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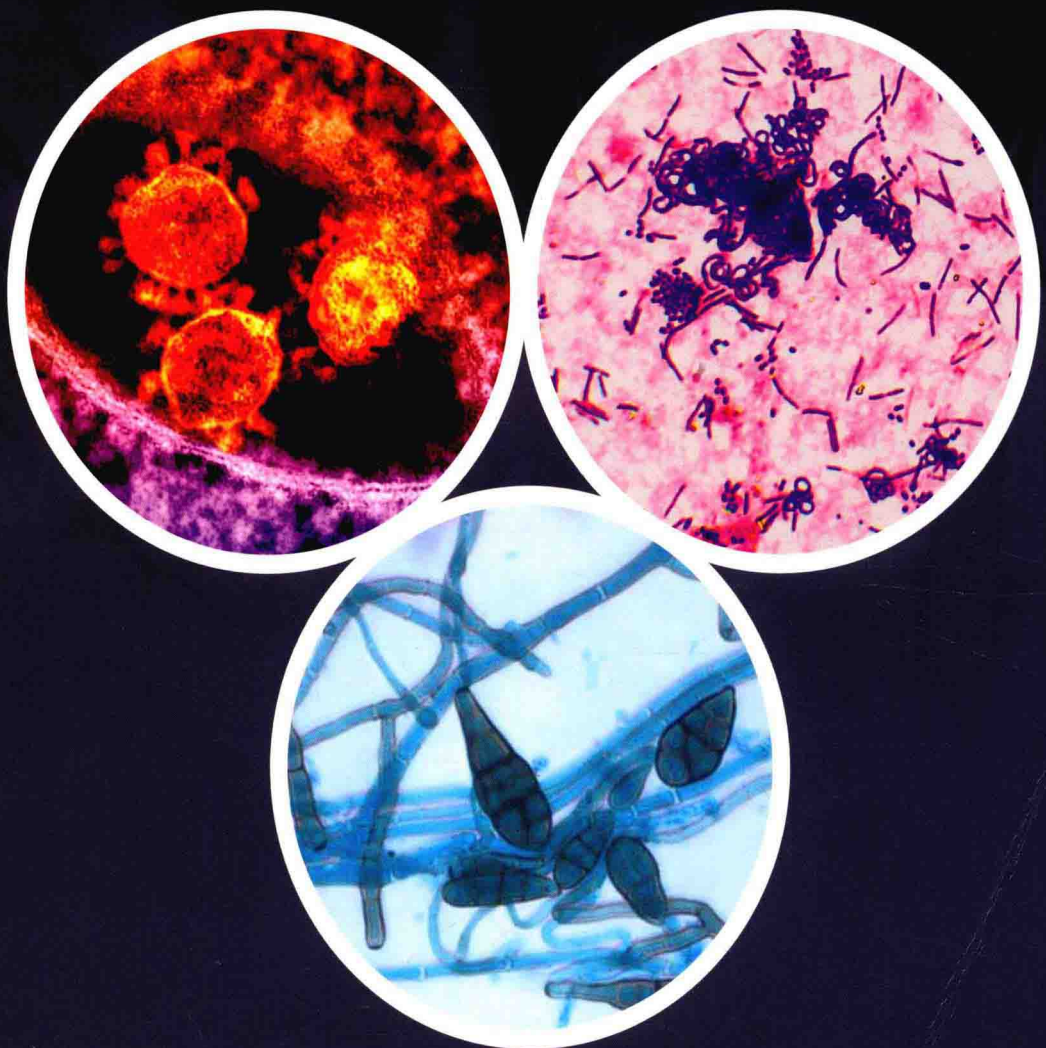

MEDICAL MICROBIOLOGY

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8e

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8TH EDITION

MEDICAL MICROBIOLOGY

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PREFACE

Our knowledge about microbiology and immunology is constantly growing, and by building a good foundation of understanding in the beginning, it will be much easier to understand the advances of the future.

Medical microbiology can be a bewildering field for the novice. We are faced with many questions when learning microbiology: How do I learn all the names? Which infectious agents cause which diseases? Why? When? Who is at risk? Is there a treatment? However, all these concerns can be reduced to one essential question: **What information do I need to know that will help me understand how to diagnose and treat an infected patient?**

Certainly, there are a number of theories about what a student needs to know and how to teach it, which supposedly validates the plethora of microbiology textbooks that have flooded the bookstores in recent years. Although we do not claim to have the one right approach to teaching medical microbiology (there is truly no one perfect approach to medical education), we have founded the revisions of this textbook on our experience gained through years of teaching medical students, residents, and infectious disease fellows, as well as on the work devoted to the seven previous editions. We have tried to present the basic concepts of medical microbiology clearly and succinctly in a manner that addresses different types of learners. The text is written in a straightforward manner with, it is hoped, uncomplicated explanations of difficult concepts. In this edition, we challenged ourselves to improve the learning experience even more. We are using the new technology on StudentConsult.com (e-version) to enhance access to the material. New to this edition, **chapter summaries** and learning aids are placed at the beginning of each of the microbe chapters, and on the e-version these are keyed to the appropriate sections in the chapter. In addition, many of the **figures** are enhanced to assist learning. **Details** are summarized in tabular format rather than in lengthy text, and there are colorful illustrations for the visual learner. **Clinical Cases** provide the relevance that puts reality into the basic science. **Important points** are emphasized in **boxes** to aid students, especially in their review, and the **study questions,** including Clinical Cases, address relevant aspects of each chapter. Each section (bacteria, viruses, fungi, parasites) begins with a chapter that summarizes microbial diseases, and this also provides **review material.**

Our understanding of microbiology and immunology is rapidly expanding, with new and exciting discoveries in all areas. We used our experience as authors and teachers to choose the most important information and explanations for inclusion in this textbook. Each chapter has been carefully updated and expanded to include new, medically relevant discoveries. In each of these chapters, we have attempted to present the material that we believe will help the student gain an interest in as well as a clear understanding of the significance of the individual microbes and their diseases.

With each edition of *Medical Microbiology* we refine and update our presentation. There are many changes to the eighth edition, both in the print and e-versions of the book. The book starts with a general introduction to microbiology and new chapters on the human microbiome and epidemiology of infectious diseases. The human microbiome (that is, the normal population of organisms that populate our bodies) can now be considered as another organ system with 10 times as many cells as human cells. This microbiota educates the immune response, helps digest our food, and protects us against more harmful microbes. Additional chapters in the introductory section introduce the techniques used by microbiologists and immunologists and are followed by chapters on the functional immune system. The immune cells and tissues are introduced, followed by an enhanced chapter on innate immunity and updated chapters on antigen-specific immunity, antimicrobial immunity, and vaccines. The sections on bacteria, viruses, fungi, and parasites have also been reorganized. Each section is introduced by the relevant basic science chapters and then the specific microbial disease summary chapter before proceeding into descriptions of the individual microbes, "the bug parade." Each chapter on the specific microbes begins with a summary (including trigger words), which is keyed to the appropriate part of the chapter in the e-version. As in previous editions, there are many summary boxes, tables, clinical photographs, and original clinical cases. **Clinical Cases** are included because we believe students will find them particularly interesting and instructive, and they are a very efficient way to present this complex subject. Each chapter in the "bug parade" is introduced by relevant questions to excite students and orient them as they explore the chapter. Finally, students are provided with access to the new Student Consult website, which provides links to additional reference materials, clinical photographs, animations (including new animations), and answers to the introductory and summary questions of each chapter. Many of the figures are presented in step-by-step manner to facilitate learning. A very important feature on the website is access to more than 200 **practice exam questions** that will help students assess their mastery of the subject matter and prepare for their course and licensure exams. In essence, this edition provides an understandable

text, details, questions, examples, and a review book all in one.

• To Our Future Colleagues: The Students

On first impression, success in medical microbiology would appear to depend on memorization. Microbiology may seem to consist of only innumerable facts, but there is also a logic to microbiology and immunology. Like a medical detective, the first step is to know your villain. Microbes establish a niche in our bodies; some are beneficial and help us to digest our food and educate our immune system, while others may cause disease. Their ability to cause disease, and the disease that may result, depend on how the microbe interacts with the host and the innate and immune protective responses that ensue.

There are many ways to approach learning microbiology and immunology, but ultimately the more you interact with the material using multiple senses, the better you will build memory and learn. A **fun** and **effective** approach to learning is to **think like a physician and treat each microbe and its diseases as if it were an infection in your patient. Create a patient for each microbial infection, and compare and contrast the different patients.** Perform role-playing and ask the seven basic questions as you approach this material: Who? Where? When? Why? Which? What? and How? For example: Who is at risk for disease? Where does this organism cause infections (both body site and geographic area)? When is isolation of this organism important? Why is this organism able to cause disease? Which species and genera are medically important? What diagnostic tests should be performed? How is this infection managed? Each organism that is encountered can be systematically examined. Use the following acronym to create a clinical case and learn the essential information for each microbe: **DIVIRDEPT.** How does the microbial ***d***isease present in the patient and the differential diagnosis? How would you confirm the diagnosis and ***i***dentify the microbial cause of disease? What are the ***v***irulence properties of the organism that cause the disease? What are the helpful and harmful aspects of the ***i***nnate and ***i***mmune response to the infection? What are the specific conditions or mechanisms for ***r***eplicating the microbe? What are all the ***d***isease characteristics and consequences? What is the ***e***pidemiology of infection? How can you ***p***revent its disease? What is its ***t***reatment? Answering the DIVIRDEPT questions will require that you jump around in the chapter to find the information, but this will help you learn the material. For each of the microbes, learn three to five words or phrases that are associated with the microbe—words that will stimulate your memory (**trigger words,** provided in the new chapter summary) and organize the diverse facts into a logical picture. Develop **alternative associations.** For example, this textbook presents organisms in the systematic taxonomic structure (frequently called a "bug parade," but which the authors think is the easiest way to introduce the organisms). Take a given virulence property (e.g., toxin production) or type of disease (e.g., meningitis) and list the organisms that share this property. Pretend that an imaginary patient is infected with a specific agent and create the case history. Explain the diagnosis to your imaginary patient and also to your future professional colleagues. In other words, do not simply attempt to memorize page after page of facts; rather, use techniques that stimulate your mind and challenge your understanding of the facts presented throughout the text and **it will be more fun.** Use the summary chapter at the beginning of each organism section to **review** and help refine your "differential diagnosis" and classify organisms into logical "boxes." Get familiar with the textbook and its bonus materials and you will not only learn the material but also have a review book to work from in the future.

No textbook of this magnitude would be successful without the contributions of numerous individuals. We are grateful for the valuable professional help and support provided by the staff at Elsevier, particularly Jim Merritt, Katie DeFrancesco, and Rhoda Howell. We also want to thank the many students and professional colleagues who have offered their advice and constructive criticism throughout the development of this eighth edition of *Medical Microbiology.*

Patrick R. Murray, PhD; Ken S. Rosenthal, PhD; and Michael A. Pfaller, MD

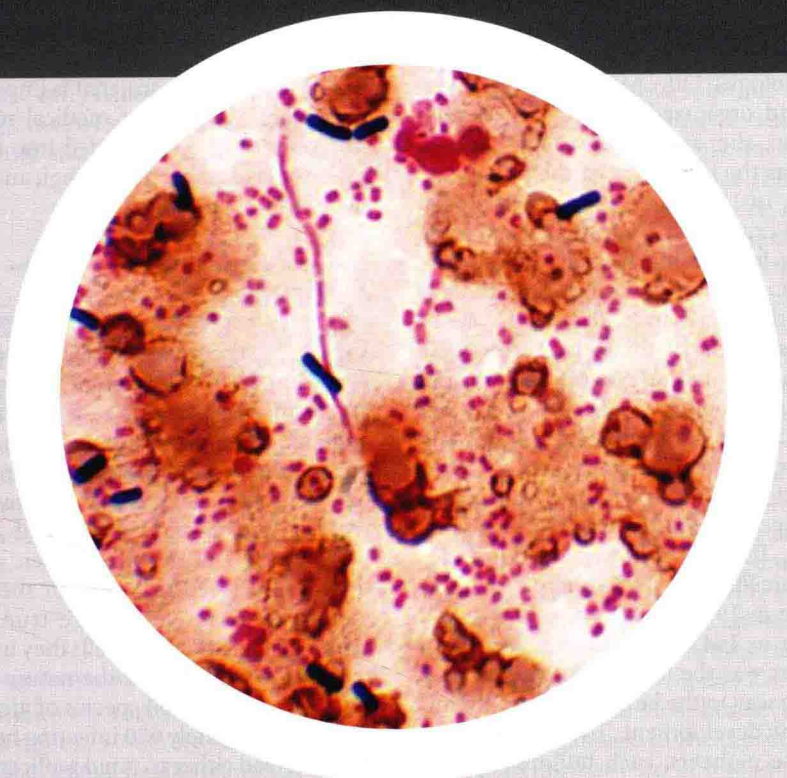
CONTENTS

SECTION 6
Mycology

SECTION 7
Parasitology

SECTION

1



INTRODUCTION

CHAPTER

1 INTRODUCTION TO MEDICAL MICROBIOLOGY

Imagine the excitement felt by the Dutch biologist Anton van Leeuwenhoek in 1674 as he peered through his carefully ground microscopic lenses at a drop of water and discovered a world of millions of tiny "animalcules." Almost 100 years later, the Danish biologist Otto Müller extended van Leeuwenhoek's studies and organized bacteria into genera and species according to the classification methods of Carolus Linnaeus. This was the beginning of the taxonomic classification of microbes. In 1840, the German pathologist Friedrich Henle proposed criteria for proving that microorganisms were responsible for causing human disease (the "germ theory" of disease). Robert Koch and Louis Pasteur confirmed this theory in the 1870s and 1880s with a series of elegant experiments proving that microorganisms were responsible for causing anthrax, rabies, plague, cholera, and tuberculosis. Other brilliant scientists went on to prove that a diverse collection of microbes was responsible for causing human disease. The era of chemotherapy began in 1910, when the German chemist Paul Ehrlich discovered the first antibacterial agent, a compound effective against the spirochete that causes syphilis. This was followed by Alexander Fleming's discovery of penicillin in 1928, Gerhard Domagk's discovery of sulfanilamide in 1935, and Selman Waksman's discovery of streptomycin in 1943. In 1946, the American microbiologist John Enders was the first to cultivate viruses in cell cultures, leading the way to the large-scale production of virus cultures for vaccine development. Thousands of scientists have followed these pioneers, each building on the foundation established by his or her predecessors, and each adding an observation that expanded our understanding of microbes and their role in disease.

Our knowledge of microbiology is now undergoing a remarkable transformation founded in the rapid technologic advances in genome analysis. The Human Genome Project was a multinational program that concluded in 2005 with the comprehensive sequencing of the human genome. The techniques developed for this program have rapidly moved into the research and clinical laboratories, leading to microbial sequencing and revealing previously unappreciated insights about pathogenic properties of organisms, taxonomic relationships, and functional attributes of the endogenous microbial population. Clearly, we are at the early stages of novel approaches to diagnostics and therapeutics based on the monitoring and manipulations of this population (the microbiome).

The world that van Leeuwenhoek discovered was complex, consisting of protozoa and bacteria of all shapes and sizes. However, the complexity of medical microbiology we know today rivals the limits of the imagination. We now know that there are thousands of different types of microbes that live in, on, and around us—and hundreds that cause serious human diseases. To understand this information and organize it in a useful manner, it is important to understand some of the basic aspects of medical microbiology. To start, the microbes can be subdivided into the following four general groups: viruses, bacteria, fungi, and parasites, each having its own level of complexity.

• Viruses

Viruses are the smallest infectious particles, ranging in diameter from 18 to 600 nanometers (most viruses are < 200 nm and cannot be seen with a light microscope). Viruses typically contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) but not both; however, some viral-like particles do not contain any detectable nucleic acids (e.g., prions), whereas the recently discovered Mimivirus contains both RNA and DNA. The viral nucleic acids required for replication are enclosed in a protein shell with or without a lipid membrane coat. Viruses are true parasites, requiring host cells for replication. The cells they infect and the host response to the infection dictate the nature of the clinical manifestation. More than 2000 species of viruses have been described, with approximately 650 infecting humans and animals. Infection can lead either to rapid replication and destruction of the cell or to a long-term chronic relationship with possible integration of the viral genetic information into the host genome. The factors that determine which of these takes place are only partially understood. For example, infection with the human immunodeficiency virus, the etiologic agent of the acquired immunodeficiency syndrome (AIDS), can result in the latent infection of CD4 lymphocytes or the active replication and destruction of these immunologically important cells. Likewise, infection can spread to other susceptible cells, such as the microglial cells of the brain, resulting in the neurologic manifestations of AIDS. The virus determines the disease and can range from the common cold to gastroenteritis to fatal catastrophes such as rabies, Ebola, smallpox, or AIDS.

• Bacteria

Bacteria are relatively simple in structure. They are **prokaryotic** organisms—simple unicellular organisms with no nuclear membrane, mitochondria, Golgi bodies, or

endoplasmic reticulum—that reproduce by asexual division. The bacterial cell wall is complex, consisting of one of two basic forms: a gram-positive cell wall with a thick peptidoglycan layer, and a gram-negative cell wall with a thin peptidoglycan layer and an overlying outer membrane. Some bacteria lack this cell wall structure and compensate by surviving only inside host cells or in a hypertonic environment. The size (1 to 20 μm or larger), shape (spheres, rods, spirals), and spacial arrangement (single cells, chains, clusters) of the cells are used for the preliminary classification of bacteria, and the phenotypic and genotypic properties of the bacteria form the basis for the definitive classification. The human body is inhabited by thousands of different bacterial species—some living transiently, others in a permanent parasitic relationship. Likewise, the environment that surrounds us, including the air we breathe, water we drink, and food we eat, is populated with bacteria, many of which are relatively avirulent and some of which are capable of producing life-threatening disease. Disease can result from the toxic effects of bacterial products (e.g., toxins) or when bacteria invade normally sterile body tissues and fluids.

• Fungi

In contrast to bacteria, the cellular structure of fungi is more complex. These are **eukaryotic** organisms that contain a well-defined nucleus, mitochondria, Golgi bodies, and endoplasmic reticulum. Fungi can exist either in a unicellular form **(yeast)** that can replicate asexually or in a filamentous form **(mold)** that can replicate asexually and sexually. Most fungi exist as either yeasts or molds; however, some fungi can assume either morphology. These are known as **dimorphic** fungi and include such organisms as *Histoplasma, Blastomyces,* and *Coccidioides.*

• Parasites

Parasites are the most complex microbes. Although all parasites are classified as eukaryotic, some are unicellular and others are multicellular. They range in size from tiny protozoa as small as 4 to 5 μm in diameter (the size of some bacteria) to tapeworms that can measure up to 10 meters in length and arthropods (bugs). Indeed, considering the size of some of these parasites, it is hard to imagine how these organisms came to be classified as microbes. Their life cycles are equally complex, with some parasites establishing a permanent relationship with humans and others going through a series of developmental stages in a progression of animal hosts. One of the difficulties confronting students is not only an understanding of the spectrum of diseases caused by parasites but also an appreciation of the epidemiology of these infections, which is vital for developing a differential diagnosis and an approach to the control and prevention of parasitic infections.

• Immunology

It is difficult to discuss human microbiology without also discussing the innate and immune responses to the microbes. Our innate and immune responses evolved to protect us from infection. At the same time, the microbes that live in our bodies as normal flora or disease-causing organisms must be able to withstand or evade these host protections sufficiently long to be able to establish their niche within our bodies or spread to new hosts. The peripheral damage that occurs during the war between the host protections and microbial invaders contributes to or may be the cause of the symptoms of the disease. Ultimately, the innate and immune responses are the best prevention and cure for microbial disease.

• Microbial Disease

One of the most important reasons for studying microbes is to understand the diseases they cause and the ways to control them. Unfortunately, the relationship between many organisms and their diseases is not simple. Specifically, most organisms do not cause a single well-defined disease, although there are certainly ones that do (e.g., *Clostridium tetani* [tetanus], Ebola virus [Ebola], *Plasmodium* species [malaria]). Instead, it is more common for a particular organism to produce many manifestations of disease (e.g., *Staphylococcus aureus*—endocarditis, pneumonia, wound infections, food poisoning) or for many organisms to produce the same disease (e.g., meningitis caused by viruses, bacteria, fungi, and parasites). In addition, relatively few organisms can be classified as always pathogenic, although some do belong in this category (e.g., rabies virus, *Bacillus anthracis, Sporothrix schenckii, Plasmodium* species). Instead, most organisms are able to establish disease only under well-defined circumstances (e.g., introduction of an organism with a potential for causing disease into a normally sterile site such as the brain, lungs, and peritoneal cavity). Some diseases arise when a person is exposed to organisms from external sources. These are known as **exogenous infections,** and examples include diseases caused by influenza virus, *C. tetani, Neisseria gonorrhoeae, Coccidioides immitis,* and *Entamoeba histolytica.* Most human diseases, however, are produced by organisms in the person's own microbial flora that spread to normally sterile body sites where disease can ensue **(endogenous infections).**

The interaction between an organism and the human host is complex. The interaction can result in transient colonization, a long-term symbiotic relationship, or disease. The virulence of the organism, the site of exposure, and the host's ability to respond to the organism determine the outcome of this interaction. Thus the manifestations of disease can range from mild symptoms to organ failure and death. The role of microbial virulence and the host's immunologic response is discussed in depth in subsequent chapters.

The human body is remarkably adapted to controlling exposure to pathogenic microbes. Physical barriers prevent invasion by the microbe; innate responses recognize molecular patterns on the microbial components and activate local defenses and specific adapted immune responses that target the microbe for elimination. Unfortunately, the immune response is often too late or too slow. To improve the human body's ability to prevent infection, the immune system can be augmented either through the passive transfer of antibodies present in immune globulin preparations or through

active immunization with components of the microbes (vaccines). Infections can also be controlled with a variety of chemotherapeutic agents. Unfortunately, microbes can mutate and share genetic information, and those that cannot be recognized by the immune response because of **antigenic variation** or those that are resistant to antibiotics will be selected and will endure. Thus the battle for control between microbe and host continues, with neither side yet able to claim victory (although the microbes have demonstrated remarkable ingenuity). There clearly is no "magic bullet" that has eradicated infectious diseases.

• Diagnostic Microbiology

The clinical microbiology laboratory plays an important role in the diagnosis and control of infectious diseases. However, the ability of the laboratory to perform these functions is limited by the quality of the specimen collected from the patient, the means by which it is transported from the patient to the laboratory, and the techniques used to demonstrate the microbe in the sample. Because most diagnostic tests are based on the ability of the organism to grow, transport conditions must ensure the viability of the pathogen. In addition, the most sophisticated testing protocols are of little value if the collected specimen is not representative of the site of infection. This seems obvious, but many specimens sent to laboratories for analysis are contaminated during collection with the organisms that colonize mucosal surfaces. It is virtually impossible to interpret the testing results with contaminated specimens, because most infections are caused by endogenous organisms.

The laboratory is also able to determine the antimicrobial activity of selected chemotherapeutic agents, although the value of these tests is limited. The laboratory must test only organisms capable of producing disease and only medically relevant antimicrobials. To test all isolated organisms or an indiscriminate empirical selection of drugs can yield misleading results with potentially dangerous consequences. Not only can a patient be treated inappropriately with unnecessary antibiotics, but also the true pathogenic organism may not be recognized among the plethora of organisms isolated and tested. Finally, the in vitro determination of an organism's susceptibility to a variety of antibiotics is only one aspect of a complex picture. The virulence of the organism, site of infection, and patient's ability to respond to the infection influence the host-parasite interaction and must also be considered when planning treatment.

• Summary

It is important to realize that our knowledge of the microbial world is evolving continually. Just as the early microbiologists built their discoveries on the foundations established by their predecessors, we and future generations will continue to discover new microbes, new diseases, and new therapies. The following chapters are intended as a foundation of knowledge that can be used to build your understanding of microbes and their diseases.

CHAPTER

2

HUMAN MICROBIOME IN HEALTH AND DISEASE

Up until the time of birth, the human fetus lives in a remarkably protected and for the most part sterile environment; however, this rapidly changes as the infant is exposed to bacteria, archaea, fungi, and viruses from the mother, other close contacts, and the environment. Over the next few years, communities of organisms (**microbiota** or **normal flora** [Table 2-1]) form on the surfaces of the skin, nares, oral cavity, intestines, and genitourinary tract. The focus of this chapter is to gain an understanding of the role these communities play in the metabolic and immunologic functions of healthy individuals, factors regulating the composition of these communities, and how disruption of these communities can result in disease states.

• Human Microbiome Project

Our current knowledge of the **microbiome** is rooted in the successful completion of the Human Genome Project, a 13-year international effort initiated in 1990 that determined the sequences of the approximately 3 billion nucleotides that make up the 23,000 protein-encoding genes in human DNA. Much like efforts to send a man to the moon, the greatest legacy of this work was the development of technologies and informatic solutions that allow the generation and analysis of tremendous amounts of DNA and messenger RNA sequencing data.

The Human Microbiome Project was a 5-year multinational study to analyze the genetic composition **(microbiome)** of the microbial populations that live in and on healthy adults. To put the complexity of this program into perspective, it is estimated that bacterial cells outnumber human cells in the host by 10:1, and the bacterial population contributes at least 300-fold more protein genes.

The Human Microbiome Project was launched in 2007 with the collection of samples from the nose, mouth, skin, gut, and vagina from healthy adult volunteers. The microbes were identified by sequencing targeted regions of the 16S ribosomal RNA gene, and information about the gene content of the entire population was determined by sequencing the whole genome of a subset of specimens. These analyses showed that there is substantial variation in the species and gene composition for individuals and at different body sites. For example, bacteria colonizing the gut are different from those in the mouth, skin, and other body sites. The body site with the greatest taxonomic and genetic diversity was the intestine, and the vagina was the least complex. Microenvironments such as different regions of the mouth, gut, skin surface, and vagina also had their own unique microbiome (Figure 2-1).

• Core Microbiome

Most individuals share a **core microbiome,** arbitrarily defined as the species that are present at a specific site in 95% or more of individuals. The greatest numbers of shared species are present in the mouth, followed by the nose, intestine, and skin, and the fewest shared species are found in the vagina. Additionally, the small numbers of species that comprise the core microbiome are the most numerous, representing the majority of the total population, whereas the remaining portion of the population **(secondary microbiome)** consists of small numbers of many species that may not be widely shared by individuals. This would imply that the members of the core microbiome are critically important, providing essential functions that must be retained for normal metabolic and immunologic activities, and the functions provided by the secondary microbiome are also critically important but can be provided by a variety of organisms. In other words, although there is tremendous variation of species among individuals, there is less variation in the genetic composition at each site. The **taxonomic diversity** of a population is great, but the functional properties are highly conserved **(functional redundancy)** in microbiomes associated with health. This is not surprising if we consider that the microbiome is a community that exists in a symbiotic relationship with its host, providing needed metabolic functions, stimulating innate immunity, and preventing colonization with unwanted pathogens. Thus interpersonal variations of the microbiome can exist in healthy individuals as long as the needed functions are satisfied.

• Evolution of the Microbiome and Normal Flora

The **normal flora** of a particular site of the body consists of a unique community of core and secondary microbiota that evolved through a symbiotic relationship with the host and a competitive relationship with other species. The host provides a place to colonize, nutrients, and some protection from unwanted species (innate immune responses). The microbes provide needed metabolic functions, stimulate innate and regulatory immunity, and prevent colonization with unwanted pathogens (Figure 2-2). The ability to tolerate

Table 2-1 Glossary of Terms

Term	Definition
Microbiota	Community of microbes that live in and on an individual; can vary substantially between environmental sites and host niches in health and disease
Normal flora	Microbiota
Microbiome	Aggregate collection of microbial genomes in the microbiota
Core microbiome	Commonly shared microbial species among individuals at specific body sites; although typically represented by a limited number of species, these comprise the largest proportion of the microbial population
Secondary microbiome	Microbial species that contribute to the unique diversity of individuals at specific body sites; typically present in proportionately small numbers
Functional redundancy	Required functions (e.g., metabolism of nutrients, regulation of the immune response) that are provided by the diverse members of the microbiota
Taxonomic diversity	The diverse number of species that comprise the microbiota
Prebiotic	Food ingredient that supports the growth of one or more members of the microbiota
Probiotic	Live organism that when ingested is believed to provide benefit to the host

the amount of oxygen or lack thereof (redox state) and the pH and salt concentration, as well as to scavenge essential minerals and harvest and metabolize the available nutrients, determines the numbers and nature of the species that populate a site of the body. Anaerobic or facultative anaerobic bacteria colonize most of the sites of the body because of the lack of oxygen in sites such as the mouth, intestine, and genitourinary tract.

The composition of the microbiota is influenced by personal hygiene (e.g., use of soap, deodorants, mouthwash, skin peels, enemas, vaginal douches), diet, water source, medicines (especially antibiotics), and exposure to environmental toxins. Drinking well water versus chlorinated city water or a diet consisting of more or less fiber, sugar, or fats can select for different intestinal bacteria based on their ability to utilize the essential minerals (e.g., iron) and nutrients. Alteration of the environment with foods or medicines can also alter the microbiota (Figure 2-3). These changes can be acceptable if the core microbiome and critical functional properties of the microbiome are maintained but can result in disease if these functions are lost. Historically, the greatest concern with the use of broad-spectrum antibiotics was the selection of resistant bacteria; however, a greater concern should be the disruption of the microbiome and loss of essential functions.

Of the approximately 200 unique species of bacteria that colonize the gut, most are members of the Actinobacteria (e.g., *Bifidobacterium*), Bacteroidetes (e.g., *Bacteroides*), and Firmicutes (e.g., *Eubacterium, Ruminococcus, Faecalibacterium, Blautia*). Interestingly, the importance of many of these bacteria was not appreciated before gene sequencing was used to identify and quantitate the gut microbiota. Within the colon, some bacteria wage interspecies warfare to establish their niche with bacteriocins (e.g., colicins produced by *Escherichia coli*), other antibacterial proteins, and metabolites that deter other species from growing. These molecules also benefit the host by eliminating invading bacteria including *Salmonella, Shigella, Clostridium difficile, Bacillus cereus,* and other pathogens. The bacteria must also resist antimicrobial peptides and immunoglobulin (Ig)A produced by the host and released into the bowel.

Metabolism of nutrients plays a major role in the symbiotic relationship between the human host and microbe. Bacteria in the human gut are responsible for metabolizing complex carbohydrates (including cellulose) to provide small-chain fatty acids such as acetate, propionate, and butyrate that can be readily transported and used by the cells of our body. These acids also limit the growth of undesirable bacteria. Other bacteria graze on the carbohydrates, the mucins that line the epithelium, or the oils released in our sweat. Bacteroidetes and Firmicutes are more efficient than others at breaking down complex carbohydrates, including plant cell wall compounds (cellulose, pectin, xylan) as well as host-derived carbohydrates, including those attached to the mucins or chondroitin sulfates of the protective mucous layer of the intestine. Increases in the ratio of these bacteria in the gut microbiome can lead to a higher efficiency in storage of the metabolic byproducts. This can be a benefit for malnourished populations or patients with debilitating diseases such as cancer, or can lead to obesity in well-nourished populations.

• Role of the Microbiome in Disease

If the normal microbiome characterizes health, alterations in the microbiome can signify disease, a relationship we are only beginning to understand. In 1884 Robert Koch and Friedrich Loeffler defined the relationship between an organism and infection. The **Koch postulates** were based on the concept of one organism: one disease. Microbiome research has introduced a new concept—disease caused by a community of organisms rather than a single species of bacteria, and the influence extends beyond traditional "infectious" diseases to include immunologic and metabolic disorders such as inflammatory bowel disease, obesity, type 2 diabetes, and celiac disease. We are now at the forefront of a new era of defining infectious diseases.

Disruption of the normal microflora (commonly referred to as **dysbiosis**) can lead to disease by the elimination of needed organisms or allowing the growth of inappropriate bacteria. For example, following exposure to antibiotics and suppression of the intestinal normal flora, *C. difficile* is able to proliferate and express enterotoxins, leading to inflammation of the colon **(antibiotic-associated colitis).** Another disease of the colon, **ulcerative colitis,** is associated with an increased level of bacteria producing mucin-degrading sulfatases, leading to degradation of the protective mucosal lining of the intestinal wall and stimulation of inflammatory immune responses. Individuals with an intestinal microbiota that is more efficient at breaking down complex carbohydrates internalize rather than void these nutrients and are therefore susceptible to **obesity** and a predisposition to metabolic syndromes such as **type 2 diabetes.** Not all patients genetically predisposed to **celiac disease,** an

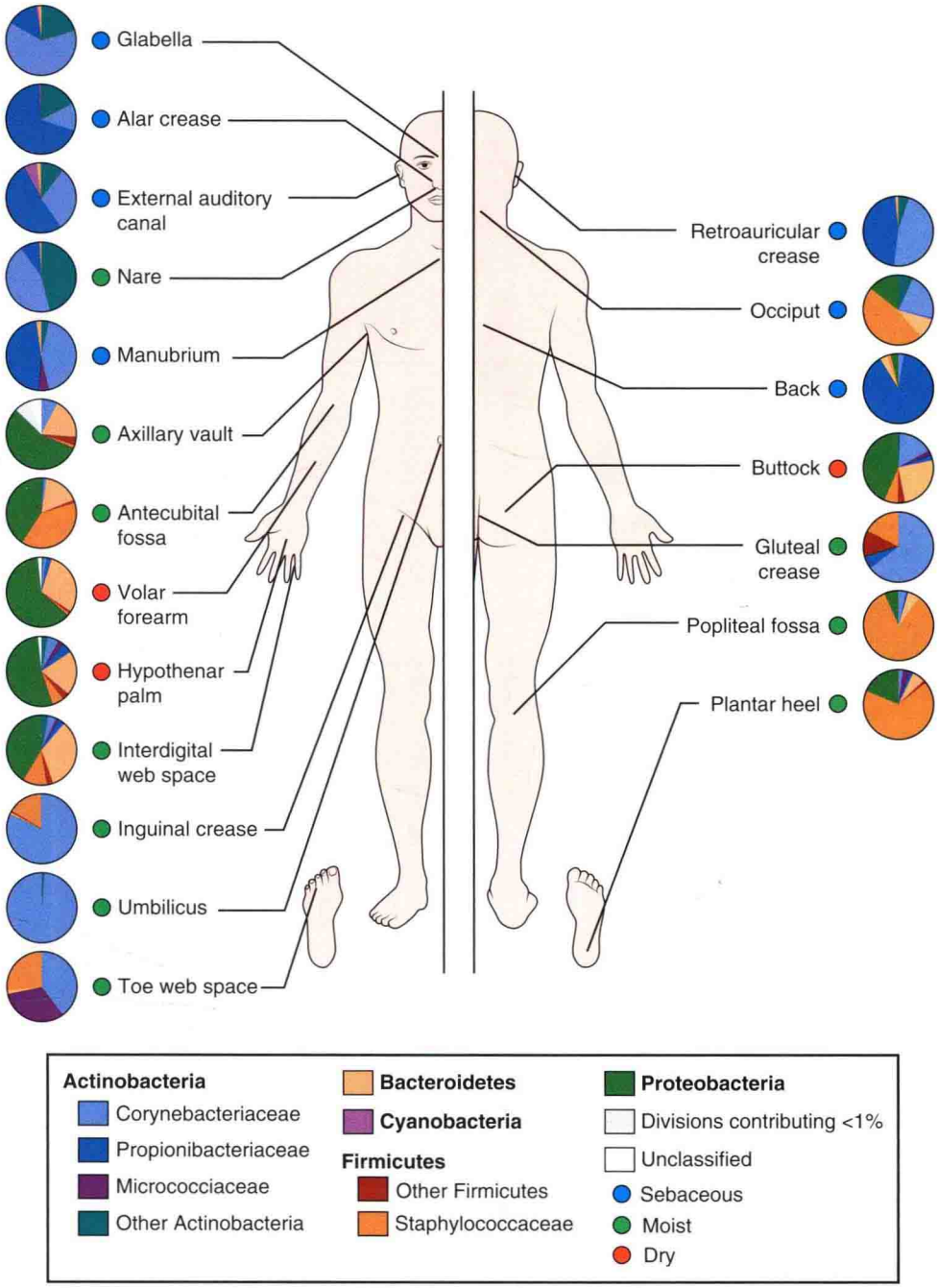


FIGURE 2-1 Topographical distribution of bacteria on skin sites. As at other body sites, the distribution of the skin microbiome is dependent on the microenvironment of the sampled site, such as sebaceous or oily *(blue circles),* moist *(green circles),* and dry, flat surfaces *(red circles).* (From Grice E, Segre J: The skin microbiome, *Nat Rev Microbiol* 9:244–253, 2011.)

immune-mediated enteropathology precipitated by exposure to gluten proteins, are symptomatic. The intestinal microbiota of most individuals is composed of bacteria capable of digesting glutens, which may be sufficient to protect these genetically predisposed individuals. In the absence of these bacteria, disease may occur. Shifts in the skin microbiome are associated with progression to **chronic wound infections** and episodic exacerbations of **atopic dermatitis.** Alteration in the vaginal microbiome from relatively few predominant organisms to a heterogeneous mixed population is associated with the progression to **vaginitis.**

• Diagnostics and Therapeutics

An understanding of the influence of dysbiosis on disease pathology can lead to both advanced diagnostic tests and paths for therapeutic intervention. Just as the presence of *Salmonella* or *Shigella* signifies disease, changes in the diversity and composition of the fecal microflora can also indicate susceptibility to or onset of disease. The most obvious example is *C. difficile* disease—clinical disease is preceded by a depletion of the normal flora owing to antibiotic use. Interestingly, patients with chronic relapsing *C. difficile* infections

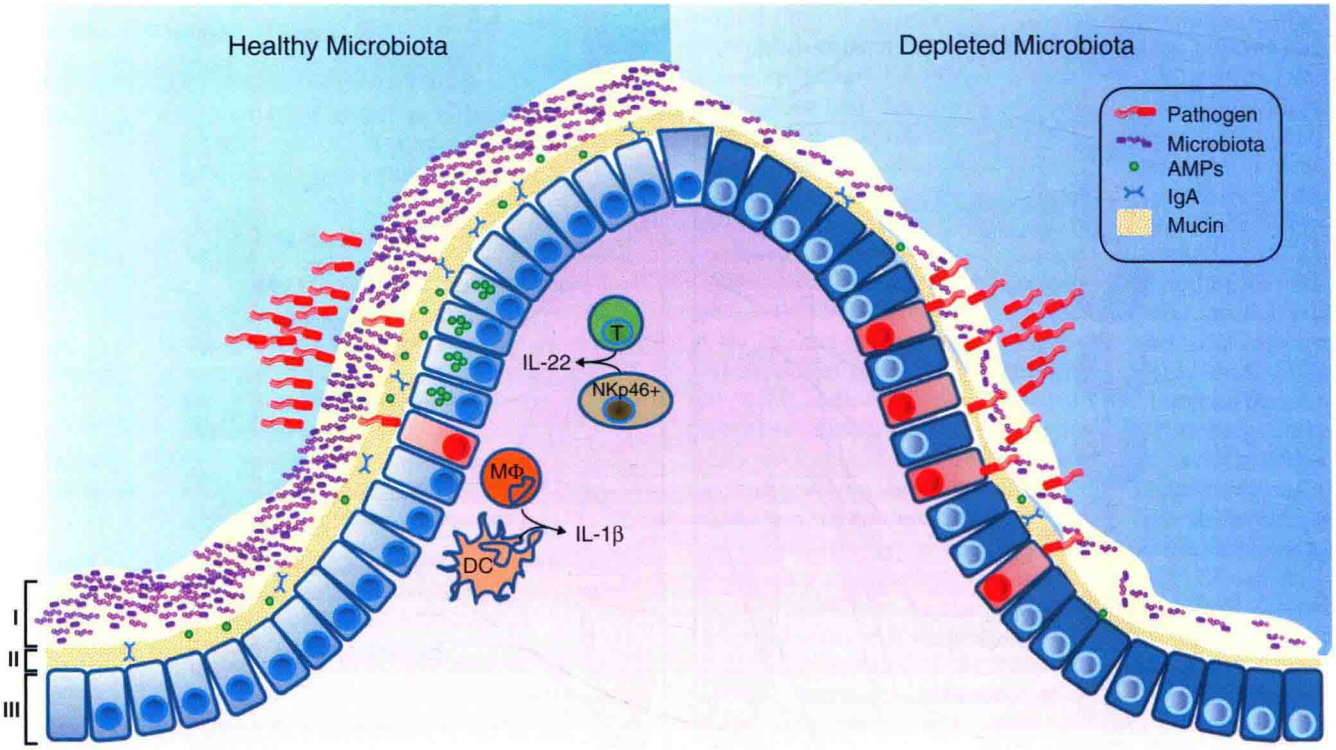


FIGURE 2-2 Intestinal microbiota protection against enteric infections. (I) Saturation of colonization sites and consumption of nutrients limit pathogen access to host tissues; (II) the microbiota prime innate immunity by stimulating mucin production, immunoglobulin *(Ig)*A, and antimicrobial peptides *(AMPs);* and (III) the microbiota stimulate interleukin *(IL)*-22 expression, which increases epithelial resistance, and IL-1β production, which promotes recruitment of inflammatory cells. (From Khosravi A, Mazmanian S: Disruption of the gut microbiome as a risk factor for microbial infections, *Curr Opin Microbiol* 16:221–227, 2013.)

are treated successfully by repopulating (some say **"repoopulating"**) the intestines with stool transplants from a healthy spouse or close relative, or with artificially created stool specimens consisting of a complex mixture of aerobic and anaerobic fecal organisms.

More subtle alterations in the gut microbiome may predict development of diseases such as **necrotizing enterocolitis (NEC),** inflammatory bowel disease, and a predilection for obesity. NEC is a devastating intestinal disease that afflicts preterm infants. Prospectively collected stool samples from infants younger than 29 weeks' gestational age who develop NEC demonstrate a distinct dysbiosis prior to the development of disease. Infants with early-onset disease have a dominance of Firmicutes (predominantly *Staphylococcus*), whereas infants with late-onset NEC have a dominance of Enterobacteriaceae.

The effects of microbiome alterations have also been described for the pathogenesis of inflammatory bowel disease and colorectal cancer. Proliferation of bacteria such as *Akkermansia muciniphila* that produce mucin-degrading sulfatases is responsible for degradation of the intestinal wall lining. Additionally, an increase in members of the anaerobic family Prevotellaceae leads to up-regulation of chemokine-mediated inflammation. Enterotoxigenic *Bacteroides fragilis* can also induce T helper cell–mediated inflammatory responses that are associated with colitis and are a precursor to colonic hyperplasia and colorectal tumors. Finally, *Methanobrevibacter smithii,* a minor member of the gut microbiome, enhances digestion of dietary glycans by *Bacteroides thetaiotaomicron* and other core intestinal bacteria, leading to accumulation of fat.

• Probiotics

Probiotics are mixtures of bacteria or yeast that upon ingestion colonize and proliferate, even temporarily, the intestine. Consumers of probiotics believe they act by rebalancing the microbiome and its functions, such as enhancing digestion of food and modulating the individual's innate and immune response. The most common reason people use over-the-counter probiotics is to promote and maintain regular bowel function and improve tolerance to lactose. Probiotics are commonly gram-positive bacteria (e.g., *Bifidobacterium, Lactobacillus*) and yeasts (e.g., *Saccharomyces*). Many of these microbes are found in ingestible capsules and as food supplements (e.g., yogurt, kefir). Probiotics have been used to treat *C. difficile*–associated diarrhea and inflammatory bowel disease, to provide protection from *Salmonella* and *Helicobacter pylori* disease, as therapy for pediatric atopic dermatitis and autoimmune diseases, and even for reduction in dental caries, although the value of probiotics for many of these conditions is unproven. Although probiotics are safe dietary supplements, not all probiotics are effective and for all people. The species, mixture of species, and dose and viability of the probiotic organisms within a probiotic formulation influence its potency, efficacy, and therapeutic potential. What is clear is that much like the use of complex artificial mixtures of

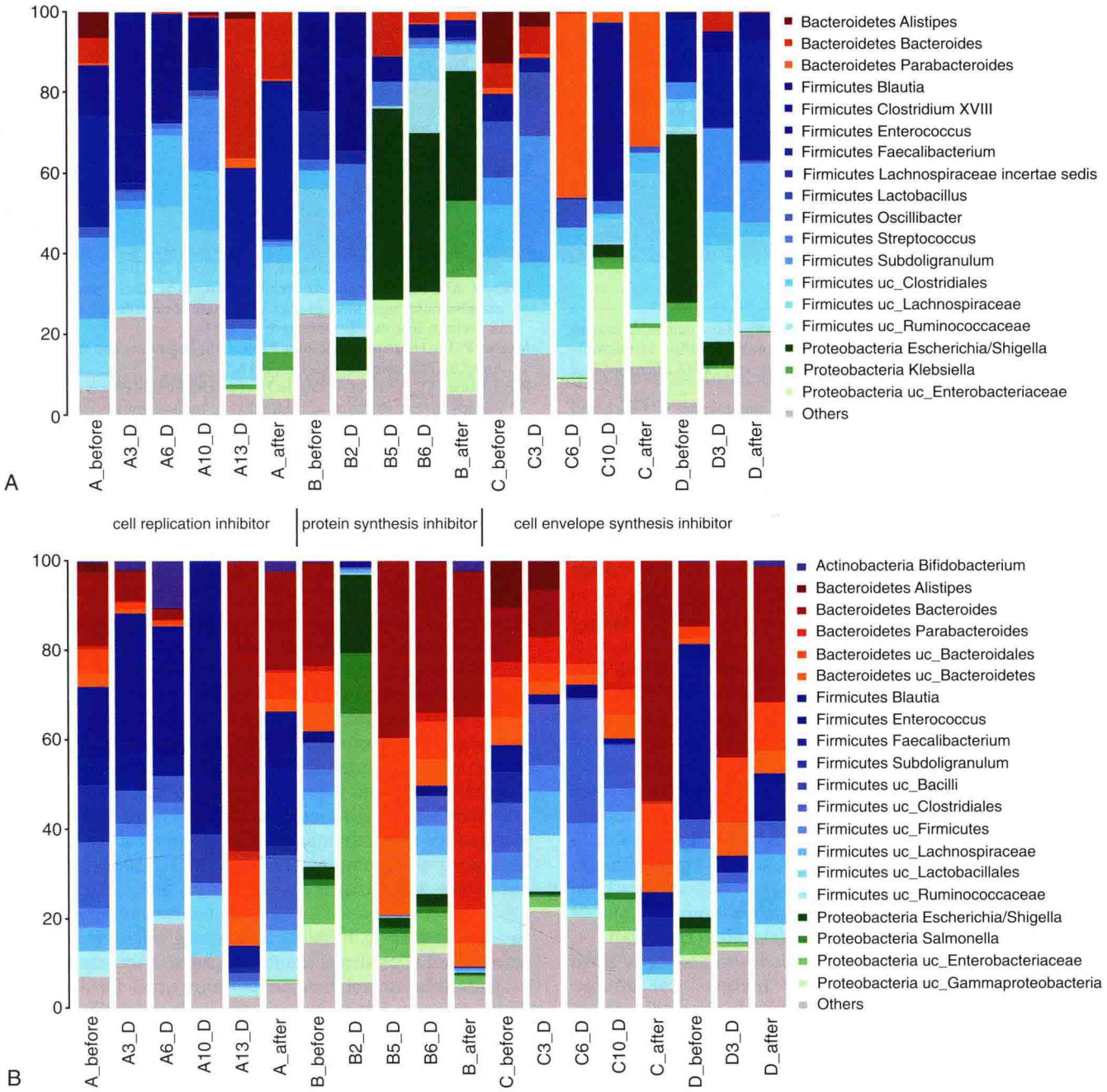


FIGURE 2-3 Effect of antibiotics on the gut microbiota. Fecal samples were collected from four patients treated with antibiotics: patient A, moxifloxacin; patient B, penicillin + clindamycin; patient C, cefazolin followed by ampicillin/sulbactam; patient D, amoxicillin. Fecal samples collected before, during (e.g., 3_D is day 3 of therapy), and after therapy were used to assess the total microbiota. Changes are noted both during therapy and after therapy is discontinued. **A,** Total microbiota (16S rRNA gene). **B,** Metabolically active microbiota (16S rRNA transcripts). (From Perez-Cobas AE, Artacho A, Knecht H, et al: Differential effects of antibiotic therapy on the structure and function of human gut microbiota, *PLoS One* 8:e80201, 2013.)

organisms to treat recurrent *C. difficile* disease, carefully designed "smart probiotics" will likely be an important adjunct to medical therapy in the future.

• Perspective

In the near future, with faster and cheaper DNA sequencing procedures, analysis of a person's microbiome may become a routine diagnostic test for predicting and treating a wide range of diseases. However, a number of questions remain to be resolved, including: can we predict disease in an individual by monitoring changes in the microbiome; which changes are most important—taxonomic or genetic function; can we prevent disease or treat disease by reestablishing a healthy microbiome; can this be done by prescribing specific replacement microbes (e.g., fecal transplant) or with a universal mixture (probiotic); can the use of metabolic

supplements (**prebiotics**) promote a healthy microbiota; and will use of antibiotics be replaced by use of "smart microbiome" therapies? Other questions include: what is the role of the host genome, environmental factors, and our hygienic practices in shaping the microbiome; and what will be the informatic requirements for guiding diagnostics or therapeutics? Regardless of the answers to these and other questions, it is certain that we are witnessing the beginning of a new era of microbiology that can radically change our approach to prediction, diagnosis, and treatment of disease.

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