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Immunological tolerance :-

Remarkable properties of the normal immune system is that it can react to an enormous variety of microbes but does not react against the individual's own (self) antigens. This unresponsiveness to self antigens, called immunological tolerance.

These mechanisms are responsible for one of the cardinal features of the immune system—namely, its ability to discriminate between self and nonself (usually microbial) antigens. Example: immune system of a pregnant female has to accept the presence of a fetus that expresses antigens derived from the father.

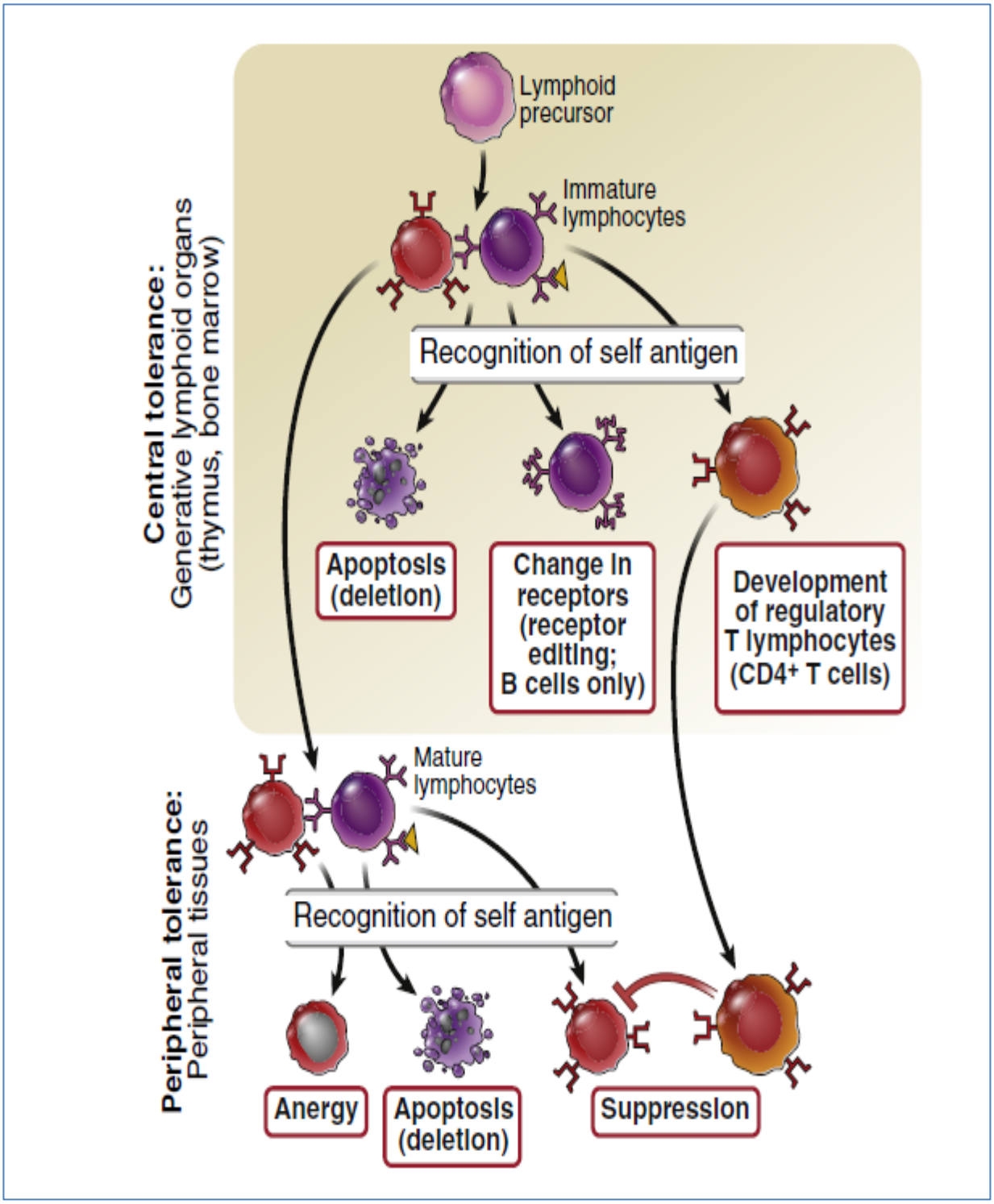
IMMUNOLOGICAL TOLERANCE MECHANISMS:-

The choice between lymphocyte activation and tolerance is determined largely by the nature of the antigen and the additional signals present when the antigen is displayed to the immune system.

When lymphocytes with receptors for a particular antigen encounter this antigen, any of several outcomes is possible. The lymphocytes may be activated to proliferate and to differentiate into effector and memory cells, leading to a productive immune response; antigens that elicit such a response are said to be immunogenic. The lymphocytes may be functionally inactivated or killed, resulting in tolerance.

The phenomenon of immunological tolerance is important for several reasons. First, as we stated at the outset, self antigens normally induce tolerance, and failure of self-tolerance is the underlying cause of autoimmune diseases. Second, if we learn how to induce tolerance in lymphocytes specific for a particular antigen, we may be able to use this knowledge to prevent or control unwanted immune reactions. Strategies for inducing tolerance are being tested to treat allergic and autoimmune diseases and to prevent the rejection of organ transplants.

Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, a process called central tolerance, or when mature lymphocytes encounter self antigens in peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance.



T cell Tolerance :-

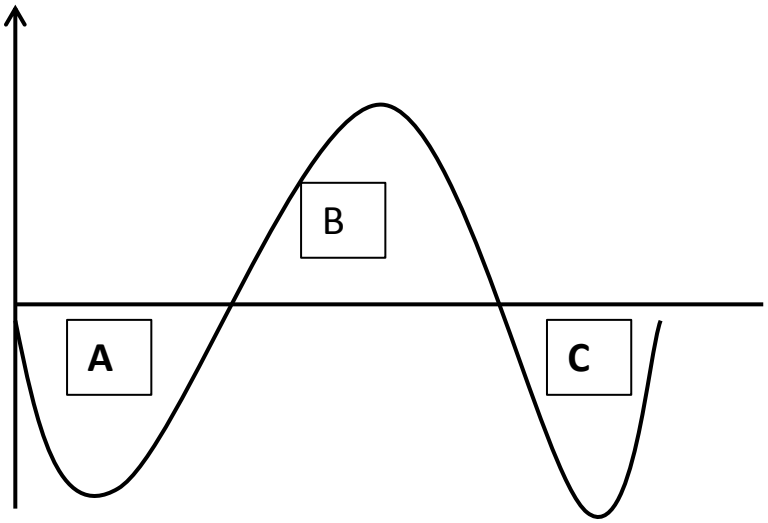
Peripheral tolerance is induced when mature T cells recognize self antigens leading to functional inactivation (anergy) or death, or when the self-reactive lymphocytes are suppressed by regulatory T cells. Antigen recognition without adequate costimulation results in T cell anergy or death, or makes T cells sensitive to suppression by regulatory T cells.

B cell tolerance:-

When immature B lymphocytes interact strongly with self antigens in the bone marrow, the B cells either change their receptor specificity (receptor editing) or are killed (deletion), Mature B lymphocytes that encounter self antigens in peripheral lymphoid tissues become incapable of responding to that antigen B cells recognize an antigen and do not receive T cell help

Also repeated exhaustive to the Ag stimulation and might be stimulated and differentiate in to short lived plasma cell then no memory cell will remain to

Antibody production



A: low dose of antigen cause tolerance.

B: moderate dose of antigen cause immune response.

C: excess dose of antigen cause immune paralysis .

In general tolerance is the ability of an animal to mount an immune response against a specific Ag .

substance that induce tolerance:-

Some type of Ag like pneumococcus bacteria can bind to B- cell these types of Ag freeze the B- cell membrane and block any further response by these cell , oral administration of some types of Ag may induce tolerance.

Transplantation :-

transfer of many tissues or organs between different parts of the body or between different individuals.

Autograft:- graft moved to a different part of an animal's own body, such transplants do not trigger an immunresponse. Examples of autografting include the use of skin to cover a burn in plastic surgery and the use of a segment of vein to bypass blocked cardiac arteries.

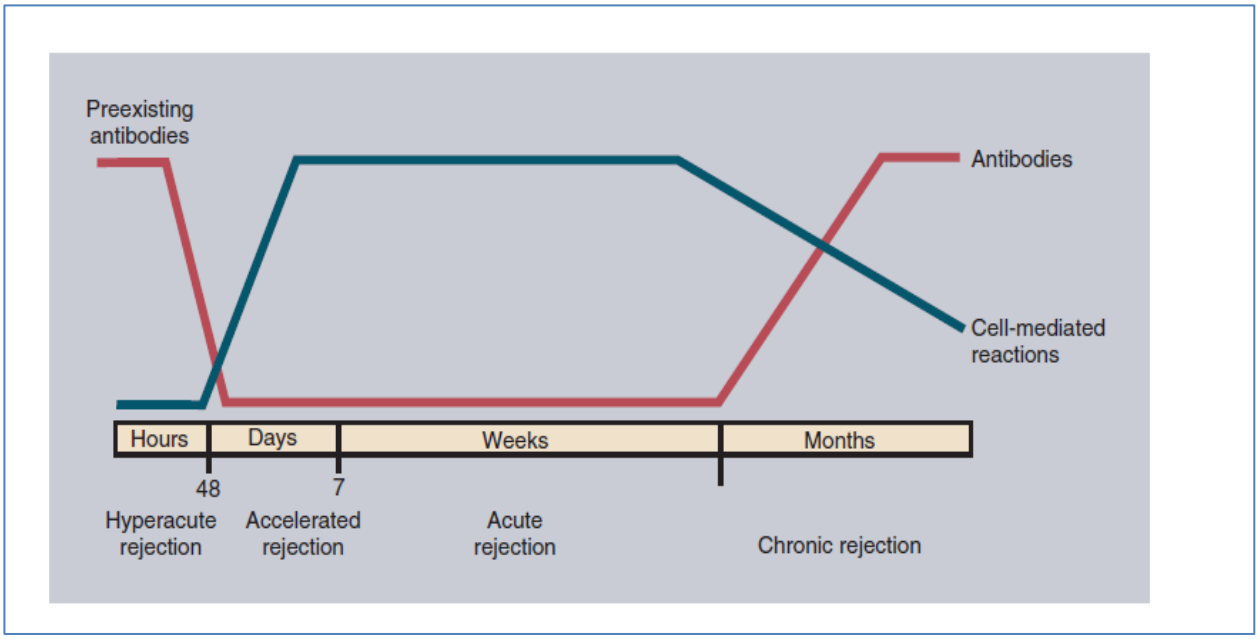
Isografts:- are grafts transplanted between two genetically identical individuals. Thus a graft between identical twins is an isograft. Similarly, Since the animals are identical, the immune system of the recipient does not differentiate between the graft and normal body cells.

Allografts:- are transplanted between genetically different members of the same species. Most grafts performed on animals or humans for therapeutic reasons are of this type because tissues are obtained from a donor who is usually unrelated to the graft recipient. Because the major Histocompatibility complex (MHC) and blood group molecules on the allograft are different from those of their host, allografts induce a strong immune response that causes graft rejection.

Xenografts:- are organ grafts transplanted between animals of different species. Thus, the transplant of a baboon heart into a human infant is a xenograft. Xenografted tissues differ from their host both biochemically and immunologically. As a result, they can provoke a rapid, intense rejection response that is very difficult to suppress

Mechanisms of tissue rejection :-

Allografted organs represent a major source of these foreign molecules. They include antigens such as the foreign blood group and MHC molecules expressed on the grafted cells **The response to MHC antigens on another individual's cells is one of the strongest immune responses known**. The acute response to donor histocompatibility antigens causes acute rejection and is mainly mediated by cytotoxic T cells attacking graft vascular endothelium. Chronic rejection and rejection directed against donor blood groups are mainly antibody mediated. The mechanisms of allograft rejection are basically depended on synergism action between antibodies and T cells.



Autoimmunity:-

Is defined as an immune response against self (autologous) antigens ,Most autoimmune diseases result from a failure to ensure that tolerance is maintained against self-antigens .

Induction of Autoimmunity

1- they can result from a normal immune response to an unusual or abnormal antigen .

2- they can result from an abnormal immune response to a normal antigen.

Many autoimmune responses simply reflect a normal immune response to an antigen that has been previously hidden or are a result of cross-reactivity between an infectious agent such as virus infections, vaccination, and some drugs and a normal body component. There may be a strong genetic predisposition to develop autoimmunity.

Mechanism of autoimmune

1- Antigens Hidden in Cells:-
Many auto antigens are found in places where they never counter circulating lymphocytes. For example, in the testes, cornea any disturbance make them visible to T cell and autoimmune disease occurs.

2- Antigens Generated by Molecular Changes:-

The production of some autoantibodies may be triggered by the development of completely new epitopes on normal proteins. examples of autoantibodies generated in this way are the rheumatoid factors.

3- Receptor Editing immature B or T cell.

4- Failure of Regulatory Control This may result from a failure of the normal control mechanisms of the immune system.

Infection-Induced Autoimmunity Autoimmune diseases are triggered by many environmental factors, and infectious agents are among the most important. Such as virus , parasite ,or evenly fetus.

5- Mechanisms of Tissue Damage in Autoimmunity:-

Autoimmune disease results when tissues are damaged by auto reactive T cells or antibodies. This damage is a result of hypersensitivity reactions. However, multiple mechanisms may be involved in any such disease, and these may vary with time.

Diseases of autoimmune

Diseases that mainly affect a single organ or tissue result from an abnormal response to a small number of self-antigens .

significant loss of control of the immune system as a whole. It is likely that all organs of the body are potentially susceptible to this form of immunological attack and cause generalized disease.

1- Equine Recurrent Uveitis:-

The most common cause of blindness in horses is recurrent uveitis (or periodic ophthalmia). Horses suffer recurrent attacks of uveitis, retinitis, and vasculitis. In acute cases, they develop blepharospasm, lacrimation, and photophobia. Each attack gets progressively more severe and gradually spreads to involve other eye tissues until complete blindness results. Treatment: Systemic and topical corticosteroid therapy

Autoimmune Nephritis:-

Horses may develop autoantibodies to glomerular basement membranes that result in glomerulonephritis and renal failure.

Systemic Lupus Erythematosus:

Equine Lupus Equine lupus presents as a generalized skin disease (alopecia, dermal ulceration, and crusting), accompanied by an antiglobulin-positive anemia. The disease is remarkable in sofar as affected horses may be almost totally

Hairless . Affected horses may also have glomerulonephritis, synovitis, and lymphadenopathy.

Treatment of reported cases has been unsuccessful.

Dog Lupus Erythematosus:-

Lupus affects middle-aged dogs (between 2 and 12 years of age) and affects males more than females. The disease is commonly seen in Collies, German Shepherds, Nova Scotia Duck Tolling Retrievers, and Shetland Sheep dogs . Dogs may present with one or more signs of disease. However, the disease is progressive, so the severity of the lesions and the number of organ systems involved gradually increases in untreated cases. The most characteristic presentation is a
fever accompanied by a symmetrical, polyarthritis. . Other common presenting signs include renal failure, skin disease , lymphadenopathy or splenomegaly , leukopenia , hemolytic anemia, and thrombocytopenia . Dogs may also show myositis or pericarditis and neurological abnormalities
The skin lesions are highly variable It is characterized by vesicular erosive
and ulcerative skin lesions, sub epidermal vesicles but are commonly restricted to areas exposed to sunlight. Young adult dogs develop scaling and
alopecia on the muzzle, pinnae, and dorsum

It may be treated with aggressive immunosuppressive therapy.

Treatment
Lupus in animals usually responds well to high doses of corticosteroids
(prednisolone or prednisone), accompanied, if necessary, by cyclophosphamide, azathioprine,. Levamisole has also been used with success.

Erosive Polyarthritis:-
Rheumatoid Arthritis The most important immunemediated erosive polyarthritis

Dogs with rheumatoid arthritis may present with chronic depression, anorexia,
and pyrexia in addition to lameness, which tends to be most severe after rest (e.g., immediately after waking in the morning).
The disease mainly affects peripheral joints, which show symmetrical swelling and stiffness. Rheumatoid arthritis tends to be progressive and eventually leads to severe joint erosion and deformities. In advanced cases affected joints may fuse as a result of the formation of bony ankyloses.

Treatment
high doses of corticosteroids, and replacement therapy ,also antibiotic may be used.

Immune response :-

Is the body's response originating from immune system activation by antigens. Immune response can be innate (natural, nonadaptive, or nonspecific)or adaptive (acquired or specific).

Immune response also can be defined as :

Defense against microbes is mediated by the effector mechanisms of innate and adaptive immunity.

The survival and pathogenicity of microbes in a host are critically influenced by the ability of the microbes to evade or resist the effector mechanisms of immunity.

Inherited and acquired defects in innate and adaptive immunity are important causes of susceptibility to infections.

1- Bacterial immunity :-

The principal mechanisms of innate immunity to extracellular bacteria are complement activation, phagocytosis, and the inflammatory response.

There are basic mechanisms by which the adaptive immune responses combat bacterial infections:

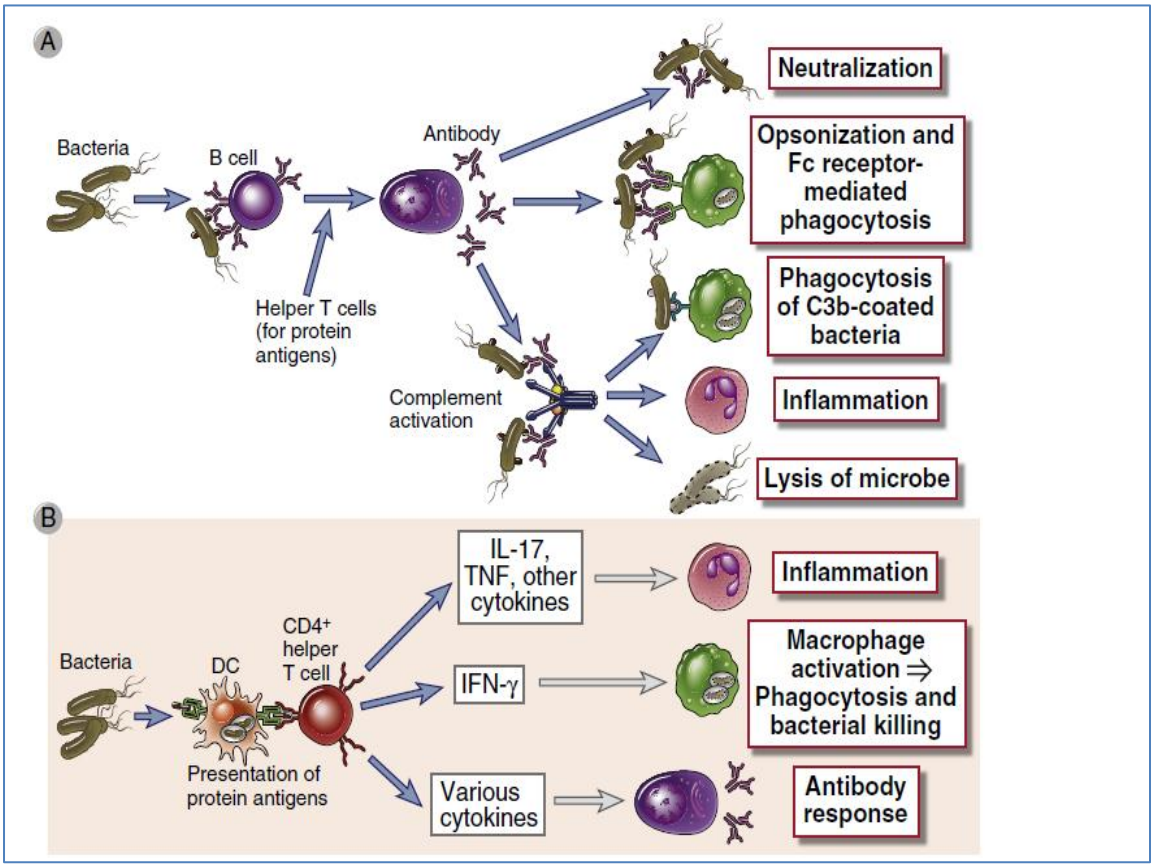
(1) neutralization of toxins or enzymes by antibody.

(2) killing of bacteria by the classical complement pathway.

(3) opsonization of bacteria by antibodies and complement, resulting in their Phagocytosis and destruction.

(4) destruction of intracellular bacteria by activated macrophages.

(5) direct killing of bacteria by cytotoxic T cells and NK cells.



Bacteria evade Immune System by :

1- Presence of capsule.

2- Multiplication of bacteria inside the macrophages, like salmonella, Brucella, Listeria, and Mycoplasma.

3- Changing of surface antigens: some bacteria like *Campylobacter fetus*.

4- Suppression of T lymphocytes: some bacteria have the ability to inhibit T cells, like *Mycoplasma mycoides*

5- Production of aphlatoxins: This toxin inhibits immune responses.

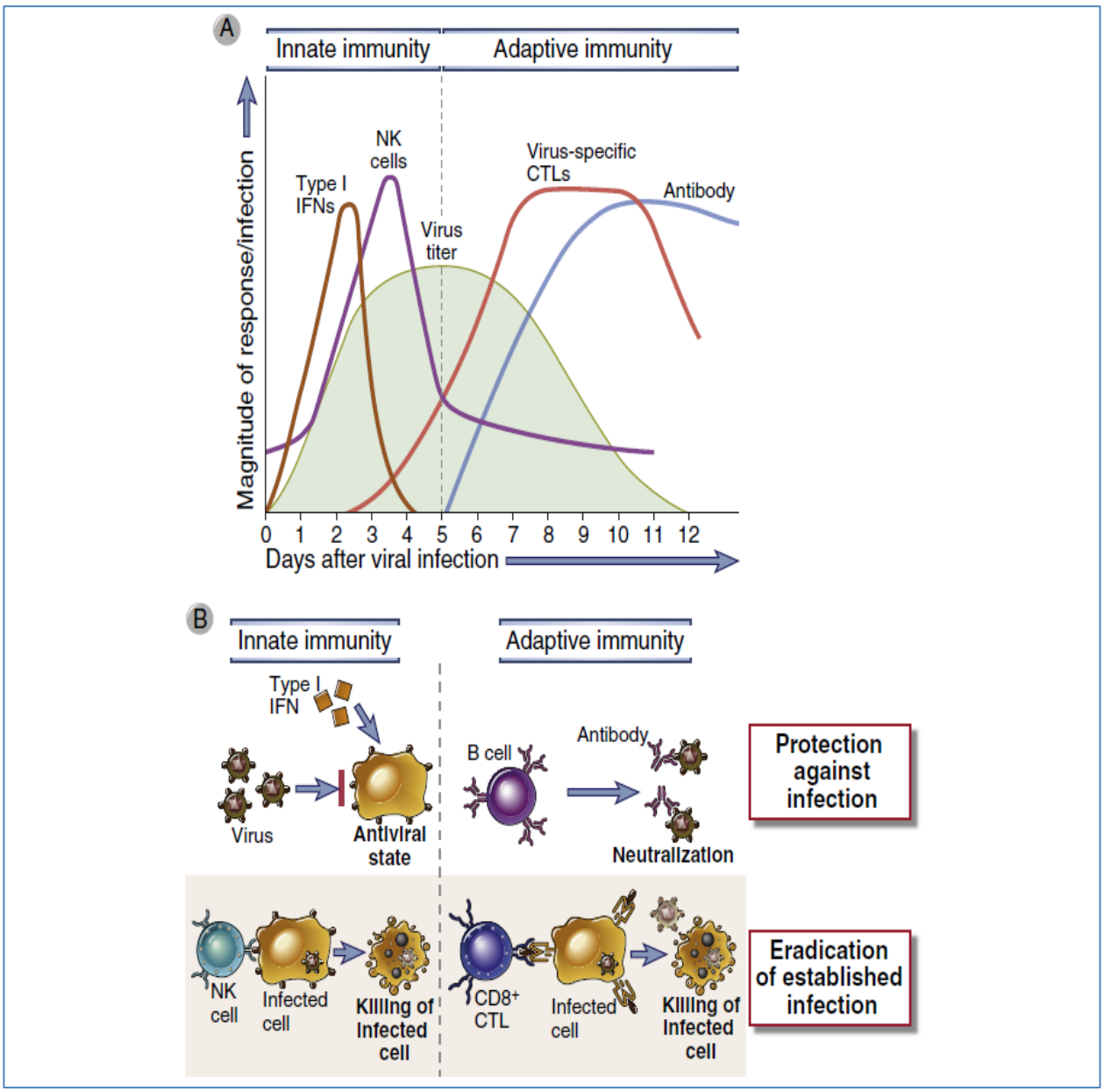
6- Release of cAMP (cyclic adenine monophosphate): This prevents fusion of lysosomes with phagosomes.

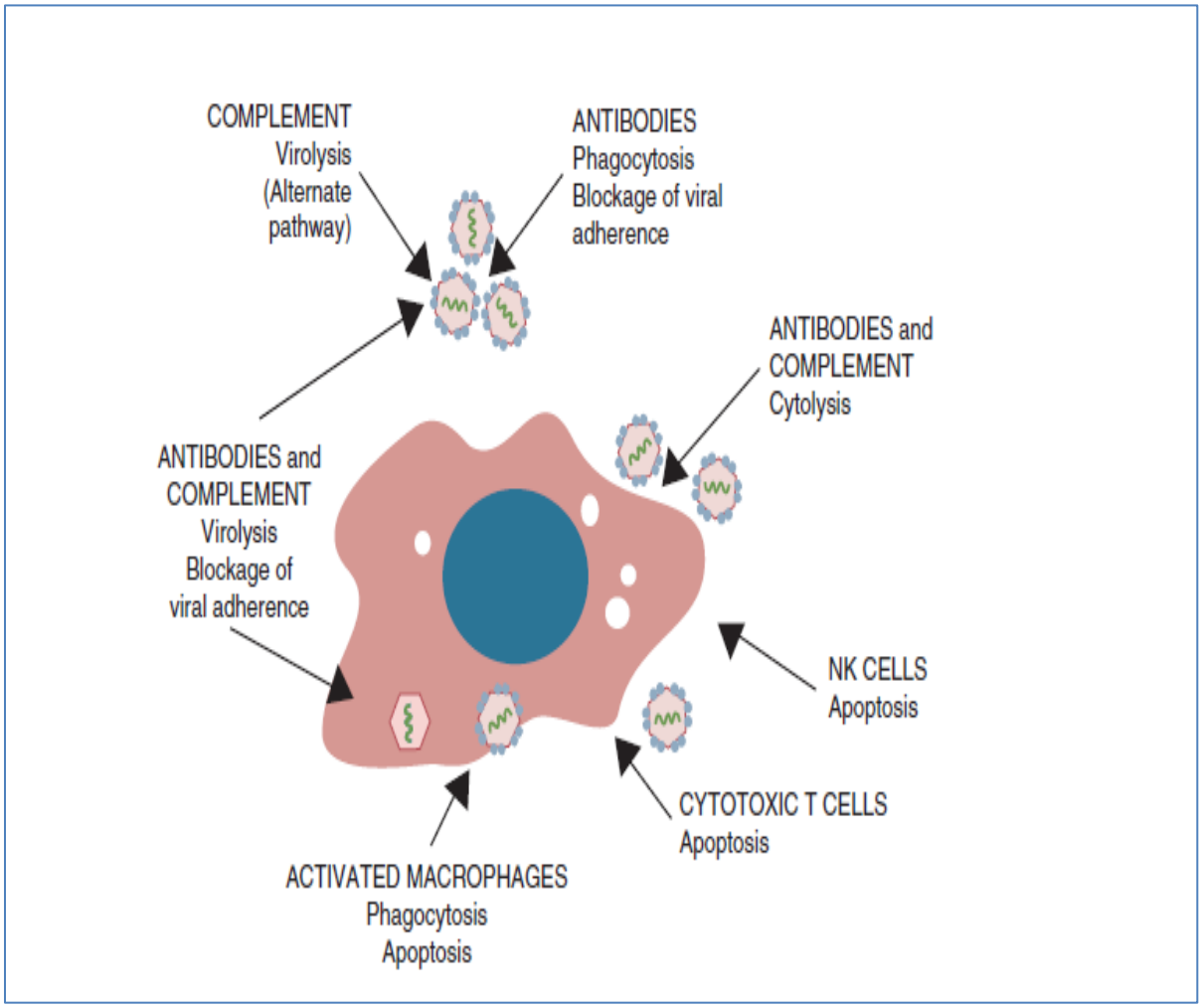
2- IMMUNITY TO VIRUSES :-

A-Innate immunity to virus occurs by interferon.

B- ***Adaptive immunity against viral infections is mediated by antibodies, which block virus binding and entry into host cells*** (neutralizing them)***, and*** Cell-mediated responses are primarily responsible for antiviral immunity. The major mechanism involved is the killing of virus infected cells by cytotoxic T cells. •

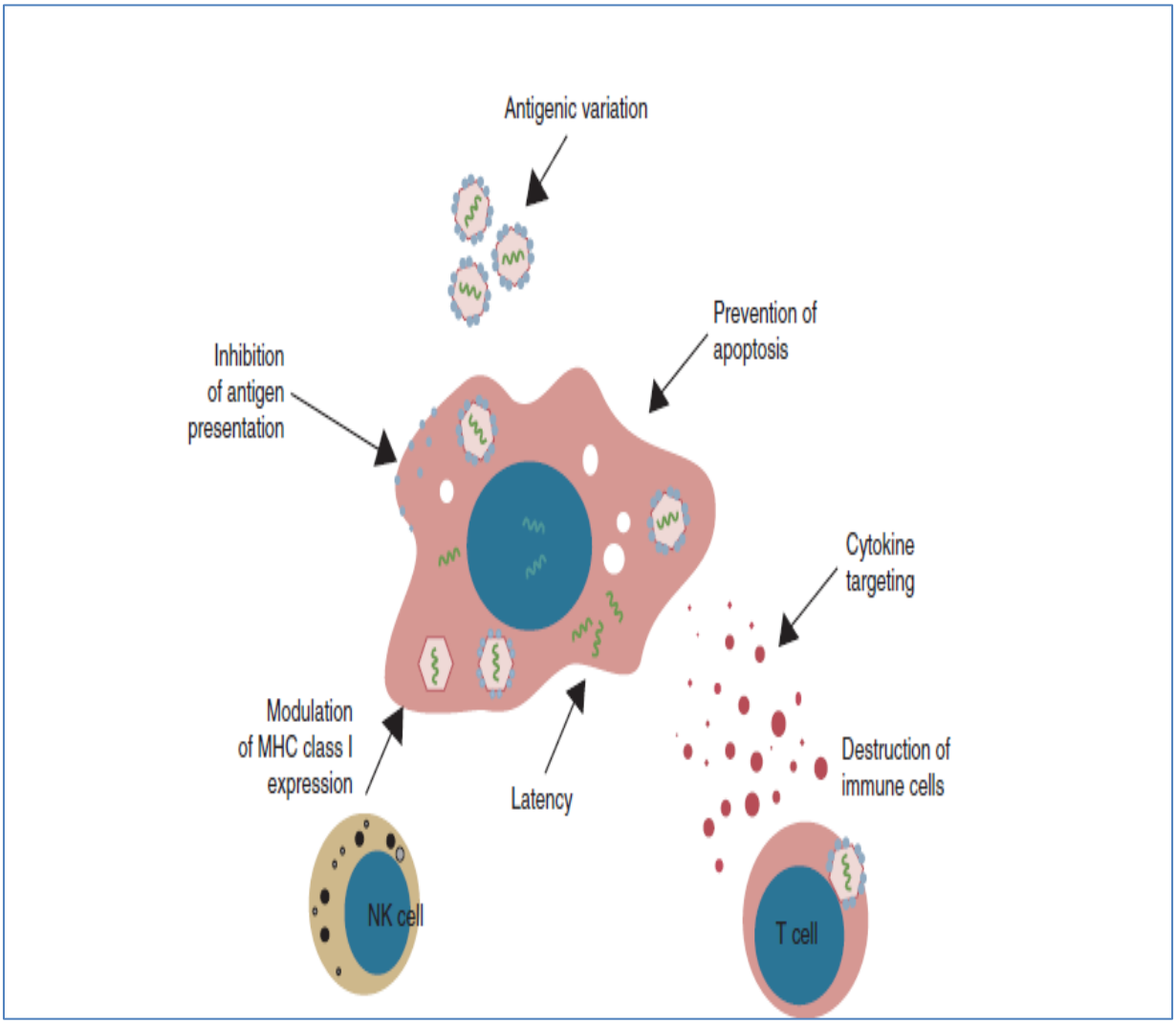
Because viruses are obligate intracellular parasites, they employ a wide variety of methods of evading the immune response . •





Viruses evade Immune system by :

1. Changing of viral surface antigens: like influenza viruses.
2. Changing of cellular surface anti gens: like measles viruses.
3. Integration of viral N.A. with cellular N.A.: like HIV virus in AIDS.
4. Immuno-suppression due to lymphatic tissue infection.
5. Stress factors and Steroids



3-Parasite immunity:-

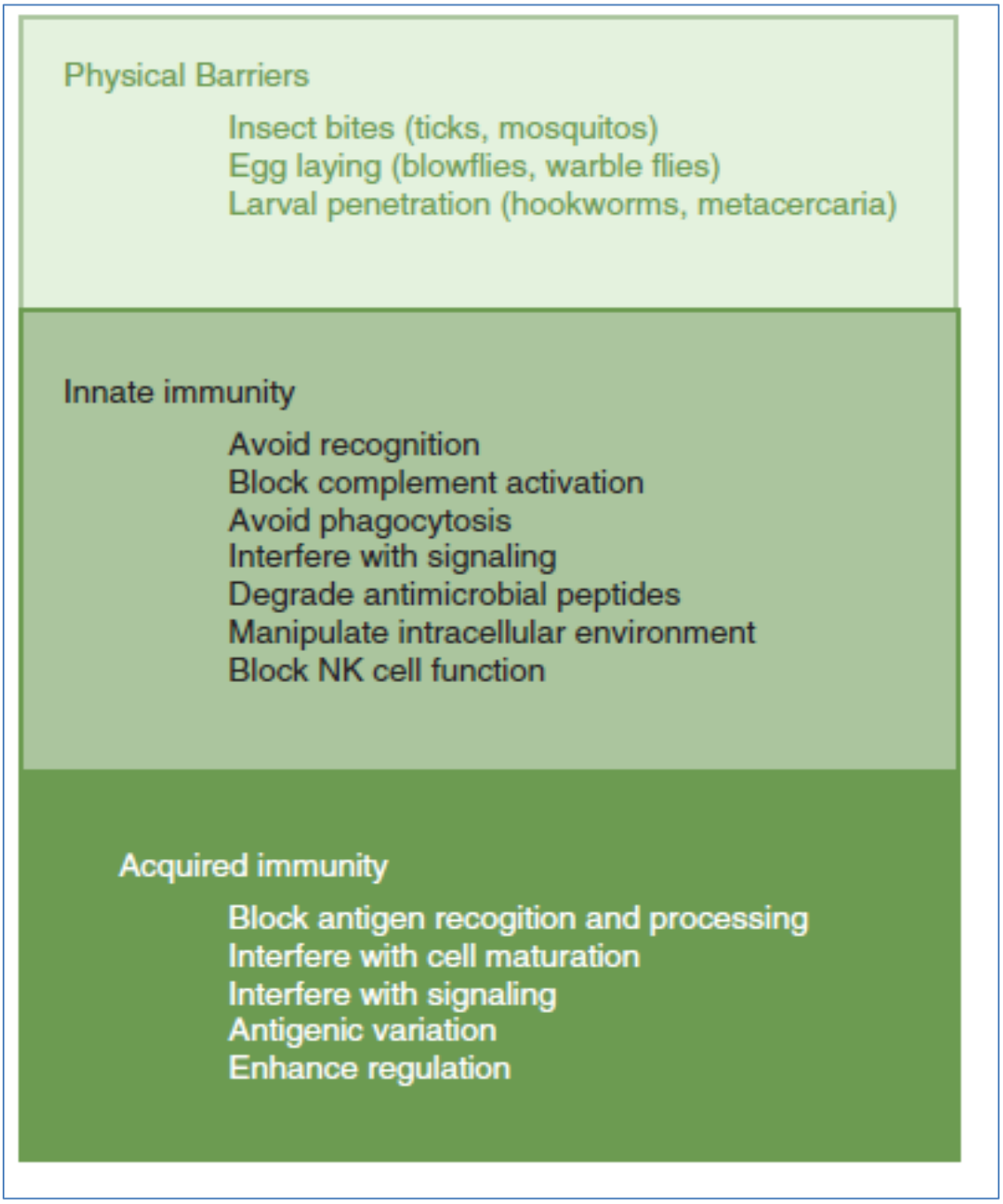
Parasites, by definition, are able to evade their host's immune response for at least sufficient time for the parasite to reproduce.

In general antibody-mediated immune responses protect against extracellular protozoa, where as cell-mediated responses control intracellular protozoa..

Helminth parasites have a unique ability to trigger T responses and immunoglobulin E (IgE) production. IgE may have evolved as an antiparasite antibody.

Parasitic worms have a thick cuticle that protects them against damage caused by most protective cells. However, Eosinophil appear to be uniquely able to damage and kill helminthes.

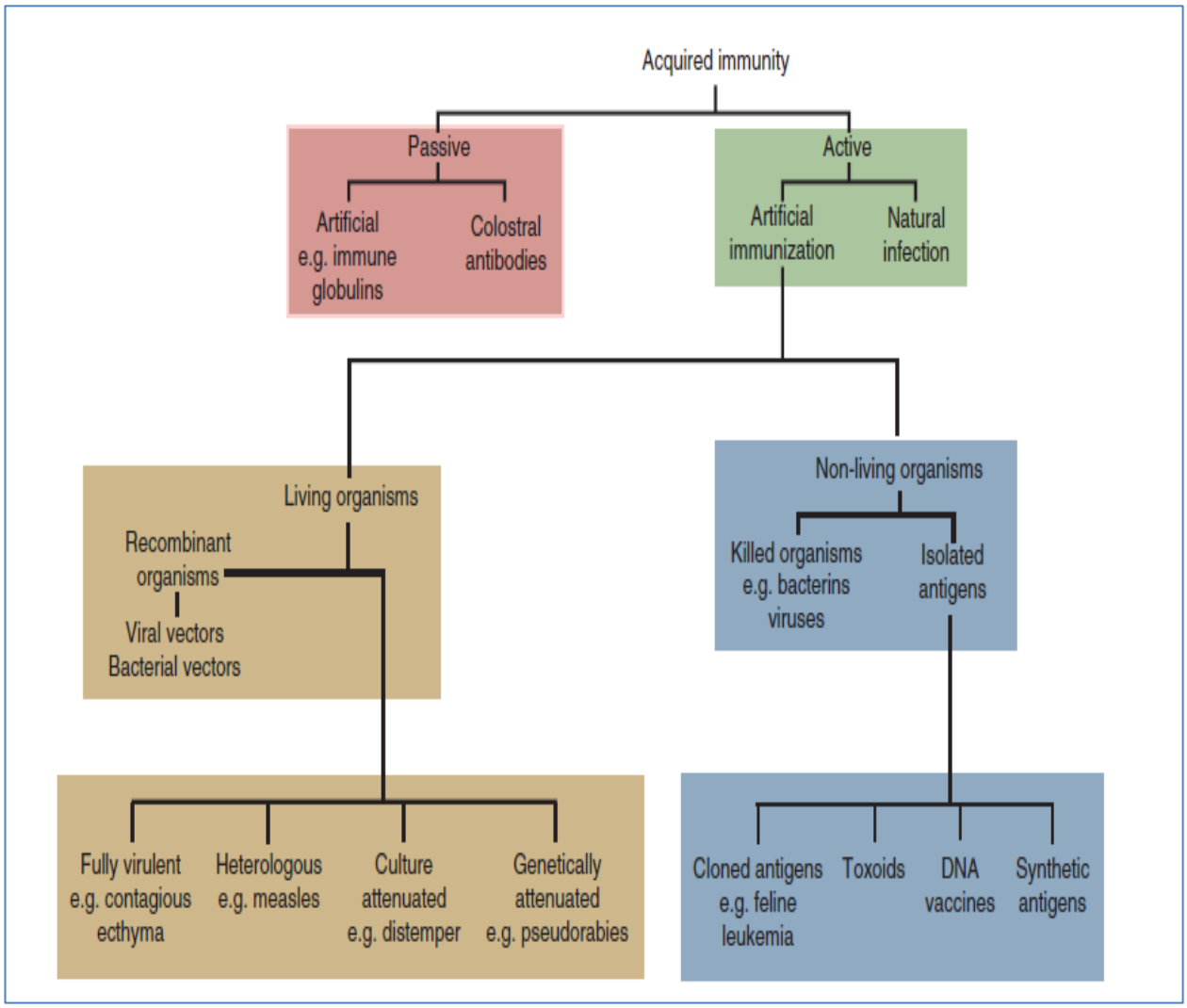
Parasite Evade immune system by :

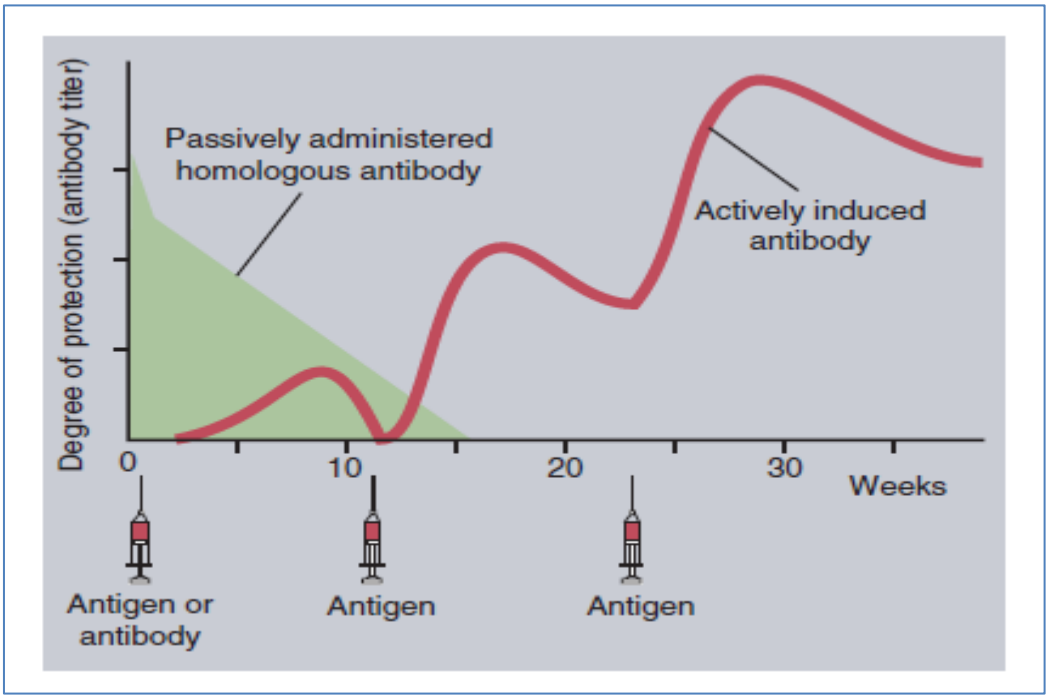


An animal can be made immune to infection in two general ways:-
passive immunization and active immunization.

1- . Passive immunization produces temporary immunity by transferring antibodies from a resistant to a susceptible animal. These passively transferred antibodies give immediate protection, but since they are gradually catabolized, this protection wanes, and the recipient eventually becomes susceptible again. Ex: anthrax infection

2- Active immunization, in contrast, involves administering antigen to an animal so that it responds by mounting an immune response. reimmunization or exposure to infection in the same animal will result in a secondary immune response and greatly enhanced immunity. The disadvantage of active immunization is that, as with all adaptive immune responses, protection is not conferred immediately. However, once established, immunity is long-lasting and capable of restimulation. EX: Pox vaccination





characteristic of vaccine :-

1- vaccines must obtaining strong immunity
2- free of adverse side effects. (In effect it should stimulate adaptive immunity without triggering the inflammation associated with innate immunity.)
3- cheap, stable, and adaptable to mass vaccination
4- should stimulate an immune response distinguishable from that due to natural infection

critical properties of vaccination

1- antigen must be delivered efficiently so that antigen-presenting cells can process antigen and release appropriate cytokines.
2- both T and B cells must be stimulated.
3- helper and effector T cells must be generated to several epitopes in the vaccine so that individual variations

are minimized.

4- the antigen must be able to stimulate memory cells in such a way that protection will last as long as possible.

Type of vaccine :

A- live vaccines:-
we obtain it by attenuation antigen in deferent method and infect host cells and undergo antigen replication and and characterized by

1- Fewer doses required Stable on storage
2- Adjuvants unnecessary
3- Less chance of hypersensitivity
4- Induction of interferon
5- Relatively cheap

6- Can be given by natural route
7- Stimulate both humoral and cell-mediated response

B- Killed organisms:-
and we obtain it by killing the antigen ,the vaccine act as exogenous antigens. This may not be the most appropriate response to some organisms but its characterized by :

1- Stable on storage
2- Unlikely to cause disease through residual virulence
3- Do not replicate in recipient Unlikely to contain live contaminating organisms
4- Will not spread to other animals
5- Safe in immunodeficient patients
6- Easier to store
7- Lower development costs
8- No risk of reversion