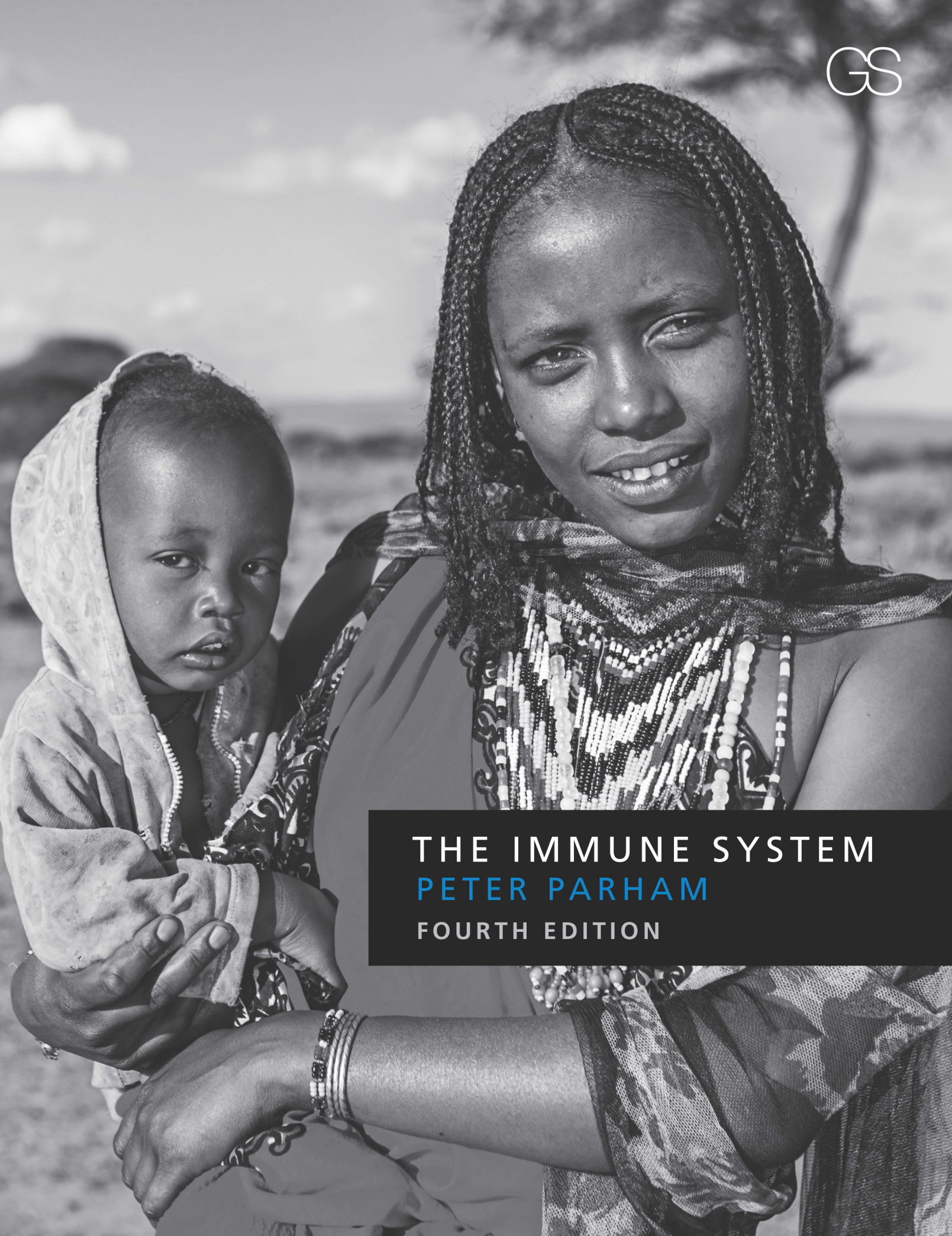

THE IMMUNE SYSTEM

PETER PARHAM

FOURTH EDITION

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PETER PARHAM

FOURTH EDITION

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Preface

This book is aimed at students of all types who are coming to immunology for the first time. The guiding principle of the book is a focus on human immune systems—how they work and how their successes, compromises, and failures affect the daily life of every one of us. In providing the beginning student with a coherent, concise, and contemporary narrative of the mechanisms used by the immune system to control invading microbes, the emphasis has had to be on what we know, rather than how we know it. In other words, our emphasis here is more on the work of nature than on the work of immunologists.

Nevertheless, since the third edition of *The Immune System* was published in 2009 the work of immunologists has dramatically advanced the boundaries of knowledge. Following close behind the discovery of immunological mechanisms has been the rational design of new drugs and therapies based on this knowledge. Other important developments have been an increasing understanding of the numerous idiosyncrasies of human immune systems and the importance of studying immune-system cells in the tissues where they function. While working on this fourth revision of *The Immune System* I was not infrequently struck and excited by the extent to which phenomena that were loose ends in 2009 are now connected and making sense in ways that were unpredictable. As a result, substantial changes have been made in this fourth edition. For readers and instructors familiar with the third edition, what follows is a guide to the major changes. For those who are new to the book it will provide an overview of its contents.

Chapter 1 provides a focused introduction to the cells and tissues of the immune system, and to their place and purpose within the human body. The two following chapters describe the innate immune response to infection. These replace the single chapter in the previous edition, reflecting how innate immunity continues to be a rich area for discovery. Particularly relevant is the now widespread appreciation that the vast majority of microorganisms inhabiting human bodies are essential for human health, for the development of the immune system, and for preventing the growth and invasion of pathogenic microorganisms. These concepts are introduced in Chapter 2, along with the immediate, front-line defenses of complement, defensins, and other secreted proteins. The induced cellular defenses of innate immunity—macrophages, neutrophils, and natural killer cells—are the topic of Chapter 3. In the previous edition of the book, there was an introductory chapter on adaptive immunity at this point. This has been dropped in the fourth edition, partly because of overlap with Chapter 1 and partly on the advice of the book's users.

The next six chapters cover the fundamental biology of the adaptive immune response. Chapters 4 and 5 describe how B lymphocytes and T lymphocytes

detect the presence of infection. These chapters introduce antibodies, the variable antigen-binding receptors of B cells and T cells, and the polymorphic major histocompatibility complex (MHC) class I and II molecules that present peptide antigens to T-cell receptors.

Chapters 6 and 7 describe and compare the development of B cells and T cells, including the gene rearrangements that generate the antigen receptors and the selective processes that eliminate cells with potential for causing autoimmunity. At the end of these two chapters, mature but naive B cells and T cells enter the circulation of the blood and the lymph in the quest for their specific antigens. Chapters 8 and 9 describe how these naive lymphocytes respond to infections and use diverse effector mechanisms to get rid of them. Here we look in detail at the dendritic cells that activate naive T cells, how immune responses are generated in secondary lymphoid organs, the differentiation of activated T cells into various effector subsets, and the generation of antibodies by B cells. The order and scope of these six chapters are the same as in previous editions of the book, but they have undergone significant revision, particularly to account for the increased knowledge and understanding of the functional diversity of both CD4 T cells and the classes and subclasses of human antibodies.

In the previous edition, Chapter 10 was divided into three parts that dealt with mucosal immunity, immunological memory, and the connection between innate and adaptive immunity. These three important areas have been given a chapter each in this edition. Chapter 10 now describes the nature of the immune response in mucosal tissue, where most immune activity takes place, and the ways in which it differs from the systemic immune response, with emphasis on the gut and the mucosal immune system's interactions with commensal microorganisms.

Chapter 11 is a new chapter that combines two related topics—immunological memory and vaccination—that were in different chapters in the previous edition. Users of the book have for some years suggested bringing these two topics together. Now is an opportune time to do so, because vaccine research and development is undergoing a renaissance after a period of considerable decline.

The more we learn about the immune system, the more blurred the distinction between innate and adaptive immunity becomes. On reflection this should not be surprising, because the two systems have been coevolving in vertebrate bodies for the past 400 million years. The largely new content of Chapter 12, entitled 'Coevolution of Innate and Adaptive Immunity', concentrates on several populations of lymphocyte that combine characteristics of innate and adaptive immunity. These include natural killer cells, γ:δ cells, natural killer T cells, and mucosa-associated invariant T cells. After years of being a cipher, the ligands that bind to the variable antigen receptors of γ:δ are now being discovered and defined.

The first part of Chapter 13, 'Failures of the Body's Defenses', describes the ways in which some pathogens change and avoid the immunological memories gained by their human hosts during previous infections. The second part of the chapter describes the inherited genetic defects that segregate in human populations and cause a wide range of immunodeficiency diseases. An invaluable by-product of identifying such patients and treating their diseases has been the ability to define the physiological functions of the component of the human immune system that is missing or nonfunctional in each different immunodeficiency disease. The third part of the chapter is devoted to the human immunodeficiency virus (HIV). At this time there is renewal of hope for HIV vaccines and immunotherapies based upon the results of studying the successful immune responses in exceptional individuals who maintain health despite having been infected with HIV.

Chapter 14 in this edition, 'IgE-mediated Immunity and Allergy', has evolved from Chapter 12 in the previous edition, 'Over-reactions of the Immune System'. After introducing the four types of hypersensitivity reaction, the chapter focuses on the immunology of IgE and how it provides protection against parasitic worms in the people of developing countries and causes type I hypersensitivity reactions (allergies) in the people of industrialized countries. Much of this chapter is new and explains how IgE and its powerful receptor on mast cells, eosinophils, and basophils constitute an entire arm of the immune system that evolved specifically to control multicellular parasites, notably helminth worms. In-depth consideration of the type II, III, and IV hypersensitivity reactions is now given in Chapter 15, 'Transplantation of Tissues and Organs', and Chapter 16, 'Disruption of Healthy Tissue by the Adaptive Immune Response', which cover transplantation and autoimmunity, respectively. As users of the book have pointed out, different forms of transplant rejection and different types of autoimmune disease provide good examples of the type II, III, and IV hypersensitivity reactions. In these two chapters and also Chapter 17, on 'Cancer and its Interactions with the Immune System', the amount of clinical description has been reduced so as to accommodate examples of promising new immunotherapies that are being used to treat transplant rejection, graft-versus-host disease, autoimmune disease, and various types of cancer. Although the order of the chapters on transplantation and autoimmunity has been changed in the fourth edition, the scope of these chapters has not changed.

In addition to these major changes, all chapters have been subject to revision aimed at bringing the content up to date and improving its clarity. Exemplifying the extent of these changes, about 20% of the figures are new and they include new images generously donated by colleagues.

I thank and acknowledge the authors of *Janeway's Immunobiology* and of *Case Studies in Immunology* for giving me license with the text and figures of their books. I have been fortunate to work with a collegial team of experts on this fourth edition. Sheryl L. Fuller-Espie (Cabrini College, Radnor, Pennsylvania) superbly composed the questions and answers for the end-of-chapter questions. Eleanor Lawrence expertly edited the text and the figures as well as the end-of-chapter questions. Nigel Orme created all the new illustrations for this edition, Bruce Goatly was a critical, creative copyeditor, and Yasodha Natkunam provided some superb new micrographs. Emma Jeffcock did wonders with the layout. I am indebted to Janet Foltin for her valuable contributions to this revision and to Denise Schanck, who has led the team and orchestrated the entire operation. Frances Brodsky has not only been a loyal user of the book but has generously given of her advice, suggestions, and much else to this Fourth Edition of *The Immune System*.

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Resources for Instructors and Students

Case Studies in Immunology

by Raif Geha and Luigi Notarangelo

The companion book, *Case Studies in Immunology*, provides an additional, integrated discussion of clinical topics to reinforce and extend the basic science. In *The Immune System* diseases covered in *Case Studies* are indicated by a clipboard symbol in the margin. *Case Studies in Immunology* is sold separately.

INSTRUCTOR RESOURCES

Instructor resources are available on the Garland Science Instructor's Resource Site, located at http://www.garlandscience.com/instructors. The password-protected website provides access to the teaching resources for both this book and all other Garland Science textbooks. Qualified instructors can obtain access to the site from their sales representative or by emailing science@garland.com.

Art of *The Immune System*, Fourth Edition

The images from the book are available in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. Figures are searchable by figure number, by figure name, or by keywords used in the figure legend from the book.

Figure-integrated Lecture Outlines

The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations. These will be useful for instructors who would like a head start in creating lectures for their course. Like all of our PowerPoint presentations, the lecture outlines can be customized. For example, the content of these presentations can be combined with videos and questions from the book or 'Question Bank,' to create unique lectures that facilitate interactive learning.

Question Bank

Written by Sheryl L. Fuller-Espie, PhD, DIC, Cabrini College, the revised and expanded question bank includes a variety of question formats: multiple-choice, true–false, matching, essay, and challenging 'thought' questions.

USMLE-style questions help prepare students for medical licensing examinations. There are more than 900 questions, and a large number of the multiple-choice questions are suitable for use with personal response systems (that is, clickers). The questions are organized by book chapter and provide a comprehensive sampling of concepts that can be used either directly or as inspiration for instructors to write their own test questions.

Diploma® Test Generator Software

The questions from the question bank have been loaded into the Diploma test generator software. The software is easy to use and can scramble questions to create multiple tests. Questions are organized by chapter and type, and can be additionally categorized by the instructor according to difficulty or subject. Existing questions can be edited and new ones added. It is compatible with several course management systems, including Blackboard® .

STUDENT RESOURCES

The resources for students are available on *The Immune System* Student Website, located at http://www.garlandscience.com/IS4-students.

Flashcards

Each chapter contains a set of flashcards, built into the website, that allow students to review key terms from the text.

Glossary

The complete glossary from the book is available on the website and can be searched or browsed.

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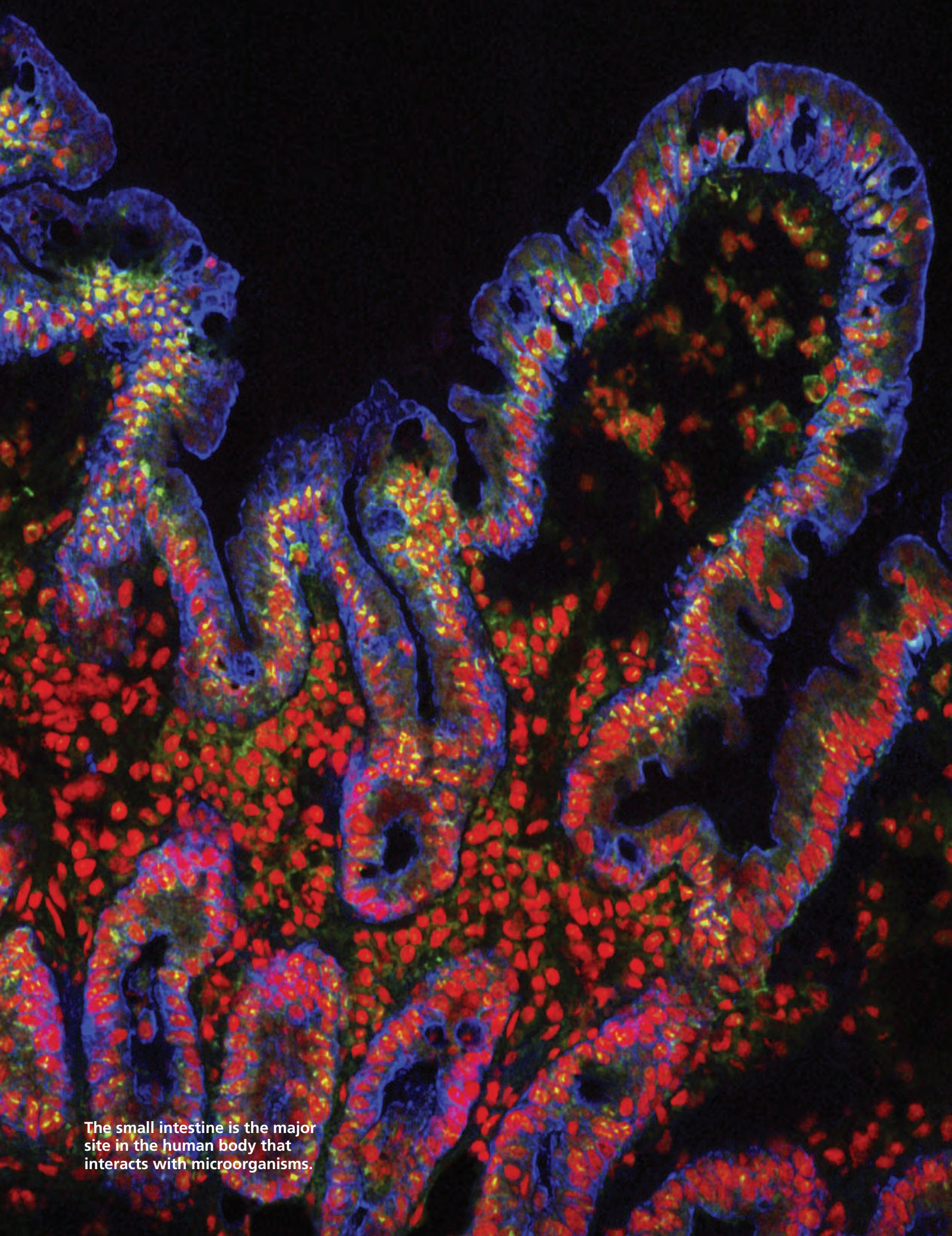


The small intestine is the major site in the human body that interacts with microorganisms.

Chapter 1

Elements of the Immune System and their Roles in Defense

Immunology is the study of the physiological mechanisms that humans and other animals use to defend their bodies from invasion by all sorts of other organisms. The origins of the subject lie in the practice of medicine and in historical observations that people who survived the ravages of epidemic disease were untouched when faced with that same disease again—they had become **immune** to infection. Infectious diseases are caused by microorganisms, which have the advantage of reproducing and evolving much more rapidly than their human hosts. During the course of an infection, the microorganism can pit a vast population of its species against an individual *Homo sapiens*. In response, the human body invests heavily in cells dedicated to defense, which collectively form the **immune system**.

The immune system is crucial to human survival. In the absence of a working immune system, even minor infections can take hold and prove fatal. Without intensive treatment, children born without a functional immune system die in early childhood from the effects of common infections. However, in spite of their immune systems, all humans suffer from infectious diseases, especially when young. This is because the immune system takes time to build up its strongest response to an invading microorganism, time during which the invader can multiply and cause disease. To provide **immunity** that will give future protection from the disease, the immune system must first do battle with the microorganism. This places people at highest risk during their first infection with a microorganism and, in the absence of modern medicine, leads to substantial child mortality, as witnessed in the developing world. When entire populations face a completely new infection, the outcome can be catastrophic, as experienced by indigenous Americans who were killed in large numbers by European diseases to which they were suddenly exposed after 1492. Today, infection with human immunodeficiency virus (HIV) and the acquired immune deficiency syndrome (AIDS) it causes are having a similarly tragic impact on the populations of several African countries.

In medicine the greatest triumph of immunology has been **vaccination**, or **immunization**, a procedure whereby severe disease is prevented by prior exposure to the infectious agent in a form that cannot cause disease. Vaccination provides the opportunity for the immune system to gain the experience needed to make a protective response with little risk to health or life. Vaccination was first used against smallpox, a viral scourge that once ravaged populations and disfigured the survivors. In Asia, small amounts of smallpox virus had been used to induce protective immunity for hundreds of years before 1721, when Lady Mary Wortley Montagu introduced the method into Western Europe. Subsequently, in 1796, Edward Jenner, a doctor in rural

Figure 1.1 The eradication of smallpox by vaccination. Upper panel: smallpox vaccination was started in 1796. In 1979, after 3 years in which no case of smallpox was recorded, the World Health Organization announced that the virus had been eradicated. Since then the proportion of the human population that has been vaccinated against smallpox, or has acquired immunity from an infection, has steadily decreased. The result is that the human population has become increasingly vulnerable should the virus emerge again, either naturally or as a deliberate act of human malevolence. Lower panel: photograph of a child with smallpox and his immune mother. The distinctive rash of smallpox appears about 2 weeks after exposure to the virus. Photograph courtesy of the World Health Organization.

England, showed how inoculation with cowpox virus offered protection against the related smallpox virus with less risk than the earlier methods. Jenner called his procedure vaccination, after vaccinia, the name given to the mild disease produced by cowpox, and he is generally credited with its invention. Since his time, vaccination dramatically reduced the incidence of smallpox worldwide until it was eventually eliminated. The last cases of smallpox were seen by physicians in the 1970s (Figure 1.1).

Effective vaccines have been made from only a fraction of the agents that cause disease, and some are of limited availability because of their cost. Most of the widely used vaccines were first developed many years ago by a process of trial and error, before very much was known about the workings of the immune system. That approach is no longer so successful for developing new vaccines, perhaps because all the easily won vaccines have been made. But deeper understanding of the mechanisms of immunity is spawning new ideas for vaccines against infectious diseases and even against other types of disease such as cancer. Much is now known about the molecular and cellular components of the immune system and what they can do in the laboratory. Current research seeks to understand the contributions of these immune components to fighting infections in the world at large. The new knowledge is also being used to find better ways of manipulating the immune system to prevent the unwanted immune responses that cause allergies, autoimmune diseases, and rejection of organ transplants.

In this chapter we first consider the microorganisms that infect human beings and then the defenses they must overcome to start and propagate an infection. The individual cells and tissues of the immune system are described, and how they integrate their functions with the rest of the human body. The first line of defense is innate immunity, which includes physical and chemical barriers to infection, and responses that are ready and waiting to halt infections before they can barely start. Most infections are stopped by these mechanisms, but when they fail, the more flexible and forceful defenses of the adaptive immune response are brought into play. The adaptive immune response is always targeted to the specific problem at hand and is made and refined during the course of the infection. When successful, it clears the infection and provides long-lasting immunity that prevents its recurrence.

1-1 Numerous commensal microorganisms inhabit healthy human bodies

The main purpose of the immune system is to protect the human body from infectious disease. Almost all infectious diseases of humans are caused by microorganisms smaller than a single human cell. For both benign and dangerous microorganisms alike, the human body constitutes a vast resource-rich environment in which to live, feed, and reproduce. More than 1000 different

microbial species live in the healthy adult human gut and contribute about 10 pounds (4.5 kilograms) to the body's weight; they are called **commensal** species, meaning they 'eat at the same table.' The community of microbial species that inhabits a particular niche in the human body—skin, mouth, gut, or vagina—is called the **microbiota**, for example the 'gut microbiota.' Many of these species have not yet been studied properly because they cannot be propagated in the laboratory, growing only under the special conditions furnished by their human hosts.

Animals have evolved along with their commensal species and in so doing have become both tolerant of them and dependent upon them. Commensal organisms enhance human nutrition by processing digested food and making several vitamins. They also protect against disease, because their presence helps to prevent colonization by dangerous, disease-causing microorganisms. In addition to competing for their space, *Escherichia coli*, a major bacterial component of the normal mammalian gut flora, secretes antibacterial proteins called colicins that incapacitate other bacteria and prevent them from colonizing the gut. When a patient with a bacterial infection takes a course of antibiotic drugs, much of the normal gut microbiota is killed along with the disease-causing bacteria. After such treatment the body is recolonized by a new population of microorganisms; in this situation, opportunistic disease-causing bacteria, such as *Clostridium difficile*, can sometimes establish themselves, causing further disease and sometimes death (Figure 1.2). *C. difficile* produces a toxin that causes diarrhea and, in some cases, an even more serious gastrointestinal condition called pseudomembranous colitis.

1-2 Pathogens are infectious organisms that cause disease

Any organism with the potential to cause disease is known as a **pathogen**. This definition includes not only microorganisms such as the influenza virus or the typhoid bacillus that habitually cause disease if they enter the body, but also ones that can colonize the human body to no ill effect for much of the time but cause illness if the body's defenses are weakened or if the microbe gets into the 'wrong' place. The latter microorganisms are known as **opportunistic pathogens**.

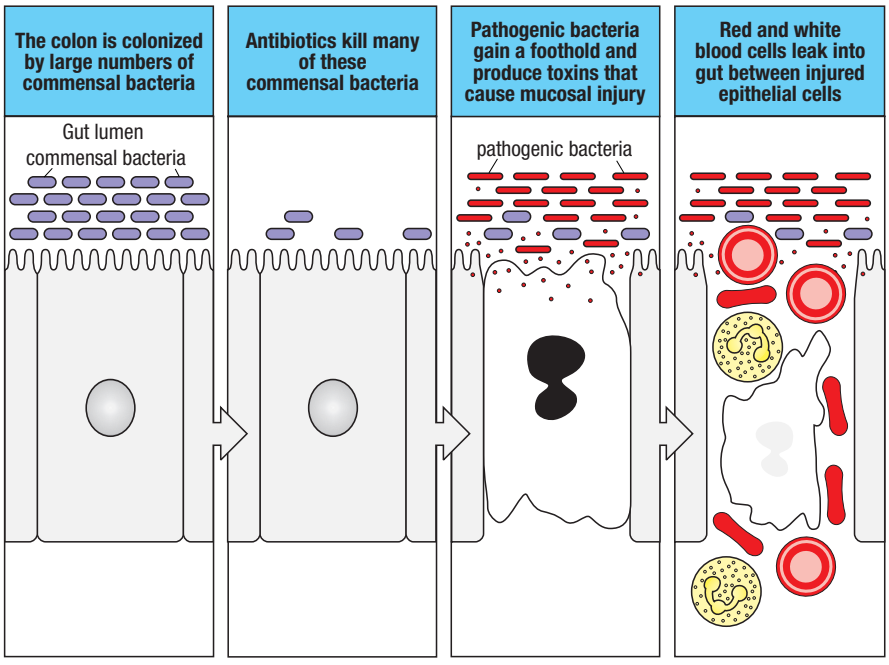


Figure 1.2 Antibiotic treatments disrupt the natural ecology of the colon. When antibiotics are taken orally to counter a bacterial infection, beneficial populations of commensal bacteria in the colon are also decimated. This provides an opportunity for pathogenic strains of bacteria to populate the colon and cause further disease. *Clostridium difficile* is an example of such a bacterium; it produces a toxin that can cause severe diarrhea in patients treated with antibiotics. In hospitals, acquired *C. difficile* infections are an increasing cause of death for elderly patients.

Pathogens can be divided into four kinds: **bacteria**, **viruses**, and **fungi**, each of which is a group of related microorganisms, and internal **parasites**, a less precise term used to embrace a heterogeneous collection of unicellular protozoa and multicellular invertebrates, mainly worms. In this book we consider the functions of the human immune system principally in the context of controlling infections. For some pathogens this necessitates their complete elimination, but for others it is sufficient to limit the size and location of the pathogen population within the human host. Figure 1.3 illustrates the variety in shape and form of the four kinds of pathogen. Figure 1.4 lists common or well-known infectious diseases and the pathogens that cause them. Reference to many of these diseases and the problems they pose for the immune system will be made in the rest of this book.

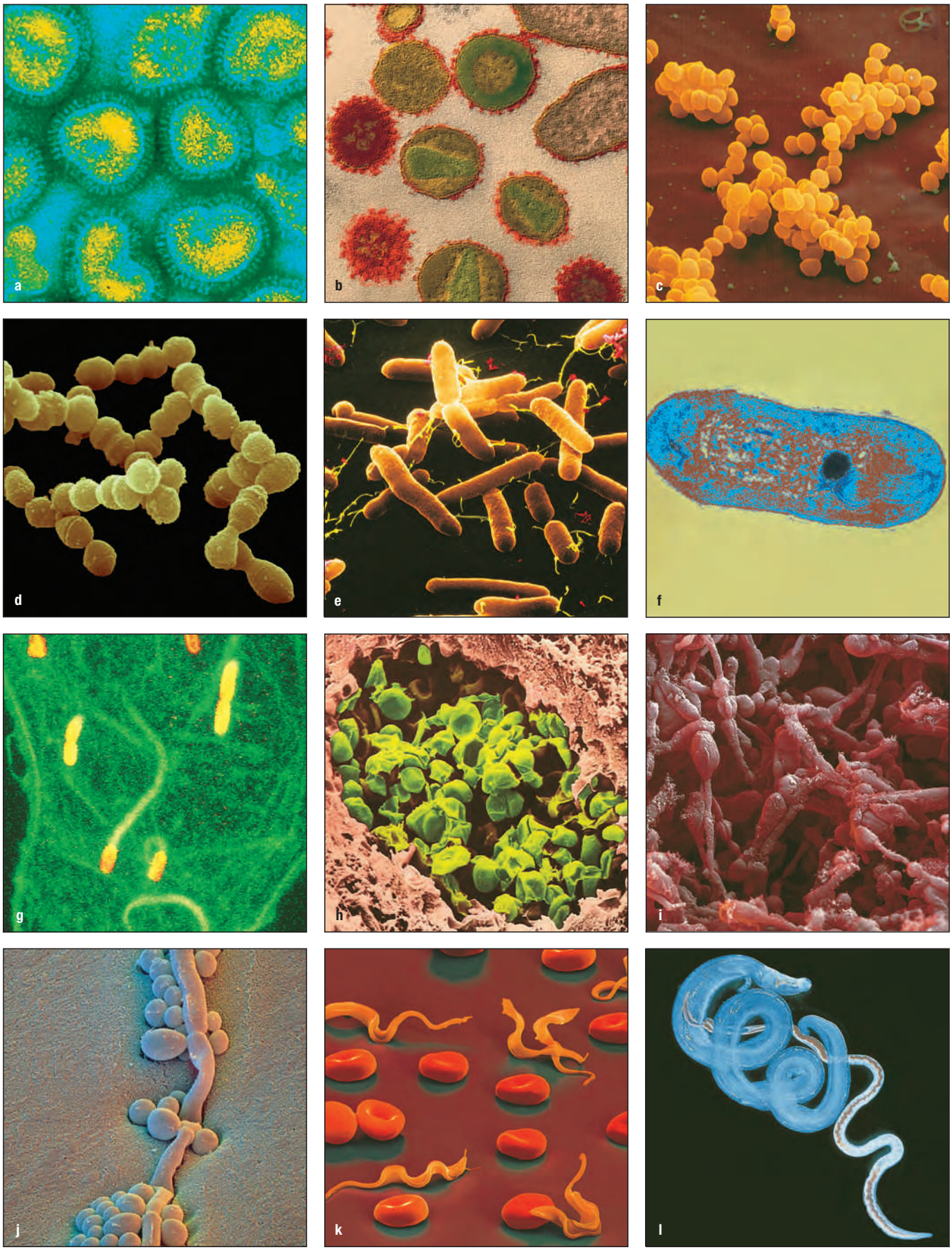
Over evolutionary time, the relationship between a pathogen and its human hosts inevitably changes, affecting the severity of the disease produced. Most pathogenic organisms have evolved special adaptations that enable them to invade their hosts, replicate in them, and be transmitted. However, the rapid death of its host is rarely in a microbe's interest, because this destroys its home and source of food. Consequently, those organisms with the potential to cause severe and rapidly fatal disease often evolve toward an accommodation with their hosts. In complementary fashion, human populations evolve a degree of built-in genetic resistance to common disease-causing organisms, as well as acquiring lifetime immunity to endemic diseases. Endemic diseases are those, such as measles, chickenpox, and malaria, that are ubiquitous in a given population and to which most people are exposed in childhood. Because of the interplay between host and pathogen, the nature and severity of infectious diseases in the human population are always changing.

Influenza is a good example of a common viral disease that, although severe in its symptoms, is usually overcome successfully by the immune system. The fever, aches, and lassitude that accompany infection can be overwhelming, and it is difficult to imagine overcoming foes or predators at the peak of a bout of influenza. Nevertheless, despite the severity of the symptoms, most strains of influenza pose no great danger to healthy people in populations in which influenza is endemic. Warm, well-nourished, and otherwise healthy people usually recover in a couple of weeks and take it for granted that their immune system will accomplish this task. Pathogens new to the human population, in contrast, often cause high mortality in those infected—between 60% and 75% in the case of the Ebola virus.

Figure 1.3 Many different microorganisms can be human pathogens. (a) Human immunodeficiency virus (HIV), the cause of AIDS. (b) Influenza virus. (c) *Staphylococcus aureus*, a bacterium that colonizes human skin, is the common cause of pimples and boils, and can also cause food poisoning. (d) *Streptococcus pneumoniae*, is the major cause of pneumonia and is also a common cause of meningitis in children and the elderly. (e) *Salmonella enteritidis*, the bacterium that commonly causes food poisoning. (f) *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. (g) A human cell (colored green) containing *Listeria monocytogenes* (colored yellow), a bacterium that can contaminate processed food, causing disease (listeriosis) in pregnant women and immunosuppressed individuals. (h) *Pneumocystis carinii*, an opportunistic fungus that infects patients with acquired immunodeficiency syndrome (AIDS) and other immunosuppressed individuals. The fungal cells (colored green) are in lung tissue. (i) *Epidermophyton floccosum*, the fungus that causes ringworm. (j) The fungus *Candida albicans*, a normal inhabitant of the human body that occasionally causes thrush and more severe systemic infections. (k) Red blood cells and *Trypanosoma brucei* (colored orange), a protozoan that causes African sleeping sickness. (l) *Schistosoma mansoni*, the helminth worm that causes schistosomiasis. The adult intestinal blood fluke forms are shown: the male is thick and bluish, the female thin and white. All the photos are false-colored electron micrographs, with the exception of (l), which is a light micrograph.

1-3 The skin and mucosal surfaces form barriers against infection

The skin is the human body's first defense against infection. It forms a tough, impenetrable barrier of **epithelium** protected by layers of keratinized cells. Epithelium is a general name for the layers of cells that line the outer surface and the inner cavities of the body. The skin can be breached by physical damage, such as wounds, burns, or surgical procedures, which exposes soft tissues and renders them vulnerable to infection. Until the adoption of antiseptic procedures in the nineteenth century, surgery was a very risky business, principally because of the life-threatening infections that the procedures introduced. For the same reason, far more soldiers have died from infection acquired on the battlefield than from the direct effects of enemy action. Ironically, the need to conduct increasingly sophisticated and wide-ranging warfare has been the major force driving improvements in surgery and medicine. As an example from immunology, the burns suffered by fighter pilots during the Second World War stimulated studies on skin transplantation that led directly to the understanding of the cellular basis of the immune response.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Type	Disease	Pathogen	General classification*	Route of infection
Viruses	Severe acute respiratory syndrome	SARS virus	Coronaviruses	Oral/respiratory/ocular mucosa
	West Nile encephalitis	West Nile virus	Flaviviruses	Bite of an infected mosquito
	Yellow fever	Yellow fever virus	Flaviviruses	Bite of infected mosquito (*Aedes aegypti*)
	Hepatitis B	Hepatitis B virus	Hepadnaviruses	Sexual transmission; infected blood
	Chickenpox	Varicella-zoster	Herpes viruses	Oral/respiratory
	Mononucleosis	Epstein–Barr virus	Herpes viruses	Oral/respiratory
	Influenza	Influenza virus	Orthomyxoviruses	Oral/respiratory
	Measles	Measles virus	Paramyxoviruses	Oral/respiratory
	Mumps	Mumps virus	Paramyxoviruses	Oral/respiratory
	Poliomyelitis	Polio virus	Picornaviruses	Oral
	Jaundice	Hepatitis A virus	Picornaviruses	Oral
	Smallpox	Variola	Pox viruses	Oral/respiratory
	AIDS	Human immunodeficiency virus	Retroviruses	Sexual transmission, infected blood
	Rabies	Rabies virus	Rhabdoviruses	Bite of an infected animal
	Common cold	Rhinoviruses	Rhinoviruses	Nasal
	Diarrhea	Rotavirus	Rotaviruses	Oral
	Rubella	Rubella	Togaviruses	Oral/respiratory

Figure 1.4 ***(opposite page and above)*** **Diverse microorganisms cause human disease.** Pathogenic organisms are of four main types—viruses, bacteria, fungi, and parasites, which are mostly protozoans or worms. Some important pathogens in each category are listed along with the diseases they cause. *The classifications given are intended as a guide only and are not taxonomically consistent; families are given for the viruses; general groupings often used in medical bacteriology for the bacteria; and higher taxonomic divisions for the fungi and parasites. The terms Gram-negative and Gram-positive refer to the staining properties of the bacteria; Gram-positive bacteria stain purple with the Gram stain, Gram-negative bacteria do not.

Continuous with the skin are the epithelia lining the respiratory, gastrointestinal, and urogenital tracts (Figure 1.5). On these internal surfaces, the impermeable skin gives way to tissues that are specialized for communication with their environment and are more vulnerable to microbial invasion. Such surfaces are known as **mucosal surfaces**, or **mucosae**, as they are continually bathed in the **mucus** they secrete. This thick fluid layer contains glycoproteins, proteoglycans, and enzymes that protect the epithelial cells from damage and help to limit infection. In the respiratory tract, mucus is continuously removed through the action of epithelial cells that bear beating cilia and is replenished by mucus-secreting goblet cells. The respiratory mucosa is thus continually cleansed of unwanted material, including infectious microorganisms that have been inhaled.

All epithelial surfaces secrete antimicrobial substances. The sebum secreted by sebaceous glands associated with hair follicles contains fatty acids and lactic acids, both of which inhibit bacterial growth on the surface of the skin. All epithelia produce **antimicrobial peptides** that kill bacteria, fungi, and enveloped viruses by perturbing their membranes. Tears and saliva contain lysozyme, an enzyme that kills bacteria by degrading their cell walls. Microorganisms are also deterred by the acidic environments within the stomach, the vagina, and the skin.

Type	Disease	Pathogen	General classification*	Route of infection
Bacteria	Trachoma	*Chlamydia trachomatis*	Chlamydias	Oral/respiratory/ocular mucosa
	Bacillary dysentery	*Shigella flexneri*	Gram-negative bacilli	Oral
	Food poisoning	*Salmonella enteritidis, S. typhimurium*	Gram-negative bacilli	Oral
	Plague	*Yersinia pestis*	Gram-negative bacilli	Infected flea bite, respiratory
	Tularemia	*Pasteurella tularensis*	Gram-negative bacilli	Handling infected animals
	Typhoid fever	*Salmonella typhi*	Gram-negative bacilli	Oral
	Gonorrhea	*Neisseria gonorrhoeae*	Gram-negative cocci	Sexually transmitted
	Meningococcal meningitis	*Neisseria meningitidis*	Gram-negative cocci	Oral/respiratory
	Meningitis, pneumonia	*Haemophilus influenzae*	Gram-negative coccobacilli	Oral/respiratory
	Legionnaire's disease	*Legionella pneumophila*	Gram-negative coccobacilli	Inhalation of contaminated aerosol
	Whooping cough	*Bordetella pertussis*	Gram-negative coccobacilli	Oral/respiratory
	Cholera	*Vibrio cholerae*	Gram-negative vibrios	Oral
	Anthrax	*Bacillus anthracis*	Gram-positive bacilli	Oral/respiratory by contact with spores
	Diphtheria	*Corynebacterium diphtheriae*	Gram-positive bacilli	Oral/respiratory
	Tetanus	*Clostridium tetani*	Gram-positive bacilli (anaerobic)	Infected wound
	Boils, wound infections	*Staphylococcus aureus*	Gram-positive cocci	Wounds; oral/respiratory
	Pneumonia, scarlet fever	*Streptococcus pneumoniae*	Gram-positive cocci	Oral/respiratory
	Tonsillitis	*Streptococcus pyogenes*	Gram-positive cocci	Oral/respiratory
	Leprosy	*Mycobacterium leprae*	Mycobacteria	Infected respiratory droplets
	Tuberculosis	*Mycobacterium tuberculosis*	Mycobacteria	Oral/respiratory
	Respiratory disease	*Mycoplasma pneumoniae*	Mycoplasmas	Oral/respiratory
	Typhus	*Rickettsia prowazekii*	Rickettsias	Bite of infected tick
	Lyme disease	*Borrelia burgdorferi*	Spirochetes	Bite of infected deer tick
	Syphilis	*Treponema pallidum*	Spirochetes	Sexual transmission
Fungi	Aspergillosis	*Aspergillus* species	Ascomycetes	Opportunistic pathogen, inhalation of spores
	Athlete's foot	*Tinea pedis*	Ascomycetes	Physical contact
	Candidiasis, thrush	*Candida albicans*	Ascomycetes (yeasts)	Opportunistic pathogen, resident flora
	Pneumonia	*Pneumocystis carinii*	Ascomycetes	Opportunistic pathogen, resident lung flora
Protozoan parasites	Leishmaniasis	*Leishmania major*	Protozoa	Bite of an infected sand fly
	Malaria	*Plasmodium falciparum*	Protozoa	Bite of an infected mosquito
	Toxoplasmosis	*Toxoplasma gondii*	Protozoa	Oral, from infected material
	Trypanosomiasis	*Trypanosoma brucei*	Protozoa	Bite of an infected tsetse fly
Helminth parasites (worms)	Common roundworm	*Ascaris lumbricoides*	Nematodes (roundworms)	Oral, from infected material
	Schistosomiasis	*Schistosoma mansoni*	Trematodes	Through skin by bathing in infected water

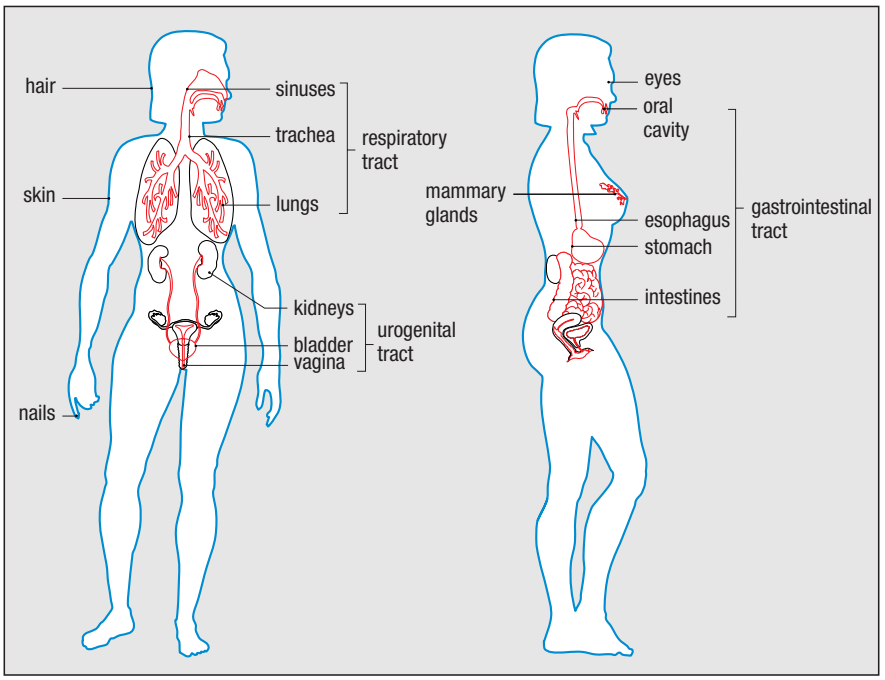

Figure 1.5 Physical barriers separate the body from its external environment. In these images of a woman, the strong barriers to infection provided by the skin, hair, and nails are colored blue and the more vulnerable mucosal membranes are colored red.

The fixed defenses of skin and mucosa provide well-maintained mechanical, chemical, and microbiological barriers that prevent most pathogens from gaining access to the cells and tissues of the body. When those barriers are breached and pathogens gain entry to the body's soft tissues, the defenses of the innate immune system are brought into play.

1-4 The innate immune response causes inflammation at sites of infection

Cuts, abrasions, bites, and wounds provide routes for pathogens to get through the skin. Touching, rubbing, picking and poking the eyes, nose, and mouth help pathogens to breach mucosal surfaces, as does breathing polluted air, eating contaminated food, and being around infected people. With very few exceptions, infections remain highly localized and are extinguished within a few days without illness or incapacitation. Such infections are controlled and terminated by the **innate immune response**, which is ready to react quickly. This response consists of two parts (Figure 1.6). The first is recognition that a pathogen is present. This involves soluble proteins and cell-surface receptors that bind either to the pathogen and its products or to human cells and serum proteins that become altered in the presence of the pathogen. Once the pathogen has been recognized, the second part of the response involves the recruitment of destructive **effector mechanisms** that kill and eliminate the pathogen. The effector mechanisms are provided by **effector cells** of various types that engulf bacteria, kill virus-infected cells, or attack protozoan parasites, and a battery of serum proteins called **complement** that help the effector cells by marking pathogens with molecular flags but also attack pathogens in their own right. Collectively, these defenses are called **innate immunity**. The word 'innate' refers to qualities a person is born with, and innate immunity comprises a genetically programmed set of responses that can be mobilized immediately an infection occurs. Many families of receptor proteins contribute to the recognition of pathogens in the innate immune response. They are of several different structural types and bind to chemically diverse ligands: peptides, proteins, glycoproteins, proteoglycans, peptidoglycan, carbohydrates, glycolipids, phospholipids, and nucleic acids.

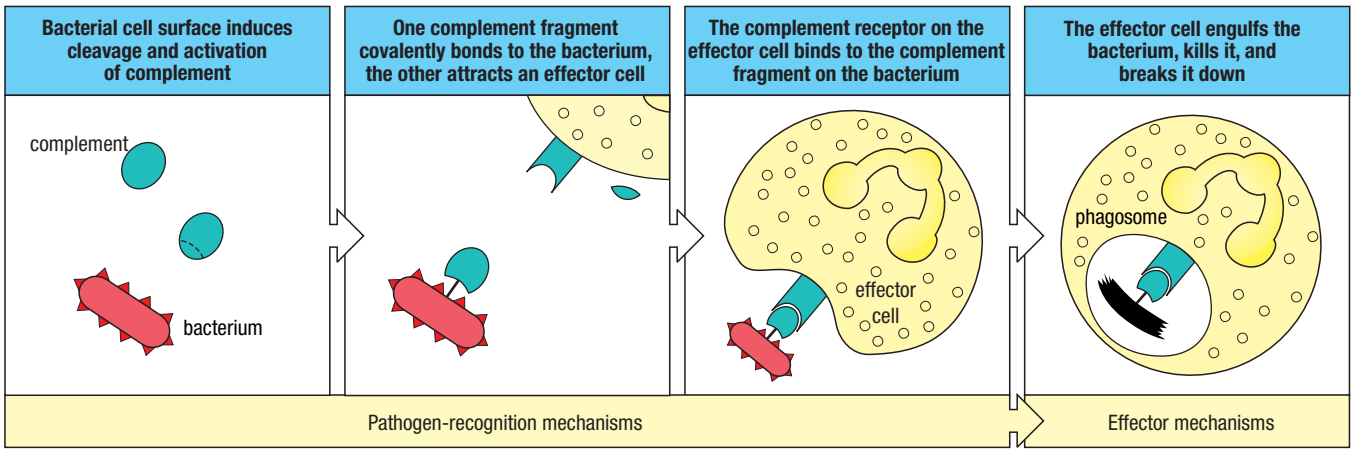

Figure 1.6 Immune defense involves recognition of pathogens followed by their destruction. Almost all components of the immune system contribute to mechanisms for either recognizing pathogens or destroying pathogens, or to mechanisms for communicating between these two activities. This is illustrated here by a fundamental process used to get rid of pathogens. Serum proteins of the complement system (turquoise) are activated in the presence of a pathogen (red) to form a covalent bond between a fragment of complement protein and the pathogen. The attached piece of complement marks the pathogen as dangerous. The soluble complement fragment summons a phagocytic white blood cell to the site of complement activation. This effector cell has a surface receptor that binds to the complement fragment attached to the pathogen. The receptor and its bound ligand are taken up into the cell by phagocytosis, which delivers the pathogen to an intracellular vesicle called a phagosome, where it is destroyed. A phagocyte is a cell that eats, 'phago' being derived from the Greek word for eat.

An infection that would typically be cleared by innate immunity is that experienced by skateboarders when they tumble onto a San Francisco sidewalk. On returning home the graze is washed, which removes most of the dirt and the associated pathogens of human, soil, pigeon, dog, cat, raccoon, skunk, and possum origin. Of the bacteria that remain, some begin to divide and set up an infection. Cells and proteins in the damaged tissue sense the presence of bacteria, and the cells send out soluble proteins called **cytokines** that interact with other cells to trigger the innate immune response. The overall effect of the innate immune response is to induce a state of **inflammation** in the infected tissue. Inflammation is an ancient concept in medicine that has traditionally been defined by the Latin words *calor*, *dolor*, *rubor*, and *tumor*: for heat, pain, redness, and swelling, respectively. These symptoms, which are part of everyday human experience, are not due to the infection itself but to the immune system's response to the pathogen.

Cytokines induce the local dilation of blood capillaries, which by increasing the blood flow causes the skin to warm and redden. Vascular dilation (vasodilation) introduces gaps between the cells of the **endothelium**, the thin layer of specialized epithelium that lines the interior of blood vessels. This makes the endothelium permeable and increases the leakage of blood plasma into the connective tissue. Expansion of the local fluid volume causes **edema** or swelling, putting pressure on nerve endings and causing pain. Cytokines also change the adhesive properties of the vascular endothelium, inviting white blood cells to attach to it and move from the blood into the inflamed tissue (Figure 1.7). White blood cells that are usually present in inflamed tissues and release substances that contribute to the inflammation are called **inflammatory cells**. Infiltration of cells into the inflamed tissue increases the swelling, and some of the molecules they release contribute to the pain. The benefit of the discomfort and disfigurement caused by inflammation is that it enables cells and molecules of the immune system to be brought rapidly and in large numbers into the infected tissue. The mechanisms of innate immunity are considered in Chapters 2 and 3.