Immunology : It is the science which deals with the study of defense mechanisms of the host body against harmful agents, infections, chemicals etc. Immunology began in 1798 when Dr. Jenner vaccinated humans with cow pox crusts to protect them against human pox .

Immunity: means all the physiological reactions which result with the body recognition of the invading material, hence react with it wither the reaction neutralize it and the end result is protection or tissue injury. Any immune response involves, firstly, recognition of the pathogen or other foreign material, and secondly a reaction to eliminate it. The different types of the immune response fall into two categories:

1-Innate (non-specific) immune response: which is the first line of defense against infection and it does not alter on repeated exposure to a given infectious agent and it react in the same manner with each pathogen. It is nonspecific immunity of different mechanisms:

Innate Immunity

Innate immunity can be seen to include four types of defensive barriers:
1- anatomic,2- physiologic, 3-phagocytic, and 4-inflammatory

1-**Physical and anatomic barriers** that tend to prevent the entry of pathogens are an organism's first line of defense against infection**.**

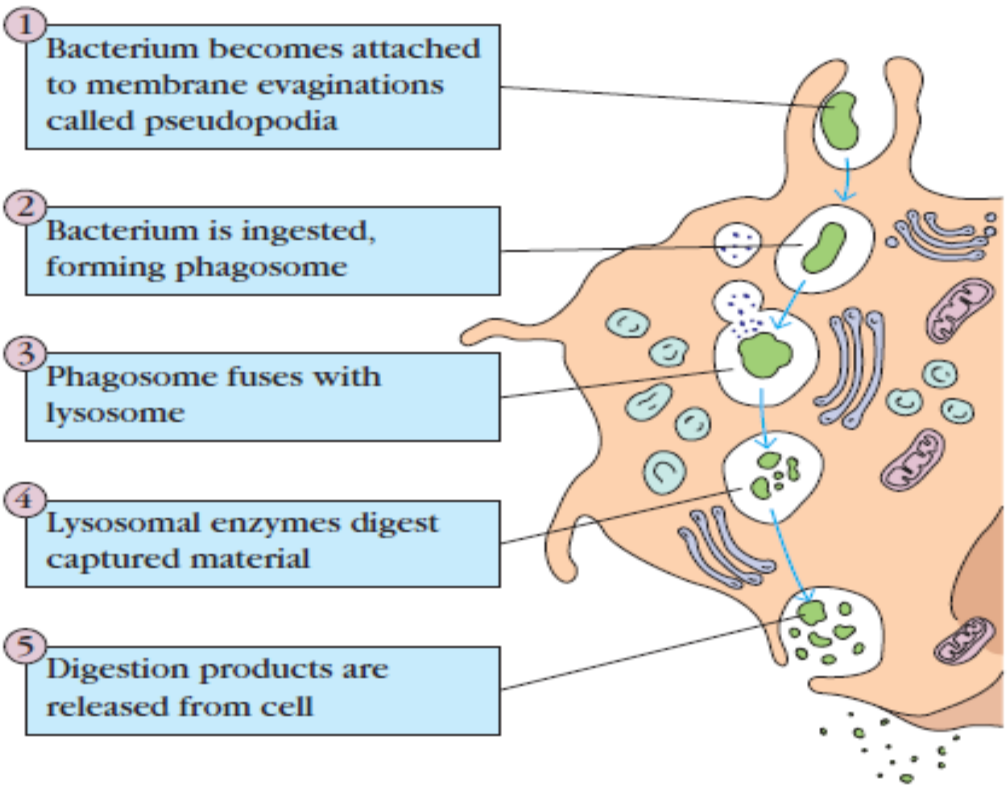
1-The outer epidermal layer consists of dead cells and is filled with a waterproofing protein called keratin.
2- Sebum consists of lactic acid and fatty acids, which maintain the pH of the skin between 3 and 5; this Ph inhibits the growth of most microorganisms.
3-The conjunctivae and the alimentary, respiratory, and urogenital tracts are lined by mucous membranes, not by the dry, protective skin that covers the exterior of the body.
4-Normal flora competes with microbes for attachment sites and nutrients.
5-Mucus entraps foreign microorganisms.
6-Cilia push microorganisms out of body.

2-Physiologic barriers

1-Temperature: Normal body temperature inhibits growth of some pathogens.
Fever response inhibits growth of some pathogens.
2-Low pH Acidity of stomach contents kills most ingested microorganisms.
3-peristalsis of intestine. Urine flow, , tears etc
4-Chemical mediators:* Lysozyme cleaves bacterial cell wall.
*Interferon induces antiviral state in uninfected cells.

*Complement lyses microorganisms or facilitates phagocytosis.

3-Phagocytosis -Another important innate defense mechanism is the ingestionof extracellular particulate material by **phagocytosis.** Phagocytosis is one type of **endocytosis,** the general term for the uptake by a cell of material from its environment. Phagocytosis is the process by which cells engulf microorganisms and particles. Firstly, the phagocyte must move towards the microbe under the influence of chemotactic signals, e.g. complement (see later). For the process to continue, the phagocyte must attach to the microbe either by recognition of the microbial sugar residues (e.g. mannose) on its surface or complement/antibody, which is bound to the pathogen. Following attachment, the phagocyte's cell surface invaginates and the microbe becomes internalized into a phagosome. The resultant phagosome fuses with multiple vesicles containing O2 free radicals and other toxic proteins known as lysosomes to form a phagolysosome. The microbe is subsequently destroyed.



Inflammation Represents a Complex Sequence of Events That Stimulates Immune Responses

Tissue damage caused by a wound or by an invading pathogenic

microorganism induces a complex sequence of events collectively known as the **inflammatory response.** a molecular component of a microbe, such as LPS, may trigger an inflammatory response via interaction with cell surface receptors. The end result of inflammation may be the marshalling of a specific immune response to the invasion or clearance of the invader by components of the innate immune system.
The Roman physician Celsus described the "four cardinal signs of inflammation" as *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain).
The cardinal signs of inflammation reflect the three major events of an inflammatory response

1. *Vasodilation*—an increase in the diameter of blood vessels—of nearby capillaries occurs as the vessels that carry blood away from the affected area constrict, resulting in distension of the capillary network. The puffy capillaries are responsible for tissue redness (*erythema*) and an increase in tissue temperatureAn
2. *increase in capillary permeability* facilitates an influx of fluid and cells from the engorged capillaries into the tissue. The fluid that accumulates **(exudate)** has a much higher protein content than fluid normally released from the vasculature. Accumulation of exudate contributes to tissue swelling **(edema)**.

3. *Influx of phagocytes* from the capillaries into the tissues is facilitated by the increased permeability of the capillaries. The emigration of phagocytes is a multistep process that includes adherence of the cells to the endothelial wall of the blood vessels **(margination)**, followed by their emigration between the capillaryendothelial cells into the tissue **(diapedesis** or **extravasation)**, and, finally, their migration through the tissue to the site of the invasion **(chemotaxis)**. As phagocytic cells accumulate at the site and begin to phagocytose bacteria, they release lytic enzymes, which can damage nearby healthy cells. The accumulation of dead cells, digested material, and fluid forms a substance called pus.

Among the chemical mediators released in response to tissue damage are various serum proteins called **acute-phase proteins.** The concentrations of these proteins increase dramatically in tissue-damaging infections. C-reactive protein is a major acute-phase protein produced by the liver in response to tissue damage.
One of the principal mediators of the inflammatory response is **histamine,** a chemical released by a variety of cells in response to tissue injury. Histamine binds to receptors on nearby capillaries and venules,

causing vasodilation and increased permeability. Another important group of inflammatory mediators, small peptides called **kinins,**

2-Adaptive (specific) immune response: it is a highly specific for a particular pathogen and the immune response improves with each successive encounter with the same antigen. Adaptive immunity displays four characteristic attributes:

_ Antigenic specificity
_ Diversity
_ Immunologic memory
_ Self/nonself recognition

Specific immune mechanisms were acquired either actively or passively

a- Active immunity :

It occurs when an active process of immunity induced by actual infection followed by recovery or followed vaccination process, like DPT. vaccine protects children from Diphtheria, Pertusis and Tetanus. Also short life immunity followed influenza infection.

b- passive immunity

Passive immunity is acquired by giving already immune factors from one person to another. Like immunity of the baby via consumption of mother's milk, also during fetal life, immunoglobulin G (IgG) pass from the mother to the fetus through placenta.

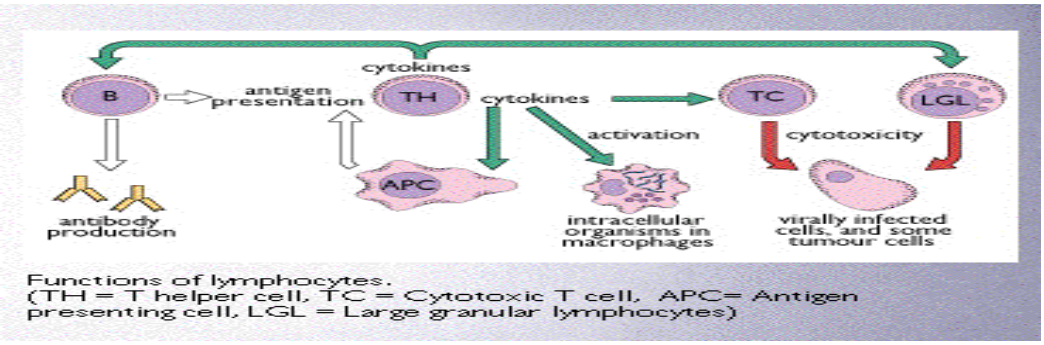
*Another example of passive immunization is the transfer of hyperimmune sera.

-lymphocytes: they are responsible for the specific immune recognition of the pathogens.T-cell mediates the adaptive cell-mediated immunity and B-cell mediate the adaptive (specific) humoral-mediated immunity.

A) ***B-cells***: are genetically programmed to encode a surface receptor specific for a particular Ag. Having recognized its specific Ag they multiply and differentiated into plasma cell, which produce large amounts of antibodies. Like thymic selection during Tcell maturation, a selection process within the bone marrow eliminates B cells with self-reactive antibody receptors. It is estimated that 90% of the B cells produced each

day die without ever leaving the bone marrow. Some of this loss is attributable to **negative selection** and subsequent elimination **(clonal deletion)** of immature B cells that express auto-antibodies against self-antigens in the bone marrow.

B) *T-cells*: are different types and they have a variety of functions. One group interacts with PMN and helps them destroy intracellular pathogens-Th-1-. Another group interacts with B-cells and help them to divide, differentiate and make Ab these are Th-2. a third group of T-cells is responsible for the destruction of host cells which have become infected by viruses or other intracellular pathogen T-cytotoxic cell (Tc). Other T-cells can suppresss the immune response and this might operate through direct killing of APCs or through suppressive cytokines like TGFb.



Functions of lymphocytes.
(TH = T helper cell, TC = Cytotoxic T cell, APC= Antigen presenting cell, LGL = Large granular lymphocytes)

C-***cytotoxic cells:*** those recognize and destroy other cells i.e they have the capacity to kill other cells like:

a- *large granular lymphocytes* which recognize the surface changes that occur on a variety of tumor cells and virally infected cells; They recognizing cells which lack, or have lost their MHC-molecules-NK-cells- or like (macrophage, neutrophil & NK) large granulocyte lymphocytes recognize and destroy some target cells which have become coated with specific Ab in what is called Ab-dependent cell-mediated cytotoxicity (ADCC).

b- *Eosinophil PMN*: they comprise 2-5% of leucocyte and their cytoplasmic granules stain acidic dye. It is engage and damage large extracellular parasites, they damage their different targets by releasing the contents of their intracellular granules close to them. eosinophiles also release histamine and aryle-sulphatase which inactivate histamine and

some of the leukotrienes (SRS-A), thus to damper down the inflammatory response and reduce granulocyte migration into the site of invasion.

Ag-presenting cells (APCs): are required for T-cells to enable them to respond to Ags. APC are a heterogeneous population of leucocytes with very efficient immunostimulatory capacity. They are the interface between the innate and adaptive immune systems. **They are found primarily in the skin, lymph node, spleen, within or underneath most mucosal epithelia and in thymus. Langerhan's cells in the skin and interdigitating cells** (IDCs) which is a migrating cell provides an efficient mechanism for carrying Ag from the skin and mucosa to the Th-cells located in the lymph node. These APC are rich in classII MHC-molecules, which are important for presenting Ag to Th-cells. They bind Ag via complement receptor (CD21, CD35) and Fc-gamma Receptor. Macrophage and classical B-cells are rich in MHC-II, thus able to present Ag to T-cells and these cell also called proffesional APCs.

Somatic cells do not normally express MHC-II but cytokines such as IFN-gamma and TNF-alpha can induce the expression of MHC-II on some of these cells and become able to present Ag like the skin and thyroid epithelium and endothelia (known as non-professional APCs).

Soluble mediators of the immune system:

A wide variety of molecules are involved in the development of the immune response. These include Abs, complements and cytokines.

A-***complement*** proteins; about 30 serum protein, present in an inactive state, activated by different mechanisms to mediate variable functions in the immune system like; opsonization (enhanced phagocytosis), chemotaxis (unidirectional migration of the inflammatory cells), anaphylaxis (mast cells degranulation and release of further inflammatory mediator) and lysis of targeted cells.

B-***cytokines;*** large group of molecules involved in signaling between cells.

C- ***Antibodies;*** they also called immunoglobulin (Igs), they are group of serum molecules produced by B-cells, it's a soluble form of B-cells surface Ag-receptors. In general each Abs can bind specifically to just

one Ag. The part of an AB molecule that bind to Ag called Fab-portion and the other part called constant portion (Fc) which interact with other cells of immune system and act as opsonin which enhance phagocytosis.

Antigenes:-

Any molecule that can be specifically recognized by the adaptive elements of the immune system, that is by B-cells or T-cells or both. Each Ag molecule have a set antigenic determinants, also called epitopes. Epitopes are molecular shapes recognized by Ab. The epitope on one antigen are usually different from those another. Some Ags have repeated epitope. Each Ab recognizes one epitope rather than the whole Ag. Even simple microorganism has many different Ags which may be protein, lipid or carbohydrate.

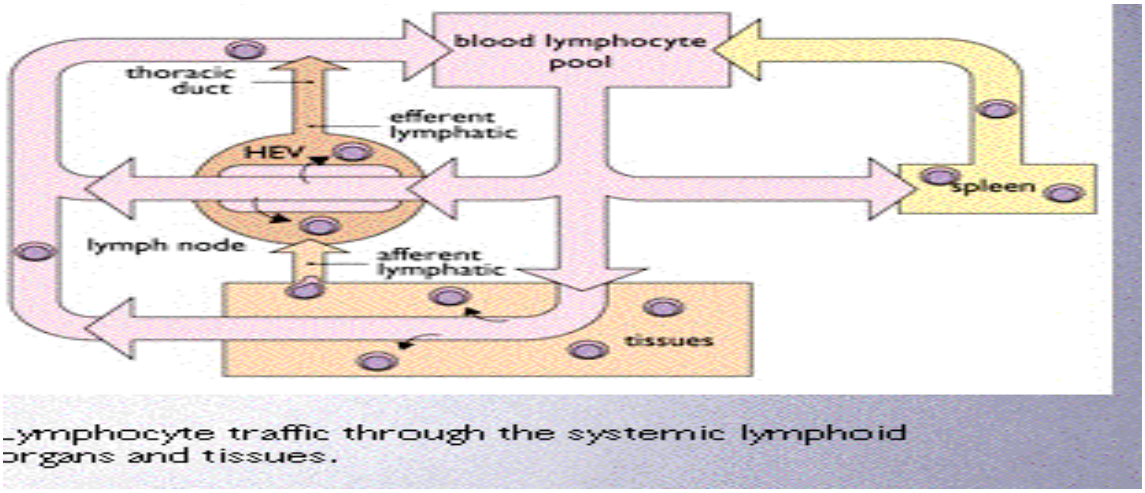
Each lymphocyte B or T is genetically programmed to be capable of recognizing essentially only one particular Ag. The immune system as a whole can recognized any particular Ag and the lymphocytes recognizing any Ag must represent only a minute proportion of the total.

When Ag binds to the few cells that can recognize, they are induced to proliferate rapidly within few days. There are a sufficient number to mount an adequate immune response. I.e the Ag select for and generates specific clone of its own Ag-binding cells this what called clonal selection. The cells usually go through a number of a cycles of division, before differentiating into mature cells. After the infection been overcome some of the newly produced cells remain and these cells called memory cells and it could confer the lasting immunity to a particular pathogen.

About 1-2% of the lymphocyte pool recirculates each hour,in what is called lymphocyte trafficking, this process allow a large numbert of Ag-specific lymphocytes to come into contact with their appropriate Ag. This is specifically important, as lymphoid cell are monospecific and there is only a limited number of lymphocytes capable of recognizing any particular Ag.

Ag-specific lymphocytes are preferentially retained in the lymph nodes draining the source of the Ag.

The lymphocyte trafficking is mediated by the interaction between lymphocyte and the endothelial cell adhesion molecules of postcapillary venules of mucosa or the high endothelial venules (HEV) of the lymph nodes.



ymphocyte traffic through the systemic lymphoid rgans and tissues.

An immunogene is a substance that causes a detectable immune response. Generally, an immunogen is a substance of high molecular weight, greater than 10000 daltons. There are two major classes of immunogen; thymic-dependent and thymic independent immunogens.

Factors affecting immunogenicity:

There are several characteristics of a molecule contribute to it is immunogenicity, these are;, , ,

1- **Foreignness** generally, the greater the phylogenic difference,

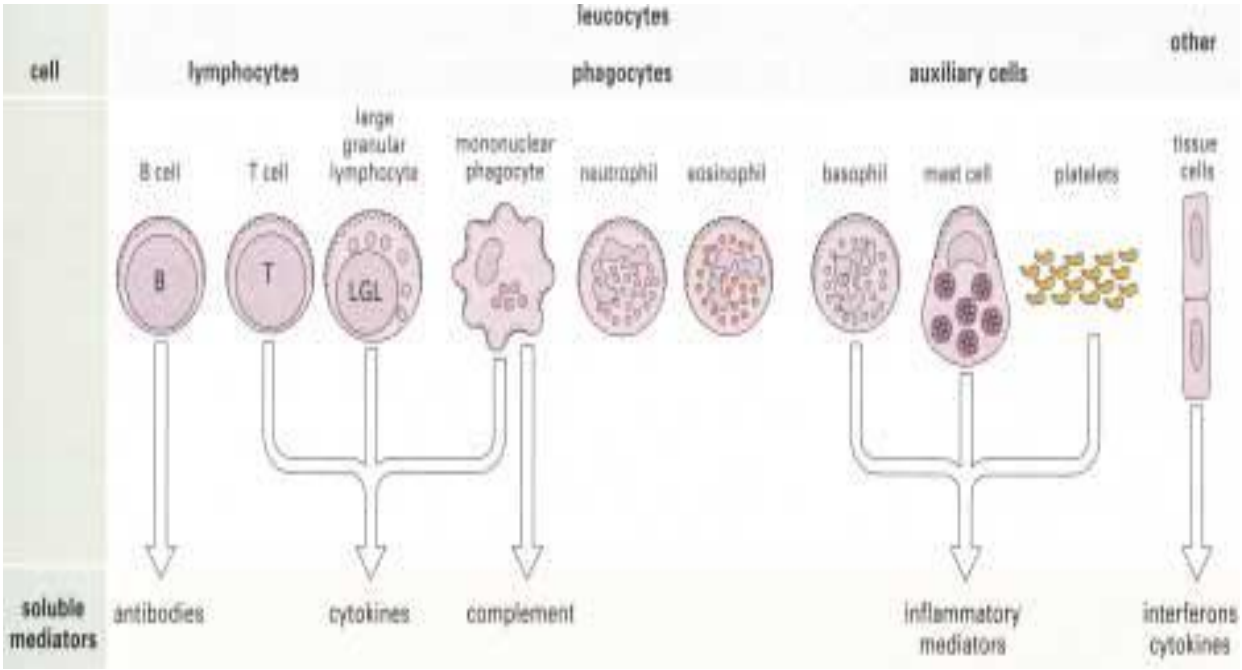
2- molecular size a substance with molecular weight of more than 100000 daltons are usually very immmunogenic and those less than 10000 daltons are non-immunogenic and called **haptens** and required a carrier protein be attached to induce a response.

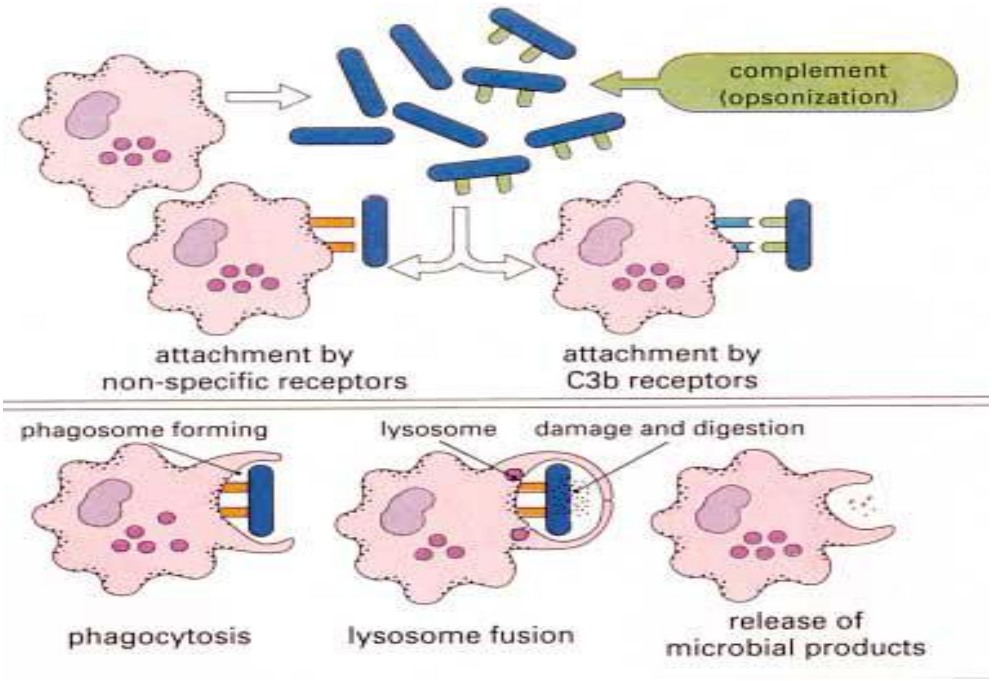
3-chemical composition and complexity Protein and cabohydrate provide the best response, lipid and nucleic acids are weak immunogenic and the more complex the molecule is, the better the immunogene. Hydrophilicity another factor in chemical composition and complexity, which influences immunogenicity. Hydrophilic molecules are more

immunogenic and the hydrophilic portions of immunogen are the antigenic determinants.

4-Genetic composition of the host, it contributes to the ability to respond to an immunogen e.g. a particular polyscharied will be immunogenic when injected in human but will cause no immune response when it's injected into a guinea pig.

5- **The route, dosage, and timing of immunogen adminstration.** Generally, soluble immunogens injected intramuscularly or subcutaneously exhibit a better response than those same immunogens taken intravenously or orally and small dose of immunogen will produce little or no response.




complement
(opsonization)
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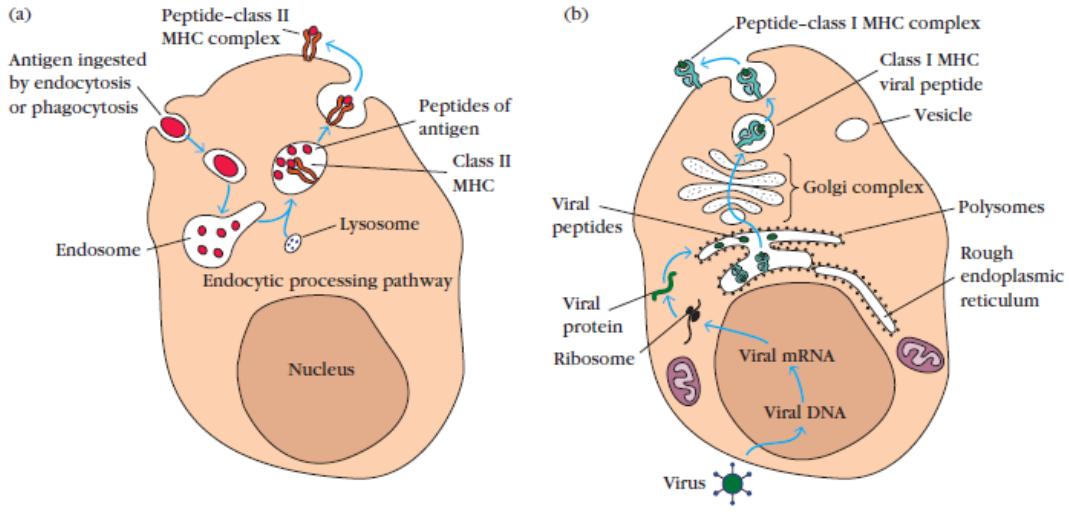
(a)
Peptide–class II
MHC complex
Antigen ingested
by endocytosis
or phagocytosis
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Class II
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Endocytic processing pathway
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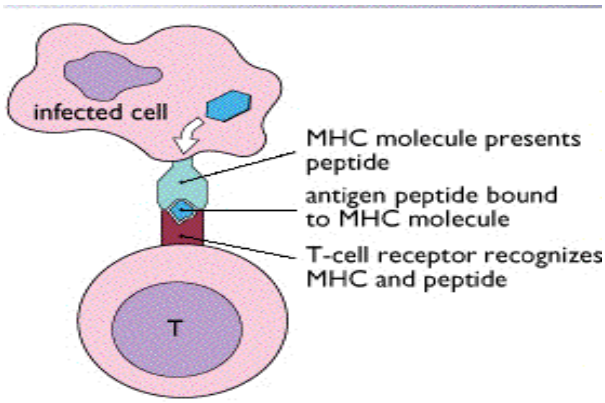

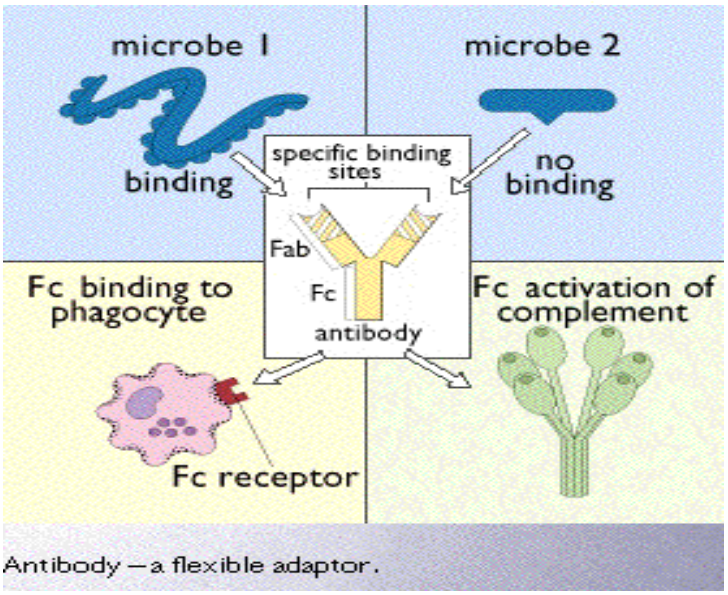

Antibody—a flexible adaptor.