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Sherris
MEDICAL MICROBIOLOGY

SIXTH EDITION

Kenneth J. Ryan • C. George Ray

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Sixth Edition

SHERRIS
MEDICAL MICROBIOLOGY

EDITORS

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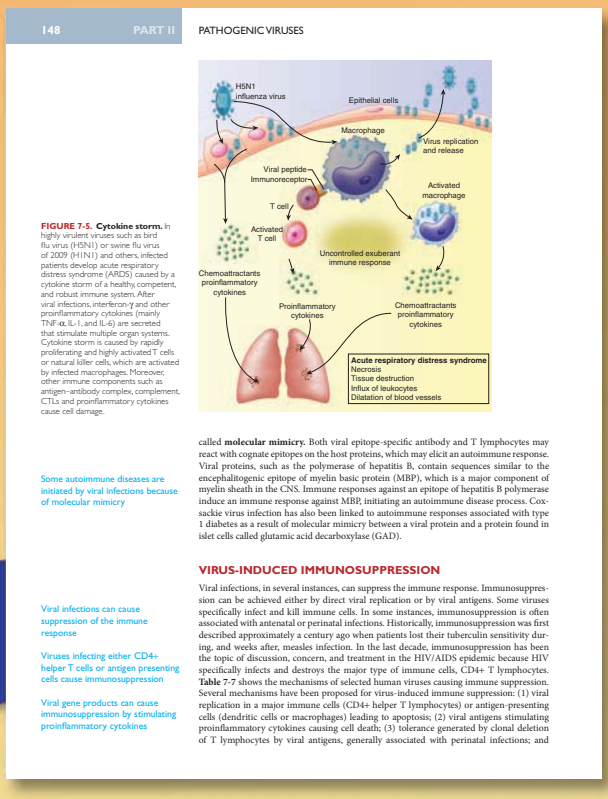
Key Features of Sherris Medical Microbiology, 6th Edition

- **57 chapters** simply and clearly describe the strains of viruses, bacteria, fungi, and parasites that can bring about infectious diseases
- **Core sections on viral, bacterial, fungal, and parasitic diseases open with new chapters** detailing basic biology, pathogenesis, and antimicrobial agents and feature a consistent presentation covering Organism, Disease, and Clinical Aspects
- **Explanations** of host-parasite relationship, dynamics of infection, and host response
- **USMLE-style questions and a clinical case** conclude each chapter on the major viral, bacterial, fungal, and parasitic diseases
- **Full-color** tables, photographs, and illustrations
- **Clinical Capsules** cover the essence of the disease(s) caused by major pathogens
- **Margin Notes** highlight key points within a paragraph to facilitate review



148 PART II PATHOGENIC VIRUSES

FIGURE 7-5. Cytokine storm. In highly virulent viruses such as bird flu virus (H5N1) or swine flu virus of 2009 (H1N1) and others, infected patients develop acute respiratory distress syndrome (ARDS) caused by a cytokine storm of a healthy, competent, and robust immune system. After viral infections, interferon-γ and other proinflammatory cytokines (mainly TNF-α, IL-1, and IL-6) are secreted that stimulate multiple organ systems. Cytokine storm is caused by rapidly proliferating and highly activated T cells or natural killer cells, which are activated by infected macrophages. Moreover, other immune components such as antigen–antibody complex, complement, CTLs and proinflammatory cytokines cause cell damage.

Some autoimmune diseases are initiated by viral infections because of molecular mimicry

called **molecular mimicry**. Both viral epitope-specific antibody and T lymphocytes may react with cognate epitopes on the host proteins, which may elicit an autoimmune response. Viral proteins, such as the polymerase of hepatitis B, contain sequences similar to the encephalitogenic epitope of myelin basic protein (MBP), which is a major component of myelin sheath in the CNS. Immune responses against an epitope of hepatitis B polymerase induce an immune response against MBP, initiating an autoimmune disease process. Coxsackie virus infection has also been linked to autoimmune responses associated with type 1 diabetes as a result of molecular mimicry between a viral protein and a protein found in islet cells called glutamic acid decarboxylase (GAD).

VIRUS-INDUCED IMMUNOSUPPRESSION

Viral infections can cause suppression of the immune response

Viruses infecting either CD4+ helper T cells or antigen presenting cells cause immunosuppression

Viral gene products can cause immunosuppression by stimulating proinflammatory cytokines

Viral infections, in several instances, can suppress the immune response. Immunosuppression can be achieved either by direct viral replication or by viral antigens. Some viruses specifically infect and kill immune cells. In some instances, immunosuppression is often associated with antenatal or perinatal infections. Historically, immunosuppression was first described approximately a century ago when patients lost their tuberculin sensitivity during, and weeks after, measles infection. In the last decade, immunosuppression has been the topic of discussion, concern, and treatment in the HIV/AIDS epidemic because HIV specifically infects and destroys the major type of immune cells, CD4+ T lymphocytes. **Table 7-7** shows the mechanisms of selected human viruses causing immune suppression. Several mechanisms have been proposed for virus-induced immune suppression: (1) viral replication in a major immune cells (CD4+ helper T lymphocytes) or antigen-presenting cells (dendritic cells or macrophages) leading to apoptosis; (2) viral antigens stimulating proinflammatory cytokines causing cell death; (3) tolerance generated by clonal deletion of T lymphocytes by viral antigens, generally associated with perinatal infections; and

New full-color art illuminates important concepts

Each agent has its own mode of spread

Poor socioeconomic conditions foster infection

Modern society may facilitate spread

Anthrax and smallpox are new bioterrorism threats

outbreaks or recognizing new epidemiologic patterns have usually pointed the way to the isolation of new agents.

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 AIDS pandemic, but the prospect of recurrence of old pandemic infections (influenza, cholera) remains. Modern times and technology have introduced new wrinkles to epidemiologic spread. Intercontinental 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.

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 products. Under natural conditions, it produces a nasty, but not 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.

PATHOGENESIS

Pathogenicity is multifactorial

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 a 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.

Pathogens have molecules that bind to host cells

Invasion requires adaptation to new environments

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**.

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 *Streptococcus 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

Margin Notes speed your review and highlight must-know points

CHAPTER 5

Emergence and Global Spread of Infection

Epidemiology, the study of the distribution of determinants of disease and injury in human populations, is a discipline that includes both infectious and noninfectious diseases. Most epidemiologic studies of infectious diseases have concentrated on the factors that influence acquisition and spread, because this knowledge is essential for developing methods of prevention and control. Historically, epidemiologic studies and the application of the knowledge gained from them have been central to the control of the great epidemic diseases, such as cholera, plague, smallpox, yellow fever, and typhus.

An understanding of the principles of epidemiology and the spread of disease is essential to all medical personnel, whether their work is with the individual patient or with the community. Most infections must be evaluated in their epidemiologic setting. For example, what infections, especially viral, are currently prevalent in the community? Has the patient recently traveled to an area of special disease prevalence? Is there a possibility of nosocomial infection from recent hospitalization? What is the risk to the patient's family, schoolmates, and work or social contacts?

The recent recognition of emerging infectious diseases has heightened appreciation of the importance of epidemiologic information. A few examples of these newly identified infections are cryptosporidiosis, hantavirus pulmonary syndrome, and severe acute respiratory syndrome (SARS) coronavirus disease. In addition, some well-known pathogens have assumed new epidemiologic importance by virtue of acquired antimicrobial resistance (eg, penicillin-resistant pneumococci, vancomycin-resistant enterococci, carbapenem-resistant enterobacteraciae, and multiresistant *Mycobacterium tuberculosis*).

Over the past two decades, powerful new molecular methods have been developed that have greatly enhanced the ability to even more clearly understand the origins, evolution and spread of a wide variety of infectious agents. This discipline is called **molecular epidemiology**. The fundamental methodologies are described in Chapter 4, and their specific applications are discussed in many other chapters throughout this book.

Factors that increase the emergence or reemergence of various pathogens include:

- Population movements and the intrusion of humans and domestic animals into new habitats, particularly tropical forests
- Deforestation, with the development of new farmlands and exposure of farmers and domestic animals to new arthropods and primary pathogens
- Irrigation, especially primitive irrigation systems, which fail to control arthropods and enteric organisms
- Uncontrolled urbanization, with vector populations breeding in stagnant water
- Increased long-distance air travel, with contact or transport of arthropod vectors and primary pathogens
- Social unrest, civil wars, and major natural disasters, leading to famine and disruption of sanitation systems, immunization programs, etc.

Important new global considerations of infectious disease

ubiquitous and have been found in humans, simians, rodents, cattle, and a variety of other hosts. They have been studied in great detail as experimental models, revealing much basic knowledge about viral genetics and pathogenesis at the molecular level. Three serotypes are known to infect humans; however, their role and importance in human disease remain uncertain. Reoviruses causing arboviral diseases are discussed in Chapter 16.

Association with human disease is uncertain

CASE STUDY

AN INFANT WITH RESPIRATORY DISTRESS

This 9-month-old boy was born prematurely, requiring treatment in a neonatal intensive care unit for the first month of life. After discharge, he remained well until 3 days ago, when symptoms of a common cold progressed to cough, rapid and labored respiration, lethargy, and refusal to eat.

On examination, his temperature was 38.5°C, respiratory rate 60/min, and pulse 140/min. Auscultation of the chest revealed coarse crackles and occasional wheezes.

Abnormal laboratory findings included hypoxemia and hypercarbia. A chest radiograph showed hyperinflation, interstitial perihilar infiltrates, and right upper lobe atalectasis.

QUESTIONS

■ Which of these viruses is the least likely cause of this baby's illness?

A. Influenza A
B. Parainfluenza 3
C. Influenza C
D. Respiratory syncytial virus
E. Adenovirus

■ The mechanism of "antigenic drift" in influenza viruses includes all but one of the following:

A. Can involve either H or N antigens
B. Mutations caused by viral RNA polymerase
C. Can predominate under selective host population immune pressures
D. Reassortment between human and animal or avian reservoirs
E. Can involve genes encoding structural or nonstructural proteins

■ Which of the following agents can be used to prevent RSV pneumonia?

A. Amantadine
B. Vaccine to F protein
C. Oseltamivir
D. Zanamivir
E. Monoclonal antibody

ANSWERS

1(C), **2**(D), **3**(E)

Case Studies put the material in clinical context

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CONTENTS

PREFACE

With this 6th edition, *Sherris Medical Microbiology* enters its fourth decade. We are pleased to welcome new authors, Michael Lagunoff (virology) and Paul Pottinger (antibiotics, parasitology) from the University of Washington; L. Barth Reller (laboratory diagnosis, bacteriology) from Duke University; and Charles R. Sterling (parasitology) from the University of Arizona. Jim Plorde, an author since the first edition, is enjoying a well-deserved rest. 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-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 aspects of the **Disease** (epidemiology, pathogenesis, immunity) the organism causes are explained; the sequence concludes with the **Clinical Aspects** (manifestations, diagnosis, treatment, prevention) of the disease. The opening of each section is marked with an icon and a snapshot of the disease(s) called the **Clinical Capsule,** which is placed at the juncture of the Organism and Disease sections. 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. The **Glossary** gives brief definitions of medical and microbiologic terms which appear throughout the book.

STUDY AIDS

The **marginal notes**, a popular feature since the first edition, are nuggets of information designed as an aid for the student during review. If a marginal note is unfamiliar, the relevant

text is in the paragraph immediately adjacent. The supplementary materials at the end of the book now include two new additions. The first is **Infectious Diseases: Syndromes and Etiologies**, a set of tables which re-sort the material in the rest of the book in a clinical context. Here you will find the common infectious etiologies of the major presentations of infectious diseases whether they are viral, bacterial, fungal, or parasitic. It is hoped these will be of value when the student prepares for case discussions or sees patients. A set of 100 **Practice Questions** is also included. These are in USMLE format and in addition to the ones following the case studies at the end of the organism-oriented chapters in Parts II-V.

For any book, lecture, case study, or other materials aimed at students, 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 5th 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 an intelligent discussion may require using the names and abbreviations of genes, their products, and multiple regulators to tell the complete story. Whenever possible we have tried to tell the story without all the code language. The exciting insights offered by genomics must be tempered by the knowledge that they begin with inferences based on the identification of sequences characteristic for a particular gene. The gene product itself may or may not have been discovered. Here, we have tried to fully describe some of the major genetic mechanisms and refer to them later when the same mechanism reappears with other organisms. For example, *Neisseria gonorrhoeae* is used as an example of genetic mechanisms for antigenic variation in the general chapter on bacterial pathogenesis (Chapter 22), but how it may influence 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 name but also the antigenic formulas of *E coli* and Influenza virus along with their emerging threats. Resistance to antimicrobial agents is a regular topic on the evening news. It 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 confident that the basis for understanding these changes is laid out in the pages of this book.

Kenneth J. Ryan
C. George Ray
Editors

PART I

Infection

C. George Ray,
L. Barth Reller, and
Kenneth J.Ryan

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CHAPTER 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

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

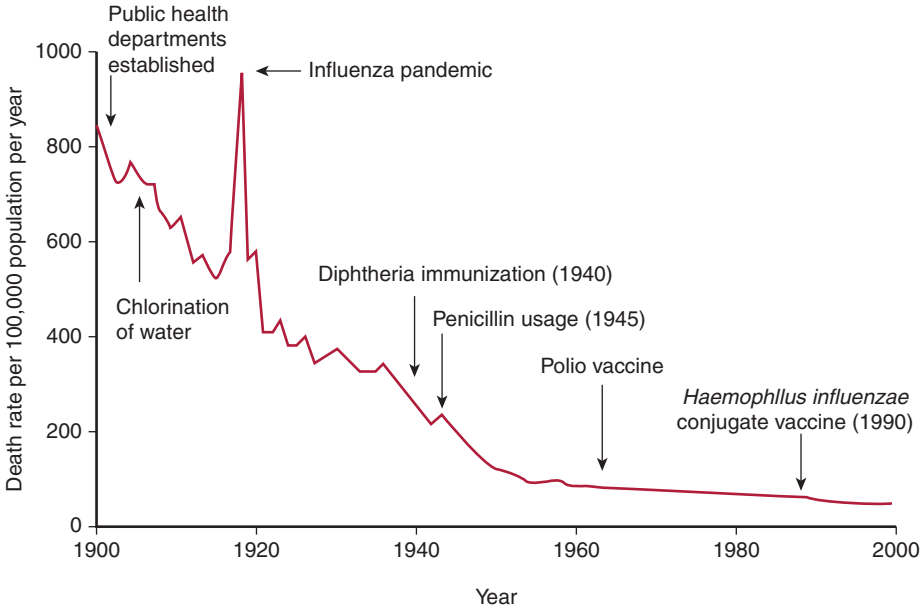

FIGURE 1–1. Death rates for infectious disease in the United States in the 20th century. Note the steady decline in death rates related to the introduction of public health, immunization, and antimicrobial interventions.

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 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.

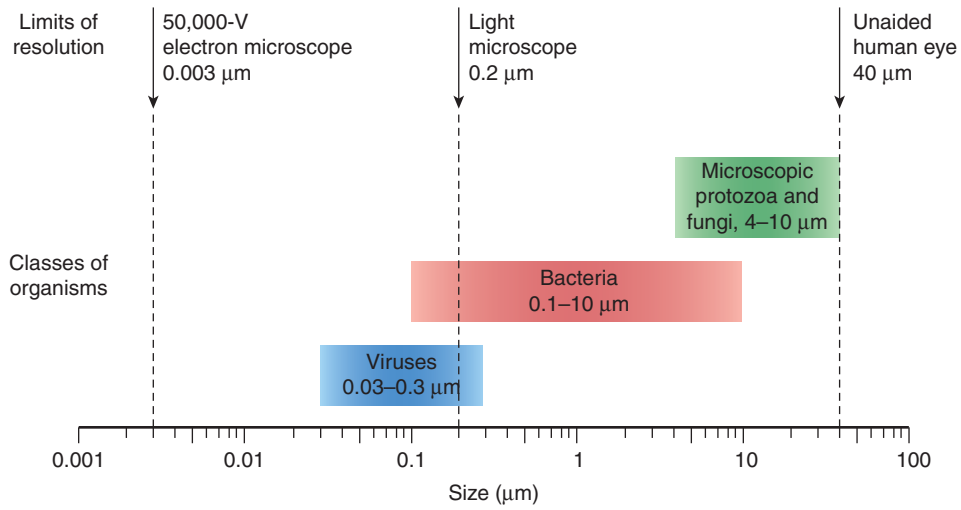

FIGURE 1–2. Relative size of microorganisms.

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.

Products of microbes contribute to the atmosphere

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).

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[b]	No	No/yes

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

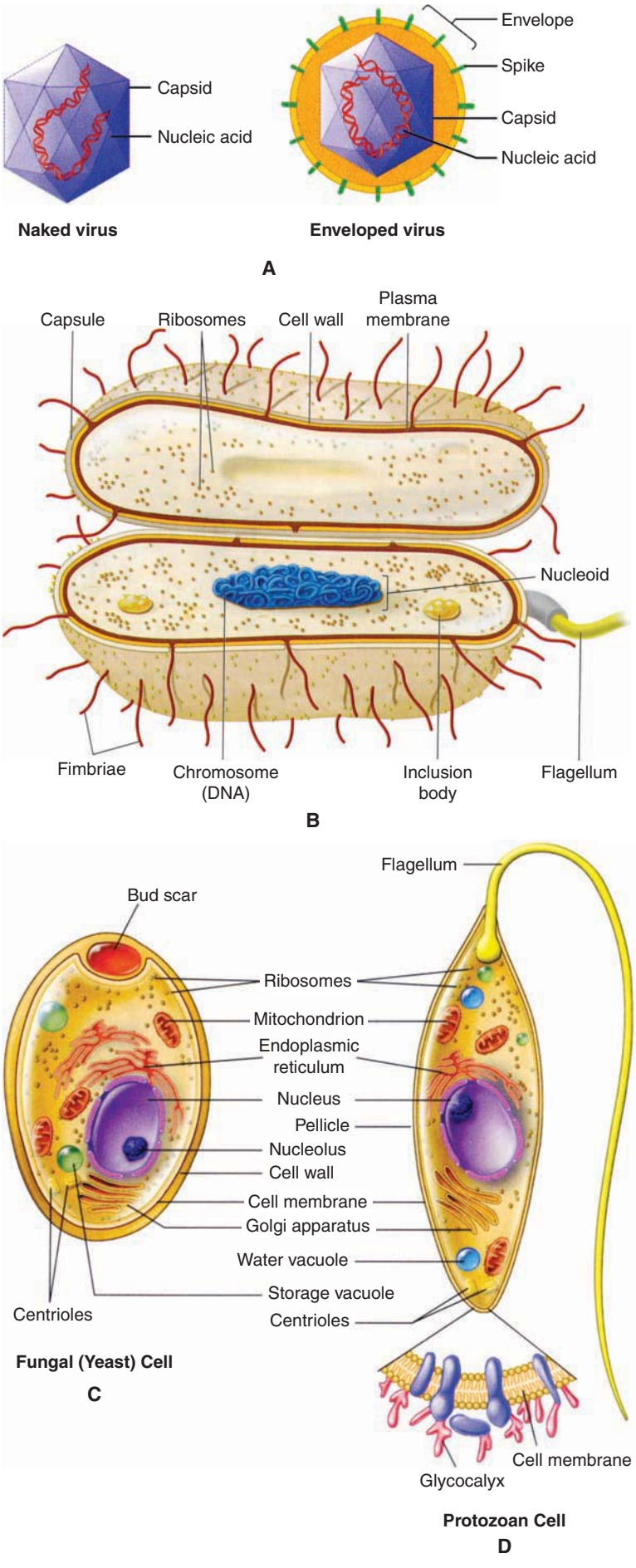

FIGURE 1–3. Infectious agents. **A.** Virus. **B.** Bacterium. **C.** Fungus. **D.** Parasite. (Reproduced with permission from Willey JM: *Prescott, Harley, & Klein's Microbiology*, 7th edition. McGraw-Hill, 2008.)

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 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

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

Yeasts and molds are surrounded by cell wall

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.

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 as we do human cells. This population formerly called the normal flora is now referred to as our **microbiota.** 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. 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.

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 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 potentially pathogenic organisms 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 impossible to determine in advance.

Flora may stay for short or extended periods

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

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,
Epistle to a Godson

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.

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 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