infoaging guides

BIOLOGY OF AGING

IMMUNE RESPONSE

An introduction to aging science brought to you by the American Federation for Aging Research

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The immune system is composed of an interdependent set of organs and cells, as well as the proteins and other chemicals they produce. Following is a brief review of what these components are and what they do.

ORGANS OF THE IMMUNE SYSTEM

Skin and mucous membranes
The skin is a critical barrier that helps to prevent invasion by germs and foreign substances. The various mucous membranes that come into contact with the outside world also serve to protect against invasion. Saliva, tears, and mucus contain antibacterial substances. The small hairs or cilia that line the trachea (windpipe) beat upwards to move foreign matter that has been inhaled back out of the respiratory tract. Germ-killing cells line the mucous membranes and skin and prevent germs from establishing themselves as infections. Also, mucous membranes, and in particular the those in the gut, are densely populated by useful microorganisms (gut flora), which not only help us digest food and maintain health but also serve as a barrier against harmful microorganisms.

Lymphatic system
Lymph is a clear, watery fluid which bathes cells of the body and carries nutrients to them. After supplying the cells with essential substances, lymph collects waste and foreign materials and conveys them to the lymphatics, vessels that lead to the lymph nodes. After being filtered through the lymph nodes, lymph re-enters the blood stream as plasma. This liquid part of the blood is composed of lymph, rather than of red and white blood cells. Plasma carries nutrients from the blood to the cells.

Lymph nodes
These small oval structures are found along the lymphatic system. Immune cells collect in them, and they filter out foreign substances. In inflammation and infection, they enlarge and are sometimes referred to as "swollen glands." They enlarge because the immune cells in them divide very rapidly, in order to multiply and defeat infection.

Thymus
The thymus is an organ in the chest, under the breastbone. It produces immune cells called T cells and is important in their maturation. The thymus is critical for the development of the immune system of infants. It also has important functions in adult immunity, but adults can live without a thymus. The thymus drastically shrinks with age and produces only very small numbers of new T cells after puberty, potentially setting the stage for T-cell aging. New research shows that while adults can live without the thymus, removing thymus in early childhood may accelerate the decline in immunity with aging.

Spleen
The spleen is an organ in the upper left quadrant of the abdomen that filters out foreign cells. It is an important containment area for white blood cells called lymphocytes. It is particularly important in protecting against infection with certain bacteria, such as *Pneumococcus*, that have cell capsules—anatomical structures, layered over the bacteria's cell wall. Cell capsules make germs slippery and harder to kill. While a person can live without a spleen, he or she would be at a higher risk of developing certain infections.

Bone marrow
The bone marrow is the home of blood stem cells, the cells that give rise to the various circulating blood cells. The marrow produces red blood cells, which carry oxygen to our tissues, and platelets, small cells critical for proper blood clotting. The marrow also produces white blood cells, of which there are several different kinds, including B cells (B lymphocytes), which make antibodies. White blood cells are the critical immune cells of the body.

CELLS OF THE IMMUNE SYSTEM

The various white blood cells include granulocytes, lymphocytes, and monocytes.

Granulocytes
These constitute about half of your circulating white blood cells. They contain granules, or little spots visible under a microscope. Types of granulocytes include:

- *Neutrophils*
  These are the most common white cells we have. They live less than a day, and their job is to react immediately to the presence of foreign matter. They locate the foreign matter through chemotaxis, a response to the release of chemicals in the presence of foreign substances. They will surround a germ or foreign body (such as a splinter), engulf it, and release other chemicals such as hydrogen peroxide to destroy it. Pus is simply a large volume of dead neutrophils and foreign matter.

- *Eosinophils*
  These granulocytes account for one to three percent of all white cells in the blood. Their numbers rise in the presence of certain parasites. However, in the absence of parasites,

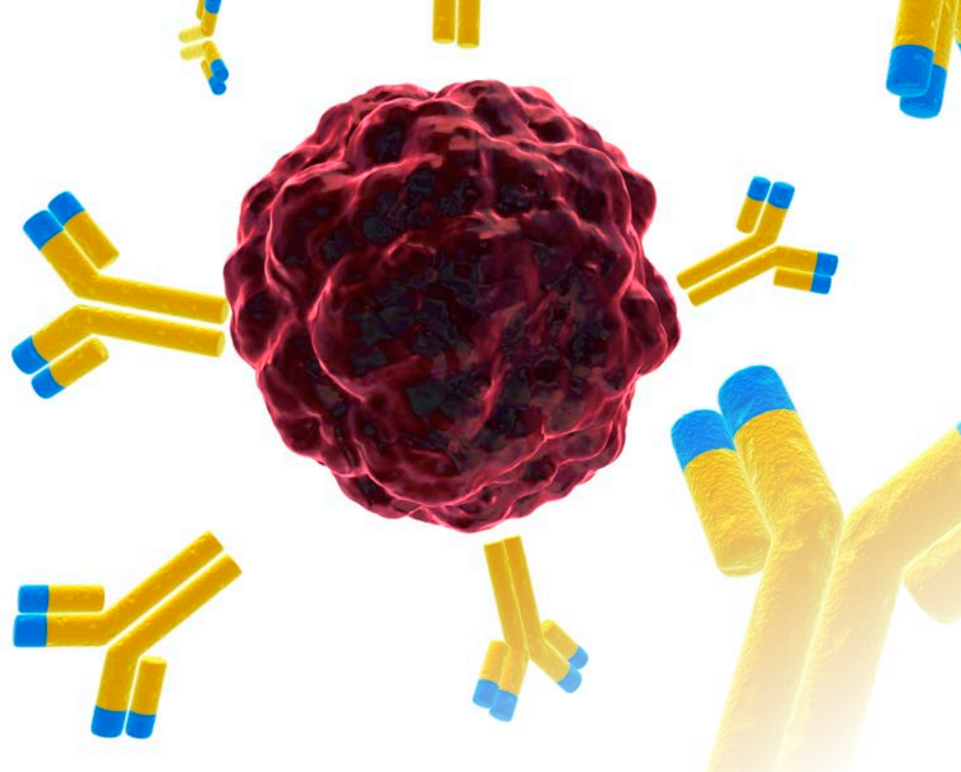
hey also participate in allergic responses.

- *Basophils*
  These cells carry the chemical histamine, the source of the woes associated with allergies (hence the value of antihistamines). They participate in inflammation.

Lymphocytes
These white blood cells are called into action to defeat bacterial and viral infections. There are two major categories of lymphocytes: B lymphocytes and T lymphocytes, often called simply B cells and T cells. Unlike granulocytes and monocytes, which will respond to any infection, each T or B cell is highly specific and will respond only to one or a handful of similar microorganisms.

- *B cells*
  B cells mature in the bone marrow. They "recognize" specific microorganisms, (i.e. bacteria , viruses, etc.), and in the presence of those specific organisms, reproduce rapidly as identical clones. B cells eventually mature into plasma cells, which are responsible for producing antibodies, infection-fighting proteins also specific to the particular germs that have invaded the body.

- *T cells*
  T cells. T cells also come in subcategories. The two main types are the killer (or cytotoxic) T cells, which can kill tumor cells and virus-infected cells, and helper T cells, which provide help to the killer T cells, to B cells, and to macrophages (see below). Some T cells also serve as regulators to stop immune responses before they go too far. Like B cells, they "recognize" specific microorganisms.



Antibodies are shaped like the letter Y. The very tips of the arms of the Y vary and can stick to the foreign invader at which they are aimed.

Monocytes
These cells are produced in the bone marrow and released into the circulatory system. They make their way to various organs in the body and mature into macrophages. Macrophages "eat" foreign matter such as bacteria, parasites, inhaled fibers and dusts, and anything else they find in organs that does not belong there, including pus. Unlike neutrophils, they are hardier and much larger, able to "eat" more efficiently and without being destroyed themselves in the process.

PROTEINS AND CHEMICALS OF THE IMMUNE SYSTEM

The various immune cells make a variety of proteins and chemicals that are also important components of the immune and inflammatory responses. These include:

Antibodies or immunoglobulin
Antibodies are proteins, made by B cells, shaped like the letter Y. There are five major forms of antibodies or immunoglobulin (abbreviated Ig): IgG, IgD, IgE, IgA, and IgM. The base of the Y-shaped protein is similar for all molecules within these five categories. The very tips of the arms of the Y vary and can stick to the foreign invader at which they are aimed, making them easier for macrophages to find.

- *IgD*
  This immunoglobulin is found on the surface of B cells and is involved in activating them to participate in the immune response.

- *IgE*
  This immunoglobulin participates in the allergic response.

- *IgA*
  IgA molecules generally come in pairs and are found in body secretions, such as saliva. They are also found inside the stomach and intestines.

- *IgM*
  IgM molecules gather in clusters and are involved in killing bacteria.

Cytokines and chemokines
These are chemicals that are secreted by cells of the immune system. Chemokines are chemical messengers that recruit other immune cells to where they are needed to fight infection and even cancers. Cytokines are used to augment or diminish the immune response and inflammation, and some can also directly kill or inhibit germs. Because they communicate between white blood cells, also called leukocytes, cytokines are sometimes called interleukins.

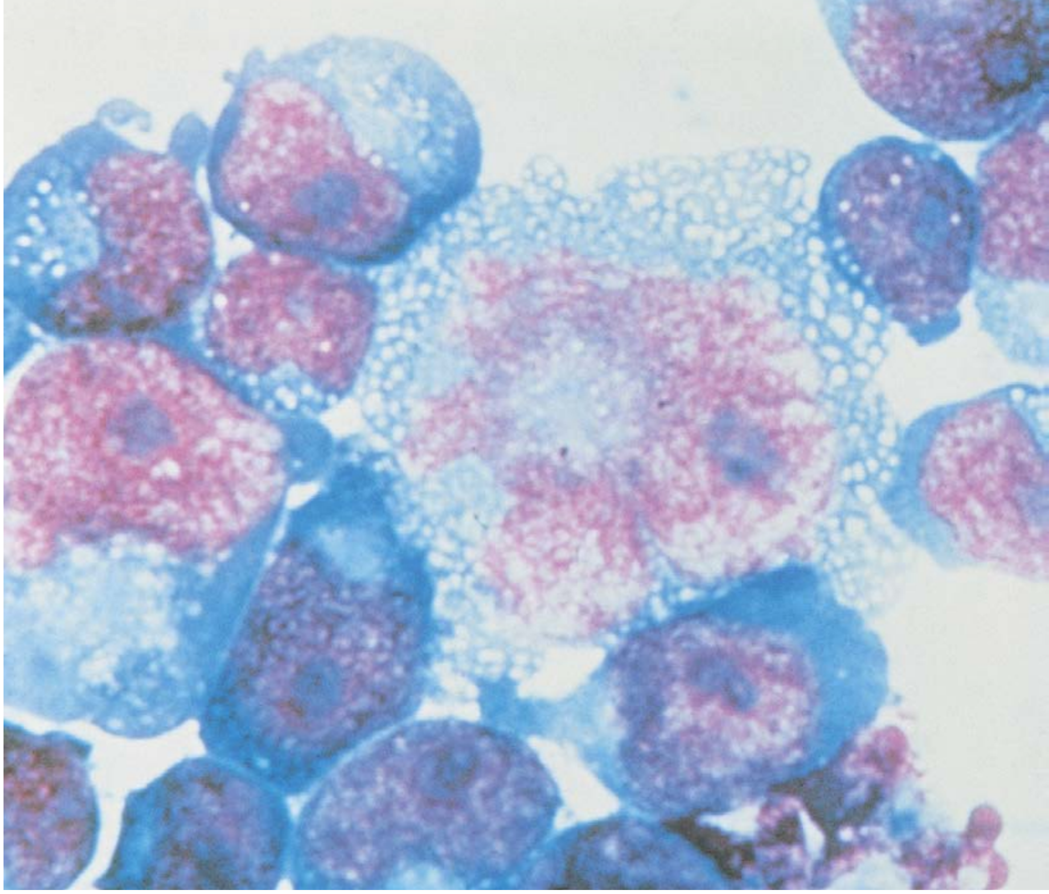
Complement proteins
These proteins are manufactured in the liver. They circulate in the bloodstream and are activated by the presence of antibodies (thus they complement their activity). They act to puncture and thus burst, or lyse, foreign cells.

Antigens
Antigens are the chemicals on the surfaces of microorganisms or foreign cells that are recognized by the immune system. Antibodies are created to specific antigens. B cells have antigen-receptor sites on their surfaces, which are proteins that recognize those antigens. T cells have more sophisticated antigen-sensing systems and do not recognize "naked" antigen. Instead, they recognize chopped pieces of an antigen that has been processed by other immune cells.

IMMUNE-RELATED DISEASES

There are a few diseases that are related to disorders within the immune system. Among these are:

The human immunodeficiency virus, or HIV, destroys helper T cells, limiting the body's ability to fight infection.



Autoimmune disease
The loss of the recognition of some body tissue as "self" is part of autoimmune disease. Antibodies and T cells attack the body's own tissue. Some examples of this include some forms of diabetes, rheumatoid arthritis, and lupus.

Immune complex disease
Normally, the clumps of antibodies and antigens that form as we fight infection or invasion are cleared from the circulation and destroyed. If that clearance does not occur, those clumps can lodge in tissues or small blood vessels and cause damage.

AIDS
The human immunodeficiency virus or HIV destroys helper T cells, limiting the body's ability to fight infection.

Cancer and its treatments
Cancer is a disease of out-of-control cell proliferation. Sometimes this disease becomes manifest because of a failure of the immune system to destroy cancerous cells. Also, chemotherapy and radiation given to people with cancer can destroy or weaken the cells and organs of the immune system as an inadvertent side effect, and this can reduce our resistance to infection. Boosting the ability of the immune system to fight cancer is one of the newest forms of anticancer therapy.

CHARACTERIZATION OF IMMUNE RESPONSE

Scientists characterize the immune response based on which aspects of it they are studying. Those aspects include:

Innate immunity
This is the nonspecific part of immunity, or the generalized response the body has to the presence of an invader. But innate immunity also alerts the T and B cells that they should mount an immune response to eradicate infection.

Adaptive or acquired immunity
This refers to the very specific response that comes in the presence of specific antigens. This includes the recruitment of B cells that make the antibodies aimed at those antigens, and activated T cells that also recognize the specific invader. While very specific, adaptive immunity also takes much longer to develop than the nearly immediate innate immunity. Thus, very often, innate immunity holds and slows down the germ until adaptive immune response develops and is ready to eradicate the infection.

Humoral immunity
This describes the production of antibodies by B cells.

Cellular immunity
This refers to the immunity that is controlled by T cells.

Mucosal immunity
This is a term that refers to the immune cells and tissues found within the mucous membranes (mouth, intestines).

Allergic reactivity
This is the immune system's response to allergens, substances such as pollen or foods that incite an inflammatory response.

AGE-RELATED CHANGES IN THE IMMUNE SYSTEM

Some scientists refer to immune senescence, a term that describes the progressive decline in function of the immune system with age. Various aspects of the immune system respond to aging in different ways. While some components lose function, others increase function inappropriately.

Natural, or innate, immunity and aging
One component of natural immunity is the macrophage, the cell whose job it is to engulf and destroy invading cells. With aging, the balance between the macrophages that enhance the immune response and the ones that suppress it is altered, and suppressive macrophages tend to dominate. Also, weak T cells in older adults can slow the activation of macrophages. Neutrophil function declines with aging, and they are not able to destroy as many microorganisms. Dendritic cells are a cell type that senses infection, picks up the germ, and fragments it to activate T-cells. It is unclear at the present whether and to what extent aging impairs their function.

Adaptive immunity and aging
The thymus gland is the organ in the chest that assists in the maturation of T cells. The thymus involutes, or shrinks, and these changes are already evident by puberty. As we mature, the thymus can become nonfunctional by age 50 to 60. How significant this is to immunity in old age is under investigation. How significant this is to immunity in old age is under investigation. While many T cells are made by the thymus before the thymus shrinks and involutes, the problem remains how to maintain these cells for six to seven decades or longer. There is compelling evidence that the naive T cells, which are made by

We might be fortunate enough to outgrow our allergies as we age.

the thymus, disappear in old age; also, these cells protect against new infection, and it is precisely those infections (a new strain of flu or a new germ we have not seen before, such as the West Nile virus or SARS) that are most dangerous to older adults. Rejuvenation of the thymus is therefore regarded by some as the "holy grail" of preventing immune decline in old age.

Older adults not only produce fewer T helper cells, but the ones they do have are often less effective than they were in earlier life. Others show aberrant function.

Finally, it appears that many autoimmune diseases arise in older adults, though the incidence of new cases likely peaks in our 30s and 40s. The immune system's ability not to attack "self" diminishes as we age, and we can begin to produce autoimmune antibodies. This may be due to age-related changes that take place within cells, such as oxidative damage from free radicals and glycation, the inappropriate insertion of glucose (sugar molecules) into DNA and other cell components. Such small changes to our cells may cause our immune systems to fail to recognize them as our own, and lead to the production of auto-antibodies. It is not clear whether these auto-antibodies produce disease as often in older adults as they do in younger adults.

MUCOSAL IMMUNITY AND AGING

IIn humans, the production of antibodies by cells located in mucosal tissues, such as those found in the mouth and intestines, falls with age, reducing mucosal immunity. Also, changes occur in the normal gut flora, so that different bacteria less compatible with health now colonize the gut (and possibly other mucosal membranes).

Vaccines are available to protect against some infectious diseases that are particularly deadly for older adults.

ALLERGIC RESPONSE AND AGING

This is perhaps the only instance in which there is good news for older adults. We tend to produce less IgE, the antibody associated with the allergic response to such items as pollen and animal danders. Thus, we might be fortunate enough to outgrow our allergies as we age.

DISEASES CAUSED BY CHANGES IN THE IMMUNE SYSTEM

In addition to autoimmune diseases (described above) other types of diseases also become more prevalent as we grow older because of our aging immune systems.

Infectious diseases
Immune senescence can permit the reactivation of old infections, such as Herpes zoster or shingles, which is caused by the chicken pox virus. Immune senescence can also cause the reactivation of latent tuberculosis.

The decline in adaptive immunity can cause infectious agents to be far more potent in older adults than in younger people. This is seen in the high death rates associated with pneumonia and influenza in older adults.

Other physical changes associated with aging contribute to the decline in resistance to infection. These include the decreased cough reflex, which allows bacteria entry into the lungs, and changes in kidney function, and in men, prostate enlargement, which can lead to an increased risk of urinary tract infections. Loss of the ability to secrete acid in the stomach in older adults can also predispose the digestive tract to certain infections.

Cancer
There is speculation that the increasing incidence of cancer in aging adults may be related to the decreased ability of the aging immune system to recognize and destroy cancerous cells before they proliferate to uncontrollable levels.

VACCINES FOR AGE-RELATED DISEASES

No vaccines yet exist for heart disease, diabetes, cancer, Alzheimer's disease, or other diseases most often associated with aging, although vaccines for Alzheimer's disease and certain types of cancer are in development. Fortunately, vaccines are available to protect against some infectious diseases that are particularly deadly for older adults. Unfortunately, even the best current vaccines are less effective in older adults. Among them are:

Pneumococcal vaccine
The Pneumococcus bacterium (*Streptococcus pneumoniae*) is the major cause of bacterial pneumonia. It can be lethal in older adults (and in some younger ones as well). Pneumococcus is called an encapsulated organism, and such organisms can be filtered out of the bloodstream by the spleen. The pneumococcal vaccine protects against 23 different forms of pneumococcus. When it was first used, it covered fewer subtypes, and its protection was thought to be lifelong. We know now that the duration of protection by that vaccine is more limited, and older adults at particular risk should be revaccinated. Those at particular risk include those with diabetes and other chronic illnesses that can reduce immune response.

Influenza vaccine
Influenza (the flu) is caused by a virus. How deadly the flu virus is depends on what strain is passing through a population in a given year, and the immune strength of those who contract the illness. The most infamous influenza outbreak occurred in 1918 and killed somewhere between 20 and 40 million people worldwide.

The flu vaccine is an annual vaccination. That is, a new vaccine is developed each year in response to the variant of the virus that has arisen for that year; thus, individuals need re-inoculation every year.

Tetanus
Tetanus, a bacterial infection, can be deadly, especially in older adults. The vaccine against tetanus is given in multiple doses in infancy, with boosters given about every ten years in adults. It is important for older adults to remain up to date on tetanus vaccinations, since loss of sensation in the feet, as can happen with diabetes or poor circulation, can mean that a dirty wound may go unnoticed, increasing the risk for the tetanus bacterium to penetrate broken skin.

Of all the vaccines above, not a single one has been produced to protect older adults specifically and take into account the changes occurring in an aging immune system. As we now have more knowledge about the challenges that can plague an old immune system, we should be able to improve the above vaccines and generate new ones, that will be tailored specifically for seniors.

AUTOIMMUNITY AND AGING

Autoimmunity refers to the unfortunate phenomenon in which our bodies start attacking our own organs and cells as if they were foreign materials. Research suggests that autoimmunity increases as we age, though the incidence of new autoimmune diseases peaks in middle age.

Autoimmune diseases
There are a great many autoimmune diseases that can occur when the human immune system turns on itself. Some of these include rheumatoid arthritis, lupus, autoimmune thyroiditis, polymyalgia rheumatica, giant cell arteritis, and a host of others with long, often difficult-to-pronounce names.

Some of the autoimmune diseases seen more commonly among older adults include polymyalgia rheumatica, which produces joint and muscle pains, and temporal arteritis, an inflammatory problem that damages the arteries near the temples. While rheumatoid arthritis can occur in young adults, there is a recognized, late-onset rheumatoid arthritis as well.

Many scientists recommend that the best diet comprises a wide variety of fruits and vegetables, which contain natural antioxidants.

Some background

Antibodies are proteins our immune system makes to attack foreign substances, such as bacteria and viruses.

Auto-antibodies are immune proteins that we mistakenly make against some part of ourselves. We can sometimes erroneously make antibodies against our own DNA (anti-nuclear antibodies or ANA); our own mitochondria, the powerhouses of our cells (AMA); and cells in our stomachs called parietal cells (PCA), among other tissues. When these auto-antibodies are organ-specific, they attack our organs and cause disease. When they are not organ-specific, they appear to circulate harmlessly in our blood.

Aging-related changes

In a small study that compared younger subjects (under age 60) to older adults (up to age 93) and centenarians (six men and 20 women, ages 101 to 106), scientists in Palermo, Italy, found that organ-specific auto-antibodies, the ones that can cause clinically significant disease, are found at the highest rate among the older adults. Centenarians had about the same number of organ-specific auto-antibodies as the younger subjects. Non-organ-specific auto-antibodies, however, were found at relatively high levels among the centenarians. The study suggests a provocative theory: that those older adults with organ-specific auto-antibodies are less likely to survive to become centenarians. The authors also speculate that the non-organ specific auto-antibodies the centenarians have were not made to attack native tissue erroneously, but perhaps were made in response to damage in those tissues as a result of aging. More research, of course, is needed to further clarify these ideas.

Boosting the immune system as we age

Many experimenters have attempted to boost immunity through a variety of interventions. Most research into adding vitamin and antioxidant supplements to the diet has not shown that these supplements improve immunity. It is clear, however, that malnutrition contributes to the depression of the immune response. Thus, many scientists recommend that the best diet, for a variety of reasons—perhaps including maintaining immune response—comprises a wide variety of fruits and vegetables, which contain natural antioxidants.

Other lifestyle changes can improve immune function, as well. For example, it is never too late to quit smoking. Smoking raises the risk of a variety of infectious diseases, such as pneumonia and bronchitis, as well as a whole raft of age-related diseases and conditions including heart disease and cancer.

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