

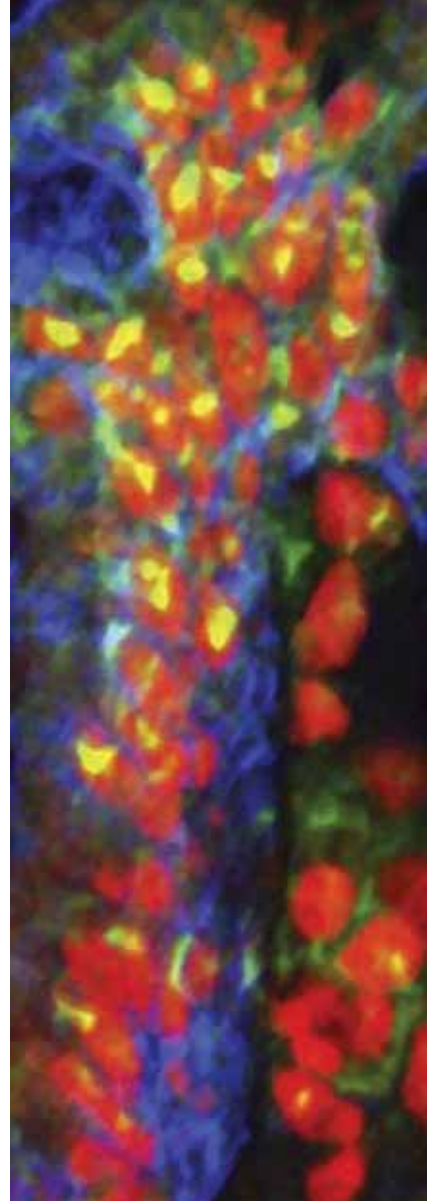
Chapter 1

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 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 enormous populations 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 provide protection from the disease in the future, 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 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 has dramatically reduced the incidence of smallpox worldwide, with the last cases being 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 will be 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 suffered by 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 500 microbial species live in the healthy adult human gut and contribute about two pounds 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 flora, for example the gut flora. 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 simple competition for space, *Escherichia coli*, a major bacterial component of the normal mammalian gut flora, secretes antibacterial



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.

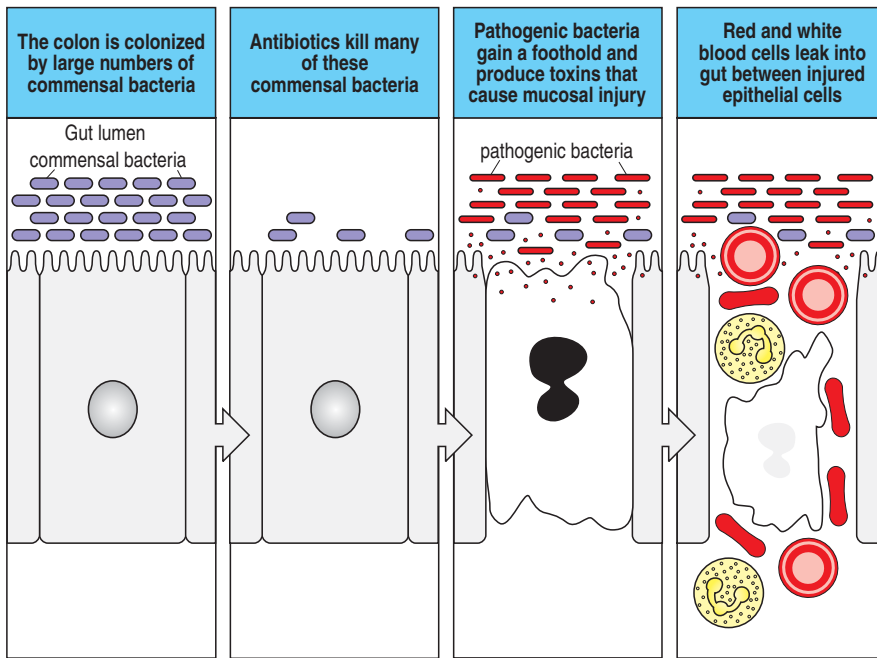


Figure 1.2 Antibiotic treatments disrupt the natural ecology of the colon. When antibiotics are taken orally to counter a bacterial infection, beneficial populations of commensal bacteria in the colon are also decimated. This provides an opportunity for pathogenic strains of bacteria to populate the 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.

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 flora 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 can cause 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 like 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 kinds of pathogen are known as **opportunistic pathogens**.

Pathogens can be divided into four kinds: **bacteria**, **viruses**, and **fungi**, which are each 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 provides a list of 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

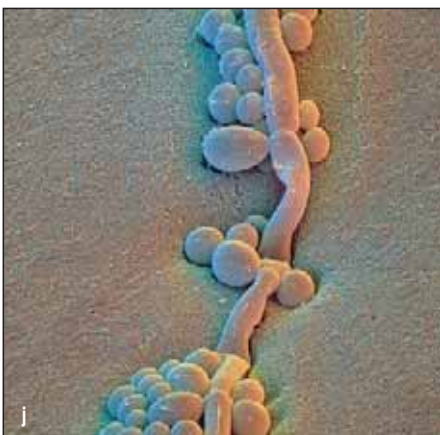
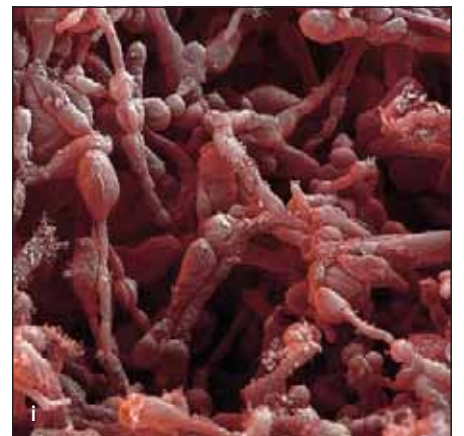
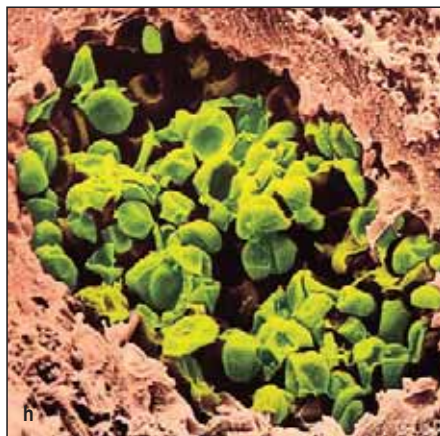
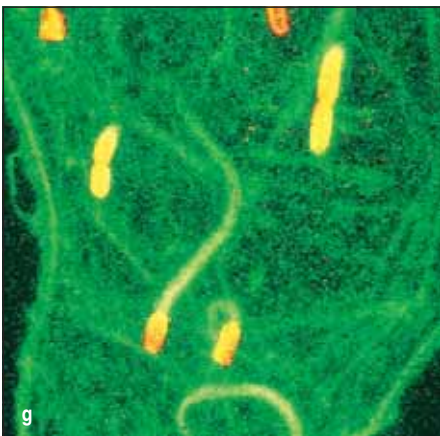
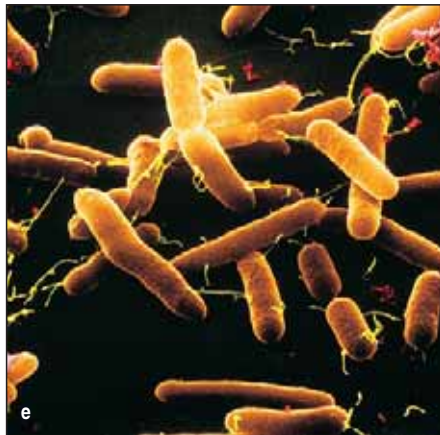
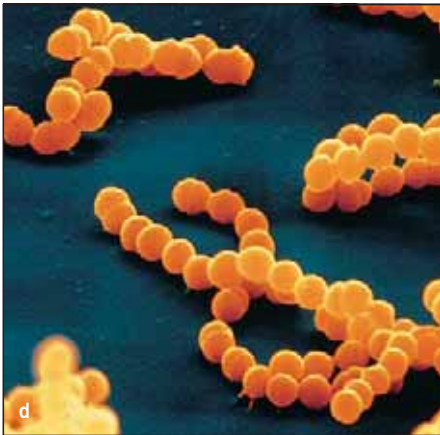
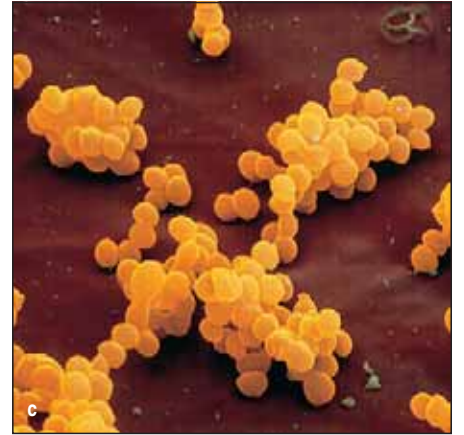
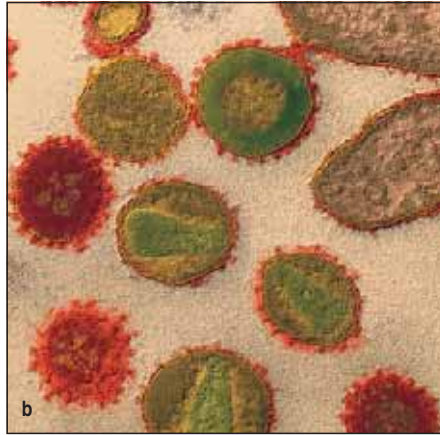
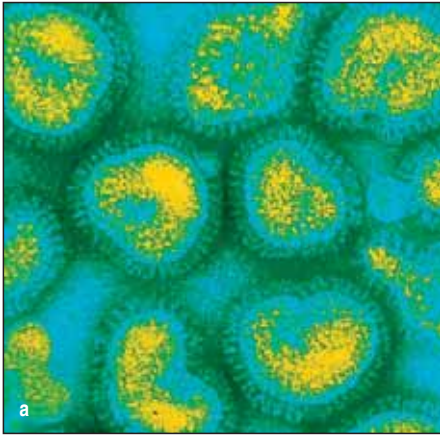


Figure 1.3 The diversity of microorganisms that are human pathogens. (a) Human immunodeficiency virus (HIV), the cause of AIDS. (b) Influenza virus. (c) *Staphylococcus aureus*, a bacterium that colonizes human skin, is the common cause of pimples and boils, and can also cause food poisoning. (d) *Streptococcus pyogenes*, the bacterium that is the principal cause of tonsillitis and scarlet fever and can also cause ear infections. (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.

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 both its home and its source of food. Consequently, those organisms with the potential to cause severe and rapidly fatal disease often tend to evolve towards an accommodation with their hosts. In complementary fashion, human populations have evolved 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.

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

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 (<i>Aedes aegypti</i>)
	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	

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 World War II stimulated studies on skin transplantation that led directly to the understanding of the cellular basis of the immune response.

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** that 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 bearing 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 breathed in.

All epithelial surfaces also 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 called **defensins** 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 of the stomach, the vagina, and the skin.

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

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.

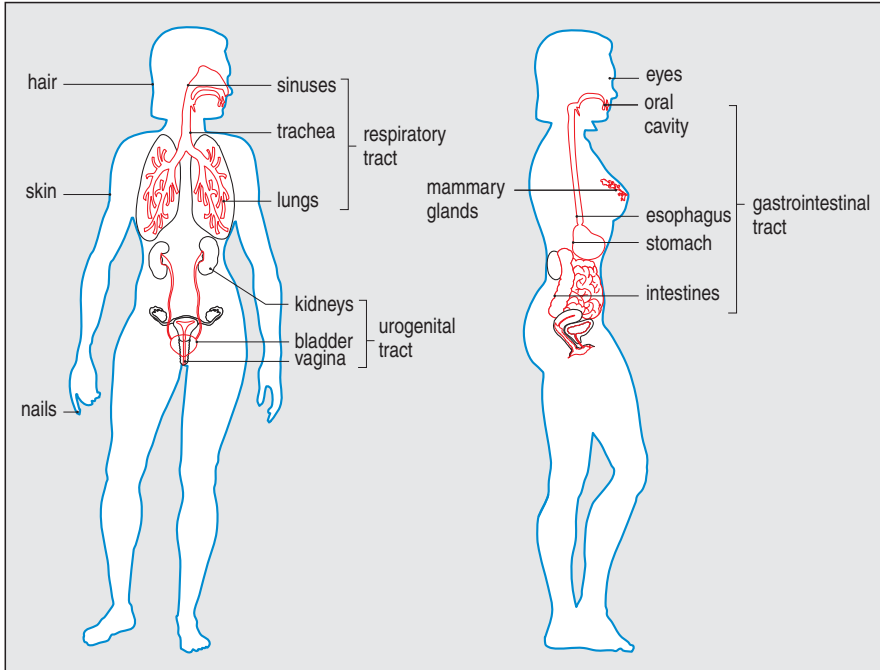


Figure 1.5 The physical barriers that separate the body from its external environment. In these images of a woman, the strong barriers to infection provided by the skin, hair, and nails are colored blue and the more vulnerable mucosal membranes are colored red.

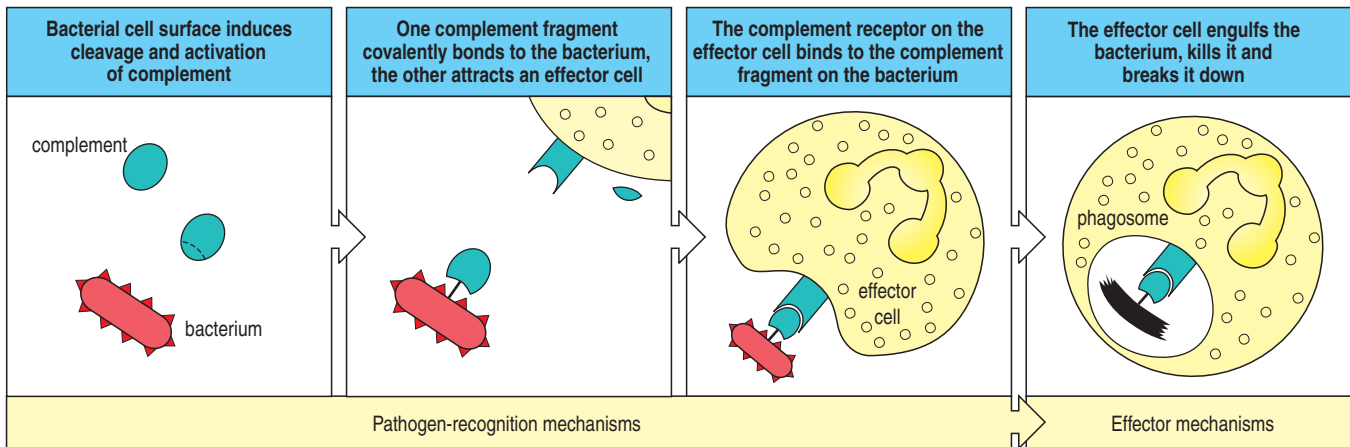
With such defenses, skin and mucosa provide well-maintained mechanical, chemical, and microbiological barriers (see Section 1-1) that prevent most pathogens from gaining access to the cells and tissues of the body (Figure 1.6). When that barrier is breached and pathogens gain entry to the body’s soft tissues, the fixed 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.

	Skin	Gastrointestinal tract	Respiratory tract	Urogenital tract	Eyes
Mechanical	Epithelial cells joined by tight junctions				
	Flow of fluid, perspiration, sloughing off of skin	Flow of fluid, mucus, food, and saliva	Flow of fluid and mucus, e.g., by cilia Air flow	Flow of fluid, urine, mucus, sperm	Flow of fluid, tears
Chemical	Sebum (fatty acids, lactic acid, lysozyme)	Acidity, enzymes (proteases)	Lysozyme in nasal secretions	Acidity in vaginal secretions Spermine and zinc in semen	Lysozyme in tears
	Antimicrobial peptides (defensins)				
Microbiological	Normal flora of the skin	Normal flora of the gastrointestinal tract	Normal flora of the respiratory tract	Normal flora of the urogenital tract	Normal flora of the eyes

Figure 1.6 Various barriers prevent bacteria from crossing epithelia and colonizing tissues. Surface epithelia provide mechanical, chemical, and microbiological barriers to infection.



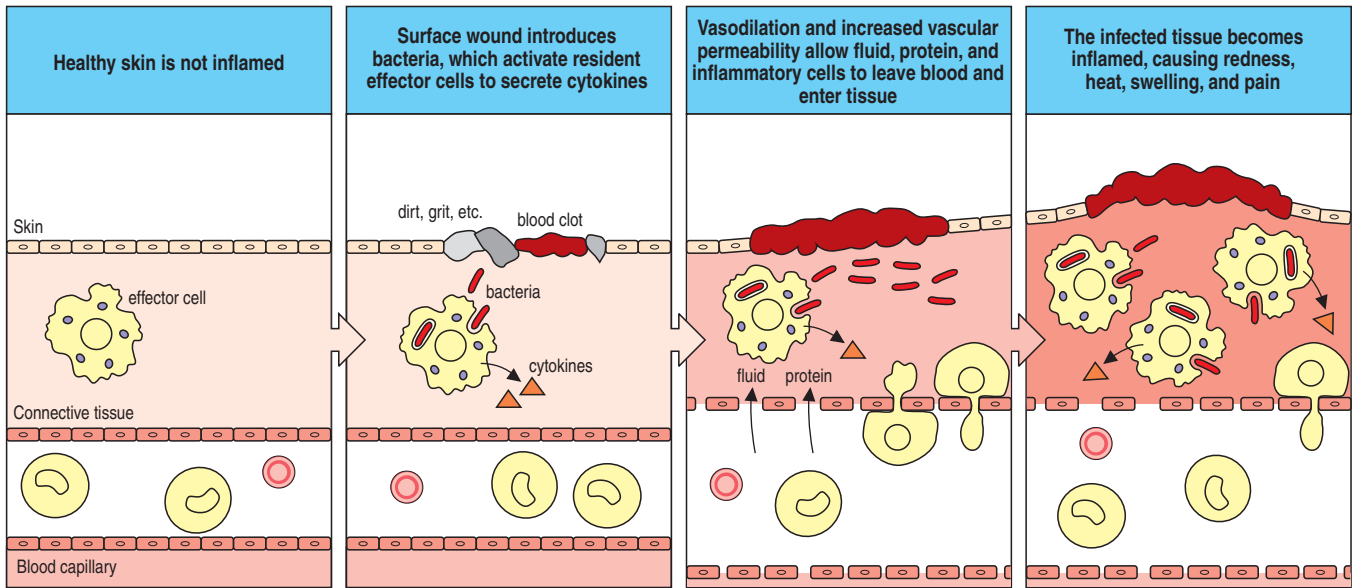
This response consists of two parts (Figure 1.7). First is recognition that a pathogen is present. This involves soluble proteins and cell-surface receptors that bind either to the pathogen and its products or to human cells and serum proteins that become altered in the presence of the pathogen. Once the pathogen has been recognized, the second part of the response involves the recruitment of destructive **effector mechanisms** that kill and eliminate it. 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 the fact that they are all determined entirely by the genes a person inherits from their parents. 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.

An infection that would typically be cleared by innate immunity is of the sort 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 it.

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 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.



(Figure 1.8). 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.

Figure 1.8 Innate immune mechanisms establish a state of inflammation at sites of infection. Illustrated here are the events following an abrasion of the skin. Bacteria invade the underlying connective tissue and stimulate the innate immune response.

1-5 The adaptive immune response adds to an ongoing innate immune response

Human beings are exposed to pathogens on a daily basis. The intensity of exposure and the diversity of the pathogens encountered increase with crowded city living and the daily exchange of people and pathogens from international airports. Despite this exposure, innate immunity keeps most people healthy for most of the time. Nevertheless, some infections outrun the innate immune response, an event more likely in people who are malnourished, poorly housed, deprived of sleep, or stressed in other ways. When this occurs, the innate immune response works to slow the spread of infection while it calls upon white blood cells called **lymphocytes** that increase the power and focus of the immune response. Their contribution to defense is the **adaptive immune response**. It is so called because it is organized around an ongoing infection and adapts to the nuances of the infecting pathogen. Consequently, the long-lasting **adaptive immunity** that develops against one pathogen provides a highly specialized defense that is of little use against infection by a different pathogen.

The effector mechanisms used in the adaptive immune response are similar to those used in the innate immune response; the important difference is in the cell-surface receptors used by lymphocytes to recognize pathogens (Figure 1.9). In contrast to the receptors of innate immunity, which are of many different types but are not specific for a particular pathogen, the receptors of adaptive immunity are all of the same molecular type and are highly pathogen-specific. They are not encoded by conventional genes but by genes that are cut, spliced, and modified to produce billions of variants of the basic receptor type, so that different lymphocytes bear different variants. During infection, only those lymphocytes bearing receptors that recognize the infecting pathogen are selected to participate in the adaptive response. These then proliferate and differentiate to produce large numbers of effector cells specific for

Recognition mechanisms of innate immunity	Recognition mechanisms of adaptive immunity
Rapid response (hours)	Slow response (days to weeks)
Fixed	Variable
Limited number of specificities	Numerous highly selective specificities
Constant during response	Improve during response

Common effector mechanisms for the destruction of pathogens

Figure 1.9 The principal characteristics of innate and adaptive immunity.

that pathogen (Figure 1.10). These processes, which select a small subset of lymphocytes for proliferation and differentiation into effector lymphocytes, are called **clonal selection** and **clonal expansion**, respectively. As these processes take time, the benefit of an adaptive immune response only begins to be felt about a week after the infection has started.

The value of the adaptive immune response is well illustrated in influenza, which is caused by infection of the epithelial cells in the lower respiratory tract with influenza virus. The debilitating symptoms start 3 or 4 days after the start of infection, when the virus has begun to outrun the innate immune response. The disease persists for 5–7 days while the adaptive immune response is being organized and put to work. As the adaptive immune response gains the upper hand, fever subsides and a gradual convalescence begins in the second week after infection.

Some of the lymphocytes selected during an adaptive immune response persist in the body and provide long-term **immunological memory** of the pathogen. These memory cells allow subsequent encounters with the same pathogen to elicit a stronger and faster adaptive immune response, which terminates infection with minimal illness. The adaptive immunity provided by immunological memory is also called **acquired immunity** or **protective immunity**. For some pathogens such as measles virus, one full-blown infection can provide immunity for decades, whereas for influenza the effect seems more short-lived. This is not because the immunological memory is faulty but because the influenza virus changes on a yearly basis to escape the immunity acquired by its human hosts.

The first time that an adaptive immune response is made to a given pathogen it is called the **primary immune response**. The second and subsequent times that an adaptive immune response is made, and when immunological memory applies, it is called a **secondary immune response**. The purpose of vaccination is to induce immunological memory to a pathogen so that subsequent

Figure 1.10 Selection of lymphocytes by a pathogen. Top panel: during its development from a progenitor cell (gray) a lymphocyte is programmed to make a single species of cell-surface receptor that recognizes a particular molecular structure. Each lymphocyte makes a receptor of different specificity, so that the population of circulating lymphocytes includes many millions of such receptors, all recognizing different structures, which enables all possible pathogens to be recognized. Lymphocytes with different receptor specificities are represented by different colors. Center panel: upon infection by a particular pathogen, only a small subset of lymphocytes (represented by the yellow cell) will have receptors that bind to the pathogen or its components. Bottom panel: these lymphocytes are stimulated to divide and differentiate, thereby producing an expanded population of effector cells from each pathogen-binding lymphocyte.

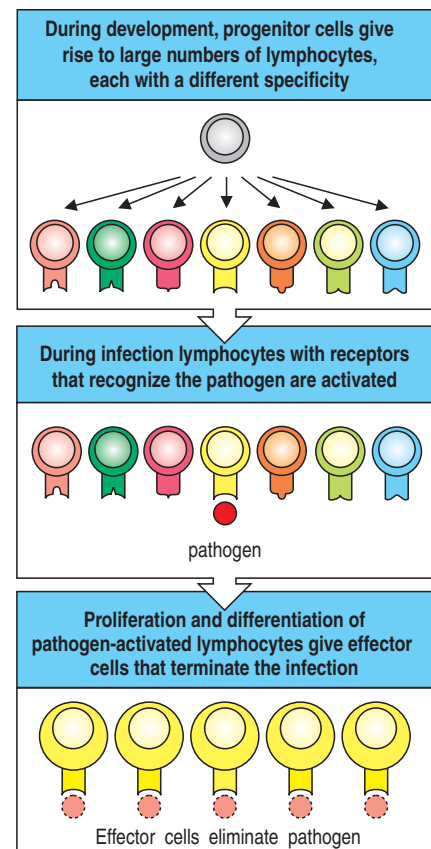


Figure 1.11 The benefits of having both innate and adaptive immunity. In normal individuals, a primary infection is cleared from the body by the combined effects of innate and adaptive immunity (yellow line). In a person who lacks innate immunity, uncontrolled infection occurs because the adaptive immune response cannot be deployed without the preceding innate response (red line). In a person who lacks adaptive immune responses, the infection is initially contained by innate immunity but cannot be cleared from the body (green line).

infection with the pathogen elicits a strong fast-acting adaptive response. Because all adaptive immune responses are contingent upon an innate immune response, vaccines must induce both innate and adaptive immune responses.

1-6 Adaptive immunity is better understood than innate immunity

The proportion of infections that are successfully eliminated by innate immunity is difficult to assess, mainly because such infections are overcome before they have caused symptoms severe enough to command the attention of those infected or of their physicians. Intuitively, it seems likely to be a high proportion, given the human body's capacity to sustain vast populations of resident microorganisms without these causing symptoms of disease. The importance of innate immunity is also implied by the rarity of inherited deficiencies in innate immune mechanisms and the considerable impairment of protection when these deficiencies do occur (Figure 1.11).

Much of medical practice is concerned with the small proportion of infections that innate immunity fails to terminate and in which the spread of the infection results in overt disease such as pneumonia, measles, or influenza and stimulates an adaptive immune response. In such situations the attending physicians and the adaptive immune response work together to effect a cure, a partnership that has historically favored the scientific investigation of adaptive immunity over innate immunity. Consequently, less has been learnt about innate immunity than adaptive immunity. Now that immunologists realize that innate immunity mechanisms are fundamental to every immune response, this gap in knowledge is being filled.

1-7 Immune system cells with different functions all derive from hematopoietic stem cells

The cells of the immune system are principally the white blood cells or **leukocytes**, and the tissue cells related to them. Along with the other blood cells, they are continually being generated by the body in the developmental process known as **hematopoiesis**. Leukocytes derive from a common progenitor called the **pluripotent hematopoietic stem cell**, which also gives rise to red blood cells (**erythrocytes**) and **megakaryocytes**, the source of **platelets**. All these cell types, together with their precursor cells, are collectively called **hematopoietic cells** (Figure 1.12). The anatomical site for hematopoiesis changes with age (Figure 1.13). In the early embryo, blood cells are first produced in the yolk sac and later in the fetal liver. From the third to the seventh month of fetal life the spleen is the major site of hematopoiesis. As the bones develop during the fourth and fifth months of fetal growth, hematopoiesis begins to shift to the **bone marrow** and by birth this is where practically all hematopoiesis takes place. In adults, hematopoiesis occurs mainly in the bone marrow of the skull, ribs, sternum, vertebral column, pelvis, and femurs. Because blood cells are short-lived, they have to be continually renewed, and hematopoiesis is active throughout life.

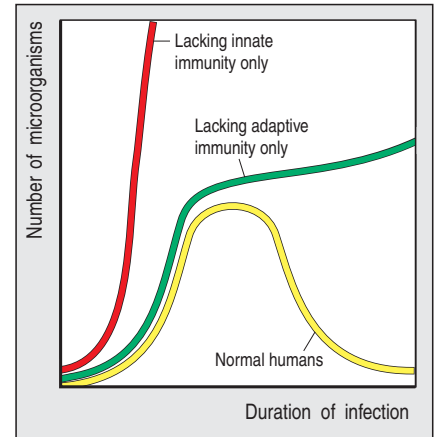
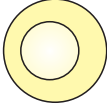

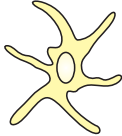
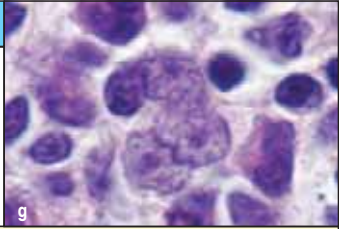


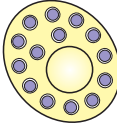



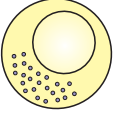

Figure 1.12 (opposite page) Types of hematopoietic cell. The different types of hematopoietic cell are depicted in schematic diagrams, which indicate their characteristic morphological features, and in accompanying light micrographs. Their main functions are indicated. We shall use these schematic representations for these cells throughout the book. Megakaryocytes (k) reside in bone marrow and release tiny non-nucleated, membrane-bound packets of cytoplasm, which circulate in the blood and are known as platelets. Red blood cells (erythrocytes) (l) are smaller than the white blood cells and have no nucleus. Original magnification $\times 15,000$. Photographs courtesy of Yasodha Natkunam.



Small lymphocyte	
	
	a
Production of antibodies (B cells) or cytotoxic and helper functions (T cells)	

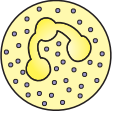

Dendritic cell	
	
	g
Activation of T cells and initiation of adaptive immune responses	

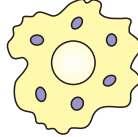
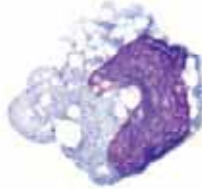
Plasma cell	
	
	b
Fully differentiated form of B cell that secretes antibodies	

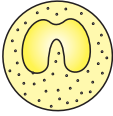
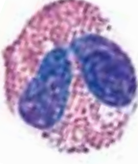
Mast cell	
	
	h
Expulsion of parasites from body through release of granules containing histamine and other active agents	

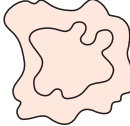
Natural killer cell	
	
	c
Kills cells infected with certain viruses	


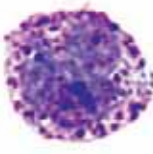
Monocyte	
	
	i
Circulating precursor cell to macrophage	



Neutrophil	
	
	d
Phagocytosis and killing of microorganisms	

Macrophage	
	
	j
Phagocytosis and killing of microorganisms. Activation of T cells and initiation of immune responses	

Eosinophil	
	
	e
Killing of antibody-coated parasites through release of granule contents	

Megakaryocyte	
	
	k
Platelet formation, wound repair	

Basophil	
	
	f
Controlling immune responses to parasites	

Erythrocyte	
	
	l
Oxygen transport	

Hematopoietic stem cells can divide to give further hematopoietic stem cells, a process called **self renewal**; they can also become more mature stem cells that commit to one of three cell lineages: the erythroid, myeloid, and lymphoid lineages (Figure 1.14). The erythroid progenitor gives rise to the erythroid lineage of blood cells—the oxygen-carrying erythrocytes and the platelet-producing megakaryocytes. Platelets are small non-nucleated cell fragments of plate-like shape that maintain the integrity of blood vessels. They initiate and participate in the clotting reactions that block badly damaged blood vessels to prevent blood loss. Megakaryocytes are giant cells that arise from the fusion of multiple precursor cells and have nuclei containing multiple sets of chromosomes (megakaryocyte means cell with giant nucleus). Megakaryocytes are permanent residents of the bone marrow. Platelets are small packets of membrane-bounded cytoplasm that break off from these cells.

The **myeloid progenitor** gives rise to the **myeloid lineage** of cells. One group of myeloid cells consists of the **granulocytes**, which have prominent cytoplasmic granules containing reactive substances that kill microorganisms and enhance inflammation. Because granulocytes have irregularly shaped nuclei with two to five lobes, they are also called **polymorphonuclear leukocytes**. Most abundant of the granulocytes, and of all white blood cells, is the **neutrophil** (Figure 1.15), which is specialized in the capture, engulfment and killing of microorganisms. Cells with this function are called **phagocytes**, of which neutrophils are the most numerous and most lethal. Neutrophils are effector cells of innate immunity that are rapidly mobilized to enter sites of infection and can work in the anaerobic conditions that often prevail in damaged tissue. They are short-lived and die at the site of infection, forming **pus**, the stuff of pimples and boils (Figure 1.16). The second most abundant granulocyte is the **eosinophil**, which defends against helminth worms and other intestinal parasites. The least abundant granulocyte, the **basophil**, is also implicated in regulating the immune response to parasites but is so rare that relatively little is known of its contribution to immune defense. The names of

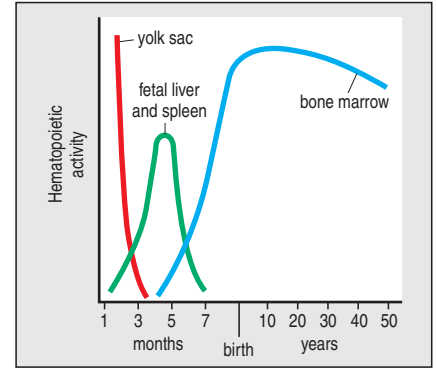


Figure 1.13 The site of hematopoiesis in humans changes during development. Blood cells are first made in the yolk sac of the embryo and subsequently in the embryonic liver. They start to be made in the bone marrow before birth, and by the time of birth this is the only tissue in which hematopoiesis occurs.

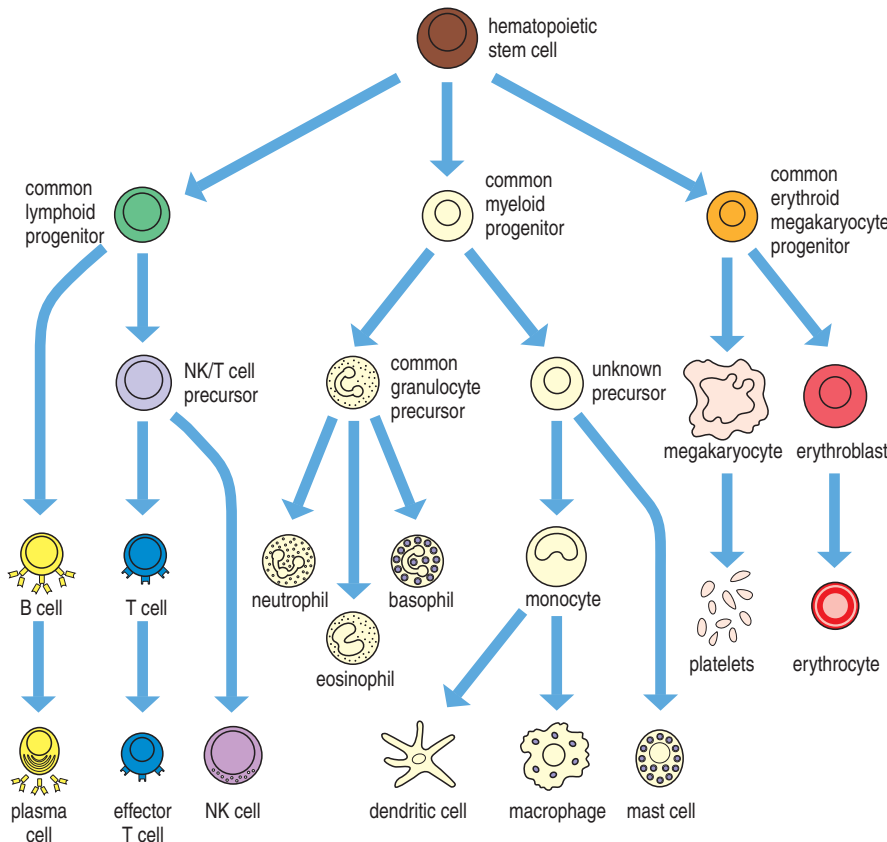


Figure 1.14 Blood cells and certain tissue cells derive from a common hematopoietic stem cell. The pluripotent stem cell (brown) divides and differentiates into more specialized progenitor cells that give rise to the lymphoid lineage, the myeloid lineage, and the erythroid lineage. The common lymphoid progenitor divides and differentiates to give B cells (yellow), T cells (blue), and NK cells (purple). On activation by infection, B cells divide and differentiate into plasma cells, whereas T cells differentiate into various types of effector T cell. The myeloid progenitor cell divides and differentiates to produce at least six cell types. These are: the three types of granulocyte—the neutrophil, the eosinophil, and the basophil; the mast cell, which takes up residence in connective and mucosal tissues; the circulating monocyte, which gives rise to the macrophages resident in tissues; and the dendritic cell. The word myeloid means ‘of the bone marrow.’

the granulocytes refer to the staining of their cytoplasmic granules with commonly used histological stains: the eosinophil's granules contain basic substances that bind the acidic stain eosin, the basophil's granules contain acidic substances that bind basic stains such as hematoxylin, and the contents of the neutrophil's granules bind to neither acidic nor basic stains.

The second group of myeloid cells consists of monocytes, macrophages, and dendritic cells. **Monocytes** are leukocytes that circulate in the blood. They are distinguished from the granulocytes by being bigger, by having a distinctive indented nucleus, and by all looking the same: hence the name monocyte. Monocytes are the mobile progenitors of sedentary tissue cells called **macrophages**. They travel in the blood to tissues, where they mature into macrophages and take up residence. The name macrophage means 'large phagocyte,' and like the neutrophil, which was once called the microphage, the macrophage is well equipped for phagocytosis. Tissue macrophages are large, irregularly shaped cells characterized by an extensive cytoplasm with numerous vacuoles, often containing engulfed material (Figure 1.17). They are the general scavenger cells of the body, phagocytosing and disposing of dead cells and cell debris as well as invading microorganisms.

If neutrophils are the short-lived infantry of innate immunity, then macrophages are the long-lived commanders who provide a warning to other cells and orchestrate the local response to infection. Macrophages present in the infected tissues are generally the first phagocytic cell to sense an invading microorganism. As part of their response to the pathogen, macrophages secrete the cytokines that recruit neutrophils and other leukocytes into the infected area.

Dendritic cells are resident in the body's tissues and have a distinctive star-shaped morphology. Although they have many properties in common with macrophages, their unique function is to act as cellular messengers that are sent to call up an adaptive immune response when it is needed. At such times, dendritic cells that reside in the infected tissue will leave the tissue with a cargo of intact and degraded pathogens and take it to one of several lymphoid organs that specialize in making adaptive immune responses.

The last type of myeloid cell is the **mast cell**, which is resident in all connective tissues. It has granules like those of the basophil, but it is not developmentally derived from the basophil and the nature of its blood-borne progenitor is not yet known. The activation and degranulation of mast cells at sites of infection make a major contribution to inflammation.

Cell type	Proportion of leukocytes (%)
Neutrophil	40–75
Eosinophil	1–6
Basophil	<1
Monocyte	2–10
Lymphocyte	20–50

Figure 1.15 The relative abundance of the leukocyte cell types in human peripheral blood. The values given for each cell type are the normal ranges found in venous blood taken from healthy donors.

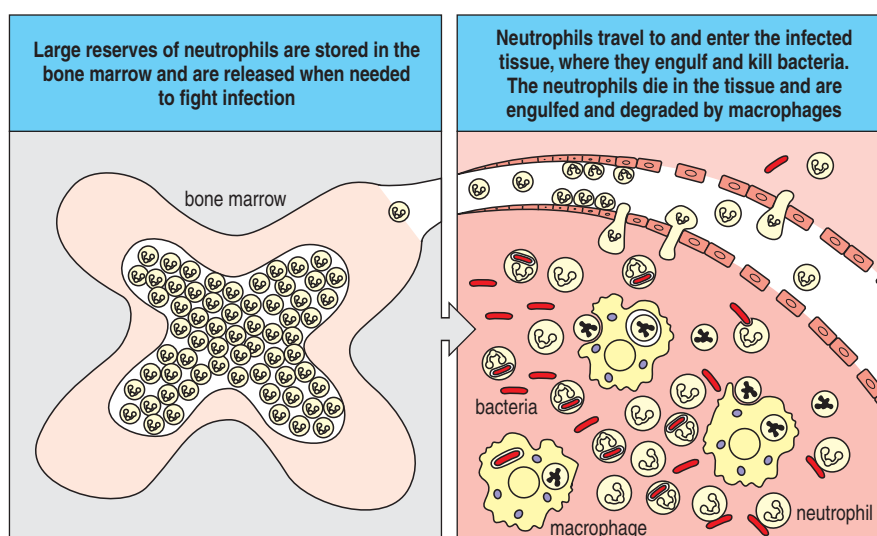
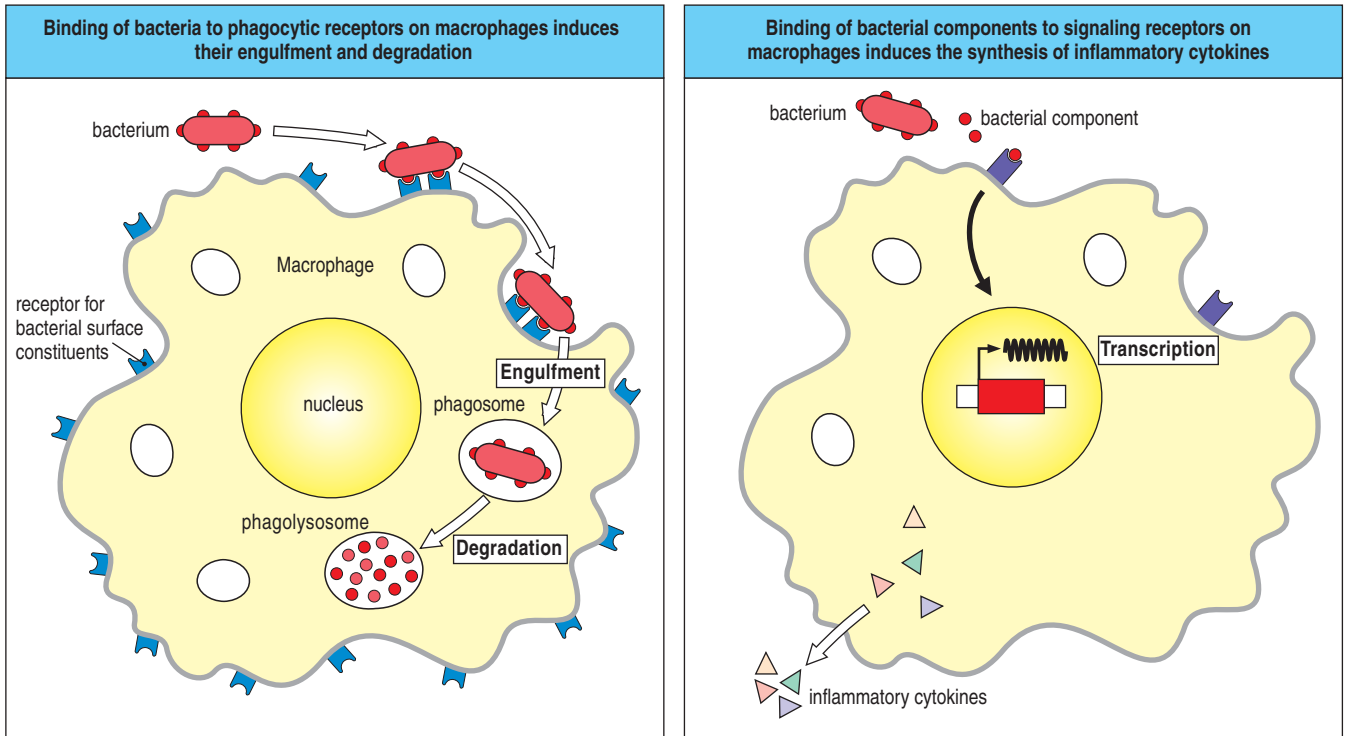


Figure 1.16 Neutrophils are stored in the bone marrow and move in large numbers to sites of infection, where they act and then die. After one round of ingestion and killing of bacteria, a neutrophil dies. The dead neutrophils are eventually mopped up by long-lived tissue macrophages, which break them down. The creamy material known as pus is composed of dead neutrophils.



The **lymphoid progenitor** gives rise to the **lymphoid lineage** of white blood cells. Two populations of blood lymphocytes are distinguished morphologically: large lymphocytes with a granular cytoplasm and small lymphocytes with almost no cytoplasm. The **large granular lymphocytes** are effector cells of innate immunity called **natural killer cells** or **NK cells**. NK cells are important in the defense against viral infections. They enter infected tissues, where they prevent the spread of infection by killing virus-infected cells and secreting cytokines that impede viral replication in infected cells. The **small lymphocytes** are the cells responsible for the adaptive immune response. They are small because they circulate in a quiescent and immature form that is functionally inactive. Recognition of a pathogen by small lymphocytes drives a process of lymphocyte selection, growth and differentiation that after 1–2 weeks produces a powerful response tailored to the invading organism.

The small lymphocytes, although morphologically indistinguishable from each other, comprise several sublineages that are distinguished by their cell-surface receptors and the functions they are programmed to perform. The most important difference is between **B lymphocytes** and **T lymphocytes**, also called **B cells** and **T cells**, respectively. For B cells the cell-surface receptors for pathogens are **immunoglobulins**, whereas those of T cells are known as **T-cell receptors**. Immunoglobulins and T-cell receptors are structurally similar molecules that are the products of genes that are cut, spliced, and modified during lymphocyte development. As a consequence of these processes each B cell expresses a single type of immunoglobulin and each T cell expresses a single type of T-cell receptor. Many millions of different immunoglobulins and T-cell receptors are represented within the population of small lymphocytes in one human being.

T cells are further subdivided into two kinds, called **cytotoxic T cells** and **helper T cells** according to the effector functions they perform after they have become activated. Cytotoxic T cells kill cells that are infected with either viruses or bacteria that live and reproduce inside human cells. NK cells and cytotoxic T cells have similar effector functions, the former providing such functions during the innate immune response, the latter during the adaptive

Figure 1.17 Macrophages respond to pathogens by using different receptors to stimulate phagocytosis and cytokine secretion. The left panel shows receptor-mediated phagocytosis of bacteria by a macrophage. The bacterium (red) binds to cell-surface receptors (blue) on the macrophage, inducing engulfment of the bacterium into an internal vesicle called a phagosome within the macrophage cytoplasm. Fusion of the phagosome with lysosomes forms an acidic vesicle called a phagolysosome, which contains toxic small molecules and hydrolytic enzymes that kill and degrade the bacterium. The right panel shows how a bacterial component binding to a different type of cell-surface receptor sends a signal to the macrophage's nucleus that initiates the transcription of genes for inflammatory cytokines. The cytokines are synthesized in the cytoplasm and secreted into the extracellular fluid.

immune response. Helper T cells secrete cytokines that help other cells of the immune system become fully activated effector cells. For example, some subsets of helper T cells help activate B cells to become **plasma cells**. Plasma cells are effector cells that secrete soluble forms of immunoglobulin called **antibodies** that bind to pathogens and the toxic products they make.

1-8 Most lymphocytes are present in specialized lymphoid tissues

Although doctors and immunologists usually sample and study human lymphocytes from blood samples taken from their patients and voluntary donors, the vast majority of lymphocytes are to be found in specialized tissues known as **lymphoid tissues** or **lymphoid organs**. The major lymphoid organs are bone marrow, thymus, spleen, adenoids, tonsils, appendix, lymph nodes, and Peyer’s patches (Figure 1.18). Less organized lymphoid tissue is also found lining the mucosal surfaces of the respiratory, gastrointestinal, and urogenital tracts. The lymphoid tissues are functionally divided into two types. **Primary or central lymphoid tissues** are where lymphocytes develop and mature to the stage at which they are able to respond to a pathogen. The bone marrow and the **thymus** are the primary lymphoid tissues; B and T lymphocytes both originate from lymphoid precursors in the bone marrow (see Section 1-7, p. 12), but whereas B cells complete their maturation in the bone marrow before entering the circulation, T cells leave the bone marrow at an immature stage and migrate in the blood to the thymus and mature there. Apart from the bone marrow and the thymus, all other lymphoid tissues are known as **secondary or peripheral lymphoid tissues**; they are the sites where mature lymphocytes become stimulated to respond to invading pathogens.

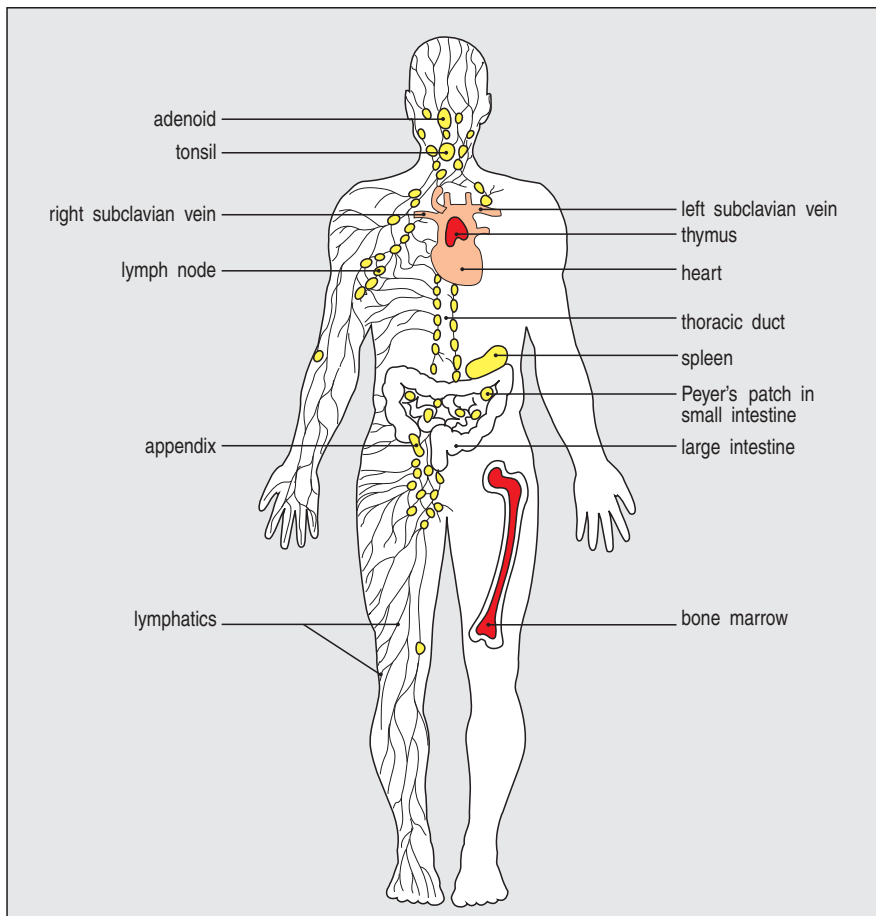


Figure 1.18 The sites of the principal lymphoid tissues within the human body. Lymphocytes arise from stem cells in the bone marrow. B cells complete their maturation in the bone marrow, whereas T cells leave at an immature stage and complete their development in the thymus. The bone marrow and the thymus are the primary lymphoid tissues and are shown in red. The secondary lymphoid tissues are shown in yellow and the thin black branching lines are the lymphatics. Plasma that has leaked from the blood is collected by the lymphatics as lymph and is returned to the blood via the thoracic duct, which empties into the left subclavian vein.

Lymph nodes lie at the junctions of an anastomosing network of **lymphatic vessels** called the **lymphatics**, which originate in the connective tissues throughout the body and collect the plasma that continually leaks out of blood vessels and forms the extracellular fluid. The lymphatics eventually return this fluid, called **lymph**, to the blood, chiefly via the thoracic duct, which empties into the left subclavian vein in the neck. Unlike the blood, the lymph is not driven by a dedicated pump and its flow is comparatively sluggish. One-way valves within lymphatic vessels, and the lymph nodes placed at their junctions, ensure that net movement of the lymph is always in a direction away from the peripheral tissues and towards the ducts in the upper body where the lymph empties into the blood. The flow of lymph is driven by the continual movements of one part of the body with respect to another. In the absence of such movement, as when a patient is confined to bed for a long time, lymph flow slows and fluid accumulates in tissues, causing the swelling known as edema.

A unique property of mature B and T cells, which distinguishes them from other blood cells, is that they move through the body in both blood and lymph. Lymphocytes are the only cell type present in lymph in any numbers; hence their name. When small lymphocytes leave the primary lymphoid tissues in which they have developed, they enter the bloodstream. When they reach the blood capillaries that invest a lymph node, or other secondary lymphoid tissue, small lymphocytes can leave the blood and enter the lymph node proper. If a lymphocyte becomes activated by a pathogen it remains in the lymph node; otherwise it will spend some time there and then leave in the efferent lymph and eventually be returned to the blood. This means that the population of lymphocytes within a node is in a continual state of flux, with new lymphocytes entering from the blood while others leave in the efferent lymph. This pattern of movement between blood and lymph is termed **lymphocyte recirculation** (Figure 1.19). It allows the lymphocyte population to continually survey the secondary lymphoid organs for evidence of infection. An

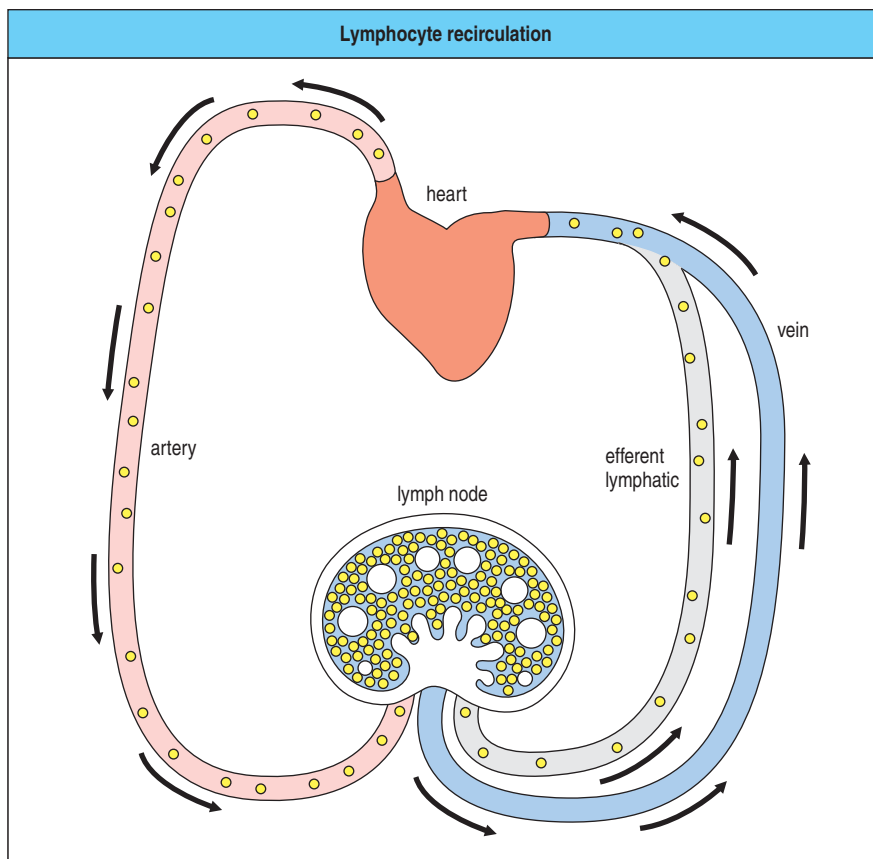


Figure 1.19 Lymphocyte recirculation.

Small lymphocytes are unique among blood cells in traveling through the body in the lymph as well as the blood. That is why they were named lymphocytes. Lymphocytes leave the blood through the walls of fine capillaries in secondary lymphoid organs. A lymph node is illustrated here. After spending some time in the lymph node, lymphocytes leave in the efferent lymph and return to the blood at the left subclavian vein. If a lymphocyte in a lymph node encounters a pathogen to which its cell-surface receptor binds, it stops recirculating.

exception to this pattern is the spleen, which has no connections to the lymphatic system. Lymphocytes both enter and leave the spleen in the blood.

The secondary lymphoid organs are dynamic tissues in which lymphocytes are constantly arriving from the blood and departing in the lymph. At any one time only a very small fraction of lymphocytes are in the blood and lymph; the majority are in lymphoid organs and tissues.

1-9 Adaptive immunity is initiated in secondary lymphoid tissues

Experiments involving deliberate infection of volunteers show that a large initial dose of pathogenic microorganisms is usually necessary to cause disease. To establish an infection a microorganism must colonize a tissue in sufficient numbers to overwhelm the cells and molecules of innate immunity that are promptly recruited from the blood to the site of invasion. Even in these circumstances the effects will usually be minor unless the infection can spread within the body. Frequent sites of infection are the connective tissues, which pathogens penetrate as a result of skin wounds. From such sites intact pathogens, components of pathogens and pathogen-infected dendritic cells are carried by the lymphatics to the nearest **lymph node**. The lymph node receiving the fluid collected at an infected site is called the **draining lymph node** (Figure 1.20).

The anatomy of the lymph node provides meeting places where lymphocytes coming from the blood encounter pathogens and their products brought from infected connective tissue (Figure 1.21). Arriving lymphocytes segregate

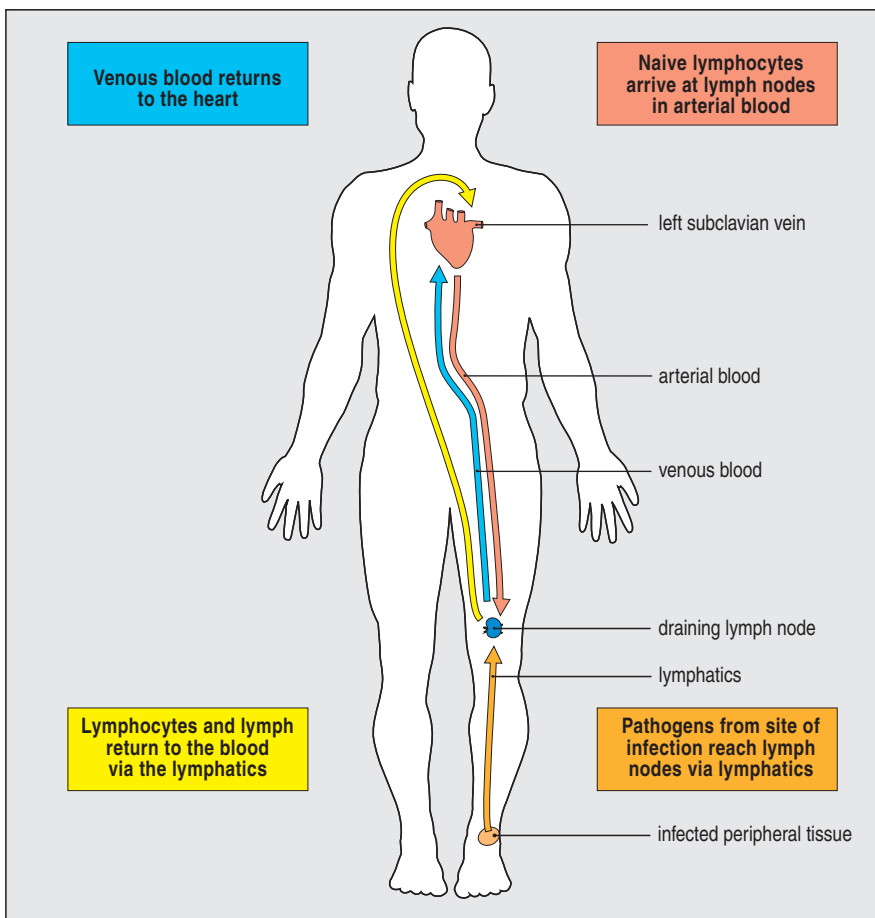


Figure 1.20 Circulating lymphocytes meet lymph-borne pathogens in draining lymph nodes. Lymphocytes leave the blood and enter lymph nodes, where they can be activated by pathogens in the afferent lymph draining from a site of infection. The circulation pertaining to a site of infection in the left foot is shown here. When activated by pathogens, lymphocytes stay in the node to divide and differentiate into effector cells. If lymphocytes are not activated, they leave the node in the efferent lymph and are carried by the lymphatics to the thoracic duct (see Figure 1.18), which empties into the blood at the left subclavian vein. Lymphocytes recirculate all the time, irrespective of infection. Every minute, 5×10^6 lymphocytes leave the blood and enter secondary lymphoid tissues.

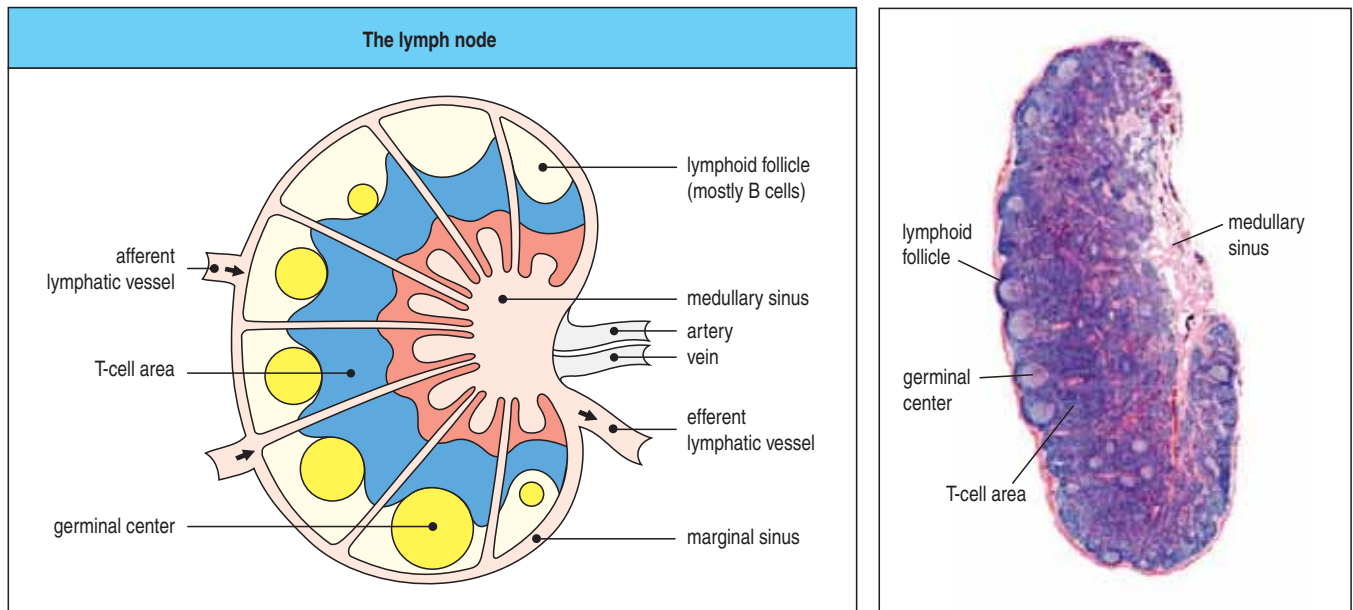


Figure 1.21 Architecture of the lymph node, the site where blood-borne lymphocytes respond to lymph-borne pathogens. Human lymph nodes are small kidney-shaped organs about 1.2 centimeters long and weighing 1 gram or less. They are located at junctions in the lymphatic system where a number of afferent lymph vessels bringing lymph from the tissues unite to form a single, larger efferent lymph vessel that takes the lymph away from the lymph node. A micrograph of a lymph node in longitudinal section is shown on the right and a lymph node is shown schematically in longitudinal section in the panel on the left. A lymph node is composed of a cortex (the yellow and blue areas on this panel) and a medulla (shown in dark pink). Lymph arrives via the afferent lymphatic vessels (pale pink), and during an infection pathogens and pathogen-laden dendritic cells arrive from infected tissue in the draining afferent lymph.

The lymph node is packed with lymphocytes, macrophages and other cells of the immune system, between which the lymph percolates until it reaches the marginal sinus and leaves by the efferent lymphatic vessel. Lymphocytes arrive at lymph nodes in the arterial blood. They enter the node by passing between the endothelial cells that line the fine capillaries within the lymph node (not shown). Within the lymph node, B cells and T cells tend to congregate in anatomically discrete areas. T cells populate the inner cortex (paracortex) and B cells form lymphoid follicles in the outer cortex. During an infection, the expansion of pathogen-specific B cells forms a spherical structure called a germinal center within each follicle. Germinal centers are clearly visible in the photograph. Original magnification $\times 40$. Photograph courtesy of Yasodha Natkunam.

to different regions of the lymph node: T cells to the T-cell areas and B cells to B-cell areas known as **lymphoid follicles**. Pathogens and pathogen-laden dendritic cells from the infected tissue arrive at a lymph node in **afferent lymphatic vessels**. Several of these unite at the node and then leave it as a single **efferent lymphatic vessel**. As the lymph passes through the node, the dendritic cells settle there and pathogens and other extraneous materials are filtered out by macrophages. This prevents infectious organisms from reaching the blood and provides a depot of pathogen and pathogen-carrying dendritic cells within the lymph node that can be used to activate lymphocytes. During an infection, pathogen-specific B cells that have bound the pathogen proliferate to form a dense spherical structure called a **germinal center** in each follicle. A lymph node draining a site of infection increases in size as a result of the proliferation of activated lymphocytes, a phenomenon sometimes referred to as “swollen glands.”

In the lymph node the small fraction of B and T cells bearing receptors that bind to the pathogen or its products will be stimulated to divide and differentiate into effector cells. T cells are activated by dendritic cells, whereupon some of the T cells move to the associated lymphoid follicle where they help activate the B cells to become plasma cells. Other effector T cells and the antibodies secreted by plasma cells are carried by efferent lymph and blood to the infected tissues (Figure 1.22). There the effector cells and molecules of adaptive immunity work with their counterparts of innate immunity to subdue the

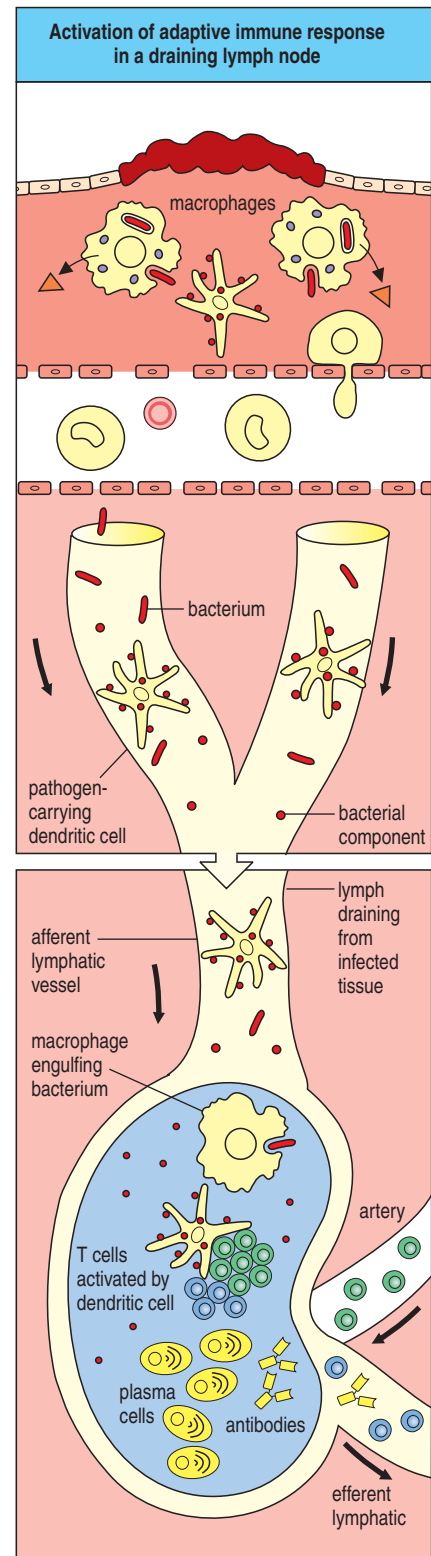
Figure 1.22 Activation of adaptive immunity in the draining lymph node. Pathogens, pathogen components, and dendritic cells carrying pathogens and molecules derived from them arrive in the afferent lymph draining the site of infection. Free pathogens and debris are removed by macrophages; the dendritic cells become resident in the lymph node and move to the T-cell areas, where they meet small lymphocytes that have entered the node from the blood (green). The dendritic cells specifically stimulate the division and differentiation of pathogen-specific small lymphocytes into effector lymphocytes (blue). Some helper T cells and cytotoxic T cells leave in the efferent lymph and travel to the infected tissue via the lymph and blood. Other helper T cells remain in the lymph node and stimulate the division and differentiation of pathogen-specific B cells into plasma cells (yellow). Plasma cells move to the medulla of the lymph node, where they secrete pathogen-specific antibodies, which are taken to the site of infection by the efferent lymph and subsequently the blood. Some plasma cells leave the lymph node and travel via the efferent lymph and the blood to the bone marrow, where they continue to secrete antibodies.

infection. Recovery from an infection involves clearance of infectious organisms from the body and repair of the damage caused by both infection and the immune response. A cure is not always possible. Infection can overwhelm the immune system, with death as the consequence. In the United States, some 36,000 deaths each year are associated with influenza. In intermediate situations the infection persists but its pathological effects are controlled by the adaptive immune response, as usually occurs with herpes viruses (see Figure 1.4).

1-10 The spleen provides adaptive immunity to blood infections

Pathogens can enter the blood directly, as occurs when blood-feeding insects transmit disease or when lymph nodes draining infected tissue have failed to remove all microorganisms from the lymph returned to the blood. The **spleen** is the lymphoid organ that serves as a filter for the blood. One purpose of the filtration is to remove damaged or senescent red cells; the second function of the spleen is that of a secondary lymphoid organ that defends the body against blood-borne pathogens. Any microorganism in the blood is a potential pathogen and source of dangerous systemic infection. Microorganisms and microbial products in the blood are taken up by splenic macrophages and dendritic cells, which then stimulate the B and T cells that arrive in the spleen from the blood. The spleen is made up of two different types of tissue: the red pulp, where red blood cells are monitored and removed, and the white pulp, where white blood cells gather to provide adaptive immunity. The organization and functions of splenic white pulp are similar to those of the lymph node, the main difference being that both pathogens and lymphocytes enter and leave the spleen in the blood (Figure 1.23).

Rare individuals have no spleen, a condition called asplenia (Figure 1.24). The underlying cause of asplenia is known to be genetic, because the condition runs in families, but the gene involved has yet to be defined. Children with asplenia are unusually susceptible to infections with so-called **encapsulated bacteria** such as *Streptococcus pneumoniae* (the pneumococcus) or *Haemophilus influenzae*, whose cells are surrounded by a thick polysaccharide capsule. A close relative of *S. pneumoniae*, *S. pyogenes*, which causes tonsillitis, can be seen in Figure 1.3d. Children with asplenia can be protected from these infections by immunization with vaccines incorporating the capsular polysaccharides of these bacteria. For good effect the vaccines are injected subcutaneously, into the connective tissue under the skin. From there they stimulate an immune response in the draining lymph nodes,



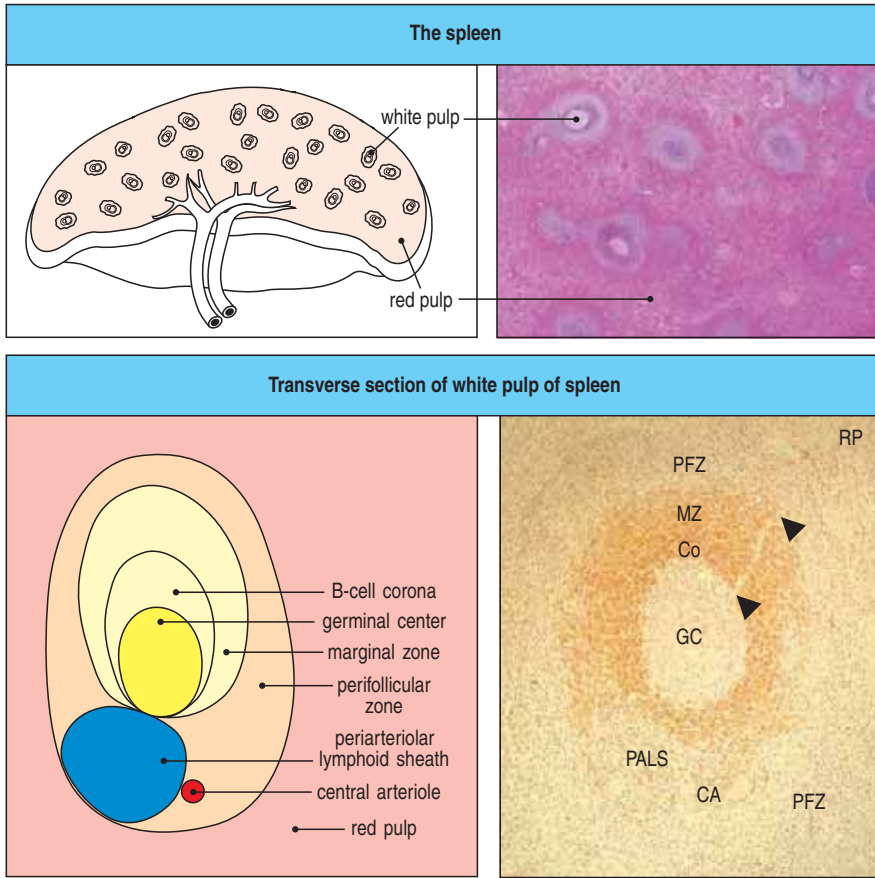


Figure 1.23 The spleen has aggregations of lymphocytes similar to those in lymph nodes. The human spleen is a large lymphoid organ in the upper left part of the abdomen, weighing about 150 grams. The upper diagram depicts a section of spleen in which nodules of white pulp are scattered within the more extensive red pulp. The red pulp is where old or damaged red cells are removed from the circulation; the white pulp is secondary lymphoid tissue, in which lymphocyte responses to blood-borne pathogens are made. The bottom diagram shows a nodule of white pulp in transverse section. It consists of a sheath of lymphocytes surrounding a central arteriole (CA). The sheath is called the periaarteriolar lymphoid sheath (PALS). The lymphocytes closest to the arteriole are mostly T cells (blue region); B cells (yellow regions) are placed more peripherally. Lymphoid follicles each comprise a germinal center, a B-cell corona (Co) and a marginal zone (MZ), which contains differentiating B cells and macrophages. Both the follicle and the PALS are surrounded by a perifollicular zone (PFZ) abutting the red pulp and containing a variety of cell types, including erythrocytes, macrophages, T cells and B cells. Photographs courtesy of H.G. Burkitt and B. Young (top) and N.M. Milicevic (bottom).

secondary lymphoid organs that have normal immunological functions in asplenic individuals. When a person's spleen is damaged as a consequence of traumatic accidents or wounds, it will often be surgically removed to prevent life-threatening loss of blood into the abdominal cavity. Children who have this procedure, called splenectomy, can be as vulnerable to bacterial infections as asplenic children. For adults, who have already been infected by these pathogens and have developed protective immunity, the consequences of splenectomy are usually slight, but protective vaccination against some pathogens, especially *S. pneumoniae*, is advised.

1-11 Most secondary lymphoid tissue is associated with the gut

The parts of the body that harbor the largest and most diverse populations of microorganisms are the respiratory and gastrointestinal tracts. The extensive mucosal surfaces of these tissues make them particularly vulnerable to

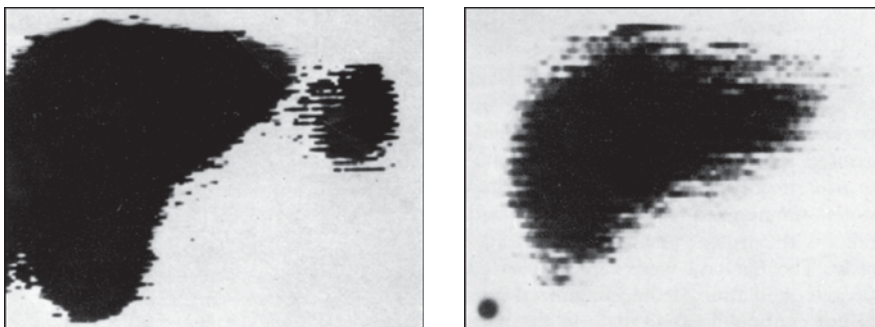


Figure 1.24 Diagnosis of a child with asplenia. The photos show scintillation scans of the abdomen of a mother (left panel) and child (right panel) after intravenous injection with radioactive colloidal gold. The large irregularly shaped organ to the left is the liver, which is seen in both panels. The smaller more rounded organ to the right in the mother is the spleen, which is not present in the child. Photographs courtesy of F. Rosen and R. Geha.

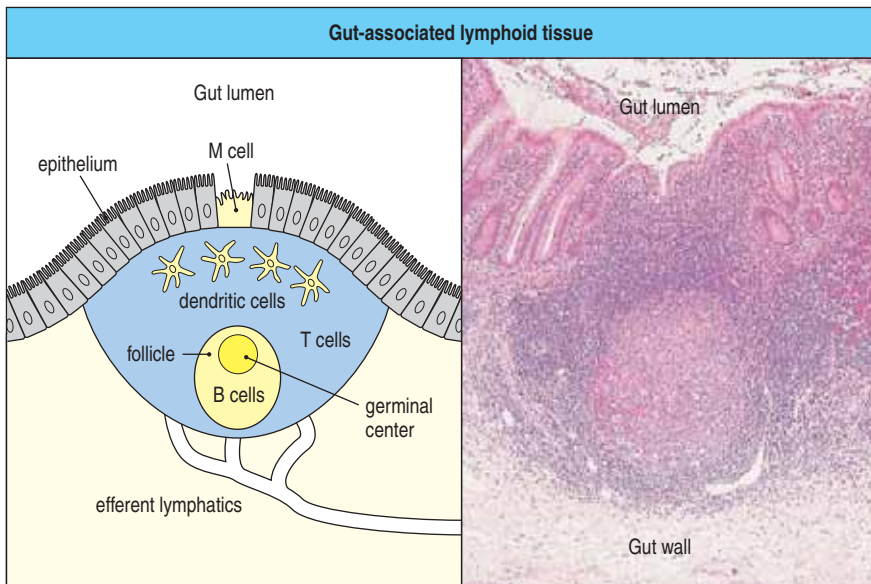


Figure 1.25 A typical region of gut-associated lymphoid tissue (GALT). A schematic diagram (left panel) and a light micrograph (right panel) of a typical region of organized GALT such as a Peyer's patch. M cells of the gut epithelial wall deliver pathogens from the luminal side of the gut mucosa to the lymphoid tissue within the gut wall. The lymphoid tissue is organized similarly to the lymph node and the white pulp of the spleen, with distinctive B- and T-cell zones, lymphoid follicles, and germinal centers. White blood cells, including lymphocytes, are delivered from the blood through the walls of small blood capillaries, as in the lymph node. Lymphocytes activated in the GALT leave in the efferent lymphatics and are delivered via the mesenteric lymph nodes (not shown) into the thoracic duct and back into the blood, from which they specifically reenter the gut as effector lymphocytes. Photograph courtesy of N. Rooney.

infection and they are therefore heavily invested with secondary lymphoid tissue. The **gut-associated lymphoid tissues (GALT)** include the **tonsils, adenoids, appendix**, and the **Peyer's patches** which line the small intestine (see Figure 1.18). Similar but less organized aggregates of secondary lymphoid tissue line the respiratory epithelium, where they are called **bronchial-associated lymphoid tissue (BALT)**, and other mucosal surfaces, including the gastrointestinal tract. The more diffuse mucosal lymphoid tissues are known generally as **mucosa-associated lymphoid tissue (MALT)**.

Although different from the lymph nodes or spleen in outward appearance, the mucosal lymphoid tissues are similar to them in their microanatomy (Figure 1.25) and in their function of trapping pathogens to activate lymphocytes. The differences are chiefly in the route of pathogen entry and the migration patterns of their lymphocytes. Pathogens arrive at mucosa-associated lymphoid tissues by direct delivery across the mucosa, mediated by specialized cells of the mucosal epithelium called **M cells**. Lymphocytes first enter mucosal lymphoid tissue from the blood and, if not activated, leave via lymphatics that connect the mucosal tissues to draining lymph nodes. Lymphocytes activated in mucosal tissues tend to stay within the mucosal system, either moving directly out from the lymphoid tissue into the lamina propria and the mucosal epithelium, where they perform their effector actions, or reentering the mucosal tissues from the blood as effector cells after being recirculated.

1-12 Adaptive immune responses generally give rise to long-lived immunological memory and protective immunity

Clonal selection by pathogens (see Figure 1.10) is the guiding principle of adaptive immunity and explains the features of immunity that perplexed physicians in the past. The severity of a first encounter with an infectious disease arises because the primary immune response is developed from very few lymphocytes; the time taken to expand their number provides an opportunity for the pathogen to establish an infection to the point of causing disease. The clones of lymphocytes produced in a primary response include long-lived **memory cells**, which can respond more quickly and forcefully to subsequent encounters with the same pathogen.

The potency of such secondary immune responses can be sufficient to repel the pathogen before there is any detectable symptom of disease. The individual therefore appears immune to that disease. The striking differences between a primary and secondary response are illustrated in **Figure 1.26**. The immunity due to a secondary immune response is absolutely specific for the pathogen that provoked the primary response. It is the difference between the primary and the secondary response that has made vaccination so successful in the prevention of disease. **Figure 1.27** shows how the introduction and availability of vaccines against diphtheria, polio, and measles have dramatically reduced the incidence of these diseases. In the case of measles there is also a corresponding reduction of subacute sclerosing panencephalitis, an infrequent but fatal spasticity caused by persisting measles virus that becomes manifest 7–10 years after measles infection and usually affects children who were infected as infants. When vaccination programs are successful to the point at which the disease is unfamiliar to physicians and public alike, then concerns can arise with real or perceived side effects of a vaccine that affect a very small minority of those vaccinated. Such concerns lead to fewer children being vaccinated and can lead to increasing occurrence of the disease.

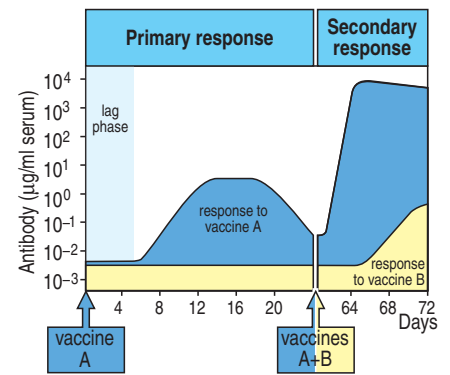


Figure 1.26 Comparison of primary and secondary immune responses. This diagram shows how the immune response develops during an experimental immunization of a laboratory animal. The response is measured in terms of the amount of pathogen-specific antibody present in the animal’s blood serum, shown on the vertical axis, with time being shown on the horizontal axis. On the first day the animal is immunized with a vaccine against pathogen A. The levels of antibodies against pathogen A are shown in blue. The primary response reaches its maximum level 2 weeks after immunization. After the primary response has subsided, a second immunization with vaccine A on day 60 produces an immediate secondary response, which in 5 days is orders of magnitude greater than the primary response. In contrast, a vaccine against pathogen B, which was also given on day 60, produces a typical primary response to pathogen B as shown in yellow, demonstrating the specificity of the secondary response to vaccine A.

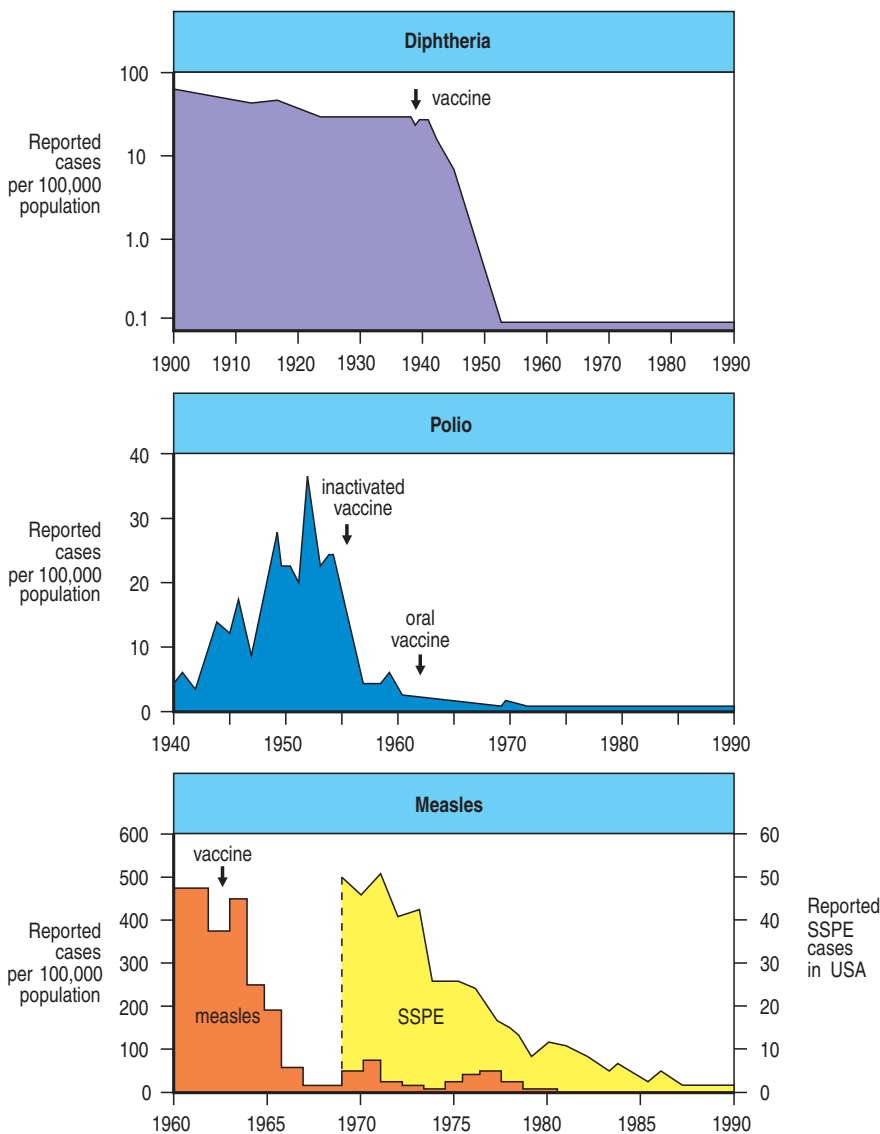


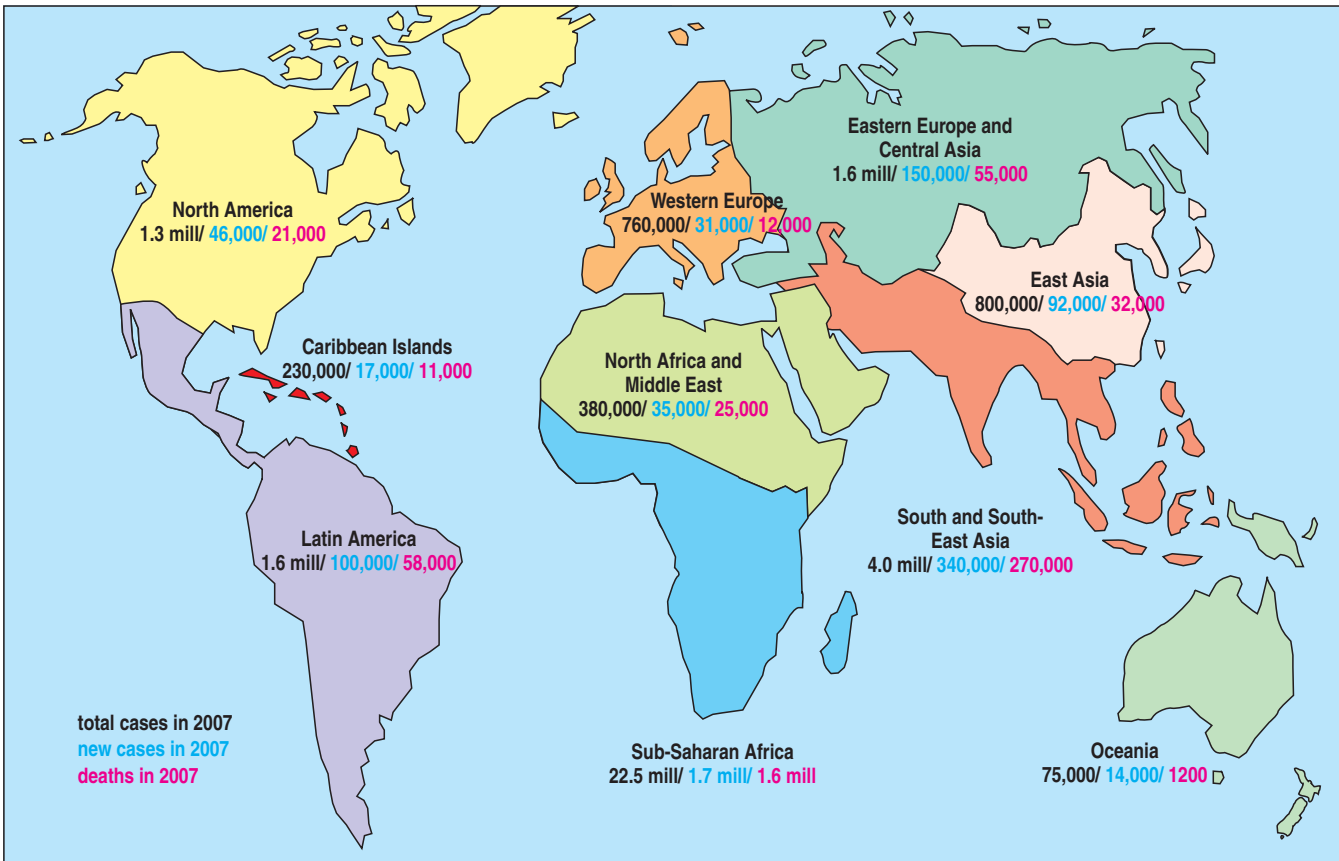
Figure 1.27 Successful vaccination campaigns. Diphtheria, poliomyelitis and measles have been virtually eliminated from the USA, as shown by these three graphs. The arrows indicate when the vaccination campaigns began. Subacute sclerosing panencephalitis (SSPE) is a brain disease that is a late consequence of measles infection for a minority of patients. Reduction of measles was paralleled by a reduction in SSPE 15 years later. Because these diseases have not been eradicated worldwide and the volume of international travel is so high, immunization must be maintained in much of the population to prevent recurrence of epidemic disease.

1-13 The immune system can be compromised by inherited immunodeficiencies or by the actions of certain pathogens

When components of the immune system are either missing or do not work properly, this generally leads to increased susceptibility to microbial infection. One cause of defective immune responses is inherited mutations in genes encoding proteins that contribute to immunity. Most people who carry a mutant gene are healthy because their other, normal, copy of the gene provides sufficient functional protein; the small and unfortunate minority who carry two mutant copies of the gene lack the function encoded by that gene. Such deficiencies lead to varying degrees of failure of the immune system and a wide range of **immunodeficiency diseases**, of which asplenia is one (see Section 1-10). In some of the immunodeficiency diseases, only one aspect of the immune response is affected, leading to susceptibility to particular kinds of infection; in others, adaptive immunity is completely absent, leading to a devastating vulnerability to all infections. These latter gene defects are rare, showing how vital is the protection normally afforded by the immune system. The discovery and study of immunodeficiency diseases has largely been the work of pediatricians, because such conditions usually show up early in childhood. Before the advent of antibiotics and, more recently, the possibility of bone marrow transplants and other replacement therapies, immunodeficiencies would usually have caused death in infancy.

Immunodeficiency states are caused not only by nonfunctional genes but also by pathogens that subvert the human immune system. An extreme example of an immunodeficiency due to disease is the **acquired immune deficiency syndrome (AIDS)**, which is caused by infection with the **human immunodeficiency virus (HIV)**. Although the disease has been recognized by clinicians only in the past 25 years, it is now at epidemic proportions, with around 33 million people infected worldwide (Figure 1.28). HIV infects helper

Figure 1.28 HIV infection is widespread on all the inhabited continents. Worldwide in 2007 there were about 33 million individuals infected with HIV, including about 2.5 million new cases, and about 2.1 million deaths from AIDS. Data are estimated numbers of adults and children living with HIV/AIDS at the end of 2007 (*AIDS Epidemic Update*, UNAIDS/World Health Organization; 2007).



T cells, a cell type essential for adaptive immunity. During the course of an extended infection, which can last for up to 20 years, the population of helper T cells gradually diminishes, eventually leading to collapse of the immune system. Patients with AIDS become increasingly susceptible to a range of infectious microorganisms, many of which rarely trouble uninfected people. Death usually results from the effects of one or more of these opportunistic infections rather than from the direct effects of HIV infection.

Summary to Chapter 1

Throughout their evolutionary history, multicellular animals have been colonized and infected by microorganisms. To restrict the nature, size, and location of microbial infestation, animals have evolved a series of defenses, which humans still use today. The skin and contiguous mucosal surfaces provide physical and chemical barriers that confine microorganisms to the external surfaces of the body. When pathogens manage to breach the barriers and gain entry to the soft tissues, they are sought out and destroyed by the immune system. The cells of the immune system are principally the various types of leukocyte and allied tissue cells, such as dendritic cells, which all derive from a common stem cell in the bone marrow.

In responding to infection, the immune system starts with innate immune mechanisms that are fast, fixed in their mode of action, and effective in stopping most infections at an early stage. The cells and molecules of innate immunity identify common classes of pathogen and destroy them. Four key elements of innate immunity are: proteins such as mannose-binding lectin that noncovalently bind to the surfaces of pathogens; proteins such as complement that bond covalently to pathogen surfaces, forming ligands for receptors on phagocytes; phagocytic cells that engulf and kill pathogens; and cytotoxic cells that kill virus-infected cells. The cells and molecules of innate immunity have counterparts in vertebrates and invertebrates.

Vertebrates have evolved the additional defenses of adaptive immunity, which are brought into play when innate immunity fails to stop an infection. Although slow to start, the adaptive immune response eventually becomes powerful enough to terminate almost all of the infections that outrun innate immunity. The mechanisms of adaptive immunity are ones that improve pathogen recognition rather than pathogen destruction. They involve the T and B lymphocytes, which collectively have the ability to recognize the vast array of potential pathogens, and are initiated in specialized lymphoid tissues such as lymph nodes and spleen, to where infections that elude innate immunity spread. In these secondary lymphoid organs, small recirculating B and T lymphocytes with receptors that bind to pathogens or their macromolecular components are selected and activated. Because each individual B or T lymphocyte expresses receptors of a single and unique binding type, a pathogen stimulates only the small subset of lymphocytes that express receptors for the pathogen, focusing the adaptive immune response on that pathogen. When successful, an adaptive immune response terminates infection and provides long-lasting protective immunity against the pathogen that provoked the response. Failures to develop a successful response can arise from inherited deficiencies in the immune system or from the pathogen's ability to escape, avoid, or subvert the immune response. Such failures can lead to debilitating chronic infections or death.

Adaptive immunity builds on the mechanisms of innate immunity to provide a powerful response that is tailored to the pathogen at hand and can be rapidly reactivated on future challenge with that same pathogen, providing life-long immunity to many common diseases. Adaptive immunity is an evolving process within a person's lifetime, in which each infection changes the make-up of that individual's lymphocyte population. These changes are neither inherited nor passed on but, during the course of a lifetime, they

determine a person's fitness and their susceptibility to disease. The strategy of vaccination aims at circumventing the risk of a first infection, and in the twentieth century successful campaigns of vaccination were waged against several diseases that were once both familiar and feared. Through the use of vaccination and antimicrobial drugs, as well as better sanitation and nutrition, infectious disease has become a less common cause of death in many countries.

Questions

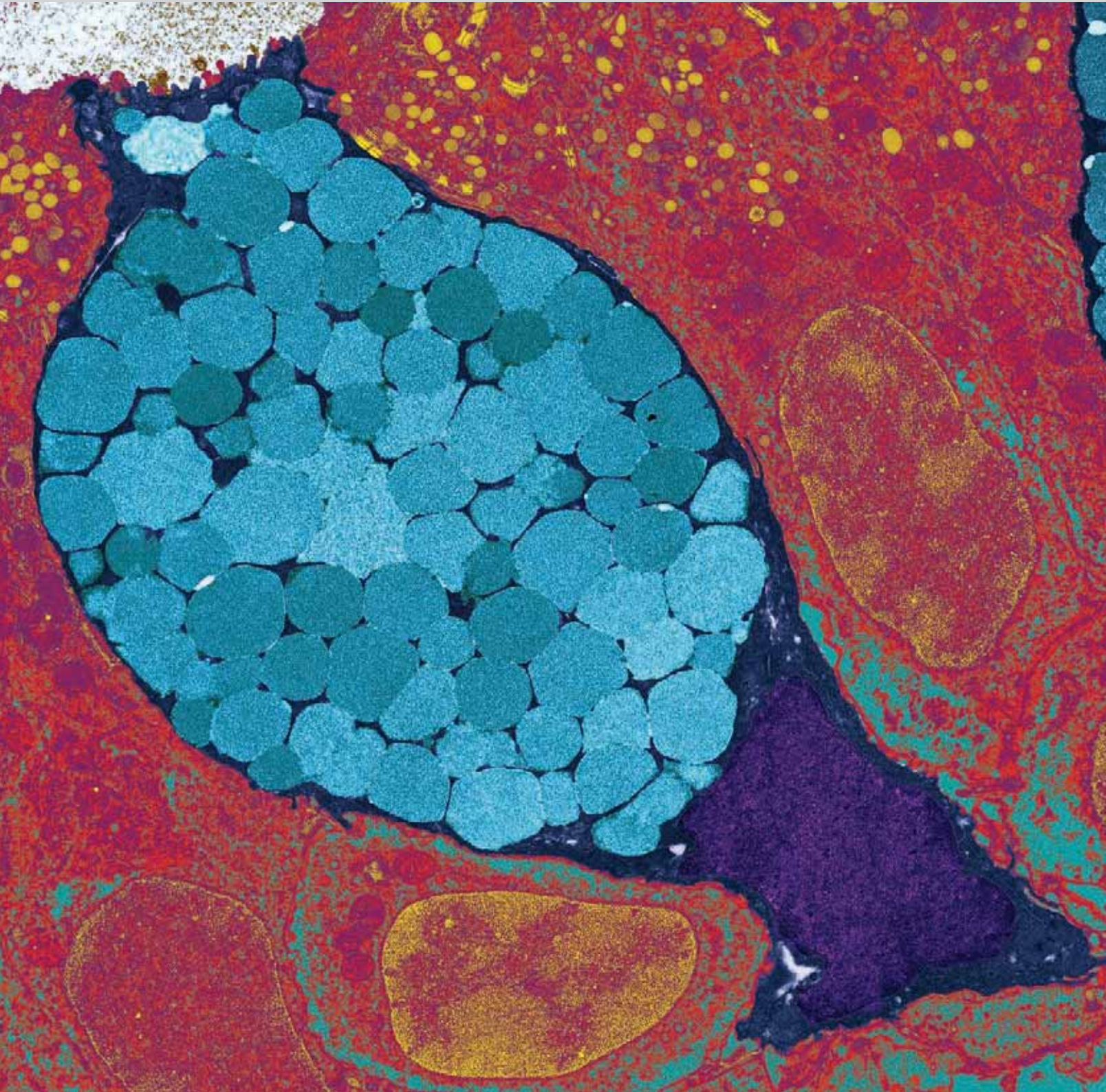
- 1-1** Identify the four classes of pathogen that provoke immune responses in our bodies and give an example of each.
- 1-2** A bacterium that causes a common disease in a population that has been previously exposed to it is called:
- opportunistic
 - resistant
 - commensal
 - endemic
 - attenuated.
- 1-3**
- Name three of the epithelia in the human body that act as barriers to infection.
 - Describe the three main ways in which epithelia carry out this barrier function, giving details of the mechanisms employed.
- 1-4** An antimicrobial peptide that protects epithelial surfaces from pathogens is called:
- glycoprotein
 - defensin
 - proteoglycan
 - lysozyme
 - sebum.
- 1-5** How can antibiotics upset the barrier function of intestinal epithelia? Give a specific example.
- 1-6** Describe the characteristics commonly associated with inflammation and what causes them.
- 1-7** Which of the following are characteristics of innate immunity? (Select all that apply.)
- inflammation
 - recognition of the pathogen improves during the response
 - fast response
 - highly specific for a particular pathogen
 - cytokine production.
- 1-8** Which of the following statements regarding neutrophils is false?
- Neutrophils are mobilized from the bone marrow to sites of infection when needed.
 - Neutrophils are active only in aerobic conditions.
 - Neutrophils are phagocytic.
 - Neutrophils form pus which is comprised of dead neutrophils.
 - Dead neutrophils are cleared from sites of infection by macrophages.
- 1-9** What are the main differences between innate immunity and adaptive immunity?
- 1-10**
- Identify the two major progenitor subsets of leukocytes.
 - Where do they originate in adults?
 - Name the white blood cells that differentiate from these two progenitor lineages.
- 1-11** Primary lymphoid tissues are the sites where lymphocytes _____, whereas secondary lymphoid tissues are the sites where lymphocytes _____.
- are stimulated; develop and mature
 - encounter pathogens; undergo apoptosis
 - develop and mature; become stimulated
 - undergo clonal selection; differentiate from hematopoietic stem cells
 - die; are phagocytosed after death.
- 1-12** The spleen differs from other secondary lymphoid organs in which of the following ways?
- It does not contain T cells.
 - It filters blood as well as lymph.
 - It is populated by specialized cells called M cells.
 - It receives pathogens via afferent lymphatic vessels.
 - It has no connection with the lymphatics.
- 1-13** What are clonal selection and clonal expansion in the context of an adaptive immune response, and describe how they shape the adaptive immune response.
- 1-14** What would be the consequence of a bioterrorist attack that released smallpox virus into a city?
- 1-15** Tim Schwartz, age 16, was hit by a car while riding his motorcycle. At the hospital he showed only minor abrasions and no bone fractures. He was discharged later that day. In the morning he experienced severe abdominal pain and returned to the hospital. Examination revealed tachycardia, low blood pressure, and a weak pulse. He received a blood transfusion without improvement. Laparoscopic surgery confirmed peritoneal hemorrhage due to a ruptured spleen. In addition to a splenectomy and a course of antibiotics, which of the following treatments would be administered?

- a. plasmapheresis to remove autoantibodies (antibodies generated against self constituents)
- b. regular intravenous injections of gamma globulin
- c. vaccination and regular boosters with capsular polysaccharides from pathogenic pneumococcal strains
- d. booster immunization with DPT (diphtheria toxoid, killed *Bordetella pertussis*, and tetanus toxoid)
- e. regular blood transfusions.

1-16 Eileen Ratamacher is 83 years old and has been chronically ill with recurrent bacterial infections over the past year. Her physician prescribed broad-spectrum antibiotics which she had been taking for the past four months. This morning she suffered from severe

abdominal cramping, vomiting, offensive smelling non-bloody diarrhea and a fever. Which of the following is not likely to be associated with her condition?

- a. The gut flora has undergone a change in composition during the course of antibiotic treatment with displacement of commensal bacteria from the intestinal lumen.
- b. There has been a reduction in colicin production by *Escherichia coli*.
- c. There is food poisoning caused by enterohemorrhagic *Escherichia coli*.
- d. There is toxin production by *Clostridium difficile* causing deterioration of the mucosal epithelium of the gastrointestinal tract.
- e. The appearance of 'pseudomembranes' on the rectal surface seen on colonoscopy.



Goblet cells secrete the mucus that protects epithelial surfaces from invasion by microorganisms.