Understanding the Immune System
How It Works
Artwork by Jeanne Kelly
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**Note:** Words in **bold** are defined in the glossary at the end of this booklet.
The immune system is a network of cells, tissues, and organs that work together to defend the body against attacks by “foreign” invaders. These are primarily microbes—tiny organisms such as bacteria, parasites, and fungi that can cause infections. Viruses also cause infections, but are too primitive to be classified as living organisms. The human body provides an ideal environment for many microbes. It is the immune system’s job to keep them out or, failing that, to seek out and destroy them.

When the immune system hits the wrong target, however, it can unleash a torrent of disorders, including allergic diseases, arthritis, and a form of diabetes. If the immune system is crippled, other kinds of diseases result.

The immune system is amazingly complex. It can recognize and remember millions of different enemies, and it can produce secretions (release of fluids) and cells to match up with and wipe out nearly all of them.

The secret to its success is an elaborate and dynamic communications network. Millions and millions of cells, organized into sets and subsets, gather like clouds of bees swarming around a hive and pass information back and forth in response to an infection. Once immune cells receive the alarm, they become activated and begin to produce powerful chemicals. These substances allow the cells to regulate their own growth and behavior, enlist other immune cells, and direct the new recruits to trouble spots.
The key to a healthy immune system is its remarkable ability to distinguish between the body’s own cells, recognized as “self,” and foreign cells, or “nonself.” The body’s immune defenses normally coexist peacefully with cells that carry distinctive “self” marker molecules. But when immune defenders encounter foreign cells or organisms carrying markers that say “nonself,” they quickly launch an attack.

Anything that can trigger this immune response is called an antigen. An antigen can be a microbe such as a virus, or a part of a microbe such as a molecule. Tissues or cells from another person (except an identical twin) also carry nonself markers and act as foreign antigens. This explains why tissue transplants may be rejected.

Antigens carry marker molecules that identify them as foreign.
In abnormal situations, the immune system can mistake self for nonself and launch an attack against the body’s own cells or tissues. The result is called an **autoimmune disease**. Some forms of arthritis and diabetes are autoimmune diseases. In other cases, the immune system responds to a seemingly harmless foreign substance such as ragweed pollen. The result is allergy, and this kind of antigen is called an **allergen**.

**The Structure of the Immune System**

The organs of the immune system are positioned throughout the body. They are called **lymphoid organs** because they are home to **lymphocytes**, small white blood cells that are the key players in the immune system. Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including lymphocytes. The thymus is a lymphoid organ that lies behind the breastbone. Lymphocytes known as **T lymphocytes** or **T cells** (“T” stands for “thymus”) mature in the thymus and then migrate to other tissues. **B lymphocytes**, also known as **B cells**, become activated and mature into **plasma cells**, which make and release **antibodies**.
The organs of the immune system are positioned throughout the body.
The lymph node contains numerous specialized structures. T cells concentrate in the paracortex, B cells in and around the germinal centers, and plasma cells in the medulla.

**Lymph nodes**, which are located in many parts of the body, are lymphoid tissues that contain numerous specialized structures.

- T cells from the thymus concentrate in the paracortex.
- B cells develop in and around the germinal centers.
- Plasma cells occur in the medulla.

Lymphocytes can travel throughout the body using the **blood vessels**. The cells can also travel through a system of **lymphatic vessels** that closely parallels the body’s **veins** and **arteries**.
Immune cells and foreign particles enter the lymph nodes via incoming lymphatic vessels or the lymph nodes’ tiny blood vessels.

Cells and fluids are exchanged between blood and lymphatic vessels, enabling the lymphatic system to monitor the body for invading microbes. The lymphatic vessels carry lymph, a clear fluid that bathes the body’s tissues.

Small, bean-shaped lymph nodes are laced along the lymphatic vessels, with clusters in the neck, armpits, abdomen, and groin. Each lymph node contains specialized compartments where immune cells congregate, and where they can encounter antigens.

Immune cells, microbes, and foreign antigens enter the lymph nodes via incoming lymphatic vessels or the lymph nodes’ tiny blood vessels. All lymphocytes exit lymph nodes through outgoing lymphatic vessels. Once in the bloodstream, lymphocytes are transported to tissues throughout the body. They patrol
everywhere for foreign antigens, then gradually drift back into the lymphatic system to begin the cycle all over again.

The spleen is a flattened organ at the upper left of the abdomen. Like the lymph nodes, the spleen contains specialized compartments where immune cells gather and work. The spleen serves as a meeting ground where immune defenses confront antigens.

Other clumps of lymphoid tissue are found in many parts of the body, especially in the linings of the digestive tract, airways, and lungs—territories that serve as gateways to the body. These tissues include the tonsils, adenoids, and appendix.

**Immune Cells and Their Products**

The immune system stockpiles a huge arsenal of cells, not only lymphocytes but also cell-devouring phagocytes and their relatives. Some immune cells take on all intruders, whereas others are trained on highly specific targets. To work effectively, most immune cells need the cooperation of their comrades. Sometimes immune cells communicate by direct physical contact, and sometimes they communicate releasing chemical messengers.

The immune system stores just a few of each kind of the different cells needed to recognize millions of possible enemies. When an antigen first appears, the few immune cells that can
respond to it multiply into a full-scale army of cells. After their job is done, the immune cells fade away, leaving sentries behind to watch for future attacks.

All immune cells begin as immature stem cells in the bone marrow. They respond to different cytokines and other chemical signals to grow into specific immune cell types, such as T cells, B cells, or phagocytes. Because stem cells have not yet committed to a particular future, their use presents an interesting possibility for treating some immune system disorders. Researchers currently are investigating if a person’s own stem cells can be used to regenerate damaged immune responses in autoimmune diseases and in immune deficiency disorders, such as HIV infection.

**B Cells**

B cells and T cells are the main types of lymphocytes. B cells work chiefly by secreting substances called antibodies into the body’s fluids. Antibodies ambush foreign antigens circulating in the bloodstream. They are powerless, however, to penetrate cells. The job of attacking target cells—either cells that have been infected by viruses or cells that have been distorted by cancer—is left to T cells or other immune cells (described below).

Each B cell is programmed to make one specific antibody. For example, one B cell will make an antibody that blocks a virus that causes the common cold, while another produces an antibody that attacks a bacterium that causes
pneumonia. When a B cell encounters the kind of antigen that triggers it to become active, it gives rise to many large cells known as plasma cells, which produce antibodies.

- **Immunoglobulin G**, or IgG, is a kind of antibody that works efficiently to coat microbes, speeding their uptake by other cells in the immune system.
- IgM is very effective at killing bacteria.
- IgA concentrates in body fluids—tears, saliva, and the secretions of the respiratory and digestive tracts—guarding the entrances to the body.
- IgE, whose natural job probably is to protect against parasitic infections, is responsible for the symptoms of allergy.
- IgD remains attached to B cells and plays a key role in initiating early B cell responses.

**T Cells**

Unlike B cells, T cells do not recognize free-floating antigens. Rather, their surfaces contain specialized antibody-like receptors that see fragments of antigens on the surfaces of infected or cancerous cells. T cells contribute to immune defenses in two major ways: some direct and regulate immune responses, whereas others directly attack infected or cancerous cells.

**Helper T cells**, or **Th cells**, coordinate immune responses by communicating with other cells. Some stimulate nearby B cells to produce antibodies, others call in microbe-gobbling cells called phagocytes, and still others activate other T cells.

**Cytotoxic T lymphocytes (CTLs)**—also called killer T cells—perform a different function. These cells directly attack other cells carrying certain foreign or abnormal molecules on their surfaces. CTLs are especially useful for attacking viruses because viruses often hide from other parts of the immune system while they grow inside infected cells. CTLs recognize small fragments of these viruses peeking out from the cell membrane and launch an attack to kill the infected cell.

In most cases, T cells only recognize an antigen if it is carried on the surface of a cell by one of the body’s own **major histocompatibility complex**, or **MHC**,
molecules. MHC molecules are proteins recognized by T cells when they distinguish between self and nonself. A self-MHC molecule provides a recognizable scaffolding to present a foreign antigen to the T cell. In humans, MHC antigens are called **human leukocyte antigens**, or HLA.

Although MHC molecules are required for T cell responses against foreign invaders, they also create problems during organ transplantations. Virtually every cell in the body is covered with MHC proteins, but each person has a different set of these proteins on his or her cells. If a T cell recognizes a nonself-MHC molecule on another cell, it will destroy the cell. Therefore, doctors must match organ recipients with donors who have the closest MHC makeup. Otherwise the recipient’s T cells will likely attack the transplanted organ, leading to **graft rejection**.

Some T cells are helper cells; others are killer cells.
Killer cell makes contact with target cell, trains its weapons on the target, then strikes.

**Natural killer (NK) cells** are another kind of lethal white cell, or lymphocyte. Like CTLs, NK cells are armed with **granules** filled with potent chemicals. But CTLs look for antigen fragments bound to self-MHC molecules, whereas NK cells recognize cells lacking self-MHC molecules. Thus, NK cells have the potential to attack many types of foreign cells.

Both kinds of killer cells slay on contact. The deadly assassins bind to their targets, aim their weapons, and then deliver a lethal burst of chemicals.

T cells aid the normal processes of the immune system. If NK T cells fail to function properly, asthma, certain autoimmune diseases—including type 1 diabetes—or the
growth of cancers may result. NK T cells get their name because they are a kind of T lymphocyte that carries some of the surface proteins, called “markers,” typical of NK T cells. But these T cells differ from other kinds of T cells. They do not recognize pieces of antigen bound to self-MHC molecules. Instead, they recognize fatty substances (lipids and glycolipids) that are bound to a different class of molecules called CD1d. Scientists are trying to discover methods to control the timing and release of chemical factors by NK T cells, with the hope they can modify immune responses in ways that benefit patients.

Phagocytes and Their Relatives
Phagocytes are large white cells that can swallow and digest microbes and other foreign particles. Monocytes are phagocytes that circulate in the blood. When monocytes migrate into tissues, they develop into macrophages. Specialized types of macrophages can be found in many organs, including the lungs, kidneys, brain, and liver.

Macrophages play many roles. As scavengers, they rid the body of worn-out cells and other debris. They display bits of foreign antigen in a way that draws the attention of matching lymphocytes and, in that respect, resemble dendritic cells (see page 15). And they churn out an amazing variety of powerful chemical signals, known as monokines, which are vital to the immune response.

Granulocytes are another kind of immune cell. They contain granules filled with potent chemicals, which allow the granulocytes to
Phagocytes, granulocytes, and mast cells, all with different methods of attack, demonstrate the immune system's versatility.

Phagocytes destroy microorganisms. Some of these chemicals, such as histamine, also contribute to inflammation and allergy.

One type of granulocyte, the neutrophil, is also a phagocyte. Neutrophils use their prepackaged chemicals to break down the microbes they ingest. Eosinophils and basophils are granulocytes that “degranulate” by spraying their chemicals onto harmful cells or microbes nearby.

Mast cells function much like basophils, except they are not blood cells. Rather, they are found in the lungs, skin, tongue, and linings of the nose and intestinal tract, where they contribute to the symptoms of allergy.
Related structures, called blood **platelets**, are cell fragments. Platelets also contain granules. In addition to promoting blood clotting and wound repair, platelets activate some immune defenses.

Dendritic cells are found in the parts of lymphoid organs where T cells also exist. Like macrophages, dendritic cells in lymphoid tissues display antigens to T cells and help stimulate T cells during an immune response. They are called dendritic cells because they have branchlike extensions that can interlace to form a network.

**T Cell Receptors**

T cell receptors are complex protein molecules that peek through the surface membranes of T cells. The exterior part of a T cell receptor recognizes short pieces of foreign antigens that are bound to self-MHC molecules on other cells of the body. It is because of their T cell receptors that T cells can recognize disease-causing microorganisms and rally other immune cells to attack the invaders, or kill the invaders themselves.

Toll-like receptors (TLRs), which occur on cells throughout the immune system, are a family of proteins the body uses as a first line of defense against invading microbes. Like T cell receptors, some TLRs peek through the surface membranes of immune cells, allowing them to respond to microbes in the cells’ environment.

Some TLRs are activated by molecules that make up viruses, whereas other TLRs respond to molecules that make up the cell walls of
bacteria. Once activated, TLRs relay the alarm to other actors in the immune system. For example, some TLRs play important roles in the all-purpose “first-responder” arm of the immune system, also called the innate immune system. In short order, the innate immune system responds with a surge of chemical signals that together cause inflammation, fever, and other responses to infection or injury. Other TLRs help initiate responses from genetically identical groups of lymphocytes, called clones, that are already programmed to recognize specific antigens. Such responses are called adaptive immunity.

Overall, the cellular receptors important for the first-line responses of innate immunity are encoded by genes people inherit from their parents. In contrast, adaptive immune responses rely on antigen receptors that are pieced together in the genomes of lymphocytes during their development in various tissues of the body. In addition to TLRs, other kinds of innate immune receptors can stimulate phagocytosis by macrophages, trigger the inflammatory responses that help control local infections, and play a range of crucial roles in defending the body against invading microbes.

Cytokines
Cells of the immune system communicate with one another by releasing and responding to chemical messengers called cytokines. These proteins are secreted by immune cells and act on other cells to coordinate appropriate immune responses. Cytokines include a diverse assortment of interleukins, interferons, and growth factors.
Cytokines include lymphokines, produced by lymphocytes, and monokines, made by monocytes and macrophages.

Some cytokines are chemical switches that turn certain immune cell types on and off. One cytokine, interleukin 2 (IL-2), triggers the immune system to produce T cells. IL-2’s immunity-boosting properties have traditionally made it a promising treatment for several illnesses. Clinical studies are underway to test its benefits in diseases such as cancer, hepatitis C, and HIV infection and AIDS. Scientists are studying other cytokines to see whether they can also be used to treat diseases.

One group of cytokines chemically attracts specific cell types. These so-called chemokines are released by cells at a site of injury or infection and call other immune cells to the region to help repair the damage or fight off the invader. Chemokines often play a key role in inflammation and are a promising target for new drugs to help regulate immune responses.
The complement system is made up of about 25 proteins that work together to assist, or “complement,” the action of antibodies in destroying bacteria. Complement also helps to rid the body of antibody-coated antigens (antigen-antibody complexes). Complement

![Diagram of complement system]

The interlocking steps of the complement cascade end in cell death.
proteins, which cause blood vessels to become dilated and then leaky, contribute to the redness, warmth, swelling, pain, and loss of function that characterize an inflammatory response.

Complement proteins circulate in the blood in an inactive form. When the first protein in the complement series is activated—typically by antibody that has locked onto an antigen—it sets in motion a domino effect. Each component takes its turn in a precise chain of steps known as the complement cascade. The end products are molecular cylinders that are inserted into—and that puncture holes in—the cell walls that surround the invading bacteria. With fluids and molecules flowing in and out, the bacterial cells swell, burst, and die. Other components of the complement system make bacteria more susceptible to phagocytosis or beckon other immune cells to the area.

Mounting an Immune Response

Infections are the most common cause of human disease. They range from the common cold to debilitating conditions like chronic hepatitis to life-threatening diseases such as AIDS. Disease-causing microbes (pathogens) attempting to get into the body must first move past the body’s external armor, usually the skin or cells lining the body’s internal passageways.

The skin provides an imposing barrier to invading microbes. It is generally penetrable only through cuts or tiny abrasions. The digestive and respiratory tracts—both portals of entry for a number of microbes—also have
When challenged by a virus or other microbe, the immune system has many weapons to choose. Their own levels of protection. Microbes entering the nose often cause the nasal surfaces to secrete more protective mucus, and attempts to enter the nose or lungs can trigger a sneeze or cough reflex to force microbial invaders out of the respiratory passageways. The stomach contains a strong acid that destroys many pathogens that are swallowed with food.

If microbes survive the body’s front-line defenses, they still have to find a way through the walls of the digestive, respiratory, or urogenital passageways to the underlying cells. These passageways are lined with tightly packed epithelial cells covered in a layer of mucus, effectively blocking the transport of many pathogens into deeper cell layers.
Mucosal surfaces also secrete a special class of antibody called IgA, which in many cases is the first type of antibody to encounter an invading microbe. Underneath the epithelial layer a variety of immune cells, including macrophages, B cells, and T cells, lie in wait for any microbe that might bypass the barriers at the surface.

Next, invaders must escape a series of general defenses of the innate immune system, which are ready to attack without regard for specific antigen markers. These include patrolling phagocytes, NK T cells, and complement.

Microbes cross the general barriers then confront specific weapons of the adaptive immune system tailored just for them. These specific weapons, which include both antibodies and T cells, are equipped with singular receptor structures that allow them to recognize and interact with their designated targets.

**Bacteria, Viruses, and Parasites**

The most common disease-causing microbes are bacteria, viruses, and parasites. Each uses a different tactic to infect a person, and, therefore, each is thwarted by different components of the immune system.

Most bacteria live in the spaces between cells and are readily attacked by antibodies. When antibodies attach to a bacterium, they send signals to complement proteins and phagocytic cells to destroy the bound microbes. Some bacteria are eaten directly by phagocytes, which signal to certain T cells to join the attack.
The combination of antigen fragment and MHC molecule attracts the help of a mature, matching T cell.

Antibodies are triggered when a B cell encounters its matching antigen.

The B cell takes in the antigen and digests it,

then it displays antigen fragments bound to its own distinctive MHC molecules.

The combination of antigen fragment and MHC molecule attracts the help of a mature, matching T cell.

Lymphokines secreted by the T cell allow the B cell to multiply and mature into antibody-producing plasma cells.

Released into the bloodstream, antibodies lock onto matching antigens. These antigen-antibody complexes are soon eliminated, either by the complement cascade or by the liver and the spleen.

B cells are triggered to mature into plasma cells that produce a specific kind of antibody when the B cell encounters a specific antigen.
T cells are mobilized when they encounter a cell such as a macrophage or a B cell that has digested an antigen and is displaying antigen fragments bound to its MHC molecules. Lymphokines help the T cell to mature. The T cell, alerted and activated, secretes lymphokines.

Some lymphokines attract immune cells—fresh macrophages, granulocytes, and other lymphocytes—to the site of infection. Yet other lymphokines direct the recruits once they arrive on the scene. Some T cells become killer cells and track down body cells infected by viruses. Some lymphokines spur the growth of more T cells.

T cells become active through a series of steps and then activate other immune cells by secreting lymphokines.
All viruses, plus a few types of bacteria and parasites, must enter cells of the body to survive, requiring a different kind of immune defense. Infected cells use their MHC molecules to put pieces of the invading microbes on their surfaces, flagging down CTLs to destroy the infected cells. Antibodies also can assist in the immune response by attaching to and clearing viruses before they have a chance to enter cells.

Parasites live either inside or outside cells. Intracellular parasites such as the organism that causes malaria can trigger T cell responses. Extracellular parasites are often much larger than bacteria or viruses and require a much broader immune attack. Parasitic infections often trigger an inflammatory response in which eosinophils, basophils, and other specialized granule-containing cells rush to the scene and release their stores of toxic chemicals in an attempt to destroy the invaders. Antibodies also play a role in this attack, attracting the granule-filled cells to the site of infection.
Immunity: Natural and Acquired

Long ago, physicians realized that people who had recovered from the plague would never get it again—they had acquired immunity. This is because some of the activated T and B cells had become **memory cells**. Memory cells ensure that the next time a person meets up with the same antigen, the immune system is already set to demolish it.

Immunity can be strong or weak, short-lived or long-lasting, depending on the type of antigen it encounters, the amount of antigen, and the route by which the antigen enters the body. Immunity can also be influenced by inherited genes. When faced with the same antigen, some individuals will respond forcefully, others feebly, and some not at all.
An immune response can be sparked not only by infection but also by immunization with vaccines. Some vaccines contain microorganisms—or parts of microorganisms—that have been treated so they can provoke an immune response but not full-blown disease. (See “Vaccines” on page 27.)

Immunity can also be transferred from one individual to another by injections of serum rich in antibodies against a particular microbe (antiserum). For example, antiserum is sometimes given to protect travelers to countries where hepatitis A is widespread. The antiserum induces passive immunity against the hepatitis A virus. Passive immunity typically lasts only a few weeks or months.

Infants are born with weak immune responses but are protected for the first few months of life by antibodies they receive from their mothers before birth. Babies who are nursed can also receive some antibodies from breast milk that help to protect their digestive tracts.

**Immune Tolerance**

Immune tolerance is the tendency of T or B lymphocytes to ignore the body’s own tissues. Maintaining tolerance is important because it prevents the immune system from attacking its fellow cells. Scientists are hard at work trying to understand how the immune system knows when to respond and when to ignore an antigen.
Tolerance occurs in at least two ways—central tolerance and peripheral tolerance. Central tolerance occurs during lymphocyte development. Very early in each immune cell’s life, it is exposed to many of the self molecules in the body. If it encounters these molecules before it has fully matured, the encounter activates an internal self-destruct pathway, and the immune cell dies. This process, called **clonal deletion**, helps ensure that “self-reactive” T cells and B cells, those that could develop the ability to destroy the body’s own cells, do not mature and attack healthy tissues.

Because maturing lymphocytes do not encounter every molecule in the body, they must also learn to ignore mature cells and tissues. In peripheral tolerance, circulating lymphocytes might recognize a self molecule but cannot respond because some of the chemical signals required to activate the T or B cell are absent. So-called **clonal anergy**, therefore, keeps potentially harmful lymphocytes switched off. Peripheral tolerance may also be imposed by a special class of regulatory T cells that inhibits helper or cytotoxic T-cell activation by self antigens.

**Vaccines**

For many years, healthcare providers have used vaccination to help the body’s immune system prepare for future attacks. Vaccines consist of killed or modified microbes, components of microbes, or microbial **DNA** that trick the body into thinking an infection has occurred.
A vaccinated person’s immune system attacks the harmless vaccine and prepares for invasions against the kind of microbe the vaccine contained. In this way, the person becomes immunized against the microbe. Vaccination remains one of the best ways to prevent infectious diseases, and vaccines have an excellent safety record. Previously devastating diseases such as smallpox, polio, and whooping cough have been greatly controlled or eliminated through worldwide vaccination programs.

Disorders of the Immune System

Allergic Diseases
The most common types of allergic diseases occur when the immune system responds to a false alarm. In an allergic person, a normally harmless material such as grass pollen, food particles, mold, or house dust mites is mistaken for a threat and attacked.

Allergies such as pollen allergy are related to the antibody known as IgE. Like other antibodies, each IgE antibody is specific; one acts against oak pollen and another against ragweed, for example.

Autoimmune Diseases
Sometimes the immune system’s recognition apparatus breaks down, and the body begins to manufacture T cells and antibodies directed against self antigens in its own cells and tissues. As a result, healthy cells and tissues
The first time the allergy-prone person runs across an allergen such as ragweed, he or she makes large amounts of ragweed IgE antibody.

These IgE molecules attach themselves to mast cells.

The second time that person has a brush with ragweed, the IgE-primed mast cell will release its powerful chemicals,

and the person will suffer the wheezing and/or sneezing, runny nose, watery eyes, and itching of allergy.

An allergic reaction occurs after plasma cells produce IgE antibody against a specific antigen and mast cells become activated.
Misguided T cells can attack insulin-producing cells of the pancreas, contributing to an autoimmune form of diabetes.

are destroyed, which leaves the person’s body unable to perform important functions.

Misguided T cells and autoantibodies, as they are known, contribute to many autoimmune diseases. For instance, T cells that attack certain kinds of cells in the pancreas contribute to a form of diabetes, whereas an autoantibody known as rheumatoid factor is common in people with rheumatoid arthritis. People with systemic lupus erythematosus (SLE) have antibodies to many types of their own cells and cell components. SLE patients can develop a severe rash, serious kidney inflammation, and disorders of other important tissues and organs.

No one knows exactly what causes an autoimmune disease, but multiple factors are likely to be involved. These include elements in the environment, such as viruses, certain drugs, and sunlight, all of which may damage
or alter normal body cells. Hormones are suspected of playing a role because most autoimmune diseases are far more common in women than in men. Heredity, too, seems to be important. Many people with autoimmune diseases have characteristic types of self-marker molecules.

**Immune Complex Diseases**

Immune complexes are clusters of interlocking antigens and antibodies. Normally, immune complexes are rapidly removed from the bloodstream. Sometimes, however, they continue to circulate and eventually become trapped in the tissues of the kidneys, lungs, skin, joints, or blood vessels. There, they set off reactions with complement that lead to

Antigen-antibody complexes can become trapped in, and damage, the kidneys and other organs.
inflammation and tissue damage. Immune complexes work their mischief in many diseases. These include malaria and viral hepatitis, as well as many autoimmune diseases.

**Immune Deficiency Disorders**

When the immune system is missing one or more of its parts, the result is an immune deficiency disorder. These disorders can be inherited, acquired through infection, or produced as a side effect by drugs such as those used to treat people with cancer or those who have received transplants.

Temporary immune deficiencies can develop in the wake of common virus infections, including influenza, infectious mononucleosis, and measles. Immune responses can also be depressed by blood transfusions, surgery, malnutrition, smoking, and stress.

Some children are born with poorly functioning immune systems. Some have flaws in the B cell system and cannot produce antibodies. Others, whose thymus is either missing or small and abnormal, lack T cells. Very rarely, infants are born lacking all of the major immune defenses. This condition is known as severe combined immune deficiency disease or SCID. (See “Gene Therapy” on page 39.)
AIDS is an immune deficiency disorder caused by a virus (HIV) that infects immune cells. HIV can destroy or disable vital T cells, paving the way for a variety of immunologic shortcomings. The virus also can hide out for long periods in immune cells. As the immune defenses falter, a person develops AIDS and falls prey to unusual, often life-threatening infections and rare cancers.
Each year thousands of lives in the United States are prolonged by transplanted organs including the kidneys, heart, lung, liver, and pancreas. For a transplant to “take,” however, the body’s natural tendency to rid itself of foreign tissue must be overridden.

One way to avoid the rejection of transplanted tissue is tissue typing, which ensures that markers of self on the donor’s tissue are as similar as possible to those of the recipient. Every cell in the body has a double set of six major tissue antigens, and each of the antigens exists, in different individuals, in as many as 20 varieties. The chance of two people having identical transplant antigens is about one in 100,000.

A second way to avoid transplant rejection is to lull the recipient’s immune system into a less active state. This can be done with powerful immunosuppressive drugs such as cyclosporine A, or by using laboratory-manufactured antibodies that attack mature T cells.

Bone Marrow Transplants
When the immune response is severely depressed—in infants born with immune disorders or in people with cancer, for example—one possible remedy is a transfer of healthy bone marrow. Once introduced into the circulation, transplanted bone marrow cells can develop into functioning B and T cells.
In bone marrow transplants, a close match is extremely important. Not only is there a danger that the body will reject the transplanted bone marrow cells, but mature T cells from the bone marrow transplant may counterattack and destroy the recipient’s tissues. To prevent this situation, known as **graft-versus-host disease**, scientists use drugs or antibodies to “cleanse” the donor marrow of potentially dangerous mature T cells.

**The Immune System and the Nervous System**

Evidence is mounting that the immune system and the nervous system are linked in several ways. One well-known connection involves the **adrenal glands**. In response to stress messages from the brain, the adrenal glands release hormones into the blood. In addition to helping a person respond to emergencies by mobilizing the body’s energy reserves, these “stress hormones” can stifle the protective effects of antibodies and lymphocytes.

Another link between the immune system and the nervous system is that the hormones and other chemicals that convey messages among nerve cells also “speak” to cells of the immune system. Indeed, some immune cells are able to manufacture typical nerve cell products, and some **lymphokines** can transmit information to the nervous system. Moreover, the brain may send messages directly down nerve cells to the immune system. Networks of nerve fibers have been found connecting to the lymphoid organs.
Scientists are now able to mass-produce immune cell secretions, both antibodies and lymphokines, as well as specialized immune cells. The ready supply of these materials not only has revolutionized the study of the immune system itself but also has had an enormous impact on medicine, agriculture, and industry.

**Monoclonal antibodies** are identical antibodies made by the many clones of a single B cell.

Monoclonal antibody technology makes it possible to mass produce specific antibodies to order.
Because of their unique specificity for different antigens, monoclonal antibodies are promising treatments for a range of diseases. Researchers make monoclonal antibodies by injecting a mouse with a target antigen and then fusing B cells from the mouse with other long-lived cells. The resulting hybrid cell becomes a type of antibody factory, turning out identical copies of antibody molecules specific for the target antigen.

Mouse antibodies are “foreign” to people, however, and might trigger an immune response when injected into a human. Therefore, researchers have developed “humanized” monoclonal antibodies. To construct these molecules, scientists take the antigen-binding portion of a mouse antibody and attach it to a human antibody scaffolding, greatly reducing the foreign portion of the molecule.

Because they recognize very specific molecules, monoclonal antibodies are used in diagnostic tests to identify invading pathogens or changes in the body’s proteins. In medicine, monoclonal antibodies can attach to cancer cells, blocking the chemical growth signals that cause the cells to divide out of control. In other cases, monoclonal antibodies can carry potent toxins into certain cells, killing the dangerous cells while leaving their neighbors untouched.

**Genetic Engineering**

Genetic engineering allows scientists to pluck genes—segments of DNA—from one type of organism and combine them with genes of a second organism. In this way, relatively simple
Genetic engineering transforms simple organisms into factories for making human proteins.
organisms such as bacteria or yeast (a type of fungus) can be induced to make quantities of human proteins, including hormones such as insulin as well as lymphokines and monokines. They can also manufacture proteins from infectious agents, such as the hepatitis virus or HIV, for use in vaccines.

**Gene Therapy**

Genetic engineering also holds promise for gene therapy—replacing altered or missing genes or adding helpful genes. One disease in which gene therapy has been successful is SCID, or severe combined immune deficiency disease.

SCID is a rare genetic disease that disables a person’s immune system and leaves the person unable to fight off infections. It is caused by mutations in one of several genes that code for important components of the immune system. Until recently, the most effective treatment for SCID was transplantation of blood-forming stem cells from the bone marrow of a healthy person who is closely related to the patient. However, doctors have also been able to treat SCID by giving the patient a genetically engineered version of the missing gene.

Using gene therapy to treat SCID is generally accomplished by taking blood-forming cells from a person’s own bone marrow, introducing into the cells a genetically changed virus that carries the corrective gene, and growing the modified cells outside the person’s body. After the genetically changed bone marrow cells
begin to produce the **enzyme** or other protein that was missing, the modified blood-forming marrow cells can be injected back into the person. Once back inside the body, the genetically modified cells can produce the missing immune system component and begin to restore the person’s ability to fight off infections.

Cancer is another target for gene therapy. In pioneering experiments, scientists are removing cancer-fighting lymphocytes from the cancer patient’s tumor, inserting a gene that boosts the lymphocytes’ ability to make quantities of a natural anticancer product, then growing the restructured cells in quantity in the laboratory. These cells are injected back into the person, where they can seek out the tumor and deliver large doses of the anticancer chemical.

**Immunoregulation**
Research into the delicate checks and balances that control the immune response is increasing knowledge of normal and abnormal immune system functions. Someday it may be possible to treat autoimmune diseases such as systemic lupus erythematosus by suppressing parts of the immune system that are overactive.
The SCID-hu mouse provides a means of studying the human immune system in action.

Scientists are also devising ways to better understand the human immune system and diseases that affect it. For example, by transplanting immature human immune tissues or immune cells into SCID mice, scientists have created “humanized” mice, a living model of the human immune system. Scientists are manipulating the immune system of humanized SCID mice to discover ways to benefit human health. Humanized mice are also being used in research on transplantation and autoimmune and allergic diseases, and to manufacture molecules that help regulate immune system function and immune tolerance.
Although scientists have learned much about the immune system, they continue to study how the body launches attacks that destroy invading microbes, infected cells, and tumors while ignoring healthy tissues. New technologies for identifying individual immune cells are now allowing scientists to determine quickly which targets are triggering an immune response. Improvements in microscopy are permitting the first-ever observations of living B cells, T cells, and other cells as they interact within lymph nodes and other body tissues.

In addition, scientists are rapidly unraveling the genetic blueprints that direct the human immune response, as well as those that dictate the biology of bacteria, viruses, and parasites. The combination of new technology and expanded genetic information will no doubt reveal even more about how the body protects itself from disease.
Glossary

**adenoids**—see tonsils.

**adrenal gland**—a gland located on each kidney that secretes hormones regulating metabolism, sexual function, water balance, and stress.

**allergen**—any substance that causes an allergy.

**antibody**—a molecule (also called an immunoglobulin) produced by a mature B cell (plasma cell) in response to an antigen. When an antibody attaches to an antigen, it helps the body destroy or inactivate the antigen.

**antigen**—a substance or molecule that is recognized by the immune system. The antigen can be from foreign material such as bacteria or viruses.

**antiserum**—a serum rich in antibodies against a particular microbe.

**appendix**—lymphoid organ in the intestine.

**artery**—a blood vessel that carries blood from the heart to other parts of the body.

**autoantibody**—an antibody that reacts against a person’s own tissue.

**autoimmune disease**—disease that results when the immune system mistakenly attacks the body’s own tissues. Examples include multiple sclerosis, type 1 diabetes, rheumatoid arthritis, and systemic lupus erythematosus.
**B cell** or **B lymphocyte**—a small white blood cell crucial to the immune defenses. B cells come from bone marrow and develop into blood cells called plasma cells, which are the source of antibodies.

**bacteria**—microscopic organisms composed of a single cell. Some cause disease.

**basophil**—a white blood cell that contributes to inflammatory reactions. Along with mast cells, basophils are responsible for the symptoms of allergy.

**blood vessel**—an artery, vein, or capillary that carries blood to and from the heart and body tissues.

**cell**—the smallest unit of life; the basic living unit that makes up tissues.

**chemokine**—a small protein molecule that activates immune cells, stimulates their migration, and helps direct immune cell traffic throughout the body.

**clonal anergy**—the process of switching off the ability of potentially harmful T or B cells to participate in immune responses. Clonal anergy is essential for generating the tolerance of T and B cells to the body’s “self” tissue antigens.
**clonal deletion**—the genetically controlled process of eliminating immune cells that could destroy the body’s own cells and tissues. The elimination process removes immature T and B lymphocytes that have receptors for cells with “self” MHC or HLA antigens, and could therefore attack and destroy the body’s own cells.

**clone**—a group of genetically identical cells or organisms descended from a single common ancestor; or, to reproduce identical copies.

**complement**—a complex series of blood proteins whose action “complements” the work of antibodies. Complement destroys bacteria, produces inflammation, and regulates immune reactions.

**complement cascade**—a precise sequence of events, usually triggered by antigen-antibody complexes, in which each component of the complement system is activated in turn.

**cytokines**—powerful chemical substances secreted by cells that enable the body’s cells to communicate with one another. Cytokines include lymphokines produced by lymphocytes and monokines produced by monocytes and macrophages.

**cytotoxic T lymphocyte (CTL)**—a subtype of T cells that carries the CD8 marker and can destroy body cells infected by viruses or transformed by cancer.
**dendritic cell**—an immune cell with highly branched extensions that occurs in lymphoid tissues, engulfs microbes, and stimulates T cells by displaying the foreign antigens of the microbes on their surfaces.

**DNA (deoxyribonucleic acid)**—a long molecule found in the cell nucleus. Molecules of DNA carry the cell’s genetic information.

**enzyme**—a protein produced by living cells that promotes the chemical processes of life without itself being altered.

**eosinophil**—a white blood cell containing granules filled with chemicals damaging to parasites and enzymes that affect inflammatory reactions.

**epithelial cells**—cells that make up the epithelium, the covering for internal and external body surfaces.

**fungus**—a member of a class of relatively primitive vegetable organisms. Fungi include mushrooms, yeasts, rusts, molds, and smuts.

**gene**—a unit of genetic material (DNA) inherited from a parent that controls specific characteristics. Genes carry coded directions a cell uses to make specific proteins that perform specific functions.

**genome**—a full set of genes in a person or any other living thing.
**graft rejection**—an immune response against transplanted tissue.

**graft-versus-host disease**—a life-threatening reaction in which transplanted cells attack the tissues of the recipient.

**granule**—a membrane-bound organelle (specialized part) within cells where proteins are stored before secretion.

**granulocyte**—a phagocytic white blood cell filled with granules. Neutrophils, eosinophils, basophils, and mast cells are examples of granulocytes.

**growth factors**—chemicals secreted by cells that stimulate proliferation of or changes in the physical properties of other cells.

**helper T cells (Th cells)**—a subset of T cells that carry the CD4 surface marker and are essential for turning on antibody production, activating cytotoxic T cells, and initiating many other immune functions.

**hepatitis**—the name of several viruses that cause liver diseases. These viruses include hepatitis A, hepatitis B, and hepatitis C.

**histocompatibility testing**—a test conducted before transplant operations to find a donor whose MHC molecules are similar to the recipient’s; helps reduce the strength of transplant rejection.
HIV (human immunodeficiency virus) — the virus that causes AIDS.

human leukocyte antigen (HLA) — a protein on the surfaces of human cells that identifies the cells as “self” and, like MHC antigens, performs essential roles in immune responses. HLAs are used in laboratory tests to determine whether one person’s tissues are compatible with another person’s, and could be used in a transplant. HLAs are the human equivalent of MHC antigens; they are coded for by MHC genes.

immune response — reaction of the immune system to foreign substances. Although normal immune responses are designed to protect the body from pathogens, immune dysregulation can damage normal cells and tissues, as in the case of autoimmune diseases.

immunoglobulin — one of a family of large protein molecules, also known as antibodies, produced by mature B cells (plasma cells).

immunosuppressive — capable of reducing immune responses.

inflammation — an immune system reaction to “foreign” invaders such as microbes or allergens. Signs include redness, swelling, pain, or heat.

inflammatory response — redness, warmth, and swelling produced in response to infection; the result of increased blood flow and an influx of immune cells and their secretions.
**innate**—an immune system function that is inborn and provides an all-purpose defense against invasion by microbes.

**interferon**—a protein produced by cells that stimulates antivirus immune responses or alters the physical properties of immune cells.

**interleukins**—a major group of lymphokines and monokines.

**lymph**—a transparent, slightly yellow fluid that carries lymphocytes, bathes the body tissues, and drains into the lymphatic vessels.

**lymph node**—a small bean-shaped organ of the immune system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are garrisons of B and T cells, dendritic cells, macrophages, and other kinds of immune cells.

**lymphatic vessels**—a bodywide network of channels, similar to the blood vessels, which transports lymph to the immune organs and into the bloodstream.

**lymphocyte**—a small white blood cell produced in the lymphoid organs and essential to immune defenses. B cells, T cells, and NK T cells are lymphocytes.
**lymphoid organ**—an organ of the immune system where lymphocytes develop and congregate. These organs include the bone marrow, thymus, lymph nodes, spleen, and various other clusters of lymphoid tissue. Blood vessels and lymphatic vessels are also lymphoid organs.

**lymphokines**—powerful chemical substances secreted by lymphocytes. These molecules help direct and regulate the immune responses.

**macrophage**—a large and versatile immune cell that devours invading pathogens and other intruders. Macrophages stimulate other immune cells by presenting them with small pieces of the invaders.

**major histocompatibility complex (MHC)**—a group of genes that controls several aspects of the immune response. MHC genes code for “self” markers on all body cells.

**mast cell**—a granulocyte found in tissue. The contents of mast cells, along with those of basophils, are responsible for the symptoms of allergy.

**memory cells**—a subset of T cells and B cells that have been exposed to antigens and can then respond more readily when the immune system encounters those same antigens again.
microbe or microorganism—a microscopic living organism. Examples include bacteria, protozoa, and some fungi and parasites. Viruses are also called microbes.

molecule—the smallest amount of a specific chemical substance. Large molecules such as proteins, fats, carbohydrates, and nucleic acids are the building blocks of a cell, and a gene determines how each molecule is produced.

monoclonal antibody—an antibody produced by a single B cell or its identical progeny that is specific for a given antigen. Monoclonal antibodies are used as research tools for binding to specific protein molecules, and are invaluable in research, medicine, and industry.

monocyte—a large phagocytic white blood cell which, when entering tissue, develops into a macrophage.

monokines—powerful chemical substances secreted by monocytes and macrophages. These molecules help direct and regulate the immune responses.

natural killer (NK) cell—a large granule-containing lymphocyte that recognizes and kills cells lacking self antigens. These cells’ target recognition molecules are different from T cells.

NK T cell—a T cell that has some characteristics of NK cells. It produces large amounts of cytokines when stimulated, and is activated by fatty substances (lipids) bound to non-MHC molecules called CD1d.
neutrophil—a white blood cell that is an abundant and important phagocyte.

organ—a part of the body that has a specific function, such as the lungs.

organism—an individual living thing composed of one or more cells.

parasite—a plant or animal that lives, grows, and feeds on or within another living organism.

passive immunity—immunity resulting from the transfer of antibodies or antiserum produced by another person.

pathogen—a disease-causing organism or virus.

phagocyte—a large white blood cell that contributes to immune defenses by ingesting microbes or other cells and foreign particles.

phagocytosis—process by which one cell engulfs another cell or large particle.

plasma cell—a large antibody-producing cell that develops from B cells.

platelet—a cellular fragment critical for blood clotting and sealing off wounds.

serum—the clear liquid that separates from the blood when it is allowed to clot. This fluid contains the antibodies that were present in the whole blood.
spleen—a lymphoid organ in the abdominal cavity that is an important center for immune system activities.

stem cell—an immature cell from which other cells derive. Bone marrow is rich in the kind of stem cells that become specialized blood cells.

T cell or T lymphocyte—a small white blood cell that recognizes antigen fragments bound to cell surfaces by specialized antibody-like receptors. “T” stands for the thymus gland, where T cells develop and acquire their receptors.

T cell receptor—complex protein molecule on the surfaces of T cells that recognizes bits of foreign antigen bound to self-MHC molecules.

Toll-like receptor (TLR)—a family of proteins important for first-line immune defenses against microbes.

tissue typing—see histocompatibility testing.

tissue—a group of similar cells joined to perform the same function.

tolerance—a state of immune nonresponsiveness to a particular antigen or group of antigens.

tonsils and adenoids—prominent oval masses of lymphoid tissues on either side of the throat.

toxin—an agent produced in plants and bacteria, normally very damaging to cells.
vaccine—a preparation that stimulates an immune response that can prevent an infection or create resistance to an infection. Vaccines do not cause disease.

vein—a blood vessel that carries blood to the heart from the body tissues.

virus—a particle composed of a piece of genetic material—RNA or DNA—surrounded by a protein coat. Viruses can reproduce only in living cells.