Methods of Studying Endocrine Functions and their Manipulations

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Methods of Studying Endocrine Functions and their Manipulations

- Two general types of investigations –

1. **augmenting the function in question.**

a. administration of extracts or organ substance by mouth

b. Grafting

c. increasing the output from the individual glands as by massage or stimulation of their secretory nerves.

2. **decreasing the function in question.**

a. Gland extirpations

b. by injecting substances to cause bland infarcts in the glands

c. by ligating the blood vessels supplying the organs in question

- Clinical observations of patients with spontaneous or surgical gland deficiencies are also of great value

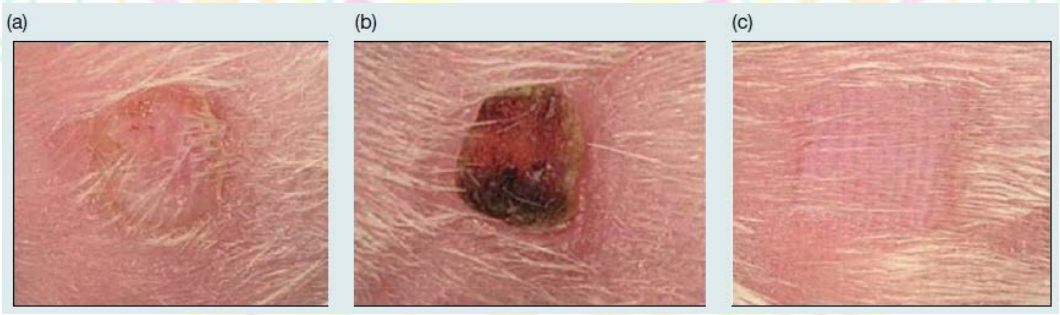


Fig. 1- Appearance of skin grafts in mice. (a) Graft undergoing rejection;
(b) complete rejection (scab); and, for comparison,
(c) a completely healed skin graft without evidence of rejection

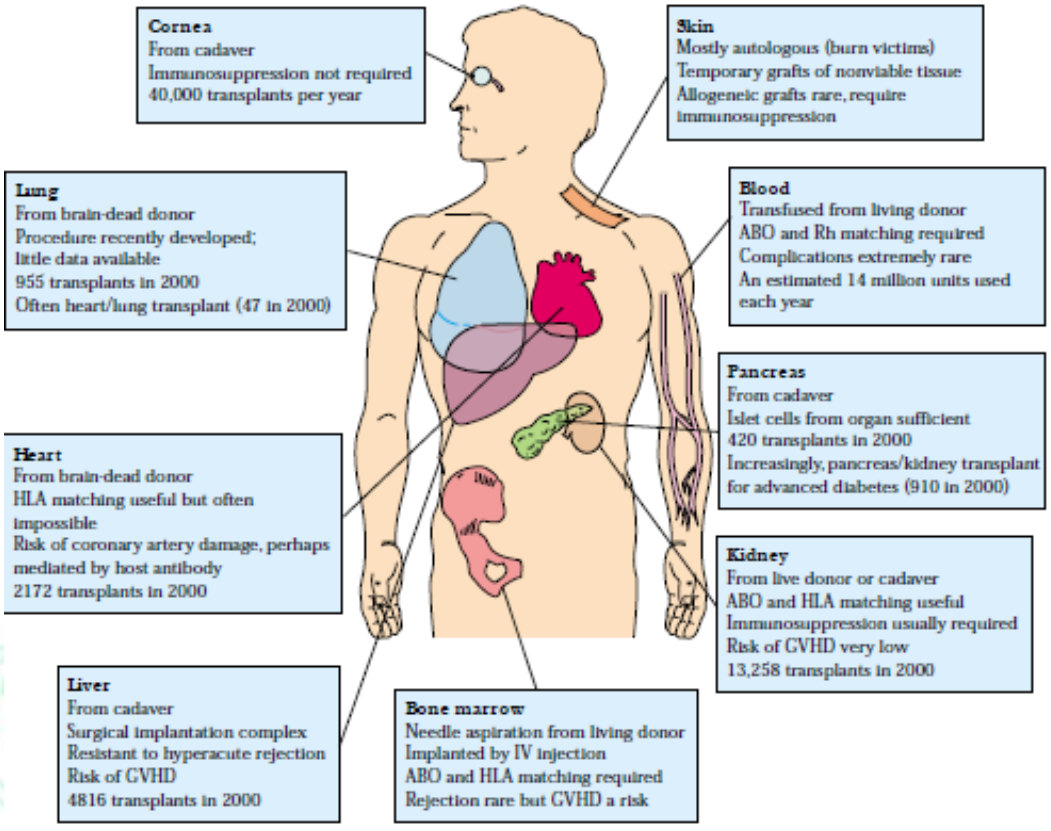


Fig.2- Transplantation

Immunosuppression

- potentially toxic immunosuppressive drugs given in order to limit immunological rejection.
- patients on immunosuppressive therapy tend to be susceptible to opportunistic infections with a variety of viral, bacterial, fungal, and parasitic diseases and virus induced cancers such as lymphomas, cervical cancer, and Kaposi sarcoma.
- Employed in 3 phases-
  - Induction therapy: Anti-T-cell antibodies and/or IL-2 receptor antagonists.
  - Maintenance therapy: calcineurin inhibitors (tacrolimus or cyclosporine), purine metabolism inhibitors (azathioprine or mycophenolate mofetil), and mTOR inhibitors (rapamycins)
  - are used, often together with steroids
  - Treatment of rejection episodes: intravenous immunoglobulin

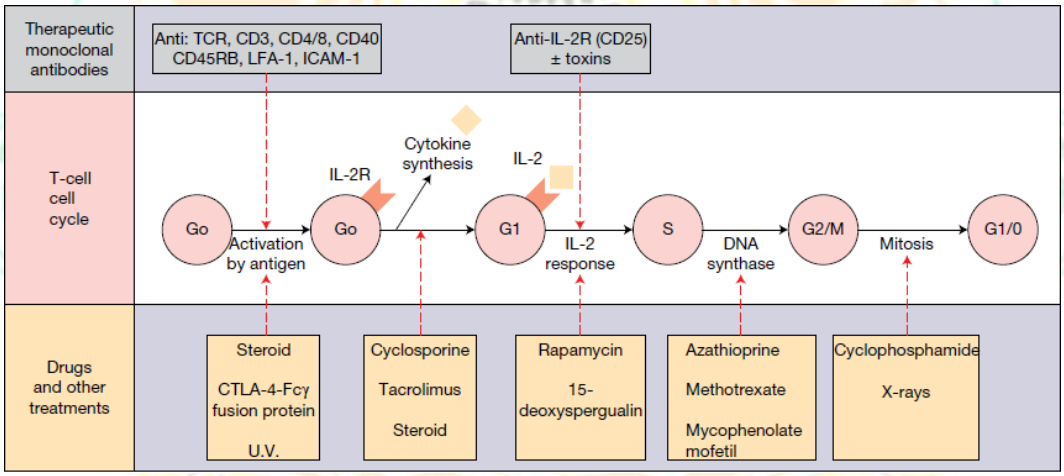


Fig. 3- Immunosuppressive agents that block the cell cycle of T-cells

Foetus as an Allograft

- Lack of both conventional class I and class II MHC antigens on the placental syncytiotrophoblast and cytotrophoblast.
- The unique expression of the nonclassical HLA-E, -F, and -G proteins on the extravillous cytotrophoblast, may protect the trophoblast from killing by uterine endometrial NK cells that would normally attack cells lacking MHC class I molecules.

- **Inhibition of complement activation**- Maternal IgG anti-paternal MHC is found in 20% of first pregnancies and this figure rises to 75–80% in multiparous women. Some of these antibodies cross-react with HLA-G, but the vulnerability of the trophoblast cells to complement is blocked by the presence on their surface of the control (complement regulatory) proteins that inactivate C3 convertase.
- The presence of Fas-ligand at the trophoblast maternal–fetal interface may contribute towards limiting immunological aggression towards the fetus.
- Suppression of T-cell, B-cell, and NK cell activity also occurs through the generation of toxic tryptophan metabolites by the catabolic enzyme indoleamine 2,3-dioxygenase, which is present in trophoblast cells and macrophages.
- the production of growth factors such as CSF-1 and GM-CSF, which have a trophic influence on the placenta, and of transforming growth factor-β (TGFβ), which could help to damp down any activation of NK cells by potentially abortive events such as intrauterine exposure to lipopolysaccharide (LPS) or to interferons.
- Production of immunosuppressive IL-10 and TGFβ by regulatory T-cells may play a central role in limiting any immunological attack on the fetus.
- Cells bearing the hallmark of naturally occurring. regulatory T-cells (i.e., CD4+CD25+CTLA-4+GITR+FoxP3+ cells) are present in increased numbers, both in the circulation and in the decidua, during the first and second trimester of human pregnancy. The absence of such T-regulatory cells has been shown to result in immunologically mediated rejection of the fetus in mice.

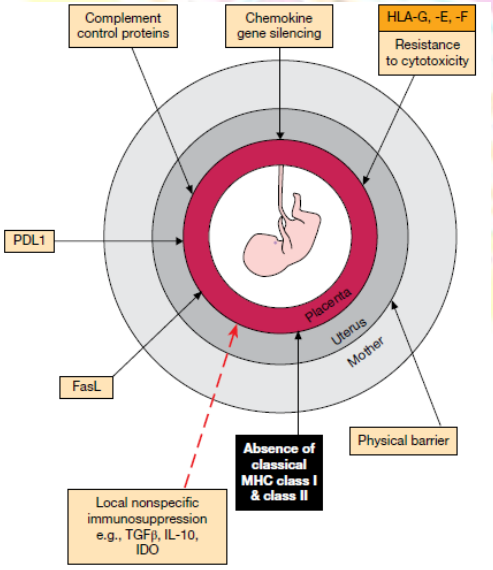


Fig.4-Foetus as an Allograft.

Ablation

- Ablation is a term used in medicine to describe the **removal of tissue** either by surgery or less invasive techniques with **the aim of restoring normal function.**
- **Surface Ablation**
- Surface ablation of the skin involves the removal of a layer of tissue to treat discoloration, improve skin texture, or remove superficial lesions, warts, or tumors. When used for cosmetic purposes to induce skin regeneration, it is referred to as **dermabrasion.**
- There are several techniques used for skin ablation:
  - *Laser ablation* used primarily for superficial lesions or discoloration
  - *Chemoablation* in which topical acids are used to peel skin or remove warts
  - *Cryoablation* which freezes the skin using cold gases like liquid nitrogen or argon
  - *Fulgeration* using high-frequency electrical currents remove small lesions or warts
- Eye laser treatments used to treat astigmatism.
- The technique, also known as Lasik surgery, removes the surface cells of the cornea which then regrow to correct the vision disorder.
- Surface ablation can also be applied to otolaryngologic procedures involving the ear, nose, or throat. One such procedure strips away excess soft palate tissue to treat snoring or sleep apnea.

Cardiac Ablation

- Cardiac ablation is a technique primarily used to correct heart rhythm problems (arrhythmias). Rather then removing tissue to enable regeneration, cardiac ablation aims to destroy tissue in the heart associated with irregular heartbeats. By blocking specific nerve pathways, the electrical signals that trigger the arrhythmias are effectively stopped.
- Cardiac ablation is typically performed by inserting a thin, flexible tube (called a catheter) through a vein or artery in the groin and threading it to the heart. When in place, a form of energy is used to either freeze or burn the area of tissue. The technique, commonly referred to a **catheter ablation**, can be used to treat arrhythmias of either the upper chambers (atria) or lower chambers (ventricles) of the heart.
- They include:
  - Atrial flutter ablation (involving the atria)

  - Pulmonary vein isolation (involving the atria)
  - Supraventricular tachycardia ablation (involving the atria)
  - Ventricular tachycardia ablation (involving the ventricles)
- A similar technique can be applied to arterial blockages that don't respond to standard balloon angioplasty. Known as rotoablation, the procedure involves the use of a tiny, diamond-tipped drill that removes fatty deposits and restores blood flow.

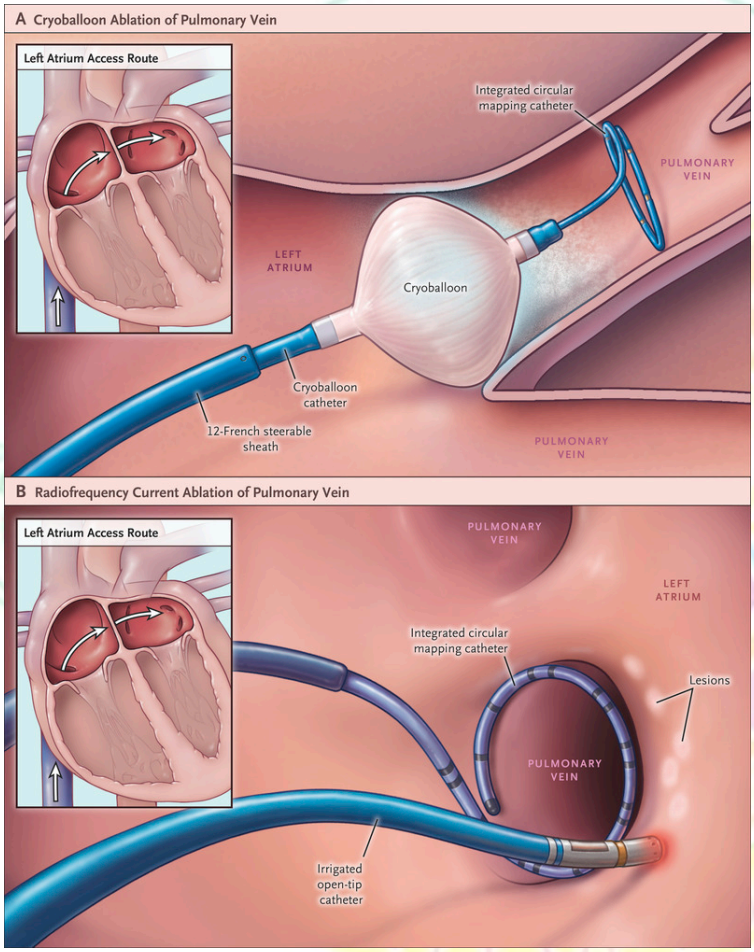


Fig.5- cardiac ablation

Endometrial Ablation

- Endometrial ablation is a minimally invasive procedure that destroys the lining of the uterus (known as the endometrium).
- The aim of the procedure is to reduce or stop the abnormal bleeding of the uterus.
- The ablation itself can be carried out in several ways:
  - High-energy radiofrequency which elevates the temperature of the uterus to destroy endometrial tissue.
  - Thermal balloon ablation in which a balloon is inserted into the uterus and filled with 190^{o}F fluid.
  - Microwave endometrial ablation (MEA) which increases the temperature of the endometrium using microwaves
  - Cryoablation in which a probe is inserted into the uterus and superchilled to -4^{o}F to create an ice ball which destroys endometrial tissue.
  -

Other Types of Ablation

- Bone marrow ablation is commonly used to remove bone marrow in advance of a bone marrow transplant.
- It is not performed mechanically but rather with a combination of chemotherapy and radiation.
- Ablative brain surgery is used to treat certain neurological disorders such as Parkinson's disease and cluster headaches.

Immunization

- Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.

Key facts

- Global measles mortality has declined by 73%
- Most children today receive lifesaving vaccines
- Uptake of new and underused vaccines is increasing.
- Immunization currently prevents 2-3 million deaths every year
- An estimated 19.4 million children under the age of one year did not receive basic vaccines

Passive immunization	**Active immunization**
• administration of preformed antibodies either intravenously or intramuscularly. • Transfer of maternal antibodies through placenta. • Transfer of maternal • Antibodies Through milk. • Following administration of Immunoglobulin or antiserum	• administration of vaccines containing microbial products with or without adjuvants in order to obtain long term immunological protection against the offending microbe. • Following clinical infection • Following subclinical infection • Following vaccination

Table 1- Passive immunization: source of antiserum and indications for various infections

Infection	**Source of Antiserum**	**Indications**
Tetanus	Immune human; horse	Post exposure (plus vaccine)
Diptheria	Horse	Post-exposure
Gas gangrene	Horse	Post-exposure
Botulism	Horse	Post-exposure
Varicella-Zoster	Immune human	Post-exposure in immunodeficiency
Rabies	Immune human	Post exposure (plus vaccine)
Hepatitis B	Immune human	Post-exposure prophylaxis
Hepatitis A	Pooled human Ig	Prophylaxis
Measles	Immune human	Prophylaxis
Snakebite	Horse	Post-bite
Some	Pooled human ig	Acute thrombocytopenia

autoimmune disease		and neutropenia

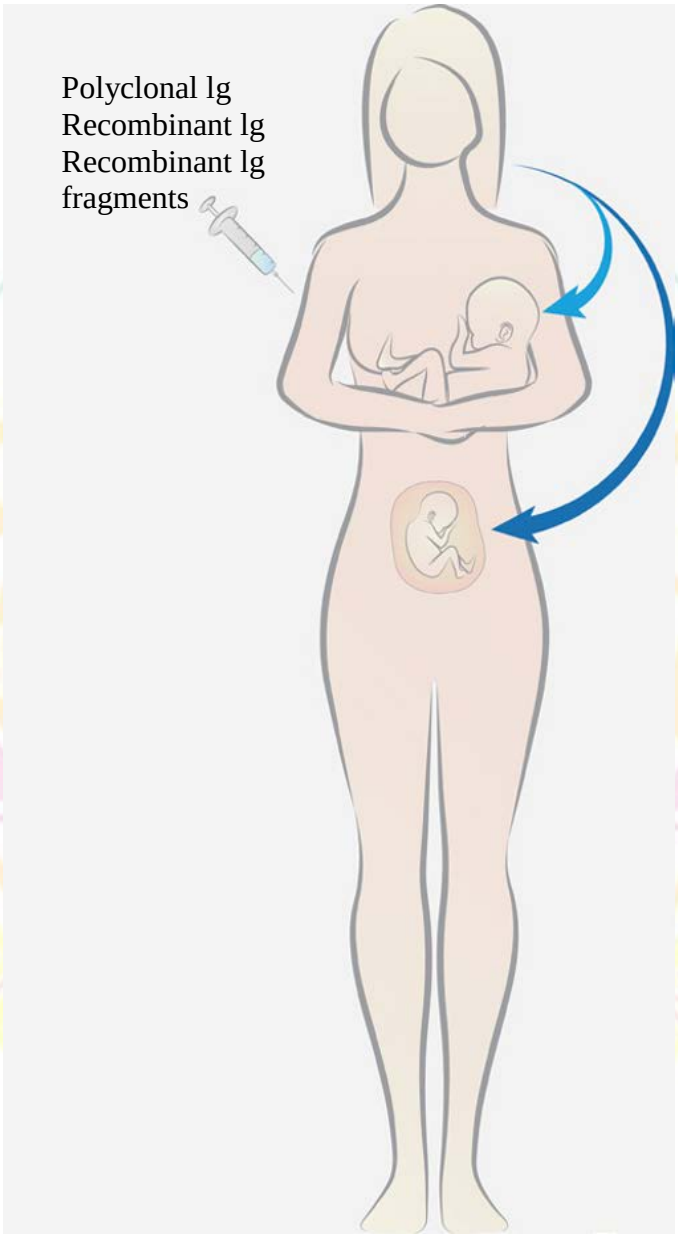
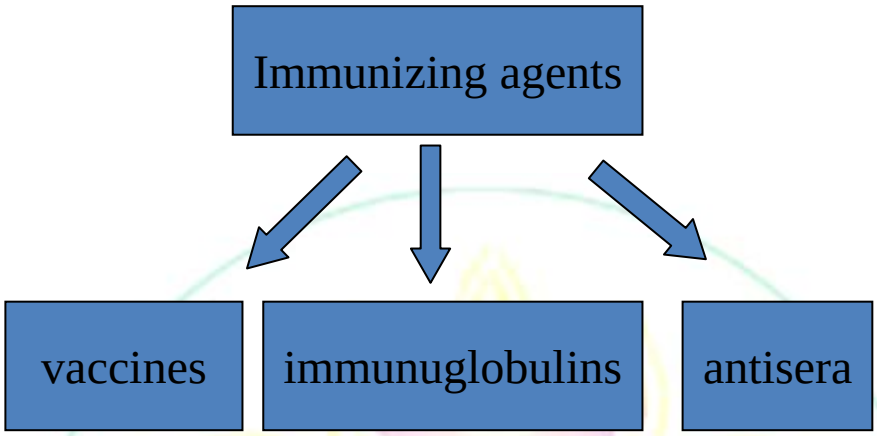


Fig.6- Passive immunization produced by: transplacentalvpassage of IgG from mother to fetus, acquisition of IgA from mother's colostrum and milk by the infant, and injection of polyclonal antibodies, recombinant monoclonal antibodies, or antibody fragments

Immunizing agents



Immunoglobulins

- There are 5 major classes: IgM, IgA, IgG, IgE, IgD.
- Two types of immunoglobulin preparations are available for passive immunization:
  - Normal human immunoglobulin
  - Specific (hyper-immune) human immunoglobulin

Antisera or antitoxins

- These are materials prepared in animals or non human sources such as horses.

Table 2- Immunoglobulin and antiserum

Human normal immunoglobulin	Human specific immunoglobulin	Non human Ig (antisera)
Hepatitis A Measles Rabies Tetanus Mumps	Hepatitis B Varicella Diphtheria	Diphtheria Tetanus Gas gangrene Botulism Rabies

Vaccination

- Vaccination is a method of giving antigen to stimulate the immune response through active immunization.
- A vaccine is an immuno-biological substance designed to produce specific protection against a given disease.
- A vaccine is “antigenic” but not “pathogenic”.

Types of vaccines

- Live vaccines
- Attenuated live vaccines
- Inactivated (killed vaccines)
- Toxoids
- Polysaccharide and polypeptide (cellular fraction) vaccines
- Surface antigen (recombinant) vaccines.

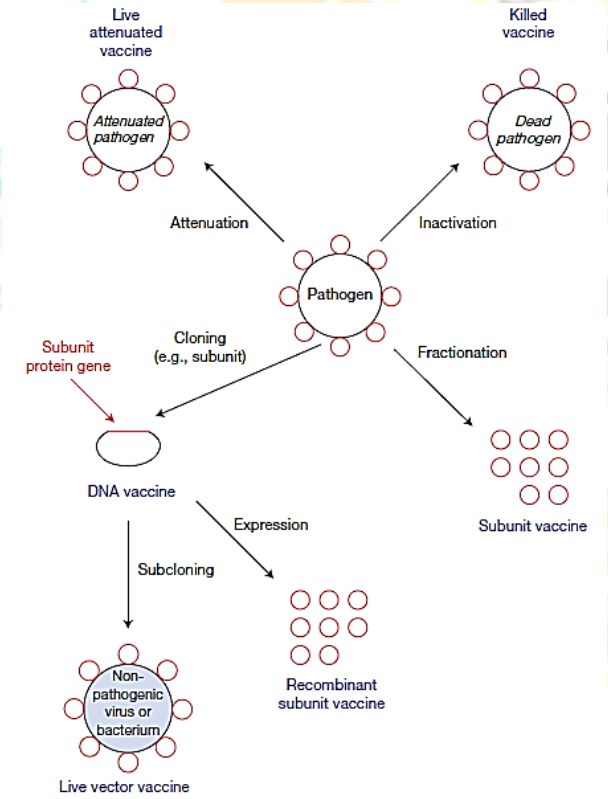


Fig.7- Classical vaccine approaches.

Live vaccines

- Live vaccines are made from live infectious agents without any

amendment.

- The only live vaccine is “Variola” small pox vaccine, made of live vaccinia cow-pox virus (not variola virus) which is not pathogenic but antigenic, giving cross immunity for variola.

Live attenuated (avirulent) vaccines

- Virulent pathogenic organisms are treated to become attenuated and avirulent but antigenic. They have lost their capacity to induce full-blown disease but retain their immunogenicity.
- Live attenuated vaccines should not be administered to persons with suppressed immune response due to:
  - Leukemia and lymphoma
  - Other malignancies
  - Receiving corticosteroids and anti-metabolic agents
  - Radiation
  - Pregnancy

Inactivated (killed) vaccines

- Organisms are killed or inactivated by heat or chemicals but remain antigenic. They are usually safe but less effective than live attenuated vaccines. The only absolute contraindication to their administration is a severe local or general reaction to a previous dose.

Toxoids

- They are prepared by detoxifying the exotoxins of some bacteria rendering them antigenic but not pathogenic. Adjuvant (e.g. alum precipitation) is used to increase the potency of vaccine.
- The antibodies produces in the body as a consequence of toxoid administration neutralize the toxic moiety produced during infection rather than act upon the organism itself. In general toxoids are highly efficacious and safe immunizing agents.

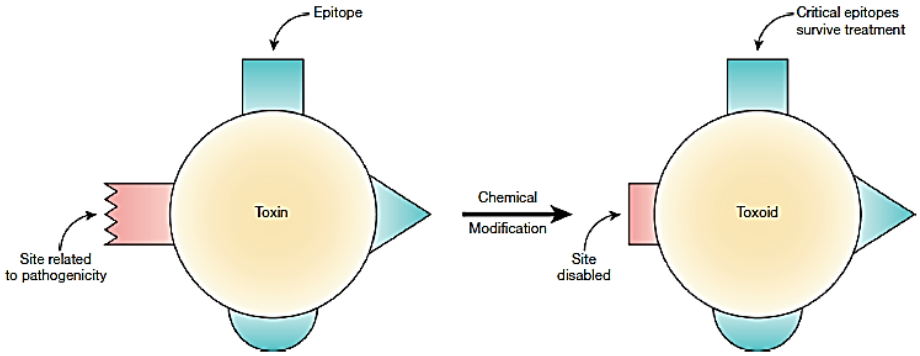


Fig.8- Modification of toxin to harmless toxoid without losing many of the antigenic determinants

Polysaccharide and polypeptide (cellular fraction) vaccines

- They are prepared from extracted cellular fractions e.g. meningococcal vaccine from the polysaccharide antigen of the cell wall, the pneumococcal vaccine from the polysaccharide contained in the capsule of the organism, and hepatitis B polypeptide vaccine.
- Their efficacy and safety appear to be high.

Surface antigen (recombinant) vaccines

- It is prepared by cloning HBsAg gene in yeast cells where it is expressed. HBsAg produced is then used for vaccine preparations.
- Their efficacy and safety also appear to be high.

Table 3- Types of vaccines

Live vaccines	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
Small pox, variola vaccine	BCG, Typhoid oral, Plague, Oral polio, Yellow fever, Measles,	Typhoid, Cholera, Pertussis, Plague, Rabies, Salk	Diphtheria, Tetanus	Meningococcal, polysaccharide vaccine, Pneumococcal	Hepatitis B vaccine

	Mumps, Rubella, Intranasal, Influenza, Typhus	polio, Intra-muscular influenza, Japanise encephalitis		polysaccharide vaccine, Hepatitis B polypeptide vaccine	

Routes of administration

- Deep subcutaneous or intramuscular route (most vaccines)
- Oral route (sabine vaccine, oral BCG vaccine)
- Intradermal route (BCG vaccine)
- Scarification (small pox vaccine)
- Intranasal route (live attenuated influenza vaccine)

Scheme of immunization

- Primary **vaccination**
  - One dose vaccines (BCG, variola, measles, mumps, rubella, yellow fever)
  - Multiple dose vaccines (polio, DPT, hepatitis B)
- **Booster vaccination**
  - To maintain immunity level after it declines after some time has elapsed (DT, MMR).

Sources:

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