Immunity

Is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion or is defined as an enhanced state of responsiveness to a specific substance, induced by prior contact with that substance.

A. Immunity classify as:

- Natural immunity (Innate immunity)
  - Is present from birth and is nonspecific.
  - Consists of various barriers to external insults; for example, skin, mucous membranes, macrophages, monocytes, neutrophils, eosinophils, and the contents of these cells.
  - This innate immunity is not improved by repeated exposure to infection and does not retain a "memory" of the infection.
- Acquired immunity(Adaptive immunity)
  - Is expressed after exposure to a given substance and is specific.
  - Involves specific receptors on lymphocytes and the participation of macrophages for its expression.
  - Consists of: 1-Humoral immunity, mediated by antibodies. 2-Cell-mediated immunity, mediated by lymphocytes.

  (Specific immunity to infections develops over time and white blood cells called lymphocytes play a central role. Lymphocytes retain a "memory" of virus infections and produce many special molecules called antibodies).

B. Immune system:

is a system of biological structures and processes within an organism that protects against disease by identifying and killing pathogens and tumor cells.

Immune system consists of: Cellular and **molecular** components derived from the **central** and **peripheral** lymphoid organs.

- Central lymphoid organs
  - Consist of the bone marrow and thymus.
  - Are the location of **maturation** of lymphoid cells
- Peripheral lymphoid organs
  - Consist of the spleen, lymph nodes and lymphatic channels, tonsils, adenoids, Peyer's patches, and appendix.
  - Are the location of **reactivity** of lymphoid cells

Cells of the immune system:

- include the white blood cells (approximately 4000 - 11000/mm^3 of blood), which are composed of:
- Granulocytes(50% - 70%) of white blood cells
- Lymphocytes(20% - 45%) of white blood cells
- Monocytes and macrophages(3% - 8%)of white blood cells

Molecules of the immune system:

- Antibodies (immunoglobulins) are protein products of certain lymphocytes with a precise specificity for a particular antigen.
- Lymphokines are secreted lymphocyte products that play a role in the activation of the immune response.

C. Development of the immune system

- Involves the maturation of **pluripotential stem cells** in the bone marrow or thymus into B cells and T cells, respectively.
- Includes the generation of specific receptors on the cell surface of B cells and T cells.
- Pluripotential stem-cell sources
  - Embryonic yolk sac
  - Fetal liver
  - Adult bone marrow

- B cells
  - Mature in the bursa (hence the name of B cells) of Fabricius in birds and in the fetal liver and adult bone marrow in humans (bursal equivalents).
  - Are involved in the generation of humoral immunity.
  - Have specific receptors (immunoglobulins) on their surface for antigen recognition.
  - Mature into antibody-producing **plasma cells**.
  - Are sessile and located predominantly in the germinal centers of the lymph nodes and spleen.
- T cells
  - Mature in the thymus.
  - Are involved in helping of B cells become antibody-producing plasma cells.
  - Have specific receptors (T-cell receptors) on their surface for antigen recognition.
  - Are involved in cell-mediated immunity.
  - Participate in suppression of the immune response.
  - Are the predominant (95%) lymphocytes in the circulation.
  - Are found in the para-cortical and inter-follicular areas of the lymph nodes and spleen.

D. Physiology of immunity

- involves the following series of events that culminate in B-cell or T-cell activation (or both) and response to the introduction of a foreign entity into the circulation:
  - Processing of the foreign entity by a macrophage or B cell
  - Recognition of this foreign entity by specific, preformed receptors on certain B cells and T cells
  - Proliferation of these B cells and T cells, as stimulated by soluble signals (interleukins) between macrophages, B cells, and T cells
  - Blast transformation and a series of mitotic divisions (from B cells) leading to the generation of plasma cells that produce immunoglobulins and (from T cells) of sensitized T cells and all capable of interacting with the original foreign stimulus

E. Antigens (Immunogens)

1. Characteristics

- Immunogenicity: is the capacity to stimulate production of specific, protective humoral or cellular immunity.
- Specific reactivity: is the capacity to be recognized by the antibodies and T cells produced.
- Foreignness: is the recognition of a body as nonself (foreign proteins are excellent antigens).
- Size: must be at least approximately 10 kilodaltons (kd) to be recognized.
- Shape: tertiary and quaternary structure determines the extent of antigenicity.

2. Definitions

- **Epitope**
  - is the restricted portion of an antigen molecule that determines the specificity of the reaction with an antibody.
  - is the antibody-binding site on an antigen for a specific antibody.
  - Generally contains four to six amino acid or sugar residues.
- **Hapten**
  - Is a small foreign molecule that is not immunogenic by itself but can bind to an antibody molecule already formed to it.
  - Can be immunogenic if coupled to a sufficiently large carrier molecule.

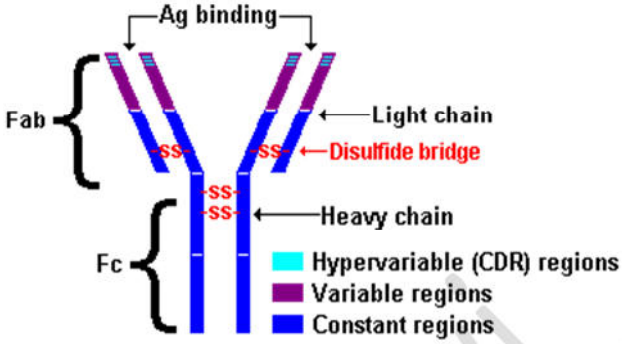
F. Antibodies (Immunoglobulins)

1.Characteristics of antibodies

- are a heterogeneous group of proteins that contain carbohydrate.
- have sedimentation coefficients ranging from 7S to 19S.
- are found predominantly in the gamma globulin fraction of serum.
- consist of polypeptide chains linked by disulfide bonds, such that each antibody contains a minimum of **two** identical heavy (H) chains and **two** identical light (L) chains.
- have inter-chain disulfide bonds holding the chains together (i.e., L to H and H to H).

- have **antigen-binding capacity** defined by their specific H and L chains.

2. Structure of antibody molecules



- **H chains**
  - are polypeptide chains of 440 - 550 amino acid residues in length.
  - have intra-chain domains of approximately 110 amino acid residues, formed by intra-chain disulfide bonds.
  - have an amino-terminal variable domain, followed by three to four constant domains.
  - are structurally different for each of the defined classes of antibody [mu , gamma , alpha , delta and epsilon].
- **L chains**
  - are polypeptide chains of approximately 220 amino acid residues in length.
  - have intrachain domains of approximately 110 amino acid residues, formed by intrachain disulfide bonds.
  - have an amino-terminal variable domain and a carboxy-terminal constant domain.
  - have two structurally distinct classes: kappa chains and lambda chains.

3. Immunoglobulin classes

The immunoglobulins can be divided into **five different classes**, based on differences in the amino acid sequences in the constant region of the heavy chains.

1. IgG –Gamma heavy chains. 2. IgM -Mu heavy chains. 3. IgA -Alpha heavy chains. 4. IgD -Delta heavy chains. 5. IgE -Epsilon heavy chains.

4. Properties of immunoglobulins

1. IgG

- All IgG's are monomers (7S immunoglobulin).
- IgG is the most versatile immunoglobulin because it is capable of carrying out all of the functions of immunoglobulin molecules.
- IgG is the major Ig in serum - 75% of serum Ig is IgG
- IgG is the major Ig in extra vascular spaces
- Placental transfer - IgG is the only class of Ig that crosses the placenta.
- Fixes complement
- Binding to cells - Macrophages, monocytes, PMNs and some lymphocytes have Fc receptors for the Fc region of IgG.

2. IgM

- IgM normally exists as a pentamer (19S immunoglobulin) .
- IgM is the third most common serum Ig.
- IgM is the first Ig to be made by the fetus and the first Ig to be made by a virgin B cells when it is stimulated by antigen.
- As a consequence of its pentameric structure, IgM is a good complement fixing Ig. Thus, IgM antibodies are very efficient in leading to the lysis of microorganisms.
- IgM binds to some cells via Fc receptors.

3. IgA

- Serum IgA is a monomer but IgA found in secretions is a dimer.
- IgA is the 2nd most common serum Ig.
- IgA is the major class of Ig in secretions - tears, saliva, colostrum, mucus. Since it is found in secretions secretory IgA is important in local (mucosal) immunity.
- Normally IgA does not fix complement, unless aggregated.
- IgA can binding to some cells - PMN's and some lymphocytes

4. IgD

- IgD exists only as a monomer.
- IgD is found in low levels in serum; its role in serum uncertain.
- IgD is primarily found on B cell surfaces where it functions as a receptor for antigen.
- IgD does not bind complement.

5**. IgE**

- IgE exists as a monomer and has an extra domain in the constant region.
- IgE is the least common serum Ig since it binds very tightly to Fc receptors on basophils and mast cells even before interacting with antigen.
- Involved in allergic reactions
- IgE also plays a role in parasitic helminth diseases.
- IgE does not fix complement.

G. The Complement System

1. Complement-mediated cell cytotoxicity

- causes lysis of a target cell.
- may be initiated by antibody fixation to a cell-surface antigen.
- may be caused by antigen-antibody complex formation.
- occurs by activation of either:
  -Classic complement cascade mediated by IgG, IgG2, IgG3, or IgM antibody
  -Alternative pathway initiated by certain antigens (i.e., lipopolysaccharide, endotoxin, zymosan) or antigen antibody complexes

2. Complement components

- is a collective term for a group of heterogeneous proteins involved in a sequential activation, culminating in target cell lysis.
- are not immunoglobulins.
- are present in normal serum.
- do not increase as a result of antigen stimulation.
- are manufactured early in ontogeny (first trimester).
- are made in macrophages and liver (except C1, which is made and assembled in gastrointestinal epithelium).
- are heat labile.
- are defined by number (C1, C2, C3) and letter (factor B, factor D) designations.

H. Hypersensitivity Reactions: are categorized according to the Gell and Coombs classification to.

1. Type I hypersensitivity (anaphylaxis)

- occurs in atopic persons.
- occurs in response to environmental antigens (e.g., allergens) or administered antigens (e.g., penicillin).
- is mediated by IgE (reaginic) antibody bound to the surface of mast cells or basophils.
- may be localized or systemic.
- IgE in immediate hypersensitivity
  - is produced in response to environmental antigens.
  - binds by the Fc portion of IgE to mast cells or basophils.
  - causes release of vasoactive and chemotactic factors from mast cells upon cross-linking of antigen on the surface.
  - can also be measured for specific idiotypes by **RAST** (**radio allergosorbent test**) allergy blood testing.
- Products released by mast cells upon stimulation of surface IgE
  - Vasoactive mediators
    - Histamine causes smooth muscle contraction in bronchioles and small blood vessels and increased permeability of capillaries; molecular weight is 111 daltons.

- Platelet-activating factor (PAF) a activates platelets.
- Chemotactic factors
  - Eosinophil chemotactic factor of anaphylaxis (ECF-A) causes influx of eosinophils; molecular weight is 2 kd.
  - Neutrophil chemotactic factor has a high molecular weight (660 kd); is chemotactic for neutrophils.

2. Type II hypersensitivity cytotoxic reactions

- involve the production of antibody to specific cell-surface epitopes, which cause destruction of the cell.
- Antibody to cell-surface antigen
  - can cause reduction in cell-surface charges.
  - can cause opsonic adherence via the Fc region of antibody to neutrophils, macrophages, and K cells (the cells responsible for ADCC); enhances cell phagocytosis and promotes cell death.
  - can activate complement to cause cell lysis.
- Examples of type II hypersensitivity reactions
  - Transfusion reactions ABO incompatibility involving IgM antibodies against A or B alloantigens
  - Rh incompatibility IgG antibodies against the D antigen on fetal red blood cells
  - Hemolytic anemia antibody to red blood cell epitopes
  - Myasthenia gravis antibody to muscle acetylcholine receptors.

3. Type III hypersensitivity immune complex reactions

- involve soluble antigen that becomes bound antigen antibody complexes, which, especially in antigen excess, can cause a series of events that lead to pathologic expression, edema, neutrophil infiltrate, and lesions in blood vessels and kidney glomeruli.
- Consequences of antigen antibody complex formation:
  - Platelet aggregation, leading to formation of microthrombi and release of vasoactive amines
  - Activation of complement and release of anaphylatoxins (causing histamine release) and chemotactic factors (for neutrophils)
  - Clotting factor XII activation, leading to fibrin, plasmin, and kinin formation
- Examples of type III hypersensitivity reactions
  - Arthus reaction immunization of rabbits with horse serum .
  - Farmer's lung antibody to inhaled aspergillus mold
  - Rheumatoid arthritis rheumatoid factor (IgM) against the Fc portion of self-IgG

4. Type IV hypersensitivity delayed-type hypersensitivity

- is differentiated from immediate-type hypersensitivity reactions (types I, II, and III).
- is an example of cell-mediated immunity; types I, II, and III are mediated by antibody and are examples of humoral immunity.
- Sequence of events in a type IV reaction
  - An appropriate antigen (tuberculin, purified protein derivative of Mycobacterium tuberculosis, tumor cell, transplanted cell, virally transformed cell) is processed by macrophages; epitopes of antigen are expressed on the macrophage surface via class II HLAs; macrophages produce IL-1.
  - T_H cells react to antigen epitope and class II antigens via TCR and CD4, respectively.
  - T_H cells are also stimulated by IL-1 from macrophages.
  - T_H cells produce IL-2, and IL-2 receptors become fully activated and release lymphokines, having an effect on T cells and macrophages.
- Lymphokines
  - that affect macrophages
  - that affect $CD8^+$ cells include IL-2, which activates them to become fully cytotoxic.

- that are produced by $CD4^+$ and $CD8^+$ cells include TNF, osteoclast-activating factor (OAF), and histamine-releasing factor (HRF).

- $CD8^+$ cytotoxic cells
  - react to viral and tumor antigens and class I HLAs via TCR and CD8 molecules, respectively.
  - are further stimulated by IL-2 from T_H cells.
  - produce IL-2 themselves.
  - produce IFN-ϒ.