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LECTURE I
Topic: HUMAN IN THE SYSTEM OF NATURE

Plan

1. Concept of life. Its definition.
2. Properties and characters of living things.
3. Organization levels of living things.
4. Biology as a subject. Its significance for medicine.
5. Human's standing in the animal world system.
6. Human as a biological and social being.

DEFINITION OF LIFE CONCEPT

Life is one of the highest forms of matter motion and organization. The bases of a natural origin of life are in the works of F. Engels who wrote, "Life is the way of existence of proteins, the basic moment of which is constant exchange of substances with the environment". American researcher J. Bernal defined life as a function of proteins and nuclear acids". Any living system is constantly exchanging energy, substances and information with the environment. Renewal of living systems is associated with flows of substances and energy; reproduction ensures communication between generations due to a flow of information. Thus three flows, i.e. the flow of substances, energy and information, participate in regulation of all processes taking place in a living system.

PROPERTIES AND CHARACTERS OF LIVING THINGS

Life is characterized by three fundamental properties: self-regeneration, self-reproduction and self-regulation. The signs of living things are determined by:

- exchange of substances and energy;
- heredity and variation;
- multiplication (reproduction);
- individual and historic development (ontogenesis and phylogenesis);
- irritability;
- homeostasis;
- discretion.

Exchange of substances and energy with the environment is a necessary condition for existence of living systems, which supports all processes of vital activity, restoration of disrupted components and their replacement with new structures. The normal course of these processes is ensured by catalytic activity of proteins and hereditary information encoded in nuclear acids.

Heredity ensures transmission of characters from one generation to the next one during reproduction. **Variation,** unlike heredity, results in appearing new characters when the conditions of the environment change. These char-

acters may be unfavorable for the organism causing its death. If changed information is useful, a new character is consolidated by evolutionary selection.

Suspension of life at any level of biologic systems is associated with **reproduction** (**multiplication**), as existence of organisms is limited in time. Life does not stop due to reproduction, and all the species are preserved.

During reproduction every organism gets hereditary information concerning characters which are formed in the process of individual development. Ontogenesis or individual development is the development of the organism from a zygote formation to death (germination and development of various organ systems when their functions become more and more complicated and the sizes of the body enlarge).

Phylogenic development of **phylogenesis** is a historic development of species. Ch. Darwin established its basic laws — from unicellular organisms to complicated multicellular organisms.

Irritability is a property characteristic of all living things. This is a reaction of the organism, organ and cell to factors of the environment. A response of unicellular moving organisms is also called *taxis*. Attached organisms — plants — react with movements of their body parts. Such reactions are called *tropisms*. Both taxis and tropisms are motor reactions towards or from the stimulus. For example, the movement of an euglena to an illuminated part of the water pond is a positive phototaxis, while the movement of an *infusoria* from a drop of some chemical substance is a negative chemotaxis. The root in plants has a negative phototropism, the stem — a positive one. Reflexes — a defense reflex, a posterity caring reflex, reveal a response of organisms with the nervous system to environmental factors, etc.

Getting information from the environment is necessary for **self-regulation in biological systems;** it is realized by feedback. Thus are regulated metabolic processes, genetic information is decoded; all organ systems of a multicellular organism are functioning. The ability of the organism to support the balance between the internal environment and the structural organization is called *homeostasis*. Homeostasis is also sustained in higher organisms systems — population-species, biocenotic and biospheric homeostasis.

At the same time, life is characterized by **integrity and discretion**. All links of the organic world are interconnected and interdependent in their existence and development. For example, green plants in the process of photosynthesis release oxygen necessary for respiration of aerobic organisms. In respiration, organisms release carbon dioxide, which is used by plants for synthesizing organic substances. The organic world consists of separate organisms or species. Every organism has organs and tissues consisting of cells. This is called discretion of living things (latin *discretus* — discontinuous).

ORGANIZATION LEVELS OF LIVING THINGS

Based on discretion we can define 3 organization levels of living things.

Molecular genetic level. At this level gene is an elementary unit. It is a part of a nuclear acid molecule that carries definite genetic information. The information about polypeptides, signs is preserved and transferred due to an RNA property, which is called replication or self-reproduction. Proteins of all living organisms contain combinations of the same 20 amino acids, while DNA and RNA molecules of all organisms consist of 5 types of nucleotides. Lipids and carbohydrates have also a similar composition. All organisms store energy in ATP molecules but genetic information is transcripted in molecules of nuclear acids.

Cellular level. All living organisms consist of cells. The cell is a structural-functional and genetic unit of all living things. It contains genetic information about the development of the entire organism. It is in the cell where all processes of vital activity take place.

Tissue level. A group of cells with the same structure, performing the same functions, forms the *tissue*. Animal organisms have 4 kinds of tissues: epithelial, connective, muscular and nervous.

Organism level. The organism is an elementary unit of life. There is a great variety of all kinds of organisms on the Earth (the amount only of animals runs to about 2 million species). The organism level is characterized by ontogenic processes (individual development), and its nervous and humoral regulation.

Population-species level. A group of individuals belonging to one species, occupying a definite territory for a long time, freely crossing and relatively isolated from individuals of other groups of the same species, form a population. At the level of populations the processes of formation of species start. The population is an elementary unit of evolution.

Biospheric-biogeocenotic level. Biogeocenosis is a group of populations of organisms from various species that are historically related and have a definite territory of residence. There is a constant exchange of substances, energy and information between populations and the environment. In total biogeocenoses form the biosphere — an area of the planet occupied by living organisms.

BIOLOGY AS A SUBJECT. ITS SIGNIFICANCE FOR MEDICINE

Biology (greek *bios* — life, alive; *logos* — study, science) studies life as a particular form of matter movement. The subject of its study is all living organisms, from unicellular to multicellular ones including the human, and all organization levels of living things. Modern Biology is a complex science. As to the objects of the study, it is subdivided into Microbiology (bacteria study), Botany (plants study), Zoology (animals study), and Human Biology. Specific

sections of these sciences are devoted to Anatomy, Morphology and Physiology. Such disciplines as Genetics, Parasitology and Ecology refer to the greatest trends in Biology. As to organization levels of living things we can distinguish Molecular Biology, Cytology (cell study), Histology (tissue study), Population Biology.

Studying Biology is of great importance for training doctors of any specialty. The knowledge of Parasitology, Genetics, Cytology and Molecular Biology often help diagnose the disease and render effective help to a patient. The development and achievements of genetic engineering ensure the production of a number of medicines (antibiotics, vitamins, hormones). Studying Parasitology is necessary for treating infectious and invasive diseases and for elaboration of prophylactic methods.

HUMAN'S STANDING IN THE ANIMAL WORLD

The human as a biological species refers to the type of *Chordates*, subtype of V*ertebrates*, class of *Mammals*, subclass of *Placentals*, order of *Primates*, suborder of *Anthropoids* (narrow-nosed apes), family of *Hominids* (people), gender of *Homo* (man), species of *Homo sapiens* (a sensible person).

HUMAN AS A BIOLOGICAL AND SOCIAL BEING

The human has signs both of a biological and social being. Just like all *Chordates,* the human in an embryonic period undergoes the formation of axial organs: a chord, a nervous tube above it, and a gastrointestinal tube under it. Under the gastrointestinal tube, on the abdominal side is the heart. In all representatives of the *subphylum of Vertebrates*, including the human, the chord transforms into the spinal column, there is the heart on the abdominal side and 2 pairs of extremities.

Belonging to the *class of Mammals*, the human has a four-chamber heart, warm-bloodiness, a well-developed brain cortex, mammary glands, and the presence of hair on the skin. The development of a human fetus in the mother's body and its feeding through the placenta are the signs characteristic of *placental* animals. Relative ties of the human with *primates* are reflected in the following signs: a thumb is opposed to the other fingers, there are nails on fingers, one pair of mammary glands, well-developed clavicles, teeth of three types and replacement of milk teeth with permanent ones, and giving birth to one child in most cases.

The evidence of the animal origin of the human is also the presence of rudiments and atavisms. *Rudiments* are organs that undergo reverse development due to their dysfunction (for example, a vermiform process and the third lid). *Atavisms* are signs of return to ancestors (for example, the presence of a tail in children, when the number of caudal vertebrae is increased; a full hair covering of the upper part of the body — "lion boys", the presence of several pairs of mammary glands).

The following **signs** are characteristic only of the species of Homo sapiens: vertical walking, mobile hand, a spinal column with 4 curves, a large volume of the brain with a well-developed cortex, the cranial part is bigger than the facial one, abstract thinking, the presence of the 2nd signal system, producing working tools.

The progress of humankind obeys social laws — the laws of the society. Appearance of distinct speech was associated with the need of communication during joint hunting and defense from enemies. Appearance of fire and using thermally cooked food resulted in the decrease of the masticating apparatus and the facial part of the skull, and to the increase of the cranial part.

The development of social relations was due to producing working tools and hunting. The brain, thinking, consciousness were developing. Speech and working activity improved. Social factors began playing an important role in the development of the human. Knowledge, skills and spiritual values in the human society are passed to a young generation through teaching and educating.

LECTURE 2
Topic: CELL. CELLULAR THEORY. ORGANIZATION OF SUBSTANCES AND ENERGY FLOWS IN THE CELL

Plan

1. Cell as an elementary unit of living things.
2. Cellular theory; its modern status.
3. Basic forms of cellular organization.
4. Structure, properties and functions of an elementary membrane.
5. Organization of a substances flow in the cell.
6. Organization of an energy flow in the cell.

In 1665 an English physicist R. Hook studying a slice of corks from the bark of a tree noticed little boxes which he called *"cellula"*, a cell. Studying the cell ran alongside with the development of microscopic techniques. A Dutchman A. van Levenhook revealed unicellular organisms in water. In 1825 a Chech scientist Ya. Purkine described a semi-fluid, jelly-like content of the cell and called it "protoplasm" (greek *protos* — the first, *plasma* — formation). In 1831 an English Botanist R. Brown revealed a *nucleus* in the cell.

In 1838–1839 German researchers T. Schwann (a zoologist) and M. Schleiden (a botanist) joined the received findings and formulated a cellular theory. Its basic issues are as follows: 1) the cell is a basic structural unit of animals and plants; 2) the process of cell formation results in growth, development and differentiation of tissues of plants and animals.

In 1858 the paper “Cellular pathology” by a German pathologist R. Virchov was published. It had two important issues: 1) every cell originates from another cell due to division; 2) all diseases of the organism are due to some changes of the cellular structure and function.

The basic issues of a modern cellular theory:

1. The cell is a structural, functional and genetic unit of all living things, an open self-regulating system constantly passing flows of substances, energy and information.
2. Cells of all organisms have a similar structure, chemical composition and processes of vital activity.
3. Cells of a multicellular organism perform various functions and form tissues.
4. When a mother cell divides, new cells are formed.

Cytology (latin *cytos* — a cell, *logos* — a science) studies the structure, chemical composition, multiplication and development, cellular interaction in a multicellular organism.

Non-cellular forms of life

Viruses	Bacteriophages
(causative agents of human, animal and plant diseases)	(bacterial parasites)

Viruses (latin *vira* — poison) discovered by D. I. Ivanovsky in 1892 are widely spread in nature. Sizes of viruses range from 20 to 300 nm (are seen only under an electron microscope).

Viruses are intercellular parasites. The properties of living things, such as metabolism and multiplication, manifest only in a host cell. A dormant form of a virus that passes from one cell to another is called a *virion*.

The genetic apparatus of a virus (a DNA or RNA molecule) is in its head that is covered by a *“protein cover”*. A *virus tail* has a hollow core, a spiral protein outside and tail filaments at the end (fig. 1).

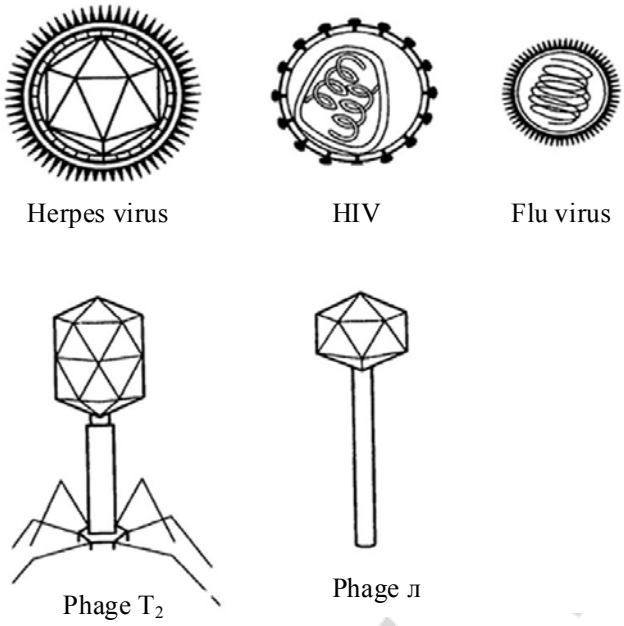


Fig. 1. External structure of viruses and bacteriophages

Over 3000 viruses that cause diseases of man (flu, hepatitis, encephalitis, HIV etc.), of animals (leucosis, brucellosis etc.) and plants (tobacco mosaic disease, dwarfism etc.) are described. In humans and animals, viruses affect the lymphatic, blood-vascular and nervous systems.

Basic forms of cellular organization

Prokaryots (prenuclear)			Eukaryots (nuclear)	
Mycoplasms	Bacteria	Cyanobacteria	Unicellular organisms (protists)	Cells of multicellular organisms

Prokaryots do not have a formed nucleus. Their genetic apparatus is a ring structure of DNA that is not linked with proteins-histones and is called a *nucleotide*.

The most primitive of prokaryots are *mycoplasms*. Their age is 3 billion years; the diameter is 0.1–0.25 μm.

The majority of them are symbionts and facultative parasites of mammals, insects and plants. Unlike viruses, they are capable of self-reproduction, and unlike bacteria, they do not have a cell wall.

Affection of human fetuses with mycoplasms causes *mycoplasmoses*. They affect the lungs and the central nervous system. They can produce a teratogenic action, causing chromosomal defects. In adults mycoplasmoses occur in the lungs, respiratory and urogenital organs (table 1).

Table 1

Cellular differences of prokaryots and eukaryots

Prokaryots	Eukaryots
No nucleus, nucleotide	There is a well-formed nucleus
DNA is not linked with proteins-histones	DNA is bound with proteins-histones

No membrane structures and organoids*, mitotic division	There are membrane structures and organoids, mitotic division

* Mesosomes perform their function — drawing in the cellular membrane.

Eukaryots have a formed nucleus surrounded by a nuclear membrane. The genetic apparatus is a complex structure of DNA linked with protein-histones (fig. 2).

The internal content of the cell is presented by a *cytoplasm* and *karyoplasm* (nucleus). In the cytoplasm, we can see a *gialoplasm* (cytoplasmatic matrix), *organelles* and *inclusions*. From outside the cell is covered with a membrane, the basic component of which is an elementary (biologic) membrane.

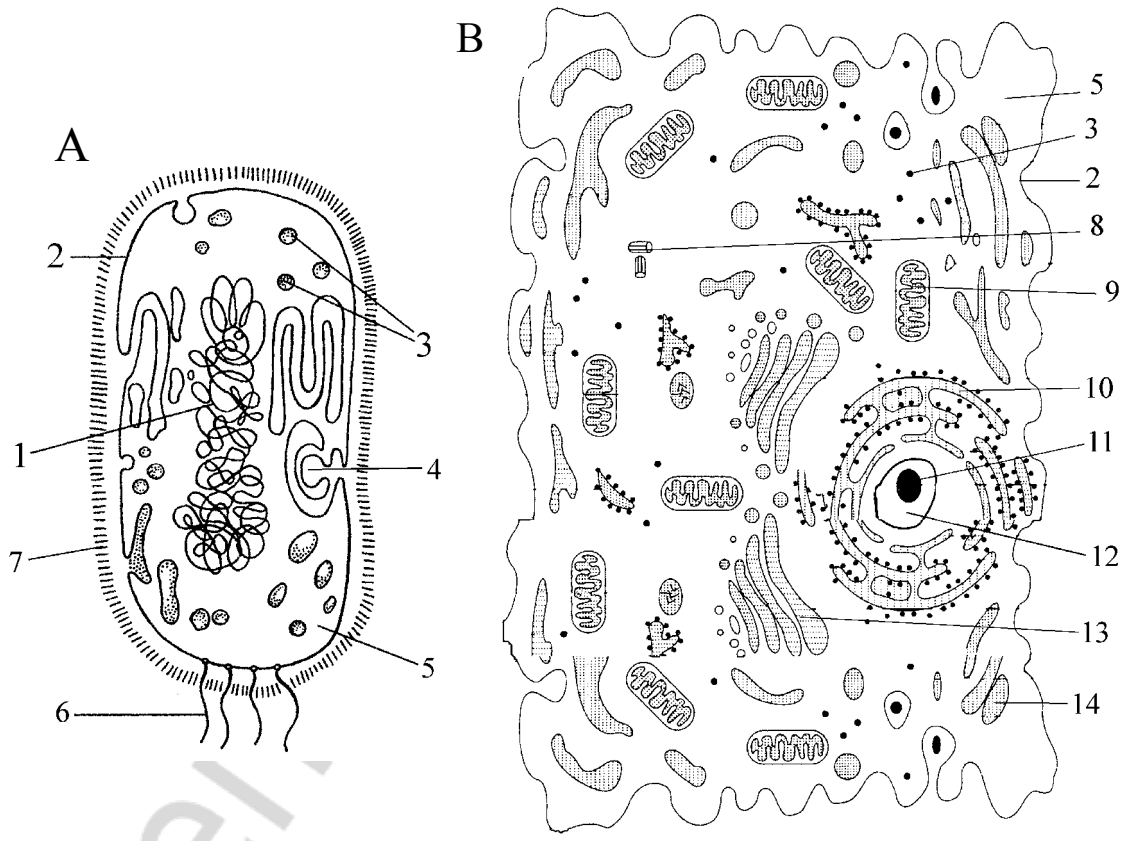


Fig. 2. Structure of prokaryotic (A) and eukaryotic (B) cells:
1 — nucleoid; 2 — plasma membrane; 3 — ribosomes; 4 — mesosome; 5 — cytoplasm; 6 — filaments; 7 — cell wall; 8 — cell center; 9 — mitochondria; 10 — granular ER (endoplasmic reticulum); 11 — nucleolus; 12 — nucleus; 13 — Golgi complex; 14 — smooth ER

ELEMENTARY MEMBRANE

N. Dawson and R. Danielly proposed the first model of the elementary membrane in 1943. It was a "**sandwich**" **model** (fig. 3A).

Two layers of lipid molecules are located between two layers of protein molecules. Each lipid molecule has two ends — a *hydrophilic* (soluble in water) and *hydrophobic* (insoluble in water). Hydrophobic parts of the molecule are directed to each other, while hydrophilic parts are directed to protein molecules.

In 1972 S. Singer and G. Nicolson proposed a better **fluid-mosaic** model which answers to properties and functions of the elementary membrane (fig. 3B).

Basic membrane components, *lipids*, comprise 20–80 % of their mass. They are phospholipids, lecithin and cholesterol. Protein molecules are in a double layer of lipid molecules that form a "lipid sea". Protein molecules passing through the two layers of lipid molecules are *integral*. Those molecules, some of which are in a bilipid layer, are called *semi-integral*. *Peripheral proteins* are on the surface of lipids. The third component of the elementary membrane is glycoproteins forming a receptor apparatus (*glycocalix*) on its surface.

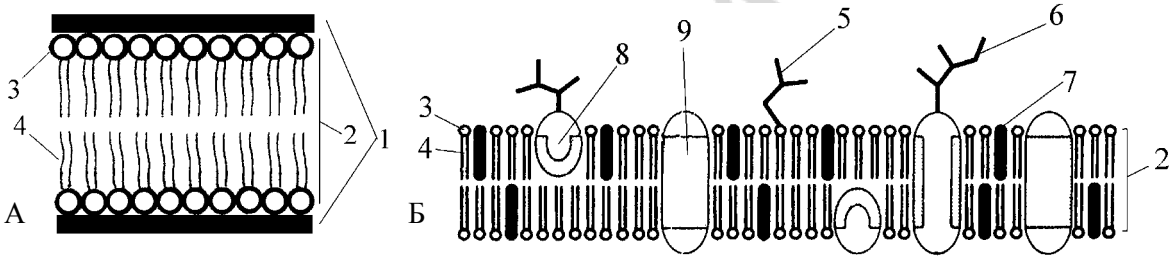


Fig. 3. Diagram of elementary membrane models:
А — "sandwich"; В — fluid-mosaic: 1 — solid protein layers; 2 — bilipid layer; 3 — hydrophilic heads of phospholipids; 4 — hydrophobal tails of phospholipids; 5 — oligosacharide chain of glycolipids; 6 — oligosacharid chain of glycoprotein; 7 — cholesterole molecule; 8 — semi-integral protein; 9 — integral protein; 10 — peripheral proteins

Properties of the elementary membrane:

- plasticity (restores quickly after injury; also stretches and compresses in cell movements);
- semi-permeability (selectively passes specific molecules);
- ability for self-locking (formation of phagosomes and vacuoles in feeding an amoeba).

Functions of the elementary membrane:

- structural (a membrane concept of the organelle structure is that all cellular organelle, except ribosomes and centrosomes, include membranes);
- barrier (defends the cell from external effect and sustains its composition);
- participates in metabolic processes (many biochemical reactions take place on membranes);
- receptor (receiving and differentiating signals, substances).

ORGANIZATION OF A SUBSTANCE FLOW IN THE CELL

The substance flow in the cell undergoes three phases:

a) passing of substances into the cell (membrane transport);
b) transformation and distribution of substances in the cell;
c) excretion of metabolites from the cell.

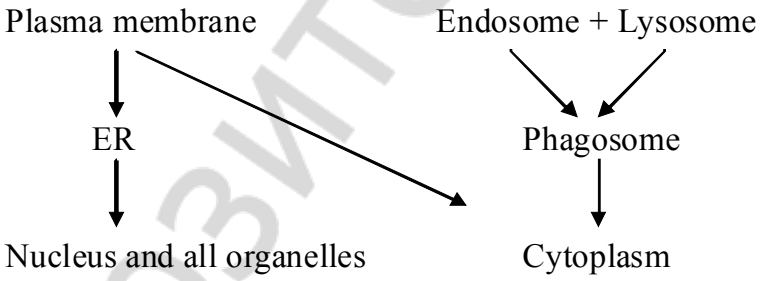
MECHANISMS OF MEMBRANE TRANSPORT

Passive transport runs on a concentration gradient without any waste of energy. Water and small molecules can pass into the cell by osmosis and diffusion, through pores or during dissolution in lipids. Lighted diffusion is associated with participation of molecular protein-carriers in transport and is called permeasis. In this way amino acids, sugars, fatty acids get into the cell.

Active transport requires waste of energy, as it runs against a concentration gradient. Such transport needs enzymes, ATP molecules and formation of special ional channels. A sodium-potassium pump is an example of such mechanism.

Cytosis is participation of the membrane itself in capturing particles or molecules and transferring them into the cell (*endocytosis*) or excreting them from the cell (*exocytosis*). Cytosis means reversible changes of architectonics (outlines) of the membrane. Transport of macromolecules or hard particles is called phagocytosis, while transport of fluid drops is called *pinocytosis*.

Substances and molecules that have passed the plasma membrane are distributed throughout the cell.



Assimilation reactions take place in the anabolic system of the cell. It includes organelles: ribosomes, endoplasmic reticulum (ER), Golgi's complex.

Organelles are differentiated areas of the cytoplasm with a constant structure and performing specific functions (fig. 4).

Ribosomes are spherical bodies (15–35 nm in diameter) consisting of a large and small subunits. They may stay freely in the cytoplasm, on the external nuclear membrane, on ER channels. A *large subunit* of a ribosome contains 3 various rRNA molecules and 40 protein molecules. A *small subunit* contains 1 rRNA molecule and 33 protein molecules. A ribosome arrangement takes place in the pore area of the nuclear membrane. The information about the rRNA structure and ribosome proteins is stored in "nucleolus organizers"

(parts of a DNA molecule in the area of secondary constrictions of satellite chromosomes). Ribosomes take direct part in arranging protein molecules. Free ribosomes synthesize protein for vital activity of the cell itself, the attached ones — proteins for excretion from the cell.

Endoplasmic reticulum (ER) are tubes and flattened membranous sacs located throughout the cell and connected with a perinuclear space of the nucleus and the cavities of a Golgi's complex. The interior compartment of the ER, referred to as the *lumen*, is separate and distinct from the surrounding cytoplasm. ER membranes perform the function of compartmentalization of the cytoplasm of the cell, its division into parts where various biochemical reactions take place. *Granular (rough) ER* (ribosomes are located on its membranes) participate in biosynthesis of proteins that are later transported to a Golgi's complex. Carbohydrates (glycogen) and lipids (cholesterol) are synthesized on membranes of a *smooth ER*. It participates in synthesis of steroid hormones, in excretion of chlorine ions (epithelial cells of the stomach), in detoxication by hepatic cells.

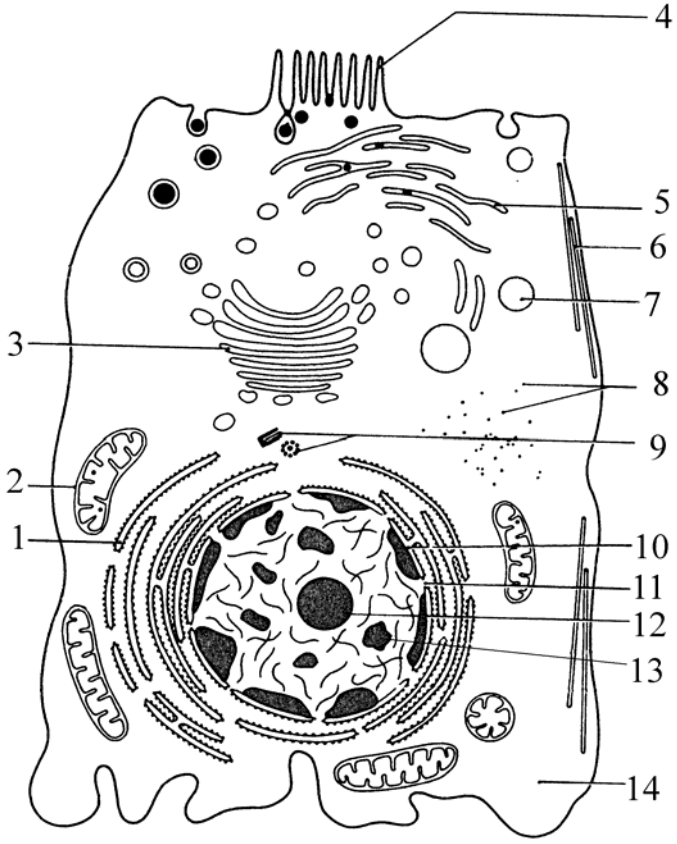


Fig. 4. Diagram of a thin cell structure:
1 — granulation ER; 2 — mitochondria; 3 — Golgi's complex; 4 — microcillia; 5 — smooth ER; 6 — microtubes; 7 — lysosome; 8 — ribosomes; 9 — cell center; 10 — nuclear membrane; 11 — nuclear pore; 12 — nucleous; 13 — chromatin; 14 — cytoplasm

Golgi's complex (Golgi apparatus) consists of vesicles, tubes, sacs. Dictisomes are basic elements of the complex. Dictisomes are piles of 10–15 elemen-

tary membranes that are dilated at the ends. These dilations form vesicles that are separated and transformed into lysosomes and vacuoles. Some of these vesicles excrete secrets and metabolites from the cell. Golgi's complex has the following functions: 1) sorting out and packing substances, synthesized in ER, into vesicles; 2) formation of complex compounds (lipoproteins, glycoproteins); 3) arranging elementary membranes; 4) formation of lysosomes, glyoxisomes and vacuoles; 5) secretion of substances.

Dissimilation reactions take place in the catabolic system of the cell. It includes: mitochondria, lysosomes, microbodies (peroxisomes and glioxisomes).

Primary lysosomes are formed in Golgi's complex. They look like rounded bodies (0.2–0.4 μm in diameter), covered with an elementary membrane. They include approximately 50 various hydrolytic enzymes. Breaking down of substances takes place in *secondary lysosomes* that are formed by fusing with a *primary lysosome* and *phagosome*. Lysosomes are capable of dissolving the structures of separate organoids.

Peroxisomes are formed in ER. Their enzymes (oxidizes) oxidize amino acids and form peroxide (H_2O_2).

Glyoxisomes are formed in Golgi's complex. Their enzymes transfer fats into carbohydrates.

Mitochondria under a light microscope have a form of rods, filaments, granules. The size of mitochondria is from 0.5 to 7 μm. Their number is different in cells with different activity. A mitochondria wall has an *inner* and *outer* membrane. Growths on the *inner* membrane form *cristae* enclosing a homogenic *internal matrix*. The interspace between wall membranes of mitochondria is filled with an *external matrix*. There are *3 enzyme systems* in mitochondria: enzymes of *Crebs' cycle* or the cycle of a citric acid in the internal matrix; enzymes of tissue respiration on the *inner* membrane and in the external matrix; enzymes of *oxidative phosphorilizing* in ATP-somes (cristae). Mitochondria have an autonomous system for protein biosynthesis. There are ribosomes, various RNA and ring molecules of DNA in its internal matrix.

Functions of mitochondria: ATP synthesis (transformation of energy of broken down compounds into that of phosphate bonds), synthesis of specific proteins and steroid hormones.

Energy exchange has three stages:

I — preparatory

II — withot oxygen (anaerobic)

III — with oxygen (aerobic)

The primary source of energy at our planet is the Sun.

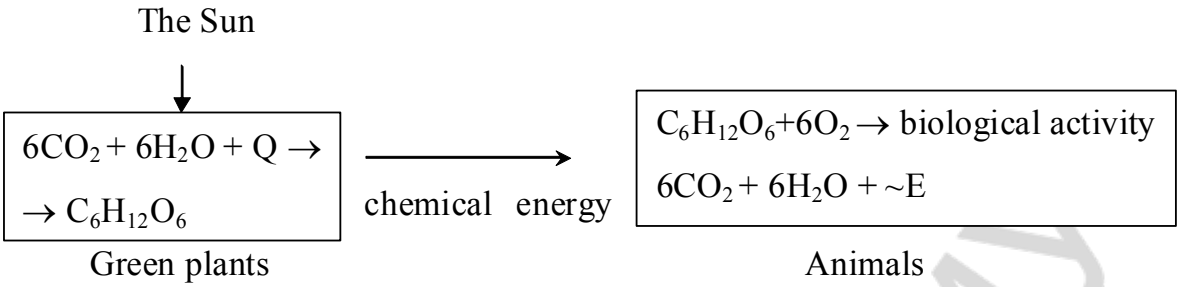


Diagram 1. Organization of an energy flow

Preparatory stage takes place in the digestive system of organisms and in cellular phagosomes where complex organic compounds break down into simple ones: polysaccharides to monosaccharides, proteins to amino acids, fats to glycerol and fatty acids.

Anaerobic stage takes place in the cellular cytoplasm. It involves 10 enzymes. Glucose is broken down into pyroacemic acid (pyruvate) and 2 ATP molecules are formed. The pyruvate may pass into mitochondria (for further transformations). During muscular activity, the lactic acid is formed there.

Aerobic stage of energy exchange takes place in mitochondria. Pyruvate in combination with coenzyme A (CoA) passes into the internal matrix of mitochondria. Hydrogen atoms are split from an activated form of an acetic acid (Acetyl CoA).

The resulting CO_2 is released from a mitochondria while protons and electrons (from hydrogen atoms) pass to the enzyme system of tissue respiration (fig. 5). Protons are accumulated on the outer surface of the internal membrane while electrons — on the inner one. On achieving a critical potential protons pass through the channels in ATP-somes.

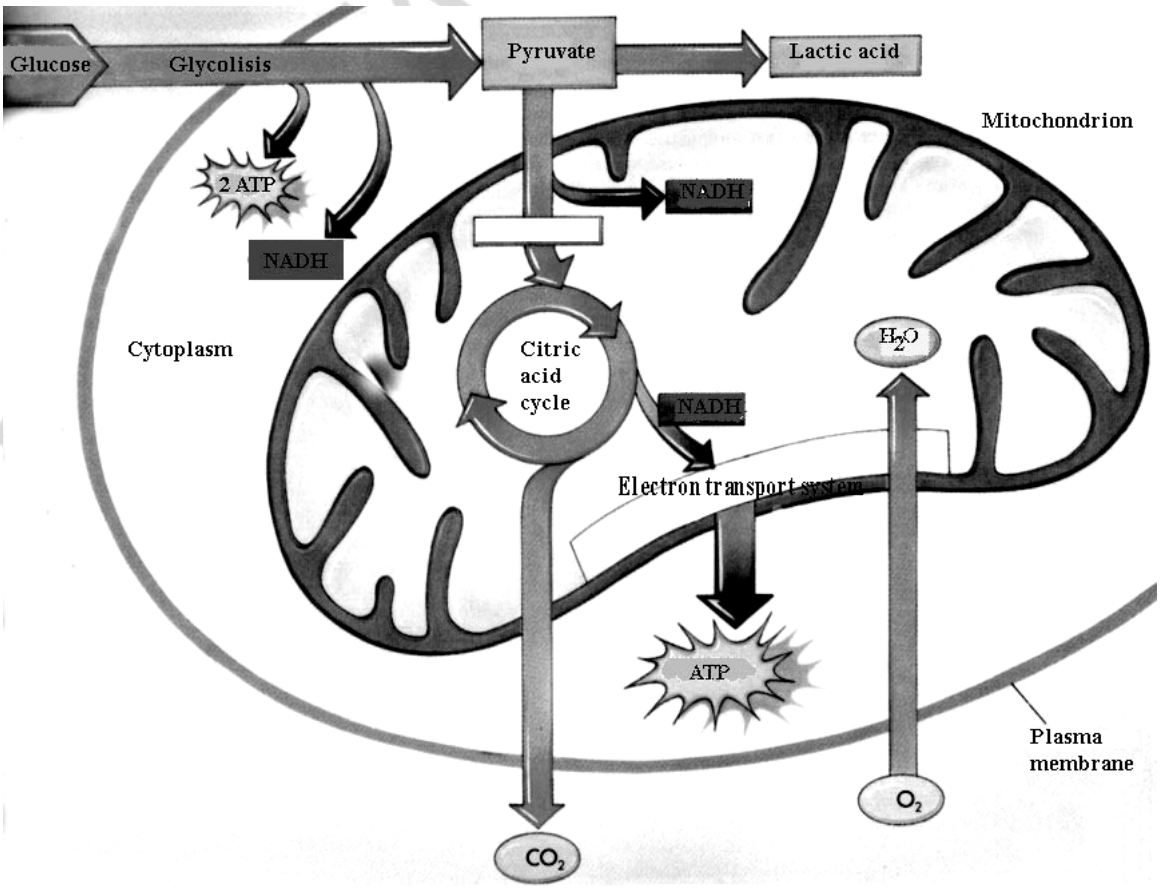


Fig. 5. Organization of an energy flow

Electrons give energy for attaching the remains of a phosphoric acid to ADP and for forming ATP, and then they join the protons. Hydrogen atoms are formed and in association with oxygen, they give water molecules. Because of all transformations of 1 glucose molecule 36 molecules of ATP +2 molecules of the anaerobic stage are formed, in total 38 molecules of ATP (fig. 5).

LECTURE 3
Topic: ORGANIZATION OF A GENETIC INFORMATION FLOW

Plan

1. Structure and functions of a cell nucleus.
2. Chromosomes: their structure and classification.
3. Cell and mitotic cycles.
4. Mitosis, meiosis: their cytological and cytogenic characteristic, significance.

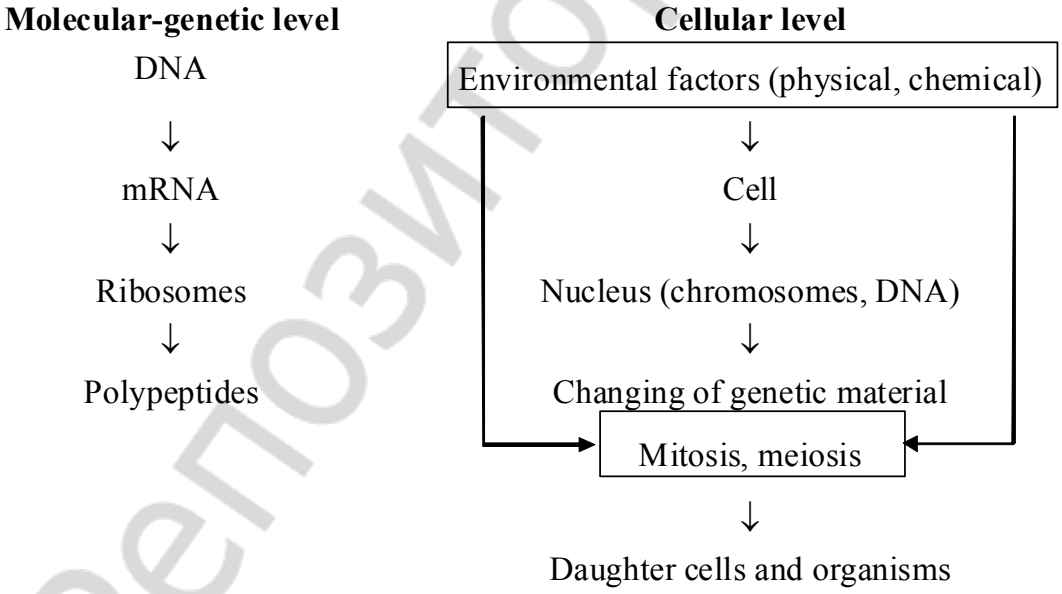


Diagram 2. Genetic information flow

STRUCTURE AND FUNCTIONS OF THE CELL NUCLEUS

The cell nucleus contains the basic genetic information.

Cell nucleus (Latin — *nucleus*; Greek — *karyon*) was described in 1831 by R. Brown. The shape of the nucleus depends on of the shape and functions of the cell. Sizes of nuclei change depending on the metabolic activity of cells.

The nucleus is surrounded by two membranes, which together form the **nuclear envelope**. The two membranes of the nuclear envelope are separated by 10–20 nm. The *perinuclear space* is in between inner and outer membranes. This membranes are perforated by **nuclear pores** approximately 9 nm in diameter, which connect the interior of the nucleus with the cytoplasm. At these pores, the outer membrane is continuous with the inner membrane. Each pore is surrounded by a pore complex made up of eight large protein granules. During active metabolic processes in the cell, the majority of pores are open. They pass a substance flow from the cytoplasm to the nucleus and back. RNA and proteins pass through these pores to enter or leave the nucleus. The number of pores in one nucleus amounts to 3–4 thousand. The outer nuclear membrane is linked with ER. It is there that *ribosomes* are located. Proteins of the internal surface of the inner nuclear membrane form a *nuclear lamina*. The nuclear lamina maintains the shape of the nucleus by its attachment to both the chromatin and the nuclear envelope (fig. 6).

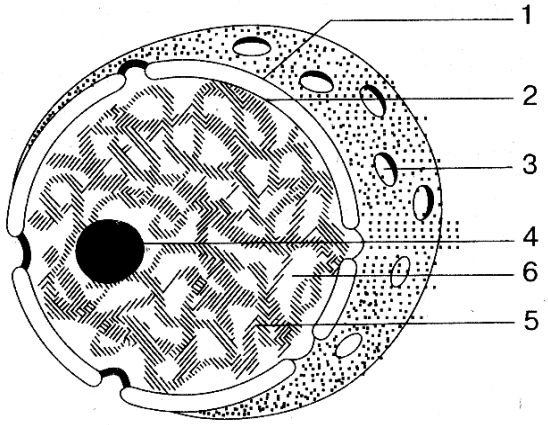


Fig. 6. Structure of a cell nucleus:
1 and 2 — outer and inner membranes of the nuclear envelope; 3 — nuclear pore; 4 — nucleolus; 5 — chromatin; 6 — nucleoplasm

Inside the nucleus, DNA combines with proteins (DNP – deoxyribonucleoprotein) to form a fibrous complex called chromatin. They contain DNA, proteins-histones and RNA in proportion 1:1.3:0.2. Prior to cell division, the chromatin aggregates to form discrete, readily visible structures called chromosomes.

Surrounding the chromatin are water and dissolved substances (proteins, lipids, carbohydrates, RNA, nucleotides, enzymes) collectively referred to as the **nucleoplasm**. Within the nucleoplasm, a network of apparently structural proteins called the *nuclear matrix* organizes the chromatin.

Nucleolus is a component of the nucleus that is not always present. It disappears at the beginning of cellular division and restores at its end. The chemical

composition of nucleoli is protein (~90 %), RNA (~6 %), lipids, enzymes. The nucleoli are formed in the area of secondary constrictions of satellite chromosomes. The function of nucleoli is to arrange ribosomal subunits.

During most of a cell's life cycle, the nuclear envelope is a stable structure. When the cell divides, however, the nuclear envelope fragments into pieces of membrane with attached pore complexes. The envelope re-forms when distribution of the duplicated DNA to the daughter cells is completed.

Functions of the cell nucleus:

1) the nucleus is the region of the cell were genetic information is stores;
2) the nucleus is the site of DNA duplication;
3) the nucleus is the site of genetic control of the cell's activities;
4) a region within the nucleus, the nucleolus, begins the assembly of ribosomes from specific proteins and RNA.

CHROMOSOMES: THEIR STRUCTURE AND CLASSIFICATION

Chromosomes (greek *chromo* — color, *soma* — body). Chromatin is diffuse throughout the nucleus until just before cell division, when it condenses to form chromosomes. Their length is 0.2–5.0 μ m, 0.2–2 μm in diameter.

A metaphase chromosome consists of two *chromatids* that are linked with a *centermere (the primary constriction)*. It divides the chromosome into two *arms*. Some chromosomes have *secondary constrictions*. An area that they separate is called a *satellite* and these chromosomes are called satellite chromosomes. The end parts of chromosomes are called *telomeres*. Under a microscope, two kinds of chromatin can be distinguished in the stained interphase nucleus: *euchromatin* and *heterochromatin*. **Euchromatin** is diffuse and stains lightly; it contains the DNA that is transcribed into mRNA. **Heterochromatin** stains densely and is generally not transcribed; any genes that it contains are thus inactivated.

The types of chromosomes are detected by the location of the centermere (fig. 7).

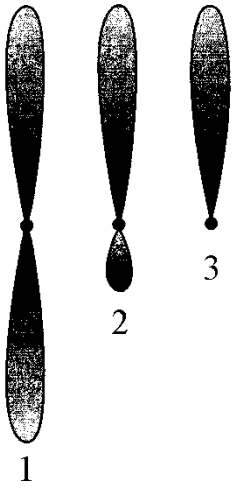


Fig. 7. Types of chromosomes

1. *Metacentric chromosomes*. The centermere is located in the middle, the arms are of the same length. A part of the arm near the centermere is called proximal while the opposite one — distal.

2. *Submetacentric chromosomes*. The centermere is biased from the center and the arms are of the same length.

3. *Acrocentric chromosomes*. The centermere is very biased from the center and one arm is very short, while the other is very long.

The cells of salivary glands of insects (Drosophila) sometimes have gigantic, *polytenic chromosomes* (multithread chromosomes).

There are 4 rules for chromosomes of all organisms:

1. *Constancy of the number of chromosomes*. In norm, the organisms of some species have a constant, characteristic of this species number of chromosomes. For example, humans have 46, dogs — 78, while Drosophilae — 8 chromosomes.

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

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

4. *Continuity of chromosomes*. In duplication of genetic material, one chromosome is formed from the other.

The number, shapes, and sizes of chromosomes in a somatic cell, which together constitute its **karyotype**.

Classification of chromosomes is performed according to different signs.

1. Chromosomes, identical in cells of a male and female organism, are called *autosomes*. A human has 22 pairs of autosomes in the karyotype. Chromosomes opposite in cells of a male and female organism are called *heterochromosomes* or *sex chromosomes*. In males they are X and Y-chromosomes and in females — X and X.

2. Arrangement of chromosomes in a descending order is called an *ideogram*. This is a systematized karyotype. Chromosomes are arranged in pairs (homologous chromosomes). The first pair includes the largest chromosomes while the 22^{nd} — small ones and 23^{rd} — sexual chromosomes.

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

Group A includes 1^{st}–3^{rd} pairs of chromosomes. These are large metacentric and submetacentric chromosomes. Their CI is 38–49 %.

Group B includes 4th and 5th pairs of chromosomes, large metacentric chromosomes. CI is 24–30 %.

Group C includes 6th–12th pairs of chromosomes of a medium size, submetacentric ones. CI is 27–35 %. This group comprises an X-chromosome.

Group D. 13th–15th pairs of chromosomes. Chromosomes are acrocentric. CI is about 15 %.

Group E. 16th–18th pairs of chromosomes. They are relatively short, metacentric or submetacentric. CI is 26–40 %.

Group F. 19th–20th pairs. Short, submetacentric chromosomes, CI — 36–46 %.

Group G. 21st–22nd pairs. Small, acrocentric chromosomes. CI is 13–33 %. This group comprises and Y-chromosome.

4. *The Paris classification of human chromosomes* was established in 1971. This classification helps in locating genes in a specific pair of chromosomes. Using special staining methods one can detect a characteristic sequence order of dark and light bands (segments) in every chromosome. The segments are marked according to the names of methods that help revealing them: Q-segments — staining with acrichinyperite; G-segments – staining with Gimza's stain; R-segments — staining after thermal denaturizing and others. A short arm of the chromosome is denoted with *p* and a long one — with *q*. Each arm of the chromosome is divided into loci and denoted with figures from the centermere to the telomere. The bands inside loci are numbered from the centermere. For example, the gene location of esterase D — 13p14 — is the 4th strand of the 1st locus of a short arm of the 13th chromosome.

Function of chromosomes is to store, to reproduce and transmit genetic information in multiplication of cells and organisms.

CELL AND MITOTIC CYCLES

There is a cell and mitotic cycle in life of the cell.

Cell's life cycle is a period from the cell appearance to its death or to the next cell division. Somatic cells undergo the following life cycles: growth, differentiation, performing specific functions, preparation for cell division (multiplication).

The majority of cells are characterized by a **mitotic cycle**, a period of their preparation for division (interphase) and division itself (mitosis).

Interphase consists of three subphases, identified as G_1, S, and G_2. The cell's DNA replicates during the S phase (the S stands for synthesis). The period between the end of mitosis and the onset of the S phase is called G_1 *(presynthetic)*, or Gap 1. Another gap phase — G_2 (*postsynthetic)* — separates the end of the S phase and the beginning of mitosis, when nuclear and cytoplasmic division take place and two new cells are formed. Mitosis and cytokinesis are referred to as the M phase of the cell cycle (diagram 3). During the inter-

phase the genetic material content is changing in the cell: n — a complement of chromosomes, chr – the number of chromatids in the chromosome, c — the number of DNA.

The G_1 period starts immediately after cellular division. The content of genetic material is 2n1chr2c. On an average, this period lasts 12 hours, but it may take several months. During this period the cell is growing, it starts functioning; active processes of synthesis of RNA, proteins, DNA nucleotides are taking place. The number of ribosomes increases, the energy is being stored in ATP molecules.

The cell cycle consists of a mitotic (M) phase, during which nuclear division (mitosis) and then cell division (cytokinesis) take place. The M phase is followed by a long period of growth known as interphase. Interphase has three subphases (G_1, S, and G_2) in cells that divide.

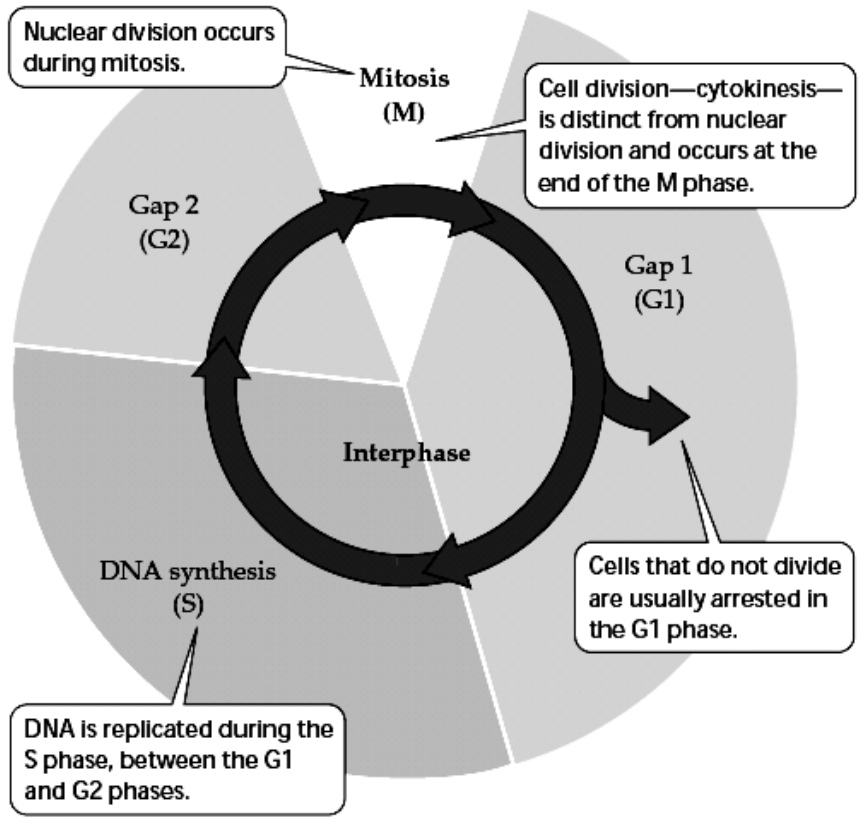
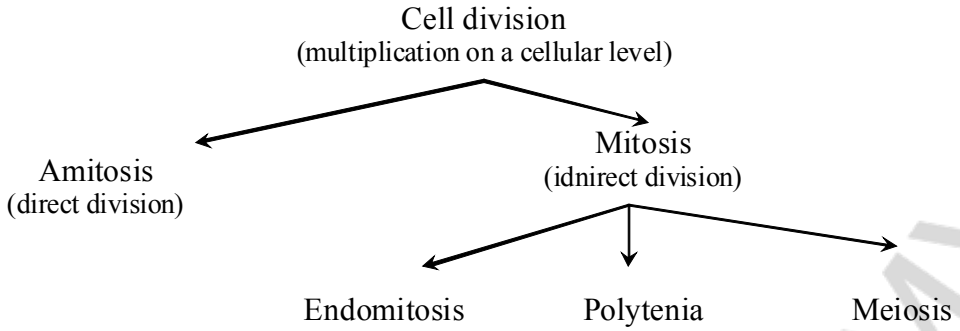


Diagram 3. The Eukaryotic Cell Cycle

During the *S period* replication of DNA molecules starts, every chromatid builds up its twin. The content of genetic material becomes 2n2chr4c. Centrioles of the centrosome ("central body") duplicate. RNA, ATP, and proteins-histones are being synthesized. The cell continues performing its functions. The duration of the period is up to 8 hours.



During the G_2 *period,* the cell is getting ready for mitotic division. Energy is being stored; RNA and predominantly nuclear proteins and protein of achromatic spindle division are being synthesized. The content of genetic material does not change: 2n2chr4c. By the end of the period all synthetic processes slow down, the cytoplasm viscosity changes, the nuclear/cytoplasm ratio reaches its critical value. The cell starts dividing.

During *amitosis,* chromatin in the nucleus does not coil, division spindle is not formed. The nucleus and cytoplasm are divided by a constriction into two. It is proved, that genetic material is uniformly distributed between daughter cells. Non-specific cells are usually divided by amitosis; these are epithelial cells of mucous membranes, cancer cells (genetic information may be distributed there unevenly) and cells participating in regeneration. Amitosis may cause the appearance of multinuclear cells (the nucleus has been divided but the cytoplasm has not).

MITOSIS, MEIOSIS
CYTOLOGIC AND CYTOGENETIC CHARACTERISTIC

Mitosis is the basic division of somatic cells. Reasons for mitosis:

- changing the nucleus/cytoplasm ratio from 1/6–1/8 to 1/69–1/89;
- presence of "mitogenetic rays", that stimulate division of adjacent cells;
- action of "wound hormones" that identify injured cells and stimulate division of intact cells.

Mitosis purpose:

- to sustain the constancy of the chromosome number, to provide genetic heredity in cellular populations;
- to support uniform distribution of chromosomes and genetic information between daughter cells.

A continuous mitosis has 4 stages: a prophase, metaphase, anaphase and telophase (fig. 8).

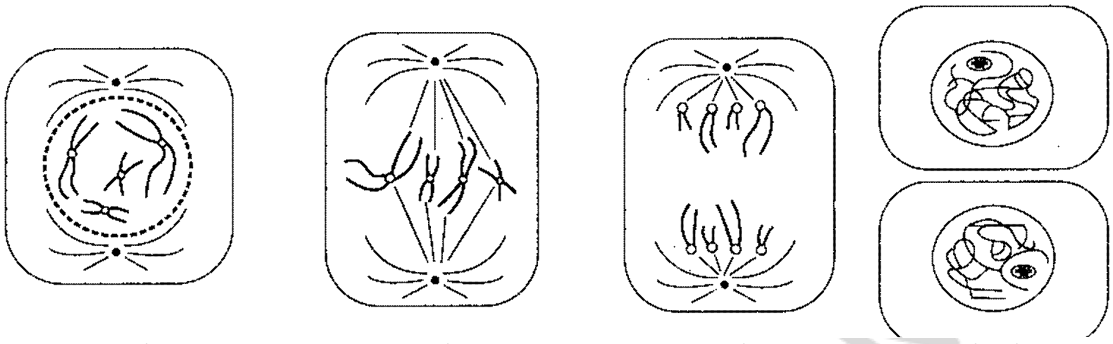


Fig. 8. Mitotic cellular division

Prophase starts with condensation of chromatin: long chromatin filaments become shorter and thicker forming chromosomes. Centrioles diverge to cellular poles, spindle filaments of division are formed. The volume of the nucleus enlarges, nucleoli and the nucleus membrane dissolve. Chromosomes pass into the cytoplasm of the cell. The content of genetic material is 2n2chr4c.

Metaphase. Chromosomes are oriented to cellular equator forming a metaphase plate. Spindle filaments of division are attached to chromosomal centermeres. One can see that every chromosome consists of two chromatids. The content of genetic material is not changed: 2n2chr4c.

Anaphase. Spindle filaments of division contract. Chromatids are divided in the area of centermeres and diverge to poles. They are called daughter chromosomes. The content of genetic information, 2n1chr2c, is at every pole of the cell.

During the *telophase* the formation of daughter nuclei occurs. Nucleus membranes are formed, restore nucleoli. The chromosomes begin to uncoil, continuing until they become the diffuse tangle of chromatin that is characteristic of interphase.

The final stage of mitosis is *cytokinesis* (division of cytoplasms). The formation of daughter membranes in animals start with the periphery of the mother cell, while in plants — from the center to the periphery. The cellular membrane is formed in fusion of ER vesicles. If the cytokinesis is inhibited, multinuclear cells are formed.

The impact of environmental factors on the cell during mitotic division may cause injuries of chromosomes, impairment of spindle division or cytokinesis which, in its turn, will result in mutations — polyplodia or heteroplodia.

The varieties of mitosis are endomitosis, polytenia and meiosis.

Endomitosis is reproduction (duplication) of chromosomes without division of the nucleus. It results in the formation of polyploid cells.

In *polytenia* reiterative duplication of chromatids takes place. Chromatids do not diverge forming polytenic (multithread) chromosomes. They occur in salivary glands of Drosophila.

Meiosis is a special division of somatic cells of genitals that results in the formation of gametes. Meiosis consists of 2 divisions: meiosis I and meiosis II. Every division has 4 phases: prophase I and prophase II; metaphase I and metaphase II; anaphase I and anaphase II; telophase I and telophase II (fig. 9).

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

1) *leptotene*: chromatin is condensed, thin chromatin filaments are formed and start their movement to each other with their centromere region; genetic material is 2n2chr4c.

2) *zygotene*: the conjugation of short, thick chromatin filaments (chromosomes) starts, they are connected along the full length, genetic information is not changed – 2n2chr4c.

3) *pachytene*: homologous chromosomes are tightly connected along the full length; the formed figures are called bivalents of chromosomes or tetrads of chromatids; genetic material may be expressed as 1nbiv4chr4c; by the end of this stage in the area of centermeres repulsion forces arise and crossing over takes place (exchange of areas of homologous chromosomes);

4) *diplotene*: repulsion forces continue their action, but chromosomes stay connected in the region of *chiasm*; the content of genetic material is preserved — 1nbiv4chr4c;

5) *diakinesis*: condensation of chromosomes is completed, the nuclear envelope and nucleolus disappear; bivalents of chromosomes connected with their ends pass into the cytoplasm and move to the equator of the cell; spindle filaments of division are attached to centermeres of chromosomes; 1nbiv 4chr4c.

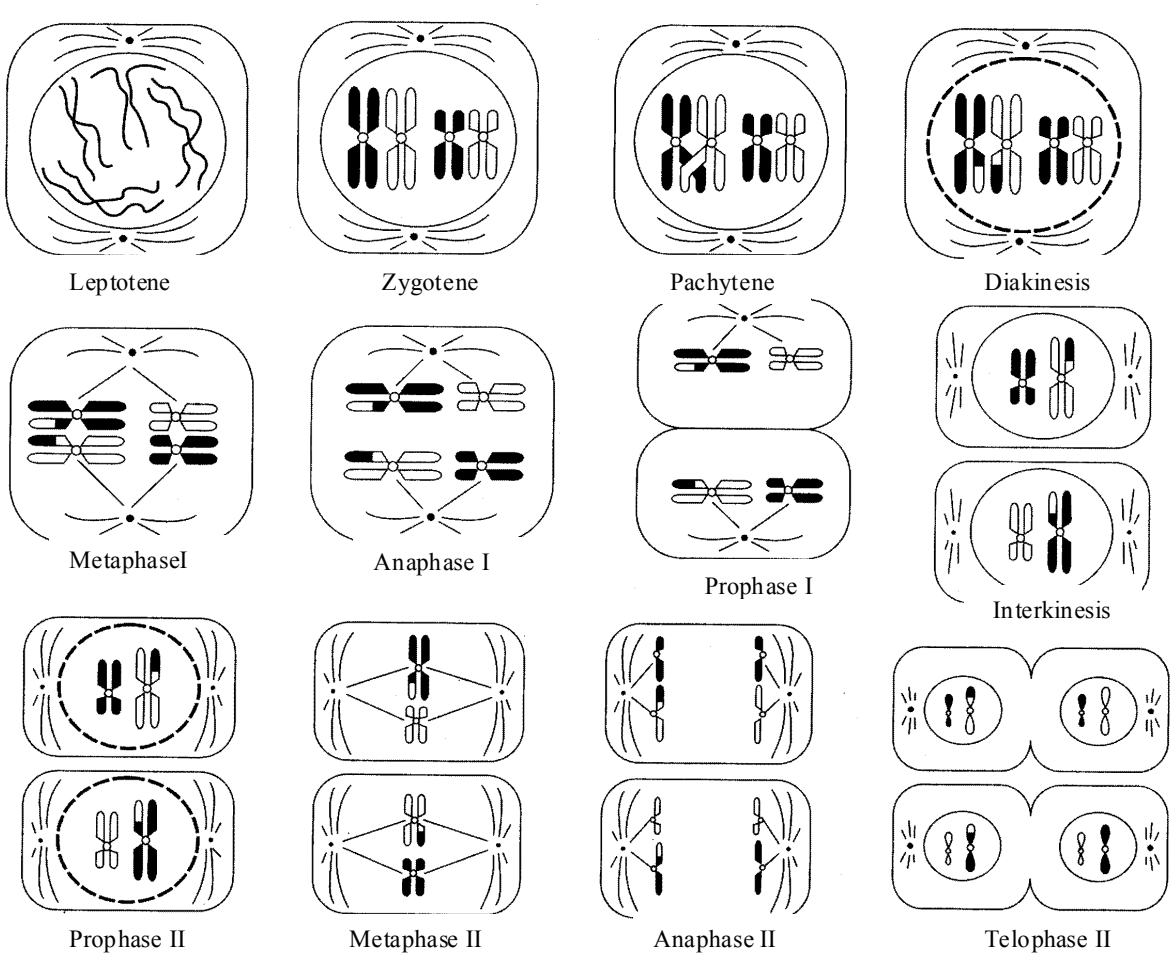


Fig. 9. Meiosis

In *the metaphase of meiosis I* bivalents are located along the equator of the cell; separate chromosomes are clearly seen; genetic material — 1nbiv 4chr4c.

Anaphase I: bivalents break into separate homologous chromosomes that diverge to the poles of the cell; each chromosome contains 2 chromatids; the content of genetic material at every pole is 1n2chr2c; reduction of the number of chromosomes has taken place — a diploid complement of chromosomes became a haploid one. That is why the 1st division of meiosis is called *reducing*.

During the *telophase* of meiosis I the cytokinesis takes place and 2 daughter haploid cells are formed — 1n2chr2c; unlike mitosis, decondensation of chromosomes does not occur.

After meiosis I comes interkinesis, a short interval between 2 divisions, then meiosis II starts. DNA replication does not occur.

The 2nd division of meiosis doesn't differ from mitosis, but in prophase II the condensation of chromosomes (1n2chr2c) does not take place, and in anaphase II chromatids (daughter chromosomes) branch to the poles of the cell. Every daughter cell gets a complement of genetic information 1n1chr1c. A hap-

loid complement of chromosomes is preserved. The second division of meiosis is called *equalizing*.

Four cells (gametes) with a haploid number of chromosomes are formed from 1 mother diploid cell.

Significance of meiosis:

- it is a mechanism of gamete formation;
- sustaining of a constant number of chromosomes in sexual reproduction;
- insurance of combinative variation as a result of crossing over, independent assortment of chromatids and chromosomes during gamete formation.

LECTURE 4
Topic: ORGANIZATION OF GENETIC MATERIAL (I)

Plan

1. Heredity and variation are fundamental properties of living things.
2. Gene: an evolution concept.
3. Evidence of a DNA role for transmission genetic information.
4. Structure and functions of nuclear acids.
5. Genetic code and its properties.
6. Properties of genes.
7. Classification of genes.

HEREDITY AND VARIATION ARE FUNDAMENTAL PROPERTIES OF LIVING THINGS

Heredity is the property of living things to preserve likeness of structural-functional organization in a number of generations.

Variation is the property of living things to acquire new characters under the influence of the environment.

Heredity is conservative. It consolidates and preserves characters of the organism and species. Variation, vice versa, permits organisms to acquire new characters and differ from parents.

The process of transmitting information from one generation to the other during sexual reproduction is called *inheritance* while the likeness degree of parents and children is called *inheritability*.

GENE: AN EVOLUTION CONCEPT

Ch. Darvin was the first to have written about heredity units. He called them heredity factors. In 1865 the work “Experiments with plant hybrids” by H. Mendel was published. He wrote there about *hereditary inclinations* that parental species pass to their off springs in sexual reproduction. Mendel made

experiments on peas. He wrote that hereditary inclinations are in gametes of parents; on fertilization they come together and form a zygote. Mendel's results were unusual for that time and scientists recognized them only in 1900 when H. de Freeze in the Netherlands, E. Chermak in Austria and K. Korrens in Germany got similar results and "rediscovered" Mendel's laws. 1900 is considered a year when the science of Genetics was born. In 1902 T. Bovery, E. W. Wilson and D. Setton proposed that hereditary factors were assocoated with chromosomes. In 1906 W. Betson introduced into Biology the term "genetics", and in 1909 W. Yohansen introduced the term "gene". In 1911 T. Morgan et al., conducting experiments on Drosophila, came to the conclusion, that genes were located in chromosomes in a linear order, and formulated a chromosomal theory of heredity. One question was unclear: what is the substance of heredity? In 1928 N. K. Koltsov presumed that the chromosome is a large protein molecule the radicals of which perform functions of genes.

EVIDENCE OF A DNA ROLE FOR TRANSMITTING GENETIC INFORMATION

Experiments on bacterial transformation (Griffith, 1929) gave one of the proofs of a DNA role for transmitting hereditary information.

F. Griffith made experiments on mice with 2 bacterial strains (diagram 5). Capsuliferous bacteria were virulent and caused death of mice of pneumonia, while uncapsuliferous ones were avirulent and mice stayed alive.

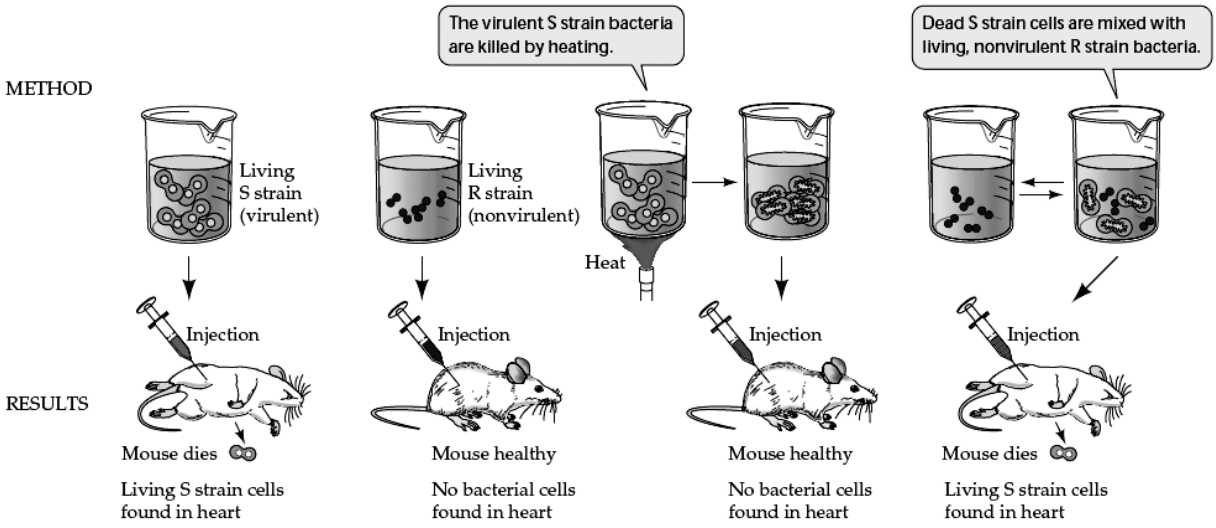


Diagram 5. Experiments of Griffith

In 1944 O. Every, K. MacLeod and M. MacCarty divided S strain bacteria into components. They were lipids, carbohydrates and DNA. Only when a rectified DNA was added to R-strain, they could observe that uncapsuliferous bacteria formed a capsule (character of virulence).

Bacterial transformation is the inclusion of parts of a bacterial DNA of one strain into a DNA of the other strain and transmitting its characters.

The experiments of N. Tsinder and J. Lederberg (195) on *transduction* in bacteria (fig. 10) gave one more proof of a DNA role for the transmission of hereditary information.

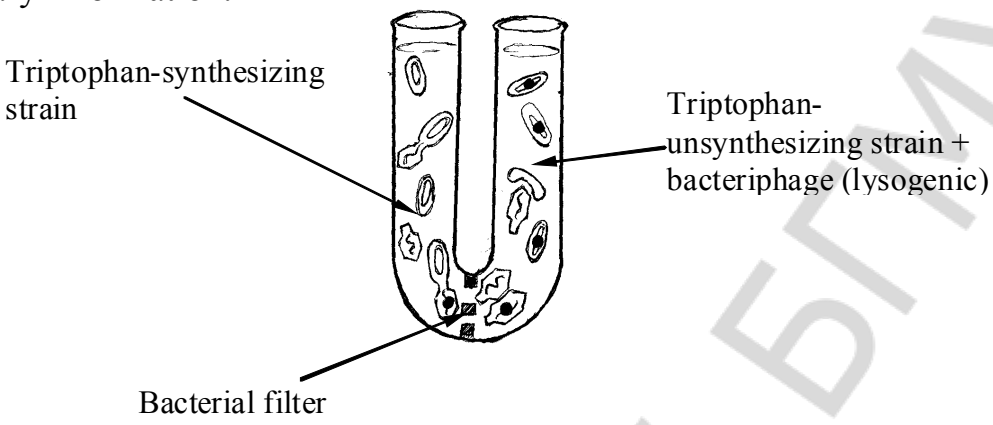
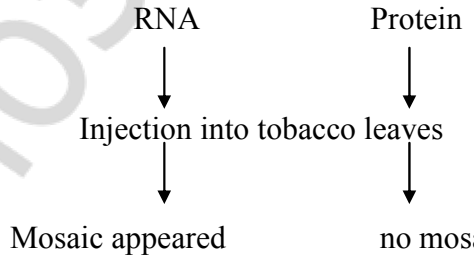


Fig. 10. Experiments of N. Tsinder and J. Lederberg

During the experiment two bacterial strains were placed into a U-shaped tube with some culture and a bacterial filter in the middle, the left bend was triptophan-synthesizing, the right one triptophan-unsynthesizing. The filter was impassable for bacteria and they did not mix. When a bacteriophage was introduced to the bend with triptophan-synthesizing bacteria, some time later they were revealed among triptophan-unsynthesizing bacteria. Thus, the filter was permeable for the bacteriophage. This event got the name of transduction.

Transduction is the ability of a bacteriophage to transfer DNA sections from one bacterial strain to the other and to pass its characters.

In 1950 H. Frenkel-Konrat obtained one more proof of the fact that the nuclear acid (RNA) participates in passing characters. A tobacco mosaic virus (TMV) was broken into RNA and protein



In the 40-s G. Biddle and E. Tatum proposed a hypothesis “one gene – one enzyme” on that basis that genes are responsible for synthesizing enzymes. However, the gene not always determines the synthesis of the whole protein mass. That is why the hypothesis was made more precise: “one gene – one polypeptide”.

STRUCTURE AND FUNCTIONS OF NYCLEIC ACIDS

In 1870 I. Misher described macromolecules in the nucleus and called them nucleic acids. They were DNA (deoxyribonecleic acid)) and RNA (ribonucleic acid). The molecular structure of DNA was decoded in 1953 by J. Watson, F. Kreek and M. Wilkinson. They called it a “life thread”.

Nucleic acids are polymers. Their monomers are *nucleotides*. A nucleotide contains a *nitrogenous basis*, sugar *deoxyribose* or *ribose* and the *phosphoric acid residue*. There are 5 types of *nitrogenous bases*: adenine, cytosine, thymine, uracil. DNA nucleotides contain adenine, guanine, cytosine and thymine. RNA nucleotides contain adenine, guanine, cytosine, uracil. Nitrogenous bases are denoted by the first letters: A, G — purine, T, C, U — pyrimidine.

The DNA molecule consists of two helixes. C*o-valent phosphodietheral links* between deoxyribase of one nucleotide and the phosphoric acid residue of the other form a sequence of nucleotides. Nitrogenous bases linked according to a *complement* principle (self-supplementation) are located inside the helix: A-T — 2 hydrogen bonds; G-C — 3 hydrogen bonds (fig. 11).

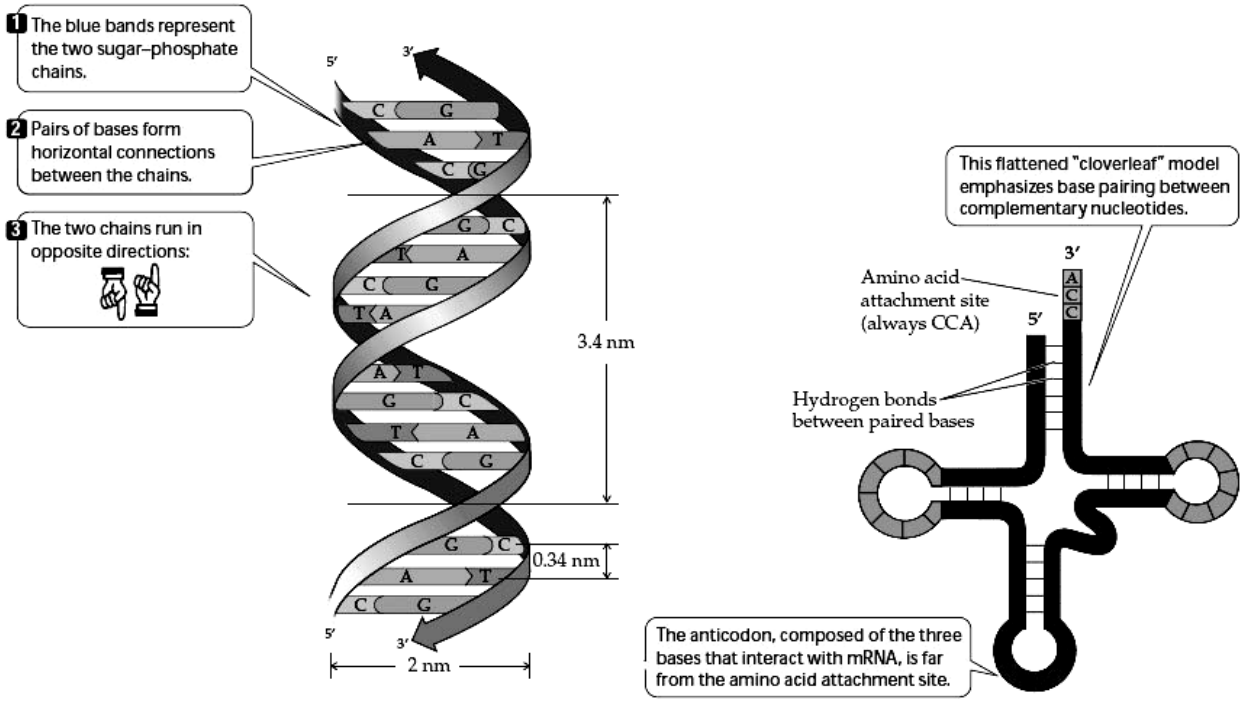


Fig. 11. Structure of a DNA molecule and tRNA

The character of complentarity of nitrogenous bases is expressed in the rules of Chargaff:

- the amount of purine bases is equal to the amount of pyrimidine bases: A + G = C + T;
- the amount of adenine is equal to that of thymine (A = T), the amount of guanine is equal to that of cytosine (G = C).

DNA is contained in a cellular nucleus, mitochondria and plastids.

DNA possesses the *properties* of replication (self-reproduction) and the ability to repair (restoration of its structure after molecular impairment).

The DNA function is to store and transmit genetic information during multiplication of cells and organisms.

The RNA molecule is also a polynucleotide but it has one sequence. Instead of thymine, it includes uracil and instead of deoxyribose it has sacharribose.

In some viruses, RNA is a store of hereditary information and has 2 sequences in the molecule.

There are 3 types of RNA in the cell. 3–4 % of the whole RNA is *messenger RNA* (mRNA): it "transcribes" genetic information from DNA and transmits it to ribosomes, where protein molecules are being arranged. *Ribosomal RNA* (r-RNA) comprises 80–85 % of the whole RNA. It is contained in ribosomes and ensures special interlocation of mRNA and r-RNA. *Transport RNA* (t-RNA) transports amino acids from the cytoplasm to ribosomes. T-RNA comprises 10–20 % of the whole RNA.

Ribonucleic acids are in the nucleus, cytoplasm, mitochondria and plastids.

Functions of RNA: participation in the synthesis of protein molecular structures (polypeptide molecules).

GENETIC CODE AND ITS PROPERTIES

- *Tripletness:* 1 codon corresponds to one amino acid in the molecule;
- *universality*: one and the same codon determines identical amino acids in all living organisms;
- *no overlapping*: one nucleotide comes into the composition of only one triplet;
- *degeneracy* or redundancy: several triplets may code one amino acid (there are 20 amino acids, but 64 possible triplets;
- *continuity* (no dividing signs between nucleotides);
- *unidirection* (formation of an mRNA goes in the direction from end 3' to end 5').
- the presence of *codons-initiators* among triplets (they start protein biosynthesis), codons-*terminators* (they denote the completion of protein biosynthesis).

The correspondence of the nucleotide order in a DNA molecule to the amino acid order in a polypeptide molecule is called *co-linearity*.

GENES CHARACTERS

1. *Specificity* is a unique sequence of nucleotides for every structural gene.
2. *Integrity* — gene as a functional unit (programming protein synthesis) is indivisible.

3. *Discretion.* A gene has subunits: amuton is responsible for mutation; arecon is responsible for recombination. A pair of nucleotides is their minimal number.

4. *Stability.* Genes are relatively stable. The incidence of self-mutation of a single gene is about $1{:}10^{-5}$ per generation.

5. *Liability.* Stability of genes is not absolute. They may alter, mutate.

6. *Pleotropia* is a multiple action of a gene (one gene is responsible for several characters.

7. *Expressivity* is a degree of phenotypical appearance of a gene. It is associated with environmental factors and the influence of other genes.

8. *Penetrance* is the incidence of appearing a gene: the ratio (in percents) of the number of species having this character to the number of species having this gene.

CLASSIFICATION OF GENES

According to function, genes are classified into structural and functional.

Structural genes contain information about proteins-enzymes, histones, sequences of nucleotides in various kinds of RNA. Functional genes affect the function of structural genes. Genes-modulators and genes-regulators are functional. *Genes-modulators* are inhibitors, intensifiers, modifiers. They enhance, attenuate or change the function of structural genes. *Genes-regulators* and *genes-operators* regulate structural genes.

The genotype of all somatic cells of the organism of one species is identical. However, cells of various tissues differ from one another. It is probably associated with functioning of various blocks of genes. The action area of this gene is called a *field of its action* (for example, the distribution of hair covering on the human body). As a rule, genes determining specific characters, do not "work" permanently (for example, genes determining the synthesis of sex hormones); their function considerably decreases with age. The functioning period of the gene is called the *time of its action*.

According to the place of action, genes are divided into 3 groups:

1. Genes functioning in all cells (for example, genes coding the enzymes of the energy exchange);

2. Genes functioning in cells of one tissue (determining the protein synthesis of miosine in muscular tissue);

3. Genes specific for one type of cells (genes of hemoglobin in immature erythrocytes).

Genes perform two main functions in the cell. A *hetezrosynthetic function* is programming biosynthesis of protein in the cell. An *autosynthetic function* is DNA replication (self-duplication of DNA).

DNA r*eplication* occurs during the synthetic period of the interphase of mitosis. The synthesis of a DNA molecule is semi-conservative: one sequence is

a mother one ("old") and a new "daughter" sequence is arranged on it. This new sequence is arranged according to the complementary concept. The basic enzyme of the synthesis is a DNA polymerase (A. Korenberg, 1956).

The DNA helix uncoils and divides into two sequences, each performing a role of the matrix (fig. 12). Replication starts immediately in several points of a DNA molecule. The DNA area from the beginning of one replication to the beginning of the other is called a *replicon*. A chromosomal eukaryote has many replicons, while a bacterial nucleoid — 1 replicon. The DNA polymerase in the replicon may move along a mother thread only in the direction from end 3' to end 5'. That is why the arrangement of mother DNA threads goes *antiparallel*, in opposite directions. The process takes place in all replicons simultaneously. The replication area is called *a replication fork*. DNA sequences in every fork assemble simultaneously several DNA-polymerases.

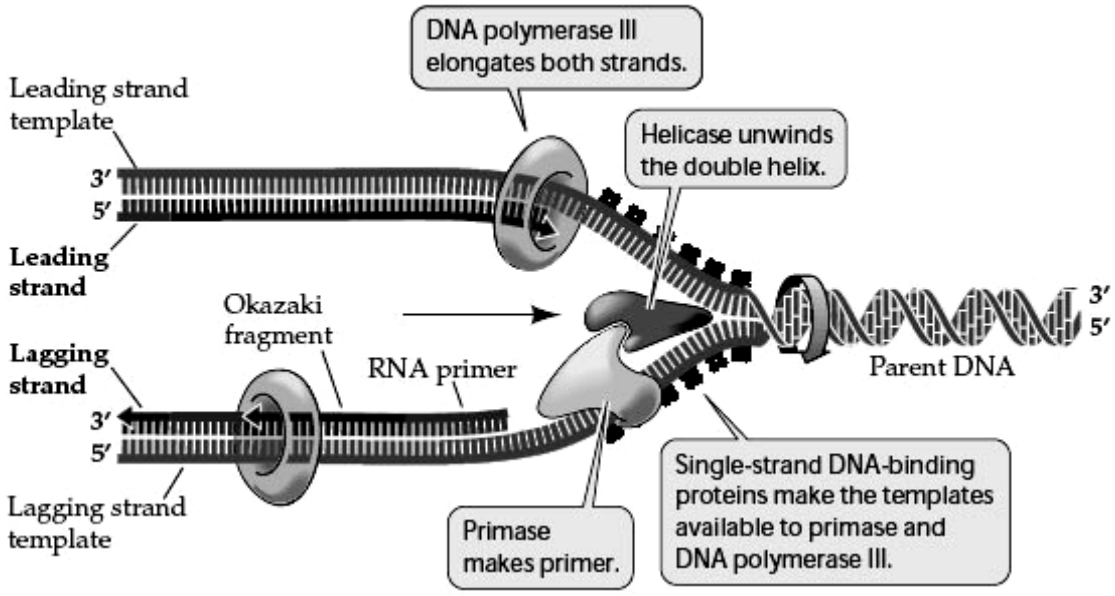


Fig. 12. Replication of a DNA molecule

In every replication fork, a DNA polymerase may gradually and continuously assemble one new DNA sequence (as it moves in one direction). The second sequence, a daughter one, is synthesized in small areas containing 150–200 nucleotides under the action of the DNA-polymerase that moves in the opposite direction. These areas are called Okazaki's fragments. All synthesized fragments of the polynucleotide sequence are linked with a lygase enzyme. A complete cellular genome is replicated once during the mitotic cycle.

LECTURE 5
Topic: ORGANIZATION OF GENETIC MATERIAL (II)

Plan

1. Packing levels of genetic material.
2. Levels of structural-functional organization of hereditary material.
3. Protein biosynthesis in the cell.
4. Transcription regulation in prokaryots and eukaryots.
5. Cytoplasmatic heredity.
6. Genetic engineering.

Chromosomes of the interphasal nucleus are represented by lumps of chromatin. *Chromatin*, DNP-deoxyribonucleoprotein, is DNA nucleoprotein fibrils linked with proteins. Their common length in the nucleus of a somatic human cell is up to 2 m. The length of all chromosomes in the metaphase comprises approximately 150 μm.

Such length reduction is due to 4 packing levels of the genetic material based on helixazation.

The 1st packing level is *nucleosomal*. The nucleosome is a globule consisting of 8 histone molecules (per 2 histone molecules of H_{2A}, H_{2B}, H_3 and H_4). A DNA helix makes about two turns (about 200 pairs of nucleotides) and passes to the next globe. The diameter of a nucleosomal thread is about 10 nm. The length of DNA reduces by 6–7 times. The same occurs in the interphase (fig. 13).

The 2nd packing level (fig. 14) is *supernucleosomal* (or solenoidal). The nucleosomal thread condenses and a helix forms. Nucleosomes "are sewn" by a histone H_1. One turn of the helix contains 6–10 nucleosomes. The helix diameter is about 25 nm. The thread length reduces by 7 times. The supernucleosomal packing level can be seen under the electron microscope in the interphase and during mitosis.

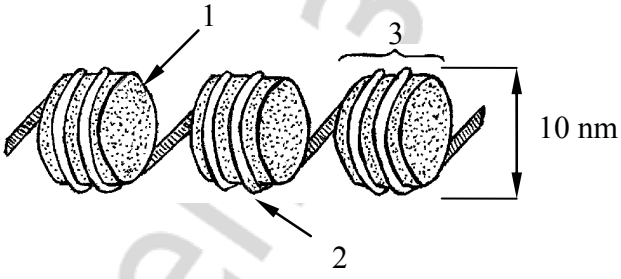


Fig. 13. Diagram of the nucleosomal packing level:
1 — octamere (histones H_{2A}, H_{2B}, H_3 and H_4);
2 — double DNA helix; 3 — nucleosome

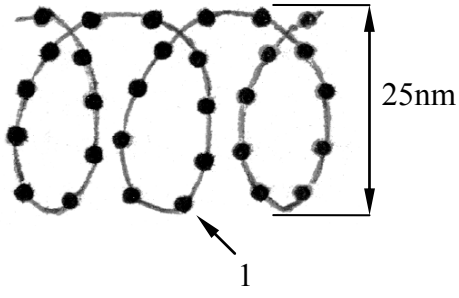


Fig. 14. Diagram of the supernucleosomal packing level: 1 — nucleosome

The 3rd packing level is *chromatidic*. The helixazation is continued and a supernucleosomal thread forms bends and loops. It is the basis of the chro-

matid. The diameter of loops is 50 nm. The DNA thread reduces by 10–20 times. Such packing level can be seen in the prophase of mitosis (fig. 15).

The 4th packing level is the *level of a metaphasal chromosome*. During the metaphase chromatids are still being helixazed. The thread length reduces by 20 times. The length of metaphasal chromosomes ranges from 0.2 to 150 μm, the diameter is 0.2–5.0 μm (fig. 16). The total DNA condensation is 10 000 times (10^4).

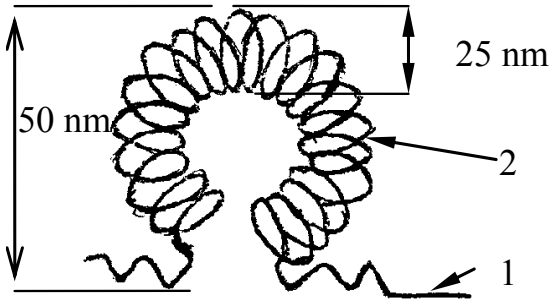


Fig. 15. Diagram of the chromatid packing level: 1 — chromatid axis; 2 — loop

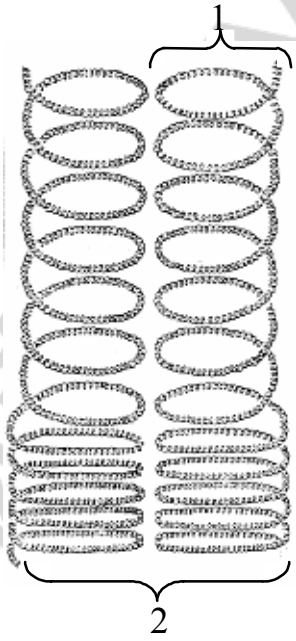


Fig. 16. Diagram of the packing level of a metaphasal chromosome: 1 — chromatid; 2 — chromosome

Ring DNA molecules ("chromosomes") of prokaryotic cells contain 5×10^6 pairs of nucleotides and form complexes with non-histone proteins.

STRUCTURAL-FUNCTIONAL ORGANIZATION LEVELS OF THE HEREDITARY MATERIAL

Structural-functional organization levels of the hereditary material are genic, chromosomal and genomic.

Gene is an elementary structure of a *gene organization level*. As genes are relatively independent from each other, there is possibility for discrete (separate) and independent inheritance (according to Mendel's 3rd law) and alteration of individual characters of gene mutations.

Genes of eukaryotes are in chromosomes forming a *chromosomal organization level of* hereditary materials. All genes of one chromosome form a coupling group and are transmitted together with this chromosome. It is at this level that recombination of parental genes in fillies and structural alterations of individual chromosomes take place in sexual reproduction.

A complement of genes received by follies from their parents comprises a genotype. The genome presents genes of a haploid chromosomal complement. The action of genes in various genotypes is revealed in various ways. The genes both of one chromosome and various chromosomes come into interaction. The impairment of a chromosomal complement results in genomic mutations.

PROTEIN BIOSYNTHESIS IN THE CELL

Protein biosynthesis in the cell is a complex process. Nucleic acids play a major role in it. In the cellular nucleus on one of DNA sequences (a coding one) r-RNA is synthesized in association with a RNA-polymerase enzyme. It "transcribes" the number of nucleotides arrangement in a DNA molecule (according to the rule of complementarity). This process is called *transcription*.

The messenger RNA enters the cellular cytoplasm through nuclear pores and moves to ribosomes.

The process of recognition (tRNA recognition of its own amino acid) occurs in the cytoplasm. The transport RNA has a specific structure (fig. 13). One end of the molecule contains a triplet of nucleotides. It is called an *anti-codon* and corresponds to a definite amino acid. There is a section for the amino acid attachment and 2 ends of a tRNA molecule on the opposite to the anti-codon end. At end 3' a CCA is fixed while at end 5'–G (guanine).

A specific amino acid is attached to its "own" tRNA in association with the enzyme of *aminoacyl-tRNA synthetase* and ATP. The amino acids pass into a large subunit of a ribosome.

The process of *translation* starts in ribosomes; the sequence of nucleotides and mRNA determines the sequence of amino acids of the peptide molecule.

The beginning of translation is *initiation*; the completion of translation is *termination*. The formation process of peptide links between amino acids is called *elongation*.

2 ends of an mRNA codon are present simultaneously in the ribosome: one is opposite to the *aminoacylic center*, the second — opposite to the *peptide center* (fig. 17).

The amino acid together with its own tRNA forms a complex of amino-acyl-tRNA. If a tRNA anti-codon and an mRNA codon, that is opposite to the aminoacyclic center, are complementary, then the aminoacyl-tRNA forms a temporary link with the codon and the mRNA. The ribosome moves to one triplet and amino acyl-tRNA passes to the peptide center. The second tRNA with the amino acid passes to the aminoacyclic center. Between the 1^{st} and 2^{nd} amino acids a peptide link is set up. The ribosome passes one triplet, the released tRNA leaves to take another amino acid. The 2^{nd} tRNA passes into the peptide center. A new tRNA with an amino acid comes to the amino acyclic center. A peptide link is formed between the amino acids, and a peptide molecule is being arranged according to mRNA information. The completion of

polypeptide synthesis (termination) determines codons UAA, UAG, UGA (stop codons). Identical polypeptides are synthesized in every ribosome of a polysome.

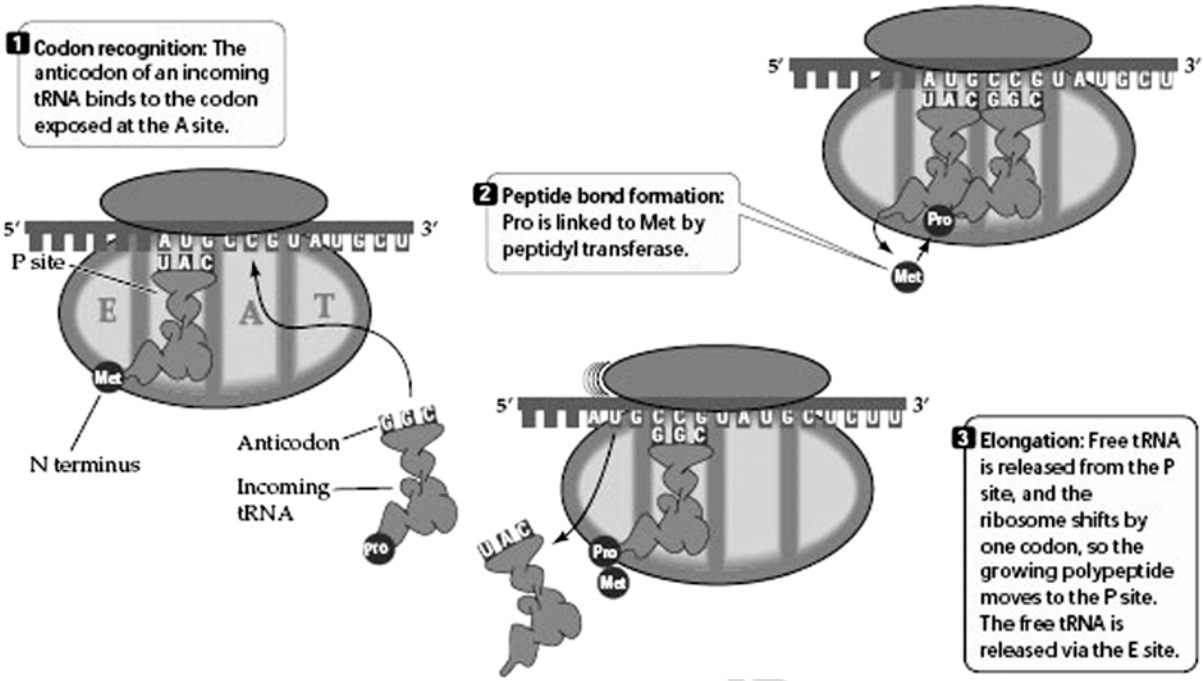


Fig. 17. Elongation

TRANSCRIPTION REGULATION IN PROKARYOTS AND EUKARYOTS

F. Jacob and J. Mono described regulation action of genes in prokaryotes in 1961. The DNA strand is presented as a straight line with structural-functional sections: a group of *structural genes* (A, B, C), a gene-operator being on one side. The *gene-operator* starts and stops the action of structural genes. Structural genes are not permanently active genes. The place of attachment of a RNA-polymerase, a promoter, is near the gene-operator. The operon includes also an initiator (a sequence of nucleotides which starts the transcription) and a terminator of the transcription (it disconnects the RNA polymerase and DNA).

The unit of prokaryotes transcription is called an operon and includes a promoter, gene-operator and structural genes (fig. 18).

The *gene-regulator* is some distance from the operon. It is permanently active. The *protein-repressor* blocking the gene-operator is synthesized according to its information. Structural genes are inactive. The operon doesn't act.

If the *inductor* passes into the cell (enzymes for its splitting are encoded in the operon), it links the protein repressor. The gene-operator is released, RNA-polymerase breaks hydrogen links between DNA sequences of structural genes. MRNA is synthesized on one of the sequences (according to complementarity principle. According to its information proteins-enzymes are synthesized on ribosomes of the cytoplasm. They break down the inductor.

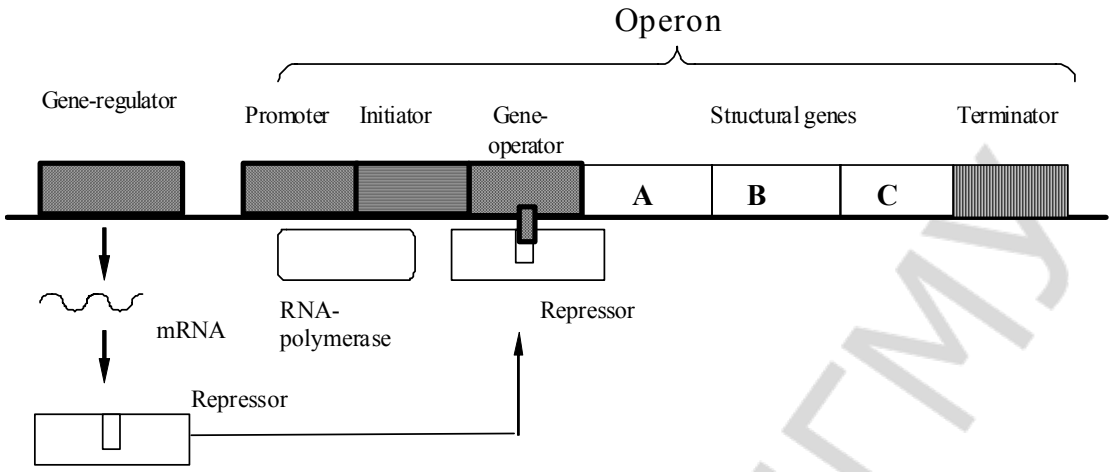


Fig. 18[a].Transcription regulation in prokaryotes. Operon "doesn't act"

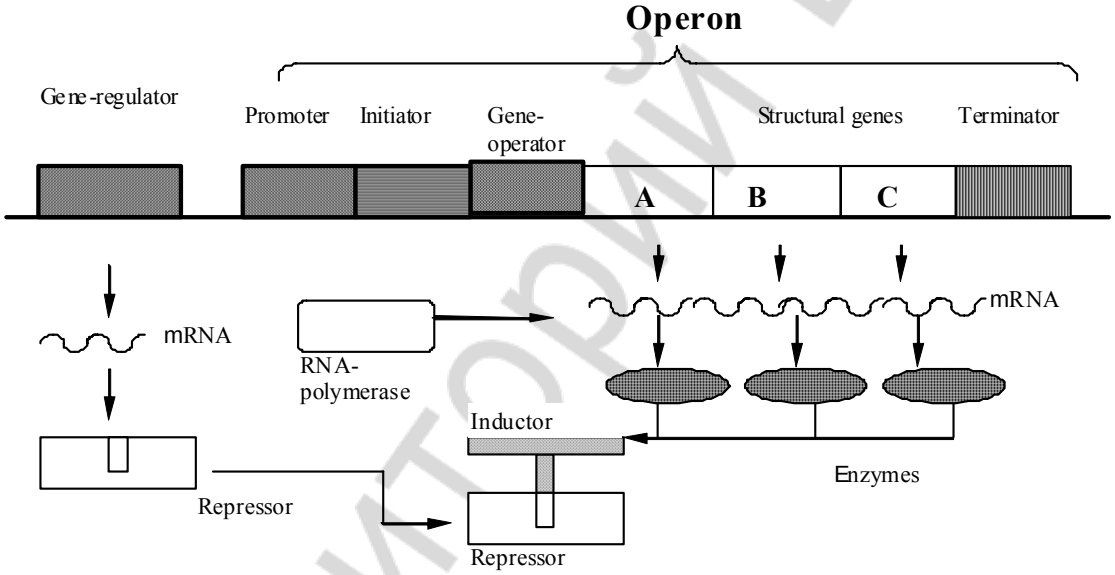


Fig. 18[b].Transcription regulation in prokaryotes. Operon "acts"

The operon acts unless the whole inductor is broken down. After its breaking down, the protein-repressor is released and blocks the gene operator again. Structural genes are switched off and proteins-enzymes are not synthesized. Every operon has its specific inductor (for example, lactose and fructose).

In 1972 G. P. Georgiev proposed a *regulation scheme of genes action in eukaryotes*. Conceptually it does not differ from that of prokaryotes. However, the structure of the scheme itself and the mechanism of its action become more complicated.

The transcription unit in eukaryotes is called a *transcripton*. It consists of a non-informative and informative zone. The *non-informative* or *acceptoral* zone includes a promoter, initiator and a block of genes-operators. The *informative* zone contains a structural gene with a terminator at the end. The structural

gene includes *introns*, non-informative sections of the DNA, and *exons*, informative zones. A *block of genes-regulators* regulates transcripton action. Several *proteins-repressors*, blocking genes-operators, are synthesized according to their information. Just as in case with the operon, reading of information from the structural gene occurs when *inductors* get into the cell. In this very case, the inductors are substances with complex composition (for example, hormones), so that for their splitting one needs several enzymes. The inductors release genes-operators from proteins-repressors. On one of DNA strands an mRNA is synthesized according to the complentarity principle, but it takes the information from the whole transcripton and presents a pre-mRNA. The processing of the pre-mRNA takes place in the nucleus under the action of exo- and endonucleasis, breaking down of the non-informative zone and slitting it into fragments. An mRNA, corresponding to exons, is formed because of splicing (sewing) of informative sections by lygasa enzymes. After such transformations, mRNA passes into the cytoplasm on ribosomes where proteins-enzymes for breaking down of inductors are synthesized. As soon as the inductors have been broken down, blocking of genes-operators by proteins-repressors is restored and the transcripton is switched off (fig. 19).

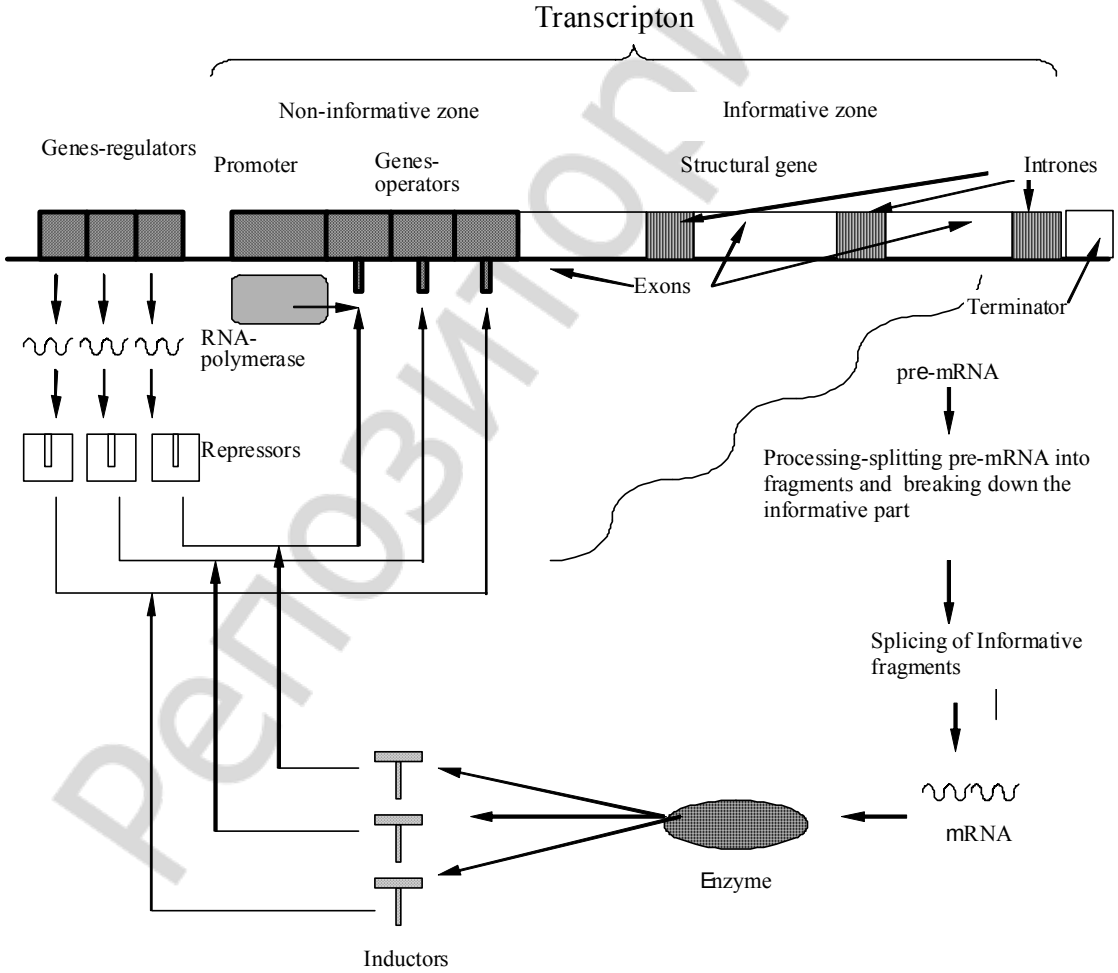


Fig. 19. Transcription regulation in eukaryotes

The complexity of the regulation action of genes in eukaryotes and the structure of this scheme is as follows:

1. It participates in the action of genes-regulators and genes-operators.
2. The structural gene of exons has informative sections and introns, non-informative sections.
3. Initial formation of a pre-mRNA. Maturation of the mRNA is associated with processing and splicing.

CYTOPLASMATIC HEREDITY

The basic genetic information of the organism is contained in a cellular nucleus. In 1908 K. Korrens described an *exonuclear (cytoplasmatic) heredity*. The genetic material contains mitochondria and plastids. These units, unlike nuclear genes, are called plasmogenes. There may be present DNA of viruses and plasmids of bacteria (ring bisequencial DNA) in the cellular cytoplasm.

Humans with cytoplasmatic heredity may suffer from Leber's disease (neuritis with atrophy of the ophthalmic nerve) and anencephalitis.

Cytoplasmatic inheritance is maternal; it is passed through ova, because sperms practically don't contain a cytoplasm.

The criteria of cytoplasmatic inheritance are:

- the absence of splitting of characters in fillies according to Mendel's laws;
- impossibility to reveal groups of coupling;
- various results of reverse crossing; in nuclear heredity they are identical:

$P: ♀AA \times ♂aa$ and $P: ♀aa \times ♂AA$

There are several types of cytoplasmatic heredity.

In 1949 B. Efrussi described *mitochondrial heredity*. He revealed that about 1 % of bread yeast form dwarf colonies. Their growth is inhibited due to a mutation of plasmogenes, and their mitochondria have no respiration enzymes. There are data about some human diseases that are caused by mutation of mitochondrial genes (for example, mitochondrial cytopathy, no fusion between upper arches of vertebrae, senility etc.).

In 1908 K. Korrens described *plastidic heredity*. The plant "night beauty" has motley leaves. A mutation has occurred, and no chlorophyll forms in some plastids. During multiplication, plastids are distributed unevenly. Some cells get normal plastids and green leaves, some cells get plastids without chlorophyll — leaves are white and the plant dies; some cells get both green (normal) and mutated plastids — the plants have molted leaves (green with white molts).

Pseudocytoplasmatic heredity is associated with passing a virus or a strange (bacterial) DNA into the cell. The predisposition of some mice to mammary tumors may be an example. If a female from a "cancerous line" feeds normal little mice, all mice will have mammary tumors. And vice versa: if little

mice of a "cancerous line" are fed by a healthy female, all little mice will be healthy. The reason of milk factor in mice was a virus. The second example may be the death of XY-zygotes of Drosophila, which was caused by a Spirochete getting into male's gametes.

GENETIC ENGENEERING

The achievements of molecular biology, biochemistry and genetics put the beginning to a new branch of science — **genetic engineering**. Methods of genetic engineering help create new genetic structures, organisms with a new genetic program according to a previously made plan. It became possible due to elaborating methods of transferring genetic information from one organism to the other.

The 1st stage of genetic engineering methods is **obtaining the genetic material**. Small genes of prokaryotes *can be synthesized chemically*; if a nucleotide sequence is completely known. Thus for the first time in 1970 G. Korana synthesized a gene of an alaninic t-RNA. Synthesis of complex genes is accomplished with *reverse transcriptio*n by enzymatic synthesis. An isolated mRNA is used as a matrix. To synthesize a coding DNA strand on it he used the enzyme of *reverse transcriptase (revertase)*, which was then replicated (for obtaining the 2nd complementary DNA strand). Genes, obtained in this way, do not function in cells, as they have neither a promoter nor a regulatory part. When it is transferred into a bacterium, an operon promoter joins structural genes, and initiates the transcripton.

Genes necessary for transplantation can be obtained using restrictases. Restrictases are enzymes discovered in 1964. Over 500 of them have been isolated by now. They can recognize definite sequences of nucleotides and cut out these sections from DNA sequences. Unisequential "sticky ends" appear at the ends of a DNA fragment.

The obtained genes are linked with vector molecules. They may be plasmids of bacteria, viruses and phages. The restrictase breaks a ring DNA of the plasmid, and a gene (DNA section) is introduced in it. The lygase enzyme connects sticky ends of the plasmid with sticky ends of a gene resulting in a *molecule with a recombinant DNA*. Such DNA is capable to permeate a cell-recipient.

DNA recombinant molecules do not get into all cells. That is why **selection of transformed cells** with an injected gene is performed on special cultures. Then *multiplication of cells* with a recombinant DNA is done, and a clone of cells with definite properties is obtained.

Genetic engineering helped receive clones of cells of enteric bacterium that can produce insulin and somatotropin necessary for patients in great amounts. There were elaborated methods of producing anti-viral serum, VIII factor of blood coagulation, anti-genes of HIV, serum against hepatitis B. Under way are

clinical trials of therapeutic methods for treatment of some malignant diseases, immunodeficient conditions and enzymopathies. The genetic engineering helped create plants capable of assimilating nitrogen from the atmosphere, microorganisms synthesizing food proteins from carbohydrates of mineral oil.

The methods of genetic engineering are widely used for establishing genes banks of humans, animals and plants.

The future of genetic engineering is the development of genotherapy and genosurgery of hereditary diseases of man which is associated with transplantation of somatic cells of normal (instead of mutated) or lacking genes into the germ; the development of cloning embryonic cells for obtaining organs and tissues for transplantation.

All this will be possible when safety of newly built genes for humans and the environment is proved.

The genetic therapy can also be used for humans to correct genetic defects in somatic cells or in embryonic cells and at early development stages of the zygote.

LECTURE 6
Topic: INHERITANCE LAWS. INTERACTIONS AND COUPLING OF GENES

Plan

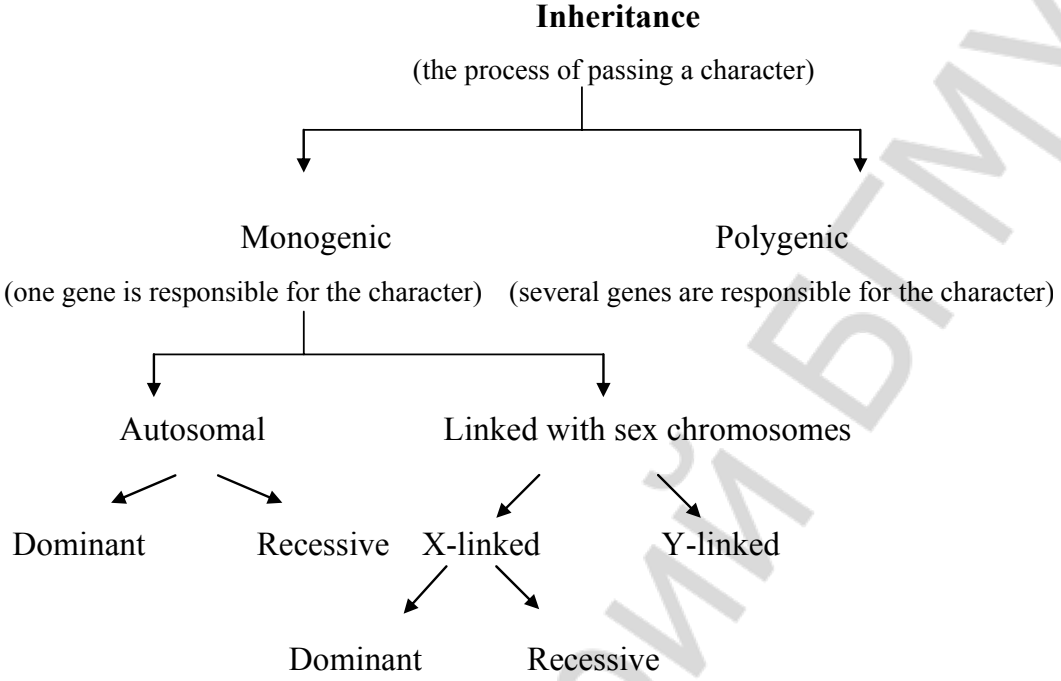
1. Genetics as a science. Types of characters inheritance.
2. Inheritance laws in monohybrid and polyhybrid cross.
3. Interaction and coupling of genes as a factor limiting Mendel's laws.

Genetics is a science about the laws of inheritance and variation. It was U. Batson who introduced the term "genetics" into Biology in 1906. General genetics includes human genetics, animals genetics, plants genetics, genetics of bacteria. General genetics includes also the sections of molecular genetics, cytogenetics, population genetics etc. Medical genetics is an important section of human genetics.

The basic inheritance laws were discovered by G. Mendel (1822–1884). G. Mendel made experiments on pea plants. During 8 years of work he studied about 20 000 of these plants. Pea plants proved to be the most suitable plant for his experiments: they had many off-springs (seeds), they were self-pollinated and had clearly marked characters (e. g. the color or the surface of seeds).

G. Mendel used a hybridological method in his work: he selected pairs of plants for crossing, analyzed inheritance of individual characters in off-springs of several generations and made their accurate quantitative account. He presented the results of his research in his work: "Experiments with plant hybrids"

(1865). G. Mendel started crossing pea plants that were distinctly different in one character — yellow peas (seeds) and green peas. Such characters are called *alternative* (two states of one character). Allelic genes that are located in identical loci of homologous chromosomes determine them.



Daigram 6. Types of characters inheritance

At present, the following designations are used:

P	AA x aa	P (parents)
G	A a	G (gametes)
F_1	Aa	F (fillies)

The genotype of a female organism is always recorded first:

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	

A phenotype ratio was 3:1 — three quarters of plants were with yellow peas and one quarter with green ones; a genotype ratio was 1:2:1. Capital letters denote dominant genes, written ones — recessive genes. Characters are *dominant* when they appear in a homozygous and heterozygous state. *Recessive* characters appear only in a homozygous state.

If the genotype contains identical allelic genes, this individual is called *homozygous* or a pure line. It produces one type of gametes and there occurs no splitting during a cross with an individual having an identical genotype. In crossing two homozygous individuals (according to dominant and recessive characters), the next generation will have individuals Aa.

They are *heterozygous* because they have two various genes of one allele. Being crossed they give splitting according to the phenotype: three quarters of yellow peas and one quarter of green peas.

INHERITANCE LAWS IN MONOHYBRID AND POLYHYBRID CROSSING

Cross is *monohybrid* if one pair of alternative characters is analyzed, *dihybrid* — if two pairs are analyzed, and if there are more than two pairs — it is *polyhybrid*.

Two Mendel's laws were formulated according to the results of monohybrid crossing.

The 1st law is *the law of hybrids uniformity of the 1st parental generation*: in crossing homozygous individuals and analyzing one pair of alternative characters, one can observe the uniformity of hybrids in their phenotype and genotype.

The 2nd law is the law of characters splitting in hybrids of the 2nd generation. In self-cross of the 1st generation hybrids, analyzed by one pair of alternative characters, splitting may occur in the 2nd generation.

According to phenotype it gives a ratio 3:1 (3 quarters of individuals with a dominant character, 1 quarter of individuals with a recessive character) and according to genotype — a ratio 1:2:1 (one part of individuals are dominant homozygotes (AA), 2 parts — heterozygotes (Aa), one part — recessive homozygotes (aa)).

In dihybrid cross, when plants were distinguished by two alternative characters, Mendel obtained the following results:

A — green seeds B — smooth seeds
A — green seeds b — wrinkled seeds
Yellow smooth green wrinkled
P AABB x aabb $P(F_1)$ AaBb x AaBb
G AB ab

homozygotes form one type of gametes — one gene goes to the gamete from every pair of genes

diheterozygotes form four types of gametes — genes from various pairs are freely combinated

Pennet's lattice is usually used to record the results of a polyhybrid cross:

♂/♀	AB	Ab	aB	ab
AB	AABB	AABb	AaBB	AaBb
Ab	AABb	AAвb	AaBb	Aabb
aB	AaBB	AaBb	aaBB	aaBb
ab	AaBb	Aabb	aaBb	aabb

In total there are 16 combinations: 9 parts A-B-: 3 parts A-bb: 3 parts aaB-: 1 part aabb. Such pattern of recording is called a phenotypic radical (recording

a genotype using a phenotype). A-B- or A-bb record means that a phenotype does not depend on what gene will replace a dash (dominant or recessive) — a dominant character will appear. If we estimate separately the ratio by pairs of characters 12A-: 4aa, 12B-: 4bb, we'll get a ratio 3:1 in both cases. On the basis of obtained results one can make a conclusion that in crossing heterozygous individuals, analyzed by several pairs of alternative characters, splitting is observed in fillies according to phenotype in ratio $(3+1)^n$, where n is the number of characters in a heterozygous state.

Mendel's 3rd law is a law of independent inheritance of characters: in crossing homozygous individuals, analyzed by several pairs of alternative characters, independent inheritance of characters and their respective genes is observed in the 2nd generation.

In 1902, to explain the results of crossings, performed by Mendel, U. Batson suggested a hypothesis of gamete purity: hybrid genes are not hybridized and are in a pure allele state. The mechanism of meiosis is a cytological basis for Mendel's laws. Homologous chromosomes diverge in meiosis, and one gene from an allele pair gets into a gamete.

Significance of Mendel's laws:

1. The laws are universal and are applicable for all living organisms.
2. G. Mendel introduced a mathematical approach into Biology. His laws have a statistical significance; they are the laws of great numbers.

INTERACTION AND COUPLING OF GENES AS A LIMITATION OF MENDEL'S LAWS

A number of factors cause limitations in manifesting Mendel's laws:

1. Impairment of equal probability for the formation of gametes and zygotes of various types.
2. Various survivals of individuals with different phenotypes (the presence of lethal and semi-lethal genes). Lethal genes cause death of organisms before birth or at birth. Semi-lethal genes reduce the life span of the organism.
3. Interaction of genes (except complete domination).
4. Coupling of genes.
5. Cytoplasmatic inheritance.

P Aa x Aa

G (A) (a) (A) (a)

F_1 ~~AA~~ Aa Aa aa

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

Interallelic interactions of genes

1. *Complete domination*: coloration of pea-seeds, brown and blue eyes in humans, straight and curly hair, 5 and 6 fingers on the hand and other characters. They are called mendelizing because splitting goes by Mendel's laws.

2. *Incomplete domination* or intermittent inheritance.

Gene A — red flowers

Gene a — white flowers

P AA x aa → Aa

Red white pink

3. *Superdomination*: due to interaction of by-products of gene activity, the action of a gene in a heterozygous state is more intensive than in a homozygous state. For example in Drosophilae: a lethal gene is recessive, and according to this gene homozygotes die; vitality in heterozygotes is greater, they are more fertile than homozygous individuals according to a dominant gene.

4. *Co-domination*. For an example, blood groups in AB_0 system: two allelic genes are identical to each other, but being together in a genotype, they cause the appearance of a new character — both produce their action (IV blood group).

Alleles of a gene I: I^0, I^A, I^B. The presence of gene I^0does not cause synthesis of anti-genes in erythrocytes (I group). Genes I^A and I^B are dominant relative to gene I^0. Occurring in the genotype in a homozygous I^AI^A; $I^B I^B$ or heterozygous $I^AI^{0;}$ I^BI^0 state they cause synthesis of anti-genes either A or B in erythrocytes. A — II blood group; B — III blood group. If they occur in the genotype together, both types of anti-genes A and B are synthesized in erythrocytes — IV (AB) blood group.

5. *Allelic exclusion*: In a heterozygous organism, various alleles of one gene are active in different cells. Example: In humans and mammals, every plasmatic cell synthesizes its own sequence of immunoglobulines (anti-bodies).

Interallelic interactions of genes

Interallelic interactions are interactions of non-allelic genes of different alleles:

1. *Complementarity* is interaction when a gene of one allele supplements the action of a gene of the other allele. Coloration of flowers in sweet 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

G AB Ab AB Ab

aB ab aB ab

F_1 9A-B-; 3A-bb; 3aaB-; 1aabb (according to Mendel's law a ratio 9:3:3:1, splitting

Red white white white obtained according to phenotype is 9:7)

2. *Epistasis* is the interaction when a dominant (recessive) gene of one allele suppresses the action of a gene of the other allele. A suppressing gene is called epistatic (inhibitor or suppressor); a suppressed gene is called hypostatic.

An example of a dominant epistasis is coloration of feathering in hens. Coloration of feathering is determined by gene C; a dominant gene of allele I suppresses its action.

Genotype of hens with colored feathering C – ii
Genotype of hens with white feathering C-I-, cc-I-, ccii
P Cc Ii x Cc Ii
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)

An example of a *recessive epistasis* is a *"Bombay phenomenon"* (inheritance of blood groups).

Phenotypically blood group I was determined in women with allele I^B. It was established that synthesis of anti-body B in erythrocytes suppressed a rare recessive gene.

3. *Polymeria* — several non-allelic genes intensify the appearance of one character. Thus are inherited some quantitative and qualitative human characters: body mass, height, pigmentation of the skin, blood pressure. Usually polymeric genes are denoted with the same letters but with different digital indices. For example, skin pigmentation in humans:

Negroids	$P_1P_1P_2P_2P_3P_3$
Europeoids	$p_1p_1p_2p_2p_3\ p_3$
Mulattos	$P_1p_1P_2\ p_2P_3p_3$

The more dominant genes are in genotype, the more intensive is the character. It is an *additive action* – summarizing the action of a gene. A minimum number of polygenes, when their action is revealed, give a *threshold effect*.

4. A "*position effect*" is a mutual effect of genes from different alleles of adjacent loci of one chromosome. It is revealed when their functional activity changes.

Coupling of genes

In 1911–1918, the laboratory of T. Morgan conducted experiments on Drosophila. It is suitable for genetic investigations, as it has few chromosomes (4 pairs), early sexual maturation, fast change of generations, a great number of fillies. It is easy to provide identical existence conditions of Drosophilae.

During the cross of Drosophilae the inheritance of two pairs of alternative characters was analyzed.

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 B-V-

All hybrids were with dominant characters — they acquired uniformity of individuals of the 1st generation.

To determine the genotype of hybrids they performed an analyzing cross — cross of individuals with a dominant character and a recessive homozygote.

I	$P(F_1)$	B-V-	x	bbvv		II	$P(F_1)$	bbvv	x	B-V-
F_2	B-V-	bbV-		B-vv	bbvv	F_2		bbvv		B-V-
	41.5 %	8.5 %		8.5 %	41.5 %			50 %		50 %

The 1st cross makes it possible to say that a female Drosophila is diheterozygous (BbVv) and genes of the body color and wings length are in one pair of homologous chromosomes — they are coupled with this pair of chromosomes. If they were located in various pairs of chromosomes, the number of individuals with different genotypes would be 25 % each. Individuals comprising 8.5 % were formed in the process of crossing-over and are called *crossoverous*. The total number of crossoverous individuals is 17 % and corresponds to the distance between genes of the body color and wing length — 17 *morganids*.

Unlike independent combining, when genes are located in one pair of homologous chromosomal pairs (1) and 25 % of individuals of each genotype are formed and during the cross, in the process of coupling genes are located in one pair of homologous chromosomes.

Crossoverous gametes are gametes containing chromatids that underwent crossing-over. Unchanged chromatids are included into non-*crossoverous gametes*.

Coupling of genes — is joint passing genes of one chromosome from generation to generation. Coupling is *complete* if crossoverous individuals are not formed (a male Drosophila). If crossoverous individuals (a female Drosophila) are formed, coupling will be *incomplete*. Crossing-over occurs not always, that is why the number of crossoverous individuals is always less than non-crossoverous ones. The force of coupling between genes (crossing-over frequency) depends on the distance between them: the greater is the distance, the weaker are the forces of coupling, the more frequently crossing-over occurs.

The results of experiments on Drosophila helped formulate the *basic issues of the chromosomal theory of inheritance*:

1. Genes are located in a linear order in definite loci. Allelic genes are in identical loci of homologous chromosomes.

2. All genes of one chromosome form a group of coupling and are inherited together.

3. Crossing-over (exchange of allelic genes) is possible between homologous chromosomes.

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

Coupling can be autosomal (groups of coupling autosomes) and gonosomal (groups of coupling sex chromosomes).

Knowing the distance between genes, one can compose maps of chromosomes.

A *genetic map*: a chromosome is presented as a straight line on which genes are conditionally located according to the results of an analyzing cross.

A cytological map is a precise drawing or a chromosome photo. The order of locating genes is determined comparing the results of an analyzing cross and chromosomal rearrangement.

LECTURE 7
Topic: VARIATION

Plan

1. Variation and its forms.
2. Mutagenic factors and mutagenesis.
3. Repair of genetic material.
4. Biological bases of cancerogenesis.

VARIATION AND ITS FORMS

Variation is a characteristic of living organisms to acquire characters that make them different from their parents in the process of ontogenesis

The genetic information received from parents determines potencies (possibilities) to develop characters. Their realization depends on specific environmental conditions. Identical genetic information in various conditions may behave differently (e.g. monozygotic twins who live in different conditions). It is a type of response to environmental effects that is inherited, and not a specific character.

The degree of phenotypical manifestation of a specific gene is *expressivity*, and the frequency of its manifestation is penetrance. The penetrance is expressed in percents: a ratio of the number of individuals with this character to the number of individuals with this gene.

The phenomenon of phenocopies and genocopies is associated with variation. *Genocopies* are identical phenotypical manifestations of mutations in various genes (example: various types of hemophilia associated with deficiency of factors VIII and IX of the coagulating system). Phenocopies — is the case when a character under the influence of some external factors modifies and copies

characters of another genotype (example: taking alcohol during pregnancy results in a complex of impairments that may copy the symptoms of Down's disease).

Forms of variation		
Phenotypic (non-hereditary, or definite group)	Genotypic (hereditary, individual or indefinite)	
↓	↓	↓
Modificatory	combinative	mutative

Modificatory variation (or modification) is associated with changing the phenotype without changing the structure of the genotype. That is why it is *non-hereditary*. Modifications occur under the influence of environmental factors and variations can be predicted to a whole group of individuals. As a rule, modifications have an *adaptive character*.

A *range of reaction* determines the limits of modificatory variation. It is controlled by the genotype and is inherited. If some character has a *narrow range of reaction*, it modifies insignificantly (e. g. the content of fat in milk of the dairy cattle). The character with a *wide range of reaction* modifies in great limits (e. g. body weight).

Combinative variation is a recombination of parental genes in fillies without any modification of the genetic material structure. Here are the *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. Random occurrence of gametes of different types during fertilization.

MUTAGENIC FACTORS AND MUTAGENESIS

Mutative variation or mutations are sudden modifications of genetic material under environmental factors. Mutations are inherited, they can't be predicted, they are individual and are the material for selective evolution.

Mutagens are factors causing mutations: exomutagens — environmental factors, endomutagens — metabolites of the human organism.

Mutagenic factors are subdivided into physical, chemical and biological.

Physical mutagens are various types of radiation, temperature, humidity and others. They cause:

– structure impairment of genes and chromosomes;
– formation of free radicals interacting with DNA;
– formation of dimer of adjacent pyrimidine bases of one DNA sequence (T-T, T-C) etc.

Chemical mutagens:

– natural organic and inorganic compounds (alkaloids, nitrates);
– by-products of coal and oil production;
– synthetic substances which have not occurred in nature (domestic chemicals, chemical compounds for agriculture, food conservation substances);
– various medicines (some antibiotics, narcotic substances, hormonal preparations) which may cause congenital development defects in humans.

Supermutagens (yperite, ethylenimin) — substances of a chemical origin that act stronger than penetrating radiation.

Chemical mutagens act in the period of DNA replication and are usually a cause of gene mutations. They cause deamination and alkylation of nucleotides, replacement of nitrogenous bases with their analogues; they inhibit synthesis of nucleic acids predecessors.

Biological mutagens are metabolites of various parasitic agents:
– parasites of non-viral origin (ricketcies, mycoplasms, bacteria);
– viruses of German measles, flu, measles, small pox;
– metabolites of protists (toxoplasm) or multicellular (cat's sucker) parasites.

Non-viral and viral agents are a cause of infectious mutagenesis. They cause the impairment of DNA synthesis, process of crossing-over, divergence of chromosomes and chromatids in the anaphase of meiosis and mitosis. Waste products of parasites act as chemical mutagens. They disrupt chromosomal telomeres and the process of crossing-over.

Mutagenesis is the process when mutations are formed. Mutagenesis may be spontaneous and induced. *Spontaneous* or self-produced mutagenesis is due to mistakes in replications and repair of DNA and under the action of metabolites (e. g. peroxide and aldehydes). *Induced* or purposefully caused mutagenesis arises due to a specific mutagen — UV or ionizing radiation.

Classification of mutations

According to *mutated cells,* mutations can be *somatic* (e. g. different eye color in one person) and *generative* (or gametic). Generative mutations are hereditary, somatic are manifested in an individual himself. They are inherited only in vegetative multiplication.

According to *outcome* (significance) *for the organism,* mutations can be positive, neutral and negative. *Positive mutations* appear rarely. They enhance vitality of the organism and are important for evolution (e. g. mutations causing the development of a 4-chamber heart in the chordates). *Neutral mutations* have practically no impact on vital processes (e. g. mutations causing freckles). *Negative mutations* are divided into lethal and semi-lethal. *Semi-lethal mutations* decrease vitality of the organism, reduce its life span (e. g. mutations causing Down's disease). *Lethal mutations* cause death either before birth or at birth (e. g. mutations causing the absence of the brain).

According to *modification of the phenotype*, mutations can be *morphological* (e.g. diminishing of eyeballs, 6 fingers on the hand) and *biochemical* (e. g. albinism, hemophilia).

According to *modification of the genotype*, mutations can be genomic, chromosomal and genic.

Genomic mutations occur when the number of chromosomes modify under the impact of environmental factors. Haploidy is a chromosomal complement 1n. In nature, it occurs in drones (males)-bees. Vitality of such organisms is decreased, as they reveal all recessive genes. Polyplody is an increase of a haploid chromosomal complement (3n, 4n, 5n). Polyplody is used in plant-growing. It increases fruitfulness. For humans, haploidy and polyplody are lethal mutations. Aneuplody is modification of the number of chromosomes in separate pairs (2n±1, 2n±2 etc.). *Trisomy*: if an X-chromosome is added to a pair of sex chromosomes of a female organism, a trisomy syndrome will develop X (47, XXX). If it is added to sex chromosomes of a male organism, Klinfelter's syndrome will develop (47, XXY). *Monosomy*: absence of one chromosome in the pair — ♀45, X0 causes Shereshevsky–Terner's syndrome. *Nullisomy*: the absence of a pair of homologous chromosomes (lethal mutation for humans).

A chromosomal mutation (or chromosomal aberrations) is a modification of the structure of chromosomes (interchromosomal or intrachromosomal). Recombinations inside one chromosome are called inversions (deficiencies and deletions), duplications. Interchromosomal recombimations are called translocations (diagram 8).

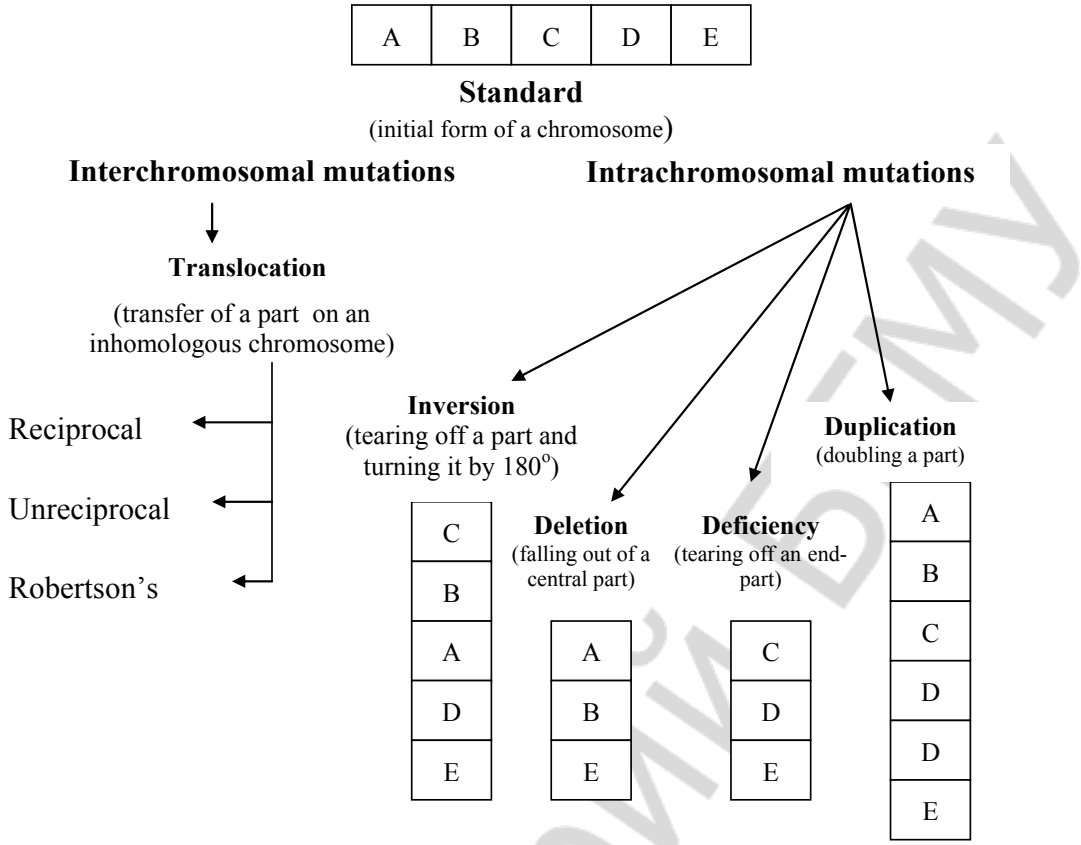


Diagram 8. Modifications of the chromosomal structure

Examples: *deletion* may cause a cat's cry in a human; *duplication* — appearance of strip-like eyes in Drosophila; *inversion* — modification of genes arrangement order. Translocations may be *reciprocal* when two chromosomes exchange segments; *non-reciprocal* when segments of one chromosome are translocated to the other; *Robertson's* — two acrocentric chromosomes are tied by their centermerous parts.

Deficiencies and duplications are always revealed phenotypically, when a complement of genes is modified. Inversions and translocations not always manifest. In such cases, conjugation of homologous chromosomes is hampered and distribution of genetic material between daughter cells is impaired.

Gene mutations are called point mutations or transgenations. They are associated with structural modification of genes and cause the development of metabolic diseases (their incidence is 2–4 %).

Structural modifications of genes:

1. *Bias of a reading frame* occurs in case of falling out or insertion of one or several pairs of nucleotides into a DNA molecule.

2. *Transition* is a mutation when a purine base is replaced by a purine or pyrimidine one (A↔G or C↔T). This replacement causes modification of codons.

3. *Transversion* is a replacement of a purine or pyrimidine base by a purine one (A↔C; G↔T) — it results in modification of codons.

Modification of codons meaning leads to *missense-mutations*. If meaningless codons are formed (UAA, UAG, UGA), they cause *nonsense-mutations*. These codons do not determine amino acids but are terminators and determine the end of reading the information.

Modifications of functional genes

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

2. The gene-repressor is tightly joined with the gene-operator and is not "taken off" by an inductor. Structural genes permanently do not work.

3. The sequence of the processes of repression and induction is impaired. If the inductor is absent, a specific protein is synthesized, as it is not synthesized in the presence of the inductor. Such impairments of transcripts function are observed in mutations of the gene-regulator or gene-operator.

At present about 5000 metabolic diseases are described, they are due to genic mutations. Their examples are phenylketonuria, albinism, galactosemia, various types of hemophilia, crescent cell anemia, achondroplasia etc.

In the majority of cases, genic mutations are revealed phenotypically.

REPAIR OF GENETIC MATERIAL

Anti-mutagenesis is an impact on the cell and organism that blocks or decreases the probability of mutation events. *Anti-mutation mechanisms ensure the stability of genetic material*.

1. Natural barriers: a diploid complement of chromosomes (parity of chromosomes), double DNA helix, redundancy (degeneracy) of the genetic code, re-iteration of some genes.

2. Repair of the DNA structure is an intracellular process of restoration of an impaired DNA molecule. The impairments can be disruption of DNA threads, sewing (connecting) DNA threads or DNA-histone, impairment of nitrogenous bases. Repair may take place: a) before duplication of a DNA molecule (*pre-replicative*); b) in the process of duplicating a molecule (*replicative*) c) after replication of a DNA molecule (*post-replicative*).

In 1962 K. Rupert described *photoreactivation* or light repair. He established that during radiation of phages, bacteria and protists with ultra-violet, their vitality sharply decreased. However, if they were exposed to a visible light, their vitality restored. During UV radiation dimers are formed in a DNA molecule (chemical links between bases T-T of one sequence). This inhibits reading the information. Visible light activates enzymes that disrupt links of dimers.

More often dark or excisional repair (A. Gerren described it in 50s of the XX century) occurs. It means that enzymes are found and the impaired part of

a DNA thread "is excised" and replaced by a synthesized intact part. Four groups of enzymes participate in these processes:

a) *endonuclease* "recognizes" the impaired part, and the DNA thread breaks nearby;

b) *exonuclease* removes the impaired part;

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

d) *Lygase* ties the ends of the inserted part with the basic DNA thread.

The impairment of the repair process may cause the development of such diseases as *pigment xeroderma* and Fanconi's anemia. In pigment xeroderma, under the influence of sunrays, there appear burns on the skin; ulcers, horny epidermis, eye diseases and malignant tumors develop. Fanconi's anemia is associated with functional impairment of the red bone marrow, which results in decrease of corpuscular elements and development of hyperpigmantation.

3. The presence of anti-mutagens. They are substances of various origin that in small concentrations can stabilize the process of mutation. Their examples are biologically active compounds: histamine and serotonine, anti-oxidants, sulphanilamide preparations, fresh vegetable juices and some other. The most effective anti-mutagen is α-tocopherol, which decreases the number of both genic and chromosomal mutations. The more tocopherol is in plants, the higher is the stability of their genetic apparatus to the action of mutagenic factors.

BIOLOGICAL BASES OF CANCEROGENESIS (GENETIC CONCEPTIONS)

Cancerogenesis is the process of formation and development of tumors. Changes occur at a molecular-genetic level. They are due to mechanisms controlling growth, reproduction and differentiation of cells.

G. de Freeze was the first to suggest the idea (1901) that tumors develop due to mutations in somatic cells. It is a *mutational conception of cancerogenesis*.

A. Borrel and F. Bosk (1903) presented the *bases of a viral-genetic conception*. They believed that viruses were causative agents of leucosis and sarcoma in hens. L. A. Zilbet (1945) called viruses a universal cause of malignant growth. Mutagens and cancerogens activate viruses, their genome invades DNA cells and modifies their properties.

Yu. M. Olenov (1967) and A. Yu. Bronovitsky (1972) suggested an *epigenomic conception*. They considered that transformation of a normal cell into a tumor is due to the impairment of the structure of functional genes.

The latest is a genic conception, a *conception of protooncogens* (R. Hubner, 1969; G. I. Abelev, 1975). A DNA of any cell contains inactive parts — pro-

tooncogens. They may be passed from parents and are introduced into the cell by a virus. Protooncogens are activated during mutations or when a virus promoter gets into the cell they pass into an active form — oncogens. A normal cell is transformed into a tumor cell.

LECTURE 8
Topic: BIOLOGY AND GENETICS OF SEX

Plan

1. Sex as a biological character.
2. Theory of sex determination.
3. Differentiation and sex re-determination.
4. Sexual chromatin and the hypothesis of Mary Lion.
5. Chromosomal diseases of sex

Sex is a complex of morphological, physiological, biochemical and behavioral characteristics of the organism that ensures the process of reproducing similar selves and transfer of genetic information from generation to generation.

Sex characters may be primary and secondary.

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

Secondary sex characters appear in puberty when sex hormones start passing into the blood (in humans it is at 10–15 years). They do not participate in reproduction directly, but stimulate the attraction and meeting of individuals of opposite sex. Secondary sex characters include specificities of the bony-muscular system, distribution of the adipose cellular tissue and hair covering, voice tembre, peculiarities of the nervous system and behavior, etc.

Among somatic characters related to sex, one can mark out sex characters restricted and controlled by sex, and characters linked with sex chromosomes.

Both sexes possess genes of *characters restricted by sex*, but they show only in one sex (e.g. genes of lactation in the dairy cattle; a gene of gout occurs only in males). Genes of *characters controlled by sex* are also found in both sexes, but the degree of their manifestation is different (a gene of alopecia shows differently in males and females). *Characters linked with sex chromosomes* include characters linked with an X-chromosome and holandric ones. Genes located in the inhomologous part of an X-chromosome determine the characters linked *with an X-chromosome (linked with sex)*. 200 of them are described (examples: gene of hemophilia, gene of daltonism). Genes located in the inhomologous part of an Y-chromosome determine *holandric characters*; 6 of them

are described (examples: a gene of ichthyosis, gene of webbed toes). They are inherited by males and show only in males.

THEORIES OF SEX DETERMINATION

Sex in the majority of animals is determined at the moment of fertilization by a combination of sex chromosomes (hetero-chromosomes) — X and Y.

P XX x XY

G (X) (X)(Y)

F_1 XX XY

XX is a female *homogametal sex*, it forms one type of gametes. XY is a male *heterogametal sex*, it forms two types of gametes. This is the way to determine sex of humans and all mammals. In birds, fish and butterflies a male sex is homogametal and a female sex is heterogametal.

♀ZW ♂ZZ

In grasshoppers and locust a female sex is XX, a male one is X0.

This theory of sex determination got the name of a chromosomal theory. It was proposed by K. Korrens in 1907.

Studying sex inheritance in Drosophila, K Bridges established in 1922 that males might have complements of XY- and X0-chromosomes. Males with an X0-complement will be sterile. He made a conclusion that Y-chromosomes in Drosophila are of no particular importance for determination of a male sex. Sex in Drosophila is determined by a ratio of the number of X-chromosomes to a complement of autosomes (1A, 2A, 3A). This theory got the name of a ***balanced sex theory***.

2X : 2A normal females
1X : 2A normal males
3X : 2A super female } sterile
1X : 3A super male }
2X : 3A intersex

The more X-chromosomes has a Drosophila female in its karyotype, the more intensively expressed are the characters of a male sex.

DIFFERENTIATION AND RE-DETERMINATION OF SEX

In humans *germination of a sex gland*, internal and external sex organs starts on the 4th week of embryogenesis. Initially one X-chromosome provides it. That is why it goes similarly in embryos with chromosomal complements 47, XX; 46, XY; 45, X0; all embryos are anatomically neutral. Primary embryonic cells in humans can be revealed on the 3rd week of embryonic development in the ectoderm of the yoke sac. Later on, under the influence of chemotaxis,

they migrate into a sex fold where they participate in the formation of an undifferentiated gonad, which consequently develops into ovaries or testes.

Differentiation of germinations into sexual glands and sexual organs of embryos and fetus occurs from the 4th till the 12th weeks of intrauterine development, and at this stage it completely depends on the 2nd sex chromosome. If it is X chromosome, the primary sex cells develop into oogonia and the whole system develops according to a female type. The development of primary sexual germinations according to a male type is determined by the presence of Y-chromosomes in the complement. The primary sex cells are differentiated in spermatogonia; testes and external sex organs are formed.

Sexual differentiation of gonads occurs between the7th and 10th weeks of embryogenesis. By the10th week it is possible to determine sex of an embryo.

Physical (morpho-physiological) determinants of sex are common for humans and animals.

Social-psychological determinants are of great importance for the formation of sexual consciousness and ideas about the sex role, which influence the selection of a sexual partner. In the majority of cases, it is an opposite sex (*heterosexualism*), rarely — *homosexualism* (identical sex).

Social-psychological determinants are very important for such events as transsexualism and transvestism. *Transsexualism* is a person's realization that he/she belongs to an opposite sex, despite the right formation of gonads and secondary sexual characters. *Transvestism* is a sexual perversion, when one reaches excitation and satisfaction putting on clothes of the opposite sex.

In the cattle during the development of two twins of different sexes, bull-calves are usually normal, while heifers are *intersexual*. It is because a male sexual hormone is excreted earlier and it influences sex determination of the second twin.

XY	Genetic sex	XX	← fertilization
↓		↓	
Testis	Gonadic sex	Ovary	← 2-12th weeks of embryogenesis
↓		↓	
Spermatozoon	Gametic sex	Ova	
↓		↓	
Androgens	Hormonal sex	Estrogens	Puberty
↓		↓	
Male sex	Morphological sex	Female sex	
↓		↓	
Male sex	Civil sex	Female sex	

↓

Sex of education

↓

Sex self-consciousness

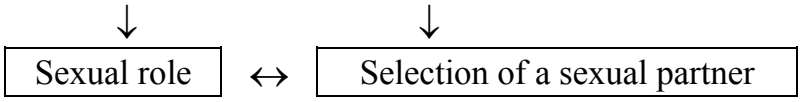


Diagram 9. Formation of sex in humans

In humans sometimes occurs *Morris's syndrome*, manifestation of a male phenotype when the genotype is XX, and manifestation of a female phenotype when the genotype is XY (*testicular feminization*). In Morris's syndrome male sex hormones are secreted after germination of testes, but there is no protein-receptor in germs that makes cells sensitive to these hormones. The development according to a male type stops, and a female phenotype develops.

SEX CHROMATIN AND MARY LION'S HYPOTHESIS

In 1949 M. Barry and Ch. Bertram discovered a large *lump of chromatin* in nuclei of neurons of a cat. It was revealed in females and was absent in males. Later it was established that it was a helixized X-chromosome. This lump of chromatin got the name a *Barr body*. It may be attached to a nucleolus, nuclear membrane, may freely occur in the karyoplasm or present a nuclear process in blood cells ("drumsticks").

In 1962 Mary Lion suggested a hypothesis of inactivation of one X-chromosome in mammal females (diagram 10). Every cell of a female embryo contains two X-chromosomes: one maternal (X_m) and the other — paternal (X_f). Up to the 16th day of embryogenesis 2 active X-chromosomes get into every cell during splitting. On the 16th day, inactivation of one X-chromosome takes place — a maternal or paternal with equal probability. The process of inactivation is random, that is why in one-half of all cells a paternal X-chromosome stays active, and in the other half of cells a maternal X-chromosome will be active. Maternal and paternal X-chromosomes contain allelic genes (dominant and recessive). Two variants of enzymes can be synthesized in cells; they differ in their relation to the substrate or according to pH-indices. It helps female organisms better adapt to the environment. The essence of *female mosaicism according to sex chromosomes* is the content of different active X-chromosomes in different cells — from father and mother.

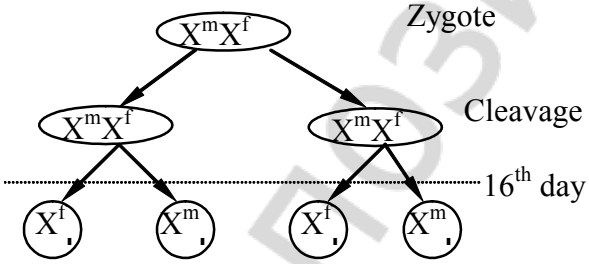


Diagram 10. Inactivation of one X-chromosome

Theoretically, a ratio of male and female gametes (ratio of sexes) at the moment of fertilization is approximately 1:1.

P XX x XY

G X X Y

F_1 XX XY
1 : 1

The primary sex ratio at the moment of fertilization: 100 female zygotes: 140–150 male zygotes. It is because spermatozoa with an Y-chromosome are lighter, more movable, have a negative charge (in ova it is positive).

The secondary sex ratio (at the moment of birth): 100♀ : 106♂.

A greater vitality of female zygotes (according to the hypothesis of M. Lion), hemozygoteness of male zygotes (all recessive genes show there) and alienation (according to proteins) of a male zygote for a maternal organism can explain such a ratio. The secondary ratio of sexes can depend on a number of factors:

1. Mother's age (during pregnancy) — at the age of 18–20♀ it is 100–120♂; at the age of 32–40 years — 100♀–90♂;
2. Boys are born more frequently during first deliveries;
3. Girls are born more often in gestational toxicosis and stress situations.

The tertiary ratio (postnatal period):

By 20 years — 100♀ : 100♂

By 50 years — 100♀ : 85♂

By 80 years — 100♀ : 50♂

A greater vitality of the female organism and greater death of males in the postnatal period (due to diseases, during wars, hard physical labor, from harmful habits, in automobile accidents) explains these ratios.

CHROMOSOMAL DISEASES OF SEX

The impairment of combinations of sex chromosomes is possible when something goes wrong during the course of mitosis and meiosis. In Drosophilae there may appear individuals called gynandromorphs. In various cells they contain a different number of sex chromosomes: X or Y or only X. Accordingly, various parts of the body may have characters of a male or female sex.

In some organisms there occurs *hermaphrodism* (bisexuiality). If *hermaphrodism is true*, then sex glands produce male and female gametes (e. g. flat worms). In case of a *false hermaphrodism* (it occurs in humans), there is inconsistency of primary and secondary sex characters. False hermaphrodites are more often sterile.

When sex chromosomes diverge in the process of human meiosis, sexual *chromosomal diseases* can occur.

♀/♂	X	XX	0
X	XX	XXX	X0
Y	XY	XXY	$Y0^v$
XY	XXY	XXXY	XY*
0	X0	XX*	00

XX and XY — a normal male and female organism.

XX* — a normal female organism which inherited both sex chromosomes from mother. $Y0^{v}$, 00 — non-vital individuals.

XXX — a syndrome of X-trisomy. Karyotype — 47, XXX. Phenotype is female. Incidence — 1:800–1:1000. Nuclei of somatic cells have 2 Barr bodies. This syndrome has no specific characters. In 75 % of cases, dementia, hot temper and irritability occur, patients degrade quickly. The risk to develop schizophrenia is increased. A tall height may take place. The function of ovaries is impaired, they are sterile. However, sometimes they may have children. The more X-chromosomes are in the genotype, the more severe is the impairment of brain functions.

X0 — a Shershevsky-Terner syndrome. Karyotype — 45, X0. Phenotype is female. The incidence is 1:2000–1:3000. Nuclei of somatic cells do not have Barr bodies. Infants have a small weight and height at birth. The height of adults is 135–145 cm. By 7 years somatic characters appear: a short neck; a skin fold goes down from the occiput to shoulders, a low position of earflaps and a hair line on the occiput, changed joints of fingers and toes, 25 % of patients have congenital heart defects and renal abnormalities. They are aging early. Sexual infantilism is clearly marked, ovaries are underdeveloped, secondary sexual characters are absent. Such patients are sterile. In this syndrome, intellect is rarely impaired. Treatment: hormonotherapy, stimulation of body height.

XXY, XXXY — Klinefelter's syndrome. Karyotype — 47, XXY; 48, XXXY. Male phenotype. The incidence is 1:400–1:500. Nuclei of somatic cells contain Barr bodies. The height is tall. Female constitution. Gynecomastia (mammary glands are enlarged) is present. Hair covering is poorly developed. Testes are underdeveloped, the process of spermatogenesis is absent (individuals are sterile), but sex reflexes are preserved. Sometimes the intellect is normal, more often mental retardation is present. In these patients, inhibition processes become weak; they are easily suggestible. Due to deficiency of hormones, they age early.

The more X-chromosomes are in the genotype, the more severe is the impairment of intellect.

LECTURE 9
Topic: BASES OF HUMAN GENETICS (I)

Plan

1. Human genetics: the subject and tasks.
2. Specificity of human genetics.
3. Methods of studying human genetics.

HUMAN GENETICS: THE SUBJECT AND TASKS

Human genetics or **anthropogenetics** (Greek *antropos* — human) studies phenomena of inheritance and variation, laws of inheriting characters, their modifications under the influence of the environment. At present, there are a number of independent sections of human genetics: cytogenetics, biochemical and molecular genetics, radiation genetics, immune genetics, pharmacogenetics, population genetics.

One of the most important sections is *medical genetics* that has become an independent science. The subject of this science is studying hereditary pathology, development of diagnostic methods, treatment and prophylaxis of hereditary diseases.

There are about 5000 metabolic hereditary diseases in humans. Various development defects are revealed in every 30–40 per 1000 newborns. About 100 forms of skeletal hereditary defects are known. The incidence of congenital development defects after the Chernobyl accident increased by 40 % in Belarus. 10 % of all *congenital development defects (CDD)* are due to chromosomal aberrations.

Examples of CDD: *agenesia* — absence of an organ (e. g., an extremity); *hypogenesia* — underdevelopment of an organ (e. g., ghonads); *hypergenesia* — overdevelopment of an organ (e. g., polydactylism); *atresia* — imperforation of natural orifices and canals (e. g., epigastrium); *ectopy* — unusual position of an organ (e. g., the heart on the right side) etc.

The tasks of human genetics are:

1. Improving methods for early diagnosis of hereditary pathology.
2. Studying the pathogenesis, treatment and prophylaxis of human hereditary diseases.
3. Wide usage of medical-genetic consultations.
4. Elaborating genetic aspects of immunity, transplantation, allergy and cancerogenesis.
5. Setting up a database bank, elaboration of genic therapeutic methods based on genic engineering.
6. Elaborating methods for protecting the human gene pool.

SPECIFICITY OF HUMAN GENETICS

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

The specificity of human genetics:

1. Impossibility to use a hybridological analysis and experimentation for humans.
2. The karyotype complexity — there are many chromosomes and groups of linkage.

3. Late puberty, a small number of fillies in the family, slow change of generations.

4. Diversity of ecological and social conditions; impossibility to establish identical conditions of life.

Advantages of the human as a genetic object:

1. Numerous individuals in human populations.
2. International cooperation of geneticists and exchange of obtained information.
3. Humans are better clinically studied than other objects.
4. Elaboration of special methods to overcome difficulties while studying human genetics.

METHODS OF STUDYING HUMAN GENETICS

F. Galton suggested a **twin method of investigation** in 1875. It allows determining a correlative role of heredity and environment in manifestation of the character.

The birth rate of twins is 1 %. Twins may be *monozygotic (unioval*) (MT). They develop from one zygote, have an identical genotype. If twins are *dizygotic (polyoval)* (DT), they develop from different simultaneously fertilized zygotes. They have different genotypes, just as in siblings.

Criteria of zygosity in twins: MT have always an identical sex, blood groups, skin patterns. In DT these parameters are different; in rare cases they may coincide (except skin patterns).

The similarity of twins according to a studied character is called *concordance*, differences according to this character — *discordance* (table 2).

Table 2

Concordance according to some characters in MT and DT

Character	Concordance of MT, %	Concordance of DT, %
Tuberculosis	66.7	23
Oligophrenia	97	37
Schizophrenia	69	10
Blood group (AB0)	100	46
Eye color	99.5	25
Hypertension	20.2	10
Diabetes mellitus	65	18

The formula of Holtsinger is used to determine a share of heredity and environment in the development of a specific character:

$$H = \frac{CMT\% - CDT\%}{}$$

$$\frac{}{100\ \% - CDT\%}$$

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 development of the character; if the amount of H approximates to 0, then the environment is mostly responsible for the character development.

F. Halton suggested a genealogic analysis in 1876. It became a basis for a **clinical-genealogical method** — making up genealogies and analyzing inheritance of characters in a number of generations. This method allows establishing:

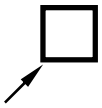
- a degree of relationship;
- if the character is hereditary or not (the presence of a family disease);
- type of inheritance (dominant, recessive, autosomal, linked with sex, holandric);
- zygosity of the genealogy members (homozygotes or heterozygotes);
- genic penetrance ;
- probability of showing the character in fillies.

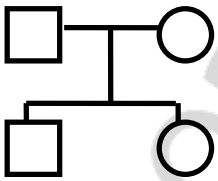
Designations used in making up a genealogy:


- a female organism (the analyzed character is absent)


- a male organism (the analyzed character is present)


- sex of the individual is not known to the proband


- a male proband


- marriage (parents)

- children (siblings)


- a heterozygotic carrier of the analyzed character

A *proband* is a person from whom a genealogy starts, it is marked with an arrow.

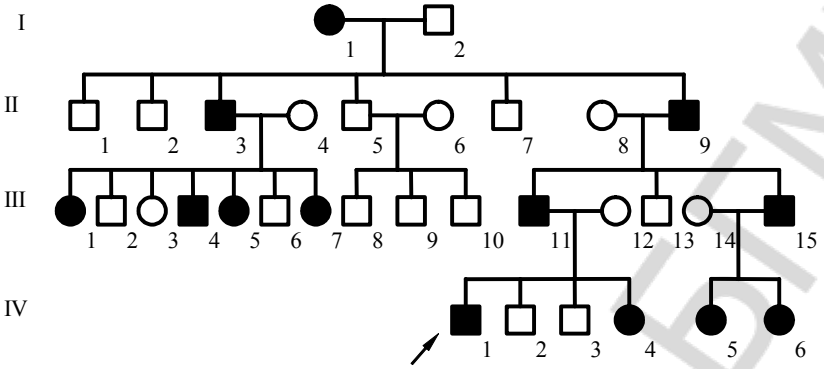
Stages of the genealogical analysis:

- Taking information about relatives of the proband;
- Making up and analyzing the genealogy; making conclusions.

Autosomal-dominant type of inheritance:

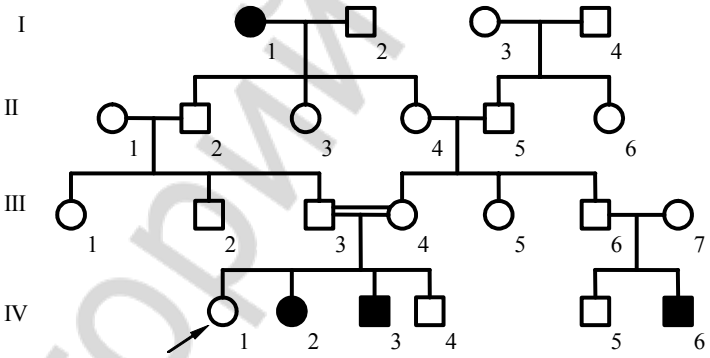
- Both males and females fall ill;
- patients are in every generation;

- Sick parents have a sick child;
- Probability of inheriting the character is 100 %, if one of the parents is homozygotic; — 75 % if both parents are heterozygotic, the gene being completely dominant and penetrated, — 100 and 50 % if one parent is heterozygotic, while the second is homozygotic according to a recessive gene.

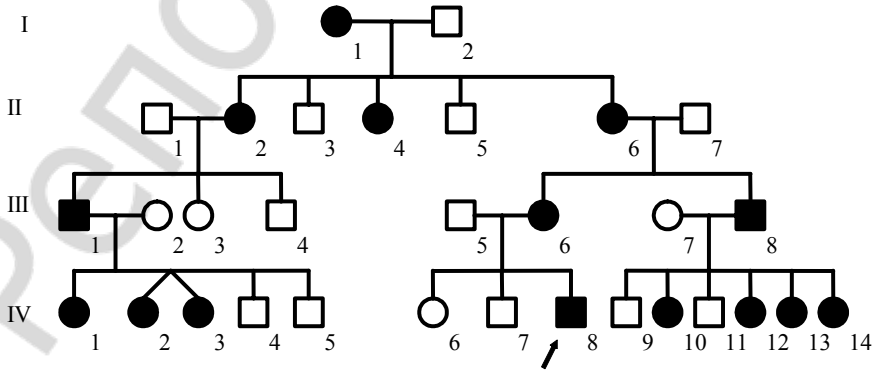


Autosomal-recessive type of inheritance:

- Both males and females fall ill;
- Patients are not in every generation;
- Healthy parents have a sick child; probability of inheriting the character is 25 %, if both parents are heterozygotic, — 50 %, if one parent is heterozygotic, the second is homozygotic according to a recessive character and — 100 %, if both parents are homozygotic according to a recessive character.



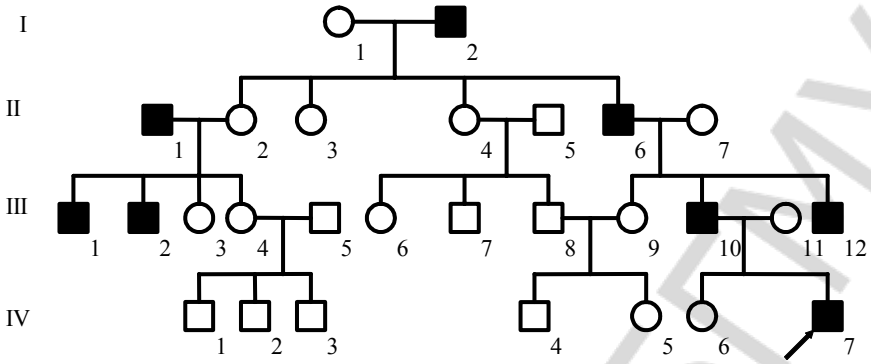
Linked with an X-chromosome dominant type of inheritance is similar to an autosomal-dominant one, except the fact that a male passes this character (with an X-chromosome) only to daughters.



Linked with an X-chromosome recessive type of inheritance:

- predominantly males fall ill;
- patients are not in every generation;

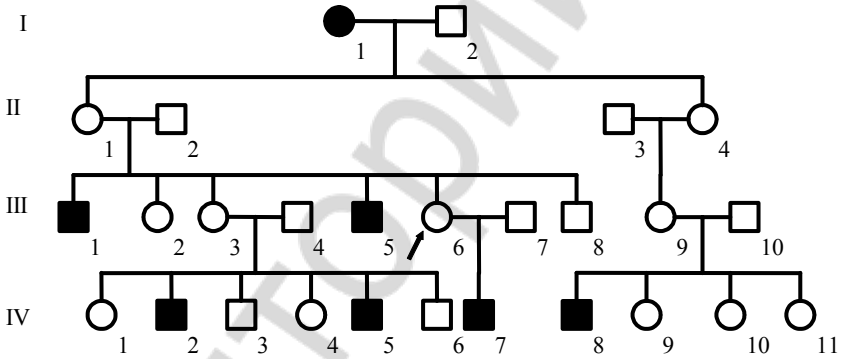
- healthy parents have a sick child;
- probability of inheriting the character is 25 % in boys and 0 % in girls from all children, if both parents are healthy.



Over 200 X-linked recessive diseases are known, when males are affected and females are carriers.

A *holandric type of inheritance:*

- only males fall ill;
- sick father has sick sons.



A population-statistical method of human genetics is based on the law of Hardy–Wineberg. The method was proposed by an English mathematician J. Hardy in 1908 and a German doctor-geneticist G. Wineberg.

The method allows studying the structure of human populations, determine the frequency rate of genes and genotypes in the population and the rate of heterozygotic carriage of a gene. Using this method one can study genic geography of diseases. The incidence of hereditary diseases highly varies in different populations and geographical zones. The incidence of schizophrenia in common population is 1 %, in the population of relatives it is 7–16 %.

The stages of the method:

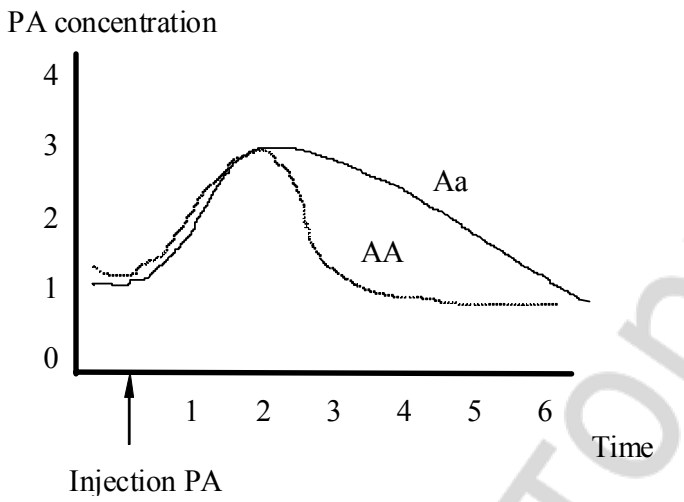
– selection of the population;
– taking material;
– statistical analysis.

A cytogenetic method is based on a microscopic study of the karyotype and determination of Barr bodies in nuclei of somatic cells. Cells of the bone marrow, lymphocytes and tumors are received and cultured. Mitotic division is stimulated, stopped at the stage of metaphase; then the cells are treated with

a hypotonic solution of NaCl, and the chromosomes are stained. After making their photos, idiograms are composed and analyzed. An autoradiographic method is used for identification of chromosomes. A fluorescent analysis is used for making precise the karyotype and mapping chromosomes.

The method reveals genomic and chromosomal mutations. Special designations are used for transcribiong these mutations: *q* — a long arm of the chromosome, *p* — a short arm of the chromosome, "+" — redundancy of genetic material, "–" — deficiency of genetic material. A male with Down's syndrome — 47, XY+21. A female with monosomy of the 21st pair — 45, XX-21. Translocation (t) — 45, XXt (13q, 21q), the presence of a ring (*r*) X-chromosome — 46, X*r* (X).

Biochemical methods are used to reveale metabolic hereditary diseases estimating enzyme activity or a quantitative final product of the reaction, which this enzyme catalyzes. Chromatographic, fluorometric, radioimmunological methods help revealing genic mutations (causes of metabolic diseases). For example, phenylketonuria is an impairment of phenylalanine exchange (PA). The incidence of this disease is 1:10000. Phenylketonuria can be revealed by the blood content of phenylalanine: in healthy people, it is 1–2 mg%, in the sick — 50–60 mg%. Every 30–40th person is a carrier of a phenylketonuria gene. Heterozygosity can be revealed when phenylalanine is injected and its content in the blood is determined. If, after injecting PA, the curve of its content in the blood is slowly returning to its norm, then a person is heterozygotic according to a phenylketonuria gene.



Genetics methods of somatic cells. It was developed by G. Barsky in 1960. The fibroblasts or leucocytes culture of the human were investigated. The cells are cloned (clones are cells with an identical genotype). Then *selection* is performed — selection of cells with given (definite) characters. It is possible to make cellular *hybridization* of both one organism and different types of them. The method of cellular hybridization allows studying linkage groups and mapping chromosomes, determining primary by-products of genes activity, the mechanism of genes interaction and regulation of their activity. It is possible to study mutagenic action of different chemical substances on the cellular culture.

Molecular-genetic methods are to reveal structure variations of the investigated DNA part and to decode the primary nucleotide sequence. In the majority of cases, it is sufficient to diagnose a disease or a heterozygotic state.

To make the analysis it is necessary to get (amplify, multiply) a sufficient number of DNA fragments. It is done using a *polymerase* chain reaction (PCR) — in several hours one can obtain any number of fragments. The cycle of amplification includes 3 stages: temperature denaturation of DNA (separation of a 2-sequence molecule into single-sequence ones) → joining single-sequence molecules to complementary parts → synthesizing polynucleotide sequences on single-sequence molecules using the polymerase. Restictases help obtain DNA fragments (per 4–6 pairs of bases). The fragments are separated using electrophoresis on the surface of polyacrylamide gel, then they are identified.

Modeling

- Biological: studying hereditary human pathologies on animals. For example, hemophilia in dogs, diabetes in rats, cleft lip and palate in mice. The theoretical basis of applying the results, obtained on animals, for humans is a *law of homologous series* of N. I. Vavilov (genetically close species and genders have similar series of hereditary variation). The biological modeling is used for studying mutagenic and teratogenic effect of new medicines.
- Mathematical: is used in population genetics while determining the frequency rate of genes and genotypes in populations under various environmental conditions.

Express-methods — are fast (screening-tests) preliminary methods (for example, examination of a newborn for phenylketonuria).

These methods must be economic, reliable, diagnostically significant; the material for investigation should be taken in small amounts and be easily accessible (blood, urine).

Biochemical and chemical methods (colored reactions) are used for quick preliminary diagnosis of metabolic diseases.

Determination of X- and Y-sex chromatin

Epithelial cells of the cheek mucus	
coloration	
acetorcein	acrychin-yperite
↓	↓
light microscope	luminescent microscope
↓	↓
determination of a number of X-chromosomes in the presence of Barr bodies (they exceed the number of lumps of X-chromatin by 1)	determination of a number of Y-chromosomes in the karyotype (an Y-chromosome gives bright green fluorescence)

Gatri's microbiological test. A drop of blood from the heel of a newborn is placed on the blotting paper and then on the agar bacterial culture containing a definite anti-metabolite of phenylalanine. The anti-metabolite inhibits growth of bacteria. However, if there is a lot of phenylalanine in the blood, anti-

metabolite is broken down and microbes start growing. Changing metabolites, one can determine definite amino acids and carbohydrates in the blood.

A dermatoglyphic analysis is studying papillary patterns (skin patterns) of fingers, palms and feet. Dermatoglyphic patterns are strictly individual and do not change during life. There are patterns of three types on fingertips: an arch (A), loop (L) and whirl (W). Patterns may be combined too.

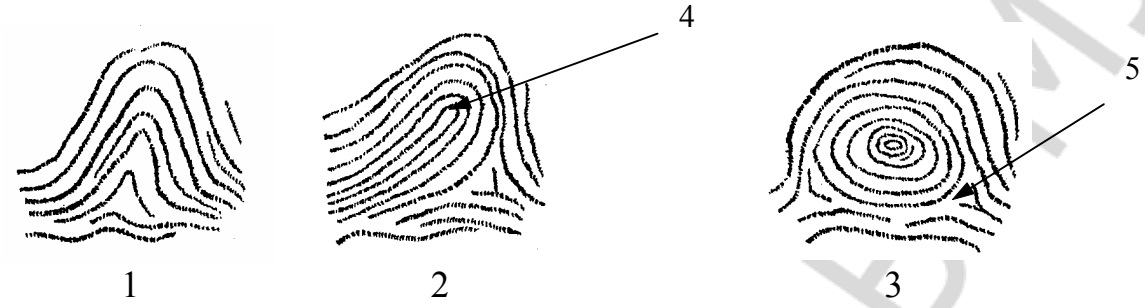


Fig. 21. Types of papillary patterns on the fingertips:
1 — arch; 2 — loop; 3 — whirl; 4 — the center of the pattern; 5 — delta

For the majority of cases, delta (triradius) is most characteristic. It is a place, where three differently oriented papillary lines converge. There are triradii a, b, c, d in interdigital spaces. A palm triradius t is located near the bracelet fold. If we connect triradii a, d, t, we shall get the main palm angle; in norm, it is not bigger than 57^{o}.

The difficulties of the dermatoglyphic analysis in medicine are due to the absence of specificity of modifications in hereditary diseases. Some relationships take place however. E. g., the distribution of basic patterns in a human population is: L — 62 %, W — 32 %, A — 6 %. In trisomy 18 arches occur on all fingers. The main palm angle in Down's syndrome is 81^{o}. A transverse furrow (on the palm) is 1 % in norm, in Down's syndrome — 40 %.

A method of prenatal diagnosis of hereditary diseases is making diagnosis of a disease or development defects before birth. When it is incurable, birth prevention of such a child is discussed (interruption of pregnancy with the woman's consent). A modern level of development of prenatal diagnosis allows making a diagnosis of all chromosomal diseases, the majority of congenital development defects and diseases associated with the impairment of enzyme functions, if a biochemical defect is known.

Methods of prenatal diagnosis can be *indirect* (examination of a pregnant woman — obstetrical-gynecological, genealogical, bio-chemical) and *direct* (examination of the fetus).

One of indirect methods is determination of α–phetoprotein (APP) in the blood serum of a pregnant woman. The APP concentration reduces in chromosomal diseases. It may increase on the $13–15^{th}$ week, when there is a menace

of a miscarriage, intrauterine death of the fetus, multiple pregnancy, defects of the nervous tube, congenital nephrosis.

Direct non-invasive methods (without tissue injury) include *ultrasonography* that is done for all pregnant women.

Ultrasonography is using ultrasound to get an image of the fetus and its membranes. The method is not dangerous for the fetus and can be re-used. Ultrasonographic diagnosis, made at different stages of pregnancy, reveals the fetus vitality, twin pregnancy, development defects of the brain (anencephaly, hydrocephaly, microcephaly), cranial and spinal hernias, hydronephrosis, polycyctosis, hypoplasia or anaplasia of kidneys, esophageal atresia, impairments of the bony system development. About 90 % of congenital defects are supposed to be revealed by ultrasound examination.

Direct invasive methods (with tissue injury): chorion biopsy, amniocetesis.

Chorionbiopsy is taking chorion celia through the uterine cervix (transcervically) for cytogenetic and biochemical investigations and DNA analysis. It is done on the 8–13th week of gestation with an ultrasound apparatus. The method *allows revealing all mutations*: genic, chromosomal and genomic.

Amniocentesis gives the best results. On the 15–17th week a puncture of the amniotic sac is made under the control of an US apparatus, and 15–20 ml of the amniotic fluid with fetal cells are taken by a syringe. The fluid is used for biochemical investigations. In fetal cells, one can determine genomic and chromosomal mutations, X- and Y-chromatin. DNA analysis determines genic mutations. While using the amniocentic method, complications do not exceed 1 %.

Indications for diagnosis by direct invasive methods are:

- the presence in the family of a hereditary disease;
- mother's age over 37 years (a mean risk value to have a fetus with a chromosomal anomaly for women at this age is 2–3 %, at the age of 45 years and over — 5–10 %);
- the presence of a gene X-linked recessive disease in the mother;
- spontaneous abortions at early terms of gestation, still birth, birth of children with multiple development defects and with chromosomal pathology;
- heterozygosity of both parents having one pair of genes with an autosomal recessive type of inheritance;
- pregnant women from the zone with an elevated adiation background.

LECTURE 10
Topic: BASES OF HUMAN GENETICS

Plan

1. Genic, chromosomal and genomic mutations as causes of hereditary human pathology.
2. Medical-genetic consultations.

GENETICALLY DETERMINED DISEASES

Genic mutations phenotypically manifest in humans as hereditary metabolic diseases, *enzymopathies*. About 5000 such diseases are described. Their incidence in human populations comprises 2–4 %.

Genic diseases occur in two types of protein changes. In case of mutations of structural genes, one can observe qualitative changes of proteins and then anomalous proteins (e. g., hemoglobin molecules) are formed. When functional genes are mutated, the content of normal protein in the cell increases or decreases, and *its quantitative changes* caused by the impairment of gene regulation occur.

The substances that accumulate in the impairment of enzyme activity may produce a toxic effect or cause definite impairments of the structure and function of the cell.

Genic diseases are classified according to the character of a metabolic defect.

Impairment of amino acids exchange

Phenylketonuria and albinism are most common diseases.

In norm: phenylalanine $\xrightarrow{\text{enzyme}}$ tyrosine $\xrightarrow{\text{enzyme}}$ melanin

When phenylalaninehydroxylase enzyme is absent, tyrosine is not formed. But as phenylpyroracemic acid accumulates in the blood serum, **phenylketonuria** develops. The frequency rate in populations is 1:6000–1:10000. Inheritance is autosomal-recessive. The symptoms of the disease: a smell of mice (phenylpyroracemic acid is excreted with urine and sweat), increased excitability and muscular tremor, convulsive epileptiformal attacks, microcephaly, mental retardation. The phenylpyroracemic acid is a neurotropic poison. Diagnosis: by biochemical methods (revealing of the phenylpyroracemic acid in urine, of phenylalanine — in blood: in norm — 1–2 mg%, in disease — 50–60 mg%). At child's birth the express-method with $FeCl_3$, microbiological Gatry's test is used.

Treatment: special diet — food without phenylalanine from the fist weeks to the age of 7–10 years.

Albinism develops in the absence of the *tyrosinase* enzyme. A melanin pigment does not form. The frequency incidence is 1:5000–1:25000. An autosomal-recessive type of inheritance. Clinical manifestations of albinism: milk-

white color of the skin, absence of pigment spots, light hair, a light-grey iridic membrane of the eyes, a red pupil, diminished eyesight, elevated sensitivity to ultraviolet radiation (inflammatory processes develop on the skin). Diagnosis of the disease: clinical examination. Treatment is not elaborated.

Impairment of carbohydrate exchange

Galactosemia. The frequency rate is 1:100000. An autosomal-recessive type of inheritance. The disease is caused by insufficiency of the enzyme that transforms galactoso-1-phosphate into uridin-diphosphogalactose.

Galactose enters the infant's organism with mother's milk and accumulates in the blood and in various tissues. Galactose is excreted with urine. The impairment of glucose exchange is observed in the liver, kidneys, the brain. The content of glucose in the blood is decreased. The basic signs of the disease: jaundice of newborns, vomiting, diarrhea, enlargement of the liver and spleen, development of mental retardation, general dystrophy, cataract. In laboratory examination galactose and protein are revealed in urine. If not treated, patients die during the first months of life. Early dietotherapy is effective — lactose is excluded from the food of newborns.

Impairment of lipid exchange

Hyperlipoproteinemia is caused by the impairment of lipid exchange in the blood serum (fatty acids, triglycerides, cholesterol) due to a defect of enzymes or cellular receptors. The frequency rate of the disease is 1:500. The type of inheritance is autosomal-dominant. An elevated cholesterol level causes the development of atherosclerosis, ischemic heart disease, early myocardial infarctions (33–45 years). Diagnosis: determination of the lipoproteins content in the blood serum.

Impairment of purines exchange

Lesch-Nyhan syndrome. The incidence frequency is 1:300 000. A recessive, linked with an X-chromosome character. The disease is caused by insufficiency of the enzyme, which catalyzes the attachment of purine bases to nucleotides, and they break down to a lactic acid. Signs of the disease: muscular hypertone, deposition of the uric acid in joints, formation of calculi in ureters, development of olygophrenia. Diagnosis: determination of the uric acid content and its salts in the blood.

Impairment of mineral exchange (copper exchange)

Wilson's disease. The incidence frequency — 2:100 000. The type of inheritance — autosomal-recessive, linked with an X-chromosome. The cause — insufficiency of the cerulloplasmine protein that provides transport of copper in the organism. The concentration of copper in the blood, brain and liver increases. The disease occurs more often at school age. Signs of the disease: enlargement of the liver and spleen, jaundice, vomiting, impairment of swallowing and motor

development in children, sometimes — deterioration of intellect. Diagnosis: determination of the cerulloplasmine content in the blood.

Impairment of coagulation mechanisms

Hemophilia A. The incidence frequency — 1:6500 newborn boys. The type of inheritance — recessive linked with an X-chromosome. The cause of the disease — decrease of coagulation factor VIII activity. The disease is revealed on the 2–3rd year of life, sometimes — at birth (by bleeding from the umbilical cord and intracutaneous hemorrhages). The disease is characterized by multiple hematomas, hemorrhages into large joints of extremities (knee, ulna), intramuscular hematomas, bleeding in injuries and the presence of blood in urine. Diagnosis: determination of the coagulation factor.

Impairment of the hemoglobin molecule structure (hemoglobinopathies)

Drepanocytic anemia (HbS): in the 6th position of a hemoglobin ß-chain, valine is substituted by a glutaminic acid. Erythrocytes are sickle-like in shape. The solubility of hemoglobin is reduced, it does not link and does not transfer oxygen. Heterozygotic carriers of gene HbS are clinically healthy under usual conditions. Already in childhood, homozygotes on this gene have chronic hypoxia and anemia with the impairment of blood circulation and thromboses. In such patients hemolysis and break down of erythrocytes are noted. Hemoglobin HbS occurs more often in areas where there are foci of malaria, because changed erythrocytes are not affected by plasmodia, and heterozygotes on gene HbS are resistant to malaria.

Chromosomal diseases

Chromosomal diseases are due to chromosomal and genomic mutations. The incidence frequency is 0.24–0.4 %. About 40 % of chromosomal diseases are autosomal trisomies. For people polyplodia, haploidy, trisomy and monosomy on large chromosomes are lethal. The diagnosis of chromosomal diseases is made after studying the karyotype by cytogenetic methods. In humans trisomies of the 13, 18 and 21st pairs of chromosomes occur most commonly.

Patau syndrome (trisomy 13): the form may be trisomal and translocational. Phenotypically they are identical. The incidence frequency — 1:6000. An average mass of children at birth is 2500 g. Phenotypical signs: anomalies of the skull and face (moderate microcephaly, a low oblique forehead, narrow eyes, a wide basis of the nose and a sunken nose-bridge, low positioned and deformed ear flaps, clefts of the lip and palate. Polydactyly and syndactyly. Bilateral microphthalmia and cornea opacity. Brain defects (aplasia and hypoplasia of optic nerves and callous body, cerebellum process). In 80 % of cases, congenital heart defects are noted. In more than 60 % cases — defects of the urinary system

(enlarged kidneys, cysts). In 50 % of cases — development defects of the alimentary system. In ¾ boys — cryptorchidism, hypoplasia of the penis; in girls — doubling of the uterus and vagina, a bicornuate uterus. 98 % of infants die before 1 year (first days and weeks).

Edward's syndrome (trisomy 18). For women older than 45 years the risk to give birth to a sick child is 0.7 %. Girls are affected more often than boys. Infants at birth have a small weight. Phenotypical signs: anomalies of the cranial and facial parts of the skull ("an overhanging" occiput, a small lower jaw and mouth opening, narrow and short eye slits; deformed ear flaps, often a lobe of the ear and tragus are absent, sometimes an external auditory passage is absent). The breastbone is short, costal interspaces are diminished. Feet anomalies ("rocking" foot, the 1st toe is shortened). Defects of the heart and large vessels. Spinal hernias and lip clefts; microphthalmia. Defects of digestive organs. Half of the patients have defects of the urinary system (a fused kidney, doubling of ureters etc.). 60 % of children with Edward's syndrome die under the age of 3 months; 1 of 10 infants lives to 1 year.

Down's syndrome (trisomy 21). It is the most common form of chromosomal human pathology (1:750). It was revealed in 1866 under the name of "mongoloid idiocy" by an English doctor Langdon Down. A small part of a long arm $21q^+$ is responsible for phenotypical manifestations of the syndrome. The probability of a sick child is about 4 %, if the parents' age is 41–46 years and older. An average mass of infants at birth is less than normal. The height of adult patients is about 20 cm less than an average one. An average life span is 36 years. Phenotypical signs: a flattened occiput, narrow forehead, broad and flat face, mongoloid eyes, the presence of an epicanthus and light spots on the iridic membrane of the eye, thick lips, a tongue protruding from the mouth. Deformity of the breastbone, shortening and dilation of wrists and feet. A low position of small ear flaps, a short neck. In 60 % of cases — heart defects, in 20 % — defects of the urinary system, in 15 % — defects of the gastrointestinal tract. Deep mental retardation is characteristic of more than 90 % of patients. Abstract thinking is highly impaired, esthetic feelings are absent. With age, insufficiency of intellect becomes more marked.

Partial monosomies

A syndrome of "cat's cry" (5p) — deletion of a short arm of the 5th chromosome or translocation of a part of the 5th chromosome to the 15th chromosome. The incidence frequency is 1:45 000 (more often in girls). The life span of such children is 5–10 years. The most permanent sign of the syndrome — "cat's cry" instead of child's crying — is caused by a defect of the larynx structure (narrowing, softness of cartilages, edema or folding of the mucus, diminishing of the epiglottis). Other phenotypical signs: microcephaly, development retardation, squinted eyes, anti-mongoloid eyes (external corners of eye slits are pulled

down), a cleft lip and palate, a low position of deformed ear flaps, a short neck. Atrophy of an optical nerve is observed.

Diseases with hereditary predisposition

Diseases with hereditary predisposition have a double nature. *A combination of hereditary factors and a complex of environmental factors* is necessary for their manifestation. By their genetic nature, they form two groups of diseases. The diseases of the first group are *monogenic*, and predisposition is determined by one gene. They are relatively few in number, and can be analyzed by Mendel's genetic analysis. They are hereditarily conditioned pathologic reactions to the action of external factors: perverted reaction to environmental pollution, medicines, food substances and supplements, physical and biological factors (vaccines, allergens). The second group includes *polygenic* or multifactoral diseases. Many genes determine hereditary predisposition to them. A relative role of genetic and environmental factors differs not only for a given disease, but also for every individual case of the disease. Genetic polymorphism explains the variety of reactions to external factors.

Multifactoral diseases comprise 90 % of chronic non-infectious diseases of various human systems and organs. They include atherosclerosis, hypertension, epilepsy, schizophrenia. Polymorphic alleles are different in different people. Such variation of genes sets up a basis for various degrees of hereditary predisposition to diseases, enhanced by environmental factors.

MEDICAL-GENETIC CONSULTATIONS

The basic trend of solving problems of congenital and hereditary diseases is prophylaxis, because in the majority of cases, pathologic changes have already been formed by this moment, and the treatment may be effective in rare cases. To prevent birth of children with hereditary pathology *methods of prenatal diagnosis are used*.

Medical-genetic consulting is an obligatory component of prenatal prophylaxis of congenital and hereditary diseases. Establishing a net of medical-genetic consultations is one of the most effective methods to reduce a genetic burden in human populations.

The aim of medical-genetic consulting is to determine a degree of genetic risk in the examined family and to explain the results of medical-genetic conclusion to spouses.

Genetic risk is the probability of appearing in fillies a hereditary pathology. Risk may be low — up to 5 %, moderate — to 10 %, increased — to 20 % and high — over 20 %. Depending on the severity of medical and social consequences of this pathology (e. g., Down's syndrome and Patau syndrome), a moderate, increased and high risks are indications for the interruption of pregnancy.

The decision to interrupt pregnancy is taken by spouses. The doctor only gives his recommendation.

Medical-genetic consultations should also:

- consult families and patients with hereditary pathology;
- to perform prenatal diagnosis of congenital and hereditary diseases;
- help doctors of other specialties to make a diagnosis, if genetic investigation methods are necessary;
- introduce a territory register of families with hereditary and congenital pathology and their following-up;
- permanent popularization of medical-genetic knowledge among the population.

Indications for referring families to a medical-genetic consultation:

- the presence of hereditary pathology in several members of the family;
- the first pregnancy;
- mental and physical retardation of the child;
- giving birth to the 1st child with development defects;
- primary amenorrhea (absence of periods) when secondary sex characters are underdeveloped;
- blood relationship of the spouses.

Therapy of hereditary human diseases

At present, the following methods of treating hereditary diseases and diseases with hereditary predisposition are marked out:

1. Symptomatic treatment. In all hereditary diseases, symptoms are treated with medicines: antibiotics for inflammatory processes, painkillers — for relieving pains, in the state of excitation — sedatives. In congenital defects, surgical treatment is often used: in constriction and atresia of vessels, in polydactyly, heart defects, defects of the facial part of the skull.

2. Pathogenetic treatment (in metabolic diseases):

– *Correction of exchang*e (dietotherapy in phenylketonuria and galactosemia, hemosorbtion);

– *Metabolic inhibition* — suppression of synthesizing a by-product which is not excreted from the organism (uric acid in Lesch-Nihan syndrome);

– *Replacement therapy* — injection of the product into the organism, which is not produced (growth hormone in dwarfism, insulin — in diabetes).

3. Etiological treatment — elimination of the cause of the disease. A very perspective method — a possibility to replace mutated genes for normal ones, using methods of genetic engineering.

Trends of prophylaxis of hereditary pathology:

1) protection of the environment, exclusion of mutagens, teratogens and cancerogens from it;

2) family planning with the account of optimal terms for child birth;

3) improving the methods of prenatal diagnosis of hereditary diseases and congenital development defects;

4) regulation of gene activity using methods of genic engineering.

LECTURE 11
Topic: GENETICS OF POPULATIONS

Plan

1. The species and its criteria. The population structure of a species.
2. Genetic processes in large and small populations.
3. Synthetic theory of evolution.
4. Elementary evolutionary factors.

THE SPECIES AND ITS CRITERIA

The term "species" was introduced into Biology by a botanist D. Ray. The species is a group of individuals having a common origin, occupying the same territory (areal), having a similarity of morphological, functional, genetic, behavioral characters, crossing with each other and giving fertile fillies. The species is a major category of biological classification.

Criteria of the species:

1) *reproductive isolation* and as a result — genetic isolation: individuals of one species cross with each other only;

2) *morphological*: structural similarity of individuals of one species;

3) *physiological*: similarity of physiological processes in individuals of one species;

4) *biochemical*: specificity of proteins, enzymes and metabolic processes in individuals of one species;

5) *etological*: similarity of behavioral reactions in individuals of one species;

6) *ecological:* similar living conditions in individuals of one species;

7) *geographical:* similar settling of individuals of one species on a definite territory.

None of these criteria defines the species separately. They define the species only in a complex.

The population structure of the species

While settling on an occupied territory, the species falls into smaller groups, which are relatively isolated from each other. These groups are populations. The term "population" was introduced into Biology by B. Johansen in 1903.

The population is a group of individuals of one species, having a common gene pool, capable of free crossing, populating the same territory for a long time and isolated from other individuals of the species.

The *gene pool* is an aggregation of all genes in the population. Gene exchange is going on between populations of the species. The sum of population gene pools comprises a *species gene pool*. Individuals of the population are characterized by *genetic polymorphism*: they comprise dominant homozygotes (AA), recessive homozygotes (aa) and heterozygotes (Aa). Such genetic polymorphism is due to panmixia — free crossing in animals and the freedom to choose a marriage partner in human populations.

Populations may be large and small, depending on the number of individuals in the population. *Large human populations* contain over 4000 individuals. Dems and isolates are *human subpopulations*. The number of individuals in *dems* is about 1.5–4 thousand people, intermarriage there comprises 80–90 %, the inflow of genes from other groups is 1–2 %. Dems are relatively transitory and unstable unions of individuals. *Isolates* are small populations with 1.5 thousand of people; intermarriage is over 90 %, the inflow of genes from other groups is less than 1 %.

Human populations are characterized by *demographic factors*: birth rate and mortality rate (the difference between them gives an increase of population), age structure, occupation, economic status of the society, ecological condition of the environment. Human populations increase in number, their evolutional selection reduces, isolates break down, and there appear similarity of living conditions in various climatic zones.

GENETIC PROCESSES IN LARGE AND SMALL POPULATIONS

Large populations are called *panmixed* or incidental, because there occurs an unrestricted cross of individuals or selection of a marriage partner.

Small populations are non-*panmixed* or non-incidental. They have definite restrictions for crossing individuals or a marriage partner.

A large in its number population approaches an *ideal* one, which is characterized by:

- an infinitely large number;
- isolation from other populations of the species;
- complete panmixia;
- absence of mutations and evolutionary selection.

There are no such populations in nature, but large in their number human populations are close to ideal ones in their characteristics.

Large (ideal) populations live according to the law of Hardy-Weinberg: in an ideal population the frequency of genes and genotypes (heterozygotes, dominant and recessive homozygotes) are in balance and do not change in a number of generations.

Large populations are characterized by genetic polymorphism (AA, Aa, aa according to a definite character) and unrestricted panmixia. Under such conditions, 9 variants of marriages are possible (taking into account genotypes):

Genetic records of marriages and fillies:

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

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

Итого: 4AA + 8Aa + 4aa или AA + 2Aa + aa

If gene frequency is denoted by A – p, a – q, genotypes AA – p^2, 2AA – 2pq, aa – q^2, then we shall get the following: p+q = 1 (100 %):

$$p^2 + 2pq + q^2 = 1 \ (100\ \%).$$

In small populations a *genic drift* appears. It is accumulation of homozygotes or homozygotic individuals. In the 1st generation (AA + 2Aa + aa) heterozygotes comprise 50 %, in F_2 their number will be 25 %, in F_3 — 12.5 % etc. In the presence of lethal genes due to homozygotization, the population is dying out. The evolution in small populations is impossible and there is no genetic variety.

The theory of genetic-automatic processes (genic drift) was presented in the works of N. P. Dubinin, D. D. Romashov, S. Right and R. Fisher in 1930. The genic drift, according to T. Dobzhansky (1951), presents incidental fluctuations of frequency of genic alleles, which were not caused by selection.

THE SYNTHETIC THEORY OF EVOLUTION. ELEMENTARY EVOLUTION FACTORS

The modern (synthetic) theory of evolution was developed in the works of S.S. Chetverikov and T. Dobzhansky. They joined the bases of Darvin's evolution theory with basic issues of population genetics, molecular biology, mathematical analysis and information theory.

The basic issues of the synthetic theory of evolution:

1. The least unit of evolution is a population.
2. The species consists of multiple subspecies and populations. Exchange of alleles is possible only within the species; the species is a genetically integral system.
3. The evolution has a permanent and prolonged period.
4. Mutation variation, which has an incidental character, presents the material for selection.

5. The basic stimulus of evolution is evolutional selection; it selects incidental and small mutations.

6. The elementary evolutionary factors include mutations, population waves, isolation. All of them change the frequency of genes in populations.

Realization of the evolutionary process is accomplished by transformation of a genetic program for organisms; frequency of genes in the population is changed by mutations of various types.

The process of mutation is a non-incidental and undirected process. Being an evolutionary factor, it supports high heterogeneity of natural populations. Mutations are not predictable and do not depend on each other. They may be neutral, negative or positive for the organism. When environmental conditions change, neutral mutations may become positive or negative. The frequency of gene mutation is 10^{-5}–10^{-7} per a generation. Taking into account a great number of genes in a human, about 10 % of his gametes have mutation genes. Dominant mutations are revealed in the 1st generation, and they immediately fall under the action of evolutional selection. Recessive mutations are revealed phenotypically only after recessive homozygotes have appeared; then the evolutionary selection affects them. The saturation of the population with recessive mutations, which diminish the adaptability of some individuals to the environment, is called a genetic load of the population. The degree of its phenotypical manifestation is not identical in various hereditary diseases (e. g., hemophilia and daltonism). Mutations are an elementary evolutionary material in natural populations.

Population waves or life waves, according to S. S. Chetverikov (1905) are periodical fluctuations of the number of natural populations due to factors of the external environment (e. g., fruitful and fruitless years). Population waves change the genetic structure of populations, removing less adapted individuals.

Isolation is restriction of the cross freedom. It results in divergence — separation of the population into groups, differing from each other, and modification of the genotype frequency.

Types of isolation:

1. Geographical or territorial-mechanical (mountain ridges, rivers);
2. Biological:

- genetic or defective hybrids (lethal effect; sterility of fillies);
- ecologo-etologic (diminishing of the probability for partners to meet; drift of reproductive periods);
- morpho-physiologic — when the probability of a favorable cross is reduced (morphological differences in sex organs; non-coincidence of marriage periods).

Etologic isolation in human populations is due to religious and moral-ethical restrictions of marriages. There are marriages between relatives in dems and isolates, inbreeding and inbred depression (hereditary pathology as a result

of homozygotization on recessive genes). Marriages between relatives may be incestuous and consanguineous.

Incestuous marriages, or forbidden, are marriages between relatives of the 1st degree of relationship (siblings, father and daughter, mother and son). Religion and law in many countries forbid them. The 2nd variety of marriages, *consanguineous*, are marriages between relatives of the2nd and 3rd degree of relationship (cuisines, uncle — niece, aunt — nephew). As the probability of heterozygosity on one and the same pathologic gene is high, manifestation of inbred depression is possible. Autobreeding are non - consanguineous marriages. They support a high level of heterozygosity. Hereditary pathology in autobreeding is much less frequent.

Table 3

Disease	Incidence frequency in fillies	
	Non- consanguineous marriages	Consanguineous marriages
Phenylketonuria	1:15 000	1:7 000
Albinism	1:40 000	1:3 000
Microcephaly	1:77 000	1:4 200

The degree of heterozygosity in human populations may considerably change *migration of the population*. *Immigration* "introduces" new alleles or new combinations of genotypes into the population.

Emigration changes a ratio of different genotypes in the population at cost of "extracting" some of them from it.

The most important evolutionary factor is evolutionary selection. It occurs within populations, differentially preserves genotypes, i. e. removes less favorable combinations of genes from the population. Selective evolution has very important forms: stabilizing, stimulating, disrupting.

I. I. Schmalgausen described *stabilizing selection*, which preserves average variants of the phenotype or character in the population, fixes a narrower standard of reaction. E. g., during storm birds with long and short wings die; while birds with wings of average sizes survive.

The stabilizing selection removes all deviations of an adaptive standard from the population. It manifests under relatively stable external conditions.

I. I. Schmalgausen developed a theory of *stimulating selection*. When environmental conditions change, a change of the reaction standard or its enlargement occurs. Example: Coloration of butterfly wings (especially under city conditions) changes depending on the color of tree trunks, where they settle. Pollution of atmospheric air makes tree trunks darker, butterfly wings also become darker.

The 3rd form of selection is *disruptive or breaking down*. It is described by G. Simpson. It is opposite to a stabilizing one and arises, when surrounding conditions sharply change.

The disruptive selection is directed against an average meaning of the character and preserves extreme variants of the standard reaction. Example: On open oceanic islands, either wingless insects or insects with overdeveloped wings are preserved, they can tolerate strong gusts of wind.

We can mark out three directions in the evolutionary study: microevolution, macroevolution and megevolution.

Microevolution is a core of the synthetic theory of evolution. It is an organism level of changes, the process of species formation itself.

Macroevolution studies the laws of historic development at a population-species level. It involves great spaces during considerable time intervals and causes the formation of over-specious taxonomic units.

Megevolution is the youngest in time direction. It considers the laws of biospheric evolution. Megevolution is a level of ecosystems. One of its main ideas is that transformations of the organic world never stop.

LECTURE 12
Topic: REPRODUCTION OF ORGANISMS

Plan

1. Reproduction as a universal feature of living things.
2. Forms of organisms' reproduction.
3. Evolution of the sex process.
4. Gametogenesis. The structure of sex cells (gametes).
5. Insemination. Fertilization.
6. Specificities of human reproduction.

Reproduction is one of the major universal features of living things, providing self-reproduction based on transmission of genetic information from generation to generation. Reproduction *on a molecular level* is replication of DNA (self-doubling), *on a subcellular level* — doubling of some organoids, on a *cellular* — amitosis, mitosis (cellular division). Cellular division is the basis of *organism's reproduction*.

Forms of organisms' reproduction

Asexual reproduction of organisms is the most ancient method. In parasites, asexual reproduction is a method of settling and increasing the number of species.

<table>
<tr><td colspan="4">Asexual reproduction</td></tr>
<tr><td colspan="3">Vegetative(with body parts)</td><td>Sporulation(with special cells — spores)</td></tr>
<tr><td rowspan="2">in unicellular</td><td colspan="2">in multicellular</td><td rowspan="2"></td></tr>
<tr><td>in plants</td><td>in animals</td></tr>
</table>

Vegetative reproduction of unicellular organisms:

a) *half-and-half division* — the nucleus is divided mitotically, then the cytoplasm is divided in two by constriction; longitudinal division — in euglena, transverse — in infusoria.

b) *schizogony* — multiple division — at first the nucleus is divided into many parts, then the cytoplasm (in malaria plasmodium);

c) *budding* — a projection with a nucleus is formed on a mother cell (a bud); the bud is growing and separates from the maternal cell (in yeast fungi and in sucking insects).

Vegetative reproduction in multicellular organisms:

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

B. *In animals*:

a) budding (in hydra);

b) fragmentation — division of the body by constrictions into several parts (celiac; and ring worms);

c) polyembryony — division of the fetus into several parts, each forming a whole organism (suckers).

Sporulation: specially formed cells — spores — give a start to a new organism (in water-plants, mushrooms, moss, lycopodium, horsetail and ferny). Spores in plants are formed in special organs — sporangia.

Sexual reproduction		
with fertilization (gametic copulation)	without fertilization (partenogenesis)	
	androgenesis	gynogenesis

EVOLUTION OF THE SEX PROCESS

The sex process is the basis of sexual reproduction. It may take a form of conjugation (exchange of genetic information between two cells) or copulation — joining of genetic information of two cells. Conjugation is characteristic of infusoria and bacteria. During conjugation, infusoria join by a cytoplasmatic bridge and exchange parts of the micronucleus. Then they diverge and reproduce by asexual way.

At a definite period of the life cycle, individuals of protists perform the function of gametes. They fuse (copulation occurs) and then they reproduce by division. If there is fusion of cells, identical in size and mobility, the process is called *isogamy* (example: amoebas with shells). The process is called *anisogamy* if one cell is larger and immobile and the other — smaller and mobile (example: malaria plasmodia).

Copulation in sexual reproduction of multicellular organisms is *gametic*. Special cells, gametes, form in gonads (sex glands). Female gametes are formed in ovaries, male gametes — in testicles.

Ova have a round or a bit oval shape. They have 60 μm — some centimeters in diameter. They are immobile. Ova contain organoids and a store of nutrients (yoke). Their cytoplasm is specific for definite species. Ova are covered with various membranes, in mammals — also with cells of the follicular epithelium.

A **spermatozoon** consists of a head, neck and tail. It is mobile, has small sizes (40–500 μm). The sizes of a human spermatozoon are 52–70 μm. An *acrosome*, a modified Golgi's complex, is at the end of the head. It provides passing of the spermatozoon into the ovum. The nucleus occupies the most part of the head; a thin layer of the cytoplasm surrounds it. There is a centersome in the neck and a helix, consisting of mitochondria. They produce energy for the tail to move (fig. 22).

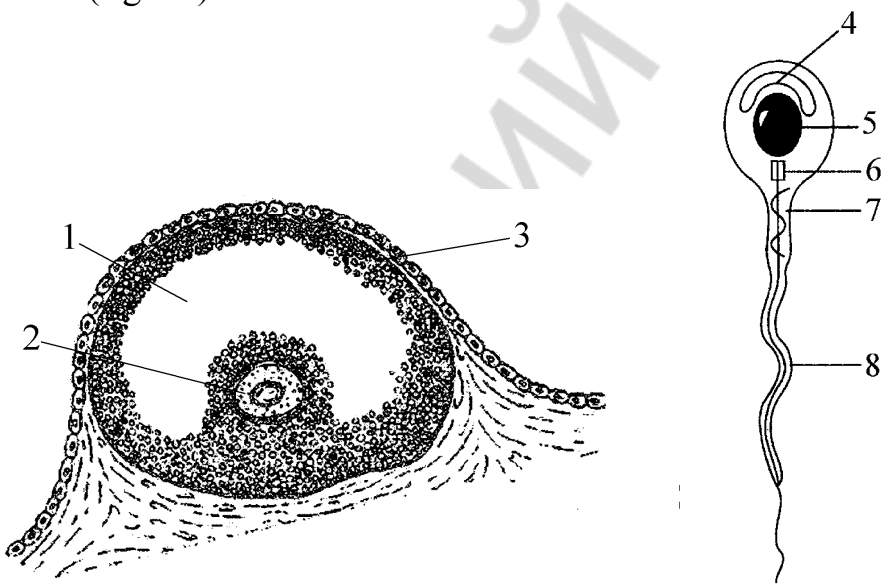


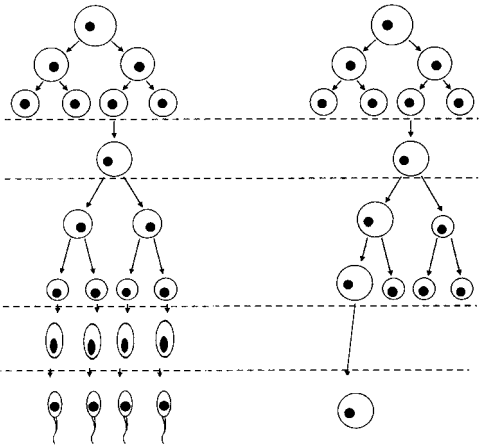
Fig. 22. The structure of an ovum and a spermatozoon:
1 — follicular cavity; 2 — ovum; 3 — follicular membrane; 4 — acrosome; 5 — nucleus; 6 — centriole; 7 — neck; 8 — tail

GAMETOGENESIS

Gametogenesis is a process of gamete formation: *ovogenesis* is formation of an ovum, *spermatogenesis* — formation of a spermatozoon. In gametogenesis, (table 4) gaploidal gametes are formed from diploid somatic cells of sex glands (gonads).

Table 4

Gametogenesis

Genetic information	Cells names	Spermatogenesis	Ovogenesis	Cells names	Periods
2n2chr4c	spermatogonies			ovogonia	Reproduction (mitosis)
2n2chr4c	Spermatocytes of the 1st order			Ovocytes of the 1st order	Growth
1n2chr2c 1n1chr1c	Spermatocytes of the 2nd order			Overcytes of the 2nd order and reductive bodies	Maturation (meiosis)
1n1chr1c	spermatides				Formation
1n1chr1c	Spermatozoa			Ovum	Gametes

Specificities of human gametogenesis

1. Mitotic division of ovogonia is completed before birth of the organism. Mitosis of spermatogonia starts from the maturation period.

2. In ovogenesis, a growth zone is particularly marked, in spermatogenesis a growth zone is practically unmarked.

3. In ovogenesis, the 1st meiotic division stops at diakinesis of the prophase till puberty. The 2nd meiotic division stops at the metaphase and is completed after fertilization.

4. In ovogenesis a formation zone is not marked, in spermatogenesis it is considerably marked.

A newborn girl has about 30 000 ovocytes in her ovaries, 300–6000 (about 13 cells per year) of them reach their maturation. During the period of sex life a male organism produces up to 500 billion spermatozoa (several billion per one ovocyte of the II order).

At present, the last stages of ovogenesis reproduce outside the organism and give the possibility of "conception" in vitro. At the stage of 8–16 blastomeres, the germ is transferred into the uterus of a woman-recipient.

In lower animals, sex cells are produced during all their life, in higher — during the period of their sexual activity.

The major advantage of sexual reproduction before asexual one is the enlargement of genetic variety of species and populations (table 5).

Depending on the presence and functioning of sex glands (gonads) in the organism, we differentiate hermaphrodism and sexual dimorphism.

A hermaphrodite is an organism, which has male and female gonads producing sex cells in one individual. Such hermaphrodism occurs in flat and ring worms. It is a *true hermaphrodism*. Its variety may be hermaphrodism of mollusks, the sex gland of which periodically produces either male or female gametes. In case of a *false hermaphrodism,* one individual develops external sex

organs and secondary characters of both sexes, but gonads of one sex (either male or female).

Table 5

Differences of reproduction forms

	Asexual	**Sexual**
Parental individual	1	2
Gamete production	–	+
Source of development of daughter individuals	Continuation of the development stage of a parental individual	Development starts with one cell — a zygote (fusion of haploid gametes → a diploid zygote
Genetic variety	–	+

Organisms with sexual dimorphism have either female or male gonads. Their sex organs are germinated in embryogenesis. Males and females are characterized by such signs of *sex dimorphism* as: differences in body dimensions, coloration, structure, voice characteristics, behavior and other features. *The signs of human sexual dimorphism are*: peculiarities of the bony-muscular system; distribution of subcutaneous adipose cellular tissue; the degree of hair covering development; voice tembre; specificities of the nervous system and behavior, etc.

INSEMINATION

A number of processes that provide a contact of female and male gametes is called *insemination*. In most of water animals insemination is external: gametes are excreted into the external environment, and their fusion occurs in water. In *internal insemination* (in ground animals) male gametes are introduced into sex ways of a female during intercourse.

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

– various charges of gametes;

– movement of spermatozoa and contraction of the walls of female sex ways;

– excretion of special chemical substances, gamones, by an ovum; spermatozoa react to them with a positive chemotaxis.

The process of fertilization has an external and internal phases.

During the *external fertilization phase,* an ovum is activated and a spermatozoon is passing into it. There is an opening in the membrane of some ovum, a *micropile*, through which a spermatozoon enters an ovum. In the majority of cases, its passing into the ovum occurs due to an *acrosomal reaction*. During the contact with an ovum, the membrane of the acrosome breaks down and the enzyme of *hyaluronidase* is excreted. It dissolves the ovum membrane, the acrosome throws out an acrosomal thread and permeates through the egg membranes and fuses with the ovum membrane. A *receiving prominence*

is formed on this part of the ovum; it grasps and brings the head, centriole and mitochondria of the spermatozoon into the cytoplasm of the ovum. If one spermatozoon enters the ovum (in mammals), the process is called *monospermy*. If several spermatozoa pass into the ovum (in insects, fish, birds), the process is called *polyspermy*. Activation of the ovum is associated with complex structural and physical-chemical changes: reconstruction of the cytoplasm, changed permeability of the membrane and metabolism. After the spermatozoon has passed into the ovum, a membrane of fertilization is formed on the surface of the ovum, and other spermatozoon cannot get inside. The external phase of fertilization is completed.

Synkaryogamy, the 2nd important process associated with *the internal phase of fertilization*, is fusion of haploid nuclei and formation of a diploid nucleus of the zygote. Colloidal features of the ovum cytoplasm change, its viscosity increases. *A male pronucleus* (spermatozoon nucleus) swells to the sizes of *a female pronucleus* (ovum nucleus), turns by 180° and moves to a female pronucleus with its centersome.

Partenogenesis and its varieties represent a special form of sexual reproduction: gynogenesis and androgenesis — the development of organisms from unfertilized ovum.

Partenogenesis (Greek *partenos* — virgin, *genos* — birth) was described in the middle of the XVIII century by a Swiss naturalist Sh. Bonne. *Natural partenogenesis* occurs in lower cancroids, bees, butterflies, rock lizards. Nuclei of somatic cells of such individuals will be haploid. A diploid complement sometimes restores in fusion of ovum nuclei with the nucleus of a directive body. In 1886 A. A. Tikhomirov described *a natural partenogenesis*. He induced splitting of unfertilized eggs of a bombyx, affecting them with physical and chemical stimuli. B. L. Astaurov developed an industrial method of obtaining partenogenetic fillies in a bombyx.

Gynogenesis (Greek *gyne* — woman) is the development of the organism based on the information of a female pronucleus. A spermatozoon is an activator of the development. The spermatozoon nucleus does not take part in fertilization. If it gets into the ovum, it becomes broken down. Gynogenesis occurs in some fish species (e.g., silver crucian). Their fillies consists only of females.

Androgenesis (Greek *andros* — man, *genesis* — birth) — the development of the germ occurs at cost of nuclei of one or two male gametes, which permeated into the cell with a broken nucleus. Such individuals are obtained in a bombyx and some wasps. All of them had only paternal characters.

SPECIFICITIES OF HUMAN REPRODUCTION

Specificities of human reproduction are associated with the fact that the human is not only a biological, but also a social being. The ability for reproduction in humans appears with puberty. Its signs are periods in girls (at an av-

erage age of 12–15 years) and pollution in boys (at 13–16 years). The duration of the reproductive period in women is to 40–45 years, in men — to old age. During one intercourse, about 200 million of spermatozoa are excreted with seminal fluid. Ovocytes in ovaries, precursors of future ovum, are germinated in embryogenesis. When puberty has come, once in a moon month an ovocyte of the 2nd order is formed. Fertilization in humans occurs in the upper parts of uterine tubes, usually during the first 12 hours after ovulation. Spermatozoa preserve their ability for fertilization during 1–2 days after their entering the female sex ways.

Human reproduction, unlike that of animals, has no seasonal prevalence. It depends on a number of social-economic factors. As a social being, the human can regulate the childbirth.

LECTURE 13
Topic: BASES OF ONTOGENESIS (EMBRYONIC DEVELOPMENT)

Plan

1. Periods of ontogenesis.
2. Embryogenesis.
3. Realization of genic actions in ontogenesis.
4. Critical periods of development. Teratogenesis.

Ontogenesis is individual development from a zygote formation until death of the organism.

Periods of ontogenesis		
prezygotic (pre-embryonic or progenetic) period	embryonic (prenatal) period	postembryonic (postnatal) period

Prezygotic period or progenesis is the period of formation and maturation of parental gametes, which will form a zygote. The quality of gametes, the presence of mutated cells there will have a considerable influence on the health of future fillies.

Embryonic or prenatal period starts with the moment of a zygote formation and ends with birth of a new organism or its going out of ovum membranes.

Postembryonic or postnatal period starts with birth of an organism or going out of ovum membranes and to its death.

EMBRYOGENESIS

Human embryogenesis includes:

- Germinative or initial period — the 1st week after fertilization, when splitting of a zygote takes place;
- Embryonic period — the 2nd-3rd weeks after fertilization, when a blastula and gastrula are formed; germination of germination sheets and axial organs take place;
- Prefetal period — the 4th-8th weeks, when germination of organ systems and placenta takes place;
- Fetal period — from the 9th week an embryo is called a fetus; growth of the fetus and formation of organs and organ systems take place.

A zygote is a unicellular stage of development of multicellular organisms that is formed in zygosis (fusion of a male and a female gamete).

The type of splitting a zygote is determined by the ovum type, which depends on the quantity of nutrients (yoke) and their distribution (fig. 23).

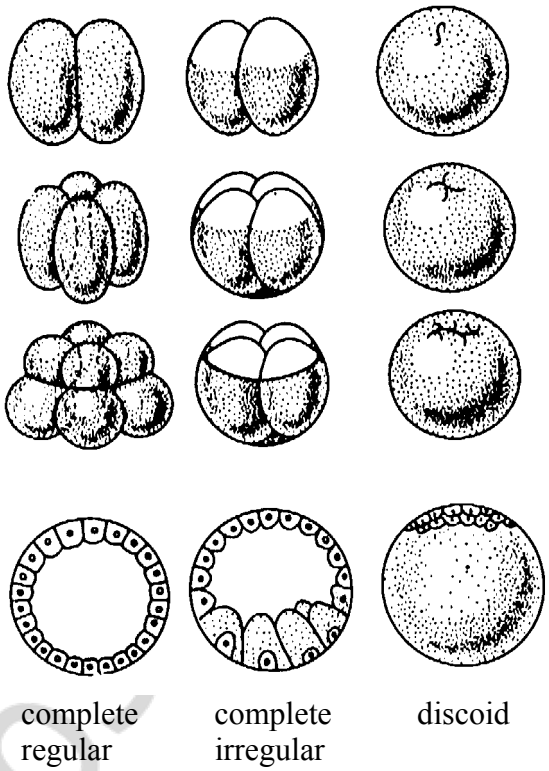


Fig. 23. Splitting types of various zygotes

Isolecytal ova: insufficient quantity of yoke, it is distributed regularly in the cell. Splitting of such eggs is complete, regular and synchronous (human).

Moderately telolecytal ova: moderate content of yoke at the pole, which is called vegetative. The pole, where the cytoplasm with the nucleus is placed, is called animal. Splitting is complete, irregular (amphibian).

Sharply telolecytal ova: a great amount of yoke is placed at the vegetative pole. A germinal disc is split; it is a small part of the cytoplasm with the nucleus. The splitting is called discoid (birds).

Centerlecytal ova: the center of the cell is occupied by the yoke; the cytoplasm forms a peripheral layer, where splitting takes place. It is called superficial (insects).

Cells that are formed during splitting of a zygote are called *blastomeres*. The germ of some animals reminds a raspberry or a mulberry in the process of splitting. It got the name of *morula*. Blastomeres of the morula are distributed on the periphery in one layer and form a *blastula* — a one-layer germ. A layer of cells is called a *blastoderm*. Cells of the blastoderm are called embryonic cells. The cavity of a blastula got the name of a primary cavity, *blastocele*. The germs of all types of animals undergo the blastula stage.

Gastrulation, formation of a gastrula, follows the blastula stage. Layers of gastrula cells got the name *germinal sheets*. There are four types of gastrulation (fig. 24):

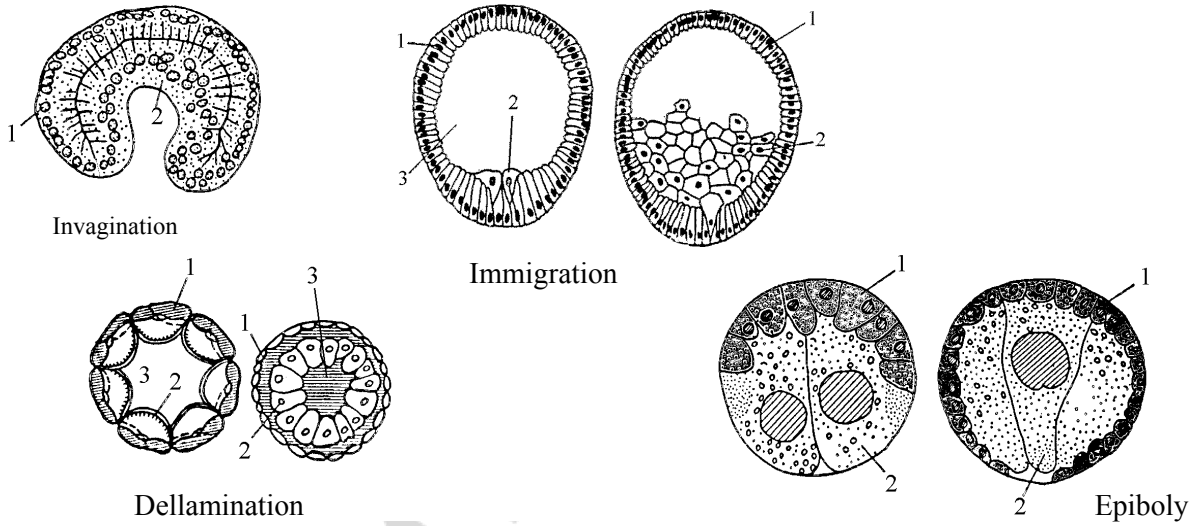


Fig. 24. Ways of gastrulation:
1 — ectoderm; 2 — entoderm; 3 — gastrocele

1. *Invagination* — drawing in. The vegetative pole of the blastula is drawn inside, settling below the animal pole. A two-layer germ is formed. The external sheet gets the name of an *ectoderm*, the internal — an *entoderm*. The gastrula cavity is called a *gastrocele* or a primary intestine. The entrance to this intestine is a primary mouth or a blastopore. Its edges form *an upper and lower lip of the blastopore*. In the secondary-mouthed (echinodermata, chordates) it becomes an anal opening, while the mouth is formed at an opposite end of the germ.

2. *Immigration* — "eviction" of some cells to a germinal cavity and formation of a second layer (endoderm) there. This way is characteristic of coelenterate.

3. *Epiboly* — becoming covered (in a telolecytal type of ova). Cells of the animal pole divide faster than cells of the vegetative pole, which form an endoderm.

4. *Dellamination* — splitting. All cells of one germinal layer divide parallelly to its surface and form two layers – an ectoderm and an entoderm.

In humans gastrulation goes according to a mixed type — several types are combined simultaneously.

At the stage of two germinal sheets, the development of sponges and coelenterate is completed. They refer to two-layer animals. All other animals, occupying higher evolution stages, are three-layer beings. Germination of the 3rd (middle) germination sheet, mesoderm, occurs in two ways — teloblastic and enterocelic (fig. 25).

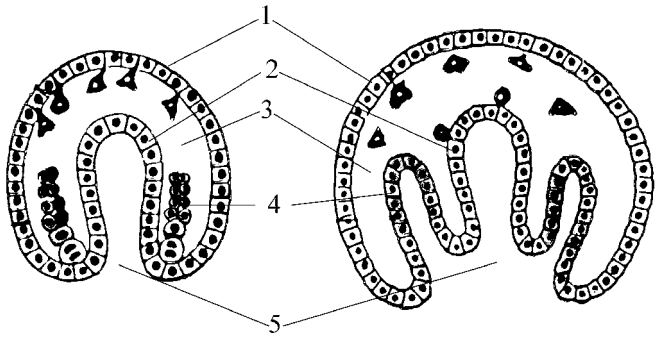


Fig. 24. Formation of 3rd germinal sheet:
1 — ectoderm; 2 — entoderm; 3 — gasrtocoel; 4 — mesoderm; 5 — blastopore

The teloblastic way is characteristic of many invertebrates. During gastrulation, one large cell, a teloblast, is formed at each of the two sides of the blastopore. They start dividing; small cells occupy the space between the ectoderm and entoderm and form the mesoderm.

The enterocelic way of germinating the mesoderm is characteristic of the chordates. On both side of the primary intestine, bulges (celomic sacs) are formed. They separate from the primary intestine, spread out between the ectoderm and entoderm and give a start to the mesoderm.

After the formation of germinal sheets, germination of axial organs occurs, *histogenesis* — the process of tissue formation and *organogenesis* — the process of organ formation.

Derivatives of germination sheets:

The *ectoderm* gives a start to external coverings, the central nervous system, initial and final parts of the gastrointestinal tube.

From the *entoderm* a chord, a middle part of the gastrointestinal tube and respiratory system are formed.

From the *mesoderm* the bony-muscular, cardio-vascular and urinary-genital systems are formed.

REALIZATION OF GENIC ACTIONS IN ONTOGENESIS

Genetic information (sequence of DNA nucleotides) provides the synthesis of mRNA, proteins-enzymes, which cause the development of characters. Manifestation of genic action depends on other genes. They may affect the given gene, proteins-enzymes that are coded by this gene, manifestation of the character. The given gene may affect the realization of action of other genes. The realization of genic action also depends on environmental factors that may change the structure of DNA, mRNA, proteins-enzymes and phenotypical manifestations of the gene (diagram 11).

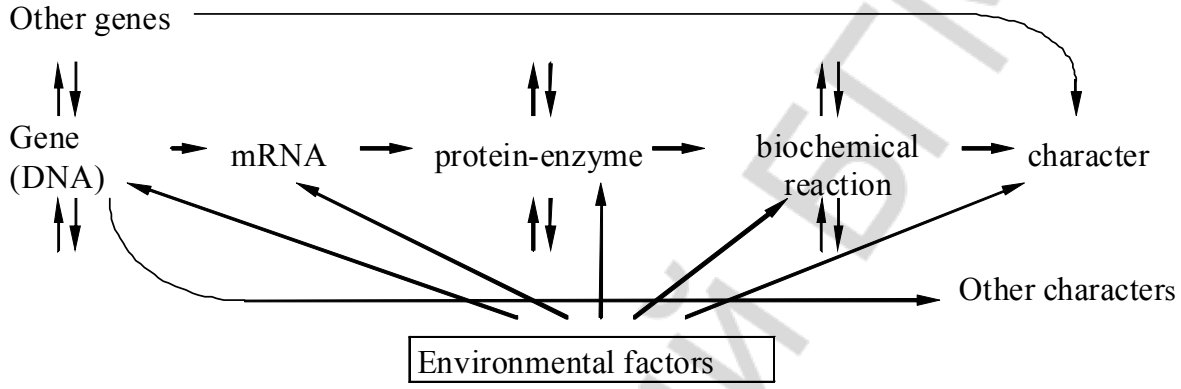


Diagram 11. Realization of genetic information

Mechanisms ensuring embryogenesis:

1. Differential genic activity — during the embryonic development, various blocks of genes have a definite order of repression and derepression.

2. Determination — the choice of a specific way of development, the acquisition by cells the ability to develop in a definite direction and simultaneous restriction of their future development possibilities. At the beginning of embryogenesis, blastomeres are totipotent (they may give a start to a whole organism) and their development depends on external inductors and adjacent cells. At later stages of embryogenesis, the cells become determinated (their development is predetermined), and they develop according to a definite plan.

3. Differentiation — biochemical, functional and morphological specialization of cells; modification of a developing structure, when relatively uniform formations become more and more different.

Differentiation phases:

- dependent (till the stage of an early gastrula);
- independent (at the stage of a late gastrula).

4. Morphogenesis — when new structures appear and their forms change in the process of ontogenesis.

Genetic bases of differentiation

Genetic differentiation is associated with uniqueness of the ovum. It shows in heterogeneity of the cytoplasm — different parts of the cytoplasm have different complements of chemical substances and have different potencies (fig. 26).

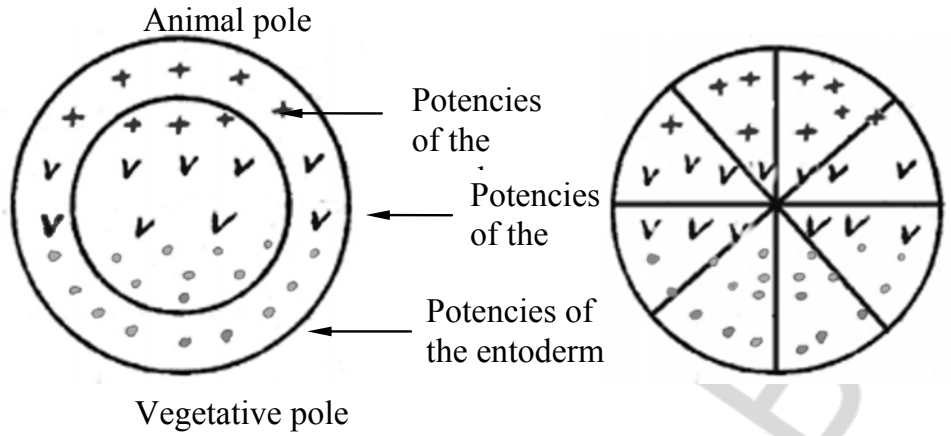


Fig. 26. Heterogeneity of the ovum cytoplasm and its subsequent splitting (various signs denote different chemical content of the cytoplasm)

Stages of differentiation

Chemical heterogeneity of the ovum cytoplasm (enhances after fertilization).

↓

Chemical heterogeneity of the blastomere cytoplasm.

↓

In different blastomeres are different inductors.

↓

Different inductors include different transcriptones.

↓

Different proteins-enzymes are synthesized; they catalyze different types of biochemical reactions.

↓

The synthesis of different typo- and tissue-specific proteins in different blastomeres.

↓

Different types of cells are formed, morphological heterogeneity is created.

↓

Different types of cells form different tissues.

↓

Different tissues form different organs.

Mechanisms of morphogenesis:

1. Embryonic induction — the impact of a group of embryonic cells on adjacent cells (G. Shpeman, G. Mangold). The primary inductor (upper lip of a blastopore) determines the formation of a nervous tube, then a chord is induced, and then — a gastrointestinal tube.

2. Morphogenetic fields (A. G. Gurvich) — distant interactions of cells having an electric or gravitational nature.

3. Gradient of physiological activity (Ch. Child) — intensity of metabolism is higher in a head part of the germ as compared to a tail part; it produces a regulating action on morphogenesis.

4. Positional information of the cell — using intercellular interactions every cell assesses its position in the germ of the organism, then it differentiates itself according to this position.

CRITICAL PERIODS OF DEVELOPMENT

The periods of the greatest sensitivity of the germ to environmental factors are called **critical periods**.

The human has three basic critical periods in embryogenesis:

1) *implantation* — instillation of the embryo into the mucus of the uterus (6^{th}-7^{th} day after fertilization);

2) *placental* — the beginning of the placenta formation (14^{th}–15^{th} day after fertilization);

3) *delivery* — the outcome from the mother's organism, adaptation of the function of all organ systems, modification of feeding (39^{th}–40^{th} week).

Critical periods coincide with transitions from one period of development to the other and changes in living conditions of the germ.

The impairment of the natural course of embryogenesis under environmental conditions is called teratogenesis (Greek *teras* — monster). Factors causing teratogenesis are teratogenes. Teratogenes may be groups of medicines (antibiotics, quinine, chloridine and anti-depressants), alcohol, nicotine, "toxins" of parasites, various types of radiation. The action of teratogenes causes development defects. Teratogenes affect gametes, causing *gametopathies*, and different stages of embryogenesis causing the development of *embryopathies*. Congenital defects may be primary due to a direct action of teratogenes (example: atresia of the Sylvian aqueduct) and secondary — because of complications of primary defects (example: hydrocephaly).

The science *teratology* studies causes, mechanisms of development and prophylaxis of development defects.

The occurrence frequency of development defects in human populations is 1–2 %.

The variety of congenital development defects includes:

- agenesia — absence of an organ (e. g., an extremity);
- hypogenesia — underdevelopment of an organ (e. g., gonads);

- hypergenesia — overdevelopment (e. g., polydactily);
- atresia — imperforation of natural openings and canals (e. g., esophagus, anus);
- ectopy — changing of the organ position (e. g., the heart on the right side).

The reasons of congenital defects:

1) genetic (various mutations);
2) exagenic (environmental factors);
3) multifactoral (joint action of factors of the 1st and 2nd groups);
4) interaction of the germ's parts (embryonic induction).

LECTURE 14
Topic: BASES OF ONTOGENESIS (POSTEMBRYONIC DEVELOPMENT)

Plan

1. Periods of postnatal ontogenesis.
2. Growth: laws and growth regulation.
3. Constitution and habitus.
4. Aging and old age. Theories of aging.
5. Death, clinical and biological.
6. Reanimation and euthanasia.

The postembryonic (postnatal) period is a period from the moment of birth or going out of ova membranes and to death. After morphogenesis is completed, puberty starts followed by reproduction and a final stage of ontogenesis — aging and death.

Table 6

Types of ontogenesis

Direct development	Indirect development (with metamorphosis)
a) laying eggs with a great amount of yoke (birds)	a) incomplete metamorphosis-stages: egg – larva – mature individual (intestinal helminthes)
b) intrauterine (mammals)	B) complete metamorphosis-stages: egg – larva – chrysalis – mature individual (butterflies, 2-wing insects)

Periods of human postnatal ontogenesis

The neonatal period (1–10 days): a complex period of reconstruction of the whole organism, adaptation to new existence conditions.

The breast-feeding (infant) period (11 days–12 months): feeding the infant with mother's milk; intensive growth.

The period of early childhood (toddle) (1–3 years): the child learns to walk and speak, gets acquainted with the surrounding world.

The 1st period of childhood (4–6 years): the child is interested in everything and tries to understand everything, learns elementary working skills.

The 2nd period of childhood (7–11 years in girls, 7–12 years in boys): growth becomes slower and the muscular system develops intensively.

The adolescent period (12–15 years in girls, 13–16 years in boys): puberty starts and growth intensity increases.

The juvenile period (16–20 years in girls and 7–20 years in boys): puberty, growth and physical development are completed.

Middle age, the 1st period (21–35 years in women, 22–35 years in men): an optimal age for childbirth.

Middle age, the 2nd period (36–55 years in women, 36–60 years in men): the period of the most active professional activity. After 35 years the first signs of aging appear — some biochemical reactions and physiological functions change.

Advanced age (56–75 years in women, 61–75 years in men): the processes of aging go on, though the majority of people preserve their professional working ability.

Senile age (76–90 years): senile changes are clearly marked; some people at this age preserve their ability for creative activity.

The age of long-livers (over 90 years): it is women who more often live to this age.

There are critical moments in the postnatal period:

1. *The natal period* (first days after birth) — all organ systems are adapted to a new environment.
2. *The puberty period* (12–16 years) — the hormonal adaptation, secretion of sex hormones into the blood and formation of secondary sex characters.
3. *Period of sex wasting away* (on an average at about 50 years) — functional failing of sex glands (gonads) and glands of internal secretion.

There are three periods of postnatal ontogenesis in animals and men:

1) prereproductive (juvenile);
2) reproductive (mature);
3) postreproductive (aging).

GROWTH: LAWS AND GROWTH REGULATION

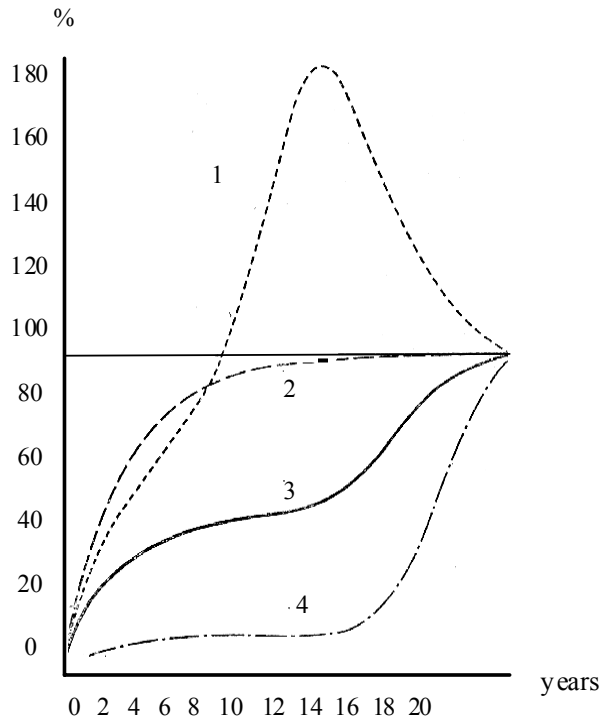
Growth is the enlargement of dimensions and body mass. Growth can be unrestricted (indefinite) — it lasts all life (crustacean, fish and amphibian) and restricted (definite) — it stops by a definite age (insects, birds, mammals). The process of growth in humans is irregular; the periods of fast growth alternate with the periods of slowed growth.

Laws of growth

The highest intensity of human growth is marked during the 1st year of life — the increment is 25 cm. On the 2nd year of life it is 10–11 cm, on the third — 8 cm. At the age of 4–7 years — it is 5–7 cm per year. At junior

school age — 4–5 cm per year, during puberty the growth intensity increases up to 7–8 cm per year. Then the human growth slows down and up to 25 years it increases 1–2 cm per year (fig. 27).

Basic types of tissue and organs growth:



1 — *lymphoid*; thymus, lymphatic nodules, lymphoid tissue of the intestines, spleen, tonsils; the maximum increment of their mass goes to 11–12 years.

2 — *cerebral*: the brain and spinal cord, eyes, the head develop earlier than other body parts — after birth and till 11–12 years.

3 — *general*: the whole body, muscles, the skeleton, respiratory organs, liver — a maximum growth during the first year of life and in the puberty period.

4 — *reproductive*: various parts of the genital system — a fast growth in the puberty period.

Regulation of growth							
Hormones			**Environmental factors**				
Chondotropic hormone (hypophysiotropic hormone);	Thyroxin (thyroid-stimulating hormone)	Sex hormones	Light	Nutrition	Vitamins (A, B, D)	Micro-elements	Social-economic factors

The *somatotropic* (chondotropic) hormone is secreted from the moment of birth till 13–16 years. When the function of the gland is decreased, hypopituitary dwarfism develops. When it is increased, gigantism develops; the height of a person reaches 2 m and over. Secretion of this hormone in adulthood gives acromegaly — enlargement of the bones of the wrist, foot and face. *Thyroxin* increases energy exchange in the organism. The functional decrease of the gland results in growth retardation, impairment of body proportions, inhibition of sex development, mental impairment. *Sex hormones* affect all the processes of metabolism.

Environmental factors have a great effect on growth. For normal growth of a child, he should have a well-balanced nutrition including vitamins and microelements. A very important role for the synthesis of vitamin D (calciferol) plays the sun light.

During the last decades there was marked *acceleration* of physical and physiological development of children. It shows already at the stage of intrauterine development — an increase of the body length in neonates by 0.5–1.0 cm, body mass — by 50–100 g, the terms of teeth eruption change. During the last 100 years the height of adult people increased on an average by 8 cm. Acceleration may be caused by the following factors: interracial marriages (heterozygosity increases), urbanization, enhancement of the radiation background, modification of the Earth magnetic field and a number of social factors.

Human age	
Biologic — the age he looks	Chronological — the number of years he/she has lived

The biological and chronological age do not always coincide.

Criteria for determination of the biological age:

- maturity of the skeleton: ossification of various parts of the skeleton occurs at a different age;
- teeth maturity: eruption of milk teeth and their substitution with permanent ones occur at a definite age.
- the time of appearance and the degree of development of secondary sex characters.

CONSTITUTION AND HABITUS

The constitution of a person presents genetically conditioned specificities of morphology, physiology and behavior.

In 1927 M. V. Chernorutsky advanced a classification which distinguished three main constitutional types.

An ectomorphic type (asthenics). They have a narrow chest, a low position of the diaphragm, lengthened lungs, relatively short intestines with low absorption, thin bones and long extremities, a thin layer of fat deposits. Asthenics are characterized by increased excitability, inclination to neuroses, hypotonia, ulcers, and tuberculosis.

Mesomorphic types (normosthenics) have a proportional constitution, moderately developed subcutaneous cellular tissue. The people of this type are energetic, mobile and prone to neuralgia, atherosclerosis and diseases of the upper respiratory tract.

An endomorphic type (hypersthenics) are characterized by a broad chest, a high position of the diaphragm, a voluminous stomach and long intestines with high absorption, a considerable layer of fat. The heart has relatively large dimensions; the blood contains an increased content of cholesterol, uric acid, erythrocytes and hemoglobin. In hypersthenics dominate the processes of assimilation; they are prone to atherosclerosis, obesity, diabetes, hypertension, the diseases of kidneys and gall bladder. The people of this type are well balanced, calm, and sociable.

As to the types of constitution, the majority of people occupy an intermediate position.

Peculiarities of morphology, physiology and behavior at a definite period constitute a habitus. Habitus reflects how a person feels, his health state at a given moment. It includes peculiarities of the constitution, carriage and gait, color of skin coverings, expression of the face, correspondence of biological and chronological age.

AGING AND OLD AGE

Aging is a general biological law, characteristic of all living organisms. Old age is a final stage of ontogenesis. The science about old age is called *gerontology*. Gerontology studies laws of aging of various organ systems and tissues. It includes the sections of gerontal hygiene and gerontal psychology.

Geriatrics is a science about diseases of old age; it studies peculiarities of their development, course, treatment and prophylaxis.

The process of aging includes all levels — a molecular, subcellular, cellular, tissue, organ and organism level. It results in decrease of vitality of the organism, weakening of homeostasis and adaptation mechanisms. The biological meaning of aging is inevitability of death.

Signs of aging in organs and organ systems

1. Cardio-vascular system. Vascular elasticity of blood vessels changes; the connective tissue in the heart and vascular walls grows out instead of the muscular tissue; blood circulation in tissues and organs becomes impaired. Functioning of blood-forming organs deteriorates.

2. Respiratory system. Interalveolar septa become disrupted, the respiratory surface of the lungs decreases; their vital capacity becomes less; the connective tissue grows out.

3. Gastrointestinal system. Loss of teeth, functional decrease of gastric glands, impairment of the motor function of the intestines.

4. Urinary system. Death of a part of nephrons, decrease of filtration intensity of kidneys.

5. Muscles and the skeleton. Atrophy of skeletal muscles, lessening of bone strength, domination of mineral substances in their composition.

6. Nervous system. Death of neurons, impairment of functional regulation of organs, slowing down the speed of impulse conduction, memory weakening. Functional decrease of all sensitive organs.

7. Weakening of the mechanisms of humoral and cellular immunity.

External manifestations of aging signs: carriage, body shape and gait change; grey hair appear, skin elasticity is being lost (wrinkles appear), sight and hearing deteriorate.

Gerontology proposes over 300 hypotheses of aging. The most common are:

1. *Energetic* (M. Rubner, 1908): the organism of every species has a definite energetic background. After it has been spent during life, the organism dies.

2. *Intoxicational* (I. Mechnikov, 1903): self-poisoning of the organism because of accumulation of nitrogenous waste and purification products in the colon of an individual.

3. *Associated with the connective tissue* (A. Bogomolets, 1922): As the connective tissue is a trophic regulator of cells and tissues, its changes impair interactions of tissues and cause aging.

4. *Overstraining of the central nervous system* (I. Pavlov, 1912; G. Selie, 1936): nervous shocks and prolonged nervous overstrains cause untimely aging.

5. *Changing of colloidal properties of the cellular cytoplasm* (V. Ruzhichka, M. Marinesku, 1922): the changed cytoplasm poorly retains water, that is why colloids from hydrophilic become hydrophobic, colloidal particles become larger and their biological properties change.

6. *The programmed number of cellular mitoses (A. Khaflick, 1965):* various species have an unequal number of cellular mitoses — the longer is life the greater number of them they have (fibroblasts of human embryos give about 50 generations, they are about 15 in mice and hens).

7. *Genetic:* accumulation of mutations; decrease of intensity and impairment of the processes of transcription, translation and repair; impairment of self-renewal of proteins.

Social factors produce a considerable effect on the process of human aging as well as conditions and style of life, various diseases. Human aging and life span also depend on the ecologic situation.

The science that studies a healthy style of life and conditions to prolong its duration is called *valeology*.

A theoretically possible human age is 150–200 years; a maximum registered is 115–120 years. An average life span in Republic of Belarus for men is 64–74 years, for women — 74–79 years. In some countries, an average life span is 35–40 years.

DEATH, CLINICAL AND BIOLOGICAL

Aging of the organism is finished with *death*. Death provides a change of generations. Causes of death may be different. A *physiological* or natural death occurs due to aging. A *pathological* or untimely death is a result of disease or an accident.

A clinical death occurs due to a failure of vital functions (heart and respiration failure), but metabolic processes in cells and organs are preserved.

A biological death occurs when the processes of self-renewal in cells and tissues stop, chemical processes are impaired, and autolysis and break down of cells take place. Necrotic changes in the most sensitive cells of the brain cortex

occur already in 5–6 minutes. It is possible to delay the period of a clinical death by general hypothermia, which slows down metabolic processes and enhances the persistence to oxygen deficiency.

Reanimation and euthanasia

Reanimation is a possibility to return a person to life after a clinical death (when vital organs are not impaired) in 5–6 minutes, while cells of the brain cortex are "alive". Reanimation methods are used in medicine in any threatening circumstances.

In the middle of the XX century there appeared a trend in medicine, which was called euthanasia. *Euthanasia* is a medical aid to pass from life for a seriously and terminally ill person according to his wish and request of his relatives. Euthanasia is legitimate in several countries. It requires solving many juridical and moral ethical problems.

LECTURE 15
Topic: BASES OF ECOLOGY

Plan

1. Ecology as a science.
2. Environmental factors.
3. Biological aspects of human ecology.
4. Nutrition chains. Forms of biotic links.
5. Parasitism as a biological phenomenon. Age and origin of parasitism.
6. Amoebas of the Limax group, their medical significance.

A German biologist E. Geckel suggested **the term "ecology"** in 1866. Ecology studies interactions and interrelations of organisms (plants, animals and humans) and the environment. It also studies problems and laws of interrelations between humans and nature.

Sections of ecology are classified:

– according to studied objects (ecology of plants, ecology of animals, ecology of humans);

– according to habitation of organisms (ecology of the land, ecology of the lake, sea, etc.);

– according to organization levels of living things (autecology, synecology).

Autecology studies interaction of individuals or their groups (populations) with the environment. *Synecology* studies interaction of over-organisms systems: biocenoses, biogeocenoses.

Geographically homogenous parts of land or water ponds inhabited by animals and plants are called biotopes (*bios* — life, living; *topes* — place). For example, a forest biotope, a marsh biotope.

A historically established society of this biotope organisms (bacteria, protists, mushrooms, plants, animals) form a *biocenosis*.

A complex of "a biotope + a biocenosis" is called *biogeocenosis*. The *anthropobiogeocenosis* is a biocenosis including the human population (from Greek anthropos — human).

The section of ecology that studies biogeocenoses (ecosystems) is called *biogeocenology*.

Environmental elements that affect organisms are called **ecologic factors**. They include abiotic, biotic and anthropogenic factors.

Abiotic factors are factors of inanimate nature: light, temperature, humidity, geomagnetic field of the Earth, gravitation, physical and chemical characteristics of the environment, alternation of seasons, wind direction, etc. In the process of evolution, every species has adapted to a definite combination of abiotic factors. For example, adaptability to:

– inhabitation conditions (water, soil, air); accordingly — specificities of the structure, functions of organ systems, way of life (fish and dolphins, birds and bats);

– chemical composition of the environment (animal world of sweet and salted water ponds);

– light and temperature regime: photoperiodism — reaction of live organisms to changes of the light day; there are light-requiring plants (steppe and meadow grass) and shade-requiring plants (plants of lower coniferous-forest circles); reaction of organisms to changes of temperature and humidity — winter and summer hibernation, anabiosis.

Hibernation is inhibition of a number of physiologic processes: in winter when the environmental temperature lowers down (bears, reptiles), in summer, when the temperature is high and during draught (rodents). Anabiosis (Greek *ana* — back, *bios* — life) — is a temporary absence of apparent signs of life: spores and plant seeds, eggs of parasites, fish and frog in winter water ponds.

Biotic factors are the effect of other living beings directly (predators — prey, parasite — host) or indirectly (through changes of inhabitation) on the organism. Biotic links and nutrition chains underlie these factors.

Antropogenic factors are the effect of humans and their productive activity on other species and their inhabitation.

At present **human ecology** exists and develops as an independent discipline. It studies laws of interaction and mutual impact of the biosphere (the environment) and anthroposystems (human populations). Medical ecology and social ecology are sections of human ecology.

Medical ecology studies the impact of environmental factors on health state of humans (so-called "civilization diseases"). *Social ecology* studies interrelation laws of social population groups and the environment. Keeping in mind that the human is not only a biological but also a social being, abiotic and biotic factors of human ecology are supplemented by *a group of social factors*. The specificity of human ecology is determined by the specificity of his habitation, which he creates himself.

Levels of interaction of the human and environment:

1. Organisms level. Fluctuation of factors of various physiologic processes (the blood pressure level, the account of blood cells, the CNS state) under the influence of environmental factors modification (magnetic and sun storms, fluctuations of atmospheric pressure).

2. Population-species level. For example, formation of large human races in the upper paleolith epoch — Europeoid, Mongoloid and Negroid. At present, when people live in different climatic zones, *adaptive types of people* have been formed. They are groups of individuals with similar characteristic features that arise in different populations in identical environment (an arctic type, a tropic type).

3. Biocenotic level. The human is a component of biocenoses. He establishes his relations both with live and unanimated nature.

The basis of organisms interrelations in biogeocenoses are trophic links or nutrition chains. Nutrition chains are a number of interrelated species, when a previous one is the food for the next one. Trophic links are determined by flows of energy and nutritious elements from one organism to the other. *The first link* of nutrition chains composes *producents* of the organic substance — autotrophic organisms (plants). *The second link* is *consuments* or consumers of the organic substance. They are heterotrophic organisms (animals). *The third link* is reducents or destruents — destructors of the organic substance. They include bacteria, fungi, insects and worms, animals that eat decaying organic remains.

An example of a nutrition chain: plants → insects → insect eating birds → predators.

Interrelations between organisms in nature are revealed as **biotic links**. Their varieties include competition, predatoriness, antibiosis, symbiosis.

Competition is interrelation of organisms of one or different species that require identical existence conditions. For example, thickly sown seeds of a plant from one species; locust, rodents, herbivorous animals (competition for food).

Predatoriness — interrelations of organisms of different species, when a representative of one (predator) kills the other (prey) and uses it for one meal. For example, a cat and a mouse, a fox and a hare.

Antibiosis (Greek *anti* — against, *bios* — life) — interrelations of organisms from different species when metabolic wastes of one species oppress the development or organisms of the other species. These substances have

a chemical nature. Lower fungi (moulds) produce *antibiotics*, biomycin, etc.). Higher plants (pine, cedar, onion, garlic) secrete volatile substances — *phytoncides* (Greek *phyton* — plant, *caedo* — kill). Antibiotics and phytoncides are used in medicine for treating various diseases.

Symbiosis is any form of co-habitation of organisms from different species. The term was introduced into biology by de Barry in 1879 (Greek *sym* — near, *bios* — life). The following forms of symbiosis are distinguished:

– *synoikia* or hosting (Greek *syn* — together, *oikos* — house) — co-habitation of place: a representative of one species uses a representative of the other species as habitation without any harm or benefit for him (e. g., cancroid sea acorns on a mollusks' shells);

– *commensalism* (French *commensal* — co-eater) or parasitism — permanent or temporary co-habitation of individuals of different species, when one of the partners eats food remains or excretion products of the other without any harm for him (e. g., a shark and a sticking fish);

– *mutualism* (French *mutuus* — mutually beneficial) — mutually beneficial co-habitation of organisms of various species (examples: filamentous organisms that break down the cellular tissue in the intestines of thermites; lishen — protists and hyphae of the mushroom);

– *parasitism* (*para* — near; *sitos* — feeding) is antagonistic sybiosis. The most common form of symbiosis is one variety of interspecies relations.

The founders of Parasitology are a German zoologist P. Leucart and a Russian academician E. N. Pavlovsky. According to E. N. Pavlovsky, "**parasites are animals** that live at cost of individuals of other species due to tight biological or ecological connections in their life cycle, which may have a shorter or longer duration. Parasites feed on body juices, tissues or digested food of their hosts. This way of life is a specific species character of this organism that repeatedly uses the organism of his host for feeding. Besides, temporally or permanently, parasites use the host organism as a place for their habitation".

Criteria of parasitism:

1) territorial relations with the host;
2) feeding at cost of the host;
3) pathogenic effect on the host (inflicted harm).

The host of a parasite is an organism, which provides him with inhabitation and food and suffers a definite harm from him.

The parasite has a specific inhabitation. The 1st order inhabitation is the host's organism. This environment actively reacts to the presence of the parasite. The 2nd order inhabitation is an external environment. During transition to parasitism the relations of the organism and the environment become simpler. The host is a link between the parasite and the external environment.

Parasitism is a universal natural phenomenon, a most common form of symbiosis. Parasites include all viruses, many bacteria, some (fungi) mushrooms and

higher plants. There are 55 000 types of protists, 7 000 types of arthropoda, 20 000 types of helminthes in the animal world. Some classes are wholly represented by parasitic organisms. They include cryptogamers, suckers and tapeworms. Only the types of Sponges and Coelenterata have no parasitic representatives.

The parasite's impact on the host's organism, as a rule, results in the development of a disease of various severity. Diseases caused by viruses are called *infections* or infectious diseases (the flue, hepatitis, AIDS, tuberculosis, etc.). Protists and representatives of the animal world — helminthes — cause *invasions* or invasive diseases (ascariasis, teniasis, enterobiasis, filariasis, etc.). Diseases caused by arthropoda (ticks and insects) are called infestations (pediculosis, myiasis, scabies, etc.).

The age of parasitism is impossible to establish, because after death they are quickly destroyed and are not preserved in geologic layers (strata). Academician E. N. Pavlovsky considered that "parasitism is a little bit younger that life on the Earth". Theoretically, one can suppose that parasites appeared simultaneously with protists, because parasitic bacteria were discovered in the body of amoeba. Multicellular parasites existed already in the paleozoic era. Imprints of sea lilies (echinodermata), the stems of which had gall-like growths caused by nematodes, prove it.

Independent organism may come to parasitic way of life in the process of evolution by different ways:

1. Predator → saprophage → ectoparasite (leeches, larva of flies). Medical leeches are a temporary parasite for the human (it feeds on blood), for small animals it may be a predator — it sucks out a large amount of blood, then the animal dies.

Larva of many flies are saprophages (they feed on decaying organic remains, animals' corpses). Larva of Volfart's fly (inhabits the hairy part of the head in humans) and larva of the gadfly (subcutaneous, gastric and abdominal) are obligate parasites.

2. Independent way of life → attached way of life → ectoparasitism. Independently living cirripedia may pass to an attached way of life fixing themselves to underwater parts of wooden buildings or bottoms of ships. They pass to ectoparasitism if they become attached to living objects — to shells of mollusks or fish bodies.

3. Commensalism → ectoparasitism. Commensalism → endoparasitism. If a commensal inhabits body coverings of the partner, it may become an ectoparasite. It becomes an endoparasite, when it gets inside the organism into body cavities connected with external environment. An enteric amoeba is a commensal in the human organism.

4. Transit through the gastrointestinal tract (larva of a filth fly)

↓

Facultative intestinal parasitism

↓

Adaptation

↓

Obligate intestinal parasitism (larva of a gadfly)

High and clearly marked *pathogenicity* is usually revealed in new parasites or in representatives of independently living species and incidentally getting into a human organism. They are probably on the way of passing from an independent way of life to a parasitic one.

Soil amoebas (Limax group) are such an example. They were described for the first time as pathogenic for the human in 1958. Representatives of the Acanthamoeba genus and Naegleria genus (fig. 28) occur in humans.

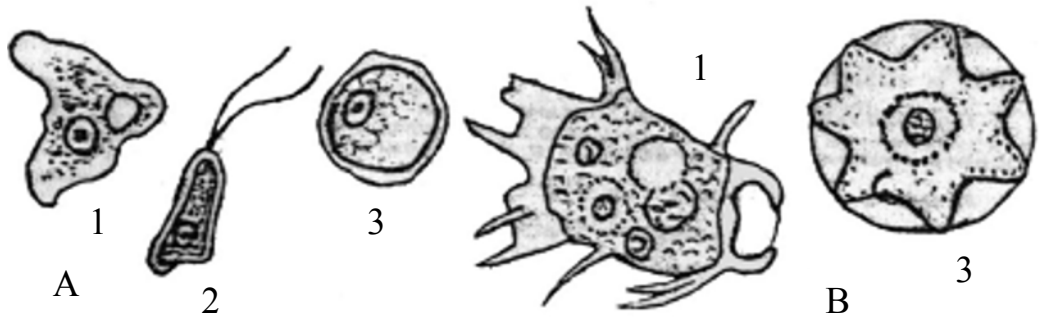


Fig. 28. Amoebas of the Limax group:
A — Naegleria; B — Acanthamoeba; 1 — amoebic stage; 2 — filamentous stage; 3 — cyst

The Acanthamoeba genus. Over 10 species are described, 6 of them are pathogenic for humans. They also affect rats, guinea pigs, monkeys. Inhabitation places: open water ponds, silt, wet soil, dust. They are revealed on contact lenses and in solutions for their storage. They exist in two stages: a thophozoit (a vegetative form with thorn-like pseudopodia) and a cyst.

Infection: through the respiratory tract by cysts with dust, trophosoits with contaminated water during bathing, through injuries on the cornea. Having got into the organism amoebas multiply and are brought into the brain, liver, heart, kidneys.

Pathogenic action: inflammation of the cornea, chronic affection of the lungs and cerebral membranes, necroses and hemorrhages in organs. The disease caused by *Acanthamoeba* amoebas are called *acanthamoebiasis*. The incubation period is from several weeks to several months. The outcome is lethal.

The Naegleria genus. 5 species are described, one is pathogenic for humans. Inhabitation places: soil, water and silt from fields irrigated by drained waters, hospital hydrothermal facilities, swimming pools. They exist in three stages: an amoeboid throphozoit (with obtuse pseudopodia), a 2-filament trophozoit, a cyst.

Infection: through the respiratory tract by cysts with dust, trophozoits with water; they multiply at the amoebic stage in the mucus of the nasal cavity, and they get into the brain along nerves.

The disease is called negleriosis. It starts as a light cold followed by nausea, vomiting, and seizures. It *affects* the cerebellum, the cortex of the brain, cerebral membranes and causes amoebic meningoencephalitis. The incubation period is 2–3 days, rarely — 7–15 days. Death occurs due to pulmonary edema and respiration failure.

The cerebrospinal fluid investigation for the presence of amoebas helps in *diagnosing* the affection of a person with soil amoebas.

The treatment of acanthomoebiasis and negleriosis is not completely elaborated.

LECTURE 16
Topic: ECOLOGICAL PARASITOLOGY

Plan

1. The subject of ecological parasitology.
2. Classification of parasites and their hosts.
3. The system "parasite – host".
4. Parasitic system.
5. About biological bases of parasitic diseases prophylaxis.

Parasitism is an ecological phenomenon. Ecological parasitology became an independent science in 1930s thanks to works by Russian scientists B. A. Dogel, V. N. Beklemishev, E. N. Pavlovsky. It studies relations between parasites and their population, with the host organism and the environment. The work of E. N. Pavlovsky "The organism as an inhabitation medium" (1934) was very significant for the development of ecological parasitology. It determined the concept of "parasitocenosis" including all parasites (of various types) of only one host organism. For example, protists, flat- and ringworms, various bacteria may inhabit the digestive system.

There are definite interrelations between them:

– *synergism*: a combination of helminthes and viruses, bacteria and protists; dysentery amoeba, having left the cyst, consumes bacteria of the host's intestine, otherwise it won't become pathogenic;

– *antagonism*: for the most part of helminthes, increase of one species number results in decrease of the other species number;

– *antibiosis*: several species cannot live in one environment due to their excretion of metabolites (cholera agent in hen does not go with tape worms, malaria plasmodia and ascarids).

THE SYSTEM «PARASITE – HOST»

The system "parasite – host" includes one host individual and one or a group of parasitic individuals of a definite species. To form this system one needs the following conditions:

a) a contact between the parasite and the host;
b) the host must provide conditions for the development of the parasite;
c) the ability of the parasite to resist reactions from the host part.

The basic development of evolution is elaboration of a balanced system; antagonism between partners is smoothed down and reliability of the system increases. The dualism of the system "parasite – host" means that from one side partners relations are antagonistic, from the other — they are stabilized. Smoothing down of the antagonism occurs due to co-adaptation ("co" means mutual):

- in the parasite — morphologic and biologic adaptations occur;
- in the host — complication of defense mechanisms takes place.

Evolutionary directions (co-evolution) are also different:

- in the parasite — it is complication of adaptation mechanisms to the host;
- in the host — mastering of defense reactions on all levels (for destruction of the parasite).

CLASSIFICATION OF PARASITES

1. According to their relations with the host:

- *true parasites* — this way of life is characteristic of all representatives of the given species (Ascaris, flat band, lice);
- *false or pseudoparasites* — as a rule, independently living but, having got into the human or animal organism, they may exist there producing harm (larva of filthy flies);
- *hyperparasites or superparasites* — they are parasites of parasites (bacteria in parasitic protists).

2. According to localization in the host:

- *ectoparasites* — they inhabit coverings of the host's organism (lice, fleas);
- *endoparasites* — they live inside the host's organism;

a) intercellular (malaria plasmodia);
b) interabdominal (helminthes of the intestines);
c) tissue (liver sucker);
d) intradermal (scabies tick).

3. According duration of its relation with the host:

- *Permanent* — they live their whole life cycle in the host (ascarids, fish tapeworm);
- Temporal — a part of their life cycle they live in the host (larval parasitism — gadfly's larvae; immarginal parasitism — mosquitoes, fleas — only sexmature individuals parasitize).

CLASSIFICATION OF HOSTS

1. According a stage of the parasite development:

a) *definitive or final host* — the parasite reaches its sex maturation in his organism and undergoes its sexual reproduction (a human for flat band, liver sucker);

b) *intermediate host* — parasite larvae inhabit his organism and undergo their asexual reproduction (mollusks for suckers, humans for malaria plasmodia);

c) *additional host* or the 2nd intermediate (predatory fish for larvae of fish tapeworm);

d) *reservoir host* — accumulation of invasion stages of the organism (wild rodents for leishmania).

2. According to conditions of the parasite development:

a) obligate or natural hosts — provide optimal conditions for the parasite development in the presence of biocenotic relations (natural ways of infecting the human with ascarids and pinworm);

b) optional hosts — the presence of biocenotic links, but the absence of biochemical conditions for the parasite development (a human for a pig ascarids);

c) potential hosts — the presence of chemical conditions, but the absence of biocenotic links (a guinea pig for a trichinella).

Ways of parasite intervention into the host organism:

1) alimentally (with food) — the basic way: helminthes eggs, protists cysts, helminthes' larvae;

2) with air drops and through the respiratory way — cysts of soil amoeba, some viruses and bacteria;

3) percutaneously (through the skin) — larvae of suckers;

4) transplacentally (through the placenta) — toxoplasma, malaria plasmodia;

5) trasfusally (on transfusion of infected blood) — trypanosomes, malaria plasmodia;

6) with mother's milk (ascarids larvae);

7) contact-domestic way (through a contact with a sick person or a sick animal, through domestic objects — scabies tick);

8) transmissively (by a sucking carrier — arthropoda):

– inoculation (through the proboscis of a carrier during blood sucking) — trypanosomes, malaria plasmodia;

– contamination (contamination of the skin by excrements of a carrier, which contain a causative agent and are rubbed into the skin during itching) — a trypanosome of Chagas' disease, plague bacillus;

9) by a sexual way (during sex contacts) — vaginal Trichomonads.

Parasites are highly specialized organisms with maximum adaptation to their environment. On one side, there occurred simplification of some of their organs, on the other — complication of the other.

Morphological adaptation of parasites

a) progressive:

- *enlargement of body sizes* (up to 20 m in tape worms);
- of all organ systems *the reproduction system reached its greatest development*;
- *hermaphrodism*;
- *various fixation organs* (sucking discs in lamblia, suckers of sucking insects, bothria, hooks of tape worms; claws of lice, mouth apparatus of ticks;
- *external coverings* (tegument, cuticle defend from the action of host's enzymes);
- *"molecular mimicry"* (resemblance of the protein structure and enzymes of the host and parasite);
- *excretion of anti-enzymes by enteric parasites* — which defend from digestion by host's juices;
- *encapsulation of parasites larvae* as a defense reaction to the effect of host enzymes;

b) regressive:

- simplification of the structure of the SNS and sensorial organs; as to sensorial organs endoparasites have tactile organs and organs of chemical feeling, in suckers larvae — light-sensitive eyes.

Biological adaptations are associated with peculiarities of the structure of the reproductive system, reproduction and development cycles of parasites:

a) *high fertility* (free living turbilation excretes 5–10 eggs, flat band with every mature chain — 100 000 eggs, Ascaris — 250 000 eggs per day);

b) *various forms of asexual reproduction* (shisogonia and sporogonia in malaria plasmodia; polyembryony in suckers);

c) *migrations over the host's organism* (flat band and ascarids larvae);

d) *complex development cycles* with changing of larva stages and intermediate hosts.

"Results" of the parasite and host interaction may be different on the organism level:

A. *Parasite's death*, if defense of the host organism is rather strong.

B. *Host's death*, if parasite pathogenicity is high and the host organism is weakened or its defense mechanisms are insufficiently strong. The parasite dies together with the host.

C. *Parasitism* develops, when the relations between the host and the parasite are balanced. Clinical signs are absent.

Every parasite has pathogenicity. Pathogenicity of the parasite is expression of extreme parasitism, its ability to cause the disease. Pathogenicity depends on a number of factors:

- *Parasite genotype*, its belonging to a species;
- *Host age* (children and elderly people are more sensitive to infection);

- *Diet* (parasitic protists are more numerous in the gastrointestinal tract of herbivorous animals; unwholesome diet of the host increases the number of parasites in the organism and their sizes, reduces the terms of parasites development;
- *Doses and invasion degrees* (the more eggs or parasite larvae are introduced into the host organism, the more severe will be the disease);
- *Resistance degrees of the host organism;*
- *Presence of other parasites and diseases,* which will weaken the host organism.

The following pathogenicity grades are marked out: carriage, subclinically and clinically marked parasitic diseases and lethality. Host pathogenicity is sharply marked in phylogenically young systems "parasite-host".

The second parasite characteristic is specificity, i. e. manifestation of historically established adaptation degree of the parasite to the host. Forms of specificity manifestation:

a) *hostal* (of the host): monohostal — the parasite has one type of the host (human Ascaris), polyhostal — the parasite has hosts of different types (leischmania, trichinella);

b) *topical* (place of parasitism): ascarids (intestines), fasciole (liver);

c) *relating to age* (the peak of parasitic diseases is marked in pre-school children);

d) *seasonal* (outbursts of amoebic dysentery — the end of spring – summer; of trichinosis — autumn – winter).

Pathogenic action of parasites on the host organism is due to their morpho-physiological peculiarities and it is in the range from an immunological reaction to clinical symptoms of the disease and fatal outcome.

1. Parasites produce *mechanical action* by their body mass (a ball of ascarids in the intestines, echinococcus bladder in the brain), by their fixation organs (incarceration of the intestinal mucous membrane by suckers and tissue necrosis, integrity impairment of the mucus by hooks and irritation of nerve endings – spasm and obstruction of the intestines), integrity impairment of skin coverings by suckers larvae, proboscis of blood sucking arthropoda.

2. *Toxic-allergic action* is produced by parasites metabolites, being antigens for the host; excreted by parasites hemolysins, histolysins and waste products of ruined parasites; ectoparasites saliva action during blood sucking. Manifestations of this action in the host: skin eruption, dermatitis, eosinophilia, allergic reaction of various severities (up to anaphylactic shock).

3. *Absorption of nutrients and vitamins* in the host organism leads to avitaminosis (mainly A and C), loss of weight, emaciation.

4. *Impairment of metabolic processes* in the host organism causes weakening of resistivity and raise of sensitivity to causative agents of other diseases.

5. Biologically active substances of the parasite produce *immune-depressive action*. They suppress phagocytic activity of leukocytes.

6. Some *parasites stimulate oncogenesis*, formation of malignant tumors: clonorchs and opisthorchs — cholangiocarcinoma, schistosomas — cancer of the gall bladder and rectum.

7. Parasites may produce *unfavorable effect on the course of pregnancy and fetus development* (malaria plasmodium, toxoplasma, opisthorch): cause gestational toxicosis, miscarriage, delivery complications (hemorrhages), impairment of the fetus development (congenital defects).

Responses of the host organism

The basis of all reactions is immune defense of the host. Allergy is a kind of immunological reactivity.

The first reaction to a parasite — is an attempt to kill it with enzyme action, free radicals, and then — to neutralize factors of its "aggression" by proteases, enzyme inhibitors.

Defense reactions of the host manifest at a cellular, tissue and organism level. *Reactions on a cellular level*: hypertrophy and modification of affected cells (erythrocytes in malaria). *Tissue defense reactions* (toxoplasmosis, trichinellosis): isolation of the parasite from healthy tissue — capsule formation from the connective tissue, dilation of blood vessels and accumulation of leukocytes around the parasite — incapsulation of a trichinella larvae, formation of the membrane of a toxoplasmatic pseudocyst. *On an organism level,* defense mechanisms manifest by humoral reactions (producing anti-bodies) and various forms of immunity: absolute – relative, active – passive, congenital – acquired. Absolute immunity is formed on leishmaniasis and trypanosomiasis, in malaria — relative. The most intense immunity arises at a larva stage. Immune reactions of the host decrease the speed of parasites reproduction and inhibit their development.

PARASITIC SYSTEM

Parasitic system (Beklemishev, 1956) forms on the population level. It includes a parasitic population of one species and one or several populations of the host or the host and the environment necessary for their existence. There are the following adaptations of parasites at the population level:

- *High fertility* is particularly important considering circulation of larva stages in the external environment and "search" of intermediate hosts;
- A movable larva or free living stages are for *active search of the host* in the cycle of parasites development;
- *The presence of dormant stages* (cysts, eggs) for waiting till unfavorable conditions are over;
- *Using reservoir hosts* for accumulation of invasive stages and transportation to their final hosts;

- *Synchronization of parasite development cycles and host's behavior.* For example, contamination of a human with schistosomes occurs during bathing, when suckers' cercaria get into blood vessels through the skin. A person comes into a water pond for bathing at the hottest time of the day, and just at this time one can observe a numerous excretion of cercaria from an intermediate host — a mollusk.

The result of the parasite impact on the host at the organism level, as a rule, is a disease, at the population level — morbidity (the number of sick individuals in a specific population). Mass diseases in human populations are epidemics, in animal populations — epizootics. Despite a clearly marked effect of the parasite on an individual host, its general influence on the host population may be insignificant.

Parasites are obligate components of biocenosis. V. N. Beklemishev proposed a conception "usefulness" of the parasite, i. e. the role of parasites in nature is stabilization of ecosystems. Parasitic diseases are a strong selective factor. The animal population without parasites will be doomed for death. Parasitism promotes the improvement of the host's immune defense.

Regulation of the number of host populations in parasitic systems follows a feedback principle a (diagram 12).

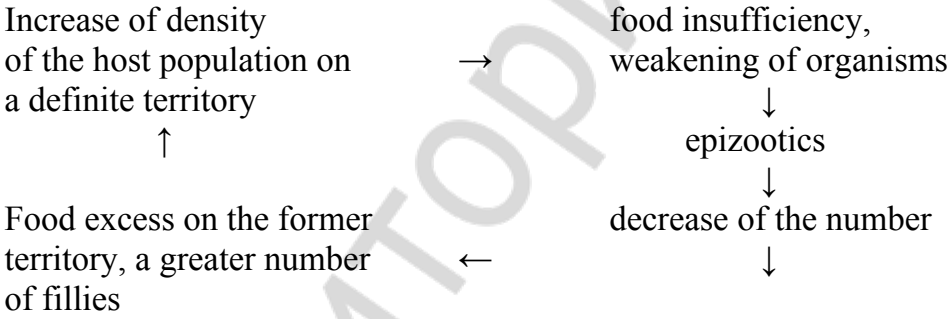


Diagram 12. Regulation of the host population quantity

Parasites bring considerable losses to plant-growing, cattle-breeding. All age groups of the population all over the world suffer from them. A number of objective causes hamper fighting against parasitic diseases: wide spreading of parasites, their great adaptive possibilities, the development of resistivity to antiparasitic preparations, difficulties of making vaccines.

Academician K. I. Skryabin developed *biological prophylactic bases* for fighting parasites. It is "a complex of preventive measures based on detailed studying of causative agent's biology, migration ways of its development stages, biology of intermediate hosts that will make it possible to interrupt some link of a parasite development cycle".

The final practical aim of Parasitology is the defense of humans, animals and plants from parasites affect and stamping out parasitic diseases.

LECTURE 17
Topic: BIOLOGICAL BASES OF TRANSMISSIBLE AND NATURAL-FOCAL DISEASES

Plan

1. Conception of transmissible diseases.
2. Natural focus and its structure.
3. Arthropod components of natural foci, their medical significance.
4. Biological prophylactic bases of transmissible and natural focal diseases.

CONCEPTION OF TRANSMISSIBLE DISEASES

Parasitic diseases (parasitoses) are divided into groups according to pathogens:

- *protozoonoses* (pathogens are protists);
- *helminthoses* (pathogens are worms-helminthes);
- *ascarioses* (caused by ticks);
- *insectoses* (caused by insects).

Zoonoses are diseases, pathogens of which are transmitted from one animal to the other. Animals may infect humans (example: plague of birds and mammals).

Anthroponoses are diseases, pathogens of which are transmitted only from human-to-human (measles, scarlet fever).

Transmissible are diseases, causative agents of which are transmitted with blood by a carrier, an arthropod (ticks and insects).

Carriers may be mechanical and specific. *Mechanical carriers* (flies, cockroaches) carry pathogens on body coverings, extremities and mouth apparatus parts. Pathogens in the organism of *specific carriers* undergo specific development stages (malaria plasmodia in a female of the malaria mosquito, plague bacillus in the flea organism). Transmission of a pathogen occurs during blood sucking through the proboscis (*inoculation*), contaminated host's covering (*contamination*) and eggs during sexual reproduction (*transovarially*).

In *obligate-transmissible diseases*, only a carrier (e. g., leishmanioses) transmits the causative agent. A carrier and other means (through the respiratory organs, animal food products) transmit *optional-transmissible diseases* (plague, tularemia, anthrax).

A transmissible disease is characterized by the presence of:

1) a parasite-pathogen;
2) a vertebrate-host;
3) an arthropod-carrier.

NATURAL FOCUS AND ITS STRUCTURE

In 1940 E. N. Pavlovsky joined the findings of parasitology, ecology and epidemiology and formulated the **study of a natural focus of the disease**. Natural-focal diseases are associated with a complex of natural conditions and exist in definite biocenoses independently on the human. A natural focus is a definite geographic landscape, where circulation of a pathogen from a donor to a recipient occurs through a carrier (diagram 13). Pathogenic donors are big animals; pathogenic recipients are healthy animals that after contagion become donors.

Flea – specific carrier

↓ ↓

Rodents (rats) Human

↓↑ ↓↑

Rodents (rats) Human

Diagram 13. The diagram of a natural plague focus

The natural focus includes the following components:

- a pathogen of the disease;
- a carrier of the pathogen;
- a donor of the pathogen;
- a recipient of the pathogen;
- a definite biotope.

The final result (outcome) of infecting the recipient in the natural focus depends on the pathogenicity degree of the pathogen, "attack" frequency of a carrier on the recipient, pathogen dose and degree of previous vaccination.

Natural foci are classified according to the origin and the extent (area):

- natural (foci of leishmaniasis and trichenellosis);
- synantropic (a focus of trichinellosis));
- anthropurgic (a focus of western tick encephalitis in Belarus);
- mixed (combined foci of trichinellosis: natural + synantropic).

According to the extent they are:

- tightly limited (a pathogen occurs in the bird's nest or in the rodent's hole);
- diffuse (the whole taiga may be a focus of tick encephalitis);
- conjugated (there are components of a plague and tularemia focus in one biotope).

Medical significance of arthropoda:

1. Carriers of pathogens of diseases (mechanic and specific).
2. Pathogens of diseases (scabbies tick, lice).

3. Intermediate hosts of helminthes (two-wing insects — for filaria, fleas — for some tape worms).

4. Venomous animals (scorpions, spiders, wasps, bees).

ARTHROPODA AS COMPONENTS OF NATURAL FOCI

Acari Order — ticks

Ixodidae Family — ixodic ticks

Representatives: *Ixodes ricinus* — dog's tick, *Ixodes persulcatus* — taiga tick, *Dermacentor pictus*, *Dercentur marginatus.*

Body dimensions of ixodic ticks are from 5 to 25 mm. They inhabit open spaces (forests). The body has no divisions. They have 4 pairs of walking extremities. The first two pairs of extremities form a mouth apparatus — "head". There is a chitin corselet which covers a dorsal part in the male and only a front part in the female. Ixodes ticks have a dark-brown corselet, while in Dermacentor ticks it has a marble pattern. The "head" is seen from the dorsal side. There are eyes (fig. 29).

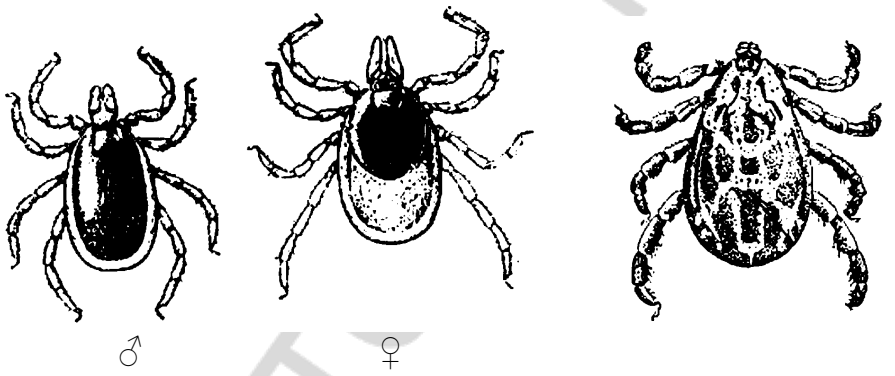


Fig. 29. Ticks of the Ixodidae family

Peculiarities of biology. Blood sucking lasts up to several days. They are capable of fasting up to 3 years. "Bites" of ticks are painless, as their saliva contains an anesthetic. A female lays up to 17 000 eggs. Development stages: an egg → a 6-leg larva (stigmas, tracheas and sexual orifice are absent) → some nymph stages (the reproductive system is underdeveloped) → imago. Blood sucking occurs at every stage, that is why the development cycle is genotrophic.

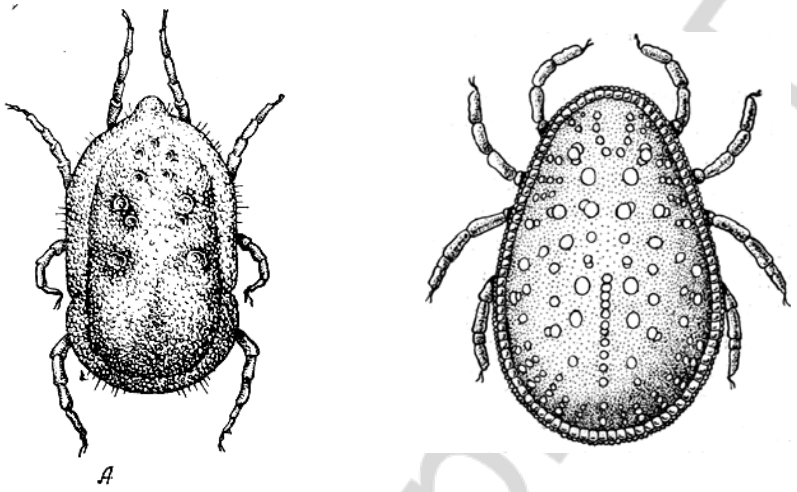
Medical significance. They are specific carriers of spring-summer and taiga encephalitis pathogens. Encephalitis virus affects salivary glands and gonads of ticks; transmission of the pathogen is possible during blood sucking (inoculation) and through eggs (transovarially). Goats are perceptive to encephalitis, that is why the virus can be transmitted with goat milk. Birds, wild rodents are reservoirs of encephalitis virus. Ixodic ticks transmit hemorrhagic fevers (affect the walls of blood vessels, kidneys, coagulation systems) brucellosis, tick typhus,

sustain foci of plague and tularemia. Ticks of the Dermacentor genus carry a Scotch encephalitic pathogen (viral turn-sichness) when the cerebellum is affected; it occurs in humans.

Argaisadae family — argasic ticks

Representative: tick Ornithodorus papillipes.

Body dimensions of the tick are from 2 to 30 mm. A chitin corselet is absent. The "head" is not seen from the back side. There is a marginal welt. Vision organs are absent (fig. 30).



Ornithodorus papillipes Argas persicus

Fig. 30. Ticks of the Argasidae family

Argasic ticks are sheltered forms (caves, rodent holes, abandoned human dwellings). Inhabitation places — steppe, forest-steppe, semi-desert.

Peculiarities of biology: blood sucking lasts up to 50 minutes. They can fast up to 12–15 years. Ovipositor contains 50–200 eggs. Transovarial transmission of a disease pathogen is possible.

Medical significance: specific transmitters of tick recurrent typhus (tick spirochetosis). Natural reservoirs of pathogens are cats, dogs, wild rodents. The incubation period of the disease is 6–8 days. Ticks' saliva has toxic action; persistent ulcers are formed at the sites of bites. Bites of ticks may cause death of lambs and sheep.

Gamasidae family — gamasic ticks

Representative: Dermanissus gallinae — chicken tick.

Body dimensions — 0.2–0.3 mm. The body is covered with bristles. Eyes are absent. Inhabit rodents' holes, birds' nests. They are permanent or temporary ectoparasites. Ticks of doves are dangerous for humans when they get into houses. Ticks saliva is poisonous and causes the development of dermatitis.

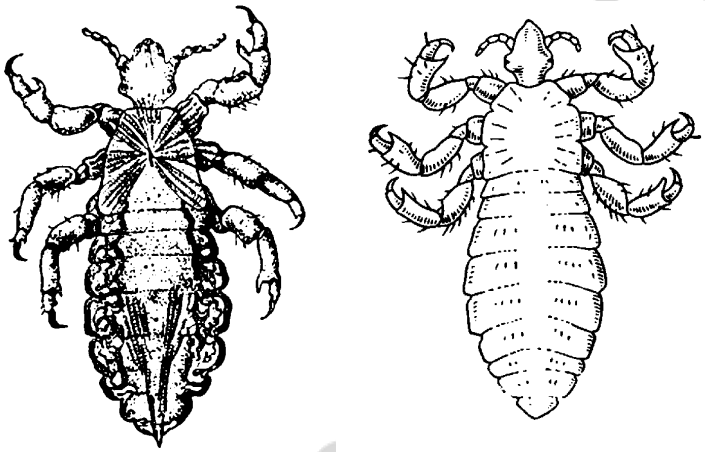
They transmit tick spirochetosis, encephalitis, hemorrhagic fevers. May transmit pathogens of the plague and tularemia.

The Anoplura order — louse

Representatives: Pediculus humanus — louse of the human.

Species *P. humanus* has two subspecies: *p. humanus capitis* — human head louse and *P. humanus humanus* — human body louse.

Permanent ectoparasites. Inhabit the hairy part of the head or folds of clothes. The length of the head louse: ♂ 2.0–3.0 mm, ♀2.4–4.0 mm; of the body louse ♂2.1–3.7 mm, ♀2.2–4.7 mm. Feed on human blood (fig. 31).



P.humanus capitis P.humanus humanus

Fig. 31. Head and body louse

Eggs of the louse are called nits. The head louse sticks them up to hairs with sticky secrete, the body louse — to hairs of clothes. The development has incomplete metamorphosis. A larva resembles a mature louse. The life span of the head louse is up to 38 days, body louse — up to 48 days. The head and body louse are specific transmitters of epidemic and recurrent typhus (louse-borne typhus). Human perceptibility to typhus is absolute.

The pathogen of epidemic typhus — Provachek's ricketsy — multiplies in epithelial cells of the stomach of the louse and is excreted with excrements of the carrier. Infection of the human occurs during rubbing of parasite's excrements into a bite wound during scratching (*contamination*). A persistent immunity is produced in the human who has suffered the disease.

The pathogen of recurrent typhus — Obermaier's Spirochaeta — penetrates into the body cavity with the patient's blood from the louse's stomach. Infection of the human occurs when the louse is squashed and its hemolymph is rubbed into the skin during scratching (*specific contamination*). The immunity after the disease is not produced, relapses are possible.

The disease caused by lice of the *Pediculus* genus is called pediculosis (or the disease of tramps). Lice saliva causes itching, in very sensitive persons — elevation of body temperature. Pigmentation and hardening of the skin are characteristic of pediculosis. Complications of pediculosis are eczema, conjunctivitis, plica (affection of the hairy part of the head).

The Aphaniptera order — fleas

Representatives: fleas of the *Oropsylla and Xenopsylla* genus (rats' fleas), *Pulex irritans* — a human flea.

Fleas are temporary ectoparasites. Imago feed on human and animal blood, larvae — on organic remains. The flea body, flattened on the sides, is covered with dense chitin and a great number of hairs and bristles. Short feelers and simple eyes are on the head. The mouth apparatus is of a stabbing-sucking type (fig. 32).

Fig. 32. A human flea (*Pulex irritans*)

The development passes with a complete metamorphosis. Larvae develop in floor slits, in dusty corners. The term of development is 19 days.

Rats' fleas are specific transmitters of the plague, they transmit tularemia, rats' epidemic typhus. Fleas are intermediate hosts of rat's and dwarf tapeworm. Plague foci still occur in India, Pakistan and Burma. Natural plague foci are sustained by wild rodents. Human perceptibility to plague is absolute. Natural reservoirs of the plague are various wild rodents — rats, gophers, marmots, etc. A plague bacillus multiplies in the stomach of the flea forming a "plague block" which closes its lumen. During blood sucking, the blood is regurgitated into the wound together with bacteria.

The *Diptera* order — two-winged insects

The wings in the first pair are membranous translucent, the second pair is transformed into rudiments — halteres — an organ steering the flight. Big facete eyes are located on the head. The mouth apparatus is licking, sucking or stabbing-sucking.

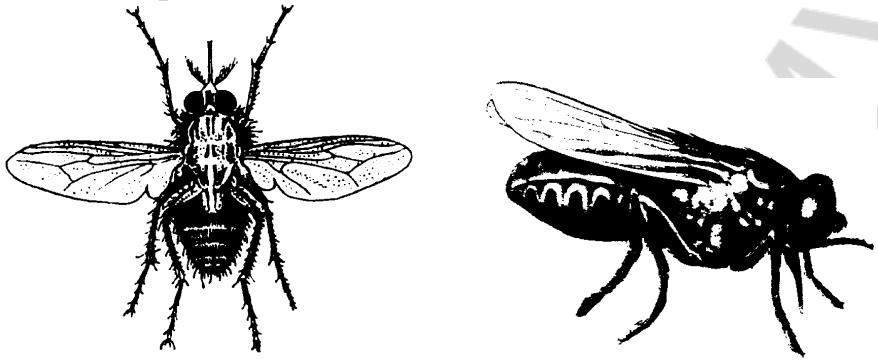
The *Muscidae* family — flies

Stomoxys calcitrans (fig. 33).

It scrapes epidermis with chitin teeth of the proboscis and licks the blood. Its saliva contains poisonous substances and causes severe irritation. Bites of Stomoxys calcitrans are painful. They are most numerous in August-September.

Stomoxys calcitrans transmits pathogens of anthrax, tularemia, staphylococcus infections.

Glossina palpalis — tsetse fly (fig. 33) is a specific transmitter of trypanosomes of the sleeping disease. It feeds on human and animal blood. It is viviparous. Body sizes are up to 13 mm. It is met in western areas of Africa.



Stomoxys calcitrans Glossina palpalis

Fig. 33. Stomoxys calcitrans and tsetse fly

The Tabanidae family — horse-flies (fig. 34).

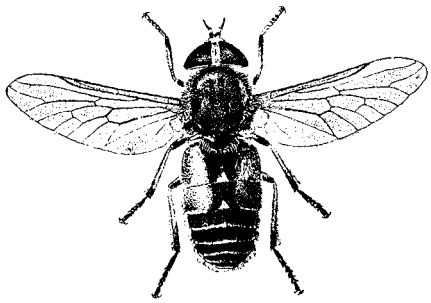


Fig. 34. A horse-fly (Tabanus autumnalis)

Big flies (up to 3 cm). Males feed on plant juices, females — on human and animal blood. The saliva is poisonous and a swelling forms around the bite. The development is with metamorphosis, occurs on the bottom of a water reservoir in wet soil. Horse-flies are mechanical transmitters of pathogens of tularemia and anthrax, intermediate hosts and specific transmitters of loaiasis.

The *Simuliidae* family — midges. Body sizes are from 2 to 6 mm (fig. 35).

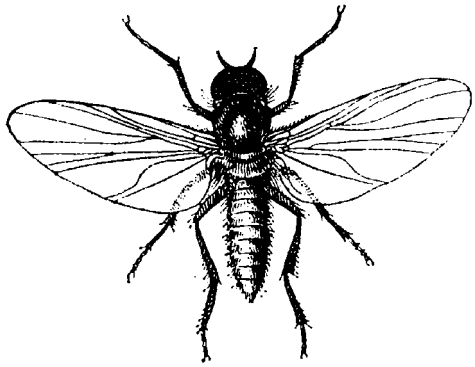


Fig. 35. A midge (Simuliidae)

The development occurs in water. Females feed on blood. Saliva of midges is toxic. Bites are painful. Midges are transmitters of tularemia and onchocercosis.

The *Ceratopogonidae* family — wood-louse. Body sizes are 1–2,5 mm (fig. 36).

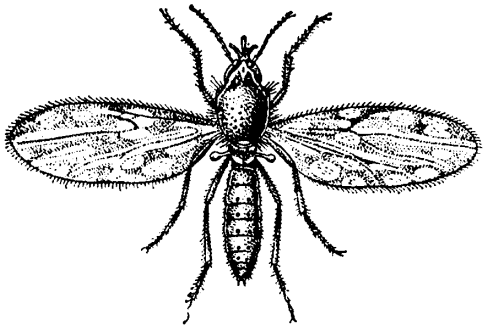


Fig. 36. A wood-louse (Ceratopogonidae)

Females feed on blood. The development occurs in wet soil and small stagnant water reservoirs. Wood-lice transmit pathogens of tularemia and some filariatoses. They participate in transmitting viruses of Japanese encephalitis.

The *Phlebotomidae* family — mosquitoes. Body sizes — 1.5–3.5 mm (fig. 37).

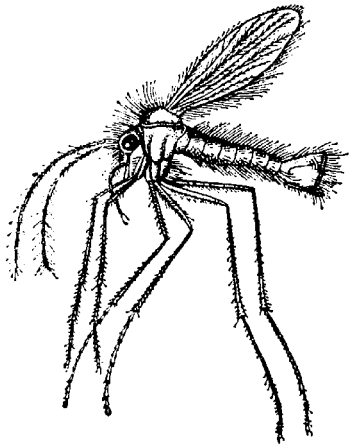


Fig. 37. A Mosquito (*Phlebotomidae*)

They lay eggs in rodents' holes, birds' nests, in caves, in garbage. Males feed on plants juices, females — on blood. The saliva is poisonous. Bites are painful, ulcerated dermatitis develops in the bites sites. Mosquitoes are specific transmitters of leishmanioses and pappataci fevers (transovarial transmission). They transmit also yellow fever and filariatoses.

The *Culicidae* family — gnats (fig. 38).

The representatives of *Anopheles*, *Culex*, *Aedes* are most widely spread. The mouth apparatus in males is sucking, they feed on flower nectar. The mouth apparatus in females is stabbing-sacking, they feed on blood. The development occurs in small water ponds with a complete metamorphosis. Maturation of eggs occurs after blood sucking during digestion of the blood (*a gonotrophic cycle*). Gnats are temporary ectoparasites of humans and animals. They transmit up to 50 various diseases. Gnats p. *Anopheles* are specific transmitters and final hosts of malaria pathogens — malaria plasmodia, they also transmit pathogens of filariatoses. Gnats p. *Culex* transmit Japanese encephalitis, tularemia, wuchreriosis; gnat of the *Aedes* genus transmit tularemia, yellow fever, dandy fever, Japanese encephalitis, anthrax, wuchereriosis. Bites of gnats are painful and cause severe itching.

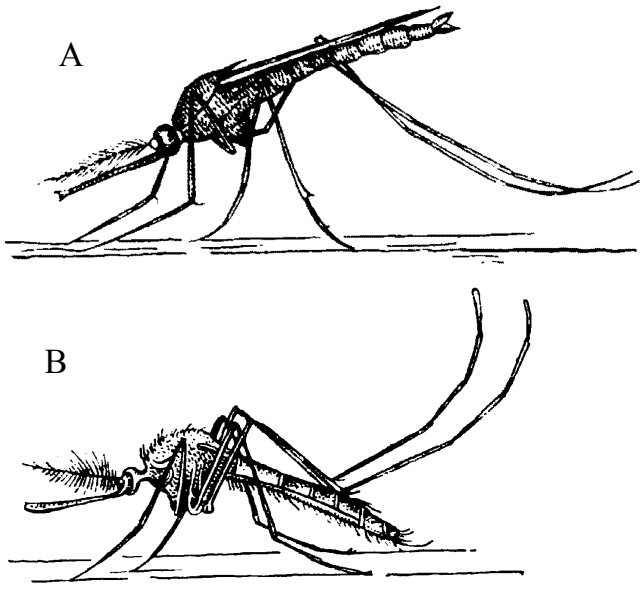


Fig. 38. Gnats (*Culicidae*):
A — *p. Anopheles*; B — *p. Culex*

BIOLOGICAL PROPHYLACTIC BASES OF TRANSMISSIBLE AND NATURAL-FOCAL DISEASES

Blood-sucking arthropod produce great damage to the health of people, they bring away a great number of lives. According to E.N. Pavlovsky, "probos-

cises of gnats, lice and fleas killed more people than were killed in battles that have ever taken place". Agriculture also suffers substantial losses.

The development and accomplishment of measures against blood-sucking Arthropod is of great importance.

A. Biological measures: using their "natural" enemies. For example, breeding the mosquitofish, which feeds on larvae of malaria mosquitoes.

B. Chemical measures: using insecticides (against flies, cockroaches and fleas); disinfecting places, where mosquitoes and small blood-sucking insects hibernate (basements, sheds, garrets); closing garbage collectors, toilets, manure depositaries, removing wastes (against flies); dispersing poisonous chemicals in water reservoirs if they have no industrial importance (against gnats); deratization (against ticks and fleas).

C. Individual preventive measures from blood-sucking arthropod: protective liquids, ointments, special protective clothes; cleanness in the rooms, wet cleaning; putting nets on dwellings windows; cleanness of the body and clothes.

LECTURE 18
Topic: BIOLOGICAL BASES OF PARASITIC TROPICAL DISEASES

Plan

1. Specificity of parasitic tropical diseases.
2. Malaria and trypanosomoses are basic protozoan tropical diseases.
3. Schistosomiasis and filariatosis — are major tropical helminthoses.

High prevalence, a great variety of diseases and their high incidence are factors, which determine the health level and population life span in Asia, Africa and South America.

Tropical pathology is characterized by peculiarities associated with specific disease courses, with direct effect of the environment and social factors. A number of factors create an unfavorable background for parasitic diseases.

Firstly, it is *early age of primary infection* — children are more perceptive to the diseases and their course is more severe in children than in adults.

Secondly, a *mass character of infection* — high doses of pathogens associated with definite factors of the environment.

Thirdly, *polyparasitism* (the organism is simultaneously affected by some species of parasites).

Climate produces a considerable effect on tropical parasitoses. High temperature and high humidity provide optimal conditions for the development of a richer fauna of parasites.

The same factors stimulate changes of water-salt exchange and catarrhal diseases, which weaken the human organism and make it easier to infest with parasites.

Water of stagnant reservoirs is also favorable for infecting humans. Frequent droughts lead to drying of reservoirs, the concentration of invasive stages increases raising the possibility of infecting humans.

Soil is also a source of infecting the human with parasites. In the absence of the sewerage system the soil is constantly contaminated by domestic wastes and drains. Untreated human feces containing protist cysts and helminthes eggs are used as fertilizers.

The probability of infecting humans increases due to a constant contact of hands and bare feet with soil.

The level of welfare and health of the population is determined by social-economic conditions.

The countries of Africa and South Asia are mainly agricultural states. 40 % of the developing countries population live in absolute poverty. 450 million people have no wholesome nutrition, ⅔ of the population are not provided with good water and a wastes removing system.

A high level of parasitic diseases in the population is also due to avitaminoses, a low level of hygienic culture, unavailability of medical care.

According to the data of the World Health Organization (WHO), which develops Special Programs of preventing parasitic diseases, malaria and trypanosomoses — of protozoan diseases, schistosomiasis and filariatoses — of helminthoses are most widely spread in tropical countries.

Malaria

Malaria occurs in 70 countries of the world. Annually about 110 million people fall ill with malaria in the world, from 1 to 2 million people die, 50 % of them are newborns. In 1880 A. Laveral described a malaria pathogen, and in 1897 R. Ross established that gnats of the *Anopheles* family are its transmitters.

Malaria pathogens are referred to **Apicomplexa phylum, Sporozoa class. Coccidia order**.

Four species of malaria plasmodia parasitize in the human:

Plasmodium vivax — a 3-day malaria pathogen;

Pl. ovale — a 3week malaria pathogen;

Pl. falciparum — a tropical malaria pathogen;

Pl. malaria — a 4-day malaria pathogen.

Ways of infecting the human with malaria:

- a bite of an Anopheles female(inoculation);
- transfusion of donor's infected blood;
- transplacentally.

An *Anopheles* female is a transmitter and a definitive host; plasmodia in its organism undergo gametogony and sporogony.

Pathogenic action of malaria plasmodia is marked during the period of erythrocytic schizogony. Due to their mechanical action massive destruction of erythrocytes occurs. Plasmodia metabolites pass into the blood plasma causing an attack of malaria. It starts with a *prolonged chill* (from 0,5 to 2–3 hours), followed by a *sharp elevation of body temperature* up to 40–41 ^{o}C. Patients complain of a bad fever, headache, nausea, vomiting and dizziness. The patients' skin is hot and dry. There is observed tachycardia, hypotension and decrease of diuresis. In 6–8 hours the body temperature sharply falls down to 35–36 ^{o}C, the body covers with *cold sticky perspiration*, intoxication decreases and the patient's condition improves (till the next attack).

Symptoms of malaria: periodicity of attacks, signs of anemia, impairment of the liver and spleen.

Gnat's bite
↓
(sporozoits → liver)
Human — intermediate host
↓
Exoerythrocytic (tissue) schizogony
In hepatic cells (the incubation period is from 7 to 25 days)
↓
Erythrocytic schizogony (2–3 days)
↓
In erythrocytes
Gamonts (micro- and macrogametocytes) — immature sexual forms
↓
The stomach of a female gnat
Development of micro- and macrogamets, formation of a zygote (ookinete)
↓
Oocyst → sporocyct
↓
Sporozoum

Diagram 14. The development cycle of a malaria plasmodium

Tropic malaria has the most severe course due to developing complications:

a) obstruction of the brain blood vessels by stuck together erythrocytes; this cerebral form gives up to 98 % of all fatal malaria cases;

b) acute renal insufficiency;

c) malaria coma;

d) impairment of microcirculation and inflammation of internal organs.

To choose the proper treatment the doctor should determine a pathogen species, which affected a person. *Laboratory diagnosis* of malaria is performed while examining a blood smear or a thick blood drop for the presence of various parasitic stages. The blood for the test is taken during or immediately after the attack.

Prevention of malaria. Personal prophylaxis — defense from gnats' bites. Social prophylaxis — revealing and treating patients and parasite-carriers, combating *Anopheles* gnats (on all development stages).

SARCOMASTIGOPHORA PHYLUM ZOOMASTIGOTA CLASS

There are free living filamentous and parasites of humans and animal among the representatives of this class, which cause severe diseases.

African trypanosomiasis or sleeping disease. Pathogens: *Trypanosome gambiense* (the West of Africa). *Trypanosome rhodesiense* (the eastern part of Africa). Morphological peculiarities of trypanosomes: a curved body, narrowed at the ends. In the center of the cell lies the nucleus. A filament follows the margin of the undulating membrane. The body length is 13–40 μm, the width — 1.5–2 μm. Nutrition is osmotic. Multiplication is asexual by longitudinal division into halves.

African trypanosomiasis is a transmissive disease. A natural focus is Equatorial Africa. Natural reservoirs for trypanosomes of the sleeping disease are domestic pigs and cattle, wild ungulate animals of Africa. The *tsetse fly* (*Glossina palpalis*) is a specific transmitter. Multiplication of trypanosomes occurs in its alimentary tract. They undergo a number of development stages and accumulate in salivary glands of flies.

Ways of infecting the human:

- a bite of a tsetse fly (inoculation);
- transfusion of infected blood;
- transplacentally.

The first 9–10 days after infection, trypanosomes are in the subcutaneous cellular tissue and then they accumulate in the lymphatic system, multiply, in 20–35 days pass into the blood and are carried through out the organism.

Localization of trypanosomes: the blood, lymphatic vessels and nodes, cerebrospinal fluid, the brain and the spinal cord.

Pathogenic action: The development of a trypanosomic chancre at a bite site. A toxic-allergic action of trypanosomes' waste products. Chill, weakness, exhaustion, dizziness. A fatal outcome if not treated.

Laboratory diagnosis: revealing of trypanosomes in the peripheral blood smear, punctuates of lymphatic nodes and cerebrospinal fluid.

Prophylaxis: personal — taking medications preventing from infection in bites of a tsetse fly and defense from fly's bites; social — revealing and treating patients and parasite-carriers, fighting against transmitters.

American trypanosomiasis (Chagas' disease) is spread in South and Central America. About 10 million people suffer from it.

Pathogen — *Trypanosoma cruzi Chagas*. Morphologically *T. cruzi* does not differ from *T. gambiense*, but has 2 life stages — filamentous and filamentless.

Natural reservoirs — wild mammals (armadillos, ant-eaters). *Specific carrier* — a bug of the *Triatoma* genus (kissing bug). Trypanosomes get into the bug's intestines with blood, multiply there and are passed away with excrements.

Ways of infecting the human:

– contamination;
– transfusion of infected blood;
– transplacentally;
– with mother's milk.

Trypanosomes multiply in skin cells or mucous membranes of the human organism; pass into the blood and affect various organs (the liver, spleen, kidneys, intestines, cardiac muscle and lymphatic nodes). The affected cells are destroyed; trypanosomes pass again into the blood and affect healthy cells.

Pathogenic action and symptoms of the disease. A swelling appears at the site of penetrating trypanosomes into the human skin, and chagoma develops (the diameter is 10–15 cm). The main affect on the host is toxic-allergic (reaction to parasite's metabolites and decay of affected cells). Edema of tissues and enlargement of lymphatic nodes are noted. In an acute period of the disease appear pains in the heart, arrhythmia, signs of cardiac insufficiency. Muscular hypertrophy leads to dilatation of the esophagus and intestines. Chagas' disease may be complicated by meningoencephalitis.

Laboratory diagnosis: revealing of trypanosomes in blood smears, cerebrospinal fluid, in punctuates of the spleen and lymphatic nodes. Immunological methods are used.

Prophylaxis of American trypanosomiasis. Revealing and treating patients, fighting against transmitters, defense against their attacks on the human (using scary ointments and fluids).

FLATHELMIONETHES PHYLUM — FLAT WORMS
TREMATODA CLASS — FLUKERS

Schistosomes or blood flukers

They occur in tropic and subtropic countries (Africa, Asia and Latin America). Diseases caused by blood flukers are called *schiostosomoses* (about 200 million people in the world suffer from them).

9 species of blood flukers parasitize on the human, 4 species are most common:

Schistosoma haematobium — a pathogen of urogenital schistosomosis;

Sch. Japonicum
Sch. Mansoni } — pathogens of enteric schistosomosis

Sch. Intercolatum

Blood flukers have different sexes, and this is their peculiarity. The male's body is wide and short (10–15 mm), a female's — 20 mm. Young individuals live separately till 6 months, then they conjugate in pairs (a female is placed in the gynecoforous canal on the abdominal side of a male (fig. 39).

Localization of schistosomes: large veins of the mesentery, intestines and the urogenital system. Eggs are excreted into the external environment from the bladder with urine or from the intestines with feces. The development starts in water: intermediate hosts — sweet water mollusks. There develop two generations of *sporocysts* and *cercaria* in their organism. Cercaria are an invasion stage for a definitive host. They leave the mollusk and swim in the water; may get into the human organism by various ways: invade the skin or mucous membranes during bathing, work in rice plantations, with drinking water from an open reservoir. Having got into the organism cercaria migrate through lymphatic and blood vessels into the rights heart chamber, the lungs and abdominal veins.

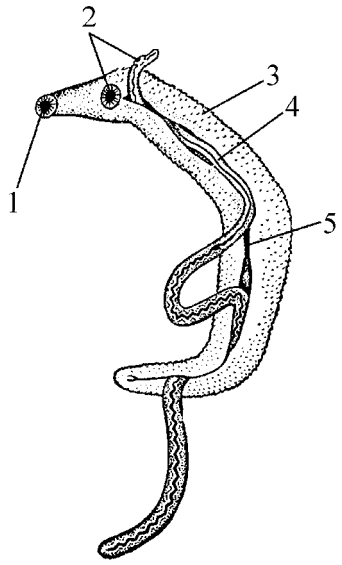


Fig. 39. Blood flukers:
1 — a mouth flukers; 2 — an abdominal flukers; 3 — a male; 4 — a female; 5 — a gynecoforous canal

Urogenital schistosomosis is called *bilharziosis*. Sex mature forms of flukers are localized in the veins of the bladder, uterus and the vagina upper part. Besides humans, apes may be principle hosts. Flukers live in the human organism up to 40 years.

Pathogenic action and symptoms of the disease. At early stages of invasion — predominantly a toxic-allergic action of larvae (skin eruptions, eosinophilia, fever, enlargement of the liver and spleen). At a chronic stage of the disease, predominates a mechanical action of eggs (there is a short thorn on their membrane) on tissues of the urogenital system (fig. 40).

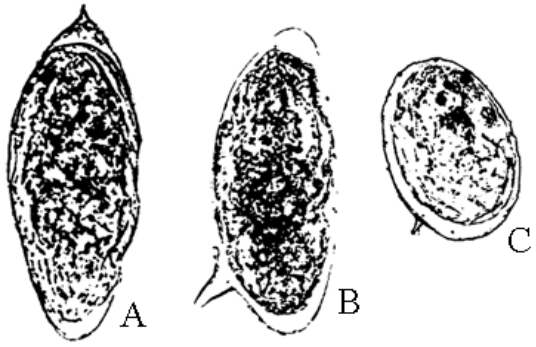


Fig. 40. Eggs of blood flukers:
A — S. haematobium; B — S. mansoni; C — S. japonicum

The first signs of having infected schistosomosis — itching at the site of cercaries' invasion and the development of dermatitis. In the migration period of young schistosomes, cough with mucus and blood and symptoms of bronchial asthma appear. Along the way of invasion one can observe the inflammation of the bladder mucus, impairment of ureters, excretion of blood with urine, impairment of the male and female genital system. Urogenital schistosomosis can be complicated by cancerous diseases of the bladder and urinary ways. Rare complications are severe impairments of the liver, spleen, lungs and CNS. The pathogen of intestinal schistosomosis *Sch. mansoni* does not differ from *Sch. haematobium* in its structure and development cycle. Definitive hosts: humans, cattle, dogs, rodents; intermediate hosts — sweet water mollusks. The parasite's life span in the human organism ranges from 8 to 30 years. Eggs from small venules pass into the intestinal cavity and are excreted with feces. The development occurs in water reservoir.

At an initial stage of the disease it is noted a toxic-allergic action as itching, skin eruptions and dermatitis. Later, changes in the colon, liver and other organs appear, i.e. pains in the stomach, rectal hemorrhages, its obstruction. There may develop bronchitis caused by allergic reactions due to decay of dead schistosomes in the lungs. In severe cases patients die of cardio-vascular insufficiency.

Japanese schistosomosis (Katayama's disease) is a variety of enteric schistosomosis with severe impairments of the intestines, liver, sometimes CNS.

Morphological difference from other schistosomes is the absence of thorns on the body. The development cycle is similar. Definitive hosts are humans, apes, cattle, horses, pigs, rats and other mammals. These schistosomes stay permanently in one place. Their localization is the hepatic and mesentery veins.

Pathogenic action and symptoms of the disease. A chronic stage of the disease leads to the liver impairment. Penetration of helminthes' eggs into the brain causes allergic reactions and the impairment of CNS (cerebral schistosomosis). *Laboratory diagnosis of schistosomoses*: revealing of schistosomes' eggs and impurities in the blood and human feces. Sometimes bioptates of the bladder mucus or the colon are tested. *Prophylaxis of schistosomose*s: personal — to

avoid contacts with water, where schistosomes larvae may be (not to enter the water and not to use it for domestic needs).

NEMATHELMINTHES PHYLUM — RING WORMS
NEMATODA CLASS — RING WORMS PROPER

Filariatoses — diseases caused by representatives of the Nematoda class — filarias. This group of human pathogens is widely spread in tropic and subtropic countries. There are approximately 650 million people ill with filariatoses in the world.

A filament body shape is characteristic of all *filarias* (fig. 41).

They are *biohelminthes*. The definitive host is a human and some mammals. *Intermediate hosts* and transmitters are two-wing blood sucking insects. Sexually mature parasites are localized in tissues and cavities of the human body, larvae (microfilarias) — in the blood or in tissues. Microfilarias migrate along blood vessels depending on the day time. Filarias are viviparous.

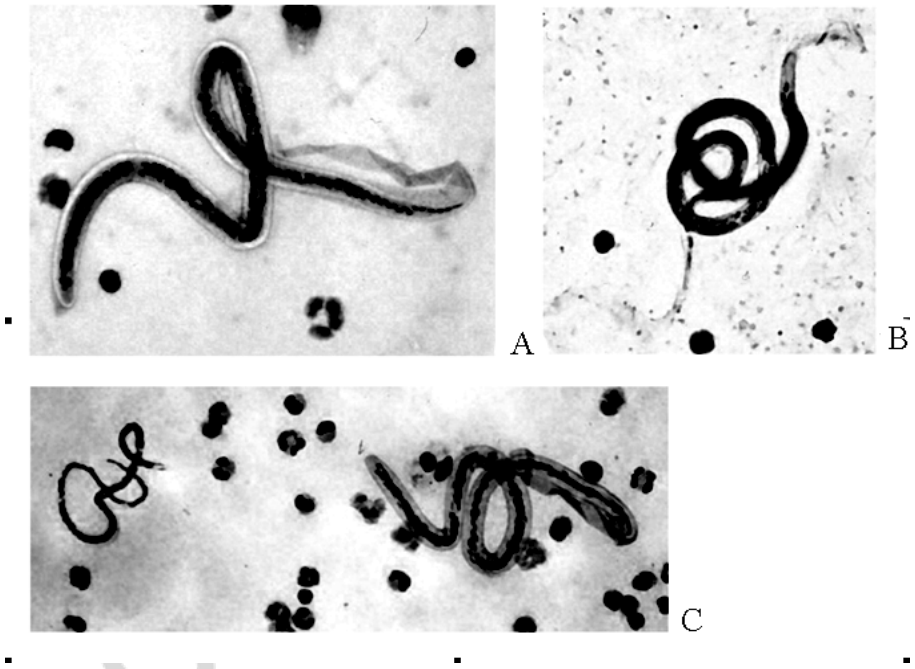


Fig. 41. Filarias:
A — Brugia malayi; B — Loa loa; C — Wuchereria bancrofti

Wuchereria bancrofti is a pathogen of wuchereriosis. The principal host is only the human, intermediate hosts and transmitters — are gnats of the *Culex*, *Anopheles*, *Aedes* and *Mansonia* genus. Localization of semi-mature forms is lymphatic vessels and nodes.

Females lay larvae here; they migrate into blood vessels (at day time they are in deep internal organs, at night they rise to peripheral vessels). The development of microfilarias in the gnat's organism ranges from 8 to 35 days (depending on the environment temperature). When a gnat bites a human,

microfilarias get again into the blood, migrate to the lymphatic system and reach their sexual maturity in 3–18 months.

Pathogenic action and symptoms of the disease. In early stages of the disease — a toxic-allergic action of parasites' metabolites. Later — a mechanical action: obstruction of lymphatic vessels, the impairment of the lymph outflow. The volume of the affected organ sharply enlarges (lower extremities, external sex organs, in women — mammary glands). Wuchereriosis is known as elephantiasis. In early stages of the disease there are bronchopneumonias, the syndrome of "tropical eosinophylia", in late stages — destructive changes in the lymphatic system, diarrhea, urine with lymph, secondary pyelonephritis, elefantism of organs.

Diagnosis: revealing of microfilarias in the blood (the blood for test is taken at night).

Brugia malaji is a pathogen of *brugiosis*. It is morphologically similar to W.bancrofti, but a bit larger in size. The life cycle does not differ from the wuchereria's cycle. The definitive host is human, apes, cats, dogs. Intermediate hosts and transmitters are more often gnats of the *Mansonia* genus. In brugiosis, predominantly upper and lower extremities are affected. The pathogenic action, symptoms and laboratory diagnosis are the same as in wuchereriosis.

Onchocerca volvulus is a pathogen of *onchocercosis*. The definitive host is only the human. Intermediate hosts and transmitters of microfilarias are midges. There are affected superficial layers of the skin, eyes and peripheral lymphatic vessels. Mobile dense nodes, onchocercomas, form under the skin. They may be in the armpits, near large joints, on the ribs, on the head. There are alive and dead nematodes under their capsule. Produced by females microfilarias are placed in the periphery of the node, they penetrate into lymphatic nodes, into the eyes, superficial layers of the skin. In the midge's stomach, larvae become invasive during 6–12 days and through a transmitter's bite they get into the definitive host where they reach their sexual maturity.

Pathogenic action and symptoms of the disease. A toxic-allergic action of parasites' metabolites. Parasitizing of microfilarias in the skin causes the development of onchopcercosic dermatitis (itching, skin eruptions, its thinning, loss of elasticity, forming of small wrinkles — an "orange skin" or a "crocodile skin", an "elephant skin". Very rarely there occurs elefantism of the face ("lion's muzzle") in onchocercosis. Onchocercosis is most seriously complicated by the impairment of eyes, which leads to the loss of eyesight.

Laboratory diagnosis: revealing of microfilarias in microscopic sections of superficial areas of the skin or sexually mature forms — in onchcercomas.

Loa loa is a pathogen of *loaosis*. The definitive host is humans, apes, the intermediate host and transmitter are horse flies. Sexually mature forms of the loana are localized in subcutaneous cellular tissue, serous cavities of eyes,

larvae — in the blood circulation system. Microfilarias in horse flies become invasive in 7–10 days. The human is infected with laosis through a horse fly‘s bite.

Pathogenic action and symptoms of the disease. A toxic-allergic action of metabolites and decay products of dead parasites. A mechanical action on tissues of the host are produced by parasites during migration over the organism. There are marked pains in extremities, paresthesias (impairments of sensitivity), temporal and quickly resolved edemas, hypereosinophylia, anemia. When the eyes are affected, there are observed edemas and hyperemia of the lids, severe pains, eyesight impairment. Due to secondary infection there develop abscesses in muscles and lymphatic nodes.

Laboratory diagnosis: revealing microfilarias in blood smears and in a thick drop of blood. Parasites are seen under the conjunctiva with a naked eye.

Prophylaxis of filariatosis: defense from of transmitters-suckers’ bites; social — sanitary-instructive activity among the population, revealing patients, fighting against transmitters.

LECTURE 19
Topic: PHYLOGENESIS OF THE ORGAN SYSTEM IN CHORDATE ANIMALS (I)

Plan

1. Association between ontogenesis and phylogenesis. The biogenetic law.
2. Phylembryogeneses.
3. Methods of organogenesis. Correlations.
4. Phylogenesis of coverings and the skeleton of chordate animals.

Ontogenesis is individual development, a complex of development processes of an individual from a zygote formation to death. The development occurs due to realization of genetic information received from parents. Environmental conditions produce a considerable effect on its realization. **Phylogenesis** is a historical development of a species, evolutionary development of organisms.

Ontogenesis and phylogenesis are closely connected. Knowing the trends and modifications of organs and their systems in the process of their historic development, one can understand and explain the development defects arising in the process of embryogenesis.

The association of ontogenesis and phylogenesis got its reflection in a number of biological laws and regularities. In 1828 Carl Barr formulated three laws.

The first law is a law of embryonic similarity — an embryo of some higher animal never resembles any other animal, but resembles its embryo.

The second law is a law of successive appearance of characters — general characters characteristic of this large group of animals are revealed in their embryo earlier than more specific characters.

The third law is a law of embryo divergence — every embryo of this form of animals does not go through other forms, but gradually separates from them.

These laws mean the following. In early stages of embryogenesis, animals embryos of various classes of vertebrates (for example, fish, birds, mammals) are alike. In time there appear differences between them within the classes, and then — within the orders (for example, a pig embryo and a human embryo).

The parallelism law of Mekkel-Serre says that every being in its embryonic development repeats adult forms of lower animal development stages.

Ch. Darvin confirmed the association of ontogenesis and phylogenesis and developed a study about recapitulations. *Recapitulation* is repetition of ancestral characters in embryos. For example, in the process of germination and development of the respiratory system a mammal embryo undergoes the stages of forming branchia slots on the pharynx, then branchiae are formed and then the organs of external respiration — the lungs.

In 1866 E. Gekkel formulated the *biogenetic law*: ontogenesis is a short and fast repetition of phylogenesis, but not adult ancestral stages are repeated here, but their embryonic ones.

It turned out, that recapitulation in ontogenesis may not always occur. On this basis Gekkel marked out two groups of characters — palingeneses and cenogeneses. *Palingeneses* mean repetition of ancestral characters in embryos (germination of a chord and branchia slots on the pharynx, a two-chamber heart in ground vertebrates). Cenogeneses are embryonic adaptations that are only in embryos and are absent in adult organisms (embryonic membranes in higher vertebrates — aminion, chorion, allantois).

PHYLEMRYOGENESES

The study of A. N. Severtsov about phylembryogeneses is of great importance for explanation of the association between ontogenesis and phylogenesis. Phylembryogeneses are embryonic neoplasms that have a phylogenic significance. The time of their appearance and the ways may be different.

The time of appearance of phylembryogeneses

Initial stages of morphogenesis	Intermediate stages of morphogenesis	Final stages of morphogenesis
Archalaxis — complete change of organ development (recapitulation is absent)	Deviation — deviation in organ development (partial recapitulation — in early stages)	Anabolism — extension in organ development recapitulation is present, a new character is germinated at early development stage

Example: from the shark scales develop:

1) corneous corselets of reptiles by deviation;
2) bird's feather by anabolism;
3) hair in mammals by archallaxis.

The most frequent way of evolution is anabolism, that is why recapitulations are observed.

WAYS OF ORGANOGENESIS. CORRELATIONS

Main principles of evolutionary organ transformations:

1. Differentiation: subdivision of the initially homogenous structure. Example: a digestive tube in mammals is subdivided into: the oral cavity, pharynx, esophagus, stomach, intestiness.

2. Integration: enhancement of mutual dependence of organism parts. For example: interdependence of the respiratory and circulatory systems in mammals.

A. N. Severtsov describes basic ways of morphofunctional changes of organs in phylogenesis. *Alternation of organ functions* is most frequently observed in the process of evolution. Simultaneously with function alternation occurs modification of the structure organ, for example, a swimming bladder of crossopterygian fish is transformed into an organ of external respiration — the lungs; skin scales of fish is transformed into teeth of mammals in the process of evolution; a sting is formed from the oviduct of the arthropod.

The next way is *extension of functions* due to changing conditions. At first thoracic fins in fish fulfilled the function providing body steadiness in water at a definite level, then they started determining the movement direction. In bottom fish they serve for support and movement around the bottom of the reservoir.

In some cases there is marked *enhancement of organ functions*. The organ sizes enlarge, and its histological structure changes. For example: The development of the frontal lobe of the brain in vertebrate mammals.

Phylogenic transformations may occur by *replacement of organs and functions*. One organ disappears or becomes rudimental and then it is replaced by another organ. An example: replacement of a chord by a spinal column, replacement of a head kidney in vertebrates by a body one, and then by a pelvic one.

The principle of functional compensation: muscular stomach of birds compensates the absence of teeth; participation of the skin in amphibians in respiration compensates insufficient lung respiration.

Interrelations of the organism parts, compliance of phylogenetic transformations of its organs and parts is called **correlations**. Correlations may be genomic, morphogenetic and ergontic or functional.

Genomic correlations are determined by interaction of genes, pleotropy and linkage of genes. An example: the combination of fair and straight hair, dark and curly hair; reduction of wings in Drozophila and simultaneous shortening of a back pair of limbs.

Morphogenetic correlations are determined by internal factors at early stages of embryonic development, when functional links between parts of an embryo have not been established. In the basis of these correlations is embryonic induction — germs of structures that form earlier, determine the direction and character of germs modifications, which form later. For example: a dorsal lip of a blastopore induces the development of a nerve tube, chord and somites.

Ergontic correlations are determined by interdependence of functions of specific organs. For example, a link between a gonadotropic function and the hypophysis and sex glands development.

PHYLOGENESIS OF BODY COVERINGS IN CHORDATE ANIMALS

External coverings or skin are subdivided into 2 layers: *epidermis* (of an ectodermal origin) and corium — *derma* or the skin proper (of a mezodermal origin). Body coverings fulfill the following functions:

- protective (from environmental factors);
- participation in excreting wastes (urea, mineral salts);
- is a sensory organ (contains receptors of perception, temperature, pain);
- blood depot;
- participation in respiration (amphibian).

The Lancelet has poorly developed coverings: one-layer epidermis with separate glandular cells; corium is a layer of a jelly-like connective tissue (fig. 42).

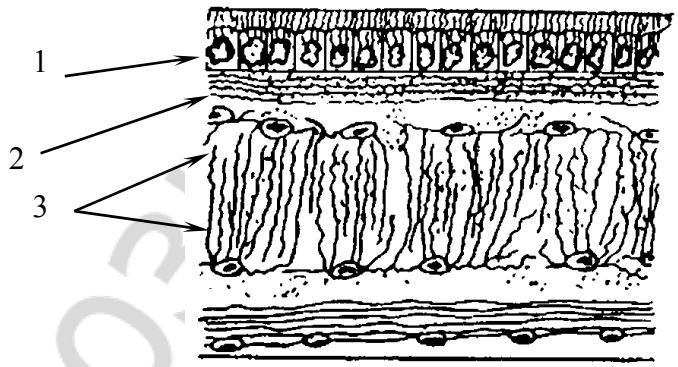


Fig. 42. The structure of the Lancelet's skin:
1 — cuticle; 2 — epidermis; 3 — corium

Evolutionary directions of body coverings:

- differentiation between epidermis and derma, derma thickness enlargement;
- from a one-layer epidermis to a multilayer one;
- differentiation of skin derivatives;
- from unicellular skin glands to multicellular ones;

- development of subcutaneous adipose cellular tissue and improvement of thermoregulation mechanisms.

Skin derivatives:

- scales in reptiles, feathers in birds, hair in mammals;
- glandular cells in fish, multicellular glands in ground vertebrates (sebaceous, sweat and mammary);
- claws, nails, horns and hooves).

Ontophylogenetically conditioned defects of coverings development in the human (recapitulation and parallelism): absence of sweat glands, ichtiosis (enhanced development of a corneous layer), multinippleness (in norm humans have 2 nipples, the number of nipples in animals is from 1–8 to 22–25).

PHYLOGENESIS OF THE SKELETON IN CHORDATES

The Lancelet's axial skeleton is a chord (of an entodermal origin) and hardbands of fibrous tissue, which give support to fins and branchial slots. The chord is an elastic band of fibrous tissue of special vacuolized cells.

The skeleton of vertebrates is of a mezodermal origin. It consists of 3 parts: the axial skeleton, the skeleton of the head, the skeleton of extremities and their girdles.

Functions of the skeleton:

- locomotion;
- protective (for internal organs);
- blood-forming;
- participation in metabolism (the depot of calcium and phosphorous salts).

Directions of the axial skeleton evolution:

- replacement of the chord by the spine;
- differentiation of the spine into departments, increase of the number of vertebrae in every department;
- formation of the chest.

Roundmouthed and lower (cartilaginous) fish retain the chord all their life. Over and under the chord vertebral arches appear.

In higher (bony) fish the spine has two departments — the body and tail. Vertebrae have bodies, arches and processes. There are ribs in the body and they have free ends on the abdominal side of the body.

The spinal departments of amphibians: the cervical and sacral departments have 1 vertebra each, the thoracic — 5 vertebrae, the caudal department may have various numbers of vertebrae. The cervical and thoracic departments carry short ribs that are free at the ends. The breastbone is cartilaginous.

Reptiles have 5 spinal departments. There appears a lumber department. The number of vertebrae in spinal departments increases to 8–12. In the cervical department the ribs become reduced, there are rudimental ribs in the lumber department. Well-developed ribs of the thoracic department are connected with

the breastbone. The caudal department of reptiles contains various numbers of vertebrae.

The spine of mammals consists of 5 departments: a cervical department (7 vertebrae), thoracic department (9–24 vertebrae), lumber department (2–9 vertebrae), sacral department (4–10 and more vertebrae), caudal department (various numbers of vertebrae). Ribs are reduced in the cervical and lumber departments. 10 pairs of ribs together with the breastbone form the chest.

Ontophylogenetic defects of the human axial skeleton:

- additional (cervical) ribs;
- increase of the vertebrae number in the caudal department (the length of the tail is up to 20 cm);
- increase of the sacral vertebrae number;
- splitting of back processes of vertebrae.

Evolution of the skeletal extremities. The basis for the extremities formation in vertebrates were metapleural (skin) folds located on both sides of the body in Lancelet.

Metapleural folds in Lancelet → paired (thoracic and abdominal) fins in fish → a five-digit extremity of a ground type.

Directions of evolution:

- reduction of the number of bony elements of fins and their enlargement by their fusion;
- increase of mobility in combination with the shoulder girdle.

Extremities in fish — thoracic and abdominal fins. The internal skeleton of fins is composed of cartilaginous and bony rays, tightly fixed together and with the shoulder girdle. In the majority of fish the fins serve for changing the movement direction.

In crossopterygian fish, the fins became used for moving over the ground, and conjugaction with the shoulder girdle has become mobile.

A five-digit extremities appeared in amphibians. A fixed connection of elements in the fins was replaced by a mobile conjugation forming joints. The extremity transformed into a complex lever. The shoulder bones, forearm and fingers became longer. Extremity girdles (scapulas, coracoideum and clavicles) look like an arch enveloping the body from the sides and bottom.

Ontophylogenetically conditioned development defects of the extremity skeleton in the human:

- additional bones of the wrist and tarsus;
- polydactyly (more than 5 fingers);
- syndactyly (fusion of finger phalanges);
- brachydactylia (shortening of finger phalanges).

The skeleton of the head (the skull) in vertebrates consists of the cranial and facial (visceral) parts. The skull protects the brain and sense organs.

The facial part forms a support for the front part of the digestive tract. Germination of the *cranial part* in embryos of all vertebrates occurs below the brain as two pairs of cartilages. There are elongated laminas on both sides of the front chordal end — *parachordalias*, in front of the chord — a pair of cartilages — *trabeculae*. Parachordalias and trabeculae fuse forming a fundus and lateral parts of the scull. *Olfaction and hearing capsules* adhere to it, and from the sides — *eyeball cartilages* (fig. 43).

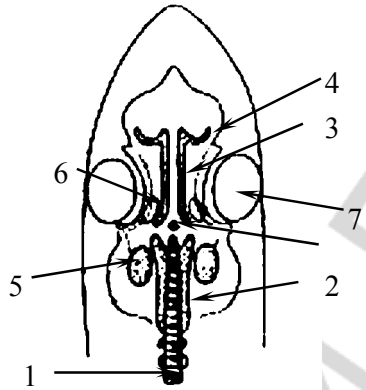


Fig. 43. Distribution of cartilages germs in the shark's skull (from the back):
1 — a chord; 2 — parachordalias; 3 — trabeculae; 4 — olfaction capsules; 5 — a hearing capsule; 6 — eyeball cartilages; 7 — an eye

Directions of the skull evolution:

- replacement of cartilaginous elements by bony ones;
- decrease of the number of bones due to their fusion;
- enlargement of the volume;
- modification of the shape (predomination of the cranial part over the facial one).

The visceral department is germinated from metamerically arranged cartilaginous arches around the front end of the digestion tube.

The evolution direction of the visceral department is differentiation of visceral arches.

In fish the 1st arch (mandible) consists of two cartilages — palatal–square and Meckel', which fuse and form the function of jaws. The 2nd arch (sublingual) contains a hyomandibular cartilage serving for the attachment to the skull (a hyosltyle skull). The rest arches are branchial — they support the respiratory apparatus (fig. 44).

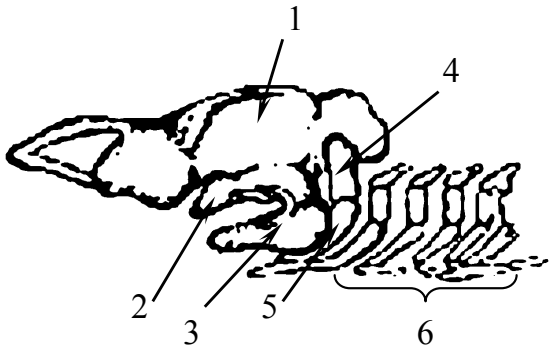


Fig. 44. The cartilaginous skeleton of the shark:
1 — the axial skull; 2 — palatal-square cartilage; 3 — the lower cartilage of the 1st arch; 4 — a hyomandibular cartilage; 5 — a hyoid; 6 — 6th–10th branchial arches

In ground vertebrates:

- the mandibular arch fuses with the skull fundus;
- the sublingual arch gives start to hearing bones;
- the 3rd–6th branchial arches give start to a shield-like cartilage and other cartilages of the larynx.

A mobile conjugation of the cranial part and the spine is characteristic of all ground vertebrates (*an autostilic type of the skull*).

In mammals the number of cranial bones decreases due to their fusion and its volume enlarges. The mandible is connected with the skull by a joint. The sizes of the facial part are considerably less than those of the cranial part.

Ontophylogenetically conditioned development defects of the head skeleton in the human:

- increase of the number of bony elements;
- non-atresia of the hard palate (cleft palate);
- frontal suture;
- one or two hearing bones;
- rudiments of cartilaginous elements in the skull ("fontanels").

LECTURE 20
Topic: PHYLOGENESIS OF ORGAN SYSTEMS IN CHORDATE ANIMALS (II)

Plan

1. Phylogenesis of the nervous, circulation and respiratory, digestive and urogenital systems.
2. Ontophylogenetic conditioning of development defects of organ systems in chordate animals.

EVOLUTION OF THE NERVOUS SYSTEM OF CHORDATE ANIMALS

The nervous system has an ectodermic origin.

Functions of the nervous system:

- regulates functioning of all organ systems;
- provides communication of the organism with the environment;
- integrates the organism into a whole;
- determines psychic activity of the human as a social being.

The nervous system of the Lancelet is a tube, which is placed over the chord. The nervous tube cavity is called a neurocele. In the frontal dilated part of the tube is an olfactory pit. Hesse's eyes (light-sensitive cells) are located along the tube.

In the process of evolution the frontal part of the Lancelet's nervous tube forms the brain, and cerebral ventricles are formed from the neurocele. The ventricles communicate with each other and the spinal cord. Over the ventricles are parts of the brain that compose its roof, the base (or fundus of the brain) is below the ventricles.

Initially three brain vesicles are germinated. Then the 1st and 3rd vesicles are divided into two — and 5 brain vesicles are formed, which are then transformed into 5 departments of the brain: 1 — *telencephalon* — the cerebrum proper (hemispheres and lateral ventricles); 2 — *diencephalon* — oliencephalon (its cavity is the 3rd ventricle); 3 — *mesencephalon* — the midbrain; 4 — *metencephalon* (cerebellum); 5 — *myelencephalon* (medulla oblongata).

The nervous system evolution follows the way of differentiation of the nervous tube into the brain and spinal cord (the central nervous system) and differentiation of the peripheral nervous system (ganglia and nerve fibers).

Directions of the brain evolution are more complex:

- enlargement of its volume;
- differentiation of departments and curves (the frontal curve — in the area of the midbrain, the middle one — a pontine (pontile) curve, a back curve — in the area of the medulla;
- the development of front brain cortex, fissures and convolutions;
- the development and improvement of sense organs.

The front brain of Fish is not divided into hemispheres; its major part composes the fundus where striate bodies are located. Small olfactory lobes branch from the frontal brain, so it is an olfactory center. The central department of the brain is most developed. It is represented by vision lobes and is an vision center. Information coming from all sense organs is analyzed in the central department of the brain. It is an integral center. Such type of brain got the name of ichthyopsidic. The cerebellum is well developed in fish due to movement complexity. 10 pairs of cerebral nerves branch from the cerebellum.

The brain of Amphibia has a poorly developed cerebellum (small mobility and monotonous movements). Their hemispheres are better developed than in

Fish and are separated, the midbrain preserves the integrating center function. Just as in Fish, 10 pairs of cerebral nerves branch off the cerebrum.

Due to various habitation conditions, *Reptiles*' frontal brain becomes larger. Olfactory lobes and striate bodies are well developed. Primitive cortical areas appear on the cerebrum hemispheres. This ancient cortex is called archypallium. The integration function is fulfilled by striate bodies of the cerebrum (sauropsid type of the brain). The sizes of the midbrain are reduced. The cerebellum is better developed than in Amphibia. There are 12 pairs of cerebral nerves.

The cerebrum in *Mammals* is considerably developed. Its sizes increased at cost of the mantle which is completely covered with the cortex. This cortex got the name of a new cortex or *neopallium*. It has a complex structure and consists of some layers of various types of cells. The new cortex forms fissures and convolutions. It contains centers of sense organs and psychic activity. The cortex becomes an integrating center, and this type of brain is called *mammal*. The middle brain is considerably reduced; instead of two vision lobes it has a quadrigerminal plate. The front protuberances of the quadrigerminal plate are linked with vision receptors, the back ones — with hearing receptors. The cerebellum is enlarged in sizes, its structure became more complex (fig. 45).

The brain of the human and Mammals has a functional asymmetry. The right hemisphere of the cerebrum (front brain) is responsible for imagination, the left one — for abstract thinking, the centers of written and oral speech are in the left hemisphere.

Ontophylogenetically conditioned development defects of the human brain:

- incomplete separation of the cerebrum hemispheres;
- absence of large hemispheres (anencephaly);
- microcephaly (decrease of the brain sizes);
- absence of separation between the cerebellum and medulla;
- congenital dropsy of the brain (hydrocephaly).

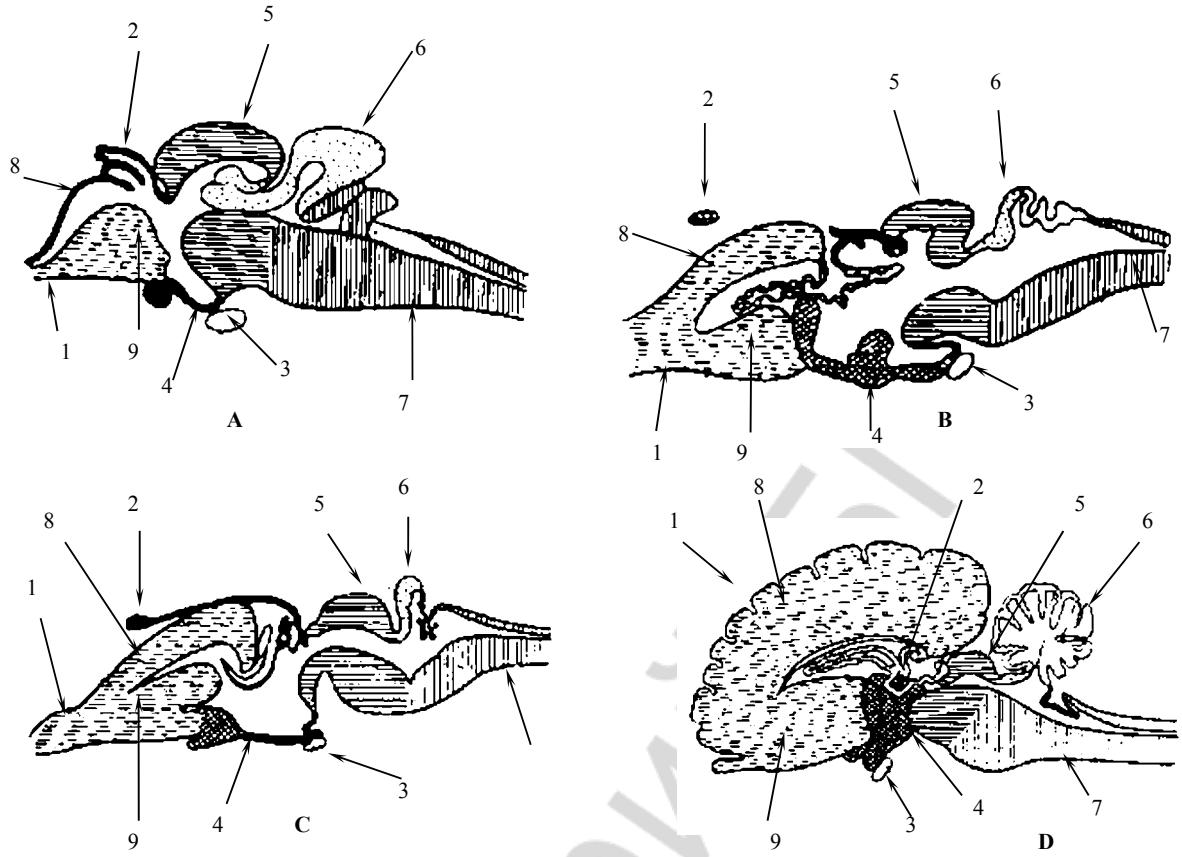


Fig. 45. The brain of Vertebrates (longitudinal section):
A — a bony fish; B — an amphibian; C — a reptile; D — a mammal; 1 — the front brain (cerebrum); 2 — epiphysis; 3 — hypophysis; 4 — oliencephalon; 5 — central brain; 6 — the cerebellum; 7 — the medulla; 8 — the mantle (roof); 9 — striate bodies of the cerebrum (front brain)

EVOLUTION OF THE RESPIRATORY SYSTEM IN CHORDATE ANIMALS

The respiratory system is germinated from the entoderm. The function of respiration in Lancelet's is fulfilled by branchial orifices (100–150 pairs). Gas exchange takes place in blood vessels of interbranchial septa. Arteries do not branch into capillaries.

Functions of the respiratory system:

- saturation of blood with oxygen and removing carbon dioxide from it (the function of gas exchange);
- depositing of blood;
- taking part in the voice box functioning.

Evolution directions of the respiratory system:

- decrease of the branchia number and increase of the respiratory surface of branchial lobes;
- formation of branchial capillaries; transfer of branchia into lungs;
- increase of the respiratory organs surface (the human lungs square is 90 m^2);

- development and differentiation of the respiratory ways, formation of a bronchial “tree”;
- formation of a thoracic cavity and appearance of a diaphragm.

The transfer of Vertebrates to an active life demands a high level of oxidizing processes in the organism. It requires a progressive reconstruction of the respiratory system.

Branchiae in *Fish* were formed, when brancial lobes appeared on interbranchial septa. Branchial arteries form a net of capillaries in these lobes. In *some species of fish* the function of respiration is fulfilled by a swimming bladder, the walls of which are rich in blood vessels.

In *Amphibia* an organ of the ground respiration appears — the lungs, which are homologous to a swimming bladder in Fish. They are thin-walled sacks with a cellular structure. There are choanas (internal nostrils) and a pharyngo-tracheal chamber. The respiration function is also fulfilled by the skin that has a great number of blood vessels and mucous glands.

The lung structure in *Reptiles* becomes more complex. There appear a multiple of cellular bars on their walls, where blood vessels pass. It considerably increases the respiratory surface of the lungs. There are changes in the respiratory ways too: cartilaginous rings in the trachea and branched bronchi. The thoracic cavity is formed, intercostal muscles develop.

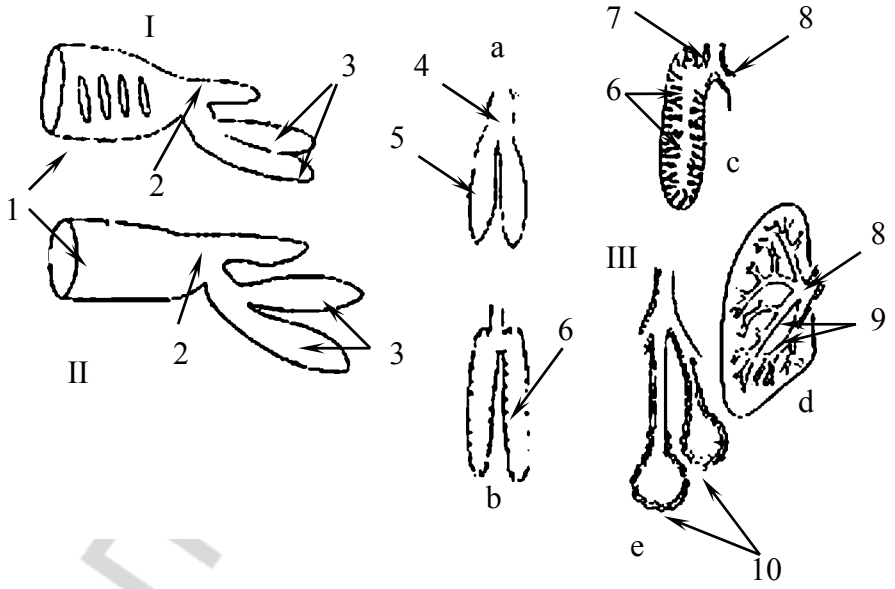


Fig. 46. Evolution of the lungs in Vertebrates:
I — a pharynx and a swimming bladder (lungs) in crossopterygian fish; II — the pharynx and the lungs in Amphibia; III — the lungs: a — a caudate amphibian; b — a caudateless amphibian; c — a reptile; d, e — a mammal. 1 — a pharynx; 2 — an unpaired chamber connecting the swimming bladder with the pharynx; 3 — sacs of the swimming bladder; 4 — a pharyngo-tracheal chamber; 5 — lung sacs; 6 — interlung septa; 7 — a trachea; 8 — a bronchus; 9 — bronchial branches; 10 — alveoli

In *Mammals* (fig. 46) the formation of a bronchial tree is completed; there appear bronchi of the 2nd, 3rd and 4th orders, bronchioles and alveoli. Gas ex-

change occurs in capillaries of alveoli, the number of which in humans is approximately 500 million. The thoracic cavity is limited by the diaphragm, it participates in respiration. Respiration ways start with a nasal cavity followed by a nasal pharynx and larynx (a shield-like cartilage appears there).

Ontophylogenetically conditioned development defects of the human respiratory system:

- underdevelopment of the pharynx or lungs;
- impairment of bronchial branching;
- hypoplasia of the lungs (decrease of the volume);
- trachea stenosis.

EVOLUTION OF THE CIRCULATORY SYSTEM IN CHORDAATE ANIMALS

The circulatory system is germinated from the mesoderm. It consists of the heart and blood vessels.

Functions of the circulatory system:

- Participation in gas exchange (transfer of oxygen and carbon dioxide);
- Trophic (transfer of nutrients to cells and tissues); excretory (transfer of dissimilation products to kidneys);
- Humoral (transfer of hormones and biologically active substances);
- Protective (phagocytosis and anti-bodies formation);
- Thermoregulatory and homeostatic (maintenance of permanent body temperature and participation in sustaining homeostasis of the organism internal environment).

The circulation system of Lancelet's is locked, has one circulation. The pulsing abdominal aorta fulfills the role of the heart. Venous blood passes to interbranchial septa through the abdominal aorta and carrying branchial arteries; there it is saturated with oxygen. Arterial blood drains into carotid arteries through deferent branchial arteries (they carry blood into the frontal department of the Lancelet's body) and into the dorsal aorta, which distributes the arterial blood throughout the body. The venous blood is accumulated by paired frontal and back cardinal veins and discharges into the abdominal aorta. Lancelet has a developed portal circulation of the liver (fig. 47).

Evolution directions of the circulatory system:

- germination of the heart and its differentiation (from 2-chambered in Fish to 3-chambered in Amphibia and Reptiles, to 4-chambered in higher Vertebrates);
- increase of oxygen content in the blood (formation of the second circulation);
- transformation of arterial arches and differentiation of vessels branching off the heart.

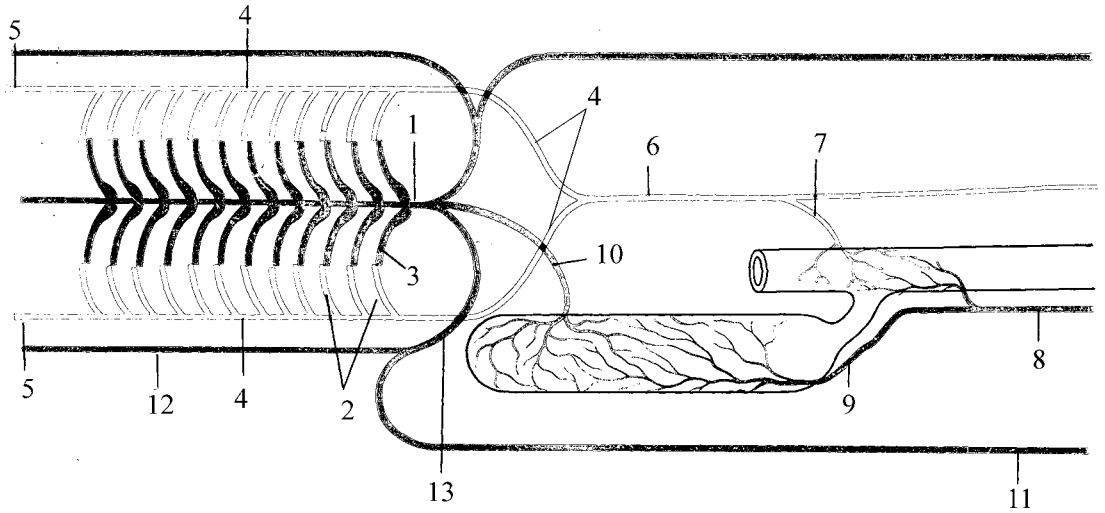


Fig. 47. The circulation system of Lancelet:
1 — the abdominal aorta; 2 — afferent branchial arteries; 3 — deferent branchial arteries; 4 — roots of the dorsal aorta; 5 — carotid arteries; 6 — a dorsal aorta; 7 — an enteric artery; 8 — a subenteric artery; 9 — a portal vein; 10 — a liver vein; 11 — a right back cardinal vein; 12 — a right front cardinal vein; 13 — a right Cuvier's duct

There appears a two-chamber heart in Fiish (an atrium and a ventricle). An arterial cone (its walls are capable of pulsating) goes off the ventricle and passes into the abdominal aorta. A venous sinus is located at the atrium. The heart contains venous blood. There is one circulation. Gas exchange occurs in branchiae. Arterial blood is carried by arteries throughout the body.

The circulation system becomes more complex, when lung respiration appears. The heart becomes 3-chambered (2 atria, one ventricle). A venous sinus adjoins the right atrium, an arterial sinus branches off the ventricle (fig. 48).

The right part of the *frog* ventricle contains venous blood, the left one — arterial blood. In the central part of the ventricle the blood is mixed. The blood brought through an arterial cone is distributed between three pairs of vessels: venous blood goes to the skin and the lungs through dermo-pulmonary arteries, the mixed blood – to all organs and tissues through the aortal arches, the arterial blood goes to the brain through carotid arteries. The second circulation appeared with the lungs.

The heart in Reptiles is 3-chambered, but an incomplete septum appears in the ventricle (in crocodiles the ventricular septum is solid). A pulmonary artery branches off the right part of the ventricle, the right aortal arch — from the left half. A left aortal arch branches off the central part of the ventricle. Venous blood goes to the lungs through the pulmonary artery. Arterial blood is carried to the brain and upper extremities by the right aortal arch. The mixed blood goes to all organs of the body through the left aortal arch.

Mammals have a 4-chamber heart, two circulations and a solid separation of arterial and venous blood. The right half of the heart contains venous blood, and the left one — arterial blood.

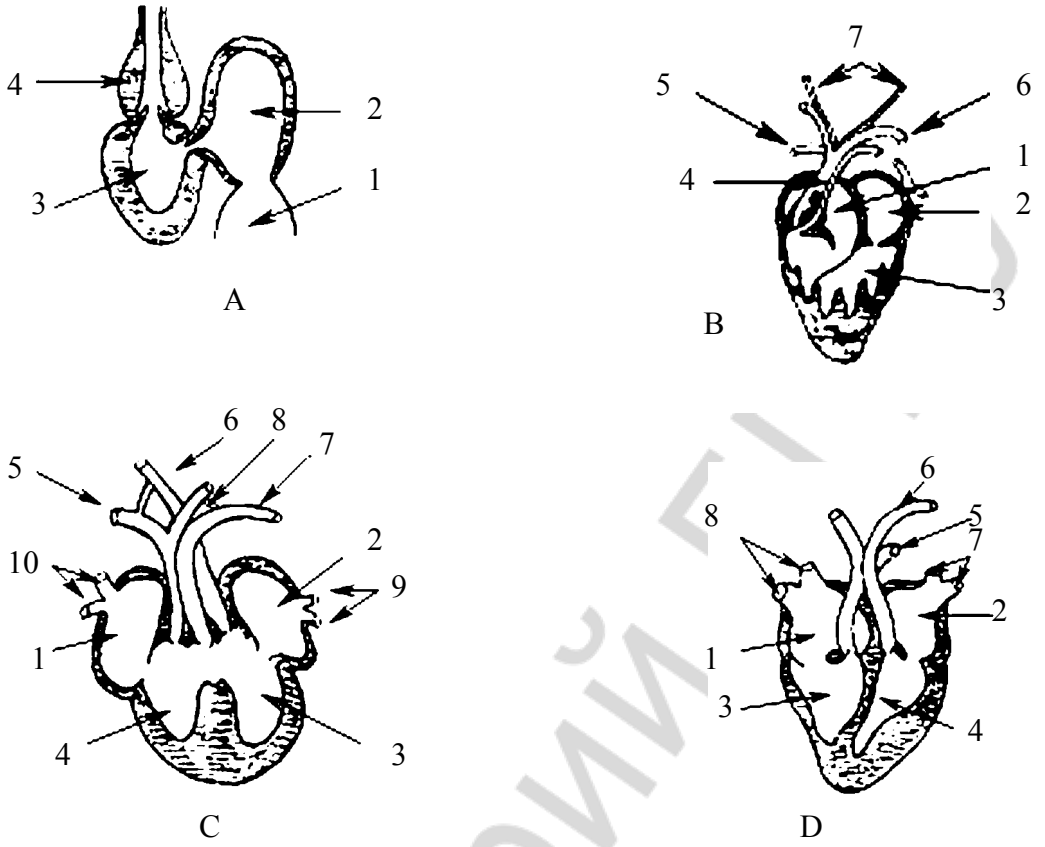


Fig. 48. The heart evolution in Vertebrates.
A — a fish: 1 — a venous sinus, 2 — an atrium, 3 — a ventricle, 4 — an aortal bulb; B — an amphibian: 1 — a right atrium, 2 — a left atrium, 3 — a ventricle, 4 — an arterial cone, 5 — a left cutaneous-pulmonary artery, 6 — a left arch of the aorta, 7 — carotid arteries; C — Reptiles: 1 — a right atrium, 2 — a left atrium, 3 — a left half of the ventricle, 4 — a right half of the ventricle, 5 — a right pulmonary artery, 6 — a right arch of the aorta, a left arch of the aorta, 7 — ; 8 — a left duct of Botallo, 9 — pulmonary veins, 10 — vena cava; D — Mammals: 1 — a right atrium, 2 — a left atrium, 3 — a right ventricle, 4 — a left ventricle, 5 — a left pulmonary artery, 6 — a left arch of the aorta, 7 — pulmonary veins; 8 — vena cava

In Ground Vertebrates 6 pairs of arterial arches are germinated. In the process of embryogenesis the 1st and the 2nd pairs are reduced, the 3rd pair gives carotid arteries, the 4th — forms arches of the aorta, the 5th pair is reduced, pulmonary arteries are formed from the 6th pair.

Ontophylogenetically conditioned development defects of the heart and vessels in the human:

- non-atresia of the interventricular and interatrial septa;
- formation of a 3-chamber heart, rarely — a 2-chamber heart;
- development of two aortal arches (the “aortal ring” envelopes the trachea and esophagus and constricts with age);
- non-atresia of the duct of Botallo (preserving the connection between the pulmonary artery and aortal arch);

- preservation of a common arterial trunk, which is not divided into the aorta and pulmonary artery by a septum (blood mixing).

EVOLUTION OF THE DIGESTIVE SYSTEM IN CHORDATE ANIMALS

The initial and terminal departments of the digestive system in chordate animals have an ectodermal origin, its central department — an entodermal one.

The designation of the digestive system is mechanical and chemical processing of food, splitting complex organic substances into monomers and their absorption into the blood and lymph.

The digestive system of Lancelet is presented by a tube that has two departments — the pharynx and intestines. The oral funnel is surrounded by tentacles; a mouth is in its depth. There pharyngeal wall is pierced with branchial slots. The intestine is not divided into departments; it terminates with the anus. A blind process of the intestines fulfills the function of the liver. Nutrition is active: water is filtered; food particles fall out in the endosteal (a deepening on the abdominal side of the pharynx) and are digested.

Evolution directions of the digestive system:

- differentiation of the digestive tube into the departments and its elongation;
- appearing of cilia in the intestines and enlargement of its absorbing surface;
- development of digestive glands; appearing and differentiation of teeth.

In the oral cavity of *Fish* are jaws where identical teeth are located (*a homodental system*), the tongue is primitive. Salivary glands are absent. The oral cavity is followed by the pharynx, esophagus, poorly developed stomach, small and large intestines, which are terminated with the anus. There is a well-developed liver, gall bladder and pancreas.

In *Amphibia* the oral cavity is not separated from the pharynx, they have a pharyngo-oral cavity. The dental system is homodental. There is a muscular tongue and salivary glands (the saliva does not contain digestive enzymes) in the pharyngo-oral cavity. One can mark out the esophagus, small and large intestines (ending with the cloaca). The liver and pancreas are well developed. Two new departments appear in the intestiness — duodenum and rectum.

The oral cavity in *Reptiles* is separated from the pharynx. The dental system is mainly homodental, in some reptiles venomous teeth are differentiated. Germs of the caecum appear on the border of a small and large intestine. The intestines end with the cloaca.

The highest differentiation of the intestines occurs in *Mammals*. The dental system is *heterodental*. The stomach has departments and digestive enzymes of various types. The length of a large intestine is considerably increased; the caecum and a vermiform process are developed. The intestinal wall has folds,

and the mucus of a small intestine — multiple cilia. All digestive glands are well developed.

Ontophylogenetically conditioned development defects of the human digestive system:

- the esophagus: stenosis, hypoplasia, atresia;
- the stomach: hypoplasia;
- additional hepatic lobes;
- germination of two rows of teeth;
- enlargement of the vermiform process length.

EVOLUTION OF THE EXCRETORY SYSTEM IN CHORDATE ANIMALS

The excretory system develops from the mesoderm. It consists of kidneys (the organs of excretion), the bladder and urinary ducts. Functions of excretory organs:

- formation of urine;
- participation in sustaining homeostasis, in regulation of blood pressure, blood volume and tissue fluid;
- synthesis of biologically active substances (renine, prostoglandines, etc.).

Evolution directions of the excretory organs:

- appearance of a compact excreting organ — a kidney;
- successive changing of three types of kidneys;
- evolution of a nephron: approaching to the circulatory system and elongation of renal canaliculi;
- enlargement of the renal absorbing surface at cost of increased number of nephrons.

The excretory system of Lancelet is presented by nephridias. There are up to 100 pairs of nephridias in the area of branchial slots, one end of which (a funnel) opens into the secondary body cavity, the other end (a short twisted canal) — into the parabranchial cavity.

A nephron is a structural unit of any kind of kidney.

A prokidney or a principal kidney — pronephos — functions in Fish and Amphibia. It consists of 6–12 nephrons. Every funnel (a nephrostoma) opens into a celom (fig. 49). Short canaliculi of funnels open into the pronephric canal which serves as a ureter. Not far from the nephrostoma in the celom wall is a vascular (capillary) glomerule. Metabolites get into the nephrostoma from the blood through the celom, then through a canaliculus into the ureter. The ureter opens into the cloaca.

A primary or bodily kidney — *mesonephros* — functions in adult Fish and Amphibia. It is germinated behind the prokidney and contains about 100 nephrons. In nephrons a growth of a canaliculus wall is formed around some part of a capillary glomerule; it looks like a 2-walled capsule. Here the dissimi-

lation products pass from the blood directly into the nephron canaliculus. They pass into the celom and then into the nephrostoma from the part of a capillary glomerule, which is not enveloped by a canaliculus process. The nephrons canaliculi are elongated and begin differentiation. At later embryogenesis stages the pronephric canal (the ureter of the kidney) splits longitudinally into two ducts — a Wolffian and a Muller's one. In females of lower Vertebrates the *Wolffian* duct transfers into a ureter, and a *Muller's* one — into an oviduct. In males of lower Vertebrates the Wolffian duct functions simultaneously as a ureter and a semen duct, while the Mullers's duct becomes atrophied.

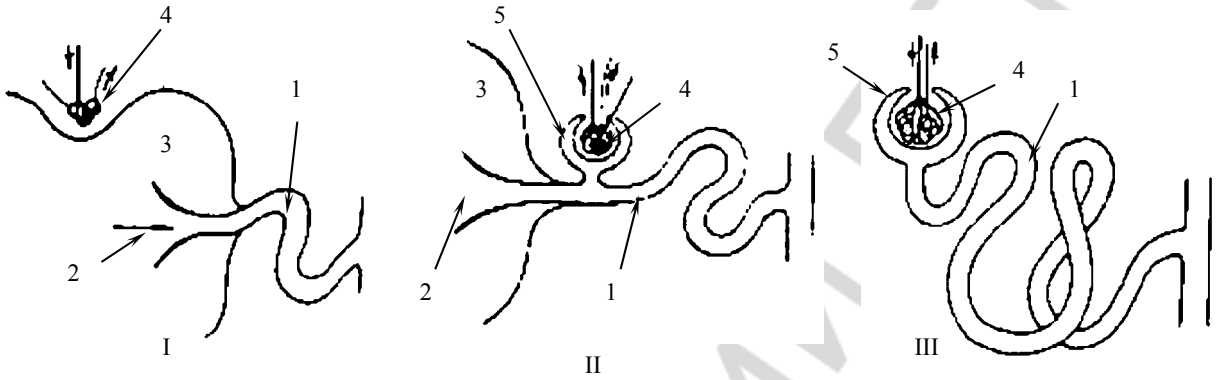


Fig. 49. Evolution of the nephron:
I — a nephron of the prokidney; II — a nephron of the kidney with an internal vascular glomerule; III — a nephron of the secondary kidney; 1 — a nephron canaliculus; 2 — a nephrostoma opening into the celom; 3 — a celom; 4 — a vascular glomerule; 5 — a capsule; 6 — a twisted canaliculus

In higher Vertebrates the secondary kidney is germinated behind the primary one, it is a pelvic kidney — *metanephros*. It contains about 1 million nephrons. The nephrons have no funnels, communication with the celom disappears completely. The nephron starts with a capsule, where a *vascular* Malpighian *glomerule* is located. Differentiation of canaliculus departments occurs: proximal and distal twisted departments of the canaliculus and a nephron loop. There occurs filtration in vascular glomerule, and in canaliculi — reabsorption of water, amino acids and glucose from primary urine into the blood.

The enlargement of the back part of the ureter forms a bladder. The wolffian duct in males of higher Vertebrates is transformed into a semen duct, the Muller's duct in females functions as an oviduct.

Ontophylogenetically conditioned development defects of the human excretory system:

- one or three kidneys;
- different levels of kidney position;
- double ureter (from one or from both sides).

EVOLUTION OF THE GENITAL SYSTEM IN CHORDATE ANIMALS AND ITS ASSOCIATION WITH THE EXCRETORY SYSTEM

The genital or reproductive system has a mesodermal origin. The majority of chordal animals have separate sexes.

Evolution directions of the genital system:

- from hermafrodism to separate sexes and sexual differentiation;
- from external insemination to internal one and intrauterine development;
- development and differentiation of sexual ways.

There are about 25 pairs of gonads (sex glands) in Lancelet, which have no sexual ducts. Gametes get into a parabranchial slot through ruptures in gonads walls, then they pass into water, where fertilization and development of the embryo takes place. The development goes with incomplete metamorphosis.

Gonads in Vertebrates are germinated as paired folds on ventral margins of bodily kidneys. At first male and female gonads have identical structure, their specialization occurs later and communication with different parts of the excretory organs is established.

In females of lower Vertebrates an oviduct is formed from the prokidney ureter. The most complex differentiation of oviducts is in Mammals. They form 3 departments — uterine tubes, the uterus and vagina. In placental Mammals atresia of distal parts of oviducts at different levels gives different variants of the uterus:

- a simple uterus (half-apes, apes, humans, some bats);
- double uterus (rodents);
- a bicornuate uterus (predators, artiodactyla).

The ovary in Fish is usually un-paired, testicles are more often paired and have semen ducts. Deferent ducts in Fish are closely connected with excretory canals of the kidneys. In the majority of Fish *insemination is external*.

Deferent *semen ducts of Amphibia testicles* pass through the kidney and open into the ureter — a wolffian duct, which is a semen duct too. Ova of females pass into the body cavity and get into oviducts — Muller's ducts. Both Wolffian and Muller's ducts open into the cloaca. In caudalless Amphibia insemination is external, in caudal ones — internal.

In *higher Vertebrates* insemination is internal. In Reptiles paired gonads are germinated, but they develop irregularly. The left ovary is less developed in Reptiles.

Complication of the *genital system of mammals* is associated with formation of a placenta and intrauterine development. Dilatation of the back part of oviducts and their fusion form a uterus. In males of some Mammals, testicles may be in the abdominal cavity. Gonads of mammals are germinated in front of the kidney and then they move into the pelvis. Ovaries stay in the back part of

the abdomen, while testicles descend into an external sac-like formation — a scrotum — through the abdominal canal.

The phylogenetical relation of the excretory and genital systems is expressed by:

– the gonads of Vertebrates are germinated as paired folds on ventral parts of the primary kidney;

– canaliculi of the prokidney and its ureter form a funnel and an oviduct in females; a ureter of the primary kidney serves as a semen duct in males (fig. 50).

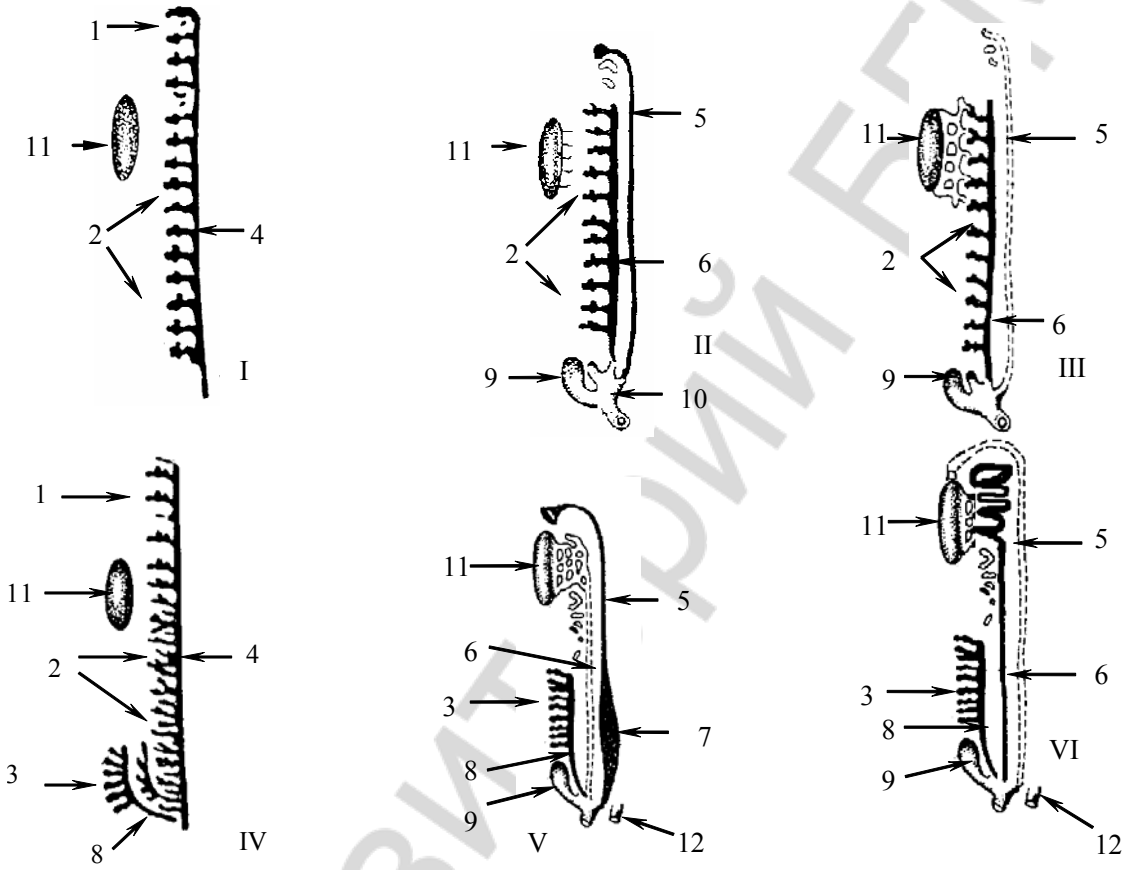


Fig. 50. The development of the excretory and genital systems in Vertebrates:
I — a neutral embryonic state in a lower Vertebrate; II — a lower vertebrate female; III — a higher vertebrate male; IV — a neutral embryonic state of a higher Vertebrate; V — a higher Vertebrate female; VI — a higher Vertebrate male. 1 — a pronephros; 2 — a mesonephros; 3 — a metanephros; 4 — a pronephric canal; 5 — a Muller's duct serving as an oviduct in females; 6 — a Wolffian duct serving as a semen duct in males; 7 — a uterus; 8 — a ureter; 9 — a bladder; 10 — a cloaca; 11 — a gonad; 12 — an anus

Otnophylogenetically conditioned development defects of the human genital system:

– a true hermaphrodism (development of both gonads);

– underdevelopment of uterine tubes; impairment of Muller's ducts atresia (anomaly in the uterus structure and vagina);

– anomaly of testicles position (they do not descend into the scrotum).

ONTOPHYLOGENETIC CONDITIONING OF DEVELOPMENT ANOMALIES (DEFECTS) OF ORGAN SYSTEMS IN CHORDATE ANIMALS

Ontogenesis and morphogenesis reflect the evolution history of the animal world development. Historic interrelations of organisms are the basis of their systematization.

The *Chordata* phylum — Chordates in divided into subtypes: *Acrania* — and *Craniota* (*Vertebrates*). The Vertebrates subphylum is divided into the lower Vertebrates **(**Anamniota) and higher Vertrebrates (Amniota). Anamniota include the Cyclostomats, Fishs and Amphibians classes. Amniota include the Reptiles, Birds, Mammals classes.

The class of Mammals includes orders: Bats, Rodents, Predators, Carnivora, Whales, Artiodactyla, Inarctiodactyla, Primates, etc.

In some development defects and diseases there appear signs in the human that are characteristis of other systematic categories close in phylogenesis (to orders or classes of the Chordate phylum).

The presence of such signs can be explained by the following ontophylogenetic mechanisms: recapitulations and parallelisms.

Recapitulations arise as a result of insufficiency or absence of anabolia. It is caused by the effect of environmental factors on the genotype of the developing organism. Due to their action gene blocks responsible for the development of specific development stages of some organ are not initiated in critical period of development. The examples of defects due to recapitulations are: defects of interventricular and interatrial septa, a 3-chamber heart, retaining of two aortal arches, etc.

Parallelism is an independent development of similar characters in the evolution of congenerous groups of organisms (for example, in humans and animals with familial origin). They arise by three ways:

1) a parallel development of characters abnormal for the human but normal for animals; for example, anomalies in the uterus structure and vagina (a bicornuate uterus is normal for predators, artiodactyla; a double uterus is normal for rodents);

2) a parallel development of characters abnormal for the human and animals, which are hereditary; for example, a cleft lip (abnormality for the human and mice) cyclopia (abnormality for the human and many animals);

3) a parallel development of similar diseases that are not hereditary; for example, thyroid cancer (in humans and dogs), nephroblastoma (in humans and sucking-pigs).

One more mechanism causing development defects is **convergence**, independent acquisition of similar characters by incongenerous organisms (for example, a lobster-claw hand in the human and in crawfish). But this mechanism is not ontophylogenetically conditioned.

LECTURE 21
Topic: HOMEOSTASIS AND CHRONOBIOLOGY

Plan

1. Homeostasis definition.
2. Chronobiology, its medical aspects.

Living organisms are in constant contact with their habitation. Environmental factors of their habitation are changing all the time. The organism adapts to them preserving the constancy of its morphology, physiology, physicochemical parameters of cells, tissues, tissue fluid and blood.

Homeostasis is the property of living systems to sustain a relative constancy of their internal environment and main organization features under changing surrounding conditions. The term "homeostasis" (Greek *homois* — identical; *stasis* — immobility) was introduced into biology by an American physiologist W. Cannon in 1932.

Homeostasis mechanisms provide thermoregulation, regulation of the blood pressure level in the organism and ions concentration in tissue fluids.

The following components participate in sustaining homeostasis:

1. *Substances*, which meet the demands of the cell (proteins, fats, carbohydrates, oxygen, inorganic compounds, etc.).
2. *Environmental factors* affecting cellular activity (osmotic pressure, temperature and concentration of hydrogen ions).
3. *Mechanisms* ensuring structural and the organism functional integrity (heredity, regeneration and repair, immunobiological reactivity).

From the point of view of cybernetics, a science about control, a living organism is an interaction system of input (a stimulus, irritant, cause) and output (an effect, reaction, response) variables (diagram 15). The system is a sum of all elements meeting a definite behavioral law. The basis of the system functioning is registration of variables deviations at the output depending on the information received at the input. For all that, the system behavior changes according to the information coming to the control block through feedback channels.

A positive feedback enhances the action of input variables. This connection gives instability of the system and extreme conditions. A negative feed back weakens the action of input variables. In living organisms, a negative feedback enhancing the system stability is widely spread.

Levels of homeostasis:

- *molecular-genetic*: DNA molecular repair, regulation of operon and transcripton functioning;
- *cellular, tissue, organ*: regeneration processes (mitochondria cysts, myofibrils. Cisterns of Golgi's complex, increase of the organiod number, cellular division, modifications of cells and intercellular substance);
- *organism*: neurohumoral regulation and the organizing role of the nervous system;

- *population-specious*: the action of Hardy-Weinberg's law;
- *biocenotic*: celf-regulation of the population number;
- *biospheric*: ensures a dynamic balance of living systems with the environment by trophic connections (nutrition chains) and circulation of substances in nature.

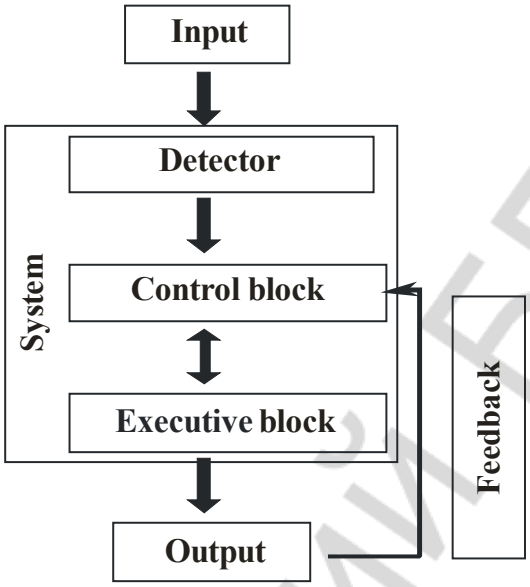


Diagram 15. Basic components of the control system

Adaptation of a biological system to changed conditions of internal or external environment has in its basis a "metabolic adaptation" — quantitative changes of metabolic process in cells.

Ensuring the constancy of internal environment of the organism and discontinuous adaptations to constantly changing external conditions occurs due to the action of the nervous and endocrine systems. *The nervous system* provides quick changes of the organism state. *The effect of hormones* acts slower bur stays longer (diagram 16).

Immune mechanisms of homeostasis provide the organism defense from alien genetic information (viruses, bacteria, protists, helminthes, proteins and modified cells of the organism itself). Homeostasis is regulated by the immune system consisting of the thymus, spleen, lymphatic nodes and red bony marrow.

The organism reacts to unusual and strong effects of external environment with *a stress-reaction* (stress), which changes the condition of the majority organ systems. The stress-reaction includes: the cortex of the brain, hypothalamus, hypophysis, adrenal glands (they excrete adrenalin).

Stress-reaction stages:

1) mobilization of defense mechanisms;
2) improvement of the organism resistance;
3) exhaustion of defense mechanisms.

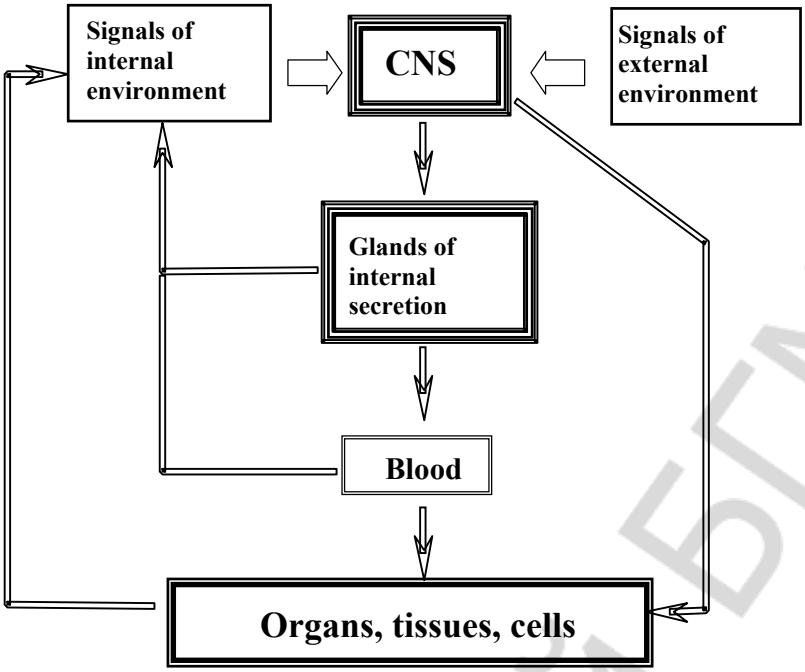


Diagram 16. Neurohumoral mechanisms of homeostasis

The 1st and 2nd links preserve homeostasis mechanisms, appearing of the 3rd link processes causes failure of homeostatic mechanisms and development of pathologic changes in the organism.

Homeostasis mechanisms are maximally reliable in mature age. In childhood and in the process of aging their efficiency decreases and in this period of ontogenesis general resistance of the organism to the action of unfavorable environmental factors becomes less.

CHRONOBIOLOGY, ITS MEDICAL ASPECTS

Living organisms are surrounded by inanimate nature characterized by rhythmic processes. Rhythms are repeated deviations and return to the initial state in equal time intervals. For example, alternation of day and night, taking turns of seasons. Living organisms have adapted to them — rhythmic processes of vital activity or biological rhythms (biorhythms). Rhythmic processes are at all organization levels of living things — from a molecular-genetic to biospheric.

K. Barr was the first who formulated the problem of biologic time in 1861. The time associated with live phenomena is biological time. Chronobiology, a section of Biology, studies biological time and biorhythms (Greek *chronos* — time).

When rhythms are regulated by external factors, they are *exogenic* rhythms. *Endogenic rhythms* are regulated by internal factors. More often rhythms are mixed.

In many cases the main external regulating factor of functional rhythmic activity of living organisms is changes of light day duration (a *photoperiod*). For

example, flowers of the majority of plants open in the morning and close in the evening; Drosophilae come out of a chrysalis at dawn; 59 % of deliveries take place at night.

There are 5 types of biorhythms:

The 1st type — *rhythms of high frequency* (from fractions of a second to 30 minutes); examples: heart contractions, respiration movements, peristalsis of the intestines;

The 2nd class — *rhythms of moderate frequency* (circadian — from 30 minutes to 28 hours); examples: changes of respiration and growth in plants; changes of activity in animals (day-time and night-time animals). About 69 physiological processes of the human are associated with circadian fluctuations, the digital amounts of which can change during 24 hours by 3–5 and more times. Examples of different circadian rhythm of physiological functions in the human:

- contractile myocardial function is higher at day-time;
- maximum temperature of the body is at 18 o'clock;
- arterial pressure in the human is higher at day-time, at night it is lower;
- blood coagulation is higher at day-time;
- cellular division speed is more intensive in the morning than at night.

People can be divided according to their workability fluctuations into:

	"larks"	"doves"	"owls"
♀	25 %	50 %	25 %
♂	50 %		50 %

It is explained by the fact that a genetic marker of the human circadian rhythm is localized in an X-chromosome.

The regulation of circadian rhythms is accomplished at a hypothalamus level.

The 3rd class is *month rhythms* (an example: periods in women);

The 4th class is *annual or seasonal* (from some months to 1 year): Light, the length of a light day is its synchronizer. Examples: transmigration of birds; winter and summer hibernation in animals; maximum activity of adrenal glands in the human in summer; arterial pressure is higher in an autumn-winter period; incidence of bronchial asthma attacks is higher in January and April and less in summer months.

The 5th class — *rhythms of low frequency*: 3, 7, 11, 80–90-year changes of solar activity. With them are associated:

– 3-year rhythms of tuberculosis recurrence incidences in humans;

– epidemics of some infectious diseases; cardio-vascular and psychic diseases (their number increases at maximum solar activity). The dependence of physiological processes on solar activity cycles is studied by *heliobiology*.

There is a lot of data about the influence of the Moon and its phases on living organisms in literature. The Moon phases are repeated in 29, 53 earthly days. The Earth surface ascends 35,6 cm maximum and descends 17,8 cm *under*

the influence of the Moon. *Under the influence of the Sun*, ascending of the surface is 16,4 cm and descending — 8,2 cm. It is the Earth's "respiration" under the action of gravitation.

The human workability, irritability of his nervous system, irritation rise during a full moon. And there is marked weakness, lowering of activity, creative energy and abilities during a new moon. Association of psychic diseases with the Moon phases was authentically proved. The least frequency of child birth is marked in a new moon, the greatest — in a full moon.

From the moment of birth 3 activity cycles are marked out in every human:

1 — *physiological* activity (23-day periodicity);

2 — *emotional* activity (28-day periodicity);

3 — *intellectual* activity (33-day periodicity).

There is a critical (zero) day in the middle of every period.

The first half of the cycle is a positive period, the 2nd half of the cycle is a negative period. All critical days coincide once a year.

Applied sections of chronobiology are chronomedicine and more common sections — chronopathology, chronopharmacology, chronotoxicology and chronotherapy.

A *chronobiological* approach allows predicting exacerbations of chronic diseases and acceleration of patients' recovery.

Chronomedicine studies biological rhythms of a healthy and sick organism.

Chronopathology studies changes in the organism in the impairment of biorhythms. Discordance of biorhythms — *desynchronosis* — may be a sign of pathology in the organism or it may lead to some pathology. It causes gastritis, ulcers, tumors, nervous impairments. Desynchronosis produces a considerable effect on person's workability.

Chronopharmacology studies various efficiency of medicines at different time of the day — sensitivity may fluctuate from 0 to 100 %. Studying the organism sensitivity to medicines at different time of the day is the subject of *chronotoxicology*. Foe example, application of cyclophosphan at 18 o'clock increased the frequency of curing mice from leucosis by 5 times as compared to its effect at 9 o'clock. Taking into consideration chronobiology, chronotherapy should revise medicines' doses, their administration at time, when they are most effective. For example, to prevent cardiac asthma and lung edema, which occur more often at night, the increasing of glycosides and prednisolone doses should be done not in the morning but in the evening.

Achievements of chronobiology and chronomedicine are used for elaborating *chronoprophylactic measures*:

– compilation of day chronograms of a norm;

– taking into account biorhythms for making up a rational regimen of work and rest, rational nutrition of people of various occupations — workers of night shifts, pilots and cosmonauts;

– prognosis of exacerbations of various diseases; settling the problems of acclimatization and adaptation.

LECTURE 22
Topic: REGENERATION AND TRANSPLANTATION OF ORGANS AND TISSUES

Plan

1. Regeneration: its forms, levels and methods.
2. Transplantation of organs and tissues.

Regeneration (from greek *regeneratio* — restoration) — restoration of lost structures by the organism itself.

The first experiments on regeneration were carried out by a French scientist R. Reomur in 1712 (he obtained regeneration of a craw-fish claw); in 1740 a Switzerland investigator A. Tramble described regeneration of a hydra.

FORMS OF REGENERATION

Physiological regeneration is inherent in all organisms. In the process of vital activity disruption of definite structures and their necessary restoration takes place. For example, change of a chitin covering or molt in arthropoda, shedding of feathers and hair in birds and mammals, molt in snakes, replacement of epithelial cells of the gastrointestinal tract (almost every day). Renewal of blood cells is going on too. Every second about 4 million erythrocytes die in the human body and almost the same quantity are formed in the red bone marrow.

Physiological regeneration is a process of cellular renewal.

According to their regeneration ability cells are divided into:

- *Labile* (epithelial cells of the skin and gastro-intestinal tract);
- *Stable* (hepatic cells);
- *Static* (nerve cells).

Restorative regeneration is restoration of organs and tissues destroyed or lost as a result of a trauma or pathologic changes. Restorative regeneration is due to impairment of the organ or tissue structural integrity (for example, restoration of the lizard's tail). Physiological and restorative regeneration have qualitatively identical mechanisms. Any disease starts with the impairment of physiological regeneration. Restorative regeneration is a response to this impairment.

Pathological regeneration: there are formed tissues, which are not identical to the lost ones (a scar tissue is formed at the site of a burn).

REGENERATION LEVELS

1. The "*lowest*" level of regeneration is molecular or biochemical regeneration. It is renewal of chemical cellular components, its molecular composition (for example, restoration of DNA molecules).

2. The next level is *subcellular regeneration* or ultra-structural: restoration of the initial structure of organoids, which were impaired by pathogenic factors or functional overstrain. Restoration of mitochondrial chrysts, Golgi's complex cisterns, regeneration of integral organoids are possible.

3. *Cellular regeneration* is a mitotic or amitotic cellular formation instead of destroyed ones (replacement of epithelial cells). One of their forms is cellular hypertrophy.

4. *Tissue or organ level of regeneration* (for example, regeneration of muscles and the lizard's tail). Compensatory hypertrophy at an organ level means that a destroyed organ is not restored, but its remaining part grows or the enlargement of one of paired organs occurs when the other is affected (examples: the liver, kidneys of mammals).

5. *Organism level* of regeneration. Some species of lower animals are capable of restoring the whole organism from its small part. For example, 1/200 part may restore the whole hydra, or 1/450 part of the planarian's body restores the whole organism. A ring worm can be cut into some parts, and each part will restore the whole organism. According to B.P. Tokin (1958), these cases present examples of somatic embryogenesis — the development of a new organism from separate somatic cells or their groups. It is a variety of vegetative multiplication in lower animals.

METHODS OF RESTORATIVE REGENERATION

Restoration of the organ after its structural integrity impairment occurs in different ways.

The presence of a wound surface, where regeneration processes occur, is a necessary condition.

1. Epimorphosis (extension) — regeneration, when a lost organ grows from the wound surface. Cells multiply forming a regeneration germ. Differentiation of cells restores the organ. An example: restoration of the lizard's tail.

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

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

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

Regeneration may be typical (restoration of one extremity after its amputation in lower vertebrates) — it is called *homomorphosis* — and atypical (*heteromorphjosis*).

Forms of atypical regeneration:

- *Heteromorphosis* — a new organ is formed at the site of a lost one (a feeler in a craw-fish instead of an eye; an extremity instead of a feeler);
- *Hypotypia* — incomplete development of a regenerating organ (a less number of fingers on the extremity);
- *Hypermorphosis* — redundant regeneration (a greater number of organs, redundancy of bony tissue at the site of a fracture);
- *Substitution or a full regeneration*: if the parenchyma is necrotized in the liver, a full regeneration is possible; if the stroma dies — a scar tissue forms, a dense connective tissue from collagen fibers.

A scar tissue or a scar is the result of pathologic tissue regeneration. The significance of scarring is closing of a pathologic foci or its isolation from surrounding healthy tissues.

It is necessary to differentiate regeneration and regenerative ability. For example, regeneration may not occur in denervation of the organ (when a nerve is cut), though a regenerative ability is preserved. The regenerative ability sharply varies not only within one type or class, but within a genus, family and order. That is why a position of the animal in the system does not determine the level of its regenerative ability.

"Progress" in the animal world was followed by continuous development, differentiation and complication of regenerative ability forms.

All *arthropoda* have the ability to regenerate eyes, feelers, parts of the oral apparatus, extremities, branchial apparatus, and some representatives can regenerate back parts of the body.

Mollusks are capable of regenerating a shell, mantle, siphon, tentacles, eyes, branchii and head parts (when a cerebral ganglion is preserved). Fish regenerate scales, fins, lower jaws, parts of a body wall; caudal amphibian — a tail, extremities, skin, spleen, liver, lungs, gonads; birds — skin, parts of the beak, muscles, bones, parts of the liver, ovaries and testicles.

Mammals can regenerate the skin, epithelium of internal organs, eye cornea, liver, parts of ovaries, kidneys, spleen, lungs, and endocrine glands.

In vertebrates the regenerative ability is limited by internal organs and physiological regeneration. The initial shape of organs is often not restored and in the site of injury a scar is formed.

Regenerative processes in the central nervous system and in myocardium are expressed only in intercellular regeneration at cost of the enlargement of the organelles mass in preserved cells.

The efficiency of regenerative processes depends on many factors. In mammals and humans regenerative processes run more actively at young age, by old age they become weaker. Denervation and X-rays *inhibit regeneration processes*. Nuclear acids, hormones, introduction of tissues into a regenerating organ *stimulate regeneration*. An example: "bone dust" in case of regeneration of a bony tissue. When the skull-cap bones are restored in the human, bone dust mixed with blood is introduced. In a week this mass is dissolved, and the excreted substances stimulate transformation of connective tissue cells into bony cells.

When parts of the trachea, bronchi and large blood vessels are regenerated after their surgical excision, prostheses, carcasses are used.

Stem cells may serve as an origin of organ or tissue regeneration. They are unspecialized cells, which undergo asymmetric division in mitosis — one cell stays a stem cell and the second one transforms into a specific tissue cell. Besides, stem cells are capable of migrating to a zone of organ or tissue injury.

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

– *humoral* regeneration: action of hormones, prostoglandines and other biologically active substances on mitotic cellular activity;

– *immunological* regulation associated with transfer of "regenerative information" by lymphocytes; it stimulates proliferation (multiplication) of cells of various internal organs.

The regeneration problem is a part of a wider and more common problem of compensation and restoration of impaired functions.

TRANSPLANTATION OF ORGANS AND TISSUES

Transplantation is replanting of organs and tissues from one organism to the other. The beginning of transplantation was set in Italy, when in 1804 the skin was transplanted in sheep. In 1818 a German surgeon F. Reisinger transplanted the cornea in a rabbit. At the end of XIX century a Russian doctor V. G. Grigoryev was a success in transplanting the whole organ in female rabbits, the ovary; and he put the beginning of transplanting organs. In 1967 an American surgeon K. Barnard made the first operation for transplanting a human heart (the patient lived over a month).

At present they transplant kidneys, liver, lungs, endocrine glands; in plastic operations the skin, cartilages, muscles, tendons, blood vessels are transplanted to patients.

In the process of development and improvement of transplantation the doctors faced a serious problem of obtaining and conservation of organs for transplantation. In 1902 a Russian physiologist A. A. Kuliabko reanimated the human heart in 20 hours after death. The scientists discussed a possibility of using

cadaver material for transplantation, reanimation of isolated organs, freezing of tissues and organs (bones, cartilage, eye cornea, bone marrow). The first in the world transplantation of a kidney from a cadaver was performed by a Russian surgeon V. V. Voronoi in 1934.

TYPES OF TRANSPLANTATION

A transplanted part of an organ or tissue is called a transplant. The organism, from which the tissue for transplantation is taken, is called a *donor*; the organism, where the transplant is transplanted, is a *recipient*.

Autotransplantation is transplantation of one's own organs and tissues; for example, the skin in burns.

Homo- (or allo-) transplantation: both a donor and a recipient are individuals of the same species. An example: blood transfusion in humans.

Hetero- (or xeno-) transplantation: a donor and a recipient belong to different biological species; in such cases the transplanted organ, as a rule, is not accepted due to a reaction of tissue incompatibility.

In 1923 a Russian surgeon N. V. Sokolov proved that the transplant acts upon the organism of a recipient as an antigen and causes a response with formation of antibodies. A rejection reaction occurs and the organ does not get accepted.

In 1958 a French immunologist J. Dosse isolated the first *transplantation (leukocytic) antigen* — in short TLA. At present over 40 TLA are isolated, which play an important role in reactions of tissue incompatibility. The content of TLA in various tissues is not alike, that is why the transplantation immunity behaves differently depending on transplanted tissue. Rejection reactions are not clearly marked, when the bone or cartilage is transplanted, stronger — when the skin or different organs are transplanted. Of all organs the bone is an ideal biological prosthesis by which one's own structure is restored.

For successful transplantation of organ and tissues it is necessary to settle such problems as prevention of transplant rejection and obtaining donor's organs.

There are the following ways of overcoming tissue incompatibility:

1. Selection of maximum compatible tissue among close relatives of the recipient: a) according to *blood group*; b) according to *transplant antigens*, which are contained mainly in lymphocytes; these are HLA systems (human lymphocyte antigen) and histological compatibility of tissues connected by receptors on the surface of cells, which recognize "own – foreign"; their genes are localized on a short lever of the 6^{th} chromosome — 6p23.

2. Suppression of tissue incompatibility by immune-suppressive methods: removal of the spleen and thymus, injection of ALS (anti-lymphocyte serum), injection of corticosteroids and anti-metabolites suppressing protein synthesis; simultaneously a general immunity is suppressed, which increases the risk of oncological diseases.

3. Exposing the bone marrow and lymphatic glands to X-rays — transplant rejection is slowed down at cost of suppressing of T-lymphocytes formation, but the defense function of blood becomes weaker and there is a risk of various infections.

4. Injecting *monoclonal anti-bodies*, which recognize and destroy transplant antigens, into the recipient's blood or red bone marrow.

The ways of obtaining organs and tissues for transplantation are different. *Conservation of cadaver material* is widely used: bones, skin, cartilage, vessels, nerves, hard cerebral membrane, cornea, etc. It is possible to cultivate isolated organs on special physiologic solutions (isolated fingers, ear flaps, some glands). Now they create and apply *artificial organs* during transplantation: heart valves, electric cardiostimulators, joints prostheses, which may work from the patient's bio-impulses.

The most perspective may be *"growing" of organs* for transplantation (by cloning human cells).

Transplantation of organs and tissues in the human is associated with a mass of legal and moral-ethical issues, when there is a necessity to take a transplant from a perished or deceased person, or one of paired organs (for example, a kidney) from a close relative.

LECTURE 23
Topic: THE BIOSPHERE AND THE HUMAN

Plan

1. The biosphere and its structure.
2. Evolution of the biosphere.
3. Interrelations of the human and nature.
4. Medico-biological aspects of the biosphere. Protection of the environment.

THE BIOSPHERE AND ITS STRUCTURE

Jan Batist Lamark was the first to define the *biosphere as an aspect of life* (Latin *bios* — alive, *sphaira* — region, ball). In 1875 an Austrian geologist E. Zuss called the biosphere a special envelope of the Earth, which is formed by living organisms. In 1920s a Russian academician V.I. Vernadsky elaborated a study about the biosphere and a geological role of living organisms in the history of our planet. He wrote, "*The biosphere* is a field of active life, an integral self-regulating open system, a general planet envelope; it became isolated by the development of life on the Earth"

The biosphere border limits spreading of living organisms in three envelopes of the Earth — air, water and stone.

An aerial envelope *of the Earth* includes lower atmospheric layers: 8–10 km in polar latitudes and 16–18 km at the equator. *Its composition* consists of gas-like substances (oxygen, nitrogen, carbon dioxide and ozone), water vapors, cosmic particles and dust particles from the Earth. *Limiting factors of* spreading living things are ultraviolet radiation, low temperature, insufficiency of water and oxygen. Spores and bacteria are mainly met here. To the altitude of 7 km birds (for example, eagles) may rise, in mountains (up to 6 km) one can observe insects and some species of plants.

A water envelope of the Earth is called the hydrosphere of the world ocean (it takes 70.8 % of the globe surface). A medium depth of the world ocean is 4 km, a maximum one — up to 11.5 km. The first life appeared in the ocean. *Water* is an important part of all components of the biosphere. It is necessary for existence of living organisms. The world ocean is a warmth regulator: it accumulates warmth fast and gives it back slowly. It is also an energy transformer. The solar energy is transformed into the energy of chemical compounds by autotrophic water organisms. Transformation of energy occurs, when water is evaporated from the ocean surface in the process of tides. *Limiting factors* for living things in the ocean are water pressure, oxygen content and light penetration. The depth of 200 m is most saturated with life. In the thickness of water habituate organisms of plankton in weighted state and passively carried by the flow. They may be unicellular seaweeds, representatives of lower crustacean (daphnia, Cyclops), larva of various species of living organisms. Organisms living a bottom life come into the group of bentos (representatives of multicellular seaweeds, sponges, echinodermata, coelenterate, mollusks and fish).

Stone or hard envelope of the Earth is called the lithosphere. Its extension is up to 100 km. An upper layer is represented by sedimentary rocks and granite, the lower one — by basalt. A *soil layer* in the lithosphere (about 10 m) is the inhabitance of many animals. *Penetration of living organisms* into the lithosphere depth is limited by high temperature, absence of light and pressure. It is the soil that connects everything into an integral biosphere. It is the habitation of many species of bacteria, protists, animals and practically all plants. Circulations of all chemical substances and their compounds in nature are associated with soil.

The biosphere substance:

- living substance (the sum of all living organisms) — 0.25 % of all biospheric substance;
- biogenic substance produced and processed during life activity of organisms (atmospheric gases, oil, coal, etc.);
- bony substance formed without participation of living organisms (products of tectonic activity);

- dispersed atoms and molecules formed from earthly substance under the influence of cosmic rays;
- substances released in radioactive break-down;
- substances of a cosmic origin as molecules and atoms.

By V. I. Vernadsky, "living substance" is all living organisms of the biosphere. Their main functions are binding and storing of solar energy and providing geochemical processes in the biosphere. The living substance consists of 500 thousand of prokaryotic plant species of 30–60 thousand protists, about 100 thousand of fungi and 2 million species of animals. Living organisms in the process of photosynthesis on the planet synthesize 46 billion t of organic carbon containing substances and 123×10^9 t of oxygen.

Biological structures of the biosphere

Organisms (individuals) of definite species are united into *populations*. *Biogeocenoses* contain populations. Trophic links are a functional similarity basis of biogeocenoses. The system "atmosphere – soil – plants – animals – microorganisms – atmosphere" is constantly functioning in biogeocenoses. The circulation of chemical elements goes on thanks to this system. V. V. Dokuchaev called it a biogeochemical circulation. Interrelations of biological systems in the biosphere help understand the mechanism of ecological homeostasis: impairments in one system result in impairments of other interrelated systems.

EVOLUTION OF THE BIOSPHERE

The first stages of the biosphere evolution went on under the effect of natural geoclimatic changes and changes of the species content and the number of living organisms. Later with the advent of human society, an anthropogenic factor joined them.

6 stages of the biosphere evolution are marked out:

1. *Coming into existence and development of life in wate*r — the first organisms were hydrobionts. The biosphere formation started.

2. Parasites and symbionts appear in hydrobionts. *The host organism, a new life environment, is formed*. There appear a photosynthesis, oxidative atmosphere and aerobic microorganisms.

3. *Organisms come from water onto land* and assimilate the land-aerial living environment and soil. The soil is being formed.

4. *All living environments are developing* — water, soil, air and organism. *The human appears*. He becomes a biosocial being. *Biogenesis* (evolution under the action of biological factors) *goes into sociogenesis*.

5. The laws of nature are intertwined with social-economic laws of the society — *a social stage of evolution is going on*. A new envelope of the Earth, the *noosphere*, is being formed.

6. With the advent of the noosphere, *sociogenesis is replaced by noogenesis*. The human becomes a mighty geological power in the biosphere.

The term "**noosphere**" was suggested by French scientists-philosophers E. Lerua and P. Teyar de Charden in 1927. They defined the noosphere as "*the sphere of intelligence*". In 1944 V. I. Vernadsky in his work "Some words about the noosphere" gave a more detailed definition, "the *noosphere* is a development stage of the biosphere connected with the advent of humanity. It includes the human society with its technique, science, culture, language and various kinds of intelligent activity".

INTERRELATIONS OF HUMANS AND NATURE

There are two aspects of human activity: biological and chemical. They are expressed as an "Anthropogenic press", which results in exhaustion of natural resources, contamination of the environment and misbalance of ecological homeostasis.

Contamination of the environment affects the gene pool of the planet (of humans, animals and plants). Anthropogenic changes in the biosphere go on alongside with the Earth population number growth and decrease of natural resources (table 7).

Table 7

Natural resources

Exhausted		**Unexhausted**		
Impossible to restore: fossils, fresh water	Possible to restore: soil, variety of plants and animals	Waters of the world ocean	Resources of cosmic origin	Climatic factors: atmospheric air, energy of the wind, water and Sun

All history of the humanity development is the development history of mercenary attitude to nature. *The biological aspect of human activity* manifests in limiting the species content and extinction of animal species and plants. One animal species dies on the globe annually. 25 thousand of plant species, 600 species of birds and 120 species of mammals are under the threat of extinction. The reasons, which cause such state of nature, are a decrease of forest areas (cutting down of forests), extinction of animals (hunting, transport vehicles) and results of productive human activity (occupied areas for building towns and roads).

Zoos, preserves, national parks deal with restoration *of disappearing animal species*. Red books control the process of restoring the disappearance of animal and plant species.

Chemical contamination of the environment

Up to 2 thousand new chemical compounds are emitted into the environment annually; about 60 thousand of then affect the human. Anthropogenic

sources of contamination: burning of fuel (oil, coal, slates, gas, fire wood and peat); transport discharges (sulphur, nitrogen oxides, carbon dioxides); agriculture (processing of cattle-breeding wastes).

Chemical substances cause the ozone layer impairment. Climatic changes or a greenhouse effect is the result of accumulation of carbon dioxide in atmosphere (7 billion t are discharged into the atmosphere annually) and methane. Climate warming increases the number of droughts and forest fires. Green plants are killed by acid rains, which destroy chlorophyll. The forest destroyed by fire demands for restoration about 500 years. The area of world forests becomes 25 million hectare every year.

Contamination sources of salted and fresh water basins are different. Sewage waters of productive enterprises bring to the ocean salts of heavy metals, chlorides, arsenic and mercury. Domestic sewage waters contaminate fresh reservoirs on the coasts. Radioactive contamination is associated with underwater explosions, submarines and containers with radioactive substances located at the bottom of seas and oceans (17.5 thousand in Northern seas, 8 thousand in the Far East; up to 25 thousand containers in the North Arctic and Pacific oceans). Contamination of water basins affects water animals, kills fish, dolphins and all living things. Settling the problem of fresh water depends on cleanness of water reservoirs.

Acid rains, salts of heavy metals, radionuclides and chemical substances used in agriculture produce a negative effect on the soil covering of the Earth. Developments of fossils, water and wind erosion lead to *soil destruction*. 1000 years are necessary to restore the structure of 2.5 cm of destructed soil. Great territories are occupied by building cities and roads.

Military destruction of the biosphere also has heavy consequences. Bomb and shells explosions destroy soil, a green covering and all living things, Depth bombs, which were thrown into the ocean during World War II, have an action radius of 300 m. There have been developed special methods of "geophysical wars": artificial formation of ozone holes (an ultraviolet radiation flow goes to the Earth); conducting directed underwater explosions (to destroy coastal population settlements); using defoliants (to destroy a green covering). In 1965 during the war in Viet-Nam Americas poured down 42 million l of defoliants; they contained dioxin (cellular poison and teratogen), the period of half-decay of which in the human organism is 608 years.

MEDICO-BIOLOGICAL ASPECTS OF THE BIOSPHERE

J. Buffon at the end of the XVIII century and J. B. Lamark in the first half of the XIX century pointed out to unfavorable consequences of human activity on the biosphere. Anthropogenic impacts on the inhabitation environment may be positive and negative. At present *negative effects* predominate, and the hu-

manity faces the danger of *ecological crisis* — such a condition of the environment, which threatens human health and normal life.

Human ecology studies regularities of the biosphere development and the state of human populations, human effect on nature and influence of the nature on human health. Ecohygiene (geohygiene) is a study about people's health on the planet alongside with ecological situation and methods of its preservation and strengthening. Now a new section of human ecology, noogenetics, a science controlling interrelations between the human society and nature, is being developed.

According to WHO data, up to 80 % of human diseases are associated with one's way of life and the environment state. More than 1 billion of people breathe with polluted air. Respiratory disease brings away 3.5 million residents of the planet annually. Every lost percent of ozone of the planet at large increases the number of the skin cancer diseases by 2.6 % (every launching of a space ship, like Shuttle, destroys 0.3 % of ozone).

The main share of air pollution in cities (60–80 %) comprises exhausts of carbon and nitrogen oxides. CO sharply decreases oxygen absorption by blood and causes the development of bronchitis and asthma. Nitrogen oxidate destroys the lung tissue and causes cancer diseases.

23 % of all diseases and 25 % of cancer are caused by environmental effects.

Data on ecology and state of the population health in the Republic of Belarus are unfavorable. According to data of 2004, there were only 27 % of absolutely healthy school-children (in 1977 this factor was 33 %). Children suffer from hereditary pathology and development retardation. 95 % of parturient women have pesticides in breast milk. Women are noted to have miscarriages and preterm deliveries. The incidence of cardio-vascular, oncological and allergic diseases is growing.

After the Chernobyl accident the number of children with chronic pathology increased (by 22 %) in Belarus. The rate of oncological diseases in children increased by 50 times, in adults — more than twice.

Ecologists, analyzing the state of nature, say that in the nearest future *Homo faber* (a human productive) will annihilate *Homo sapiens* (a human intelligent).

Nature protection — is a system of scientifically based international, state and social measures directed to rational usage and restoration of natural resources, protection of the environment from contamination and destruction.
The tactics of nature protection:

1. Ecologization of policy and thinking. A number of organizations deal with issues of protection of the human inhabitation: UNO, UNESCO, MAGATE, International Union of biological sciences, Scientific committee for the problems of the environment, scientific program "Human and biosphere" (MAB) and

a number of other organizations. All educational establishments give students the bases of ecological education.

2. Development of legislative acts regulating interrelations of humans and nature, and control over their execution. They are laws about land, water, forests, etc. They are consolidated by the Constitution of the country.

3. Protection of genetic pool of all living world. It can be achieved, when the environment is clean, it has no contaminating substances, mutagens, cancerogens and teratogens.

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