Antigen: is any substance that may be binding specifically to components of the immune system, such as lymphocytes, the B-cell receptor (BCR) on lymphocytes or the T cell receptor on T cells, or soluble antibodies.

Immunogen: is a complete antigen, which is composed of the macromolecules carrier and antigenic determinants (epitopes) that can induce an immune response.

The difference between the two terms is important because many compounds are incapable of inducing an immune response, yet they are capable of binding with components of the immune system that have been induced specifically against them. In general all immunogens are antigens, but not all antigens are immunogens.

Immunogenicity :

It means the ability of antigens to induce humoral and/or cellular immune response.

Types of immunogenicity: Their are tow types

a- Wanted immunogenicity: ex. Vaccine (for bacterial or virus)

b- Unwanted immunogenicity: when organs of the immune system produce an immune response against an antigen which is undesired, like in cases of Autoimmune diseases.

Requirements for immunogenicity:-

A substance must possess the following characteristics to be immunogenic and produce immunogenicity:-

1- Foreignness

2- High molecular weight

3- Chemical complexity

4- Degradability(solubility)

1- Foreignness:-

In general, molecules recognized as self are not immunogenic, so animals normally do not respond immunologically to self.

The immunogenicity of molecules depends on the degree of foreignness; the greater the difference in structure between foreign antigens and the animal's body, the greater intensity of the immune response, and the antigen becomes more immunogenic.

For example:

a- -if the rabbit is injected with its own serum albumin, it will not mount an immune response, it recognises the albumin as self. but if rabbit serum albumin is injected into a guinea pig, the later recognises the rabbit serum albumin as foreign and mounts an immune response against it.

2-High molecular weight:-

All immunogens have a large molecular weight, the antigens must have a certain minimal molecular weight to be considered as immunogens

1- Small compounds with a molecular weight less than 1000 Dalton, as (penicillin & aspirin) are not immunogenic.
2- The substance with molecular weight between 1000-6000 Dalton, as insulin, may or may not be immunogenic.
3- The substance with a molecular weight more than 6000 Dalton in general is immunogenic.

In general, small substances have decreased immunogenicity whereas large substances have increased immunogenicity. (Protein is excellent immunogen, polysaccharide is good, lipid and nucleic acid are not immunogens).

3-Chemical complexity:-

a certain degree of physiochemical complexity is required for an antigen to be immunogenic. simple molecules such as homopolymers of amino acid with a

molecular weight 30000 Dalton(polymer of lysine) is good immunogen but homodimers of others amino acid (D- glutamic acid polymer) in the capsule of *Bacillus anthracis* with a molecular weight 50000 Dalton is not immunogenic, because it have high molecular weight are not sufficient chemically complex.

An increase of the chemical complexity of a compound means an increase in the immune response, leading to an increase in immunogenicity and vice versa.

4-Degradability (solubility**):-**

Most protein antigens need to be processed and represented by antigen-presenting cells (APC) to T cells to initiate the immune response.

Degradation processes of the antigen, called enzymatic degradation of antigen. This leads to expressing antigenic epitopes to the surface of representing cells (APC), and bound to the major histocompatibility antigen, lead to the formation of the complex which binds to T cell.

Antigens are divided into two types according to the enzymatic degradation:-

1- Antigens are stable to the enzymatic degradation. These antigens are not immunogenic (carbohydrates that are not processed and represented, they bind to B cells to produce antibody directly).
2- Antigens are sensitive to the enzymatic degradation; these are good immunogenic.

All these factors are required to consider antigen as immunogen and produce its immunogenicity.

Epitopes (antigenic determinants):-

is a small part of a complex antigen that is capable of binding to the antibody or is present with the major histocompatibility antigen on the surface of the presenting cell's surface.

Antigens may have one or more than one antigenic determinants. The epitopes consist of roughly 5 amino acid or sugar molecules the size of the epitopes is related to the size of the antigen (protein usually has one epitope for each 5 kDa)

Hapten:- it's the substance that fails to induce immune responses in its native form because of its low molecular weight(less than 100 Dalton) and their chemical simplicity. These substances are not immunogenic, unless they are attached chemically or conjugated to a large high molecular weight, physiochemically complex substance called **carriers** to form high molecular weight complex carriers for inducing immune response.

Example: hapten like penicillin drugs , aniline; carrier like protein

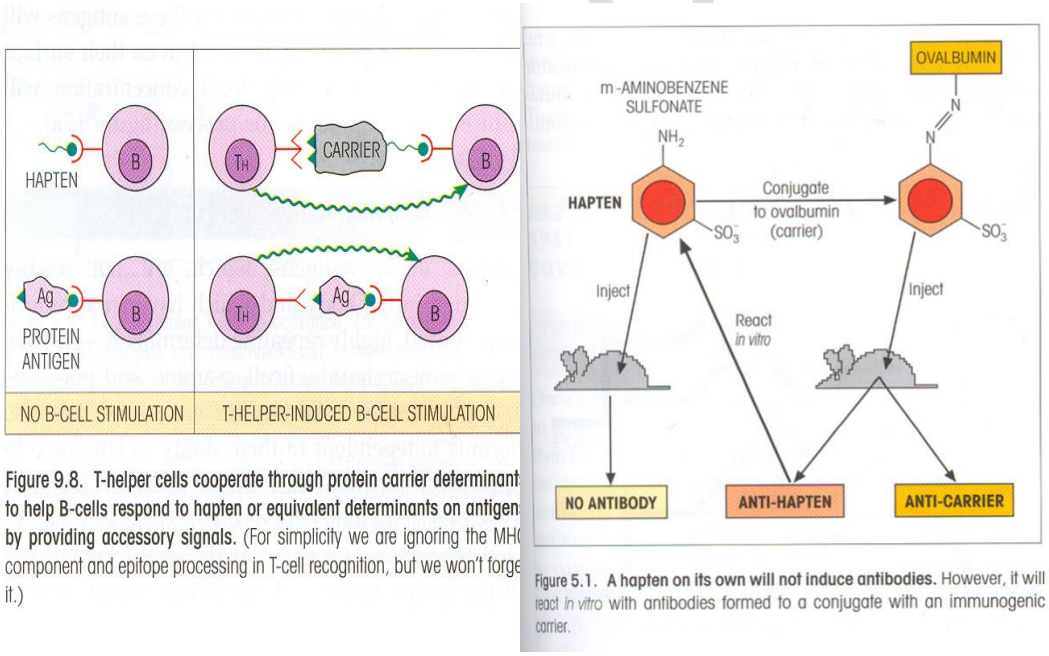

Figure 9.8. T-helper cells cooperate through protein carrier determinant to help B-cells respond to hapten or equivalent determinants on antigen by providing accessory signals. (For simplicity we are ignoring the MH component and epitope processing in T-cell recognition, but we won't forge it.)

Figure 5.1. **A hapten on its own will not induce antibodies.** However, it will react *in vitro* with antibodies formed to a conjugate with an immunogenic carrier.

Adjuvants:-

is a substance that enhances the immune response to a given immunogen, various derivatives or vehicles are often used as Adjuvants.

The name Adjuvants is in the Latin language, meaning " to aid ", so when it's mixed with an immunogen, it enhance immune response against that immunogen.

Difference between Adjuvants and Hapten:

No.	Hapten	Adjuvants
1	Its not immunogenic by itself	It's an immunogen by itself
2	Must be attached chemically to the carrier before administration	It's injected with immunogen in the same site (not required attached with it)
3	Not used in vaccine	Used in the vaccination process
4	Attached to the carrier to be the immunogen	Increase immune response to immunogen

The mechanisms of adjutants are:-

1- increase the biological or immunological half life of antigen
2- Increasing the production of local inflammatory cytokines .
3- Improving and helping to absorb antigen, antigen delivery and processing and presentation by antigen presenting cells.
4- Increase and activate macrophage and lymphocyte.

Examples:-

a- Aluminum hydroxide or aluminum phosphate (alum) is used as an adjuvant in the vaccines , inorganic salts are used in the precipitation & preparation of vaccines, causing the increase in inflammatory response & increase immunogenicity.

b- Freund's complete adjuvant contains oil in water with killed mycobacteria that enhanced uptake of antigen by antigen presenting cells. Or Freund's incomplete adjuvant just contains oil in water.

Classification of antigen :

1- according to its origin

2- according to its dependence of the T cell

Antigen classified according to its origin to:-

i. exogenous antigen (external)

ii. endogenous antigen (internal)

Exogenous antigens include:-

a- bacterial antigen :- which include:

I. Somatic antigen (O Ag): lipopolysaccharide (endotoxin), which is part of the cell wall in Gram-negative bacteria.

II. Flagellar antigen and pili antigen: protein in nature, which cover some of the Gram-negative bacteria.

III. Capsular antigen or virulence antigen (V or K antigen): the capsule of bacteria is important to prevent Phagocytosis and consists of polysaccharide.

IV. Antigens secreted or produced by bacteria: exotoxin and enzymes

Exotoxin: a toxic protein secreted by bacteria and released in surrounding environments when they die, especially in Gram-positive bacteria.

It's a very high immunogenic protein that stimulates the production of antibodies called antitoxin.

Toxoid: is the toxin of bacteria that has been treated to lose its toxicity but retain its immunogenicity

Super antigen: is an antigen causing nonspecific activation of T cells (pyrogenic toxin A of *Streptococcus pyogenes*)

b- Viral antigens:- which include:

i. Viral proteins which represented the capsid
ii. Enveloped viruses have lipoprotein and glycoprotein, which produce antibodies
iii. Viral nucleic acid
iv. Complete virions which produce immune response.

c- Fungal and Parasite Antigen:- parasite worms, protozoa and fungi composed of different proteins, carbohydrates, lipid, and nucleic acids, which can serve as antigen to produce an immune response.

d- Non microbial antigen:-

i. Food containing foreign molecules can cause an allergic reaction.
ii. Dust, fungal spores, pollen grains
iii. Chemical substance like dye
iv. Snake bite or mosquito bites (contain foreign molecules)

Endogenous antigen include :-

a- Cell body structure like cytoplasmic membrane or protein

b- Viral molecules: because virus replication inside the cell some new viral protein which produced by cell are carried to the surface of these infected cell and its recognized by immune system and provide immune responce.

c- **Autoantigens** some situation, and not always, an immune response may be directed against normal body components. This is called an autoimmune

response. Antigens that induced this autoimmune response are called autoantigens.

They can include hormones such as thyroglobulin, structural components such as basement membranes, complex lipids such as myelin, intracellular components such as the mitochondrial proteins, nucleic acids or nucleoproteins and cell surface proteins such as hormone receptors.

The reaction between the Autoantigen and the autoantibody leads to the cause of autoimmune disease.

d- Major Histocompatibility antigen: is an organized cluster of genes encoding polymorphic cell surface molecules that control the antigen presentation by the antigen presenting cells (macrophage, lymphocytes). They act to the activation of T cells.

Major Histocompatibility antigens appear as specialized receptor glycoproteins in the cell surface and differ between species of animals and between individuals in the same animal species.

This are two types of Major Histocompatibility antigen:

i. Major Histocompatibility antigen type I (MHC I): they are associated with representing the antigen by antigen-presenting cells to T cells with aid of CD8. In case of virus infection or tissue rejection

ii. Major Histocompatibility antigen type II (MHC II), they are associated with representing antigen by antigen-presenting cells to T cells with aid of CD4 in case of exogenous antigen.

T cells are a part of lymphocytes that are specialized in the thymus and can be divided into: **cytotoxic T cells,** which act with MHC I to kill body cells, and **T helper** cells, which act with MHC II to promote immune responses by providing Co-stimulation from cytokines and co-stimulator receptors. And **T memory** cell which provides immunological memory.

c- Tumor antigen: occurs only in the tumor cell

Difference between exoantigen and endo-antigen

	Exogenous antigen	Endogenous antigen
1	From outside the body	From inside the body (self-structure)
2	Stimulate T helper cell	Stimulate cytotoxic T cell
3	Assist with the CD4 of the complement	Assist with the CD8 of complement
4	Have been involved with MHC II	Have been involved with MHC I
5	Occur in case of infection or injection of antigen	Mostly in the case of autoimmune disease

Antigen classified according to its dependence of T cell into:

i. Thymic dependent **required** help from the T helper cell to produce B cell stimulation.

ii. Thymic independent, **not required** help from the T helper cell to produce B cell stimulation.

In general, when a foreign antigen enters the body, it first must be trapped and processed so that it can be recognized as being foreign. Then this information must be converted either to the antibody–forming system or to the cell-mediated immune system. These systems must then respond by the production of specific antibodies and/or cells that are capable of eliminating the antigen.