Kenneth J. Ryan / C. George Ray

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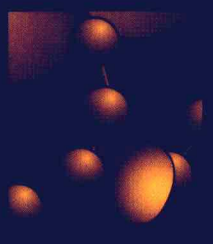
Sherris MEDICAL MICROBIOLOGY

An Introduction to Infectious Diseases




4TH EDITION

SHERRIS MEDICAL MICROBIOLOGY

AN INTRODUCTION TO INFECTIOUS DISEASES

KENNETH J. RYAN, MD
C. GEORGE RAY, MD

EDITORS

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Dedication

To Fritz[a]

[a] Fritz D. Schoenknecht, MD, American microbiologist (1931–1996). Your wit, intellect, music, and twinkle-eyed warnings remain a cherished part of our lives.

PREFACE

With this fourth edition, *Sherris Medical Microbiology,* which began almost two decades ago as *Medical Microbiology* (1984), retains the same team as the third edition with some redistribution in assignments. The most significant of these is the decision of George Ray to join Ken Ryan as editor. John Sherris continues to act as an advisor to all of us.

The goal of *Sherris Medical Microbiology* remains unchanged from that of the first edition. 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. The organization is the same as the third edition with basic topics followed by chapters on the major bacterial, viral, fungal, and parasitic pathogens. We have tried to strengthen the pathogen presentation style introduced in the third edition. For each virus, bacterium, fungus, or parasite, the most important features of the organism (structure, metabolism, genetics), the disease (epidemiology, pathogenesis, immunity), and the clinical aspects (manifestations, diagnosis, treatment, prevention) are placed in distinct sections and in the same order. The opening to each of these sections is now marked by an icon for the organism  , disease  , or clinical aspects  . At the juncture between the organism and disease sections, a new feature, the Clinical Capsule, has been introduced. This brief snapshot of the disease is intended to orient the first-time reader before they dive into discussions of pathogenic mechanisms. Fourteen brief chapters at the end summarize the relevant clinical, diagnostic, and therapeutic information into the most common clinical infectious syndromes without the addition of new material. It is hoped that these chapters will be of particular value when the student prepares for case discussions or sees patients.

In *Sherris Medical Microbiology,* the emphasis is on the text narrative, which is designed to be read comprehensively, not as a reference work. In this regard all the pathogenic microorganisms we feel are important are included at a level of detail relevant for medical students. Any added detail in tables and figures is for example or explanation and not intended to be learned. Marginal notations throughout the text have been revised to capsulize major points as an aid for the student during review. A student scanning the red marginal notes will encounter all the major points in a chapter. If a note looks unfamiliar, the relevant text is immediately adjacent.

An overview chapter on the immune response to infection is included for continuity, but it is assumed this subject will be covered by one of the many excellent immunology

texts available. The chapter on dental microbiology has been updated to serve the needs of dental students.

Much new material has been included, but in order to keep the student from being overwhelmed, older or less important information has been deleted to keep the size of this book approximately the same as the previous edition. As a rule of thumb, material on classic microbial structures, toxins, and the like has been trimmed unless its role in disease will be explained in the following sections. At the same time, we have tried not to eliminate detail to the point of becoming synoptic and uninteresting. For example, adequate explanation of the pathogenesis of an infectious disease may require discussion of the roles played by multiple proteins, genes, and regulators. Where these features form a coherent picture we have tried to tell the complete story, particularly if it is instructive as a general principle. When details such as the names of proteins and genes have been placed in parentheses, it is a sign the authors feel they need not be memorized.

A saving grace is that our topic is important, dynamic, and fascinating. Who could have predicted that AIDS, which occupied less than a page in the first edition, would in the 1990s become the leading cause of death in young American men and, with this edition, enter a period of drug suppression and hope? Gastritis and ulcers attributed to stress in the past are now being cured by antimicrobial therapy directed against *Helicobacter pylori,* but this bacterium has now been officially declared a carcinogen due to additional links with gastric cancer. Just as we were about to hit the presses, an apparently new infectious disease emerged from the Far East in the form of the severe acute respiratory syndrome (SARS). Never a dull moment! These and many other infectious agents and diseases old and new are described and explained in these pages. The student is invited to read them and begin a lifetime of learning in microbiology, infectious diseases, and medicine.

Kenneth J. Ryan
C. George Ray
Editors

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New illustrations for this edition were prepared under the direction of Becky Hainz-Baxter and Alexander Teshin Associates, whose skill and ability to respond creatively to the diverse needs of this text are gratefully acknowledged. Illustrations prepared by Sam Eng for the mycology and parasitology sections in the first edition have been carried over to this edition, as have many of the illustrations prepared for the second edition by Marilyn Pollack-Senura, and for the third edition by Cindy Tinnes.

Finally, we wish to acknowledge our students, past and present, who provide the stimulation for continuation of this work, and our families who provide the encouragement and support that make it possible.

CONTENTS

CHAPTER 1

Overview

KENNETH J. RYAN

> 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 antimicrobials changed this fact (Fig 1-1), but only for the nations that could afford the improvements. As the 21st century begins, the world is divided into countries in which heart attacks, cancer, and stroke have surpassed infection as a cause of death and those in which infection is still the leading cause of death.

A new uneasiness that is part evolutionary, part discovery, and part diabolic has taken hold. Infectious agents once conquered have demonstrated resistance to established therapy, such as multiresistant *Mycobacterium tuberculosis,* and new diseases, such as acquired immunodeficiency syndrome (AIDS), have emerged. The spectrum of infection has widened, with discoveries that organisms once 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, 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

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

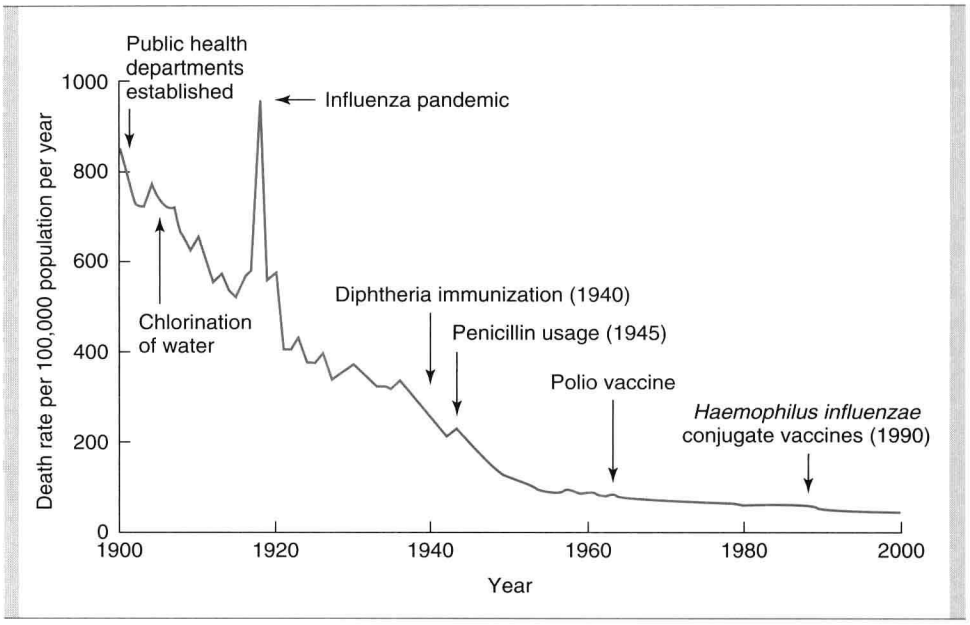

FIGURE 1–1
Death rates for infectious disease in the United States in the 20th century. Note the steady decline in death rates related to the introduction of public health, immunization, and antimicrobial interventions.

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 where it is possible to know not only the genes involved but 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 antimicrobics to counter these chemotherapeutic agents.

THE INFECTIOUS AGENTS: THE MICROBIAL WORLD

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, some bacteria) and others have macroscopic forms (eg, fungal molds, parasitic worms).

Microbes are small

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, and some can survive and multiply in hot springs at temperatures above 75°C.

Most play benign roles in the environment

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.

Products of microbes contribute to the atmosphere

TABLE 1–1

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

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.

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 eukaryotic cell plan of our own cells. 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 their cell plan is prokaryotic (Table 1–1) and lacks the organelles of eukaryotic cells. Viruses have a genome and some structural elements but must take over the machinery of another living cell (eukaryotic or prokaryotic) in order to replicate.

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, but never both. 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 many thousands of viral particles, which can be assembled almost simultaneously under the direction of the viral nucleic acid. With many viruses, cell death and infection of other cells by the newly formed viruses result. Sometimes, viral reproduction and cell reproduction proceed

Replication is by control of the host cell metabolic machinery

Some integrate into the genome

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.

Bacteria

Bacteria are the smallest (0.1 to 10 μm) 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. In fact, most bacteria are about 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 a day. The Archaebacteria differ radically from other bacteria in structure and metabolic processes; they 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 to 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. 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

Parasites

Parasites are the most diverse of all microorganisms. They range from unicellular amoebas of 10 to 12 μm to multicellular tapeworms 1 meter in length. The individual cell plan is eukaryotic, but the organisms such as worms are highly differentiated and have their own organ systems. Most of the 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.

Range from tiny amoebas to meter-long worms

INFECTIOUS DISEASE

Of the thousands of species of viruses, bacteria, fungi, and parasites, only a tiny portion are involved in disease of any kind. These are called pathogens. There are plant pathogens, animal pathogens, fish pathogens, as well as the subject of this book, human pathogens. Among pathogens, there are degrees of potency called virulence, which sometimes makes the dividing line between benign and virulent microorganisms difficult to draw. Many bacteria and some fungi are part of a normal flora that colonizes the skin and mucosal surfaces of the body, where most of the time they appear to do no harm. In extreme circumstances, a few of these organisms are associated with mild disease, making them low-virulence pathogens at best. Other pathogens are virtually always associated with disease of varying severity. *Yersinia pestis,* the cause of plague, causes fulminant disease and death in 50 to 75% of individuals who come in contact with it. 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

Pathogens are rare

Virulence varies greatly

how a pathogen causes disease, the better they will be prepared to intervene and help their patients.

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 data analysis alone determined how streptococcal puerperal fever was transmitted. He even devised a means to prevent it decades before the organism itself was discovered (see Chapter 72). Since then each organism has built its own profile of vital statistics. Some agents are transmitted by the air, others by food, others by insects, and some spread by the person-to-person route. 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 are crucial to understanding the disease. It is also essential to discovering the emergence of "new" diseases, whether they are truly new (AIDS) or just undiscovered (Legionnaires' disease). Solving mysterious outbreaks or recognizing new epidemiologic patterns have usually 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. In previous centuries, epidemics, sometimes caused by the introduction of new organisms of unusual virulence, often resulted in high morbidity and mortality. The possibility of recurrence of old pandemic infections remains, and, in the case of AIDS, we are currently witnessing a new and extended pandemic infection. 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 (cholera). The efficiency of the food industry has sometimes backfired when the distributed products are contaminated with infectious agents. The well-publicized outbreaks of hamburger-associated *Escherichia coli* O157:H7 infection are an example. The nature of massive meatpacking facilities allowed organisms from infected cattle on isolated farms to be mixed with other meat and distributed rapidly and widely. By the time outbreaks are recognized, cases of disease are widespread, and tons of meat must be recalled. In simpler times, local outbreaks from the same source would 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 of animals or animal products with humans. Under natural conditions, it produces a nasty but usually 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 so long ago that most of the population has never been exposed or immunized and are thus vulnerable to its reintroduction. We do not know if infectious bioterrorism will work on the scale contemplated by its perpetrators, but in the case of anthrax we do know that sophisticated systems have been designed to attempt it. We hope that we will never learn whether bioterrorism will work on a large scale.

Anthrax and smallpox are new bioterrorism threats

PATHOGENESIS

Once 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 pathogen is very complicated. Multiple features, called virulence factors, are required to persist, cause disease, and escape to repeat the cycle.

Pathogenicity is multifactorial

The variations are many, but the mechanisms used by many pathogens are now being dissected at the molecular level.

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, they are usually exploiting some molecule important for essential functions of the cell. For some toxin-producing pathogens, this attachment is all they need 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 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.

Pathogens have molecules that bind to host cells

Invasion requires adaptation to new environments

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 gases. 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. Cholera is caused by a bacterial toxin, which causes intestinal cells to hypersecrete water and electrolytes leading to diarrhea. 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.

Inflammation alone can result in injury

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 8) 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 evade the immune response. Some pathogens attack the immune effector cells, and others undergo changes that confound 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 humoral (antibody) or cell-mediated immunity (CMI). 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 above for gonorrhea. The antigen against which protective antibodies are directed (M protein) is stable but naturally exists in over 80 types. Each requires its own specific antibody. Knowing the molecule against which the protective immune response is directed is particularly important for devising preventive vaccines.

Antibody or cell-mediated mechanisms may be protective

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

Body system(s) involved dictate clinical findings