cadherins** from adjacent cells use a calcium-dependent mechanism to span wider intercellular spaces than can the zona occludens. Loss of E-cadherin may allow cancer cells to metastasize.

Macula Adherens

As opposed to the beltlike distribution of the zonula occludens and adherens, desmosomes resemble spot welds—single rivets erratically spaced below the apical surface of the epithelium. Intracellularly, they are associated with keratin intermediate filaments, providing strength and rigidity to the epithelial surface. Like the zonula adherens, macula adherens are also mediated by calcium-dependent cadherin interactions.

Hemidesmosomes

These asymmetrical anchors provide epithelial adhesion to the underlying connective tissue layer, the **basement membrane.** The hemidesmosomes contain **integrin** (instead of cadherins), an anchoring protein filament that binds the cell to the basement membrane. Although the intracellular portion structurally resembles that of the desmosome, none of the protein components are conserved, except for the cytoplasmic association with intermediate filaments.

Gap Junctions

These intercellular junctions allow for rapid transmission of electrical or chemical information from one cell to the next. A connexon is formed from a complex of six **connexin** proteins. Each single **connexon** exists as a hollow cylindrical structure spanning the plasma membrane. When a connexon of one cell is bound to a connexon of an adjacent cell, a gap junction is formed, creating an open channel for fluid and electrolyte transport across cell membranes.

CLINICAL CORRELATION

Pemphigus vulgaris: An autoimmune disease of the skin due to anti-desmosome antibodies. This disrupts the cohesion between keratinocytes, leading to fragile blisters. The antibodies are distributed in a reticular or "net-like" pattern. Nikolsky sign is positive.

CLINICAL CORRELATION

Bullous pemphigoid: An autoimmune disease of the skin due to anti-hemidesmosome antibodies. These disrupt the dermal-epidermal junction resulting in separation of the layers in the form of tense bullae. The antibodies are distributed linearly along the basement membrane. Nikolsky sign is negative.

FLASH FORWARD

Gap junctions allow for "coupling" of cardiac myocytes, enabling the rapid transmission of electrical depolarization and coordinating contraction during the cardiac cycle.

HEMATOPOIESIS

Hematopoietic cells are stem cells residing in the bone marrow that can give rise to all mature components of circulating blood cells and immune systems.

Blood

Blood is composed of cells suspended in a liquid phase. This liquid phase, which consists of water, proteins, and electrolytes is known as **plasma.** O_2-carrying red blood cells, known as **erythrocytes,** make up about 45% of blood by volume. This percentage is known as the **hematocrit.** Erythrocytes can be separated from white blood cells, or **leukocytes,** and **platelets** by centrifugation. Erythrocytes form the lowest layer, and leukocytes form the next layer, also known as the **buffy coat.** Plasma from which the platelets and clotting factors have been extracted is called blood **serum.**

The Pluripotent Stem Cell

The hematopoietic stem cell is the grandfather of all major blood cells. These cells reside within the bone marrow, where **hematopoiesis** (blood cell production) occurs. They are capable of asymmetrical reproduction: simultaneous self-renewal and differentiation.

- **Self-renewal,** integral to the maintenance of future hematopoietic potential, preserves the pool of stem cells.
- **Differentiation** leads to the production of specialized mature cells, necessary for carrying out the major functions of blood.

CLINICAL CORRELATION

RBC cytoskeletal abnormalities (eg, hereditary spherocytosis, elliptocytosis) and hemoglobinopathies (eg, thalassemias, sickle cell anemia) cause significant morbidity and mortality.

Two differentiated cell lines derive from the pluripotent stem cell: **myeloid** and **lymphoid** (Figure 1-7). These cells are considered committed, meaning that they have begun the process of differentiation and have lost some of their potential to become cells in an alternate lineage. The myeloid lineage produces six different types of colony-forming units (CFUs), each ending in a distinct mature cell: erythroid (producing erythrocytes), megakaryocyte (producing platelets), basophil, eosinophil, neutrophil, and monocyte (differentiates into macrophage). The lymphoid lineage produces two cell lines: T cells and B cells.

Erythrocytes

CLINICAL CORRELATION

The reticulocyte count increases when the bone marrow increases production to replenish red cell levels in the blood in response to anemia.

Erythrocytes are nonnucleated, biconcave disks designed for gas exchange. These cells measure approximately 8 μm in diameter, and their biconcave shape increases their surface area for gas exchange, and allows them to squeeze through narrow capillaries. These cells lack organelles, which are extruded shortly after they enter the bloodstream. Instead, they contain only a plasma membrane, a cytoskeleton, hemoglobin, and glycolytic enzymes that help them survive via **anaerobic respiration** (90%) and the hexose monophosphate shunt (10%). This limits the red blood cell life span to approximately 120 days, after which they are mainly removed via macrophages in the spleen, and to a lesser extent, via the liver. Mature erythrocytes are replaced by immature **reticulocytes** produced in the bone marrow. Reticulocytes are distinguished from mature erythrocytes by their slightly larger diameter and reticular (mesh-like) network of ribosomal RNA. Erythropoietin is the hormone that stimulates erythroid progenitor cells to mature by binding to JAK2, a nonreceptor tyrosine kinase.

RBCs are highly dependent on glucose as their energy source, and glucose is transported across the RBC membrane via the glucose transporter (GLUT-1). They are susceptible to free radical damage, but can synthesize glutathione, an important antioxidant. Hemoglobin's ability to transport oxygen is closely associated with the production of 2,3-bisphosphoglycerate (2,3-BPG); 2,3-BPG decreases the affinity of hemoglobin for oxygen, thus improving oxygen delivery to tissues. The iron in hemoglobin is maintained in the ferrous state; ferric iron (Fe^{3+}) is reduced to the ferrous (Fe^{2+}) state via an NADH-dependent methemoglobin reductase system. Finally, RBCs contain certain enzymes

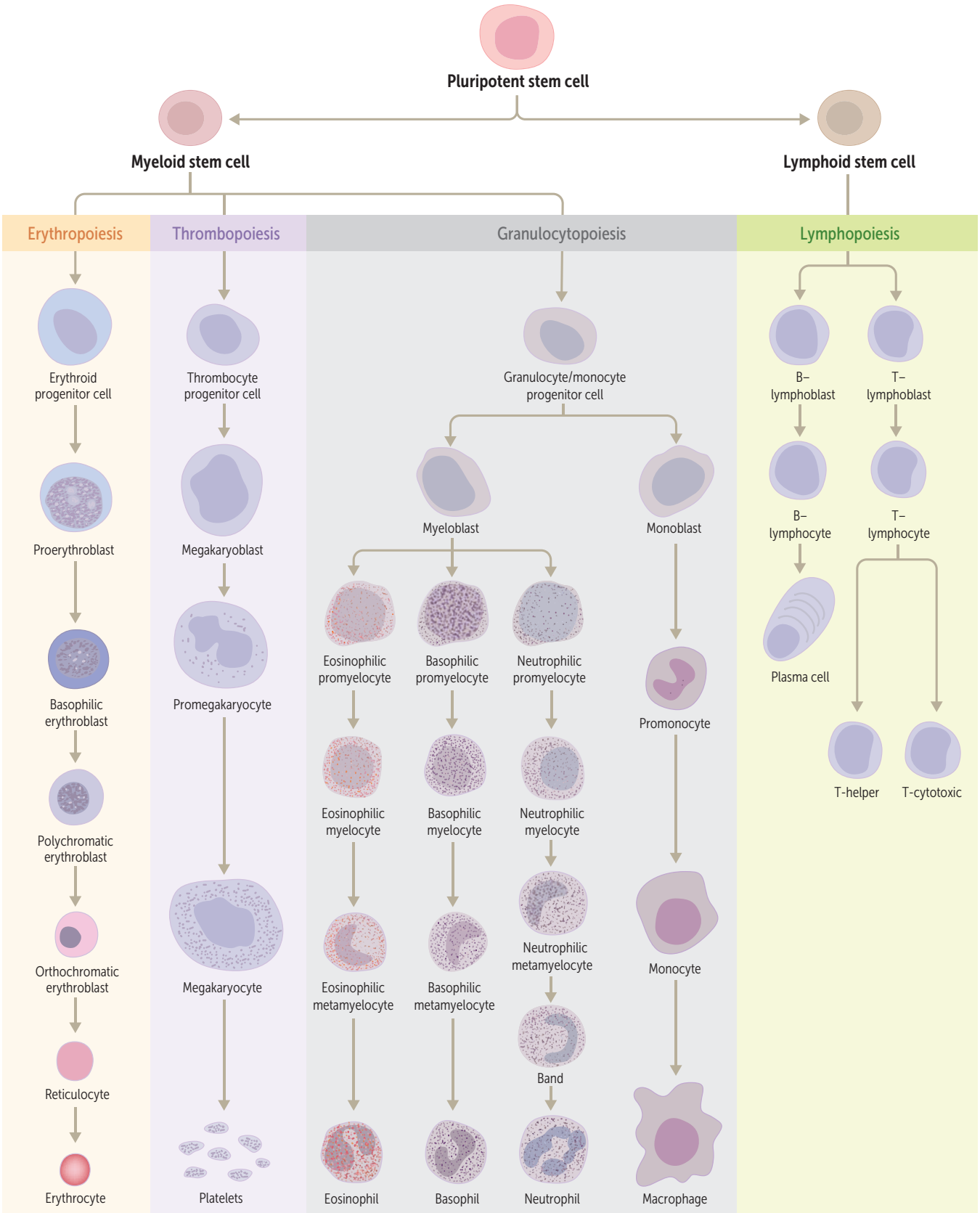


FIGURE 1-7. **Blood cell differentiation.** A chart of the pluripotent hematopoietic stem cell's differentiation potential.

CLINICAL CORRELATION

Activating mutations in JAK2 can cause myeloproliferative disorders like polycythemia vera, essential thrombocythemia, and myelofibrosis. The most common mutation for polycythemia vera is V617F (Figure 1-8).

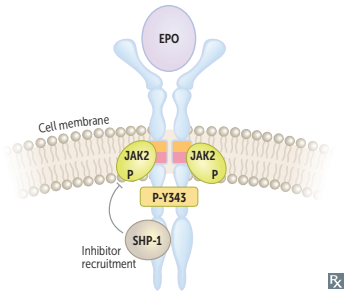


FIGURE 1-8. Erythropoietin (EPO) receptor.

KEY FACT

Leukos = Greek for white.
Cytos = Greek for cell.

CLINICAL CORRELATION

Chronic granulomatous disease: Congenital deficiency of NADPH oxidase impedes the oxidative burst in neutrophils, causing a difficulty in forming the reactive oxygen compounds used to kill pathogens. This results in recurrent bouts of bacterial infection, most commonly pneumonia and skin abscesses.

KEY FACT

Important neutrophil chemotactic agents: C5a, IL-8, leukotriene B4 (LTB_4), kallikrein, platelet-activating factor.

of nucleotide metabolism, and a deficiency in these enzymes (eg, adenosine deaminase, pyrimidine nucleotidase, and adenylate kinase) is involved in some of the hemolytic anemias.

Leukocytes

Leukopoiesis is the process of white blood cell production from hematopoietic stem cells. **Neutrophils, basophils, mast cells,** and **eosinophils** develop through a common promyelocyte lineage. **Monocytes** develop from a monoblast. Lymphocytes, although separate from myeloid cells, are also considered leukocytes and arise from the lymphoid stem cell.

All leukocytes are involved in some aspect of the immune response:

- **Neutrophils** affect **nonspecific innate immunity** in the acute inflammatory response.
- **Basophils and mast cells** mediate **allergic responses.**
- **Eosinophils** help fight **parasitic infections.**
- **Lymphocytes** are integral to both **cellular** and **humoral immunity.**

Neutrophils

These products of the myeloid lineage act as acute-phase granulocytes. They begin in the bone marrow as myeloid stem cells (Figure 1-7) and mature over a period of 10–14 days, producing both primary and secondary granules (promyelocyte stage; Figures 1-9 and 1-10). Once mature, these leukocytes are vital to the success of the innate immune system and are especially prominent in the acute inflammatory response.

Histologically, these cells are distinguished by their large spherical size, multilobed nuclei, and **azurophilic** primary granules **(lysosomes).** These cells have earned the alternative name **polymorphonucleocytes (PMNs)** due to their multilobed nucleus. The key to their immune function lies in the ability of PMNs to phagocytose microbes and destroy them via **reactive oxygen species** (superoxide, hydrogen peroxide, peroxyl radicals, and hydroxyl radicals). Neutrophils contain several enzymes, most notably **NADPH oxidase,** which produces O_2^- radicals, directing the oxidative burst, as well as the **myeloperoxidase (MPO) system,** which uses hydrogen peroxide and chloride to generate hypochlorous acid (HOCl), a potent bactericidal oxidant.

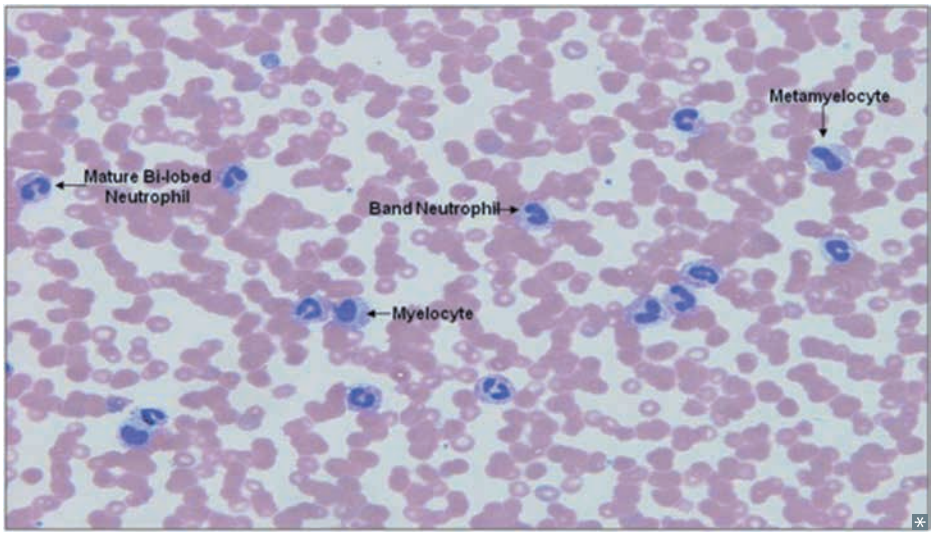


FIGURE 1-9. Peripheral blood smear with neutrophilia. This peripheral blood smear displays an extreme leukemoid reaction (neutrophilia). Most cells are band and segmented neutrophils.

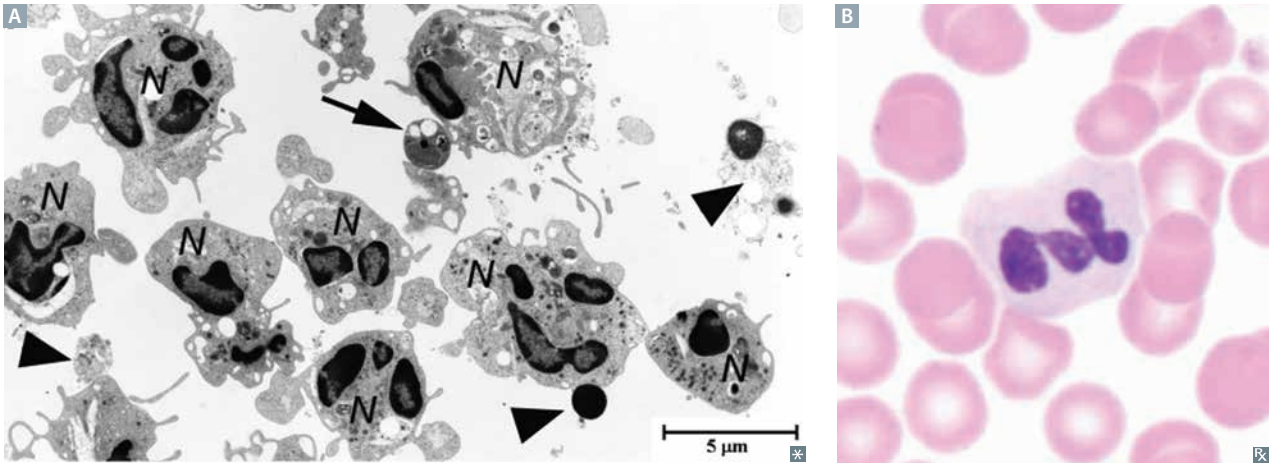


FIGURE 1-10. Electron microscopy of neutrophils. A Highly activated neutrophils (N) with apoptotic neutrophils (black arrow) and cell debris (black arrowhead). B Neutrophil.

Eosinophils

Eosinophils follow the same pattern of maturation as neutrophils, beginning in the bone marrow as eosinophilic CFUs. Eosinophils also contain granules with eosinophil peroxidase. However, they differ in that they are slightly larger than neutrophils with cationic proteins, such as **major basic protein** (antiparasitic) and **eosinophilic cationic protein** (antiparasitic) within **acidophilic** (ie, **eosinophilic**) granules. Once fully mature, eosinophils possess a large, bilobed nucleus (not multi-segmented like neutrophils) and sparse endoplasmic reticulum and Golgi vesicles (Figure 1-11).

MNEMONIC

Causes of eosinophilia—
NAACP
Neoplasia
Asthma
Allergic processes
Chronic adrenal insufficiency
Parasites (invasive)

Basophils and Mast Cells

Distinguished by large, coarse, darkly staining granules, basophils produce peroxidase, **heparin,** and **histamine** (Figure 1-12). Basophils also release **kallikrein,** which acts as an eosinophil chemoattractant during hypersensitivity reactions, such as contact allergies and skin allograft rejection. Because they share a great deal of structural similarities, basophils can be considered the blood-borne counterpart of the **mast cell,** which resides within tissues, near blood vessels. Both mast cells and basophils produce histamine and

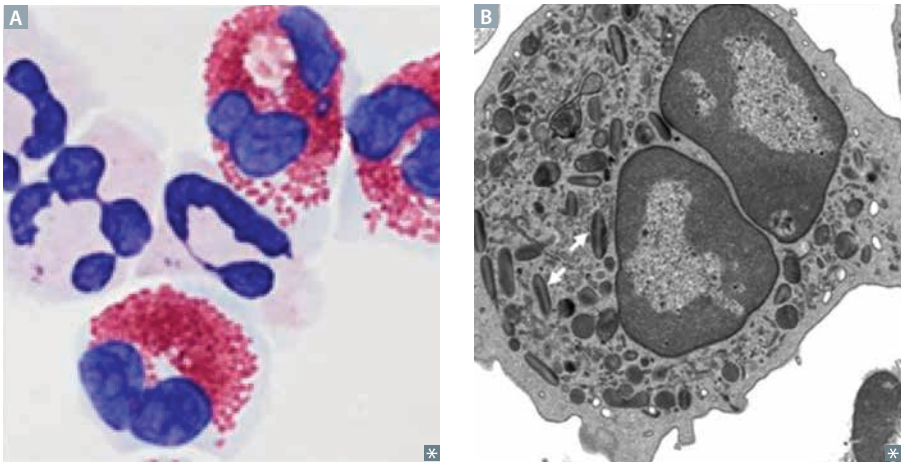


FIGURE 1-11. Eosinophil microscopy. A Mature eosinophil with bright red granules. B Electron microscopy of eosinophils with bilobed nuclei and specific granules in the shape of a football with a crystalline core made from major basic protein.

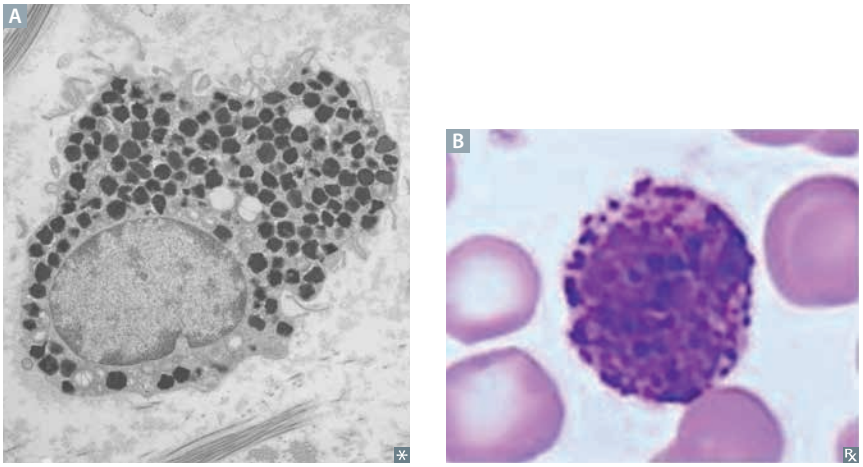


FIGURE 1-12. **Basophil microscopy.** A Electron micrograph of a normal intact mast cell with homogenous electron-dense granules. B Basophil.

CLINICAL CORRELATION

Mast cells release histamine, which leads to type I allergic reactions, resulting in unpleasant allergy symptoms and anaphylaxis.

heparin, but mast cells also contain serotonin (5-HT), which basophils lack. Mast cells degranulate during the acute phase of inflammation, acting, via their released granule contents, on the nearby vasculature. This leads to vasodilation, fluid transudation, and swelling of interstitial tissues.

Monocyte Lineage

Monocytes

KEY FACT

In tissue = macrophage
In blood = monocyte

Monocytes are the myeloid precursor to the mononuclear phagocyte, the tissue macrophage. Morphologically, they appear as spherical cells with scattered small granules, akin to lysosomes. The blood monocyte is a large (10–18 μm), motile cell that marginates along the vessel wall in response to the expression of specific cell adhesion proteins. During an inflammatory response, these cell adhesion proteins (namely, platelet endothelial cell adhesion molecule, or **PECAM-1**) facilitate monocyte **diapedesis** (transmigration) across vessel walls into surrounding tissues. Once in close proximity to the inflammatory foci, the monocyte differentiates into a macrophage with increased phagocytic and lysosomal activity (Figure 1-13).

Macrophages

During differentiation, monocyte cell volume and lysosome numbers increase. These lysosomes fuse with phagosomes to degrade ingested cellular and noncellular material.

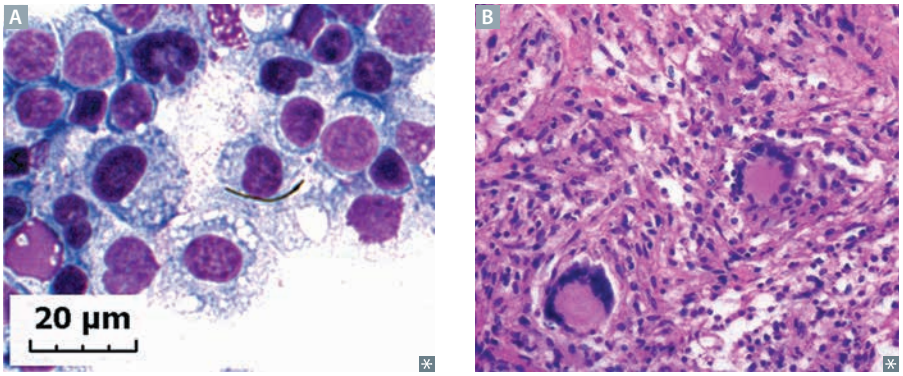


FIGURE 1-13. **Macrophage microscopy.** A Active macrophage and B multinucleated giant cell.

Macrophages (20–80 μm) also contain a large number of cell surface receptors. These differ, depending on the tissue in which the macrophage matures, contributing to the diversity of macrophage functions (Table 1-1).

As described in Table 1-1, monocyte-derived cells are distributed among several organs and tissues (including connective tissue and bone) where they reside (termed tissue-resident macrophages). Alternatively, monocytes can migrate into tissues during an acute inflammatory response and, there, transform into reactive macrophages to aid the innate immune system. Once out of the circulation, monocytes have a half-life of up to 70 hours. Their numbers within inflamed tissues begin to overcome those of neutrophils after approximately 12 hours.

Multinucleated Giant Cells

At sites of chronic inflammation, such as tuberculous lung tissue, macrophages sometimes fuse to produce multinucleated phagocytes (Figure 1-13). These microbicidal cells can be produced in vitro via interferon-γ (IFN- γ) or interleukin-3 (IL-3) stimulation.

Antigen-Presenting Cells

Antigen-presenting cells (**APCs**) are essential to the adaptive immune system. These monocyte-derived phagocytic cells take up antigens (primarily protein particles), process them, display them bound to the **major histocompatibility complex (MHC) II** cell surface marker, and travel to lymph nodes, where they recruit other cells of the immune system into action. Dendritic cells are especially important in the initial exposure to a new antigen. Successful differentiation from monocytes depends on an endothelial cell signal that is secondary to foreign antigen exposure. In the absence of this second signal, these sensitized monocytes transform into macrophages.

Lymphocytes

Lymphocytes are easily distinguished from other leukocytes by their shared morphology (Figures 1-14 and 1-15). After differentiating from lymphoblasts within the marrow, they migrate to the blood as spherical cells, 6–15 μm in diameter. Typically, the nucleus contains tightly packed chromatin, which stains a deep blue or purple and occupies approximately 90% of the cell cytoplasm.

As the primary actors in the adaptive immune response, lymphocytes undergo biochemical transformation into active immune cells via coordinated stimulatory signals. These activated lymphocytes then enter the cell cycle, producing a number of identical daughter cells. They eventually settle into G_0 as a memory cell while they await the

CLINICAL CORRELATION

Lipid A from bacterial lipopolysaccharide (LPS) binds CD14 on macrophages to induce cytokine release. Toxic shock syndrome is caused by preformed *Staphylococcus aureus* toxic shock syndrome toxin (TSST-1), which acts as a superantigen and causes massive cytokine release.

KEY FACT

Macrophages are activated by IFN-γ. They can function as antigen-presenting cells via MHC II.

FLASH FORWARD

Dendritic cells are the most important APCs in the body and they are responsible for initiation of adaptive immunity.

TABLE 1-1. Distribution of Mononuclear Phagocytes

Marrow	Monoblasts, promonocytes, monocytes, macrophages
Blood	Monocytes
Body cavities	Pleural macrophages, peritoneal macrophages
Inflamm tory tissues	Epithelioid cells, exudate macrophages, multinucleated giant cells
Tissues	Liver (Kupffer cells), lung (alveolar macrophages), connective tissue (histiocytes), spleen (red pulp macrophages), lymph nodes, thymus, bone (osteoclasts), synovium (type A cells), mucosa-associated lymphoid tissue, gastrointestinal tract, genitourinary tract, endocrine organs, central nervous system (microglia), skin (dendritic cells)

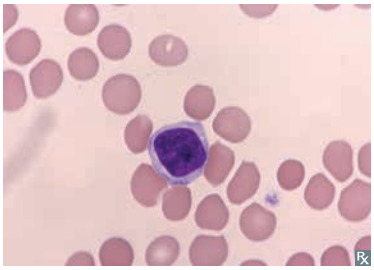


FIGURE 1-14. Light microscopy of a lymphocyte from a blood smear. Medium-sized agranular lymphocyte (stained purple) with a high nuclear to cytoplasmic ratio and a condensed chromatin pattern.

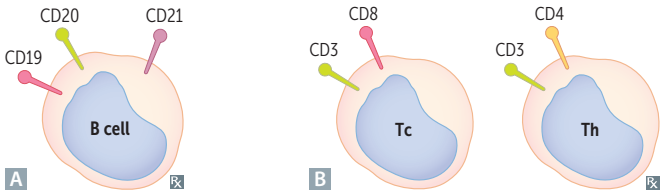


FIGURE 1-15. Lymphocytes. A B cell and B T cell.

next stimulation event. Alternatively, following replication, daughter cells can become terminally differentiated lymphocytes, primed for effector and secretory roles in immunologic defense of the host organism.

B Cells and Plasma Cells

B cells are the "long-range artillery" in the adaptive immune response. After the lymphoblast stage, the lymphocyte lineage diverges into B cells and T cells, each performing separate roles in the adaptive, or **humoral, immune response.** Once committed, **B** cells develop in the **B**one marrow and then migrate to other lymphoid organs. As they develop, B cells express immunoglobulins (IgM and IgD) on their surface, in association with costimulatory proteins. These **B-cell antigen receptor complexes** allow for the recognition of foreign antigens and subsequent activation of the B cell. Downstream cell signaling leads to the expression of necessary genes for terminal differentiation to **plasma cells** that produce and secrete antibodies to aid the specific immune response. B cells that recognize self-antigens are triggered to undergo programmed cell death, or **apoptosis,** to reduce the chance of autoimmunity.

MNEMONIC

MHC × CD = 8 (eg, MHC II × CD4 = 8, and MHC I × CD8 = 8).

T Cells

T cells are the "infantry" of the adaptive immune response. During maturation in the **T**hymus, early T cells begin expressing several surface receptors simultaneously, including the T-cell receptor (**TCR**), **CD4,** and **CD8.** If one of these CD receptors recognizes **receptors** of thymic APCs, either **MHC II** or **I,** respectively, then this T cell is **positively selected,** proliferates, and matures. If a T cell recognizes self-antigen, then it is **negatively selected,** and undergoes apoptosis. All T cells express CD3, and either CD4 (helper T cells), or CD8 (cytotoxic T cells).

KEY FACT

Helper T cells "help" by mediating the specificity of the adaptive immune response. They act as a messenger between APCs and B cells, triggering humoral immunity.

Helper T Cells

Two subtypes of T helper cells are derived from the CD4+ progenitor: Th1 and Th2. Th1 responses occur in the presence of intracellular pathogens. Helminthic or **parasitic infections,** on the other hand, drive Th2-mediated immune responses.

Helper T cells spring into action when they recognize foreign antigens bound to MHC II. Once activated, they secrete **cytokines,** chemical messengers that recruit and activate other immune effector cells. These cytokines, also called **interleukins,** specifically attract B cells, which, in turn, divide and differentiate into plasma cells. After the immune response is complete, some helper T cells become **memory cells**—quiescent immune cells that retain their specificity in case of a rechallenge with the same antigen in the future. The presence of memory cells increases the speed and efficiency of future immune responses.

Cytotoxic T Cells

CD8+ T cells also proliferate in response to cytokines; however, they only recognize antigens in association with class I MHC. These cells are actively involved in immune surveillance of intracellular pathogens.

Every human cell contains MHC I, but only APCs contain MHC II.

- A cell infected by an intracellular pathogen (ie, a virus) processes viral proteins and presents them on the surface via MHC I.
- A roving CD8+ T cell recognizes this signal and attaches to the infected cell via cell adhesion molecules.
- The activated cytotoxic T cell releases **perforins,** which are proteins that form holes in the plasma membrane of targeted cells.

FLASH FORWARD

Cytotoxic T cells also destroy target cells via the **Fas-Fas ligand** interaction. The interaction of Fas ligand of CD8+ T cells with the Fas receptor of the infected cell leads to apoptosis of the target cell.

KEY FACT

Th1 cells are associated with **innate** immunity and **cytolytic** responses. **Th2** cells are associated with **humoral** immunity and **asthma.**

Gross Anatomy and Histology

ABDOMINAL WALL ANATOMY

Layers of the Abdominal Wall

The order of the layers of the anterior abdominal wall differs depending on location. They are depicted in Figure 1-16.

The abdominal muscle aponeuroses comprising the rectus sheath differ above and below the arcuate line. The arcuate line is a horizontal line at the level where the inferior epigastric vessels perforate the rectus abdominis (Figure 1-16). Above the umbilicus, the rectus abdominis muscle is enveloped in the aponeurosis of the internal oblique muscle, with the aponeurosis of the external oblique anterior to the rectus sheath. Below the arcuate line, the anterior rectus sheath is composed of all three abdominal muscle aponeuroses (external oblique, internal oblique, and transversus abdominis). Deep to the muscle layer is the extraperitoneal tissue and transversalis fascia. The parietal peritoneum is deep to that fascia.

CLINICAL CORRELATION

An indirect inguinal hernia enters the deep inguinal ring lateral to the inferior epigastric vessels. A direct inguinal hernia enters the superficial inguinal ring via a weakness in the abdominal muscles medial to the inferior epigastric vessels.

Inguinal Canal

The inguinal canal is an oblique, inferomedially directed channel through which the testes and its vessels and nerves traverse the abdominal wall to reach the scrotum (Figure 1-17). As the testis descends, it carries a sheath of peritoneal sac (tunica vaginalis) into which it invaginates acquiring a partial covering. The inguinal canal lies superior and parallel to the **inguinal ligament,** allows the passage of the **round ligament** of the uterus in women and the **spermatic cord** (ductus deferens and testicular vessels) in men. The canal has two openings: the **internal** (or **deep**) and **external** (or **superficial**) **inguinal rings.** The transversalis fascia evaginates through the abdominal wall and continues as a covering of structures passing through the abdominal wall. The superficial ring is actually an opening through the external oblique aponeurosis. If the protrusion occurs at the site of the deep inguinal ring, the hernia is indirect (Figure 1-18). If the weakness occurs medial to the inferior epigastric vessels, the hernia is direct (Figure 1-18).

CLINICAL CORRELATION

Internal hemorrhoids are painless because they occur above the pectinate line where the innervation is visceral. External hemorrhoids occur below the pectinate line and are painful because they receive somatic innervation. The pectinate line is also a site for portal systemic anastomosis—rectal bleeding is therefore possible in patients with portal hypertension.

Retroperitoneum

The posterior abdominal cavity contains several important structures situated between the parietal peritoneum and the posterior abdominal wall. This region, the retroperitoneum, contains portions of the gastrointestinal, genitourinary, endocrine, and vascular systems (Figure 1-19).

The Pectinate Line

The pectinate (dentate) line is the mucocutaneous junction where the endoderm meets the ectoderm in the anal canal. In the developing embryo, the endodermally derived hindgut fuses with the ectodermally derived external anal sphincter (Figure 1-20). Tissues on each side of this boundary are fed by separate neurovascular sources (Table 1-2).