Some glossary in Immunology……

Immunology: The word immunity was derived from the Latin word "immunis" meaning exempt. Immunology is the branch of biomedical science that deals with the response of an organism to antigenic challenge and its recognition of what is self and what is not. It deals with physiological functioning of the immune system in states of both health and disease as well as malfunctions of the immune system in immunological disorders like allergies, hypersensitivities, immune deficiency, transplant rejection and autoimmune disorders.

Antibody (Ab): a glycoprotein molecule produced as a result of interaction with an antigen, It has the ability to combine with the antigen that stimulated its production**.**

Immunoglobulin: a glycoprotein composed of (H) heavy and (L) light, that function as antibody. All antibodies are immunoglobulins, but not all immunoglobulins have antibody function.

Opsonin: A substance capable of enhancing phagocytosis. Antibodies and complement are the two main opsonins.

Monoclonal Ab: each B lymphocyte produces antibody of a single specificity. If B cells are fused to a myeloma cell by somatic cell hybridization, the fused cell known as a hybridoma and immortalized monoclonal antibodies producing cell line.

Antigen (Ag): A substance that can react with an antibody. Not all antigens can induce antibody production, that can are also called immunogens.

Hapten: A molecule that is not immunogenic by itself but can react with specific antibody after being joined to a suitable carrier molecule called adjuvant.

Epitope: site on an antigen recognized by an antibody . also known as antigenic determinant.

Paratope: site on the variable region of the antibody recognized by an antigen epitope and represented the site of reaction between Ab & Ag.

Immune response: development of resistance (immunity) to a foreign substance (eg. Infectious agent). It can be antibody – mediated (humoral), cell mediated (cellular) or both.

Humoral immunity: pertaining to immunity in a body fluid and used to denote immunity mediated by antibody and complement.

Cell – mediated (cellular) immunity: immunity in which the participation of lymphocytes and macrophages is predominant. It is a term generally applied to the type IV hypersensitivity reaction.

Immunity and immune response: it is the state of protection from infectious disease, it is either:

A. Innate immunity:

- Provides the first line of defense.
- Less specific or not specific to a particular pathogen.
- Has obvious barriers include the skin (antimicrobial peptides & fatty acids in sebum), mucosal membrane, the stomach (low pH, digestive enzymes and fluid flow toward intestine, large intestine (contain normal flora and fluid expelled from rectum, lysozyme enzymes which is present in tears, cilia sweep mucus outward in airway and lung & host cells such as the phagocytes in alveoli of lungs and soluble molecules contribute to innate immunity like interferon and complement as well as inflammatory mediators.
- Many of molecule in innate immunity have the property of pattern recognition (the ability to recognize a given molecules this is a strong feature of innate immunity.
- Response time for hours.

B. Adaptive (acquired) immunity:

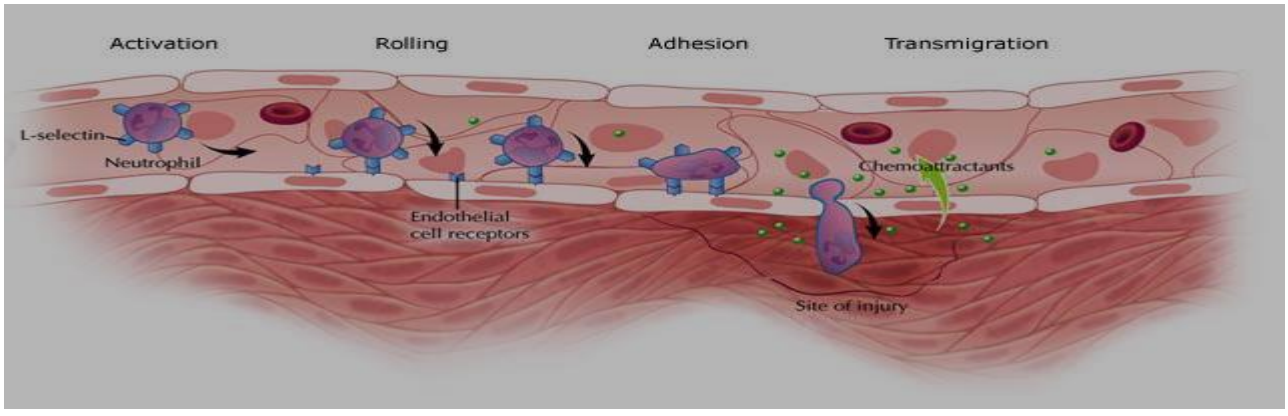
- In contrast to the broad reactivity of the innate immunity, it dose not come into play until there is a recognized antigenic challenge to the organism.
- Response to the challenge with a high degree of specificity with remarkable property of the memory.
- The major agents of adaptive immunity are lymphocyte and the antibodies.
- Display four characteristic attributes: antigenic specificity, diversity, immunological memory and self – non self recognition.
- Response time for days.
- It can be passive or active.

Passive immunity…. Immunity acquired by the transfer of antibody from one individual to another such as from mother to offspring. There are two ways to acquired passive immunity natural acquired passive immunity happens when a mother transfer antibodies to her offspring via a placental route during pregnancy and via colostrum during breastfeeding and artificially acquired passive immunity is done by injecting antibodies or sensitized lymphocytes to an organism via vaccination. *The main advantage* of passive immunity is the prompt availability a large amounts of antibody, *disadvantages* are the short life span of these antibodies and possible hypersensitivity reaction if antibodies (Igs) from another species administered.

Active immunity…. Immunity developed in an organism by its own production of antibodies in response to an antigen a pathogen or to a vaccine. It is generally long term and acquired by infection followed B cells and T cell activation or artificially by vaccines in immunization process, active immunity involves humoral immunity (B-cells) and cell – mediated immunity (T- cells). *Advantage* include long term protection based on memory of prior contact with antigen, *disadvantage* include the slow onset of protection and the need for prolonged or repeated contact with antigen.

Inflammatory response (Inflammation):

When pathogens breach the outer barriers of innate immunity (skin and mucosa membrane) the attending infection or tissue injury can induce a complex cascade of events known as the inflammatory response. Inflammation may be acute for example in response to tissue damage or it may be chronic leading to pathologic consequences such as arthritis.
Within minutes after tissue injury there is increase in vascular diameter (vasodilation) resulting in a rise of blood volume in the area. Higher blood volume heats the tissue and causes it redden. Vascular permeability also increases, leading to leakage of fluid from the blood vessels particularly at postcapillary venules. This results in an accumulation of fluid (edema) that swells the tissue. Within a few hours, leukocytes adhere to endothelial cells in inflamed region and pass through the wall of capillaries and into the tissue space this process called extravasation which can be divided into four steps… rolling, activation by chemoattractant stimulus, arrest and adhesion and transendothelial migration.
These leucocytes phagocytos invading pathogens and release molecular mediators that contribute to the inflammatory response and the recruitment and activation of effector cells. Among the mediators are low molecular weight called cytokines. Cytokines are secreted by white blood cells and various other cells in the body in response to stimuli and play major roles in regulating the development and behavior of immune effector cells. Other important chemoattractants are the by products of complement (C5a, C3a) and N-formyl peptides produced by the breakdown of bacterial protein during an infection.
Binding of chemokines or other chemoattractants to receptors on the membrane of neutrophil cells triggers an activating signal that induces a conformational changes in a molecule of the neutrophil membrane called integrin, increase its affinity for intracellular adhesion molecules (ICAMs) on the endothelium. Chemokines cause leukocytes to move into various tissue sites by inducing the adherence of these cells to the vascular endothelium lining the walls of blood vessels. After migrating in tissues, leukocytes move by chemotaxis toward the higher localized concentrations of chemokines at the site of infection, thus targeted phagocytes and effector lymphocyte populations are attracted to the focus of the inflammation to invade organisms.



Rolling is mediated by transient binding of selectins on the vascular endothelium to mucins on the neutrophil. Chemokines and other chemoattracnts that bind to a specific receptor on the neutrophil activate a signal transduction pathway, resulting in a conformational change in integrin that enables them to adhere firmly to ICAMs on the surface of endothelial cells.

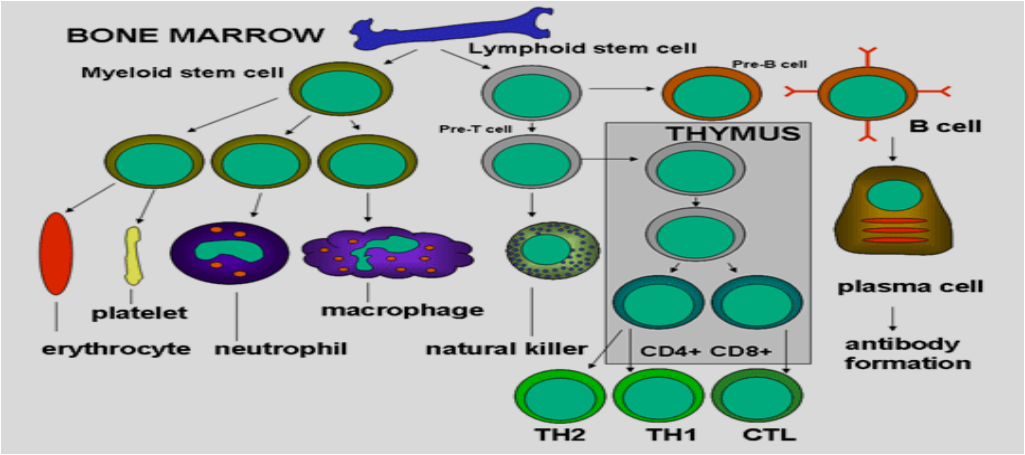
Cells & organs of immune system:

The cells, organs & tissues of the immune system are found throughout the body.... They can be classified functionally into 2 main groups (Primary and Secondary lymphoid organs). Blood vessels and lymphatic systems connect these organs united them into a functional whole.

cells of the immune system……

All the types of blood cells derived from hematopoietic stem cell (HSC) which mainly self renewing by hematopoiesis process **Hematopoiesis** is a steady state process in which mature blood cells are produced at the same rate at which they are lost. The stem cell differentiate s along one of two pathways, giving rise to either….

- **lymphoid progenitor cell …** give arise to NK cell, T- cell, B -cell.
- **Myeloid progenitor cell…** give arise to macrophage, granulocyte (Neutrophil, Eosinophil and Basophil)., Megakaryocyte (platelets) and erythrocyte.



Lymphoid cells…..

formed about 20-40% of WBCs and 99% of lymph. It is the central cell of adaptive immunity and subdivided into….

- **B cell**: derived and mature in bursa, produce antibodies molecule (Igs) and differentiate into effector cell (plasma cell) and memory cell.
- **T cell**: mature in thymus and express on their membrane T- cell receptors (Ag binding site molecule). T- cell receptors only recognize Ag that bond to major histocompatibility complex (MHC).

  T- cell can be classified into:

  - **Tc (CD8) …..**cytotoxic**.**
  - **Th (CD4)…..** helper**.**
  - **T reg …..**regulatory**.**
- **Natural killer cell**: Large granular lymphocyte form 5-10% of peripheral blood , display cytotoxic activity against tumor cell & some viral infection. Play important role in the innate immunity , destroyed target cell by (ADCC) processes.

❖ ***Myeloid cells*****…..**

- **Mononuclear phagocytes:** Monocyte circulating in the peripheral blood & differentiate into macrophage when enter tissues. It has phagocytic ability, secrets hydrolytic enzymes. Macrophage may be stimulated by particular Ag or cytokines secreted by Th cell. According to their tissue location macrophage named..
- Intestinal Mq…..gut
- Alveolar Mq…. Lung
- Histocytes….tissue
- Kupffer cell….liver
- Mesangial cell….kidney
- Microglial cell….brain
- Osteoclasts….bone.

- **Granulocytic cells**:
  - **1- Neutrophil:** formed 50-70% of the peripheral blood circulate in the blood stream for 7-10 hr. It is the first cell arrive to the site of inflammation by movement called extravasation . (Neutrophil phagocyte like Mq) digest by primary granules..lysozyme & Secondary granules..collagenous.
  - **2- Eosinophile:** formed 1-3% , bilobed & granulated it is also phagocytic cell play important role during parasitic infection.
  - **3- Basophile:** formed 0-1%, lobes & granulated stained with basic stain. It is not phagocytic cell but play important role during allergy response.
- **Mast cells:** Arise from bone marrow , still undifferentiated in the blood until reach to tissues. They found in the skin , connective tissue , mucosal , respiratory , genitourinary & digestive tract tissues . It contain histamine (pharmacologically active substances play important role in the allergies.
- **Dendritic cells:** were the first cell of immune system discovered. There are at least 4 categories of Dendritic cell recognized:

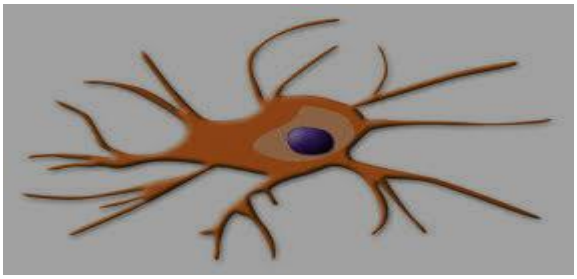
  1-Langerhans DC…epidermal of skin.

  2-Interstitial DC… Interstitial spaces except brain.

  3-Monocyte derived DC…migrate from blood to tissue then back to the blood.

  4- Plasmacytoid derived DC… act as Ag presenting cell , play important role in innate immune response.

  immature Dendritic cells take on their cargo of Ag in 3 ways: **-they engulf it by phagocytosis, internalize it by receptor – mediated endocytosis or imbibe it by pinocytiosis.**



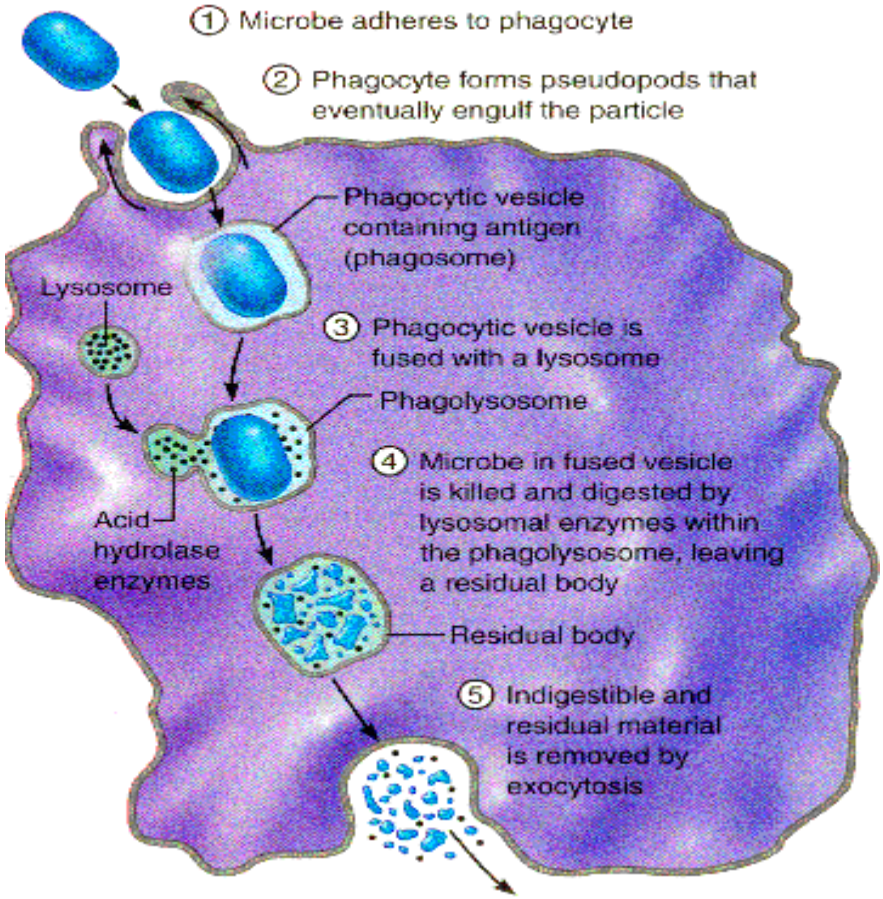
Phagocytosis:

Several types of cells in the immune system engulf microorganisms via **phagocytosis**.

- **Neutrophils**. Neutrophils are abundant in the blood, quickly enter tissues, and phagocytize pathogens in acute inflammation.
- **Macrophages**. Macrophages are closely related to monocytes in the blood. These longer-lived cells predominate in chronic inflammation. They also release some important inflammatory mediators.
- **Dendritic Cells**. Phagocytosis in these cells is important for the elaboration of a specific immune response rather than for directly destroying the pathogens.
- **B Lymphocytes**. A small amount of phagocytosis in these cells is often necessary in order for them to develop into cells that release antibodies.

Sequence of phagocytosis events

- Phagocytosis begins with the neutrophil or macrophage flowing around the pathogen and engulfing it so that it winds up enclosed in a **phagosome** (phagocytic vesicle). But this is only the first step, because the more challenging task of destroying the microorganisms remains. Indeed, some pathogens have special, effective mechanisms for frustrating this destruction step.
- The next step is the fusion of **lysosomes** with the phagosome. The result is called a **phagolysosome**. Lysosome are derived from the Golgi apparatus, much like secretion vesicles, but their contents are focused on destroying microorganisms.



Organs of the immune system…..

These organs can be distinguished by functions as…..

1- **Primary lymphoid organs:**

A -Thymus: Site of T- cell maturation, bilobed organ consist of cortex (site of immature thymocyte) & Medulla (site of thymocyte) .If the thymus removed for example T- cell level decrease in the body & cell – mediated immunity absent this called DiGeorge's syndrome in human. Size of Thymus… In infants(30 gm) & in elderly(3 gm).

B -Bone marrow: Complex tissue of hematopoiesis, it is the site of B- cell development & origin. Arising from lymphoid progenitors, immature B cell proliferate and differentiate within the bone marrow and stromal cells within the bone marrow interact directly with the B cells are the source of about 90% of the immunoglobulins IgG and IgA in plasma.

2- **Secondary lymphoid organs:**

A -Lymph nodes: It is the site when I.R are mounted Ag in lymph , bean in shape encapsulated consist of ... Lymphocytes, Dendritic cell & Macrophage. Lymph node function is the trap of bacterial cells & particular Ag carry by lymph.

It consist of 3 regions:

1- Cortex: B-cell, Mq, DC
2- Paracortex: T-cell , Mq, DC
3- Medulla: Plasma cell…Ab

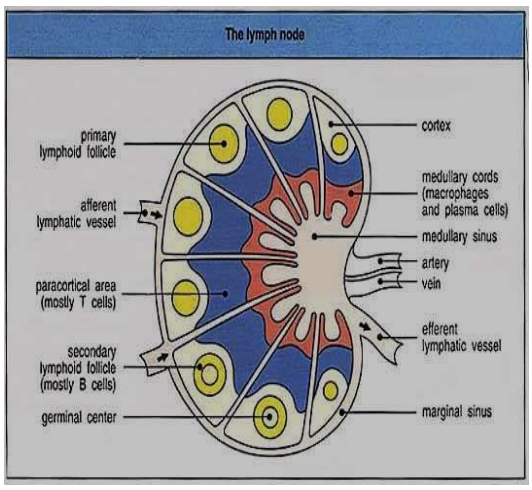
B- Spleen: It is ovoid structure , situated at the left high level of the abdominal cavity… play major role in the mounting of I.R in blood stream . (Splenectomy) in children leading to sepsis & in adult leading to bacteremia.

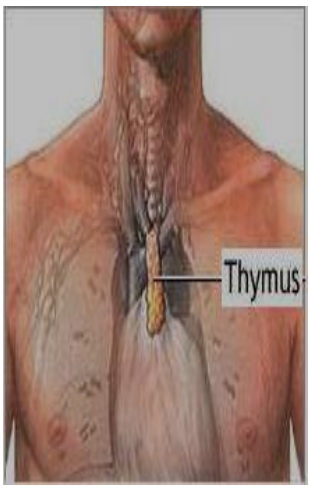
It consist of 2 regions:

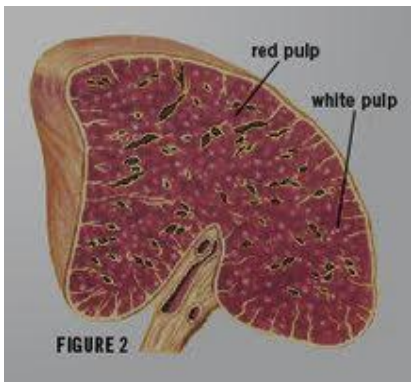
1- Red pulp: Lymphocyte, Mq, RBCs (site of old & destroy RBCs)
2- White pulp: population T- lymphocyte.

Separated by marginal zone: Mq & lymphocyte

C -Mucosa associated lymphoid tissue (MALT). Tonsils & Appendix
D - Bronchus associated lymphoid tissue (BALT). Respiratory epithelium
E - Gut associated lymphoid tissue (GALT). Digestive tract.
F - Cutaneous associated lymphoid tissue (CALT). Skin.

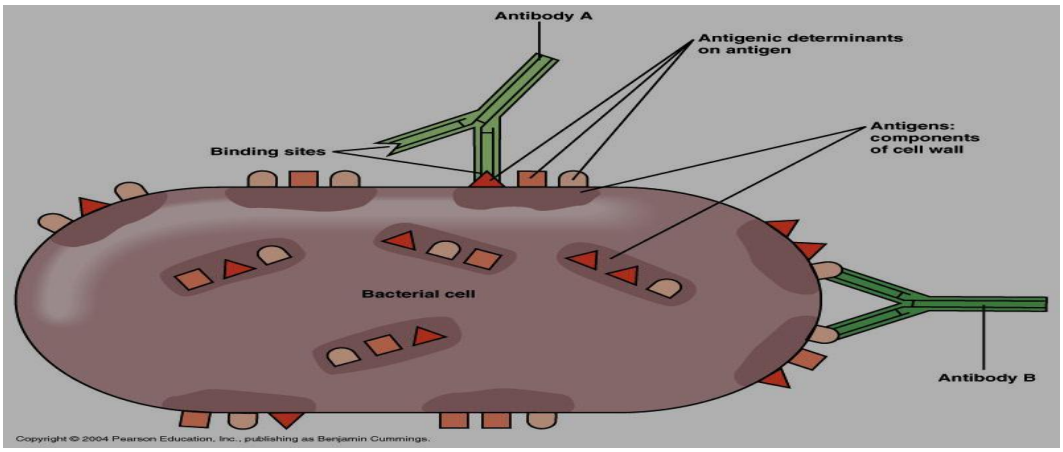






Antigens

Antigens are defined specifically as molecules that interact with the immunoglobulin receptor of B cells (or with the T- cell receptor when complexed with MHC molecules).
Immune cells do not interact with, or recognize an entire immunogen molecule instead lymphocytes recognize discrete sites on the macromolecule called **epitopes** or **antigenic determinants**. B and T cells can be recognize different epitopes on the same antigenic molecule.
Lymphocytes may interact with a complex antigen on several levels of antigen structure. An epitope on a protein antigen may involve elemnts of the primary, secondary, tertiary and quaternary structure of protein. In polysaccarides, branced chain point contribute to the conformation of epitopes. B cells recognize soluble antigen when it binds to antibody molecules in the B- cell membrane B- cell epitopes must be accessible in order to be able to bind to an antibody are usually composed of hydrophilic amino acids, while pathogen proteins are recognized by the T- cell receptor only when in complex with an MHC molecule.



Immunogenicity Vs Antigenicity:

Immunogenicity is the ability to induce a humoral and/or cell mediated immune respons and a substane that induce a specific immune response is usually called an **immunogen**.

Antigenicity: is the ability to combine specifically with the secreted antibodies of B-cell and /or surface receptors on T- cells. Although all molecules that have the property of immunogenicity also have the property of antigenicity, the reverse is not true.

Haptens: are small molecules antigenic but incapable by themselves of inducing a specific immune response (they lack immunogenicity). Haptens can be coupling chemically to a large immunogenic substances called a carier or **adjuvant**, yield an immunogenic hapten carrier conjugate to enhance the immunogenicity of antigen.

Properties of the immunogen contribute to immunogenicity:

1-Foreignness: to elicit an immune response, a molecule must be recognized as nonself by a biological system. The flip side of the capacity to recognize nonself is tolerance of self, a specific unresponsiveness to self antigens. When antigen is introduce into an organism, the degree of its immunogenicity depends on the degree of its foreignness. For example experimental antigen of bovin serum albumin (BSA) is not immunogenic when injected into a cow but is strongly immunogenic when injected into a rabbit.

2-Molecular size: there is a correlation between the size of a macromolecule and its immunogenicity. The most active immunogens tend to have a molecular mass of > 100.000 Da.

3-Chemical composition and heterogeneity: size and foreignness are sufficient to make a molecule immunogenic other properties are needed like synthetic homopolymers (like polymers composed of multiple copies of single amino acid or sugar) tend to lack immunogenicity regardless to their size, so heteropolymers are usually more immunogenic than homoplymers.

4-Susceptibility to antigen processing and presentation: large, insoluble, or aggregated macromolecules generally are more immunogenic than small, soluble ones because the larger molecules are more readily phagocytosed and processed. Macromolecules that can not be degraded and presented with MHC molecules are poor immunogen, so the degradative enzymes within antigen – presenting cells can degrade only proteins containing L- amino acids but not D- amino acid which consider poor immunogen.

5-The biological system contributes to immunogenicity:

a- Genotype of the recipient animal: a major factor determining immune responsiveness can be the genotype of the recepient. The genitic constitution (genotype) of an immunizied animal influences the type of immune response the animal manifests as wel as the degree of the response, for example the two different inbred strains of mice responded very differently after exposure to a synthetic polypeptide immunogen.

The response of an animal to an antigen is also influenced by the genes that encode B- cell and T- cell receptors and by genes that encode B- cell and T- cell receptors and by genes that encode various protiens involved in immune regulatory mechanisms.

b- ***Immunogen dosage and route of adminstration:*** an insufficient dose will not stimulate an immune response either because it fails to activate enough lymphocytes or because, in some cases certain ranges of low doses can induce a state of immunologic unresponsiveness or tolerance. Conversely, an excessively high dose can also induce tolerance.

A single dose of most immunogens will not induce a strong response, rather, repeated administration over a period of weeks is usually required this boosters dose increase the clonal proliferation of antigen – specific B cells or T cells thus increase the lymphocyte populations specific for the immunogen. Adminstrition route strongly influences which immune organs and cell populations will be imvolved in the response, Ag administered intravenously is carried first to the spleen, whereas Ag administered subcutanously moves firest to local lymph nodes, (im) into a muscle, (id) into the skin and (ip) into the peritoneal cavity.

c- ***Adjuvants:*** a large immunogenic substances called a carier or **adjuvant**, yield an immunogenic hapten carrier conjugate to enhance the immunogenicity of antigen.There are two types of adjuvants (Freund's incomplete adjuvant) contains antigen in aqueous solution like mineral oil, the dispreses of oil into small droplets surrounding the antigen permit the very slowly released of antigen from the site of injection.. Aluminum potassium sulfate (alum) is an adjuvant that prolongs the persistence of antigen and is the only adjuvant approved for general human use, while (Freund's complete adjuvant), it is highly effective and containing heat – killed *Mycobacteria* as ingredient which contain Muramyl dipeptide acomponent of cell wall that can activated dendritic cell and macrophage.