



SCIENCE
EDUCATION

Understanding the Immune System How It Works



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
National Cancer Institute

Understanding the Immune System How It Works

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

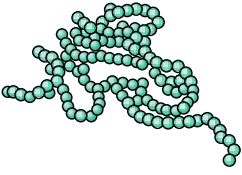
National Institute of Allergy and Infectious Diseases
National Cancer Institute

NIH Publication No. 03-5423
September 2003
www.niaid.nih.gov
www.nci.nih.gov

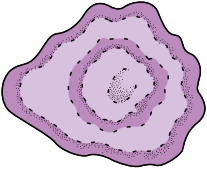
Contents

- 1** Introduction
- 2** Self and Nonself
- 3** The Structure of the Immune System
- 7** Immune Cells and Their Products
- 19** Mounting an Immune Response
- 24** Immunity: Natural and Acquired
- 28** Disorders of the Immune System
- 34** Immunology and Transplants
- 36** Immunity and Cancer
- 39** The Immune System and the Nervous System
- 40** Frontiers in Immunology
- 45** Summary
- 47** Glossary

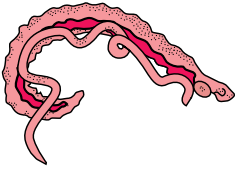
Introduction



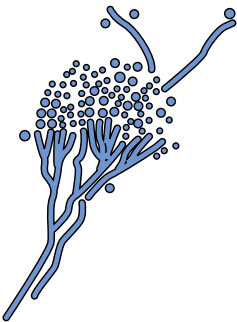
Bacteria:
streptococci



Virus:
herpes virus



Parasite:
schistosome



Fungus:
penicillium mold

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* (germs)—tiny, infection-causing *organisms* such as *bacteria*, *viruses*, *parasites*, and *fungi*. Because the human body provides an ideal environment for many microbes, they try to break in. 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 or is crippled, however, it can unleash a torrent of diseases, including *allergy*, *arthritis*, or *AIDS*.

The immune system is amazingly complex. It can recognize and remember millions of different enemies, and it can produce secretions and cells to match up with and wipe out each one of them.

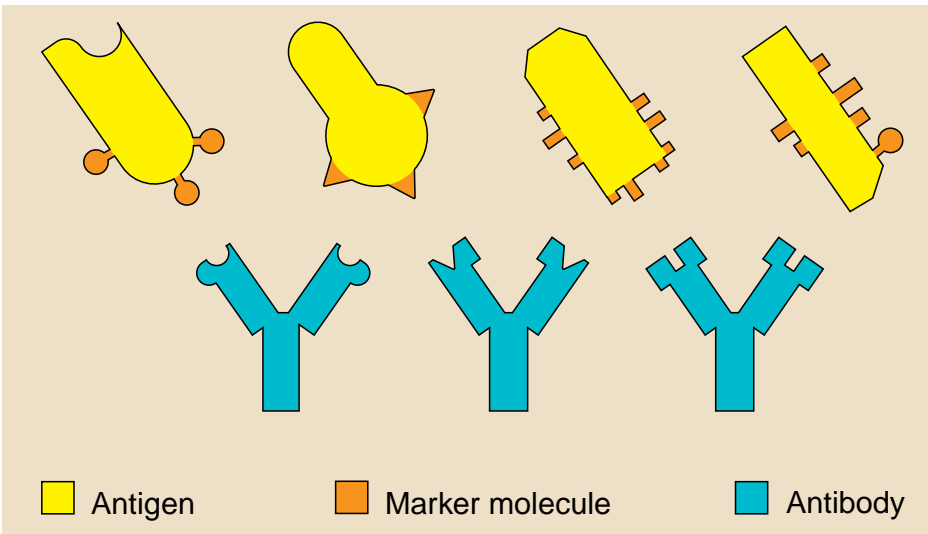
The secret to its success is an elaborate and dynamic communications network. Millions and millions of cells, organized into sets and subsets, gather like clouds of bees swarming around a hive and pass information back and forth. Once immune

*Definitions of words printed in italics are listed in the Glossary on page 47.

cells receive the alarm, they undergo tactical changes and begin to produce powerful chemicals. These substances allow the cells to regulate their own growth and behavior, enlist their fellows, and direct new recruits to trouble spots.

Self and Nonself

The key to a healthy immune system is its remarkable ability to distinguish between the body's own cells—self—and foreign cells—nonself. The body's immune defenses normally coexist peacefully with cells that carry distinctive “self” marker molecules. But when immune defenders encounter cells or organisms carrying



Antigens carry marker molecules that identify them as foreign.

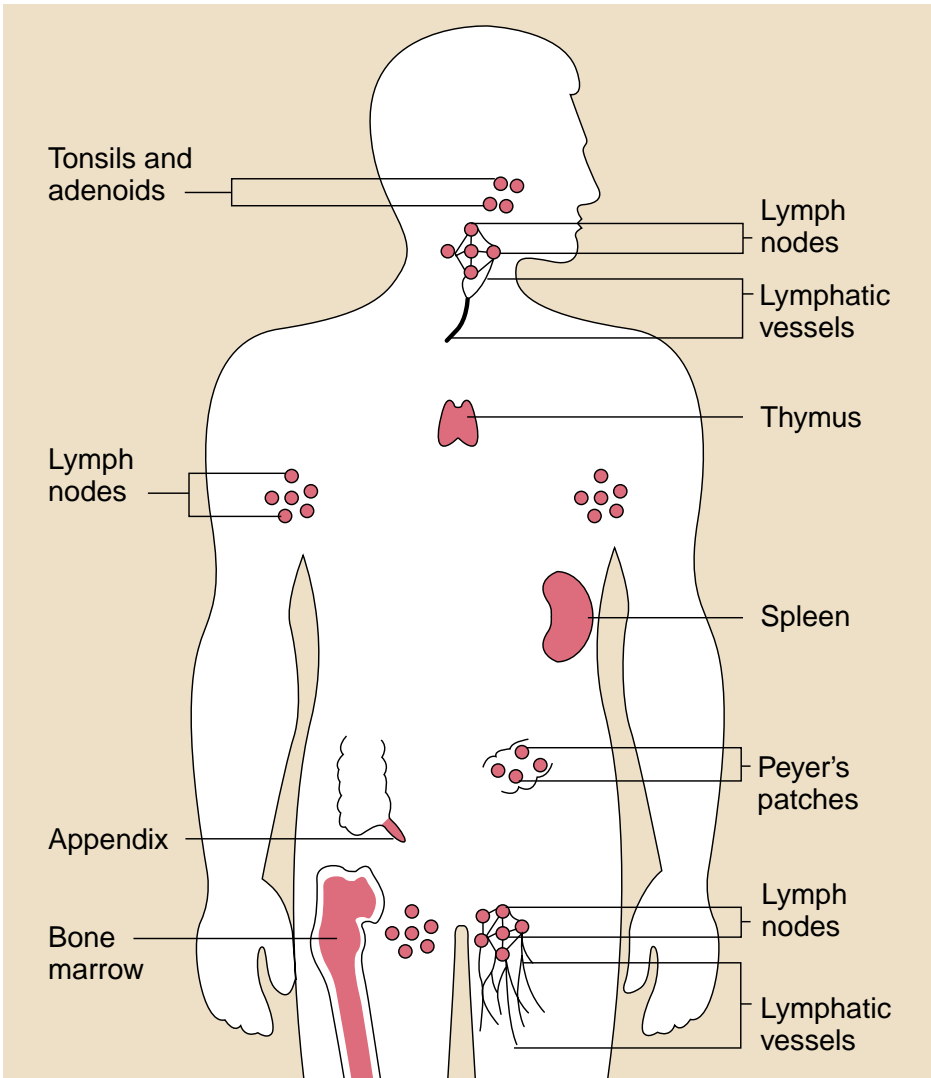
markers that say “foreign,” they quickly launch an attack.

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

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

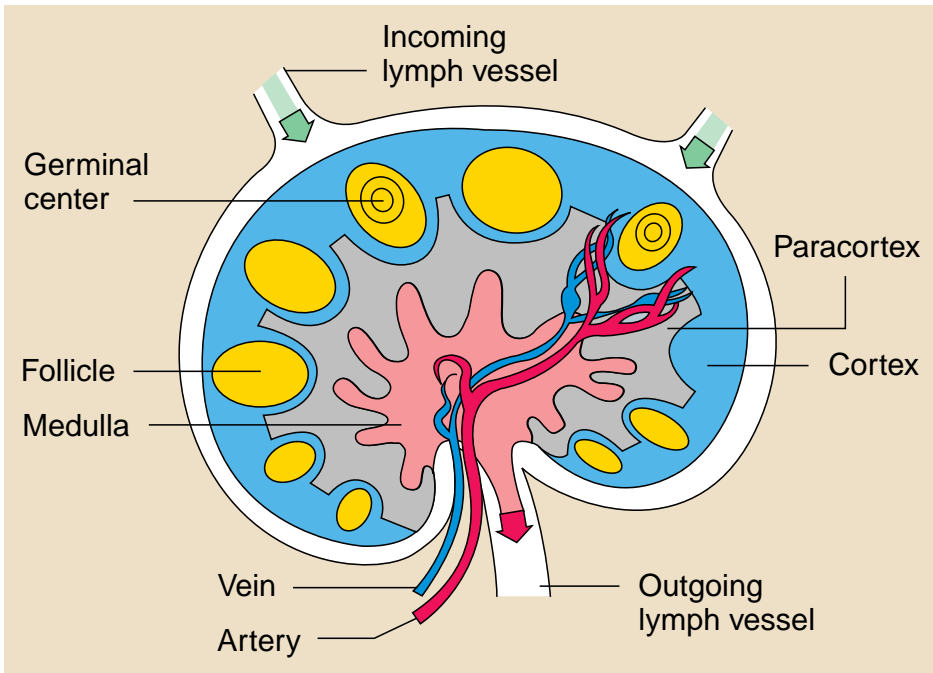
The organs of the immune system are positioned throughout the body. They are called *lymphoid organs* because they are home to *lymphocytes*, small white blood cells that are the key players in the immune system.



The organs of the immune system are positioned throughout the body.

Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including white blood cells destined to become immune cells.

The *thymus* is an organ that lies behind the breastbone; lymphocytes known as



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.

T lymphocytes, or just "*T cells*," mature in the thymus.

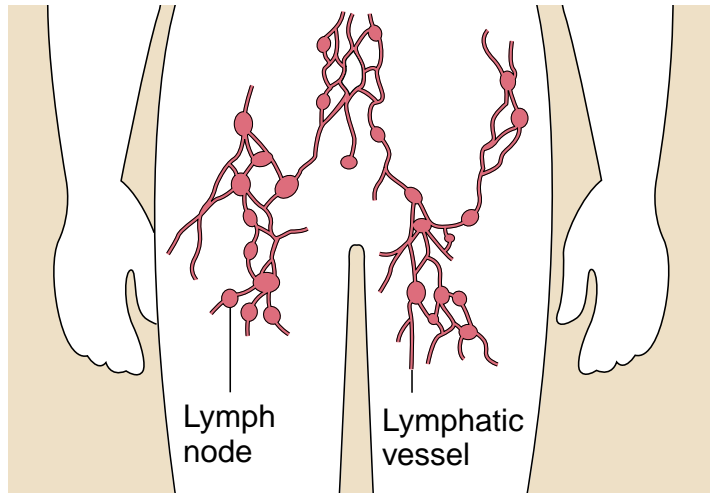
Lymphocytes can travel throughout the body using the *blood vessels*. The cells can also travel through a system of *lymphatic vessels* that closely parallels the body's veins and arteries. Cells and fluids are exchanged between blood and lymphatic vessels, enabling the lymphatic system to monitor the 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 and foreign particles 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, they 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, and serves as a meeting ground where immune defenses confront antigens.

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

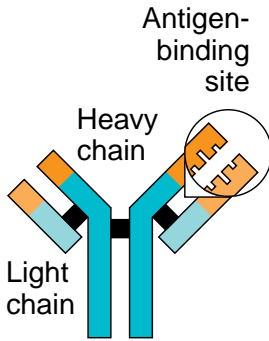


Immune cells and foreign particles enter the lymph nodes via incoming lymphatic vessels or the lymph nodes' tiny blood vessels.

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 comers, while 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, sometimes by 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 appears, those few matching cells multiply into a full-scale army. After their job is done, they fade



- Variable region
- Constant region

An antibody is made up of two heavy chains and two light chains. The variable region, which differs from one antibody to the next, allows an antibody to recognize its matching antigen.

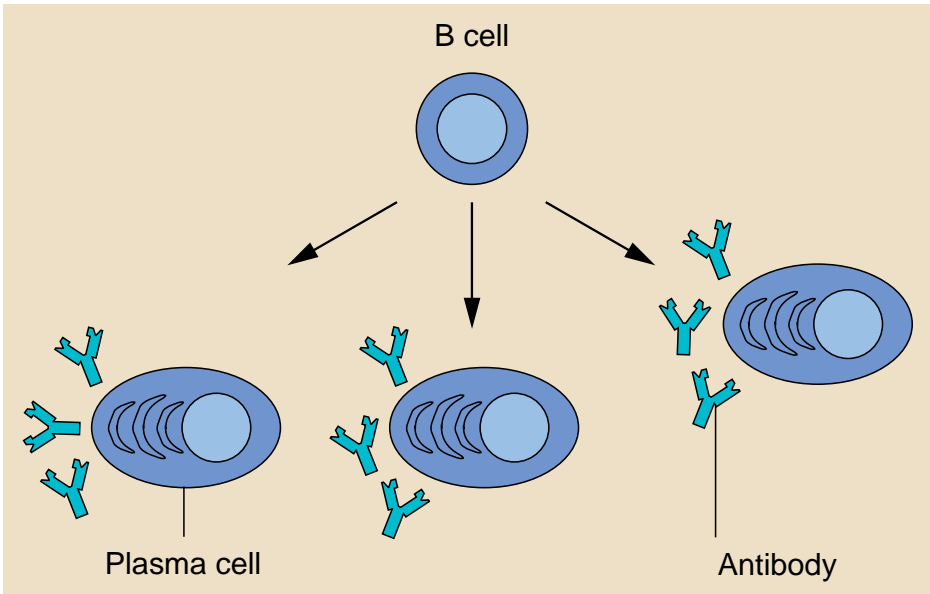
away, leaving sentries behind to watch for future attacks.

All immune cells begin as immature *stem cells* in the bone marrow. They respond to different *cytokines* and other 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, they are 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 immune deficiency diseases.

B Lymphocytes

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 antigens circulating 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).

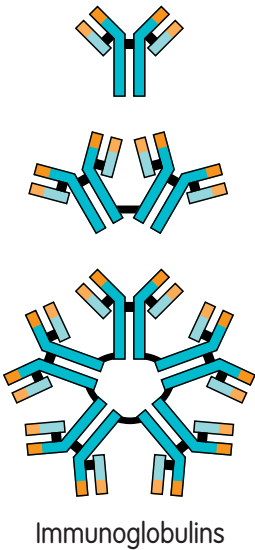


B cells mature into plasma cells that produce antibodies.

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 its triggering antigen, it gives rise to many large cells known as *plasma cells*. Every plasma cell is essentially a factory for producing an antibody. Each of the plasma cells descended from a given B cell manufactures millions of identical antibody molecules and pours them into the bloodstream.

An antigen matches an antibody much as a key matches a lock. Some match exactly; others fit more like a skeleton key. But whenever antigen and antibody interlock, the antibody marks the antigen for destruction.



Antibodies belong to a family of large molecules known as *immunoglobulins*. Different types play different roles in the immune defense strategy.

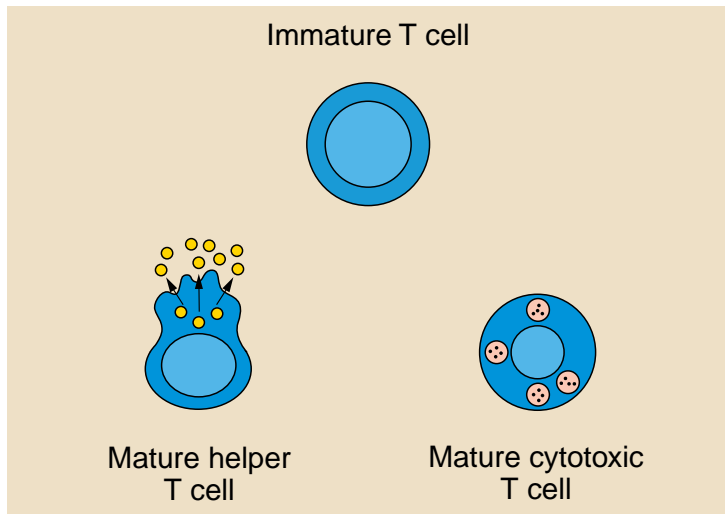
- Immunoglobulin G, or IgG, works efficiently to coat microbes, speeding their uptake by other cells in the immune system.
- IgM is very effective at killing bacteria.
- IgA concentrates in body fluids—tears, saliva, the secretions of the respiratory tract and the digestive tract—guarding the entrances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

T Cells

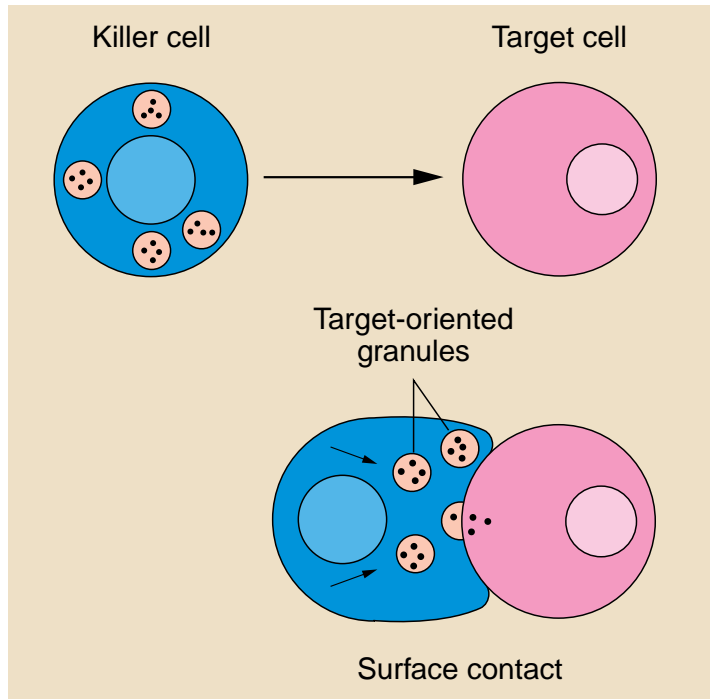
Unlike B cells, T cells do not recognize free-floating antigens. Rather, their surfaces contain specialized antibody-like receptors that see fragments of antigens on the surfaces of infected or cancerous cells. T cells contribute to immune defenses in two major ways: some direct and regulate immune responses; 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 antibody, others call in microbe-gobbling cells called phagocytes, still others activate other T cells.

Killer T cells—also called *cytotoxic T lymphocytes* or *CTLs*—perform a different function. These cells directly attack other



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.

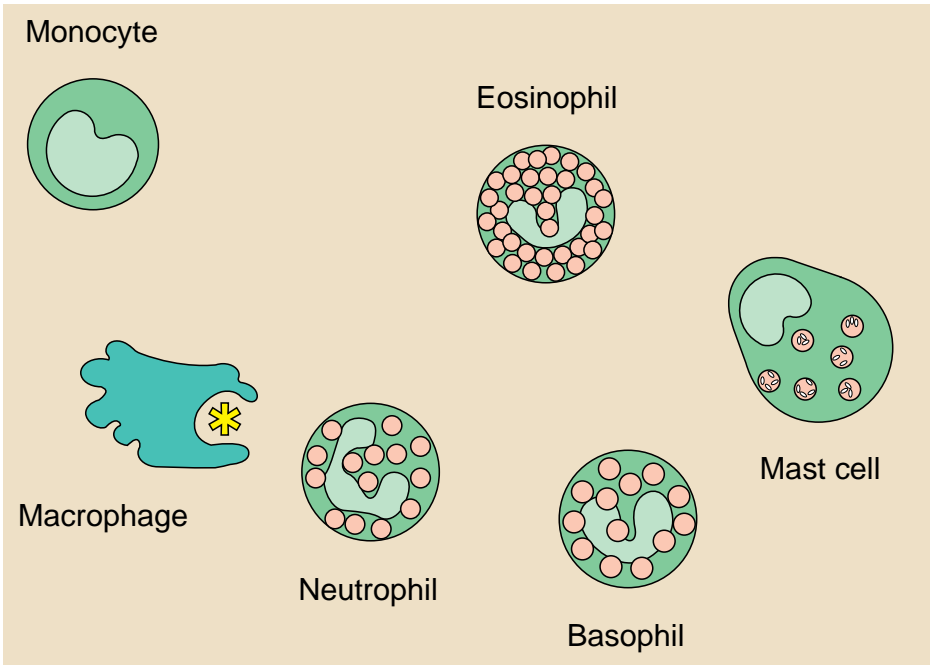
cells carrying certain foreign or abnormal molecules on their surfaces. CTLs are especially useful for attacking viruses because viruses often hide from other parts of the immune system while they grow inside infected cells. CTLs recognize small fragments of these viruses peeking out from the cell membrane and launch an attack to kill the 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 *MHC*, or *major histocompatibility complex*, molecules. MHC molecules are proteins

recognized by T cells when distinguishing between self and nonself. A self MHC molecule provides a recognizable scaffolding to present a foreign antigen to the T cell.

Although MHC molecules are required for T-cell responses against foreign invaders, they also pose a difficulty 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*.

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



Phagocytes, granulocytes, and mast cells, all with different methods of attack, demonstrate the immune system's versatility.

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.

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 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 they churn out an amazing variety of powerful chemical signals, known as *monokines*, which are vital to the immune responses.

Granulocytes are another kind of immune cell. They contain granules filled with potent chemicals, which allow the granulocytes to 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; it uses its prepackaged chemicals to break down the microbes it ingests. *Eosinophils* and *basophils* are granulocytes that “degranulate,” spraying their chemicals onto harmful cells or microbes nearby.

The *mast cell* is a twin of the basophil, except that it is not a blood cell. Rather, it is found in the lungs, skin, tongue, and linings of the nose and intestinal tract, where it is responsible for the symptoms of allergy.

A related structure, the blood *platelet*, is a cell fragment. Platelets, too, contain

granules. In addition to promoting blood clotting and wound repair, platelets activate some of the immune defenses.

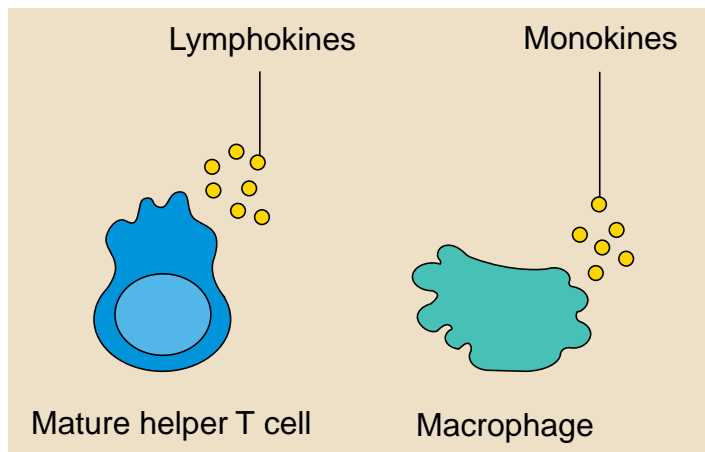
Cytokines

Components of the immune system communicate with one another by exchanging chemical messengers called cytokines. These proteins are secreted by cells and act on other cells to coordinate an appropriate immune response. Cytokines include a diverse assortment of *interleukins*, *interferons*, and *growth factors*.

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 ongoing to test its benefits in other diseases such as cancer, hepatitis C, and

Cytokines include lymphokines, produced by lymphocytes, and monokines, made by monocytes and macrophages.



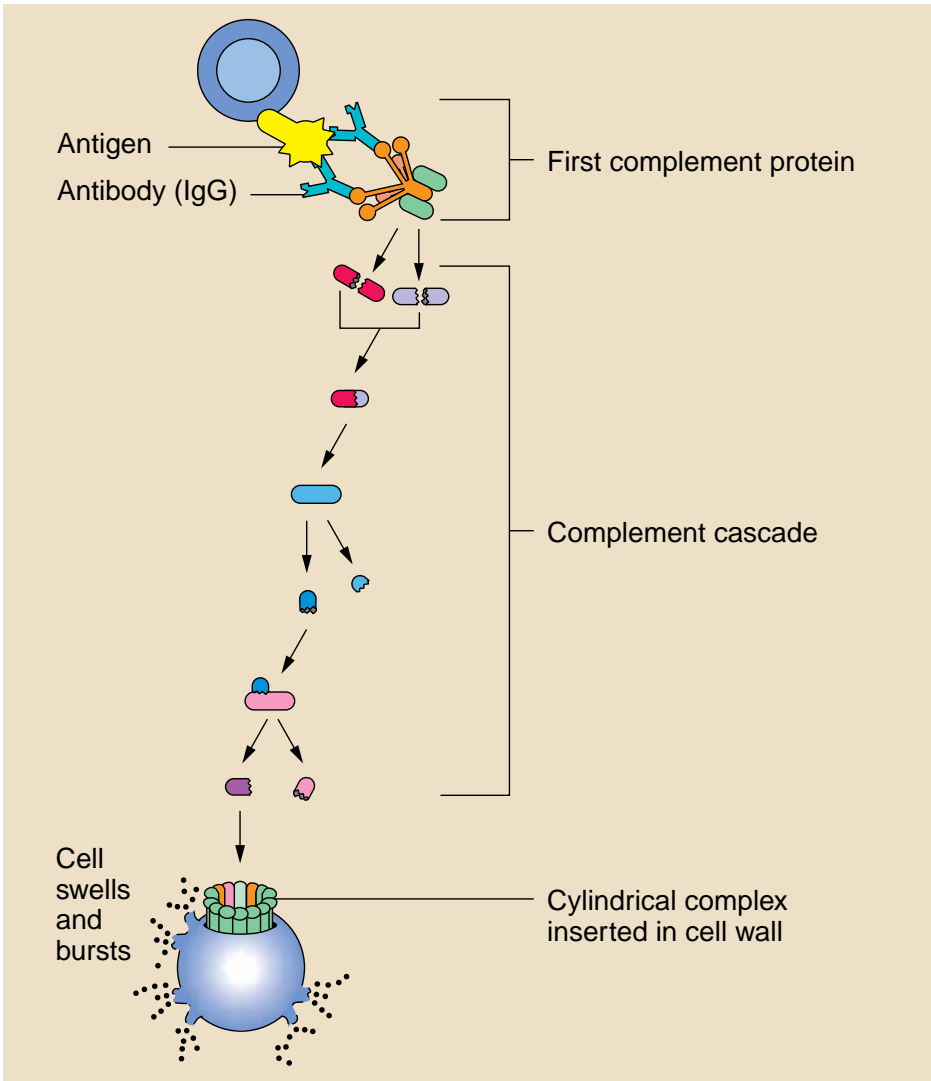
HIV infection and AIDS. Other cytokines also are being studied for their potential clinical benefit.

Other cytokines chemically attract 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.

Complement

The *complement* system is made up of about 25 proteins that work together to “complement” the action of antibodies in destroying bacteria. Complement also helps to rid the body of antibody-coated antigens (antigen-antibody complexes). Complement 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 product is a



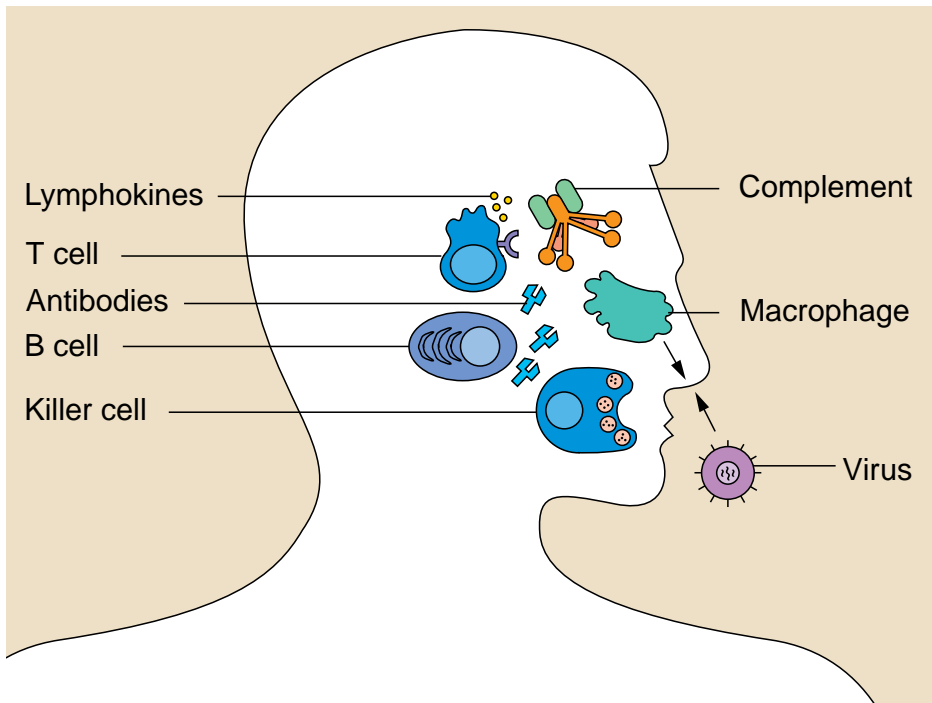
The interlocking steps of the complement cascade end in cell death.

cylinder inserted into—and puncturing a hole in—the cell’s wall. With fluids and molecules flowing in and out, the cell swells and bursts. Other components of the complement system make bacteria more susceptible to *phagocytosis* or beckon other 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



When challenged, the immune system has many weapons to choose.

tracts—both portals of entry for a number of microbes—also have 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 organisms. 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 number of cells, including macrophages, B cells, and T cells, lie in wait for any germ that might bypass the barriers at the surface.

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

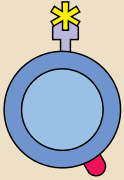
Microbes that cross the general barriers then confront specific weapons tailored just for them. Specific weapons, which include both antibodies and T cells, are equipped with singular receptor structures that allow them to recognize and interact with their designated targets.

Bacteria, Viruses, and Parasites

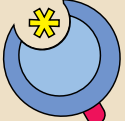
The most common disease-causing microbes are bacteria, viruses, and parasites. Each uses a different tactic to infect a person, and, therefore, each is thwarted by a different part of the immune system.

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.

All viruses, plus a few types of bacteria and parasites, must enter cells to survive, requiring a different approach. Infected cells use their MHC molecules to put pieces of the invading microbes on the cell's surface, flagging down cytotoxic T lymphocytes to destroy the infected cell. Antibodies also can assist in the immune



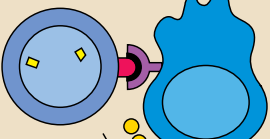
Antibodies are triggered when a B cell encounters its matching antigen.



The B cell takes in the antigen and digests it,

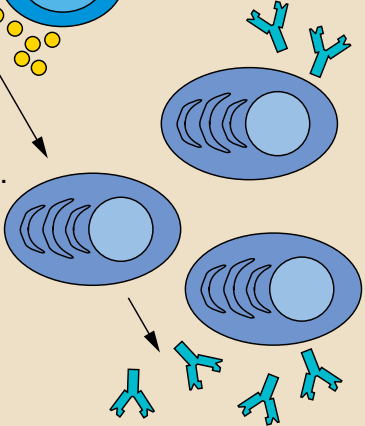


then it displays antigen fragments bound to its own distinctive MHC molecules.

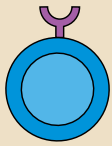


The combination of antigen fragment and MHC molecule attracts the help of a mature, matching T cell.

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.



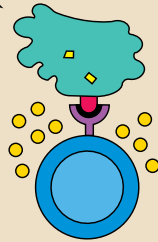
T cells are mobilized



when they encounter a cell such as a macrophage or a B cell that has digested an antigen

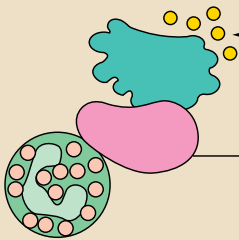


and is displaying antigen fragments bound to its MHC molecules.



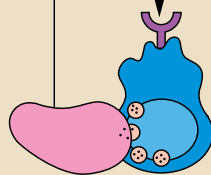
Lymphokines help the T cell to mature

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.

Infected cells



Some T cells become killer cells and track down body cells infected by viruses.

Some lymphokines spur the growth of more T cells.

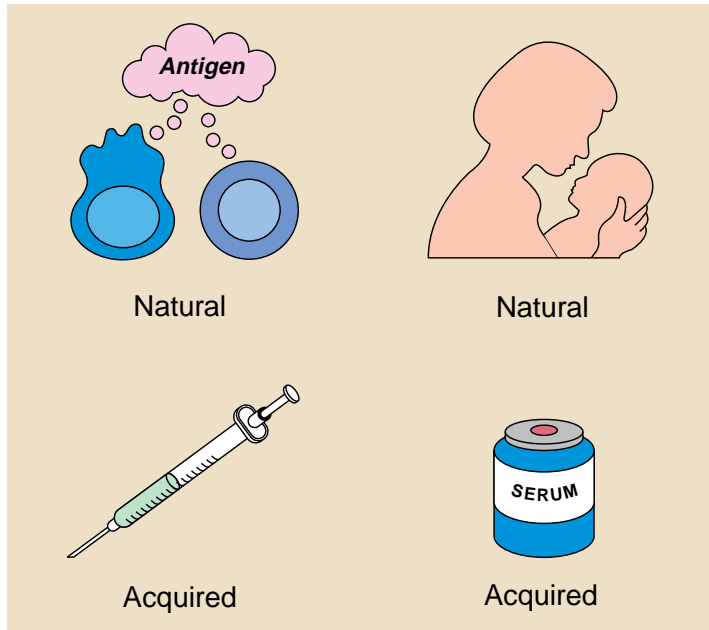
response, attaching to and clearing viruses before they have a chance to enter the cell.

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 when eosinophils, basophils, and other specialized granular cells rush to the scene and release their stores of toxic chemicals in an attempt to destroy the invader. Antibodies also play a role in this attack, attracting the granular 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 become *memory cells*. The next time an individual meets up with the same antigen, the immune system is set to demolish it.

Immunity can be strong or weak, short-lived or long-lasting, depending on the type of antigen, the amount of antigen, and the route by which it 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*. Vaccines contain microorganisms—or parts of microorganisms—that have been treated so they can provoke an immune response but not full-blown disease.

Immunity can also be transferred from one individual to another by injections of *serum* rich in antibodies against a particular microbe (*antiserum*).

For example, immune serum is sometimes given to protect travelers to countries where hepatitis A is widespread. Such *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 received 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.

Tolerance occurs in at least two ways. 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 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

Medical workers have long helped the body's immune system prepare for future attacks through vaccination. Vaccines consist of killed or modified microbes, components of microbes, or microbial *DNA* that trick the body into thinking an infection has occurred. An immunized person's immune system attacks the harmless vaccine and prepares for subsequent invasions. Vaccines remain one of the best ways to prevent infectious diseases and 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

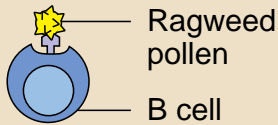
Allergic Diseases

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 or house dust is mistaken for a threat and attacked.

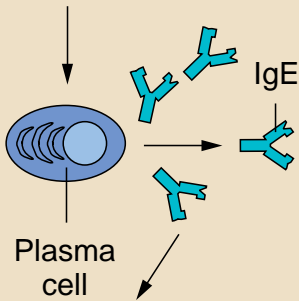
Allergies such as pollen allergy are related to the antibody known as IgE. Like other antibodies, each IgE antibody is specific; one acts against oak pollen, another against ragweed.

Autoimmune Diseases

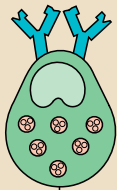
Sometimes the immune system's recognition apparatus breaks down, and the body begins to manufacture T cells and antibodies directed against its own cells and organs. Misguided T cells and *autoantibodies*, as they are known, contribute to many diseases. For instance, T cells that attack pancreas cells contribute to diabetes, while an autoantibody known as rheumatoid factor is common in people with rheumatoid arthritis. People with systemic lupus erythematosus (SLE) have



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.

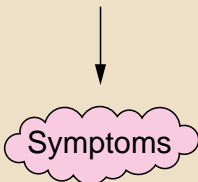
Mast cell



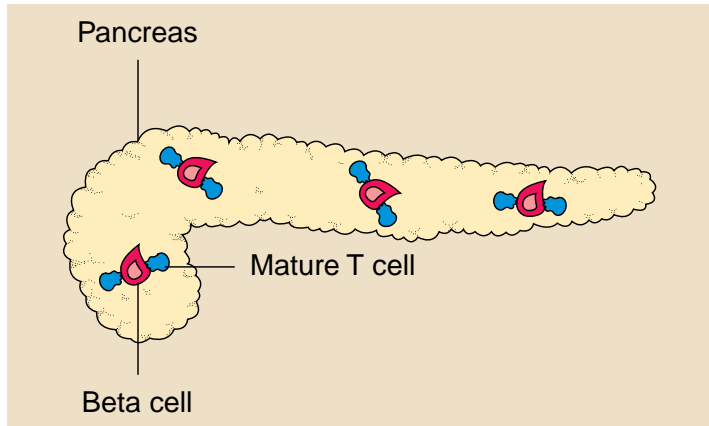
The second time that person has a brush with ragweed,

the IgE-primed mast cell will release its powerful chemicals,

Chemicals



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



Misguided T cells can attack insulin-producing cells of the pancreas, contributing to diabetes.

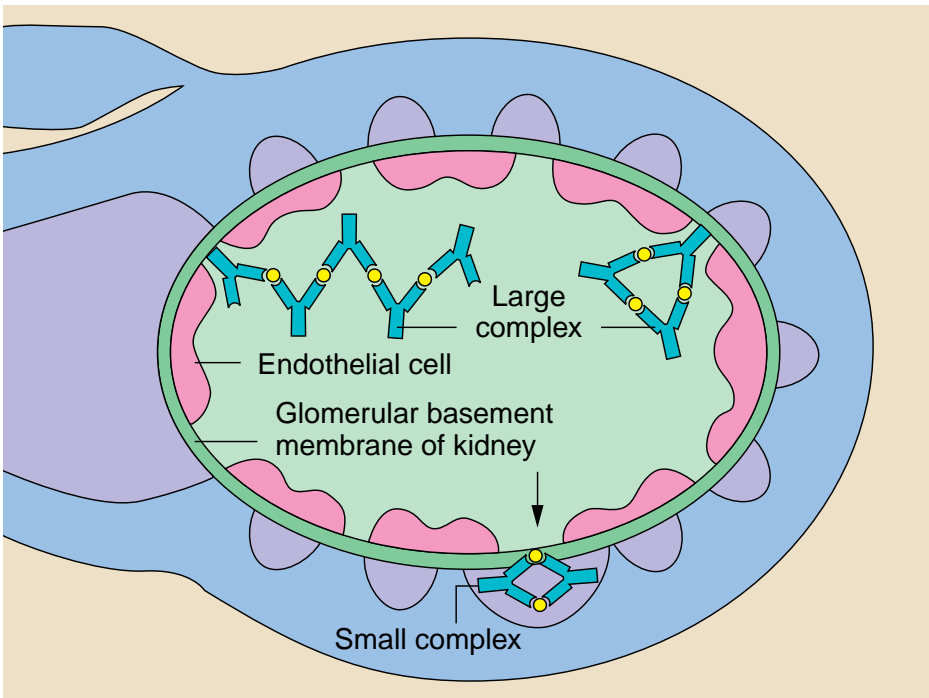
antibodies to many types of their own cells and cell components.

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, since 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, the lungs, skin, joints, or blood vessels. There they set off reactions with complement that lead to inflammation and tissue damage.

Immune complexes work their mischief in many diseases. These include malaria and viral hepatitis, as well as many autoimmune diseases.



Antigen-antibody complexes can become trapped in, and damage, the kidneys and other organs.

Immunodeficiency Disorders

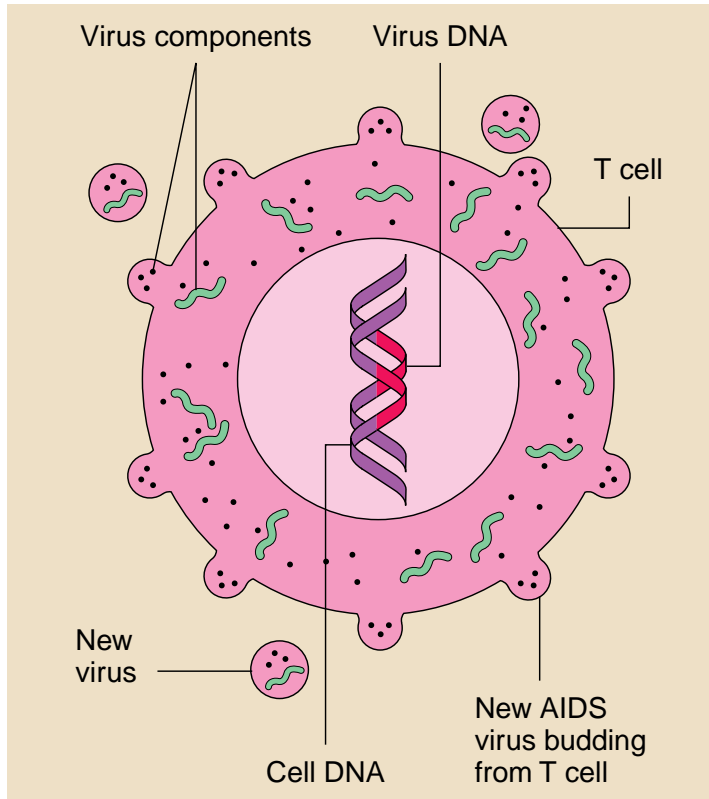
When the immune system is missing one or more of its components, the result is an immunodeficiency disorder.

Immunodeficiency disorders can be inherited, acquired through infection, or produced unintentionally 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 immunodeficiency disease or SCID.

AIDS is an immunodeficiency 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. HIV also can hide out for long periods in immune



The AIDS virus takes over the machinery of the T cells it infects, using it to make new viruses.

cells. As the immune defenses falter, a person with AIDS falls prey to unusual, often life-threatening infections and rare cancers.

A contagious disease, AIDS is spread by intimate sexual contact, transfer of the virus from mother to infant during pregnancy, or direct blood contamination. There is no cure for AIDS, but newly developed antiviral drugs can slow the advance of the disease, at least for a time. Researchers also are testing HIV vaccines in clinical studies.

Cancers of the Immune System

The cells of the immune system, like other cells, can grow uncontrollably, resulting in cancer. Leukemias are caused by the proliferation of white blood cells, or *leukocytes*. The uncontrolled growth of antibody-producing plasma cells can lead to multiple myeloma. Cancers of the lymphoid organs, known as lymphomas, include Hodgkin's disease.

Immunology and Transplants

Each year thousands of American lives are prolonged by transplanted organs—kidney, 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.

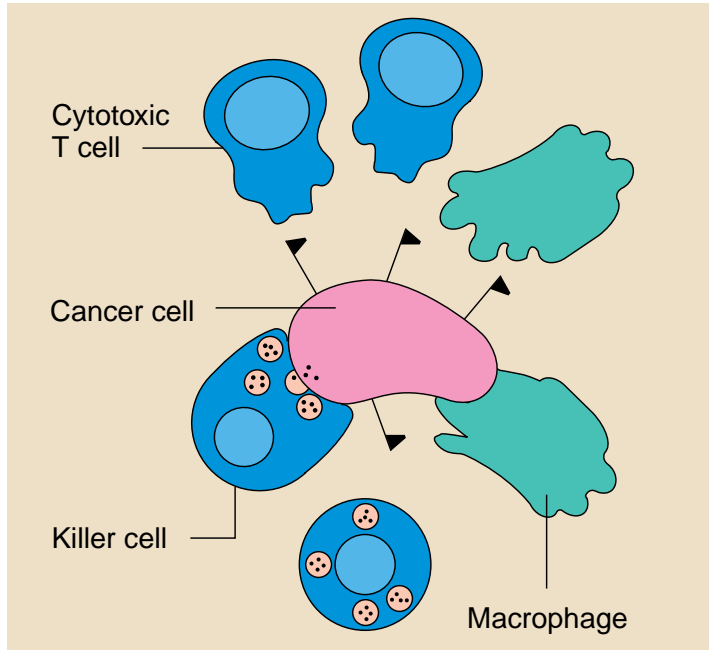
One way, *tissue typing*, makes sure markers of self on the donor's tissue are as similar as possible to those of the recipient. Each cell has a double set of 6 major tissue antigens, and each of the antigens exists, in different individuals, in as many as 20 varieties. The chance of 2 people having identical transplant antigens is about 1 in 100,000.

A second way is to lull the recipient's immune system. 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—one possible remedy is a transfer of healthy bone marrow. 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.



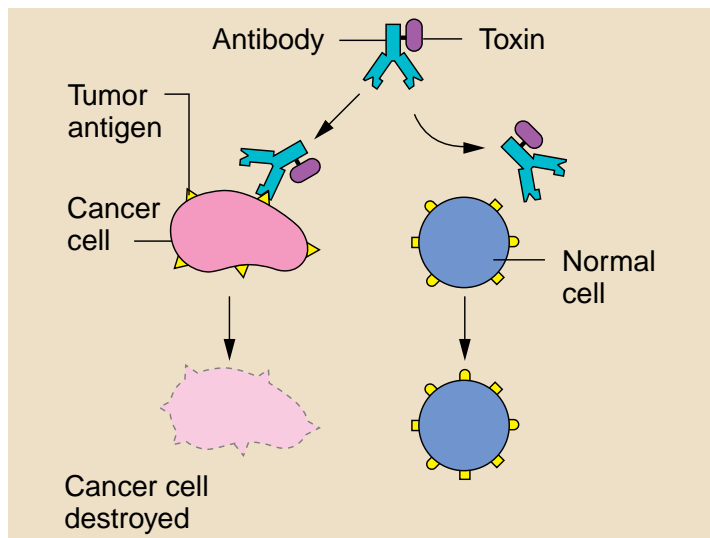
A cancer cell can rouse several types of immune defenses.

Immunity and Cancer

When normal cells turn into cancer cells, some of the antigens on their surface may change. If the immune system notices the foreign antigens, it launches the body's defenders, including killer T cells, NK cells, and macrophages. But the immune system cannot patrol everywhere to provide bodywide surveillance, flushing out and eliminating all cells that become cancerous. Tumors develop when the system breaks down or is overwhelmed.

Scientists are shaping immune cells and substances into ingenious new anticancer weapons. They are using substances known as *biological response modifiers*, including lymphocytes and *lymphokines*, to bolster the patient's immune responses. In some cases, biological response modifiers are injected directly into the patient. They can also be used in the laboratory to transform some of the patient's own lymphocytes into tumor-hungry cells, which are then injected back into the patient so they can attack the cancer cells.

Antibodies specially made to recognize specific cancers can be coupled with drugs, *toxins*, or radioactive materials, then sent off like “magic bullets” to deliver their lethal cargo directly to the target cancer



Antibodies targeted against cancer cells can be linked with toxins, drugs, or radioactive substances, which they can deliver directly to the cancer cell.

cells. Alternatively, toxins can be linked to a lymphokine and routed to cells equipped with receptors for the lymphokine.

Radioactively labeled antibodies can also be used to track down hidden nests of cancer cells (metastases).

Still other researchers are testing therapeutic cancer vaccines. These differ from traditional vaccines, which are given before disease onset to protect a person from future infections. Cancer vaccines are used after the cancer has arisen, and are designed to help the immune system fight off the illness.

The immune system often responds weakly or not at all to cancer cells. Cancer vaccines try to improve on the natural anticancer response by stimulating strong killer T-cell responses against a tumor. Although such vaccines are generally not able to destroy a tumor if given as the only form of treatment, research suggests they can be effective partners if administered along with other forms of treatment.

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.

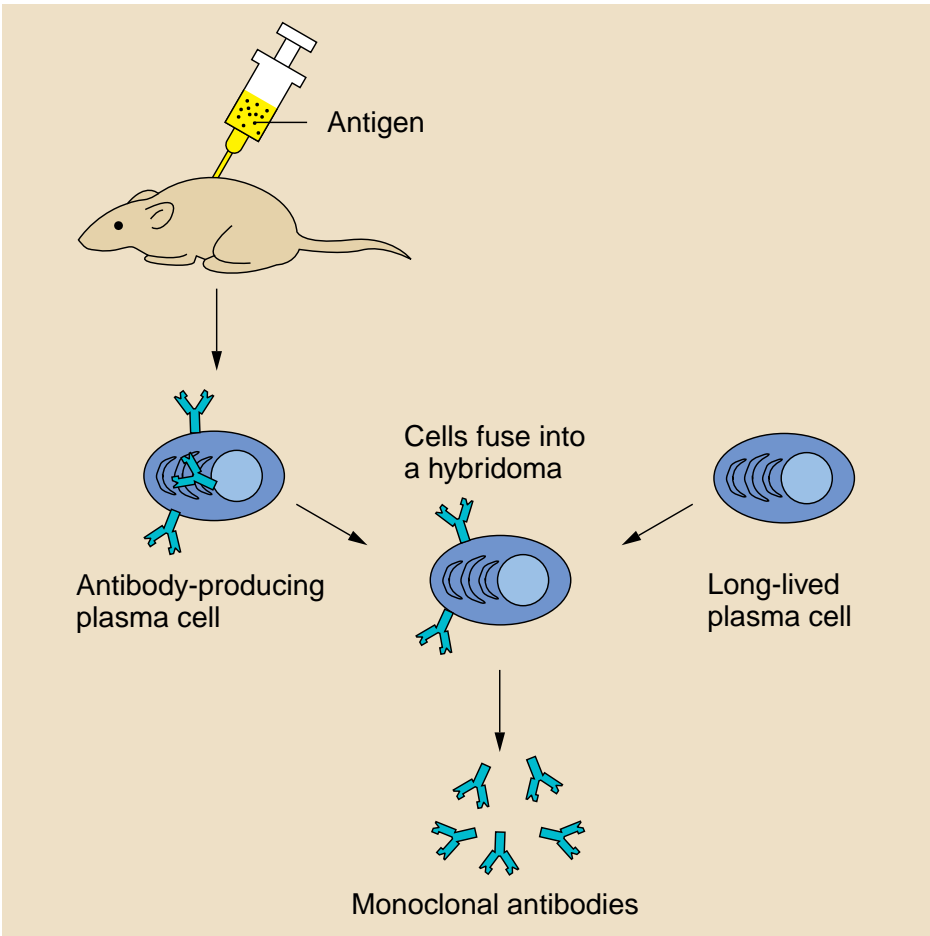
Hormones and other chemicals known to convey messages among nerve cells have been found to "speak" to cells of the immune system. Indeed, some immune cells are able to manufacture typical nerve cell products, while some lymphokines can transmit information to the nervous system. What's more, the brain may send messages directly down nerve cells to the immune system. Networks of nerve fibers have been found connecting to the lymphoid organs.

Frontiers in Immunology

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 descendants (*clones*) of a single B cell. Because of their unique specificity for different molecules, 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 another long-lived cell. 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 their own immune response when injected into a human. Therefore, researchers have begun to study “humanized” monoclonal antibodies. To construct these molecules, scientists take the antigen-binding portion of a mouse antibody and attach it to a



Monoclonal antibody technology makes it possible to mass produce specific antibodies to order.

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,

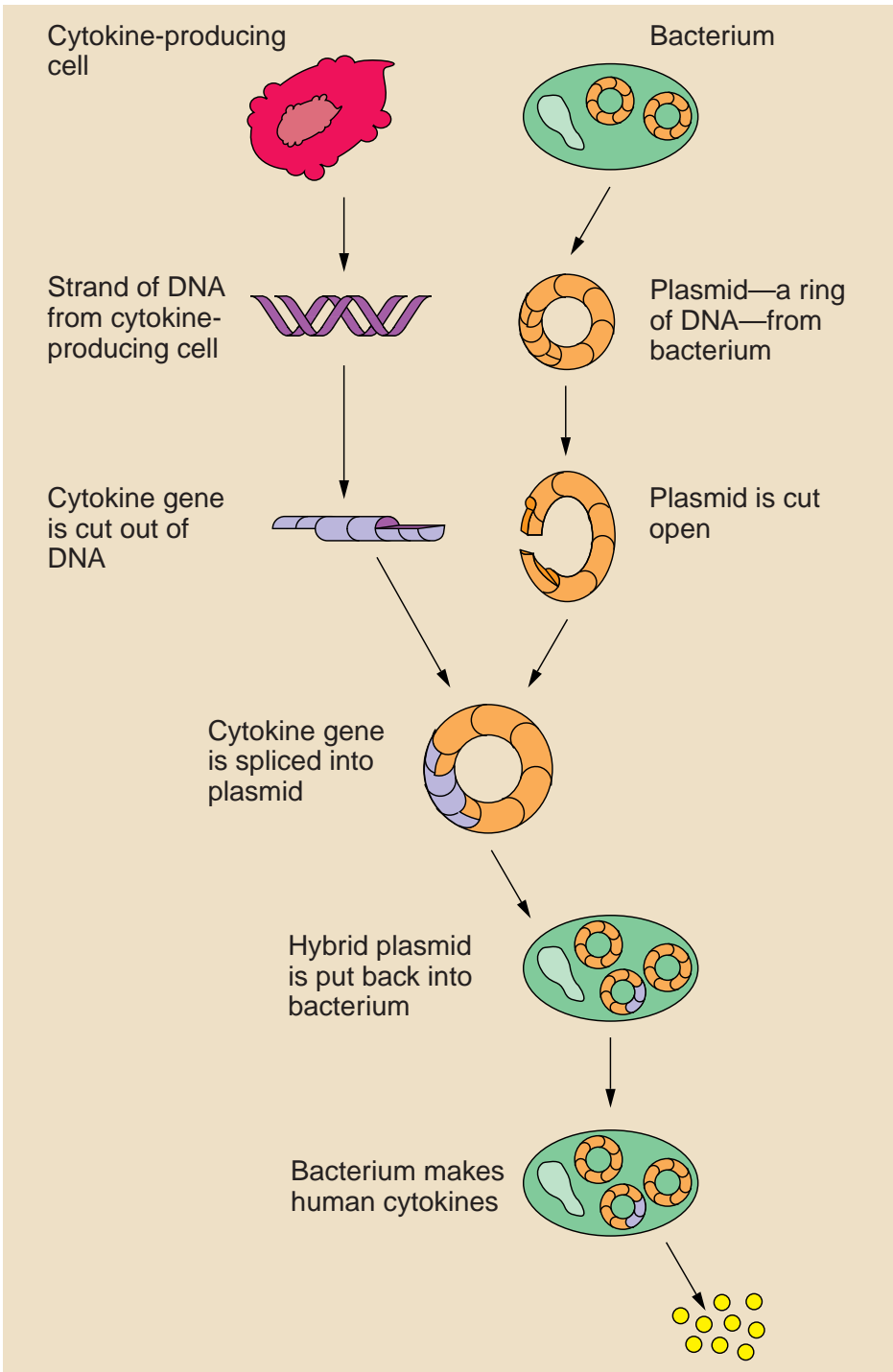
blocking the chemical growth signals that cause the cells to divide out of control. In other cases, monoclonal antibodies can carry potent toxins into select cells, killing the cell while leaving its neighbors untouched.

Genetic Engineering

Genetic engineering allows scientists to pluck genes—segments of the hereditary material, DNA—from one type of organism and combine them with genes of a second organism. In this way relatively simple organisms such as bacteria or yeast 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. Severe combined immunodeficiency disease is a prime candidate for gene therapy. SCID is caused by the lack of an *enzyme* due to a single missing gene. A genetically engineered version of the missing gene can be introduced into cells taken from the patient's bone marrow. After treated marrow cells begin to produce the enzyme, they can be injected back into the patient.



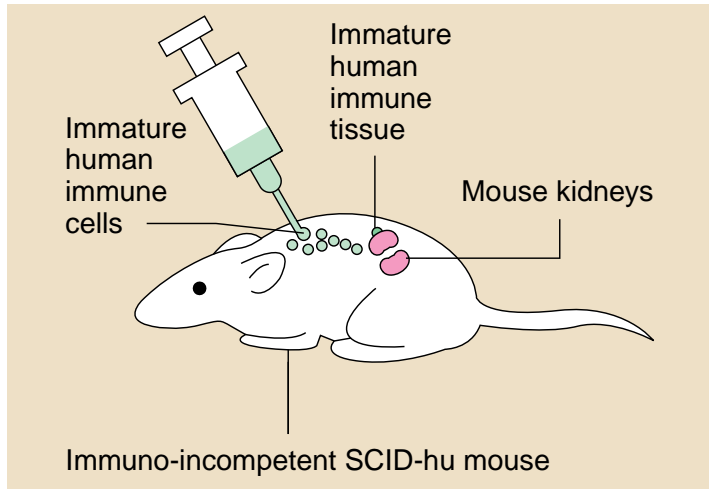
Genetic engineering transforms simple organisms into factories for making human proteins.

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 patient, 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 functions. Someday it may be possible to treat diseases such as systemic lupus erythematosus by suppressing parts of the immune system that are overactive.

By transplanting immature human immune tissues or immune cells into SCID mice, scientists have created a living model of the human immune system. This animal model promises to be immensely valuable in helping scientists understand the immune system and manipulate it benefit human health.



The SCID-hu mouse provides a means of studying the human immune system in action.

Summary

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 letting scientists quickly determine which targets are triggering an immune response. Improvements in microscopy are permitting the first-ever observations of 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 teach us even more about how the body protects itself from disease.

Glossary

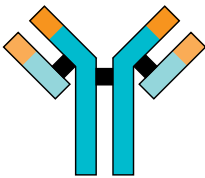
AIDS (acquired immunodeficiency syndrome)—life-threatening disease caused by the human immunodeficiency virus, which breaks down the body’s immune defenses.

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.

allergy—a harmful response of the immune system to normally harmless substances.



antibodies—molecules (also called immunoglobulins) produced by a B 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 molecule 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.

autoantibodies—antibodies that react 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 I diabetes, rheumatoid arthritis, and systemic lupus erythematosus.

B cells—small white blood cells crucial to the immune defenses. Also known as B lymphocytes, they 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.

basophils—white blood cells that contribute to inflammatory reactions. Along with mast cells, basophils are responsible for the symptoms of allergy.

biological response modifiers—substances, either natural or synthesized, that boost, direct, or restore normal immune defenses. They include interferons, interleukins, thymus hormones, and monoclonal antibodies.

blood vessels—arteries, veins, and capillaries that carry blood to and from the heart and body tissues.

bone marrow—soft tissue located in the cavities of the bones. Bone marrow is the source of all blood cells.

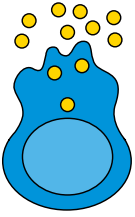
chemokines—certain proteins that stimulate both specific and general immune cells and help coordinate immune responses and inflammation.

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.

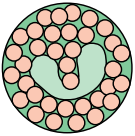
cytokines—powerful chemical substances secreted by cells that enable the body’s cells to communicate with one another. Cytokines include lymphokines produced by lymphocytes and monokines produced by monocytes and macrophages.



cytotoxic T lymphocytes (CTLs)—a subset of T cells that carry the CD8 marker and can destroy body cells infected by viruses or transformed by cancer.

DNA (deoxyribonucleic acid)—a long molecule found in the cell nucleus; it carries the cell's genetic information.

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



eosinophils—white blood cells that contain granules filled with chemicals damaging to parasites, and enzymes that affect inflammatory reactions.

epithelial cells—cells making up the epithelium, the covering for internal and external body surfaces.

fungi—members of a class of relatively primitive vegetable organisms. They include mushrooms, yeasts, rusts, molds, and smuts.

genes—units of genetic material (DNA) inherited from a parent. Genes carry the directions a cell uses to perform a specific function.

graft rejection—an immune response against transplanted tissue.

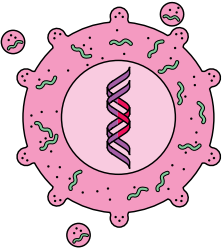
graft-versus host disease (GVHD)—a life-threatening reaction in which transplanted cells attack the tissues of the recipient.

granules—membrane-bound organelles within cells where proteins are stored before secretion.

granulocytes—phagocytic white blood cells filled with granules organisms. 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.



HIV (human immunodeficiency virus)—the virus that causes AIDS.

immune response—reaction of the immune system to foreign substances.

immunoglobulins—a family of large protein molecules, also known as antibodies, produced by B cells.

immunosuppressive—capable of reducing immune responses.

inflammatory response—redness, warmth, and swelling produced in response to infection, as the result of increased blood flow and an influx of immune cells and secretions.

interferons—proteins produced by cells that stimulate anti-virus immune responses or alter the physical properties of immune cells.

interleukins—a major group of lymphokines and monokines.

leukocytes—all white blood cells.

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

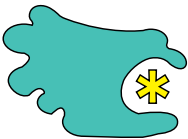
lymph nodes—small bean-shaped organs of the immune system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are garrisons of B, T, and other immune cells.

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

lymphocytes—small white blood cells produced in the lymphoid organs and paramount in the immune defenses. B cells and T cells are lymphocytes.

lymphoid organs—the organs of the immune system, where lymphocytes develop and congregate. They 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.

microbes—microscopic living organisms, including bacteria, viruses, fungi, and protozoa.

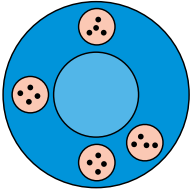
microorganisms—microscopic organisms, including bacteria, virus, fungi, plants, and parasites.

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 antibodies—antibodies produced by a single cell or its identical progeny, specific for a given antigen. As tools for binding to specific protein molecules, they are invaluable in research, medicine, and industry.

monocytes—large phagocytic white blood cells which, when entering tissue, develop into macrophages.

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



natural killer (NK) cells—large granule-containing lymphocytes that recognize and kill cells lacking self antigens. Their target recognition molecules are different from T cells.

neutrophil—white blood cell that is an abundant and important phagocyte.

organisms—individual living things.

parasites—plants or animals that live, grow, and feed on or within another living organism.

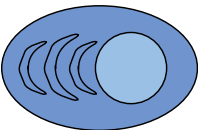
passive immunity—immunity resulting from the transfer of antibodies or antiserum produced by another individual.

pathogen—a disease-causing organism.

phagocytes—large white blood cells that contribute to the immune defenses by ingesting microbes or other cells and foreign particles.

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

plasma cells—large antibody-producing cells that develop from B cells.



platelet—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 cells—immature cells from which all cells derive. The bone marrow is rich in stem cells, which become specialized blood cells.

T cells—small white blood cells (also known as T lymphocytes) that recognize antigen fragments bound to cell surfaces by specialized antibody-like receptors. “T” stands for thymus, where T cells acquire their receptors.

T lymphocytes—see T cells.

thymus—a primary lymphoid organ, high in the chest, where T lymphocytes proliferate and mature.

tissue typing—see histocompatibility testing.

tissues—groups 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.

toxins—agents produced in plants and bacteria, normally very damaging to cells.

vaccines—preparations that stimulate an immune response that can prevent an infection or create resistance to an infection. They do not cause disease.

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



NIAID □

NATIONAL[®]
CANCER
INSTITUTE

NIH Publication No. 03-5423
September 2003
www.niaid.nih.gov
www.nci.nih.gov