BTY 203 IMMUNOLOGY

UNIT 1

Organs of immune system

An extensive network of tissues, organs, proteins, and cells make up the body's immune system.

An immune system working correctly can distinguish healthy tissue and foreign objects. It will initiate a complex attack to defend the body from invaders if it identifies an unwanted element. Also, it detects and removes damaged and dead cells.

But, the immune system is not always reliable. For example, when a person has a medical condition or needs medications that alter how the system functions, it may be unable to fight efficiently.

In autoimmune disorders and allergies, the immune system misinterprets healthy tissue and starts an unwanted attack, resulting in painful and life-threatening symptoms.
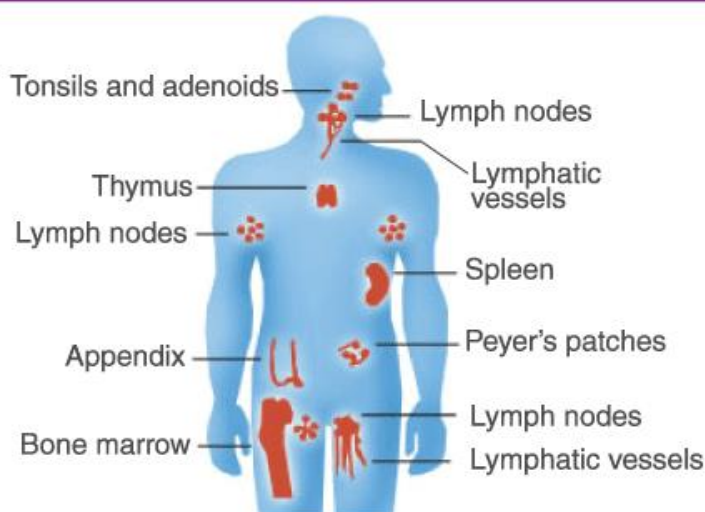
n general, exposure to many pathogens strengthens the immune system. By adulthood, most people will have been exposed to several pathogens and strengthened their immune systems.

When the body creates an antibody, it stores a copy so that it can respond more quickly the next time the same antigen surfaces.

The immune system is composed of two basic parts:

    1.**The innate immune system:** Individuals are born with this immune system.

    2.**The adaptive immune system:** Individuals develop this immunity when exposed to organisms or chemicals released by microorganisms.

The Innate Immune System

People have some immunity from birth, ready to fight against invaders immediately.

The external barriers of our body, which serve as the first line of defence against pathogens, such as the skin and gut and throat mucous membranes, are a part of our innate immunity.

This response is non-specific and generic.

Macrophages will engage in combat with infections if they can evade the innate immune system. In addition, cytokines produced by macrophages help the body respond to inflammation.

The Adaptive (Acquired) Immune System

The ability to defend against infections improves over time.

The body produces a variety of antibodies to various pathogens due to immunisations and exposure to various diseases. Immunological memory is a term used by doctors to describe this condition when the immune system recalls earlier enemies.
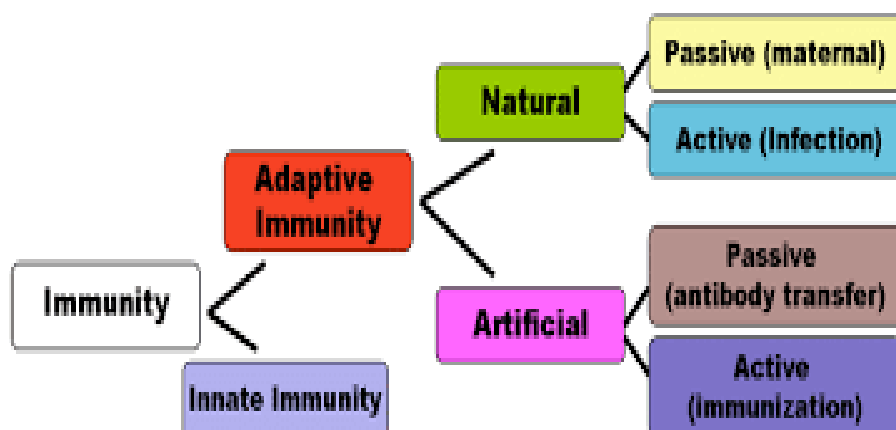
Active Immunity

Active immunity involves the body's immediate reaction to a foreign antigen. The body keeps track of the infections it has already encountered in the acquired or adaptive immune system. This is a direct effect of the active immune system.

We develop active immunity when we contact the pathogen or its antigen. When a pathogen enters the body for the first time, some antibodies that combat it are stored in case the pathogen attacks again. This is referred to as natural active immunity.

Passive Immunity

Antibodies acquired from outside the body trigger an immunological response known as passive immunity. The first encounter with a disease is always a little tough on the body because the body's initial response to it is relatively weak.

This sort of immunity is temporary and comes from a third party. For instance, a newborn acquires antibodies from their mother through the placenta before birth and breast milk after birth.

This passive immunity protects infants from several infections throughout their early years.
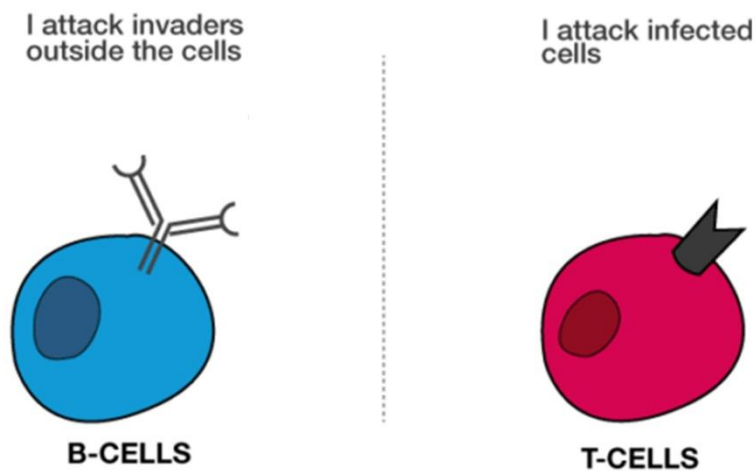
Organs of the Immune System

The thymus and bone marrow are important primary lymphoid organs. Secondary lymphatic tissues like the spleen, lymph arteries, tonsils, lymph nodes, skin, adenoids, and liver are all important parts of the immune system.

Primary Lymphoid Organs

The primary sites of lymphocyte development, or lymphopoiesis, are known as primary lymphoid organs (PLO). Lymphocytes develop from lymphoid stem cells, multiply, and mature into useful cells known as immuno-competent cells. B-cell maturation occurs in the bone marrow of animals, whereas T-cell maturation occurs in the thymus.

Thymus

This tiny organ, located in the upper chest below the breast bone, helps to mature a particular type of white blood cell. The particular task of this cell is to recognise and memorise an intruder so that a counter-attack can be easily mounted the next time this intruder attacks.

The thymus provides an inductive environment for forming T lymphocytes from haematopoietic stem cells. Thymic stromal cells also enable the selection of a useful and self-tolerant T cell repertoire. As a result, the thymus' induction of central tolerance is one of its most significant functions.

Bone Marrow

Red blood cells, plasma cells, several types of white blood cells, and other immune cells are all produced from stem cells found in the spongy interior of the bones. Every day, the bone marrow produces billions of new blood cells and releases them into the blood.

The primary site of B-cell maturation and propagation in adults is the bone marrow, where all other circulating blood cells are produced. The process of producing all blood cells throughout foetal development is known as haematopoiesis. It first occurs in the blood island of the yolk sac and para-aortic mesenchyme, followed by the liver and spleen.

Secondary Lymphoid Organs

In addition to the primary lymphoid organs, there are a few other lymphoid organs known as secondary lymphoid organs. The spleen and lymph nodes are the two most significant and well-organised secondary lymphoid organs.

The secondary (or peripheral) lymphoid organs (SLO) sustain and initiate an adaptive immune response. Antigen-induced lymphocyte activation takes place in the secondary lymphoid organs. Until they come into contact with their particular antigen, mature lymphocytes travel back and forth between the blood and secondary lymphoid organs. Clonal growth and affinity maturation are produced by activation.

Lymph Nodes

The network of lymphatic channels (also known as lymphatic vessels) and lymph nodes are connected by lymphatic nodes.

Immune cells found in lymph nodes examine foreign pathogens introduced into the body. These tiny glands filter and kill them to prevent germs from spreading to other body areas. They are a component of the lymphatic system in our body. The individual lymphocytes (white blood cells) are then activated, replicated, and sent to combat that specific invader.

Numerous lymph nodes can be found throughout the body, especially in the groin, armpits, and neck. Lymph nodes that are swollen and painful are a sign that the body is fighting infections.

Spleen

The secondary lymphoid organ, the spleen, is situated high in the left abdominal area. Spleens are designed to filter blood, capture blood-borne antigens, and react to systemic infections.

The primary functions of the spleen are:

- Production of immune cells to fight antigens
- Removal of particulate matter and aged blood cells (red blood cells)
- Production of blood cells during foetal life.

The spleen has primarily efferent lymphatic channels, similar to the thymus. It receives blood from both the splenic artery and the short gastric arteries. The spleen produces antibodies in its white pulp and eliminates antibody-coated blood cells and germs through lymph nodes and blood circulation.

Mucosal-Associated Lymphoid Tissue

Along with lymph nodes, the spleen's mucosal-associated lymphoid tissue (MALT) is also regarded as a secondary lymphoid organ. Lymphoid tissues on a thin layer surround the mucous membranes of the urogenital, respiratory, and digestive systems.

MALTs are designed to produce massive, antibody-producing plasma cells, which are essential for the body's defence mechanism.

Lymphatic Vessels

The lymphatic vessels, also known as lymph vessels, are tubes with thin walls transporting lymph between various body parts. They consist of the tubular lymph capillary vessels, the larger collecting vessels, the right lymphatic duct, and the left lymphatic duct (thoracic duct).

Interstitial fluid in the tissues is mostly absorbed by lymph capillaries, which then move the fluid into larger collecting ducts, where it is ultimately returned to the bloodstream via a subclavian vein.

Other Lymphoid Tissues

To protect the body against infections and the growth of tumours, lymphoid tissue connected to the lymphatic system performs immunological activities. It is made up of connective tissue composed of

reticular fibres (that have a variety of leukocytes or white blood cells, primarily lymphocytes) through which the <u>lymph</u> passes. Lymphoid follicles are areas of lymphoid tissue that are densely filled with lymphocytes.

UNIT-II

MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGEN PRESENTATION AND PROCESSING MECHANISM

Major Histocompatibility Complex Molecules

The major histocompatibility complex (MHC) is a collection of genes coding for MHC molecules found on the surface of all nucleated cells of the body. In humans, the MHC genes are also referred to as human leukocyte antigen (HLA) genes. Mature red blood cells, which lack a nucleus, are the only cells that do not express MHC molecules on their surface.

There are two classes of MHC molecules involved in adaptive immunity, MHC I and MHC II **(Figure 19.11).** MHC I molecules are found on all nucleated cells; they present normal self-antigens as well as abnormal or non-self pathogens to the effector T cells involved in cellular immunity. In contrast, MHC II molecules are only found on macrophages, dendritic cells, and B cells; they present abnormal or non-self pathogen antigens for the initial activation of T cells.

Both types of MHC molecules are transmembrane glycoproteins that assemble as dimers in the cytoplasmic membrane of cells, but their structures are quite different. MHC I molecules are composed of a longer α protein chain coupled with a smaller β_2 microglobulin protein, and only the α chain spans the cytoplasmic membrane. The α chain of the MHC I molecule folds into three separate domains: α_1, α_2 and α_3. MHC II molecules are composed of two protein chains (an α and a β chain) that are approximately similar in length. Both chains of the MHC II molecule possess portions that span the plasma membrane, and each chain folds into two separate domains: α_1 and α_2, and β_1, and β_2. In order to present abnormal or non-self-antigens to T cells, MHC molecules have a cleft that serves as the antigen-binding site near the "top" (or outermost) portion of the MHC-I or MHC-II dimer. For MHC I, the antigen-binding cleft is formed by the α_1 and α_2 domains, whereas for MHC II, the cleft is formed by the α_1 and β_1 domains
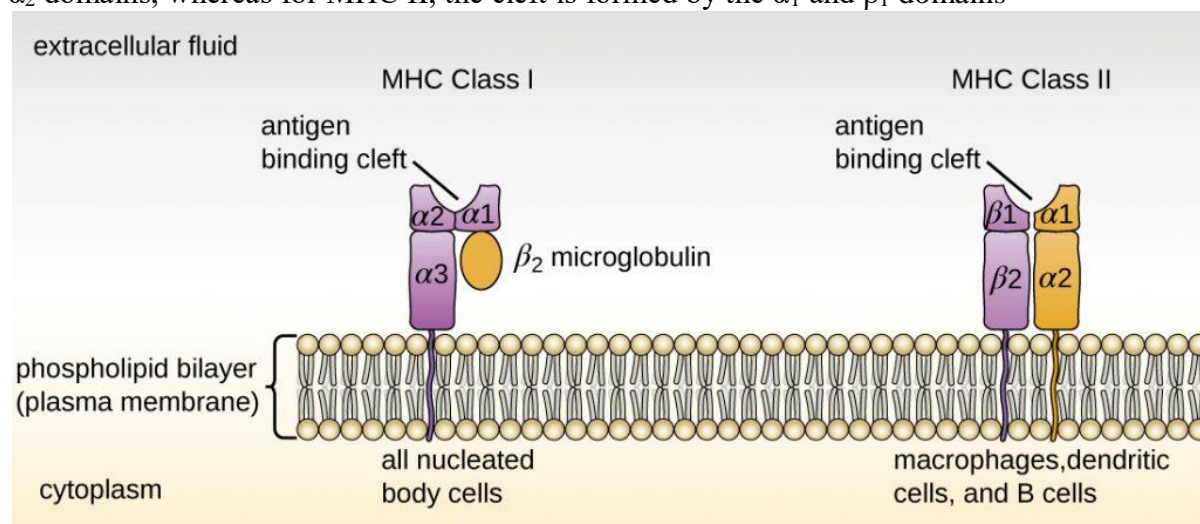
MHC I are found on all nucleated body cells, and MHC II are found on macrophages, dendritic cells, and B cells (along with MHC I). The antigen-binding cleft of MHC I is formed by domains $\alpha1$ and $\alpha2$. The antigen-binding cleft of MHC II is formed by domains $\alpha1$ and $\beta1$.

- Compare the structures of the MHC I and MHC II molecules.

Antigen-Presenting Cells (APCs)

All nucleated cells in the body have mechanisms for processing and presenting antigens in association with MHC molecules. This signals the immune system, indicating whether the cell is normal and healthy or infected with an intracellular pathogen. However, only macrophages, dendritic cells, and B cells have the ability to present antigens specifically for the purpose of activating T cells; for this reason, these types of cells are sometimes referred to as antigen-presenting cells (APCs).
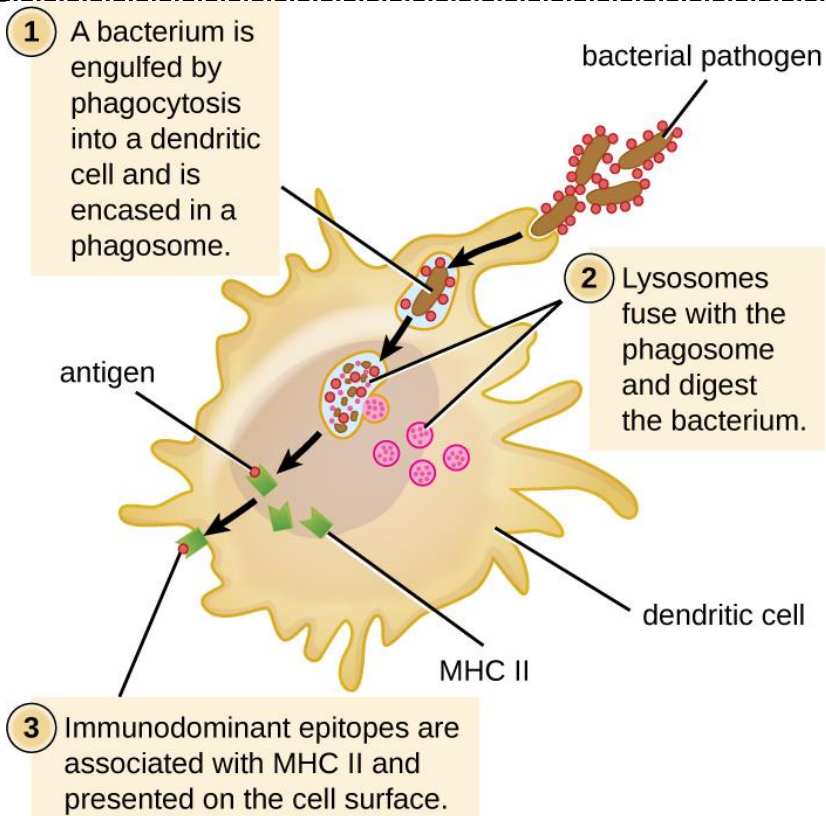
While all APCs play a similar role in adaptive immunity, there are some important differences to consider. Macrophages and dendritic cells are phagocytes that ingest and kill pathogens that penetrate the first-line barriers (i.e., skin and mucous membranes). B cells, on the other hand, do not function as phagocytes but play a primary role in the production and secretion of antibodies. In addition, whereas macrophages and dendritic cells recognize pathogens through nonspecific receptor interactions (e.g., PAMPs, toll-like receptors, and receptors for opsonizing complement or antibody), B cells interact with foreign pathogens or their free antigens using antigen-specific immunoglobulin as receptors (monomeric IgD and IgM). When the immunoglobulin receptors bind to an antigen, the B cell internalizes the antigen by endocytosis before processing and presenting the antigen to T cells.

Antigen Presentation with MHC II Molecules

MHC II molecules are only found on the surface of APCs. Macrophages and dendritic cells use similar mechanisms for processing and presentation of antigens and their epitopes in association with MHC II; B cells use somewhat different mechanisms that will be described further in **B Lymphocytes and Humoral Immunity.** For now, we will focus on the steps of the process as they pertain to dendritic cells.

After a dendritic cell recognizes and attaches to a pathogen cell, the pathogen is internalized by phagocytosis and is initially contained within a phagosome. Lysosomes containing antimicrobial enzymes and chemicals fuse with the phagosome to create a phagolysosome, where degradation of the pathogen for antigen processing begins. Proteases (protein-degrading) are especially important in antigen processing because only protein antigen epitopes are presented to T cells by MHC II

APCs do not present all possible epitopes to T cells; only a selection of the most antigenic or immunodominant epitopes are presented. The mechanism by which epitopes are selected for processing and presentation by an APC is complicated and not well understood; however, once the most antigenic, immunodominant epitopes have been processed, they associate within the antigen-binding cleft of MHC II molecules and are translocated to the cell surface of the dendritic cell for presentation to T cells.

1 A bacterium is engulfed by phagocytosis into a dendritic cell and is encased in a phagosome.

bacterial pathogen

2 Lysosomes fuse with the phagosome and digest the bacterium.

antigen

dendritic cell

MHC II

3 Immunodominant epitopes are associated with MHC II and presented on the cell surface.

A dendritic cell phagocytoses a bacterial cell and brings it into a phagosome. Lysosomes fuse with the phagosome to create a phagolysosome, where antimicrobial chemicals and enzymes degrade the bacterial cell. Proteases process bacterial antigens, and the most antigenic epitopes are selected and presented on the cell's surface in conjunction with MHC II molecules. T cells recognize the presented antigens and are thus activated.

- What are the three kinds of APCs?
- What role to MHC II molecules play in antigen presentation?
- What is the role of antigen presentation in adaptive immunity?

Antigen Presentation with MHC I Molecules

MHC I molecules, found on all normal, healthy, nucleated cells, signal to the immune system that the cell is a normal "self" cell. In a healthy cell, proteins normally found in the cytoplasm are degraded by proteasomes (enzyme complexes responsible for degradation and processing of proteins) and processed into self-antigen epitopes; these self-antigen epitopes bind within the MHC I antigen-binding cleft and are then presented on the cell surface. Immune cells, such as NK cells, recognize these self-antigens and do not target the cell for destruction. However, if a cell becomes infected with an intracellular pathogen (e.g., a virus), protein antigens specific to the pathogen are processed in the proteasomes and bind with MHC I molecules for presentation on the cell surface. This presentation of pathogen-specific antigens with MHC I signals that the infected cell must be targeted for destruction along with the pathogen.

Before elimination of infected cells can begin, APCs must first activate the T cells involved in cellular immunity. If an intracellular pathogen directly infects the cytoplasm of an APC, then the processing and presentation of antigens can occur as described (in proteasomes and on the cell surface with MHC I). However, if the intracellular pathogen does not directly infect APCs, an alternative strategy called cross-presentation is utilized. In cross-presentation, antigens are brought into the APC by mechanisms normally leading to presentation with MHC II (i.e., through phagocytosis), but the antigen is presented on an MHC I

molecule for CD8 T cells. The exact mechanisms by which cross-presentation occur are not yet well understood, but it appears that cross-presentation is primarily a function of dendritic cells and not macrophages or B cells.

- Compare and contrast antigen processing and presentation associated with MHC I and MHC II molecules.
- What is cross-presentation, and when is it likely to occur?

- Major histocompatibility complex (MHC) is a collection of genes coding for glycoprotein molecules expressed on the surface of all nucleated cells.
- MHC I molecules are expressed on all nucleated cells and are essential for presentation of normal "self" antigens. Cells that become infected by intracellular pathogens can present foreign antigens on MHC I as well, marking the infected cell for destruction.
- MHC II molecules are expressed only on the surface of antigen-presenting cells (macrophages, dendritic cells, and B cells). Antigen presentation with MHC II is essential for the activation of T cells.
- Antigen-presenting cells (APCs) primarily ingest pathogens by phagocytosis, destroy them in the phagolysosomes, process the protein antigens, and select the most antigenic/immunodominant epitopes with MHC II for presentation to T cells.
- Cross-presentation is a mechanism of antigen presentation and T-cell activation used by dendritic cells not directly infected by the pathogen; it involves phagocytosis of the pathogen but presentation on MHC I rather than MHC II.

Humoral and cell mediated immunity resonase

Humoral immunity is an antibody-mediated response that occurs when foreign material - <u>antigens</u> - are detected in the body. This foreign material typically includes extracellular invaders such as bacteria. This mechanism is primarily driven by <u>B cell lymphocytes</u>, a type of immune cell that produces antibodies after the detection of a specific antigen.

Naïve B cells are lymphocytes that circulate throughout the body in the lymphatic system. These lymphocytes express a variety of antigen-specific molecules that are essential for the detection of infectious agents in the human body. Whenever naïve B cells encounter an antigen in the lymphatic system, they undergo a differentiation process that leads to the creation of memory B cells and effector B cells.

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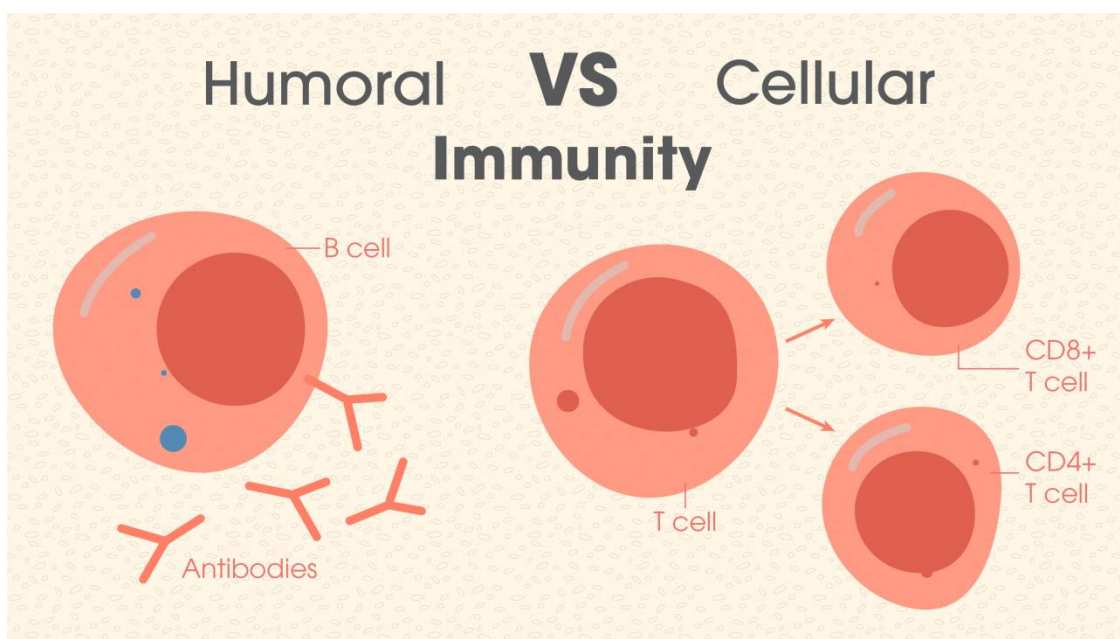
During this underlined differentiation, memory B cells and effector B cells produce the same antigen-specific molecules as their parent naïve B cell. With the help of T cell lymphocytes, in turn activated by MHC class II receptors that recognize microbial-associated antigens, the activated memory B cells express these antigen-specific molecules on their surface while the effector B cells secrete these molecules in the blood to bind the antigen of interest.

What is cell-mediated immunity?

Unlike humoral immunity, **cell-mediated immunity** does not depend on antibodies for its adaptive immune functions. Cell-mediated immunity is primarily driven by mature T cells, macrophages, and the release of cytokines in response to an antigen.

T cells involved in cell-mediated immunity rely on antigen-presenting cells that contain membrane-bound MHC class I proteins in order to recognize intracellular target antigens. The binding specificity between MHC proteins and foreign antigens is essential for the maturation and differentiation of naïve T cells into helper or killer T cells.

Cell-mediated immunity typically comes into play at body sites where cells are infected by a virus, bacteria, or fungi (intracellular invaders). With the assistance of MHC class I proteins, T cells can also recognize cancerous cells.

What lymphocytes are involved in cell-mediated immunity?

The main types of lymphocytes involved in cell-mediated immunity include naïve T cells, helper T cells, killer T cells, and macrophages. Naïve T cells, which have not yet become activated, circulate in the bloodstream and the lymphatic system. When they encounter an antigen-presenting cell, these naïve cells become activated, rapidly proliferating into different T-cell subsets. These subsets perform different functions – CD4+ helper T cells, for example, release a set of signaling proteins called cytokines. These cytokines can damage the target cell directly or help activate "killer" T cells and macrophages. CD8+ killer T cells, also called cytotoxic T cells, perform direct lysis of target cells, while macrophages, which are a type of antigen-presenting cell, also play an important role in T-cell activation.

Humoral vs cell-mediated immunity: table

	Humoral	**Cell Mediated**
Type	Antibody-mediated response	T cell-mediated response
Site of Activity	Extracellular fluids	Location of antigen-presenting tissue
Main Cell Types Involved	B cells	T cells
Speed of Onset	Fast response upon detection	Slow response
Antigen Type	Extracellular pathogens	Intracellular pathogens, cancer

		cells
Method of Removal	Antibody-mediated destruction or neutralization	Cell lysis and programed death
MHC Proteins Involved	MHC class II proteins	MHC class I proteins

Humoral and Cell-Mediated Immune Responses

The immune system distinguishes two groups of foreign substances. One group consists of antigens that are freely circulating in the body. These include molecules, viruses, and foreign cells. A second group consists of self cells that display aberrant MHC proteins. Aberrant MHC proteins can originate from antigens that have been engulfed and broken down (exogenous antigens) or from virus-infected and tumor cells that are actively synthesizing foreign proteins (endogenous antigens). Depending on the kind of foreign invasion, two different immune responses occur:

The humoral response (or antibody-mediated response) involves B cells that recognize antigens or pathogens that are circulating in the lymph or blood ("humor" is a medieval term for body fluid). The response follows this chain of events:

1. Antigens bind to B cells.
2. Interleukins or helper T cells costimulate B cells. In most cases, both an antigen and a costimulator are required to activate a B cell and initiate B cell proliferation.
3. B cells proliferate and produce plasma cells. The plasma cells bear antibodies with the identical antigen specificity as the antigen receptors of the activated B cells. The antibodies are released and circulate through the body, binding to antigens.
4. B cells produce memory cells. Memory cells provide future immunity.

- The cell-mediated response involves mostly T cells and responds to any cell that displays aberrant MHC markers, including cells invaded by pathogens, tumor cells, or transplanted cells. The following chain of events describes this immune response:

1. Self cells or APCs displaying foreign antigens bind to T cells.
2. Interleukins (secreted by APCs or helper T cells) costimulate activation of T cells.
3. If MHC-I and endogenous antigens are displayed on the plasma membrane, T cells proliferate, producing cytotoxic T cells. Cytotoxic T cells destroy cells displaying the antigens.
4. If MHC-II and exogenous antigens are displayed on the plasma membrane, T cells proliferate, producing helper T cells. Helper T cells release interleukins (and other cytokines), which stimulate B cells to produce antibodies that bind to the antigens and stimulate nonspecific agents (NK and macrophages) to destroy the antigens.

Unit-III

ANTIGEN -ANTIBODY INTERACTIONS AND VARIOUS TECNIQUES

Antigen-antibody reaction or antigen-antibody interaction is a particular chemical interaction between antibodies generated by B cells of the white blood cells and antigens during the immune reaction. The process of agglutination combines antigens and antibodies.

It is the basic biological process that the body uses to defend itself against various foreign particles like viruses and their toxic chemicals. An antigen-antibody complex is formed in the blood when antibodies specifically and strongly bind to antigens. The immunological complex is subsequently transferred to cellular systems where it can be eliminated or deactivated

Antigen (Ag)

(Anti = opposite; gen = anything that causes)

Immunogens are any foreign substances that, once entering our bodies, frequently cause a sequence of immunological responses. While others, known as haptens, require the assistance of other molecules (carrier proteins) to activate an immunological response. All of the immunogens and haptens are referred to as antigens.

- They could be polysaccharides, lipids, proteins, or peptides.
- An epitope is an antibody-binding location.

Antibody (Ab)

An antibody is a component that the immune system produces in response to antigens. Thus, antigens result in the production of antibodies. They act together to exhibit an immunological response. The general characteristics of an antibody are as follows:

- An antibody is also known as an immunoglobulin (Ig)
- They are Y-shaped
- Glycoproteins
- Generated by plasma B-cells.
- Paratope is the name of the antigen binding site.
- Five types: IgG, IgA, IgM, IgE, and IgD.

Antigen-Antibody Reaction

Antigens and antibodies combine specifically with each other. Antigen-Antibody reaction is the term used to describe this interaction between them. Ag-Ab reaction is a common acronym for it. These serve as the building blocks of humoral or antibody-mediated immunity.

These reactions serve as the foundation for the detection of both specific and non-specific Ags, such as enzymes that cause non-specific diseases. Serological reactions are referred to as Ag-Ab reactions when they occur in vitro.

Stages of Antigen-Antibody Reaction

There are three stages to the interactions between Ag and Ab.

- The first stage of the reaction entails the formation of the Ag-Ab complex.
- The second stage results in visible phenomena like agglutination, precipitation, etc.
- The third stage involves the destruction of Ag or neutralisation of Ag.

Properties of Antigen-Antibody Reaction

- Significantly specific reaction
- Occurs in a noticeable manner
- Non-covalent reactions (Ionic bonds, Van der Waals forces, Hydrophobic interactions, Hydrogen bonds)
- Antibodies and antigens are not denatured
- Reversible
- Affinity: This refers to how strongly an antigen binds to a certain antigen-binding site on an antibody.
- Avidity: It is a more general concept than affinity. It represents the Ag-Ab complex's total strength. It depends on:

1. The antibody's affinity
2. Antibody and antigen valencies (the number of binding sites)
3. How epitopes and paratopes are structurally arranged.

- Cross-Reactivity: This term describes an antibody's capacity to bind to similar epitopes on other antigens.

Types of Antigen-Antibody Reaction

The types of antigen-antibody reactions are as follows:

- Precipitation Reaction
- Agglutination Reaction
- Complement Fixation
- Immunofluorescence
- ELISA – Enzyme-Linked ImmunoSorbent Assay

Precipitation Reaction

An insoluble precipitate of Ag-Ab complex is produced when a soluble Ag and its Ab combine in the presence of an electrolyte (NaCl) at a specific pH and temperature. Precipitin is the Ab that causes precipitation, and the reaction is termed a precipitation reaction.

The precipitation reaction occurs in both liquid and gel media.

- **Liquid Precipitation:** An antigen-antibody reaction is carried out by adding increasing amounts of antigen to tubes containing a constant amount of antibody. Precipitation results from the combined reaction of the antigen and antibody.
- **Gel Precipitation:** Petri plates or plates with agar gel or a similar gel are used in these methods. In the gel system, both Ag and Ab rapidly diffuse in all directions. A zone of equivalency, observed as visible precipitation, will form at a specific point depending on the diffusion rate and concentration of reactants.

Multiple bands develop in complex Ag or Ab preparations. They fall into two methods: single diffusion and double diffusion.

Agglutination Reaction

The particles are clustered or agglutinated when a certain Ag is combined with its Ab in the presence of electrolytes at an appropriate temperature and pH. The clumps of cellular Ag formed by the serum's Ab are known as agglutinins.

Agglutinogens are the name for the aggregated particulate antigens.

- **Slide Agglutination:** This is a fast and convenient way to identify the presence of agglutinating antibodies.
- **Tube Agglutination:** This is a common technique for estimating the quantity of Ab. A constant volume of the Ag suspension is introduced after serially diluting the Ab-containing serum with saline in multiple small test tubes.

A control tube is retained that contains no antiserum. The tubes are incubated up until observable agglutination. The tube demonstrating the highest agglutination is known as the titre.

- **Passive Agglutination Test:** This test is equivalent to the haemagglutination test, but the physical characteristics of the reaction are different.

A carrier particle has Ag coated on its surface, making the reaction more sensitive by assisting in the transformation of a precipitation process into an agglutination reaction. RBC, latex particles, or bentonite can be used as carrier particles. Sometimes, tanned RBC (polystyrene coated RBC) might be used.

Complement Fixation

Some non-specific, unstable fresh serum components known as complements are required for the lysis of RBC or microorganisms.

Every person has the 11 proteins that comprise the complement system. They attach to the Fc subunit of Ab in the Ag-Ab complex. Complement fixation tests make use of the Ag-Ab complex's capacity to fix complement.

In the first step, the test Ag and the antiserum, which have been heated to 56°C to inactivate complement, are combined with a known quantity of complement. This is incubated for 18 hours at 4°C.

If the serum contains Ab that is specific for the Ag, an Ag-Ab complex will develop and fix the complement.

Immunofluorescence

Fluorescence is the ability to absorb light rays of a certain wavelength and emit light rays of a different wavelength.

Fluorescent dyes emit intense visible light when exposed to UV radiation.

In 1942, Albert Coons and coworkers demonstrated how labelled dyes could be coupled to antibodies, allowing for the detection of antigens using these labelled dyes.

Commonly used dyes include:

The most used label for immunofluorescence operations is fluorescein, an organic dye that absorbs blue light (490 nm) and emits a strong yellow-green fluorescence (517 nm).

As a strong emitter of red fluorescence and an effective light absorber (30 times more effective than fluorescein), phycoerythrin is often used as a label for immunofluorescence.

ELISA – Enzyme-Linked Immunosorbent Assay

In 1971, enzyme-labelled Ag's and Ab's were created as serological reagents for the testing of antibodies and antigens.

When compared to radioimmunoassay (RIA), they are more simple, sensitive, affordable, and risk-free.

The ligand used is a molecule that is covalently attached to an enzyme like peroxidase, beta-galactosidase, alkaline phosphatase, etc. and is capable of detecting the Ab.

There are three types of ELISA:

- **Indirect ELISA:** HIV can be detected using the indirect ELISA method. The surface of the microtiter plates is coated with envelope proteins developed using recombinant technology. Unbound proteins are washed out when suspect serum is added.
- **Sandwich ELISA:** This method is used for determining whether there is Ag in a sample. The suspect serum is added and given time to react after the well has been coated with Ag-specific Ab. Unbound Ag is removed from the wells through washing.

The next step is to add a labelled Ab against a different Ag epitope. Washing is used to remove unbound Ab's, followed by the addition of coloured substrate and colour development. The colour intensity is directly proportional to the Ag concentration in the serum.

- **Competitive ELISA:** Competitive ELISA is another variant for estimating antigen concentrations. In this method, the antibody is initially incubated in solution with the sample containing the antigen.

What are the Different Types of Vaccines and production vaccine

Vaccines are medications that are used to make people immune to certain diseases. They contain the bacteria or virus, or parts of the bacteria or virus, that cause illness and disease.

The bacteria or virus is included in the vaccine so that the immune system can be taught to recognize and produce antibodies against it if a person is exposed to it naturally, without the person ever experiencing any symptoms of illness or disease.

The main types of vaccines that act in different ways are:

- Live-attenuated vaccines
- Inactivated vaccines
- Subunit, recombinant, conjugate, and polysaccharide vaccines
- Toxoid vaccines
- mRNA vaccines
- Viral vector vaccines

There is a risk of side effects with all vaccines, but some are less likely to cause side effects than others.

Live-attenuated vaccines

Live-attenuated vaccines inject a live version of the germ or virus that causes a disease into the body. Although the germ is a live specimen, it is a weakened version that does not cause any symptoms of infection as it is unable to reproduce once it is in the body.

Live-attenuated vaccines can be made to create immunity against viruses or bacteria, but they are more commonly used for viruses.

This type of vaccine works by allowing a virus or germ to reproduce enough for the body to make memory B-cells, which are a type of cell that can recognize and remember a virus and generate an immune response against it for many years after their initial response.

Live-attenuated vaccines trigger an immune response that is similar to what would occur during a natural infection, but the person is not able to pass on the virus to other people and will not become ill with the disease the virus causes.

A person will usually get lifelong immunity from disease through live-attenuated vaccines, and only one or two doses of the vaccine are usually needed to provide this immunity.

The types of diseases that live-attenuated vaccines are used for include:

- Measles, mumps, and rubella (MMR combined vaccine)
- Rotavirus
- Smallpox
- Chickenpox
- Yellow fever

As a live version of the virus or bacteria is included in this type of vaccine, medical advice should be sought before the vaccine is given as it may not be suitable for people with weakened immune systems or long-term health conditions.

Live-attenuated vaccines also need to be kept cool while they are stored, so they may not be suitable for use in environments where there is little access to refrigeration.

Inactivated vaccines

An inactivated vaccine uses a strain of a bacteria or virus that has been killed with heat or chemicals. This dead version of the virus or bacteria is then injected into the body.

Inactivated vaccines are the earliest type of vaccine to be produced, and they do not trigger an immune response that is as strong as that triggered by live-attenuated vaccines.

Inactivated vaccines do not offer lifelong immunity and need topping up over time, but they may cause fewer side effects than live-attenuated vaccines.

The types of diseases that inactivated vaccines are used for include:

- Hepatitis A
- Flu
- Polio
- Rabies

Subunit, recombinant, conjugate, and polysaccharide vaccines

Subunit, recombinant, conjugate, and polysaccharide vaccines use particular parts of the germ or virus. They can trigger very strong immune responses in the body because they use a specific part of the germ.

Although the immune responses are strong, these types of vaccines may need topping up over time. They are suitable for people with weakened immune systems and long-term health conditions.

These types of vaccines are used to create immunity against the following diseases:

- Hib (Hemophilus influenza type b)
- Hepatitis B
- Human papillomavirus (HPV)
- Whooping cough
- Pneumococcal disease
- Meningococcal disease
- Shingles

Subunit vaccines

Antigens from the surface of the germ or virus are responsible for triggering an immune response in the body. Subunit vaccines isolate specific antigens from a germ or virus for use in the vaccine, and these antigens are specifically chosen according to the strength of the immune response they generate.

Subunit vaccines do not cause many side effects because they are so specifically targeted.

Recombinant vaccines

Recombinant vaccines are made through genetic engineering. The gene that creates the protein for a bacteria or virus is isolated and placed inside another cell's genes. When that cell reproduces, it produces vaccine proteins that mean the immune system will recognize the protein and protect the body against it.

Conjugate vaccines

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Conjugate vaccines use two different components. Conjugate vaccines use parts from the outer antigen coat of the bacteria or virus, which are not strong enough to cause illness or generate an immune response in the body.

These weak antigen coats are linked to a stronger carrier protein using chemicals, and this combination of the weak antigen coat and stronger carrier proteins triggers the immune system to act more aggressively against the weak antigen.

.**Toxoid vaccines**

Toxoid vaccines use toxins created by the bacteria or virus to create immunity to the specific parts of the bacteria or virus that cause disease, and not the entire bacteria or virus. The immune response is focused on this specific toxin.

Toxoid vaccines do not offer lifelong immunity and need to be topped up over time.

Toxoid vaccines are used to create immunity against diphtheria and tetanus.

mRNA vaccines

This technology has been in development for decades. mRNA vaccines have benefits such as short manufacturing times and low manufacturing costs. However, they have to be kept at low temperatures due to the fragility of the mRNA.

mRNA vaccines work by triggering an immune response from proteins they synthesize. They induce both cellular and humoral immunity.

The first mRNA vaccine was approved this year for COVID-19. There is some misinformation that mRNA vaccines can alter a person's DNA. However, they are not able to do this.

Viral vector vaccines

Viral vector vaccines modify another virus and use it as a vector to deliver protection from the intended virus. Some of the viruses used as vectors include adenovirus, influenza, measles virus and vesicular stomatitis virus (VSV).

Recent uses of viral vector technology have been in Ebola virus and COVID-19, and studies into its use for Zika, flu and HIV are ongoing.

DNA and recombinant vector vaccines

DNA and recombinant vector vaccines (also known as platform-based vaccines) are two new types of vaccines currently under development.

DNA vaccines include DNA that creates specific antigens from a germ. Once injected into the body, the DNA for the germ is reproduced by the body and is recognized by the immune system. The immune response will then protect the body against further infection and will continue to protect the future.

DNA vaccines are thought to be more effective than protein- or antigen-based vaccines because the antigen can sometimes be degraded or consumed by the body before the immune system can generate a full attack against the antigen.

Recombinant vector vaccines work as a natural infection and are good at training the immune system to recognize and attack germs. They work by reproducing a live virus that has been engineered to carry extra genes from the germ infecting the body.

The extra number of genes produce the proteins that the immune system needs to recognize and protect against.

Unit-IV

Our <u>immune system</u> works continuously to keep us healthy and protect us against <u>bacteria</u>, <u>viruses</u>, and other germs. Sometimes, however, this system becomes too sensitive, causing **hypersensitivity reactions** that can be harmful or even deadly.

Hypersensitivity reactions are categorized into four major types: **type I**, **type II**, **type III**, and **type IV**. Type I, II, and III reactions are the result of <u>antibody</u> actions, while type IV reactions involve T cell lymphocytes and cell-mediated immune responses.

Type I Hypersensitivity Reactions

This image is depicting hay fever showing pollen grains (yellow) entering the nasal cavity (left) of a hay fever sufferer. The symptoms are caused by a massive release of the chemical histamine in the body in response to the pollen. Claus Lunau/Science Photo Library/Getty Images

Type I hypersensitivities are immune reactions to allergens. **Allergens** can be anything (<u>pollen</u>, mold, peanuts, medicine, etc.) that triggers an allergic reaction in some individuals. These same allergens do not normally cause problems in most individuals.**1**

Type I reactions involve two types of <u>white blood cells</u> (mast cells and basophils), as well as immunoglobulin E (IgE) antibodies. Upon the initial exposure to an allergen, the immune system produces IgE antibodies which bind to the <u>cell membranes</u> of mast cells and basophils. The antibodies are specific to a particular allergen and serve to detect the allergen upon subsequent exposure.

A second exposure results in a rapid immune response as IgE antibodies attached to mast cells and basophils bind allergens and initiate degranulation in the white blood cells. During degranulation, mast cells or basophils release granules that contain inflammatory molecules. The actions of such molecules (heparin, histamine, and serotonin) result in allergy symptoms: runny nose, watery eyes, hives, coughing, and wheezing.**1**

Allergies can range from mild hay fever to life-threatening anaphylaxis. **Anaphylaxis** is a serious condition, resulting from inflammation caused by histamine release, that impacts the <u>respiratory</u> and <u>circulatory</u> <u>systems</u>. The systemic inflammation results in low blood pressure and blockage of air passages due to swelling of the throat and tongue. Death may occur quickly if not treated with epinephrine.**1**

Type II Hypersensitivity Reactions

This image shows type A blood (A antigen) that was agglutinated (clumped) by mixing the blood with a serum containing anti-A antibody. An antigen-antibody reaction agglutinated the red blood cells forming a large clump. Ed Reschke/Photolibrary/Getty Images

Type II hypersensitivities, also called **cytotoxic hypersensitivities**, are the result of antibody (IgG and IgM) interactions with <u>body cells</u> and <u>tissues</u> that lead to cell destruction. Once bound to a cell, the antibody initiates a cascade of events, known as complement, that causes inflammation and cell lysis. Two common type II hypersensitivities are hemolytic transfusion reactions and hemolytic disease of newborns.

Hemolytic transfusion reactions involve blood transfusions with incompatible blood types. ABO blood groups are determined by the antigens on red blood cell surfaces and the antibodies present in blood plasma. A person with blood type A has A antigens on blood cells and B antibodies in blood plasma. Those with blood type B have B antigens and A antibodies. If an individual with type A blood were given a blood transfusion with type B blood, the B antibodies in the recipients plasma would bind to the B antigens on the red blood cells of the transfused blood. The B antibodies would cause the type B blood cells to clump together (**agglutinate**) and lyse, destroying the cells. Cell fragments from the dead cells could obstruct blood vessels leading to damage of the kidneys, lungs, and even death.[2]

Hemolytic disease of newborns is another type II hypersensitivity that involves red blood cells. In addition to A and B antigens, red blood cells may also have Rh antigens on their surfaces. If Rh antigens are present on the cell, the cell is Rh positive (Rh+). If not, it is Rh negative (Rh-). Similar to ABO transfusions, incompatible transfusions with Rh factor antigens can lead to hemolytic transfusion reactions. Should Rh factor incompatibilities occur between mother and child, hemolytic disease could occur in subsequent pregnancies.[3]

In the case of an Rh- mother with an Rh+ child, exposure to the child's blood during the final trimester of pregnancy or during childbirth would induce an immune response in the mother. The mother's immune system would build up antibodies against the Rh+ antigens. If the mother became pregnant again and the second child was Rh+, the mother's antibodies would bind to the babies Rh+ red blood cells causing them to lyse. To prevent hemolytic disease from occurring, Rh- mothers are given Rhogam injections to stop the development of antibodies against the blood of the Rh+ fetus.

Type III Hypersensitivity Reactions

Arthritis is an inflammation of the joints. This colored X-ray shows the hands of an 81 year old female patient with rheumatoid arthritis. Credit: Science Photo Library/Getty Images

Type III hypersensitivities are caused by the formation of immune complexes in body tissues. Immune complexes are masses of antigens with antibodies bound to them. These antigen-antibody complexes contain greater antibody (IgG) concentrations than antigen concentrations. The small complexes can settle on tissue surfaces, where they trigger inflammatory responses. The location and size of these complexes make it difficult for phagocytic cells, like macrophages, to remove them by phagocytosis. Instead, the antigen-antibody complexes are exposed to enzymes that break down the complexes but also damage underlying tissue in the process.

Immune responses to antigen-antibody complexes in blood vessel tissue causes blood clot formation and blood vessel obstruction. This can result in inadequate blood supply to the affected area and tissue death. Examples of type III hypersensitivities are serum sickness (systemic inflammation caused by immune complex deposits), lupus, and rheumatoid arthritis.[1]

Type IV Hypersensitivity Reactions

Contact dermatitis is a type IV hypersensitivity that results in severe skin rash. Smith Collection/Stone/Getty Images

Type IV hypersensitivities do not involve antibody actions but rather T cell lymphocyte activity. These cells are involved in cell mediated immunity, a response to body cells that have become infected or carry foreign antigens. Type IV reactions are delayed reactions, as it takes some time for a response to occur. Exposure to a particular antigen on the skin or an inhaled antigen induces T cell responses that result in the production of **memory T cells**.

Upon subsequent exposure to the antigen, memory cells induce a quicker and more forceful immune response involving macrophage activation. It is the macrophage response that damages body tissues. Type IV hypersensitivities that impact the skin include tuberculin reactions (tuberculosis skin test) and allergic reactions to latex. Chronic asthma is an example of a type IV hypersensitivity resulting from inhaled allergens.**1**

Some type IV hypersensitivities involve antigens that are associated with cells. **Cytotoxic T cells** are involved in these types of reactions and cause apoptosis (programmed cell death) in cells with the identified antigen. Examples of these types of hypersensitivity reactions include poison ivy induced contact dermatitis and transplant tissue rejection.

Autoimmune diseases result when your immune system is overactive, causing it to attack and damage your body's own tissues.

Normally, your immune system creates proteins called antibodies that work to protect you against harmful substances such as viruses, cancer cells, and toxins. But with autoimmune disorders, your immune system can't tell the difference between invaders and healthy cells.

Doctors have identified more than 100 different autoimmune diseases, which together affect over 24 million people in the U.S. It's not clear exactly what causes or triggers them. Treatment usually focuses on reducing immune system activity.

Types of Autoimmune Diseases

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Types of Autoimmune Diseases

Some examples of autoimmune diseases are:

- **Rheumatoid arthritis** (RA). Your immune system produces antibodies that attach to the linings of your joints. Your immune system cells then attack the joints, causing inflammation, swelling, and pain. If left untreated, RA gradually causes permanent joint damage. Treatments include various medications that reduce immune system overactivity. You might take them by mouth or as a shot. See charts that list rheumatoid arthritis drugs and their side effects.
- **Systemic lupus erythematosus** (lupus). When you have lupus, you develop autoimmune antibodies that can attach to tissues throughout your body. This disease most often attacks your joints, lungs, blood cells, nerves, and kidneys. Treatment often includes daily oral prednisone, a steroid that reduces immune system function. Read an overview of lupus symptoms and treatments.
- Inflammatory bowel disease (IBD). Your immune system attacks the lining of your intestines, causing bouts of diarrhea, rectal bleeding, urgent bowel movements, abdominal pain, fever, and weight loss. Ulcerative colitis and Crohn's disease are the two main forms of IBD. Immune-suppressing medicines, taken by mouth or as a shot, can treat IBD. Learn about the differences between ulcerative colitis and Crohn's disease.
- **Multiple sclerosis** (MS). Your immune system attacks nerve cells, causing symptoms that may include pain, blindness, weakness, poor coordination, and muscle spasms. Your doctor can use

medicines that suppress your immune system to treat it. Read more on multiple sclerosis drugs and their side effects.

- **Type 1 diabetes**. Your antibodies attack and destroy insulin-producing cells in your pancreas. People with type 1 diabetes need insulin shots to survive. Learn about the symptoms to look for in <u>type 1 diabetes</u>.
- **Guillain-Barre syndrome** (GBS). Your immune system attacks the nerves controlling the muscles in your legs and sometimes those in your arms and upper body. This leads to weakness, which can sometimes be serious. Filtering the blood with a procedure called plasmapheresis is the main treatment.
- **Chronic inflammatory demyelinating polyneuropathy** (CIDP). Similar to Guillain-Barre, this disease also involves the immune system attacking the nerves. But the symptoms last much longer. If it's not treated early, about 30% of people with this condition will eventually need to use a wheelchair. Treatment for CIDP and GBS are essentially the same. Find out what the treatment options are for CIDP.
- **Hashimoto's thyroiditis**. Antibodies from your immune system attack your thyroid gland, slowly destroying the cells that produce thyroid hormone. You develop low levels of thyroid hormone (hypothyroidism), usually over months to years. Symptoms include <u>fatigue</u>, constipation, weight gain, depression, dry skin, and sensitivity to cold. Taking a synthetic thyroid hormone pill every day restores normal body functions. Find out more on treatments for an underactive thyroid.
- **Myasthenia gravis**. Antibodies bind to your nerves and make them unable to stimulate your muscles properly. The main symptom is weakness that gets worse with activity. A drug called pyridostigmine (Mestinon) is most often used to treat myasthenia gravis. Read an overview of the symptoms of myasthenia gravis.
- **Scleroderma**. Also known as systemic sclerosis, this chronic connective disease causes inflammation in your skin and other places in your body. As a result, your body makes too much collagen. This leads to visible hardening of the skin and damage to your blood vessels and organs, such as your heart, lungs, and kidneys. There's no cure. Treatment aims to relieve symptoms and stop the disease from getting worse.
- **Vasculitis.** In this group of autoimmune diseases, your immune system attacks and damages blood vessels. Vasculitis can affect any organ, so symptoms vary widely and can happen almost anywhere in your body. Treatment involves reducing immune system activity, usually with prednisone or another corticosteroid. Learn more about <u>vasculitis symptoms and treatments</u>.

Immuno deficiency diseases types

Severe Combined Immunodeficiency (SCID)

Severe combined immunodeficiency (SCID) is a group of rare disorders caused by mutations in different genes involved in the development and function of infection-fighting immune cells. Infants with SCID appear healthy at birth but are highly susceptible to severe infections. The condition is fatal, usually within the first year or two of life, unless infants receive immune-restoring treatments, such as transplants of blood-forming stem cells, gene therapy, or enzyme therapy. More than 80 percent of SCID infants do not have a family history of the condition. However, development of a newborn screening test has made it possible to detect SCID before symptoms appear, helping ensure that affected infants receive life-saving treatments.

More than a dozen genes have been implicated in SCID, but gene defects are unknown in approximately 15 percent of newborn-screened SCID infants, according to an NIH-funded study. Most often, SCID is inherited in an <u>autosomal recessive pattern</u>, in which both copies of a particular gene—one inherited from the mother and one from the father—contain defects. The best-known form of autosomal recessive SCID is caused by adenosine deaminase (ADA) deficiency, in which infants lack the ADA enzyme necessary for T-cell survival. X-linked SCID, which is caused by mutations in a gene on the X chromosome, primarily affects male infants. Boys with this type of SCID have white blood cells that grow and develop abnormally.

As a consequence, they have low numbers of <u>T cells</u> and <u>natural killer cells</u>, and their <u>B cells</u> do not function.

Symptoms of SCID occur in infancy and include serious or life-threatening infections, especially viral infections, which may result in pneumonia and chronic diarrhea. *Candida* (yeast) infections of the mouth and diaper area and pneumonia caused by the fungus *Pneumocystis jirovecii* also are common.

The SCID newborn screening test, originally developed at NIH, measures T cell receptor excision circles (TRECs), a byproduct of T-cell development. Because infants with SCID have few or no T cells, the absence of TRECs may indicate SCID. To confirm a SCID diagnosis, a doctor will evaluate the numbers and types of T and B cells present and their ability to function. Research supported by NIAID and other organizations has shown that early diagnosis of SCID through newborn screening leads to prompt treatment and high survival rates. SCID was added in 2010 to the U.S. Department of Health and Human Services' Recommended Uniform Screening Panel for newborns. Today, all newborns in the United States are screened for SCID.

Hematopoietic (blood-forming) stem cell transplantation is the standard treatment for infants with SCID. Ideally, infants with SCID receive stem cells from a sibling who is a close tissue match. Transplants from matched siblings lead to the best restoration of immune function, but if a matched sibling is not available, infants may receive stem cells from a parent or an unrelated donor. These transplants are life-saving, but often only partially restore immunity. NIAID-supported research has shown that early transplantation is critical to achieving the best outcomes for SCID infants. Investigators analyzed data from 240 infants with SCID and found that those who received transplants before the age of 3.5 months were most likely to survive, regardless of the type of stem cell donor used.

Children who have SCID with ADA deficiency have been treated somewhat successfully with enzyme replacement therapy called PEG-ADA.

Studies also have shown that gene therapy can be an effective treatment for some types of SCID, including X-linked SCID. In gene therapy, stem cells are obtained from the patient's bone marrow, the normal gene is inserted into the stem cells using a carrier known as a vector, and the corrected cells are returned to the patient. Early efforts to treat X-linked SCID with gene therapy successfully restored children's T-cell function, but approximately one-quarter of the children developed leukemia two to five years after treatment. Scientists suspect that the vectors used in these studies activated genes that control cell growth, contributing to leukemia. Newer gene therapy strategies use modified vectors that appear effective and safe. NIAID researchers are using a novel gene therapy approach to successfully treat older children and young adults with X-linked SCID

 Acquired immunodeficiency syndrome (AIDS),

Acquired immunodeficiency syndrome (AIDS), is an ongoing, also called chronic, condition. It's caused by the human immunodeficiency virus, also called HIV. HIV damages the immune system so that the body is less able to fight infection and disease. If HIV isn't treated, it can take years before it weakens the immune system enough to become AIDS. Thanks to treatment, most people in the U.S. don't get AIDS.

HIV is spread through contact with genitals, such as during sex without a condom. This type of infection is called a sexually transmitted infection, also called an STI. HIV also is spread through contact with blood, such as when people share needles or syringes. It is also possible for a person with untreated HIV to spread the virus to a child during pregnancy, childbirth or breastfeeding.

There's no cure for HIV/AIDS. But medicines can control the infection and keep the disease from getting worse. Antiviral treatments for HIV have reduced AIDS deaths around the world. There's an ongoing effort to make ways to prevent and treat HIV/AIDS more available in resource-poor countries.

Symptoms

The symptoms of HIV and AIDS vary depending on the person and the phase of infection.

Primary infection, also called acute HIV

Some people infected by HIV get a flu-like illness within 2 to 4 weeks after the virus enters the body. This stage may last a few days to several weeks. Some people have no symptoms during this stage.

Possible symptoms include:

- Fever.

- Headache.

- Muscle aches and joint pain.

- Rash.

- Sore throat and painful mouth sores.

- Swollen lymph glands, also called nodes, mainly on the neck.

- Diarrhea.

- Weight loss.

- Cough.

- Night sweats.

These symptoms can be so mild that you might not notice them. However, the amount of virus in your bloodstream, called viral load, is high at this time. As a result, the infection spreads to others more easily during primary infection than during the next stage.

Clinical latent infection, also called chronic HIV

In this stage of infection, HIV is still in the body and cells of the immune system, called white blood cells. But during this time, many people don't have symptoms or the infections that HIV can cause.

This stage can last for many years for people who aren't getting antiretroviral therapy, also called ART. Some people get more-severe disease much sooner.

Symptomatic HIV infection

As the virus continues to multiply and destroy immune cells, you may get mild infections or long-term symptoms such as:

- Fever.

- Fatigue.

- Swollen lymph glands, which are often one of the first symptoms of HIV infection.

- Diarrhea.

- Weight loss.

- Oral yeast infection, also called thrush.

- Shingles, also called herpes zoster.

- Pneumonia.

Progression to AIDS

Better antiviral treatments have greatly decreased deaths from AIDS worldwide. Thanks to these lifesaving treatments, most people with HIV in the U.S. today don't get AIDS. Untreated, HIV most often turns into AIDS in about 8 to 10 years.

Having AIDS means your immune system is very damaged. People with AIDS are more likely to develop diseases they wouldn't get if they had healthy immune systems. These are called opportunistic infections or opportunistic cancers. Some people get opportunistic infections during the acute stage of the disease.

The symptoms of some of these infections may include:

- Sweats.

- Chills.

- Fever that keeps coming back.

- Ongoing diarrhea.

- Swollen lymph glands.

- Constant white spots or lesions on the tongue or in the mouth.

- Constant fatigue.

- Weakness.

- Rapid weight loss.

- Skin rashes or bumps.