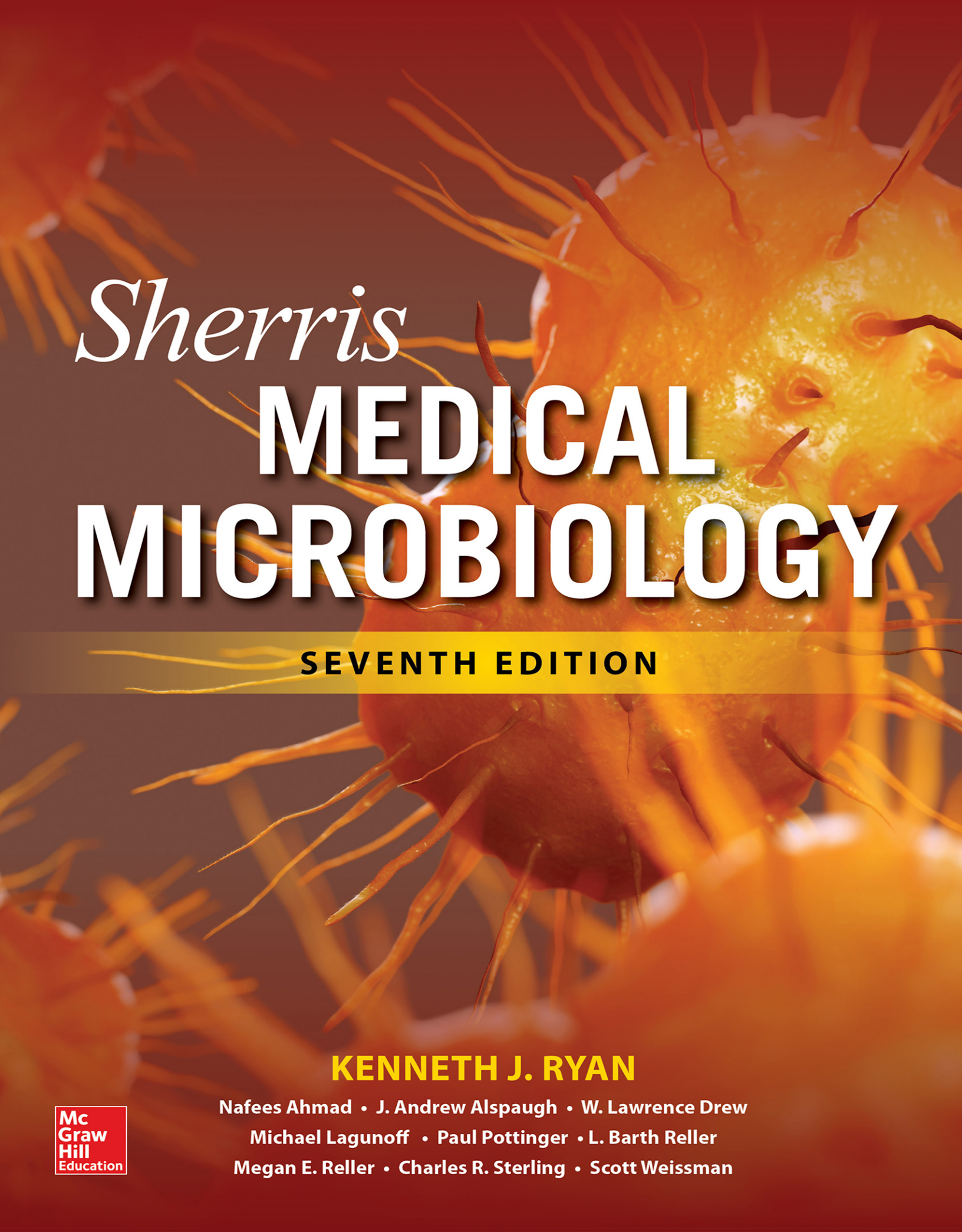

Sherris MEDICAL MICROBIOLOGY

SEVENTH EDITION

KENNETH J. RYAN

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Michael Lagunoff • Paul Pottinger • L. Barth Reller
Megan E. Reller • Charles R. Sterling • Scott Weissman

Mc Graw Hill Education

Seventh Edition

SHERRIS MEDICAL MICROBIOLOGY

EDITOR

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Mc Graw Hill Education

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NOTICE

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DEDICATION

Founders of *Sherris Medical Microbiology*

C. George Ray, MD
James J. Plorde, MD
Elizabeth Sherris
Frederick C. Neidhardt, PhD

Between the sixth and this seventh edition we have lost four scholars who significantly aided founding editor **John Sherris** in the formation and character of this book now known as *Sherris Medical Microbiology*.

George Ray was a founding author, writing on viral diseases, infectious disease syndromes, and laboratory diagnosis. For the fourth through the sixth editions, he was also coeditor of the book. Gorge, a national leader in rapid viral diagnosis, was also a decorated teacher of medical students at three medical schools, the University of Washington, the University of Arizona, and St. Louis University. At SLU, he finished his career as Chairman of Pediatrics.

Jim Plorde, also a founding author, wrote on antibiotics, bacterial diseases, parasitic diseases and infectious disease syndromes in the first through the fifth editions. Jim's Peace Corps and international experience was reflected in his writing, particularly on parasitic diseases. In his faculty career at Washington he served as Chief of Infectious Diseases and Microbiology at the Seattle Veterans Administration Medical Center.

Elizabeth Sherris not only contributed to the organization of the book, she typed the first draft at a time before computers, copiers, and the Internet. Elizabeth had a keen sense of language particularly concerning the clear use of medical language which earned her the respect of the authors and the publisher. She followed later editions closely, remarking especially on the introduction of full color artwork in the fifth edition.

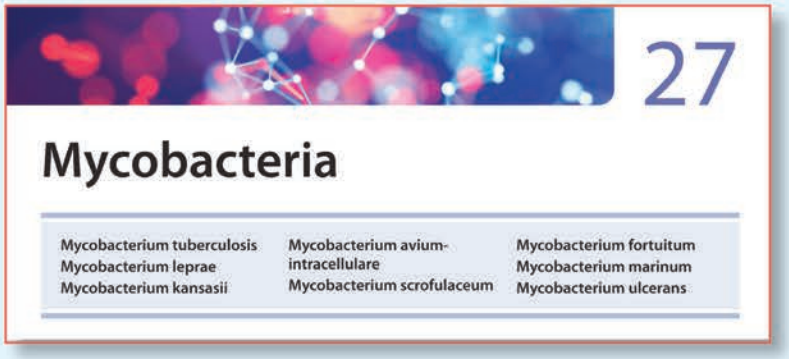
Fred Neidhardt was recruited as an author for the second edition during a sabbatical at Washington and continued through the fourth edition. Fred set the standard and style for the presentation of basic bacteriology to medical students, which continues today. A towering figure in bacterial physiology highlighted by his two-volume book on *Escherichia coli,* Fred held faculty positions at Harvard, Purdue, and Michigan, where he was Chair of Microbiology.

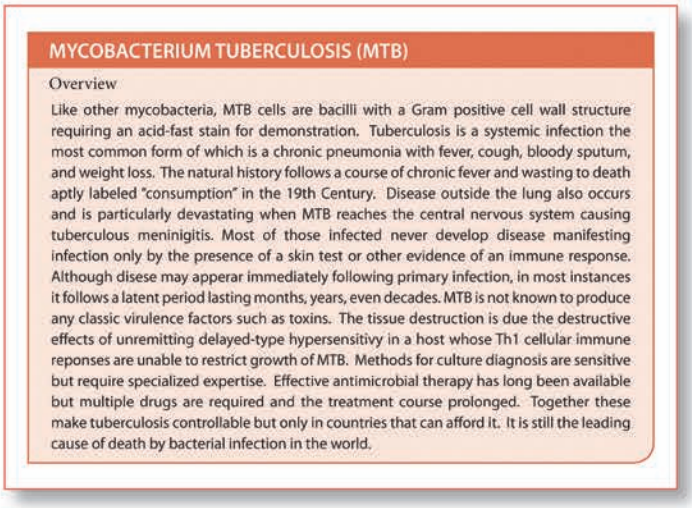
Key Features

Based on recommendations from our Student Advisory Group a number of changes in chapter presentation have been implemented in the 7th edition of *Sherris Medical Microbiology*. These changes are particularly evident in the 40 chapters which describe the microbiology, disease (epidemiology, pathogenesis, immunity) and clinical aspects (manifestations, diagnosis, treatment, prevention) of the viral, bacterial, fungal, and parasitic human pathogens. These features are designed to highlight the most important elements for both course study and preparation for USMLE examinations. Examples of each are demonstrated below.

PATHOGEN LIST

Immediately below the title the pathogens for which at least a paragraph of discussion is included in the chapter are listed.



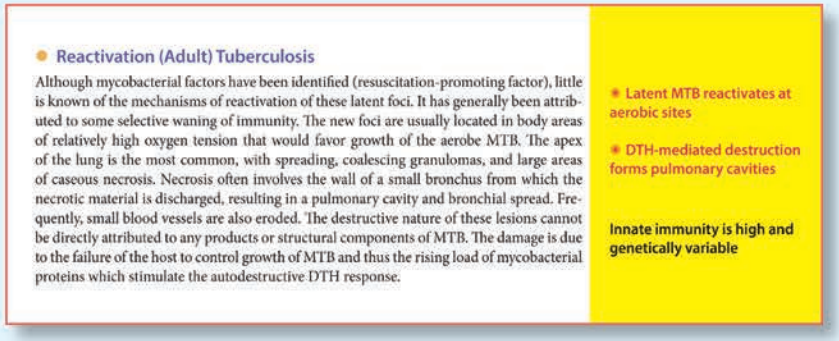


OVERVIEW

The chapter opens with a boxed narrative paragraph explaining the big picture of the organism and disease features. If the chapter contains more than one major pathogen, an OVERVIEW is given for each.

MARGINAL NOTES

Marginal notes, a feature of *Sherris Medical Microbiology* since the first edition, give a brief statement of the text material in the immediately opposite paragraph. For the 7th edition this has been enhanced by highlighting those items likely to be the subject of USMLE Step 1 questions.



Reactivation Tuberculosis

The times of life when persons infected with MTB are most likely to develop clinical disease are infancy (primary), young adult (primary or reactivation), or old age (reactivation). In Western countries, reactivation of previous quiescent lesions occurs most often after age 50.

How can it take this long for disease to develop?

and is more common in men. Reactivation is associated with a period of immunosuppression precipitated by malnutrition, alcoholism, diabetes, old age, or a dramatic change in the individual's life, such as loss of a spouse. In areas in which tuberculosis is more prevalent , reactivation is more frequently seen in young adults experiencing the immunosuppression that accompanies puberty and pregnancy. Recently, reactivation and progressive primary tuberculosis among younger adults have increased as a complication of AIDS.

DIAGNOSIS

Tuberculin Test

The tuberculin skin test (**Figure 27–6**) measures DTH to an international reference tuberculoprotein preparation called PPD. The test involves an intradermal injection that is read 48 to 72 hours later. An area of induration of 15 mm or more accompanied by erythema constitutes a positive reaction, and no induration indicates a negative reaction. A positive PPD test indicates that the individual has developed DTH through infection at some time with MTB, but carries no implication as to whether the disease is active. Persons who have been infected with another mycobacterial species or immunized with the bacillus Calmette-Guérin (BCG) vaccine may also be reactive, but the induration is usually in the 5 to 10 mm. range. Patients with severe disseminated disease, those on immunosuppressive drugs, or those with immunosuppressive diseases such as AIDS may fail to react or produce

Think ⇨ Apply 27-1. This is due to latency. The MTB have been inert but "alive". Alive all this time.

THINK → APPLY

At random points the author interrupts the text to pose a question. These are designed to challenge the student to think about what they have read earlier in the chapter and apply it to the question much as might be done during a lecture. The answer is given at the bottom of the page.

KEY CONCLUSIONS

At the end of each chapter or major section of a chapter a bulleted list of sentences giving the major conclusions the student should be able to draw from that section is displayed. This includes microbiologic, disease, and clinical features of the pathogen and is particularly intended for review during preparation for exams.

KEY CONCLUSIONS

- High lipid mycobacterial cell wall contains mycolic acids and lipoarabinomannan (LAM) which are responsible for the difficult staining property called acid-fastness.
- Infection is by inhalation of respiratory droplets coughed up by human cases.
- Primary pulmonary infection leads to systemic spread of MTB.
- MTB interferes with killing mechanisms of alveolar macrophages.
- MTB-specific macrophage activation by IFNg leads to resolution in most infected persons.
- Incomplete macrophage activation leads to progressive disease (tuberculosis).
- DTH is the sole known cause of injury.
- Entry of MTB into inactive latent state creates risk of reactivation disease in the lung or other sites (much less often) years to decades later.
- DTH response to tuberculin (PPD) indicates previous infection but not active disease.
- Definitive diagnosis is by AFB smear, culture, or NAA procedures on sputum or other tissues.
- BCG vaccine offers childhood protection but does not prevent reactivation. It also causes a DTH reponse to PPD.
- Antimicrobiol chemotherapy of tuberculosis is effective but few agents are able to penetrate the MTB cell wall. Cost and compliance limit worldwide effectiveness.
- Up to four drugs are used simultaneously to prevent expression of resistant mutants.

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Preface

With this seventh edition, *Sherris Medical Microbiology* will complete its fourth decade. We are pleased to welcome new authors, Andy Alspaugh (mycology) and Megan Reller (epidemiology) from Duke and Scott Weissman (bacteriology) from the University of Washington. Sadly, George Ray a founding author and coeditor of the last three editions is no longer with us (see Dedication). John Sherris, the founding editor, continues to act as an inspiration to all of us.

BOOK STRUCTURE

The goal of *Sherris Medical Microbiology* remains unchanged from that of the first edition (1984). This book is intended to be the primary text for students of medicine and medical science who are encountering microbiology and infectious diseases for the first time. **Part I** opens with a chapter that explains the nature of infection and the infectious agents at the level of a general reader. The following four chapters give more detail on the immunologic, diagnostic, and epidemiologic nature of infection with minimal detail about the agents themselves. **Parts II** through **V** form the core of the text with chapters on the major viral, bacterial, fungal, and parasitic diseases, and each begins with its own chapters on basic biology, pathogenesis, and antimicrobial agents.

CHAPTER STRUCTURE

In the specific organism/disease chapters, the same presentation sequence is maintained throughout the book. First, features of the **Organism** (structure, metabolism, genetics, etc.) are described; then mechanisms of the **Disease** (epidemiology, pathogenesis, immunity) the organism causes are explained; the sequence concludes with the **Clinical Aspects** (manifestations, diagnosis, treatment, prevention) of these diseases. A clinical **Case Study** followed by questions in USMLE format concludes each of these chapters. In *Sherris Medical Microbiology,* the emphasis is on the text narrative, which is designed to be read comprehensively, not as a reference work. Considerable effort has been made to supplement this text with other learning aids such as the above-mentioned cases and questions as well as tables, photographs, and illustrations.

STUDENT-DRIVEN STUDY AIDS

This edition includes a number of new study aids which are the product of a **Student Advisory** Group (see Authors page) conceived and lead by Laura Bricklin, then a second-year medical student. They include a boxed narrative **OVERVIEW** opening each disease-oriented chapter or major section, highlighted **MARGINAL NOTES** judged to be "high yield" for Step 1 preparation, and bulleted lists of **KEY CONCLUSIONS** at the end of major sections. A **THINK ➔ APPLY** feature randomly inserts thought-provoking questions into the body of the text, which are answered at the bottom of the page. These new features are explained in detail and illustrated on pages iv and v.

The back of the book includes two more review tools. **Infectious Diseases: Syndromes and Etiologies** is a set of tables that brings together the infectious agents (viruses, bacteria, fungi, parasites) discussed separately in Parts II through V as probable causes of the major infection syndromes (pneumonia, arthritis, diarrhea, etc.). It is hoped these will be of value when the student prepares for case discussion exercises or sees patients. The **100 Practice Questions** are in USMLE format and in addition to the ones at the end of earlier chapters.

For any textbook, dealing with the onslaught of new information is a major challenge. In this edition, much new material has been included, but to keep the student from being overwhelmed, older or less important information has been deleted to keep the size of this book no larger than of the sixth edition. As a rule of thumb, material on classic microbial structures, toxins, and the like in the Organism section has been trimmed unless its role is clearly explained in the Disease section. At the same time, we have tried not to eliminate detail to the point of becoming synoptic and uninteresting. Genetics is one of the greatest challenges in this regard. Without doubt this is where major progress is being made in understanding infectious diseases, but a coherent discussion may require using the names and abbreviations of genes, their products, and multiple regulators to tell a complete story. Whenever possible we have tried to tell the story without all the code language. We have also tried to fully describe the major genetic mechanisms in general chapters and then refer to them again when that mechanism is deployed by a pathogen. For example, *Neisseria gonorrhoeae* is used to explain the genetic mechanisms for antigenic variation in a general chapter on bacterial pathogenesis (Chapter 22), but how it influences its disease, gonorrhea, is taken up with its genus *Neisseria* (Chapter 30).

A saving grace is that our topic is important, dynamic, and fascinating—not just to us but to the public at large. Newspaper headlines now carry not only the new names of emerging threats like Zika virus but also the antigenic formulas of more familiar pathogens like *E coli* and influenza virus. Resistance to antimicrobial agents and the havoc created by antivaccine movements are regular topics on the evening news. I1t is not all bad news. We sense a new optimism that deeper scientific understanding of worldwide scourges like HIV/AIDS, tuberculosis, and malaria will lead to their control. We are hopeful that the basis for understanding these changes is clearly laid out in the pages of this book.

Kenneth J. Ryan
Editor

PART I
Infection

L. Barth Reller • Megan E. Reller • Kenneth J. Ryan

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1

Infection—Basic Concepts

Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever.

— Sir William Osler, 1896*

When Sir William Osler, the great physician/humanist, wrote these words, fever (infection) was indeed the scourge of the world. Tuberculosis and other forms of pulmonary infection were the leading causes of premature death among the well to do and the less fortunate. The terror was due to the fact that, although some of the causes of infection were being discovered, little could be done to prevent or alter the course of disease. In the 20th century, advances in public sanitation and the development of vaccines and antimicrobial agents changed this (**Figure 1–1**), but only for the nations that could afford these interventions. As we move through the second decade of the 21st century, the world is divided into countries in which heart attacks, cancer, and stroke have surpassed infection as causes of premature death and those in which infection is still the leader.

A new uneasiness that is part evolutionary, part discovery, and part diabolic has taken hold. Infectious agents once conquered have shown resistance to established therapy, such as multiresistant *Mycobacterium tuberculosis*, and diseases, such as acquired immunodeficiency syndrome (AIDS), have emerged. The spectrum of infection has widened, with discoveries that organisms earlier thought to be harmless can cause disease under certain circumstances. Who could have guessed that *Helicobacter pylori,* not even mentioned in the first edition of this book (1984), would be the major cause of gastric and duodenal ulcers and an officially declared carcinogen? Finally, bioterrorist forces have unearthed two previously controlled infectious diseases—anthrax and smallpox—and threatened their distribution as agents of biological warfare. For students of medicine, understanding the fundamental basis of infectious diseases has more relevance than ever.

BACKGROUND

The science of medical microbiology dates back to the pioneering studies of Pasteur and Koch, who isolated specific agents and proved that they could cause disease by introducing the experimental method. The methods they developed lead to the first golden age of microbiology (1875-1910), when many bacterial diseases and the organisms responsible for them were defined. These efforts, combined with work begun by Semmelweis and Lister, which showed how these diseases spread, led to the great advances in public health that initiated the decline in disease and death. In the first half of the 20th century, scientists studied the structure, physiology, and genetics of microbes in detail and began to answer

*Osler W. *JAMA*. 1896;26:999.

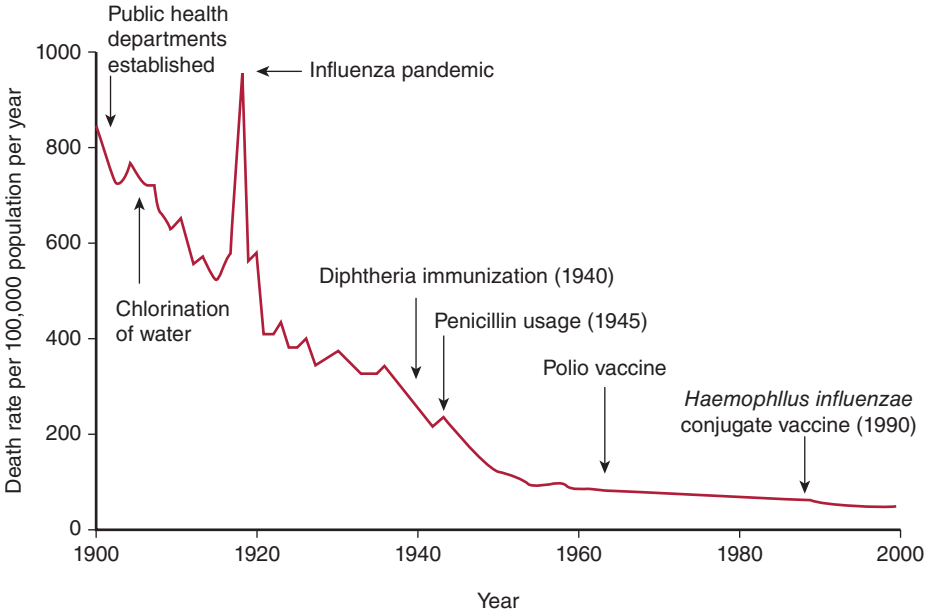

FIGURE 1–1. Death rates for infectious disease in the United States in the 20th century. Note the steady decline in death rates related to the introduction of public health, immunization, and antimicrobial interventions.

questions relating to the links between specific microbial properties and disease. By the end of the 20th century, the sciences of molecular biology, genetics, genomics, and proteomics extended these insights to the molecular level. Genetic advances have reached the point at which it is possible to know not only the genes involved but also to understand how they are regulated. The discoveries of penicillin by Fleming in 1929 and of sulfonamides by Domagk in 1935 opened the way to great developments in chemotherapy. These gradually extended from bacterial diseases to fungal, parasitic, and finally viral infections. Almost as quickly, virtually all categories of infectious agents developed resistance to all categories of antimicrobial agents to counter these chemotherapeutic agents.

INFECTIOUS AGENTS: THE MICROBIAL WORLD

Microbes are small

Microbiology is a science defined by smallness. Its creation was made possible by the invention of the microscope (Gr. *micro,* small + *skop,* to look, see), which allowed visualization of structures too small to see with the naked eye. This definition of microbiology as the study of microscopic living forms still holds if one can accept that some organisms can live only in other cells (eg, all viruses and some bacteria) and that others include macroscopic forms in their life cycle (eg, fungal molds, parasitic worms). The relative sizes of some microorganisms are shown in **Figure 1–2.**

Most play benign roles in the environment

Microorganisms are responsible for much of the breakdown and natural recycling of organic material in the environment. Some synthesize nitrogen-containing compounds that contribute to the nutrition of living things that lack this ability; others (oceanic algae) contribute to the atmosphere by producing oxygen through photosynthesis. Because microorganisms have an astounding range of metabolic and energy-yielding abilities, some can exist under conditions that are lethal to other life forms. For example, some bacteria can oxidize inorganic compounds such as sulfur and ammonium ions to generate energy. Others can survive and multiply in hot springs at temperatures higher than 75°C.

Products of microbes contribute to the atmosphere

Some microbial species have adapted to a symbiotic relationship with higher forms of life. For example, bacteria that can fix atmospheric nitrogen colonize root systems of legumes and of a few trees, such as alders, and provide the plants with their nitrogen requirements. When these plants die or are plowed under, the fertility of the soil is enhanced by nitrogenous compounds originally derived from the metabolism of the bacteria. Ruminants can use grasses as their prime source of nutrition, because the abundant flora of anaerobic bacteria in the rumen break down cellulose and other plant compounds to usable carbohydrates and amino acids and synthesize essential nutrients including some amino acids and vitamins. These few examples illustrate the protean nature of microbial life and their essential place in our ecosystem.

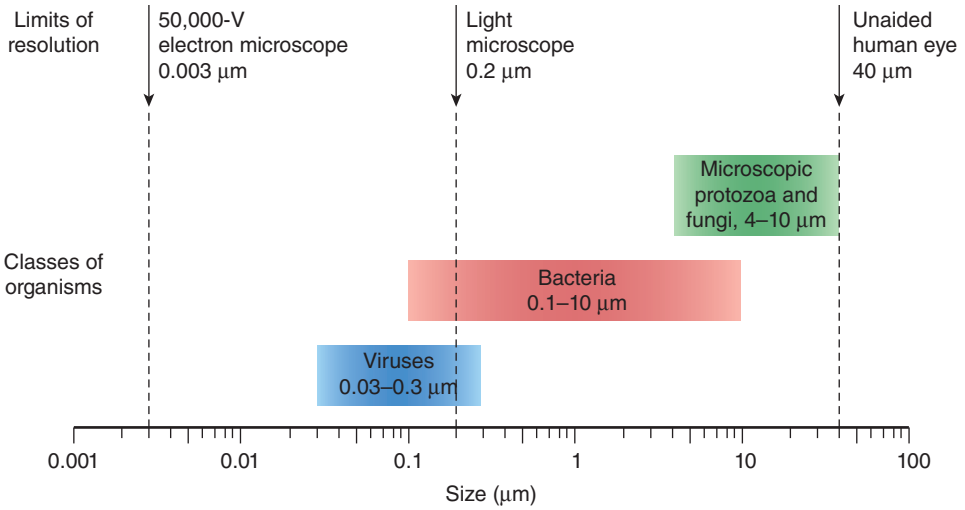

FIGURE 1–2. Relative size of microorganisms.

The major classes of microorganisms in terms of ascending size and complexity are viruses, bacteria, fungi, and parasites. Parasites exist as single or multicellular structures with the same compartmentalized eukaryotic cell plan of our own cells including a nucleus and cytoplasmic organelles like mitochondria. Fungi are also eukaryotic, but have a rigid external wall that makes them seem more like plants than animals. Bacteria also have a cell wall, but with a cell plan called "prokaryotic" that lacks the organelles of eukaryotic cells. Viruses are not cells at all. They have a genome and some structural elements, but must take over the machinery of another living cell (eukaryotic or prokaryotic) to replicate. The four classes of infectious agents are summarized in **Table 1–1,** and generic examples of each are shown in **Figure 1–3.**

Increasing complexity: viruses → bacteria → fungi → parasites

VIRUSES

Viruses are strict intracellular parasites of other living cells, not only of mammalian and plant cells, but also of simple unicellular organisms, including bacteria (the bacteriophages). Viruses are simple forms of replicating, biologically active particles that carry genetic information in either DNA or RNA molecules. Most mature viruses have a protein coat over their nucleic acid and, sometimes, a lipid surface membrane derived from the cell they infect. Because viruses lack the protein-synthesizing enzymes and structural apparatus necessary for their own replication, they bear essentially no resemblance to a true eukaryotic or prokaryotic cell.

Viruses contain little more than DNA or RNA

Viruses replicate by using their own genes to direct the metabolic activities of the cell they infect to bring about the synthesis and reassembly of their component parts. A cell infected with a single viral particle may, thus, yield thousands of viral particles, which can

TABLE 1–1 Features of Infectious Agents

	VIRUSES	BACTERIA	FUNGI	PARASITES
Size (µm)	<1	2-8	4+	2+
Cell wall	No	Yes	Yes	No/yes[a]
Cell plan	None	Prokaryotic	Eukaryotic	Eukaryotic
Free living	No	Yes[b]	Yes	Yes
Intracellular	Yes	No/yes	No	No/yes[c]

[a]Parasitic cysts have cell walls.
[b]A few bacteria grow only within cells.
[c]The life cycle of some parasites includes intracellular multiplication.

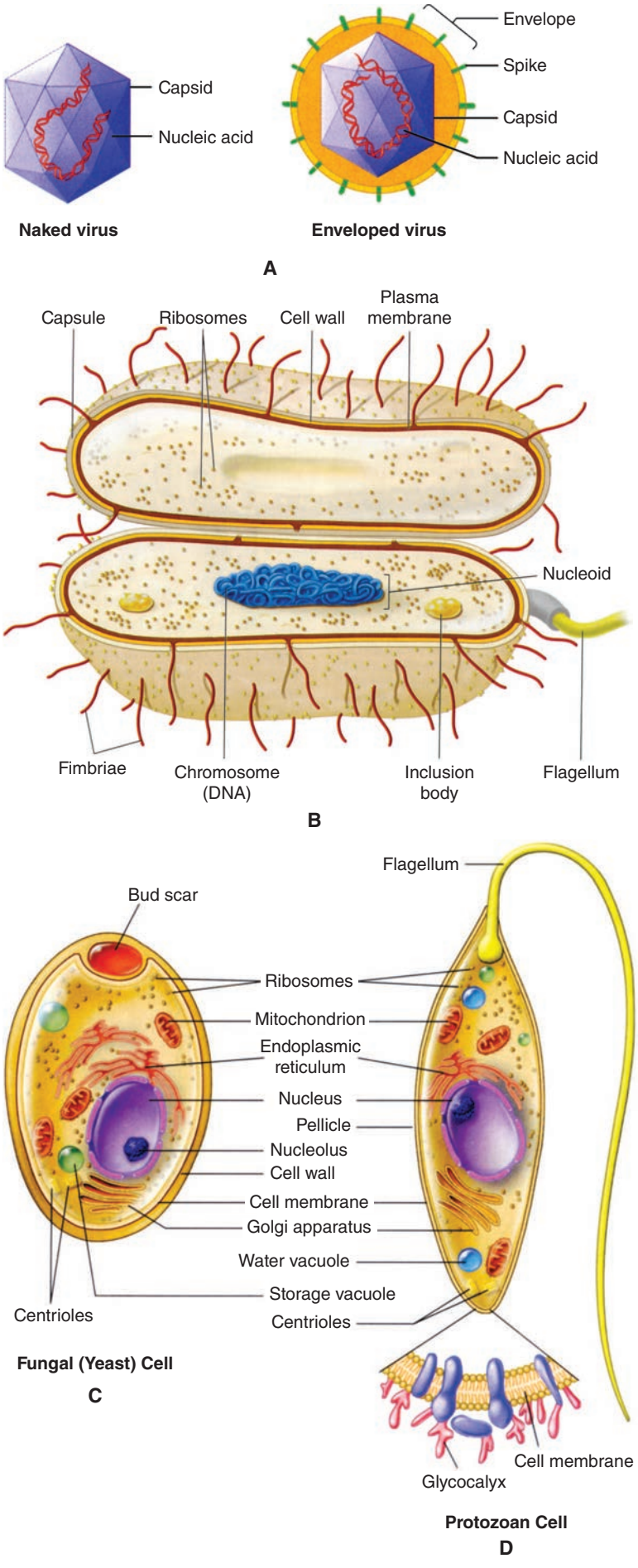

FIGURE 1–3. Infectious agents. **A.** Virus. **B.** Bacterium. **C.** Fungus. **D.** Parasite. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

be assembled almost simultaneously under the direction of the viral nucleic acid. Infection of other cells by the newly formed viruses occurs either by seeding from or lysis of the infected cells. Sometimes, viral and cell reproduction proceed simultaneously without cell death, although cell physiology may be affected. The close association of the virus with the cell sometimes results in the integration of viral nucleic acid into the functional nucleic acid of the cell, producing a latent infection that can be transmitted intact to the progeny of the cell.

Replication is by control of the host cell metabolic machinery

Some integrate into the genome

BACTERIA

Bacteria are the smallest (0.1-10 μm) independently living cells. They have a cytoplasmic membrane surrounded by a cell wall; a unique interwoven polymer called peptidoglycan makes the wall rigid. The simple prokaryotic cell plan includes no mitochondria, lysosomes, endoplasmic reticulum, or other organelles (**Table 1–2**). In fact, most bacteria are approximately the size of mitochondria. Their cytoplasm contains only ribosomes and a single, double-stranded DNA chromosome. Bacteria have no nucleus, but all the chemical elements of nucleic acid and protein synthesis are present. Although their nutritional requirements vary greatly, most bacteria are free living if given an appropriate energy source. Tiny metabolic factories, they divide by binary fission and can be grown in artificial culture, often in less than 1 day. The Archaea are similar to bacteria but evolutionarily distinct. They are prokaryotic, but differ in the chemical structure of their cell walls and other features. The Archaea (archebacteria) can live in environments humans consider hostile (eg, hot springs, high salt areas) but are not associated with disease.

Smallest living cells

Prokaryotic cell plan lacks nucleus and organelles

FUNGI

Fungi exist in either yeast or mold forms. The smallest of yeasts are similar in size to bacteria, but most are larger (2-12 μm) and multiply by budding. Molds form tubular extensions called hyphae, which, when linked together in a branched network, form the fuzzy structure seen on neglected bread slices. Fungi are eukaryotic, and both yeasts and molds have a rigid external cell wall composed of their own unique polymers, called glucan, mannan, and chitin. Their genome may exist in a diploid or haploid state and replicate by meiosis or simple mitosis. Most fungi are free living and widely distributed in nature. Generally, fungi grow more slowly than bacteria, although their growth rates sometimes overlap.

Yeasts and molds are surrounded by cell wall

TABLE 1–2 Distinctive Features of Prokaryotic and Eukaryotic Cells

CELL COMPONENT	PROKARYOTES	EUKARYOTES
Nucleus	No membrane, single circular chromosome	Membrane bounded, a number of individual chromosomes
Extrachromosomal DNA	Often present in form of plasmid(s)	In organelles
Organelles in cytoplasm	None	Mitochondria (and chloroplasts in photosynthetic organisms)
Cytoplasmic membrane	Contains enzymes of respiration; active secretion of enzymes; site of phospholipid and DNA synthesis	Semipermeable layer not possessing functions of prokaryotic membrane
Cell wall	Rigid layer of peptidoglycan (absent in Mycoplasma)	No peptidoglycan (in some cases cellulose present)
Sterols	Absent (except in Mycoplasma)	Usually present
Ribosomes	70 S in cytoplasm	80 S in cytoplasmic reticulum

PARASITES

Range from tiny amoebas to meter-long worms

Parasites are the most diverse of all microorganisms. They range from unicellular amoebas of 10 to 12 μm to multicellular tapeworms 1 m long. The individual cell plan is eukaryotic, but organisms such as worms are highly differentiated and have their own organ systems. Most worms have a microscopic egg or larval stage, and part of their life cycle may involve multiple vertebrate and invertebrate hosts. Most parasites are free living, but some depend on combinations of animal, arthropod, or crustacean hosts for their survival.

THE HUMAN MICROBIOTA

Before moving on to discuss how, when, and where the previously mentioned agents cause human disease, we should note that the presence of microbes on or in humans is not, by itself, abnormal. In fact, from shortly after birth on, it is universal; we harbor 10 times the number of microbial cells than human cells. This population formerly called the normal flora is now referred to as our **microbiota** or microbiome. These microorganisms, which are overwhelmingly bacteria, are frequently found colonizing various body sites in healthy individuals. The constituents and numbers of the microbiota vary in different areas of the body and, sometimes, at different ages and physiologic states. Their names are mostly unfamiliar because they have not (yet) been associated with disease. They comprise microorganisms whose morphologic, physiologic, and genetic properties allow them to colonize and multiply under the conditions that exist in particular sites, to coexist with other colonizing organisms, and to inhibit competing intruders. Thus, each accessible area of the body presents a particular ecologic niche, colonization of which requires a particular set of properties of the colonizing microbe.

Flora may stay for short or extended periods

If pathogens are involved, the relationship is called the carrier state

Organisms of the microbiota may have a symbiotic relationship that benefits the host or may simply live as commensals with a neutral relationship to the host. A parasitic relationship that injures the host would not be considered "normal," but, in most instances, not enough is known about the organism–host interactions to make such distinctions. Like houseguests, the members of the normal flora may stay for highly variable periods. **Residents** are strains that have an established niche at one of the many body sites, which they occupy indefinitely. **Transients** are acquired from the environment and establish themselves briefly, but they tend to be excluded by competition from residents or by the host's innate or immune defense mechanisms. The term **carrier state** is used when organisms known to be potentially pathogenic are involved, although its implication of risk is not always justified. For example, *Streptococcus pneumoniae,* a cause of pneumonia, and *Neisseria meningitidis,* a cause of meningitis, may be isolated from the throat of 5% to 40% of healthy people. Whether these bacteria represent transient flora, resident flora, or carrier state is largely semantic. The possibility that their presence could be the prelude to disease is presently impossible to determine in advance.

It is important for students of medical microbiology and infectious disease to understand the role of the microbiota because of its significance both as a defense mechanism against infection and as a source of potentially pathogenic organisms. In addition, it is important for physicians to know the typical composition of the microbiota at various sites to avoid confusion when interpreting laboratory culture results. The following excerpt indicates that the English poet W.H. Auden understood the need for balance between the microbiota and its host. He was influenced by an article in *Scientific American* about the flora of the skin.

On this day tradition allots
to taking stock of our lives,
my greetings to all of you, Yeasts,
Bacteria, Viruses,
Aerobics and Anaerobics:
A Very Happy New Year
to all for whom my ectoderm
is as Middle Earth to me.

For creatures your size I offer
a free choice of habitat,
so settle yourselves in the zone
that suits you best, in the pools

of my pores or the tropical
forests of arm-pit and crotch,
in the deserts of my fore-arms,
or the cool woods of my scalp.

Build colonies: I will supply
adequate warmth and moisture,
the sebum and lipids you need,
on condition you never
do me annoy with your presence,
but behave as good guests should,
not rioting into acne
or athlete's-foot or a boil.

—W.H. Auden, "A New Year Greeting"

ORIGIN AND NATURE

The healthy fetus is sterile until the birth membranes rupture. During and after birth, the infant is exposed to the flora of the mother's vagina and to other organisms in the environment. During the infant's first few days of life, the microbiota reflects chance exposure to organisms that can colonize particular sites in the absence of competitors. Subsequently, as the infant is exposed to a broader range of organisms, those best adapted to colonize particular sites become predominant. Thereafter, the flora generally resembles that of other individuals in the same age group and cultural milieu.

Initial flora is acquired during and immediately after birth

Local physiologic and ecologic conditions determine the microbial makeup of the flora. These conditions are sometimes highly complex, differing from site to site, and sometimes with age. Conditions include the amounts and types of nutrients available, pH, oxidation–reduction potentials, and resistance to local antibacterial substances such as bile and lysozyme. Many bacteria have adhesin-mediated affinity for receptors on specific types of epithelial cells; this facilitates colonization and multiplication and prevents removal by the flushing effects of surface fluids and peristalsis. Various microbial interactions also determine their relative prevalence in the flora. These interactions include competition for nutrients and inhibition by the metabolic products of other organisms.

Physiologic conditions such as local pH influence colonization

Adherence factors counteract mechanical flushing

Ability to compete for nutrients is an advantage

MICROBIOTA AT DIFFERENT SITES

At any one time, the microbiota of a single person contains hundreds if not thousands of species of microorganisms, mostly bacteria. The major members known to be important in preventing or causing disease, as well as those that may be confused with etiologic agents of local infections, are summarized in **Table 1–3** and are described in greater detail in subsequent chapters. The **Human Microbiome Project** is an ongoing effort to bring this information together.

Blood, Body Fluids, and Tissues

In health, the blood, body fluids, and tissues are sterile. Occasional organisms may be displaced across epithelial barriers as a result of trauma or during childbirth; they may be briefly recoverable from the bloodstream before they are filtered out in the pulmonary capillaries or removed by cells of the reticuloendothelial system. Such transient bacteremia may be the source of infection when structures such as damaged heart valves and foreign bodies (prostheses) are in the bloodstream.

Tissues and body fluids such as blood are sterile in health

Transient bacteremia can result from trauma

Skin

The skin surface provides a dry, slightly acidic, aerobic environment. It plays host to an abundant flora that varies according to the presence of its appendages (hair, nails) and the activity of sebaceous and sweat glands. The flora is more abundant on moist skin areas (axillae, perineum, and between toes). Staphylococci and members of the *Propionibacterium* genus occur all over the skin, and facultative diphtheroids (corynebacteria) are found in moist areas. Propionibacteria are slim, anaerobic, or microaerophilic gram-positive rods that grow in subsurface sebum and break down skin lipids to fatty acids. Thus, they are most numerous in the ducts of hair follicles and of the sebaceous glands that drain into them. Even with antiseptic scrubbing, it is difficult to eliminate bacteria from skin sites, particularly those bearing pilosebaceous units. Organisms of the skin flora are resistant to

Propionibacteria and staphylococci are dominant bacteria

Skin flora is not easily removed

Conjunctiva resembles skin

TABLE 1–3 Predominant and Potentially Pathogenic Microbiota of Various Body Sites

BODY SITE	POTENTIAL PATHOGENS (CARRIER)	LOW VIRULENCE (RESIDENT)
Blood	None	None[a]
Tissues	None	None
Skin	*Staphylococcus aureus*	*Propionibacterium, Corynebacterium* (diphtheroids), coagulase-negative staphylococci
Mouth	*Candida albicans*	*Neisseria* spp., viridans streptococci, *Moraxella, Peptostreptococcus*
Nasopharynx	*Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae,* group A streptococci, *Staphylococcus aureus* (anterior nares)	*Neisseria* spp., viridans streptococci, *Moraxella, Peptostreptococcus*
Stomach	None	Streptococci, *Peptostreptococcus,* others from mouth
Small intestine	None	Scanty, variable
Colon	*Bacteroides fragilis, E coli, Pseudomonas, Candida, Clostridium (C perfringens, C difficile)*	*Eubacterium, Lactobacillus, Bacteroides, Fusobacterium,* Enterobacteriaceae, *Enterococcus, Clostridium*
Vagina		
Prepubertal and postmenopausal	*Candida albicans*	Diphtheroids, staphylococci, Enterobacteriaceae
Childbearing	Group B streptococci, *C albicans*	*Lactobacillus,* streptococci

[a]Organisms such as viridans streptococci may be transiently present after disruption of a mucosal site.

the bactericidal effects of skin lipids and fatty acids, which inhibit or kill many extraneous bacteria. The conjunctivae have a very scanty flora derived from the skin flora. The low bacterial count is maintained by the high lysozyme content of lachrymal secretions and by the flushing effect of tears.

Intestinal Tract

***Oropharynx has streptococci* and Neisseria**

The **mouth** and **pharynx** contain large numbers of facultative and anaerobic bacteria. Different species of streptococci predominate on the buccal and tongue mucosa because of different specific adherence characteristics. Gram-negative diplococci of the genus *Neisseria* and coccobacillary *Moraxella* make up the balance of the most commonly isolated organisms. Strict anaerobes and microaerophilic organisms of the oral cavity have their niches in the depths of the gingival crevices surrounding the teeth and in sites such as tonsillar crypts, where anaerobic conditions can develop readily.

***H pylori* turned out to be a stomach pathogen**

The total number of organisms in the oral cavity is very high, and it varies from site to site. Saliva usually contains a mixed flora of about 10^8 organisms per milliliter, derived mostly from the various epithelial colonization sites. The genera include *Actinomyces, Bacteroides, Prevotella, Streptococcus*, and others. The stomach contains few, if any, resident organisms in health because of the lethal action of gastric hydrochloric acid and peptic enzymes on bacteria. One species, *H pylori*, long thought to be a common resident is now known to be the primary cause of ulcers. The small intestine has a scanty resident flora, except in the lower ileum, where it begins to resemble that of the colon.

Small intestinal flora is scanty but increases toward lower ileum

Adult colonic flora is abundant and predominantly anaerobic

The colon carries the most abundant and diverse microbiota in the body. In the adult, feces are 25% or more bacteria by weight (about 10^{10} organisms per gram). More than 90% are anaerobes, predominantly members of the genera *Bacteroides, Fusobacterium, Eubacterium,* and *Clostridium*. The remainder of the flora is composed of facultative organisms such as *Escherichia coli,* enterococci, yeasts, and numerous other species. There are considerable

Diet affects species composition

differences in adult flora depending on the diet of the host. Those whose diets include substantial amounts of meat have more *Bacteroides* and other anaerobic gram-negative rods in their stools than those on a predominantly vegetable or fish diet. Recent studies have suggested the composition of the colonic microbiota could play a role in obesity.

Respiratory Tract

S aureus is carried in anterior nares

The external 1 cm of the anterior nares has a flora similar to that of the skin. This is the primary site of carriage of a major pathogen, *Staphylococcus aureus*. Approximately 25% to 30% of healthy people carry this organism as either resident or transient flora at any given time. The nasopharynx has a flora similar to that of the mouth; however, it is often the site of carriage of potentially pathogenic organisms such as pneumococci, meningococci, and *Haemophilus* species.

Lower tract is protected by mucociliary action

The respiratory tract below the level of the larynx is protected in health by the action of the epithelial cilia and by the movement of the mucociliary blanket; thus, only transient inhaled organisms are encountered in the trachea and larger bronchi. The accessory sinuses are normally sterile and are protected in a similar fashion, as is the middle ear by the epithelium of the eustachian tubes.

Genitourinary Tract

Bladder and upper urinary tract are sterile

The urinary tract is sterile in health above the distal 1 cm of the urethra, which has a scanty flora derived from the perineum. Thus, in health, the urine in the bladder, ureters, and renal pelvis is sterile.

Hormonal changes affect the vaginal flora

The vagina has a flora that varies according to hormonal influences at different ages. Before puberty and after menopause, it is mixed, nonspecific, and relatively scanty, and it contains organisms derived from the flora of the skin and colon. During the childbearing years, it is composed predominantly of anaerobic and microaerophilic members of the genus *Lactobacillus,* with smaller numbers of anaerobic gram-negative rods, gram-positive cocci, and yeasts (**Figure 1–4**) that can survive under the acidic conditions produced by the lactobacilli. These conditions develop because glycogen is deposited in vaginal epithelial cells under the influence of estrogenic hormones and metabolized to lactic acid by lactobacilli. This process results in a vaginal pH of 4 to 5, which is optimal for growth and survival of the lactobacilli, but inhibits many other organisms.

Use of epithelial glycogen by lactobacilli produces low pH

Bacterial Vaginosis

BV is associated with a shift in vaginal microbiota

Bacterial vaginosis (BV) is a long known and unfortunately common syndrome which is still poorly understood. Its dominant feature is an uncomfortable vaginal discharge with a "fishy" odor which contains epithelial cells coated with bacteria (clue cells). This change is associated with a shift in the vaginal microbiota away from the acidic *Lactobacillus* flora to one with a higher pH and a greater mixture of species including more anaerobes. Over the years several of these newcomers have been tagged as the cause of BV, particularly

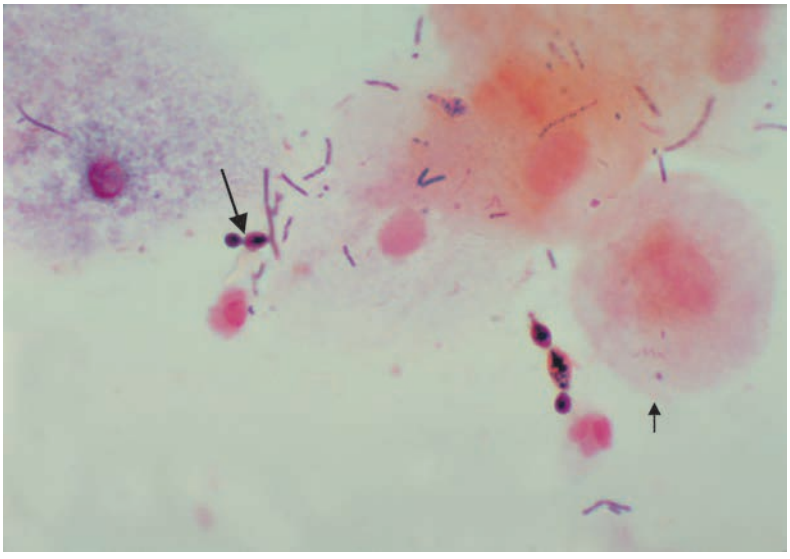

FIGURE 1–4. Vaginal flora. Vaginal Gram smear showing budding yeast (long arrow), epithelial cells (short arrow) and a mixture of other bacterial morphologies. The long gram-positive rods are most likely lactobacilli. [Redrawn from Centers for Disease Control and Prevention (CDC).]

Gardnerella vaginalis and *Mobiluncus*. The BV situation appears to be more complex than this, involving complex interactions of the vaginal microbiota.

ROLES IN HEALTH AND DISEASE

Opportunistic Infection

Flora that reach sterile sites may cause disease

Virulence factors increase the opportunity for invasion

Mouth flora plays a major role in dental caries

Many species among the microbiota are opportunists in that they can cause infection when they reach protected areas of the body in sufficient numbers. For example, certain strains of *E coli* can reach the urinary bladder by ascending the urethra and cause acute urinary tract infection. Perforation of the colon from a ruptured diverticulum or a penetrating abdominal wound releases feces into the peritoneal cavity; this contamination may be followed by peritonitis or intraabdominal abscesses caused by members of the flora which have virulence factors allowing them to exploit this situation. There are now examples of the microbiota supplying a step in the pathogenesis of a classic pathogen. Attachment of *Neisseria gonorrhoeae* to the cervix has been shown to be enhanced when an enzyme produced by the cervicovaginal microbiota unmasks a crucial receptor (see Chapter 30). Caries and periodontal disease are caused by organisms that are members of the oral microbiota (see Chapter 41).

Exclusionary Effect

Competing with pathogens has a protective effect

Antibiotic therapy may provide a competitive advantage for pathogens

Balancing the prospect of opportunistic infection is the tendency of the resident microbiota to produce conditions that compete with extraneous newcomers who happen to be pathogens and thus reduce their ability to establish a niche in the host. The microbiota in the colon of the breastfed infant produces an environment inimical to colonization by enteric pathogens, as does a vaginal flora dominated by lactobacilli. The benefit of this exclusionary effect has been demonstrated by what happens when it is removed. Antibiotic therapy, particularly with broad-spectrum agents, may so alter the microbiota of the gastrointestinal tract that antibiotic-resistant organisms multiply in the ecologic vacuum. Under these conditions, the spore-forming *Clostridium difficile* has a selective advantage that allows it to survive, proliferate, and produce a toxic colitis.

Priming of Immune System

Sterile animals have little immunity to microbial infection

Low exposure correlates with asthma risk

Organisms of the microbiota play an important role in the development of immunologic competence. Animals delivered and raised under completely aseptic conditions ("sterile" or gnotobiotic animals) have a poorly developed reticuloendothelial system, low serum levels of immunoglobulins, and lack antibodies to antigens that often confer a degree of protection against pathogens. There is evidence of immunologic differences between children who are raised under usual conditions and those whose exposure to diverse flora is minimized. Some studies have found a higher incidence of immunopathologic states, such as asthma in the more isolated children.

PROMOTING A GOOD MICROBIOTA

Intestinal lactobacilli may protect against diarrheal agents

The field of probiotics is based on the notion that we can manipulate the microbiota by promoting colonization with "good" bacteria. Elie Metchnikoff originally suggested this in his observation that the longevity of Bulgarian peasants was attributable to their consumption of large amounts of yogurt; the live lactobacilli in the yogurt presumably replaced the colonic flora to the general benefit of their health. This notion persists today in capsules containing freeze-dried lactobacilli sold by the sizable probiotics industry and by promotion of the health benefit of natural (unpasteurized) yogurt, which contains live lactobacilli. Because these lactobacilli are adapted to food and not the intestine, they are unlikely to persist, much less replace, the typical microbiota of the adult colon. In some clinical studies, administration of preparations containing a particular strain of *Lactobacillus* (*Lactobacillus rhamnosus* strain GG, LGG) has been shown to reduce the duration of rotavirus diarrhea in children. The use of similar preparations to prevent relapses of antibiotic-associated diarrhea caused by *C difficile* has shown little success but fecal transplant (a whole new microbiota) has blocked recurrences of pseudomembranous colitis, the most serious form of this disease.

Research into the role of the microbiota in health and disease is one of the most exciting topics in science. This is by no means limited to topics related to infectious disease. Currently the most active areas involve mechanisms of obesity, autoimmune disorders (arthritis, asthma) and more subjective subjects like human cravings. Much of the work involves the interactions between multiple species many of which can only be detected by genomic methods. Obviously, it is going to take considerable time to sort these relationships out.

INFECTIOUS DISEASE

Of the thousands of species of viruses, bacteria, fungi, and parasites, only a tiny portion is involved in disease of any kind. These are called **pathogens.** There are plant pathogens, animal pathogens, and fish pathogens, as well as the subject of this book, human pathogens. Among pathogens, there are degrees of potency called **virulence,** which sometimes makes drawing the dividing line between benign and virulent microorganisms difficult. Pathogens are associated with disease with varying frequency and severity. *Yersinia pestis,* the cause of plague, causes fulminant disease and death in 50% to 75% of persons who come in contact with it. Therefore, it is highly virulent. Understanding the basis of these differences in virulence is a fundamental goal of this book. The better students of medicine understand how a pathogen causes disease, the better they will be prepared to intervene and help their patients.

Pathogens are rare

Virulence varies greatly

For any pathogen, the basic aspects of how it interacts with the host to produce disease can be expressed in terms of its epidemiology, pathogenesis, and immunity. Usually, our knowledge of one or more of these topics is incomplete. It is the task of the physician to relate these topics to the clinical aspects of disease and be prepared for new developments which clarify, or in some cases, alter them. We do not know everything, and not all of what we believe we know is correct.

EPIDEMIOLOGY

Epidemiology is the "who, what, when, and where" of infectious diseases. The power of the science of epidemiology was first demonstrated by Semmelweis, who by careful analysis of statistical data alone determined how streptococcal puerperal fever is transmitted. He even devised a means to prevent transmission (handwashing) decades before the organism itself (*Streptococcus pyogenes*) was discovered. Since then, each organism has built its own profile of vital statistics. Some agents are transmitted by air, some by food, and others by insects; many spread by the person-to-person route. **Figure 1–5** presents some of the variables in this regard. Some agents occur worldwide, and others only in certain geographic locations or ecologic circumstances. Knowing how an organism gains access to its victim and spreads is crucial to understanding the disease. It is also essential in discovering the emergence of "new" diseases, whether they are truly new (HIV/AIDS) or just recently discovered (Legionnaires disease). Solving mysterious outbreaks or recognizing new epidemiologic patterns have often pointed the way to the isolation of new agents.

Each agent has its own mode of spread

Epidemic spread and disease are facilitated by malnutrition, poor socioeconomic conditions, natural disasters, and hygienic inadequacy. Epidemics, caused by the introduction of new organisms of unusual virulence, often result in high morbidity and mortality rates. We are currently witnessing a new and extended Zika virus pandemic, but the prospect of recurrence of old pandemic infections (influenza, cholera) remains. Modern times and technology have introduced new wrinkles to epidemiologic spread. Air travel has allowed diseases to leap continents even when they have very short incubation periods. The efficiency of the food industry has sometimes backfired when the distributed products are contaminated with infectious agents. The outbreaks of hamburger-associated *E coli* O157:H7 bloody diarrhea and hemolytic uremic syndrome are an example. The nature of massive meat-packing facilities allowed organisms from infected cattle on isolated farms to be mixed with other meat and distributed rapidly and widely. By the time outbreaks were recognized, cases of disease were widespread, and tons of meat had to be recalled. In simpler times, local outbreaks from the same source might have been detected and contained more quickly.

Poor socioeconomic conditions foster infection

Modern society may facilitate spread

Of course, the most ominous and uncertain epidemiologic threat of these times is not amplification of natural transmission but the specter of unnatural, deliberate spread. Anthrax is a disease uncommonly transmitted by direct contact with animals or animal

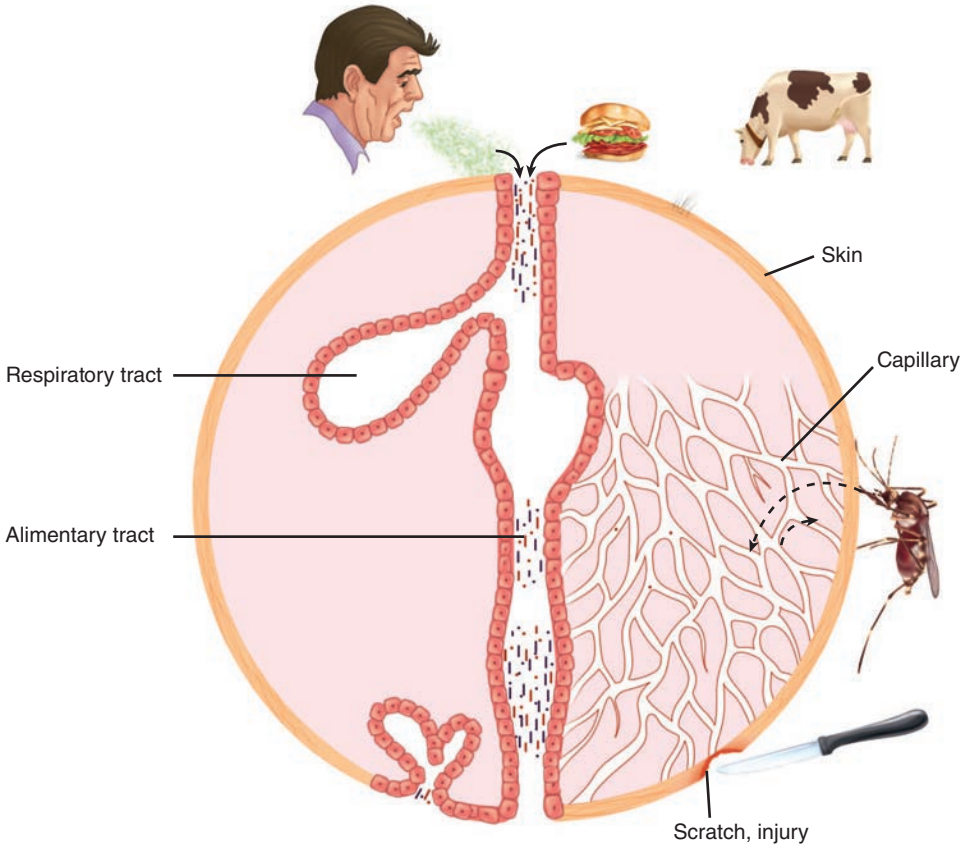

FIGURE 1–5. Infection overview. The sources and potential sites of infection are shown. Infection may be endogenous from the internal flora or exogenous from the sources shown around the outside.

products. Under natural conditions, it produces a nasty, but not usually life-threatening, ulcer. The inhalation of human-produced aerosols of anthrax spores could produce a lethal pneumonia on a massive scale. Smallpox is the only disease officially eradicated from the world. It took place sufficiently long ago that most of the population has never been exposed or immunized and is, thus, vulnerable to its reintroduction. We do not know whether infectious bioterrorism will work on the scale contemplated by its perpetrators; however, in the case of anthrax, we do know that sophisticated systems have been designed to attempt it. We hope never to learn whether bioterrorism will work on a large scale.

Anthrax and smallpox are new bioterrorism threats

PATHOGENESIS

When a potential pathogen reaches its host, features of the organism determine whether or not disease ensues. The primary reason pathogens are so few in relation to the microbial world is that being successful at producing disease is a very complicated process. Multiple features, called virulence factors, are required to persist, cause disease, and escape to repeat the cycle. The variations are many, but the mechanisms used by many pathogens have now been dissected at the molecular level.

Pathogenicity is multifactorial

The first step for any pathogen is to attach and persist at whatever site it gains access. This usually involves specialized surface molecules or structures that correspond to receptors on human cells. Because human cells were not designed to receive the microorganisms, the pathogens are often exploiting some molecule important for some other essential function of the cell. For some toxin-producing pathogens, this attachment alone may be enough to produce disease. For most pathogens, it just allows them to persist long enough to proceed to the next stage—invasion into or beyond the surface mucosal cells. For viruses, invasion of cells is essential, because they cannot replicate on their own. Invading pathogens must also be able to adapt to a new milieu. For example, the nutrients and ionic environment of the cell surface differs from that inside the cell or in the submucosa. Some of the steps in pathogenesis at the cellular level are illustrated in **Figure 1–6.**

Pathogens have molecules that bind to host cells

Invasion requires adaptation to new environments

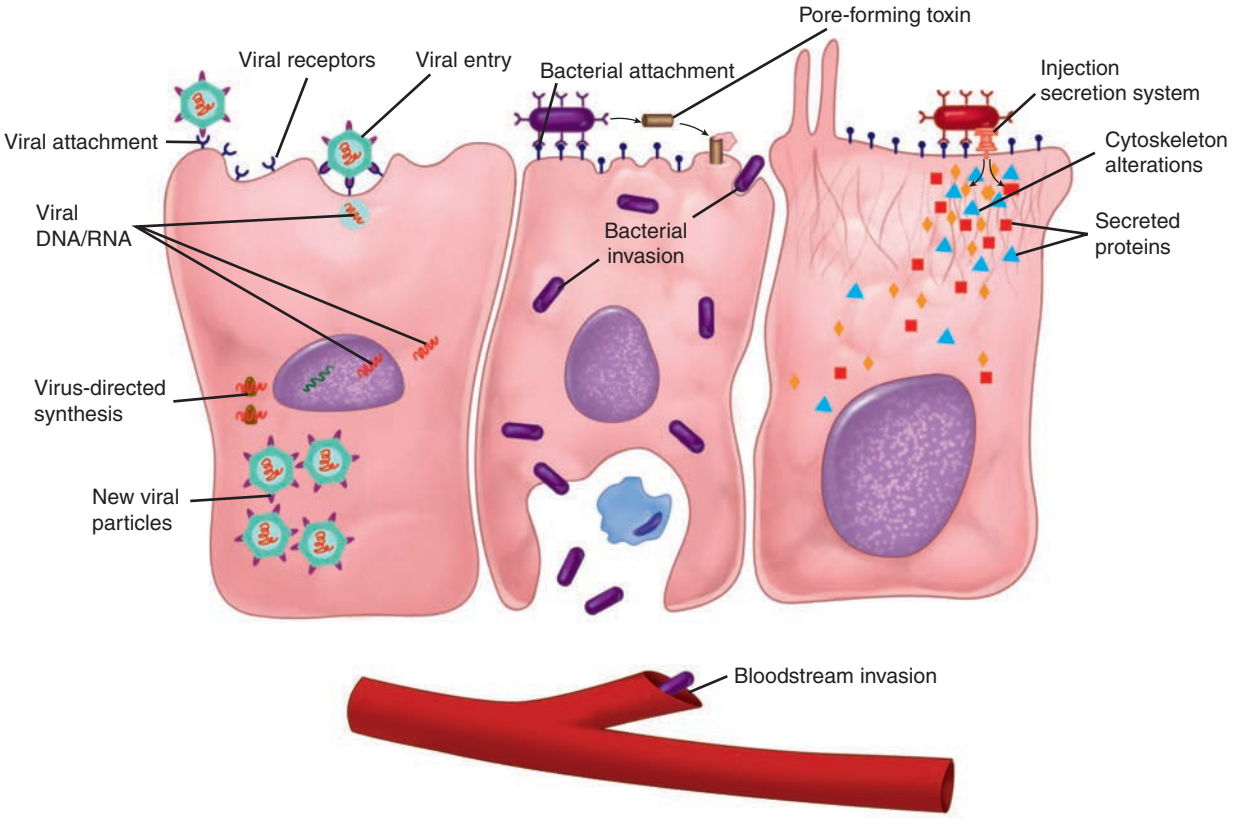

FIGURE 1–6. Infection cellular view. *Left.* A virus is attaching to the cell surface but can replicate only within the cell. *Middle.* A bacterial cell attaches to the surface, invades, and spreads through the cell to the bloodstream. *Right.* A bacterial cell attaches and injects proteins into the cell. The cell is disrupted while the organism remains on the surface.

Inflammation alone can result in injury

Persistence and even invasion do not necessarily translate immediately to disease. The invading organisms must disrupt function in some way. For some, the inflammatory response they stimulate is enough. For example, a lung alveolus filled with neutrophils responding to the presence of *S pneumoniae* loses its ability to exchange oxygen. The longer a pathogen can survive in the face of the host response, the greater the compromise in host function. Most pathogens do more than this. Destruction of host cells through the production of digestive enzymes, toxins, or intracellular multiplication is among the more common mechanisms. Other pathogens operate by altering the function of a cell without injury. Diphtheria is caused by a bacterial toxin that blocks protein synthesis inside the host cell. Details of the molecular mechanism for this action are illustrated in **Figure 1–7.** Some viruses cause the insertion of molecules in the host cell membrane, which cause other host cells to attack it. The variations are diverse and fascinating.

Cells may be destroyed or their function altered

IMMUNITY

Although the science of immunology is beyond the scope of this book, understanding the immune response to infection (see Chapter 2) is an important part of appreciating pathogenic mechanisms. In fact, one of the most important virulence attributes any pathogen can have is an ability to neutralize the immune response to it in some way. Some pathogens attack the immune effector cells, and others undergo changes that evade the immune response. The old observation that there seems to be no immunity to gonorrhea turns out to be an example of the latter mechanism. *Neisseria gonorrhoeae,* the causative agent of gonorrhea, undergoes antigenic variation of important surface structures so rapidly that antibodies directed against the bacteria become irrelevant.

Evading the immune response is a major feature of virulence

For each pathogen, the primary interest is whether there is natural immunity and, if so, whether it is based on cell-mediated (T_H1, CMI) or humoral (T_H2, antibody) mechanisms.

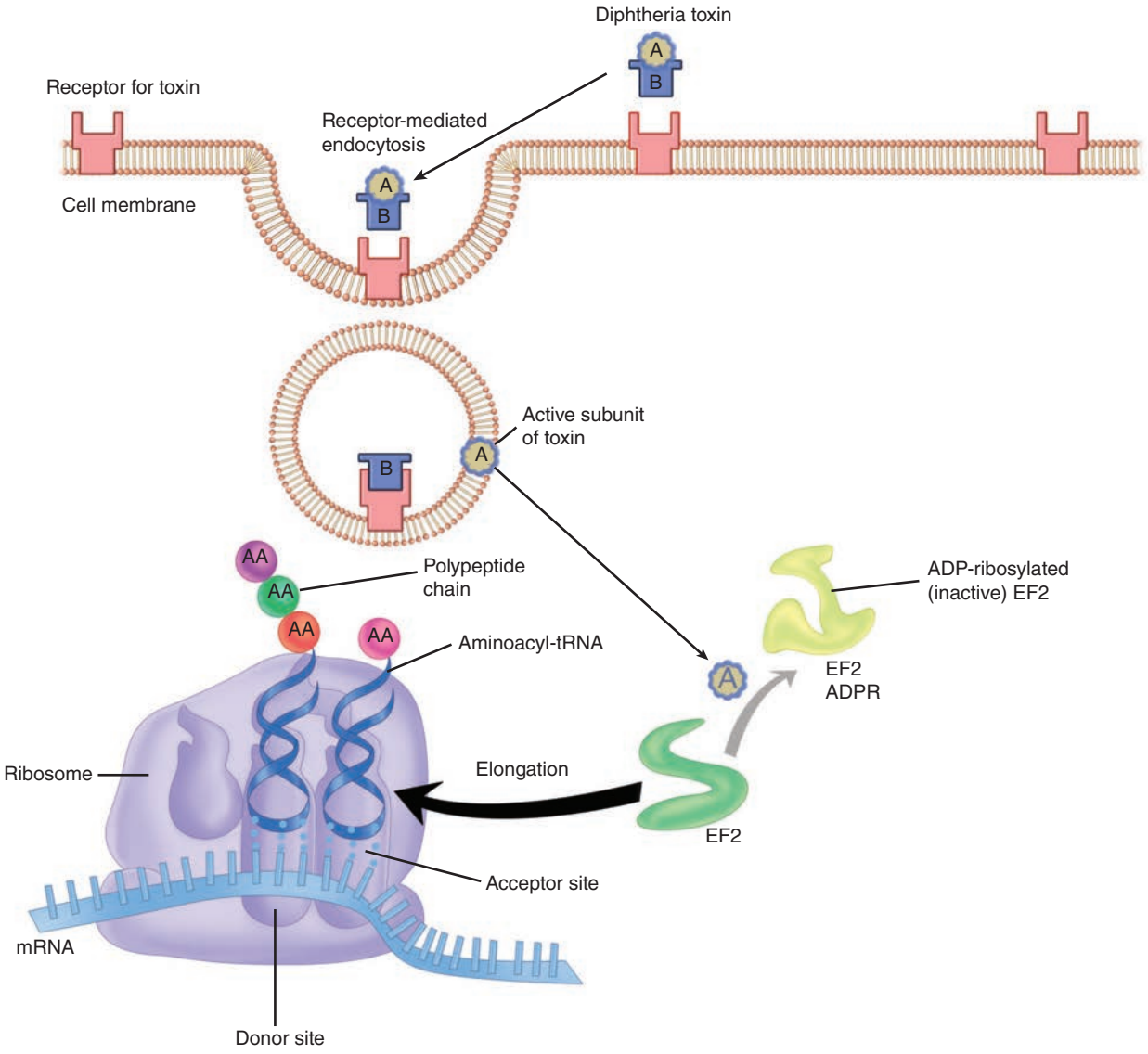

FIGURE 1–7. Action of diphtheria toxin, molecular view. The toxin-binding (B) portion attaches to the cell membrane, and the complete molecule enters the cell. In the cell, the A subunit dissociates and catalyzes a reaction that ADP-ribosylates (ADPR) and, thus, inactivates elongation factor 2 (EF-2). This factor is essential for ribosomal reactions at the acceptor and donor sites, which transfer triplet code from messenger RNA (mRNA) to amino acid sequences via transfer RNA (tRNA). Inactivation of EF-2 stops building of the polypeptide chain.

Antibody or cell-mediated mechanisms may be protective

Humoral and CMI responses are broadly stimulated with most infections, but the specific response to a particular molecular structure is usually dominant in mediating immunity to reinfection. For example, the repeated nature of strep throat (group A *streptococcus*) in childhood is not due to antigenic variation as described for gonorrhea. The antigen against which protective antibodies are directed (M protein) is stable, but naturally exists in more than 80 types. Each type requires its own specific antibody. Knowing the molecule against which the protective immune response is directed is particularly important for devising preventive vaccines.

CLINICAL ASPECTS OF INFECTIOUS DISEASE

Manifestations

Fever, pain, and swelling are the universal signs of infection. Beyond this, the particular organs involved and the speed of the process dominate the signs and symptoms of disease.

Cough, diarrhea, and mental confusion represent disruption of three different body systems. On the basis of clinical experience, physicians have become familiar with the range of behavior of the major pathogens. However, signs and symptoms overlap considerably. Skilled physicians use this knowledge to begin a deductive process leading to a list of suspected pathogens and a strategy to make a specific diagnosis and provide patient care. Through the probability assessment, an understanding of how the diseases work is a distinct advantage in making the correct decisions.

Body system(s) involved dictate clinical findings

Diagnosis

A major difference between infectious and other diseases is that the probabilities just described can be specifically resolved, often overnight. Most microorganisms can be isolated from the patient, grown in artificial culture, and identified. Others can be seen microscopically or detected by measuring the specific immune response to the pathogen. Preferred modalities for diagnosis of each agent have been developed and are available in clinic, hospital, and public health laboratories all over the world. Empiric diagnosis made on the basis of clinical findings can be confirmed and the treatment plan modified accordingly. New methods which detect molecular or genomic markers of the agent are now realizing their potential for rapid, specific diagnosis.

Disease-causing microbes can be grown and identified

Treatment

Over the past 80 years, therapeutic tools of remarkable potency and specificity have become available for the treatment of bacterial infections. These include all the antibiotics and an array of synthetic chemicals that kill or inhibit the infecting organism, but have minimal or acceptable toxicity for the host. Antibacterial agents exploit the structural and metabolic differences between microbial and human eukaryotic cells to provide the selectivity necessary for good antimicrobial therapy. Penicillin, for example, interferes with the synthesis of the bacterial cell wall, a structure that has no analog in human cells. There are fewer antifungal and antiprotozoal agents because the eukaryotic cells of the host and those of the parasite have metabolic and structural similarities. Nevertheless, hosts and parasites do have some significant differences, and effective therapeutic agents have been discovered or developed to exploit them.

Antibiotics are directed at structures of bacteria not present in host

Specific therapeutic attack on viral disease has posed more complex problems, because of the intimate involvement of viral replication with the metabolic and replicative activities of the cell. However, recent advances in molecular virology have identified specific viral targets that can be attacked. Scientists have developed successful antiviral agents, including those that interfere with the liberation of viral nucleic acid from its protective protein coat or with the processes of viral nucleic acid synthesis and replication. The successful development of new agents for human immunodeficiency virus has involved targeting enzymes coded by the virus genome.

Antivirals target unique virus-coded enzymes

The success of the "antibiotic era" has been clouded by the development of resistance by the organisms. The mechanisms involved are varied but, most often, involve a mutational alteration in the enzyme, ribosome site, or other target against which the antimicrobial is directed. In some instances, organisms acquire new enzymes or block entry of the antimicrobial to the cell. Many bacteria produce enzymes that directly inactivate antibiotics. To make the situation worse, the genes involved are readily spread by promiscuous genetic mechanisms. New agents that are initially effective against resistant strains have been developed, but resistance by new mechanisms usually follows. The battle is by no means lost, but has become a never-ending policing action.

Resistance complicates therapy

Mechanisms include mutation and inactivation

Prevention

The goal of the scientific study of any disease is its prevention. In the case of infectious diseases, this has involved public health measures and immunization. The public health measures depend on knowledge of transmission mechanisms and on interfering with them. Water disinfection, food preparation, insect control, handwashing, and a myriad of other measures prevent humans from coming in contact with infections agents. Immunization relies on knowledge of immune mechanisms and designing vaccines that stimulate protective immunity.

Public health and immunization are primary preventive measures

Attenuated strains stimulate immunity

Live vaccines rarely cause disease

Immunization follows two major strategies—live vaccines and inactivated vaccines. The former uses live organisms that have been modified (attenuated) so they do not produce disease, but still stimulate a protective immune response. Such vaccines have been effective, but carry the risk that the vaccine strain itself may cause disease. This event has been observed with the live oral polio vaccine. Although this rarely occurs, it has caused a shift back to the original Salk inactivated vaccine. This issue has reemerged with a debate over strategies for the use of smallpox immunization to protect against bioterrorism. This vaccine uses vaccinia virus, a cousin of smallpox, and its potential to produce disease on its own has been recognized since its original use by Jenner in 1798. Serious disease would be expected primarily in immunocompromised individuals (eg, from cancer chemotherapy or AIDS), who represent a significantly larger part of the population than when smallpox immunization was stopped in the 1970s. Could immunization cause more disease than it prevents? Despite the claims of those who oppose the use of all vaccines as "unnatural" the risk/benefit ratio of all currently licensed vaccines is greatly on the positive side.

Purified components are safe vaccines

The safest immunization strategy is the use of organisms that have been killed or, better yet, killed and purified to contain only the immunizing component. This approach requires much better knowledge of pathogenesis and immune mechanisms. Vaccines for meningitis use the polysaccharide capsule of the bacterium, and vaccines for diphtheria and tetanus use only a formalin-inactivated protein toxin. Pertussis (whooping cough) immunization has undergone a transition in this regard. The original killed whole-cell vaccine was effective, but caused a significant incidence of side effects. A purified vaccine containing pertussis toxin and a few surface components has reduced side effects, but its efficacy compared with the previous vaccine is now in question.

Vaccines can be genetically engineered

The newest approaches for vaccines require neither live organisms nor killed, purified ones. As the entire genomes of more and more pathogens are being reported, an entirely genetic strategy is emerging. Armed with knowledge of molecular pathogenesis and immunity and the tools of genomics and proteomics, scientists can now synthesize an immunogenic protein without ever growing the organism itself. Such an idea would have astonished even the great microbiologists of the last two centuries.

SUMMARY

Infectious diseases remain as important and fascinating as ever. Where else do we find the emergence of new diseases, together with improved understanding of the old ones? At a time when the revolution in molecular biology and genetics has brought us to the threshold of new and novel means of infection control, the perpetrators of bioterrorism threaten us with diseases we have already conquered. Meeting this challenge requires a secure knowledge of the pathogenic organisms and how they produce disease, as well as an understanding of the clinical aspects of these diseases. In the collective judgment of the authors, this book presents the principles and facts required for students of medicine to understand the most important infectious diseases.

2

Immune Response to Infection

Within a very short period immunity has been placed in possession not only of a host of medical ideas of the highest importance, but also of effective means of combating a whole series of maladies of the most formidable nature in man and domestic animals.

—Elie Metchnikoff, 1905

The "maladies" Metchnikoff and the other pioneers of immunology were fighting infections and, for decades, their field was defined in terms of the immune response to infection. We now understand that the immune system is as much a part of everyday human biologic function as the cardiovascular or renal systems. In its adaptive and disordered states, infectious diseases are only one of the major player along with cancer and autoimmune diseases. Students of medicine take up immunology as a separate unit with its own text covering the field broadly. This chapter is not intended to fulfill that function, or to be a shortened but comprehensive version of those sources. It is included as an overview of aspects related to infection for other students and as an internal reference for topics that reappear in later pages of this book. These include some of the greatest successes of medical science. The early and continuing development of vaccines that prevent and potentially eliminate diseases is but one example. In addition, knowledge of the immune response to infection is integral to understanding the pathogenesis of infectious diseases. It turns out that one of the main attributes of a successful pathogen is evading or confounding the immune system.

The immune response to infection is presented as two major components—innate immunity and adaptive immunity. The primary effectors of both are cells that are part of the white blood cell series derived from hematopoietic stem cells in the bone marrow (**Figure 2–1**). Innate immunity includes the role of physical, cellular, and chemical systems that are in place and that respond to all aspects of foreignness. These include mucosal barriers, phagocytic cells, and the action of circulating glycoproteins such as complement. The adaptive side is sometimes called specific immunity because it has the ability to develop new responses that are highly specific to molecular components of infectious agents, called **antigens.** These encounters trigger the development of new cellular responses and production of circulating antibody, which have a component of memory if the invader returns. Artificially creating this memory is, of course, the goal of vaccines.

INNATE (NATURAL) IMMUNITY

Innate immunity acts through a series of specific and nonspecific mechanisms, all working to create a series of hurdles for the pathogen to navigate (**Table 2–1**). The first are mechanical barriers such as the tough multilayered skin or the softer but fused mucosal layers of internal surfaces. As discussed in Chapter 1, the microbiota on these surfaces presents formidable competition for space and nutrients. Turbulent movement of the mucosal surfaces and enzymes or acid secreted on their surface make it difficult for an organism to persist.

Skin, mucosa are barriers

Cells engulf, digest, and present antigens from microbes

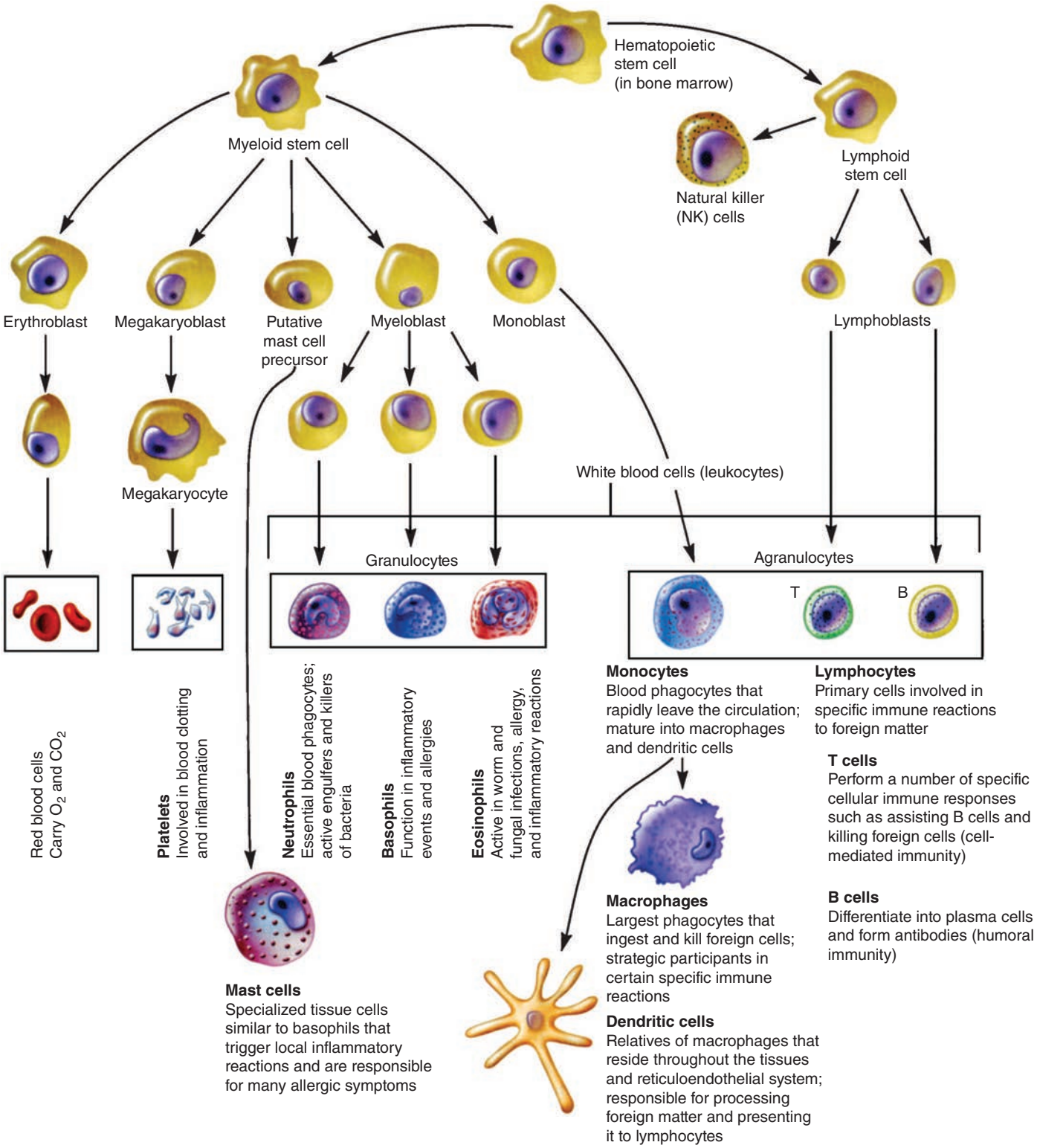

FIGURE 2–1. Human blood cells. Stem cells in the bone marrow divide to form two blood cell lineages: **(1)** the lymphoid stem cell gives rise to B cells that become antibody-secreting plasma cells, T cells that become activated T cells, and natural killer cells. **(2)** The common myeloid progenitor cell gives rise to granulocytes and monocytes that give rise to macrophages and dendritic cells. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

TABLE 2–1 Features of Innate Immunity in Infection

	LOCATION	ACTIVITY AGAINST PATHOGENS
Cells		
Macrophage	Circulation, tissues	Phagocytosis, digestion
Dendritic cell	Tissues	Phagocytosis, digestion
Polymorphonuclear neutrophil (PMN)	Circulation, tissues (by migration)	Phagocytosis, digestion
M cell	Mucus membranes	Endocytosis and delivery to phagocytes
Surface Receptors		
Lectin	Phagocyte	Recognize carbohydrates
Arginine-glycine-arginine (RGD)	Phagocyte	Recognize arginine-glycine-aspartic acid sequence
Toll-like receptor (TLR)	Phagocyte	Recognizes PAMP, such as bacterial LPS (TLR-4), peptidoglycan[a] (TLR-2)
Inflammation		
Selectins	Endothelium	Attract and attach PMNs
Integrins	PMNs	Attach to selectins
Kallikrein	Extracellular fluid	Release bradykinin, prostaglandins
Chemical Mediators		
Cathelicidin	PMNs, macrophages, epithelial cells	Ionic membrane pores
Defensins	PMN granules	Ionic membrane pores
Complement (classical, alternative, lectin)	Serum, extracellular fluid	Membrane pores, phagocyte receptors

LPS, lipopolysaccharide of gram-negative bacterial outer membrane; PAMP, pathogen-associated molecular pattern.

[a]Cell wall component of gram-positive and gram-negative bacteria.

Organisms that are able to pass the mucosa encounter a population of cells with the ability to engulf and destroy them. In addition, body fluids contain chemical agents such as complement, which can directly injure the microbe. The entire process has cross-links to the adaptive immune system. The endpoint of phagocytosis and digestion in a macrophage is the presentation of the antigen on its surface; the first step in specific immune recognition.

PHYSICAL BARRIERS

The thick layers of the skin containing insoluble keratins present the most formidable barrier to infection. The mucosal membranes of the alimentary and urogenital tract are not as tough but, often, are bathed in secretions inhospitable to invaders. Lysozyme is an enzyme that digests peptidoglycan—a unique structural component of the bacterial cell wall. Lysozyme is secreted onto many surfaces and is particularly concentrated in conjunctival tears. The acid pH of the vagina and particularly the stomach makes colonization difficult for most organisms. Only small particles (5-10 μm) can be inhaled deep into the lung alveoli because the lining of the respiratory tract includes cilia that trap and move them back toward the pharynx.

Lysozyme digests bacterial walls

Cilia move particles away from pulmonary alveoli

The skin and mucosal surfaces of the intestinal and respiratory tract also contain concentrations of lymphoid tissue within or just below their surfaces, which provide a next-level defense for invaders surviving the above described barriers. These lymphoid collections are

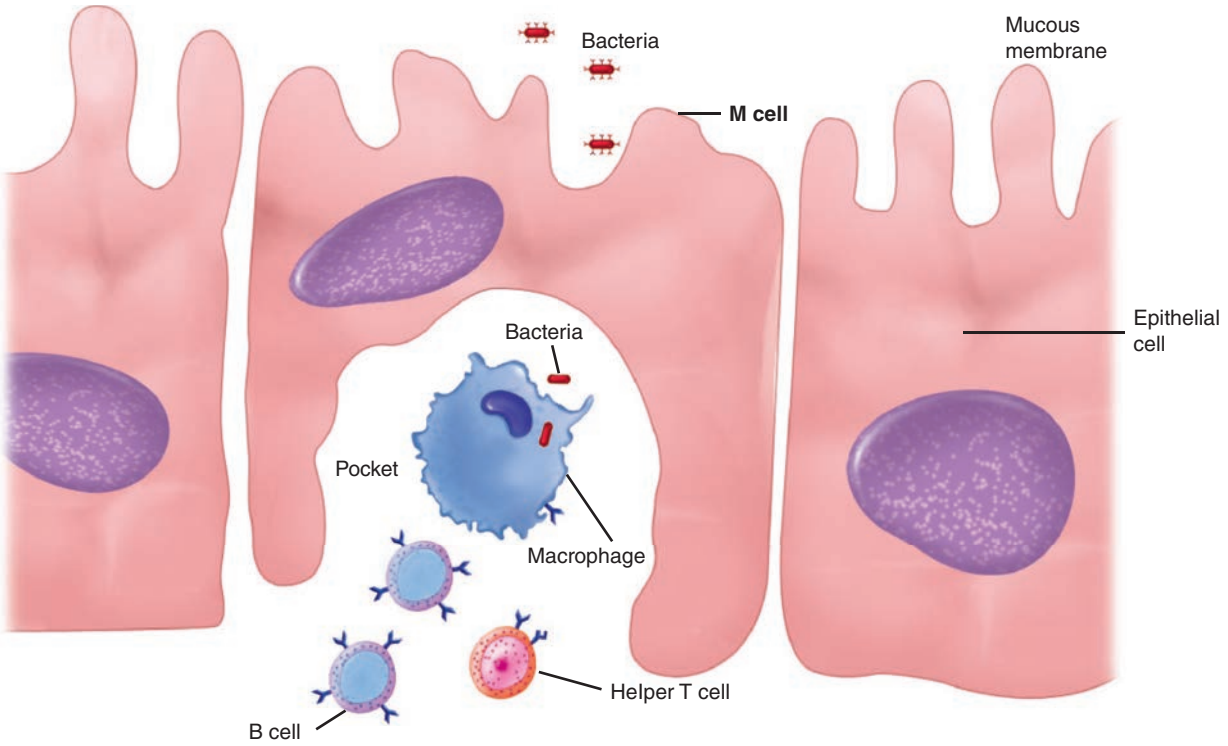

FIGURE 2–2. M cell. An M cell is shown between two epithelial cells in a mucous membrane. It has endocytosed a pathogen and released it into a pocket containing macrophages and other immune cells.

M cells deliver to macrophages and lymphocytes

designed to entrap and deliver invaders to some of the phagocytes described in the following text. For example, in the intestine, M cells (**Figure 2–2**) that lack the villous brush border of their neighbors endocytose bacteria and then release them into a pocket containing macrophages and lymphocytic components (T and B cells) of the adaptive immune system. The enteric pathogen *Shigella* exploits this receptiveness of the M cell to attack the adjacent enterocytes from the side.

IMMUNORESPONSIVE CELLS AND ORGANS

Stem cells differentiate to myeloid and lymphoid series

Thymus, spleen, and lymph nodes are immune organs

Not all the cells shown in Figure 2–1 are involved in the immune system; of those that are, not all respond to infection. What the immunoresponsive cells have in common is derivation from hematopoietic stem cells in the bone marrow, which create the myeloid and lymphoid series followed by further differentiation into their mature cell types. Of the types shown, the erythroblast and megakaryocyte do not participate in immune reactions. In the myeloid series, basophils and mast cells are primarily involved in allergic reactions rather than infection. The immunoresponsive cells are found throughout the body in the circulation or at fixed locations in tissues. They are concentrated in the lymph nodes and spleen, and form a unified filtration network designed as a sentinel warning system. In the lymphoid series, cells destined to become T cells mature in the thymus (the source of their name). Thus, the thymus, spleen, and lymph nodes might be thought of as the organs of the immune system. These are collectively referred to as the lymphoid tissues.

Cellular Receptors for Microbes

Surface receptors recognize uniquely microbial PAMPs

Fixed and circulating phagocytes express surface receptors which recognize a limited array of uniquely microbial structures based on the pattern of their molecular structure. These pathogen-associated molecular patterns (PAMPs) include bacterial cell wall peptidoglycan, the lipopolysaccharide endotoxin of gram-negative bacteria, mannose and other glycoproteins, lipids and polysaccharides. Nucleic acids are also recognized such as the double-stranded RNA found in many viruses. These PAMP-recognizing receptors may be found

on the surface of phagocytes, dendritic cells, and specialized compartments called toll-like receptors (TLRs) of which over 10 types have been described. The engagement of TLR receptors generate transcription signals that generate a range of antimicrobial cytokines specific to the TLR type.

Cytokine production triggered by TLRs

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are small peptide molecules with natural antimicrobial effects. In mammals there are two major families of AMPs called cathelicidins and defensins. They are produced by multiple cell types including leukocytes, mast cells, dendritic cells, and platelets in response to tissue damage. They exhibit broad-spectrum activity against bacteria, fungi, parasites, and some enveloped viruses. Their antimicrobial action is by electrostatic interaction with the surfaces of microbes such as bacterial outer membranes, cytoplasmic membranes, and cell walls causing rupture and death. Some AMPs may also disrupt metabolic processes like nucleic acid and protein synthesis.

Cathelicidins and defensins bind and disrupt microbial surfaces

Cells Responding to Infection

Monocytes

Monocyte is a general morphologic term for cells that include or quickly (within hours) differentiate into macrophages or dendritic cells. These are the cells of the immune system that both phagocytose invaders and process them for presentation to the adaptive immune system. **Macrophages** are found in the circulation and tissues, where they are sometimes given regional names such as alveolar macrophage. They possess surface receptors such as mannose and fructose, which nonspecifically recognize components commonly found on pathogens and more specialized receptors able to recognize unique components of microbes such as the lipopolysaccharide (LPS) of gram-negative bacteria. They also have receptors that recognize antibody and complement.

Macrophages in circulation or tissues

Surface receptors recognize pathogens

Dendritic cells have a distinctive star-like morphology, and are present in the skin and in the mucous membranes of the respiratory and intestinal tracts. Similar to macrophages, they phagocytose and present foreign antigens. Surface recognition includes PAMP recognition. After binding and phagocytosis, dendritic cells migrate to lymphoid tissues where specific adaptive immune responses are triggered. This interaction involving lymphocytes and T cells functions as a bridge between the innate and adaptive immune systems.

Star-like tissue phagocytes recognize PAMPs

In lymphoid tissues interact with adaptive immunity

Granulocytes

Of the cells in the granulocyte series, the most active is the **polymorphonuclear neutrophil** or **PMN.** These cells have a distinctive multilobed nucleus and cytoplasmic granules that contain lytic enzymes and antimicrobial substances including peroxidase, lysozyme, defensins, collagenase, and cathelicidins. PMNs have surface receptors for antibody and complement and are active phagocytes. In addition to the digestive enzymes, PMNs have other oxygen-dependent and oxygen-independent pathways for killing microorganisms. Unlike macrophages, they only circulate and are not present in tissues except by migration as part of an acute inflammatory response.

PMNs have digestive and killing pathways

In circulation unless they migrate in inflammation

Eosinophils are nonphagocytic cells that participate in allergic reactions along with **basophils** and **mast cells.** Eosinophils are also involved in the defense against infectious parasites by releasing peptides and oxygen intermediates into the extracellular fluid. It is felt that these products damage membranes of the parasite.

Eosinophils damage parasites

Lymphocytes

Lymphocytes are the primary effector cells of the adaptive immune system. They are produced from a lymphocyte stem cell in the bone marrow and leave in a static state marked to become T, B, or null cells after further differentiation (**Figure 2–3**). This requires activation mediated by surface binding, which then stimulates further replication and differentiation.

T, B, and null cells initially static

B cells mature in the bone marrow and then circulate in the blood to lymphoid organs. At these sites, they may become activated to a form called a plasma cell, which produces antibodies. **T cells** mature in the thymus and then circulate awaiting activation. Their activation results in production of cytokines, which are effector molecules for multiple immunocytes and somatic cells. Some of the uncommitted null cells become **natural killer (NK) cells,** which have the capacity to directly kill cells infected with viruses by secreting IFN-γ.

B cells make antibody

T cells secrete cytokines

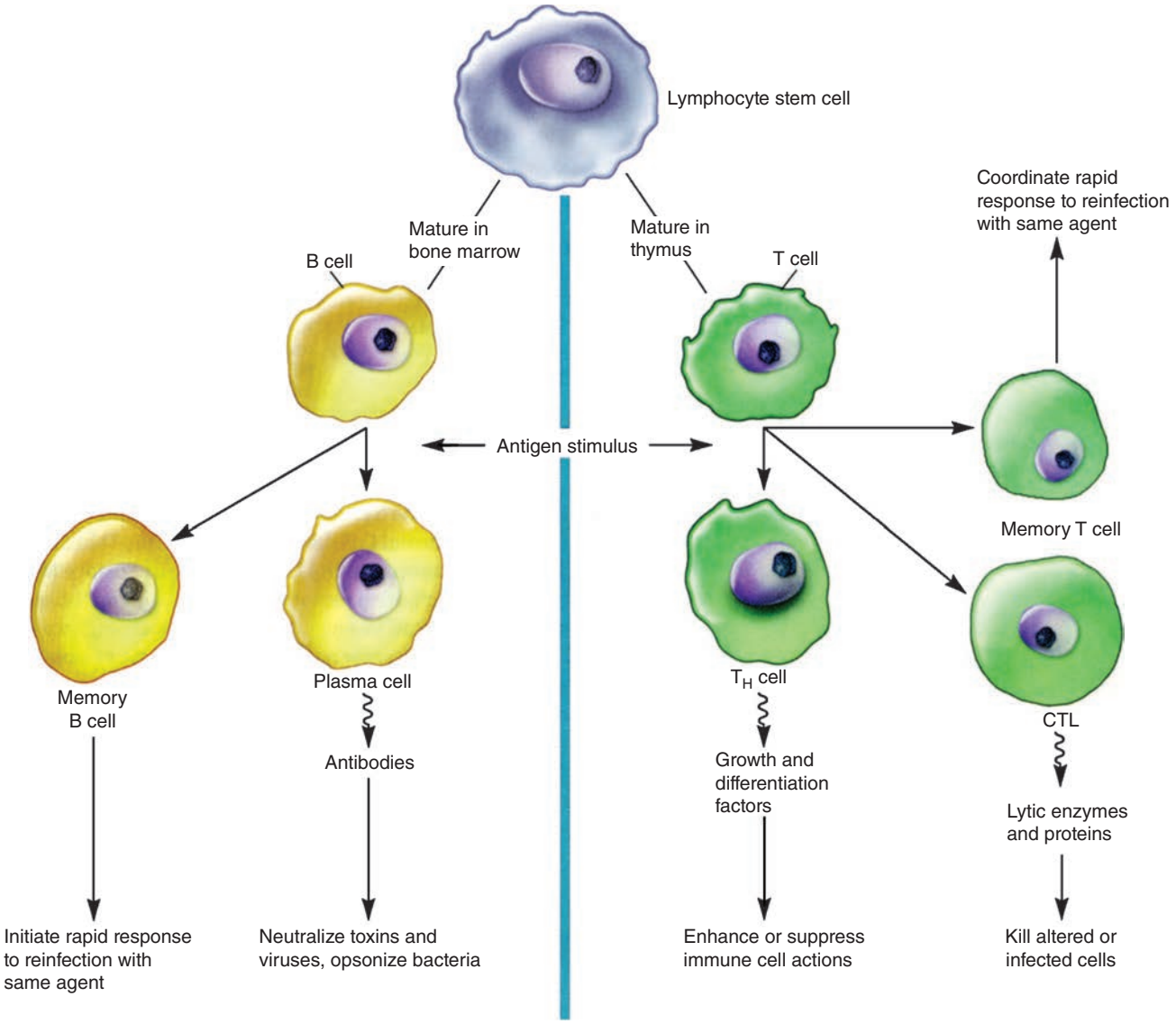

FIGURE 2–3. B and T lymphocytes. B cells and T cells arise from the same cell lineage but diverge into two functional types. Immature B cells and T cells are indistinguishable by morphology. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

Phagocytosis

Opsonization not required

Carbohydrate and peptide sequence recognized

Phagocytosis is one of the most important defenses against microbial invaders (**Figure 2–4**). The major cells involved are PMNs, macrophages, and dendritic cells. For all, the process begins with surface–pathogen recognition mechanisms, which may be either dependent on opsonization of the organism with complement or antibody or independent of opsonization. At this point, only the opsonin-independent mechanisms are considered. These use the nonspecific mechanisms already described and hydrophobic interactions between bacteria and the phagocyte surface. More powerful mechanisms include **lectins,** which bind carbohydrate moieties and protein–protein interactions based on a specific peptide sequence (arginine-glycine-aspartic-acid or RGD). These **RGD receptors** are present on virtually all phagocytes.

Enzymes digest in acidic phagolysosome

Reactive oxygen driven by respiratory burst

Bound organisms are taken inside the phagocyte in a membrane-bound phagosome destined to fuse with lysosomes inside to form a **phagolysosome.** This is the main killing ground of the phagocyte. The lysosomal enzymes include hydrolases and proteases that have maximum activity at the acidic pH inside the phagolysosome. In addition, inside the phagocyte are oxidative killing mechanisms created by enzymes that produce **reactive oxygen intermediates** (superoxide, hydrogen peroxide, singlet oxygen) driven by a metabolic respiratory burst in the cell cytoplasm. These mechanisms are particularly used for killing bacteria. Bacterial pathogens whose pathogenesis involves multiplication rather

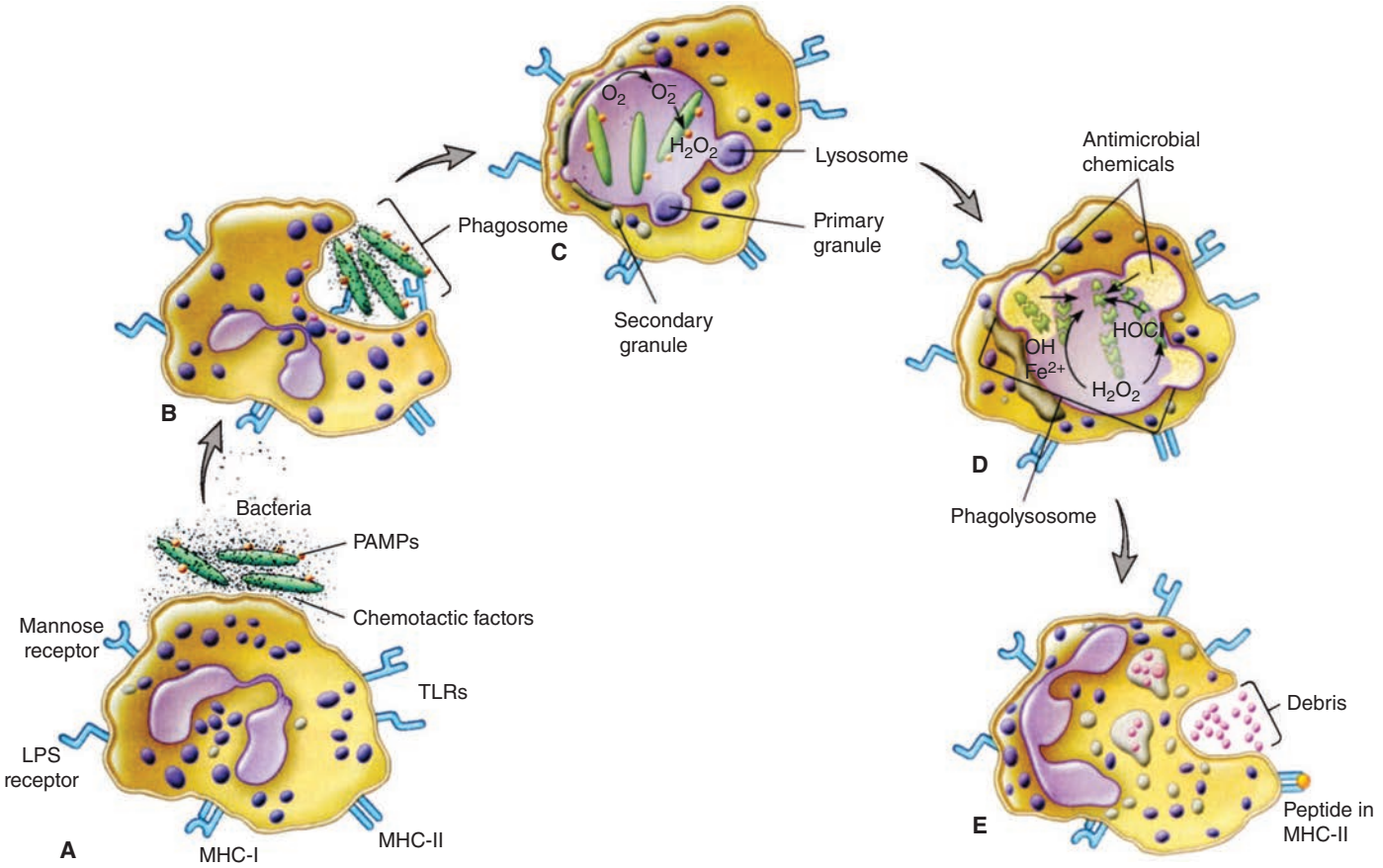

FIGURE 2–4. Phagocytosis. A. Drawing shows receptors on a phagocytic cell, such as a macrophage, and the corresponding PAMPs participating in phagocytosis. The schematic depicts the process of phagocytosis showing ingestion. **B.** Participation of primary and secondary granules. **C.** O_2-dependent killing events. **D.** Intracellular digestion. **E.** Endocytosis LPS receptor, lipopolysaccharide receptor; TLRs, toll-like receptors; MHCI, class I major histocompatibility protein; MHC II, class II major histocompatibility protein; PAMPs, pathogen-associated molecular patterns. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

than destruction inside the phagocyte have mechanisms to block one or more of the preceding steps. For example, some pathogens are able to block fusion of the phagosome with the lysosome; others interfere with the acidification of the phagolysosome.

Another mechanism effective with some viruses, fungi, and parasites is the formation of **reactive nitrogen intermediates** (nitric oxide, nitrate, and nitrite) delivered into a vacuole or in the cytoplasm. PMN granules contain a variety of other antimicrobial substances, including peptides called **defensins.** Defensins act by permeabilizing membranes and, in addition to bacteria, are active against enveloped viruses.

Reactive nitrogen affects viruses

INFLAMMATION

Inflammation encompasses a series of events in which the above mentioned cells are deployed in response to an injury—such as a new microbial invader. At the first insult, chemical signals mobilize cells, fluids, and other mediators to the site to contain, combat, and heal. In acute inflammation, the first events may be noticed in minutes, and the entire process resolved over a matter of days to a couple of weeks. Chronic inflammation may follow the incomplete resolution of an acute process or arise as a slow insidious process of its own. The natural history of infections such as tuberculosis, which follow this pattern, run for months, years, even decades.

Acute = hours to days

Chronic = weeks to months

The first event in **acute inflammation** is the release of chemical signals (chemokines) that act on adhesion molecules (selectins) in local capillaries. This slows the movement of passing PMNs and activates adhesive integrins on their surface. This leads to tight adhesion to

PMNs migrate from capillaries

Enzymes and chemical mediators facilitate swelling

the endothelium followed by squeezing past the endothelial wall to the tissues below. There, chemotactic factors released by the bacteria lead them to the primary site. Increasing acidity of local fluids releases enzymes (kallikrein, bradykinin) that open junctions in capillary walls and allow increased flow of fluids and more leukocytes. Histamine (from mast cells), arachidonic acid, and prostaglandin release complete the picture of swelling and pain.

Lymphocytes and macrophages predominate

Granulomas indicate failure to resolve by adaptive cellular mechanisms

Chronic inflammation bridges the innate and adaptive immune responses. An acute phase, if present, is usually not noticed, and the cellular infiltrate is composed of lymphocytes and macrophages with relatively few PMNs. It is generally associated with slower-growing pathogens such as mycobacteria, fungi, and parasites in which cell-mediated immunity is the primary adaptive defense. Many of these pathogens have mechanisms that allow them to multiply in nonactivated macrophages. If the macrophages are effectively activated by T cells, the multiplication ceases and the inflammation and injury are minimal. If not, multiplication and chronic inflammation continue sometimes in the form of a **granuloma,** which is an indication of a destructive hypersensitivity component to the inflammation.

CHEMICAL MEDIATORS

Peptides alter membrane permeability

Chemical mediators of innate immunity that have direct antimicrobial activity include cationic proteins and complement. The cationic proteins (cathelicidin, defensins) act on bacterial plasma membranes by the formation of ionic pores, which alter membrane permeability. The complement system is a series of glycoproteins, which can directly insert in bacterial membranes or act as receptors for antibody. Cytokines are proteins or glycoproteins released by one cell population that act as signaling molecules for another. They are generally thought of in the context of the adaptive immune system, but they can be stimulated directly by microorganisms.

The Complement System

Multiple components activated in cascade fashion when triggered

Pathways differ in initiation mechanism

Opsonization is serum coating of pathogens

The complement system consists of more than 30 distinct components and several other precursors. All are in the plasma of healthy individuals in inactive forms that must be enzymatically cleaved to become active. When this happens, a cascade of reactions is triggered, which activates the various components in a fixed sequence (**Figure 2–5**). The difference between the pathways is in the mechanisms for their initiation. Once started, any pathway can produce the same effects on pathogens, which include enhancing phagocytosis, activation of leukocytes, and lysis of bacterial cell walls. An important step in the process is coating of the organism with serum components, a process called **opsonization.** The coatings may be mannose-binding proteins, complement components, or antibody. There is no immunologic specificity in complement activation or in its effects.

Alternative Pathway

Activation is by pathogen surfaces

Membrane-attack complex inserts and provides phagocyte receptors

Factor H binding accelerates C3b degradation on capsules

The alternative pathway is activated by bacterial cell wall components with repetitive surface structures such as LPS. The multiple components come together in the formation of the **membrane-attack complex,** which inserts directly into bacterial membranes (**Figure 2–6**), particularly the outer membrane of gram-negative bacteria. This not only injures the organism, but also enhances phagocytosis because the other end of the molecule has receptors for phagocytes. Gram-positive bacteria are less affected because they have no exposed membrane (see Chapter 21). These actions are particularly important for the effectiveness of innate immunity in the early stages of acute infections before the adaptive immune system has time to act. The key complement component for alternate pathway activity is C3b. C3b activation and degradation are regulated by a number of serum factors (factors B, D, and H) that can modulate its activity. A major mechanism for pathogens to block alternate pathway attack is by binding factor H to their surface. This is accomplished by bacterial capsules and surface proteins. This concentration of factor H causes local degradation of C3b (see Chapter 22, Figure 22–4).

Lectin Pathway

Lectins bind mannose on pathogens

Another means of activating the complement system is based on the carbohydrate building of lectins. In this case, the lectins bind to mannose—a common surface component

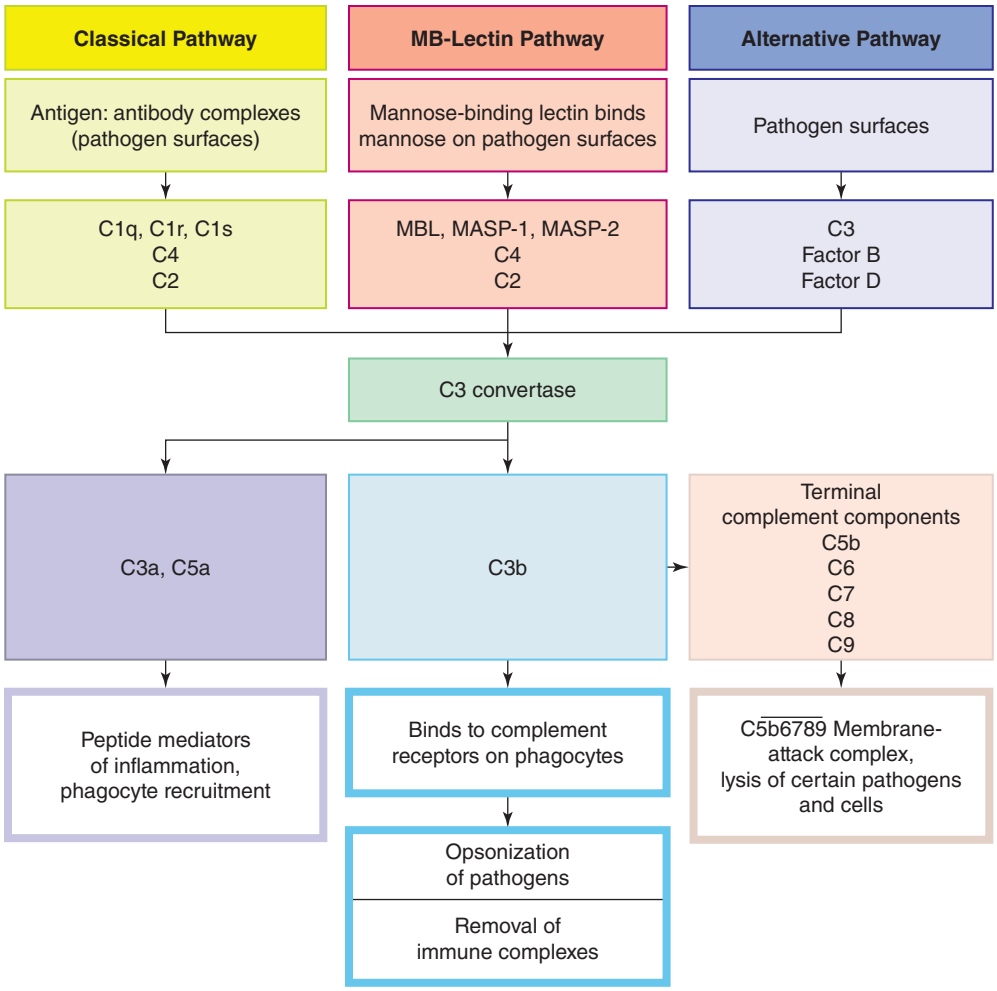

FIGURE 2–5. Components and action of complement. Complement activation involves a series of enzymatic reactions that culminate in the formation of C3 convertase, which cleaves complement component C3 into C3b and C3a. The production of the C3 convertase is where the three pathways converge. C3a is a peptide mediator of local inflammation. C3b binds covalently to the bacterial cell membrane and opsonizes the bacteria, enabling phagocytes to internalize them. C5a and C5b are generated by the cleavage of C5 by a C5 convertase. In addition, C5a is a powerful peptide mediator of inflammation. C5b promotes the terminal components complement to assemble into a membrane-attack complex. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

of bacteria, fungi, and some virus envelopes. This binding opsonizes the pathogen and enhances phagocytosis. Thus, as in the alternative pathway, the activation comes from pathogen surfaces and proceeds through the same C3 convertase (Figure 2–5).

Classic Pathway

Antigen–antibody reaction exposes complement binding sites

The classic complement pathway is initiated by the binding of antibodies formed during the adaptive immune response (as described further) with their specific antigens on the surface of a pathogen. This binding is highly specific but amounts to another case of opsonization activating the complement cascade. In this case, specific sites on the Fc portion of immunoglobulin molecules bind and activate the C1 component of complement to start the process. The pathway and sequence of individual complements are characteristic of the classic pathway, but it still reaches C3b, the common point for microbial directed action. As with the alternative pathway, this creates the membrane-attack complex, the mediators of inflammation, and receptors for phagocytes on C3b.

C3b has receptors for phagocytes

Cytokines

Cytokine is a broad term referring to molecules released from one cell population destined to have an effect on another cell population (**Table 2–2**). As these proteins and glycoproteins

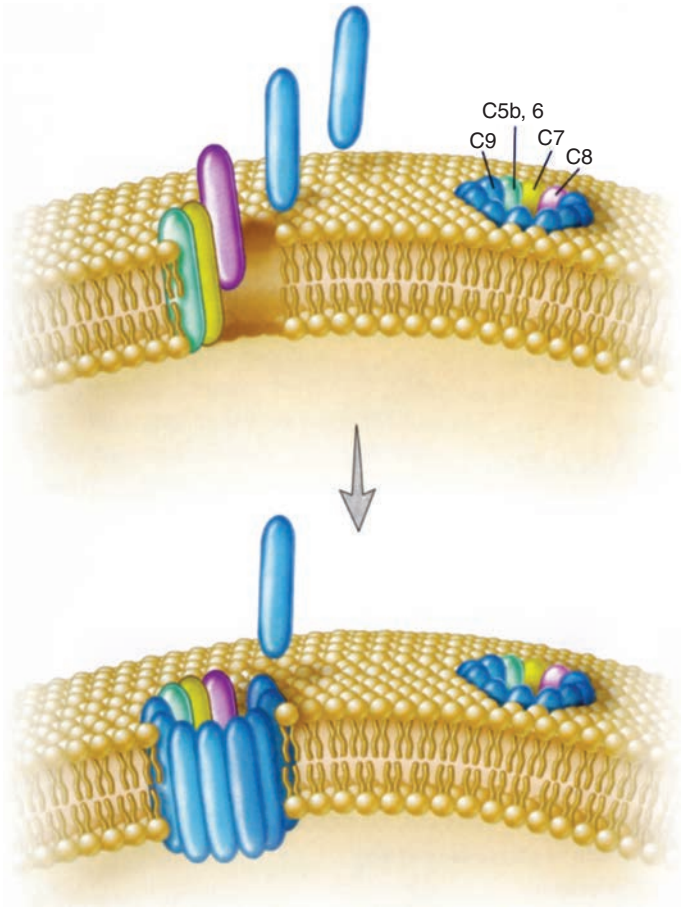

FIGURE 2–6. Complement membrane-attack complex. The membrane-attack complex (MAC) is a tubular structure that forms a transmembrane pore in the target cell's plasma membrane. The subunit architecture of the MAC shows that the transmembrane channel is formed by multiple polymerized molecules. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

TABLE 2–2 Some Cytokines Acting in Infection

	CELL SOURCE	FUNCTIONS
Interleukins (IL)		
IL-1	Macrophages, endothelium, fibroblasts, epithelial	Differentiation and function of immune effectors, PMN response (T_H17)
IL-2	T cells (T_H1)	T-cell proliferation, cytolytic activity of natural killer (NK) cells
IL-4	T cells (T_H2), macrophages, B cells	Differentiation of naïve T cells to helper T cells, proliferation of B cells
IL-5	T cells (T_H2)	Eosinophil activation
IL-8	Macrophages, endothelial, T cells, keratinocytes, PMNs	Chemoattractant for PMNs and T cells, PMN degranulation, migration of PMNs
IL-17	T cells (T_H17)	Inflammation, PMN response
IL-22	T cells (T_H17)	Antimicrobial peptides
Interferons (IFN)		
IFN-α/β	T cells, B cells, macrophages, fibroblasts	Antiviral activity, stimulates macrophages, MHC class I expression
IFN-γ	T cells (T_H1, CTLs), NK cells	T-cell activation, macrophage activation, PMNs, NK cells, antiviral, MHC class I and II expression
Tumor Necrosis Factor (TNF)		
TNF-α	T cells, macrophages, NK cells	Expression of multiple cytokines, (growth and transcription factors), stimulates inflammatory response, cytotoxic for tumor cells
TNF-β	T cells, B cells	Same as TNF-α

MHC, major histocompatibility complex; PMN, polymorphonuclear neutrophil.

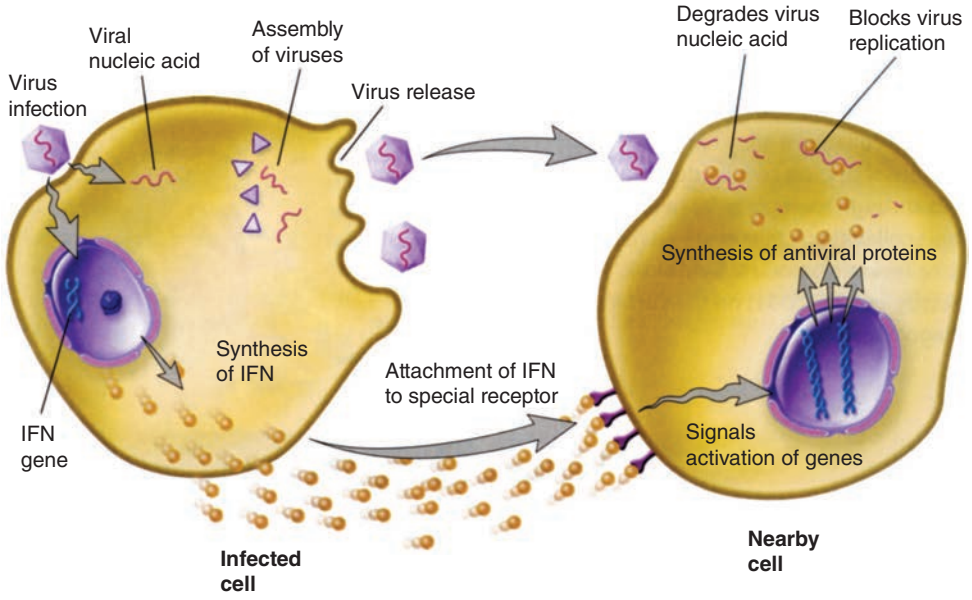

FIGURE 2–7. Antiviral action of interferon. Interferon (IFN) synthesis and release are often induced by a virus infection. IFN binds to a ganglioside receptor on the plasma membrane of a second cell and triggers the production of enzymes that render the cell resistant to virus infection. The two most important such enzymes are oligo (A) synthetase and a special protein kinase. When an IFN-stimulated cell is infected, viral protein synthesis is inhibited by an active endoribonuclease that degrades viral RNA. An active protein kinase phosphorylates and inactivates the initiation factor elf-2 required for viral protein. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

have been discovered, they have been named and classified in relation to biologic effects observed initially only to discover that they have multiple other actions. For infectious diseases, the operative subcategories are **chemokines,** which are cytokines chemotactic for inflammatory cell migration, and **interleukins** (**IL-1, -2, -3,** etc), which regulate growth and differentiation between monocytes and lymphocytes. **Tumor necrosis factor (TNF),** so named for its cytotoxic effect on tumor cells, can also induce apoptosis (programmed cell death) in phagocytes—a useful feature for pathogens they have taken in. **Interferons (INF-α, -β, and -γ)** were originally named for their interference with viral replication (**Figure 2–7**), but are now known to be central to activation of T cells and macrophages. Unless commanded to understand specific situations, cytokine is used to represent all these mediators in these pages.

ILs, IFNs, TNF, chemokines are all cytokines

THE ADAPTIVE (SPECIFIC) IMMUNE SYSTEM

The adaptive immune system differs from the innate immune response in its discrimination between self and nonself and in the magnitude and diversity of highly specific immune responses possible (**Table 2–3**). In addition, it has a **memory** function, which is able to mount an accelerated response if an invader returns. The adaptive system operates in two broad arms—**humoral immunity** and **cell-mediated immunity**. Humoral immunity comes from bone marrow-derived **B cells** and acts through the ability of the antibodies it produces to bind foreign molecules called antigens. Cell-mediated (cellular) immunity is mediated through **T cells** that mature in the thymus and respond to antigens by directly attacking infected cells or by secreting cytokines to activate other cells. As shown in **Figure 2–8,** the B-cell and T-cell systems are interactive.

Antigens and Epitopes

An antigen is any substance (usually foreign) with the ability to stimulate an immune response when presented in an effective fashion. They are usually large structurally complex proteins, polysaccharides, or glycolipids. Each antigen can contain many subregions that

TABLE 2–3 Cells Involved in the Adaptive Immune System

CELL	FUNCTION	SPECIFIC RECEPTORS FOR ANTIGEN	CHARACTERISTIC CELL-SURFACE MARKER	SPECIAL CHARACTERISTICS
B cells	Production of antibody	Surface immunoglobulin (IgM monomer)	Fc and complement C3d receptors; MHC class II	Differentiate into plasma cells
Helper T lymphocytes (T_H)	Stimulate macrophages, eosinophils, PMNs, IgE production, B cells	α/β T-cell receptor (TCR)	CD4+	Presented by MHC class II, Three subsets (T_H1, T_H2, T_H17)
Cytotoxic T lymphocytes (CTLs)	Lyse antigen-expressing cells such as virally infected cells or allografts	α/β TCR	CD8+	Presented by MHC class I
Natural killer (NK) cells	Spontaneous lysis of tumor and infected cells	Inhibitory; activating	Fc receptor for IgG	Recognize MHC class I
Macrophages (monocytes)	Phagocytosis, secretion of cytokines to activate T cells (eg, IL-1) or other accessory cells such as polymorphonuclear neutrophils (PMNs)[c]	None, but can be "armed" by antibodies binding to Fc receptors	Macrophage surface antigens	Express surface receptors for the activated third component of complement (C3), kill ingested bacteria by oxidative bursts
Polymorphonuclear leukocytes (neutrophils, eosinophils)	Phagocytosis killing	None, but can be "armed" by antibodies		Protective in bacterial and parasitic (eosinophils) infections

MHC, major histocompatibility complex.

Antigens stimulate immune response

Epitopes fit to the combining site of T-cell receptors and antibodies

are the actual antigenic determinants, or epitopes. These epitopes can consist of separate peptides, carbohydrates, or lipids of the correct size and three-dimensional configuration to fit the combining site of an antibody molecule or a T-cell receptor (TCR) (**Figure 2–9**). Approximately six amino acids or monosaccharide units provide a correctly sized epitope. Antigens presented by infectious agents typically contain multiple epitopes, including copies of the same epitope. Other small organic molecules that would not ordinarily stimulate an immune response may do so if bound to a larger carrier, such as a protein. These are called **haptens,** and the specificity of the immune response may be generated for both the hapten and its larger carrier.

B cells multiply and produce antibody

A foreign antigen entering a human host may, by chance, encounter a B cell whose surface antibody is able to bind it. This interaction stimulates the B cell to multiply, differentiate, and produce more surface and soluble antibodies of the same specificity. Eventually, the process leads to production of enough antibody to bind more of the antigen. This mechanism is most likely to operate with antigens such as polysaccharides that have repeating subunits, thus improving the possibility that exposed epitopes are recognized.

Protein antigens must be processed first

Large, complex antigens such as proteins and viruses must be processed before their epitopes can be effectively recognized by the immune system. This processing takes place in macrophages or specialized epithelial cells found in the skin and lymphoid organs, where they are adjacent to other immunoresponsive cells. The ingested antigen is degraded to peptides of 10 to 20 amino acids that are presented by major histocompatibility molecules on the host cell surface to be recognized by T cells (Figures 2–10, 2–11).

Recognition of Foreignness

MHC gene complex codes surface molecules

Distinguishing between self and nonself is obviously essential to maintaining integrity and homeostasis. The collection of genes that control these functions is called the **major histocompatibility complex (MHC),** and it codes for molecules present on the surface of almost all human cells. Of interest in infection are MHC class I and II molecules (**Figure 2–10**). **MHC class I** molecules are in the membrane of almost all cells, but **MHC class II** molecules are present only on certain leukocytes such as macrophages, dendritic cells, and some T and B cells.

MHC II on macrophages, dendritic cells

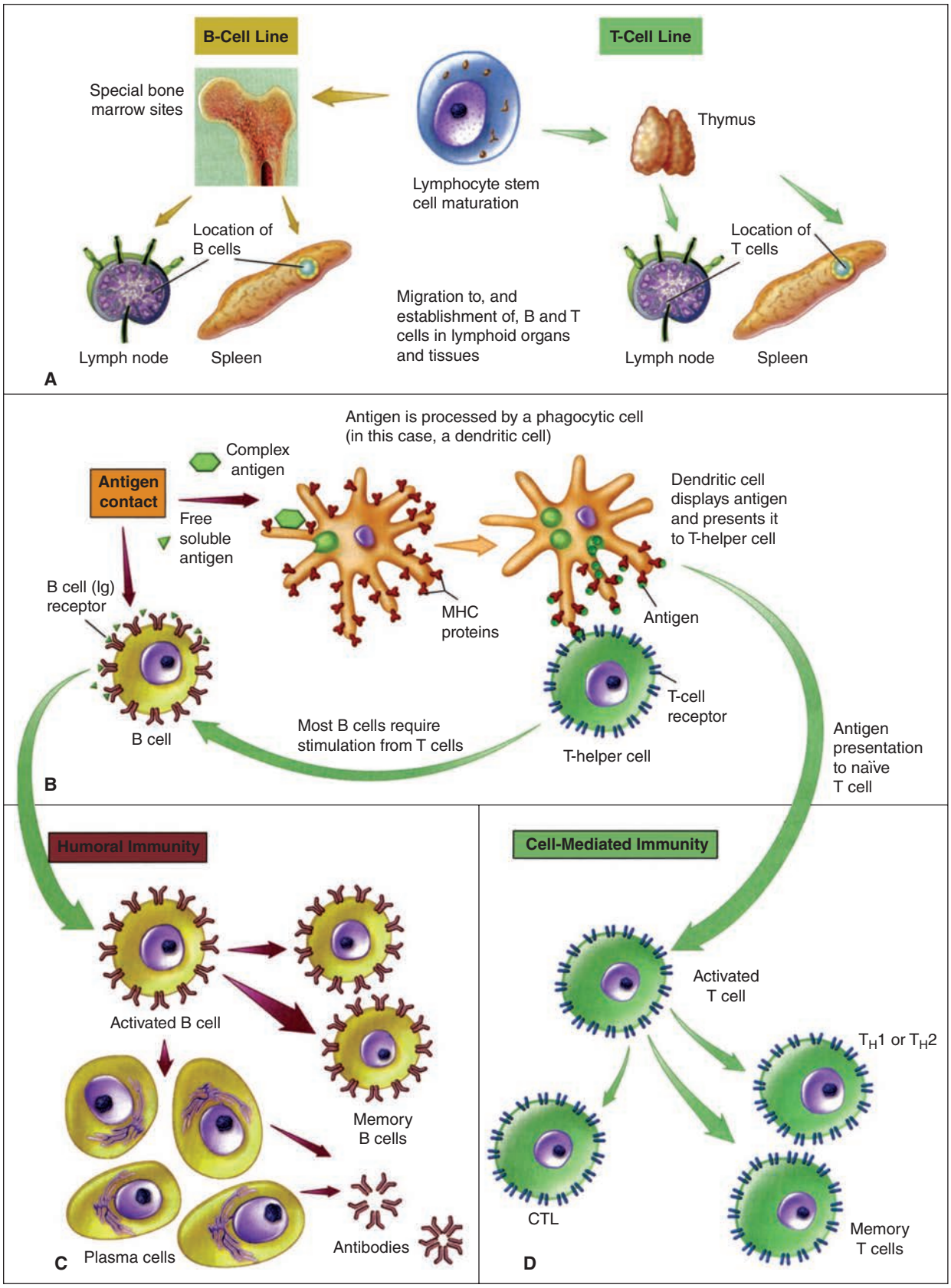

FIGURE 2–8. Acquired immune system development. A. Lymphocyte stem cells develop into B- and T-cell precursors that migrate to the bone marrow or thymus, respectively. Mature B and T cells seed secondary lymphoid tissues. **B.** Lymphocyte receptor binding of antigen activates B and T cells to become effector cells. **C.** B lymphocytes develop into memory cells and antibody-secreting plasma cells. **D.** T cells develop into memory cells, helper T cells, and cytotoxic T cells. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)

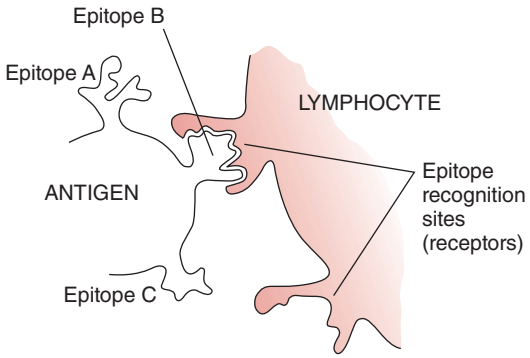

FIGURE 2–9. Epitopes. Schematic of epitope recognition by an immunoresponsive lymphocyte. Epitope B on the antigen binds to a complementary recognition site on the surface of the immunoresponsive cell. Antigens may have many different epitopes, but an immunoresponsive lymphocyte has receptors of only one specificity. In most cases, epitopes are recognized on the surface of macrophages that have processed the antigen. The receptor for antigens on B cells is the combining site of the surface immunoglobulin.

MHC I presents cytoplasmic peptides to CD8+

MHC II presents foreign peptides to CD4+

Both MHC class I and class II participate in antigen processing, but by distinctly different pathways (**Figure 2–11**). MHC class I molecules bind to products generated in the cytoplasm by a natural process or a viral infection. Viral proteins are digested to peptides in a cytoplasmic structure called the **proteasome,** and delivered to the endoplasmic reticulum. Here they find the binding site of the class I molecule and are transported to the surface for presentation of the peptide. MHC class II molecules bind to fragments that originally come from outside the cell, but have been taken into the endocytotic vacuole of a phagocyte. After digestion in the phagolysosome, peptide fragments are combined with class II molecules and move to the surface for presentation. The presented MHC class I peptides are recognized by CD8+ T cells and the MHC class II by CD4+ T cells.

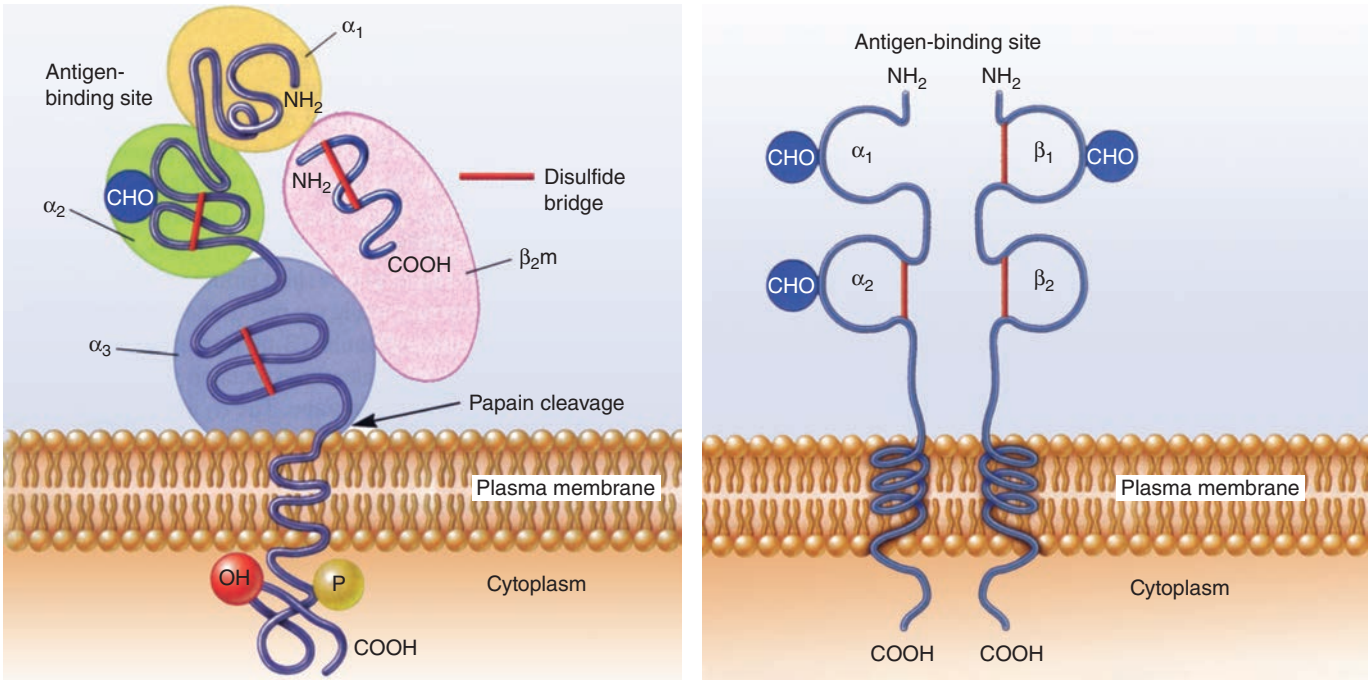

FIGURE 2–10. MHC class I and II molecules. A. The class I molecule is a heterodimer composed of the alpha protein, which is divided into three domains: α_1, α_2, and α_3, and the protein β_2 microglobulin. **B.** The class II molecule is a heterodimer composed of two distinct proteins called alpha and beta. Each is divided into two domains α_1, α_2, and β_1, β_2, respectively. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology,* 7th edition. McGraw-Hill, 2008.)