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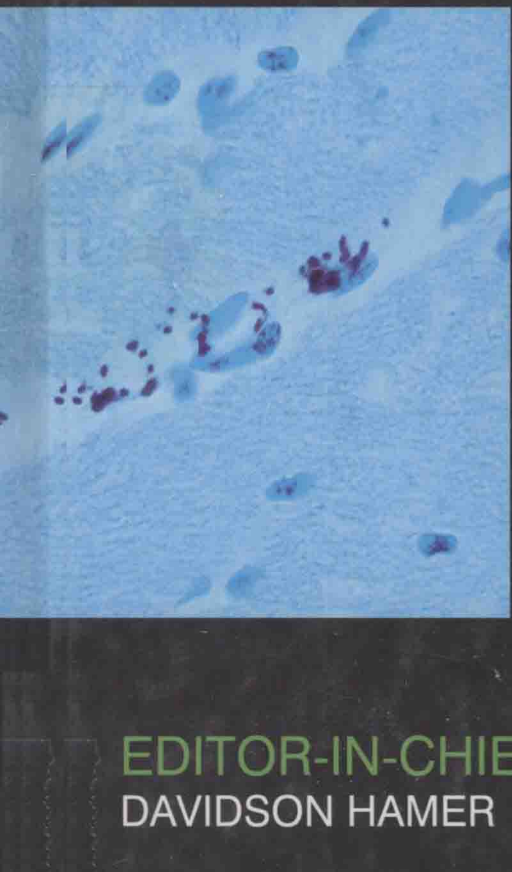
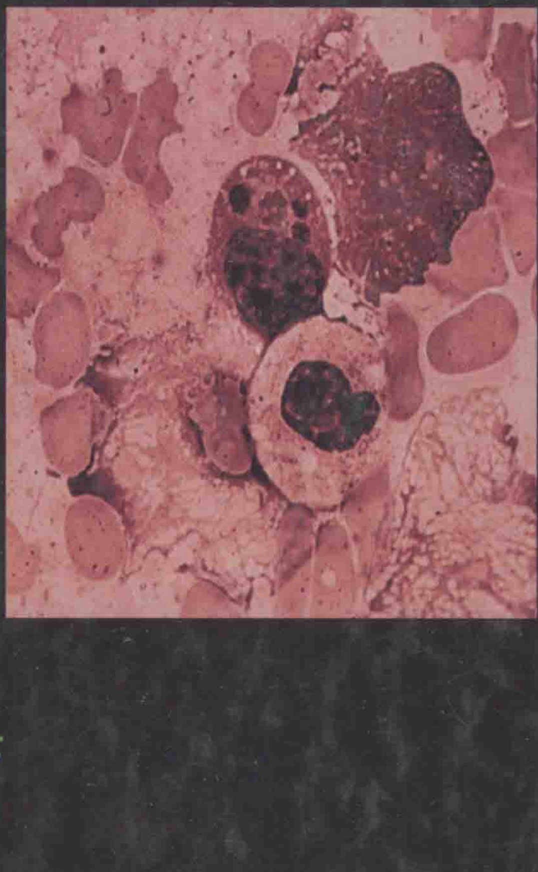
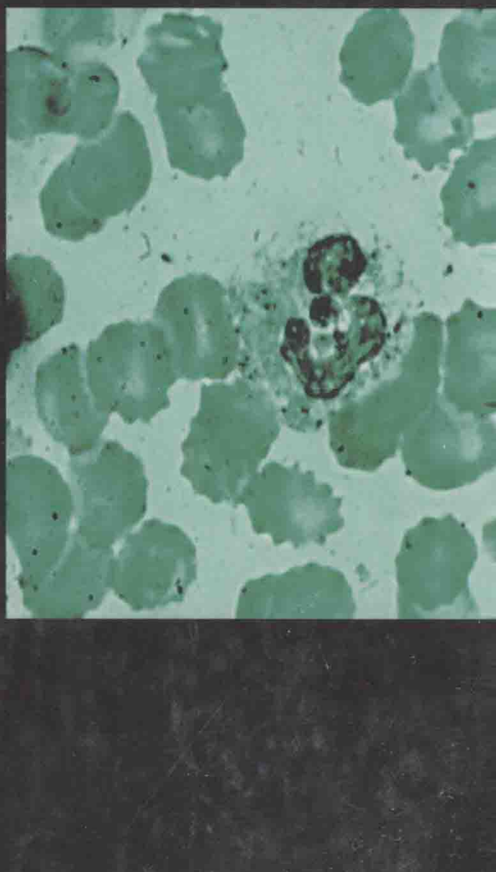

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Introduction

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Introduction

Infectious diseases are a major cause of morbidity, disability, and mortality worldwide. Substantial gains have been made in public health interventions for the treatment, prevention, and control of infectious diseases during the last century. Nevertheless, in recent decades, the world has witnessed the emergence and development of a worldwide human immunodeficiency virus (HIV) pandemic, increasing antimicrobial resistance, and the emergence of many new bacterial, fungal, parasitic, and viral pathogens, including the recent influenza A H1N1 (swine flu) pandemic (Influenza chapter).

As a result of changes in environmental, social, economic, and public health factors, morbidity and mortality due to infectious diseases have declined in industrialized countries during the last century. This advance has coincided with a gradual transition to chronic disease morbidity and mortality from ischemic heart disease, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, and cancer (Lopez et al. 2006). By contrast, in less-developed countries, infectious diseases continue to contribute substantially to the overall burden of disease although many developing countries are increasingly confronted with the double burden of death and disability due to infectious and chronic diseases.

Infectious Diseases: A Historical Perspective

At the beginning of the twentieth century, infectious diseases were the leading cause of death worldwide. Three diseases – pneumonia, diarrhea, and tuberculosis, were responsible for about 30% of deaths in the United States (Cohen, 2000). Early infant and childhood mortality from infections contributed to a low average life expectancy. A number of developments, including improved nutrition, safer food and water supplies, improved hygiene and sanitation, the use of antimicrobial agents, and widespread immunizations against important infectious diseases, resulted in decreased host susceptibility and reductions in disease transmission. During the last century, there has been a decline in infectious diseases mortality in the United States from 797 deaths per 100 000 in 1900 to 36 deaths per 100 000 in 1980. While each of the above factors played an important role in contributing to reductions in the burden of infectious diseases in developed countries, in many less-developed countries, only the benefits of vaccinations have been available to the population. Unsafe food and water, absence of sanitation, lack of access to health care or effective drug therapies, and malnutrition are still common problems. Nevertheless, the benefits of primary prevention through immunization against infectious diseases have been profound. For example, there was a worldwide decline of more than 92% of infectious disease cases and greater than 99% decrease in deaths due to diphtheria, measles, mumps, pertussis, and tetanus between the prevaccine era and the first decade of the twenty-first century (Roush, 2007). Similarly, the more recent introduction of hepatitis A and B, *Haemophilus influenzae* type b, and conjugate pneumococcal vaccines has resulted in substantial declines in morbidity and mortality from these diseases in resource-rich countries.

New infectious disease threats have emerged in the recent past to affect both developed and less-developed regions, and many neglected infectious diseases remain troublesome. Concurrent with the growth of the AIDS pandemic, there has been a rise in mortality rates among persons aged 25 years and older in developed and less-developed areas of the world. In addition, conditions in many developed countries paradoxically facilitate the emergence and transmission of some infectious diseases. Thus, from a historical view, infectious diseases are now seen to have played an unexpectedly important role globally.

Worldwide Burden of Infectious Diseases in the Early Twenty-first Century

By the late twentieth century, substantial reductions in child mortality had occurred in low- and middle-income countries. The decrease in the number of child deaths during 1960–1990 averaged 2.5% per year and the risk of dying in the first 5 years of life dropped by half – a major achievement in child survival. During the period 1990–2001, mortality rates dropped an average of 1.1% annually, mostly after the neonatal period. Unfortunately, most neonatal deaths are not recorded in formal registration systems and communities with the greatest number of neonatal deaths have the least information on mortality rates. As a consequence, the current global burden figures of newborn and young infant deaths are largely estimates. These figures suggest that 10.8 million children under the age of 5 years die annually and, of the 130 million births, about 4 million die in the first 4 weeks of life – the neonatal period, with nearly three quarters of neonatal deaths occurring in the first week after birth (Black, 2003).

During the period 2000–2003, four communicable diseases accounted for 54% of childhood deaths worldwide (Childhood infectious diseases chapter). These included pneumonia (19%), diarrhea (18%), malaria (8%), and neonatal sepsis or pneumonia (10%) (Bryce, 2005). Undernutrition is an underlying cause in more than half of all deaths in children younger than 5 years. The distribution of these four major causes of mortality was similar in World Health Organization (WHO) regions with the exception of sub-Saharan Africa where 94% of childhood malaria deaths occurred (Malaria chapter).

The south Asian region accounts for the highest number of child deaths, over 3 million, whereas the highest mortality rates are generally seen in sub-Saharan Africa. Each year, sub-Saharan Africa and South Asia share 41% and 34% of child deaths respectively (Black, 2003). Only six countries account for half of worldwide deaths and 42 for 90% of child deaths with the predominant causes being pneumonia, diarrhea, and neonatal disorders, with surprisingly little contribution from malaria and AIDS. In all, 99% of neonatal deaths occur in poor countries (estimated average neonatal mortality rate (NMR) of 33/1000 live births) and the remaining 1% is divided among 39 high-income countries (estimated average NMR of 4/1000 live births). Although HIV/AIDS and tuberculosis are important infectious causes of morbidity and death globally, the number of individuals (2.1 million adults and children; UNAIDS 2007) dying from these diseases is approximately 20% of the number of children under 5 dying of the causes listed earlier. Thus, there is substantial scope for a focus on the entire spectrum of significant infectious diseases of public health importance.

Disability-adjusted life years (DALYs) are a widely accepted metric for understanding the burden of disease. Lower respiratory tract infections are the leading cause of DALYs worldwide, accounting for 6.4% of the total (Pneumonia chapter). HIV/AIDS is third on the list accounting for 6.1% while diarrheal diseases and malaria rank fifth and ninth, accounting for 4.2% and 2.7% of DALYs respectively. In high-income countries, lower respiratory infections are the fourth leading cause of death. No communicable disease is among the top ten leading causes of DALYs in high-income countries. In contrast, pneumonia, HIV/AIDS, diarrhea, tuberculosis, and malaria rank among the top ten causes of death and DALYs in low- and middle-income countries.

What Are the Most Important Neglected Diseases?

While there are more than 30 neglected tropical diseases, 13 parasitic and bacterial infections plus dengue fever account for the greatest burden of disease (Hotez, 2009). These diseases are responsible for reduced child survival, impaired growth and cognitive development of children, adverse effects on educational and agricultural productivity, and substantial costs to families and health systems in some of the most impoverished populations in the world. When the top 13 major neglected tropical diseases are combined, they represent the sixth leading cause of life-years lost to disability and premature death (Hotez, 2007).

A broad range of parasites plague humans worldwide. Certain parasites, such as the *Plasmodium* species that cause malaria, are well recognized and have received intensive international support for research and programmatic control interventions, whereas others receive much less attention. Some of the main neglected tropical parasitic diseases include the protozoan infections: human African trypanosomiasis (African trypanosomiasis chapter), visceral leishmaniasis (Leishmaniasis chapter), and American trypanosomiasis (Chagas disease) (Chagas disease chapter), and helminthic infections, such as the soil transmitted nematodes (ascariasis, hookworms, trichuriasis) (Intestinal nematode chapter), schistosomiasis (Schistosomiasis chapter), lymphatic filariasis (Filariasis chapter), onchocerciasis (Onchocerciasis chapter), and dracunculiasis. As described later, efforts by the Carter Center and partners during the last two decades have resulted in substantial reductions in the prevalence of infections due to *Dracunculus medinensis*.

Recent global estimates indicate that more than a quarter of the world's population is infected with one or more helminths. The geographic distribution of roundworms in many tropical and subtropical regions closely parallels socioeconomic and sanitary conditions. In locales where several species of intestinal parasites are found, co-infection with *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms is common. Roundworms, members of the phylum Nematoda, are responsible for large numbers of infections. For example, the global prevalence of ascariasis is more than 800 million, trichuriasis greater than 600 million, and hookworms about 576 million (Hotez, 2007). Fortunately many of the neglected bacterial and parasitic diseases have simple, relatively low cost interventions available for their control and treatment.

Emerging Infectious Diseases

Emerging infectious diseases are significant for a number of reasons. From the purely medical view, many of these diseases are difficult to treat or have no specific effective therapy available, making prevention critically important. For most of these diseases, no vaccines are available, rendering the most important tool of the past century – immunization – irrelevant to their prevention and control. As they arise, they require social, public health, and medical mobilization as well as the diversion of human and financial resources away from other medical and societal problems. In many cases, emerging diseases have become epidemic in developed countries because of their ability to take advantage of opportunities for transmission directly related to the infrastructure of development and to their protected ecological niches. They threaten less-developed regions to an even greater extent because of the limited resources available to combat them. Furthermore, many emerging diseases have the potential to selectively kill or cause illness in specific subsets of the population, raising difficult issues of social and economic justice, and resource allocation. Lastly, many emerging diseases are harbored in economically important animal species, suggesting that this reservoir for human infection will require new approaches to prevent their spread to humans.

Emerging infectious diseases may be defined as diseases that are caused by pathogens only recently recognized to exist, such as *Cryptosporidium* (Cryptosporidiosis chapter). In addition, diseases that were rare, but that have become resurgent or spread their geographic distribution, are 'reemergent.' Such diseases include resurgent dengue (Dengue chapter) and malaria, as well as agents such as West Nile, an arbovirus that has spread to new continents (Arbovirus chapter). This group of diseases is important globally, and the experience of the last 30 years suggests that newly emerging diseases are likely to bedevil us.

Reasons for the emergence of these diseases may be understood within an ecological context of human interactions with other humans, with animals that may host human pathogens, and with a changing agricultural and industrial environment. Additional factors include increasing antimicrobial resistance, global travel, and international commerce. As the global climate changes, so does the environment which can support not only the pathogens, but also the vectors responsible for their transmission. Upland regions that were once free of malaria because they were too cold to support Anopheline mosquitoes have now warmed, allowing malaria to spread. Human behavior is intimately linked to the spread of these diseases, as humans push into new ecological zones and alter food production in ways that facilitate pathogen transmission. Behavior at the societal level includes the breakdown of public health barriers by poverty, war, and famine. The political will to devote resources required to combat diseases may be lacking, and conversely the intent to cause harm through bioterrorism is present.

Role of Zoonotic Reservoirs

Approximately 70% of recently emerged infectious diseases have animal reservoirs. These reservoirs include both domestic animals and wildlife. Factors influencing the transmission of diseases from domestic animals to humans include agricultural intensification, as well as technological advances. In many countries, domestic animals raised for their meat are housed in factory-like settings with many thousands of animals. This concentration of animal hosts may increase the likelihood of exposure for a worker in the facility, or for people exposed to animal urine or feces. In addition, technological advances, such as the use of pig heart valves to replace human heart valves, could allow for the transmission of animal pathogens through implantation (xenotransplantation).

Our era is not the first to experience novel pathogens. Measles is the descendant of rinderpest, a disease of herbivores – and thus when cattle and other animals were domesticated 10–15 000 years ago, our ancestors suffered from animal pathogens that had 'jumped' into humans. The role of domesticated animals continues as a source of emerging diseases. *Cryptosporidium* parasites infect a broad range of animal and human hosts, but were not recognized for their substantial contribution to the burden of human diarrheal disease until the early 1980s when the AIDS pandemic became evident. Enterohemorrhagic *Escherichia coli* (EHEC) bacteria contain many of the same genes that *Shigella* bacteria do, and have caused renal failure and death from the shared 'hemolytic-uremic' syndrome (HUS) (Intestinal infections overview chapter). Beef production has become industrialized in many countries, and includes the practice of grinding the meat of many cattle together into one immense batch of hamburger (beef) patties. *E. coli* O157:H7 and other EHEC bacteria live in cattle intestines, and the contamination of a single animal carcass with intestinal contents during slaughter has led to large outbreaks of HUS in people fed from the same batch of hamburger meat. Similarly, contamination of a large batch of ice cream that was distributed across the United States led to a disseminated epidemic of salmonellosis (Foodborne illnesses overview chapter).

Human intrusion into new environments leads to new exposures and occasional transmission. A classic example is that of hunters and loggers in tropical regions where yellow fever is endemic to monkeys and is maintained by mosquitoes (*Haemagoggus*, *Sabathes*, and *Aedes* species) adapted to the high forest canopy (Yellow fever chapter). When trees are felled, the mosquitoes may feed on the loggers and transmit yellow fever. When the loggers return to urban areas, then the cycle of transmission from human to mosquito to human is maintained by another mosquito species, *Aedes aegypti*, which is well adapted to urban settings. This same mosquito transmits dengue, which is epidemic in many parts of the world, and recently was the leading cause of death in children in Thailand (Dengue chapter). Sadly, in a herculean effort, *Ae. aegypti* was eradicated from the Americas before World War II, but the resources and political will required to eradicate periodic reintroductions was not made, and it is now widespread in the western hemisphere. Vector control programs in South America were often abandoned in the 1980s, allowing the return of *Ae. aegypti* to urban settings. In Africa, a third form of yellow fever transmission, maintained by people traveling between forested and urban areas, has recently been the most important one.

Antibiotic resistance has risen to frankly frightening levels. Bacteria, such as *E. coli*, *Salmonella*, and *Shigella* species which cause diarrhea; many of the bacterial etiologies of pneumonia; and others such as *Staphylococcus aureus* are resistant to inexpensive – and often improperly used – antibiotics. It has been common for individuals with hospital-acquired infections to have pathogens resistant to nearly all, or all, available antibiotics. It is becoming common to see these agents causing disease in the community. We are in a race to develop new agents to treat these diseases, and the bacteria are winning.

In the same vein, novel forms of influenza virus are causing global disease (Influenza chapter). Influenza is almost uniquely pathogenic in humans because of its ability to rapidly mutate, and to replicate in animals of major importance to humans, such as hogs, chickens, and ducks. The recent H1N1 pandemic has provided important lessons in prevention and treatment, in part by illustrating how important human behavior is at both personal (hand-washing) and societal (travel, quarantines) levels. Preparation for influenza pandemics requires political will and the allocation of resources. Our current method for influenza vaccine production (in embryonated chicken eggs), although safe, is unlikely to address the global needs for vaccination against more virulent pandemic influenza in an adequate or timely way.

These at-times dispiriting circumstances are not the complete picture. New preventive measures (insecticide-treated bed nets) and therapies for malaria (the artemesinins) have been deployed. Poliomyelitis, now endemic in only a handful of countries, is a forgotten disease for many (Polio chapter). The provision of clean water and sanitation is a Millennium Development Goal, and if achieved, will prevent many of the diarrheal diseases discussed in this volume by breaking the cycle of transmission. Recognition of the dangers in industrialized food production has led to more stringent measures to prevent bacterial contamination of beef and poultry. Efforts to immunize mothers and children against diseases such as tetanus and *Hemophilus influenzae* type b have been hugely successful in many countries.

Overview of Public Health and Infectious Diseases

The focus of this book is on diseases of major public health importance, with the important exceptions of HIV and *Mycobacterium tuberculosis*. The book is divided into four major sections. After several comprehensive chapters that provide reviews of bacterial infections, common pediatric infectious diseases, gastrointestinal infections, food- and water-borne disease, and major clinical diseases syndromes – pneumonia and viral hepatitis – there are three major sections: bacteria, parasites, and viruses. Since the focus is on diseases of public health importance, predominantly in resource-poor areas of the world, the bacterial and viral sections place less emphasis on nosocomial infections or infectious pathogens that plague highly immunocompromised individuals such as those with underlying hematological malignancies and HIV/AIDS, or who have undergone transplantation.

Given the wide range of infectious diseases responsible for human infections, it is not possible to do justice to all infections in one book. We have chosen therefore to focus on major diseases that in many cases have received less attention during recent years. Thus, HIV/AIDS, tuberculosis, and environmental mycobacteria will not be addressed. Similarly, several diseases that have been eradicated (e.g., smallpox), or have nearly been eradicated (dracunculiasis), or cause a very low burden of disease (yaws, pinta, endemic syphilis, and rare fungal infections) have also not been included.

This book is meant to address an important gap in information available to the public health and biomedical community. The focus is on diseases that form the bulk of the human burden of infectious diseases, but which have received relatively scanty attention in recent years. Thus, the main contribution of this volume is its detailed and expert information on neglected and emerging diseases. This includes highly informative reviews of the epidemiology, clinical manifestations, diagnosis, treatment, prevention, and control of these diseases with high-quality tables, figures, and informative references.

This volume will be useful to clinicians, students, and other biomedical professionals as it concisely describes the clinical manifestations, and epidemiology, of diseases which in aggregate form the majority of infectious diseases. This volume will also be useful to policy makers as it clearly delineates actions to decrease the transmission of these diseases and to improve their treatment.

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CONTENTS

SECTION 3 PARASITES

SECTION 4 VIRUSES

OVERVIEW AND SYNDROME CHAPTERS

Bacterial Infections, Overview

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Introduction

Bacteria are ubiquitous. They play an important role in maintaining the environment in which we live. Only a small percentage of the world's bacteria cause infection and disease. These bacterial infections have a large impact on public health. As a general rule, bacterial infections are easier to treat than viral infections, since the armamentarium of antimicrobial agents with activity against bacteria is more extensive. More so than with infectious diseases caused by viruses and parasites, however, bacterial resistance to antimicrobials is a rapidly growing problem with potentially devastating consequences.

Bacteria are unique among the prokaryotes in that so many of them are normal flora that colonize the host without causing infection. Once a person is infected, clinically apparent disease may or may not be seen, and only in a small subset of infections do we see clinically significant disease. Bacterial infections can be transmitted by a variety of mechanisms. In order to be spread, a sufficient number of organisms must survive in the environment and reach a susceptible host. Many bacteria have adapted to survive in water, soil, food, and elsewhere. Some infect vectors such as animals or insects before being transmitted to another human.

New species and new variants of familiar species continue to be discovered, particularly as we intrude into new ecosystems. Both Lyme disease and Legionnaire's disease, now well-known to health-care professionals, were discovered as recently as the 1970s. The recent increased prevalence of highly immunosuppressed individuals, both due to AIDS and the increasing use of immunosuppressive drugs as chemotherapy and for transplantation of organs, tissues, and cells, has led to a population of patients highly susceptible to types of bacterial infections that were comparatively rare before.

Several factors lead to the development of bacterial infection and disease. First, the infectivity of an organism determines the number of individuals that will be infected compared to the number who are susceptible and exposed. Second, the pathogenicity is a measure of the potential for an infectious organism to cause disease. Pathogenic bacteria possess characteristics that allow them to evade the body's protective mechanisms and use its resources, causing disease. Finally, virulence describes the organism's propensity to cause disease, through properties such as invasiveness and the production of toxins. Host factors are critical in determining whether disease will develop following transmission of a bacterial agent. These factors include genetic makeup, nutritional status, age, duration of exposure to the organism, and coexisting illnesses. The environment also plays a role in host susceptibility. Air pollution as well as chemicals and contaminants in the environment weaken the body's defenses against bacterial infection.

Structure and Classification of Bacteria

Bacteria are prokaryotic organisms that carry their genetic information in a double-stranded circular molecule of DNA. Some species also contain small circular plasmids of additional DNA. The cell cytoplasm contains ribosomes and there is both a cell membrane and, in all species except *Mycoplasma*, a complex cell wall. External to the cell wall, some bacteria have capsules, flagella, or pili (see **Figure 1**). Bacteria normally reproduce by binary fission. Under the proper conditions, some bacteria can divide and multiply rapidly. Consequently, some infections require only a small number of organisms to cause potentially overwhelming infection.

Bacteria are classified as Gram-positive or Gram-negative based on the characteristics of their cell wall, as seen under a microscope after stains have been administered, a procedure called Gram staining, that was developed in 1882 by Hans Christian Gram (see **Figure 2**). Most, but not all, bacteria fall into one of these two categories. Clinically, one of the main differences between gram-positive and gram-negative organisms is that gram-negative bacteria tend to produce an endotoxin that can cause tissue destruction, shock, and death. The two classes of bacteria differ in their antibiotic susceptibilities as well.

Bacteria can also be classified based on their growth responses in the presence and absence of oxygen. Aerobic bacteria, or aerobes, grow in the presence of oxygen. Obligate aerobes such as *Bordetella pertussis* require oxygen. Facultative organisms can grow in the presence or absence of oxygen. Anaerobic bacteria such as the *Clostridia* are able to grow in the absence of oxygen and obligate anaerobes require its absence.

Some bacteria are not classified as Gram-positive or Gram-negative. These include the mycobacteria, of which *Mycobacterium tuberculosis* is the most well-known, which can be seen under the microscope using a special stain

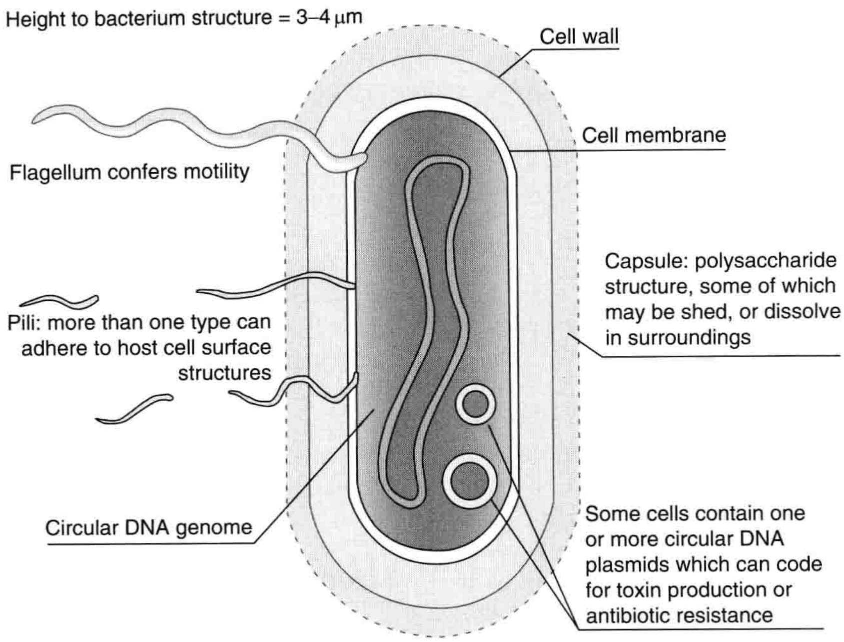

Figure 1 Structure of a bacterium. Reproduced from Bannister BA, Begg NT, and Gillespie SH (eds.) (1996) Structure and classification of pathogens. In: *Infectious Disease*, 2nd edn., ch. 2, pp. 23–34. Oxford, UK: Blackwell Science Ltd., with permission from Blackwell Publishing.

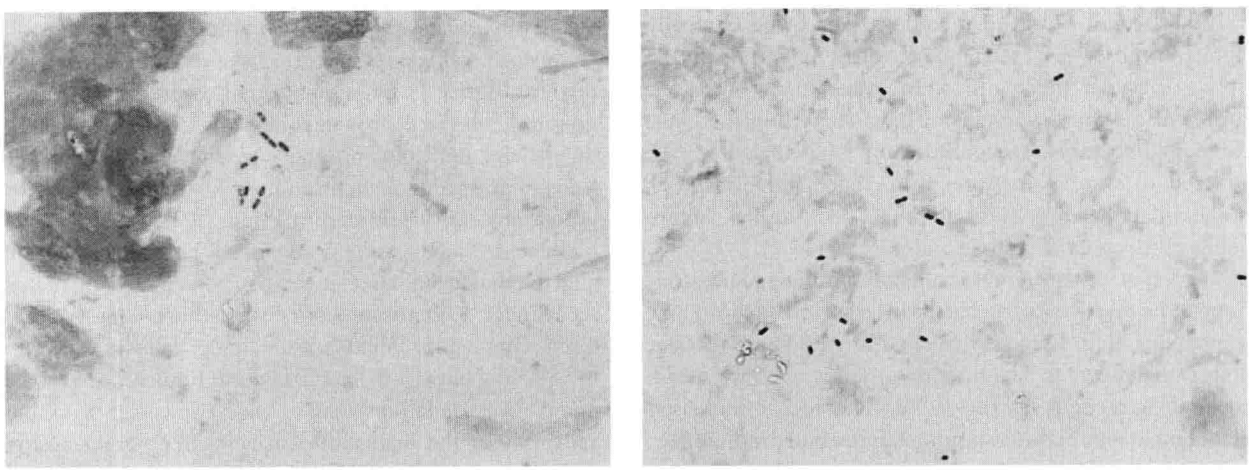

Figure 2 Gram stains of Gram-negative (left) and Gram-positive (right) bacteria (courtesy of Tufts Medical Center Microbiology Laboratory).

called the acid-fast stain; organisms that do not take up Gram stain such as the spirochetes (which cause diseases such as syphilis and Lyme disease); and the *Rickettsia* (which cause Rocky Mountain spotted fever and epidemic typhus).

Clinical Manifestations of Bacterial Infection

All of the human organs are susceptible to bacterial infection. Each species of bacteria has a predilection to infect certain organs and not others. For example, *Neisseria meningitidis* normally infects the meninges (covering) of the central nervous system, causing meningitis, and can also infect the lungs, causing pneumonia. It is not, however, a cause of skin infection. *Staphylococcus aureus*, which people typically carry on their skin or mucus membranes, often causes skin and soft tissue infections, but also spreads readily throughout the body via the bloodstream and can cause infection of the lungs, abdomen, heart valves, and almost any other site.

Disease can be caused by destruction of the body's cells by the organism or the body's immune response to the