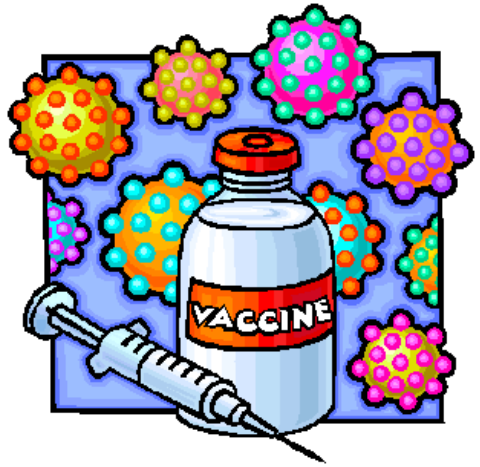

Vaccines

The modern era of vaccines and vaccination began in 1796 with **Edward Jenner's** use of cowpox as a vaccine against smallpox.

La Vaccine. French color lithograph, 1827, by Louis Leopold Boilly.

Vaccines and Immunizations

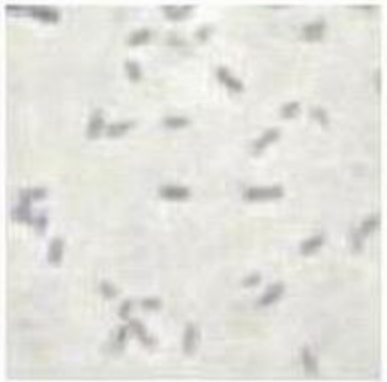


A **vaccine** [Latin *vacca,* cow] is a preparation from an infectious agent that is administered to humans and other animals to induce protective immunity.

Active immunization is the protection of susceptible humans and domestic animals from communicable diseases by the administration of **vaccines (vaccination).** Active immunoprophylaxis can be considered under two headings.

1. Routine immunization of the children which forms part of basic health care of communities.
2. Immunization of individuals or selected groups exposed to rick of particular infection.

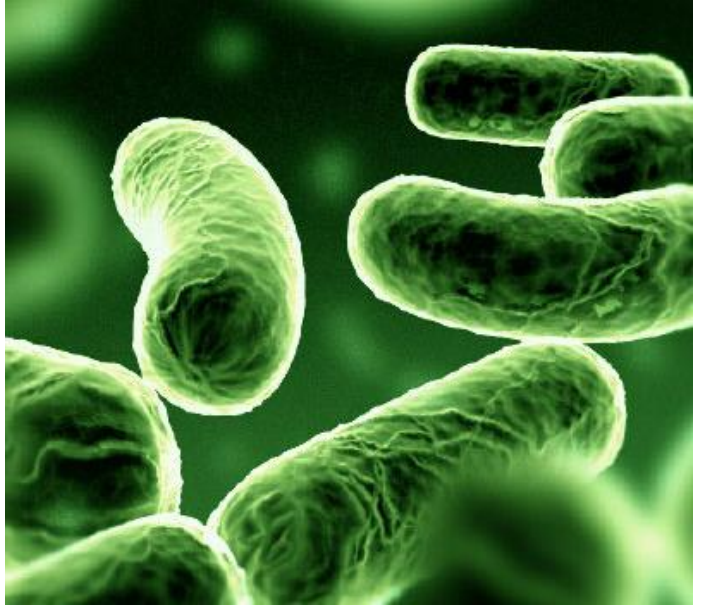
Types of Vaccines and Their Characteristi



A **vaccine** may consist of a preparation

- of killed microorganisms;
- living, weakened (attenuated) microorganisms;
- inactivated bacterial toxins (toxoids);
- chemical vaccines;
- recombinant vectors (e.g. modified polio vaccine);
- DNA vaccines (none approved yet) that are administered to an animal to induce immunity artificially.

Whole-Organism Vaccines



Many of the current vaccines in use for humans that are effective against viral and bacterial diseases consist of whole microorganisms that are either **inactivated** (killed) or **attenuated** (live but avirulent). These are termed **whole-organism vaccines.** The major characteristics of these vaccines are compared and contrasted in next slides.

A Comparison of Inactivated (Killed) and Attenuated (Live) Vaccines

Inactivated Vaccine

Booster shots:

Multiple boosters required

Production:

Virulent microorganism inactivated by chemicals or irradiation

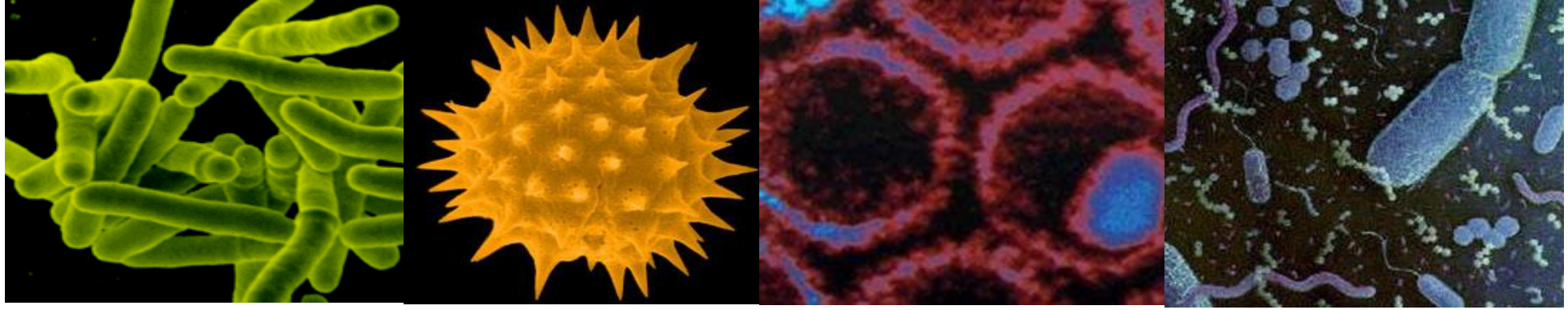
Attenuated Vaccine

Booster shots:

Only a single booster

Production:

Virulent microorganism grown under adverse conditions or passed through different hosts until avirulent



Inactivated Vaccine

Reversion tendency:

None

Stability:

Very stable, even where refrigeration is unavailable

Type of immunity induced:

Humoral

Attenuated Vaccine

Reversion tendency:

May revert to a virulent form

Stability:

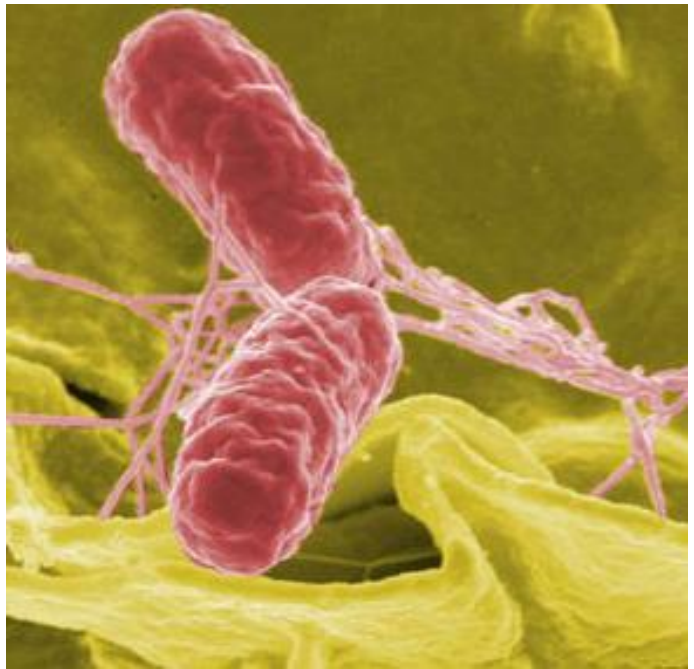
Less stable

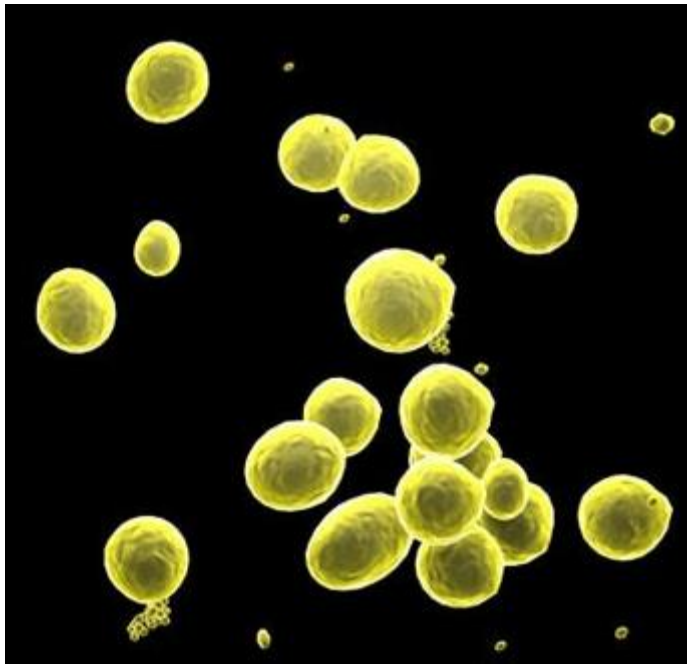
Type of immunity induced:

Humoral and cell-mediated

Autovaccines

Inactivated vaccine for personal prescription and may be prepared from microorganisms that cause disease with patient only.





Purified Macromolecules as Vaccines

A few of the common risks associated with whole-organism vaccines can be avoided by using only specific, purified macromolecules derived from pathogenic microorganisms. Currently, there are three general forms of **macromolecule vaccines:** (1) chemical vaccines (capsular polysaccharides, cell proteins)

(2) recombinant surface antigens, and

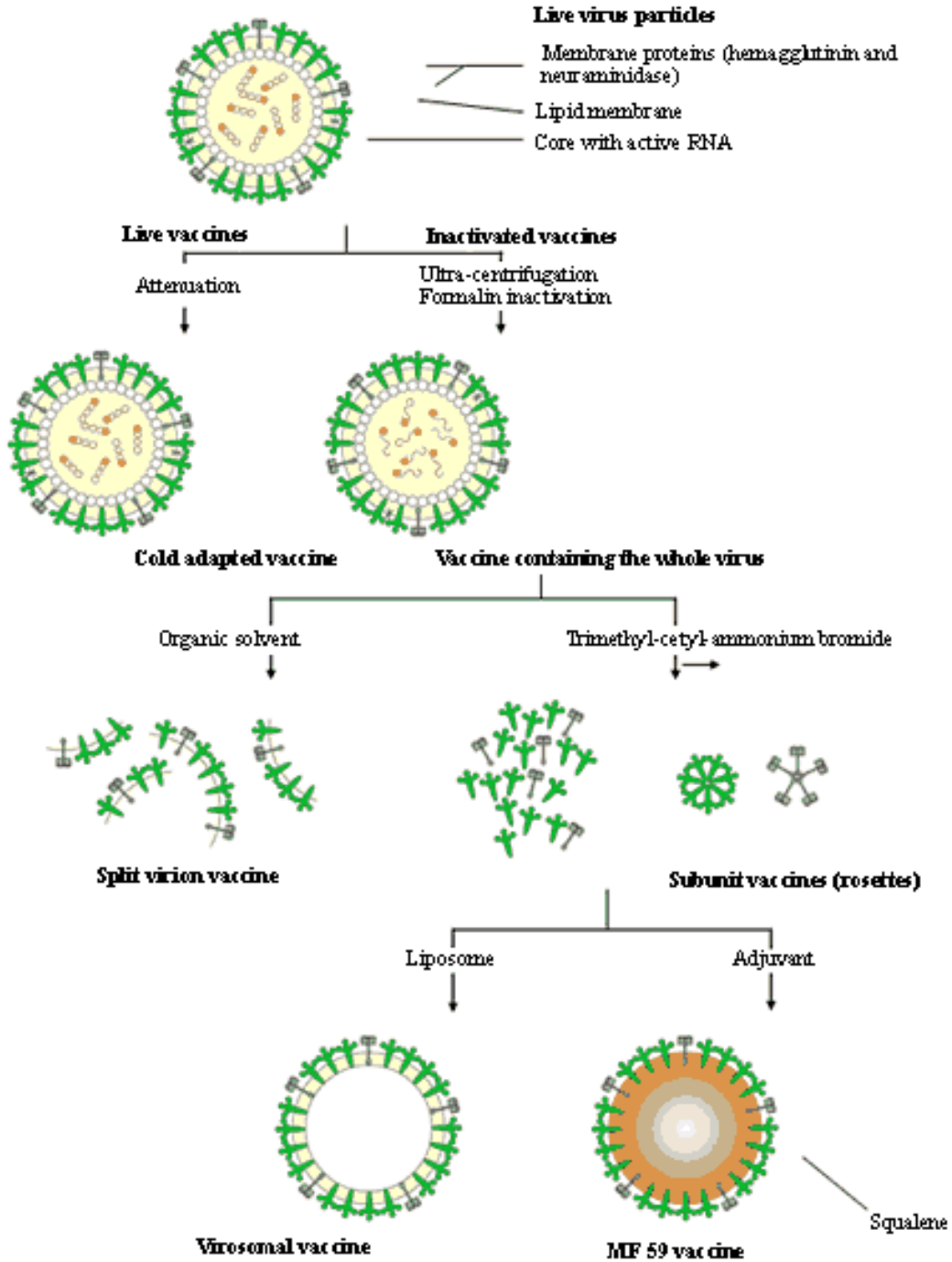
(3) inactivated exotoxins called **toxoids**.

Chemical vaccine

Chemical vaccine – is prepared of chemical substances of bacterial structures (polysaccharides, proteins and other). These chemical substances must be antigenic and immunogenic. Chemical vaccine may be bacterial (vaccines against S.pneumoniae, N.meningitidis, Haemophilus influenzae) and virus (hepatitis B vaccine, influenza vaccine).

Chemical vaccine –
is produced with chemical and physical methods.
Chemical vaccine
may be **split vaccines**
and **subunit vaccines.**

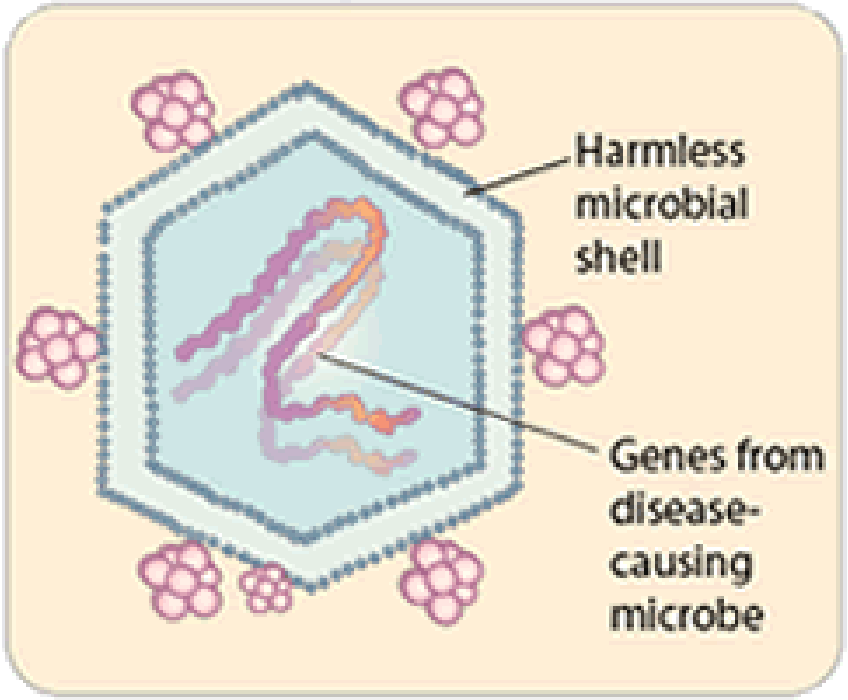
Types of influenza vaccines



Recombinant-Vector Vaccines

Genetic vaccines are quite different in structure from wholeorganism vaccines. It is now possible to isolate genes that encode major antigens from a pathogen and insert them into nonvirulent viruses or bacteria.

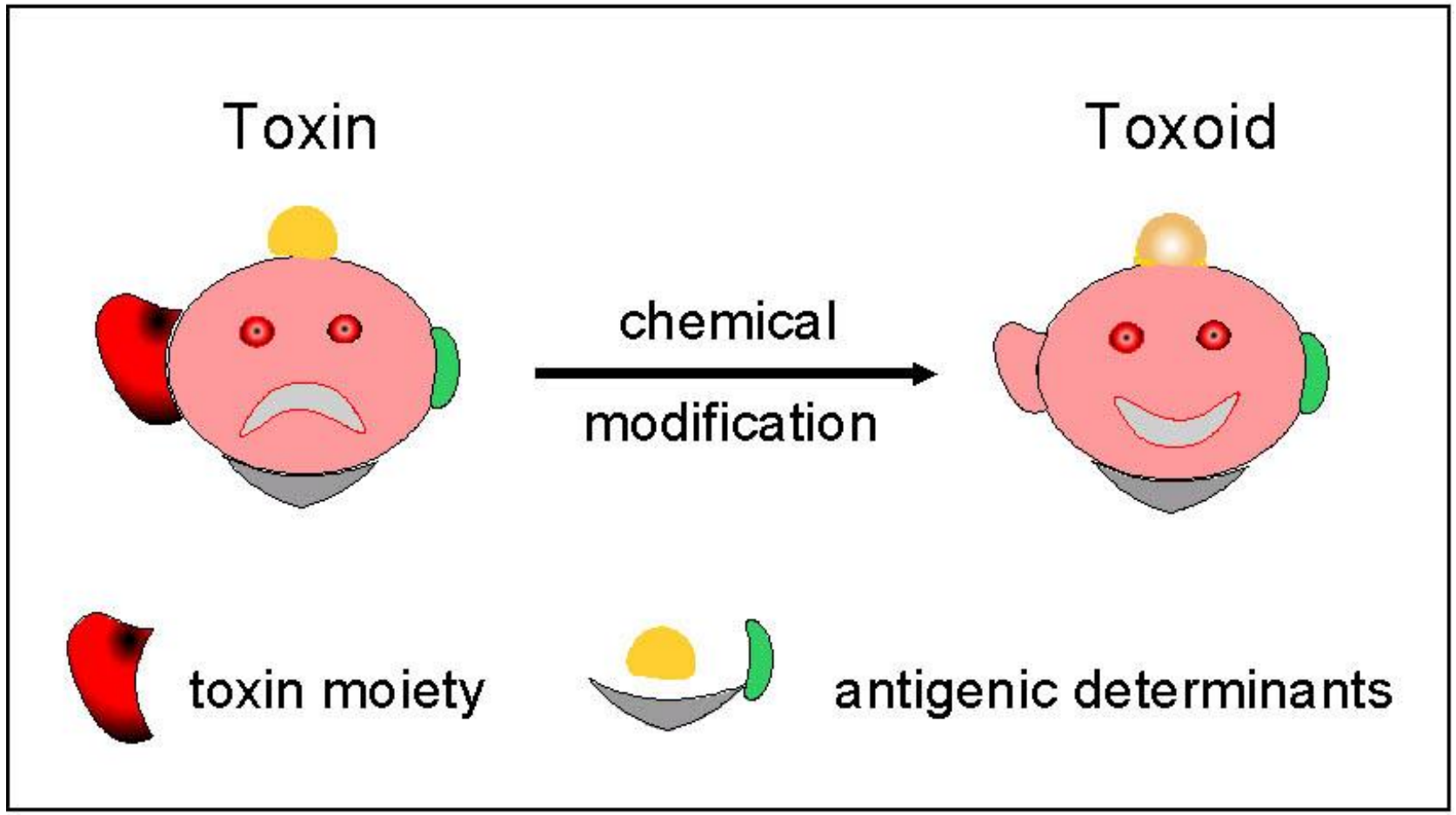
The vaccines are usually delivered by needle injection or by a device called a gene gun.



Toxoids

Toxoids are inactivated toxins that have lost their active site but have maintained their immunogenic determinants. Administration of the toxoid induces the production of antibodies capable of neutralizing the toxins by blocking their adsorption to cellular receptors.
Toxoids are effective immunogens that induce long-lasting protection.

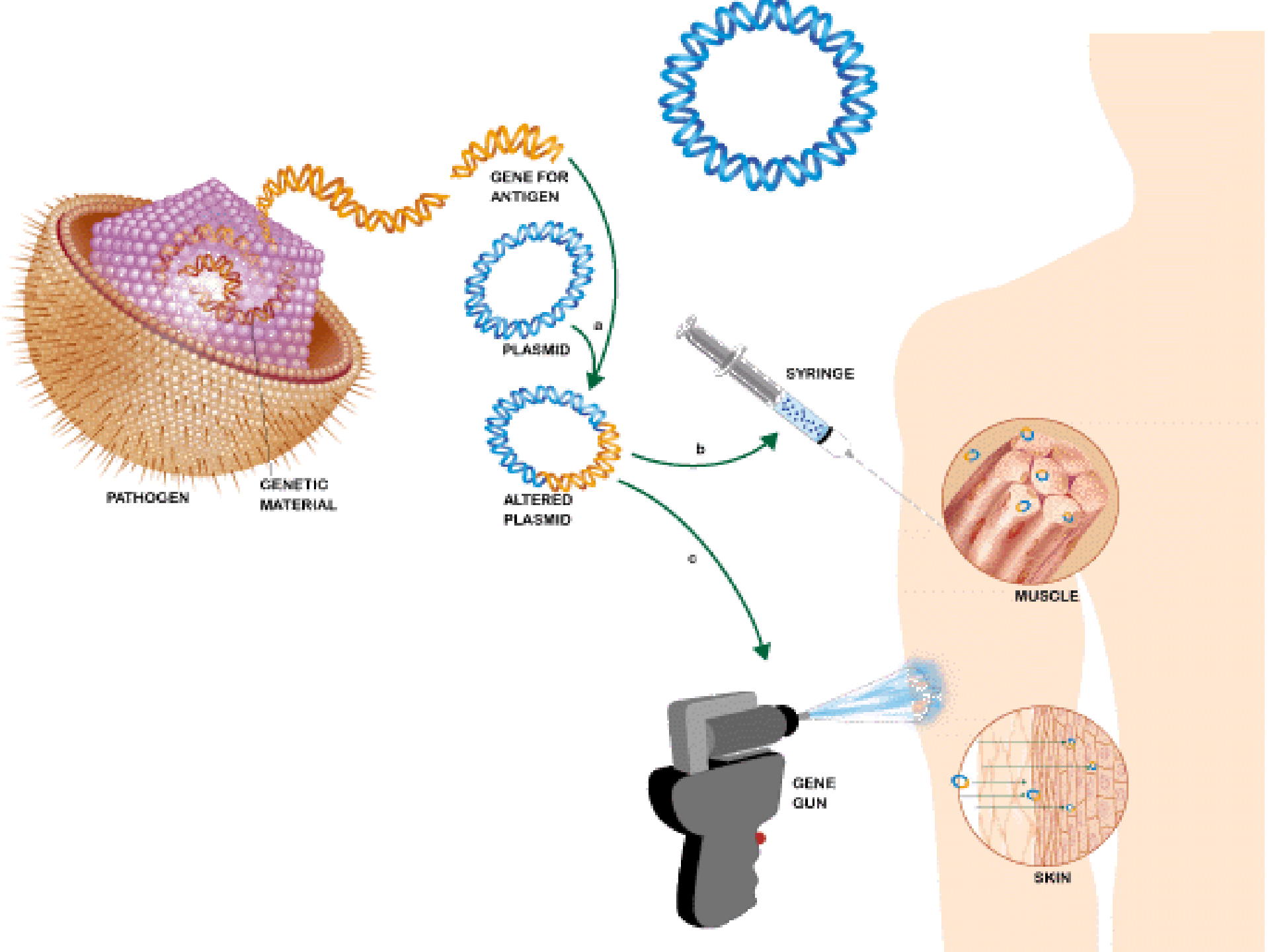
Modification of Toxin to Toxoid



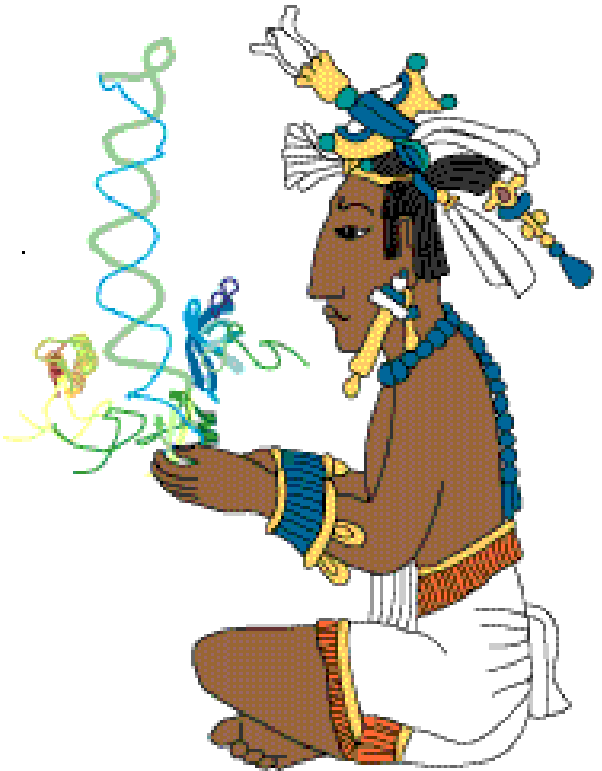
DNA Vaccines

A more complicated genetic vaccine to emerge in recent years is the DNA vaccine. A **DNA vaccine** elicits protective immunity against a microbial pathogen by activating both branches of the immune system: humoral and cellular. Long-lasting memory cells also are generated.

The immunization procedure begins with the injection into muscle of a plasmid preparation that contains genes for pathogen antigens. The plasmids are taken up by muscle cells, enter the cell nuclei, and express their antigen genes. The muscle cells commence protein synthesis and produce the pathogen's antigenic proteins.


GENE FOR
ANTIGEN
PLASMID
a
PATHOGEN
GENETIC
MATERIAL
ALTERED
PLASMID
b
SYRINGE
MUSCLE
c
GENE
GUN
SKIN

At present, there are human trials under way with several different DNA vaccines against malaria, AIDS, influenza, hepatitis B, and herpesvirus. Vaccines against a number of cancers (lymphomas, prostate, colon) are also being tested.

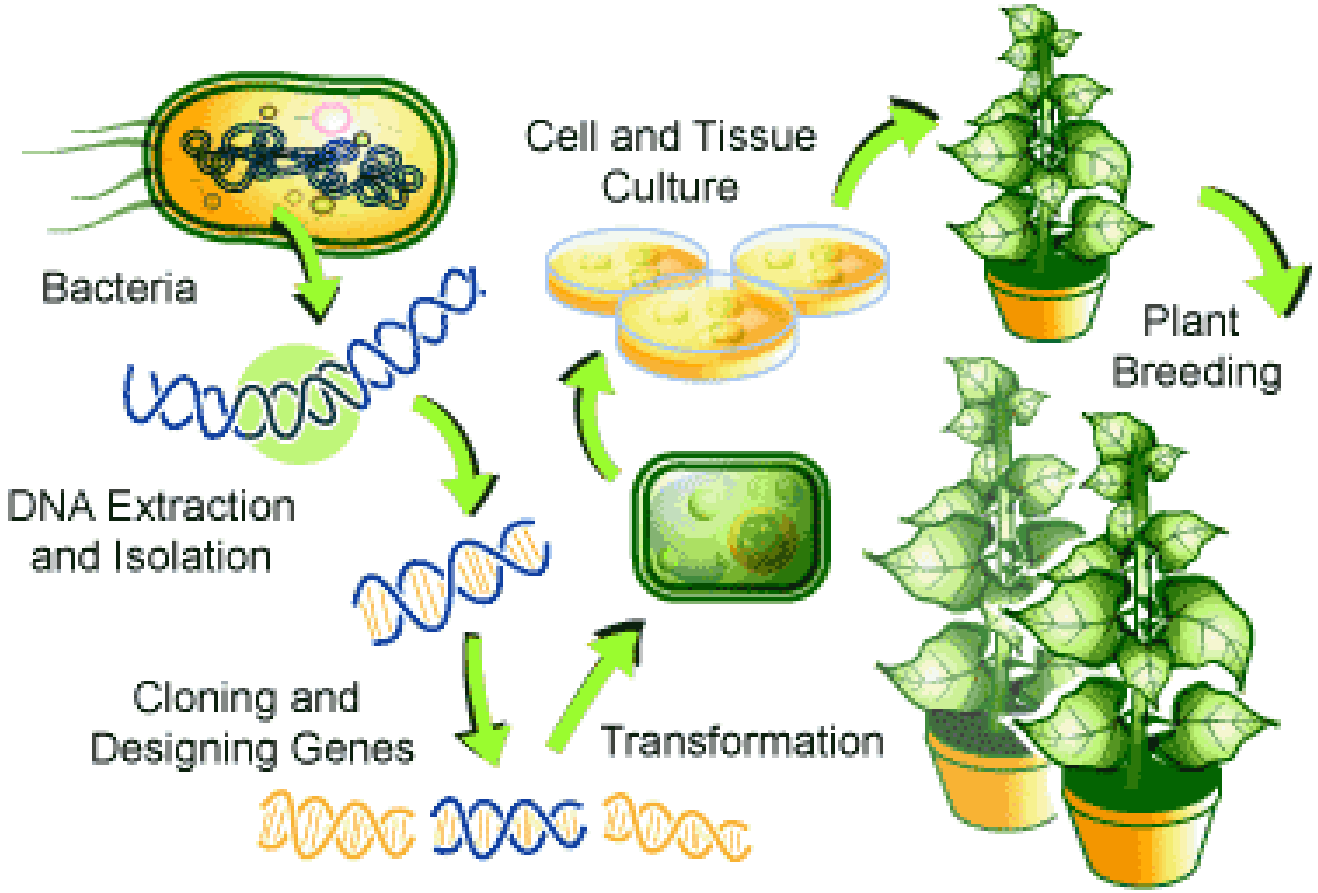


Adjuvants.

Adjuvant is a substance which, by delaying absorption of an antigen or by other means, enhances its antigenic efficiency. It is possible to boost the magnitude of an immune response by using an adjuvant to maintain the antigen in close proximity to immune cells and for keep the antigen from dissipating from the inoculation site. Different types of adjuvants are available. Such as alum (aluminum hydroxide gels, which keep the antigen from dissolving away) and microorganisms, e.g. whole B.pertussis. Two commonly used preparations are Freund's incomplete (antigen in an emulsion of mineral oil and water) and Freund's complete (complete because it adds mycobacterial antigens to the emulsion).

Food vaccine

Edible plant vaccine (EPV) requires antigen expression in transgenic plants and is then given by oral delivery.



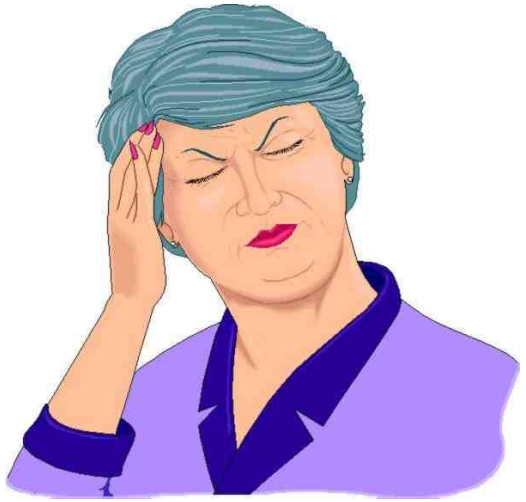
Methods of administration

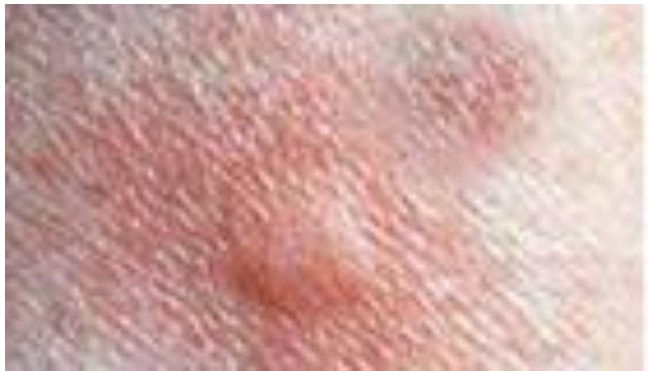
Vaccine administration may be

1. **Oral**
2. **By injection**:
   - intramuscular,
   - intradermal,
   - subcutaneous),
3. **By puncture**
4. **Transdermal**
5. **Intranasal**

The side effects of vaccines

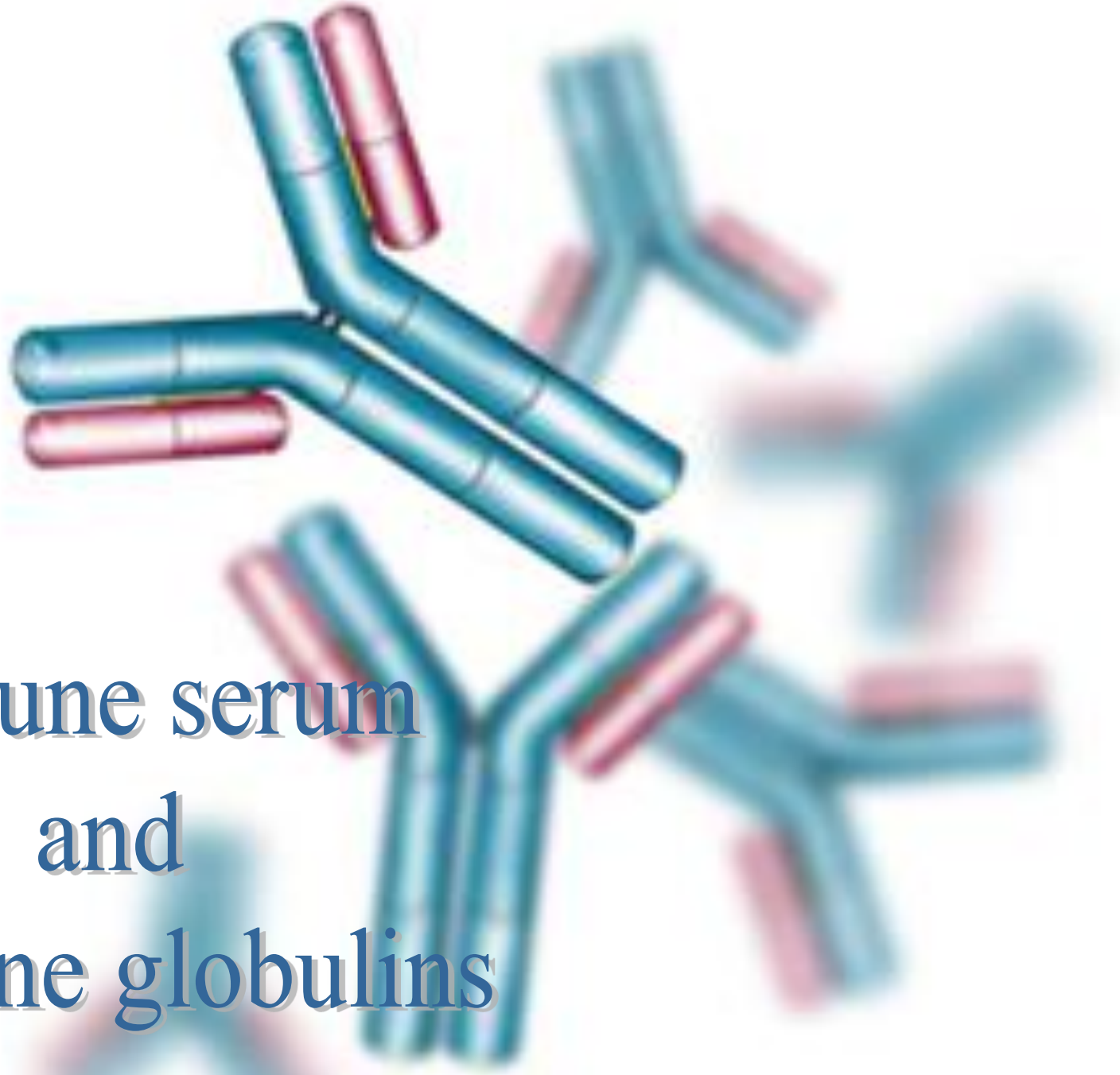
Like all medications and natural medications, vaccines may have side effects. For vaccines most side effects are short-lived and do not lead to any long-term problems.





The side effects of some vaccines

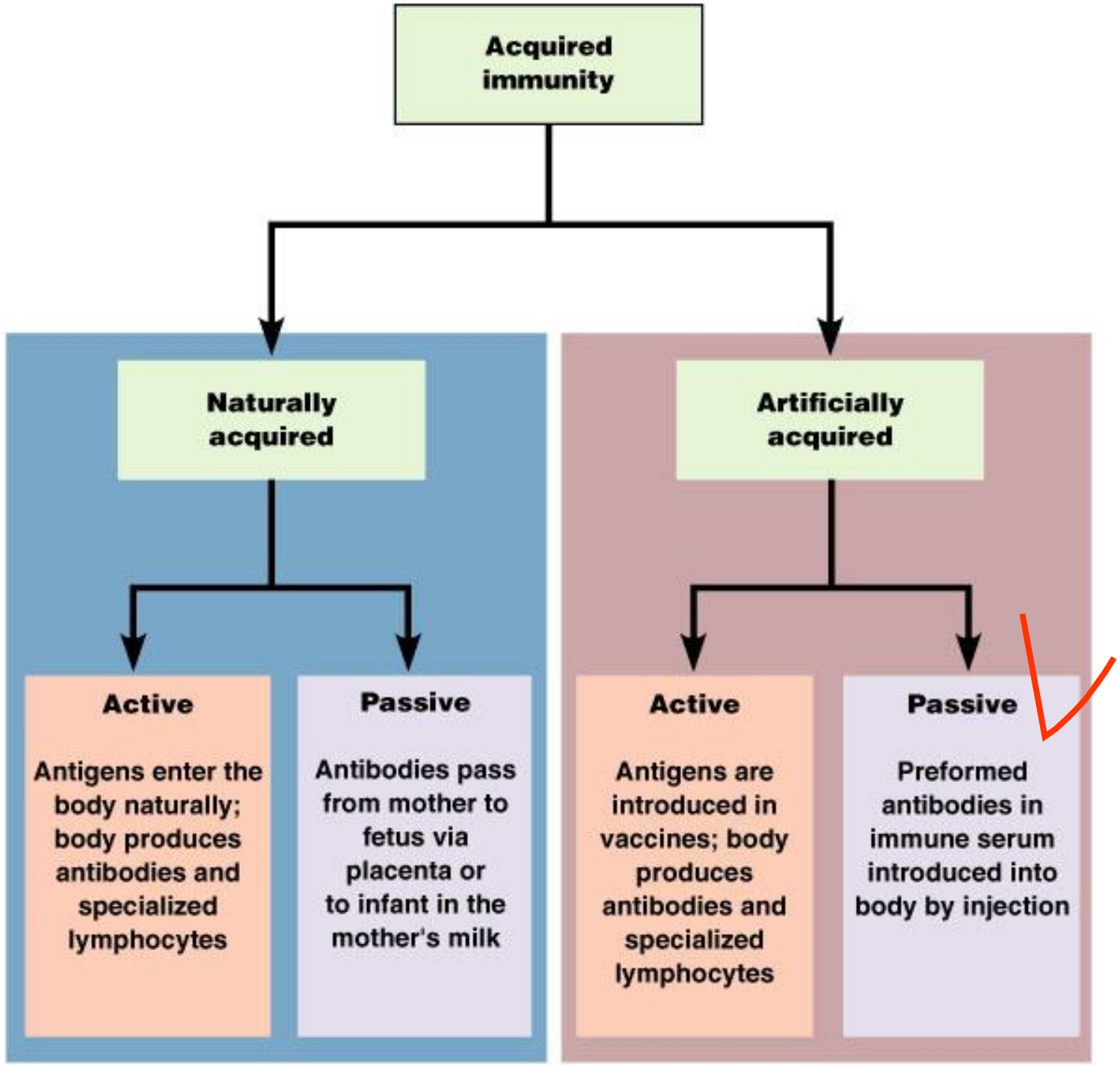
Vaccine	Side effect	When this could start
Diphtheria-tetanus-pertussis DTPa	Mild fever, unsettled, swelling or soreness at the injection site	Within 4 hours
Hepatitis B vaccine Hep B	Mild fever, unsettled, soreness at the injection site, nausea, malaise, muscle or joint pain	Within 4 hours
IPV	Pain, redness, swelling at injection site, fever, crying and lack of appetite	Within 4 hours
Oral Polio Vaccine OPV	Diarrhoea, headache, and/or muscle pain	Within 4 hours
Haemophilus influenza type b Hib	Mild fever, unsettled, swelling or soreness at the injection site	Within 4 hours
Measles Mumps Rubella MMR	Mild fever, rash, unsettled, swollen glands	Between 5 and 12 days after immunisation
Adsorbed diphtheria tetanus Td	Swelling or soreness at injection site	Within 4 hours
Influenza vaccine Flu vaccine	Mild fever, malaise, muscle pain, swelling or soreness at the site of injection	Within 4 hours
BCG TB vaccine	Swelling or slight discharge at the site of vaccination	Within 3 weeks, lasting for up to 2 months
Pneumococcal	Mild fever, swelling or soreness at injection site	Within 4 hours
Varicella	Mild fever, rash, swelling or soreness at injection site	Within 0 to 42 days
Q fever	Swelling or soreness at injection site, mild flu-like symptoms, rarely fever, chills and minor sweating	Within 12 hours to 14 days
Meningococcal C	Pain, redness, swelling at injection site, fever, irritability, lack of appetite and headaches	Within 4 hours



Immune serum and immune globulins

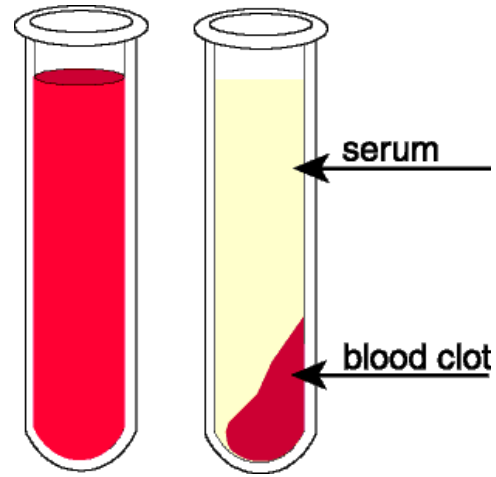
Passive immunization,
artificially acquired passive immunity,

can be produced **by injecting**
an animal or human **with preformed antibodies**
that have been **produced in another animal,**
in another human, or in vitro.
This type of immunization is called passive because protection does not require participation of the recipient's immune system. Passive immunization is routinely administered to individuals exposed to certain microbial pathogens that cause diseases such as botulism, diphtheria, hepatitis, measles, rabies, and tetanus as well as to protect them against snake and spider bites.


Acquired immunity
Naturally acquired
Artificially acquired
Active
Antigens enter the body naturally; body produces antibodies and specialized lymphocytes
Passive
Antibodies pass from mother to fetus via placenta or to infant in the mother's milk
Active
Antigens are introduced in vaccines; body produces antibodies and specialized lymphocytes
Passive
Preformed antibodies in immune serum introduced into body by injection

Some terms and definitions

- **Blood serum**, **serum** - an amber, watery fluid, rich in proteins, that separates out when blood coagulates.

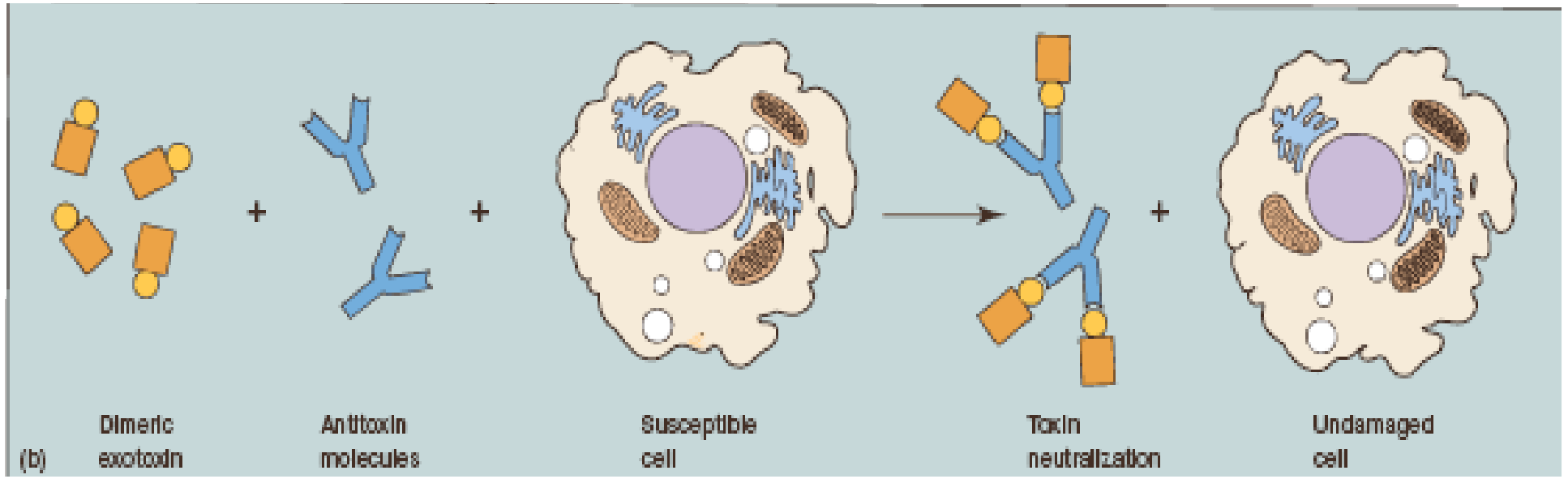


- **Antiserum** - human or animal serum containing one or more antibodies that are specific for one or more antigens and are administered to confer immunity. Also called **immune serum.** The antibodies in an antiserum result from previous immunization or exposure to an agent of disease.

Serum,Hyper Immune Serum,Prophylactic Serum,Therapautic Serum,Gamma Globulin

Another term is **hyperimmune serum** which indicates that the serum has a higher-than-normal level of a particular antibody. If the serum is used to protect against a disease, it is called **prophylactic serum**, if serum is used in therapy of an established disease, it is, called **therapeutic** serum. A common term is **gamma globulin**. Gamma globulin usually consists of a pool of sera from human donors, which should contain a mixture of antibodies including those for the disease to be treated.

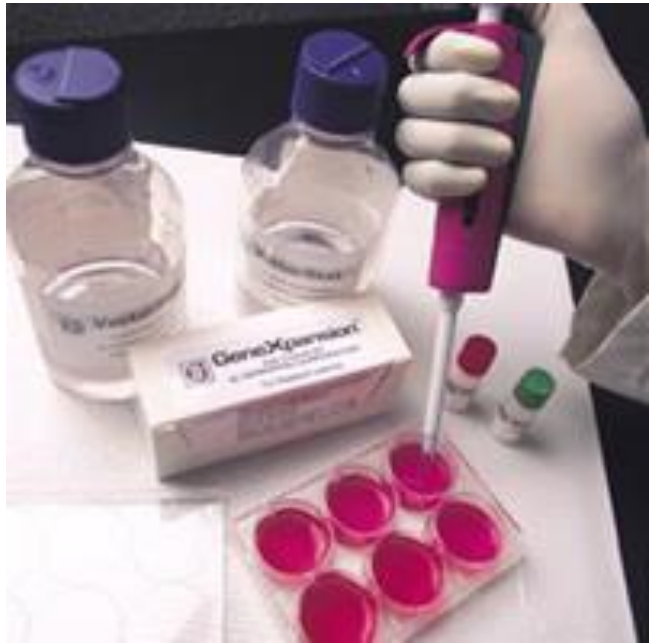
An antibody capable of neutralizing a toxin or antiserum containing neutralizing antibody against a toxin is called **antitoxin.**



Neutralization of the toxin by antitoxin.

Immune serum and immune globulins

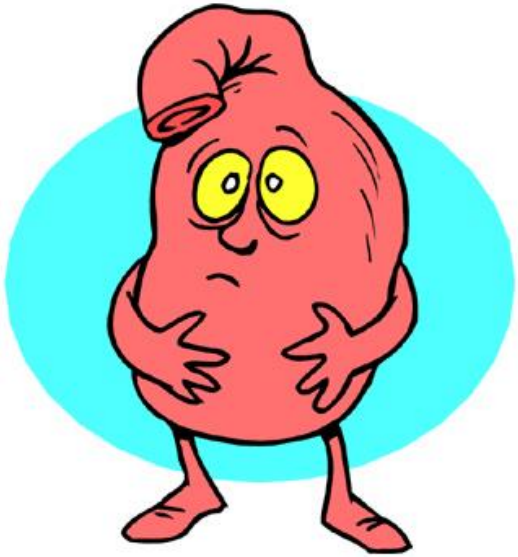
Used in the prevention, treatment or diagnosis of infectious disease.



Serotherapy -
treatment of infectious disease by injection of immune serum or antitoxin.

Seroprophylaxis - prevention of infectious disease by injection of immune serum or antitoxin.

A immune serums may be:

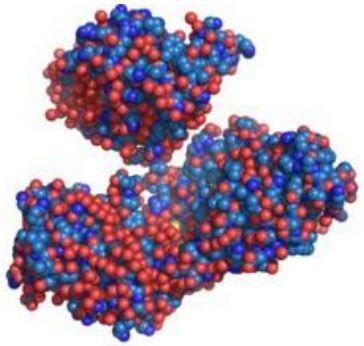


- **Antibacterial** – consist of antibody against bacteria

- **Antiviral**– consist of antibody against viruses

- **Antitoxic** – consist of antibody against a toxin

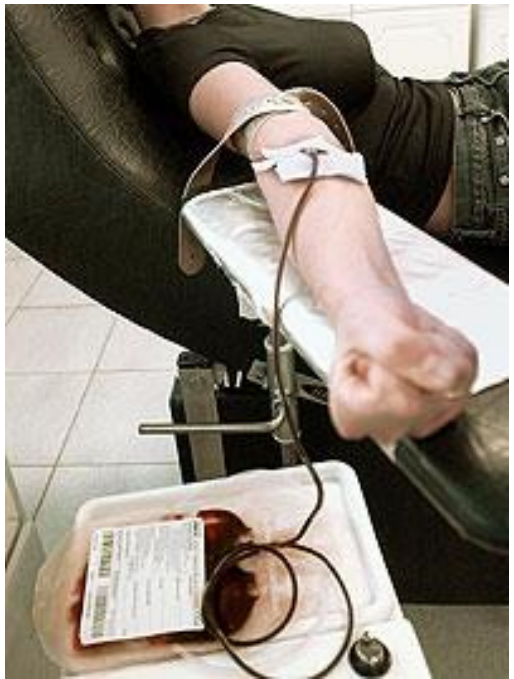
DIPHTHERIA TOXIN



A immune serums may be:

- **Heterogeneous** antiserums are produced in animals (*e.g.,* horse, sheep, ox, rabbit).

- **Homogeneous** antiserums are produced in man.



Emil von Behring and Shibasaburo Kitasato working together in Berlin in 1890 announce the discovery of diphtheria antitoxin serum, the first rational approach to therapy of infectious diseases. They inject a sublethal dose of diphtheria filtrate into animals and produce a serum that is specifically capable of neutralizing the toxin. They then inject the antitoxin serum into an uninfected animal to prevent a subsequent infection. Behring was awarded the Nobel Prize in Medicine or Physiology in 1901.

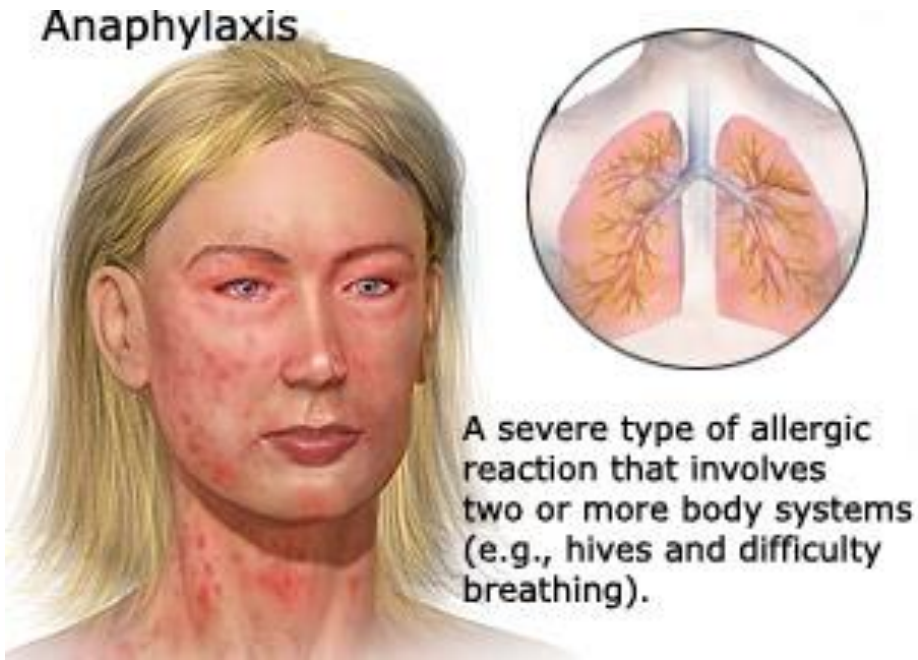
Furthermore, the protection lasts only as long as the antibody molecules survive in the recipient—**months** with antibodies from another human, but only **weeks** with antibodies from animals or in vitro methods.

Passive immunization should be used only when absolutely necessary because of the risks involved such as developing anaphylaxis, serum sickness, or a type III hypersensitivity reaction.

Anaphylaxis is an acute systemic (multi-system) allergic reaction in humans and other mammals.

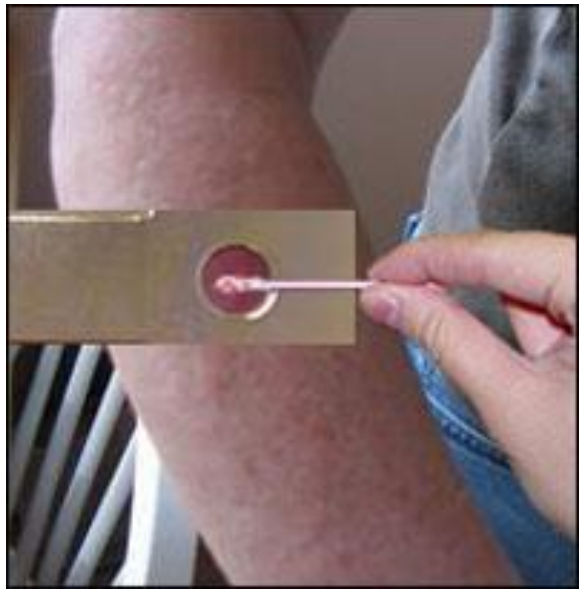
Anaphylactic shock, the most severe type of anaphylaxis.

Anaphylactic shock can lead to death in a matter of minutes if left untreated.

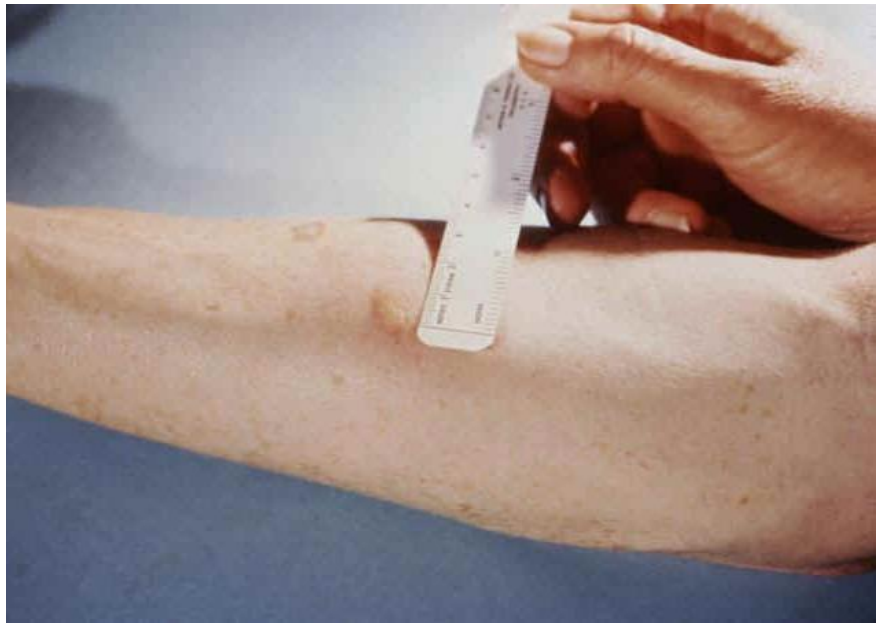


Serum sickness is a reaction to an antiserum derived from an animal source. Serum sickness typically develops up to ten days after exposure to the antiserum, and symptoms are similar to an allergic reaction. Symptoms can take as long as fourteen days after exposure to appear, and may include:

- Rashes
- Joint pain (arthralgia)
- Fever
- Lymph node swelling (lymphadenopathy)
- Shock
- Decreased blood pressure (hypotension)
- Enlarged spleen (splenomegaly)



To prevent anaphylactic shock, an intracutaneous test is made previously by injecting 0.1 ml of 1:100 diluted serum into the flexor surface of the forearm if the reaction is negative (a papule no larger than o.9 cm in diameter) the serum is injected (subcutaneously or intramuscular or even intravenous). If the intracutaneous test proves positive it's necessary to make desensitization using the method proposed by **Bezredko** (fractional injection of the serum).



Immune Globulins and Antitoxins Used for Passive Immunization against Specific Organisms and Diseases

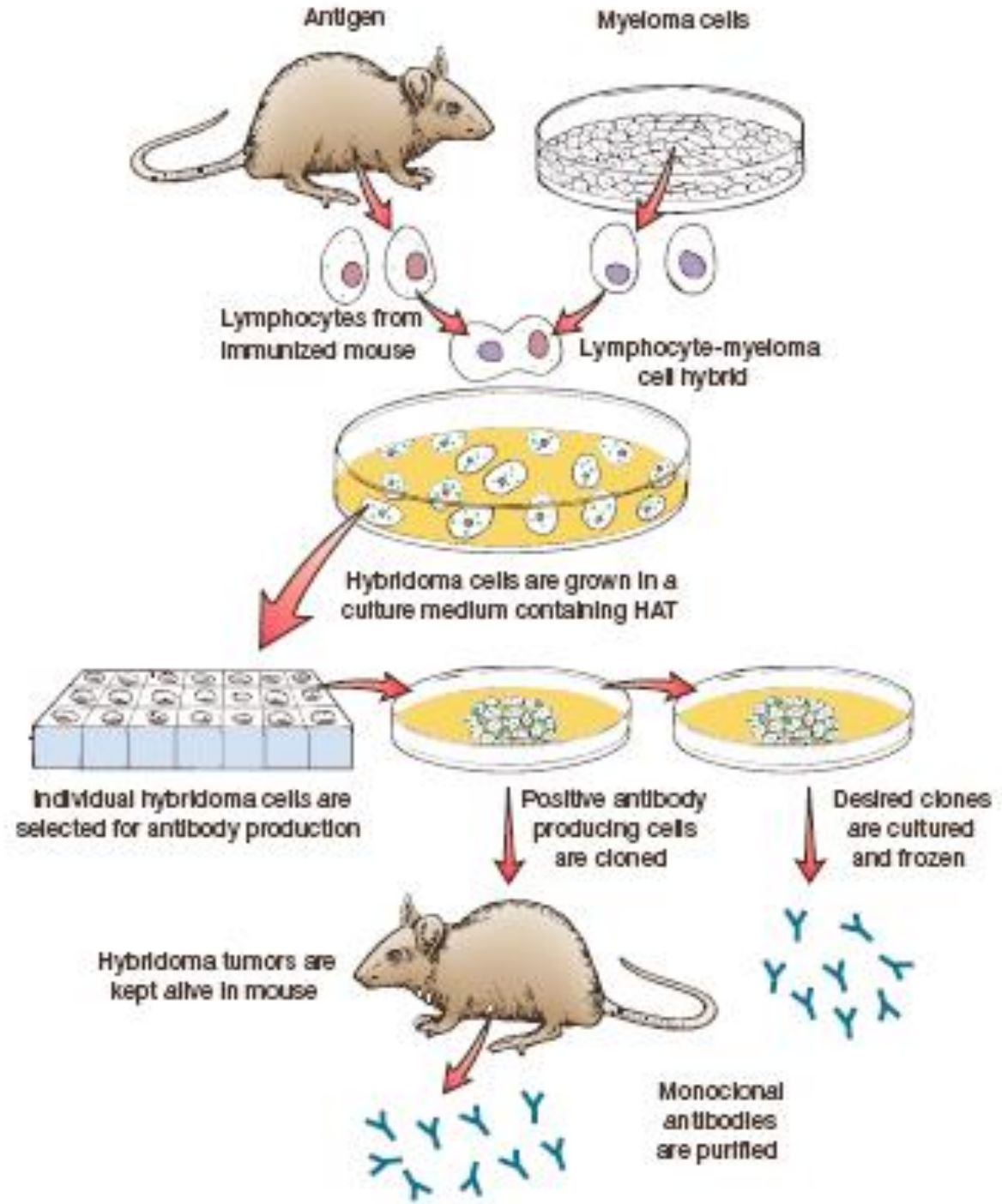
Organism/Disease	Agenta
• Black widow spider bite	• Horse antivenom
• Snakebite	• Horse antivenom
• Acute respiratory failure (respiratory syncytial virus)	• Monoclonal antibodies
• Botulism	• Botulinum antitoxin (equine)
• Diphtheria	• Diphtheria antitoxin (equine)
• Hepatitis A and B	• Pooled human immune gamma globulin
• Measles	• Pooled human immune gamma globulin

Organism/Disease	Agenta
• Rabies	• Rabies immune globulin administered around the wound in addition to being injected intramuscularly
• Tetanus • Eczema • Immunocompromised individuals	• Tetanus immune globulin • Vaccinia immune globulin • Varicella-zoster immune globulin

Hybridomas

The limitations of antiserum as a source of antibodies have been overcome with the development of hybridoma techniques to manipulate and culture various mammalian cells that synthesize antibodies in vitro. Each cell and its progeny normally produce a **monoclonal antibody (MAb)** of a single specificity.
The methodology of one of these techniques:
Animals (usually mice or rats) are immunized with antigens. Once the animals are producing a large quantity of antibodies, their spleens are removed and antibodyproducing B and plasma cells (lymphocytes) isolated. These lymphocytes are then fused with myeloma cells by the addition of polyethylene glycol, which promotes membrane fusion.

Technique for the Production of Monoclonal Antibodies.



Myeloma cells are cancerous plasma cells that can readily be cultivated; mutant myeloma cells incapable of producing immunoglobulins are used. These fused cells, derived from lymphocytes and myeloma cells, are called **hybridomas** (they are hybrids of the two cells). The fusion mixture is then transferred to a culture medium containing a combination of **h**ypoxanthine, **a**minopterin, and **t**hymidine (HAT). Aminopterin is a poison that blocks a specific metabolic pathway in cells. Myeloma cells lack an enzyme that allows their growth in the presence of aminopterin. However, the pathway is bypassed in lymphoid cells provided with the intermediate metabolites hypoxanthine and thymidine.

As a result the hybridomas grow in the HAT medium but the myeloma cells die because they have a metabolic defect and cannot employ the bypass or salvage pathway.

When the culture is initially established using the HAT medium, it contains lymphocytes, myeloma cells, and hybridomas. The unfused lymphoid cells die naturally in culture within a week or two, and the myeloma cells die in the HAT as just described.

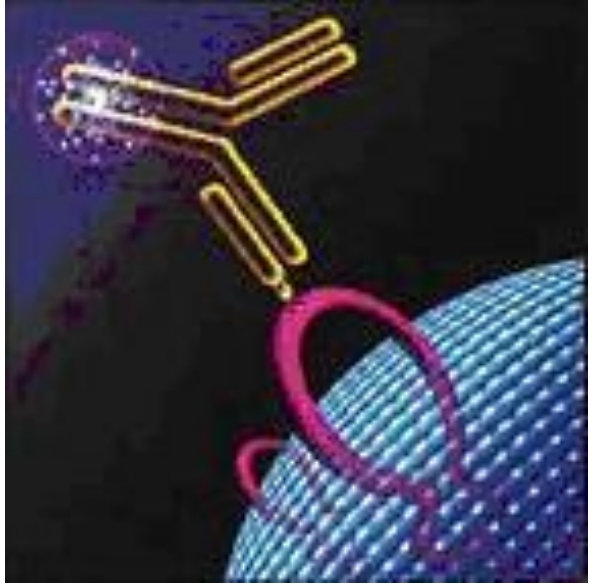
In contrast, the fused cells survive because they have the immortality of the myeloma and the metabolic bypass of the lymphoid cells. Hybridomas that have the antibody-producing capacity of the original lymphoid cells are randomly placed in culture wells.

Manufacturing monoclonal antibodies

The wells are individually tested for production of the desired antibody, and, if positive, the cells within the well provide clones of immortal cells, all producing the same monoclonal antibody.

Monoclonal antibodies currently have many applications. For example, they are routinely used in the typing of tissue, in the identification and epidemiological study of infectious microorganisms, in the identification of tumor and other surface antigens, in the classification of leukemias, and in the identification of functional populations of different types of T cells.

Anticipated future uses include



(1) **passive immunizations** against infectious agents and toxic drugs,
(2) tissue and organ **graft protection**,
(3) stimulation of tumor rejection and elimination,
(4) manipulation of the immune response,
(5) preparation of more specific and sensitive
diagnostic procedures, and
(6) delivery of antitumor agents (**immunotoxins**) to tumor cells.