REGENERATION. TRANSPLANTATION OF ORGANS AND TISSUES. EXPLANTATION.

Azerbaijan Medical University
Medical biology and genetics department
Presented by assistant professor: Suleymanova Leyla

Lecture plan:

- 1.Regeneration as a biological phenomenon: definition and general description
- 2.Types of regeneration
- 3.Levels of regeneration
- 4.Regulation of regeneration
- 5.Stem cells
- 6.Transplantation of organs and tissues
- 7. Human Leukocyte Antigens (HLA) complex
- 8.Transfusiology
- 9.Explantation

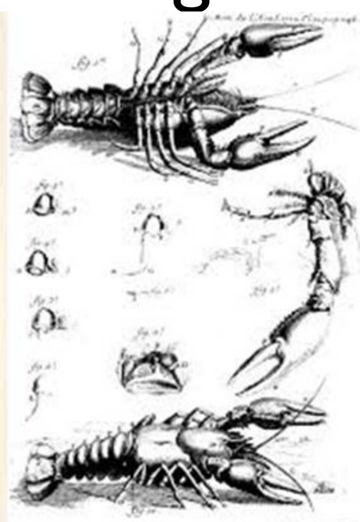
Regeneration as a biological phenomenon: definition and general description

Living organisms are characterized by a properties - the ability to:

- \- **Self-regulation** (Homeostasis) - is the ability to maintain a relatively stable internal state that persists despite changes in the world outside.
- \- **Self-reproduction** (Reproduction) - the ability of living organism to reproduce another with a similar organization to its own. It is based on the process of doubling DNA molecules with subsequent cell division.
- \- **Regeneration** (restoration) - the ability of living organisms to restore damaged tissue, and sometimes even entire lost organs.

Regeneration as a biological phenomenon: definition and general description

- The first experiments on regeneration were carried out by French scientists R. Reaumur in 1712 (he received the regeneration of claws for crayfish);
- in 1740, A. Trembley (from Geneva family) described the regeneration of a hydra.

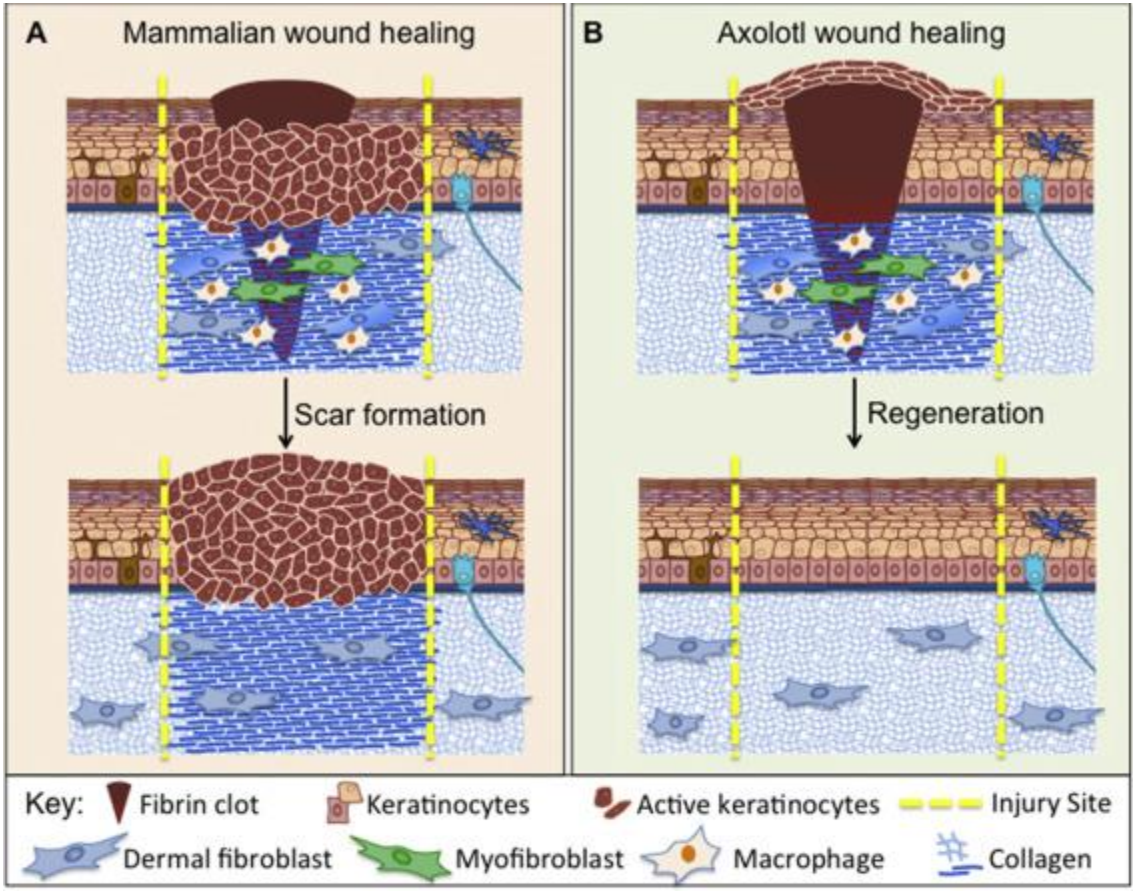


Regeneration as a biological phenomenon: definition and general description

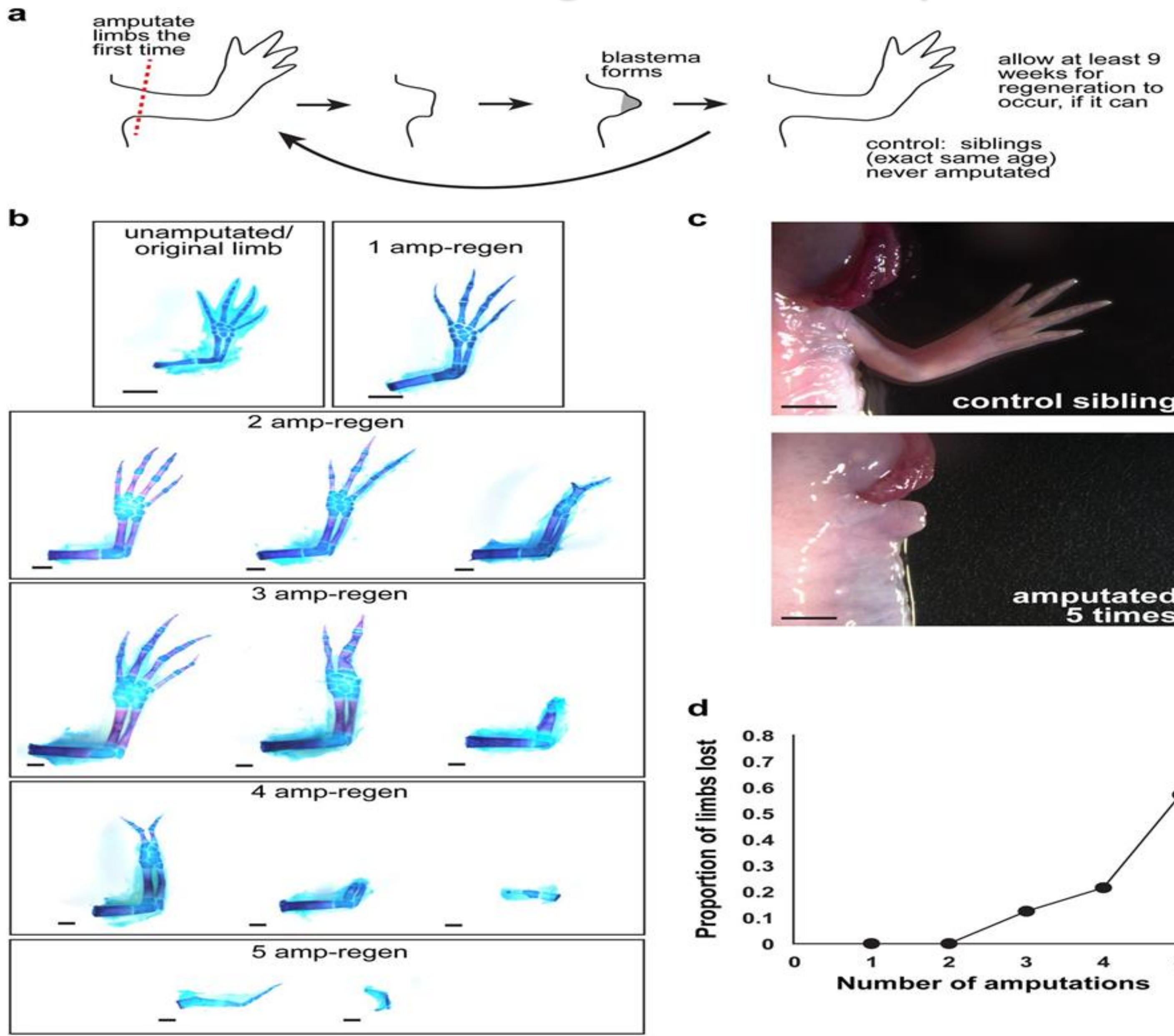
- Every species is capable of regeneration, from bacteria to humans.
- Some animals have **extensive regenerative abilities**. For example, the hydra and planarian can form two whole bodies after being cut in half. The Axolotl, or Mexican salamander, is an animal with a backbone that can regenerate the form and function of almost any limb, organ, or other body part.
- More complex animals such as mammals have **limited regenerative capacities.** These include forming thick scars in tissues and skin to promote the healing of injured or amputated body parts, regrowing hair and skin, and knitting together fractured bones.

Regeneration as a biological phenomenon: definition and general description

- Regeneration can either be **complete** where the new tissue is the same as the lost tissue, or **incomplete** where after the necrotic tissue comes fibrosis.



Regeneration as a biological phenomenon: definition and general description



Types of regeneration

The regenerative capacity of cells permits to classify them into three groups:

- **Labile cells** (epithelium of the skin and gastrointestinal tract) continue to proliferate throughout life;
- **Stable cells** (the liver, the proximal tubules of the kidney, and endocrine glands) are cells that multiply only when needed. They spend most of the time in the quiescent G0 phase of the cell cycle, but can be stimulated to enter the cell cycle when needed;
- **Permanent cells** (nerve cells, skeletal muscle cells, and cardiac muscle cells) cannot reproduce themselves after birth.

Types of regeneration

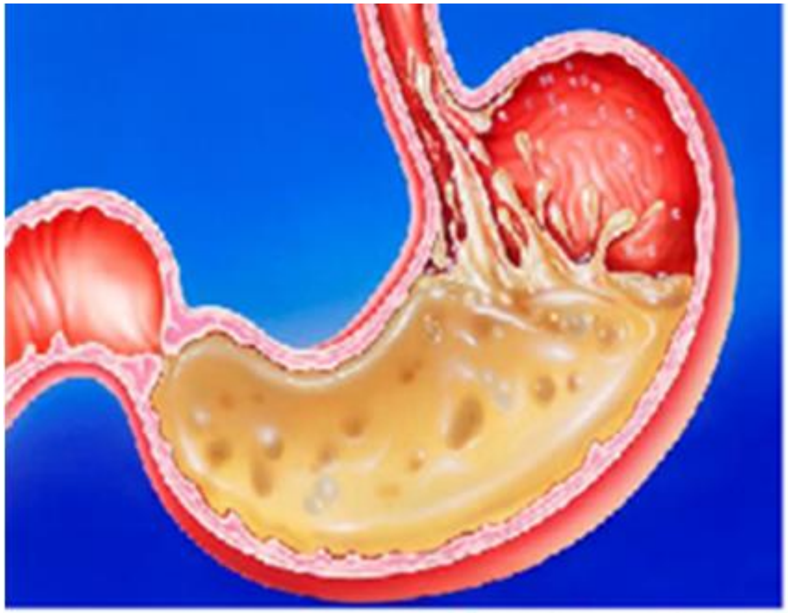
- **Physiological regeneration** is the process of normal functioning of the body, usually not associated with damage or loss of body part. Physiological regeneration is a cellular renewal process. For example: change of chitinous cover or molting in arthropods, replacement of feathers and fur in birds and mammals, molting in snakes, replacement of epithelial cells of the gastrointestinal tract (almost every day),renewal of blood cells.

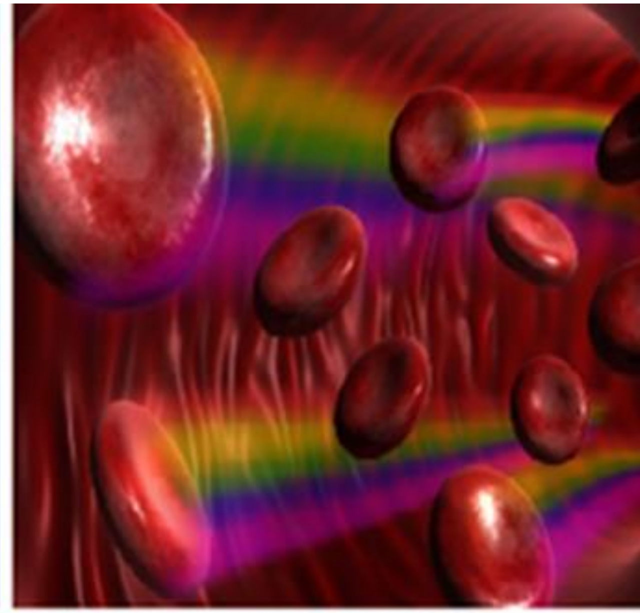
Physiological regeneration in animals





Physiological regeneration in human





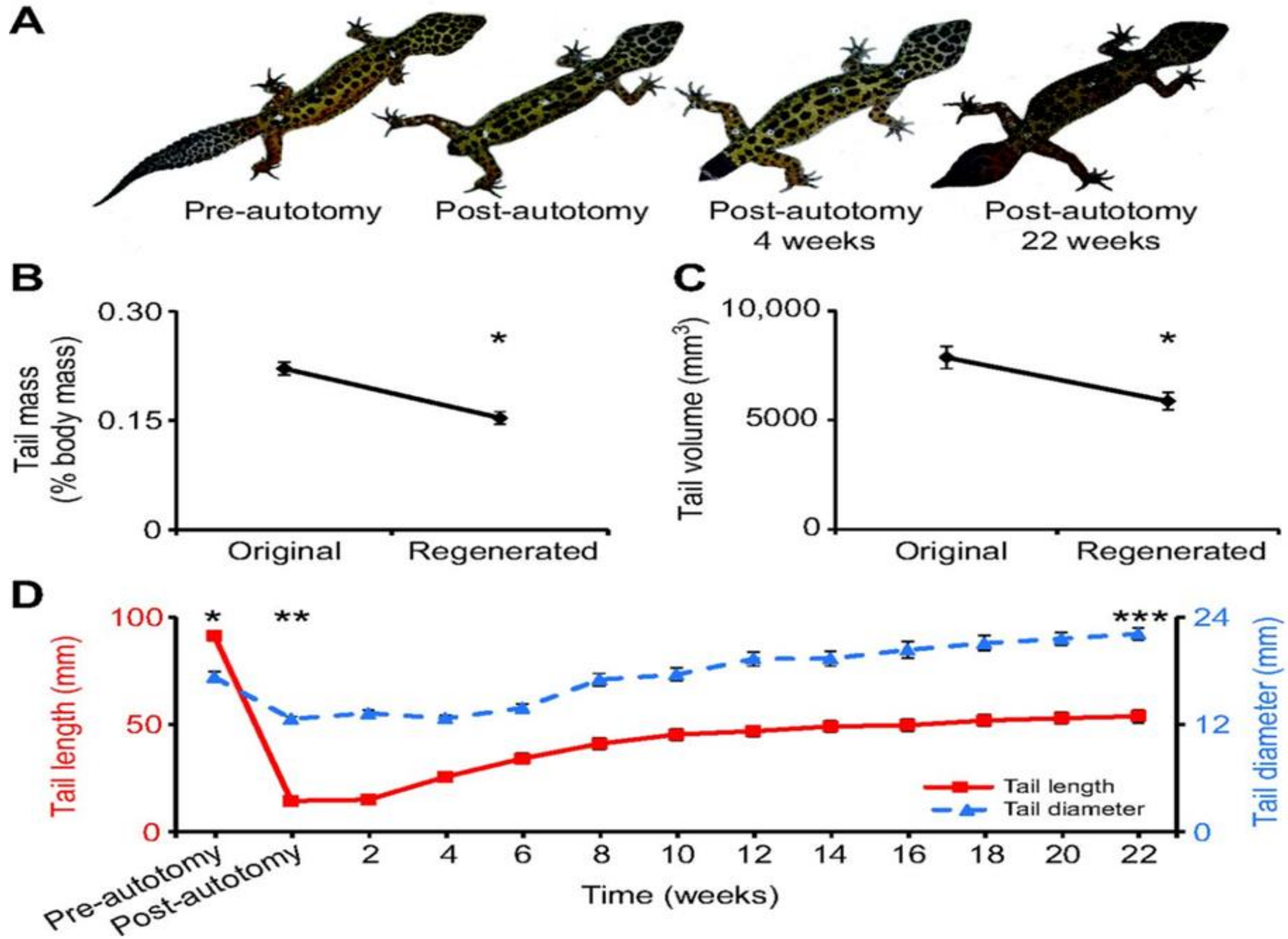
Types of regeneration

- **Reparative regeneration** is the replacement of lost parts or repair of damaged body organs. In this type of regeneration, wound is repaired or closed by the expansion of the adjoining epidermis over the wound.

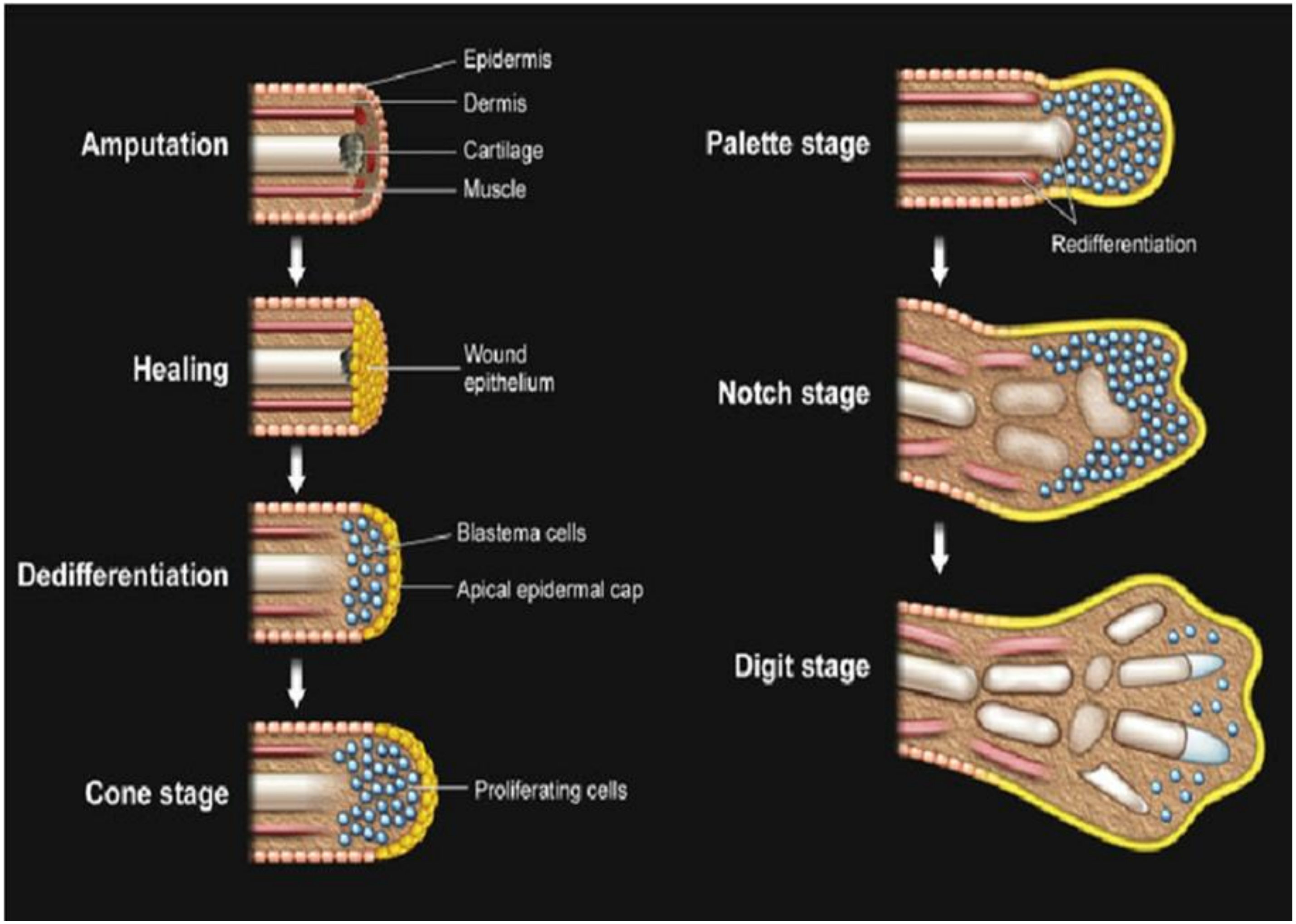
Methods of reparative regeneration

1. **Epimorphosis** is type of reparative regeneration, when a lost organ grows from the wound surface. Cells multiply forming a regeneration germ. Differentiation of cells restores the organ. An example: restoration of the lizard's tail.

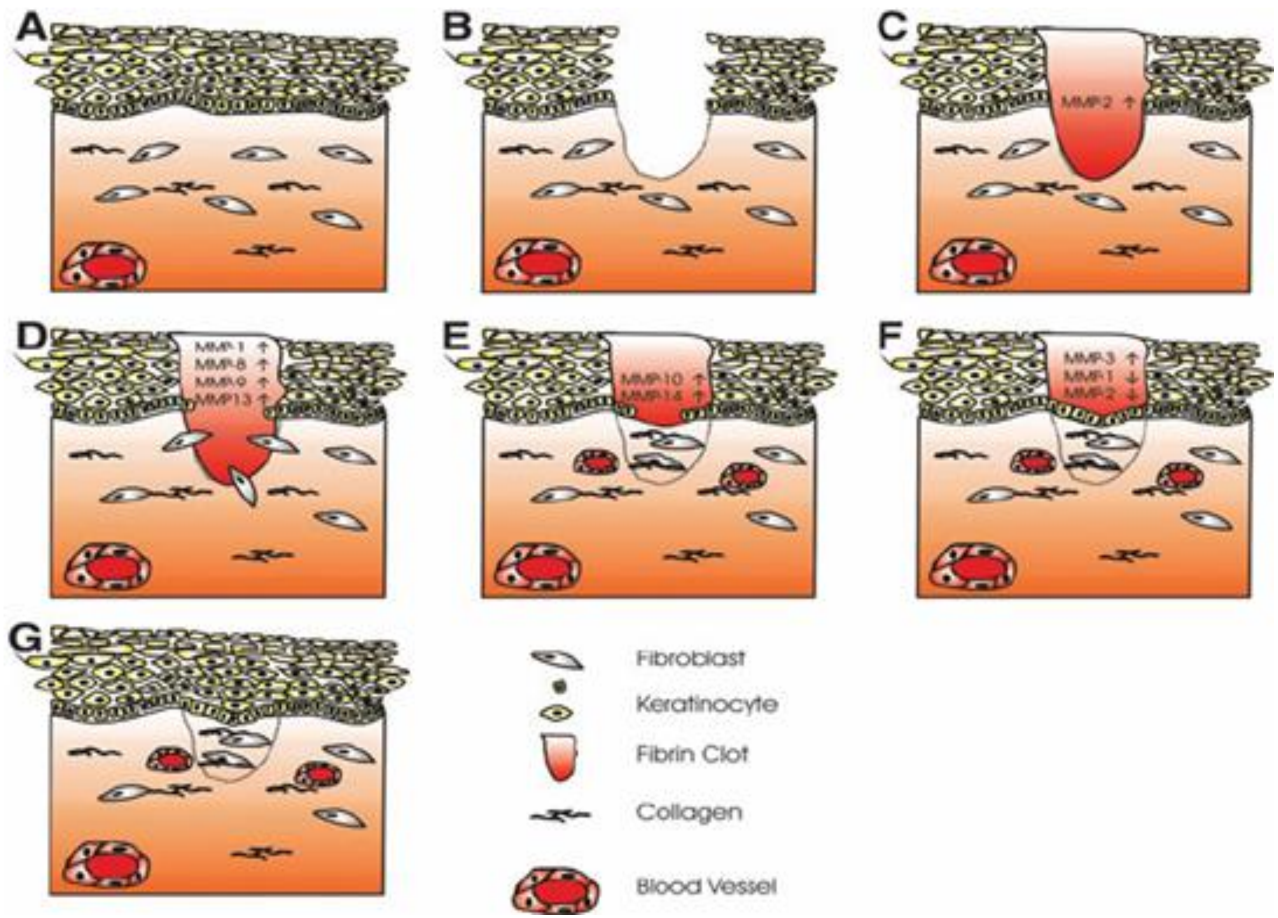
Epimorphosis



Epimorphosis

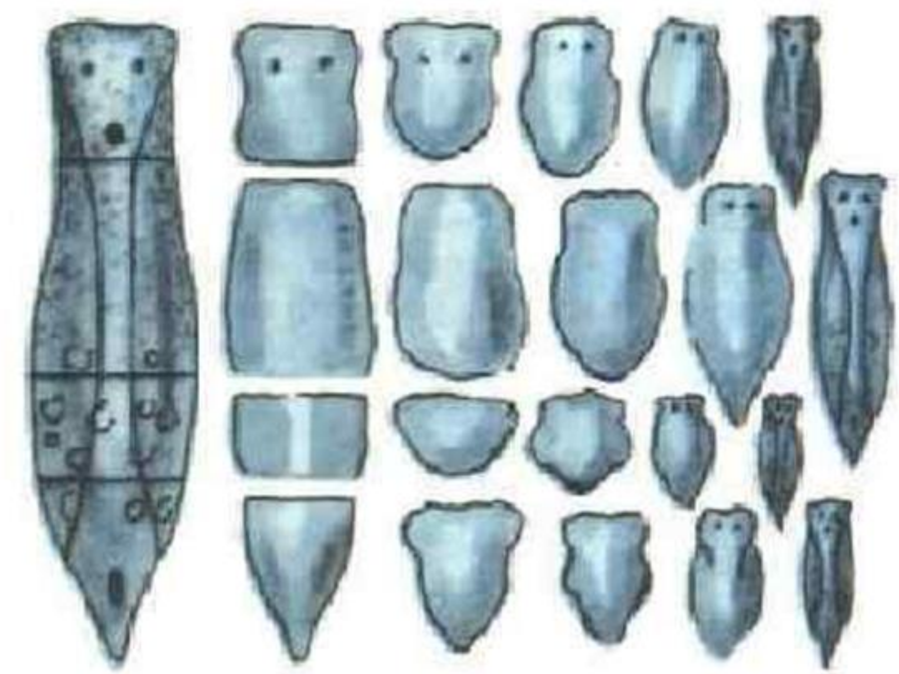


Epimorphosis: wound healing

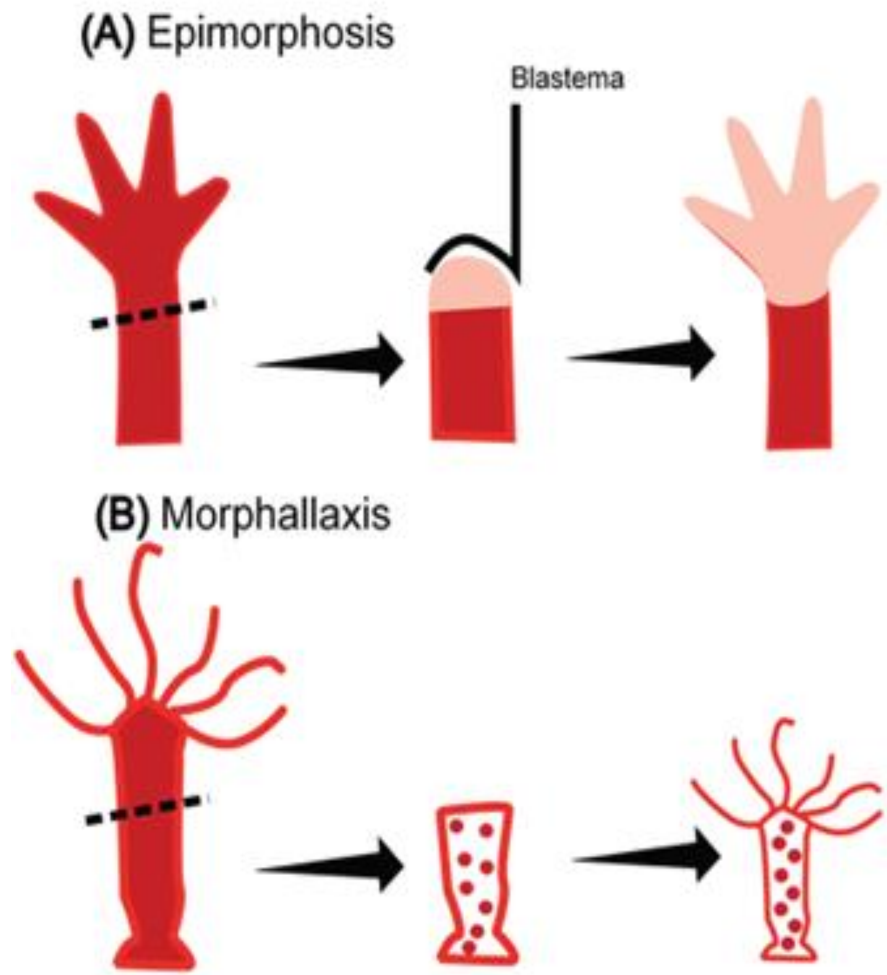


Methods of reparative regeneration

2. Morphallaxis — reconstruction of a remaining part of the organ to its initial shape (a whole hydra and planarian).

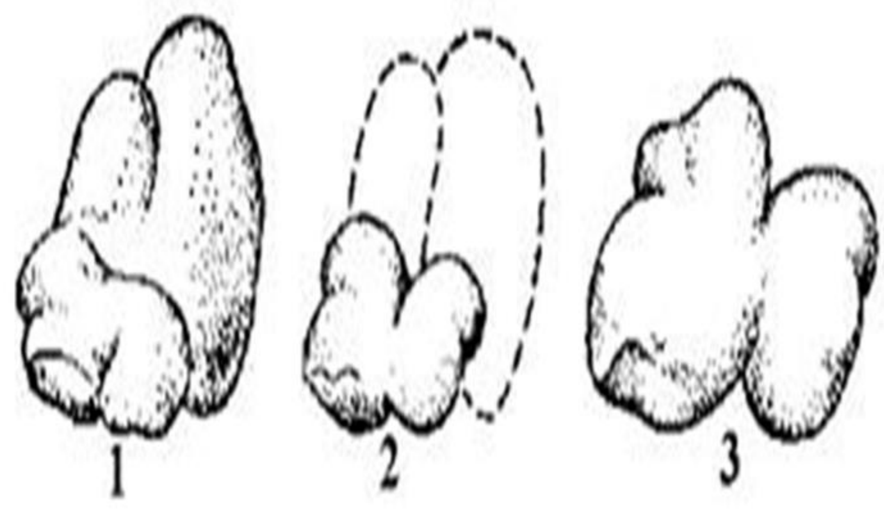


Methods of reparative regeneration



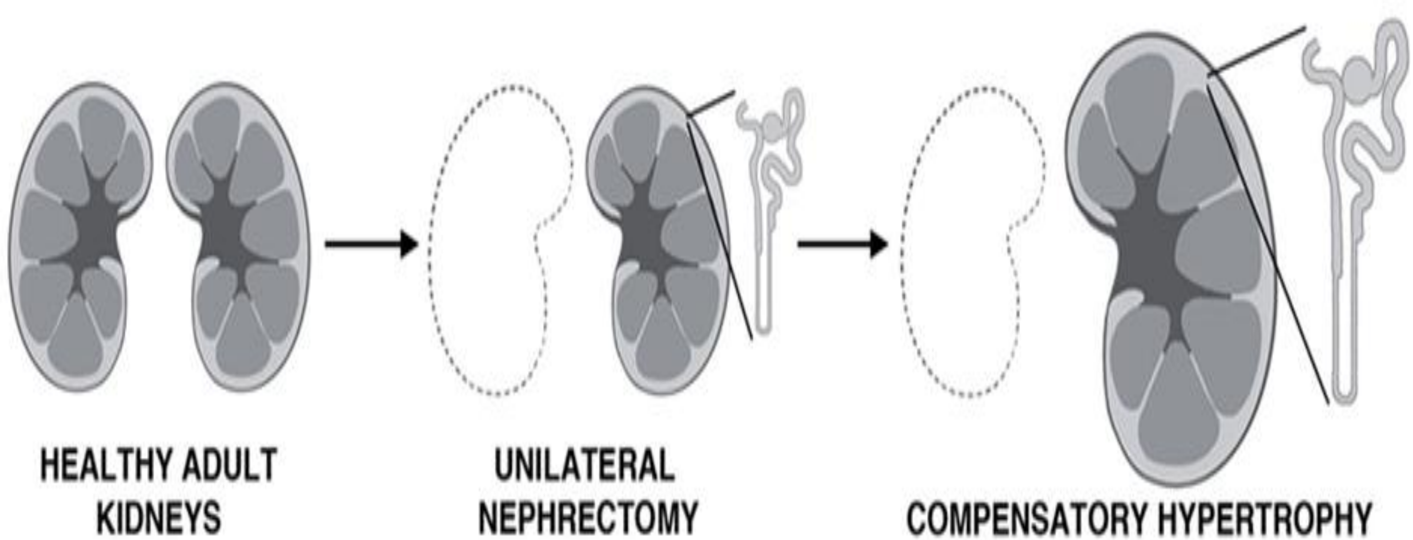
Methods of reparative regeneration

3. Endomorphosis or regenerative hypertrophy — enlargement of organ sizes after its injury. After removal of a part of the liver or spleen, a scar tissue forms on its wound surface, but a removed part is not restored. A mass of the remaining part grows and the organ reaches its former sizes.



Methods of reparative regeneration

4. Compensatory hypertrophy is a change in one of paired organs, when the other is impaired (hypertrophy of one kidney, when the other is removed).



Reparative regeneration

- There are typical and atypical reparative regeneration.

- In a *typical regeneration*, or *homomorphosis*, the lost part is replaced by the development of exactly the same part.
- In an *atypical regeneration*, or *heteromorphosis*, the lost part is replaced by a structure that quantitatively or qualitatively differs from the original one. In a tadpole that has regenerated a limb, the number of fingers may be less than the original, and in a shrimp, an antenna can grow instead of an amputated eye.

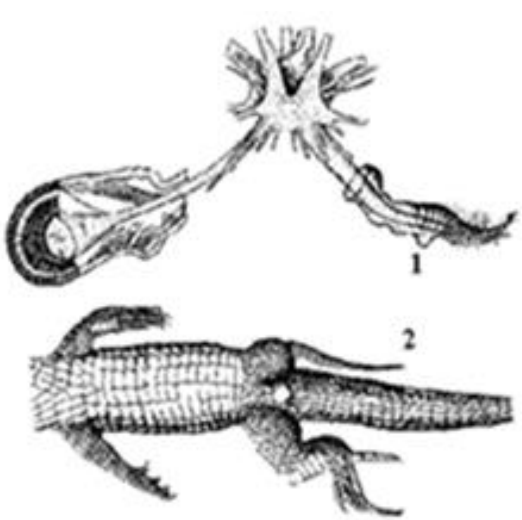
Forms of an atypical regeneration:

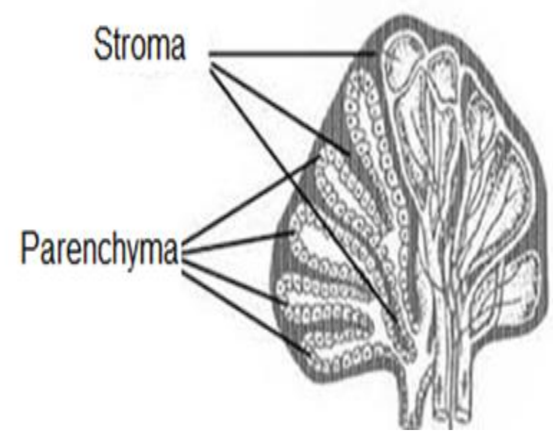
• heteromorphosis - in place of the lost organ another organ is formed (in crayfish instead of eye appears antenna; instead of antennae appears limb);

• hypotypia - incomplete development of the regenerating organ (less number of fingers on the limbs);

• hypermorphosis - excessive regeneration (more organs, excess bone tissue at the fracture site);

• substitution, or complete regeneration: if the parenchyma dies in the liver, full regeneration is possible, if the stroma dies, a scar tissue is formed - a dense connective tissue from collagen fibers.





Types of regeneration

- Certain animals have ability to release part of the body that has been grasped by an external agent. A notable example is found among lizards that break off the tail when it is seized by a predator. The phenomenon is found also among certain worms, salamanders, and spiders. This phenomenon is called **autotomy or self-amputation**.

Levels of regeneration

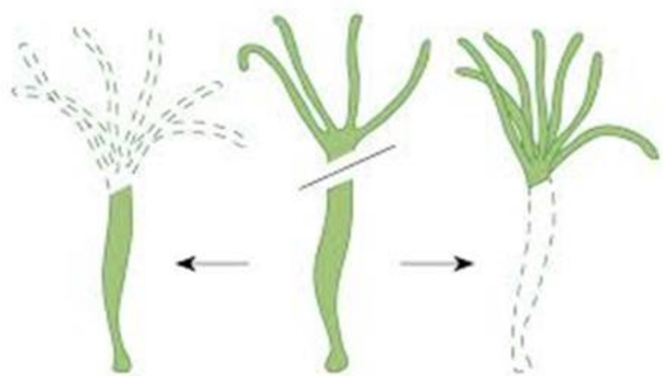
- 1. The "lower" level of regeneration is **molecular** or **biochemical regeneration**. This is an update of the chemical components of the cell, its molecular composition (for example, the repair of DNA molecules).
- 2. The next level is **subcellular regeneration**, or ultrastructural: restoration of the initial structure of organelles, disturbed by the influence of pathogenic factors or functional overvoltage (for example, restoration of mitochondrial cristae, Golgi complex cisterns, the regeneration of whole organelles).

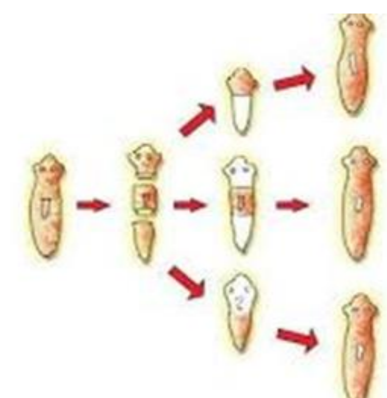
Levels of regeneration

- 3. **Cellular regeneration** is a mitotic and amitotic formation of cells instead of destroyed cells (replacement of epithelial cells). One form is cell hypertrophy.
- 4. **Tissue and organ regeneration** levels (examples: muscle and tail regeneration in a lizard). Compensatory hypertrophy at the organ level is expressed in the fact that the destroyed organ is not restored, but the remaining part grows or one of the paired organs grows when the other is damaged (examples: liver, mammalian kidneys).

Levels of regeneration

- 5. The **organism level** of regeneration. Some species of lower animals are capable of restoring the whole organism from a small part of it. For example: 1/200 part can restore the whole hydra or 1/4500 part of the planarian body restores the whole organism.
- According to B.P. Tokin (1958), these cases are examples of somatic embryogenesis - the development of a new organism from individual somatic cells or their groups. This is a type of vegetative reproduction in animals of the lower levels of organization.





Regulation of regeneration

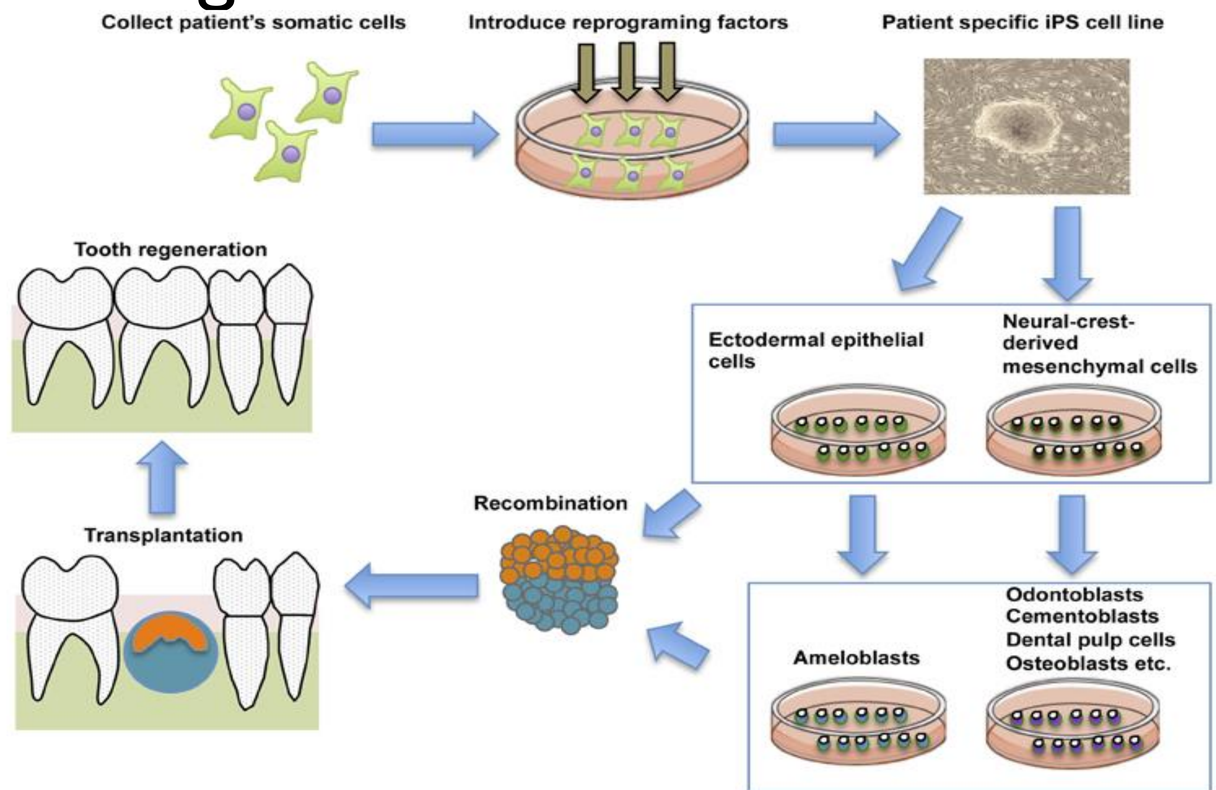
- Regeneration mechanisms are associated with the advent of new inductors and switching on new blocks of genes. The regulation of regeneration processes means:

– **humoral regeneration**: action of hormones and other biologically active substances on mitotic cellular activity. For example, the reproduction of cells in the tissue is limited by the substances of keylons (glycoproteins). Keylones - tissue-specific hormones of local action - are represented by proteins or peptides of various molecular weights. Substances that inhibit cell proliferation by inhibiting DNA synthesis in progenitor cells. Produced by all cells of higher organisms. When occurs damage, antikeylons are formed that neutralize the action of keylons, which leads to cell proliferation. In addition, the decay products of damaged cells have a stimulating effect - they affect intact cells, causing them to multiply.

– **immunological regulation** associated with transfer of «regenerative information» by lymphocytes; it stimulates proliferation (multiplication) of cells of various internal organs. The macrophages, lymphocytes, mast cells, platelets, endotheliocytes take part in restoring the structure of the functional element of the damaged organ.

Stem cells

- Stem cells are undifferentiated (immature) cells found in many species of multicellular organisms.
- Stem cells may serve as an origin of organ or tissue regeneration.

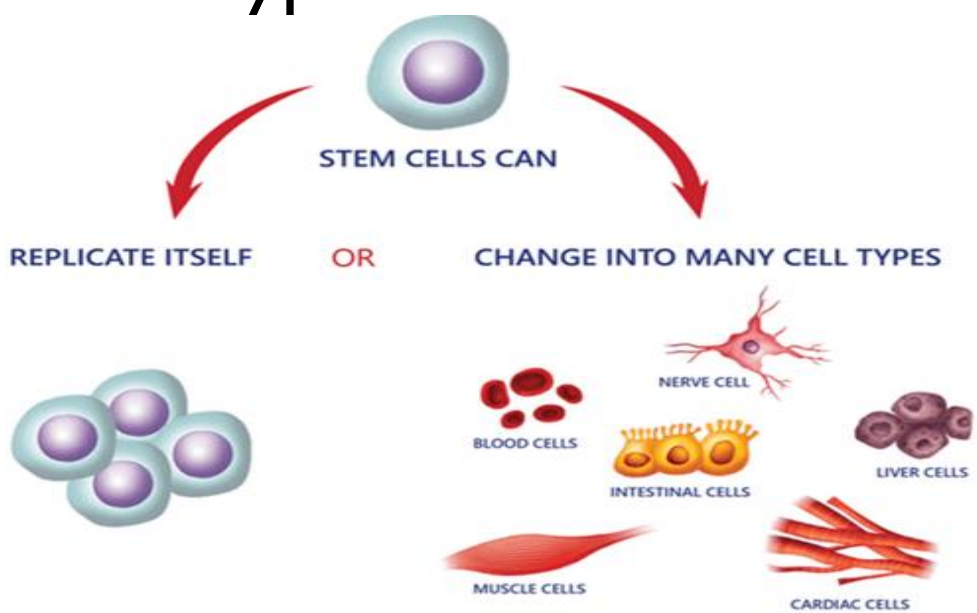


Stem cells

- Stem cells have two properties:

- self-renewal: the ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

- Potency: the capacity to differentiate into specialized cell types.



Stem cells

- Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.

\- *Totipotent stem cells* can differentiate into embryonic and extra embryonic cell types. Such cells can construct a complete, viable organism. These cells are produced from the fusion of an egg and sperm cell (zygote). Cells produced by the first few divisions of the fertilized egg are also totipotent.

\- *Pluripotent stem cells* are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers.

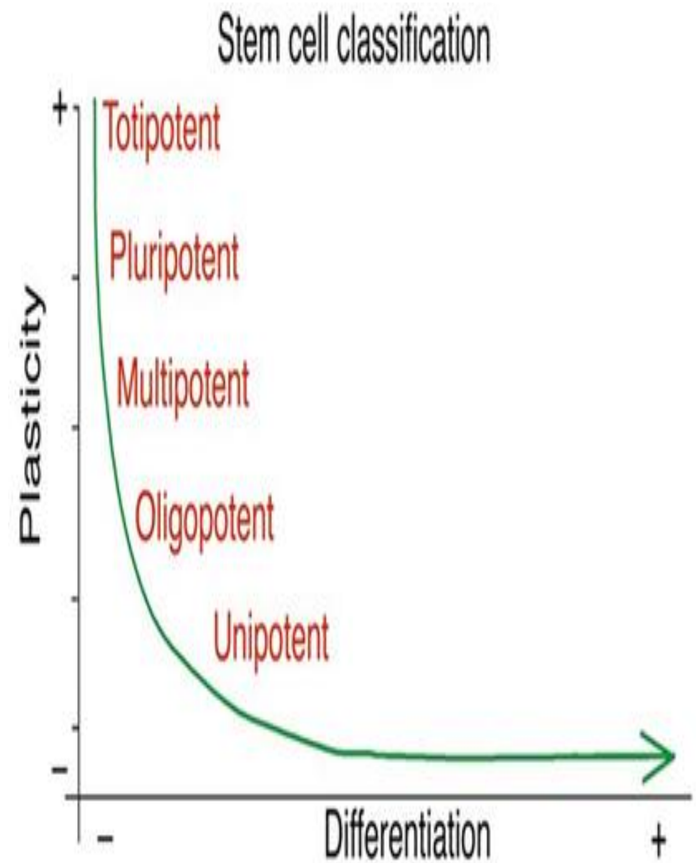
\- *Multipotent stem cells* can differentiate into a number of cell types, but only those of a closely related family of cells.

\- *Oligopotent stem cells* can differentiate into only a few cell types, such as lymphoid or myeloid stem cells.

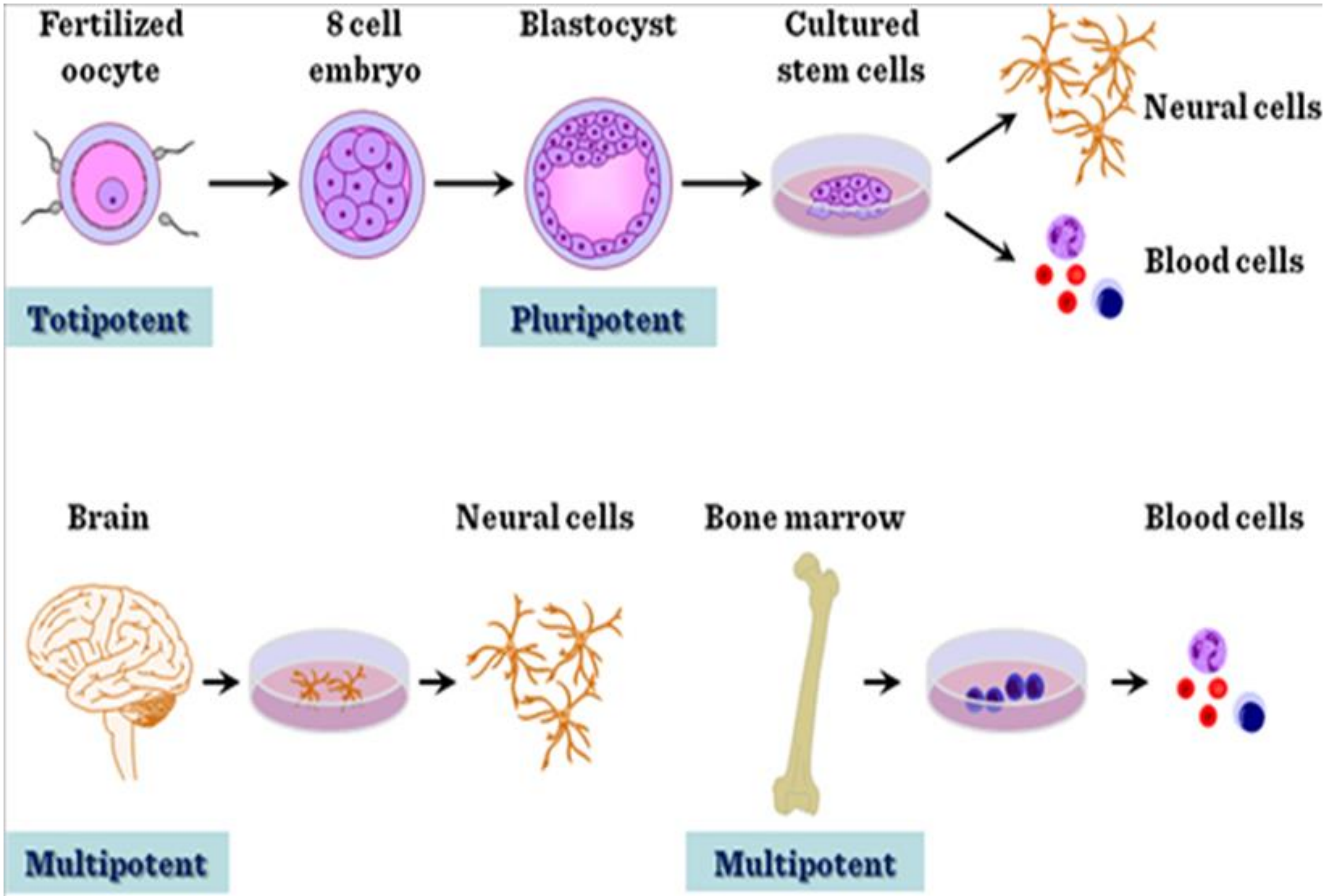
\- *Unipotent stem cells* can produce only one cell type, their own, but have the property of self-renewal, which distinguishes them from non-stem cells (e.g. progenitor cells, which cannot self-renew).

Stem cells

CELL TYPE	DESCRIPTION	EXAMPLES
Totipotent	Each cell can develop in to new individual	Cells from early (1-3) days embryo
Pluripotent	Cells can form (over) cell types	Some cells of blastocyst (5 -14 days)
Multipotent	Cells differentiated but can form a number of other types	Fetal tissue cord blood and adult stem cells
Oligo potent	Ability to differentiate in to few cells	Adult lymphoid or myeloid cell
Unipotent	Ability to produce cells	Adult muscle stem cells



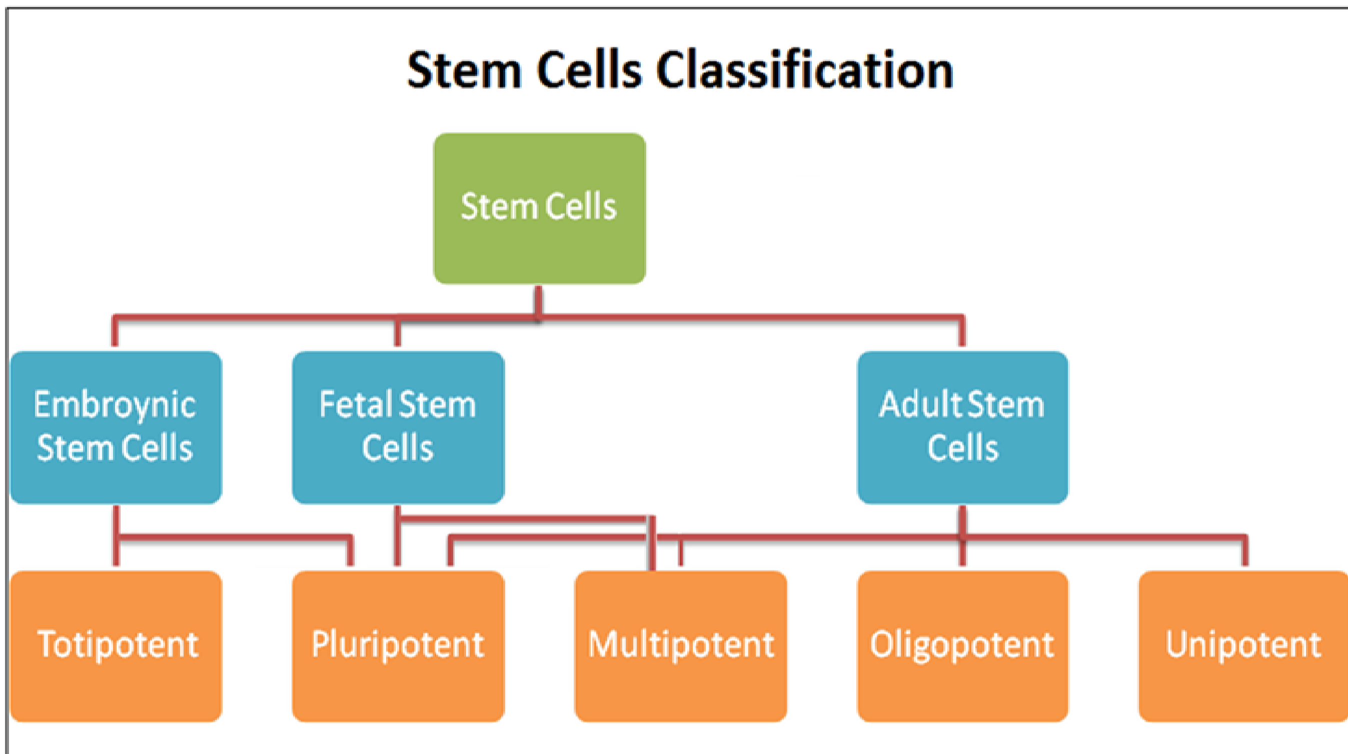
Stem cells



Fertilized oocyte
8 cell embryo
Blastocyst
Cultured stem cells
Neural cells
Blood cells
Totipotent
Pluripotent
Brain
Neural cells
Bone marrow
Blood cells
Multipotent
Multipotent

Stem cells

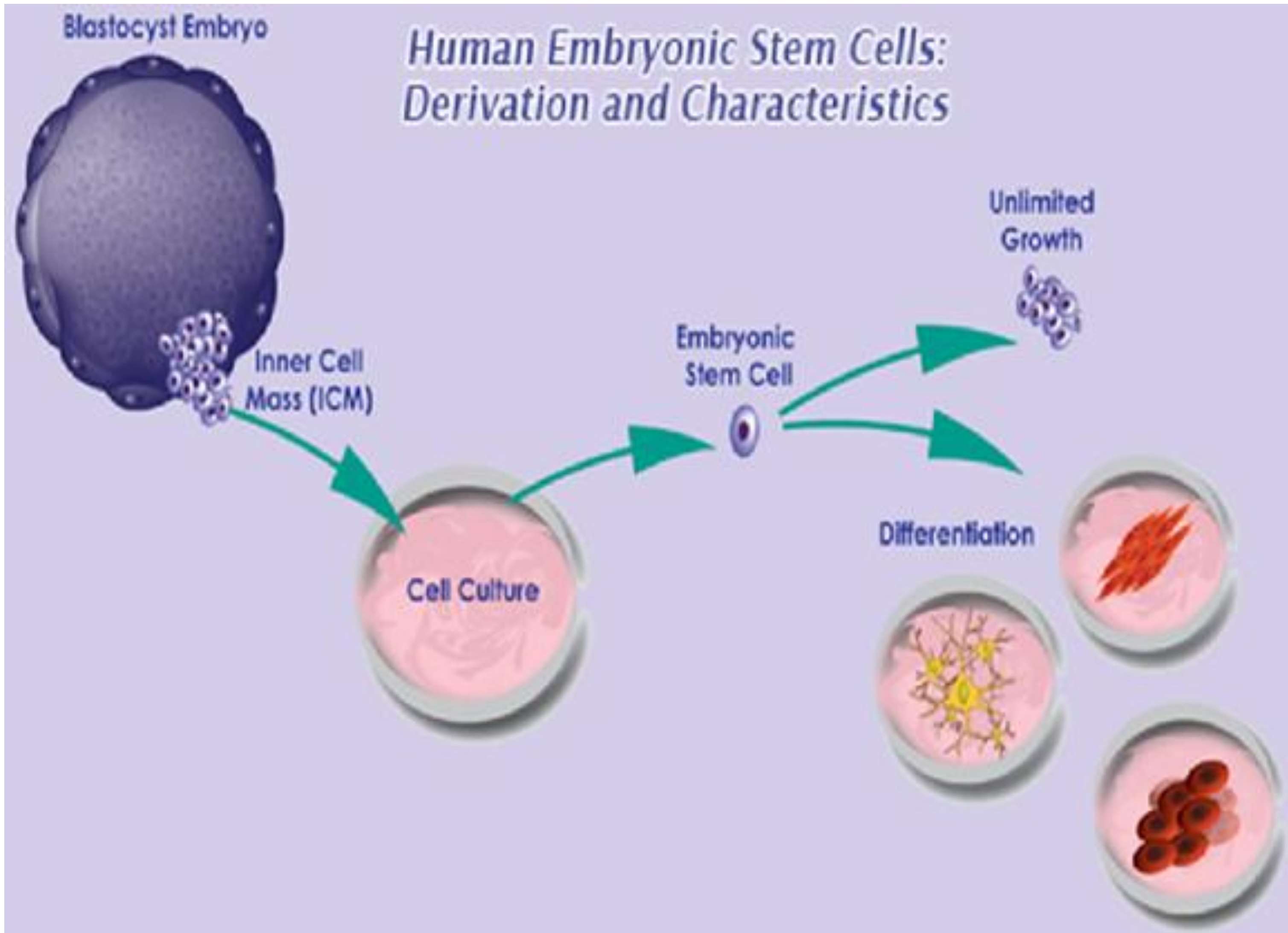
- Stem cells can be divided into three main groups depending on the source of their production: **embryonic, fetal and postnatal (somatic stem cells, or adult stem cells)**.



Stem cells

- **Embryonic stem cells** (ESCs) are the cells of the inner cell mass of a blastocyst, formed prior to implantation in the uterus. In human embryonic development the blastocyst stage is reached 4–5 days after fertilization, at which time it consists of 50–150 cells. ESCs are pluripotent and give rise during development to all derivatives of the three germ layers: ectoderm, endoderm and mesoderm.

Stem cells


Blastocyst Embryo
Human Embryonic Stem Cells:
Derivation and Characteristics
Unlimited
Growth
Embryonic
Stem Cell
Inner Cell
Mass (ICM)
Differentiation
Cell Culture

Stem cells

- **Fetal stem cells** (FSCs) are located in the organs of fetuses. There are two types of fetal stem cells:

- Fetal proper stem cells come from the tissue of the fetus proper, and are generally obtained after an abortion. These stem cells are not immortal but have a high level of division and are multipotent.

- Extra embryonic fetal stem cells come from extra embryonic membranes, and are generally not distinguished from adult stem cells. These stem cells are acquired after birth, they are not immortal but have a high level of cell division, and are pluripotent.

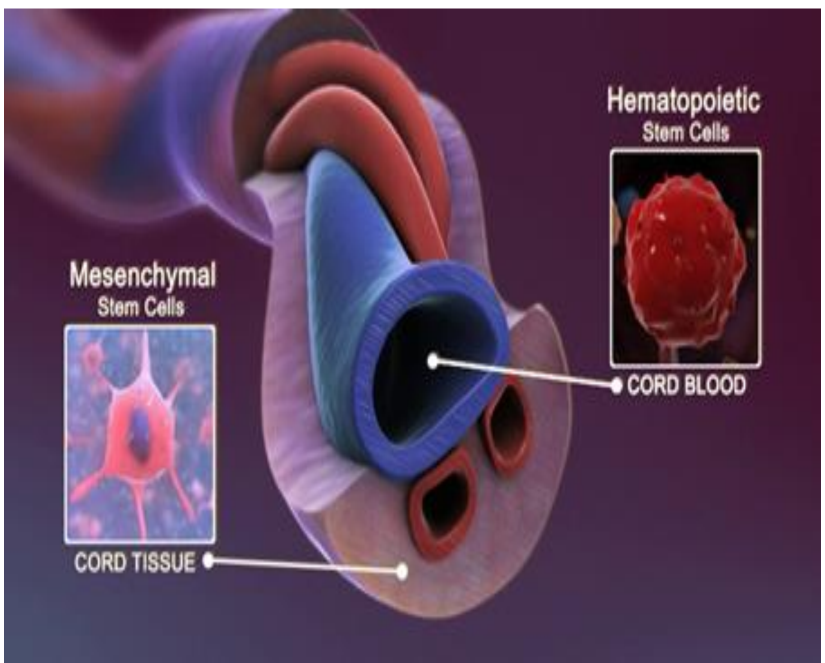
Stem cells

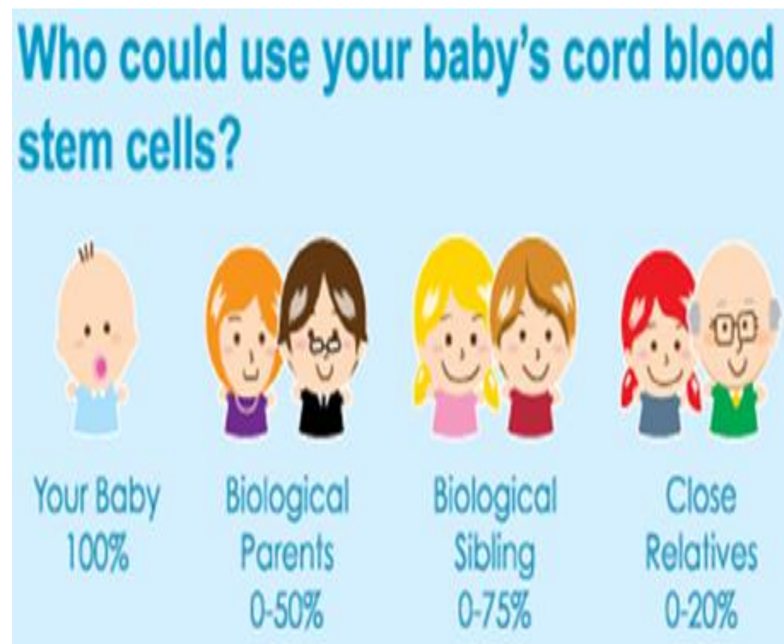
- **Postnatal or adult stem cells, also called somatic stem cells (SSCs)**, are stem cells which maintain and repair the tissue in which they are found. They can be found in children, as well as adults.
- There are three known accessible sources of adult stem cells in humans:

- Bone marrow, which requires extraction by harvesting, that is, drilling into bone (typically the femur or iliac crest).
- Adipose tissue (fat cells), which requires extraction by liposuction.
- Blood, which requires extraction through apheresis, wherein blood is drawn from the donor (similar to a blood donation), and passed through a machine that extracts the stem cells and returns other portions of the blood to the donor.

Stem cells

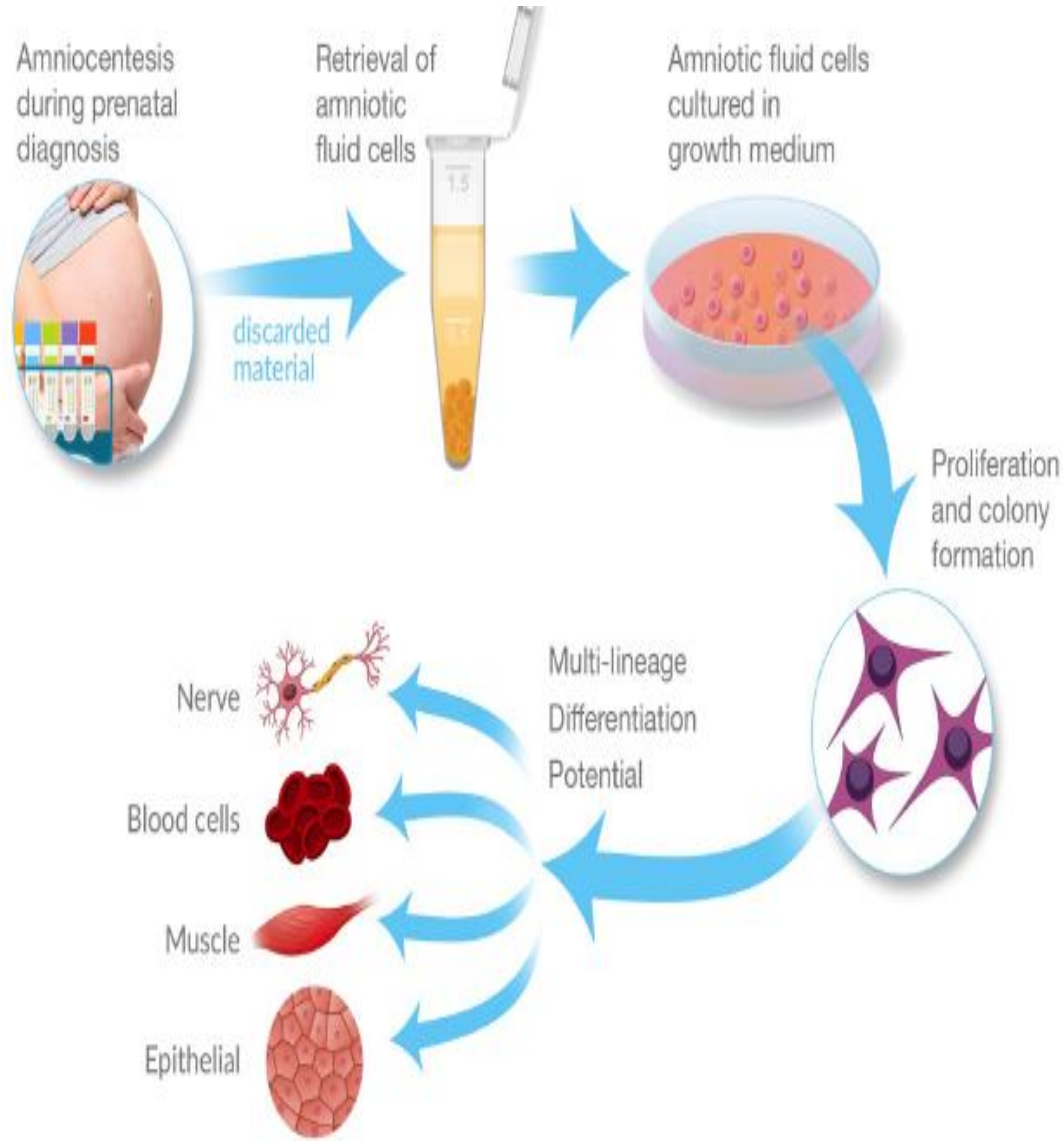
- Pluripotent adult stem cells are rare and generally small in number, but they can be found in **umbilical cord blood** and other tissues.





Stem cells

- **Amniotic stem cells** are also found in amniotic fluid. They are multipotent and can differentiate in cells of adipogenic, osteogenic, myogenic, endothelial, hepatic and also neuronal lines.

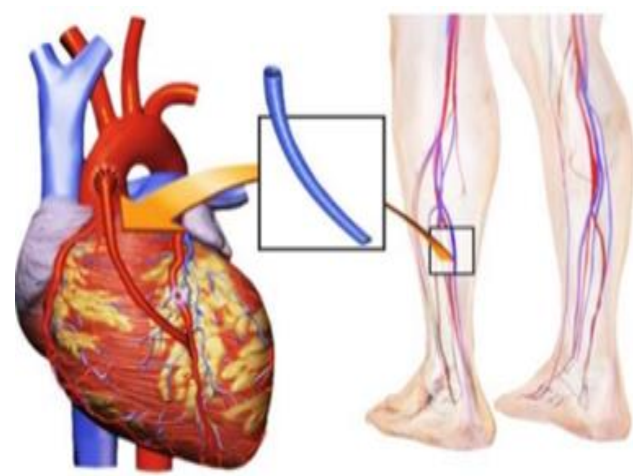


Transplantation

- **Organ transplantation** is a medical procedure in which an organ is removed from one body and placed in the body of a recipient, to replace a damaged or missing organ.
- Organs that have been successfully transplanted include the heart, kidneys, liver, lungs, pancreas, intestine, and thymus.
- Tissues include bones, tendons (both referred to as musculoskeletal grafts), cornea, skin, heart valves, nerves and veins.

Types of transplant

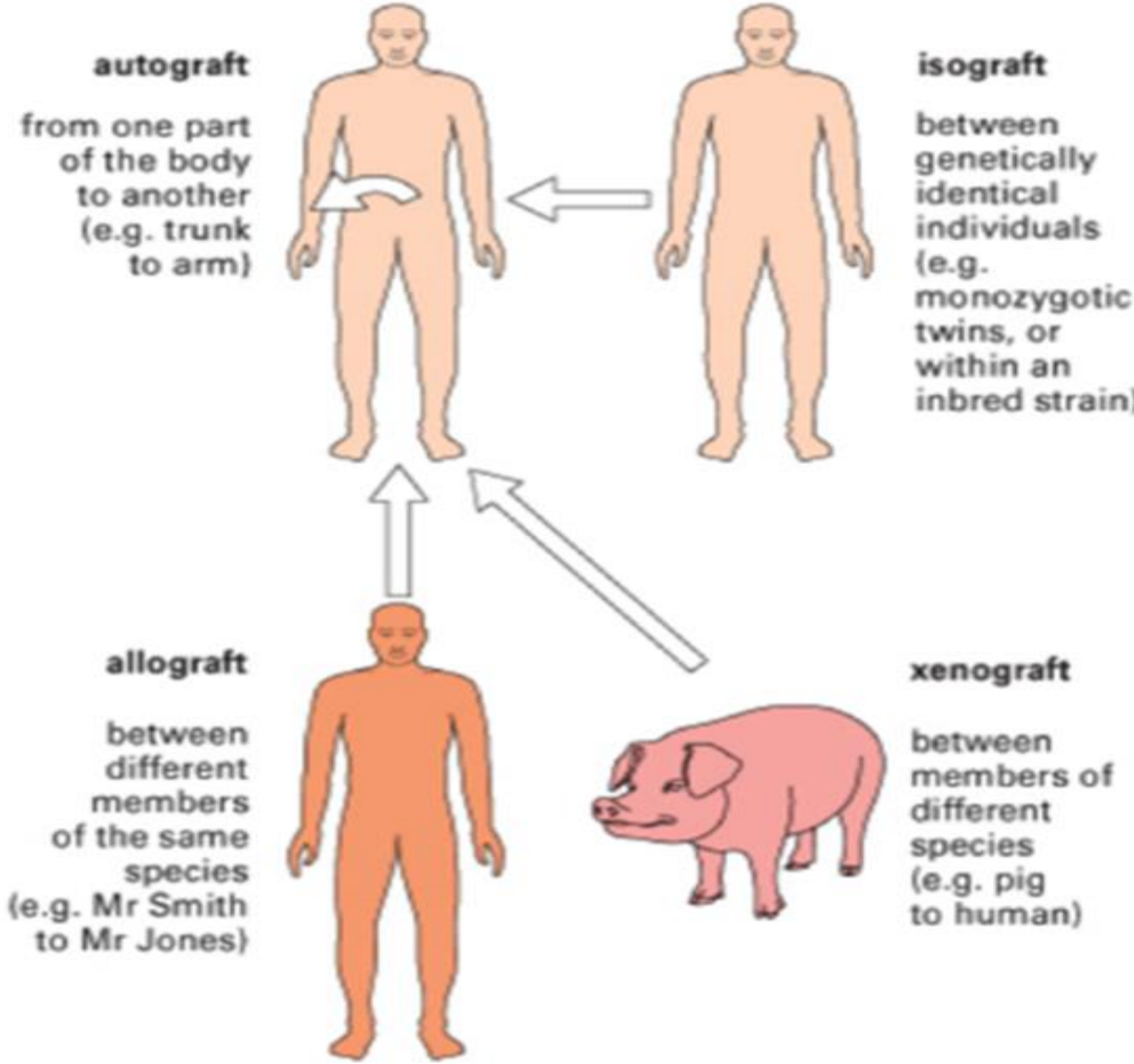
- The tissue or organ transplanted is known as the transplant or graft.
- There are mainly four different types of grafts namely Autograft, Isograft (Syngraft), Allograft (Homograft) and Xenograft (Heterograft).



Types of transplant

- **Autograft:** It is tissue transferred from one body site to another in the same individual. These grafts are often performed on patients with burns by transferring healthy skin to the burned area. Always graft is accepted.
- **Isograft:** It is the tissue transferred between genetically identical individuals. In humans, this type of graft transfer possible usually between identical (Monozygotic) twins. This type of graft was also accepted. This type of graft is formerly known as syngraft or syngenic graft.
- **Allograft:** It is the tissue transferred between genetically non-identical members of the same species. Most of the organs (grafts) transplanted in human populations are found to be allograft. Normally allografts are rejected after transplantation, but immunosuppressive drugs and immune tolerance properties utilized for the survival of graft.
- **Xenograft:** It is the tissue transferred between different species. This graft is also normally rejected. Pigs' hearth valve usually transplanted to humans. Through immunosuppressive and tolerance properties, graft survived in transplanted individuals.

Types of transplant

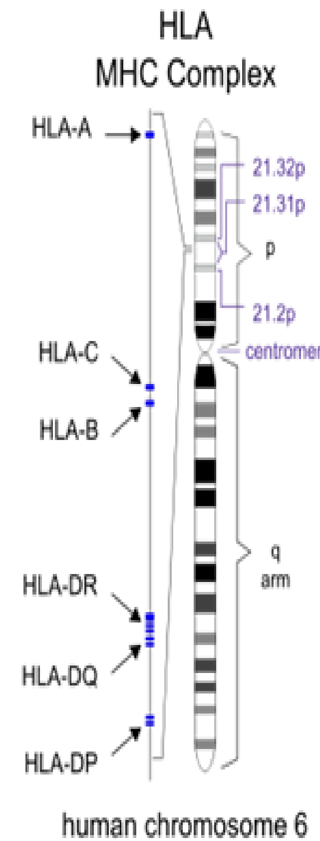


Transplant rejection

- **Transplant rejection** occurs when transplanted tissue is rejected by the recipient's immune system, which destroys the transplanted tissue.
- To reduce the risk of transplant reactions, donor selection for antigens of the *main histocompatibility complex* (MHC), often also according to *ABO* system and various *immunosuppressant drugs* are used to suppress the immune system, some of which can be prescribed for life.

Human Leukocyte Antigens (HLA) complex

- HLA is a group of histocompatibility antigens, the main histocompatibility complex in humans. Presented by more than 150 antigens. The locus located on the 6th chromosome contains a large number of genes associated with the human immune system.



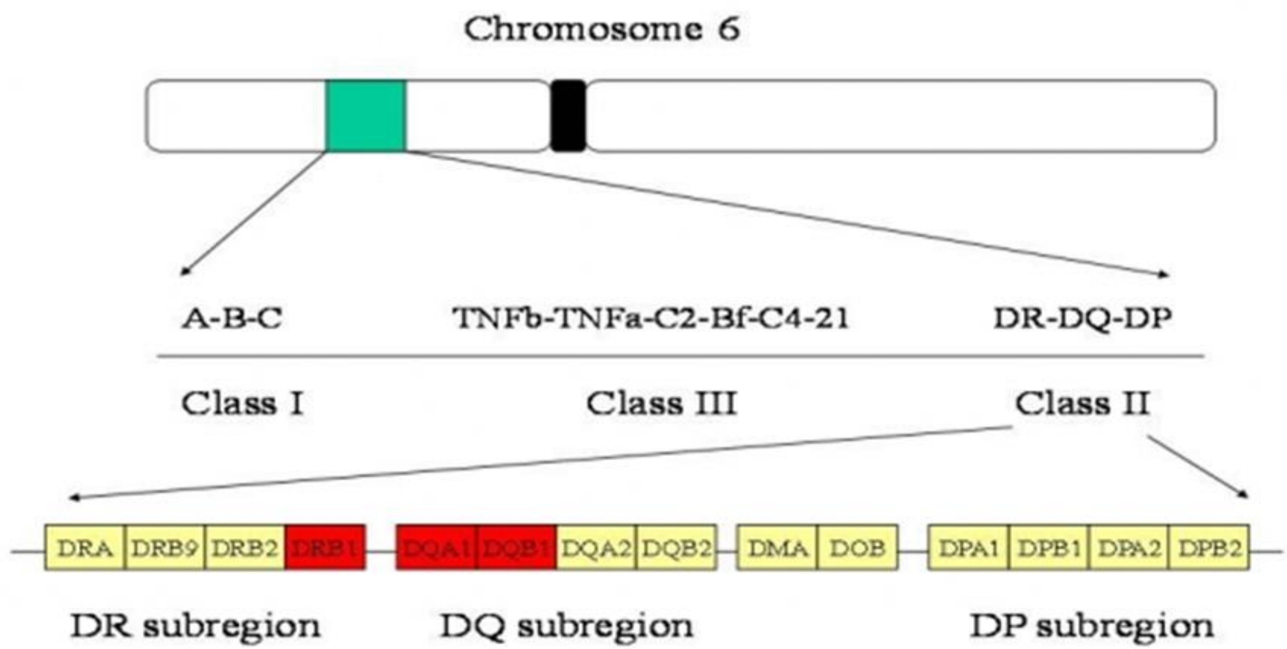
HLA complex

- **HLAs corresponding to MHC class I** (A, B, and C) which all are the HLA Class1 group present peptides from inside the cell.
- For example, if the cell is infected by a virus, the HLA system brings fragments of the virus to the surface of the cell so that the cell can be destroyed by the immune system.

HLA complex

- **HLAs corresponding to MHC class II** (DP, DM, DO, DQ, and DR) present antigens from outside of the cell to T-lymphocytes. These particular antigens stimulate the multiplication of T-helper cells (also called CD4 positive T cells), which in turn stimulate antibody-producing B-cells to produce antibodies to that specific antigen. Self-antigens are suppressed by regulatory T cells.
- **HLAs corresponding to MHC class III** encode components of the complement system.

HLA complex


Chromosome 6
A-B-C
TNFb-TNFa-C2-Bf-C4-21
DR-DQ-DP
Class I
Class III
Class II
DRA
DRB9
DRB2
DRB1
DQA1
DQB1
DQA2
DQB2
DMA
DOB
DPA1
DPB1
DPA2
DPB2
DR subregion
DQ subregion
DP subregion

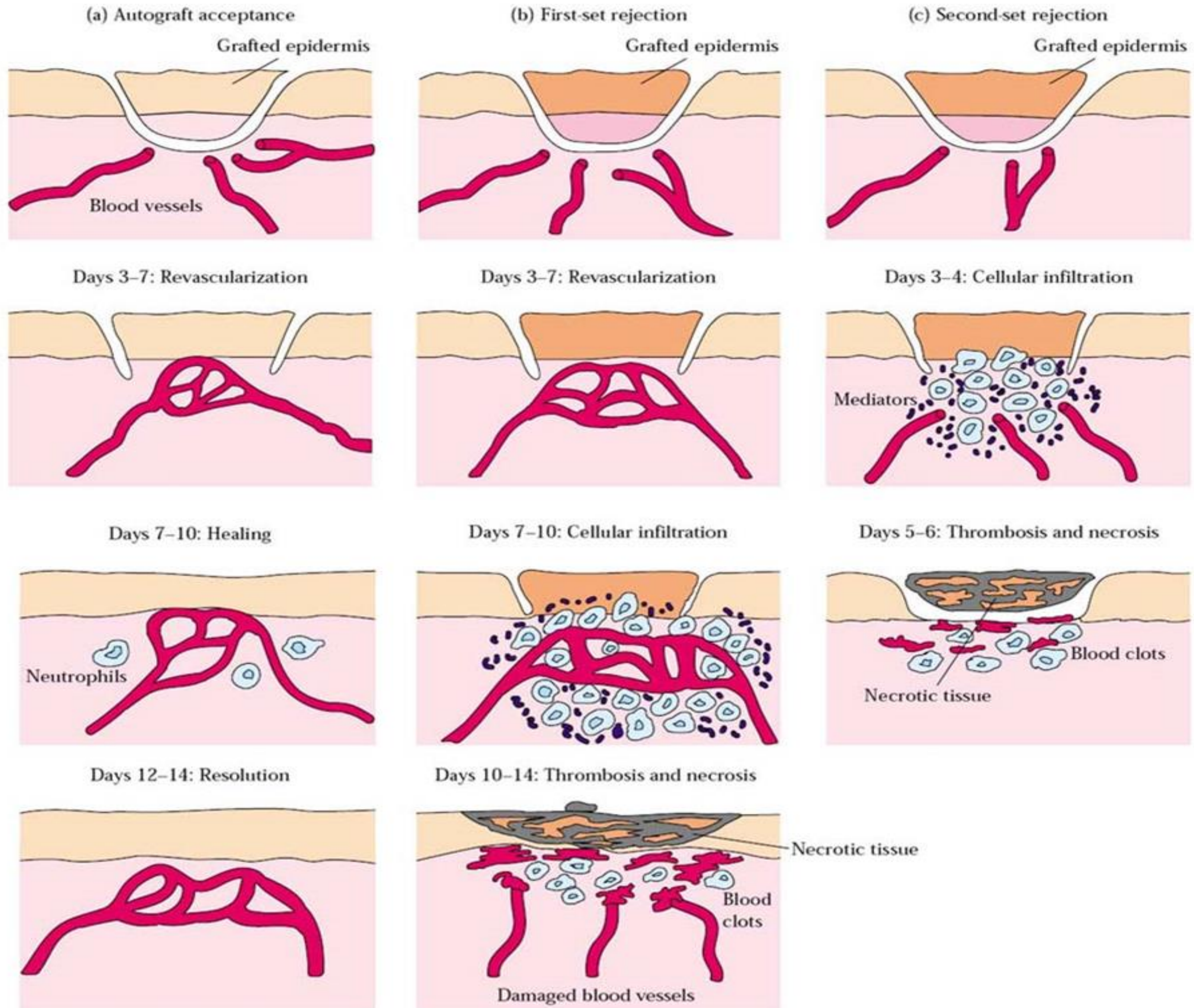
Transplant rejection

- Rejection is an adaptive immune response via cellular immunity (mediated by killer T cells inducing apoptosis of target cells) as well as *humoral immunity* (mediated by activated B cells secreting antibody molecules), though the action is joined by components of innate immune response (phagocytes and soluble immune proteins).
- Usually autografts and isografts are accepted and allograft and xenografts are rejected.

Specificity and memory of rejection

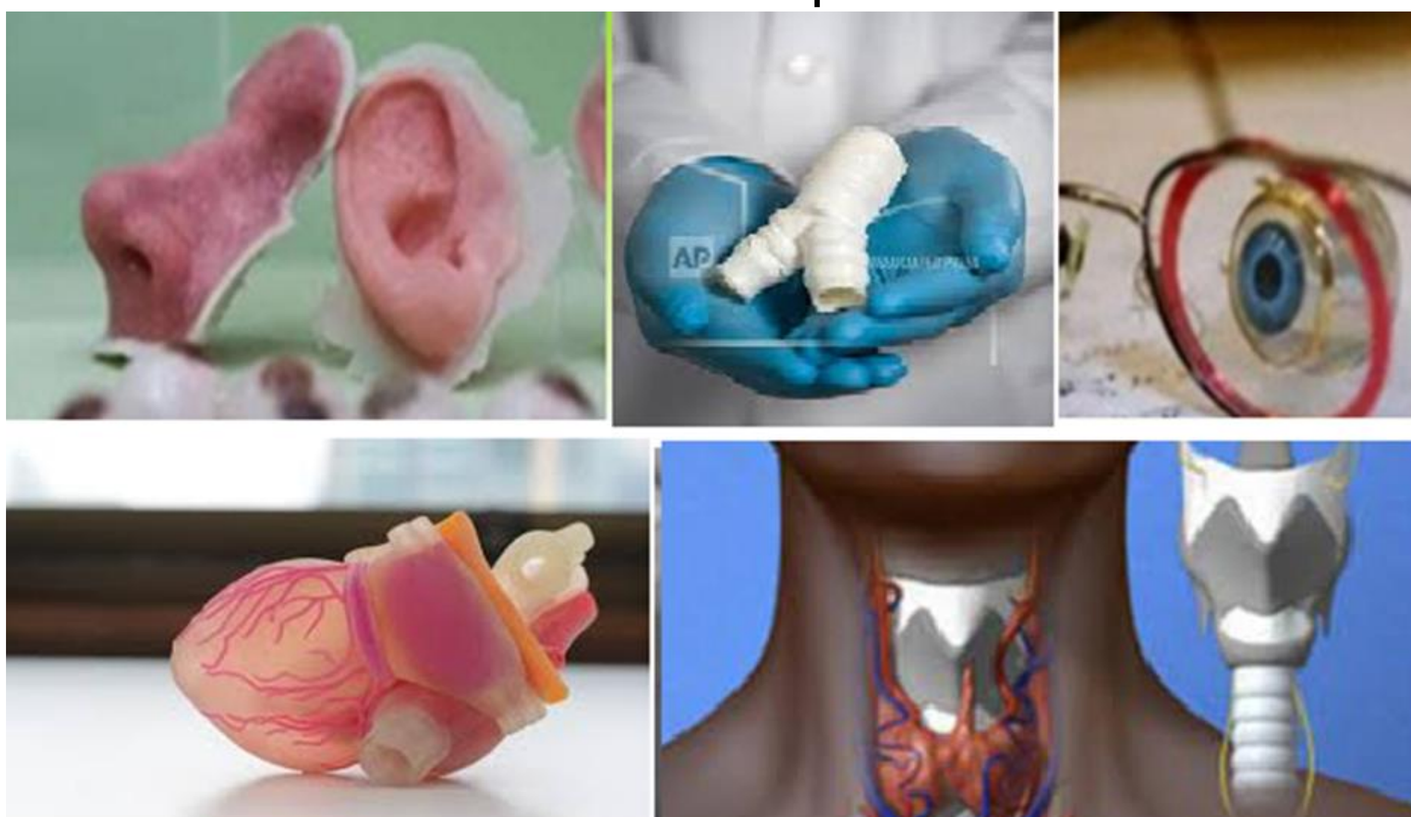
- Graft rejection can be studied in different headings like specificity and *memory* response to graft rejection, time variation in graft rejection and actual mechanism of graft rejection.
- When a graft is transplanted first time, it is referred as primary graft. If the primary graft is allograft type then it is rejected within 14 days of transplantation. The rejection type is known as first set of rejection. When another graft from same donor is transplanted second time or more then the graft is said to be secondary graft and it is rejected with 5-6 days. The rejection type is known as second set of rejection. The variation in the rejection time periods is because of immunologic memory and specificity between grafts.

Specificity and memory of rejection



Artificial organs

- An artificial organ is an engineered device or tissue that is implanted or integrated into a human — interfacing with living tissue — to replace a natural organ, to duplicate or augment a specific function or functions so the patient may return to a normal life as soon as possible.

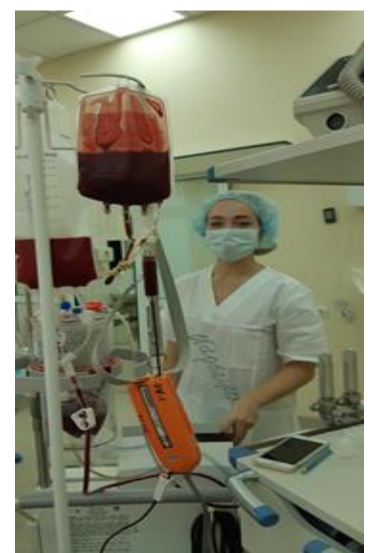


Transfusiology

- **Transfusion medicine,** or **transfusiology** is the branch of medicine that is concerned with transfusion of blood and blood components.

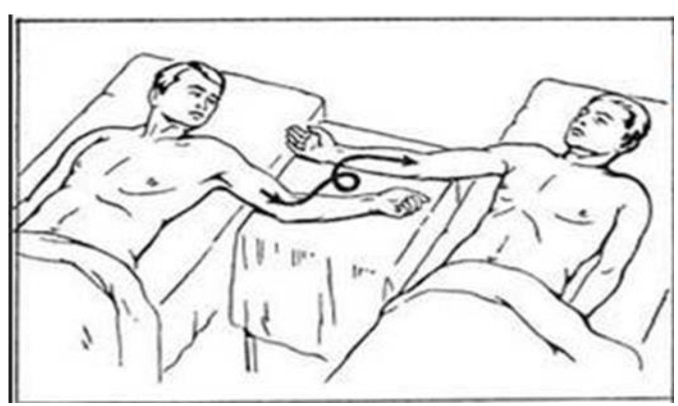
Transfusiology

- **Intraoperative reinfusion** is a method based on the collection of blood poured into the cavity (abdominal, thoracic, pelvic cavity) during surgery, and the subsequent washing of red blood cells and returning them to the bloodstream.



Transfusiology

- **Autohemotransfusion** is a method in which the patient is both a donor and a recipient of blood and its components for himself.
- **Direct blood transfusion** is a direct blood transfusion from a donor to a recipient without stabilization and preservation.



Transfusiology

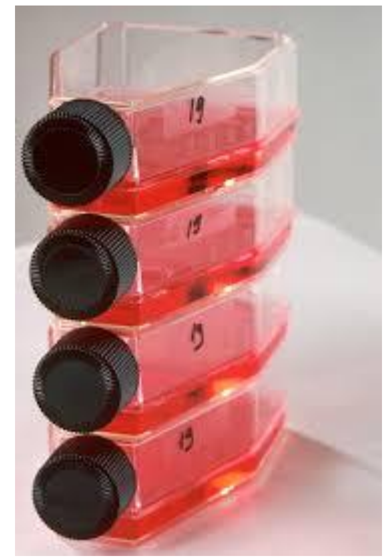
- **Indirect blood transfusion** is the main method of blood transfusion. This method uses stabilizers and preservatives (citrate, citrate-glucose, citrate-glucose phosphate preservatives, adenine, pyruvate, heparin, ion exchange resins, etc.), which makes it possible to carry out the preparation of blood components in large quantities, and also to store it for a long time.

Explantation

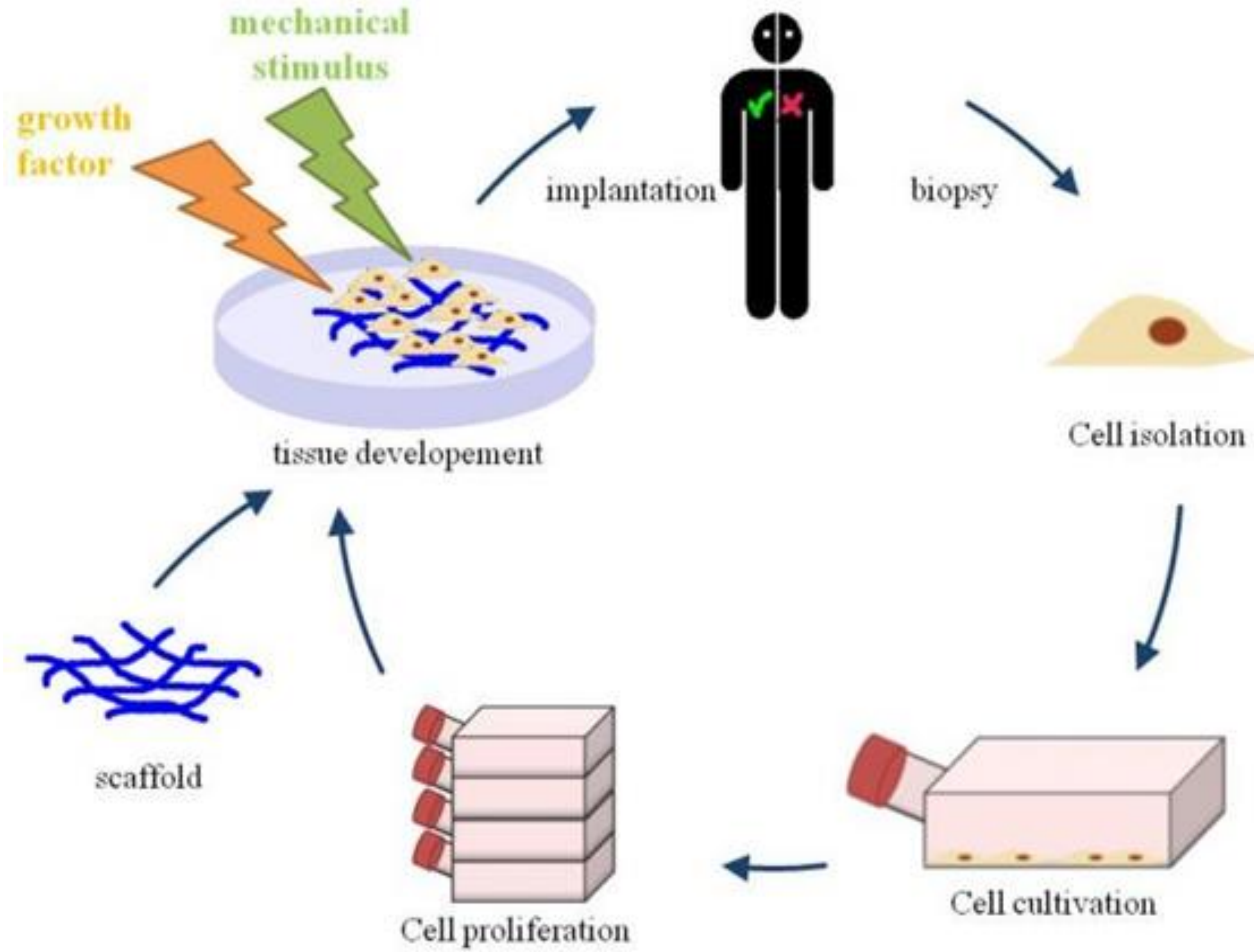
- **Explantation** is the cultivation of isolated organs and tissues.
- The cultivation of isolated organs in the body is based on the fact that in the organs separated from the whole organism (in vitro-outside the body), under certain conditions, the process of life activity can be carried out.

Explantation

- **Tissue culture** is a method that makes it possible to grow tissue pieces and even individual cells outside the body.
- For tissue culture, small pieces of organs under strictly sterile conditions are excreted from the body, placed in glass chambers on specially prepared nutrient media and create the necessary temperature regime. After a certain dormant period, cells in the culture begin to multiply intensively. The tissue receives nutrient material for growth from the environment; vital products come into it. Their accumulation leads the culture to aging. The resulting cells become smaller. If you do not timely reseed (passage) in a fresh environment, the tissue dies.



Explantation



Thanks for attention