Merck Manual
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SECTION 16

IMMUNE DISORDERS

CHAPTER 183

Biology of the Immune System

The immune system is designed to defend the body against foreign or dangerous substances that invade it. Such substances include microorganisms (commonly called germs, such as bacteria, viruses, and fungi), parasites (such as worms), cancer cells, and even transplanted organs and tissues.▲ Substances that stimulate an immune response in the body are called antigens. Antigens may be contained within or on bacteria, viruses, other microorganisms, or cancer cells. Antigens may also exist on their own—for example, as pollen or food molecules. A normal immune response consists of recognizing a foreign antigen, mobilizing forces to defend against it, and attacking it.

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Disorders of the immune system occur

- when the body generates an immune response against itself (an autoimmune disorder)▲
- when the body cannot generate appropriate immune responses against invading microorganisms (an immunodeficiency disorder)■
- when a normal immune response to foreign antigens damages normal tissues (an allergic reaction).★

The first line of defense against invaders is mechanical or physical barriers: the skin; the cornea of the eye; and the membranes lining the respiratory, digestive, urinary, and reproductive tracts. As long as these barriers remain unbroken, many invaders cannot penetrate them. If a barrier is broken—for example, if extensive burns damage much of the skin—the risk of infection is increased. In addition, the barriers are defended by secretions containing enzymes that can destroy bacteria. Examples are tears in the eyes and secretions in the digestive tract and vagina.

The next line of defense involves white blood cells that travel through the bloodstream and into tissues, searching for and attacking microorganisms and other invaders. This defense has two parts. The first part, called nonspecific (innate) immunity, involves several types of white blood cells that usually act on their own to destroy invaders. The second part, called specific (adaptive) immunity, involves white blood cells that work together to destroy invaders. Some of these cells do not directly destroy invaders but enable other white blood cells to recognize and destroy invaders.

Nonspecific immunity and specific immunity interact, influencing each other directly or through substances that attract or activate other cells of the immune system—part of the mobilization step in defense. These substances include cytokines (which are the messengers of the immune system), antibodies, and complement proteins (which form the complement system). These substances are not contained in cells but are dissolved in a body fluid, such as plasma, the liquid part of blood.

To be able to destroy invaders, the immune system must first recognize them. That is, the immune system must be able to distinguish what is nonself (foreign) from what is self. The immune system can make this distinction because all cells have identification molecules on their surface. Microorganisms are recognized because they have unique, foreign identification molecules on their surface. In people, identification molecules are called human leukocyte antigens (HLA), or the major histocompatibility complex (MHC). HLA molecules are called antigens because they can provoke an immune response in another person (normally, they do not provoke an immune response in the person who has them). Each person has unique human leukocyte antigens. A cell with molecules on its surface that are not identical to those on the body's own cells is identified as being foreign. The immune system then attacks that cell. Such a cell may be a microorganism, a cell from transplanted tissue, or one of the body's cells that has been infected by an invading microorganism.

Some white blood cells—B lymphocytes—recognize invaders directly. But others—T lymphocytes—need help from other cells of the immune system—called antigen-presenting cells. These cells ingest an invader and break it into fragments. Antigen fragments from the invader are then "presented" in a way that T lymphocytes can recognize.

The immune system includes several organs in addition to cells dispersed throughout the body. These organs are classified as primary or secondary lymphoid organs. The primary lymphoid organs—the thymus gland and bone marrow—are the sites where white blood cells are produced. In the thymus gland, T lymphocytes—a type of white blood cell—are produced and trained to recognize foreign antigens and ignore the body's own antigens. (T lymphocytes are critical for specific immunity.) The bone marrow produces several types of white blood cells, including neutrophils, monocytes, and B lymphocytes. When needed to defend the body, the white blood cells are mobilized, mainly from the bone marrow. They then move into the bloodstream and travel to wherever they are needed.

The secondary lymphoid organs include the spleen, lymph nodes, tonsils, liver, appendix, and Peyer's patches in the small intestine. These organs trap microorganisms and other foreign substances and provide a place for mature cells of the immune system to collect, interact with each other and with the foreign

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How T Lymphocytes Recognize Antigens

T lymphocytes are part of the immune surveillance system. They travel through the bloodstream and lymphatic system, looking for foreign substances (antigens) in the body. However, a T lymphocyte cannot recognize an antigen unless it has been processed and "presented" to the T lymphocyte by another white blood cell, called an antigen-presenting cell. Antigen-presenting cells consist of dendritic cells (which are the most effective), macrophages, and B lymphocytes.

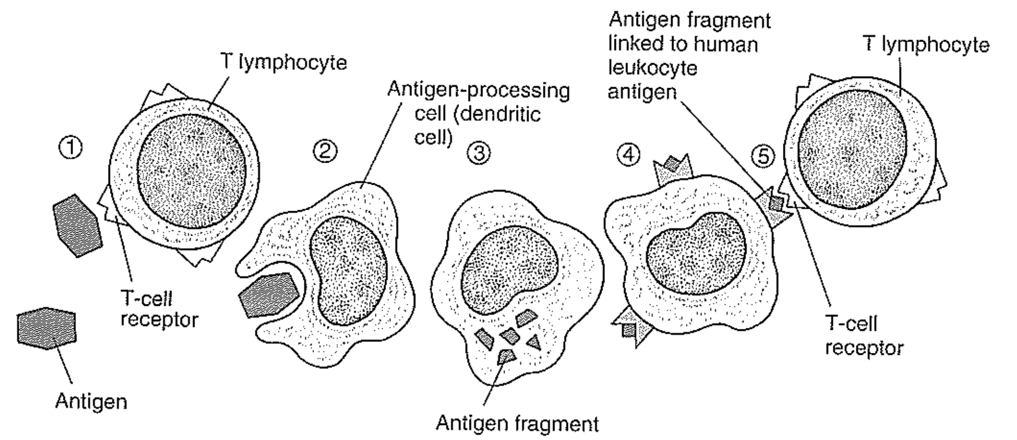
1. By itself, a T lymphocyte cannot recognize an antigen circulating in the body.

2. A cell that can process antigens, such as a dendritic cell, ingests the antigen.

3. Enzymes in the antigen-processing cell break the antigen into fragments.

4. Some antigen fragments are picked up by human leukocyte antigen (HLA) molecules as they are assembled inside the antigen-processing cell. Then the molecules with the antigen fragments are transported to the cell's surface.

5. A special molecule called a T-cell receptor, which is located on the surface of a T lymphocyte, can recognize the antigen fragment when it is attached to and presented by an HLA molecule. The T-cell receptor then attaches to the part of the HLA molecule presenting the antigen fragment, fitting in it as a key fits in a lock.



substances, and generate a specific immune response.

The lymph nodes are strategically placed in the body and are connected by an extensive network of lymphatic vessels, which act as the immune system's circulatory system. The lymphatic system transports microorganisms, other foreign substances, cancer cells, and dead or damaged cells from the tissues to the lymph nodes and then to the bloodstream. Lymph nodes are one of the first places that cancer cells can spread. Thus, doctors often evaluate lymph nodes to determine whether a cancer has spread. Cancer cells in a lymph node can cause the node to swell. Lymph nodes can also swell after an infection, because immune responses to infections are generated in lymph nodes.

Nonspecific Immunity

Nonspecific (innate) immunity is present at birth. Nonspecific immunity is so named because its components treat all foreign substances in much the same way.

The white blood cells involved in nonspecific immunity are monocytes (which develop into macrophages), neutrophils, eosinophils, basophils, and natural killer cells. Each type has a slightly different function. The complement system and cytokines also participate in nonspecific immunity.

Macrophages

Macrophages develop from a type of white blood cell called monocytes after monocytes move from the bloodstream to the tissues.

Understanding the Immune System

Antibody (immunoglobulin): A protein that is produced by B lymphocytes and that interacts with a specific antigen.

Antigen: Any substance that can stimulate an immune response.

Basophil: A white blood cell that releases histamine (a substance involved in allergic reactions) and that produces substances to attract neutrophils and eosinophils to a trouble spot.

Cell: The smallest unit of a living organism, composed of a nucleus and cytoplasm surrounded by a membrane.

Chemotaxis: The process of attracting cells by means of a chemical substance.

Complement system: A group of proteins with various immune functions, such as killing bacteria and other foreign cells, making foreign cells easier for macrophages to identify and ingest, attracting macrophages and neutrophils to a trouble spot, and enhancing the effectiveness of antibodies.

Cytokines: The immune system's messengers, which help regulate an immune response.

Dendritic cell: A white blood cell that usually resides in tissues and that helps T lymphocytes recognize foreign antigens.

Eosinophil: A white blood cell that can ingest bacteria and other foreign cells, that may help immobilize and kill parasites, that participates in allergic reactions, and that helps destroy cancer cells.

Helper T cell: A white blood cell that helps B lymphocytes recognize and produce antibodies against foreign antigens.

Histocompatibility: Literally, compatibility of tissue; determined by human leukocyte antigens (the major histocompatibility complex) and used to determine whether a transplanted tissue or organ will be accepted by the recipient.

Human leukocyte antigens (HLA): A group of molecules that are located on the surface of cells and that are unique in each organism, enabling the body to distinguish self from nonself; also called the major histocompatibility complex.

Immune response: The reaction of the immune system to an antigen.

Immunoglobulin: A synonym for antibody.

Interleukin: A type of cytokine secreted by some white blood cells to affect other white blood cells.

Killer (cytotoxic) T cell: A lymphocyte that attaches to foreign or abnormal cells and kills them.

Leukocyte: A white blood cell, such as a monocyte, a neutrophil, an eosinophil, a basophil, or a lymphocyte.

Lymphocyte: The white blood cell responsible for specific immunity, including producing antibodies (by B lymphocytes) and distinguishing self from nonself (by T lymphocytes).

Macrophage: A large cell that is derived from a white blood cell called a monocyte, that ingests bacteria and other foreign cells, and that helps white blood cells identify microorganisms and other foreign substances.

Major histocompatibility complex (MHC): A synonym for human leukocyte antigens.

Mast cell: A cell in tissues that releases histamine and other substances involved in allergic reactions.

Molecule: A group of atoms chemically combined to form a unique chemical substance.

Natural killer cell: A type of lymphocyte that, unlike other lymphocytes, is formed ready to kill certain microorganisms and cancer cells.

Neutrophil: A white blood cell that ingests and kills bacteria and other foreign cells.

Phagocyte: A cell that ingests and kills invading microorganisms, other cells, and cell fragments.

Phagocytosis: The process of a cell ingesting an invading microorganism, another cell, or a cell fragment.

Receptor: A molecule on a cell's surface or inside the cell that allows only molecules that fit precisely to it—as a key fits in its lock—to attach to it.

Suppressor T cell: A white blood cell that helps end an immune response.

When infection occurs, monocytes leave the bloodstream and move into the tissues. There, over a period of about 8 hours, monocytes enlarge greatly and produce granules within themselves. The granules are filled with enzymes and other substances that help digest bacteria and other foreign cells. Monocytes that have enlarged and contain granules are macrophages. Macrophages stay in the tissues. They ingest bacteria, foreign cells, and damaged and dead cells. (The process of a cell ingesting a microorganism, another cell, or cell fragments is called phagocytosis, and cells that ingest are called phagocytes.)

Neutrophils

Neutrophils ingest bacteria and other foreign cells. Neutrophils contain granules that release enzymes to help kill and digest these cells. Neutrophils circulate in the bloodstream and must be signaled to leave the bloodstream and enter tissues. The signal often comes from the bacteria themselves, from complement proteins, or from macrophages, all of which produce substances that attract neutrophils to a trouble spot. (The process of attracting cells is called chemotaxis.)

Eosinophils

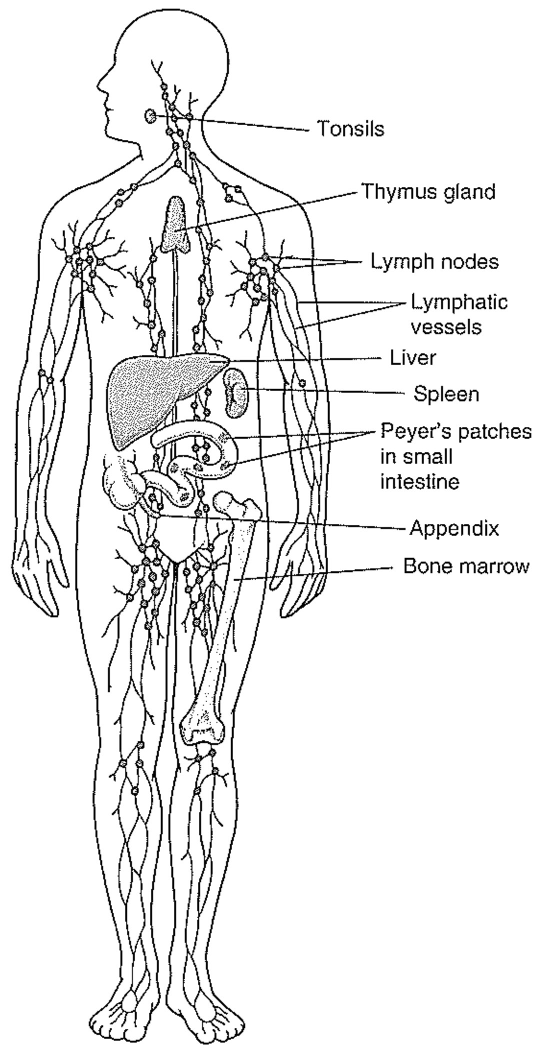
Eosinophils can ingest bacteria and other foreign cells, contain granules filled with enzymes to digest the ingested bacteria and cells, and circulate in the bloodstream. However, they are less active against bacteria than are

Lymphatic System: Helping Defend Against Infection

The lymphatic system is a vital part of the immune system, along with the thymus gland, bone marrow, spleen, tonsils, liver, appendix, and Peyer's patches in the small intestine.

The lymphatic system is a network of lymph nodes connected by lymphatic vessels. This system transports lymph. Fluids that contain oxygen, proteins, and other nutrients seep through the thin walls of capillaries into the body's tissues to nourish them. Some of these fluids enter the lymphatic vessels to be returned eventually to the bloodstream. The fluids also transport foreign substances (such as bacteria), cancer cells, and dead or damaged cells that may be present in tissues into the lymphatic vessels. Lymph also contains many white blood cells.

All substances transported by the lymph pass through at least one lymph node, where foreign substances can be filtered out and destroyed before fluids are returned to the bloodstream. In the lymph nodes, white blood cells can collect, interact with each other and antigens, and generate immune responses to foreign substances. Lymph nodes contain a mesh of tissue in which lymphocytes are tightly packed. Harmful microorganisms are filtered through the mesh, then attacked by lymphocytes and macrophages (which are also present in the lymph nodes). Lymph nodes are often clustered in areas where the lymphatic vessels branch off, such as the neck, armpits, and groin.



neutrophils and macrophages. Their main function may be to attach to and thus help immobilize and kill parasites. Eosinophils also participate in allergic reactions (such as asthma).▲

Basophils

Basophils do not ingest foreign cells. They contain granules that release histamine, a substance involved in allergic reactions. Basophils also produce substances that attract neutrophils and eosinophils to a trouble spot.

Natural Killer Cells

Natural killer cells are lymphocytes, a type of white blood cell. Natural killer cells are called "natural" killers because they are ready to kill as soon as they are formed. Natural killer cells attach to foreign cells and release enzymes and other substances that damage the outer membranes of the foreign cells. Natural killer cells kill certain microorganisms, cancer cells, and cells infected by viruses. Thus, natural killer cells are often the body's first line of defense against viral infections. Also, natural killer cells produce cytokines that regulate some of the functions of T lymphocytes, B lymphocytes, and macrophages.

Complement System

The complement system consists of more than 30 proteins that act in a sequence: One protein activates another and so on. This sequence is called the complement cascade. Complement proteins can kill bacteria directly or help destroy bacteria by attaching to them, thus making the bacteria easier for neutrophils and macrophages to identify and ingest. Other functions include attracting macrophages and neutrophils to a trouble spot, causing bacteria to clump together, and neutralizing viruses. The complement system also participates in specific immunity.

Cytokines

Cytokines are the messengers of the immune system. White blood cells and certain other cells of the immune system produce cytokines when an antigen is detected. There are many different cytokines, which affect different parts of the immune system. Some stimulate activity. They stimulate certain white blood cells to become more effective killers and to attract other white blood cells to a trouble spot. Other cytokines inhibit activity, helping end an immune response. Some cytokines, called interferons, interfere with the reproduction (replication) of viruses. Cytokines also participate in specific immunity.

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Specific Immunity

Specific (adaptive) immunity is not present at birth; it is acquired. As a person's immune system encounters antigens, it learns the best way to attack each antigen and begins to develop a memory for that antigen. Specific immunity is so named because it tailors its attack to a specific antigen previously encountered. The hallmarks of specific immunity are its ability to learn, adapt, and remember. Specific immunity takes time to develop after initial exposure to a new antigen. However, because a memory is formed, subsequent responses to a previously encountered antigen are more effective and more rapid than those generated by nonspecific immunity.

Lymphocytes are the most important type of white blood cell involved in specific immunity. Dendritic cells, antibodies, cytokines, and the complement system (which enhances the effectiveness of antibodies) are also involved.

Lymphocytes

Lymphocytes enable the body to remember antigens and to distinguish self from nonself (foreign). Lymphocytes circulate in the bloodstream and lymphatic system and move into tissues as needed.

The immune system can remember every antigen encountered because lymphocytes live a long time—for years or even decades. When lymphocytes encounter an antigen for the second time, they respond quickly, vigorously, and specifically to that particular antigen. This specific immune response is the reason that people do not contract chickenpox or measles more than once and that vaccination can prevent certain disorders.

Lymphocytes include B lymphocytes, T lymphocytes, and natural killer cells (which are involved in nonspecific immunity).

B Lymphocytes: B lymphocytes (B cells) are formed in the bone marrow. B lymphocytes have particular sites (receptors) on their surface where specific antigens can attach. When a B lymphocyte encounters an antigen, the antigen attaches to the receptor, stimulating the B lymphocyte to change into a plasma cell.

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Plasma cells produce antibodies. These antibodies are specific to the antigen that stimulated their production.

T Lymphocytes: T lymphocytes (T cells) are produced in the thymus gland. There, they learn how to distinguish self from nonself. Only the T lymphocytes that tolerate the self-identification molecules are allowed to mature and leave the thymus. Without this training process, T lymphocytes could attack the body's cells and tissues.

Mature T lymphocytes are formed and stored in secondary lymphoid organs (such as the spleen), bone marrow, and lymph nodes. They circulate in the bloodstream and the lymphatic system, where they search for particular foreign or abnormal cells, such as particular bacteria or cells infected by particular viruses. T lymphocytes can attack particular foreign or abnormal cells.

There are different types of T lymphocytes:

- **Killer (cytotoxic) T cells** attach to foreign or abnormal cells (because they recognize the antigens on these cells). Killer T cells kill foreign or abnormal cells by making holes in the cell membrane and injecting enzymes into the cells.
- **Helper T cells** help B lymphocytes recognize and produce antibodies against foreign antigens. Helper T cells also help killer T cells kill foreign or abnormal cells.
- **Suppressor T cells** produce substances that help end the immune response.

Sometimes T lymphocytes—for reasons that are not completely understood—develop without or lose the ability to distinguish self from nonself. The result is an autoimmune disorder, in which the body attacks its own tissues.▲

Dendritic Cells

Dendritic cells develop from monocytes and reside mainly in tissues. Newly developed dendritic cells ingest and break antigens into fragments so that other immune cells can recognize them—an activity called antigen processing. A dendritic cell matures after it is stimulated by cytokines at a site of infection or inflammation. Then, it moves from tissues to the lymph nodes where it shows (presents) the antigen fragments to T lymphocytes, which generate a specific immune response.

Antibodies

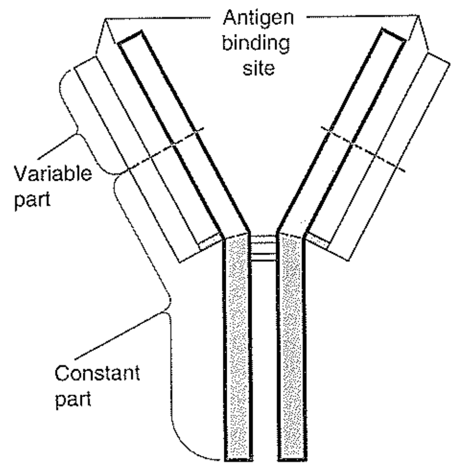
When a B lymphocyte encounters an antigen, it is stimulated to mature into a plasma cell, which then produces antibodies (also called immunoglobulins, or Ig). Antibodies protect the body by helping other immune cells ingest antigens, by inactivating toxic substances produced by bacteria, and by attacking bacteria and viruses directly. Antibodies also activate the complement system. Antibodies are essential for fighting off certain types of bacterial infections.

Each antibody molecule has two parts. One part varies; it is specialized to attach to a specific antigen. The other part is one of five structures, which determines the antibody's class—IgG, IgM, IgD, IgE, or IgA. This part is the same within each class.

IgM: This class of antibody is produced when a particular antigen is encountered for the first time. The response triggered by the

Basic Y Structure of Antibodies

An antibody molecule is basically shaped like a Y. The molecule has two parts. One part varies from antibody to antibody, depending on which antigen the antibody targets. The antigen attaches to the variable part. The other part (constant part) is one of five structures, which determines the antibody's class—IgG, IgM, IgD, IgE, or IgA. This part is the same within each class.



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Strategies for Attack

Different types of invading microorganisms are attacked and destroyed in different ways. Some microorganisms are directly recognized, ingested, and destroyed by phagocytes, such as neutrophils and macrophages. However, phagocytes cannot recognize certain bacteria, because the bacteria are enclosed in a capsule. In these cases, B lymphocytes have to help phagocytes with recognition. B lymphocytes produce antibodies against the antigens contained in the bacteria's capsule. The antibodies attach to the capsules. The phagocyte can then recognize and ingest the whole complex, including the bacteria.

Some microorganisms cannot be completely eliminated. To defend against these microorganisms, the immune system builds a wall around them. The wall is formed when phagocytes, particularly macrophages, adhere to each other. The walled microorganism is called a granuloma. Some bacteria thus imprisoned may survive in the body indefinitely. If the immune system is weakened (even 50 or 60 years later), the walls of the granuloma may crumble, and the bacteria may start to multiply, producing symptoms.

first encounter with an antigen is called the primary antibody response. Normally, IgM is present in the bloodstream but not in the tissues.

IgG: The most prevalent class of antibody, IgG is produced when a particular antigen is encountered again. This response is called the secondary antibody response. It is faster and results in more antibodies than the primary antibody response. IgG is present in the bloodstream and tissues. It is the only class of antibody that crosses the placenta from mother to fetus. The mother's IgG protects the fetus and infant until the infant's immune system can produce its own antibodies.

IgA: These antibodies help defend against the invasion of microorganisms through body surfaces lined with a mucous membrane, including those of the nose, eyes, lungs, and digestive tract. IgA is present in the bloodstream, in secretions produced by mucous membranes, and in breast milk.

IgE: These antibodies trigger immediate allergic reactions.▲ IgE binds to basophils (a type of white blood cell) in the bloodstream and mast cells in tissues. When basophils or mast cells with IgE bound to them encounter allergens (antigens that cause allergic reactions), they release substances that cause inflammation and damage surrounding tissues. Thus, IgE is the only class of antibody that often seems to do more harm than good. However, IgE may help defend against certain parasitic infections that are common in some developing countries.

IgD: Small amounts of these antibodies are present in the bloodstream. The function of IgD is not well understood.

Effects of Aging

The immune system changes throughout life. At birth, specific immunity is not fully developed. However, newborns have some antibodies, which crossed the placenta from the mother during pregnancy. These antibodies protect newborns against infections until their own immune system fully develops. Breastfed newborns also receive antibodies from the mother in the breast milk.

As people age, the immune system becomes less effective. It becomes less able to distinguish self from nonself. As a result, autoimmune disorders become more common. Macrophages destroy bacteria, cancer cells, and other antigens more slowly. This slowdown may be one reason that cancer is more common among older people. T lymphocytes respond less quickly to antigens, and there are fewer lymphocytes capable of responding to new antigens. Thus, when older people encounter a new antigen, the body is less able to recognize and defend against it.

Older people have smaller amounts of complement proteins than younger people, especially during bacterial infections. The amount of antibody produced in response to an antigen and the antibody's ability to attach to the antigen are reduced. These changes may partly explain why pneumonia, influenza, infectious endocarditis, and tetanus are more common among older people and result in death more often. Also, vaccines are less likely to produce immunity in older people.

These changes in immune function may contribute to the greater susceptibility of older people to some infections and cancers.

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