МИНИСТЕРСТВО НАУКИ И ВЫСШЕГО ОБРАЗОВАНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

ФЕДЕРАЛЬНОЕ ГОСУДАРСТВЕННОЕ БЮДЖЕТНОЕ ОБРАЗОВАТЕЛЬНОЕ УЧРЕЖДЕНИЕ ВЫСШЕГО ОБРАЗОВАНИЯ

СЕВЕРО-КАВКАЗСКАЯ ГОСУДАРСТВЕННАЯ АКАДЕМИЯ

МЕДИЦИНСКИЙ ИНСТИТУТ

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МЕДИЦИНСКАЯ БИОЛОГИЯ И ГЕНЕТИКА

Medical biology and genetic

Учебно-методическое пособие для студентов I курса обучающихся по специальности 31.05.01. «Лечебное дело» с включенным иностранным языком

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Издание содержит теоретический материал практических занятий по медицинской биологии и общей генетике, термины, предполагает закрепление теоретического материала по следующим темам: «Закономерности наследования признаков при моно- и полигенном наследовании. Формирование фенотипа как выражение единства генетических и средовых факторов», «Хромосомный и геномный уровни организации наследственного материала у про- и эукариот», «Наследственные болезни человека», «Основы молекулярной генетики». Предназначено для иностранных студентов 1-го курса, обучающихся на иностранном языке.

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CONTENTS

HUMAN IN THE SYSTEM OF NATURE

Origin of life. Evidence of the organic world evolution. Life is a way of existence of protein bodies that are constantly exchanging energy, substance and information with the environment. The complex of proteins and nuclear acids isa biochemical substrate of life (its material basis).

Hypotheses of life origin:

– **creationism** –life was created by God;

– **self–generation** –life originated many times from non–living matter;

– **stationary condition** –life existed always;

– **panspermia** –life was brought to the Earth from other planets;

– **biochemical** –life came into existence due to biochemical evolution.

The evidences of the organic life evolution are: paleonthologic (transient forms, philogenetic series); comparative– anatomic (identical structural plan of chordal animals; homologous organs, rudiments and atavisms); embryologic (the law of embryonal similarity, biogenetic law); molecular–genetic data.

1. Organization levels of living things. Properties and characters of living things.

Properties of living things:

– self–regulation – the ability to modify one's own vital activity according to environmental changes;

– self–renewal – the ability to synthesize, restore or replace its own structural–functional components;

– self–generation – the ability to reproduce identical oneselves, increasing the number of the species and providing the continuity of generations.

These properties define *characters of living things*:

– **exchange of substances and energy**;

– **heredity** – provides transmission of characters from generation to generation during reproduction;

– **variation** – causes the appearance of new characters in environmental changes;

– **reproduction** (multiplication);

– **ontogenesis** (individual development) and **phylogenesis** (historical de velopment of species);

– **growth** –enlargement in size, volume and mass of organisms**;**

– **irritability** –response of organisms to environmental factors;

– **homeostasis** – the ability to sustain the constancy of internal environ ment and structural organization;

– **integrity and discretion** (division into components).

Organization levels of living matter:

1. ***Molecular–genetic –****gene* is an elementary unit at this level.

2. ***Cellular*** – all living organisms consist of cells. The cell is a structural–functional and genetic unit of living things. It contains genetic information aboutthe development of the whole organism. All vital processes take place there.

3. ***Tissue*** – a group of cells with identical structure performing identical functions form the *tissue*.

4. ***Organism***. The organism is an elementary unit of life. The *organism* level is characterized by processes of ontogenesis (individual development), its nervous and humoral regulation.

5. ***Population–specious***. A group of individuals of one species, occupyinga definite territory for a long time, freely crossing and relatively isolated from other groups of individuals of the same species, form a *population*. The popula– tion is an elementary unit of evolution.

6. ***Biospheric–biogeocenotic***. *Biogeocenosis* – is a group of populations of organisms from different species that are historically related with each other and with a definite residential territory. There is a constant exchange of substances, energy and information between populations and the environment. All biocenoses compose a biosphere – an area of the planet occupied by living organisms.

2. Methods of studying living things (methods of biological sciences).

Integral understanding of living matter can be obtained only by complex investigation of life at all organization levels. It is the subject of Biology anda number of special disciplines (biological sciences).

Biochemistry, Biophysics and Molecular Biology study life manifesta– tions at a molecular–genetic level; Cytology – at a subcellular and cellular levels; Histology – at a tissue level.

Regulations of individual development and organisms structure are studied by Embryology, Anatomy, Physiology; historical development of living systems – by evolutionary study, Paleobiology. Genetics, Biogeography, Systematization, Ecology, etc. –study the population–specious, biogeocenotic and biospheric levels. All biological disciplines are closely connected and are a basisfor the development of other branches of national economy, selection, veterinary science and medicine. Meanwhile every science uses a great range of methods to solve topical problems: observation, description, modeling and experimentation.

3. The significance of Biology for medicine.

Studying biology is of great significance for training doctors. Using methods of biological modeling, they study mechanisms of etiology and development of many human diseases, elaborate ways of their prevention and treatment. To study the biology of parasites is necessary for successful fighting against invasive diseases. Genetic engineering (genetic designing of cells and organisms with definite characters) and biotechnologies (technological processes using liv ing organisms) helped setting up the production of antibiotics, interferon, some hormones and enzymes, many vitamins. Methods for determining the structure of human genes will allow using genotherapy of hereditary diseases in future.

4. The position of the human in the animal world system.

The human as a biologic species refers to the phylum of *Chordates*, subphylum of *Vertebrates*, class of *Mammals*, subclass of *Placentals*, order of *Pri– mates*, suborder of *Anthropoids* (narrow–nosed apes), family of *Hominids* (humans), genus of *Homo* (man), species of *Homo sapiens* (a reasonable man).

5. Humans as biological and social beings. Humans have characters bothof biological and social beings (tab. 1).

Table 1 – Similarity of humans and animals

№	Systemic group of animals	Signs characteristic of humans
1.	Phylum – chordates	Germination of axial organs occurs in the embryonic period: a chord, nervous tube, gastric tube
2.	Subphylum –Vertebrates	The chord transforms into the spine, the heart is onthe abdominal side. There are 2 pairs of extremities, 5 departments of the brain, jaws
3.	Class –mammals	4– chamber heart, warm–bloodiness, well–developed cerebral cortex, mammary glands, presence of hair onskin coverings
4.	Subclass –Placentals	Development of human fetus in the mother's womb and its feeding through the placenta
5.	Order –Primates	The thumb of the upper extremities is opposed to the others, nails on fingers, one pair of mammary glands, well–developed clavicles, teeth of three types and replacement of milk teeth by permanent ones, giving birth to one child in the majority of cases

The following **signs** are characteristic only of the species of *Homo sapiens*: straight walking, apparent thumb opposition, S–shaped spine, the brain volume of 1100–1700 cm^3, prominence of the chin, abstract thinking, speech, producing tools, etc. The progress of humankind obeys social laws –laws of the society. The human life is impossible outside the society. Social factors have playeda great role in human development. Knowledge, skills and spiritual valuables are transferred in the society through training and education of young generations.

Basic terms and concepts:

1. Self–regulation – is the ability of the organism to modify parametersof vital activity according to environmental changes.

2. Self–renewal – is the ability of the organism to restore or change its structural–functional components.

3. Self–reproduction – is the ability of the organism to reproduce its own selves.

4. Systemic position of Homo sapiens – the position of the human inthe animal world system.

5. A phylogenetic tree – is a tree–shape diagram, which presents relative and historic relations between systemic groups.

MAGNIFYING DEVICES. METHODS OF STUDYING CELLS

1. The subject, tasks and methods of cytology. Cytology (Latin *cytos* – a cell, *logos* – a science) – is a science studying the structure, chemical com–position and functions of cells, their multiplication, development and interaction in a multicellular organism.

The tasks of cytology:

– studying the structure and function of cells and their components (membranes, organoids, inclusions and nucleus);

– studying cellular division and possibilities of their adaptation to environmental changes;

– studying interrelations between cells in a multicellular organism. Methods of cytology:

1. *Microscopic* – they help study morphology of cells and their components (the methods of light and electron microscopy).

2. *Cytochemical (histochemical)* – they help determine the chemical composition or localization of substances in the cell (in tissue sections). They are based on special staining stuff.

3. *Biochemical* are used for studying the chemical composition of cells, de termination of substance concentration in tissues. They are based on the propertyto absorb light waves of a definite length by different biochemical compounds.

4. *The method of differential centrifugation* helps study the composition and properties of cellular organoids: a tissue specimen is fragmentized to destroy cellular membranes, then placed into the centrifuge, where it is divided into separate fractions.

5. *The method of autography* is used for studying the dynamics of metabolic processes in cellular structures. It means the introduction of radioactive isotopes into the cell. Molecules marked with radioactive isotopes (^{3}H, ^{32}P, ^{14}C) participate in exchange reactions. Their localization, movement, accumulation and excretion are determined by radiation registered with a photoplate.

6. *Rhoentgenostructural analysis* is performed for studying the spacious structure and arrangement of molecules in the substance. This method is based on diffraction of R–rays passing through a substance crystal.

2. Magnifying devices and their purpose. The light microscope arrangement.

A biological microscope is intended for studying microobjects in the flow of passing light. A light microscope (fig. 1) consists of 3 parts: mechanical, illuminating and optical.

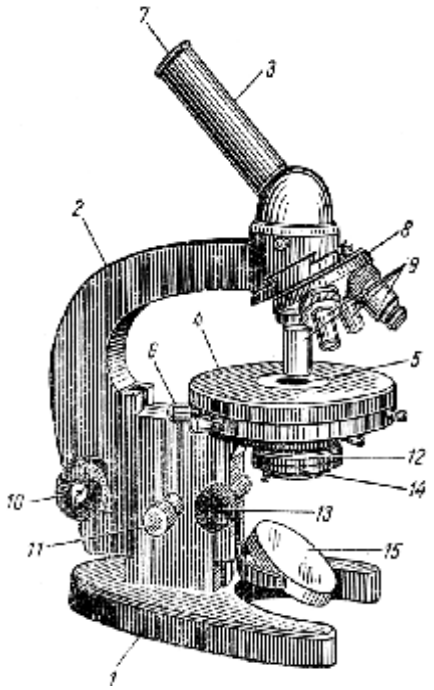


Fig. 1. The structure of a light microscope:
1 – a base; *2* – a draw–tube holder; *3* – a draw–tube; *4* – a stage; *5* – an aperture of the stage; *6* –screws for moving the stage; *7* – an ocular; *8* – a revolving device; *9* –objectives; *10* – a cremaliera; *11* – a micrometric screw (in some models it is located on the base); *12* – a condenser; *13*, *14* – a screw and diaphragm of the condenser respectively; *15* – a mirror

The *mechanical* part includes a stand, a stage, a cremaliera (a macrometric screw), a micrometric screw, a draw–tube and a revolver.

The support consists of a draw–tube holder (column) and a base. The column contains:

– a revolver – a rotating mechanism for changing objectives;

– a draw–tube – a hollow tube for fixing an ocular;

– a system of screws for rough (macrometric) and fine (micrometric) adjustment of the microscope;

– a stage for placing an investigation object.

The *illuminating* part includes a mirror (or an electric illuminator) anda condenser.

The *mirror* of the microscope is double–sided – with a convex and concave surface. A concave surface is used under natural illumination, while a flat one – under artificial illumination.

The condenser is a lens system collecting light rays into a band. The light band diameter can be regulated with a special level, changing the diaphragm lumen.

The *optical* system consists of an ocular and objectives.

The *ocular* (*oculus* – an eye) is a lens system directed towards the eye. Magnification is indicated on the ocular mount. A teaching microscope uses spare oculars with magnification 7×, 10× and 15×.

The *objective* is located at a lower end of the draw–tube – it is a lens system

directed to the investigated object. Two kinds of objectives are used: with small magnification (8×) and a large one (40×).

The total magnification of the microscope is determined by multiplying the multiple of the objective and ocular magnifications. For example, the total magnification of the microscope with 40× objective magnification and 7× ocular magnification will be equal to 280.

3. Rules of working with the microscope:

1. Put the microscope column towards yourself and the mirror towards the light origin; approximately a palm width from the stage edge.
2. Set the objective 2–3 cm from the surface of the stage rotating the *ma crometric* screw.
3. Check the adjustment of the objective with small magnification (8 ×) until it «clicks», it should be fixed opposite the aperture on the stage.
4. Put the condenser into a neutral position and open the diaphragm completely.
5. *Looking into the ocular*, direct the mirror surface to the light source for even illumination of the *field of vision*.
6. Place the micropreparation on the stage, the cover glass should be directed towards the objective!
7. *Looking on the side* (!), lower the objective 0,5 cm from the surface of the cover glass with a macrometric screw (the focal distance of the objective with 8× is *about 1 cm*).
8. Looking into the ocular, rotate *the macrometric screw towards «your–self»* slowly (!) and get a clear image of the object.
9. Study the object. Move the preparation manually.

Note: If the object is too small and is not seen at small magnification, then adjust the microscope to an edge of the cover glass. Having obtained a clear image of the glass edge, move it further to a working field in search of the object.

Rules of working with a large magnification (7 × 40) microscope:

1. Get a clear object image at small magnification (see above).
2. Center the needed area of a micropreparation – move it to the center ofthe field of vision.
3. Rotate the objective with large magnification (×40).using a revolver until it «clicks».
4. Put the condenser into an upper position. Looking from the side, *carefully* lower the large magnification objective with the macrometric screw until it touches the surface of the cover glass (the focal distance of 40 × objective is approximately 1–2 mm).
5. Looking into the ocular, turn slightly a *macrometric screw «towards yourself»* (!) until the object outlines appear.
6. Use a *micrometric screw* for getting a better image turning it towards yourself or from yourself *no more than 0,5 turn*.
7. Study the needed area of the micropreparation.

Terminating the work with the microscope:

1. Having finished studying the object, raise the drawtube 2–3 cm witha macrometric screw and take off the preparation off the stage.

2. Set a small magnification objective until it «clicks» by turning the revolver and fix it against the aperture on the stage.

3. Lower the objective to the stage level with a macrometric screw.

Basic terms and concepts:

1. Immersion –liquid that fills the space between the cover glass and the immersion objective (90×).

2. Condensor – is a lens system collecting light rays into a bundle.

3. Cremaliera – is a macrometric screw.

4. Objective – is a lens system, which are screwed into the revolver and are directed to the stage.

5. Ocular – is a lens system inserted into an upper aperture of the draw–tube and directed to the eye.

6. Resolution – is the ability of the optic device to differentiate small details: a minimum distance between two adjacent points (lines), which are possible to differentiate.

7. Revolving mechanism – is a rotating mechanism for changing objectives, which is fixed on the column of the support.

8. Draw–tube – is a hollow tube, which connects the ocular and the ob–jective.

BIOLOGY OF THE CELL. THE FLOW OF SUBSTANCEAND ENERGY IN THE CELL

1. The present state of the cellular theory.

1. The cell – is an elementary structural–functional and genetic unit of all living things, open self–regulating system, through which flows of substances, energy and information pass (fig. 2).

2. Cells of all organisms have similar structure, chemical composition and processes of vital activity.

3. New cells form, when the mother cell divides.

4. Cells of a multicellular organism differentiate and form tissues for performing various functions.

2. **Differentiating signs of pro– and eukaryotic cells** (tab. 2).

Table 2 – Pro– and eukaryotic cells

Prokaryotes	**Eukaryotes**
Differences	
Mycoplasms, bacteria, cyanobacteria	Protists, plant and animal cells
Sizes: 1–10 μm	10–100 μm
There is no nucleus, but a nucleoide	There is a formed nucleus
DNA is not linked with proteins–histones	DNA is linked with proteins–histones

There is no mitosis and membrane organoids, theirfunctions are performed by mesosomes – drawings in of the cellular membrane	There is mitosis and membraneorganoids (fig. 3)

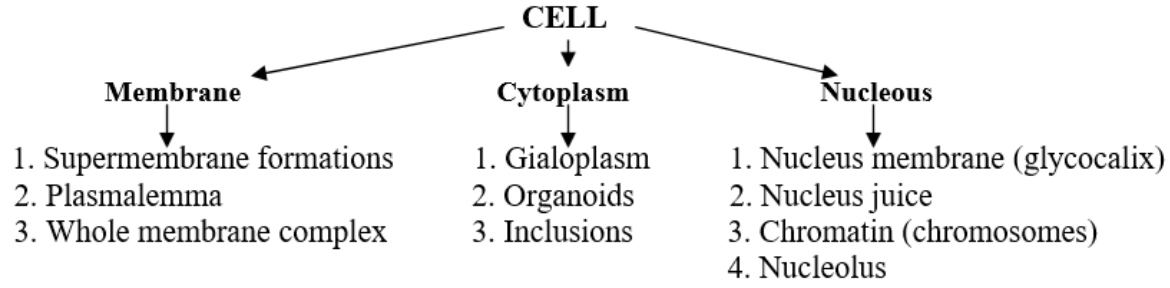


Fig. 2. The diagram of the cell structure

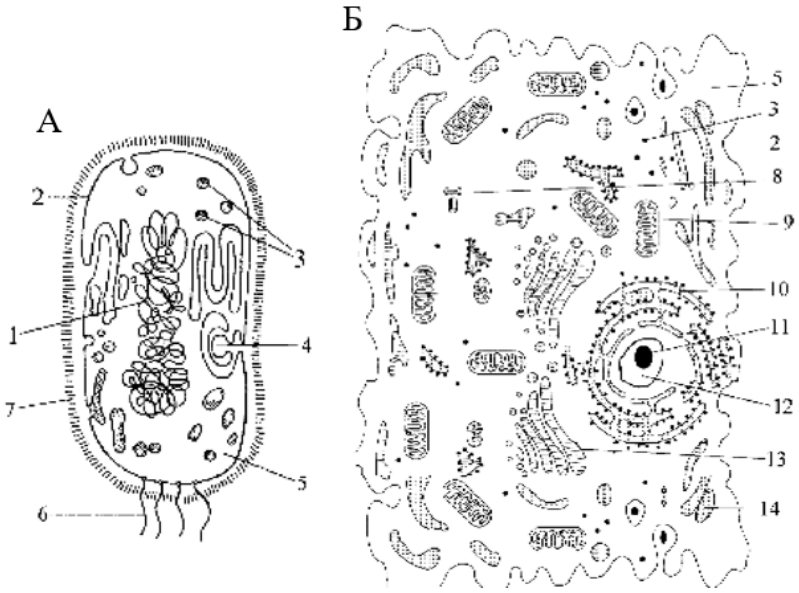


Fig. 3. The structure of a prokaryotic and eukaryotic cells:
A –prokaryotic cell, B –eukaryotic cell: 1 – a nucleoide; 2 –plasmalemma; 3 –ribosomes; 4 – a mesosome; 5 – cytoplasm; 6 – a filament; 7 – a cell wall; 8 – a cell center; 9 – a mitochondria; 10 – a granular EPR; 11 – a nucleolus; 12 – a nucleus; 13 –Golgi's complex; 14 – a smooth EPR

3. The structure of (a model) elementary membrane, its properties and functions.

In 1943 N. Dowson and P. Danielli proposed the first model of an elementary membrane. It was a **«sandwich» model**. Two layers of lipid molecules are located between two layers of protein molecules. Every lipid molecule has two ends –*hydrophilic* (water–soluble) and *hydrophobic* (water insoluble). Hydrophobic parts of molecules are directed towards each other, hydrophilic ones –towards proteins.

A fluid–mosaic model is better; it meets the requirements of properties and functions of an elementary membrane. It was proposed in 1972 by S. Singer and

G. Nikolson. The basic membrane components –lipids – compose from 20 to 80 % of its mass. They are phospholipids, lecithin and cholesterol. Protein molecules are in a double layer of lipid molecules that form a «lipid sea». Protein molecules, which penetrate 2 layers of lipid molecules, are *integral*. Those protein molecules, which are immersed into one layer, are *semi– integral*. *Peripheral proteins* are on the surface of lipids. The third component of an elementary membrane – are *glycoproteins* and *glycolipids* forming a receptor apparatus on its surface (*glycocalix*).

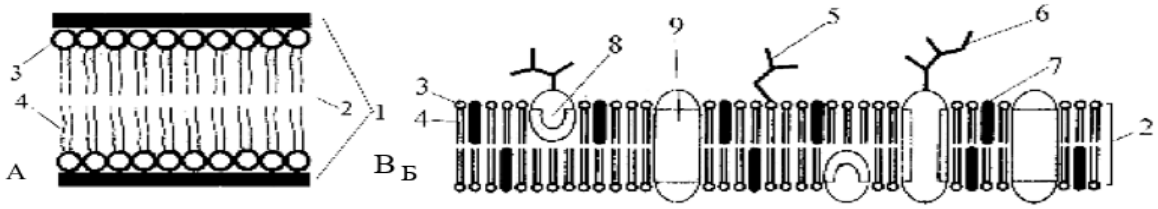


Fig. 4. The diagram of elementary membrane models:
A –sandwich, B –fluid–mosaic: 1 –solid protein layers; 2 – a bilipid layer; 3 –hydrophilic heads of phospholipids; 4 –hydrophobic tails of phospholipids; 5 –glycolipid; 6 –glycoprotein; 7 – cholesterol; 8 –semiintegral protein; 9 – integral protein

Properties of the elementary membrane:

– plasticity (it restores quickly after impairment and also stretches and constricts in cellular movements);

– semi–permeability (passes molecules selectively);

– ability for self–locking (vesicles and vacuoles are formed).Functions of the elementary membrane:

– structural (membranes are included into the composition of all cellular organoids except ribosomes and centrosomes);

– barrier (protects the cell from external factors and sustains its composition);

– metabolic (many enzymes are located on membranes);

– receptor (receives signals, recognizes substances).

4. Methods of passing substances into the cell:

1. *Passive transport* follows the concentration gradient without spending energy. Water and small molecules can pass into the cell by filtration, diffusion, through pores or in the process of solution in lipids.

2. *Lighted diffusion* is associated with participation of proteins–transmitters in transferring molecules – permeasis. Amino acids, sugar, fatty acids get into the cell in this way.

3. *Active transpoprt* demands energy expenditure, because it follows against the concentration gradient. Such transport demands enzymes, ATP molecules and formation of special ion canals. A sodium–potassium pump is an example of such transport.

4. *Endocytosis* – is participation of the membrane itself in catching particles or molecules and transporting them into the cell. *Endocytosis* – is a modified

architectonics (outlines) of the membrane. Transport of macromolecules or hard particles is *phagocytosis*, while transport of fluid is *pinocytosis*.

5. **The cell anabolic system.** The cell anabolic system performs reactions of plastic exchange or assimilation.

Organoids – are differentiated areas of the cytoplasm. They have a constant structure and perform specific functions.

Ribosomes – are spherical bodies (15–35 nm in diameter) consisting of two subunits. They may be in hyaloplasm, on the external nucleous membrane, on membranes of the endoplasmatic net. A *large subunit* of the ribosome contains three different molecules r–RNA and 40 molecules of proteins, a *small subunit* – one r–RNA molecule and 33 protein molecules. Ribosome subunits are synthesized in nucleoli. The information about the r–RNI structure is contained in «*nucleoli–organizers»* (DNA molecule areas in the region of secondary constrictions of satellite chromosomes). The final assembly of ribosomes in subunits occurs in the process of translation.

The function of ribosomes is assembling protein molecules (translation).

Endoplasmatic reticulum (EPR) – are canals located throughout the cell and connected with the perinuclear space of the nucleus and cavities of Golgi's complex. A canal wall is an elementary membrane. EPR canals perform the function of compartmentalization of the cell cytoplasm, its division into areas, where various biochemical reactions take place. The granular EPR (ribosomes are placed on its membranes) participate in protein biosynthesis, which are later transported to Golgi's complex.

Carbohydrates and lipids are synthesized on membranes of a smooth EPR (does not contain ribosomes). It takes part in synthesizing steroid hormones, in detoxication of toxic substances (liver cells).

Golgi's complex consists of vesicles, tubules, sacs. Dictyosomes are basic elements of the complex.

Dictyosomes – are piles of closed sacs of 10–15 elementary membranes that have dilations on the ends. These dilations form vesicles that separate and transform into lyzosomes and vacuoles. Part of these vesicles excrete secretes and metabolites from the cell.

Functions of Golgi's complex:

– sorting and packing substances synthesized in EPN;

– synthesizing complex compounds (lipoproteins, glycoproteins);

– assembling elementary membranes;

– forming lyzosomes, glyoxisomes and vacuoles;

– taking part in substance secretion.

6. **The cell catabolic system.** The cell catabolic system performs energy exchange or dissimilation.

Primary lyzosomes form in Golgi's complex. They are rounded bodies (0,2–0,2 μm in diameter) covered with an elementary membrane. They include approximately 50 different hydrolytic enzymes. *Secondary lyzosomes* (phagolyzosomes) contain breakable substances.

Functions of lyzosomes:

– breaking up substances passed into the cell in phagocytosis;

– destroying impaired structures and organoids of the cell.

Peroxisomes are formed in EPN. Their enzymes (oxidazes) oxidize amino acids with formation of peroxide (H_2O_2).

Glyoxisomes are formed in Golgi's complex, their enzymes transform fats into carbohydrates.

Mitochondria have a shape of rods, filaments and granules. The size of mi tochondria is from 0,5 to 7 μm. Their number is not the same in cells with dif– ferent activity. A mitochondrion wall has an external and internal membrane. Projections of the internal membrane form *crysts*, between which is an internal matrix containing enzyme systems of an oxygen stage of energy exchange andan autonomous system of protein biosynthesis (ribosomes, RNA and ring DNA molecules). The interspace between mitochondrion wall membranes is filled with perimitochondrial *space*.

Functions of mitochondria:

– ATP synthesis;

– Synthesis of specific proteins and steroid hormones.

7. **Energy exchange in the cell. Fermentation systems of mitochondria. Energy exchange** is the sum of fermentation breaking–down reactions of complex organic compounds followed by releasing energy used for ATP synthesis.

The preparatory stage goes in the digestive system and in phagosomes of cells, where complex organic compounds break down into simple ones: polysaccharides to monosacharides, proteins to amino acids, fats to glycerol and fatty acids. The released energy is dissipated as warmth.

The Anaerobic stage (glycolysis) occurs in the cytoplasm of cells. Ten en zymes participate in it. Glucose breaks down to pyroacemic (lactic) acid and2 ATP molecules form. The pyroacemic acid passes into mitochondria for fur– ther transformations.

Aerobic stage of energy exchange occurs in mitochondria. There are 3 fermentation systems in mitochondria:

– Krebs cycle (of citric acid) – in the internal matrix;

– tissue respiration –on the internal membrane;

– oxidation phosphorilizing – aTP–somes (mushroom–shaped bodies).

Pyroacemic acid comes into the internal matrix of the mitochondrion and interacts with co–enzyme A (KoA), when Acetyl KoA (an activated form of Acetic acid) forms. CO_2 and H^o chip off Acetyl KoA. CO_2 is excreted by mitochondria, and H^+ and e (from hydrogen atoms) pass to the enzyme system of tis sue respiration. Protons accumulate on the external surface of the internal membrane and electrons –on the internal one. Having reached a critical potential (200 mv), protons pass through canals into ATP–somes. Electrons give the energy away for adding the rest of phosphoric acid to ADP (ATP synthesis) and they join protons. Hydrogen atoms are formed, they mix with oxygen and form water molecules. 38 mol of ATP from 1 mol of glucose are formed as a result of all reactions of energy exchange.

Basic terms and concepts:

1. Glycocalix – is a receptor apparatus of an animal cell membrane.

2. Glycolysis – is a process of breaking down glucose without oxygen.

3. Glyoxisomes – are organoids, where transformation of fats into carbo hydrates takes place.

4. Concentration gradient – is the difference of substance concentrations.

5. Mesosomes – are drawings– in of prokaryotic cells plasmolemma,which perform a role of membrane organoids.

6. Nucleoid – is a genetic apparatus of prokaryotes.

7. Peroxisomes – are organoids, where oxidation of amino acids occurs and peroxide is formed.

8. Plasmalemma – is a membrane, which is included into the cell membrane.

9. Enzymes of oxidizing phosphorilizing – are enzymes of mitochondria localized in ATP–somes.

10. Enzymes of tissue respiration – are enzymes of mitochondria localized in crysts.

11. Enzymes of Krebs cycle – are enzymes of mitochondria localized inthe matrix.

TEMPORAL ORGANIZATION OF THE CELL

1. The structure and functions of the nucleus.

The basic genetic information is in the nucleus. R. Brown described the nucleus (Latin –nuc– leus; Greek –karyon in 1831. The shape of the nucleus depends on the shape and functions of the cell.

The *membrane* of an interphase nucleus (*karyolemma*) consists of an exter–nal and internal elementary membrane. A *prenuclear space* is between them. There are openings in membranes, *pores*. Protein molecules forming *porous complexes* are in the pores. When the cell is active, the majority of pores are open. The substance flow passes through them from the cytoplasm into the nucleus and back. The number of pores in one nucleus reaches 3–4 thousand. The external nucleus membrane is linked with endoplasmatic net canals. *Ribosomes* are usually placed on it. Proteins of the internal nuclear membrane form a *nuclear plate*. It sustains a constant shape of the nucleus and chromosomes are attached to it.

Nuclear juice – is *karyolymph*, a colloid solution in a jelly–like state, that contains proteins, lipids, carbohydrates, RNA, nucleotides, enzymes.

Nucleolus – is a temporary component of the nucleus: it disappears inthe beginning of cellular division and restores in the end of it. Chemical composition: protein (~90 %), r–RNA (~6 %), lipids, enzymes. Nucleoli form in the area of secondary constrictions of satellite chromosomes. Function: assembling ribosome subunits.

Chromatin of the nucleus – interphase chromosomes. They contain DNA, proteins–histones and RNA in ratio 1:1,3:0,2. DNA together with protein form *desoxiribonucleoprotein* (DNP). DNP spiralizes and forms chromosomes during mitotic division of the nucleus.

Functions of the nucleus:

1) forms hereditary information of the cell;

2) takes part in cellular division (multiplication);

3) regulates metabolic processes in the cell.

2. Types of chromosomes. The structure of a metaphasal chromosome. Chromosomes (Greek – c*hromo* – color, *soma* –body) – is spiralized chromatin. The chromosome length is 0,2–5,0 μm, diameter –0,2–2,0 μm.

A metaphasal chromosome consists of 2 *chromatids*, that are linked witha *centermere (primary constriction)*. It divides the chromosome into 2 *arms*. Some chromosomes have *secondary constrictions*. The area they separate is a satellite, and such chromosomes are called satellite. Terminal areas of chromo somes are telomeres. Each chromatid includes one DNA molecule together with proteins–histones. Chromosomal areas with intense staining are areas of strong spiralization (*heterochromatin*). Lighter areas – are areas of weak spiralization (*euchromatin*).

Types of chromosomes according to the centermere position:

1. *Metacentric* – the centermere is in the middle, the arms are of identical length.

2. *Submetacentric* – the centermere is biased from the center, the arms areof different length.

3. *Acrocentric* – the centermere is far from the center, one arm is very short, and the other – very long.

One can meet gigantic, *polytenous chromosomes* (polyfilament chromosomes) in cells of insects (Drosophila) salivary glands.

There are 4 rules for chromosomes of all organisms:

1. *The rule of a constant number of chromosomes*. Organisms have a constant characteristic of the species number of chromosomes. For example, inthe human – 46, in the dog –78, in Drosophila – 8.

2. *Parity of chromosomes*. In norm, every chromosome in a diploid complement has a pared chromosome – identical in shape and size.

3. *Individuality of chromosomes*. Chromosomes of different pairs differ in shape, structure and size.

4. *Continuity of chromosomes*. When genetic material is doubled, a chromosome originates from a chromosome.

Chromosomal function: storing, reproduction and transmission of genetic information, when cells and organisms multiply.

3. Cellular and mitotic cycles. There is a cellular and mitotic cycle in life of cells.

Cellular or life cycle of the cell – is a period from the appearance of the cell until its death or to the end of next cellular division. *The period of life cycle of somatic cells*: growth and differentiation, performing specific functions, preparation for division (multiplication), division. A mitotic cycle is characteristic of the majority of cells – a period of its preparation for division (interphase) and the division itself (mitosis).

4. Interphase, characteristic of periods. Reasons of mitosis.

The interphase includes three periods: G_1 *–pre–synthetic (post–mitotic),* S *–synthetic* and G_2 *–post–synthetic (pre–mitotic)*. The content of genetic material in the cell changes during the interphase: n – a haploid complement of the chromosome, chr – the number of chromatids in the chromosome, c – the number of DNA complements.

Pre–synthetic period. The cell grows, performs its functions. RNA, proteins, DNA nucleotides are synthesized in it, the number of ribosomes increases, ATP accumulates. The period lasts 12 hours but it may take several months. The content of genetic material –2n l chr 2c.

During the *synthetic period,* replication of DNA molecules occurs each chromatid adds one more identical to itself. The content of genetic material becomes 2n2chr4c. Centrioles duplicate. RNA, ATP and proteins–histones are synthesized. The cell continues performing its functions. The duration of the periodis up to 8 hours.

During the *post–synthetic period* energy of ATP accumulates; RNA, nuclear proteins and proteins–tubulines necessary for chromatin division spindle are actively synthesized. The content of genetic material does not change: 2n2chr4c. By the end of the period all synthetic processes become slower, the cytoplasm viscosity changes.

Reasons of mitosis:

– changing of the nuclear– cytoplasmatic ratio from $^1/_6$–$^1/_7$ to $^1/_{69}$–$^1/_{89}$;

– the presence of «mitogenetic rays» which stimulate division of adjacent cells;

– action of «wound hormones», which determine impaired cells and sti–mulate division of unimpaired cells.

5. Characteristic and significance of mitosis.

The basic method of dividing somatic cells is mitosis. Mitosis has four stages: a prophase, metaphase, anaphase and telophase.

The *prophase* starts with spiralization of chromatin: long chromatin filaments are shortened and thickened forming chromosomes. Centrioles diverge to cell poles; filaments of the division spindle are formed. Nucleoli and nuclear membrane dissolve, the nucleus volume enlarges. The content of genetic material is 2n2chr4c.

The metaphase: chromosomes are located at the cell equator forminga *metapasal plate*. Filaments of the division spindle are attached to the centermere of chromosomes. One can see that each chromosome consists of two chromatids. The content of genetic material does not change –2n2chr4c.

Anaphase. Filaments of the division spindle constrict. In the region of center meres, chromosomes are divided into two chromatids. The chromatids diverge to cell poles. They are daughter chromosomes. The content of genetic information at each pole of the cell –2n I chr2c.

During the *telophase* the formation of daughter nuclei continues. Nuclear membranes are formed, chromosomes are despiralized, loose their clear outlines and nucleoli are restored. The final stage of mitosis is cytokinesis (division ofthe

cytoplasm). The cellular membrane is formed by fusion vesicles of the endoplasmatic net. Two cells are formed, the content of genetic material of which –2n I chr2c.

The significance of mitosis:

– sustaining the constancy of the chromosome number, providing genetic succession in cellular populations;

– even distribution of chromosomes and genetic information between daughter cells.

6. Characteristic and significance of meiosis.

Meiosis is a variety of mitosis. Meiosis is division of somatic cells of gonads that leads to the formation of gamets. Meiosis consists of two divisions –meiosis I and meiosis II. Each division has four phases: prophase I and prophase II, metaphase I and metaphase II, anaphase I and anaphase II, telophase I and telophase II.

The prophase of meiosis I is most complicated. It has 5 stages:

1. *Leptotena*: chromatin spiralizes forming thin chromatin filaments that start moving to each other with centermere parts; genetic material –2n2chr4c.

2. *Zygotena*: *conjugation* of short and thick chromatin filaments (chromosomes) starts, they join along the whole length; genetic information does not change –2n2chr4c.

3. *Pachitena*: homologous chromosomes are tightly joined along the whole length; the formed figures are *bivalents* of chromosomes or *tetrads* of chromatids; genetic material can be recorded as ln_{biv}4chr4c; by the end of the stage antagonizing forces start acting in the area of centermeres and *crossing–over* occurs, exchange of homologous chromosomes parts.

4. *Diplotena*: antagonizing forces continue their action, but chromosomes stay joined in the area of chiasm (crossings); the content of genetic material is preserved –ln_{biv}4chr4c;

5. *Diakinesis*: chromosomal spiralization finishes, the nuclear membrane and nucleolus disappear; chromosomal bivalents linked with their ends come into the cytoplasm and move towards the center of the cell; filaments of the division spindle attach to centermeres of chromosomes; ln_{biv}4chr4c.

In the **metaphase of meiosis I,** bivalents are located along the equator of the cell; separate chromosomes are clearly seen; genetic material –ln_{biv}4chr4c.

Anaphase I: bivalents are divided into homologous chromosomes. Filaments of the division spindle constrict, that is why chromosomes diverge to cell poles. Each chromosome still contains 2 chromatids. The content of genetic material at each cell pole – is ln2chr2c. During this phase the reduction (decrease) of the number of chromosomes occurs – a diploid complement of chromosomes becomes a haploid one.

In the **telophase of meiosis I,** cytokinesis takes place, and two–daughter haploid cells form –ln2chr2c; unlike mitosis in this phase, despiralization of chromosomes does not occur.

After meiosis I comes **interkinesis** – a short interval between two divisions. DNA replication does not occur. Interkinesis is followed by meiosis II.

Meiosis II almost does not differ from mitosis. In prophase II, spiralization of chromosomes (ln2chr2c) does not occur, and in anaphase II chromatids but not chromosomes diverge to cell poles. Each daughter cell gets a complement of genetic information 1n1chr1c.

During meiosis one mother haploid cell forms 4 cells (gamets) with a haploid complement of chromosomes.

The significance of meiosis: it is a mechanism of gamete formation; it sustains the constancy of the number of chromosomes; provides combinative variation.

7. Amitosis. During amitosis chromatin is not spiralized and the division spindle is not formed. The nucleus and cytoplasm are divided by constriction into two. Usually amitosis divides epithelial cells of mucous membranes, cancer cells (genetic information there may be distributed unevenly) and cells participating in regeneration. Amitosis can lead to the formation of multinuclear cells (the nucleus has divided, but the cytoplasm has not).

Basic terms and concepts:

1. Bivalents – two homologous chromosomes, conjugated with each other during the prophase of meiosis I. Their number is equal to a haploid complement of chromosomes.

2. Karyolymph – nuclear juice.

3. Cellular cycle – is a period from the appearance of the cell to its death or to the end of next cellular division.

4. Conjugation of chromosomes –linkage of homologous chromosomes in length.

5. Crossing–over – is exchange of identical parts of chromatids of homo logous chromosomes in pachitena of the prophase of meiosis I.

6. Meiosis – is division of somatic cell of gonads, when gametes are formed.

7. Mitotic cycle – is a preparation period of the cell for division (interphase) and division itself (mitosis).

8. Telomeres of chromosomes – terminal parts of chromosomal arms.

9. Chiasms – cross of chromatids of homologous chromosomes in conjugation.

10. Chromatin – is a complex consisting of DNA and histone proteins

11. Nuclear– cytoplasmatic ratio – is a physiologically and morphologically regular ratio of the mass (volume) of the nucleus to the mass (volume) of the cytoplasm in every cell.

BASES OF CYTOGENETICS

1. The concept of karyotype and ideogram.

Karyotype is a diploid complement of chromosomes of a somatic cell characteristic of the organism of a definite species.

The human karyotype contains 46 chromosomes. Chromosomal pairs, identical in males and females, are autosomes. There are 22 such pairs in the human.

One pair of chromosomes, which differentiates male and female organisms,

are *heterochromosomes* or *sex chromosomes*. In males they are X and Y and in females – X and X.

The arrangement of chromosomes in descending order of their sizes is an ideogram. It is a systematized karyotype, where homologous chromosomes are arranged in pairs.

2. Methods of studying the human karyotype.

Cytogenetic method. It studies the karyotype by microscope. Stages of the method:

1. Obtaining cells (blood lymphocytes, skin fibroblasts).
2. Cultivating cells on artificial culture.
3. Adding PHA (phytohemoagglutinin) for stimulating mitosis.
4. Stopping the cellular division in the metaphase by colchicyne, which impairs the mitotic apparatus.
5. Treating cells with NaCl hypotonic solution (the cell is broken and chromosomes become accessible for staining).
6. Staining chromosomes with specific stains.
7. Microscoping and making photographs of chromosomes.
8. Compiling an ideogram and analyzing it.

The method is used for diagnosing genomic and chromosomal mutations to determine a genetic sex of the organism.

The autographic method is used for identification of chromosomes.

The fluorescent method is used to confirm the karyotype and to map chromosomes.

3. The Denver and Paris classification of human chromosomes.

In 1960 the Denver classification of chromosomes was proposed. It is based on the shape of chromosomes, their sizes, position of the centermere, presence of secondary constrictions and satellites. An important factor of this classification is a *centermeric index* (CI). It is a ratio of a short chromosomal arm to its full length, expressed in percents. All chromosomes are divided into 7 groups. The groups are denoted with Latin letters from A to G:

– *group A* includes 1^{th}–3^{th} pairs of chromosomes. They are large metacentric and sub-metacentric chromosomes. Their CI is 38–49 %.

– *group B.* 4^{th} and 5^{th} pairs of chromosomes – large sub-metacentric chromosomes. CI is 24–30 %.

– *group C.* 6^{th}–12^{th} pairs of chromosomes: of a moderate size, sub-metacentric, CI is 27–35 %. X– chromosome is also included into this group.

– *group D.* 13^{th}–15^{th} chromosomes. They are acrocentric. CI is about 15 %.

– *group E.* 16^{th}–18^{th} pairs of chromosomes. They are relatively short, metacentric or sub-metacentric. CI is 26–40 %.

– *group F.* 19^{th}–20^{th} pairs. Short, sub-metacentric chromosomes. CI is 36–46%.

– *group G.* 21^{st}–22^{nd} pairs. Small, acrometacentric chromosomes. CI is 13–33 %. An Y– chromosome refers to this group.

The Paris classification of human chromosomes was introduced in 1971. A characteristic order of alternating dark and light bands (segments) is revealed in every chromosome using specific staining methods. The segments are de– noted by the names of methods, which reveal them: Q–segments – after staining with acrichine–yperite; G–segments –with Gimza stain; R–segments –staining after heat denaturation, etc.

A short arm of the chromosome is denoted with ***p***, a long one –withthe letter ***q***. Each chromosomal arm is separated into areas and is denoted with figures from centermere to telomere. Bands within the areas are numbered from the centermere. For example, the gene position of D esterase can be denoted as *13p14* – the 4^{th} band of the 1^{st} region of a short arm of chromosome 13.

Basic terms and concepts:

1. Autosomes – are chromosomes identical in cells of male and female organisms.

2. Karyotype – is a chromosomal complement of a somatic cell characteristic of the organism of a definite species.

3. Colchycine – is a substance used for destroying the division spindle, when a cytogenetic method is used.

4. Sex chromosomes – are chromosomes different in cells of male and fe male organisms. In males they are X and Y chromosomes, in females –X and X.

5. Phytohemoagglutinine – a substance, which is used for stimulation of mitosis in the cytogenetic method.

6. Centeromeric index (CI) – is a ratio of a short arm length ofthe chromosome to its full length expressed in percent.

ORGANIZATION OF HEREDITARY MATERIAL
CLASSES I

1. Nucleic acids (DNA and RNA): the structure and functions. Chargaff's rules.

In 1870 I. Misher described macromolecule in nucleus and called them **nucleic acids** (from Latin *nucleus* –nucleus). DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) refer to nucleic acids. The structure of a DNA molecule was decoded in 1953 by J. Watson, F. Krik and M. Wilkinson.

The nucleic acids are biopolymeres. Their monomeres are *nucleotides*.A nucleotide consists of a nitrogenous base, 5– carbon sugar and residue ofthe *phosphoric acid*. Nitrogenous bases are of 5 types: adenine, guanine, cytosine, thymine, uracyl. Nitrogenous bases are denoted: A, G –purine, T, C, U – pyrimidine. 5– carbon sugar – is *deoxiribose* or *ribose*.

The **DNA** molecule consists of two sequences which are interwoven as spirals. Each sequence is a polynucleotide. A DNA nucleotide consists of a nitrogenous base (adenine, guanine, cytosine and thymine), deoxiribose and a residue of the phosphoric acid. The nucleotide sequence is linked by *phosphodieather bonds* between deoxiribose of and the residue of the phosphoric

acid of the other nucleotide. There are linked nitrogenous bases within the spiral; they are linked to each other according to the principle of *complementarity*:A = T –2 hydrogen bonds G ≡ C –3 hydrogen bonds.

The complementarity property of nitrogenous bases is expressed in Char–gaf's rules:

– the number of purine bases is equal to the number of pyrimidine bases: A + G = C + T;

– the amount of adenine is equal to the amount of thymine (A = T), the amount of guanine is equal to the amount of cytosine (G = C).

The DNA is in the cellular nucleus, in mitochondria and plastids. DNA properties: *replication* (self–reproduction) and ability to *repair* (restoration of the structure after impairment of the molecule). DNA functions: storing and transmitting genetic information during multiplication of cells and organisms.

The **RNA** molecule is a polynucleotide consisting of one sequence. In comparison with a DNA it includes uracil instead of thymine and sugar ribose instead of deoxiribose. In some viruses, RNA has two sequences.

The cell has 3 types of RNA, they are in the nucleus, cytoplasm, mitochondria and plastids. 3–4 % of the whole RNA compose the *messenger RNA* (mRNA): it «records» the genetic information from DNA and translocates it into ribosomes – a place, where protein molecules are assembled. The *ribosomal RNA* (r–RMNA) composes 80–85 % of the whole RNA. It is included into ribosomes and provides special interposition of i–RNA and r–RNA. The *transport RNA* (t–RNA) comprises 10–20 % of the whole RNA, it transports (transfers) amino acids from the cytoplasm to ribosomes.

2. Proofs of the nucleic acids role in transmission hereditary information. Experiments on **bacteria transformations** (Griffith, 1929) became one of the proofs of the DNA role in transmitting hereditary information.

F. Griffith investigated the action of two bacterial strains on mice. Capsulated bacteria were pathogenic (virulent) and caused death of mice of pneumonia, uncapsulated ones were not pathogenic (avirulent), and mice stayed alive. When a mixture of alive avirulent and killed by boiling virulent bacteria was introduced into the organism of mice, the mice died. F. Griffith discovered the phenomenon of bacteria transformation – appearance of a capsule and virulence in uncapculated bacteria. In 1944 year O. Every, K. McLeod and M. McCarty isolated a DNA capsule strain from bacteria; after addition of purified DNA of a virulent strain to alive bacteria of avirulent strain they observed their transformation and formation of a capsule.

Bacteria transformation is the inclusion of bacterial DNA regions of one strain into DNA of the other strain and transmission of its properties.

The next proofs of the DNA role in transmitting hereditary information were experiments of N. Cinder and J. Lederberg (1952) on **transduction** in bacteria. Two strains of bacteria were placed into a U–tube with filter and culture: into one bend –triptophansynthesizing, and into the other bend –triptopha– nunsynthesizing.

The filter was unpermeable for bacteria and they did not mix, but it was permeable for viruses. If into the bend with triptophansynthesizing bacteriaa

bacteriophage was introduces, then some time later there were revealed bacteria (among triptophanunsynthesizing bacteria in the other bend), which wereable to synthesize triptophan. The phenomenon was called transduction.

Transduction is the ability of a bacteriophage to transfer parts of DNA from one strain of bacteria to the other and transmit its properties.

3. Properties of genes.

The gene is a part of a DNA molecule coding a definite polypeptide. Genes are characterized by the following properties:

1. *Specificity* – a unique sequence of nucleotides for every structural gene.

2. *Integrity* –being a functional unit (programming of protein synthesis) the gene is integral.

3. *Discretion* – the gene includes two subunits: a muton – a subunit, which is responsible for mutations; a recon, which is responsible for recombina tion. Their minimum number – a pair of nucleotides.

4. *Stability* –genes are relatively stable. The frequency of unconditioned mutations of a gene is approximately 10^{-5} per a generation.

5. *Lability* – they can modify, mutate.

6. *Pleotropia* –multiple genic action (one gene is responsible for several characters).

7. *Expressivity* – the degree of phenotypical manifestation of the gene.It is due to environmental factors and effect of other genes.

8. *Penetration* –frequency of appearing the gene: a ratio (in percents) of the number of individuals having this character to the number of individuals having this gene.

4. DNA replication.

Genes perform two functions in the cell. A *heterosynthetic* function is programming of biosynthesis in the cell. An *autosynthetic* function – is replication of DNA (self–doubling of DNA).

Replication of DNA occurs in the synthetic period of the interphase. Synthesis of the DNA molecule is semiconservative: one sequence is motherly («old»), a new daughter sequence («new») is assembled on it. The new sequence is assembled according to complementarity of the mother sequence. The main enzyme of synthesis is a DNA–polymeraze.

The spiral of a DNA molecule under the action of the DNA–helicase enzyme is unwinded by 2 sequences, each of them performs a matrix role. Replication starts in some points of the DNA molecule. The part of DNA from the start of one replication to the start of the other is a *replicon*. Chromosomes of eukaryotes have many replicons, those of bacteria nucleoid – 1 replicon. Doubling in all replicons goes simultaneously. A replication part is called a *replication fork*.

DNA–polymerase can move along the mother sequence only from 3’ end to 5’ end. That is why assembling of daughter sequences goes *antiparallel* (in opposite directions). Several DNA polymerases work simultaneously in every replication fork. One of daughter molecule sequences (a leading one) is continuous ly duplicating. The second sequence (a retarding one) is duplicating with short parts of 150–200 nucleotides under the action of DNA–polymerase, which moves

in opposite from the first enzyme direction. These parts are called *Oka– saki's fragments*. All synthesized fragments of a polynucleotide sequence are linked with a *lygase* enzyme. The whole genome of the cell is replicated once during a mitotic cycle.

5. The genetic code and its properties. Protein biosynthesis.

Recording of genetic information as a nucleotide sequence in DNA and mRNA is a *genetic code*. A nucleotide triplet coding a specific amino acid isa *codon*. The codon is an elementary functional unit of the gene.

Properties of the genetic code:

– *tripletness* –one amino– acid is coded by three nucleotides – a codon (triplet);

– *universality* –one and the same codon defines one amino acid in all organisms;

– *no overlapping* –one nucleotide is included only in one triplet;

– *degeneration,* or redundancy –one amino acid can be coded by several triplets (there are 20 amino acids, by 64 possible triplets);

– *discontinuity* – there are no disjunctive symbols between codons;

– *single direction (m*RNA synthesis occurs in the direction from 5' end to3' end);

– *presence of codons–terminators* (they define the end of protein biosynthesis).

The correspondence of the order of nucleotides in a DNA molecule to the order of amino acids in the polypeptide molecule is **colinearity**.

6. Protein biosynthesis in the cell. Protein biosynthesis is a fermentation process, where nucleic acids play the main role. MRNA is synthesized in the cellular nucleus on one of DNA sequences (coding). RNA–polymerase «transcribes» the order of nucleotides arrangement in a DNA molecule (by complementarity rule). This process is called *transcription*. MRNA enters the cytoplasm through nucleous pores and directs to ribosomes.

Recognition (recognizing of its own amino acid by t–RNA) occurs in the cytoplasm. The transport RNA has a specific structure: one end of the molecule contains a nucleotide triplet, it is called an *anticodon* and corresponds to a definite amino acid. The ribosome moves one triplet, and the amino– acyl–t–RNA passes into the peptide center. A definite amino acid joins «its own» t–RNA with the enzyme of *amino– acyl–tRNA–synthetase* and ATP. The amino acid with its t–RNA forms a complex of amino– acyl–t–RNA.

The process of *translation* is going on in ribosomes – a nucleotide sequence of mRNA defines the amino acid sequence of the polypeptide molecule. MRNA is linked with a small ribosome unit in the cytoplasm. The complex of ribosomes, united mRNA, is called a polysome. The beginning of translation is *initiation*, the end of translation – *termination*. The formation process of peptide links between amino acids is *elongation*. There are two mRNA codons in the ribosome simultaneously: one – the *amino–acylic center*, the second – in the *peptide* one.

If a t–RNA anti– codon and an mRNA codon, which is in the amino–acylic

center, are complementary, then amino– acyl–t–RNA forms a temporary bond with an mRNA codon. The ribosome moves by one triplet, and the amino– acyl–t–RNA passes into the peptide center. The second t–RNA with the amino acid comes to the amino–acylic center. A peptide bond sets between the first and second amino acids. The ribosome moves by one triplet, the released t–RNA leaves the ribosome. The second t–RNA passes into the peptide center. The process repeats many times. Termination of polypeptide synthesis is determined by stop– codons: UAA, UAG, UGA.

7. The central dogma of Molecular Biology.

In 1958 F. Krik formulated the central dogma of Molecular Biology: DNA → RNA → protein. The genetic information, recorded in DNA, is realized in a form of proteins. This realization occurs through mRNA. DNA is synthesized on DNA providing its own replication.

In viruses, mRNA can be transcribed in DNA («back transcription»), but protein can not be a matrix for nucleic acids.

Basic terms and concepts:

1. Avirulent strain – is a group of microorganisms that cannot cause a disease.

2. Anti– codon – is a t–RNA nucleotide triplet, which is complementary to an mRNA triplet in the process of translation.

3. Bacteriophage – is a virus parasitizing on bacteria.

4. Virulent strain – are microorganisms able to cause a disease.

5. Gene – a fragment of a DNA molecule coding a definite polypeptide.

6. Initiation – an initial stage of translation.

7. Codon – a nucleotide triplet, the least functional unit of the gene.

8. Complementarity of nitrogenous bases – correspondence of nitrogenous bases to each other in a DNA molecule.

9. Lability of the gene – ability of the gene to mutate.

10. Nucleotide – a monomere of nucleic acids consisting of a nitrogenous base, sugar (pentose) and a residue of the phosphoric acid.

11. Stability of the gene – ability of the gene to preserve its structure.

12. Termination –finishing the polypeptide synthesis.

13. Transduction –transport of a DNA molecule fragment by a bacteriophage from one bacterial strain to the other.

14. Transformation – is the ability of a bacterial strain to occupy fragments of the other strain and obtain new properties and signs.

15. Elongation – is the process of translation from formation of the first peptide bond to joining the last amino acid.

CLASSES II

1. Levels of packing genetic material.

A DNA is linked with histone and non–histone proteins forming nuclear–protein fibrils (DNP). A fibril length in a human diploid chromosomal complement is 2 m, and a length of a chromosome in the metaphase is 150 μm. Packing of

genetic material is obtained by spiralization (condensation) and four package levels of DNP.

Nucleosomal level. A nucleosome is a globule containing 2 histone mole–cules: H_{2A}, H_{2B}, H_3, H_4, around which a double DNA spiral forms 2,2 turns (200 pairs of nucleotides). The nucleosomal thread has d = 10–13 nm. The DNA length reduces by 5–7 times. This level is characteristic of the interphase.

Supernucleosomal level (solenoid). The nucleosomal thread condenses, nucleosomes are «sewn» by histone H_1 and a spiral is formed with d = 25 nm. One turn of the spiral contains 6–10 nucleosomes. DNA shortens 6–fold more. The super-nucleosomal package level can be seen in the interphase and in mitosis.

Chromatid level. The super–nucleosomal filament is spiralized with formation of loops and twists and is the basis of a chromatid. The loop diameter equalsto 50 nm. The DNP thread shortens by 10–20 times. Such package level can be seen in the mitosis prophase.

Metaphasal chromosome level. Chromatids are spiralized and form euchromatin (weakly spiralized) and heterochromatin (strongly spiralized) fragments; there occurs 20–fold shortening of DNP. The length of metaphasal chromosomesis from 0,2 to 150 μm, the diameter is 0,2–5,0 μm.

The total condensation of DNP is 10 000 times.

2. Classification of genes. Classification of DNA sequences:

1. *Unique sequences* (solitary sequences in the genome are included into structural genes and carry information about the structure of polypeptides (they compose 56 % in the human genome).

2. *Repeated sequences* (are repeated ten, hundred, million times) – are promotors, they regulate DNA replication; participate in crossing–over, separate exons and introns in the transcripton.

3. *Transposones* («jumping genes») – are movable genetic elements able to invade the chromosome and to move within it.

According to their functions genes are classified into:

1. *Structural genes* contain information about structural proteins, proteins–enzymes, histones and about sequences of nucleotides in various kinds of RNA.

2. *Functional genes* produce effect on the work of structural genes. Genes–modulators and genes–regulators are functional. *Genes–modulators* are inhibitors, intensifiers, modifiers. They enhance, weaken or modify the work of structural genes. *Genes–regulators* and *genes–operators* regulate the work of structural genes.

According to their action genes are subdivided into three groups:

1. *Functioning in all cells* (genes coding enzymes of energy exchange).

2. *Functioning in cells of one tissue* (determining myosine protein synthesis in the muscular tissue).

3. *Specific for one type of cells* (genes of hemoglobin in immature erythrocytes).

3. Transcription regulation in prokaryotes.

Functional regulation of genes in prokaryotes was described in 1961 by A. L'vov, F. Jacob and J. Mono. The unit of transcription regulation in prokaryotes (*operon*) includes a group of structural genes ruled by one gene–operator (fig. 5).

A DNA sequence is presumably presented as a straight line, which contains structural–functional parts:

– *promoter* – a site of attachment of the RNA–polymerase;

– *initiator* – a nucleotide sequence, from which transcription starts;

– *gene–operator* – switches on and switches off the work of structural genes;

– *structural genes (A, B, C) – determine synthesis of proteins–enzymes*;

– *terminator* of transcription – disconnects the RNA–polymerase from a DNA.

Structural genes are active not all the time. Some distance from the operon is a *gene–regulator*. It is constantly active. According to its information, the *protein–repressor* is synthesized, it blocks the gene–operator, that is why structural genes are not active and the operon does not work.

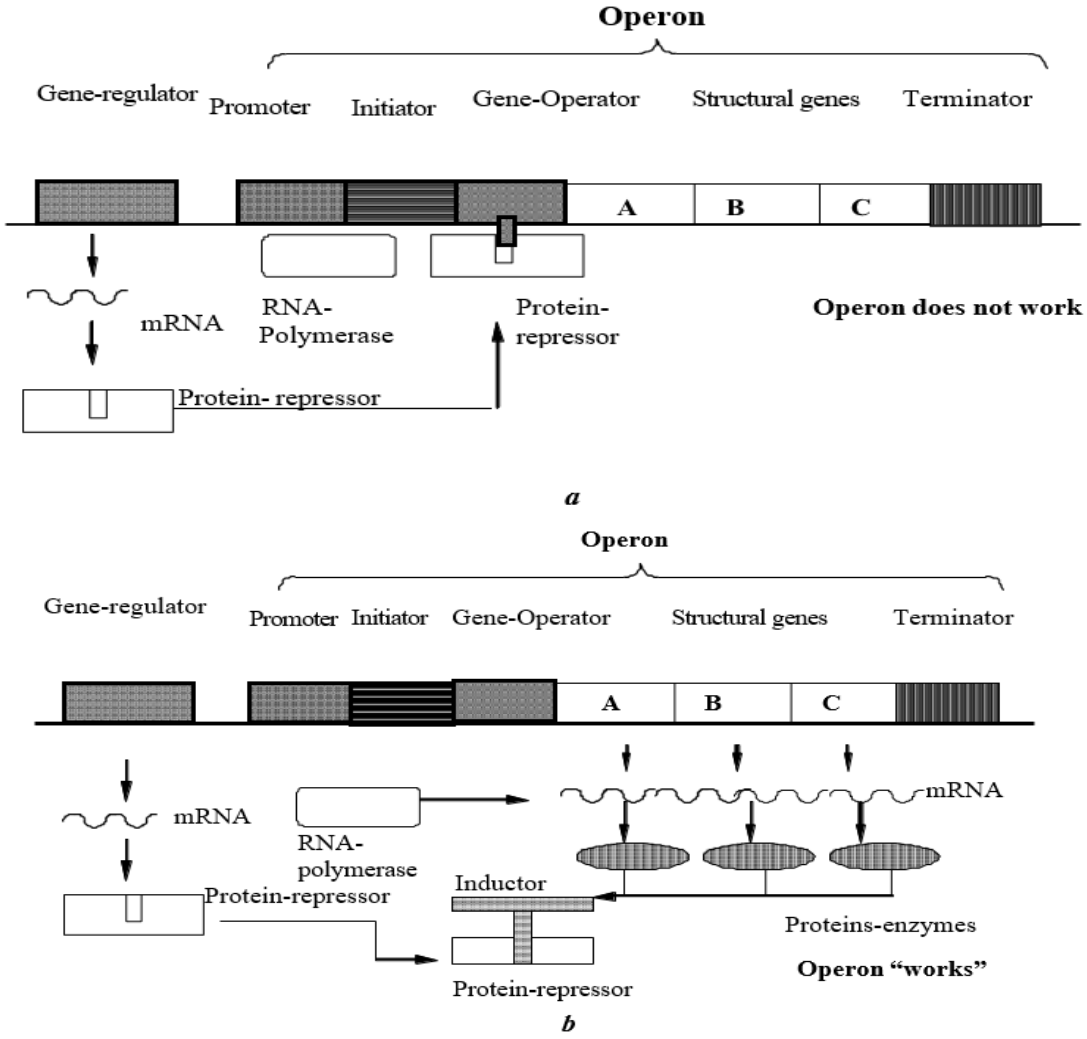


Fig. 5. The diagrams of transcription regulation in prokaryotes

If an inductor (enzymes for its breaking down are encoded in structural genes) comes into the cell, it binds the protein–repressor. The gene–operator is released, RNA–polymerase breaks hydrogen bonds between DNA sequences of structural genes and transcription occurs. An mRNA is synthesized. According to its information proteins–enzymes are synthesized on the cytoplasm ribosomes, they break down the inductor.

The operon works until the whole inductor is not destroyed. After its

destruction the protein–repressor is released, which blocks again the gene–operator. Structural genes are switched off, and proteins–enzymes are not synthesized. Each operon has its specific inductor (for example, lactose and fructose).

Transcription regulation in eukaryotes (the diagram of G. P. Georgiev).

In 1972 G. P. Georgiev proposed a diagram of genes work regulation in eukaryotes. Principally it does not differ from the diagram of regulation in prokaryotes. But the structure of the diagram itself and the mechanism of its work become more complicated (fig. 6).

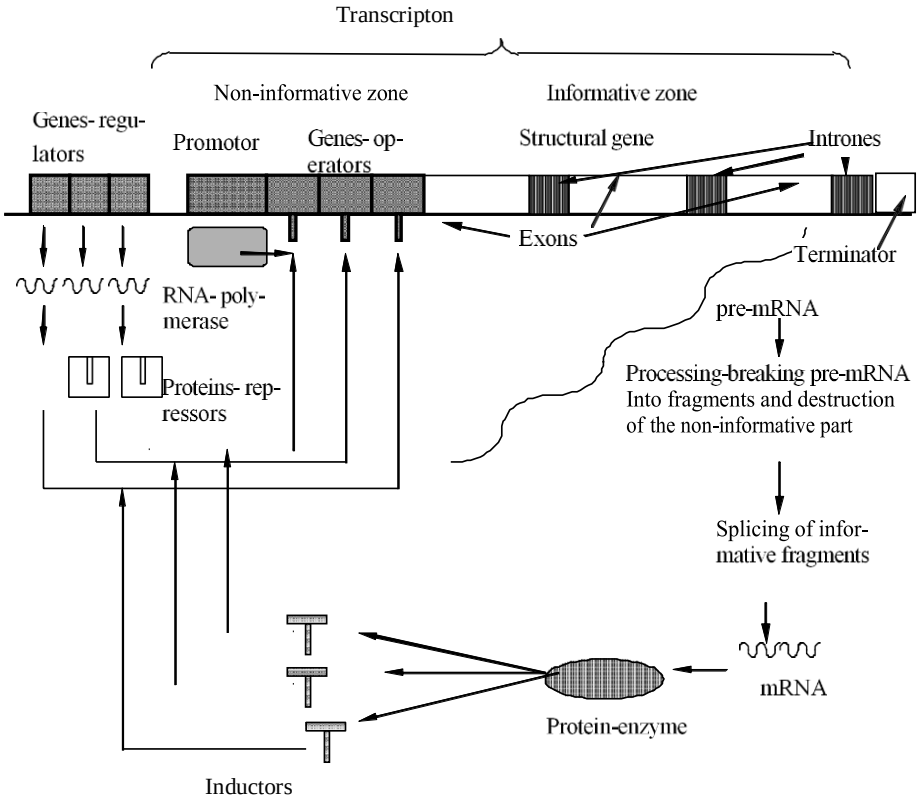


Fig. 6. The diagram of transcription regulation in eukaryots

A transcription unit in eukaryotes is called a transcripton. It consists ofa non– informative zone and an informative zone. The non– informative or acceptor zone includes a promoter, initiator and a block of genes–operators. The in–formative zone contains one structural gene having a mosaic structure: it contains exons – informative fragments and introns –non– informative DNA fragments. The structural gene is followed by a transcription terminator. The block of genes–regulators regulates the work of transcriptons. On the basis of their information several proteins–repressors are synthesized, they block genes–operators. Just as in the operon, reading of information from the structural gene occurs, when inductors get into the cell. In this case substances with a complex structure serve as inductors (for example, hormones). The inductors release genes–operators from proteins–repressors. An mRNA precursor (pre–mRNA) is synthesized, it contains information about the whole sequence of the transcripton, its informative and non– informative parts.

In the nucleus under the action of exo– and endonucleases there occurs

the processing of *pre–mRNA* –destruction of the non– informative part and splitting it into fragments corresponding to exons. The mRNA is formed as a result of *splicing* (sewing) of informative parts with *lygases* enzymes. After such transformations mRNA comes into the cytoplasm on ribosomes, where protein encoded in the transcripton is synthesized. After destruction of inductors blocking of genes–operators by proteins–repressors is restored, and the transcripton is switched off.

4. Cytoplasmatic heredity.

The basic genetic information of the organism is contained in the nucleus. Genetic material (*plasmogenes*) contain mitochondria and plastids. There may be a foreign DNA of viruses and bacteria in the cytoplasm.

Criteria of cytoplasmatic heredity:

– inheritance goes on mother's line through the ovum cytoplasm;

– absence of splitting characters in fillies according to Mendel's laws;

– impossibility to reveal linkage groups;

– different results of recurrent crossing (in nuclear inheritance they are identical).

Mitochondrial heredity was described by B. Effrussy in 1949. He discovered that about 1 % of yeast colonies form dwarf colonies. Their growth goes very slowly, because the plasmogens mutation occurred and their mitochondria have no respiratory enzymes. There is information about some human diseases that are due to mutations of mitochondrial genes (mitochondrial cytopathy, non– atresia of upper vertebrae–spina bifida, senility, Leber's disease (atrophy ofan optic nerve), anencephaly (absence of the brain0, etc.

Plastid heredity (K. Korrens, 1908).The plant Night beauty has molted leaves (green with white spots). There occurred a mutation, and chlorophyll is not produced in some plastids. Plastids are distributed unevenly during multiplication. One part of cells get normal plastids and have green leaves. The other part of cells get plastids without chlorophyll –leaves are white and the plant dies. The third one get plastids both green (normal) and mutated plastids –plants have molted leaves.

Pseudocytoplasmatic inheritance is associated with getting a viral or bacterial DNA into the cell. Some mice are predisposed to tumors of mammary glands. If normal little mice were fed by a female of a «cancer line», all mice will have tumors of the mammary gland. And vice versa: if little mice of a «can cer line» are fed by a healthy female, all little mice will be healthy. The causative agent of milk in mice was a virus.

Basic terms and concepts:

1. Gene–operator – is a gene that switches on and off the work of structural genes.

2. Inductor – is a substance coming into contact with protein–repressor and initiating the operon or transcripton.

3. Intron – is a non– informative fragment of structural genes in eukaryotes.

4. Nucleosome – is a structural unit of chromatin consisting of 8 proteins–histones and DNA nucleotides.

5. Operon – is a transcription unit in prokaryotes.

6. Promotor – is a site of attaching a RNA–polymerase.

7. Processing – is a fermentative destruction of a pro–mRNA non–informative fragment and splitting the informative part into fragments corresponding to exons.

8. Repressor – is protein encoded by the gene–regulator and which is ableto block the gene–operator.

9. Solenoid – is the second package level of genetic material

10. Splicing – is the sum of reactions of combining fragments of pre–mRNA and the formation of mRNA.

11. Transcripton – is a transcription unit of eukariotes.

12. Transposon – are nucleotides sequences of the DNA molecule with temporary localization.

13. Exon – is an informative part of structural genes of eukariotes.

GENETIC ENGINEERING

Purpose of genetic engineering – is designing of genetic structures accord ing to a given plan (creation of organisms with a new genetic program by translocation of genetic information from one organism to the other).

1. Stages of genetic engineering methods:

1. Obtaining genetic material.
2. Translocation of DNA fragments into a molecule–vector.
3. Introduction of a recombinant DNA into a cell–recipient.
4. Selection of cellular clones containing molecules of a hybrid DNA.

2. Obtaining genetic material.

Chemical–fermentative synthesis of genes. Short (8–16 nucleotides) single–sequenced DNA fragments are synthesized *in vitro*, then they are linked with lygases and treated with high temperature for the formation of double–thread DNAmolecules. The gene should be **sequenced** for this method.

Fermentative synthesis of complex genes. It is performed by recurrent transcription. An isolated m–RNA is used as a matrix. Using an enzyme revertase, a coding DNA thread is synthesized on it, then it is replicated. The obtained genes do not function in cells as they have no promoter and regulation part. During transfer into a bacterium a promoter is added to structural genes, andthe gene starts its work.

Isolating natural genes with restictases . Restrictases – are enzymes causing DNA hydrolysis with formation of shorter fragments of the molecule. They affect DNA of any organisms if it has sites of recognition (usually they recognize very specific parts for every enzyme with 4–6 pairs of nucleotides in length). These parts are called *palindromes*.

At present there are over 500 restrictases in genetic engineering, they are able to cut the DNA in approximately 120 sites and form double–thread (*obtuse*) ends or single–thread (*sticky*) ends in the DNA.

Gene isolation with restrictases has a number of disadvantages:

– it is not always possible to select restrictases, which allow to cut outa DNA part with a necessary gene;

– the cut out DNA fragment may contain introns, then recombinant DNA will not be able to work in prokaryotic cells due to disability for processing and splicing.

K. Mullis (1987) elaborated a method, which was called a polymerase chain reaction (PCR). PCR is performed in vitro using the enzyme of DNA–polymerase bacteria Thermus aquaticus, a complement of 4 nucleotides A, T, G and C and short *primings*. The enzyme is marked by its persistence to high temperature.

Thanks to primings the DNA fragment is limited, it will be copied by DNA polymerase. The PCR has 3 stages:

1. *Denaturation* – a mixture, which contains a specimen of a needed DNA, is heated to 90 °C. Meanwhile, during 15 seconds there occurs breaking of hydrogen bonds between DNA sequences, and two single–sequenced molecules are formed from one double–sequenced molecule.

2. *Hybridization of primings* – the temperature is lowered to +50 °C and primings are added. This stage lasts about 30 seconds.

3. *Polymerization* – the mixture is heated again to +70 °C. At this temperature the Taq–polymerase lengthens both primings from their 3' ends. The primings grow up to the matrix sizes. This process takes 90 sec.

As a result, the number of DNA increases by many times. During 20 cycles the number of DNA copies reaches 10^6.

3. Incorporation of DNA fragments into the molecule–vector.

Vector – is a small autonomously replicated DNA molecule, which pro vides multiplication and work of the incorporated definite gene.

Vector molecules should:

– contain points of replication origin and replicate autonomously;

– permanently be inherited by a host cell;

– be contained in a great number of copies in the cell;

– possess a sufficient capacity, which allows cloning big genes in their composition;

– contain «convenient» sites of restriction;

– contain selective markers, which could be used for selecting cells that have received a cloned DNA segment and the marker itself.

The most useful of «vector–host» systems are those, in which the host role play *bacteria E. coli,* and the vector role – **plasmids**.

Plasmids – are ring autonomously replicated DNA molecules that are contained in bacterial cells.

Phage vectors – are phage particles containing a recombinant DNA. Vec tors for E. coli are constructed on the basis of **phage λ and phage M 13**.

Phage λ contains a double–sequenced DNA of 48 500 pairs of nucleotides in size. It is packed into the head as a linear molecule with sticky ends. After pene tration into the cel, sticky ends are mutually paired, the molecule locks into a ring

and is sewn by a DNA–lygase. It is possible to clone fragments of 15 000 pairs of nucleotides long in the content of vectors on the basis of phage λ**.**

Cosmids – are vectors made on the basis of plasmids and phage λ. Cosmids have cos–sites, which are located on both ends of a DNA molecule of phage λ. Complementary single–sequenced parts are 12 nucleotides long, due to which the phage has a linear shape, they join each other through cos–sites and form a long sequence of hundreds of phage DNA or concatameres.

Phasmids – are hybrid vectors that can develop both as a phage and a plasmid. The capacity of plasmids is comparable to that of phage vectors.

4. Introduction of recombinant DNA in the cell–recipient.

The following methods are used:

1. Conjugation – transmission of genetic material in bacteria may occur in direct intercellular contact. Genetic material is transmitted only in one direction.

2. Transformation – transmission of genes with a free soluble DNA (by plasmids), isolated from cells–donors;

3. Transduction – the transmission of DNA from a cell–donor to a cell–recipient may occur with participation of b vector acteriophages;

4. Transfection – infection with phages λ, ψ174 and T4;

5. Competence – ability of cells to absorb a DNA from the environment;

6. Microinjection of DNA molecules into animal cells;

7. Using liposomes for introducing DNA into animal cells. Liposomes are vesicles surrounded by one or several layers of lipids.

5. Using methods of genetic engineering in medicine.

Southern blott hybridization. The method developed in 1975 allows identifying restriction DNA fragments (fig. 7).

A DNA treated with restrictases is placed on agar jelly in a special chamber for electrophoresis, where an electric field is formed, and under its influence DNA fragments start moving. Short fragments move faster. After electrophoresis a mixture of DNA fragments forms some fractions located some distance from each other. Each such fraction corresponds to one DNA fragment. DNA fragments separated in the agar jelly **are denaturated to single–sequenced molecules**, and then the whole electrophoresic DNA specter **is printed (blotting**) on an applied to the jelly nitrocellulose **film** and is fixed by high temperature. Then the film is placed into the culture containing a **radioactively marked DNA–probe**. The probe can hybridize only with a specific complementary to it DNA fragment. After interaction with the DNA–probe the film is applied tothe nitrocellulose membrane containing all obtained DNA fragments. After exposition there appear lighted spots corresponding to the arrangement of marked DNA fractions on the film (autoradiogram).

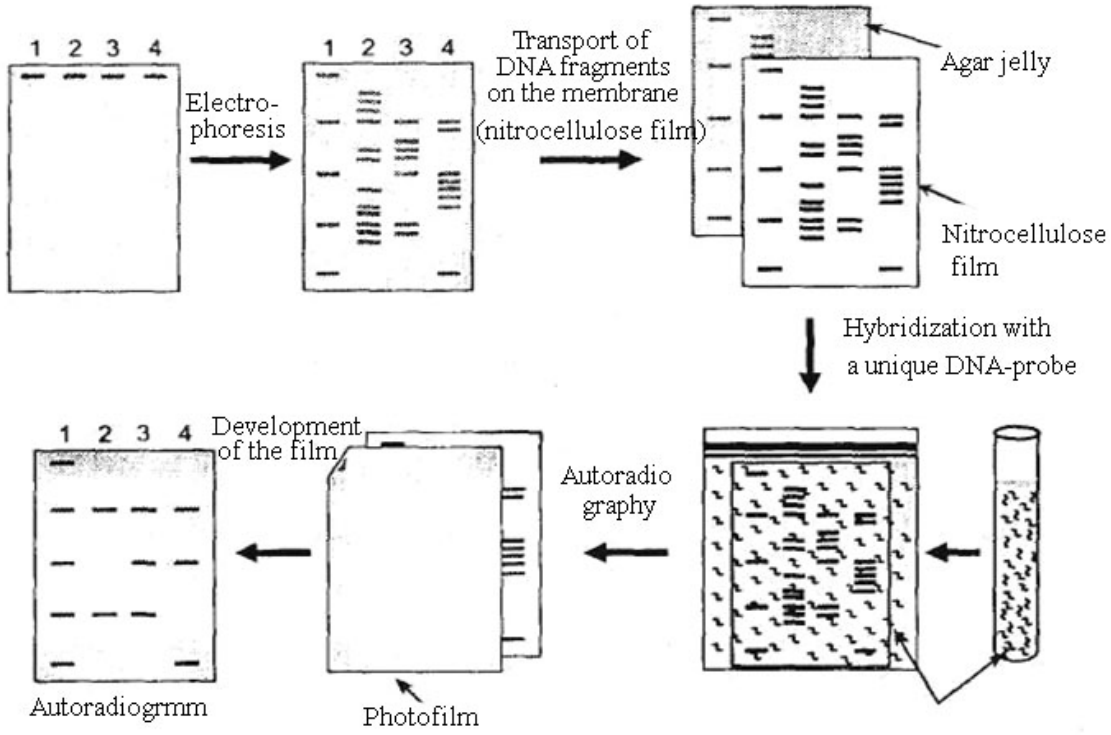


Fig. 7. Southern–blott hybridization method

The method is used for revealing DNA sequences characteristic of mutated genes, it allows diagnosing gene mutations.

Gene dactyloscopy. There is a minisatellite DNA in the human genome, which presents short (9–64 nucleotide pairs), recurrent, tandem, variable DNA sequences. A tandem recurrence – are two or more identical DNA sequences located close to each other. The human has many different tandem DNA recurrences located in different chromosomes, which in total form a unique complement of minisatellite DNA for every human. The method of analyzing these fragments got the name of **gene dactyloscopy (fingerprint of DNA)**.

The technology of gene dactyloscopy: a DNA is isolated from cells and cut into fragments of various length with the help of restrictases. Then the Southern–blott analysis is made. *Fractions containing a minisatellite DNA*, are revealed with a probe, which is complementary to a link from 13 recurrent nucleotides. The probe is radioactive, it lights a roentgen film only in definite places, giving a picture of some tens of alternating dark fractions corresponding to separate minisatellites.

Basic terms and concepts:

1. Autoradiogram – is a film, where lighted fragments corresponding to the arrangement of marked DNA fractions are revealed.

2. Vector – is a small autonomously replicated DNA molecule, which provides multiplication and the work of a gene incorporated in it.

3. Genic dactyloscopy – is a method analyzing fractions of a minisatellite DNA.

4. Hybridization of primings – is a second stage of the polymerase chain reaction resulting in hybridization of DNA chains with primings.

5. DNA–probe – is a radioactively marked short specific DNA sequence.

6. Cosmids – are artificial constructions made on the basis of plasmids and phage λ.

7. «Sticky ends» – are single–thread complementary DNA ends, which are formed by restrictases.

8. Liposomes – are vesicles surrounded by one or several layers of lipids.

9. Plasmids – are small ring autonomously replicated DNA molecules, which are in bacterial cells.

10. Restrtictases – are enzymes causing DNA hydrolysis with the formation of «sticky ends».

11. Restriction sites – are sites recognized by restrictases (there are usually recognized parts of 4–6 pairs of nucleotides in length, strictly specific for every enzyme).

12. Phasmids – are hybrid vectors, which can develop both as a phage and a plasmid.

INHERITANCE REGULARITIES. INTERACTION OF GENES

1. Genetics as a science. Basic concepts of Genetics.

Genetics is a science about laws of heredity and variation. The term «genetics» was introduced into Biology by W. Batson in 1906.

Genotype – is a sum of all genes of the organism.

Phenotype – is a sum of all characters and properties of the organism, which are determined by the genotype and environmental factors.

Alternative signs – are incompatible characters.

Allelic genes – are genes occupying identical loci of homologous chromosomes, they determine the development of one alternative character.

Non– allelic genes – are genes occupying different loci of homologous chromosomes or inhomologous chromosomes, they determine the development of different characters.

Homozygous organism – is an organism, which contains identical genes, form one type of gametes; in crossing with identical individual on the genotype no splitting of characters occurs.

Heterozygous organism – is an organism containing different allelic genes; it forms two types of gametes; in crossing with an identical on genotype individual splitting of characters occurs.

Dominant characters – are characters, which are revealed in a homozygous and heterozygous state.

Recessive characters – are characters, which are revealed only in a homozygous state.

The basic hereditary laws were described by G. Mendel (1822–1884) in his work «Experiments on vegetative hybrids» (1865). G. Mendel used a **hybridological method. Hybridization** is crossing of individuals differing on genotype and phenotype, followed by further analysis of fillies (hybrids).

2. Peculiarities of the hybridological method:

1. Crossing of pure lines (homozygotes).
2. Analysis of inheriting separate characters in fillies of some generations.
3. Precise quantitative account of fillies with different characters.

3. Inheritance regularities in monohybrid crossing.

Monohybrid crossing is crossing, when one pair of alternative characters is analyzed.

Law I – is **a law of hybrid uniformity**: in crossing of homozygous individuals analyzed by one pair of alternative characters one can observe uniformity of hybrids on phenotype and genotype.

P AA x aa P (parents)

G (A) (a) G (gametes)

F_1 Aa F (fillies)

G. Mendel crossed a homozygous plant of pea with yellow seeds and a homozygous plant of pea with green seeds. As a result of such cross G. Mendel ob tained plants only with yellow seeds. These plants were heterozygous on genotype.

Law II – is **a law of splitting characters**: in crossing heterozygous organ isms analyzed on one pair of alternative characters one can observe splitting on phenotype in ratio 3:1 and on genotype 1:2:1. Splitting **on phenotype**: 3 parts of individuals with a dominant character, 1 part with a recessive character. Splitting **on genotype**: 1 part of individuals – are dominant homozygotes (AA), 2 parts of individuals – are heterozygotes (Aa), one part of individuals – are recessive homozygotes (aa).

P (F_1) Aa x Aa

G (A)(a) (A)(a) P (F_1) –hybrids of the 1st generation are parental

F_2 AA, Aa, Aa, aa

4. Hypothesis of «purity of gametes» and its cytological foundation.

W. Batson proposed a **hypothesis of gametes purity** in 1902 to explain the results of crossing performed by G. Mendel, i. e. genes in hybrids are not hybridized and are in a pure allelic state. The mechanism of meiosis is a cytological basis of Mendel's laws. Homologous chromosomes in meiosis diverge, that is why one gene from an allelic pair gets into a gamete.

5. Analyzing cross. The concept of a phenotypical radical.

Analysing cross – is crossing of an individual having a dominant character, with a recessive zygote for determining its genotype. If in the result of analyzing cross one can observe the uniformity of hybrids, then the initial organism is homozygous (AA); if one observes splitting, then the initial organism is heterozygous (Aa).

Phenotypical radical – is a short record of the genotype made on the basis of the phenotype. Record A–B– means that the phenotype does not depend on what gene will be instead of dash – a dominant or a recessive one: a dominant character will be revealed.

6. Regularities of inheritance in polyhybrid crossing. The law of independent inheritance of characters.

Dihybrid crossing – is crossing, when two pairs of alternative characters are analyzed, if there are more than two pairs – crossing is called **polyhybrid.**

Mendel's law III – is **a law of independent inheritance of characters**: in crossing homozygous individuals analyzed by several pairs of alternative cha racters, one can observe independent inheritance of characters and corresponding genes in the second generation.

Gene	Character
A	Yellow color of seeds
a	Green color of seeds
B	Smooth shape of seeds
b	Wrinkled shape of seeds

P. AABB x aabbG.

AB ab

F_1. AaBb - 100 %

P. AaBb x AaBb

G. aB ab aB ab

AB Ab AB Ab

G	*AB*	*Ab*	*aB*	*ab*
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAbb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

In dihybrid crossing, when plants differed in two alternative pairs of characters, G. Mendel got The Pennet's lattice is used for recording results of dihybrid crossing: All in all we get 16 combinations: 9 parts A–B–: 3 parts A–bb: 3 parts aaB–: 1 part aabb. If one separately estimates the ratio of characters in pairs 12A–: 4aa–, 12B–: 4bb–, we'll get the ratio 3:1 in both cases. On the bases of obtained results one can make a conclusion that in crossing of heterozygous individuals, which are analyzed by several pairs of alternative characters, there will be observed splitting on the phenotype in fillies in the ratio $(3 + 1)^n$, where n – is the number of characters in a heterozygous state.

The significance of Mendel's laws:

1. The laws are universal, they are applicable for all living organisms.

2. G. Mendel introduced a mathematical method into Biology; they are laws of large numbers.

7. Conditions limiting the manifestation of Mendel's laws. Pleotropic action of the gene. Semi–lethal and lethal genes.

Conditions limiting the manifestation of Mendel's laws:

1. Different probability of the formation of gametes and zygotes of various types.

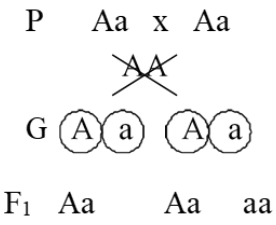
2. Different survival of individuals of different phenotypes (the presence of lethal and semi–lethal genes). *Lethal genes* cause death of organisms before birth or at the moment of birth. *Semi–lethal genes* reduce the life span of the organism.

3. Interaction of genes (except complete domination).

4. Linkage of genes.

5. Cytoplasmatic heredity.

An example of the *action of a lethal gene*. A dominant gene **A** determines a grey color of wool in sheep, and in a homozygous state, it produces a lethal action (due to underdevelopment of the stomach in lambs). A recessive gene a determines a black color of wool. Instead of an expected ratio 3:1 we get the ratio 2:1 on the phenotype and genotype.



The pleotropic action of the gene –one gene is responsible for manifestation of several characters. An example, the syndrome of «blue scleras»: a gene causes a blue color of scleras, fragile bones and congenital deafness in humans.

8. Intrallelic interaction of genes.

Intrallelic interactions of genes are interactions of genes from one allelic pair:

1. *Complete domination*: coloration of peas, brown and blue eyes in humans, straight and curly hair and other characters. They are called mendelizing – splitting obeys Mendel's laws.

2. *Incomplete domination* or intermediate inheritance.Gene A –red flowers. Gene a –white flowers.P AA x aa → Aa

Red white pink

3. *Superdomination*: Gene action in a heterozygous state is revealed stronger than in a homozygous one. For example, in Drosophila: a lethal gene is recesive and homozygotes on this gene die; vitality in heterozygotes is stronger and they are more fertile than homozygous individuals on a dominant gene.

4. *Co–domination*. An example –blood groups on the system AB0: 2 allelic genes (I^A, I^B) are equivalent to each other, but being together in the genotype they cause the appearance of a new character –both show their action (IV blood group).

9. Inheriting blood groups.

Inheriting blood groups in the human by the system AB0 is due to gene I. Alleles of gene I: I^0, I^A, I^B. The presence of gene I^0 does not cause synthesis of antigenes in erythrocytes (group I).

Genes I^A and I^B are dominant to gene I^0. Occuring in the genotype in a homo– (I^A I^A; I^B I^B) or in a heterozygous (I^AI^0; I^B I^0) state they cause synthesis of anti–genes, either A, or B in erythrocytes: A –group II, B –blood group III. If they are in the genotype together, then 2 types of anti–genes are synthesized in erythrocytes: A and B –blood group IV(AB).

Multiple alleles – are alleles that are presented in the population by more than 2 states (alleles of the gene I –I^0, I^A, I^B).

Inheriting Rh–factor. The presence of protein, Rhesus–factor, in erythrocytes is due to Gene D.

The blood of such people is Rh–positive (Ph^+). When the Rhesus–factor (d) is absent, the blood is Rhesus–negative (Rh^-).

Inheriting blood groups on system MN. This system is due to the presence of two alleles –L^N and L^M. Gene L^M causes the presence of antigene M in human erythrocytes (blood group M), and gene L^N –of antigene N (blood group N).

The simultaneous presence of both alleles in the genotype causes the presence of both anti–genes M and N in erythrocytes (blood group MN).

10. Interallelic interaction of genes.

Interallelic interaction – is the interaction of non– allelic genes.

1. **Complementarity** – is interaction, when a gene of one allele complements the action of a gene of the other allele. Coloration of flowers in fragrant peas is determined by a combination of dominant genes of allele A and allele B. The absence of one or two dominant genes in the genotype determines the formation of white flowers.

Colored flowers: A – B –; white flowers: A-BB, aaB-, aabb

P AaBb x AaBb

Red flowers Red flowers

(AB) (Ab) (AB) (Ab)

G

(aB) (ab) (aB) (ab)

F_1 9A-B-; 3A-bb; 3aaB-; 1aabb

Red White White White

(according to Mendel's law a ratio 9:3:3:1, splitting obtained according to phenotype is 9:7).

Epistasis – is interaction, when a dominant (recessive) gene of one allele suppresses the manifestation of gene action of the other allele. A suppressing gene is called *epistatic* (inhibitor or suppressor); a suppressed gene is called *hypostatic*. An example of epistasis – coloration of feathering in hens. Feather coloration is determined by gene **C**; a dominant gene of allele **I** suppresses its action.

Genotype of hens with colored feathering C – ii Genoype of hens with white feathering C–I–, cc–I–, cciiP CcIi x CcIi

White hens White hens F_1 9C–I–: 3C–ii: 3ccI–: 1ccii

White colored white white (splitting by Mendel is 9:3:3:1, Splitting obtained according to phenotype is: 13 white: 3 colored)

2. **Polymeria** –several non– allelic genes enhance the phenotypic manife station of the character.

In this way some human quantitative characters are inherited: body mass, height, skin pigmentation, blood pressure. Polymeric genes are usually denoted by identical letters but with different figure indices.

For example, skin pigmentation in the human: negroids –P $_1P_1P_2P_2P_3P_3$; europeoids –$p_1p_1p_2p_2p_3p_3$; mulates –$P_1p_1P_2p_2P_3p_3$. The more dominant genes are in the phenotype, the stronger is the character expressed.

Basic terms and concepts:

1. Allelic genes – are genes occupying identical loci of homologous chromosomes, they determine the development of different states of one character.

2. Genome – is a sum of all genes in a haploid complement of chromosomes.

3. Genotype – is a sum of all genes in the organism.

4. Homozygous organism – is an organism containing identical variants of one allele in somatic cells (AA, aa).

5. Complementarity – is interallelic interaction, when a gene of one allele complements the action of a gene of the other allele.

6. Multiple allelism – is a phenomenon, when a gene in the population is presented by more than two allelic states.

7. Polygenic inheritance – is inheritance of characters that are determined by polymeric genes.

8. Superdomination – is interaction of genes, when a dominant gene in a heterozygous state shows its action stronger than in a homozygous one.

9. Phenotuypical radical – a short record of the genotype on the basis of the phenotype.

10. Phenotype – is a sum of characters and properties of the organism.

LINKAGE OF GENES

1. Experiments of T. Morgan. Complete and incomplete linkage.

In 1911–1912 experiments on Drosophila were performed in the laborato ries of T. Morgan. It is convenient for genetic investigations, because:

– it has few chromosomes (4 pairs),

– early sex maturity, fast change of generations,

– a great number of fillies, it is easy to make similar conditions for Drosophila.

Two pairs of alternative characters were analyzed in Drosophila on crossing.

Gene B – a grey body Gene V –normal wings Gene b – a black body gene V –short wings

The 1st cross of flies was done according to Mendel's scheme: P BBVV x bbvv

F_1 BbVv –grey with normal wings –100 %

To clear out the genotype of hybrids an analyzing cross of a male of the 1 st generation was performed. It is crossing of an individual with dominant charac– ters with a recessive homozygote.

According to Mendel's law III T. Morgan expected to get an equal quantity of flies in the fillies of each phenotype –per 25 %. However he got flies of two

phenotypes (per 50 %) with parental characters. T. Morgan proposed that genes of the body color and wings length are localized in one chromosome and passed together, i. e. linked. **Linkage of genes** – is a joint transmission of genes of one chromosomal pair.

A male Drosophila has a **complete linkage of genes**. One of a pair of homologous chromosomes contains 2 dominant genes (**BV**), and the other –2 recessive (**bv**). In the process of meiosis one chromosome (with genes **BV**) gets into one gamete, and the other (with genes **bv**) in the other. Thus, there form not 4 but 2 types of gametes in a diheterozygous organism. Fillies also have such characters as their parents.

In the 3rd experiment T.Morgan crossed a hybrid female of Drosophila with a recessive male. He got 4 types of fillies: 2 types (83 %) with parental characters and 2 types (17 %) with a new combination of characters. Individuals composing per 8,5 % formed in the process of crossing–over and are called *crossoverous*. The total number of crossoverous individuals comprises 17 %, which corresponds to the distance between genes of the body color and wing length –17 morganids.

II $P(F_1)$ bbvv x B–V– III $P(F_1)$ B–V– x bbvv

F_2 bbvv B–V– F_2 B–V– bbV– B–vv bbvv

50 % 50 % 41,5 %; 8,5 %; 8,5 %; 41,5 %

In a female Drosophila, unlike a male, crossing–over impairs linkage of genes and stimulates recombination of genetic material.

Linkage is called *complete* if crossoverous individuals are not formed (a male of Drosophila). If they are formed (a female of Drosophila), linkage will be *incomplete*.

2. Autosomal and gonosomal linkage groups.

Genes localized in one chromosome (a pair of homologous chromosomes) are transmitted together and compose a *linkage group*. The number of linkage groups is equal to the *haploid number of chromosomes*. Linkage can be *autosomal* (the groups linking chromosomes) and *gonosomal* (the groups linking sex chromosomes). There are 23 linkage groups in the human: 22 *autosomal* and 1 *gonosomal* group.

3. Crossing–over, crossoverous and non– crossoverous gametes.

Linkage of genes is disturbed by a biological phenomenon – c*rossing– over*, which occurs in the prophase of meiosis I. Crossing–over is the formation of a cross and exchange of identical parts of chromatids of homologous chromo– somes in a bivalent. It does not occur in a Drosophila male and a bombyx female. Crossoverous gametes – are gametes containing chromatids that have under– gone crossing–over. Unmodified chromatids are included into *non– crossoverous gametes*. Crossing–over occurs not always, that is why there are always less crossoverous individuals than non– crossoverous. The linkage force between genes (frequency of crossing–over) depends on the distance between them: the more is the distance, the weaker are linkage forces, the more frequently crossing–over occurs.

4. Basic issues of the hereditary chromosomal theory.

1. Genes are arranged in chromosomes in a linear order in definite loci.

Allelic genes are in identical loci of homologous chromosomes.

2. All genes of one chromosome compose a linkage group and are inherited together. The number of linkage groups is equal to the number of pairs of homologous chromosomes.

3. Crossing–over (exchange of allelic genes) is possible between homolog–ous chromosomes.

4. The percentage of crossing–over depends on the distance between genes in the chromosome. 1 % of crossing–over is equal to 1 morganid – a unit ofthe distance between genes called to honor T. Morgan.

5. Maps of eukariotic chromosomes (genetic and cytological).

Knowing the distance between chromosomes one can make their maps.

A genetic map: the chromosome is presented as a straight line, along which genes are presumably located according to the results of crossing being analyzed.

A cytological map – is a precise picture or a photo of the chromosome. The arrangement order of genes is determined during comparison of analyzing cross results and chromosomal reconstructions.

Basic terms and concepts:

1. Crossoverous gametes – are gametes, into which chromatids exposedto crossing–over got.

2. Non– crossoverous gametes – are gametes, into which chromatids not exposed to crossing–over got.

3. Genetic map of the chromosome – is a part of a straight line, wherethe order of genes arrangement is marked.

4. A cytological map of the chromosome – is a photo or a picture ofthe chromosome, on which the order of genes arrangement is marked.

5. Recombinants – are organisms that are formed during the fusion of crossoverous gametes.

6. Linkage of genes – is a joint transmission of genes of one chromosome.

VARIATION

1. Variation and its types.

Variation – is a property of living organisms to obtain characters distinguishing them from their parents in the process of ontogenesis (fig. 8).

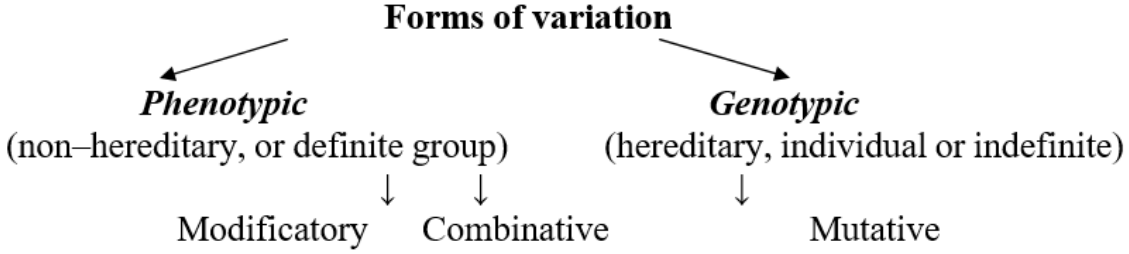


Fig. 8. Forms of variation

2. Phenotypical variation. The reaction range.

A phenotypical or modificatory variation – is modification of the phenotype

without changing the structure of the genotype. That is why it is *non– hereditary*. Modifications occur under the action of environmental factors, changes can be predicted for a *whole group of individuals*. As a rule, modifications have *an adaptive character* –enhancing of skin pigmentation (sun–tan) under ultra–violet radiation.

The reaction range determines the limits of modificatory variation. It is controlled by the genotype and is inherited. If the character has a narrow reaction range, it changes insignificantly (fatness of milk). The character with a broad reaction range changes in wide limits (body mass).

3. Genotypical variation and its forms.

A genotypical variation – is modification of the phenotype due to changing the genotype. It is inherited. It includes a *combinative* and *mutational* variation.

A combinative variation is associated with recombination of parentalgenes in fillies without changing the structure of genetic material. For example, appearance of a blue–eyed child in heterozygous brown–eyed parents.

Mechanisms of combinative variation:

1. Free combination of chromosomes and chromatids, when they diverge in meiosis.

2. Crossing–over in meiosis (recombination of genes).

3. Incidental meeting of gametes of different types during fertilization.

Mutational variation or mutations – is a sudden uneven changing of genetic material under the influence of environmental factors. It is inherited.

Differentiation of mutations from modifications (fig. 9).

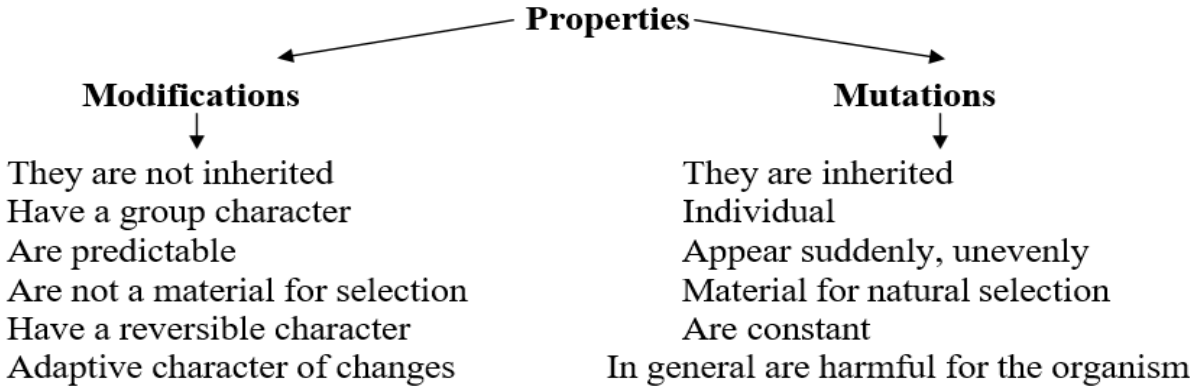


Fig. 9. Differentiation of mutations from modifications

4. Mutagenic factors.

Mutagenic factors – are factors causing mutations. Mutagenic factors are divided into physical, chemical and biological.

Physical mutagens – are various kinds of radiation, temperature, humidity, etc.

They cause impairments of the structure of genes and chromosomes; formation of free radicals interacting with DNA; cuts of the division spindle threads; formation of dimeres of adjacent pyrimidine bases of one DNA sequence (T–T), etc.

Chemical mutagens – some medicines, formalin, yperite, colchicin, food conservants, etc.

They cause desamination and alkylation of DNA molecule nucleotides; replacement of nitrogenous bases for their analogues (substances with similar structure); suppress synthesis of precursors of nucleic acids (nucleotides, ribose, deoxiribose).

*Biological mutagen*s – are viruses, bacteria, metabolites – protists and helminthes.

They cause impairments of DNA synthesis, divergence of chromosomes and chromatids in the anaphase of meiosis and mitosis; waste products of parasites act as chemical mutagens, destroy chromosomal telomeres and impair the process of crossing–over.

5. Classification of mutations.

The formation process of mutations is called *mutagenesis*.

According to etiological factors:

1. Spontaneous – appear under the influence of natural factors (mutagens) without participation of the human.

2. Induced – the result of directed effect of definite mutagenic factors.

According to mutated cells:

1. Gametic – occur in sex cells and are transmitted during sexual reproduction.

2. Somatic – occur in somatic cells, show in the individual itself and are inherited only in vegetative reproduction.

According to the outcome for the organism:

1. Negative: lethal, incompatible with life and semi–lethal, reducing vitality.

2. Neutral, affecting the vitality inconsiderably.

3. Positive, increasing the vitalality.

According to modification of the phenotype:

1. Morphological (small eyes, 6 fingers on the hand).

2. Biochemical (albinism, hemophylia).

According to modification of the genotype:

1. Genomic.

2. Chromosomal.

3. Genic.

6. Genomic, chromosomal and genic mutations.

Genomic mutations – is changing of the number of chromosomes. **Haploidy** – is a chromosomal complement ln. It occurs in drones (males) in bees. The vitality of such organisms is decreased, as all recessive genes are revealedin them. *Polyploidy* – increase of a haploid chromosomal complement (3n, 4n, 5n). Polyploidy is used in plant growing. It increases fruitfulness. For the human haploidy and polyploidy are lethal mutations.

Heteroploidy – is a change of the number of chromosomes indivisible by a haploid one (2n ± 1, 2n ± 2 and so on). *Trisomy*: an X– chromosome is added to a pair of sex chromosomes of a female organism, the trisomy syndrome develops (47, XXX); if it is added to sex chromosomes of a male organism, the

Kleinfelter's syndrome develops (47, XXY). *Monosomy*: absence of one chromosome in the pair –45, X0 –syndrome of Shereshevsky–Terner. *Nullisomy*: absence of a pair of homologous chromosomes (for humans, it is a lethal mutation).

Chromosomal mutations (or chromosomal aberrations) – are modifications of the structure of chromosomes (interchromosomal or intrachromosomal).

Rearrangements **inside one chromosome**: inversions, lacking (deficiency and deletion), duplications. *Deletion* is lacking of a middle part of the chromosome; *deficiency* –of a terminal end; *duplication* – doubling of a chromosom al part; *inversion* – changing of the genes arrangement order in the chromosome. In deletion of telomere parts of both arms of chromosomes one can observe locking of the remaining structure into a ring and forming of *ring chromosomes*.

Interchromosomal mutations are translocations. Translocations can be: *reciprocal* –2 chromosomes exchange with their parts; *non–reciprocal* –parts of one chromosome are relocated on the other; *Robertson's* –2 acrocentric chromosomes are linked with their centermeres.

Lacking and duplications are always revealed phenotypically, because a complement of genes changes. Phenotypical inversions and translocations are not always revealed. In these cases conjugation of homologous chromosomes becomes difficult and the distribution of genetic material between daughter cellsis impaired.

Genic mutations (point or transgenations). They are associated with changes of the structure of genes and cause the development of metabolicdiseases.

Mutations of structural genes:

1. *Bias of the reading frame* – deletion or insertion of one or several pairsof nucleotides into a DNA molecule.

2. *Transition* – is a mutation, when there occurs a replacement of a purine base for a purine or pyrimidine one for another pyrimidine (A ↔ G or C ↔ T). Such replacement results in changing codons.

3. *Transversion* – replacement of a purine base for a pyrimidine or a pyrimidine for a purine base (A ↔ C; G ↔ T) results in changing codons. Changing of structural genes results in *missense–mutations* (changing of the codons meaning). If senseless codons are formed (UAA, UAG, UGA), they cause *non– sense–mutations*. These codons do not determine amino acids but are terminators – they determine the end of information reading.

Mutations of functional genes:

1. The protein–repressor is modified and it does not suit the gene–operator. In this case structural genes are not switched off and work permanently.

2. The protein–repressor is tightly joined with the gene–operator and is not released by the inductor. Structural genes do not work permanently.

3. The impairment of alternation of the processes of repression and induction. If the inductor is absent, a specific protein is synthesized, in the presence ofthe inductor it is not synthesized. Such impairments of transcripton actions are observed in mutations of a gene–regulator or a gene–operator.

In the majority of cases genic mutations are revealed phenotypically.

7. Stability and repair of genetic material, anti–mutagens.

Anti–mutagenesis is the impact on the cell or organism, which blocks or reduces the probability of mutations occurrence. Stability of genetic material provides anti–mutagenic mechanisms.

1. **Natural barriers**: a diploid complement of chromosomes (parity of chromosomes), double DNA spiral, redundancy (degeneration) of the genetic code, iteration of some genes.

2. **Repair of the DNA structure** – is an intercellular process of an impaired DNA molecule restoration.

In 1962 K. Rupert described photoreactivation or light repair. He established that when phages, bacteria and protists are radiated by ultra–violet radiation, their vitality drops. But if they are exposed to visible light, their vitallity restores. Under the action of ultraviolet radiation dimeres are formed in a DNA molecule (chemical bonds between bases T–T of one sequence). This inhibits reading of information. Visible light activates enzymes, which destroy links of dimeres.

The most common is a **dark** or *excision* repair (A. Herren) Four groups of enzymes take part in it:

a) *endonuclease* «recognizes» an impaired part and cuts a DNA thread next to it;

b) *exonuclease* removes the impaired part;

c) *DNA polymerase* synthesizes a DNA fragment instead of a destroyed one according to a complementarity principle;

d) *lygase* links the ends of an inserted part with the main DNA thread.

The impairment of the repair process may result in the development of diseases such as *pigmental xeroderma* and *Fankoni's anemia*.

3. **The presence of anti–mutagens**. These are substances of various origin, that in small concentrations are able to stabilize a mutation process; biologically active compounds –histamine and serotonin, anti–oxidants, sulphanilamide preparations, fresh vegetable juices, α–tocopherol, which decreases the number of both genic and chromosomal mutations).

8. Biological bases of cancerogenesis

Cancerogenesis is a process of formation and development of tumors.

1. *Mutational conception* – in the basis of cancerogenesis are genomic or chromosomal mutations of somatic cells (G. de Freeze, 1901)**.**

2. *Viral*–genetic conception –viruses are causative agents of malignant growth. Mutagens and cancerogens stimulate the activity of viruses; their genomeis included into the cellular DNA and changes its properties (L. A. Zilber, 1945).

3. *Epigenomic conception* – in the basis of transformation of a normal cell into a tumor are persistent impairments of the structure of functional genes (Yu. M. Olenev, 1967, and A. Yu. Bronovitsky, 1972).

4. *Oncogen conception*. Cellular DNA contains definite parts – *proton – cogens*. They can be received from parents or introduced into the cell by a virus. Protooncogens are activated in mutations or when a viral promoter gets into the cell. They pass into an active form – oncogens, the cell transforms into a tumor (R. Hubner, 1969.; G. I. Abelev, 1975).

Basic terms and concepts:

1. Deletions – intrachromosomal mutations associated with a loss of a middle part of the chromosome.

2. Duplications – intrachromosomal mutations associated with doubling of a part of the chromosome.

3. Inversion – intrachromosomal mutations, when the gene arrangement order impairment occurs.

4. Cancerogenesis – a process of formation of tumor cells.

5. Ring chromosomes – chromosomes, which are formed during deletion of telomere parts and locking of the structure into a ring.

6. Reaction range – limits of modificatory variation.

7. «Bias of the reading frame» – a mutation variety of structural genes, when an insertion or deletion of nucleotides occurs.

8. Transitions – a mutation variety of structural genes, when a replace–ment of bases occurs: A for G or T for C.

9. Transgenations – genomic mutations.

10. Translocations – exchange of inhomologous chromosomes parts.

BIOLOGY AND GENETICS OF SEX

1. Sex as a biological character. Sexual characters.

Sex is a complex of morphological, physiological, biochemical and behavioral characters of the organism that provide the process of reproducing their own selves and transmission of genetic information from generation to generation.

Primary sexual characters – external and internal sex organs. They take a direct part in the process of reproduction, are germinated in the embryogenesis and are formed by the moment of birth.

Secondary sexual characters appear in the period of puberty. They include peculiarities of the bony–muscular system, distribution of the adipose tissue and hair covering, voice timbre, peculiarities of the nervous system and behavior and other characters.

2. Characters controlled and limited by sex.

Genes determining characters limited by sex are located in autosomes of individuals of both sexes, but are revealed only in individuals of one sex (a gene of lactation is revealed in females of the cattle; a gout gene is revealed only in men).

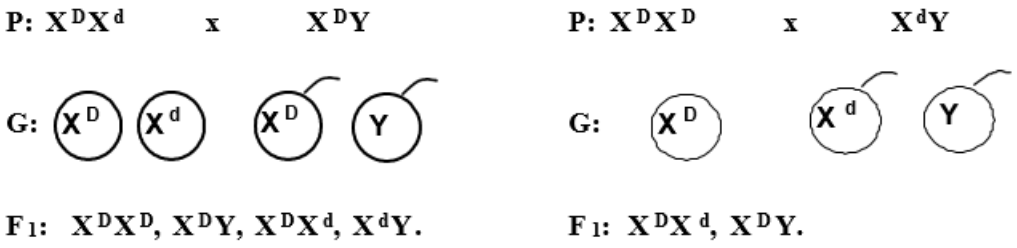
Genes determining characters *controlled by sex* are also in autosomes of individuals of both sexes, but the degree and frequency of their manifestation is different (an alopecia gene is differently revealed in men and women).

3. Characters linked with an X– chromosome and holandric ones.

Characters *linked with sex chromosomes* are divided into characters linked with an X– chromosome and holandric. Genes located in an X– chromosome non–homologous part determine characters *linked with an X– chromosome (linked with sex)*. They are about 200 (hemophilia, daltonism).They are inherited from father only to daughter and from mother both to son and daughter.

Genes located in a Y– chromosome non–homologous part determine holan–dric characters; 6 of them are described (ichthyosis, membranes between toes) they

are inherited from males and are revealed only in men.



4. Chromosomal sex theory.

The sex in majority of animals is determined at the moment of fertilization by a combination of sex chromosomes (heterochromosomes) –X and Y.

XX is a female *homogametic sex*, it forms one type of gametes; XY– is a male *heterogametic sex*, it forms two types of gametes. In this way sex of humans and animals is determined. Birds, fish, butterflies have a homogametic male sex and a heterogametic female sex. Grasshoppers and locust have a female sex XX, a male sex X0.

This theory of determination sex got the name of *chromosomal theory*.

It was proposed in 1907 by K. Korrens.

5. Peculiarities of sex determination in humans and its impairments.

In the human the *germ formation* of gonads, internal and external sex organs occurs till the 4^{th} week of embryogenesis. On the initial stage, it is provided by one X– chromosome. The primary gametes in humans can be revealed on the 3^{rd} week of the embryonic development in the ectoderm of the yolk sac.

Differentiation of germs into sex glands and sex organs in an embryo and fetus occurs from the 4^{th} to 12^{th} weeks of intrauterine development; at this stage it completely depends on the second sex chromosome. If it is an X– chromosome, primary sex cells develop into ovogonies and the whole sex system develops according to a female type. The development of primary sex germs according to a male type is determined by the presence of a Y– chromosome in the complement. Primary sex cells are differentiated in spermatogonies, forming testicles and external sex organs.

Physical sex determinants: genetic sex, gonad sex, gamete sex, hormone sex and morphological sex. *Physical (morphophysiological) determinants of sex* are common for humans and the majority of animals. **An Intermediate determinant**: civil sex. **Social–psychological determinants**: sex of brining up, sex of self– consciousness, sex role, choice of a sexual partner. *Social–psychological determinants* have a great significance in the formation of sex consciousness and ideas about sex role in the human.

Sexual chromatin.

In 1949 M. Barr and Ch. Bertram revealed in nuclei of cat's nerve cells a large *lump of chromatin*. It was revealed only in females and was absent in males. Later it was established, that it was an inactivated X– chromosome. This lump was called sex chromatin or a *Barr body*. The Barr body can be attached to a nuclear membrane, it may be freely located in the karyoplasm or present a nuclear process in nuclei of blood cells («drum sticks» in neutrophils).

6. Chromosomal sex diseases.

♂ \ ♀	X	XX	0
X	XX	XXX	X0
Y	XY	XXY	Y0
XY	XXY	XXXY	XY*
0	X0	XX*	0

1. XX and XY – a normal maleand female organism.

2. XX* – a normal female organism that got both sex chromosomes from mother.

3. XY* – a normal male organism that got both sex chromosomes from father.

4. Y0, 0 – an organism lacking vital capacity.

5. XXX – an X–trisomy syndrome. Karyotype –47, XXX. A female phenotype. Incidence frequency 1:800–1:1000. Nuclei of somatic cells have two barr bodies. Tall height. The constitution corresponds to a male type. In 75 % of cases mental retardation is marked. Secondary and primary sex characters are underdeveloped, the ovaries function is impaired. Sometimes they may have children.

6. X0 –Shereshevsky–Terner's syndrome. Karyotype –45, X0. Female phenotype. Incidence frequency 1:2000–1:3000. Nuclei of somatic cells have no Barr body. A height of an adult is 135–0145 cm. Specific characters: a short neck; a skin fold from the occiput to the shoulders, a low position of ear flaps, a low growth of hair at the occiput, changed joints of fingers and toes; 15 % have congenital defects of the heart and renal function anomalies. Ovaries and secondary sex characters are underdeveloped. Such patients are sterile. The intellect does not suffer in this syndrome. Treatment: early hormonotherapy.

7. XXY, XXXY – Klinefelter's syndrome. Karyotype –47, XXY, 48, XXXY. A male phenotype. Incidence frequency 1:400–1:500. Nuclei of somatic cells contain one or two Barr bodies. Tall height. Female type of constitution. Gynecomastia – mammary glands are enlarged. Hair covering is poorly developed, testes are underdeveloped, the process of spermatogenesis is impaired (individuals are sterile), but sex reflexes are retained. The intellect is decreased. The more are X– chromosomes in the genotype, the stronger suffers the intellect.

8. Primary, secondary and tertiary ratios of sexes.

In theory, the sex ratio at the moment of fertilization is approximately 1:1.

A real ratio of sexes differs from a theoretical one.

The *primary* sex ratio at the moment of conception is 140–150 male zygotes per every 100 female zygotes.

The *secondary* sex ratio (at the moment of birth) is ♀:♂ = 100:106. Such ratio can be explained by a greater vitality of female zygotes, homozygotenessof male zygotes (all recessive genes located on a non–homologous part of an X–chromosome, are revealed) and alienation (on proteins) for the mother's organism of a male zygote.

The *tertiary* ratio (a postnatal period): by 20 years the ratio is ♀:♂ =

100:100; by 50 years – 100:85; by 80 years –100:50. This ratio can also be explained by a greater vitality of a female organism and a greater mortality of men in the postnatal period (diseases, wars, hard physical labor, harmful habits, car crashes).

Basic terms and concepts:

1. Hermafrodism – the presence of sex characters of both sexes in one organism.

2. Holandric characters – characters determined by genes located on a non–homologous part of a Y– chromosome.

3. Characters controlled by sex – characters that appear with various frequency and degree in individuals of different sex.

4. Characters limited by sex – characters that appear only in individuals of one sex.

5. Characters linked with an X– chromosome – characters determined by genes located on a non–homologous part of an X– chromosome.

6. Klinefelter's syndrome – a chromosomal disease due to the presence of an additional X– chromosome in a male organism,

7. Morris syndrome –formation of a female phenotype in XY genotype.

8. X–trisomy syndrome – a chromosomal disease in women, when an additional X– chromosome is present.

9. Shershevsky–Terner's syndrome – a chromosomal disease in women, when one X– chromosome is absent.

10. Transsexualism – a persistent discordance of sexual self– consciousness in the human to his genetic and gonad sex (sensation of belonging to an opposite sex).

11. Physical sex determinants – morphophysiological determinants.

BASES OF HUMAN GENETICS
CLASSES I

1. Present tasks of human genetics.

Human genetics studies regularities of inheriting normal and pathologic characters, their modification under the influence of the environment. The section of **medical genetics** studies mechanisms of hereditary pathology, develops methods of diagnosis, treatment and prophylaxis of hereditary human diseases.

The tasks of medical genetics are:

1. Improvement of early diagnostic methods of hereditary diseases.
2. Wide usage of medico–genetic consulting.
3. Setting up a gene pool, development of genic therapeutic methods on the basis of genetic engineering.
4. Development of methods protecting the human gene pool.

2. The human as an object of genetic investigations.

The human as an object of genetic investigations has its peculiarities and a number of difficulties.

Peculiarities of human genetics:

1) impossibility to apply a hybridological analysis and experimentation on humans;

2) a complex karyotype –many chromosomes and linkage groups;

3) late sexual maturity, a small number of fillies in the family, slow change of generations;

4) a great variety of ecological and social conditions; impossibility tocreate identical living conditions.

Advantages of the human as a genetic object:

1) a great number of individuals in populations, the possibility of analyinge characters on vast material;

2) international co–operation of geneticists;

3) the human is better clinically studied than other objects;

4) development of special methods for overcoming difficulties during studying human genetics.

3. Clinical–genealogical methods.

A genealogic analysis was proposed by F. Halton in 1883. The **clinical–genealogical method** was developed on its basis; it is making up genealogies and analyzing the transmission mechanism of a character in a number of generations.

The method allows determining:

– a relation degree of people in one family;

– if the character is hereditary; the type of inheritance; zygosity of the members of genealogy (homozygotes or heterozygotes);

– penetration of a gene (frequency of its appearance);

– probability of revealing the character in fillies (genetic risk).

Conditional designations used in making up a genealogy, are given infig. 10.

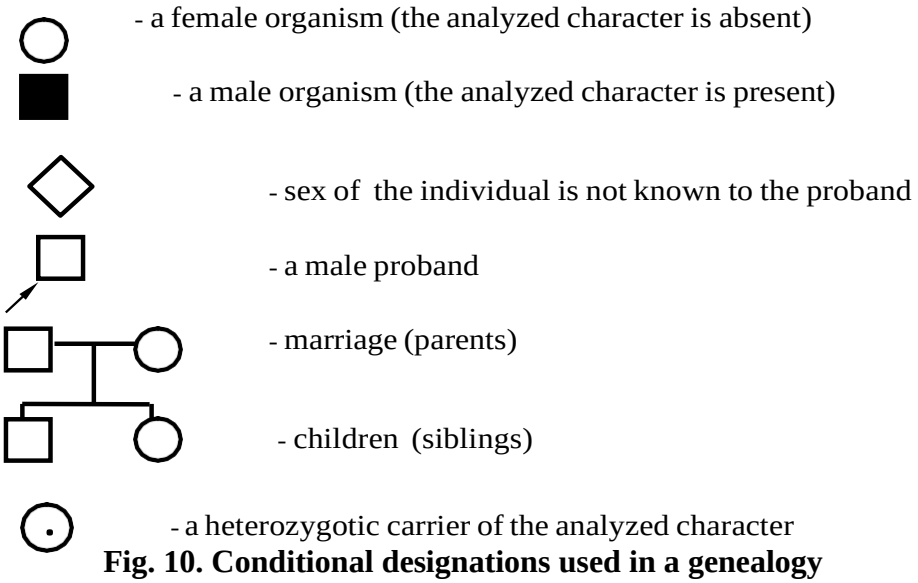


Fig. 10. Conditional designations used in a genealogy

A human, from whom a genealogy starts, is a proband and is marked with an arrow.

Genealogic analysis stages:

– taking information about relatives of the proband;

– making up a genealogy;

– analyzing the genealogy and conclusions.

Types of inheriting characters. Autosomal–dominant type of inheritance:

– both men and women fall ill in an equal degree;

– patients are in every generation;

– a sick child in sick parents;

– a probability of inheriting the character is 100 %, if one of the parents is homozygous, 75 % –if both parents are heterozygous, 50 % –if one parent is heterozygous and the other is homozygous on the recessive gene.

Autosomal–recessive type of inheritance:

– men and women fall ill in equal degree;

– patients are not in every generation;

– a sick child in healthy parents;

– a probability of inheriting the character is 25 %, if both parents are heterozygous, 50 %, if one parent is geterozygous and the other is homozygous on a recessive character, and 100 % if both parents are recessive homozygotes.

Linked with an X– chromosome dominant type of inheritance is similar to an autosomal–dominant one, except the fact that a male passes this character (with an X– chromosome) only to daughters.

Linked with an X– chromosome recessive type of inheritance:

– predominantly men fall ill;

– patients in every generation; a sick child in healthy parents

– a probability of inheriting the character is 25 % of all children; inboys – 50 %; in girls –0 %, if both parents are healthy.

Holandric type of inheritance:

– patients in all generations;

– only men fall ill;

– all sons are ill in a sick father.

4. Twin method.

In 1876 F. Halton proposed a **twin method**. The method allows determining a role of heredity and environment for revealing a character in the human. The frequency of giving birth to twins is 1 %. Twins can be *monozygous* (MT). They develop from one zygote, have an identical genotype. If the twins are *dizygous* (DT), they develop from different simultaneously fertilized ova. They have a similar but not identical as in siblings genotype.

Zygosity criteria in twins: in MT the sex, blood groups, pattern of skin coverings are always identical; in DT these factors may differ.

Similarity of twins on the studied character is called *concordance*, differences on this character –*discordance*.

To reveal a share of heredity and environment in the development ofa definite character a Holtsinge formula is used:

$$H = \frac{\text{CMT \%} - \text{CDT \%}}{100 \quad \text{\%} - \text{CDT \%}},$$

where H – a heredity share; CMT – concordance in monozygotic twins; CDT – concordance in dizygotic twins.

If H = 1,0, only heredity is responsible for the character development; if the amount of H approaches to 0 – the environment is mainly responsible for the character development.

5. Cytogenetic method.

A cytogenetic method is based on microscopic *study of the karyotype*. Lymphocytes, bony marrow cells are obtained and grown on trophic cultures. The mitotic cellular division is stimulated, stopped in the metaphase, the cells are treated with NaCl hypotonic solution, chromosomes are stained. They are studied under microscope, their pictures are taken and ideograms are analyzed. To detail a karyotype and map chromosomes a fluorescent analysis is used. The method reveals *genomic and chromosomal mutations*. Special designations are assumed to record mutations: q – a long chromosomal arm, p – a short chromosomal arm, «+» –redundancy of genetic material, «–» – insufficiency of genetic material. The record of a male karyotype with Down's syndrome –47,XY,21+.

6. Biochemical methods.

Biochemical methods are used for revealing hereditary metabolic diseases on enzyme activity or on the quantity of the final product of reaction that is catalyzed by this enzyme. Chromatographic, fluorometric, radio–immunological and other methods are used to reveal gene mutations (causes of metabolic diseases). For example, phenylketonuria – the impairment of phenylalanine exchange (PhA). Phenylketonuria can be revealed by the content of phenylalanine in blood: in healthy people it is 1–2 mg %, in sick ones –50–60 mg %. Every 30–40th person is a carrier of a phenylketonuria gene.

Heterozygosity can be revealed in injection of phenylalanine into the organism and its content in the blood is determined. If after injecting PhA the curve of its content slowly returns to its norm, a person is heterozygous ona phenylketonuria gene.

7. Methods of a recombinant DNA. The program «Human genome».

Methods of a recombinant DNA (**molecular–genetic**) allow determining a pathologic gene in the genome. Stages of the methods:

1. DNA specimen are cut by restrictases into short fragments havinga point of recognition.
2. The received fragments are separated by electrophoresis in an agar jelly into fractions differing in size (a molecular mass).
3. A needed number of copies of DNA fractions is obtained with a PCR.
4. Heat denaturation is conducted of a multiplied fraction of a double–sequenced DNA into single–sequenced fragments.
5. These fragments are placed into the culture with a radioactive probe (a single–sequenced DNA corresponding to a pathologic gene). If there is a complementary pathologic gene to the probe among these fragments, a two–sequenced DNA is formed.

6. The result is registered with an X–ray sensitive film.

In 1990 an international project on making a genetic human map (Human Genome Project) was started. The tasks of the «Human Genome» program included decoding of a nuicleotide sequence (sequencing) of a human DNA molecule. In 2000 the human genome was sequenated.

Basic terms and concepts:

1. Dizygous twins – develop from two ova fertilyzed by spermatozoa.

2. Monozygous twins – develop from one fertilized ovum.

3. Discordance – a degree of twins' difference on a studied character.

4. Concordance – a degree of twins' similarity on a studied character.

5. Proband – a person, from whom making a genealogy starts.

6. Sequencing –determination of a nucleotide sequence in the gene.

7. Genealogy – a genealogic map, where all relatives of the proband and relative ties between them are denoted by symbols.

CLASSES II

1. Modeling methods. A law of N. I. Vavilov.

Biological modeling is studying hereditary human abnormalities on animals with similar impairments (hemophilia in dogs, diabetes mellitus in rats, etc). The method is based on a law of homologous rows of N. I. Vavilov: **close genera and species have similar rows of hereditary variation. Knowing forms of variation of one species, one can presume identical forms in other species or genus**.

Mathematical modeling is used in population genetics during determination of frequency of genes and genotypes in populations under different conditions of the environment.

2. Characteristic of human populations. Types of marriage. Population is a group of species of one type having a common genotype, who are capable of free crossing, inhabit one territory for a long time and are relatively isolated from other individuals of the species.

Populations can be great and small. *Great* human populations contain over 4000 individuals. Dems and isolates – are *small populations.* The number of individuals in dems is 1500–4000 people, intergroup marriages in them compose 80–90 % and the inflow of genes from other groups is 1–2 %. *Isolates* contain up to 1500 people, intergroup marriages are over 90%, the inflow of genes from other groups is less than 1%. Marriages among relatives – in*breeding (incest marriages)* are observed in dems and isolates. There is a high probability of homozygosity in relatives on one and the same pathologic gene; manifestation of hereditary pathology is possible. Outbreeding – incongeneric marriages. They sustain a high level of heterozygosity, and hereditary pathology occurs there far more rarely.

Human populations are characterized by demographic factors: the number, birthrate, mortality rate, age and sex structure, occupation, ecologic state of the environment. The action of evolutionary selection is decreased there and destruction of isolates takes place.

3. Genetic processes in great populations. The law of Hardy–Weinberg.

Great populations are called *panmixed*, as the choice of a partner for marriage is not limited there. Great in their number populations approache to an *ideal* one, which is characterized by a great number, isolation from other populations of the species; complete panmixing; absence of mutations and evolutionary selection.

The law of Hardy–Weinberg: In an ideal population frequencies of genes and genotypes are in equilibrium and do not change in a number of generations.

Great populations are characterized by genetic polymorphism (AA, Aa ona definite character) and panmixia. Nine variants of marriages are possible undersuch conditions (taking into account genotypes):

Genetic records of marriages and fillies:

1. AA x AA → AA.
2. AA x Aa → AA + Aa.
3. AA x aa → Aa.
4. Aa x AA → AA + Aa.
5. Aa x Aa → AA + 2Aa + aa.
6. Aa x aa → Aa + aa.
7. aa x AA → Aa.
8. aa x Aa → Aa + aa.
9. aa x aa → aa.

m \ f	AA	Aa	aa
AA	1	4	7
Aa	2	5	8
aa	3	6	9

Summary: 4AA + 8Aa + 4aa or AA + 2Aa + aa

If one denotes genes frequencies as A–**p**, a–**q**, of genotypes as AA–$\mathbf{p^2}$, Aa–**2pq**, aa–$\mathbf{q^2}$, we'll get the following record: $\mathbf{p + q = 1}$ and $\mathbf{p^2 + 2pq + q^2 = 1}$.

4. Genetic processes in small populations.

There appears a **genes drift** – in**cidental fluctuations of genes frequencies**. It is the accumulation of homozygotes of homozygous individuals. In the first generation (AA + 2Aa + aa) heterozygotes comprise 50 %, in F_2 their number will be 25 %, in F_3 –12,5 %, etc. When lethal genes are present, the population comes to extinction due to homozygotization. Evolution in small populations is impossible, there is no genetic diversity.

Mutation process – is an incidental and undirected process. It sustainsa high degree of heterogeneity of populations. Mutations can be neutral, negativeor positive for the organism. When the environmental conditions change, neutral mutations can become positive or negative. Mutation frequency of a gene is 10^{-5}–10^{-7} per generation. Dominant mutations are revealed already in the first generation and are immediately exposed to evolutionary selection. At first reces sive mutations accumulate in the population and are revealed phenotypically only after the appearance of recessive homozygotes, then evolutionary selection affects them. Mutations present an **elementary evolutionary material**.

Population waves or life waves – are periodical fluctuations of the number of natural populations due to fluctuations of environmental factors. Population waves change the genetic structure of populations removing the least adapted individuals from them.

Isolation – is a limitation of free crossing. It leads to separation of the population into separate groups and changing the genotype frequency. Types of isolation:

1. Geographic or territorial (mountain ridges, rivers).

2. Biological:

– genetic or hybrids sterility;

– ecologoetological (unlikeness to meet a partner);

– morphophysiological or impossibility to cross due to morphological differences of sex organs.

Migration of the population may increase heterozygosity in human populations. *Immigration* introduces new alleles or new genotype combinations into the population. *Emigration* changes the ratio of different genotypes in the population due to the «outflow» of genes.

Evolutionary selection is the most important evolutionary factor. It removes less favorable combinations of genes from the population and selectively preserves more favorable genotypes changing genes frequency in populations. Three forms of evolutionary selection are distinguished – stabilizing, moving and disrupting.

5. Genetic load and its biological nature.

Saturation of populations with recessive mutations reducing adaptability of separate individuals to the environment, is called a *genetic load* of the population. A part of genetic load is passed from generation to generation (heterozygous carriage of pathologic recessive genes), other mutations arise in every new generation under the effect of mutagenic factors. The amount of genetic load is proportional to the contamination degree of the environment (5 %).

6. Methods of prenatal diagnosis of hereditary diseases.

Indirect methods of prenatal (before birth) diagnosis – examination of a pregnant woman (obstetric–gynecological, genealogical, biochemical) and *direct* methods – examination of the fetus.

α–Phetoprotein (APP) – is an embryo–specific protein; it is produced by fetal cells and the placenta and passes into the mother's blood. Reducing of *α–phetoprotein* at the 13–15th weeks of embryonic development is characteristic of chromosomal diseases. Its concentration is elevated in a threatening miscarriage, intrauterine death of the fetus, plural pregnancy, nerve tube defects, congenital nephrosis.

Ultrasonography is referred to *direct non– invasive methods* (without tissues injury), it is the usage of super sound for obtaining an image of the fetus and its membranes. It is used for all pregnant women, because it is safe for the fetus and can be repeated. This method reveals vitality of the fetus, twin pregnancy and severe development defects of the brain and spinal cord and the skeleton.

Indications for diagnosis using *direct invasive methods*:

– the presence of a hereditary disease in the family;

– mother's age over 37 years; presence of an X–linked recessive disease in the mother;

– presence of spontaneous abortions in women at early stages of pregnancy, cases of still births, children with multiple development defects and chromo–somal pathology;

– heterozygosity of both parents, having one pair of genes each with an autosomal–recessive type of inheritance.

Direct invasive methods (with tissue injury):

1. Chorion–biopcy –taking chorion cilia through the uterine cervical canal for cytogenetic and biochemical investigations and DNA analysis. It is performed under control of ultrasonography at the 8–13 th weeks of gestation. The method allows revealing genic, chromosomal and genome mutations.

2. Amniocentesis. At the 15–17th weeks under control of ultrasonography a puncture of the amniotic sac is made through the abdominal wall and 15–20 ml of amniotic fluid with fetal cells are taken with a syringe for diagnosis of various hereditary diseases. Complications in this method arise in 1 % of cases.

7. Express–methods.

Express–methods are methods of fast preliminary diagnosis of human hereditary diseases. These methods must be economic, safe and diagnostically significant; the material for investigation should be in small amounts and be easily accessible (blood, urine).

Gatry's microbiological test. A drop of blood of the newborn is put on blotting paper and put on the agar culture of bacteria containing anti–metabolite of phenylalanine. The anti–metabolite inhibits bacterial growth. But if the blood contains a lot of phenylalanine, anti–metabolite is destroyed, and microbes start their growth.

Determination of X– and Y–sex chromatin – the cheek epithelial cells or leukocytes are investigated. X– chromatin is determined during acetorceine staining, and Y– chromatin – with acrichine–yperite. A genetic sex is determined, chromosomal diseases of sex are diagnosed.

Biochemical and chemical (colored reactions) methods are used for fast preliminary diagnosis of hereditary metabolic diseases (10 % $FeCl_3$ solution for diagnosing phenylketonuria).

Dermatoglyphic analysis is a study of patterns on the skin of fingers, palms and feet. Dermatoglyphic patterns are very individual and do not change during life. There are patterns of three types on finger tips: an arch (A), (L) a loop and winding (W). There are tri–radii in interfinger spaces: a, b, c and d.

Near the bracelet fold is a palm tri–radius t. If one connects tri–radii a, d, t, we'll get a main palm angle; in norm it is not more than 57 %. The combination of radial loops on 4–5th fingers, amounts of the main palm angle of 60–86° and a four–finger furrow (it forms on fusion of an oblique and transverse line) allows suggesting a hereditary disease.

Basic terms and concepts:

1. Amniocentesis – a method of prenatal diagnosis: taking of amniotic fluid with fetal cells for biochemical and cytogenetic investigations.

2. α–Phetoprotein – is protein contained in amniotic fluid and blood serum of a pregnant woman.

3. Dems – are populations of people containing 1500–4000 individuals.

4. Drift of genes – incidental fluctuations of genes frequencies in small populations.

5. Panmixia – absence of limitations in choosing of a partner for marriage.

6. Population – a group of individuals of one species inhabiting the given territory, freely crossing with each other and isolated from other groups of indi viduals of this species.

7. Gatry's test – a preliminary method for diagnosis of phenylketonuria in neonates.

8. Ultrasonography – a diagnostic method using ultrasound for obtaining an image of the fetus and its membranes.

9. Chorion–biopcy – a method of prenatal diagnosis –taking of chorion cilia epithelium for cytogenetic and biochemical investigations and DNA analysis.

HUMAN GENETIC AND CHROMOSOMAL DISEASES

1. Genic mutations as a cause of metabolic diseases.

Genic mutations are revealed phenotypically in the human as hereditary metabolic diseases – *fermentopathies*. About 3000 such diseases are described. Their frequency in human populations is from 2 to 4 %.

Genic diseases may have the following causes:

1) mutations of structural genes –qualitative changes of proteins are observed, *abnormal proteins* are formed (for example, mutant forms of hemoglobin);

2) mutations of functional genes – the content of normal protein in the cell decreases, its *quantitative* changes occur.

Substances, which accumulate in the impairment of enzyme activity, may produce a toxic action or cause definite impairments of the structure and function of cells.

2. Characteristic of genic human diseases. Genic diseases are classified according to a character of metabolic impairment.

Impairments of amino acid exchange. Phenylketonuria is inherited on autosomal–recessive type. Its frequency is 1:10 000. The enzyme activity of phenylalaninehydroxilase is impaired. Phenylalanine does not transform into tyrosine and the phenylpyroacemic acid (PhPAA) forms; it is a poison for nervous cells.

Symptoms: «mice» smell, progressing mental retardation, increased excitation and muscular tone, hyperreflexia, tremor, convulsive epileptic attacks, weakpigmentation of the skin.

Diagnosis: Gatry's test, an express–method with $FeCl_3$, biochemical methods (determination of PhPAA in the urine and of phenylalanine in the blood).

Treatment: diet– therapy (food without phenylalanine from the first weeks of life till 7–10 years).

Albinism develops in the absence of the *thyrosinase* enzyme. The *melanin* pigment does not form. Incidence frequency is 1:5000–1:25 000. Autosomal–recessive type of inheritance.

Symptoms: depigmentation of the skin, hair, eyes, photophobia, decreased sharpness of vision, increased sensitivity to UV rays, inflammatory diseases of the skin develop.

Diagnosis – clinical examination. Treatment is not elaborated.

Impairment of carbohydrate exchange. Galactosemia. Incidence frequency 1:100 000. Autosomal–recessive type of inheritance. The disease is caused by insufficiency of the enzyme, galactoso–1–phosphaturidiltranspherase, which participates in metabolism of galactose.

Symptoms: hepatomegaly, jaundice, vomiting, diarrhea, retardation of psychic–motor development, cataract.

Diagnosis: a decreased content of glucose is revealed in the blood, the con–tent of protein and galactose is increased in urine.

Treatment: exclusion of lactose from the food of a newborn.

Impairment of lipid exchange. Hyperlipoproteinnemia is caused by the impairment of lipid exchange in the blood plasm (fatty acids, triglycerids, cholesterol) due to a defect of enzymes or cellular receptors. Incidence frequency of the disease 1:500. The type of inheritance is autosomal–dominant.

Symptoms: an increased level of cholesterol results in the development of artherosclerosis, ischemic heart disease, early myocardial infarctions (33–45 years).

Diagnosis: determination of lipoproteins in the blood serum.

Impairment of purines exchange. Lesch–Nyhan's syndrome. Incidence frequency is 1:300 000. A recessive, linked with an X– chromosome syndrome. The disease is caused by insufficiency of the enzyme that catalyzes the attachment of purine bases to nucleotides, and they break down to the uric acid.

Symptoms: hypertone of muscles, olygophreny, inclination of the child to self–injuries, urinary calculi, deposits of the uric acid in joints.

Diagnosis: determination of the uric acid in the blood.

Impairment of mineral exchange. The disease of Wilson–Konovalov: incidence frequency 2:100 000. The type of inheritance is autosomal–recessive. The cause of the disease – insufficiency of the enzyme resulting in the impairment of cerulloplasmine synthesis, which provides copper transport. Copper concentration in the blood increases and it accumulates in the brain tissue and liver. The disease is revealed at school age.

Symptoms: hepatomegaly, jaundice, vomiting, cirrhosis of the liver, impairment of intellect, tremor, impairment of swallowing, muscular hypertone.

Diagnosis: determination of cerulloplasmine concentration in the blood serum.

Impairment of coagulation mechanisms. Hemophilia A: incidence frequency is 1:6500 of newborn boys. The type of inheritance is recessive linked with an X– chromosome. Cause of the disease: decrease of the activity of coagulation factor VIII (anti–hemophilic globulin A). The disease is revealed on the 2–3 year of life, sometimes – on birth (by bleeding from the umbilical cord and intracutaneous hemorrhages). Symptoms: hemorrhages, a hematome type of bleeding, hemarthroses (hemorrhages into a knee, elbow, mortis joint), gliding joints, blood in urine.

Diagnosis: determination of coagulation factor VIII of the blood. Treatment: injection of coagulation factor and exchange transfusion. **Impairment of the hemoglobin molecule structure (hemoglobinopathies).**

Crescent cell anemia (HbS): in position 6 of a β – chain of hemoglobin the glutamine acid is replaced with valline. In hemozygotes on a mutant type erythrocytes take a sickle–like shape, there develops chronic hypoxia and anemia, hemolysis and breaking down of erythrocytes (a lethal outcome is possible). He terozygous carriers of a HbS gene are healthy under usual conditions.

To diagnose genic diseases biochemical methods are used and methods ofa recombinant DNA.

3. Chromosomal and genome mutations as a cause of chromosomal human diseases.

Chromosomal diseases are the result of chromosomal and genome mutations. Frequency is 0,24–0,4 %. About 90 % of chromosomal diseases are autosomal trisomies. Polyploidy, haploidy, trisomy on large chromosomes and all monosomies (except an X–monosomy) are lethal for the human. Diagnosis of chromosomal diseases is made after studying with cytogenetic methods. The most common are trisomies on the 13 st, 18 st, 21st pairs of chromosomes.

4. Characteristic of chromosomal human diseases.

Patau's syndrome (47, XX, 13+; 47, XY, 13+). Frequency is 1:6000. There are 2 cytogenetic variants: trisomy and Robert's translocation. Minimum diagnostic signs: microcephaly, polydactyly, a short neck, narrow eye slits, a sunken nose–bridge, a two–lateral cleft of the upper lip and palate, microphthalmia, deformed ear flaps. Children are born with the body mass under the norm (2500 g). In 80 % of newborns are heart defects, 65 % – abnormalities of the brain, 60 % – abnormalities of the kidneys, 50 % –defects of digestive organs. 95 % die before 1 year.

Edward's syndrome (47, XX, 18+; 47, XY, 18+) occurs with frequency of 1:7000. For women older 45 years the risk to give birth to a sick child is 0,7 %. A cytogenetic syndrome is presented by trisomy, rarely mosaic forms occur and a translocation form is an exclusion. Minimum diagnostic signs: reduced weight at birth (on an average 2100 g), abnormalities of the cranial and facial parts of the skull (step–like falling back of frontal bones in the region of the fon– tanel, the lower jaw and mouth opening are small, eye slits are narrow and short, ear flaps are deformed), a «rocking foot», defects of the heart and large vessels. Life span – 60 % of children die before the age of three months.

Down's syndrome (47, XX, 21+; 47, XY, 21+) is the most common chromosomal pathology – 1:750. Such children are more often born by mothers of 41–46 years, the probability to give birth to a sick child increases in them to 4,1 %. Cytogenetic forms: trisomy, a translocation form or mosaicism. Minimum diagnostic signs: mental retardation, muscular hypotony, a flat face, short neck, epicanthus, mongoloid eyes, thick lips, thickened tongue protruding from the mouth, defects of the cardio–vascular system and digestive organs. Life span is about 36 years.

«Cat's cry» syndrome (5p–) is due to a deletion of a short arm of the 5th chromosome. Population frequency – 1:45 000. Minimum diagnostic signs: a specific cry («cat's cry»), physical underdevelopment, mental retardation, microcephaly, a moon–like face, a broad nose–bridge, a short neck, strabismus, low–positioned ear flaps, bite abnormalities, muscular hypotony. Life span is reduced: only 14 % of patients live over 10 years.

Basic terms and concepts:

1. Hemophilia – a disease associated with blood coagulation impairment.

2. Microphthalmia –reduced sizes of the eye–ball.

3. Microcephaly –reduced sizes of the brain.

4. Monosomy – absence of one chromosome from a pair in the karyotype,a variety of aneuploidy.

5. Syndactylly – atresia of finger phalanges.

6. Trisomy – a 3rd chromosome in a pair of homologous chromosomes.

7. Fermentopathy – hereditary metabolic diseases due to the impairmentof synthesis and function of enzymes.

8. Chromosomal diseases – complexes of congenital defects caused bythe impairment of the structure and number of chromosomes.

9. Cerulloplasmia – the protein providing copper transport in the organism.

10. Epicanthus – a 3rd lid.

MEDICAL–GENETIC CONSULTATION

1. The aim and tasks of medical–genetic consulting.

Medico–genetic consulting is a compulsory component of prenatal prophy laxis of congenital defects and hereditary diseases.

The aim of medico–genetic consulting is the establishment of a genetic risk degree in the examined family and explanation of the medico–genetic conclusionto spouses.

Tasks of medico–genetic consulting:

– consulting of families and patients with hereditary pathology;

– prenatal diagnosis of congenital defects and hereditary diseases;

– assistance to doctors of various specialties in making a diagnosis, if genetic investigation methods are necessary;

– introduction of a territorial register of families and patients with hereditary and congenital pathology and their following–up;

– popularization of medical–genetic knowledge among the population.

2. Characteristic of the genetic prognosis stages.

1. *Determination of a genetic risk degree. Genetic risk* is a probability of appearing a hereditary pathology in fillies. There is a low risk degree – up to5 %, an inconsiderably increased one – to 10 %, a moderate degree –to 20 % and a high risk degree – over 20 %. Depending on severity of medical and social consequences of this pathology, a moderate, increased and high risk degree is an indication for pregnancy interruption (medical abortion).

2. *Assessment of the severity of social consequences of the anomaly.* A risk degree not always corresponds to a severity of the expected disease. For example, polydactylism (a genetic risk degree is not less than 50 %) can be easily eliminated by a surgery. Phenylketonuria (a genetic risk degree is 25 %) is a severe disease and is hardly cured. The severity degree of this disease on social and medical consequences for the patient and his family is considered to be severe.

3. Application of prenatal diagnosis methods.

The decision concerning pregnancy interruption is taken by the spouses.

The doctor only gives his recommendations.

4. Indications for referring a family couple to a medical–genetic consultation:

– the presence of similar hereditary pathology in some members of the family;

– sterility and a miscarriage in primary pregnancy;

– mental and physical retardation of the child;

– having the 1st child with development defects;

– primary amenorrhea (absence of periods) in underdevelopment of secondary sex characters;

– a contact of spouses with mutagenic factors;

– blood relationship of the spouses.

3. Treatment principles of hereditary human pathology.

At present the following approaches to treatment of hereditary diseases and diseases with hereditary predisposition are marked out.

1. **Symptomatic treatment**, when in all hereditary diseases separate symptoms are treated with medicines: antibiotics in inflammatory processes, pain killers – in pains, sedatives – in states of excitation.

Surgical treatment is often used in congenital defects: in stenosis of vessels and atresia, in polydactylism, heart defects, defects of the facial part of the skull.

2. **Pathogenic treatment** (in metabolic diseases):

– *exchange correction* –diet therapy in phenylketonuria and galactosemia);

– metabolic inhibition –synthesis suppression of the product, which is not excreted from the organism (uric acid in the Lesch–Nyhan's syndrome);

– replacement therapy – injection of the product not produced in the organism (growth hormone in dwarfism, insulin in diabetes mellitus).

– Etiological treatment – elimination of the cause of the disease. A most perspective method is the possibility to replace mutation genes using genetic engineering methods.

Genic therapy:

1. Using antisense olygonucleotides (ASOG). They are short nucleotide sequences, complement to fragments of mRNA or nuclear DNA.

Linking with a target (promoter or mRNA), ASOG blocks synthesis of apathologic protein.

2. Application of ribosimes –polyribonucleotides having enzyme (ribonuclease) activity. The presence of a specific nucleotide activity in ribosimes allows inserting nucleotides in them, complementary mRNA of viruses and

destroying them.

3. Implanting genes into a nuclear DNA of somatic cells for treating tumor diseases (the patients are injected their own tumor cells with genes of tumor necrosis or with genes of interleukins activating lymphocytes and macrophages).

Basic terms and concepts:

1. Genetic risk of a light degree – the probability of appearing a hereditary pathology in fillies is up to 10 %.

2. Genetic risk of a moderate degree – the probability of appearing a hereditary pathology in fillies is up to 20 %.

3. Genetic risk of a high degree – the probability of appearing a hereditary pathology in fillies is over 20 %.

4. Diet therapy – treatment with the help of a diet.

5. Metabolic inhibition – synthesis suppression of the product not excreted from the organism.

6. Genic therapy – treatment using genetic engineering methods

7. Replacement therapy – injection of hormones and enzymes not produced in the organism.

8. Pathogenic therapy – is used in metabolic diseases for correction of metabolic impairments.

9. Symptomatic therapy – treatment of separate symptoms (signs) of a hereditary disease or a congenital development defect.

10. Etiological therapy – treatment for elimination of the cause of the disease.

REPRODUCTION OF ORGANISMS

1. Forms of reproduction, their characteristic.

Reproduction is a universal organism property of all living things, which provides reproduction of their own selves and is based on transmission of genetic information from generation to generation.

Replication on a *molecular leve*l is a DNA replication, on a *subcellular level* – doubling of some organoids, on a *cellular one* – amitosis, mitosis. Cellular division is the basis of *organisms' reproduction*.

Forms of reproducing organisms. The characteristic of asexual reproduction: 1 parental individual takes part in reproduction; somatic cells are a source of genetic information; genotypes of daughter cells are identical to parental ones; the number of individuals grows fast; it ensures the species existence in unchanging environmental conditions (fig. 11).

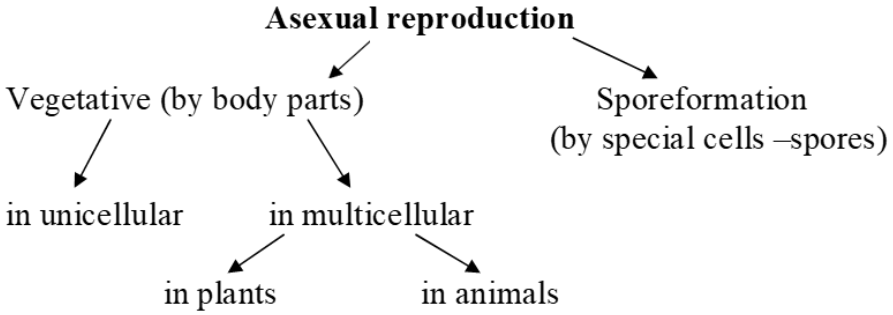


Fig. 11. Asexual reproduction

***Vegetative reproduction of unicellular organisms*:**

a) *division into two* (longitudinal division – in euglenas, transverse – in infusorians);

b) *schizogony* – is *a* multiple division – at first the nucleus is divided in–to multiple parts, then the cytoplasm (in a malaria plasmodium);

c) *budding* – a bud forms on the mother's cell, it grows and separates from the mother's individual (yeast, sucking infusorians).

***Vegetative reproduction in multicellular organisms*:**

A. *In plants* – by vegetative organs: the root, stem, leaves.

B. *Animals*:

a) *budding* (hydra);

b) *fragmentation* – division of the body by constrictions into several parts (cilia and ring worms);

c) *polyembryony* – division of the germ into several parts, each forming an integral organism (suckers).

***Sporeformation**:* in special organs (sporogonies) spores are formed, they give start to a new organism (water–plants, mushrooms, mosses, lycopodium, horse–tail, ferns).

Characteristic of sexual reproduction: 2 parental individuals take part in reproduction; parental sex cells are a source of genetic information; genotypesof daughter cells differ from the parental ones due to combinative variation; it promotes the adaptability of organisms to changing environmental conditions (fig. 12).

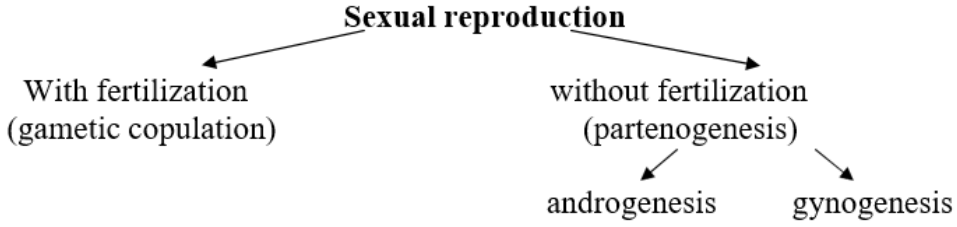


Fig. 12. Sexual reproduction

2. Evolution of the sexual process.

A sexual process is the bases of sexual reproduction. *Conjugation* is exchange of genetic information between unicellular organisms. *Copulation* is joining the genetic information of two cells. The increase of the number of

individuals is not observed in the sexual process.

Conjugation is characteristic for infusorians and bacteria. During conjugation infusorians are linked with a plasmatic bridge and exchange micronucleus parts. Then they diverge and multiply in asexual way. At a definite period of their life cycle the organisms of protists perform a function of gametes. They fuse (the copulation occurs) and then multiply by division.

The copulation in sexual reproduction is called *gametic*.

3. Gametes structure.

Ova have a rounded or oval shape from 60 μm to some cm in diameter. They are immovable, contain organoids and a store of nutrients (yolk). Their cytoplasm is species–specific. Ova are covered with membranes, in mammals – also with follicular epithelial cells.

Types of ova:

– *isolecital* – there is a small amount of yolk, it is evenly distributed (the Lancelet, mammals);

– *sharply telolecital* – there is a lot of yolk, it is located on the vegetative pole, and both the cytoplasm and the nucleus are on the animal pole (reptiles, birds);

– *moderately telolecital* – in fish and amphibians;

– *centrolecital* – there is little amount of yolk, it is in the center (insects).

A **spermatozoon** consists of a head, neck and tail. The sizes of a human spermatozoon are 52–70 μm. There is an *acrosome*, a modified Golgi's complex, at the end of the head. It provides the permeation of a spermatozoon into the ovum. The main part of the head is occupied by the nucleus surrounded by a thin layer of cytoplasm. There is a centrosome and a spiral thread consisting of mitochondria producing energy for movements of the tail in the neck.

4. Gametogenesis (oogenesis and spermatogenesis).

Depending on the presence and functioning of sex glands in the organism there are hermaphrodites and organisms with separate sexes.

The hermaphrodite is an organism having both male and female gonads forming both spermatozoa and ova. Such hermaphrodism occurs in flat and ring worms. It is a *true* hermaphrodism. In case of a *false* hermaphrodism, sex organs and secondary characters of both sexes develop in one individual and gonads are of one sex (male or female). The human may have a false hermaphrodism.

Organisms with separate sexes have either female or male gonads. Males and females are characterized by the characters of **sexual dimorphism**: differences in body sizes, coloration, structure, voice specificities, behavior and other characters. *The characters of sexual dimorphism in the human are* peculiarities of the bony–muscular system: distribution of subdermal adipose cellular tissue; the degree of hair covering development; voice timbre; peculiarities of behavior, etc.

The process of ova formation is oogenesis, that of spermatozoa – *spermatogenesis*. In gametogenesis, haploid gametes are formed from diploid somatic cells of sex glands (fig. 13).

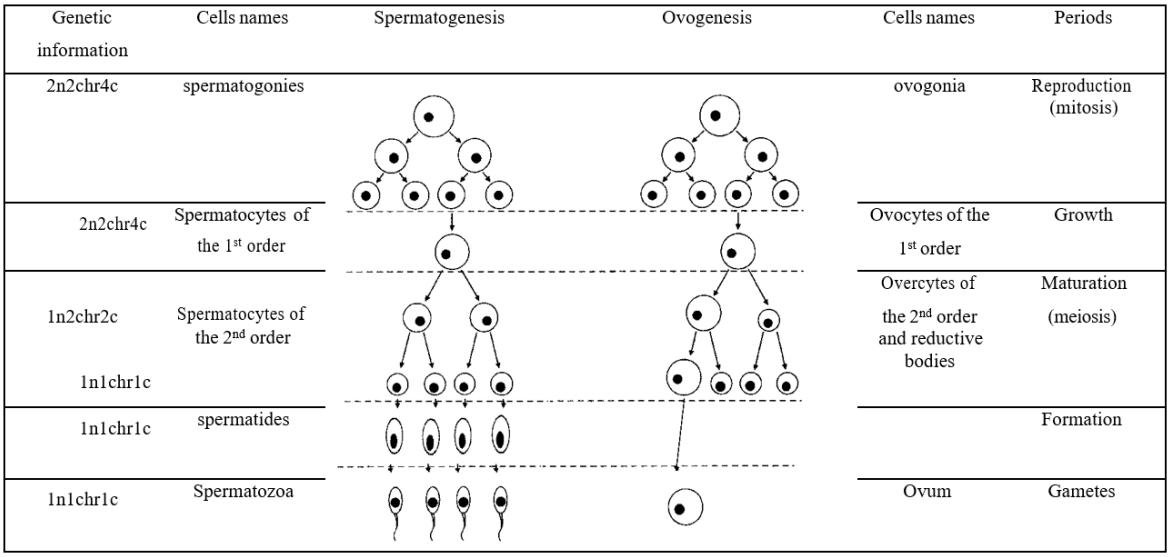


Fig. 13. Gametogenesis

Peculiarities of human gametogenesis:

1. Mitotic division of oogonies is completed before birth of the organism. Mitosis of spermatogonies starts with puberty.

2. A growth zone is clearly marked during oogenesis.

3. In oogenesis the 1st division of mitosis stops at the prophase diakinesis stage before puberty. The 2nd division of meiosis stops at the metaphase stage and completes after fertilization.

4. There is no zone of formation in oogenesis, in spermatogenesis the formation zone is clearly marked.

5. A newborn girl has about 30 000 oocytes in her ovaries, of them only 300–400 reach their maturity (about 13 cells a year).

6. During the period of sexual life a male organism produces up to 500 billion spermatozoa.

5. Insemination, its forms. Fertilization and its stages.

A number of processes that provide a contact of female and male gametesis **insemination**. Water animals have an *external insemination*: gametes are excreted into the water, where their fusion occurs.

In an *internal insemination* (in ground animals), male gametes are injected into the sexual ways of a female during an intercourse.

The insemination process is followed by fertilization: fusion of gametes with a zygote formation. A contact of gametes is provided by:

– opposite charges of gametes;

– movement of spermatozoa and wall contraction of female sexual ways;

– excretion of gammons by an ovum, to which spermatozoa have a positive chemotaxis.

An external stage of fertilization – is permeation of a spermatozoon intoan ovum. During the contact with the ovum a spermatozoon acrosomal membrane is destroyed and the enzyme *hyaluronidase* is excreted.

The enzyme dissolves the ovum membrane, an acrosomal thread is thrown

from the acrosome; it permeates through egg membranes and fuses with the ovum membrane. A *receiving protuberance* is formed in this part of the ovum; it catches and carries the head and centriole of the spermatozoon into the ovum cytoplasm. The ovum can be permeated by one spermatozoon (in mammals), then it is *monospermy*.

If several spermatozoa enter the ovum (in insects, fish and birds), it is *polyspermy*. After spermatozoon permeation a fertilization membrane forms on the surface of the ovum and other spermatozoa can not get inside.

Syncaryogamy is associated with an **internal stage**; it is fusion of gametes haploid nuclei and formation of a diploid nucleus of a zygote.

A *male pronucleus* (spermatozoon nucleus) enlarges to the sizes of a female pronucleus (ovum nucleus), turns by 180 ^{o} and moves to a *female pronucleus* with its centrosome. The pronuclei fuse, a diploid chromosomal complement restores and a zygote forms.

A special form of reproduction is **partenogenesis**, the development of organisms from unfertilized ova. A *natural partenogenesis* occurs in lower cancroids, bees, butterflies, rock lizards. Nuclei of somatic cells in such individuals can be haploid. A diploid complement restores in fusion of the ovum nucleus with the nucleus of the directing body.

6. Biological peculiarities of human reproduction.

Peculiarities are:

1. The human is not only biological but also a social being.

2. The ability for reproduction appears with puberty. Its signs are first periods in girls (on an average from 12–15 years) and pollutions in boys (from 13–16 years).

3. The duration of the reproductive period in women is to 40–45 years,in men –to an old age (gamete production by the testes occurs during the whole life).

4. During one intercourse about 200 million of spermatozoa are excreted with the semen fluid.

5. On coming puberty one oocyte of the 2nd order is formed once a moon month.

6. Fertilization occurs in upper parts of the uterine tubes, usually duringthe first 12 hours after ovulation.

7. Spermatozoa retain their ability for fertilization during 1–2 days after getting into the female sexual ways.

8. Human reproduction, unlike that of animals, is not seasonal. It depends on a number of social–economic factors.

9. The human can regulate birthrate.

Basic terms and concepts:

1. Acrosome – is a modified Golgi's complex of a spermatozoon.

2. Conjugation – a sexual process, when exchange of genetic information between two cells occurs.

3. Copulation – is a sexual process, when joining of genetic information of two individuals occurs.

4. Oogamy – is a form of copulation with a strict differentiation of gametes: a large and immovable ovum and a small and movable spermatozoon.

5. Oogenesis – is a process of development of maturation of ova.

6. Insemination – are processes ensuring gametes contact.

7. Fertilization – is fusing of an ovum and a spermatozoon with further formation of a zygote.

8. Partenogenesis – is sexual reproduction without fertilization.

9. Sexual process – is exchange of genetic information between two cells or joining the genetic information of two cells; increase of the number of individuals is not observed.

10. Syncarion – is a nucleus of a zygote formed as a result of fusion of gametic nuclei.

11. Spermatogenesis – is a process of spermatozoa development.

BASES OF ONTOGENESIS (EMBRYONIC DEVELOPMENT)

1. Ontogenesis, its types, division into periods.

Ontogenesis – is individual development of the organism from a zygote formation to its death.

Division of ontogenesis into periods (fig. 14).

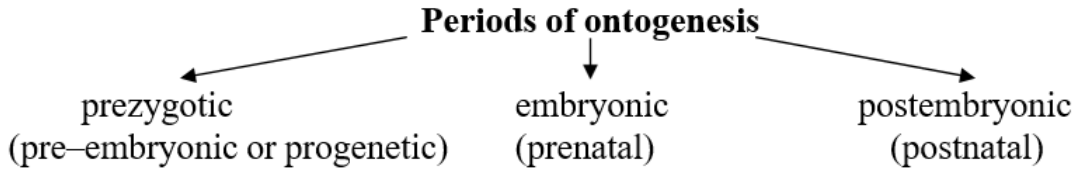


Fig. 14. Periods of ontogenesis

The pre–zygote period – is a period of formation and maturation of those parental sex cells that will form a zygote in future.

The embryonic or prenatal period starts with the moment of a zygote formation and ends with birth of a new organism or its leaving egg membranes.

The post–embryonic or post–natal period – lasts from birth of an organ ism or its leaving egg membranes and to death.

2. Characteristic of pro–genesis.

Pro–genesis of a female sex cell, that is a basis for a zygote formation, starts in the embryonic period of the mother's organism; that is why the older is the woman, the longer is this period. Usually its length coincides with the mother's age. Pro–genesis of a spermatozoon, that will be a basis for a zygote formation, is about 70 days. The quality of gametes, the presence of two mutant genes there produce a considerable effect on health of future fillies.

3. Division of the human embryonic development into periods. Embryogenesis of the human includes:

1. Germinative or initial period – the 1st week after fertilization, a zygoteis being split.

2. Embryonic period – the 2nd–3rd weeks after fertilization, a blastule anda gastrule are formed, germinal layers and axial organs are being germinated.

3. Pre–fetal period – the 4–8th weeks, formation of germs of all organ sys tems and the placenta.

4. Fetal period –from the 9th week an embryo is called a fetus; growth ofthe fetus is going on, its organs and organ systems are being formed.

4. Characteristic of embryogenesis stages. Provisional organs.

Zygote is a unicellular development stage of a multicellular organism; it was formed on fusion of a male and female gamete.

The type of **splitting a zygote** is determined by an ovum type that depends on the amount of nutrients (yolk) and their distribution. Cells that are formed in splitting are *blastomeres*. The process of splitting a germ in some animals reminds a raspberry (**morula**). Blastomeres of the morula are located on the periphery in one layer and form a **blastula** – a one–layer germ with a cavity inside. This layer of cells is called *blastoderma*. The cavity of the blastula is a *blastocele*.

The blastula stage is followed by **gastrullation** – formation of a gastrula, a two–layer germ. The cell layers of the gastrula got the name of germinal layers. There are 4 types of gastrulation (fig. 15).

Invagination – is drawing in: the vegetative pole of the blastula is drawn inside, taking place under the animal pole. A 2–layer germ is formed: an external layer got the name of *ectoderm*, an internal one –*entoderm*. The gastrula cavityis called gastrocele or a primary intestine. Entrance to the intestine is a primary mouth or a blastopore. Its edges form an upper and lower lip of the blastopore. In secondary–mouthed (echinodermata and chordates) it becomes an anal opening and the mouth is formed on the opposite end of the germ.

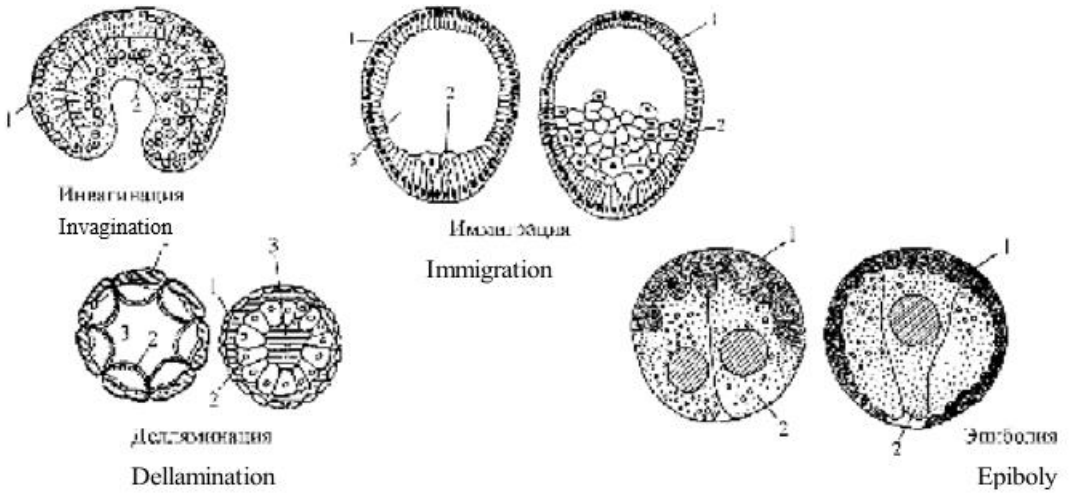


Fig. 15. Ways of gastrulation:
1 –ectoderm; 2 –entoderm; 3 –gastrocele

Immigration – is «eviction» of some cells into the germ's cavity and for mation of a second layer there – entoderm.

Epiboly – over–growing: the animal pole cells are divided faster than the vegetative pole cells that become the endoderm.

Delamination – splitting: all cells of one germinal layer are divided parallel to its surface and form 2 layers – the ectoderm and endoderm.

Gastrulation in the human goes on a mixed type –some of its forms combine simultaneously.

All animals (except sponges and coelenterate) have three layers. Germination of the 3rd germinal layer, **mesoderm**, occurs in two ways: *teloblastic* and *enterocelic*. The *teloblastic way* is characteristic of invertebrates. There forms one large cell, a *teloblast*, on both sides of the intestine near the blastopore. They start dividing; small cells take place between the ectoderm and entoderm and form the mesoderm. The *enterocelic way* is characteristic for chordates. There are formed bulges, *pockets* (celomic sacs) on two sides of the primary intestine. They become separated from the primary intestine, over–grow between the ectoderm and entoderm and give start to the mesoderm. After the formation of germinal layers germination of axial organs occurs; it is *histogenesis* – a process of tissue formation and *organogenesis* – a process of organ formation.

Derivatives of germinal layers. The ectoderm gives start to the epidermis and its derivatives, nervous system, sense organs, initial and final parts of the digestive tube.

The chord, middle part of the digestive tube, liver, pancreas and respiratory system are formed from the **entoderm**.

The following organs and systems are formed from the **mesoderm**: the connective and muscular system, skeletal muscles, the skeleton, derma, dentin, urogenital system, smooth musculature, heart, blood vessels, blood, lymphatic system.

Provisional (temporary) organs of the germ:

1. *Amnion* – is a sac filled with the fluid that forms water environment, protects the germ from drying and injuries.

2. *Chorion* (a serous membrane) is an external membrane adjacent to shell or mother's tissues. It serves for exchanging nutrients with the external environment.

3. *Yolk sac* takes part in feeding of the germ and is a blood–making organ.

4. *Allantois* is a process of the back intestine, a receptacle for urea and the uric acid. In mammals it forms the placenta together with the chorion.

5. Realization of genetic information in the prenatal period.

Genetic information (sequence of DNA nucleotides), provides synthesis of mRNA, proteins–enzymes that stipulate the development of characters. Manifestation of genes action depends on other genes. They can affect the given gene, protein–enzymes coded by this gene, manifestation of the character. This gene can affect the realization of other genes action. The realization of the gene action is also affected by environmental factors that can modify the structure of DNA, mRNA, proteins–enzymes and phenotypical manifestations of the gene (fig. 16).

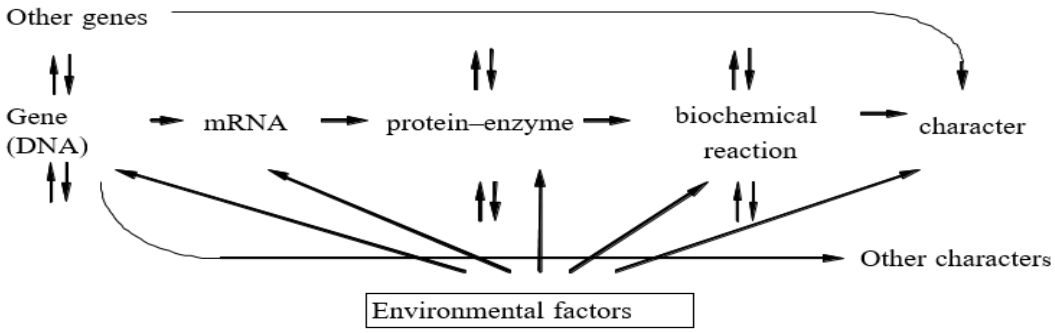


Fig. 16. Realization of genetic information

6. Mechanisms of embryogenesis. Morphogenesis. Mechanisms ensuring embryogenesis:

1. **Differential activity of genes** –various blocks of genes have a strictly definite order of repression and depression during embryonic development.

2. **Determination** –obtaining the ability to develop in a definite direction by the cells and simultaneous limitation of their future development possibilities. At the beginning of embryogenesis blastomeres are *totypotentious* (can give start to a whole organism) and their development depends on external inductors and adjacent cells. At later stages of embryogenesis cells become determinant (their development is predetermined) and they develop according to a given plan.

3. **Differentiation** – is a biochemical, functional and morphological specialization of cells; modification of a developing structure, when relatively homogenous formations become more and more different.

Phases of differentiation:

– *dependent* (to the stage of an early gastrula);

– *independent* (at the stage of a late gastrula).

Genetic bases of differentiation. Genetic differentiation is associated with universality of an ovum and inhomogeneity of its cytoplasm –different parts of the cytoplasm have a *different complement of chemical substances* and possess different development possibilities.

Stages of differentiation (fig. 17).

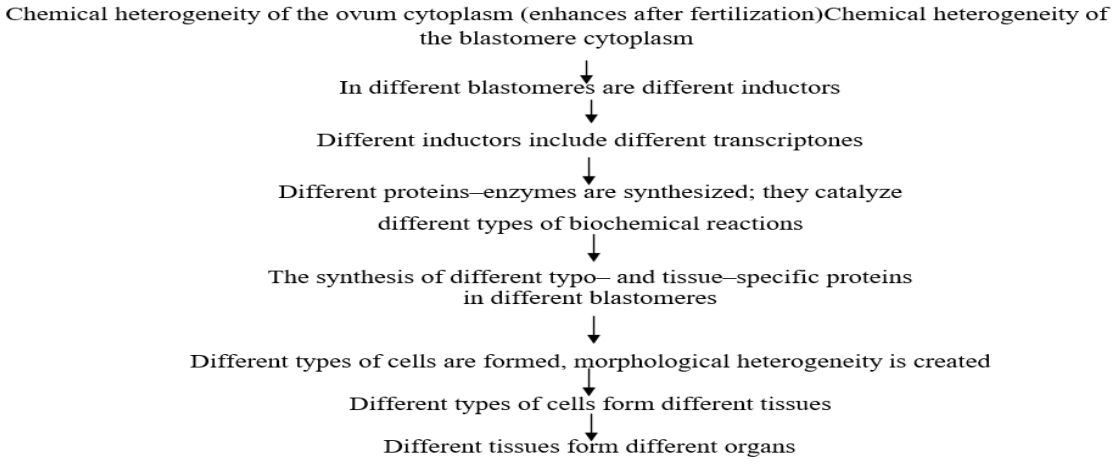


Fig. 17. Stages of differentiation

4. **Morphogenesis** – is a process of appearing new structures and modifi cation of their form in ontogenesis.

Mechanisms of morphogenesis:

1. **Embryonic induction** – is influence of a group of embryonic cells on adjacent cells (G. Shpeman, G. Mangold). The primary inductor (*an upper lip of the blastopore*) determines the nervous tube formation, then the chord development is induced, and after this –that of the digestive tube.

2. **Morphogenetic fields** (A. G. Gurvich) – are distant cellular interactions of the electric or gravitational nature.

3. **Gradient of physiologic activity** (Ch. Child) – the intensity of substances exchange in the head department of the germ is higher than in the caudal one.

4. **Positional information of the cell** –due to intercellular interactions every cell assesses its own position in the germ of an organ and then differentiates according to this position.

7. Critical periods of the prenatal ontogenesis. Teratogenesis.

Periods of the greatest sensitivity of the germ to environmental factors are called **critical periods.**

The human has 3 basic critical periods in embryogenesis:

1) *implantation* – instillation of an embryo in the mucus of the uterus (6–7th day after fertilization);

2) *placentation* – the beginning of the placenta formation (14–15th day after fertilization);

3) *delivery* – coming out of the mother's organism, reconstruction of all organ systems, modification of the way of feeding (39–40th week).

Critical periods coincide with transitions from one development period to the other and modified existence conditions of the germ.

The process of the natural course impairment of embryogenesis under environmental factors is called **teratogenesis** (Greek *teras* –monster).

Factors causing teratogenesis are *teratogens*. They are medicines (antibio–tics, quinine, chloride, anti–depressants, etc.), alcohol, nicotine, waste products of parasites, ionizing radiation.

Causes, development mechanisms of development defects are studied by teratology. Incidence frequency of development defects in human populations is1–2 %.

Variants of congenital development defects: aplasia (hypoplasia), hypo–(hyper) trophy, heterotopy, atresia, stenos, etc.

Basic terms and concepts:

1. Aplasia – absence of an organ.

2. Atresia –imperforation of natural openings and canals.

3. Balstula – a one–layer multicellular germ with a cavity inside.

4. Gradients of physiologic activity – intensity of exchange processes in the head department of the germ are higher as compared to the caudal department.

5. Critical periods – are periods of the greatest sensitivity of the germ to environmental factors.

6. Morphological fields –distant cellular interactions of the electric or gravitational nature.

7. Ontogenesis – an individual development from a zygote formationto death.

8. Progenesis – the period of formation and maturation of those sex parental cells that form a zygote.

9. Stenos –narrowing of a hollow organ canal.

10. Teratogenesis – the impairment process of a natural course of em bryogenesis under environmental factors.

11. Embryonic induction – the effect of a group of embryonic cells on adjacent cells.

BASES OF ONTOGENESIS (POSTEMBRYONIC DEVELOPMENT)

1. Postnatal ontogenesis. Types of development. Metamorphosis.

Post–embryonic (postnatal) period – is a period from the moment of birth or coming out of egg membranes and to death. After morphogenesis comes puberty and reproduction takes place; a final stage of ontogenesis is getting old and death.

Table 3 – Types of ontogenesis

Direct development	Indirect development (with metamorphosis)
Laying eggs with a great amount of yoke (birds)	Incomplete metamorphosis, stages: egg – larva – mature individual (intestinal helminthes)
Intrauterine (mammals)	Complete metamorphosis, stages: egg – larva – chrysalis – mature individual (butterflies, 2–wing insects)

2. Division of the postnatal human ontogenesis into periods.

Neonatal period (1–10 days): a complex period of reconstruction of the whole organism, adaptation to new existence conditions.

Breast–feeding period (11 days – 12 months): feeding the child with mother's milk; intensive growth.

Early childhood period (1–3 years): the child learns to walk and speak, gets a cquainted with the surrounding world.

The 1st childhood period (4–6 years): the child is interested in everything and tries to understand everything, masters elementary game skills.

The 2nd childhood period (7–11 years in girls, 7–12 years in boys): the growth becomes slow, intensive development of the muscular system; children go to school.

Adolescent period (12–15 years in girls, 13–16 years in boys): puberty starts and growth intensity increases.

Juvenile period (16–20 years in girls, 17–21 years in young men): puberty, growth and physical development have completed.

Middle age, I period (21–35 years in women, 22–35 years in men): an optimal period for childbirth; mastering professional skills.

Middle age, II period (36–55 years in women, 36–60 years in men): a period

of the most active professional activity; the first signs of getting old appear after 35 years).

Advanced age (56–75 years in women, 61–75 years in men): the processes of aging are going on; retirement.

Senile age (76–90 years): senile changes are marked; some people retain the ability for creative work at this age.

Age of long–livers (over 90 years).

3. Critical periods of postnatal ontogenesis.

There are **critical periods** in the postnatal human ontogenesis:

1. *Neonatal period* (the first days after birth) – reconstruction of all organ systems for a new environment is going on.

2. Puberty period (12–16 years) – a hormonal reconstruction, formation of secondary *sexual* characters.

3. *Period of sexual wasting away* (about 50 years in women, 60–70 years in men) – functional fading of sex glands and the glands of internal secretion).

4. Growth. Growth types of tissues and organs in the human. Acceleration.

Growth – is enlargement of sizes and body mass. The growth can be **unlimited** (indefinite) – it lasts all life (cancroids, fish and reptiles) and **limited** (definite) –stops by a definite age (insects, birds, mammals).

The growth of the human has an uneven course. The most intensive growth is marked in the first year of life – it increases by 25 cm. In the 2 nd year it increases by 10–11 cm, in the 3rd – by 8 cm. At the age from 4 to 7 years the growth increment is 5–7 cm per year. At a junior school age it is 4–5 cm per year, in puberty the growth intensity increases to 7–8 cm a year. Then the growth slows down and increases only 1–2 cm a year till the age of 20–25 years.

Basic growth types for tissues and organs:

– a *general* type: the whole body, muscles, skeleton, respiratory organs, liver have a maximum growth in the 1st year of life and in puberty;

– a *lymphoid* type: the thymus, lymphatic nodes and the lymphoid tissue of the intestine, spleen, tonsils; a maximum increase of their mass occurs till the age of 11–12 years and then involution;

– a *cerebral* type: the brain and the spinal cord, eyes, the head develop earlier than other parts of the body – after birth and to 10–12 years;

– a reproductive type: various parts of the reproductive system – a fast growth in puberty.

Growth regulation:

1. Somatotropin (a hypophysis hormone), thyroxin (a thyroid gland hormone).

2. Environmental factors: light, nutrition, vitamins (A, B, D), microelments, social–economic factors.

The somatotropic hormone is produced since the moment of birth till 13–16 years. When the gland's function is lowered, hypophysial nanism devel– ops; when it is increased, gigantism develops – the human growth reaches 2 meters and more. Excretion of the hormone in an adult person results in acromegaly –

bones enlargement of the hand, foot and face. *Thyroxin* increases energy exchange in the organism. The decrease of the gland's function leads to growth retardation, impairment of body proportions, retardation of sexual devel– opment, mental impairment. *Sexual hormones* produce effect on all metabolic processes. *Environmental factors* produce a great effect on growth. Balanced nu– trition is necessary for normal growth of the child. It should include vitamins and microelements. The sun light plays an important role in synthesis of vitamin D (calciferole).

During the last decades the **acceleration** of physical and physiological development of children and adolescents is marked. It is manifested already on the stage of intrauterine development –lengthening of the body of newborns by 0,5–1,0 cm, body mass by 50–100 g, the terms of teeth eruption change. The growth for the last 100 years has increased on an average by 8 cm. The following factors are considered to cause acceleration: mixed marriages (increase of heterozygosity), urbanization, increase of the radiation background, changes in the Earth magnet field and a number of social factors.

5. Age of the human.

Age:

1. *Biological* – the age he looks.

2. *Chronological* – the number of years a person has lived.Criteria for determination of a biological age:

– skeletal maturity: ossification of various parts of the skeleton occurs at different ages;

– teeth maturity: appearance of milk teeth and their replacement with permanent ones occurs at a definite age;

– the time of appearing and the development degree of secondary sex cha racters.

6. Constitution and the human habitus.

Constitution of the human – are genetically conditioned peculiarities of morphology, physiology and behavior. In 1927 M. V. Chernorutsky proposed the classification including three types of constitution.

Ectomorphic type (asthenics): a narrow chest, low position of the diaphragm, elongated lungs, short intestines with low absorption, thin bones and long extremities, a thin layer of fat deposits. Asthenics are characterized by high excitability, inclination to neuroses, hypotonia, ulcers, tuberculosis.

Mesomorphic type (normosthenics): proportional constitution, moderate development of the hypodermal adipose tissue. Such people are energetic, alert, inclined to neuralgias, atherosclerosis and diseases of the upper respiratory tract.

Endomorphic type (hypersthenics): a broad chest, voluminous stomach and long intestines, a considerable fat deposit. The amounts of cholesterol, uric acid, erythrocytes and hemoglobin in the blood are increased. Assimilation processes predominate, they are inclined to obesity, diabetes mellitus, hypertension, diseases of kidneys and bladder.

Habitus includes peculiarities of morphology, physiology and behavior ina definite period. Habitus reflects well–being of a person and his health state ata

given moment. It includes: peculiarities of the body build, pose, bearing, gait, color of the skin coverings, expression of the face, concordance of a biological and chronological age.

7. Ageing of the organism. Basic theories of ageing.

Ageing – is a common biological regularity characteristic of all living organisms. Old age is a final stage of ontogenesis. The science about old age is called **gerontology**. It studies regularities of ageing of various organ systems and tissues. **Geriatrics** is a science about diseases of old people; it studies pecu–liarities of their development, course, treatment and prophylaxis.

Gerontology offers more than 300 hypotheses of ageing. The most common of them are:

1. *Energetic* (M. Rubner, 1908): the organism of each species has a definite energetic fund. It is being spent during the whole life, then the organism dies.

2. *Intoxicational* (I. Mechnikov, 1903): self–poisoning of the organism due to accumulation of products of nitrogenous exchange and putrefaction in the intestines.

3. *Associated with the connective tissue* (A. Bogomolets, 1922): the connective tissue is a nutrition regulator of cells and tissues; changes taking place there impair inter–tissue interactions and result in ageing.

4. *Overstrain of the central nervous system* (I. Pavlov, 1912. G. Celie, 1936): nervous break–downs and prolonged nervous overstrain cause untimely ageing.

5. *Changes of colloidal properties of the cellular cytoplasm* (V. Ruzhichka, M. Marinesku, 1922): a modified cytoplasm does not retain water properly, colloids from hydrophilic transform into hydrophobic, colloidal particles become bigger and their biological properties change.

6. *The programmed number of cellular mitoses* (A. Heiflick, 1965): different species have different numbers of cellular divisions: fibroblasts of human embryos give about 50 generations, the mice and hen has about 15 generations).

7. *Genetic*: accumulation of mutations: decrease of intensity and impairment of the processes of transcription, translation and repair; impairment of self–renewal of proteins.

A considerable impact on the process of human ageing has *social factors*, living conditions and way of life, various diseases. Ageing and the life span de–pend also on the ecological situation.

The science that studies a healthy style of life of the human and conditions increasing his life span is called **valeology**. A theoretically possible human age is 150–200 years; a maximum registered one is 115–120 years. An average life span of men in Belarus is 62–70 years, that of women –72–79 years.

8. Clinical and biological death. Reanimation. Problems of euthanasia.

Ageing of the organism is terminated by **death**. Death ensures a change of generations. Causes of death can be different. *A physiological death*, or natural, occurs due to ageing. A *pathological death,* or untimely, is the result of a dis– ease or an accident.

A clinical death occurs as a result of termination of vital functions (heart or respiration failure), but exchange processes of substances in cells and organs are retained.

A biological death is termination of processes of self–renewal in cells and tissues, impairment of chemical processes, autolysis and decay of cells. In the most sensitive cells of the brain cortex necrotic changes are revealed already in 5–6 minutes. To prolong the period of nearing a clinical death one can using general hypothermia of the organism that slows down metabolic processes and increases the persistence to oxygen starvation.

Reanimation – is a possibility to return a human to life from the state of a clinical death (when vital organs are not impaired) in 5–6 minutes, while cortical cells of the brain are still alive. Reanimation methods are used in medicine in any threatening conditions.

Euthanasia – is a medical assistance to pass from life for a terminally ill patient according to his will or request of his relatives. Euthanasia is allowed by law only in some countries.

Basic terms and concepts:

1. Acceleration –speeding–up of physical and physiological development of children and adolescents.

2. Valeology – a science that studies a healthy style of life of the human and conditions for enlargements of its duration.

3. Biological age – the number of years a person looks.

4. Chronological age – age confirmed by documents

5. Habitus of the human –peculiarities of morphology, physiology, behavior in a definite interval.

6. Geriatrics – a science about diseases of old people; studies peculiarities of their development, course, treatment and prophylaxis.

7. Gerontology – is a science about old age.

8. Constitution of the human – is genetically conditioned peculiarities of morphology, physiology and behavior.

9. Metamorphosis – is transformation of larval organs into organs of an adult organism.

10. Reanimation – is a possibility to return a person to life from the state of a clinical death.

Euthanasia – is medical assistance for passing from life to a terminally ill patient according to his wish of request of his relatives.

EVOLUTION OF ORGAN SYSTEMS

CLASSES I

1. Biogenetic law, A. N. Severtsev's study about phylembryogeneses.

In 1866 E. Geckel formulated a biogenetic law: *ontogenesis is a short and fast recurrence of phylogenesis due to hereditary characters and adaptability*.

Ch. Darvin confirmed the association between onto – and phylogenesis and developed a study about **recapitulations** – recurrence of ancestors' characters in germs on phylogenesis in the process of ontogenesis.

Further embryological studies showed that this biogenetic law was valid only in general features: none of the germ's development stages repeated in full the structure of ancestors on phylogenesis; in ontogenesis the structure of embryos is repeated but not adult stages of ancestors.

The study of A. N. Severtsev about phylembryogenesis is very important for explanation of the relation between onto– and phylogenesis. **Phylembryogeneses** are embryonic reconstructions that are preserved in adult forms and have an adaptive significance. There are 3 types of phylembryogenesis:

1) **archalaxises** – are changes from the moment of an organ germination (the development of a hairy integument in mammals); for all that at the beginning of morphogenesis mutated genes become involved in the work and the development takes a new course (recapitulations are absent);

2) **deviations** –diverging from the middle of the organ development course (the development of scales in reptiles); initially the process goes according to phylogenesis (partial recapitulation), and in the middle of morphogenesis mutated genes interfere with the work and the course takes another direction;

3) **anabolia** –further development of the organ (from a 2– chamber heart to a 4–chamber heart); at first all preceding stages of the organ development recapitulate, and only at the end of embryogenesis mutated genes interfere and a new character is germinated.

In some development defects the human obtains characters characteristic of orders or classes of the Chordate type. They occur due to ontophylogenetic mechanisms: recapitulations, parallelisms. **Recapitulations** occur as a result of insufficiency or absence of anabolism. The examples of defects due to recapitulations: a 3– chamber heart, preservation of embryonic vessels, 2 aortal arches, retardation of kidneys development, doubling of ureters. **Parallelism** is an independent development of similar characters in the evolution of closely related groups of organisms (in the human and animals with similar origin). An example of parallelism in the human is polymastia.

2. Phylogenesis of body integuments in chordal animals.

Skin integuments develop from two germinal layers: an ectoderm (epidermis) and a mesoderm (derma).

Basic evolution directions:

1. Differentiation into 2 layers: an external layer –epidermis, an internal – derma and thickening of the derma.
2. From one–layer to multilayer epidermis.
3. Differentiation of the derma into 2 layers –papillary and net.
4. Appearance of subcutaneous adipose cellular tissue and improvement of thermoregulation mechanisms.
5. From unicellular glands to multicellular ones.
6. Development of various skin derivatives.

The Lancelet has a one–layer epidermis, it is cylindrical, has glandular cells excreting mucus. The derma is presented by a thin layer of incompletely formed connective tissue.

In lower vertebrates the epidermis is multilayer. Skin derivatives: unicellular (in fish) and multicellular (in amphibians) mucous glands; scales (in fish).

In amphibians the skin is thin, without scales, contains a great number of mucous glands, the secret of which moistens integuments and produces an antibacterial effect. The skin participates in gas exchange.

In reptiles corneous scales develop, and skin glands are absent.

In mammals: The epidermis and derma are well developed; there appears a subcutaneous adipose cellular tissue. A great number of glands are in the skin: sweat, sebaceous, lactiferous and odorous. There are also various derivatives ofa corneous layer: hair, horns, claws and hoofs. There is a net and a papillary layer in the derma. The papillary layer contains nerve receptors, blood and lymph vessels.

3. Phylogenesis of the axial skeleton of the chordates.Basic evolution directions:

1. Replacement of a chord for a spine, a cartilaginous tissue for a bony one.
2. Differentiation of the spine into departments (from 2 till 5).
3. Enlargement of the number of vertebrae in departments.
4. Formation of the chest.

Cartilaginous fish preserve a chord during all their life, but germs of vertebrae appear in them. In fish develop vertebral bodies, osteal and transverse processes and a spinal canal is formed. The spine consists of 2 departments: of the trunk and the tail. There are ribs in the trunk department that end freely inthe abdominal side of the body.

In amphibians 2 new departments appear: cervical and sacral, each containing one vertebra. There is a cartilaginous breastbone. Ribs in caudates do notreach the breastbone, in non– caudates they are absent.

In reptiles the cervical department has 8–10 vertebrae, the thoracic and lumbar department – 22 vertebrae, the sacral – 2 and the caudal –some tens of vertebrae. The first two cervical vertebrae provide mobility of the head;the last 3 vertebrae have per 1 pair of ribs. The first 5 pairs of ribs of the lumbar–thoracic department are attached to a cartilaginous breastbone forming the chest.

In mammals the spine consists of 5 departments. The cervical department has 7 vertebrae, thoracic –from 9 to 24, lumbar –from 2 to 9, sacral – 4–10 and more, in the caudal department the number of vertebrae varies. There occurs reduction of ribs in the cervical and lumbar departments. The breastbone is bony. 10 pairs of ribs reach the breastbone forming the thorax.

4. Phylogenesis of the brain and visceral departments of the skull in chordates.

Basic evolution directions:

1. Joining a visceral (facial) department to a cranial one, enlargement of the cranial department volume.
2. Decrease in the number of bones at the expense of their fusion.
3. Replacement of a cartilaginous skull for a bony one.
4. Mobile joining of the skull with the spine.

The cranial department of the skull in vertebrates develops just as continuation of an axial skeleton, the visceral department being a support for the respiratory system and an anterior part of the digestive system. Germination of an axial skull occurs from 2 basic departments: a chordal – **parachordaly** on the sidesof the chord and perichordal – **trabecula** in front of the chord (fig. 18).

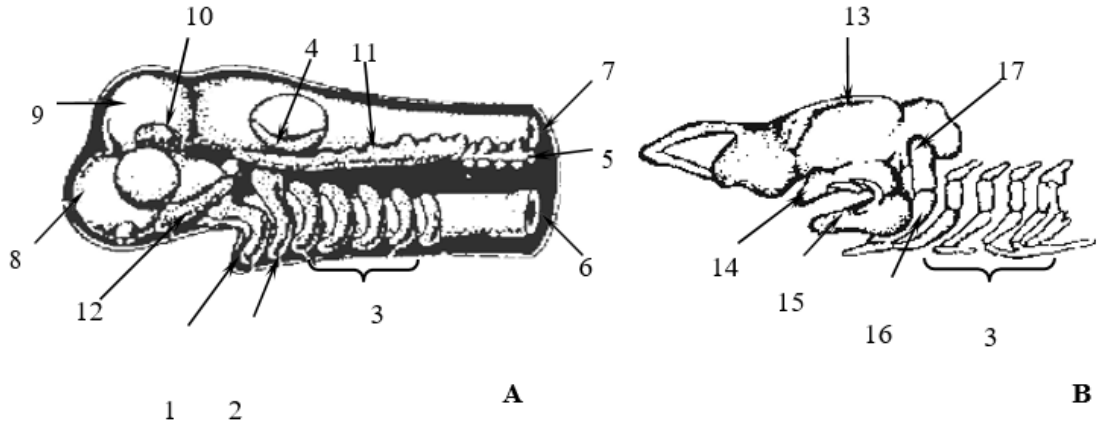


Fig. 18. A cartilaginous skeleton of the shark:
A – a germ, B – a mature species: 1 – a mandibular arch; 2 – a hyoid arch; 3 –III–IV branchial arches; 4 – a hearing capsule; 5 – a chord; 6 – an intestine; 7 –spinal cord; 8 – an anterior brain bladder; 9 – a middle brain bladder; 10 –orbital cartilages;11 –parachordalies; 12 –trabeculae; 13 – a cranial skull; 14 – a palatal quadrate carti– lage; 15 – a Meckel's cartilage; 16 – a hyoid; 17 – a hyomandibular cartilage

Trabeculae and parachordalies overgrow and fuse together forming the skull from beneath and the sides. Olfactory and hearing capsules adhere to it. Lateral sides are filled with orbital cartilages. The cranial skull undergoes development stages: that of a connective tissue, cartilaginous and bony.

Fish. The cranial skull is cartilaginous. There appears an occipital department. A visceral skull consists of 5–6 cartilaginous arches that envelope an anterior department of the digestive tube. Arch I is mandibular, consists of an upper cartilage – a palatal quadrate that forms a primary upper jaw. A lower cartilage –Meckel's, forms a primary lower jaw. Arch II –hyoid, consists of 2 upper hyomandibular cartilages and 2 lower –hyoids. The hyomandibular cartilage adheres to the base of the cranial skull from each side; the hyoid connects with the Meckel's cartilage (**a hyostyle type**). The dome of the cranial skull is tightly connected with the spine.

The skull in **ground vertebrates** has a mobile connection with the spine.

Amphibians have functioning secondary jaws. The palatal–quadrate cartilage of the 1st maxilla arch adheres to the base of the cranial skull (**an autostyle type**). The hyomandibular cartilage of the hyoid arch loses its role of a maxilla arch pendant and transforms into a hearing bone (column). The Meckel's cartilage is reduced, the hyoid transforms into processes of the hyoid. The rest visceral arches (they are 6) are preserved as a hyoid and a cartilaginous pharynx.

In reptiles the skull ossifies, there are many covering bones. The connection of the visceral and cranial skull occurs at the expense of an ossified part of the reduced palatal–quadrate cartilage. The skull is **autostylish**. The jaws are secondary. The secondary hard palate and orbital arches are formed.

In mammals the dome of the skull is formed by frontal and bregma bones. The mandible consists of one bone and its process forms a joint connecting it with the cranial skull. The palatal–quadrate and Meckel's cartilages are transformed into

an anvil and a hammer. The upper department of the hyoid arch forms a stirrup. Parts of branchial arches II and III form a shield–like pharyngeal cartilage, branchial arches IV and V are transformed into pharyngeal cartilages. **In higher mammals** the cranial skull volume is considerably increased. Inthe human the facial skull sizes are diminished as compared to the cranial department, the skull is rounded and smooth. An orbital arch is formed (**a synapcidal type** of the skull).

5. Phylogenesis of the nervous system in chordates.

The nervous system has an ectodermal origin, is built as a nervous tube.

Basic evolution directions:

1. Differentiation of the nervous tube into the brain and the spinal cord.

2. Evolution of the brain:

a) from the stage of 3 brain bladders to 5 brain bladders and 5 brain departments;

b) appearance of the brain cortex and enlargement of its surface atthe expense of furrows and convolutions;

c) from an ichthyopsidic to a sauropsidic and a mammal type of the brain.

3. Differentiation of the peripheral nervous system.

In the Lancelet CNS is presented by a nervous tube. Its anterior part is dilated, an olfactory pit is located on it. Light–sensitive cells are located through the whole length of the tube (Gesse's eyes).

On the front end of the nervous tube 3 brain bladders are germinated (anterior, middle and posterior). Then the anterior and posterior bladders are divided and 5 bladders form, from which the brain departments develop: frontal (**telencephalon**), intermediate (**diencephalon**), middle (**mesencephalon**), the cerebellum (**metencephalon)** and elongated (**myelocephalon**). There are cavities inside the departments (cerebral ventricles) that continue and pass into the spinal cord. The part of the brain located over the ventricles is called the **dome** (mantle), andbelow it – the **bottom** of the brain.

In fish the brain is small. The front brain is not divided into hemispheres. The dome is epithelial; the bottom of the brain is presented by striated bodies. Olfactory lobes are small. The intermediate brain is presented by the thymus and hypothalamus. The middle brain is large; it is an integrating center (an **ichthyocidic** type of the brain). In the area of the middle brain a convolution appears. The cerebellum is well developed. There are 10 pairs of intracranial nerves (fig. 19).

In amphibians: 1) the volume of the front brain increases; 2) the front brain is divided into 2 hemispheres; 3) a nervous tissue appears in the brain dome; 4) striated bodies are well developed. Olfactory lobes are separated from the hemispheres. The intermediate brain is presented by the thalamus and hypothalamus. The middle brain is large and is an integrating center. The cerebellum is poorly developed. The elongated brain is developed as in fish. There are 10 pairs of intracranial nerves.

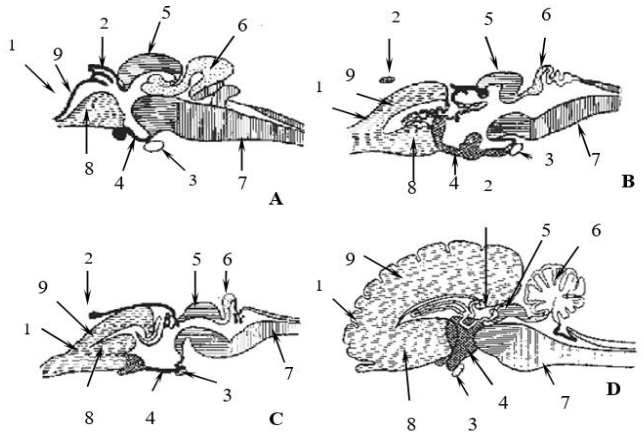


Fig. 19. The brain of vertebrates (a longitudinal section):
A – a bony fish, B – an amphibian, C – a reptile, D – a mammal: 1 – a front brain; 2 – an epyphisis; 3 – a hypophysis; 4 – an intermediate brain; 5 – a middle brain; 6 – a cerebellum; 7 – an elongated brain; 8 –striated bodies of the front brain; 9 – a mantle (dome)

In reptiles the front brain becomes the largest department. Large olfactory lobes are differentiated, sincipital lobes are separated. Hemispheres of the brain have cortex germs on lateral surfaces. The cortex has a primitive structure(3 layers of cells) – a**rchipallium**. The front brain (striated bodies) is an integrating center: such type of the brain is called **sauropsidic (striatal)**. The sizes of the middle brain are diminished (it loses the function of an integrating brain). The cerebellum is considerably enlarged. The elongated brain forms a sharp convolution in the vertical plane. There are 12 pairs of intracranial nerves.

In mammals the front brain reaches the most development at the expense of the secondary cortex (**neopallium**). In lower mammals the cortex surface is smooth, and in higher mammals furrows and convolutions form. The secondary cortex is an integrating center (a **mammal** type). The intermediate brain is covered by the front brain. The middle brain is diminished, forms a quadrihillock (2 upper prominences are subcortical centers of vision, 2 lower ones – subcortical centers of hearing). The cerebellum is considerably enlarged in sizes, is differentiated into two hemispheres and a middle part – a worm. There are 12 pairs of intracranial nerves, 3 convolutions of the brain: 1) sincipital – at the level of the middle brain, 2) occipital – in the area, where the elongated brain passes into the spinal cord, 3) pontine – in the area of the posterior part ofthe brain.

6. Phylogenesis of the digestive system of chordates.

The digestive system develops from the endoderm, its initial and final departments –from the ectoderm.

Basic evolution directions:

1. Differentiation of the digestive tube into departments.
2. Development of digestive glands.
3. Appearance of teeth and their differentiation.
4. Enlargement of the absorption surface at the expense of the intestines elongation and appearance of cilia.

In the Lancelet the digestive system is presented by a straight tube that is differentiated into a pharynx and intestines. The pharynx is pierced with branchial slits. The digestive tube forms a hepatic growth.

In fish jaws and homogenous teeth appear (a homodontal dental system), an esophagus, stomach, small and large intestine. The liver is well developed; there is a gallbladder. The pancreas is slightly separated.

Amphibians have an oral–pharyngeal cavity, homogenous teeth, esophagus, small and large intestine, liver, pancreas. There appeared a muscular tongue and salivary glands. There are no enzymes in the saliva. There appear a duodenum and rectum. The intestines end with a cloaca.

In reptiles the oral cavity is separated from the pharynx, differentiation of teeth starts (venomous teeth), stomach walls are thick, there is a caecum germ, the intestine elongates and ends with a cloaca.

Mammals have a heterodontal dental system (incisors, canines and molars). Fleshy lips appear. The saliva contains enzymes. The intestine is differentiated into a small and large intestine, the caecum is well developed, it has an appendix. The rectum is terminated with an anal opening. The mucous membrane of the intestines has a great number of folds, in a small intestinecilia.

7. Ontophylogenetic etiology of the development defects of integuments, skeleton, nervous and digestive systems in the human.

Ontophylogenetic reasons of skin defects (etiology –recapitulations): absence of sweat glands, ichthyosis, redundant hairiness of the face and the body, polymastia.

Ontophylogenetic reasons of defects of the brain (etiology – recapitula tions): absence of differentiation of hemispheres, incomplete separation of hemispheres of the front brain (prosencephalia), an ichthiopsidic, sauropsidic types of the brain.

Ontophylogenic reasons of skeleton defects: additional ribs at the 7^{th} cervical or at the 1^{st} lumbar vertebra, splitting of dorsal vertebral arches, non–atresiaof osteal vertebral processes (Spina bifida), increase of the number of sacral ver–tebrae, the presence of a tail.

Ontogenetic reasons of skull defects: increasing of bony elements, non–atresia of the hard palate «a cleft palate», frontal suture; one hearing bone; absence of the chin prominence.

Ontophyloigenetic reasons of the digestive system defects: fistulas of the neck (rupture of branchial pockets), homodontal dental system, additional lobes of the liver and pancreas, shortening of the intestines.

Basic terms and concepts:

7. Anabolia – additions to the organ development. They arise after the organ has completed its development.

8. Archallaxis – changes since the time of the organ germination; the development goes by another way.

9. Deviation – deflection from the middle of the organ development. At early stages – a partial recapitulation.

10. Sauropsidic type of the brain – an integrating center –striated bodies of the frontal brain.

11. Ichthiopsidic type of the brain – an integrating center – the middle brain.

12. Mammal type of the brain – an integrating center – a new cortex ofthe brain.

13. Parallelism – an independent development of similar characters in evolution of closely related groups of organisms.

14. Recapitulation – recurrence of ancestral characters in germs on phylogenesis in the process of ontogenesis.

15. Phylembryogenesis –embryonic reconstructions that are preserved in mature forms and have an adaptive significance.

CLASSES II

1. Phylogenesis of the respiratory system of Chordates.

The respiratory system has an entodermal origin.

Basic evolution directions of the respiratory system:

1. From branchial slits of the Lancelet to the branchial apparatus of the fish.

2. Enlargement of the respiratory surface at the expense of branchial lobes formation; formation of branchial capillaries.

3. From the branchial apparatus to organs of ground respiration –lungs.

4. Development and differentiation of respiratory ways, formation ofa bronchial tree.

5. Enlargement of the respiratory surface of the lungs, formation ofthe chest and appearance of the diaphragm.

In the Lancelet: 100–150 pairs of interbranchial septa piercing the pharynx, in the vessels of which gas exchange takes place. These are carrying to andcarrying out branchial arteries. There are no branchial capillaries.

In fish in the anterior part of the pharynx branchia develop. In the capillaries of branchial lobes gas exchange takes place. In the **crossopterygian** fish appear organs of air breathing – a germ of a lung of ground vertebrates a pairedgrowth of the pharyngeal wall with an abdominal side.

Caudalless amphibians have a common pharyngeal–tracheal chamber, in the caudates it is separated into a pharynx and a trachea (fig. 20).

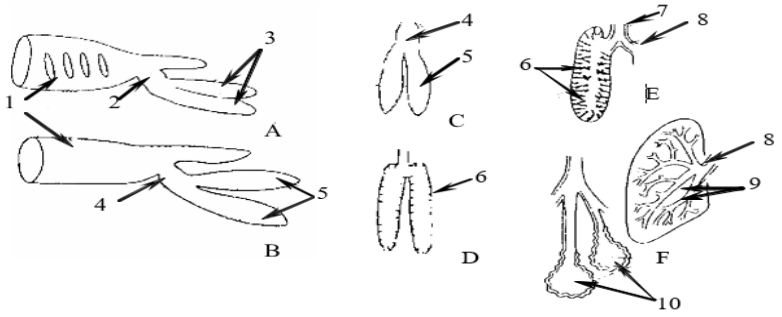


Fig. 20. Evolution of the lungs in vertebrates:

A – a pharynx and a swimming bladder (lungs) of the crossopterygian fish, B – a pharynx and lungs of the amphibians, C – a caudal amphibian, D – a caudalles amphibian, E – a reptile, F – a mammal: 1 – a pharynx; 2 – an unpaired chamber connecting the swim– ming bladder with the pharynx; 3 –sacs of the swimming bladder; 4 – a pharyngeal– tracheal chamber; 5 –lung sacs; 6 – intralung septa; 7 – a trachea; 8 – a bronchus; 9 –bronchial branches; 10 – alveoli

There appear Seiler's cartilages and voice cords in the pharynx. Caudalless amphibians have septa in the lungs. The lungs of **caudal amphibians** are presented by two thin–walled sacs without any septa. Ventilation of the lungs is weak, that's why the skin participates in respiration.

In reptiles the respiratory surface of the lungs is increased by cellular bars, where blood vessels pass. There appear out–of–lungs bronchi, in the pharynx – an innominate cartilage. Cartilaginous rings are formed in the trachea. The chest is formed: the connection of the ribs and the spine and breast is mobile, intercostal muscles develop.

In mammals a nasal cavity, a nasopharynx are formed, in the pharynx – a shield–like cartilage. A bronchial tree develops. Bronchioles and alveoli considerably increase the respiratory surface (the number of alveoli is up to 500 million). The chest separated by the diaphragm from the abdominal cavity takes part in respiration.

2. Phylogenesis of the blood circulatory system of chordates.

The blood circulatory system has a mesodermal origin.

Basic evolution directions:

1. Germination and differentiation of the heart (from a 2– chamber to a 4– chamber heart).

2. Development of the 2nd (pulmonary) blood circulation and a final separation of the venous and arterial blood.

3. Transformation of branchial arteries (arterial arches) and differentiation of vessels branching off the heart.

The Lancelet has one circulation. Through the abdominal aorta the venous blood comes into carrying– in branchial arteries, the number of which corresponds to the number of interbrachial septa (up to 150 pairs), where it gets enriched with oxygen. Through carrying–out branchial arteries the blood comes to carotid arteries (they carry blood to the anterior department of the body) and into a dorsal artery, which branches into multiple arteries, and carries the blood throughout the organism (fig. 21).

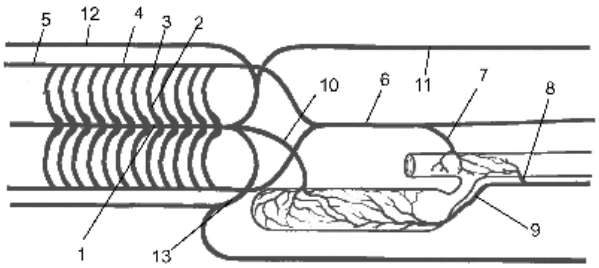


Fig. 21. The circulatory system of the Lancelet:
1 – an abdominal aorta; 2 – carrying– in branchial arteries; 3 – carrying–out branchial arte–ries; 4 –roots of a dorsal artery; 5 – carotid arteries; 6 – a dorsal artery; 7 – an intestinal artery; 8 – a subintestinal vein; 9 – a portal vein of the liver; 10 – a hepatic vein; 11 – a right posterior vein; 12 – a right anterior cardinal vein; 13 – a left Cuvier's vessel

After gas exchange the venous blood accumulates in paired anterior and posterior cardinal veins located symmetrically. The anterior and posterior cardinal

veins from each side fuse into Cuvier's ducts. They empty into the abdominal aorta. In the area of a hepatic protuberance a portal system is formed, the blood from which passes into an abdominal aorta through a hepatic vein.

Fish have one circulation. The heart is located beneath the mandible and consists of two chambers (an atrium and a ventricle) and contains venous blood. A venous sinus adjoins the atrium, an arterial cone comes off the ventricle, which passes into the abdominal aorta. During embryogenesis 5–7 pairs of branchial arteries are germinated, then the 1st, 2nd and 7th are reduced, andthe 3rd–6th pairs stop functioning.

In amphibians the 2nd circulation develops due to the appearance of the lungs. The heart consists of two atria and one ventricle. A venous sinus adjoins the right atrium, an arterial cone comes off the ventricle (fig. 22).

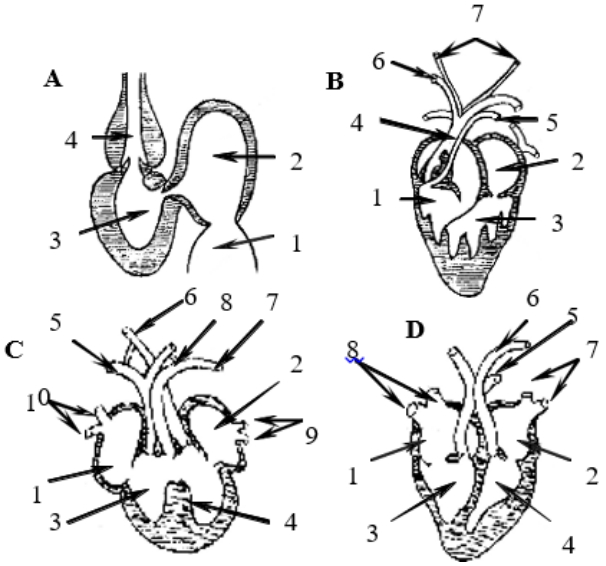


Fig. 22. Heart evolution of vertebrates:
A –fish: *1* – a venous sinus; *2* – an atrium; *3* – a ventricle; *4* – an aortal bulb; *B* – am– phibian: *1* – a right atrium; *2* – a left atrium; *3* – a ventricle; *4* – an arterial cone; *5* – a left cutaneous–pulmonary artery; *6* – a right arch of the aorta; *7* – carotid arteries; *C* –reptiles: *1* – a right atrium; *2* – a left atrium; *3* – a ventricle; *4* – an interventricular sep– tum; *5* – a right pulmonary artery; *6* – a right arch of the aorta; *7* – a left arch of the aorta;*8* – a left duct of Botallo; *9* – pulmonary veins; *10* –vena cava; *D* – a mammal: *1* – a right atrium; *2* – a left atrium; *3* – a right ventricle; *4* – a left ventricle; *5* – a left pul– monary artery; *6* – a left arch of the aorta; *7* – pulmonary veins; *8* –vena cava

The atria open into a common orifice: venous blood comes from the right atrium and arterial –from the left one. The blood in the right part of the ventricle is venous, it is mixed in the center and arterial in the left part. The blood is distributed into 3 pairs of vessels through the arterial cone: venous blood goes to the skin and lungs through the cutaneous–pulmonary arteries; mixed blood goes to all organs and tissues through aortal arches and arterial blood –to the brain through carotid arteries. 6–7 pairs of branchial arteries are geminated during embryogenesis: the 1st, 2nd, 5th and 7th are reduced, from the 3rd one carotid arteries develop, from the 4th one – arches of the aorta, from the 6th – cutaneous–pulmonary arteries (fig. 23).

In reptiles the heart consists of 3 chambers, an incomplete septum appears

in the ventricle. The pulmonary artery springs off the right part of the ventricle,it carries venous blood to the lungs; from the left part – the right arch ofthe aorta that carries arterial blood to the brain and front limbs. The left arch of the aorta springs off the center of the ventricle, it carries mixed blood. Behind the heart 2 arches of the aorta fuse into one vessel and carry mixed blood to all organs. 6 pairs of branchial arteries are germinated. They transform into the same vessels as in amphibians (the 5^{th} pair – into pulmonary arteries).

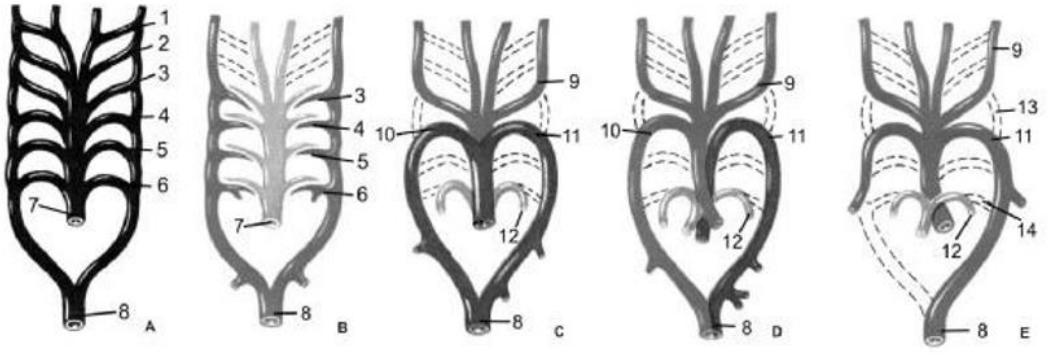


Fig. 23. Development of arterial arches in vertebrate animals:
A – a germ of a vertebrate, B – a fish, C – a caudalless amphibian, D – a reptile, E – a mammal: 1–6 – arterial (branchial arches); 7 – an abdominal aorta; 8 – a dorsal aorta; 9 – carotid arteries; 10 – a right arch of the aorta; 11 – a left arch of the aorta; 12 –pul– monary arteries; 13 – a carotid on–flow; 14 – a duct of Botallo

In mammals there is observed a complete division of the heart into the left and right halves, a complete separation of the blood into arterial and venous. The right heart part contains venous blood, while the left one – arterial blood. The pulmonary circulation starts from the right ventricle with pulmonary arteries and terminates in the left atrium with pulmonary veins. The general circulation starts from the left ventricle with a left arch of the aorta and ends in the right atrium with vena cava. 6 pairs of branchial arteries are geminated in embryogenesis, then in the process of development the 1^{st} and 2^{nd} pairs are reduced; the 3^{rd} pair gives carotid arteries; the 4^{th} right pair is reduced, the left one forms an arch of the aorta; the 5^{th} pair is reduced; the 6^{th} –forms pulmonary arteries.

3. Phylogenesis of the excretory system of chordates.

The excretory system has a mesodermal origin, it is built according toa nephridia type in the Lancelet, in vertebrates it is represented by kidneys.

Basic development directions:

1. From nephridia of the Lancelet to a compact organ – a kidney in vertebrates.

2. From a head kidney to a body and pelvic kidney at the expense of increasing the number of nephrons and coming together of the nephrons and bloodcapillaries, elongation of nephron canaliculi.

The Lancelet has 100–150 pairs of nephridia – short tubules that open with one end into a celom, and with the other – into a peribranchial cavity. A glomerule of capillaries is in the celom wall near canaliculi.

In phylogenesis of vertebrates 3 generations of kidneys change successively

each other: a head kidney –**pronephros**, a primary (body) kidney – **mesonephros**, a secondary (pelvic) kidney –**metanephros**. A nephron is a basic structural–functional unit.

The pronephros of fish and amphibian larvae has 6–12 nephrons. The nephron consists of a funnel (a nephrostoma) and a short canaliculus. Neph rostomas open into a celom, and canaliculi – into a ureter of the kidney. In the celom wall near nephrostomas a capillary glomerule is located (fig. 24).

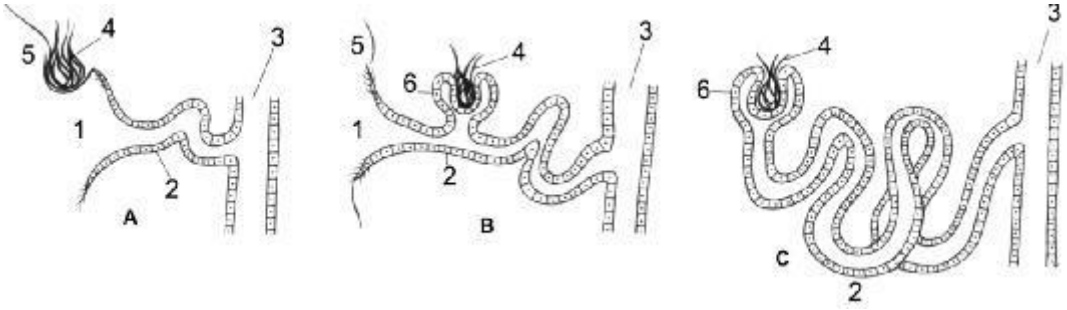


Fig. 24. Evolution of the nephron:
A – a pronephros, B – a mesonephros, C – a metanephros: 1 – a nephrostoma; 2 – a nephron canaliculus; 3 – a ureter; 4 – a glomerule; 5 – a celom; 6 – a nephron capsule

Dissimilation products pass from the blood into a celom, then througha nephrostoma into a canaliculus, and then into a ureter of the pronephros (pronephric canal). The ureter opens into the cloaca.

The mesonephros (mature fish and amphibians) contain approximately 100 nephrons. Around some capillary glomerule forms a wall growth of a canaliculus as a 2–walled capsule. Nephrostomas are preserved. Dissimilation products are removed from the blood in two ways. The 1st way –from a nephrostoma into a canaliculus, the 2nd –from a capillary glomerule into a canaliculus. Inthe process of development the perinephric canal is split longitudinally into 2 canals –Muller's and Wolf's. In the course of development the Muller's canal becomes atrophied in males of lower vertebrates, and in females it is transformed into an egg–duct. The Wolf's canal transforms into a ureter in females, in males it functions as a ureter and a semen–duct.

In amniots (higher vertebrates) a metanephros functions, it contains about 1 million nephrons. There is no nephrostoma, the canaliculus wall completely envelopes a capillary glomerule (forming a renal body: a capsule of Shumlyansky–Bowman and a capillary glomerule), then the canaliculus is differentiated into a descending part, the Henle's loop and an ascending part. Removal of dissimilation products from the blood occurs directly into a canaliculus. In vascular glomerule, filtration of blood plasma occurs, and in canaliculi – reverse absorption of water, amino acids and glucose from primary urine. The dilation of the posterior part of the ureter forms a urine bladder.

4. Ontophylogenetic reasons of development defects of the respiratory, cardio–vascular and urogenital systems in the human.

Ontophylogenetic etiology of the respiratory system in the human: underdevelopment of the pharynx or the lungs, cystic hypoplasia, abnormal branching of bronchi, hypoplasia of the diaphragm, etc.

Ontophylogenetic etiology of development defects of the cardio–vascular system: a defect of the interventricular septum, non–atresia of a Botallo's duct, an abnormality of the aortic–pulmonary septum (incomplete separation of the arterial trunk into an aorta and a pulmonary trunk), transposition of vessels, preservation of 2 aortal arches, etc.

Ontophylogenetic etiology of development defects of the urogenital system: a pelvic position of kidneys, preservation of a mesonephros, doubling of the ureter, a bicornuate uterus, a duplex uterus and vagina (on the type of par allelism).

Basic terms and concepts:

3. Arterial arches –branchial arteries.

4. Arterial cone – a muscular tube, the walls of which are capable of pul sation; it starts from the ventricle and is divided into a cutaneous–pulmonary and carotid arteries and aortal arches.

5. Botallo's duct – connects the aorta with pulmonary arteries and results in the outflow of arterial blood from the general circulation to the pulmonary circulation.

6. Venous sinus – a site, where vena cavea open in to the heart.

7. Secondary kidney (metanephros) – a pelvic kidney.

8. Capsule of Shumlyansky–Bowman – a double–layer cup surrounding a capillary glomerule.

9. Mesonephric canal – a ureter of the primary kidney.

10. Nephrostoma – a nephron funnel that opens into a celom.

11. Primary kidney (mesionephron) – a trunk kidney.

12. A front kidney (pronephros) – consists of 6–12 nephrons that have a funnel and a short canaliculi.

13. Transposition of vessels – changing the position of vessels.

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МЕДИЦИНСКАЯ БИОЛОГИЯ И ГЕНЕТИКА

Medical biology and genetic

Учебно-методическое пособие для студентов I курса
обучающихся по специальности 31.05.01. «Лечебное дело»
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