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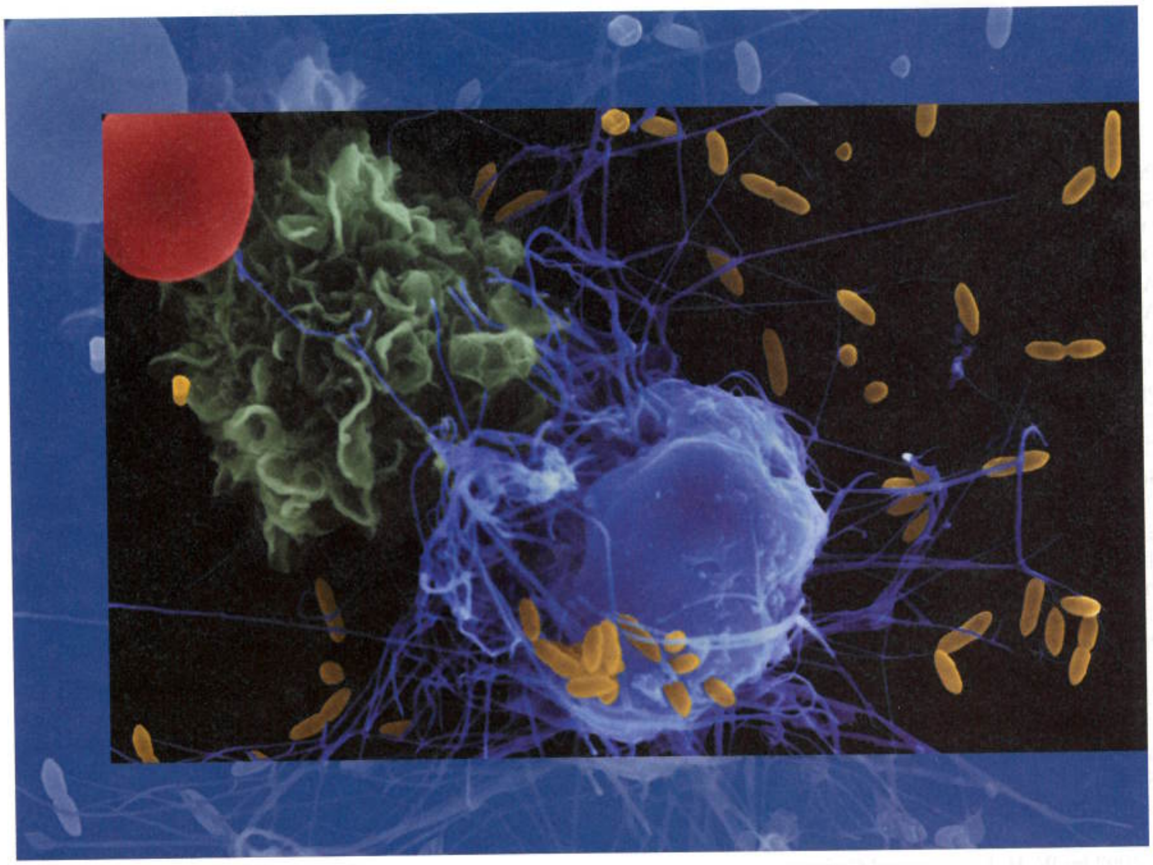

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About the Cover

The macrophage (blue) is a key player in innate immunity, sensing bacterial proteins through its pattern recognition receptors and then internalizing and digesting (phagocytosing) the invading bacteria (yellow). This encounter stimulates the macrophage to secrete soluble factors that attract other cells such as the monocyte (green) to the area of attack. (© 2004 Dennis Kunkel Microscopy, Inc.)

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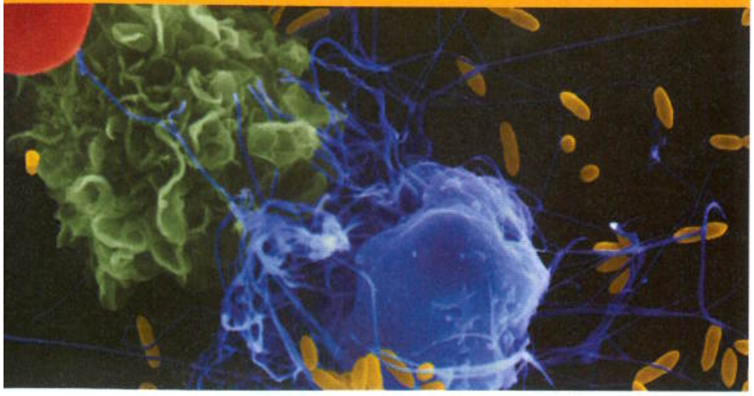
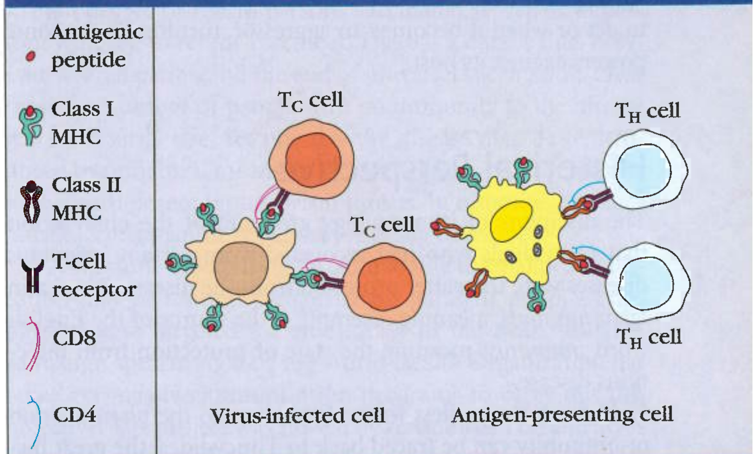


chapter 1

Overview of the Immune System



T-cell recognition of antigen-MHC.

- Historical Perspective
- Early Studies of Humoral and Cellular Immunity
- Theoretical Challenges
- Infection and Immunity
- Innate and Adaptive Immunity
- Immune Dysfunction and Its Consequences

THE IMMUNE SYSTEM EVOLVED TO PROTECT MULTICELLULAR organisms from pathogens. Highly adaptable, it defends the body against invaders as diverse as the virus that causes polio and the flatworm that causes schistosomiasis. The immune system generates an enormous variety of cells and molecules capable of specifically recognizing and eliminating foreign invaders, all of which act together in a dynamic network.

Protection by the immune system can be divided into two related activities—recognition and response. Immune recognition is remarkable for its capacity to distinguish foreign invaders from self components. The immune system is able to recognize molecular patterns that characterize groups of common pathogens and deal with these in a rapid and decisive manner. It can even detect subtle chemical differences that distinguish one foreign pathogen from another. Above all, the system is able to discriminate between foreign molecules and the body's own cells and molecules (self-nonself discrimination). In addition, the system is able to recognize host cells that are altered and that may lead to cancer. Typically, recognition of a pathogen by the immune system triggers an **effector response** that eliminates or neutralizes the invader. The multiple components of the immune system are able to convert the initial recognition event into a variety of effector responses, each uniquely suited for eliminating a particular type of pathogen. Certain exposures induce a **memory response,** characterized by a more rapid and heightened immune reaction upon later attack. It is the remarkable property of memory that prevents us from catching some diseases a second time, and immunological memory is the foundation for vaccination, which is a means of "educating" the immune system to prepare it for later attacks.

Although reference is made to the immune *system,* it must be pointed out that there are *two* systems of immunity, innate immunity and adaptive immunity, which collaborate to protect the body. **Innate immunity** includes molecular and cellular mechanisms predeployed before an infection and poised to prevent or eliminate it. This highly effective first line of defense prevents most infections at the outset or eliminates them within hours of encounter with the innate immune system. The recognition elements of the innate immune system precisely distinguish between self and pathogens, but they are not specialized to distinguish small differences in foreign molecules. A second form of immunity, known as **adaptive immunity,** develops in response to infection and adapts to recognize, eliminate, and then remember the invading pathogen. Adaptive immunity is contingent upon innate immunity and begins a few days after the initial infection. It provides a second, comprehensive line of defense that eliminates pathogens that evade the innate responses or persist in spite of them. An important consequence of adaptive immune response is memory. If the same, or a closely related, pathogen infects the body, memory cells provide the means for the adaptive immune system to make a rapid and often highly effective attack on the invading pathogen.

This chapter introduces the study of immunology from a historical perspective. The highly practical or applied aspects of immunology are outlined, emphasizing the role of vaccination in the development of immunology as a scientific field and as an important aspect of public health. A bird's-eye view of the common pathogens to which we are exposed is given, with a broad overview of the processes, cells, and molecules that make up the innate and adaptive immune systems. Last, we describe circumstances in which the immune system fails to act or when it becomes an aggressor, turning its awesome powers against its host.

Historical Perspective

The discipline of immunology grew out of the observation that individuals who had recovered from certain infectious diseases were thereafter protected from the disease. The Latin term *immunis,* meaning "exempt," is the source of the English word *immunity,* meaning the state of protection from infectious disease.

Perhaps the earliest written reference to the phenomenon of immunity can be traced back to Thucydides, the great historian of the Peloponnesian War. In describing a plague in Athens, he wrote in 430 BC that only those who had recovered from the plague could nurse the sick because they would not contract the disease a second time. Although early societies recognized the phenomenon of immunity, almost 2000 years passed before the concept was successfully converted into medically effective practice.

Early vaccination studies led the way to immunology

The first recorded attempts to induce immunity deliberately were performed by the Chinese and Turks in the fifteenth century. They were attempting to prevent smallpox, a disease that is fatal in about 30% of cases and that leaves survivors disfigured for life (Figure 1-1). Reports suggest that the dried crusts derived from smallpox pustules were either inhaled into the nostrils or inserted into small cuts in the skin (a technique called *variolation*) in order to prevent this dreaded disease. In 1718, Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople, observed the positive effects of variolation on the native Turkish population and had the technique performed on her own children. The English physician Edward Jenner, in 1798, made a giant advance in the deliberate development of immunity. Intrigued by the fact that milkmaids who had contracted the mild disease cowpox were subsequently immune to the much more severe smallpox, Jenner reasoned that introducing fluid from a cowpox pustule into people (i.e., inoculating them) might protect them from smallpox. To test this idea, he inoculated an eight-year-old boy with fluid from a cowpox pustule and later intentionally infected the child with smallpox. As predicted, the child did not develop smallpox.

Jenner's technique of inoculating with cowpox to protect against smallpox spread quickly throughout Europe. However, it was nearly a hundred years before this technique was applied to other diseases. As so often happens in science, serendipity in combination with astute observation led to the next major advance in immunology, the induction of immunity to cholera. Louis Pasteur had succeeded in growing the bacterium thought to cause fowl cholera in culture, confirming its role when chickens injected with the cultured bacterium developed fatal cholera. After returning from a summer vacation, he injected some chickens with an old bacterial culture. The chickens became ill, but to Pasteur's surprise, they recovered. Pasteur then grew a fresh culture of the bacterium with the intention of injecting it into some fresh chickens. But as the story is told, his supply of chickens was limited, and therefore he used the previously injected chickens. Unexpectedly, the chickens were completely protected from the disease. Pasteur hypothesized and proved that aging had weakened the virulence of the pathogen and that such an attenuated strain might be administered to protect against the disease. He called this attenuated strain a **vaccine** (from the Latin *vacca,* meaning "cow"), in honor of Jenner's work with cowpox inoculation.

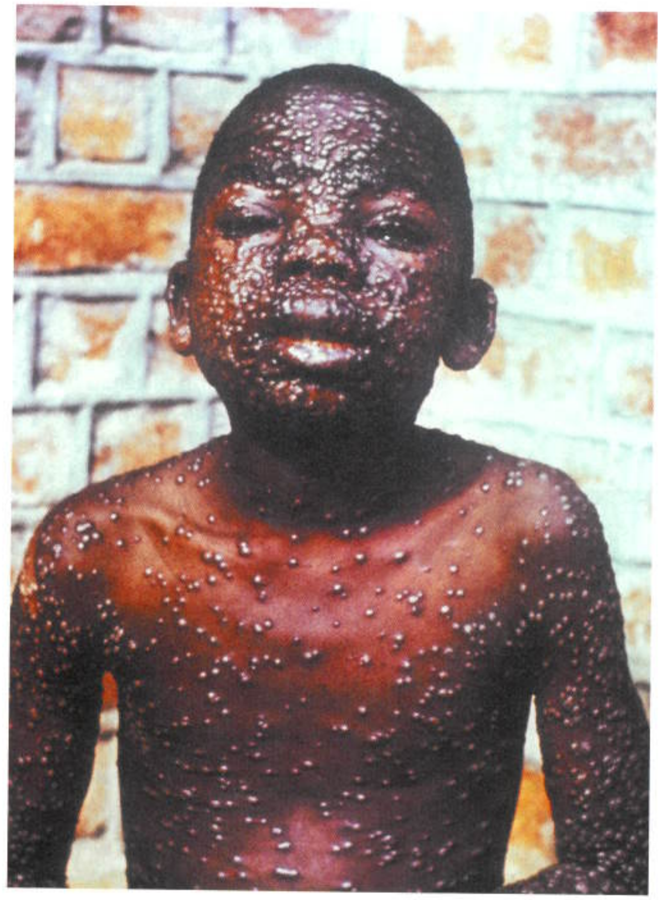


FIGURE 1-1 African child with rash typical of smallpox on face, chest, and arms. Smallpox, caused by the virus *Variola major,* has a 30% mortality rate. Survivors are often left with disfiguring scars. *[Centers for Disease Control.]*

Pasteur extended these findings to other diseases, demonstrating that it was possible to **attenuate,** or weaken, a pathogen and administer the attenuated strain as a vaccine. In

FIGURE 1-2 Wood engraving of Louis Pasteur watching Joseph Meister receive the rabies vaccine. *[From* Harper's Weekly ***29:836;*** *courtesy of the National Library of Medicine.]*

a now classic experiment performed in the small village of Pouilly-le-Fort in 1881, Pasteur first vaccinated one group of sheep with heat-attenuated anthrax bacteria *(Bacillus anthracis);* he then challenged the vaccinated sheep and some unvaccinated sheep with a virulent culture of the anthrax bacillus. All the vaccinated sheep lived, and all the unvaccinated animals died. These experiments marked the beginnings of the discipline of immunology. In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog (Figure 1-2). The boy, Joseph Meister, was inoculated with a series of attenuated rabies virus preparations. He lived and later became a custodian at the eponymous Pasteur Institute.

Vaccination is an ongoing, worldwide enterprise

The emergence of the study of immunology and the discovery of vaccines are tightly linked. The discovery, development, and appropriate use of vaccines remains a challenge to immunologists today.

In 1977, the last known case of naturally acquired smallpox was seen in Somalia. This dreaded disease was eradicated by universal application of a vaccine that did not differ greatly from that used by Jenner in the 1790s. A consequence of eradication is that universal vaccination becomes unnecessary; this is a tremendous benefit because the smallpox vaccine carried a slight degree of risk to persons vaccinated as well as to persons exposed to recent vaccinees. There is a darker side, however, to eradication and the end of universal vaccination. Over time, the number of people with no immunity to the disease will necessarily rise. Yet one day the disease may be reintroduced by unnatural means. In fact, smallpox is considered one of the most potent bioterrorism threats. In response, new and safer vaccines against smallpox are being developed.

A milestone in vaccinology comparable to smallpox eradication may be around the corner for paralytic polio, a crippling disease targeted for eradication in the near future. A campaign spearheaded by the World Health Organization has relied on massive immunization programs to carry out this objective. The project was slowed by resistance in certain areas based on rumors that immunization causes sterility in male children. The regional resurgence in polio cases in certain areas of Asia and Africa resulting from this resistance is a setback, but one that can be overcome by education and observation of the benefits of vaccination. The fact that polio is not a threat worldwide and has been eliminated in most countries is a triumph that should not be overshadowed by delays in the eradication program.

In the United States and other industrialized nations, vaccines have eliminated a host of childhood diseases that were considered a part of growing up just 50 years ago. Measles, mumps, whooping cough (pertussis), tetanus, diphtheria, and polio are extremely rare or nonexistent because of current vaccination practices (Table 1-1). One can barely estimate the savings to society resulting from the prevention of these diseases. Aside from suffering and mortality, the cost to treat these illnesses and their aftereffects or sequelae (such as paralysis, deafness, blindness, and mental retardation) is immense and dwarfs the costs of immunization.

For some diseases, immunization is the best, if not the only, effective defense. Because few antiviral drugs are now available, the major defense against influenza must be an effective vaccine. If an influenza pandemic recurs, as predicted by many experts, there will be a race between its spread and the manufacture and administration of an effective vaccine. At the time of this writing, much attention is being paid to an emerging strain of avian influenza. About 200 cases of infection in humans have been documented, of which about half were fatal. If this virus adapts to spread efficiently in humans, a major pandemic will result. Without a preventative vaccine, the devastation caused by the influenza pandemic of 1918, which left as many as 50 million dead, may be equaled or surpassed.

Despite the record of success for vaccines and our reliance on them, opponents to vaccination programs have made claims that vaccines do more harm than good and that childhood vaccination should be curtailed or even eliminated. There is no dispute that vaccines represent unique safety issues, since vaccines are given to people who

TABLE 1-1 Cases of selected infectious disease before and after the introduction of effective vaccines

	ANNUAL CASES/YR		CASES IN 2004
Disease	Prevaccine	Postvaccine	Reduction (%)
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Measles	503,282	37	99.99
Mumps	152,209	236	99.85
Pertussis (whooping cough)	147,271	18,957	87.13
Paralytic polio	16,316	0	100
Rubella (German measles)	47,745	12	99.97
Tetanus ("lockjaw")	1,314 (deaths)	26 (cases)	98.02
Invasive hemophilus influenzae	20,000	172	99.14

SOURCE: Adapted from W. A. Orenstein et al., 2005. *Health Affairs* **24**:599.

are healthy. Furthermore, there is general agreement that vaccines must be regulated and the public must have access to clear and complete information about them. Although the claims of critics must be evaluated, many can be answered by careful and objective examination of records. A recent example is the claim that the mercury-containing preservative thimerosol, previously used in some vaccine preparations, causes autism and was responsible for recent increases in the incidence of the disorder, which is marked by intense self-absorption and inability to relate to others. Autism generally manifests itself between 1 and 2 years of age, the time window in which many vaccines are given (see Chapter 19). The Danish government maintains meticulous health records on its citizens, a source of data that throws revealing light on the putative causal connection between thimerosol and autism. The records indicated that the incidence of autism increased significantly since 1992 in Denmark. However, the records also showed that the use of thimerosol as a vaccine preservative had already been stopped completely in that country several years earlier. Data such as these make it difficult to link autism to the use of thimerosol and suggest the need for further research into the causes for the increase in autism.

Perhaps the greatest current challenge in vaccine development is the lack of effective vaccines for major killers such as malaria and AIDS. It is hoped that the immunologists of today, using the tools of molecular and cellular biology, genomics, and proteomics, will make inroads into preventing these diseases. A further issue in vaccines is the fact that millions of children in developing countries die from diseases that are fully preventable by available, safe vaccines. High manufacturing costs, instability of the products, and delivery problems keep these vaccines from those they could greatly benefit. This problem could be alleviated in many cases by development of future-generation vaccines that are inexpensive, heat stable, and administered without a needle.

Early Studies of Humoral and Cellular Immunity

Pasteur proved that vaccination worked, but he did not understand how. The experimental work of Emil von Behring and Shibasaburo Kitasato in 1890 gave the first insights into the mechanism of immunity, earning von Behring the Nobel prize in medicine in 1901 (Table 1-2). Von Behring and Kitasato demonstrated that **serum** (the liquid, noncellular component recovered from coagulated blood) from animals previously immunized to diphtheria could transfer the immune state to unimmunized animals. In search of the protective agent, various researchers during the next decade demonstrated that an active component from immune serum could neutralize toxins, precipitate toxins, and agglutinate (clump) bacteria. In each case, the active agent was named for the activity it exhibited: antitoxin, precipitin, and agglutinin, respectively. Initially, different serum components were thought to be responsible for each activity, but during the 1930s, mainly through the efforts of Elvin Kabat, a fraction of serum first called gamma globulin (now **immunoglobulin**) was shown to be responsible for all these activities. The active molecules in the immunoglobulin fraction are called **antibodies.** (The terms *antibody* and *immunoglobulin* may be used interchangeably, but usually the term *antibody* is reserved for immunoglobulins with known specificity for an antigen.) Because immunity was mediated by antibodies contained in body fluids (known at the time as humors), it was called humoral immunity.

The observation of von Behring and Kitasato was applied to clinical practice. Prior to the advent of antibiotic therapy for infectious diseases, antisera, often prepared in horses, were given to patients with a variety of illnesses. Today there are therapies that rely on transfer of immunoglobulins, and with the development of monoclonal antibody technology, antibody therapy

TABLE 1-2 Nobel prizes for immunologic research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Bordet	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Dausset Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Cesar Milstein Georges E. Köhler Niels K. Jerne	Great Britain Germany Denmark	Monoclonal antibodies Immune regulatory theories
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by T cells
2002	Sydney Brenner H. Robert Horvitz J. E. Sulston	S. Africa United States Great Britain	Genetic regulation of organ development and cell death (apoptosis)

is now a well-established commercial enterprise (see Clinical Focus in Chapter 4). Emergency use of sera containing antibodies against snake or scorpion venoms for bite victims is a common practice. Whereas a vaccine is said to engender **active immunity** in the host, transfer of antibody with a given specificity confers **passive immunity.** Newborn infants benefit from passive immunization conferred by the presence of maternal antibodies in their circulation. Passive immunity may be given as a preventative (prophylaxis) to those who anticipate exposure to a given disease or to those with compromised immunity.

Antisera to certain bacterial toxins such as diphtheria or tetanus can be administered to infected individuals to stop the disease caused by the toxin. A dramatic vignette of this application was the relay of dogsleds racing over 674 miles of frozen Alaskan landscape to bring diphtheria antitoxin from Fairbanks to the affected children in the icebound city of Nome during a diphtheria outbreak in 1925. The successful outcome is commemorated annually in the Iditarod dogsled race, and there is a statue of Balto, one of the lead dogs used for the final leg of the delivery, in New York's Central Park.

In 1883, even before the discovery that a serum component could transfer immunity, Elie Metchnikoff demonstrated that cells also contribute to the immune state of an animal. He observed that certain white blood cells, which he termed **phagocytes,** ingested (phagocytosed) microorganisms and other foreign material (Figure 1-3). Noting that these phagocytic cells were more active in animals that had been immunized, Metchnikoff hypothesized that cells, rather than serum components, were the major effector of immunity. The active phagocytic cells identified by Metchnikoff were likely blood monocytes and neutrophils (see Chapter 2).

Theoretical Challenges

Whereas development of safe and effective vaccines and the use of passive immune therapy remain challenging problems in clinical (also called *translational*) research, the study of immunology also raised puzzling theoretical questions that occupied the scientific community.

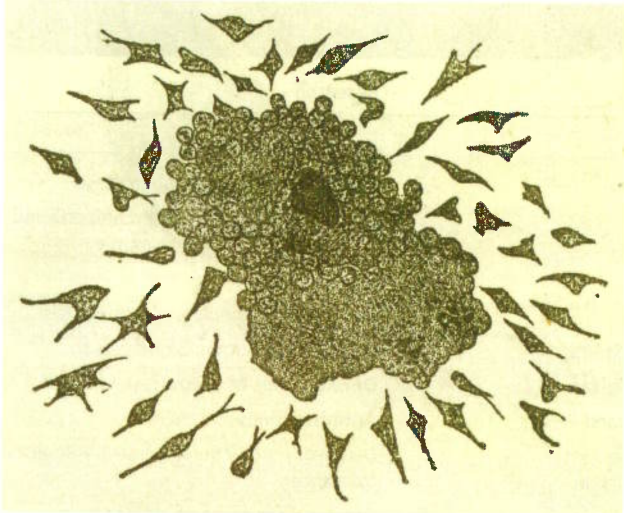


FIGURE 1-3 Drawing by Elie Metchnikoff of phagocytic cells surrounding a foreign particle. He first described and named the process of phagocytosis, or ingestion of foreign matter by white blood cells. *[By permission of The British Library:7616.h.19,* Lectures on the Comparative Pathology of Inflammation delivered at the Pasteur Institute in 1891, *translated by F. A. Starling and E. H. Starling, with plates by Il'ya Il'ich Mechnikov, 1893, p. 64, fig. 32.]*

One question that surfaced early involved the relative roles of cellular and humoral immunity. A controversy developed between those who held to the concept of humoral immunity and those who agreed with Metchnikoff's concept of **cell-mediated immunity.** It is now obvious that both are correct—the full immune response requires both cellular and humoral responses. Early studies of immune cells were hindered by the lack of genetically defined animal models and modern tissue culture techniques, whereas studies with serum took advantage of the ready availability of blood and established biochemical techniques to purify protein mediators of humoral immunity. Information about cellular immunity therefore lagged behind the unraveling of humoral immunity.

In a key experiment in the 1940s, Merrill Chase, working at The Rockefeller Institute, succeeded in transferring immunity against the tuberculosis organism by transferring white blood cells between guinea pigs. Until that point, attempts to develop an effective vaccine or antibody therapy against tuberculosis had met with failure. Thus, Chase's demonstration helped to rekindle interest in cellular immunity. With the emergence of improved cell culture techniques in the 1950s, the **lymphocyte** was identified as the cell responsible for both cellular and humoral immunity. Soon thereafter, experiments with chickens pioneered by Bruce Glick at Mississippi State University indicated that there are two types of lymphocytes: T lymphocytes, derived from thymus, mediated cellular immunity, and B lymphocytes, from the bursa of Fabricius (an outgrowth of the cloaca in birds), were involved in humoral immunity. The controversy about the roles of humoral and cellular immunity was resolved when the systems were shown to be intertwined. It became clear that both systems were necessary for the immune response.

One of the great enigmas confronting early immunologists was the specificity of the antibody molecule for foreign material, or **antigen** (the general term for a substance that binds with a specific antibody). Around 1900, Jules Bordet at the Pasteur Institute expanded the concept of immunity beyond infectious diseases by demonstrating that nonpathogenic substances, such as red blood cells from other species, could serve as antigens. Serum from an animal inoculated with noninfectious material would nevertheless react with the injected material in a specific manner. The work of Karl Landsteiner and those who followed him showed that injecting an animal with almost any organic chemical could induce production of antibodies that would bind specifically to the chemical. These studies demonstrated that antibodies have a capacity for an almost unlimited range of reactivity, including responses to compounds that had only recently been synthesized in the laboratory and had not previously existed in nature. In addition, it was shown that molecules differing in the smallest detail could be distinguished by their reactivity with different antibodies. Two major theories were proposed to account for this specificity: the selective theory and the instructional theory.

The earliest conception of the *selective theory* dates to Paul Ehrlich in 1900. In an attempt to explain the origin of serum antibody, Ehrlich proposed that cells in the blood expressed a variety of receptors, which he called "side-chain receptors," that could react with infectious agents and inactivate them. Borrowing a concept used by Emil Fischer in 1894 to explain the interaction between an enzyme and its substrate, Ehrlich proposed that binding of the receptor to an infectious agent was like the fit between a lock and key. Ehrlich suggested that interaction between an infectious agent and a cell-bound receptor would induce the cell to produce and release more receptors with the same specificity (Figure 1-4). According to Ehrlich's theory, the specificity of the receptor was determined in the host before its exposure to antigen, and the antigen selected the appropriate receptor. Ultimately, all aspects of Ehrlich's theory would be proven correct with the minor exception that the "receptor" exists as both a soluble antibody molecule and a cell-bound receptor; the soluble form is secreted rather than the bound form released.

In the 1930s and 1940s, the selective theory was challenged by various *instructional theories,* in which antigen played a central role in determining the specificity of the antibody molecule. According to the instructional theories, a particular antigen would serve as a template around which antibody would fold. The antibody molecule would thereby assume a configuration complementary to that of the antigen template. This concept was first postulated by Friedrich Breinl and Felix Haurowitz in about 1930 and redefined in the 1940s in terms of protein folding by Linus Pauling. The instructional theories were formally disproved in the 1960s, by which time information was emerging about the structure of protein, RNA, and DNA that would offer new insights into the vexing problem of how an individual could make antibodies against almost anything.

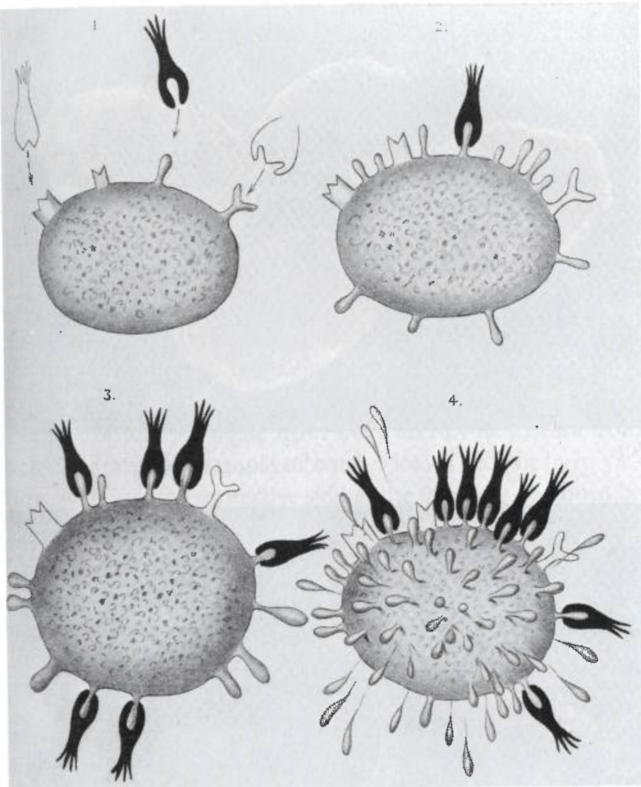


FIGURE 1-4 Representation of Paul Ehrlich's side chain theory to explain antibody formation. The cell is pluripotent in that it expresses a number of different receptors or side chains, all with different specificities; if an antigen encounters this cell and there is a good fit with one of its side chains, synthesis of that receptor is triggered and the receptor will be released. *[From Ehrlich's Croonian lecture of 1900 to the Royal Society.]*

In the 1950s, selective theories resurfaced as a result of new experimental data and, through the insights of Niels Jerne, David Talmadge, and F. Macfarlane Burnet, were refined into a theory that came to be known as the **clonal-selection** theory. According to this theory, an individual lymphocyte expresses membrane receptors that are specific for a distinct antigen. This unique receptor specificity is determined before the lymphocyte is exposed to the antigen. Binding of antigen to its specific receptor activates the cell, causing it to proliferate into a clone of cells that have the same immunologic specificity as the parent cell. The clonal-selection theory has been further refined and is now accepted as an underlying paradigm of modern immunology.

Infection and Immunity

Along with the developing field of immunology grew the study of medical microbiology, which covered the identification of infectious agents and their modes of causing disease. Organisms causing disease are termed **pathogens,** and their means of attacking the host is called **pathogenesis.** The human pathogens can be grouped into major categories, shown below and in Figure 1-5.

Major groups of human pathogens	Examples of diseases
Viruses	Polio, smallpox, influenza, measles, AIDS
Bacteria	Tuberculosis, tetanus, whooping cough
Fungi	Thrush, ringworm
Parasites	Malaria, leishmaniasis

Of major interest here are the means by which effective immunity to the pathogens can be achieved. An effective defense relies heavily on the nature of the individual microorganism. For example, because viruses require mammalian cells for their replication and multiplication, an effective defense strategy may involve recognizing and killing any cell that is virus infected before the life cycle of the virus can be completed. For organisms that replicate outside host cells, prompt recognition of these invaders by antibodies or soluble molecules can be used, followed by cellular and molecular immune mechanisms that eliminate the pathogen.

Some pathogens that pervade our environment cause no problem for healthy individuals because there is adequate preexisting immunity. However, individuals with deficiencies in immune function may be susceptible to disease caused by these ubiquitous microbes. For example, the fungus *Candida albicans,* present nearly everywhere, causes no problems for most individuals. However, in those with lowered immunity, it can cause an irritating rash and a spreading infection in the mucosa lining the oral and vaginal cavities. The rash, called thrush, may be a first sign of immune dysfunction. If left unchecked, *C. albicans* can spread, causing systemic candidiasis, a life-threatening condition. Another example is the virus *Herpesvirus simplex,* which normally causes small lesions around the lips or the genitalia. In those with deficient immunity, these lesions may spread to cover large portions of the body. Such infections by ubiquitous microorganisms, often observed in cases of immune deficiency, are termed **opportunistic infections.** Several rarely seen opportunistic infections identified in early AIDS patients were the signal that the immune systems of these patients were seriously compromised.

For some pathogens known to cause serious disease, the means to achieve immunity are well documented and allow control of the disease. For example, tetanus (commonly called lockjaw) is caused by a common soil bacterium *(Clostridium tetani),* which acts through a toxin that attacks the nervous system (neurotoxin). Untreated, tetanus leads to death within a short time. There is an effective vaccine to tetanus, and should that fail, antibodies to the toxin can be administered to offset the potentially fatal disease. Prior to the availability of these prevention and treatment measures, anyone suffering a

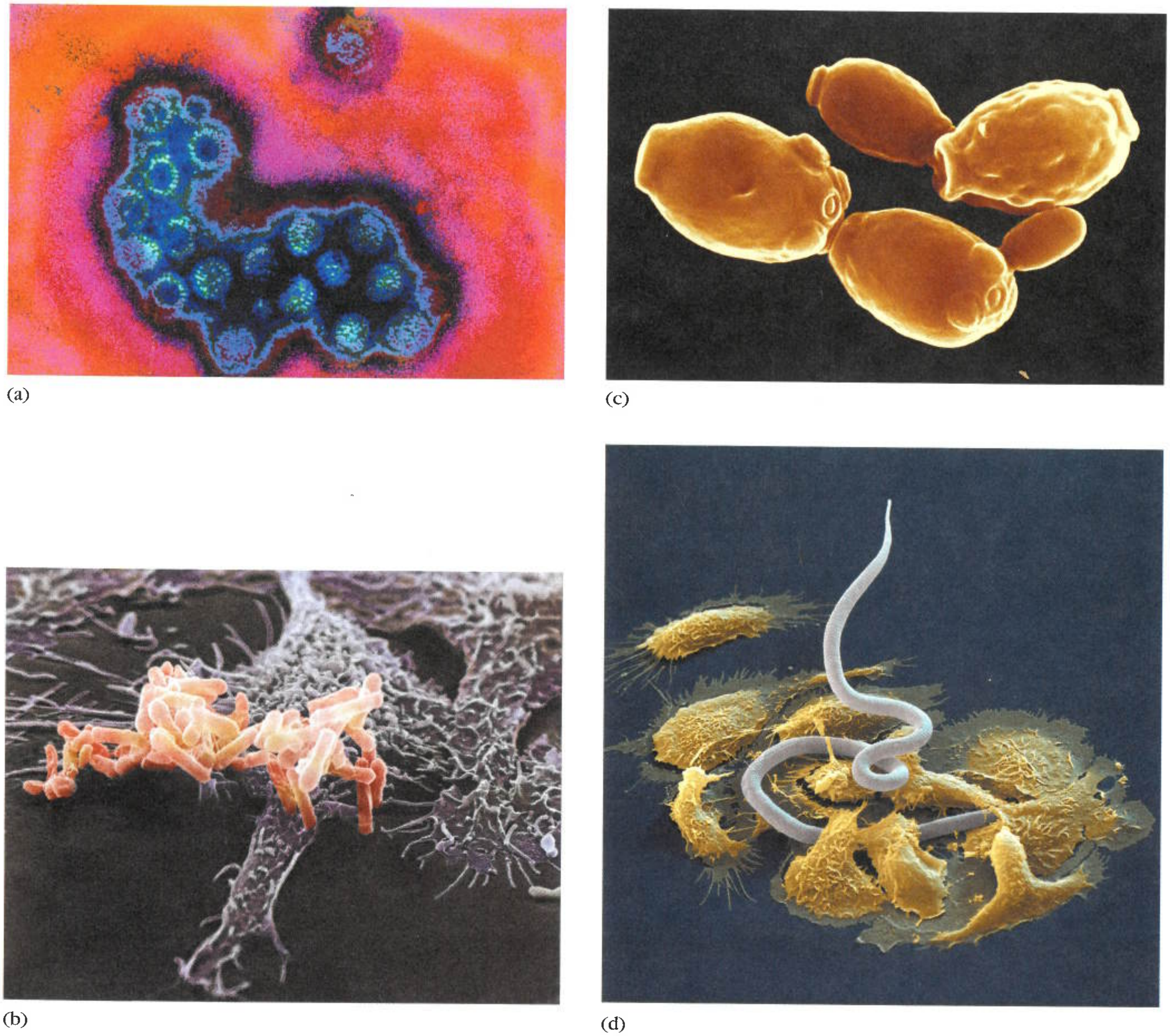


FIGURE 1-5 Pathogens representing the major categories of microorganisms causing human disease. (a) Viruses: Transmission electron micrograph of rotavirus, a major cause of infant diarrhea. Rotavirus accounts for approximately 1 million infant deaths per year in developing countries and hospitalization of about fifty thousand infants per year in the United States. *[VEM/Photo Researchers.]* (b) Bacteria: *Pseudomonas,* a soil bacterium that is an opportunistic pathogen for humans, being ingested by human macrophages. *[David M. Phillips/Photo Researchers.]* (c) Fungi: *Candida albicans,* a yeast inhabiting human mouth, throat, intestines, and genitourinary tract; *C. albicans* commonly causes an oral rash (thrush) or vaginitis in immunosuppressed individuals or in those taking antibiotics that kill normal bacterial flora. *[Stem Jems/Photo Researchers.]* (d) Parasites: The larval form of filaria, a parasitic worm, being attacked by macrophages. Approximately 120 million persons worldwide have some form of filariasis. *[Oliver Meckes/Nicole Ottawa/Eye of Science/Photo Researchers.]*

puncture wound by a dirty object, such as a rusty nail, was at risk for a fatal tetanus infection. In marked contrast to the success in controlling tetanus is the failure to devise immune strategies to control HIV infection, which leads to AIDS.

The immune system must deal with all types of pathogens and has evolved multiple strategies for dealing with invasion by a pathogen that has passed the first barriers of skin and mucosa. We will see that some of these strategies are poised to respond the instant a pathogen breaches the host's barriers; other defenses are crafted to act after infection is established.

Innate and Adaptive Immunity

Immunity—the state of protection from infectious disease—has both a less specific and a more specific component. The less specific component, **innate immunity,** provides the first line of defense against infection. Most components of innate immunity are present before the onset of infection and constitute a set of disease-resistance mechanisms that are not specific to a particular pathogen, but include cellular and molecular components that recognize classes of molecules peculiar to frequently encountered pathogens.

The first hurdle for a pathogen involves breaching the barriers that protect the host. Obvious barriers include the skin and the mucosal membranes. The acidity of the stomach contents and of perspiration poses a further barrier to organisms unable to grow in acidic conditions. Enzymes such as lysozyme, which is present in tears, attack the cell walls of certain bacteria on contact. The importance of these barriers becomes obvious when they are breached. Bites of animals or insects puncture the skin and can introduce a number of diseases. Animal bites can communicate rabies or tetanus, whereas insects carry a host of diseases, including malaria from mosquitoes, plague from fleas, and Lyme disease from ticks. A dramatic example of barrier loss is seen in burn victims, who lose the protective skin at the burn site and must be treated aggressively with drugs to prevent bacterial and fungal infection. Beyond the primary barriers, innate immunity includes a host of cells, such as the phagocytes demonstrated by Metchnikoff, as well as antimicrobial compounds synthesized by the host that can recognize and neutralize invaders based on common molecular surface markers.

Phagocytic cells are a barrier to infection

An important innate defense mechanism is the ingestion of extracellular particulate material by phagocytosis. Phagocytosis is one type of **endocytosis,** the general term for the uptake by a cell of material from its environment. In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms. Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages (see Chapter 2). Most cell types are capable of other forms of endocytosis, such as *receptor-mediated endocytosis,* in which extracellular molecules are internalized after binding to specific cellular receptors, and *pinocytosis,* the process by which cells take up fluid from the surrounding medium along with any molecules contained in it.

Soluble molecules contribute to innate immunity

A variety of soluble factors contribute to innate immunity, among them the protein lysozyme, the interferon proteins, and components of the complement system (see Chapter 7). **Lysozyme,** a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall. **Interferon** comprises a group of proteins produced by virus-infected cells. Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state.

Complement, examined in detail in Chapter 7, includes a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance. Complement occupies a position that truly straddles the innate and adaptive immune systems, in that certain components may directly deal with pathogens, whereas others require prior binding of antibodies to activate its effector system. Reactions between complement molecules or fragments of complement molecules and cellular receptors trigger activation of cells of the innate or adaptive immune systems. Recent studies on **collectins** indicate that these proteins may kill certain bacteria directly by disrupting their lipid membranes or, alternatively, by aggregating the bacteria to enhance their susceptibility to phagocytosis.

Many of the molecules involved in innate immunity have the property of **pattern recognition,** the ability to recognize a given class of molecules. Because certain types of molecules are unique to microbes and never found in multicellular organisms, the ability to immediately recognize and combat invaders displaying such molecules is a strong feature of innate immunity. Molecules with pattern recognition ability may be soluble, like lysozyme and the complement components described above, or they may be cell-associated receptors, such as those designated the **Toll-like receptors (TLRs),** described in Chapter 3.

Should the invading pathogen breach the host's physical and chemical barriers, it may then be detected by pattern recognition molecules of the host and taken up by phagocytic cells, causing the system to react with an inflammatory response (see Chapters 3 and 13). This response concentrates elements of innate immunity at the inflammation site and may result in the marshaling of a specific immune response against the invader. The specific response called upon by the inflammation is the adaptive (sometimes called acquired) immune response.

In contrast to the broad reactivity of the innate immune system, which is uniform in all members of a species, the specific component, adaptive immunity, does not come into play until there is a recognized antigenic challenge to the organism. Adaptive immunity responds to the challenge with a high degree of specificity as well as the remarkable property of "memory." Typically, there is an adaptive immune response against an antigen within five or six days after the initial exposure to that antigen. Future exposure to the same antigen results in a memory response: the immune response to the second challenge occurs more quickly than the first, is stronger, and is often more effective in neutralizing and clearing the pathogen. The major agents of adaptive immunity are lymphocytes and the antibodies they produce. Table 1-3 compares innate and adaptive immunity.

Because adaptive immune responses require some time to marshal, innate immunity provides the first line of defense during the critical period just after the host's exposure to a pathogen. In general, most of the microorganisms encountered by a healthy individual are readily cleared within a few days by defense mechanisms of the innate immune system before they activate the adaptive immune system.

Collaboration between innate and adaptive immunity increases immune responsiveness

It is important to appreciate that the innate and adaptive immune systems do not operate independently—they

TABLE 1-3 Comparison of innate and adaptive immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse; improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response
Major components	Barriers (e.g., skin); phagocytes; pattern recognition molecules	Lymphocytes; antigen-specific receptors; antibodies

function as a highly interactive and cooperative system, producing a combined response more effective than either branch could produce by itself. Certain cellular and molecular immune components play important roles in both types of immunity.

An example of cooperation is seen in the encounter between macrophages and microbes. Interactions between receptors on macrophages and microbial components generate soluble proteins that stimulate and direct adaptive immune responses, facilitating the participation of the adaptive immune system in the elimination of the pathogen. The soluble proteins are growth factor–like molecules known by the general name **cytokines.** The cytokines react with receptors on various cell types and signal the cell to perform functions such as synthesis of new factors or to undergo differentiation to a new cell type. A restricted class of cytokines have chemotactic activity and recruit specific cells to the site of the cell secreting that cytokine; these are called **chemokines.**

The type of intracellular communication mediated by cytokines is referred to by the general term **signaling.** Basically, signaling involves the reaction between a soluble molecule (ligand) and a cell membrane–bound molecule (receptor) or between membrane-bound molecules on two different cells. The interaction between a receptor and its ligand leads to metabolic adaptations in cells. There are an enormous number of different signal transduction pathways, all exhibiting common themes typical of these integrative processes:

- *Signal transduction begins when a signal binds to its receptor.* Receptors may be inside or outside the cell. Signals that cannot penetrate the cell membrane bind to receptors on the cell surface. This group includes water-soluble signaling molecules and membrane-bound ligands (MHC-peptide complexes, for example). Hydrophobic signals, such as steroids, can diffuse through the cell membrane and are bound by intracellular receptors.
- *Many signal transduction pathways involve the signal-induced assembly of pathway components.* Molecules known as adaptor proteins bind specifically and simultaneously to two or more different molecules with roles in the signaling pathway, bringing them together and promoting their combined activity.
- *Signal reception often leads to the generation within the cell of a "second messenger,"* a molecule or ion that can diffuse to other sites in the cell and stimulate metabolic changes. Examples are cyclic nucleotides (cAMP, cGMP), calcium ion (Ca^{2+}), and membrane phospholipid derivatives such as diacylglycerol (DAG) and inositol triphosphate (IP_3).
- *Protein kinases and protein phosphatases are activated or inhibited.* Kinases catalyze the phosphorylation of target residues (tyrosine, serine, or threonine) of key signal transduction proteins. Phosphatases catalyze dephosphorylation, reversing the effect of kinases. These enzymes play essential roles in many signal transduction pathways of immunological interest.
- *Signals are amplified by enzyme cascades.* An enzyme in a signaling pathway, once activated, catalyzes many additional reactions. The enzyme may generate many molecules of the next component in the pathway or activate many copies of the next enzyme in the sequence. This greatly amplifies the signal at each step and offers opportunities to modulate the intensity of a signal.

These processes are schematically represented in Figure 1-6.

The activity that results from signal transduction may be synthesis and/or secretion of certain proteins, differentiation, or the initiation or cessation of specific functions. For example, stimulated macrophages secrete cytokines that can direct adaptive immune responses of lymphocytes against specific pathogens.

In a complementary fashion, the adaptive immune system produces signals and components that increase the effectiveness of innate responses. Some T cells, when they encounter appropriately presented antigen, synthesize and secrete cytokines that increase the ability of macrophages to kill the microbes they have ingested. Also, antibodies produced against an invader bind to the pathogen, marking it as a target for attack by macrophages or by complement proteins and serving as a potent activator of the attack.

A major difference between adaptive and innate immunity is the rapidity of the innate immune response, which utilizes a preexisting but limited repertoire of responding components. Adaptive immunity compensates for its slower onset by its ability to recognize a much wider repertoire of foreign substances and also by its ability to improve during a response, whereas innate immunity remains constant.

Adaptive immunity is highly specific

Adaptive immunity is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules (i.e., foreign antigens). Unlike innate immune responses,

OVERVIEW FIGURE 1-6: Common Themes in Signal Transduction

Signal reception

1 Signaling pathways are initiated when a signal binds its receptor

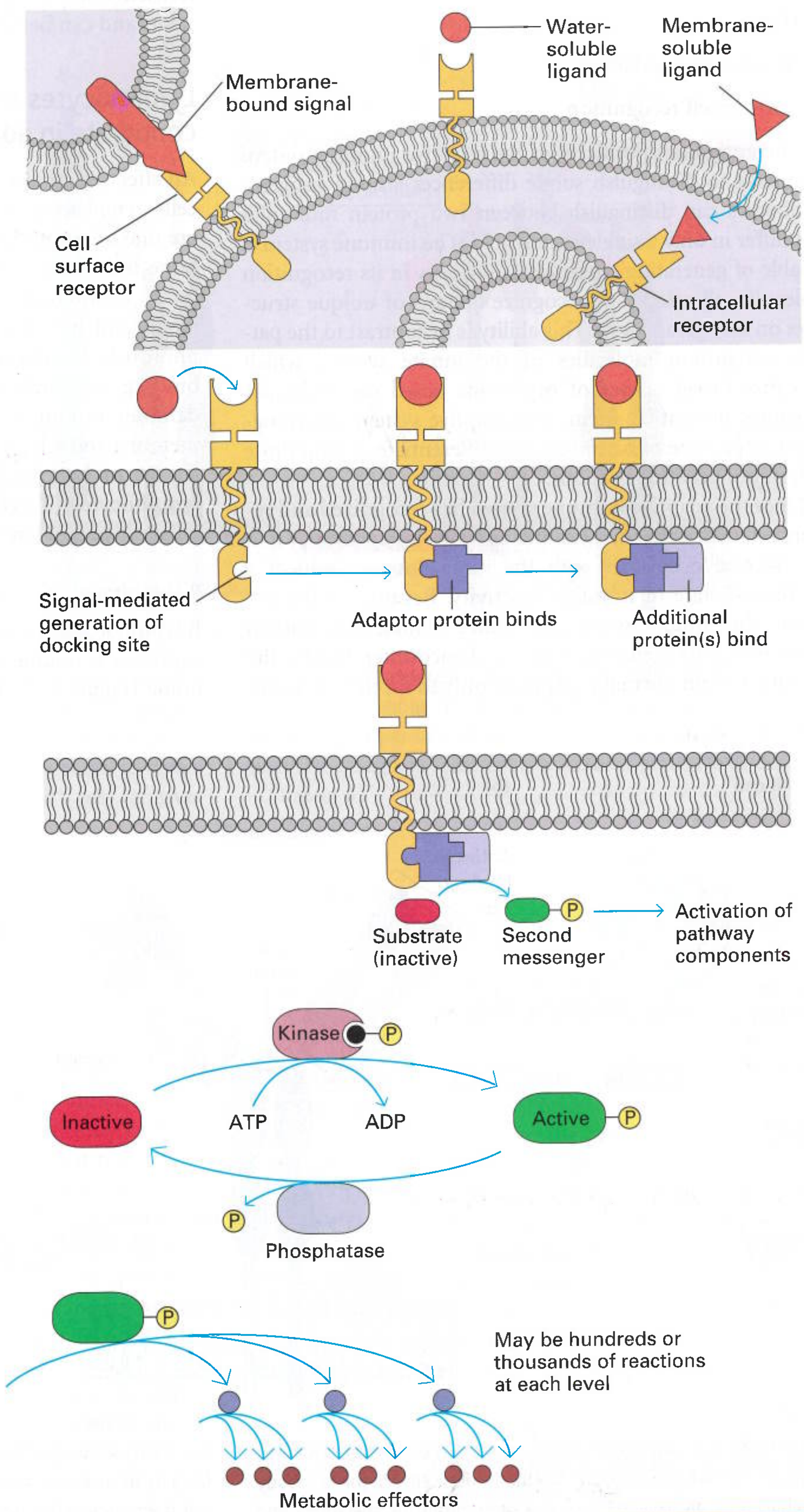
Transduction

2 Ligand binding to receptor induces assembly of signaling pathway components

3 Generation of second messenger carries signal to cell interior

4 Phosphorylation/dephosphorylation cycles under control of the signaling pathway activate/deactivate additional pathway components

5 Enzyme cascades amplify the signal, converting molecules to their active forms



adaptive responses are not the same in all members of a species but are reactions to specific antigenic challenges. Adaptive immunity displays four characteristic attributes:

- Antigenic specificity
- Diversity
- Immunologic memory
- Self-nonself recognition

The **antigenic specificity** of the adaptive immune system permits it to distinguish subtle differences among antigens. Antibodies can distinguish between two protein molecules that differ in only a single amino acid. The immune system is capable of generating tremendous *diversity* in its recognition molecules, allowing it to recognize billions of unique structures on foreign antigens. This ability is in contrast to the pattern recognition molecules of the innate system, which recognize broad classes of organisms based on molecular structures present on them. The adaptive system can recognize a single type of organism and differentiate among those with minor genetic variations.

Once the adaptive immune system has recognized and responded to an antigen, it exhibits *immunologic memory;* that is, a second encounter with the same antigen induces a heightened state of immune reactivity. Because of this attribute, the immune system can confer lifelong immunity to many infectious agents after an initial encounter. Finally, the immune system normally responds only to foreign antigens, indicating that it is capable of *self-nonself recognition.* The ability of the immune system to distinguish self from nonself and respond only to nonself molecules is essential. As described below, failure of the ability to distinguish self from nonself leads to an inappropriate response to self components and can be fatal.

Lymphocytes and antigen-presenting cells cooperate in adaptive immunity

An effective immune response involves two major groups of cells: *lymphocytes* and *antigen-presenting cells.* Lymphocytes are one of many types of white blood cells produced in the bone marrow by the process of hematopoiesis (see Chapter 2). Lymphocytes leave the bone marrow, circulate in the blood and lymphatic systems, and reside in various lymphoid organs. Because they produce and display antigen-binding cell surface receptors, lymphocytes mediate the defining immunologic attributes of specificity, diversity, memory, and self-nonself recognition. The two major populations of lymphocytes—**B lymphocytes (B cells)** and **T lymphocytes (T cells)**—are described briefly here and in greater detail in later chapters.

B Lymphocytes

B lymphocytes mature in the bone marrow; on release, each expresses a unique antigen-binding receptor on its membrane (Figure 1-7). This antigen-binding or B-cell receptor

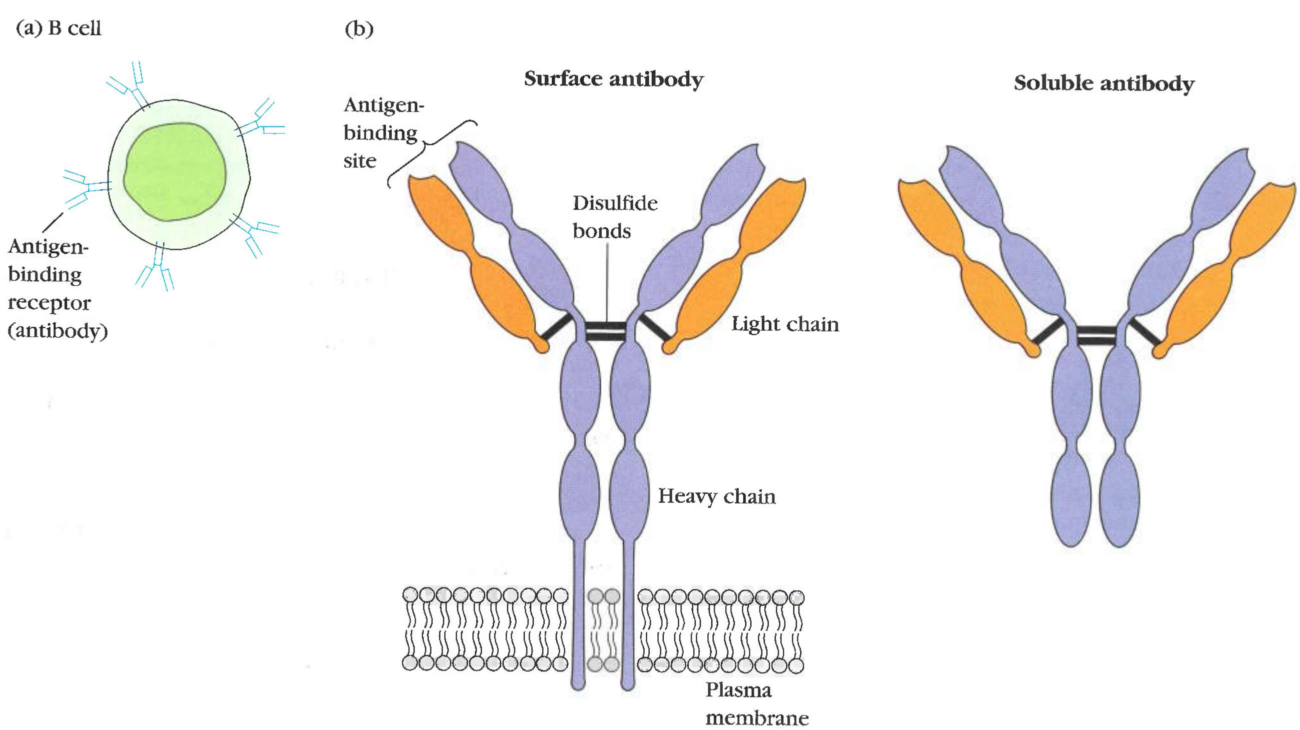


FIGURE 1-7 B cell. (a) The surfaces of B cells host about 10^5 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell have the same antigenic specificity and can interact directly with antigen. (b) Membrane-bound and soluble (secreted) antibody showing the heavy chains (blue) and light chains (red). Note that the soluble form lacks the sequences that bind the cell membrane. (The ovals in the diagrams represent characteristic protein folds called Ig domains, discussed in Chapter 4.)

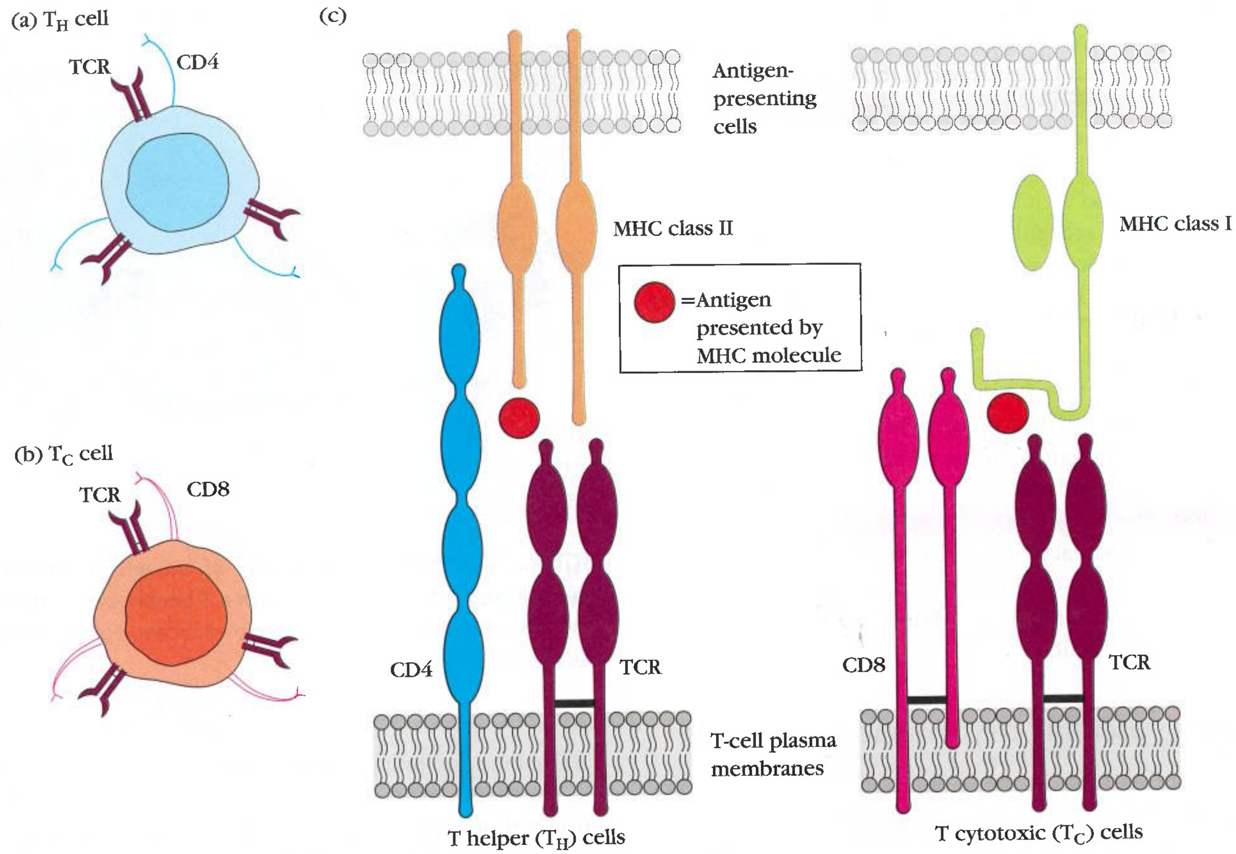


FIGURE 1-8 T cells. Key to the function of T cells is an antigen-binding molecule, the T-cell receptor (TCR). In general, T cells bearing CD4 ($CD4^+$ cells) act as (a) helper cells and $CD8^+$ cells act as (b) cytotoxic cells. (c) $CD4^+$ cells recognize only antigen bound to class II MHC molecules on antigen-presenting cells. $CD8^+$ cells recognize only antigen associated with class I MHC molecules. Both types of T cells express about 10^5 identical molecules of the antigen-binding T-cell receptor per cell, all with the same antigenic specificity. (The ovals in the diagrams represent characteristic protein folds, discussed in Chapter 4.)

is a membrane-bound **antibody molecule** (Figure 1-7b, c). Antibodies are glycoproteins that consist of two identical polypeptides called the heavy chains and two shorter, identical polypeptides called the light chains. Each heavy chain is joined to a light chain by disulfide bonds, and the heavy/light chain pairs are linked together by additional disulfide bonds. The amino-terminal ends of the pairs of heavy and light chains form a site to which antigen binds. When a naive B cell (one that has not previously encountered antigen) first encounters the antigen that matches its membrane-bound antibody, the binding of the antigen to the antibody causes the cell to divide rapidly; its progeny differentiate into **memory B cells** and **effector B cells** called **plasma cells.** Memory B cells have a longer life span than naive cells, and they express the same membrane-bound antibody as their parent B cell. Plasma cells produce the antibody in a form that can be secreted (Figure 1-7b, right) and have little or no membrane-bound antibody. Although plasma cells live for only a few days, they secrete enormous amounts of antibody during this time. A single plasma cell can secrete hundreds to thousands of molecules of antibody per second. Secreted antibodies are the major effector molecules of humoral immunity.

T Lymphocytes

T lymphocytes also arise in the bone marrow. Unlike B cells, which mature in the marrow, T cells migrate to the thymus gland to mature. Maturing T cells express a unique antigen-binding molecule, the **T-cell receptor (TCR),** on their membranes. There are two well-defined subpopulations of T cells: **T helper (T_H)** and **T cytotoxic (T_C) cells.** T helper (Figure 1-8a) and T cytotoxic (Figure 1-8b) cells can be distinguished from one another by the presence of either **CD4** or **CD8** membrane glycoproteins on their surfaces. T cells displaying CD4 generally function as T_H cells, whereas those displaying CD8 generally function as T_C cells (see Chapter 2). A recently characterized third type of T cell, called a **T regulatory (T_{reg}) cell,** carries CD4 on its surface but may be distinguished from T_H and T_C cells by cell surface markers associated with its stage of activation.

Unlike membrane-bound antibodies on B cells, which recognize free antigen, most T-cell receptors can recognize only antigen that is bound to cell membrane proteins called **major histocompatibility complex (MHC) molecules.** MHC molecules are polymorphic (genetically diverse) glycoproteins found on cell membranes (see Chapter 8). There are two major types of MHC molecules: class I MHC molecules, which are expressed by nearly all nucleated cells of vertebrate species, and Class II MHC molecules, which are expressed only by **antigen-presenting cells (APCs)** (Figure 1-8c). When a naive T cell encounters antigen combined with a MHC molecule on a cell, the T cell proliferates and differentiates into memory T cells and various effector T cells.

After a T_H cell recognizes and interacts with an antigen–MHC class II molecule complex, the cell is activated—it undergoes a metabolic transformation and begins to secrete various cytokines. The secreted cytokines play an important role in activating B cells, T_C cells, macrophages, and various other cells that participate in the immune response. Differences in the types of cytokines produced by activated T_H cells result in different patterns of immune response. One possible response is the induction of a change in T_C cells to form **cytotoxic T lymphocytes (CTLs)** that exhibit cell-killing or cytotoxic activity. CTLs have a vital function in monitoring the cells of the body and eliminating any that display antigen, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft.

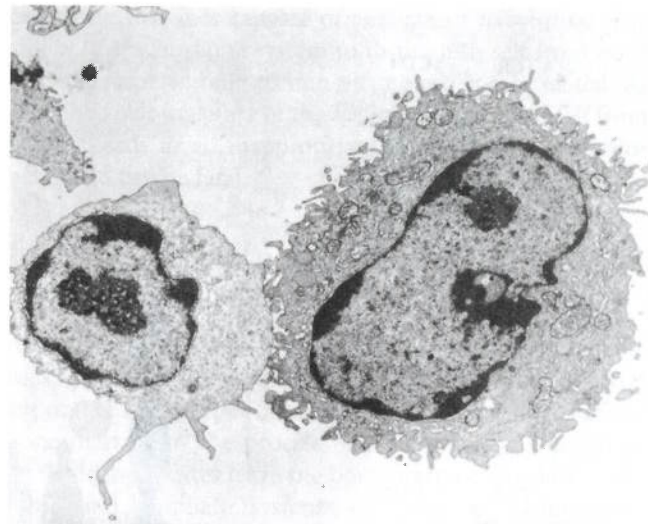


FIGURE 1-9 Electron micrograph of an antigen-presenting macrophage *(right)* associating with a T lymphocyte. *[From A. S. Rosenthal et al., 1982, in* Phagocytosis—Past and Future, *Academic Press, p. 239.]*

Antigen-presenting cells interact with T cells

Activation of both the humoral and cell-mediated branches of the immune system requires cytokines produced by T_H cells. It is essential that activation of T_H cells themselves be carefully regulated, because a T-cell response directed against self components can have fatal autoimmune consequences. One safeguard against unregulated activation of T_H cells is that the antigen receptors of T_H cells can recognize only antigen that is displayed together with class II MHC molecules on the surface of antigen-presenting cells. These specialized cells, which include macrophages, B lymphocytes, and dendritic cells, are distinguished by two properties: (1) they express class II MHC molecules on their membranes, and (2) they can produce cytokines that cause T_H cells to become activated.

Antigen-presenting cells first internalize antigen, by either phagocytosis or endocytosis, and then display a part of that antigen on their membrane bound to a class II MHC molecule. The T_H cell interacts with the antigen–class II MHC molecule complex on the membrane of the antigen-presenting cell (Figure 1-9). The antigen-presenting cell then produces an additional signal leading to activation of the T_H cell.

Humoral and cellular immune responses exhibit different effector functions

As mentioned earlier, immune responses can be divided into humoral and cell-mediated responses. Humoral immunity refers to immunity that can be conferred on a nonimmune individual by administration of serum antibodies from an immune individual. In contrast, cell-mediated immunity can be transferred only by administration of T cells from an immune individual.

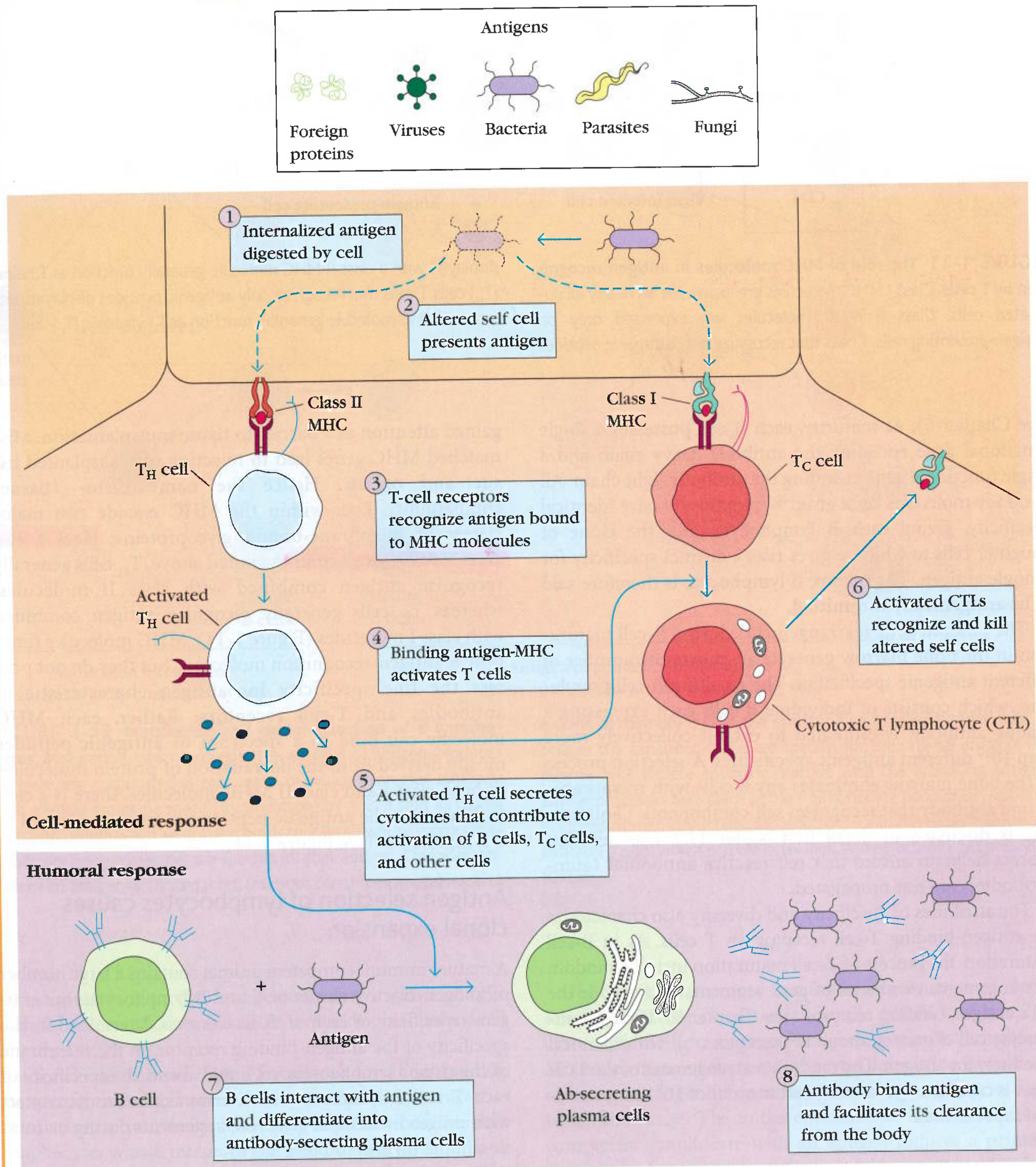
The humoral branch of the immune system is at work in the interaction of B cells with antigen and their subsequent proliferation and differentiation into antibody-secreting plasma cells (Figure 1-10). Antibody functions as the effector of the humoral response by binding to antigen and facilitating its elimination. Antigen coated with antibody is eliminated in several ways. For example, antibody can cross-link several antigens, forming clusters that are more readily ingested by phagocytic cells. Binding of antibody to antigen on a microorganism can also activate the complement system, resulting in lysis of the foreign organism. In addition, antibody can neutralize toxins or viral particles by coating them, which prevents them from binding to host cells.

Effector T cells generated in response to antigen are responsible for cell-mediated immunity (see Figure 1-10). Both activated T_H cells and cytotoxic T lymphocytes serve as effector cells in cell-mediated immune reactions. Cytokines secreted by T_H cells can activate various phagocytic cells, enabling them to phagocytose and kill microorganisms more effectively. This type of cell-mediated immune response is especially important in ridding the host of bacteria and protozoa contained by infected host cells. CTLs participate in cell-mediated immune reactions by killing altered self cells, including virus-infected cells and tumor cells.

The antigen receptors of B and T lymphocytes are diverse

The antigenic specificity of each B cell is determined by the membrane-bound antigen-binding receptor (i.e., antibody) expressed by the cell. As a B cell matures in the bone marrow, its specificity is created by random rearrangements of a series of gene segments that encode the antibody molecule

OVERVIEW FIGURE 1-10: The Humoral and Cell-Mediated Branches of the Immune System



In the humoral response, B cells interact with antigen and then differentiate into antibody-secreting plasma cells. The secreted antibody binds to the antigen and facilitates its clearance from the body. In the cell-mediated response, various subpopulations of T cells recognize antigen presented on self cells. T_H cells respond to antigen by producing cytokines. T_C cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self cells (e.g., virus-infected cells).

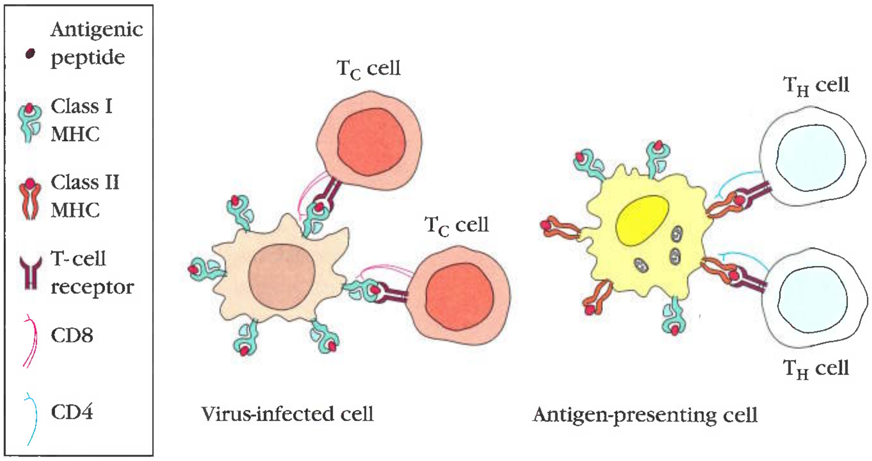


FIGURE 1-11 The role of MHC molecules in antigen recognition by T cells. Class I MHC molecules are expressed on nearly all nucleated cells. Class II MHC molecules are expressed only on antigen-presenting cells. T cells that recognize only antigenic peptides displayed with a class II MHC molecule generally function as T helper (T_H) cells. T cells that recognize only antigenic peptides displayed with a class I MHC molecule generally function as T cytotoxic (T_C) cells.

(see Chapter 5). At maturity, each B cell possesses a single functional gene encoding the antibody heavy chain and a single functional gene encoding the antibody light chain. All antibody molecules on a given B lymphocyte have identical specificity, giving each B lymphocyte, and the clone of daughter cells to which it gives rise, a distinct specificity for a single antigen. The mature B lymphocyte is therefore said to be **antigenically committed.**

The random gene rearrangements during B-cell maturation in the bone marrow generate an enormous number of different antigenic specificities. The resulting B-cell population, which consists of individual B cells each expressing a unique antibody, is estimated to exhibit collectively more than 10^{10} different antigenic specificities. A selection process in the bone marrow eliminates any B cells with membrane-bound antibody that recognizes self components. (This process is discussed in detail in Chapter 11.) The selection process helps to ensure that self-reactive antibodies (autoantibodies) are not propagated.

The attributes of specificity and diversity also characterize the antigen-binding T-cell receptor on T cells. As in B-cell maturation, the process of T-cell maturation includes random rearrangements of a series of gene segments that encode the cell's antigen-binding receptor (see Chapter 9). Each T lymphocyte cell expresses about 10^5 receptors, all with identical specificity for antigen. The random rearrangement of the TCR genes is capable of generating on the order of 10^9 unique antigenic specificities.

The major histocompatibility complex molecules bind antigenic peptides

The major histocompatibility complex is a large genetic complex with multiple loci. This group of genes first gained attention as a barrier to tissue transplantation. Mismatched MHC genes lead to rejection of transplanted tissue and organs. Hence the name histo- (tissue) compatibility. Loci within the MHC encode two major classes of membrane-bound glycoproteins: **class I and class II MHC molecules.** As noted above, T_H cells generally recognize antigen combined with class II molecules, whereas T_C cells generally recognize antigen combined with class I molecules (Figure 1-11). MHC molecules function as antigen-recognition molecules, but they do not possess the fine specificity for antigen characteristic of antibodies and T-cell receptors. Rather, each MHC molecule can bind to a spectrum of **antigenic peptides** mostly derived from the degradation of protein molecules. In both class I and class II MHC molecules, there is a cleft within which the antigenic peptide sits and is presented to T lymphocytes (see Figure 1-11).

Antigen selection of lymphocytes causes clonal expansion

A mature immunocompetent animal contains a large number of antigen-reactive clones of T and B lymphocytes; the antigenic specificity of each of these clones is determined by the specificity of the antigen-binding receptor on the membrane of the clone's lymphocytes. As noted above, the specificity of each T and B lymphocyte is determined before its contact with antigen by random gene rearrangements during maturation in the thymus or bone marrow.

The role of antigen becomes critical when it interacts with and activates mature, antigenically committed T and B lymphocytes, bringing about expansion of the population of cells with a given antigenic specificity. In this process of **clonal selection,** an antigen binds to a particular T or B cell

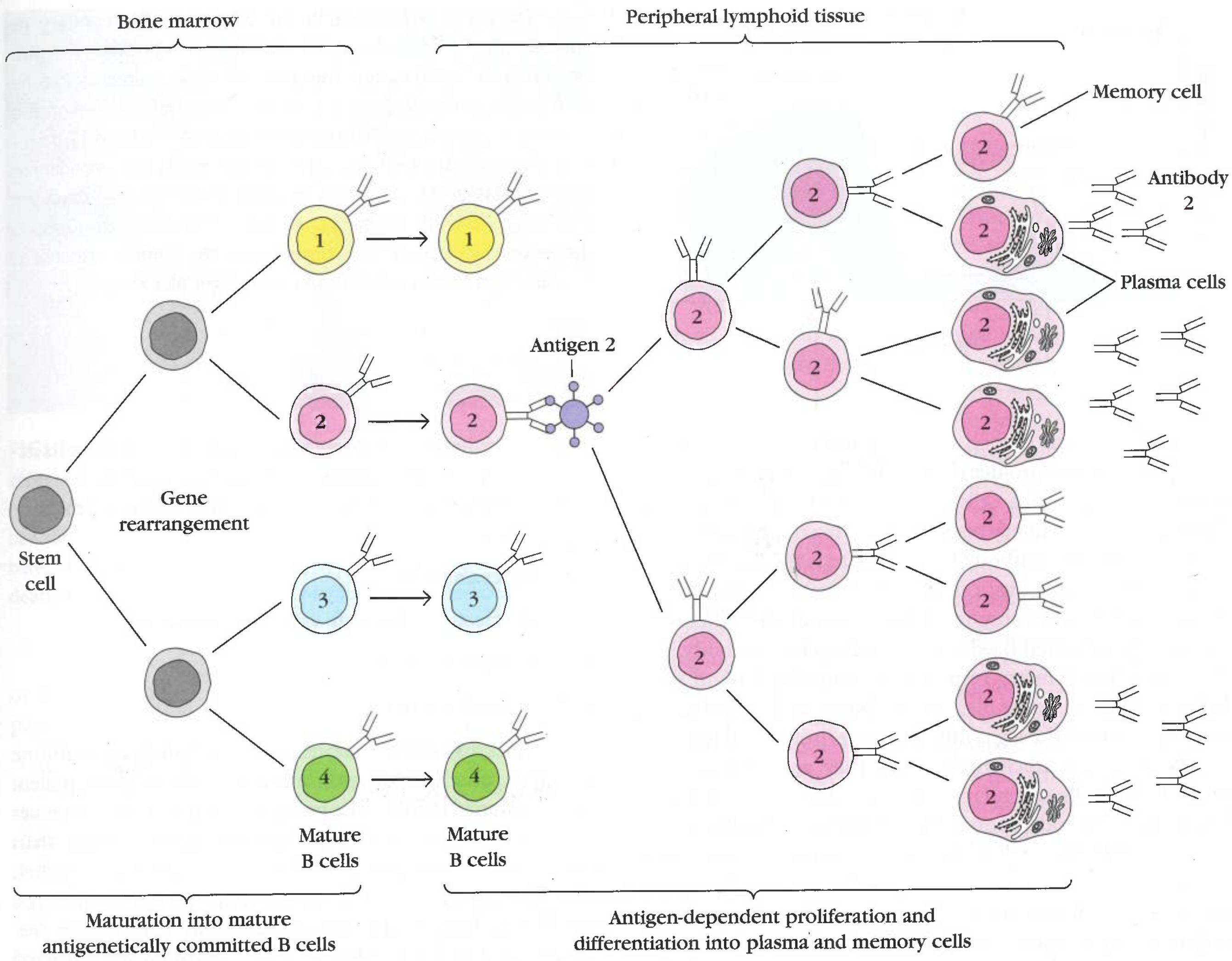


FIGURE 1-12 Maturation and clonal selection of B lymphocytes. Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity (indicated by 1, 2, 3, and 4). Clonal selection occurs when an antigen binds to a B cell whose membrane-bound antibody molecules are specific for that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen. The plasma cells secrete antibody reactive with the activating antigen. Similar processes take place in the T-lymphocyte population, resulting in clones of memory T cells and effector T cells; the latter include activated T_H cells, which secrete cytokines, and cytotoxic T lymphocytes (CTLs).

and stimulates it to divide repeatedly into a clone of cells with the same antigenic specificity as the original parent cell (Figure 1-12).

Clonal selection provides a framework for understanding the specificity and self-nonself recognition that is characteristic of adaptive immunity. Specificity is present because only lymphocytes whose receptors are specific for a given antigen will be clonally expanded and thus mobilized for an immune response. Self-nonself discrimination is accomplished by the elimination, during development, of lymphocytes bearing self-reactive receptors or by the functional suppression of these cells if they reach maturity.

Immunologic memory is another consequence of clonal selection. During clonal selection, the number of lymphocytes specific for a given antigen is greatly amplified. Moreover, many of these lymphocytes, referred to as memory cells, have a longer life span than the naive lymphocytes from which they arise. The initial encounter of a naive immunocompetent lymphocyte with an antigen induces a **primary response;** a later contact of the host with antigen will induce a more rapid and heightened **secondary response.** The amplified population of memory cells accounts for the rapidity and intensity that distinguishes a secondary response from the primary response.

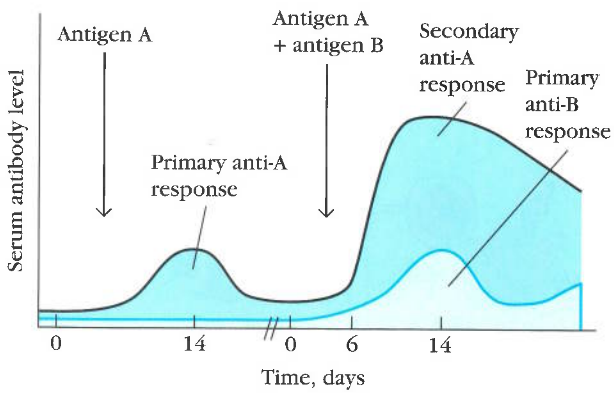


FIGURE 1-13 Differences in the primary and secondary response to injected antigen (humoral response) reflect the phenomenon of immunologic memory. When an animal is injected with an antigen, it produces a primary serum antibody response of low magnitude and short duration, peaking at about 10 to 17 days. A second immunization with the same antigen results in a secondary response that is greater in magnitude, peaks in less time (2–7 days), and lasts longer (months to years) than the primary response. Compare the secondary response to antigen A with the primary response to antigen B administered to the same mice (light blue shading).

In the humoral branch of the immune system, antigen induces the clonal proliferation of B lymphocytes into antibody-secreting plasma cells and memory B cells. As seen in Figure 1-13, the primary response has a lag of approximately 5 to 7 days before antibody levels start to rise. This lag is the time required for activation of naive B cells by antigen and T_H cells and for the subsequent proliferation and differentiation of the activated B cells into plasma cells. Antibody levels peak in the primary response at about day 14 and then begin to drop off as the plasma cells begin to die. In the secondary response, the lag is much shorter (only 1–2 days), antibody levels are much higher, and they are sustained for much longer. The secondary response reflects the activity of the clonally expanded population of memory B cells. These memory cells respond to the antigen more rapidly than naive B cells; in addition, because there are many more memory cells than there were naive B cells for the primary response, more plasma cells are generated in the secondary response, and antibody levels are consequently 100- to 1000-fold higher.

In the cell-mediated branch of the immune system, the recognition of an antigen-MHC complex by a specific mature T lymphocyte induces clonal proliferation into various T cells with effector functions (T_H cells and CTLs) and into memory T cells. As with humoral immune responses, secondary cell-mediated responses are faster and stronger than primary.

Immune Dysfunction and Its Consequences

The above overview of innate and adaptive immunity depicts a multicomponent interactive system that protects the host from invasion by pathogens that cause infectious diseases and from altered cells that can reproduce in an uncontrolled manner to cause cancer. This overview would not be complete without mentioning that the immune system can, and does at times, function improperly. Sometimes the immune system fails to protect the host adequately because of a deficiency, and sometimes it overreacts or misdirects its activities to cause discomfort, debilitating disease, or even death. There are several common manifestations of immune dysfunction:

- Allergies and asthma
- Graft rejection and graft-versus-host disease
- Autoimmune disease
- Immunodeficiency

Allergies and asthma are results of inappropriate immune responses, often to common antigens such as plant pollen, food, or animal dander. The possibility that certain substances induced increased sensitivity (hypersensitivity) rather than protection was recognized in about 1902 by Charles Richet, who attempted to immunize dogs against the toxins of a type of jellyfish, *Physalia.* He and his colleague Paul Portier observed that dogs exposed to sublethal doses of the toxin reacted almost instantly, and fatally, to subsequent challenge with minute amounts of the toxin. Richet concluded that a successful immunization or vaccination results in *phylaxis,* or protection, whereas the opposite result may occur—**anaphylaxis**—in which exposure to antigen can result in a potentially lethal sensitivity to the antigen if the exposure is repeated. Richet received the Nobel prize in 1913 for his discovery of the anaphylactic response.

Fortunately, most allergic reactions in humans are not rapidly fatal. A specific allergic or anaphylactic response usually involves a type of antibody called IgE (for *immunoglobulin E*). Binding of IgE to its specific antigen (allergen) releases substances that cause irritation and inflammation. When an allergic individual is exposed to an allergen, symptoms may include sneezing, wheezing, and difficulty in breathing (asthma); dermatitis or skin eruptions (hives); and, in more extreme cases, strangulation due to blockage of airways by inflammation (Figure 1-14). A significant fraction of our health resources is expended to care for those suffering from allergies and asthma. The frequency of allergy and asthma in the United States places these complaints among the most common reasons for a visit to the doctor's office

FIGURE 1-14 Patient suffering swelling of the right eye from effects of allergic reaction to a bee sting. Such hypersensitivity reactions result from sensitization caused by previous exposure to the bee venom. Bee stings may cause pain, redness, and swelling as shown here or may cause systemic anaphylactic reactions that result in death if not quickly treated. *[Dr. P. Marazzi/Photo Researchers.]*

or to the hospital emergency room (see Clinical Focus on page 20).

When the immune system encounters foreign cells or tissue, it responds strongly to rid the host of the invader. The same response may be raised against mutant host cells, including cancer cells. However, in some cases, the transplantation of cells or an organ from another individual, although viewed by the immune system as a foreign invasion, may be the only possible treatment for life-threatening disease. For example, it is estimated that more than 70,000 persons in the United States alone would benefit from a kidney transplant. The fact that the immune system will attack and reject any transplanted organ that it recognizes as nonself raises a formidable barrier to this potentially lifesaving treatment. An additional danger in transplantation is that any transplanted cells with immune function (for example, when bone marrow is transplanted to restore immune function) may view the new host as nonself and react against it. This reaction, which is termed graft-versus-host disease, can be fatal. The rejection reaction and graft-versus-host disease can be suppressed by drugs, but treatment with these drugs suppresses general immune function, so that the host is no longer protected by its own immune system and becomes susceptible to infectious diseases. Transplantation studies have played a major role in the development of immunology. A Nobel prize was awarded to Karl Landsteiner (mentioned above for his contributions to the concept of immune specificity) in 1930 for the discovery of the human ABO blood groups, a finding that allowed blood transfusions to be carried out safely. In 1980, G. Snell, J. Dausset, and B. Benacerraf were recognized for discovery of the major histocompatibility complex, and in 1991, E. D. Thomas and J. Murray were awarded Nobel prizes for advances in transplantation immunity. Development of procedures that would allow a foreign organ to be accepted without suppressing immunity to all antigens remains a challenge for immunologists today.

In certain individuals, the immune system malfunctions by losing its sense of self and nonself, which permits an immune attack on the host. This condition, **autoimmunity,** can cause a number of chronic debilitating diseases. The symptoms of autoimmunity differ, depending on which tissues and organs are under attack. For example, multiple sclerosis is due to an autoimmune attack on a protein in nerve sheaths in the brain and central nervous system, Crohn's disease is an attack on intestinal tissues, and rheumatoid arthritis is an attack on joints of the hands, feet, arms, and legs. The genetic and environmental factors that trigger and sustain autoimmune disease are very active areas of immunologic research, as is the search for improved treatments.

If any components of innate or specific immunity are defective because of genetic abnormality or if any immune function is lost because of damage by chemical, physical, or biological agents, the host suffers from **immunodeficiency.** The severity of the immunodeficiency disease depends on the number of affected components. A common type of immunodeficiency in North America is a selective immunodeficiency in which only one type of immunoglobulin, IgA, is lacking; the symptoms may be an increase in certain types of infections or the deficiency may even go unnoticed. In contrast, a rarer immunodeficiency called **severe combined immunodeficiency (SCID),** which affects both B and T cells, may result in death from infection at an early age if untreated. Since the 1980s, the most common form of immunodeficiency has been acquired immune deficiency syndrome, or AIDS, which results from infection with the retrovirus human immunodeficiency virus, or HIV. In AIDS, T helper cells are destroyed by HIV, causing a collapse of the immune system. It is estimated that 40 million people worldwide suffer from this disease, which if not treated is usually fatal within 8 to 10 years after infection. Although certain treatments can now prolong the life of AIDS patients, there is no known cure for the disease.

This chapter has been a brief introduction to the immune system, and it has given a thumbnail sketch of how this complex system functions to protect the host from disease. The following chapters will examine the structure and function of the individual cells, organs, and molecules that make up this system. They will describe our current understanding of how the components of immunity interact and the experiments that allowed discovery of these mechanisms. Specific areas of applied immunology, such as immunity to infectious diseases, cancer, current vaccination practices, and the major types of immune dysfunction are the subject of later chapters.

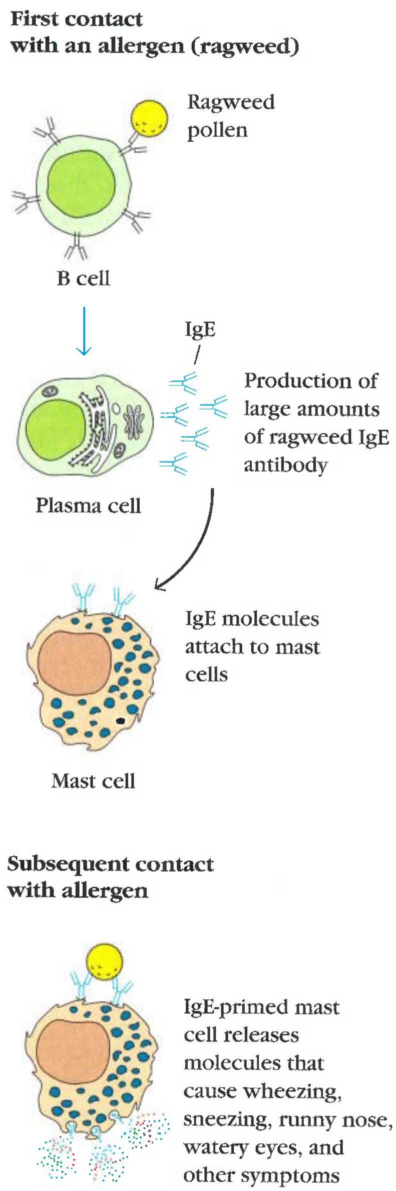
CLINICAL FOCUS

Allergies and Asthma Are Serious Public Health Problems

Although the immune system serves to protect the host from infection and cancer, inappropriate responses of this system can lead to disease. Common among the results of immune dysfunction are allergies and asthma, both serious public health problems. Details of the mechanisms that underlie allergic and asthmatic responses to environmental antigens (or allergens) will be considered in Chapter 15. Simply stated, allergic reactions are responses to antigenic stimuli that result in immunity based mainly on the IgE class of immunoglobulin. Exposure to the antigen (or allergen) triggers an IgE-mediated release of molecules that cause symptoms ranging from sneezing and dermatitis to inflammation of the lungs in an asthmatic attack. The sequence of events in an allergic response is depicted in the accompanying figure.

The discomfort from common allergies such as plant pollen allergy (often called ragweed allergy) is short-lived, consisting of sneezing and runny nose—trivial in comparison to the effects of cancer, cardiac arrest, or life-threatening infections. A more serious allergic reaction is asthma, a chronic disease of the lungs in which inflammation, mediated by environmental antigens or infections, causes severe difficulty in breathing. According to 2002 statistics from the Centers for Disease Control, 20 million people suffer from asthma in the United States, and 12 million per year experience an asthma attack. About 5000 people die each year from asthma. In the past 20 years, the prevalence of asthma in the Western world has doubled.*

The importance of allergy as a public health problem is underscored by the fact that the annual numbers of doctor visits for hypertension, routine medical examinations, or normal pregnancy are each fewer than the number of visits for allergic conditions. In fact, the most common reason for a trip to a hospital emergency room is an asthma attack, accounting for one third of all visits. In addition to those treated in the ER, there were about 160,000 hospitalizations for asthma in the past year, with an average stay of 3 to 4 days.



Sequence of events leading to an allergic response. When the antibody produced on contact with an allergen is IgE, this class of antibody reacts with a mast cell. Subsequent reaction of the antibody-binding site with the allergen triggers the mast cell to which the IgE is bound to secrete molecules that cause the allergic symptoms.

Although all ages and races are affected, deaths from asthma are 3.5 times more common among African American children. The reasons for the increases in number of asthma cases and for the higher death rate in African American children remain unknown, although recent studies of genetic factors in allergic disease may have uncovered some clues (see Clinical Focus in Chapter 15).

An increasingly serious health problem is food allergy, especially to peanuts and tree nuts (almonds, cashews, and walnuts).† Approximately 3 million Americans are allergic to these foods, and they are the leading causes of fatal and near-fatal food allergic (anaphylactic) reactions. Although avoiding these foods can prevent harmful consequences, the ubiquitous use of peanut protein and other nut products in a variety of foods makes avoidance very difficult for the allergic individual. At least 50% of serious reactions are caused by accidental exposures to peanuts, tree nuts, or their products. This has led to controversial movements to ban peanuts from schools and airplanes.

Anaphylaxis generally occurs within an hour of ingesting the food allergen, and the most effective treatment is injection of the drug epinephrine. Those prone to anaphylactic attacks often carry injectable epinephrine to be used in case of exposure.

In addition to the suffering and anxiety caused by inappropriate immune responses or allergies to environmental antigens, there is a staggering cost—estimated to be almost $20 billion—in terms of lost work time for those affected and for caregivers. These costs well justify the extensive efforts by basic and clinical immunologists and allergists to relieve the suffering caused by these disorders.

*Holgate, S. T. 1999. The epidemic of allergy and asthma, *Nature* supp. to vol. 402, B2.

†Hughes, D. A., and C. Mills. 2001. Food allergy: A problem on the rise. *Biologist* (London) **48**:201.

SUMMARY

- Immunity is the state of protection against foreign organisms or substances (antigens). Vertebrates have two types of immunity: innate and adaptive.
- Innate immunity constitutes a first line of defense, which includes barriers, phagocytic cells, and molecules that recognize certain classes of pathogens.
- Innate and adaptive immunity operate cooperatively; activation of the innate immune response produces signals that stimulate a subsequent adaptive immune response.
- Adaptive immune responses exhibit four immunologic attributes: specificity, diversity, memory, and self-nonself recognition.
- The high degree of specificity in adaptive immunity resides in molecules (antibodies and T-cell receptors) that recognize and bind specific antigens.
- Antibodies recognize and interact directly with antigen. T-cell receptors recognize only antigen combined with major histocompatibility complex (MHC) molecules.
- The two major subpopulations of T lymphocytes are the $CD4^+$ T helper (T_H) cells and $CD8^+$ T cytotoxic (T_C) cells, which give rise to cytotoxic T cells (CTLs).
- Dysfunctions of the immune system include common maladies such as allergies and asthma as well as immunodeficiency and autoimmunity.

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Useful Web Sites

http://www.aaaai.org/

The American Academy of Allergy Asthma and Immunology site includes an extensive library of information about allergic diseases.

http://www.aai.org

The Web site of the American Association of Immunologists contains a good deal of information of interest to immunologists.

http://www.ncbi.nlm.nih.gov/PubMed/

PubMed, the National Library of Medicine database of more than 9 million publications, is the world's most comprehensive bibliographic database for biological and biomedical literature. It is also a highly user-friendly site.

Study Questions

CLINICAL FOCUS QUESTION You have a young nephew who has developed a severe allergy to tree nuts. What precautions would you advise for him and for his parents? Should school officials be aware of this condition?

1. Why was Jenner's vaccine superior to previous methods for conferring resistance to smallpox?
2. Did the treatment for rabies used by Pasteur confer active or passive immunity to the rabies virus? Is there any way to test this?
3. Infants immediately after birth are often at risk for infection with group B streptococcus. A vaccine is proposed for administration to women of childbearing years. How can immunizing the mothers help the babies?
4. Indicate to which branch(es) of the immune system the following statements apply, using H for the humoral branch and CM for the cell-mediated branch. Some statements may apply to both branches.
   a. Involves class I MHC molecules
   b. Responds to viral infection
   c. Involves T helper cells
   d. Involves processed antigen
   e. Responds following an organ transplant
   f. Involves T cytotoxic cells
   g. Involves B cells
   h. Involves T cells
   i. Responds to extracellular bacterial infection
   j. Involves secreted antibody
   k. Kills virus-infected self cells
5. Adaptive immunity exhibits four characteristic attributes, which are mediated by lymphocytes. List these four attributes and briefly explain how they arise.
6. Name three features of a secondary immune response that distinguish it from a primary immune response.
7. Compare and contrast the four types of antigen-binding molecules used by the immune system—antibodies, T-cell