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Chair of Medical Biology and Genetics

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Представлен лекционный материал по медицинской биологии и генетике, читаемый студентам факультета по подготовке специалистов для зарубежных стран, которые занимаются на английском языке.

Авторами представлены сведения о молекулярно-генетическом и клеточном уровнях организации живого, биологии и физиологии клетки, размножении организмов и репродукции человека, биологии пола.

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FOREWORD

The textbook represents the text of lectures at the course of Medical biology and genetics which has been reading for English-speaking students of faculty of specialists training for foreign countries of the Gomel State Medical University. The material of the textbook corresponds to the Program in Medical biology and genetics for students of medical faculty of the high medical educational institutions № 08-14/5941, authorized by Ministry of Health Republic of Belarus at September 3, 1997.

The section «Cytology and Genetics» of Medical biology and genetics course is included in the first part of the textbook. The section includes the following material: role of biology in system of medical education, cell level of the life, cytobiology, molecular-genetic level of living things organization, physiology of a cell, reproduction of organisms, human reproduction, biology of a sex, gene level of hereditary material organization, monogenic and polygenic inheritance, the genotype expression in the phenotype, chromosome and genome level of the hereditary material organization, diversity of organisms, bases of human genetics, human hereditary diseases, and principles of genetic counseling.

Authors will be rather grateful to everyone who will consider possible to state the critical remarks to address of offered methodical recommendations which will be perceived as expression of desire to assist in its improvement at the subsequent reprinting.

ПРЕДИСЛОВИЕ

Данное пособие представляет собой конспект текста лекций по курсу медицинской биологии и генетике, которые читаются студентам факультета по подготовке специалистов зарубежных стран УО «Гомельский государственный медицинский университет», обучающихся на английском языке. Материал пособия соответствует Программе по медицинской биологии и генетике для студентов лечебного факультета высших медицинских учебных заведений № 08-14/5941, утвержденной Министерством здравоохранения Республики Беларусь 3 сентября 1997 г.

В первую часть пособия включен раздел курса медицинской биологии и генетики «Цитология и генетика», который включает следующий материал: роль биологии в системе медицинского образования, клеточный уровень организации живого, биология клетки; молекулярно-генетический уровень организации живого; физиология клетки; размножение организмов, репродукция человека; биология пола.

Авторы будут весьма благодарны всем, кто сочтет возможным высказать свои критические замечания в адрес предлагаемых методических ре-

комендаций, которые будут восприняты как выражение желания оказать помощь в его улучшении при последующем переиздании.

LECTURE 1

Theme: The role of biology in system of medical education

Plan:

1. Biology — a science about a life. Role of biology in doctor's training.
2. Properties, attributes and levels of the living things organization.
3. Cytology — a science about the basic form of the living things organization. The cell theory and its modern condition. The cell — an elementary genetic and structural-functional unit of life.
4. Features of structure of pro- and eukaryotic cells. Karyotype.

1. Biology — a science about a life. Role of biology in doctor's training

Biology — a science about a life which studies a life as the special form of movement of a matter, laws of its existence and development. A subject of biology are alive organisms, their structure, functions, and also natural communities of organisms. The term «biology» for the first time has been offered to J. B. Lamarck in 1802, and occurs from two greek words: bios — a life, logos — a science. Together with astronomy, physics, chemistry, geology, etc. the sciences studying the nature, the biology concerns to number of natural sciences.

The biology is not uniform discipline. It is set at least 50 disciplines. Among these are:

a) morphological disciplines (anatomy, histology), describing a structure of organisms;

b) physiological disciplines (physiology of a cell, animals, plants);

c) general biological disciplines (cytology, genetics, evolution);

d) ecological disciplines (biogeography, parasitology);

g) boundary disciplines (biochemistry, biophysics, anthropology).

The biology as a science has saved up a huge actual material. Knowledge of essence of a life — one of the primary goals of modern biology.

The biology in second half of 20 centuries became a leading science. It becomes the leader of natural sciences, defines the basic directions of its development in medicine, ecology, genetics.

Biological disciplines represent a theoretical basis of medicine that has great significance for a doctor's training. On the basis of morphological disciplines develops pathology. Such especially applied sections of medicine as therapy, surgery are based on the data of anatomy, physiology, biochemistry. Epidemiology bases on achievements of ecology, zoology, parasitology, microbiology, and virology.

The role of biology is defined by formation of outlook on the basis of studying fundamental disciplines of cytology, genetics, medical biology, ontogenesis, ecology and evolutionary doctrine with a way in medical practice.

2. Properties, attributes and levels of the living things organization

Properties of organisms: self-control, self-updating, self-reproduction.

Living things are characterized by a next major attributes:

1. A metabolism and energy. Any organism can be presented as the open system supporting a continuous metabolism and energy with an environment. A basis of exchange processes are reactions of plastic (anabolism) and power exchange (catabolism).

Anabolism of organisms subdivided on: autotrophic (photosynthesizing and chemosynthesizing), heterotrophic (saprotrophic and parasites), and mixotrophic.

On type catabolism organisms subdivided on aerobic and anaerobic.

2. The structural organization. Living things is constructed from the same chemical elements as lifeless, but it is characterized by the complexity of the chemical compounds caused by certain orderliness at a molecular level. The structural organization is a characteristic property of living things at all levels of its organization. A chromosome is a typical example of the ordered structure.

3. Discreteness and integrity. The organic world has integrity, since makes system of the interconnected parts, and at the same time it is discrete. The organic world is consisting of separate units — organisms or individuals. Each organism is consisting of cells, and cell is consisting of subcellular structures (organelles), but organism has functions as a single unit.

4. A reproduction — reproduction of similar to itself.

5. A heredity and variability — the major properties of living things that are related with transfer from parents to progeny of hereditary attributes and with possibility to change hereditary attributes under influence of environment.

6. Growth and development — properties of an organism to grow and develop due to cell divisions and their differentiation.

7. Irritability and movement. Properties of living things to have contact with environment and other organisms. In monocelled it is shown as taxis, in plants -— as tropisms, in the animals — as reflexes.

8. Internal regulation and homeostasis. Any organism, being open system, keeps during a long time a constancy of internal environments (homeostasis) thanking to neurohumoral regulation.

Distinguish four levels of life organization:

1. Molecular-genetic. Elementary structure of this level is a code of the hereditary information that can be transmitted from generation to generation. The elementary phenomenon is reproduction of codes by a matrix principle and synthesis of primary gene structures.

2. Ontogenetic. Elementary structure of this level is a cell, and the elementary phenomena are ontogenesis, differentiation and individual development of organisms.

3. Population. Here, elementary structures are populations of any species of organisms, and the elementary phenomenon is the directed changes of their genetic structure.

4. Biospheric. Elementary structures of this level are ecosystems, and the elementary phenomena are transitions from one condition in another. Basic indivisibility of biosphere causes necessity of the decision of many problems of wildlife management and use of its resources.

3. Cytology — a science about the basic form of the living things organization. The cell theory and its modern condition. The cell — an elementary genetic and structural-functional unit of life

The section of biology that study of the structural and functional organization of cells has received the name «cytology» (from Greek. cytos — a cell, a cavity, logos — a science). Opening of a cell is connected to names of great scientists — R. Hooke, M. Malpigi, N. Gru, which have described a cellular structure of many plants, and also with name A. Laevenhook, for the first time observing cells of animals.

In 1939 German zoologist T. Shwann has published work «Microscopic researches about conformity in structure and growth of animals and plants» in which bases of the cellular theory have been stated. In this work T. Shwann has come to two conclusions:

1. All living things are composed of cells;
2. Process of cell formations provide growth, development and a differentiation of all plant and animal tissues and organisms.

The further development of the cell theory is connected to a name of German scientist R. Virchow which in 1858 has published the work «The cellular pathology». In this work R. Virchow has added to cell theory the third conclusion: «Omnis cellula e cellula» — each cell from a cell. This conclusion has excellent proved by further development of biology. Now, it is not known different ways of occurrence of cells besides their division.

But a number of R. Virchow's conclusions was erroneous and met objections on the part of contemporaries. On R. Virchow, pathological process in an organism represents the sum of disorders of ability to live of separate cells, it is local process. R. Virchow and his followers did not see also qualitative differences between a part and the whole, considering an organism outside of its historical development and conditions of existence. This idea of R. Virchow is proved criticized by Setchenov, Botkin, Pauls which have shown, that the organism — a single whole and integration of its parts is carried out first of all CNS.

Due to researches Schwann, Schleiden, Virchow, Morgan, Nawashin, Koltsow, Nasonow, and etc. a cell consider as the elementary unit of life with such attributes as a metabolism, reproduction, reactance, and variability.

The modern cell theory includes the following positions:

1. All living things are made up of one or more cells.
2. Cells are the basic living units within organisms, and the chemical reaction of life take place within cells.
3. All cells arise from preexisting cells.
4. Cells of multicellular organisms are specialized on functions.
5. Cells form tissues, organs, organisms.

Significance of the cell theory:

— The proof of a morphological basis of unity of wildlife.
— The biology explanation of life.
— Strengthening of idea of evolution.

4. Features of pro — and eukaryotic cells structure. Karyotype

Vital forms of organisms:

1. Before cellular — kingdom of viruses.
2. Cellular:

— prokaryotic — kingdom of bacteria,
— eukaryotic — kingdom of plants, animals, and fungi.

The majority of organisms are consisting of cells. However there are before cellular forms of a life — viruses. With occurrence of a cell, living things get ability to an independent metabolism and duplication. Complication of their organization is connected with the appearance of cell and then nuclear membranes and increase in molecular weight of DNA.

Cells divided on prokaryotic and eukaryotic.

Prokaryotic cells — before nucleus cells. The hereditary apparatus is submitted by one molecule DNA of the ring shape (nucleoid). Prokaryotic cells are haploid. Molecular weight of DNA corresponds to 2000 of structural genes. The cell is bounded to a double plasmatic membrane (external and internal). Above of a membrane, the cell wall is formed. It will consist of carbohydrate murein, forming a rigid grid. Organells of membrane structures are absent in cytoplasm. Their function is carried out with embolies of an internal membrane — mesosomes. In cytoplasm there are ribosomes. Bacteria can contain fine molecules of DNA (plasmids). Photosynthesizing bacteria have photomembranes. Storage nutrients are submitted by carbohydrates.

Eukaryotic cells have the discrete nucleus, an external biological membrane — plasmalemm, and cytoplasm with organelles and inclusions.

Plasmalemm separates contents of a cell from an environment and adjusts movement of ions and macromolecules in a cell and from it. The biological membrane has a fluid mosaic structure (model Singer). It will consist of double layer of phospholipids which molecules are submitted by not polar waterproof ends and polar hydrophilic surfaces, inverted to an environment. On external surface plasmalemm animal cells is situated a polysaccharide layer —

glycocalyx. Cells of plants have cellulose, and mushrooms have chitinous shell above plasmalemm.

Chemical compound of a cell membrane is the following:

1. Proteins — 55% (from them up to 200 enzymes).
2. Lipids — 35%.
3. Carbohydrates — 5–10% (in connection with simple or complex proteins).

Functions of membrane's lipids are structural, and barrier.

Functions of membrane's proteins are structural, enzymatic, receptor, and transport.

Function of glycoprotein is receptor.

Properties of membranes: plasticity, penetrability, dynamism.

Functions of membranes:

1. Structural (are part of the majority organells).
2. Barrier (support of a constancy of a chemical compound and protect).
3. Regulation of exchange processes.
4. Receptor.
5. Transport.

Plasmalemm includes a complex of elementary membranes: 3–4 — at animal cell, 7–8 — at plant cell. Through plasmalemm transport of substances in a cell is carried out. Transport can be passive and active.

1. Passive transport occurs on a gradient of concentration without expenses of energy. It can be: diffusion of gases, osmotic movement of the water, the facilitated diffusion with help of protein-carriers (amino acid, sugar, fat acids).

2. Active transport goes against a gradient of concentration with an expense of energy. For it presence, the special ionic channels, enzymes and ATP is necessary. So *sodium — potassium pump* works. Concentration K^+ in a cell is higher, than out of cell, and, nevertheless, ions K^+ are coming in a cell, and ions of sodium are go outside. Ions of sodium form on a surface of a membrane a positive charge, inside of cell forms a negative charge. On everyone 2 coming in ion K^+, from cell 3 ions Na^+ are go outside. The charge on membrane provides transfer of a nervous pulse, absorption nutrients of intestine villus, adsorption in kidney tubules.

The Mg^{2+}/Ca^{2+} *pump* provides muscular contraction.

Large molecules of proteins**,** nucleic acids, polysaccharides are penetrated inside of a cell by **endocytosis**. Distinguish two kinds of endocytosis: *phagocytosis* and *pinocytosis.* Phagocytosis — catch of solid particles by a membrane. Then, it is formed digestive vacuole inside a cell at participation of lysosomes. Pinocytosis — digestion of liquid nutrients.

Excretion from a cell of the substances, enclosed with membrane, refers to **exocytosis.**

The substances which have come in a cell can be used:

1) For synthesis of the substances necessary for the cell (anabolic system);

2) As an energy source (catabolic system).

Anabolic (assimilation, a plastic exchange) and catabolic (dissimilation, a energy exchange) systems of a cell are related, as all processes of cell life are impossible without energy of ATP which, in turn, cannot be formed without the fermental systems builded as a result of anabolic reactions. Also flows of substance and energy are inextricably related with each other becouse heterotrophic cells are capable to use only the energy made in complex chemical compounds.

To anabolic system of a cell concern: ribosomes, endoplasmic reticulum, complex Golgi.

To cataboloic to system of a cell concern: lysosomes, peraxisom, glyoxisom, mitochondria.

Cytoplasm — contents of a cell without a nucleus. In cytoplasm distinguish hyaloplasm, organells and inclusions.

Hyaloplasm is the basic substance of a cell to which are connected colloidal properties of cytoplasm. Hyaloplasm will consist of two phases: liquid and solid. The liquid phase is submitted by colloidal solutions of proteins, carbohydrates, nucleotides, ions of inorganic substances. The solid phase is submitted by microtrabecular system, microtubules, microfilaments which form cytoskeleton cells.

Organells are the specialized constant components of the cytoplasm, which are possessing a certain structure and carrying out a function in ability to live of a cell. Organells are divided on two groups: organelles of general purpose and special purpose.

1. Organells general purpose:

a) membrane structures (mitochondria, plastids, complex Golgi, endoplasmic reticulum, lysosomes, vacuole);

b) non-membrane structures (ribosomes, the cellular center).

2. Organells special purpose: miofibrils, tonofibrils, neurofibril, cilia, flagella.

Cytoplasmic inclusions are changeable structures in the cytoplasm, representing products of living cells. On the biological significance of inclusions, it can be conditionally divided into the basic groups: trophic, secretoral, special purpose, excretory, pigmentary.

The nucleus is a constant structural component of all eukaryotic cells. The nuclear envelope of interphase nucleus will consist of two elementary membranes (external and internal), the space between which refers to perinuclear. Membranes have pores, through which there is substances exchange between nucleus and cytoplasm. The external nuclear membrane passes in walls of endoplasmic riticulum channels. On it ribosomes are located.

Nucleoplasm is the homogeneous substance that filling space between structures of nucleus. It contains proteins, nucleotides, ATP, various kinds of RNA, chromatin, and nucleolus.

Chromatin is complex of DNA and histon proteins. In process of mitosis, spiral chromatin forms chromosomes.

Nucleolus is consisting of proteins (80%), RNA (up to 15%), DNA (up to 12%). Provide synthesis of r-RNA and formation subunit of ribosomes.

Functions of nucleus: storage and transfer of the genetic information, regulation of life processes of cell.

The metaphase chromosome (spiral chromatin) is consisting of two chromatids. The form is determined by presence centromere (kinetochore). It divides a chromosome on 2 arms. The arrangement centromere determines the basic forms of chromosomes: metacentric, submetacentric, acrocentric, telocentric.

The degree of chromosomes spiralization is not identical. Sites of chromosomes with weak spiralization have name *euchromatin.* It is a site of high metabolic activity where DNA is consists of unique sequences. A site with strong spiralization is *heterochromatin.* It is site capable to a transcription. Distinguish *constitutive heterochromatin* which is genetic inert (does not contain genes, does not pass in euchromatin) and *facultative heterochromatin* which can pass in active euchromatin. Terminal parts of distal sites of chromosomes have name telomers.

Chromosomes are subdivided on autosomes and heterochromosomes (sex chromosomes).

In 1924 under the offer of G. A. Levitansky, the diploid set of chromosomes of a somatic cell has been named *karyotype.* It is characterized by number, shape, and size of chromosomes. Under S. G. Navashin offer, chromosomes are placed accordingly their size that have name *idiogramm* — systematized karyotype. In 1960 the international classification of chromosomes where suggested. Chromosome classification based on size and arrangement of centromere has been offered in Denver. In karyotype a somatic cell of human distinguish 22 pairs of autosomes and pair of sex chromosomes. A set of chromosomes in somatic cells have name *diploid*, and in sex cells — *haploid* (it is equal to half of autosome set). The human karyotype was divided into 7 groups, depending on their sizes and shape:

A. 1–3 Biggest metacentric.
B. 4–5 Biggest submetacentric.
C. 6–12 X-chromosome, average metacentric.
D. 13–15 Average acrocentric.
E. 16–18 Small submetacentric.
F. 19–20 Small metacentric.
G. 21–22 Y-chromosome, small acrocentric.

According to *Paris* classification, chromosomes are divided into groups on their sizes and the form, and also on the base their selective staining.

Chromosomes possess the following properties (a rule of chromosomes):

1. Rule of chromosome individuality — not homologous chromosomes is differed.

2. Rule of chromosome pairs — paired chromosomes is named homologous.

3. Rule of constancy of chromosome number — chromosome number is characteristic for each species.

4. Rule of continuity — an ability of chromosome to reproduction.

PART I

BASICS OF CYTOGENETICS
MOLECULAR GENETIC LIFE ORGANIZATION LEVEL

LECTURE 2

Theme: The molecular-genetic level of the life organization

Plan:

1. The evolution-caused levels of the life. A molecular-genetic level.
2. Structure of nucleic acids. Structure of DNA. Chargaff rules . Autoreproduction of DNA, its kinds. Structure of RNA, its types and kinds. Synthesis of m-RNA, its stages.
3. The organization of a hereditary material at not cellular forms, pro- and eukaryotes. The molecular organization of chromosomes. Levels of DNA packing.
4. Gene as a fragment of genome nucleic acid. A genetic code and its characteristics.

1. The evolution-caused levels of the life. A molecular-genetic level

The molecular-genetic level of the life is connected to storage and flow of the information in new generations of cells and organisms. DNA of chromosomes of a nucleus, m-RNA, t-RNA, ribosomes, and enzymes of activation of amino acids consistently participate in a cell in this flow. Furthermore, proteins of the certain structure and functions are synthesized. Studying of this level is connected to functions and structure of nucleic acids. They posess a leaging role in storage of information and its realization. They provide processes of protein synthesis, a metabolism, laws of growth, reproduction, heredity, and variability. Disorders of their structure give raise to pathology.

Two groups of nucleic acids are known: RNA and DNA.

DNA is in nucleus as part of chromatin, and also is in mitochondria, and plastids, and RNA — in nucleolus, matrix some cytoplasm, ribosomes.

The carrier of the hereditary information in a cell is DNA, and RNA — serves for transfer and realization of the genetic information at pro- and eukaryotes. To the help of m-RNA there is a translation process of DNA sequence of nucleotids in polypeptide.

At some organisms, except for DNA, the carrier of the hereditary information can be RNA, for example, at viruses of a tobacco mosaic, a poliomyelitis, AIDS virus.

2. Structure of nucleic acids. Structure of DNA. Chargaff rules. Autoreproduction of DNA, its kinds. Structure of RNA, its types and kinds. Synthesis of m-RNA, its stages

Monomeres of nucleic acids are nucleotides. It is established, that in chromosomes of eukaryotes, huge two-spiral molecule DNA is formed by 4 types of nucleotides: adenine, guanine, thymine, cytosine. Everyone nucleotide will consist of the nitrogenous basis (purines G+A or pyrimidines C+T), deoxyribose, and phosphoric acid residue.

Analyzing DNA a different origin, E. Chargaff has formulated laws of a quantitative parity of the nitrogenous bases — Chargaff rules:

1. The quantity of adenine is equal to quantity of thymine (A=T).
2. The quantity of guanine is equal to quantity of cytosine (G=C).
3. The quantity of purines is equal to quantity of pyrimidines (G+A = C+T).
4. Quantity of the bases with 6-amino groups equal to quantity of the bases with 6-ketogroupes (A+C = G+T).
5. In the same time the parity of bases A+T/G+C is strictly species-specific (for human — 0.66; mice — 0.81; bacteria — 0.41).

In 1953 biologist J. Watson and physicist F. Crick had been offered spatial molecular model of DNA. The basic postulates of model consist in the following:

1. Each molecule DNA will consist of two long antiparallel polynucleotide chains (threads) forming a double helix, twirled around of the central axis.
2. Everyone nucleoside (sugar + the nitrogenous basis) is located in a plane, a perpendicular axis of helix.
3. Two polynucleotide chains are fastened by the hydrogen bonds formed between the nitrogenous bases.
4. Pairing the nitrogenous bases is strictly specific, the purine bases bond only with pyrimidines: A—T, G—C.
5. The sequence of the bases of one chain can considerably vary, but the nitrogenous bases of other chain should be strict complementary to it.

Polynucleotide chains are formed due to covalent bond between nucleotides through the phosphoric acid residue which connects carbon in the fifth position of sugar to the third carbon of the next nucleotide. Threads have an orientation: the beginning of chain 3'OH — in the third position of carbon deoxyribose joins hydroxyl group OH, the end of chain — 5'-phosphate, the phosphoric acid residue joins the fifth carbon deoxyribose.

DNA has property of replication — autoreproductions. Replication is based on principles of semiconservativity, antiparallelity, complementarity, and discontinuity. Hereditary information of DNA is realized in result replication as matrix synthesis. It proceeds in stages: initiation, elongation, termination.

Process is related with the S-period of interphase. DNA-polymerase enzyme uses as a matrix a one-chained DNA and at the presence of 4 nucleotides and primer (RNA) builds second chain of DNA.

Synthesis of DNA is carried out by a principle complementary. Between nucleotides of DNA chain it is formed phosphodiester bonds due to connections of 3'OH groups of the last nucleotide with 5'-phosphate of the following nucleotide which should join a chain.

Distinguish three basic kinds of DNA replication: conservative, semiconservative, and disperse.

Conservative — safe the integrity of an initial two-chained molecule and synthesis affiliated of two-chained. Half of affiliated molecules are constructed completely from a new material, and half - from old parent.

Semiconservative — synthesis of DNA begins with heliase enzyme connection to a point of the beginning replication which untwines DNA parts. Each of DNA threads joins with connecting protein which interfering their connection. Unit of replication is replicon; it is a site between two points of the beginning of synthesis of affiliated chains. Interaction of enzymes with a point of the beginning replication refers to iniciation. This point goes along a chain (3'OH→5'Ph) and replicative fork is formed.

Synthesis of a new chain goes in discontinuous manner with formation of fragments in length of 700–800–2000 nucleotide residues. There are a start point and the end point of replication. Replicon goes along molecule DNA and its new parts untwine. Each of parent chains is a matrix for affiliated which is synthesized by a principle of complementarity. As a result of consecutive nucleotide connections, the DNA chain is extended (a stage elongation) with the help of DNA-ligase enzyme. Synthesis stops (termination) on reaching of the necessary length of a molecule. In eukaryotic cells works at once thousands of replication forks. In prokaryotic cells iniciation occurs in one point of DNA ring, thus two replication forks move in 2 directions. In a place of their meeting, two chained molecules of DNA are separated.

Disperse — disintegration of DNA on the nucleotide fragments; new two-chained DNA will consist of spontaneously gathered new and parental fragments.

DNA structure of eukaryotic cells is similar with DNA of prokaryotes. Distinctions concern: quantities of DNA on genes, length of DNA molecule, the order of nucleotide sequences alternation, the shape of packing (in eukaryotes — linear, in prokaryotes — ring).

For eukaryotes, a redundancy of DNA is characteristic: amount of DNA participating in coding is only 2% from total quantity of DNA. The part of redundant DNA is submitted by moderately repeating identical sets of nucleotides, repeating many times. Distinguish frequent and moderate repeated

sequences. They form constitutive heterochromatin (structural). It is built-in between unique sequences. Redundant genes can have to more than 10^4 copies.

DNA has property *of reparation* — ability to restoration of the broken structure due to mutations. In a basis of this process lays the structure of DNA molecule (double helix structure). Restoration of the sites damaged by mutations occurs by a principle complementarity.

Biological role of RNA is related to process of realization of the hereditary information from DNA in process of protein synthesis. Messenger RNA is the intermediary between the information about structure of protein on DNA nucleus and a place of synthesis of protein molecules in cytoplasm on ribosomes. RNA has no double helix structure; it is submitted by one polynucleotide chain (except for two-chained RNA-CONTAINING viruses). Depending on species, amount of RNA in a cell is changes. There are three kinds of RNA: ribosome, messenger, and transport. All kinds are synthesized on DNA molecule in a nucleus by transcription.

R-RNA (ribosome RNA) is a part of ribosomes (3000–5000 nucleotides) (80% from total RNA of a cell). From it, the skeleton of ribosomes is constructed, participated in iniciation, the termination of synthesis, and separation of protein molecules from ribosomes.

M-RNA (messenger (matrix) RNA) carries the genetic information transcribed from DNA about structure of polypeptyde chains as codes (triplets of nucleotides). The molecule includes from 300 up to 3000 nucleotides and amount of m-RNA is 3–5% of total quantity of RNA.

T-RNA (transport RNA) provides transport of the activated amino acids to ribosomes. Has secondary structure as a clover leaf, on which top situated anticodon.

The central process of cell metabolism related to a flow of substance, energy, and information is protein biosynthesis which is carried out at participation of nucleic acids.

The genetic information coded in DNA is transferred to ribosomes through m-RNA. Site of DNA containing the information on structure of polypeptide chains refers as a gene. In eukaryotes, transfer of hereditary information from genes is regulated by histon proteins which affect to this process. The beginning of the information coping is connected with clearing certain DNA site (gene) from histon proteins with the help of non histon proteins which are capable to recognize the certain genes.

All kinds of RNA are synthesized on DNA. This process refers to *a transcription*. DNA molecule is shared into the sites containing the information on structure of protein which refers to as genes and not informative sites (spacers) which separate genes. Spacers are various in lengths and regulate transcription of the following gene. *Transcribe* spacers are copied at transcription together with a gene and their complementary

copies appear on pro-m-RNA. *Untranscribed* spacers are meeting between genes which coded histon proteins and m-RNA.

Synthesis of m-RNA goes from one thread of two-chained molecule DNA by a principle of complementarity. M-RNA is a copy not whole DNA molecule but only parts of it. This part is one gene or group of genes of one function. Such group of genes refers to operon. Operon is a unit of genetic regulation. It includes the structural genes carrying the information on structure of proteins and regulatory genes managing work of structural genes. It has also promotor, operator, and terminator. The promotor is in the beginning of everyone operon. It is «airfield» for RNA-polymerase. The operator operates a transcription. Terminator includes the stop-codons which finished synthesis of m-RNA.

At eukaryotes, structural genes are divided on exons and introns. Exon — the sites carrying the information, and intron — not carrying the information.

Transcription beginning from:

1. Formation of primary transcript — the long progenitor of m-RNA with the full information from DNA molecule (pro-m-RNA).
2. Processing — shortening of primary transcript by a cutting of not informative DNA sites (introns).
3. Splicing — ligation of informative sites and formation mature m-RNA.

The transcription begins from a starting point of molecule DNA with participation of RNA — polymerase enzyme.

Synthesis of m-RNA passes in 4 stages:

1. Linkage of RNA-polymerase with the promotor.
2. Initiation — the beginning of m-RNA synthesis.
3. Elongation — growth of m-RNA chain.
4. Termination — stop of m-RNA synthesis.

3. The organization of hereditary material at not cellular forms, pro- and eukaryotes. The molecular organization of chromosomes. Levels of DNA packing

The hereditary material of viruses is submitted by two- or one-chained molecule of DNA, or RNA. In a virus of tobacco mosaic RNA forms one-chained helix in length up to 300 nanometers and diameter is 8 nanometers. Virus of AIDS has a two-chained RNA.

In prokaryotes the hereditary material is submitted by ring DNA molecule (a ring chromosome).

In eukaryotes the hereditary material is submitted by chromosomes. Chromosomes are spiral chromatin — complex DNA and proteins where 40% is DNA, 40% is histons proteins, and almost 20% is non hostons proteins and a little of RNA.

Histon is chromosomal proteins with the high content of arginine and lysine. Histons stabilize structure of a chromosome and play a role in regulation of activity of genes.

Non gistons (acid) proteins. In chromosomes their amount approximately is twice less histons. There are more than 100 kinds of non histons proteins exist. They are various on molecular weight and structure. These proteins can be responsible for replication, reparation, transcription, and probably play role in activation of genes. It is actin, miosin, enzymes of RNA synthesis, and DNA-polymerase.

From five classes histons, four histons (H2A, H2B, H3, H4) form original spherical body — nucleosome in diameter about 10 nanometers. The 8 molecules form one nucleosome of histons. Around nucleosome the part of DNA molecule (about 140 nucleotides pairs) which forms around of it almost two coils is stacked. All nucleosomes are connected with each other by short parts of DNA molucule (1–10 nanometers or 30–100 pairs of nucleotides). Molecules of histon H1 are attached to each such part. A medium-size gene composed, approximately, from six nucleosomes. It is supposed, that due to interaction H1 with nucleosomes there is a condensation nucleotide structures in special chromatin thread (elementary fibril, d=10–11 nanometers), which twists in chromatin spiral (d = 20–30 nanometers), or chromatin. The chromatin spiral, probably, is identical with chromonemm which during division is twisted in chromatid.

Thus, DNA has next levels of packing:

1. Nucleosome (2.5 coils of two-spiral DNA around of eight molecules of histon proteins).
2. Super nucleosome — a chromatin spiral (chromonemm).
3. Chromatid — spiral chromonemm.
4. Chromosome — the fourth level of DNA packing.

In an interphase nucleus, chromosomes are decondensed and submitted by chromatin. Despiralisation the site containing genes refers to euchromatin (loosened, fibrous chromatin). This is necessary condition for a transcription. During rest between divisions the certain sites of chromosomes and the whole chromosomes remain compact. These spiral and strong coloured sites refer to heterochromatin. They are inactive regarding to transcription. Distinguish facultative and constitutive heterochromatin.

Facultative heterochromatin is informative since contains genes and can pass in euchromatin. From two homology chromosomes one can be heterochromatinic. Constitutive heterochromatin always heterochromatinic, noninformative (does not contain genes) and consequently it is always inactive regarding to transcription.

Chromosomal DNA is consisting of more than 108 pair bases of which it is formed informative blocks — the genes located linearly. On their portion fall about 25% of DNA. Gene is a functional unit of DNA which contains the information for synthesis of polypeptides, or all of RNA molucules. Between genes are spacers — not informative DNA parts of different length. Redundent genes are submitted by the big number of identical copies. For example, it is genes for t-RNA, r-RNA, and histons. There are sequences same nucleotides in DNA. They can be moderately repeating and highly repeating sequences. Moderately repeating sequences reach 300 pairs nucleotides with repeatitions of $10^{2-}10^{4}$ and represent more often spacers and redundent genes.

High repeated sequences (10^{5}–10^{6}) form constitutive heterochromatin. About 75% of all chromatin does not participate in transcription; it falls on high repeated sequences and nontranscribed spacers.

4. Gene as a fragment of genome nucleic acid. Genetic code and its characteristics

The genetic information is coded in DNA. The genetic code has been found out by M. Nirenberg and H. G. Koran, for what they have been awarded with the Nobel Prize in 1968.

Genetic code is a system of arrangement of nucleotides in the nucleic acid molecule that controled sequence of amino acids in a polypeptide molecule.

The basic postulates of a code are:

1. Genetic code has a triplet structure. The triplet of mRNA is called codon.
2. One amino acid corresponds, as a rule, more than one codon. In codon first two nucleotides are identical to one amino acid more often, and the third varies.
3. The nucleotide sequence is recognized in one direction, triplet by triplet.
4. AUG represents start codon.
5. UAG, UAA, UGA are stop codons.
6. The genetic code is universal for all organisms.

Discovery of DNA structure, the material carrier of heredity, promoted the decision of many questions: reproduction of genes, the nature of mutations, and biosynthesis of protein. Discovery of mechanism of genetic code transfer promoted development of molecular biology, gene engineering, and gene therapy.

CELLULARLIFE ORGANIZATION LEVEL

LECTURE 3

Theme: The cell physiology

Plan:

1. Cell as an open system.
2. The organization of energy, substance, and information flow.
3. Life cycle of a cell.
4. Autoreproduction of cells.
5. The cell proliferation and its significance for medicine.

1. Cell as an open system

The cell is open self-regulating system. For it, the flow of substance, energy, and information are characteristic. For a cell and for a whole organism distinguish an external and internal exchange. The external exchange is an exchange with an environment: inflow of nutrients, excretion of products of a metabolism. The internal exchange is carried out by dissimilation and assimilation. Assimilation is carried out by reactions of a plastic exchange (biosynthesis of proteins, fats, carbohydrates, photosynthesis). On the base of assimilation, organisms can be divided on autotrophic and heterotrophic. Dissimilation is carried out by reactions of a power exchange (synthesis of ATP due to breakdown energy of complex organic substances). On the base of dissimilation, organisms can be divided on anaerobic and aerobic.

Energy is «ability to make external action» (M. Plank). By the form of substance or energy exchange with environment distinguish next kinds of systems:

1. Isolated — absent of any exchange of substance and energy.
2. Adiabatic — only exchange of energy is possible, except for thermal energy.
3. Closed — exchange of any energy is possible.
4. Open — any exchange of substance and energy is possible. Cells of living things are an open self-regulating systems, which has an information, energy and substance flow.

2. The organization of energy, substance, and information flow

The flow of energy in organisms is submitted by endocellular mechanisms which are capable to provide: photosynthesis, chemosynthesis, fermentation, breath.

All cells and organisms are heterogeneous open systems. A primary energy source for a life on the Earth is the solar energy. For all cells of organisms, organic substances (carbohydrates, fats, and partially proteins) with their chemical energy serve as «fuel» from which the energy necessary for function of an organism is taken. Autotrophic organisms synthesize this «fuel», heterotrophic — receive it from autotrophic. The energy, released at breakdown of organic substances, is not used in cells at once for realization of work but reserved in the form of high-energy intermediate substances, as a rule - ATP.

During photosynthesis the solar energy in plant cells turns in first to energy of chemical compounds as molecules of ATP and NADP-H^2 which is used then

in a plastic exchange (synthesis of organic substances). In cells heterotrophic organisms the flow of energy is provided with processes of fermentation and breath. Fermentation occurs in cytoplasm. Products of dissimilation of organic substances are pyruvic acid, which is rich energy, and 2 molecules of ATP. Therefore the release of energy at fermentation is insignificant.

The breath is oxidizing phosphorilation that take place in matrix and on membranes of mitochondria. Oxidizing phosphorilation gives 36 molecules of ATP. In total, energy of one molecule of glucose is transformed to energy of 38 ATPs.

Process of a power exchange has stages: preparatory, without oxygen exchange, and with oxygen exchange. In the first stage, monomeres form from organic compounds. In the second stage, more than 10 enzymes of cytoplasm are participating. At this stage the power exchange of anaerobic organisms comes to the end. Thus organic substances and energy of their chemical bonds collect in energy of ATP synthesized from ADP molecules and phosphates of cell. However the power output makes only 2 molecules of ATP. Full extraction of energy from an intermediate product of disintegration (piruvic acid) occurs at the oxygen stage, including cycle in mitochondria Quantity of ATP at this stage is 36 molecules.

On synthesis of ATP the cell uses 67% of energy of organic substances. At highly organized animals and human, glycolysis is required additional energy source to aerobiosis.

In chemosintesis, there is a transformation of energy of chemical compounds to energy of organic substances. Energy which is released at oxidation of compounds is used for restoration of carbon dioxide to organic substances.

To each cells or organism, the exchange of the information is characteristic. At a level of a cell, the organism receives the information that occurs in an environment. The continuous flow of the information acts in an organism and there is processed, other such flow of the information all time leaves an organism serving, in turn, as the transmitter. The information cannot be determined not as a matter, not as energy, but it is transferred with signals of material nature. At hormonal communication the chemical signal (hormone) gets in all parts of an organism, but only the certain organs are capable to accept the given signal. For example, tyreotropin (the hormone of anterior lobe of hypophysis) specifically influences a thyroid gland. The number of pulses in unit of time (frequency of pulses) serves in nervous system as information parameter. Quantity of the information in this or that signal measures in bits.

At human the maximal flow of information directed, mainly, on the visual analyzer to inside, is estimated in 108–109 bit/s, that makes 10^9 bits for 80 years of a life (for comparison: the book of average volume contains about 10^6 bits. For management of person behaviour and activity of its physiological functions

the day off (direction from the brain) flow of the information in size 10^7 bit/s is necessary. It is provided by connection of memory programs.

The flow of the internal information in an organism is carried out with the help of a brain cortex and glands of internal secretion. The cell perceives a flow of the external information from an intercellular liquid by means of receptors of a cell membrane. The internal information contains in DNA. In a flow of the internal information take part the nuclear and cytoplasmic DNA, RNA, and enzymes. The information flow provides hereditary continuity of generations.

Structures of organisms are not constant. They destroyed and formed anew. Turnover process is carried out due to the substance flow.

The substance flow is characterized by a plastic exchange in a cell.

- Photosynthesis: $6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$
- Chemosintesis: $H_2S + O_2 \rightarrow H_2O + S + Q$

  $NH_3 + O_2 \rightarrow H_2NO_3 + Q$
- Biosynthesis of proteins: protein → amino acid → own protein.

The sequence of protein biosynthesis processes is represented as follows:

1. Activation of amino acid by specific enzyme in presence of ATP with formation of aminoaciladenilate monophosphate.
2. Connection of the activated amino acid to specific t-RNA with forming aminoacil t-RNA and releasing of AMP.
3. Linkage of aminoacil t-RNA with ribosomes and inclusion of amino acids in the protein with releasing of t-RNA .

The ribosome contacts during each moment only to a small site of m-RNA, it is possible equal to one triplet. The ribosome goes on m-RNA by «short steps», a triplet by triplet. On m-RNA can be assembled a few ribosomes which form the polyribosome. In ribosome moving on m-RNA, t-RNA «delivers» amino acids from an environment. Amino acid is attached to t-RNA according to anticodon sequence. At complementarity of codon with anticodon the delivered amino acid is included in polypeptide chain. Transfer of the information from m-RNA on synthesized polypeptide has received name of translation.

3. Life cycle of a cell

One of the basic biological features of a cell as elementary alive system is its ability to an autoreproduction. The reproduction of cells underlies the development, growth, reproduction, and regeneration of an organism. The period of time from the ending of one cell division up to the end of the following cell division received name of life cycle or cell cycle. For not reproducible cells, the cell cycle is the period from formation of a cell to its death. In life cycle of cells can be distinguished two big periods:

1) period between divisions or interphase, when the cell grows, performs its functions, and prepared for division;

2) division of a cell or mitosis (M phase).

There is a number of processes in cell interhpase: growth of cell, reproductions of DNA, doubling of chromatid number, syntesis of proteins, formation and accumulation of energy.

It is possible to divide interphase into three periods:

1. Postmitotic or presynthetic period G1: 2n 1ch 2C.

During this period, cells grow, synthesize RNA and proteins, and store of energy. DNA synthesis is absent. This period is characterized by that the cell contains 2n chromosomes, each of which is formed by single chromatid. Chromosomes are despirilized. If quantity of DNA contained in 23 chromatids (n) to designate as «C», cell in G1 period has 2C of DNA (2n): 2n 1ch 2C.

2. Synthetic period S: 2n 2ch 4C.

There is active synthesis of DNA in cells (replication). Each chromosome completes second chromatid. In a result, concentration of DNA is 4C, kariotype is equal to 2n and any of chromosomes will consist of 2 chromatids.

3. Postsynthetic or premitotic period G2: 2n 2ch 4C

There is a synthesis of proteins, form of mitotic apparatus, and store of energy in a cell.

4. Autoreproduction of cells

CLASSIFICATION OF THE CELL DIVISIONS

Mitotic division	Amitotic division	
	By the form	By the type
1. Mitosis itself	1. Equal	1. Generative
2. Meiosis	2. Non-equal	2. Reactive
3. Endomitosis	3. Fragmentation	3. Degenerative
4. Polyteny	4. Without cytotomy	

MITOSIS is the most common way of cell reproduction. Mitosis provides formation of genetically equivalent cells and keeps continuity of chromosomes in a number of cell generations. Mitosis is a unique type of cell divisions of animals and plants at which all cells pass a number of the consecutive changes resulting in formation of two daughter cells with diploid set of chromosomes and a full set of genes.

Biological significance of mitosis:

1. Provides continuity of chromosomes in a number of cell generations and uniform their distribution in daughter cells.
2. The universal mechanism of reproduction of the eukaryotic cells.
3. Genetic continuity, formation of identical with parent daughter cells.
4. Growth of an organism.
5. Regeneration.

6. Cellular proliferation.

There are 5 phases consistently proceeding in mitosis: prophase, prometaphase, metaphase, anaphase, and telophase.

In the cell entering PROPHASE chromosomes get a dense, spirilized strings (each chromosome will consist of 2 chromatids). In this time chromosomes is shortened up to 1/25 the initial length. There is a start of destruction of nucleolus and nuclear envelope. Duplication of centriole is observed and spindle of division is starting to form.

PROMETAPHASE usually begins with destruction of a nuclear environment then in the center of cell. Chromosomes randomly move in the direction of equator of a cell.

In a METAPHASE, chromosomes in animal cells are situated in the field of equator. All chromosomes are well visible and calculation of chromosomes passes in this phase. Chromosomes are connected to strings of spindle with the help centromeres.

In ANAPHESE, strings of spindle are reduced; chromatids separated and move to the poles.

In TELOPHASE, chromatids disperse to poles, despirilized, around of them nuclear envelope are formed, nucleolus is restored, centrosome loses activity. Begins cytocinesis — division of cytoplasm.

Mitotic division in plant and animal cells is similar. But in cells of the higher plants centrosome is absent. Division of cytoplasm in animal cells occurs by constriction which, going deep, divides a cell into two parts. In cells of plants the plate is formed in the center of a spindle and then grows to periphery.

Set of processes of preparation of cells to division and itself mitotic division makes mitotic cycle of a cell. If daughter cells at once start preparation for the following mitosis them mitotic cycle coincides with life cycle (tissues of embryo). In other cases daughter cells are exposed to a differentiation and carry out various functions (presynthetic period is extended). Their life cycle comes to end with death of a cell (at nervous cells G1 — during all life).

Duration of each period of mitotic cycle is various and lasts from several minutes till several hours that depend on series of reasons: such as tissues, a physiological condition of an organism, external factors (temperature, light, chemical). Factors of the internal environment have influence also: neurohumoral mechanisms which are carried out by nervous system and hormones, and also products of tissue degradation.

ENDOMITOSIS — one of kinds of mitosis which essence consists in reduplication of chromosomes without destruction of a nuclear envelope and without division of a cell. In a cell, there is a multiplication of number of chromosomes, sometimes in tens times, in comparison with initial. Endomitosis meets in intensively functioning cells of various tissues: cells of liver, tissues of

nematods, insects, and crustaceans. Suppose, that endomitosis arises during evolution as one of variants of mitosis.

POLYTENY. Sometimes reproduction of chromonems occurs without increase of chromosoms. Each chromosome is repeatedly doubled (due to increase in quantity of chromonema), but affiliated chromosomes remain connected among themselves, chromatids do not miss. This phenomenon has received name polyteny. It is a special case of endomitosis. Polyteny meets in insects, infusorians, some plants. In cells of salivary glands of drosophila because of politeny number of chromonems in chromosomes reaches 1024 per nucleus.

MEIOSIS provide the sexual reproducing of organism.

Meiosis consisting of two consecutive divisions:

- 1-Reducing division (meiosis1).
- 2-Equalizing division (meiosis2).

In everyone distinguish 4 stages:

Meiosis 1.

Prophase consisting of five stages: 2n 2ch 4C.

The leptonemm — the chromosomes condensed. They are thing, each containing two chromatids. Chromosomes can be visible in microscope.

The zygonemm — conjugation of homologous pairs of chromosomes.

The pahynemm — homologous pairs of chromosomes become thicken and shorten, form uniform structure — bivalent, consisting of pair of homologous chromosomes, i. e. from 4 chromatids.

The number bivalents corresponds to number of pairs chromosomes and is haploid. There is an exchange of parts of homological chromosomes — crossing-over.

The diplonemm — homologous chromosomes begin to move apart remaining connected in area of centromers. These places refer to chiasms.

The diakinesis — spirilisation is maximal, bivalents settle down on periphery of nucleus. Nucleus envelope is disappeared.

Metaphase 1. Bivalents are in a cell equator. Centromers are attached to spindle of division: 2n 2ch 4C

Anaphase 1. Divergence of homologous chromosomes consisting from two chromatids to poles of cell: n 2ch 2C

Telophase 1. Chromosomes are at poles of cell, nuclear membrane is formed, cytoplasm divided. Two cells with haploid set of chromosomes are formed.

Meiosis 2.

Interphase is absent.

Prophase 2. Short. Chromosomes condense, the spindle forms, and the nuclear envelope disintegrates.

Metaphase 2. Individual chromosomes line up on the metaphase plate.

Anaphase 2. Sister chromatids separate and migrate as individual chromosomes toward the spindle poles.

Telophase 2. Chromosomes arrive at the spindle poles; the spindle breaks down and a nuclear envelope re-forms. The cytoplasm divides.

Biological significance of meiosis:

1. Provides formation of sex cells.
2. Promotes maintenance of a constancy of chromosome number.
3. Causes of a plenty new combinations of non homologous chromosomes.
4. Forms a plenty recombination of genes.
5. Is a source of combinative diversity.

AMITOTIC DIVISION, or direct division, represents nuclear division without spiralisation chromosomes and without uniform distribution of them since the mitotic apparatus is not formed. Amitotic division is described by R. Remak in 1841. Direct division is characterized by division of nucleolus, then nucleus and cytoplasms. The nucleus can shares on two uniform parts (uniform amitotic division) or two non-uniform parts (non-uniform amitotic division), or the nucleus shares on some parts. Sometimes after nuclear division cytoplasm is not divided, and there are multinuclear cells (amitotic division without division of cytoplasm). Depending on the factors causing amitotic division, distinguish three its types (with Zhilkin L.N., 1966): generative, reactive, and degenerative.

Generative amitotic division is marked at division of highly specialized polyploid cells. It is observed in infusorians at division of macronucleus, in some mammalian cells (liver, epidermis).

Reactive amitotic division revealed at various damaging influences (ionizing rays, disorder of exchange processes: starvation, disorder of a nucleic exchange, denervation tissues). This kind of amitotic division usually does not come to the end division of cell and results in formation of multinuclear cells. Probably, it is necessary to consider as the compensatory reaction resulting in increase of an exchange surface between nucleus and cytoplasm.

Degenerative amitotic division arises in growing old cells with dying away vital properties. This kind is submitted by a fragmentation and budding of nucleus. It has no relation to reproduction of cells. Occurrence of degenerative forms of amitotic division serves as attribute of necrobiotic processes.

5. The cell proliferation and its significance for medicine

Cells of animal tissues on ability to division (cellular proliferation) are divided *on three groups*:

1. Labile.
2. Stable.
3. Static.

To *labile* refer cells which are quickly and easily reproduced during of organism vital activity (blood cells, epithelial cells).

To *stable* refer cells of such organs as liver, pancreas, salivary glands, which find out have the limited ability to reproduction.

To *static* cells refer cells of cross-striped muscles of heart and nervous tissue, which cells do not divide.

Now it is established, that mitotic division is consequence of a long scheme of the reasons. First of all, the important role is played with the factors providing an opportunity of the introduction of cells in division. It is precisely proved, that all synthetic processes in the cell preparing for division are under the control of its genetic apparatus. The genes supervising this process are in different chromosomes. The Soviet scientists L. N. Bljaher (1954), I. A. Utkin (1959) have shown the important role of neurohumoral regulation to mitotic activity. They have established, that reflex character of regulation of cell divisions influences indirectly through the shift of hormonal balance. It is established, that amplification of secretion by adrenaline brakes mitotic activity whereas hormones of thyroid gland cause amplification of mitosis. On mitotic cycle also influence: a daily rhythm of mitotic activity, factors of an environment (light, temperature), neurohumoral mechanisms, and products of tissues disintegration.

Cell proliferation — increase in number of cells by mitosis, resulting in growth of a tissue, as against other way of increase in its weight (for example, a hypostasis). In nervous cells proliferation is absent.

In an adult organism, division and specialization of cells are proceeding. These processes can be both normal (physiological) and directed on restoration of an organism owing to disorder of its integrity.

Proliferation of cells underlies regeneration of the lost parts. The problem of regeneration is interested for medicine and for regenerative surgery.

Distinguish physiological, reparative and pathological regeneration.

Physiological regeneration — change of eryhtrocytes, skin epithelium.

Raparative regeneration — when in an organism there is a damage or destruction of cells and tissues.

Pathological regeneration — growth of tissues not identical to healthy tissues (growth of a scar tissue on place of burn, a cartilage on place of crisis, reproduction of cells of connective tissue on place of heart muscular tissue).

Studying of physiology of a cell has great significance for understanding of ontogenesis level of the living things organization, mechanisms of self-control of the cell providing complete function of whole organism.

ONTOGENETIC LIFE ORGANIZATION LEVEL

LECTURE 4

Theme: Reproduction and its cytologic bases

Plan:

1. Reproduction — universal property of living things.
2. Asexual reproduction, its kinds and biological significance.
3. Sexual reproduction, its kinds.
4. Gametogenesis. Laws of ovogenesis and spermatogenesis in mammals.
5. Fertilisation, its phases, biological essence. Mono- and polyspermy.
6. Features of human reproduction, its hormonal regulation.

1. Reproduction — universal property of living things

Reproduction is ability to self-reproduction; it is carried out at cell level.

Reproduction at molecular level — ability of nucleic acids to self-replication. On ontogenetic level, self-reproduction is performed in different forms: from simple division of unicells to sexual reproduction (eukaryotes).

Reproduction is ability to make progeny similar to itself, this condition of species existence in which basis is transfer of genetic material.

2. Asexual reproduction, its kinds and biological significance

There are two kinds of reproduction: asexual and sexual.

In *asexual* reproduction, one individual participates; individuals genetically identical to an initial parental individual are formed; somatic cells (division — mitosis) participate; sex cells are not formed; there is no genetic variety. Significance in evolution: strengthening of role of balancing selection, preservation of fitness in changing conditions of environment.

There are two kinds of asexual reproduction: vegetative and spore formation; a special case in vertebrates is a polyembryony: a case of asexual reproduction at early stages of embryonic developments. The splitting of blastula at medusa and development from each cell the whole organism was described in first by I. Mechnikov. The example in human is development of twins.

Reproduction on organism level
Asexual

	Vegetative: (from many somatic cells)	**Spore formation:** (from one specialized cell)
Monocellular	1. Simple division in two (prokaryotes, monocellular eukaryotes). 2. Shyzogony (monocellular: flagellata) 3. Budding (monocellular: yeast; multicellular — hydra)	At the monocellular eukaryotes, seaweed, mushrooms, mosses, horsetails.
Multicellular	4. A fragmentation (in multicellular — worms) 5. Polyembryony 6. By vegetative organs in plants (by stem and root buds, bulbs, and tubers) 7. The ordered division (uniform amitotic division in starfish, worms)	

3. Sexual reproduction, its kinds

Eukaryotes have three types of sexual reproduction. They have been formed during their evolution. They are conjugation, copulation, and irregular types of sexual reproduction. Conjugation provides an exchange of the genetic information without increase in quantity of individuals. It is characteristic for protozoa, seaweeds, and bacteries.

Sexual reproduction

With fertilisation of ovicell.	Without fertilisation of ovicell.
— Copulation (isogamy, anisogamy in monocellular and oogamy in multicellular)	Irregular types: — parthenogenesis: — ginogenesis, — androgenesis

Sexual reproduction — occurrence and development of progeny from fertilized egg (zygote). During historical development sexual reproduction of organisms became dominating in plants and animals.

Sexual reproduction has a number of advantages:

1. High rate of reproduction.

2. Full updating of genetic material. It is source of genetic variability. It gives success in competition.

3. The big adaptive potential.

Sexual reproduction is characterized by the following features:

1. Two individuals participate.

2. A source of formation of new organism is special cells — gametes (distinguish the man's and female sex cells).

3. For formation of a new organism fusion of two sex cells is necessary. It is enough 1 cell of each parent.

4. Meiosis provides an evolutionary advantage.

Sexual reproduction without fertilisation of ovicell

Parthenogenesis — development of a germ from not fertilized egg. It is peculiar to the lowest crustacea, bees, and wasps. Distinguish somatic (or diploid) and generative (or haploid) partenogenesis. At somatic parthenogenesis, ovicell does not undergo to reduction division, two haploid nucleuses merge together, restoring diploid set of chromosomes. In generative parthenogenesis (aphid, lowest crustacea), the germ develops from haploid ovicell. Male-bees develop from not fertilized haploid eggs by parthenogenesis. In wasps and ants the diploid set of chromosoms in somatic cells is restored after parthenogenesis thanks to endomitosis.

In *ginogenesis* participate sperms as stimulator of ovicell development, but fertilisation in this case does not occur. Development of germ is carried out due to a female nucleus. It is observed at round worms, at fish *Moliensia* genus. The

nucleus of sperm is destroyed and loses ability to caryogamy, but keeps ability to egg activation. The progeny receives genetic information from mother.

Androgenesis is egg development due to sperm nucleus and female's cytoplasm. Haploid germ has low viability. Viability is normalized, if diploid set of chromosomes is restored. Ar polyspermia, merge of two sperm nucleuses and formation of diploid nucleus is possible.

4. Gametogenesis. Laws of ovogenesis and spermatogenesis in mammals

Formation of sex cells is connected with meiosis. Sex cells (1n) are formed from somatic cells (2n).

Primary sex cells, as well as somatic cells carry 2n set of chromosomes in nucleus and subjected to multiple mitotic divisions in a zone of reproduction of sex glands. Primary sex cells occur from one or several germ cells and in the beginning they are similar in females and males. Then they are differentiated and turn in oogonia and spermatogonia (2n) which in a zone of growth of sex glands pass the period of growth (interphase). Oogonia turn in primary oocytes, spermatogonia — in primary spermacytes. In a zone of maturing they enter in meiosis. In result of meiosis, secondary oocyte and one polar body are formed in ovary and 2 secondary spermatocytes are formed in testicle. After the second division of meiosis, the two haploid cells are formed from each cell: in female — 1 oocyte and 3 polar bodies, in males — 4 spermatids. Then spermatides in a zone of formation turn in spermatozoa.

Differences of oogenesis from spermatogenesis

1. The reproduction period of oogonia is terminated before the moment of a birth.
2. The oogenesis growth period is longer than spermatogenesis growth period, and has subdivision to «small growth» and «big growth» periods. Oocyte becomes bigger than spermatocyte.
3. Primary oocyte may give only one gamete, whereas spermatocyte gives four gametes.
4. Oogenesis have not period of maturation.

The characteristic of sex cells

Ovicell is oval, large, and immobile cell. It is without of centrosome and it is unable to division itself.

There are three kinds of ovicells depending on the contents of a yolk:

— isolecital;

— polylecital (telolecital and centrolecital);

— alecital.

Ovicells are protected by coats. There are 3 kinds of coats:

1. Primary or yolk coat; the product of vital activity of oocyte or ovicell. It is in contact with cytoplasm. It is formed by peeling from egg surface. It is

penetrated by shoots of follicular cells and proteins. At human this coat called shining coat or «zona pellucida».

2. Secondary coat. It is formed as derivative of follicular cells which surround the oocyte (cells of a granular layer). At insects, it is chorion; at human, it is radiated coat or «corona radiate».

3. Tertiary coat. It is formed after fertilisation due to discharge of glands or mucous epithelium of sex ways in time of ovicell pass in oviduct of female. These are jellylike coat of amphibian eggs, protein coats, under shell and shell coats in birds.

Spermatozoa overcome secondary and primary environments during fertilization.

Spermatozoa have head, neck, and tail. The head is consisting from acrosome and nucleus. Acrosome is formed from elements of Golgi apparatus of spermatide. It is head cap of spermatozoa. Acrosome provides penetration of spermatozoa in ovicell and its activation with help of hyaluronidase enzyme.

The nucleus of spermatozoa contains compactly packed deoxyribonucleoproteids. Such packing of haploid set of chromosomes is connected to protamine proteins. Significance of packing: almost full inactivation of genetic material of spermatozoa.

In a neck located proximal and distal centrioles. Proximal centriole takes part in formation of spindle of division of fertilized egg; and from distal centriole the axial string of tail is formed. Mitochondria are concentrated in the average part of neck. This part provides energy and metabolic activity of spermatozoa.

Basis of tail is the axial string surrounded with a small amount of cytoplasm and cell membrane.

Viability of spermatozoa depends on their concentration, concentration of hydrogen ions (in the alkaline environment spermatozoa have the greatest activity), and temperature.

5. Fertilisation, its phases, biological essence. Mono-and polyspermy

Insemination preceded to process of fertilisation (fusion of nucleus of male and female gametes). There are two ways of insemination: external and internal. Transitive forms (skin insemination) are characteristics for leeches.

Stages of fertilization.

1. Molecules on the sperm's surface recognize the egg, and the explosion of the needlelike acrosome allows the sperm to penetrate the coatings surrounding the egg's surface.

2. Plasma membranes of sperm and egg fuse.

3. Chemical reactions cause the breakdown of the granules below the ovum's plasma membrane and the establishment of the fertilization membrane, a barrier to penetration by any other sperm.

4. Sperm and egg nuclei fuse and form the diploid nucleus.

Phases of fertilisation:

External phase.

Female and male gametes release hamons. Ovicell produce ginohamons I and II, spermatozoa — androhamons I and II. The ginohamon I activates movement of spermatozoa and provides contact to an egg; androhamon II dissolves the egg coats.

The period of egg viability in mammals is up to 24 hours and period of spermatozoa viability is up to 96 hours depending on a kind of animals. Ability of spermatozoa to fertilization is kept from 24 till 48 hours.

At the moment of contact of spermatozoa with an external egg coats begins acrosome reaction. From the side of ovicell begins cortical reaction. From acrosome the hyaluronidase enzyme is released. Tubercle of fertilization is formed in a place of contact of spermatozoa with the plasma membrane of egg. Tubercle of fertilization promotes retraction of spermatozoa inside the egg. Membranes of gametes are merging. In some cases (in mammals) spermatozoa will penetrate into an egg without active participation of tubercle of fertilization.

Internal phase.

Process of fertilisation comes to the end with unity of genetic material of male and female gametes. The coat of fertilisation is formed in 1-3 minutes after insemination.

Fusion of male and female sex cells refers to *syngamy. Synkaryogamy* is a fusion of nucleus of gametes that makes essence of fertilisation.

6. Features of human reproduction, its hormonal regulation

At human the ovicell and spermatozoa develop from primary sex cells which are formed in mesoderm. Subsequently they migrate to a place of the final localization — in developing sex glands. At human they appear in a wall of yolk sack in 24 day after fertilisation, then at 4 week germs — in mesentary of a hindgut, and a week later — in rudiment of sex glands. At many animal sites of the cytoplasm, responsible for allocation of primary sex cells, differs by pigmentation or granules. It is sex determinants. Sex cytoplasm is localized on a vegetative pole of a cell.

Specific attributes of a female become appreciable at the end of 7–8 weeks. By the end 3 months inside of gonads are formed ovocytes (prophase 1). To 7 months, fast rates are got a differentiation of ovary. To 9-th month in ovary there are 200–400 thousand of oocytes. Specific attributes of male are observed at the end of 7-th week.

In ovogenesis, mitotic division of primary female sex cells stops to 5 to month of intra-uterine development. The amount of them reaches almost 7 million. Oogonia during their development turn in oocytes I. The further intra-uterine reproduction of oogonia stops. Therefore to the moment of a girl birth the ovary contains already about 2 million oocytes in primary follicles. However among them there is an intensive process of atresia. Therefore to the beginning

of a puberty about 400–500 thousand of oocytes capable to the further development remains in ovary.

Formation of primary follicles comes to the end by the end of 3-rd month of intra-uterine development when follicular cells completely cover oocyte. By the moment of end of formation of a primary follicle the oocytes are at diplonemm stage of meiosis 1. Since this moment there comes a long interval in the further development. The stop of division of oocyte I is kept before puberty.

Shortly before ovulation the stop at the diplonemm stage is interrupt. Division quickly comes to the end with formation of oocyte II and one so-called polar body. Ovulation of oocyte refers to oocyte II. After ovulation in oocyte take place the second division of meiosis which begins lasts up to a metaphase II. If fertilisation has taken place, the phase II of meiosis comes to the end. In result arises fertilized ovicell. If during 48 hours after ovulation fertilisation has not taken place, ovulated egg is perished.

Monthly in ovary matures one follicle inside which there is a gamete capable to fertilisation. Maturing of follicle has some stages. In the beginning oocytes I are surrounded by a layer of cells and the primary follicle is formed. Further during the period before puberty the follicles increase in sizes due to oocyte growth, formations of a transparent zone, and «corona radiate». Then the secondary follicle grows, turns in tertiary follicle or mature follicle that contains oocyte I. In total for the genital period at the woman matures about 400–500 follicles.

After follicle maturing, its wall is broken off and gamete gets in a cavity of a body. Oviduct settles down near ovary; cilias provide movement eggs on oviduct where there is a fertilisation. After ovulation, destroyed follicle is reduced and as a result of divisions of follicular cells the yellow body filling a cavity of vesicle is formed. If fertilisation does not occur, it degenerates, and in the other place of ovary new follicles start to grow. In case of pregnancy the yellow body is kept, and new follicles are formed after labor. In the juvenile and mature periods of ontogenesis oocytes in ovary are in prophase I (a diplonemm stage: chromosomes as lamp brushes, intensive synthesis of RNA). Periodically, the block of prophase I is removed and oocytes then comes to the end of meiosis I and comes in meiosis II. At fertilization, meiosis II comes to the end in 24 hours, later in 10 hours it is formed syncaryon and goes syngamy.

Blocking of meiosis I has adaptive character. Conjugation and crossing-over are under protection of a parent organism that guarantees smaller quantity of anomalies. For the period of puberty matures 400–800 oocytes. In postembryonic period the organism is subject to various influences of an environment that increases frequency of formation of abnormal gametes.

Growth of follicles and their ovulation are hormone dependent processes, which are regulated by hormones of a hypophysis: follicle-stimulating hormone (FSH), luteinizing hormone (LH), and hormones of ovary (estrogen and progesterone). Under influence of FSH there is development and maturing of

follicles in ovary. At joint action of FSH and LH there is a break of mature follicle, ovulation, and formation of a yellow body. After ovulation, LH promotes development in yellow body the hormone of progesterone.

Secretion LH and FSH by hypophysis is adjusted by humoral activity of hypothalamus which release hormons oxitocyne and vasopressine. These centers in its turn are under influence of hormones of ovary — estrogens. They influence on development of secondary sex traits, on methabolic exchange (strengthening dissimilation of proteins), and termoregulation. Besides ovary develop and androgens — man's sex hormones. The androgens released as well in a cortex of adrenal glands.

Man's sex gland — testicle is consisting from seminiferous tubules, surrounded by connective and loose connective tissue that produced hormones. Seminiferous tubules are consisting of various types of cells. Primary sex cells are in internal walls of seminiferous tubules.

Spermatogenesis is a way of transformation of primary sex cells — spermatogonia in spermatozoa in testicles. It consists of three steps. The first — repeated mitosis of spermatogonia. The second — meiosis I and II. The third — spermagenesis. All three steps of development occur in seminiferous tubules of man's sex glands — testicles. Spermatogonia are situated near the external wall of seminiferous tubules. They start to grow and move from periphery to the center of tubules passing to mitotic division. Spermatogonia grow and after numerous mitotic divisions form spermatocytes which passing to meiosis. Two meiotic divisions come to the end with formation of sperm cells.

At human, the first division of meiosis continues some weeks, the second — 8 hours. During the second division of meiosis spermatocytes II give four mature haploid (1n1c) sex cells. In a zone of formation they become sperm cells.

Gametogenesis is carried out during all period of male's sexual maturity. Full maturing of a sex cell takes 72 hours.

Functions of testicle are regulated by endocrine glands and hypophysis. The main male sex hormone (testosterone) developed by testicles (cells of Leydig). In small amounts, testosterone is formed also in cortex of adrenal glands. Under influence of testosterone, the formation and disintegration of protein in male's organism are intensifying that influence on development of muscles, bone tissue, and body size.

Reaction on gonadotropic hormones is universal for diagnostics of pregnancy. In urine of women appears gonadotropic hormone of chorion at an early stage of pregnancy.

Modern human reproductive strategy

1 Artificial insemination (Leonov, 1961).

2. Fertilisation in a test tube.

3. Artificial cultivation of an embryo and its replacement in uterus.
4. Substitutive motherhood.

LECTURE 5

Theme: Biology of sex

Plan:

1. Sex as a trait. Sexual dimorphism.
2. Types of definitions of sex.
3. Differentiation of sex traits in the ontogenesis.
4. Redefinition of sex. A role of sex hormones in differentiation of sex.

1. Sex as a trait. Sexual dimorphism

The sex is a set of morphological, physiological, biochemical, behavioural and other traits of the organism which provide a reproduction.

Traits on which individuals of different sexs differ divide on primary and secondary. Primary are submitted by the organs providing formation of gametes and fertilisation (gonads, reproductive tracts, and organs). These are external and internal genitals which are formed in embryogenesis. Secondary traits do not take part in a reproduction, develop under influence of sex hormones, and appear during puberty. These are morphological features of an organism. For example, development of a certain bone-muscular system, subcutaneous fat, scalp, timbre of a voice, features of behavior.

The traits of an individual connected to a sex are possible to divide into 3 groups:

1. Limited by a sex;
2. Controllable by a sex;
3. Sex linked.

Development of traits limited by a sex is caused by the genes located in autosomes of both sexes, but shown only at one sex. So, genes of egg-laying qualities have both hens and cocks, but the genes work only at hens. Such phenomenon is observed in relation with influence of corresponding sex hormones.

Example of the traits controllable by a sex is appearance of horns in male of cattle, and poll — in female of cattle. In human: the gene of bald spot has manifestation only in men, podagra — in 40% of men and is rare in women.

Traits which development is controlled by genes of sex chromosomes refer to sex linked. The amount of these traits is about 200. For example, daltonism and hemophilia are linked to the X-chromosome; hypertrichosis is linked with the Y-chromosome.

2. Types of definitions of sex

Definitions of sex can be divided on:

1. Progamic or before fertilisation.

2. Syngamic — genetic definition of a sex at fertilisation which depends on character of combination of sex chromosomes or from a ratio of sex chromosomes and autosomes.

3. Epigamic — it is formed under influence of an environment.

The chromosomal definition of sex concerns to syngamic type of sex definition. Chromosomes responsible for a sex definition have named sex chromosomes. The normal male gamete carries X or Y chromosomes and all ova carry X-chromosome. In case of a normal divergence of chromosomes in meiosis are formed normal ovule and spermatozoa with a usual set of chromosomes X and Y. The sex of a zygote is determined at fusion of gametes. Thus distinguish homogametic and heterogametic sex. At homogametic sex zygote has identical gametes. For example, female (XX) is homogametic sex at mammals and drosophila; male (ZZ) is homogametic sex at birds, reptiles, and insects.

The chromosomal theory of sex (Korrens, 1907) consists in a combination of sex chromosomes at fertilisation. Distinguish the following types of chromosomal definition of the sex: **XY, XO, ZW, ZO.**

Chromosomal definition of sex

The homogametic sex is characterized by presence of identical sex chromosomes.	
XX — female	In vertebrates, insects, arachnida, drosophila.
ZZ — male	In birds, fishes, butterflies, reptiles, amphibious.
The heterogametic sex is characterized by presence of different sex chromosomes.	
XY — male	In vertebrates, insects, arachnida, drosophila.
ZW — female	In birds, fishes, butterflies, silkworm, reptiles, amphibious.

At abnormalities during mitosis or meiosis an individual-gynandromorph can be formed. The combination of sex chromosomes in different cells of such individuals can be miscellaneous and cases mosaicism: XX/XXX, XY/XXX; XO/XXY.

At nondisjunction of sex chromosomes their different combinations are possible. It is the reason of chromosomal aberrations in human.

Nondisjunction of sex chromosomes

♂ \ ♀	X	XX	O
X	XX	XXX	XO
Y	XY	XXY	YO

XY	XXY	XXXY	XYO
O	XO	XX	O

In case of nondisjunction of sex chromosomes at meiosis gametes XX and 0 at female, and XY and 0 at male are formed. At their participation in fertilization, zygotes with unusual combination of sex chromosomes are formed. At human such anomalies meet in 1 of 600–700 newborns. Zygote YO perishes at early stage of development; individuals XXX, XXY, XO — are viable. Excess of X-chromosomes causes constitutional anomalies and mental defects. But in the nature there are individuals in which the Y chromosome is genetically inert and does not render special influence on sex definition.

At drosophila, individuals such as XO which were males are found out but are sterile (1916, K.Bridzhes), and individuals XXY was normal female.

The balance theory of sex (K. Bridgess, 1922)

The sex is determined by a ratio of number of sex chromosomes and ploidy number of autosomes.

Genes of female organism are situated in X-chromosomes, male — in autosomes.

In norm:

- female have balance 2X: 2A=1
- male — X: 2A=0,5.

Normal balance of sex chromosomes and autosomes in human:

- Women — XX: 44A.

Debalances: XO: 44A, XXX: 44A.

- Men — XY: 44A.

Debalances: XXY: 44A, XYY:44A.

Thus, essence of the balance theory that take part in definition of a sex not only sex chromosomes, but also autosomes. One haploid set of autosomes gives to individuals the male traits. In this case the sex is determined by a ratio of autosomes and sex chromosomes.

Definition of sex on ploidy meets at bees also. Female bees are diploid and male are haploid becouse developed by parthenogenesis from not fertilized ovicells.

3. Differentiation of sex traits in the ontogenesis

Formation of sex traits is carried out under the genetic control. The genetic sex of human embryo is determined by set of sex chromosomes at fusion of gametes: XX and XY.

Rudiments of gonads at early embryos (till 5-th or 6-th week) do not differ at different sexes and will consist of an external layer — cortex and an internal layer — medulla. Primary cells of a germ track are found out in human on 3-rd week of embryo developments in ectoderm of yolk sack. Then under influence

of chemotactic signals they migrate in gonads. This migration does not depend on sex. Rudiments of gonads can develop in ovary or testicle. The differentiation of male gonad is observed on 7-th week: to 36 day of development the testicle starts to release androgens wich determine the male development. Development of female gonad is observed on 8-th week; result of that is formation of female hormones — estrogens.

Stages of a differentiation of a sex in human

The periods of intra-uterine development (week).	Development of gonads and sex characteristics.
3	Primary sex cells
5	Formation of primary gonads
6	Bisexual gonads
7–8	Development of male's gonads (testicle)
8–9	Development of female's gonads (ovary)
7–9	formation of a hormonal sex
10–12	formation of internal genitals
12–20	formation of external genitals

The direction of sex development is defined by presence of Y-chromosome. In norm, the X-chromosome contains a gene-repressor — **the gene of testicular feminization Tfm** which does not give to develop on male type. Normal allele of the gene determines synthesis of protein receptor for androgens synthesized at both sexes. Development of male phenotype depends on a gene of Y-chromosome — **h-Y antigen**. It releases by primary male cells of the germ track. H-Y antigen is responsible for development of testosteron. As soon as these cells get in rudiments of gonads, the differentiation of testicle begins. H-Y-receptor are situated on a surface of gonad cells of both types. It was considered, that the male phenotype is determined by all genes of Y-chromosome. But in 1990 the gene (**Sex Region Y**), located in Y-chromosome was open. At its absence the genotype XY gives the female phenotype.

Development of gonads

Rudimentary gonad is bisexual till 6-th week of intra-uterine development.

The XX genotype of an individual causes development of cortex and forms ovary on 8–9 weeks of intra-uterine development.

The XY genotype of an individual causes development of medulla and forms testicle on 7–8 weeks.

Gonads determine development of primary and secondary sex traits. Sex glands release hormones (estrogens, androgens) which together with hormones of endocrine glands control ways of a sex differentiation. The level of hormones is in its turn controlled by genes.

Thus, process of the sex differentiation includes:

1. The genetic control.
2. Regulation functions of hormones.

There is *a theory of hormone action* as regulation factors of genes. Hormones force on specific cells only — *targets*. In a cell, the special protein is developed. It is the receptor contacting with hormone. Then it gets properties to induce work of one or several genes in chromosomes. Cells of female organism perceive the hormones of female type in the greater degree and a cell-target of male organism perceives the male hormones.

The theory of targets — the theory of action of hormones as gene regulatory factors. The main theses of the theory:

1. A protein-receptor is produced in target cells.
2. The protein-receptor contacts with the hormone.
3. Work of several genes in chromosomes is initiated.

Formation of proteins-receptors and hormones is controlled by genes.

Mutations of such genes cause:

1. Abnormalities of synthesis of protein-receptor.
2. Absence of perception of hormones.
3. Abnormalities of sex formation.

XTfm — normal allele: controls a synthesis of a protein-receptor for androgenes.

Xtfm — the recessive mutation of a gene: receptors are not synthesized, the hormone is not recognised.

The genetic scheme of crossing at redefinition of a sex

Task

P: ♀XTfm Xtfm x ♂XTfm Y

G: (XTfm) (Xtfm) (XTfm) (Y)

F: XTfm XTfm; XTfm Xtfm; XTfm Y; Xtfm Y.

Xtfm Y — Moris syndrome: an individual with male genotype but with female phenotype. It is caused absence of receptors to testosteron.

Formation of proteins-receptors and hormones is controlled in its turn by genes. In case of mutations there is disturbance of the control causing anomalies. As an example is the Moris syndrome. Persons with this disease do not have receptors to testosteron and the hormone is not perceived. Thus, the development on male type is stop and appears female phenotype. In a number of cases, it is possible to correct such defects by injection of appropriate hormones.

Primary genetic bisexuality is a basis for redefinition of sex. The germ of a male gets the attributes peculiar to a female. Individual has male karyotype, male gonads, but female phenotype. Proportions of body in the individual are

female; it has milk glands, short vagina, and testicle in the large lips of pudendum, inguinal canal, or abdominal cavity.

4. Redefinition of sex. A role of sex hormones in differentiation of sex

As a result of influence of hormones or disorder of function of receptors of target cells there can be a redefinition of sex.

In the nature it is a lot of factors weakening action of genes which control development of sex. For example, in human gonads of one individual can develop equally testicle and ovary parts.

The human hermaphroditism — it is the phenomenon of intersexuality.

On the basis of the clinical data distinguish 3 types of intersexuality:

1. True hermaphroditism — presence in individual the gonads and sex cells of both sexs.

2. Male pseudohermaphroditism: individual has only testicle, phenotype — female.

3. Female pseudohermaphroditism: individual has only ovary, phenotype — male.

Ratio of sexes

Primary ratio of sexes: at the moment of fertilisation the ratio should be about 1:1 as the meeting of sex chromosomes is equiprobable. At investigation in human it is revealed, that on 100 female zygotes it is formed 140–160 male zygotes. Spermatozoa with Y-chromosome are easier, more movable, and also have the big negative charge while ovule has positive charge. Therefore, spermatozoa with Y-chromosome impregnate ovule more often.

Secondary ratio of sexes: to the moment of a birth 100 girls accounts for 103-105 boys are born because of vitality female gametes and protein foreignness of male germs. To 20 years 100 girls accounts for 100 young men.

Tertiary ratio of sexes: to 50 years 100 women accounts for 85 men; and to 85 years 100 women accounts for 50 men. The female organism more adapted, that can be explained alongside with other reasons by mosaicism of a female organism on sex chromosomes.

In the beginning of female germ development the both X-chromosomes functioning, i.e. in two time more than in male. It is possible explain the big viability of female zygotes.

In 1962 M. Lajon has stated a hypothesis about inactivation of one X-chromosome in female organism of mammals. At a female germ, both chromosomes function up to 16 days of embryo developments. In 16-th day occurs

inactivation of one chromosome and forms sex chromatin. This process is random, therefore approximately in 1/2 of cells the mother's X-chromosome is kept active and father's X-chromosome is inactive. In other ½ of cells the father's X-chromosome is kept active and mother's X-chromosome is inactive. A change of activation does not occur. Mother's and father's X-chromosome can contain different alleles, i.e. in one chromosome can be located dominant alleles, in another — recessive. Having additional genes, adaptive possibilities of organism are increased. The female organism is more resistant to cold, ionizing radiation, and mental stress.

If the hypothesis worked without restrictions would not be phenotypic distinctions between healthy women with two X-chromosomes and patients with X0 or XY/XXYY sex chromosomes. Obviously, the X-chromosome is not full inactivated.

The formation of sex system start from genetic sex determination by chromosomes set. The genetic sex determines the gonad sex — histological structure of sex glands. It is allows to determine gametic sex — ability of sex gland to produce spermatozoa or ovule. Gonads show an individual role in reproduction process. Also gonad sex determines the hormonal sex — the ability of sex gland to produce specific sex hormones. Then, the level and dominating directions of hormonal action determine the morphological sex. Morphological sex means features of structure and development of internal and external sex organs, and also secondary sexual characteristics. It is important to note that a term «sex» is composed from many related to each other biological, social, and psychological components.

The scheme of a sex differentiation

Genetic	Chromosomes XX and XY
Gametic	Ovule, spermatozoa
Gonad	Testicle and ovary
Hormonal	Hormones of hypophysis; male and female hormones of gonads: androgens, estrogens (progesterone)
Morphological	Secondary sex features on male and female type
Psychological	Sexual psychological dominant

PART II

BASICS OF HUMAN HEREDITY AND DIVERSITY

LECTURE 6

Theme: Genetic as ascience. Gene level of hereditary material organization

Plan:

1. Genetics — a science about heredity and diversity.
2. The general concepts of a genetic material and its properties.
3. Levels of the structural organization of genetic material.
4. Structure of gene in pro- and eukaryotes.
5. Hypothesis «one gene — one enzyme».
6. Expression of genes in prokaryotes.
7. Features expression genes in eukaryotes. Human haemoglobins.
8. Gene engineering.

1.Genetics — a science about heredity and diversity

The heredity and diversity are fundamental properties of living things. The science studying laws of heredity and diversity refers to as *genetics*.

The genetics studies the following problems:

1. Storage of the genetic information.
2. Transfer of the genetic information.
3. Realization of the genetic information.
4. Change of the genetic information.

The first stage of genetics development covers period between 1900 and 1912. It starts in 1900 from rediscovering of Mendel's laws by scientists G. de Frieze, K. Correns, A. Chermak. The second stage (1912–1925) is creation of the chromosomal theory by T. Morgan. The third stage (1925–1940) is opening artificial mutagenesis and genetic processes of evolution. The fourth stage (1940–1953) is development of works about genetic control of physiological and biochemical traits. The fifth stage (1953 to present time) is characterized by development of molecular biology.

Fragmentary data on trait inheritance were known for a long time however scientific bases of trait transfer for the first time have been stated by G. Mendel in 1865 in his work: «Experiences on plant hybrid». It was advanced ideas but contemporaries did not give the matter to its opening. The concept «gene» was not at that time and G. Mendel spoke about «hereditary inclinations» contained in sex cells which nature was unknown.

In 1900 G. de Frieze, A. Chermak, and K. Correns rediscovered G. Mendel's laws independent from each other. This year also is considered year of

genetics birth as science. In 1906 U. Batson has entered the term «genetics» and in 1909 V. Jogansen has entered the term «gene». In 1911 the basic statements of chromosomal theory of heredity was formulated by T. Morgan with coworkers. They have proved that genes are located in the certain loci of chromosomes and in the linear order; therefore a gene began to consider as the site of the chromosome responsible for manifestation of certain trait.

HEREDITY is a property of living things to transfer morphology, function, and individual development traits from parents to offspring.

DIVERSITY is an ability of progeny to be distinct from parents by morphological and physiological traits and features of individual development.

INHERITANCE is a way of transfer of the genetic information: through sex cells at sexual reproduction or through somatic cells at asexual reproduction, i.e. a material basis is ovicell and spermatozoa, or somatic cells.

HERITABILITY is a degree of a ratio between heredity and diversity.

*GEN*E is unit of heredity and diversity, it is the sequence of DNA molecule giving the information on synthesis of certain polypeptide. The set of alleles of an organism which it receives from the parents refers to as the *GENOTYPE.* The set of genes in haploid set of chromosomes termed a *GENOME.*

Set of all external and internal traits of an organism refers to *PHENOTYPE*, and a separate trait refers to *PHENE*. For example, the nose form, the auricle form, form of fingers of foots and hands, color of hair are external phenotypic traits; features of a structure of a stomach, the contents of leukocytes and erythrocytes in blood are the internal phenotypic traits.

2.The general concepts of a genetic material and its properties

The *GENETIC MATERIAL* — it is components of a cell which have a structurally-functional unity and provide storage, realization and transfer of the hereditary information at asexual and sexual reproduction. The genetic material possesses universal properties of living things: discreteness, continuity, linearity, and relative stability.

The basic properties of genetic material:

1. The gene is store and transfer the hereditary information.
2. The gene is capable to change the genetic information due to mutation.
3. The gene is capable to a reparation and its transfer to next generations.
4. The gene is capable to realization — protein synthesis.
5. The genetic material has stability. Stability of genetic material is provided by:

— diploid set of chromosomes;
— double helix structure of DNA;
— redundancy of genetic code;
— repetition of some genes;
— reparing of DNA broken structure.

3. Levels of the structural organization of genetic material

Distinguish the following levels of the structural-functional organization of genetic material: gene, chromosome, and genome levels.

The elementary structure of the *GENE* level of the organization is the gene. At this level, the structure of DNA molecule, gene expression and repression, biosynthesis of protein, and etc.

Genes of eukaryotic cells are situated in chromosomes forming the *CHROMOSOME* level. This level of the organization studied the gene linkage and segregation of genes at sexual reproduction (crossing-over).

All set of genes of an organism function as the whole and form the uniform system named GENOME. The same gene in different genotypes can express differently. The genome level explains interaction of genes both in one and in different chromosomes.

In 1928 N. K. Koltsov has assumed that the chemical basis of gene is protein molecule. However, further with opening of the phenomena of transformation of microorganisms, the role of DNA in transfer of the hereditary information has been proved.

Thus, in the beginning of 50^{th} years it has been proved that material of heredity and diversity is the gene which has the certain structural-functional organization. By modern definition, the gene is the site of DNA molecule which determines the polypeptide synthesis.

The sexual process of bacteria at which the genetic material is transfer refers to *CONJUGATION*.

TRANSFORMATION is ability of DNA of one bacterium to build into sites of DNA molecule of another bacterium and thus to transfer of inherited traits from one to another bacterium (experiences F. Griffith with pneumococcuses).

TRANSDUCTION is ability of bacteriophages to transfer fragments of DNA from one bacterium to another and to transfer of inherited traits from one to another bacterium.

The gene level is connected with successes of the chromosomal theory.

Concept of «gene» was offered first in 1909 by the Danish geneticist Wilhelm Johannsen. W. Johannsen considered that: the gene is the material particle laying in a chromosome, capable to a self-reproduction and being the minimal unit of recombination, mutations and genetic function.

Mendel has suggested to designate the hereditary inclinations (genes) by letters of the latin alphabet. *Allele* — one of the alternative forms of a gene, on which depends a development of alternative traits. Alleles are located in the same locus of homologous chromosomes and have 2 states — *dominant and recessive.*

In relation with successes of molecular genetics old ideas about the gene have subjected to essential revision. According to the modern conception, the GENE is a specific sequence of nucleotides of the DNA molecule that have the function which are distinct from function of other genes.

4.Structure of gene of pro- and eukaryotes

It was originally supposed that the gene is indivisible and integrated unit. As a whole the gene is exposed to mutations, recombinations and is responsible for function. However it was found that the gene is discrete.

Well-defined gene discreteness has been investigated by American geneticist S. Benzer on the example of thin structure of genes of phage T4 of *E. coli*. He showed that the gene can be divided by crossing-over into parts. The discrete organization of genes has been established and at eukaryotes.

At the end of 50th years S. Benzer assumed that the gene is integrated and discrete unit at same time. At realization of the basic function — programming of protein synthesis — the gene acts as integrated unit which change causes the change of structure of protein molecule. This unit S. Benzer has named *INTRON*. The size of it is approximately equal to a gene.

Discreteness of gene consists in existence of subunits. Elementary unit of a mutation is *MUTON;* and elementary unit of the recombination is *RECON*. The minimal size of muton and recon are equal to 1 pair of nucleotides and to be termed the *SITE*. Thus, the *site* is structural unit of a gene.

The sizes of genes are various. The number of nucleotide pairs in the structural gene is about thousand. The shortest well known structural genes are genes coded the transport RNA. These genes contain more than 190 nucleotide pairs. The largest gene (for example, the gene of silk fibrin of silkworm) reaches the size more than 16,000 nucleotide pairs.

Right up to the end of 70th years it was believed that genes exist as whole piece of DNA molecule. However, in 1977 it has been shown that at adenovirus some of genes exist as a fragments distributed throughout the genome.

The site of a gene carrying the genetic information is termed EXON, and the site of a gene do not carrying the genetic information is termed INTRON. For example, the globulin coding gene has 3 exons and 2 introns.

In the beginning, the DNA sequence is transcribed to pro-mRNA sequence. Then pro-mRNA is exposed to stage-by-stage splicing and only after that it turns out to mature mRNA which is ready for the subsequent translation. The explanation of the fact of existence introns is not found yet. It is supposed, that at the moment of m-RNA formation from pro-mRNA a various linkage of exons will lead to synthesis of various proteins. Probably, introns serve as a material for formation of new genes during evolution. It is shown that mutation of introns can break process of splicing, stop synthesis of protein, and change its structure.

The term «gene» at once as has been offered, was used for a designation of the hereditary inclinations determining development one or the other of external phenotype traits.

5. Hypothesis «one gene — one enzyme»

In the 40th years George Beadle and Edward Tatum offer a hypothesis: one gene — one enzyme.

Today, when researches showed that some proteins are composed of more than one polypeptide chain and that different polypeptide chains are encoded by separate genes, this model was modified to become — the one gene, one polypeptide hypothesis. Moreover, gene carries out various functions. Well known genes which control expression of genes and replication.

6. Expression of genes in prokaryotes

Genetic mechanisms of gene expression have been investigated in microorganisms by French geneticists François Jacob and Jacques Monod. In 1961, Fr. Jacob and J. Monod described the «operon model» for the genetic control of lactose metabolism in *E. coli*.

The main position of this theory is that there are two types of genes in DNA molecule — *structural* and *regulatory*.

Structural genes encode proteins that are used in metabolism or biosynthesis, or that play a structural role in the cell.

Regulatory genes are genes whose products, either RNA or proteins, interact with other sequences (structural genes) and affect their transcription or translation. In many cases, the products of regulatory genes are DNA-binding proteins.

One or several structural genes that located in bacterial or virus DNA near to group of regulatory genes are represent the unit of genetic regulation — OPERON.

Principles of operon work can be shown on the example of operon work of *E. coli*. This operon is responsible for assimilation of lactose by this bacterium.

Nucleoid of *E. coli* has various sites including lactose area (lac-operon). Lac-operon includes 3 genes coding 3 enzymes. All genes of lac-operon are transcribed in one mRNA which is translated to 3 proteins.

Operon starts from a site, to which the special protein-activator (the Cap-protein which is making active catabolic genes) is affiliated. Without this protein the RNA-polymerase enzyme cannot contact with operon and begin transcription. Cap-protein preliminary becomes more active itself with help of cyclic AMP. After this site a promotor is situated. It is the DNA sequence which identified by RNA-polymerase and attached to the promotor, and then moves along the operon and transcribes it. An operator is situated after the promotor. It is consists of 21 pairs of nucleotides and plays the important role in regulation of operon work; with it the special protein which inhibits transcription (REGULATORY PROTEIN) can affiliated. The lac-operon comes to the end with the small site of DNA serving as a stoplight, stopping moving of RNA-polymerase and transcription of operon.

The regulation of work of structural genes of lac-operon is carried out by regulatory protein which is coded by gene-regulator. This protein is synthesized continuously in the cell but in very small amount (at the same time in cytoplasm is present no more than 10 of its molecules). Regulatory protein possesses affinity with the operator of lac-operon and if in the cell there is no lactose it is

attached to the operator and inhibited the movement of RNA-polymerase from the promotor to structural genes. Thus structural genes are subjected to repression. Synthesis of coded enzymes does not go. After inflow of lactose the regulatory protein contacts with lactose earlier than its molecules achieve the operator. The structure of regulatory protein is strongly changes to what loses ability to affiliate with the operator. Lactose plays a role of effector: the low-molecular substance change the properties of protein at connection with it. Changed regulatory protein ceases the contact with the operator, RNA — polymerase freely moves along the operon and transcribes structural genes. In the cell, synthesis of all three enzymes necessary for assimilation of lactose begins, i. e. there is an induction (expression a gene).

Regulation of activity of eukaryotic genes is investigated less than in viruses and prokaryotes. It is caused by presence in eukaryotes a nucleus, complicated organization of chromosomes and celldifferentiations. It is supposed, that in a basis of regulation of action of eukaryotic genes the mechanisms basically similar to those at viruses and prokaryotic are lay. However, there are also essential differences.

7. Features of gene expression in eukaryotes. Human haemoglobins

There are differences in regulation of gene activities in eukaryotes and prokaryotes:

1. Operon of eukaryotes consists of one gene.
2. In eukaryotes, the structural genes responsible for different parts of biochemical reactions are scattered in genome instead of concentration in one operon.
3. In eukaryotes, there is a group repression of gene activity in the nucleus, in the chromosome, or in its parts.
4. There is a system of steroid hormones for regulation activity of genes in eukaryotes.
5. Eukaryotes genes may change their activity during ontogenesis.

An example of complex expression of genes is the gene control of synthesis of human haemoglobins. It is known, that the hemoglobin HbA contains a as two chains of protein α and two chains of protein β. Moreover, in 2.5% of cases there is haemoglobin HbA2 which consist of two chains of protein α and two chains of protein σ. In fetus erythrocytes about 80% of hemoglobins are in the form HbF, their molecules consist of two chains of protein α and two chains of protein γ. In addition, patients with sickle-cell an anemia have hemoglobin HbS which differs from normal HbA by amino acid substitution in one chain of protein β (in 6-th position glutamic acid is replaced by valine). These four haemoglobin types are controlled by separate genes. The locus α^A determines formation of protein α during all life in all four haemoglobins. The locus β^A supervises formation of protein β only in HbA after a birth. The locus

γ^F determines synthesis of protein γ in haemoglobin HbF during an intra-uterine life. The locus σ^{A2} determines synthesis of protein σ in haemoglobin HbA2 during all life after a birth. Combination of protein chains gives four types of haemoglobins. Loci α^A, β^A, σ^{A2}, γ^F are closely linked in a chromosome. All four specified genes are structural. In their action there is a complex cooperation due to what there are four types of haemoglobins. Expression of genes β^A, σ^{A2} is under influence of gene-regulators that is shown in the fact of replacement HbF of fetus on HbA and HbA2. The adults have repression of gene γ^F and inclusion of gene β^A. Interaction of genes α^A, β^A, and σ^{A2} determines development of normal haemoglobin (an example of intergenic interaction); and interaction β^A and β^{AI} in HbS is an example of allele interaction which determined by the pathology of haemoglobin.

Characteristics of the human haemoglobins

Type of Hb	Polypeptide chains	Gene loci
HbA	2 α, 2 β	α^A, β^A
HbA2	2 α, 2 σ	α^A, σ^{A2}
HbF	2 α, 2 γ	α^A, γ^F
Hbs	2α, β, $\beta^{6\text{-valine}}$	α^A, β^{AI}

The above-stated data have allowed to formulate the modern theory of a gene:

1. The gene occupies the certain locus in a chromosome.
2. Gene is a part of DNA molecule; a number of nucleotides in a gene is various.
3. Inside of gene can occur recombination and mutation.
4. There are structural and regulatory genes.
5. Structural genes encode structure of proteins, tRNA, and rRNA.
6. Regulatory genes regulate the activity of structural genes.
7. Arrangement of triplets in structural genes collinear to sequences of amino acids in proteins.
8. The genotype, being discrete, functions as a whole.

8. Gene engineering

One of sections of molecular genetics and molecular biology which has come nearer to a boundary of practical use is the gene engineering. The gene engineering is the sum of the methods, allowing to transfer genes from one organism to another, or it is a technology of the designing of new biological objects. The follow operations is included in gene engineering:

1. Synthesis of genes outside of an organism.
2. Isolation of single genes or genetic structures (fragments of chromosomes, the whole chromosomes, nucleus) from cells.
3. The directed reorganization of the isolated structures.

4. Copying and reproduction of the isolated genes or the synthesized genes or genetic structures.

5. Transfer and insertion of the genes or genetic structures in new genome.

6. Experimental joining of genomes in one cell.

Gene engineering include:

1. Receiving of a genetic material.

It is carried out by its isolation from the genome of donor cells, or by its chemical synthesis.

2. Introduction of a genetic material.

It is carried out by transformation, transduction, conjugation, and somatic hybridization.

3. Inclusion of new genes in the genetic material of cells, with the help of a vector. It can be plasmid vector, cosmid vector, retroviral vector and etc.

With the help of gene engineering it is solved a number of problems of biology: mosaic structure of gene, decoding of gene structure, coding antibodies. In 1980, the somatotropin hormone; in 1982, the insulin, and also interferon, vitamins, and other hormones is received by the method of gene engineering. The gene engineering is a basis of biotechnology; and in medicine provides manufacture of vaccines, serums, and also diagnostics of genetic anomalies of human at early stages of it development (gene surgery is replacement of the injured gene by new), and gene therapy.

In 2001 with help of Human genome program the quantity of the genes in human genome was open. It expands opportunities of use of genetics for the medical purposes.

However cultivation of hybrids of human and chimeras, and also all works on human cloning should be forbidden. It is opinion of the majority of geneticists.

Change of genes with the help of somatic cells should be carried out for human only in the therapeutic purposes. Application of sex cells for gene treatment is possible only at the sufficient proof of safety of such treatment in comparison with gene therapy by somatic cells.

LECTURE 7

Theme: Laws of inheritance on the ontogenetic level. Monogenic and polygenic inheritance

Plan:

1. The basic types of inheritance.
2. Laws of monogenic inheritance.
3. Solution of genetic tasks.
4. Polygenic inheritance.

1. The basic types of inheritance

Genetic processes are determining factors in ontogenesis of all organisms. An individual development of any organism is determined by its genotype. From generation to generation the information about all diverse morphological, physiological, and biochemical traits is transferred. *INHERITANCE* is a way of transfer of the genetic information: through sex cells — at sexual reproduction, or through somatic cells - at asexual reproduction.

Two basic types of inheritance are distinguished — monogenic and polygenic. At monogenic — the trait is controlled by one gene, at polygenic the trait is controlled by several genes. Genes can be located in autosomes or sex chromosomes. The mode of a gene expression can be dominant or recessive.

Now, distinguish the following types and variants of trait inheritance:

1. Monogenic.
2. Polygenic.
3. Autosomal: dominant and recessive.
4. The heredity linked with sex chromosomes: linked with X-chromosome (dominant and recessive) or Y-chromosome.

Genes can be located in different chromosomes or chromosomes represent group of linkage of genes.

The basic processes that difine the laws of inheritance:

1. Self-reproduction of chromosomes.
2. Distribution of chromosomes at gametogenesis and their combination while fertilization.
3. The gene control during ontogenesis.

2. Laws of monogenic inheritance

Material bases of heredity are studied with help of the cytology method. The combination of cytology method with the hybrid analysis gives cytogenetic method.

Laws of monogenic inheritance were open by G. Mendel, which has developed a hybrid method, stated in 1868 in work «Experiences under plant hybrids». G. Mendel first discovered the principles of heredity by crossing different varieties of pea plants and analyzing the pattern of transmission of traits in subsequent generations.

Mendel has based completely new principle of the research. Attributes of the hybrid method of G. Mendel:

1. Selection of parent pairs (pure lines) for crossing.
2. In each generation it is necessary to keep count of organisms at each pair of alternative characteristics, without taking into account other differences between crossed organisms.
3. Use the quantitative analysis of hybrid organisms.
4. Individual analysis of the offspring from each hybrid organism.

For the genetic analysis of the certain traits at sexual reproduction the crossing of two individuals is necessary. Mendel has suggested to designate hereditary inclinations (genes) by letters of the latin alphabet. One of two or more alternate forms of a gene is accepted to name as allelemorphic (from Greek. allelon — «with each other», morph — the form) or allelic. Allelic genes are located in same locus of homologous chromosomes. Each gene can have two conditions — **dominant** and **recessive**. A prevalence of attribute of one of parents in the offspring of the first generation, Mendel has named **dominance** (from an armour. dominans — to prevail). The attribute that suppressed in hybrids has received the name (from an armour. recessus — deviation) **recessive**. The dominant gene can be designated the capital letter of the latin alphabet (A), and recessive — by small letter (a). The organisms having identical alleles of one gene, for example, both dominant (AA) or both recessive (aa) refer to **homozygotes**. The organisms having different alleles of one gene (Aa) refer to **heterozygotes**.

If the organism has only one allele of a gene (X) such organism refers to **hemizygote**. At writing the scheme of crossing it is accepted to put on the first place a genotype of female organism, on the second place — male. Crossing is designated by multiplication (x). Parental individuals are writed in the first line and designated by the letter «P». Gametes, which are formed by parents, are writed in the second line and designated by the letter «G». Progeny are writed in the third line. It are named hybrids and designated by the letter «F» with the digital index corresponding to a number of hybrid generation. For example:

P: ♀ AA x ♂ aa

G: (A) (a)

F1: Aa

The essence of the first law of Mendel can be formulated as follows: **in a cross between homozygous-dominant and homozygous-recessive individuals, all hybrids of the first generation will resemble its dominant parent in their phenotype.**

Mendel's first law receive name ***the low of uniformity of hybrids of 1-st generation or the law of dominating*** (concept of dominance).

On the basis of studying of hybrids of 2-nd generation the second law has been formulated by G. Mendel: **in crossing of two heterozygous individuals (i.e. hybrids) analyzed on one alternative pair of traits, the phenotype ratio 3 : 1 and the genotype ratio 1 : 2 : 1 are expected.**

P: ♀ Aa x ♂ Aa

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

F1: AA, Aa, Aa, aa

Segregation on a phenotype — 1:2:1.

Segregation on a genotype — 3:1.

This law has been named ***the law of segregation or principle of segregation***.

For an explanation of results of the 2-nd Mendel's law, W. Batson (1902) suggested a thesis of «GAMETES PURITY»:

1. genes in gametes of hybrids are discrete (pure);

2. only one gene from the allele pair gets in a gamete due to a divergence of homologous chromosomes in the meiosis.

The reason of not mixing of genes in heterozygote state is their situation in different chromosomes. In result of meiosis chromosomes with genes get in different gametes. This phenomenon is shown with help of cytologic bases of monohybrid crossing.

To analyze a genotype of individual with a dominant phenotype carry out so-called *test crossing*. It is because of the individual with dominant phenotype may be either homozygous or heterozygous. In testcross, analyzing individual is crossed with homozygous recessive one. If all offspring appears homogeneous, an analyzed individual is homozygote on dominant allele; if there was segregation 1:1 — it is heterozygote.

For dihybrid crossings by G. Mendel was taken the homozygous organisms differing on two pairs of traits. Hybrids of the first generation were uniform to both dominant characteristics. At the analysis of inheritance of traits in the second generation (F2) the independent (free) combination of pairs attributes was observed. This conclusion has received the name **of the third law of Mendel *or the principle of independent assortment.***

This principle states that alleles at different loci separate independently of one another. The principle of independent assortment is an extension of the principle of segregation. The principle of segregation states that the two alleles of a locus separate when gametes are formed; the principle of independent assortment states that, when these two alleles separate, their separation is independent of the separation of alleles at *other* loci.

The scheme of crossing

Gene	characteristics	Genotype	P: ♀ AaBb x ♂ AaBb G: (AB) (Ab) (AB) (Ab) (aB) (ab) (aB) (ab) F1: segregation on phenotypic radical is: 9A-B-; 3A-bb; 3aaB-; 1aabb
A	yellow	AA, Aa	
a	green	aa	
B	round	BB, Bb	
b	wrinkled	bb	

The general formula of dihybrid crossings — $(3:1)^2$; for polyhybrid crossing — $(3:1)^n$.

The phenotypic radical is the part of genotype of an organism which determines its phenotype.

3. Solution of genetic tasks

Task on monohybrid crossing

At human, a gene causing one forms of hereditary surdomutism is recessive to a gene of normal hearing. What progeny is possible from a marriage of heterozygotic individuals?

Trait	Gene	Genotype	Solution:

Norm	A	AA, Aa	P: ♀ Aa x ♂ Aa F_1: AA, 2Aa, aa Answer: 75% — norm hearing, 25% — surdomutism.
Surdomutism	a	aa	
P: ♀ Aa x ♂ Aa F_1 — ?			

Ability to manage the right hand at human dominates above the ability to manage the left hand. In a marriage of two right-handed persons the left-handed child was born. What genotypes of parents?

Trait	Gene	Genotype	Solution:
Right-hander	A	AA, Aa	P: ♀ Aa x ♂ Aa F_1: AA, 2Aa, aa Answer: genotype of parents — Aa.
Left-hander	a	aa	
P: ♀ A_ x ♂ A_ F_1 — aa P — ?			

Task on dihybrid crossing

At human, short-sightedness dominates over normal sight, and brown color of eyes dominates above blue color. The single child of short-sighted brown-eyed parents has blue eyes and normal sight. Give genotypes of all members of family.

Trait	Gene	Genotype	P: ♀ AaBв x ♂ AaBв
Short-sightedness Norm Brown eyes Blue eyes	A a B в	A aa B- вв	F: 9A-B- : 3A-вв : 3aaB- : 1aaвв

Task on polyhybrid crossing

Human has some forms of a hereditary cataract: dominant and recessive. What probability of healthy child birth from the parents with the dominant hereditary form and two recessive forms of cataract. Parents are heterozygotes for all forms of cataract.

The analysis of one pair of attributes in monohybrid crossing gives segregation 3:1 on a phenotype which is provided with a divergence of homologous chromosomes in meiosis. At polyhybrid crossing the segregation of different pairs of alternative attributes is expressed by the formula $(3+1)^n$, where n — number of pairs of alternative attributes.

Attribute	Gen	Genotype	Solution:
Cataract 1	A	AA,Aa	P ♀ AaBвDd x ♂ AaBвDd F_1: aa B_D_-? P ♀ AaBвDd x ♂ AaBвDd G: (ABD), (ABd) (AвD), (Aвd) (aBD), (aBd) (aвD), (aвd)
Norm 1	A	aa	
Cataract 2	в	Bв	
Norm 2	B	BB, Bв	
Cataract 3	d	Dd	
Norm 3	D	DD, Dd	

			F_1: $(3:1)^3$ → (3A_:1aa)(3B_:1вв)(3D_:1dd) → 27A_B_D_:9A_B_dd:9A_ввD:_9aaB_D_: 3A_ввdd:3aaB_dd :3aaввD_:1aaввdd
Answer: 9/64*100=14% of healthy children.			

As well as any laws of the nature, Mendel's laws may work only in certain conditions which are:

1. Equal probability of all kinds of gamete formation by all hybrids.
2. Equal probability of all possible combinations of gametes while fertilisation.
3. Equal viability of zygotes of any genotypes.
4. Full trait expression independently from development conditions of an organism.
5. Genes location in different chromosomes in dihybrid and polyhybrid crosses.
6. Equal probability of all kinds of gamete formation on the basis of independent assortment of non homologuos chromosomes in meiosis while di- and polyhybrid cross.

4. Polygenic inheritance

As it has already been told, the mechanism causing segregation of attributes in hybrid progeny is meiosis. Meiosis provides a divergence of chromosomes at formation of gametes, i. e. segregation is carried out in haploid gametes, at a level of chromosomes and genes but the result is analyzed in diploid organisms at a level of traits.

Between these two moments passes a lot of time during which on gametes, zygotes and developing organisms the set of environment conditions operates. Therefore, if in a basis of segregation the biological mechanisms lay, the observed segregation has random or statistical character.

G. Mendel had several pairs of attributes when analyzed its inheritance in peas. About 3000 traits which inheritance submits to Mendel's laws are known in human. American geneticist V. Makkjusik has published the catalogue of hereditary traits of human which supplemented every year.These are color of eyes and hair, form of nose, lips, teeth, chin, fingers, and auricle.

Many hereditary diseases also submit to Mendel's laws. The major task of medical genetics is the knowledge and description of human hereditary diseases. It is known more than 2000 hereditary diseases and anomalies of development. They are studied on molecule, cell, ontogenetic and population levels. There are a number of heavy diseases of nervous system (schizophrenia, epilepsy), of endocrine systems (cretinism), blood (hemophilia), metabolic exchange (phenylketonuria, alkaptonuria, albinism). Studying of the reasons of these

diseases, their early diagnostics allows to develop the methods of its prevention. The medical genetics has reliable methods of diagnostics and identification of hereditary diseases. Establishment of genetic consulting centres will help the doctor to conduct early diagnostics, treatment and prevention of hereditary diseases.

Some inherited traits and diseases that submit to Mendel's laws

Dominant	Recessive
Norm	
Brown eyes	Blue eyes
Dark hair	Light hair
Mongoloid eyes	European eyes
Aquiline nose	Nose of a straight line
Dimples on cheeks	Absence
Freckles	Absence
Right — handedness	Left — handedness
Rh +	Rh-
Pathological	
Chondrodystrophia	Normal development of skeleton
Polydactylia	Norm
Brachydactyly	Norm
Normal blood clotting	Hemophilia
Normal sight	Daltonism
Pigmentation	Albinism (absence of melanin)
Normal exchange of phenylalanine	Phenylketonuria

LECTURE 8

Theme: Mechanism of development: the genotype expression in the phenotype

Plan:

1. Phenotype as result of realization of a genotype in the certain conditions of environment.
2. Allele interaction.
3. Gene interaction.
4. Quantitative and qualitative specificity of gene expression in attributes.

1. Phenotype as result of realization of a genotype in the certain conditions of environment

All organisms are characterized by suitability to various factors of environment. Among them, there is factors which operate on an organism during many geological epoch (gravitation, change of day and night, magnetic field) and factors which operate only a short time and locally (water stress, overcooling, overheating, noise).

Therefore, at human during historical development the high level of adaptation to an environment was developed due to genes determine not only a final attribute but also limits of variation of attributes. It achieves smaller dependence on environment but complexity of the genetic apparatus and complexity of the control of development of attributes raises. For development of attribute, i. e. the genotype was realized in a phenotype, corresponding conditions of environment are necessary. It is possible to illustrate with the following scheme:

ONTOGENESIS
GENOTYPE ----------> PHENOTYPE
CONDITIONS OF THE ENVIRONMENT

In ontogenesis operates more likely not separate genes but all genotype as the complete integrated system with difficult connections. Such system is not stable, it is dynamic. As a result of mutations there are new genes, new chromosomes and new genomes are formed. New genes interact with old or can change their work. Thus, genotype is complete system developed historically.

Gene expression can vary under various mutations and under influence of various factors. It has been established that many genes can influence one attribute and, on the contrary, one gene frequently influences on many attributes. Beside this, gene action can be changed by the neighbourhood genes or conditions of an environment. Mendel's laws reflect laws of inheritance under conditions: genes are located in different in pairs of homologous chromosomes and for each attribute one gene answers. However, it is not always so.

Mode of gene expressions is various and depends on properties of genes. There are:

1. The gene *is discrete* in the action: provide course of a certain biochemical reaction, a degree of the character expression or repression.
2. Each gene *is specific* in the action: it is responsible for synthesis of the primary structure of an protein molecule.
3. The gene can have a multiple action — *pleiotropy*.
4. The different genes which are located in different pairs of homologous chromosomes, can act on development of the same character, intensifying or weakening it — *polimery*.
5. The gene *can interact* with other genes, thereby its effect can vary.
6. Phenotypic expression of a gene depends on the environment factors.

At the analysis of Mendel's laws we supposed that dominant gene completely suppresses expression of recessive gene.

2. Allele interaction

The careful analysis of realization of genotype in phenotype has shown that trait expressions can be determined by interaction of alleles. Types of allele interaction:

- Dominance or complete dominance.
- Incomplete dominance.
- Codominance.
- Overdominance.

Dominance is property of a gene to cause development of an attribute in a heterozygotic condition. Whether it means, what recessive allele is completely suppressed and does not function at all? It appears — is not. The recessive gene is expressed in homozygous condition.

For the majority of attributes at animals and human there is an ***intermediate inheritance or incomplete dominance***. At incomplete expression of gene the hybrid does not reproduce completely any of parental attributes. Expression of an attribute appears intermediate with the big or smaller bias to dominant or recessive condition. Inheritance of sickle-cell anemia and anophthalmia are examples of incomplete dominance in human.

Task 1

Sickle-cell anemia is inherited as not completely dominant attribute. In natives of Africa, dominant gene S in a homozygous condition causes death of individuals from an anemia. People with a genotype ss in local conditions perish from malaria but do not suffer anemia. Heterozygotes survive, as do not suffer anemia and not ill malaria.

What probability of viable progeny birth from heterozygotic parents?

At ***overdominance*** the dominant gene in heterozygotic condition expressed more strongly, than in homozygous: Aa > AA. For example, in *Drosophila* a recessive lethal allele (a) is present:

— homozygote (aa) is dead,

— homozygote (AA) have normal viability,

— heterozygote (Aa) live longer and give more progeny, than dominant homozygotes. It is possible to explain such phenomenon by interaction of gene products.

Alleles in heterozygotic condition can be expressed both simultaneously. This phenomenon has received the name ***codominance***. For example, each of alleles encodes synthesis of the certain protein. Then at heterozygotes synthesis of both proteins is take place that it is possible to reveal by biochemically. This method has found application in genetic consuling for revealing of heterozygotic carriers of the genes causing illness of metabolic exchange. For example, inheritance of the fourth blood group with genotype I^AI^B.

For some loci, more than two alleles are present within a group of individuals — the locus has ***multiple alleles***. (Multiple alleles may also be referred to as an ***allelic series***.) Although there may be more than two alleles

present within a *group,* the genotype of each diploid *individual* still consists of only two alleles. The inheritance of characteristics encoded by multiple alleles is no different from the inheritance of characteristics encoded by two alleles, except that a greater variety of genotypes and phenotypes are possible. At human series of alleles I^0, I^A, I^B which determines polymorphism on blood groups is known. Presence in erythrocytes two antigenes A and B, and presence in blood serum two agglutinating antibodies (α and β) has been established. Be found that a human population is broken on 4 groups depending on blood groups:

Inheritance of blood groups in human (system AB0)

Blood group	Antigenes	Antibodies made by body	Gene	Genotype	Interaction of genes
I (0)	—	α,β	I^0	$I^0 I^0$	
II (A)	A	β	I^A	$I^A I^A$, $I^A I^0$,	dominance
III (B)	B	α	I^B	$I^B I^B$, $I^B I^0$,	dominance
IV (AB)	A, B	—	I^A, I^B	$I^A I^B$	codominance

Task 2

Mother has 1st blood group and the father — IV. Whether children can inherit blood group of one of the parents?

P: ♀ $I^0 I^0$ x ♂ $I^A I^B$

F_1: $I^A I^0$, $I^B I^0$

Answer: cannot.

3. Gene interaction

Frequently, the effects of genes at one locus depend on the presence of genes at other loci. This type of interaction between the effects of genes at different loci (genes that are not allelic) is termed gene interaction. Distinguish the following kinds of gene interactions: ***epistasis, hypostasis, complementation, and polymery.***

At dominance, action of one allele is suppressed by another allele the same gene: A> a, B> b. Sometimes the effect of gene interaction is that one gene masks (hides) the effect of another gene at a different locus (A> B, C> D, c> d), a phenomenon known as ***epistasis***.

In epistasis, the gene that does the masking is called the ***epistatic gene***; the gene whose effect is masked is a ***hypostatic gene***. Epistatic genes may be recessive (***recessive epistasis***) or dominant (***dominant epistasis***) in their effects.

Dominant epistasis — type of interaction when dominant allele of one gene repress the action of another non allele gene (A- > B-, A- > bb). Segregation at dominant epistasis is — 13:3 or 12:3:1.

Recessive epistasis — type of interaction when recessive allele of one gene in a homozygous condition represses dominant or recessive allele of another gene (aa> B- or aa> bb). Segregation is — 9:4:3.

Task 3

Two forms of short-sightedness is known in human: moderate and high. They is determined by two dominant non allele genes. A high short-sightedness become apparent in people with both forms.

Mother has a high form of short-sightedness (one of parents is short-sighted), father is norm, children: the daughter — with the moderate form of short-sightedness, the son — with high form of short-sightedness. What genotypes of parents and children? What proportion of children's genotypes?

Solution:

P: ♀ AaBb x ♂ aabb

G: (AB), (Ab) (ab)
(aB), (ab)

F1: AaBb, Aabb, aaBb, aabb
high, high, moderate, norm

Answer: 50% high, 25% moderate, 25% norm.

Event of recessive epistasis on the example of the Bombay phenomenon in human

In human is the gene f — epistatic. Homozygote ff suppresses action of dominant alleles I^A, I^B. At the Bombay phenomenon the genotypes I^AI^0ff and I^BI^0ff phenotypically display I(0) blood group.

F — normal allele. Genotypes I^AI^0FF, I^AI^0Ff, I^BI^0FF, and I^BI^0Ff correspond to their phenotypes.

Epistatic interaction of genes plays the basic role in hereditary diseases of human metabolism, when one gene suppresses formation of active enzymes of other gene.

Complementary, or supplementing genes be named dominant genes which at a combined presence (in genotype A-B-) cause development of a new attribute in comparison with separate action of each gene (A-вв or aaB-). The normal hearing is inherited in human on the base on a principle of ***complementation***.

Task 4

Deafness is caused by different recessive genes d and e that laying in different pairs of chromosomes. D and E are normal alleles. D — controls the normal development of a cochlea. E — controls the normal development of an acoustic nerve. Person with D-E- genotype is normal hearing. People with

genotypes E-dd and eeД- are deaf persons. In a marriage of a deaf man (ddEE) with deaf woman (ДДee), all children will healthy.

Solution:

P: ♀ DDee x ♂ ddEE

G: (De) (dE)

F1: DdEe — complementary action of genes.

Answer: 100% children will healthy.

The types of interaction of genes considered till now concerned to qualitative alternative attributes. However, organism traits like rate of growth, weight of body, length of body, arterial pressure, and degree of pigmentation is impossible to decompose on phenotype classes. These traits has name *quantitative.* Each of such traits is formed usually under influence of several equivalent genes. The phenomenon of trait formation as a result of action of several genes refers to *polymery (-ia)*, and genes has name *polymeric*. In this case the principle of unequivocal action of genes on development of an attribute is accepted. Polymeric inheritance at human provides transfer to generation of quantitative attributes.

The degree of expression of these traits depends on quantity of dominant genes in a genotype and from of environment influence. Human can have predisposition to diseases: hypertonic illness, adiposity, diabetes, schizophrenia, and etc. These attributes under favorable conditions of environment can not be expressed or be feebly marked. It differ polygenic attributes from monogenic.

Changing the environment conditions and carrying preventive actions, it is possible to reduce considerably a frequency and degree of expression of some multiple-factor diseases. Summation of «dozes» of polymeric genes and influence of environment provide existence of continuous numbers of quantitative changes.

Pigmentation of a skin at human is determined by 5–6 polymeric genes. Dominant alleles prevail at inhabitants of Africa, recessive alleles — at European races.

So, discussed three types of gene interaction (epistasis, complementation, and polymeria) modify the classical formula of phenotype segregation but it is not the disorder of the genetic mechanism of segregation because it is result of interaction of genes among themselves in ontogenesis.

Action of gene in genotype depends on its doze. In norm, each trait is encoded by two alleles of a gene. This doze of the gene provides normal development. At trisomy, doze of gene is 3; at monosomy, doze of gene is 1. The doze of gene provides normal development of female organism in inactivation of one X-chromosome at the woman after 16 day of intra-uterine development.

One gene can determine development not one but several traits — ***pleiotropy effect***. So, for example, ***Morphan syndrome*** is caused by one gene. Features of the syndrome:

- high growth due to long extremities;
- thin digits (arachnodactily);
- lens subluxation;
- heart disease;
- high level catecholamins in blood.

The other example of pleiotropic action of gene in human is the sickle-cell anemia. The mutation of normal allele results in change of molecular structure of protein of hemoglobin; erythrocytes lose ability to transport of oxygen and get the sickle form instead of rounded. Homozygotes on the gene sickle-cell perish at a birth; heterozygotes live and possess stability against malaria.

Expression of gene action has the certain characteristics, as the same gene at different organisms can show the different effect in the various environment conditions. It is caused by the genotype of organism and conditions of environment at which pass it ontogenesis.

4. Quantitative and qualitative specificity of gene expression in attributes

Incomplete penetrance and variable expressivity result from the influence of other genes and environmental factors on the phenotype.Expressivity is the degree to which a trait is expressed. Examples are brachydactyly and polydactyly in a different degree of their expressivity.

Penetrance — is the phenomenon under which the trait encoded by same gene, is expressed in one and it is not expressed in other individuals of related group. Penetrance is defined as the percentage of individuals having a particular genotype that express the expected phenotype. For example, if we examined 42 people having an allele of polydactyly and found that only 38 of them were polydactylous, the penetrance would be 38/42 = 0.90 (90%). Full penetration — 100%, the gene is expressed in each individual. At incomplete penetrance — only at a part of individuals express the expected phenotype.

Example penetrance in human is blue sclera syndrome. Penetrance of blue sclera syndrome is 100%. Syndrome of blue sclera is a thin vascular tunic of eye which is joined with otosclerosis, deafness, fragility of bones with often fractures.

- Penetrance of bone fragility — 63%.
- Penetrance of deafness — 60%.
- Penetrance of all three symptoms is 44%.

Concepts of «expressivity» and «penetrance» concern, first of all, to autosome-dominant genes and attributes. Autosome-recessive attributes are shown only at hemyzygote with full penetrance and high expressivity. Expressivity and penetrance are caused by interaction of genes in a genotype and various reaction of the genes to environment factors.

Task 5

Some forms of schizophrenia are inherited as dominant autosome characters. In homozygotes, penetrance is equal 100%, in heterozygotes — 20%. It is necessary to determine probability of disease manifestation in family, where both parents are heterozygotes.

Solution:

P: ♀ Aa x ♂ Aa

F1: AA, 2Aa, aa

25% 10%

(probability of disease manifestation of homozygotes at 100% penetrance is 25%)

(probability of disease manifestation of heterozygotes at 20% penetrance is 50×20/100=10%)

25+10=35% it is probability of disease manifestation in family.

At studying of influence of genetic and environment factors on expression of attributes there are certain difficulties at presence of ***genocopy and phenocopy.***

Genocopy — similar phenotypic expression of different genes. An example are different forms of a hemophilia (A, B, C).

Occasionally, environmental factors alone can produce a phenotype that is the same as the phenotype produced by a genotype; this phenotype is called a phenocopy. Phenocopy — are not hereditary changes of phenotype of an organism under action of environment. For example, a cataract in the child can be related either with the mother roseola disease or with hereditary disease.

The area of action of a gene refers to as an action field of a gene. The gene can control 1 trait, 2, 3 traits, etc. For example, determination of hair growth, development of dermatoglyphic patterns on fingers, palms, and foots.

Time of a gene action — the period of its functioning. For example, decrease in melanin synthesis in hair with the age and releasing of sex hormones with the age.

Thus, separate genes cause only potential of development of attributes. Expression of them depends on genetic factors, influence of environment, and individual development. Formation of phenotype has multiple-factor principle and represents unity of genetic and environment factors.

LECTURE 9

Theme: Chromosome and genome level of the hereditary material organization

Plan:

1. Role of chromosomes in transfer of hereditary traits in pro- and eukaryotes.

2. Chromosomes, as groups of linked genes. Complete and incomplete linkage.

3. Bases of the chromosomal theory of inheritance.

4. Linkage groups of genes in human.

5. The inheritance of traits linked to a sex.

6. Genome level of the hereditary material organization.

7. Cytoplasmic inheritance. Genetic system of a cell.

1. Role of chromosomes in transfer of hereditary traits in pro- and eukaryotes

The chromosomal level of the organization of a hereditary material is characterized by features of morphology and functions of chromosomes. The role of chromosomes in transfer of the hereditary information has been proved due to:

1. Opening chromosomal definition of a sex,

2. An ascertaining of groups of linked genes that corresponding to number of chromosomes,

3. Construction of genetic and cytologic maps of chromosomes.

In DNA-CONTAINING viruses, bacteria, Cyanobacteriae, and also in self replicated cell organelles of eukaryotes (plastids, mitochondria, and kinetoplasts) the hereditary material is submitted by a unique chromosome which represents two-spiral DNA molecule. This molecule at some forms is linear, but at the majority forms a ring which is usually overwinded and has supercoil form. The length of DNA molecules of DNA-CONTAINING viruses, prokayiotes and cell organelles is from 5 up to 100 μm. At the fineest viruses — from 0.4 up to 1 μm, and at bacteria — 1000–2000 μm.

At the majority of RNA-CONTAINING viruses the chromosome is submitted by one stranded RNA molecule, for example at a HIV. However viruses at which the chromosome is formed by two stranded RNA molecule are known. The sizes of chromosomes of RNA-CONTAINING viruses it is less, than at DNA-CONTAINING viruses.

In DNA viruses the information on all its structural proteins is coded. Many viruses contain genes of specific polymerases supervising replication of DNA. Fine viruses contain only 3 genes which code A-protein, replicase, and protein of membrane. Genes of viruses can exist as fragments of DNA separated by inert nucleotide sequences. At the moment of gene work the inert nucleotide sequences are cut out and integrity of the genetic information is restored.

The transcription and replication of the genetic information is carried out with participation of enzymes of the cell-owner.

Chromosomes of prokaryotes are submitted by ring molecule of DNA. Prokaryotes contain only one chromosome and are haploids. Molecular weight of DNA of prokaryotes correspond to about 2000 structural genes with length

about 1500 pairs of nucleotides. Genes are situated linearly and carry the information on structure of 3–4,5 thousands of various proteins.

Chromosomes of eukaryotes are constructed from nucleoproteins which main components are DNA and two types of proteins — histone (basic) and non histone (acid) proteins. It is established, that in chromosomes of eukaryotes (with exception of polytene chromosomes) there is only one continuous string of DNA representing a uniform huge two-spiral molecule consisting of hundreds millions pairs of nucleotides. Length of DNA in a chromosome can achieve several centimeters. The molecular organization of a chromosome has been discussed earlier. In the metaphase, the chromosomes consisting from two chromatides are well visible under the microscope, but genes in them remain inactive during all mitosis. After the termination of mitosis occurs despiralization of chromosomes. In interphase nucleus the chromosome will consist from strongly stretched chromatides. Because of small thickness (25 μm) they are not visible in an optical microscope, but well visible in an electron microscope and do not lose the individuality during all life cycle of a cell.

Structure of DNA of eukaryotes is similar to DNA of prokaryotes. They differ in amount of nucleotides in genes, in length of DNA molecule, the order of nucleotide sequences, the form of packing: at eukaryotes — the linear form, and at prokaryotes — ring; prokaryotic DNA is not surrounded by a nuclear membrane nor is the DNA complexed with *histone* proteins; eukaryotic DNA is complexed to histone proteins to form chromosomes that are located in the nucleus.

Feature of DNA of eukaryotes is its ***redundancy***. The quantity of DNA participating in coding of the hereditary information is about 2% of all DNA. It is the proof of redundancy of eukaryotic DNA.

The part of redundant DNA is submitted by identical nucleotide repetitions. Distinguish frequent and moderate repeating sequences. All of them either concentrated in the certain places of genome and form structural (constitutive) chromatine or distributed over all genome. The redundant DNA exists for gene regulation, for preventing of structural genes variability.

2.Chromosomes as groups of linked genes. Complete and incomplete linkage

From principles of the genetic analysis follows that the independent combination of attributes can be carried out only on condition that the genes determining these attributes are in different pairs of chromosomes. Hence, at each organism, the number of pairs of attributes on which independent inheritance is observed is limited to number of pairs of chromosomes. On the other hand, the number of attributes and the properties of an organism controllable by genes is obvious, that, is extremely great, and the number of pairs chromosomes at each kind is not enough and constantly. It is necessary to

admit, that in each chromosome there is not one gene but a lot of it. If it so, it is necessary to recognize, that Mendel's third rule concerns only distribution of chromosomes, instead of genes, i. e. its action is limited. The analysis of display of the third rule has shown that in some cases new combinations of genes at hybrids absolutely were absent, i. e. full linkage between genes of initial forms was observed and phenotype segregation 1:1 was observed. In other cases the combination of attributes was marked with smaller frequency than it is expected at independent inheritance.

In 1906 William Batson has described disorder of Mendel's law of independent inheritance of two attributes. There were questions: why not all attributes are inherited, and how they inherited, how much genes in chromosomes, what laws of inheritance of the genes which are situated in one chromosome? The chromosomal theory of heredity created by T. Morgan in 1911 could answer on these questions.

T. Morgan, having studied all deviations, has suggested naming the joint inheritance of genes limiting their free combination, ***linkage of genes or the linked inheritance.***

T. Morgan's researches and its school have shown, that in homologous pair of chromosomes on a regular basis there is an exchange of genes. Process of gene exchange between homologous chromosomes was named the chiasm of chromosomes or ***crossing over***. Crossing over is observed in meiosis and it provides new combinations of the genes which are situated in homologous chromosomes. The phenomena of crossing over and linkage of genes are typic for animals, plants, and microorganisms. Exceptions represent the males of drosophila and females of silkworm. Crossing over provides recombination of genes and considerably increases a role of combinative diversity in evolution. Crossing over is determined on the basis of occurrence of organisms with a new combination of attributes. The phenomenon of crossing over was open by T. Morgan on drosophila.

Record of a genotype diheterozygote at independent inheritance:

AaBb

Record of a genotype diheterozygote at the linked inheritance:

$$\frac{AB}{ab}$$

Gametes that contain only original combinations of alleles present in the parents are **nonrecombinant gametes**, or parental gametes. Gametes with new combinations of alleles are called **recombinant gametes.** With independent assortment, nonrecombinant and recombinant gametes are produced in equal proportions.

$$\frac{AB}{ab}$$

$\underline{AB}$ $\underline{ab}$ **$\underline{Ab}$ $\underline{aB}$**

Nonrecombinant gametes Recombinant gametes

Progeny that display the original combinations of traits present in the P generation are **nonrecombinant progeny,** or parental progeny. The progeny with new combinations of traits formed from recombinant gametes are termed **recombinant progeny.**

The distance calculation between genes is possible with the next equation:

$$X = \frac{a+b}{n} \times 100\%$$

- X — distance between genes, in % of recombination.
- a — quantity of individuals of 1-st recombinant group.
- b — quantity of individuals of 2-nd recombinant group.
- n — total amount of hybrids in experiment.
- 100% — percentage scaling factor.

On the basis of the linked inheritance T. Morgan formulated the thesis which was included in genetics under the name of a ***Morgan rule***:

1. The genes located in one chromosome are inherited as linked.
2. Linkage intensity are depend on distance between genes.
3. The linked genes are located in the linear order and frequency of recombination between genes is in direct proportion to distance between them.

Morgan has suggested to designate the distance between genes in percentage of crossing over between them. Distances on genetic maps are measured in map units (abbreviated m.u.); one map unit is equal to 1% of recombination. Map units are called also centimorgans (cM), in honor of T. Morgan; one morgan is equal to 100 m.u.

On frequency of crossing over between two genes it is possible to calculate the relative distance between them. So, if between genes **A** and **B** crossing over is 3%, and between genes **B** and **C** — 8 %, the crossing over between **A** and **C** should occur with frequency either 3+8=11%, or 8-3=5%, depending on order of gene localization in a chromosome.

The linked genes are located in the linear order and frequency of crossing over between them is directly proportional to distance between them. However, this thesis is characteristic only for genes close laying to each other. In a case concerning the distant genes some deviation from such dependence is observed.

The genes which are located in one chromosome and inherited as linked make ***group of linkage***, which number at each species equally to haploid set of chromosomes.

Genetic maps of chromosomes is an order of an arrangement of genes in a chromosome on relative distance of them from each other. Distance between the linked genes is calculated on frequency crossing over between them. Genetic maps of all chromosomes are made for the organisms which are most genetically investigated: drosophila, hen, mice, corn, tomato, neurospore, and etc. For the human the genetic maps of all of 23 chromosomes also are made.

The cytologic map is a map of a chromosome on which the arrangement and distance between genes (in base pairs) in the chromosome is determined. Construction of them is conducted on the basis of chromosomal reorganizations, politene chromosomes, differential staining, and radioactive labels.

For today genetic to cytologic maps are constructed and compared at drosophila. The reality of this comparison proves a principle about linear arrangement of genes in chromosomes.

3. Bases of the chromosomal theory of inheritance

1. Genes are in chromosomes. Each chromosome represents group of the linked genes. Number of linkage groups in each species is equal to a number of chromosome pairs.
2. Each gene occupied the certain locus in a chromosome. Genes in chromosomes are in linear arrangement.
3. There is allele exchange between homologous chromosomes.
4. The distance between genes in a chromosome is proportional to frequency of recombination between them.

4. Linkage groups of genes in human

Studying of the linked inheritance in human is complicated. It is carried out with use of a method of hybridization of somatic cells and DNA (cell genetics).

It is possible to separate somatic cells outside of an organism and combine them as with cells of the same organism as with another. Nucleus of cells are fused, the hereditary material is united, the part of chromosomes drops out, so the genes of the representing groups of linkage drop out together. So, can be determined groups of linked genes. Cell hybrids of human and mouse, human and mosquito are received.

The genes located in autosomes represent group of linked genes. Such linked genes refer to ***autosomal.***

Examples of the linked inheritance in human:

1. In the first autosome — loci of blood group AB0 and syndromes of nails defect and patella defect.
2. In the second autosome — loci of a Rh factor and the oval shape of erythrocyte.
3. Genes of polydactily and cataract.
4. In the X-chromosome — genes of hemophilia A and B, daltonism, and Emery muscular dystrophy.

5. Inheritance of subloci A, B, C, D / D R of HLA system that control antigene synthesis.

5. The inheritance of traits linked to a sex

Traits encoded by genes located in sex chromosomes refer to sex linked. In human, it is described more than 60 diseases linked to a sex. The majority from the diseases are recessive. Genes in sex chromosomes can be divided into 3 groups:

1. Partially sex linked genes. They are located in homologous regions of X and Y sex chromosomes. It is haemorrhagic diathesis, convulsive frustration, pigmentary retinitis, pigmentary parchment-skin, the general color blindness, and etc.
2. Completely sex linked genes. They are located in X-chromosome region non-homologous to Y-chromosome. These genes supervise diseases: atrophy of optic nerve, Duchenne muscular dystrophy, daltonism, hemophilia, and etc.
3. Holandric genes. The genes located in Y-chromosome region non-homologous to X-chromosome. It is sindactylia, hypertrichosis of auricle.

The gene of daltonism is shown at 7% of men and at 0.5% of women, but carriers of this gene are 13% of women.

Some mechanisms of inheritance of completely sex linked traits are noted:

1. Traits are criss-cross transferred (from father to daughter and from mother to son).
2. Results of crossing and backcrossing do not coincide with each other.
3. Traits of heterogametic sex are transferred in any conditions.

6. Genome level of the hereditary material organization

Genome is a set of all genes in haploid set of chromosomes of any organism. Genome level of the hereditary material organization has features at prokaryotes and eukaryotes.

In bacterial genome the majority of genes ***are unique***. Exceptions are the genes coding ***r-RNA and t-RNA***. These genes repeat in bacterial genome on some times. It is necessary to note the certain discrepancy between number of pairs of nucleotides in bacterial genome and number of genes in them. So, DNA of colon bacillus contains 3,8 billion pairs of nucleotides. Structural genes at them are about 1000 on which it is necessary 1-1.5 million pairs of nucleotides. It is necessary to assume, that the substantial parts in DNA bacteria is the parts which functions are not clear yet. Helix formation of DNA in «chromosome» prokaryotes is much less than at eukaryotes.

In eukaryotic genomes, there are:

- a large number of genes;
- a complicated system of gene expression and repression (hormonal regulation, group repression);
- a scattered distribution of genes.

DNA quantity in chromosomes is great and increases in process of complication of organisms. ***Redundancy of genes*** is also characteristic for eukaryotes**.** So, human genome contains big number of nucleotide pairs sufficient for formation more than 2 million of structural genes while in human are present about 32 000 of genes.

More than half of genome haploid set of eukaryotes is presented by ***the unique genes*** submitted only one time. Amount of unique genes in human — 64%, at calf — 55%, at drosophila — 70%.

Morgan has specified stability of structure genome and constancy of gene arrangement in chromosomes.

In 70th years at drosophila the group of the genes submitted by many wandering genes which are scattered on different sites of chromosomes is found out. 30% of genes wander on chromosomes, have no constant localization. Mobile genes make 5% of all genome.

Thus, within last 10 years was clarified that the structure of genome of pro- and eukaryotes includes genes:

1. Having either stable, or unstable localization;
2. The unique sequence of nucleotides is submitted in genome by one or small number of copies. It is: structural and regulatory genes. Unique sequences of eukaryotes, as against genes of prokaryotes, have a mosaic structure;
3. Many times repeating sequences of nucleotides are copies (recurrences) of unique sequences (at prokaryotes is not present). Copies are grouped on some tens or hundreds and form the blocks located in a certain place of a chromosome. Repetitions replicated but, as a rule, are not transcribed. They can play a role:

1. as regulators of a gene activity;
2. as the protective mechanism from point mutations;
3. in storage and transfer of the hereditary information;
4. in the mechanism of evolution.

7. Cytoplasmic inheritance. Genetic system of cell

The chromosomal theory of heredity specifies the leading part of nucleus in transfer of hereditary attributes. In process of development of genetics the data of direct participation in the phenomena of heredity of cytoplasms was collected. Such form of heredity is determined by the components of a cell capable to self-reproduction, i.e. having own DNA.

Heredity, at which elements of cytoplasm are material basis of inheritance, refers to cytoplasmic inheritance**.** Such form of heredity does not submit to Mendel's laws. Cytoplasmic inheritance is carried out on mother line since egg is rich in cytoplasm.

Hereditary factors of cytoplasm and organelles refer to ***a plasmotype or plasmon.*** Unit of cytoplasmic heredity is ***plasmagene.*** In prokaryotes, a carrier of cytoplasmic heredity is ***plasmid DNA.***

The plasmotype of eukaryotes will consist of the hereditary apparatus of plastid, mitochondria, and DNA of hyaloplasm. Cytoplasmic hereditary structures are distributed among daughter cells non-uniformly as against nuclear.

Cytoplasmic heredity
I. Actually cytoplasmic inheritance.
1. Plastid
2. Mitochondrial
3. Cytoplasmic male sterility
II. Predetermination of cytoplasms.
III. Inheritance through infections

Plastid DNA. Inheritance of foliage variegation in plants is an example of such type of inheritance. Foliage variegation in flowers of *Mirabilis jalappa* observed only at female plants. During formation of female gametes in meiosis it is found out DNA of chloroplasts, in pollen cells — it is absent. The attribute of foliage variegation is connected to mutations of DNA that results in decolouration of chloroplasts. Egg carrying genes of foliage variegation contains in cytoplasm the DNA of normal and decoloured chloroplasts.

Mitochondrial heredity. Mitochondrial genes code 2 groups of the attributes which connected with:

1) work of respiratory system;

2) resistance to antibiotics.

In mitochondria of yeast cells the genes of respiratory enzymes are found out. These genes are in plasmids. At bacteria distinguish 3 types of plasmids:

1. Containing sex factor **F**;

2. Containing factor **R**;

3. Containing factor **col** — colicinogenic factor.

Bacteria with factor **F** are male. At conjugation the factor **F** passes in a female individual and it becomes male.

Factor **R** provides stability to antibiotics and also is transferred at conjugation.

Plasmids with the factor **col** which DNA codes the proteins — colicins that killing bacteria which not contain such plasmid factor.

Cytoplasmic male sterility (CMS) is a form of extranuclear inheritance. It is characterized by presence in DNA of mitochondria and plastids the cytoplasmic gene (plasmagene) that oppress formation of chromosomes in pollen grain. In result there is the unviable pollen which is not forming of sperm. The CMS plays the big role in selection and seed-growing for exception of self-pollination and the subsequent harvest of heterotic hybrids (corn, onions, wheat, beet, and etc.).

Predetermination of cytoplasm

Not genetic factors are present at cytoplasm of egg (enzymes, protein-repressors). These factors have influence on expression of nuclear genes. There is ***«a mother effect»*** — influence of mother genotype on offspring development

transmitted through cytoplasm of egg. So the direction of a spiral of a pond snail shell determinates by genotype of mother, instead of genotype of germ.

Example:

SS, + Ss — right-handed shell,

ss — left-handed shell.

P: ♀ SS x ♂ss

F1: Ss — right-handed shell.

F2 — instead of segregation 3:1, offspring has the right-handed shell, since **ss** does not find.

DNA of plastids, mitochondria, and any yet not established factors are material base of cytoplasmic inheritance.

Genotype (all genetic apparatus of a cell)

The system of the genetic apparatus of a cell includes ***genome of nucleus*** and ***plasmotype (plasmon) of cytoplasms.*** The genetic apparatus of a cell is discrete. In genotype of nucleus it is submitted by chromosomes and the genes included in chromosomes, in a plasmotype of cytoplasm it is submitted by plasmagenes which are fragments of plastid and mitochondrial DNA.

LECTURE 10

Theme: Diversity

Plan:

1. Forms of diversity and their significance in ontogenesis and evolutions.
2. Modification diversity. Norm of reaction.
3. Genotypic diversity and its kinds: combinative and mutational
4. DNA repair.

1. Forms of diversity and their significance in ontogenesis and evolutions

The genetics studies not only the phenomena of a heredity, but also diversity of organisms. ***Diversity*** is a property of living things to change, expressing in ability to get new attributes or to lose old one. The reasons of diversity are a variety of genotypes, conditions of environment which determine a variety in expression of attributes at organisms with identical genotypes.

DIVERSITY

Phenotypic	**Genotypic**
1. Ontogenetic	1. Combinative
2. Modificational	2. Mutational

Formation of various types of diversity is consequence of interaction of an environment, a genotype, and a phenotype.

Phenotypic diversity — the diversity reflecting changes of phenotype under action of conditions of an environment not touching a genotype though the degree of its expressiveness is determined by a genotype.

Ontogenetic diversity is a constant change of attributes in development of an individual (ontogenesis of amphibious, insects, development morphophysiological and mental attributes in human).

Modificational diversity is a phenotypic differences arising due to influence of factors of an environment.

2. Modification diversity. Norm of reaction

Modification diversity is determined by a genotype. Modifications are not inherited and are seasonal and ecological.

Seasonal modifications — genetically determined change of attributes as a result of seasonal changes of climatic conditions.

Ecological modifications — adaptive changes of a phenotype as result of change of conditions of an environment. Phenotypically they are shown in a degree of expressiveness of an attribute. Ecological modifications affect the quantitative (weight of animals, amount of offspring) and qualitative (skin color in human under influence of UV-rays) attributes.

Properties of modifications:

1. Modifications are not inherited;

2. Arise gradually, have transitive forms;

3 Modifications are quantitative changes; they form continuous numbers and grouped around of average value;

4. Modifications are directed changes. Under influence of the same factor of environment the group of organisms changed similar;

5. All most widespread modifications have adaptive nature.

So increase of number erythrocytes and maintenance of Hb in blood of animals and human in mountains represent the adaptation for the best use of oxygen. Sunburn of skin — the adaptation to influence of excessive sunshine. It is established, only those modifications are adaptive which are caused by usual changes of environment. Modifications have no adaptive significance if caused by various chemical and physical factors. So, influencing in the increased temperature on a pupa of drosophila, it is possible to receive individuals with the twirled wings, with cuttings on them that looks as mutations.

6. Ecological modifications are reversible and with alternation of generations under different condition environment can not be shown (For example: fluctuations of yields of milk in cattle, change of amount erythrocytes and leukocytes at diseases or changes of conditions of environment.). If in a number of generations the environmental condition is not varied the degree of expressiveness of an attribute in offspring is kept. Such modifications refer to long-term. At change of environmental conditions the long-term modifications

are not inherited. There is erroneous opinion that education and external influence can fix a new attribute (an example of dog training) in offspring.

7. Modifications have adequate character, i.e. the degree of attribute expression is in direct dependence on a kind and duration of action of the factor. So, improvement of conditions of cattle care causes increase in weight of animals.

8. One of the basic properties of modifications is their mass character — the same factor causes identical change of the individuals with similar genotypes. The limit and a degree of expression of modifications are controlled by a genotype (an example with identical twins).

9. Modifications possess a different degree of stability: long and short-term. So, sunburn in human is over on termination of sunshine action. Other modifications which have arisen at early stages of development can be kept during all life (bow-legging after a rachitis).

Modifications are unequivocal for the most primitive and highly organized organisms. To number of such modifications concern phenotypic changes connected to a feed. Changes not only amount but also quality of food can cause occurrence of the following modifications: avitaminosis, dystrophy, and rachitis. To the most often human modifications concern the phenotypic attributes caused by physical loadings: increase in volume of muscles as a result of training, increase of blood supply, and return back of changes at an inactive life-style.

As modifications are not inherited, in medical practice is important their differences from a mutation. The modifications arising in human are submit to correction while mutational changes cause incurable pathologies.

Variations in gene expression are not boundless. They are limited to norm of reaction of an organism.

The norm of reaction is a limit of modification diversity. The norm of reaction, i.e. ability to development of an attribute and the form of its expression depending of environment conditions, is inherited. Norm of reaction — the specific quantitative and qualitative characteristic of a genotype. Distinguish attributes with wide and narrow norm of reaction. To wide norm of reaction concerned the quantitive traits: weight of cattle, productivity of crops. The narrow norm of reaction is shown at next qualitative attributes: percent of fat content of milk, the contents of proteins in blood in human. The unequivocal norm of reaction is characteristic as for the majority of qualitative attributes — color of hair and eyes.

Under influence of some harmful factors with which human does not meet during evolution, resources of the modification diversity determining by norm of reaction are excluded. There are uglinesses or anomalies which refer to ***morphoses.*** These are changes of morphological, biochemical, physiological attributes at mammal. For example: 4 hearts, one eye, two heads in cattle; in human: absence of finitenesses, impassability of intestines, and tumour of upper

lip. The reason of occurrence of such changes is teratogens. There is thalidomide, quinine, hallucinogen LSD, drugs, and alcohol. Morphosis sharply changes a new attribute as against the modifications causing change of a degree of expression of an attribute. Morphoses can arise during the critical periods of ontogenesis and do not have adaptive character.

Morphoses which are similar to mutations refer to ***phenocopy.*** The mechanism of ***phenocopy*** is disorder of realization of the hereditary information. They arise due to repression of function of the certain genes. Their expression can be similar with function of known genes but it is not inherited.

3. Genotypic diversity and its kinds: combinative and mutational

Genotypic diversity — the diversity of an organism caused by change of a genetic material of a cell or combinations of genes in a genotype which can lead to to occurrence of new attributes or to their new combination.

The diversity arising at crossing as a result of various combinations of genes and their interaction among them refers to ***combinative.*** Mechanisms of its occurrence:

1. An independent divergence of chromosomes in meiosis;
2. Crossing over
3. A random combination of gametes at fertilisation.

It is inherited according to Mendel's rules. Expression of attributes at combinative diversity is under influence of interaction of alleles and genes, multiple alleles, pleiotropic action of genes, linkage of genes, penetrance and expressivity of genes, etc.

Thanking to combinative diversity the big variety of hereditary attributes in human is provided.

Expression of combinative diversity in human is under influence of mating system or system of marriages: inbreeding and outbreeding.

Inbreeding — a related marriage which can be close in a various degree. The marriage of brothers with sisters or parents with children refers to the first degree of relationship and is the closest. Less close marriage is between cousin brothers and sisters or between nephews and aunts.

1. The first important genetic consequence of inbreeding — increase with each generation of homozygosity of progeny on all independently inherited genes.

2. The second — separation of population on a number of genetically various lines. Diversity of populations during of inbreeding will grow, whereas diversity of each line is reduced.

Frequently, inbreeding leads to weakening and even degeneration of progeny. As a rule, inbreeding in human is harmful. It increases the risk of disease and premature death of progeny. But examples of long close inbreeding,

not accompanying for harmful consequences, is exists. For example, a family tree of pharaons of Egypt is known.

Outbreeding or unrelated marriage. Individuals are considered as unrelated if there are no common ancestors in 4–6 generations.

Outbreeding increase heterozygosity of progeny unites alleles which existed at parents separately. Harmful recessive genes finding at parents in a homozygous condition are repressed at heterozygous progeny. The combination of all genes in genome of hybrids grows and accordingly will be widely shown combinative diversity.

Combinative diversity in family concerns both normal and pathological genes. The solution of questions of medical-genetic aspects in family demands on accurate establishment of disease inheritance — autosome-dominant, autosome-recessive, or sex linked. At presence of recessive abnormal gene in heterozygous condition the disease probability at the child is 25%.

Frequency of Down syndrome at children of mothers in age of 35 years is 0,33%, in age 40 years and older is more than 1,24%.

The diversity with rapid, strong changes of traits is called ***mutational***. ***Mutations*** are permanent, heritable changes of genetic information. Gene mutations affect only the genetic information of a single gene; chromosome and genome mutations alter the structure and the number of chromosomes and therefore usually affect many genes.

The term ***mutation*** for the first time has been offered by H. de-Frieze in its work «The mutational theory» (1901–1903). The main statements of this theory:

1. Mutation appears suddenly.
2. New forms are stable.
3. Mutations are qualitative changes.
4. Mutations may be useful and harmful.
5. The same mutations may appear repeatedly.

All mutations can be divided into groups:

Classifying factor	Mutations' names
According mutated cells	1. Generative 2. Somatic
According genotype change	1. Gene (point) mutation 2. Chromosome aberrations 3. Interchromosome aberrations (translocations) 4. Genome mutations 5. Cytoplasmic mutations
According adaptive significance	1. Useful 2. Harmful 3. Neutral
According reason of mutation	1. Spontaneous 2. Induced

The primary role belongs to ***the generative mutations*** arising in sex cells. Generative mutations causing change of attributes and properties of an organism can be found out, if a gamete carrying a mutant gene, participates in formation of a zygote. If a mutation is dominant, the new attribute or property are shown even at the heterozygotic individual. If mutation is recessive, it can be shown only through some generations at homozygous condition. As an example of generative dominant mutations in human the occurrence of blistering skin of footstep, cataracts of eyes, brachyphalange (brachydactyly with deficiency of phalanxes) can serve. An example of spontaneous recessive generative mutation in human can consider hemophilia.

Somatic mutations arise in somatic cells. Somatic mutations play a role at organisms with asexual reproduction. So, in vegetative reproduced plants the somatic mutation can give plants with a new mutant attribute. Inheritance of somatic mutations now has a great significance for studying the reasons of cancer in human. It is presumed for malignant tumours that the transformation of a normal cell in cancer occurs due to somatic mutations.

Molecular mechanisms of ***gene mutations*** are revealed in changes of the order of nucleotide pairs in a DNA molecule. Gene mutations can be as dominant, and recessive. The essence of local intragenic changes can be shown to four types of nucleotide reorganizations:

1. Substitution of the base pairs in DNA molecule. It may be:

а) Transition or replacement purine bases on purines or pyrimidine bases on pyrimidines;

б) Transversion or replacement purine bases on pirimidine.

2. Deletion (loss) of one pair or group of the bases in DNA molecule;

3. Insertion of one pair or group of the bases in DNA molecule;

4. Translocation of nucleotide positions inside a gene.

Changes in molecular structure of a gene conduct to a new form of genetic information necessary for biochemical processes in a cell, and results in occurrence of new properties in a cell and an organism as a whole. Apparently, point mutations are the most important for evolution.

On influence on character of coded polypeptides the point mutations can be submitted as four classes:

1. A base substitution that alters a codon the mRNA, resulting in a different amino acid in the protein, is referred to as a ***missense mutation***.

2. ***Nonsense mutation*** changes a sense codon (one that specifies an amino acid) into a nonsense codon (one that terminates translation. If a nonsense mutation occurs early in the mRNA sequence, the protein will greatly shortened and will usually be nonfunctional.

3. ***Silent mutation*** alters a codon but, thanks to the redundancy of the genetic code, the codon still specifies the same amino acid.

4. Insertions and deletions within sequences that encode proteins may lead to ***frameshift mutations***, changes in the reading frame of the gene.

Chromosomal aberrations result from break of chromosome sites and then their recombinations. Distinguish the following chromosome aberrations:

1. **Deletion** is a loss of a chromosome segment.

2. Duplication is a mutation in which part of the chromosome has been doubled.

3. **Inversion** is a mutation in which a chromosome segment is inverted — turned on 180º.

Interchromosome reorganizations.

A **translocation** entails the movement of genetic material between nonhomologous chromosomes.

Genome mutations occur due to increase or decrease in number of chromosomes or haploid set of chromosomes. Accordingly, the genome mutations can be classified into two basic types: changes in the number of individual chromosomes (***aneuploidy***) and changes in the number of chromosome sets (***polyploidy***).

Polyploids include triploids (3n) tetraploids (4n), pentaploids (5n), and even higher numbers of chromosome sets. Polyploidy results in change of attributes of an organism: increase in the sizes of cells and increase of biomass. It is used in selection of plants. Polyploidy is known in animals: infusoria, silkworm, and amphibian.

Four types of relatively common aneuploid conditions is well-known in diploid individuals: nullisomy (2n-2), monosomy (2n-1), trisomy (2n+1), and tetrasomy (2n+2). Such mutations cause pathologies in human: triplo-X syndrome, trisomy on 21-st chromosome (Down syndrome), monosomy on the X-chromosome (Terner syndrome), etc. The phenomenon of aneuploidy shows that changing in number of chromosomes results in decrease of organism viability.

Cytoplasmic mutations are plasmagene changes, resulting in changes of traits and properties of an organism. Such mutations are stable and transferred from generation to generation, for example, loss of cytochrome oxidase in mitochondria of yeast. Human diseases caused by mutations of mitochondrion DNA: congenital myopathy, anencephaly, and spina bifida.

On adaptive significance the mutations can be divided on useful, harmful (lethal and semilethal) and neutral. This division is relative. Between useful and lethal mutations there is almost continuous range owing to expressivity of gene. An example of lethal and semilethal mutations in human is epilepsy, and also presence of tumours of heart, kidneys, congenital ichthyosis, amaurotic familial idiocy, thalassemia, etc.

Spontaneous mutations arise in natural conditions without special influence of unusual agents. The mutational process is characterized by mutation rate. Spontaneous mutation rates are low for all organisms studied. The certain mutation rate is characteristic for each species of organisms. Some species possess higher mutational diversity than others. The established laws of mutation rates are reduced to the following positions:

а) Various genes in one genotype mutate with different frequency (there are genes mutable and stable);

б) Similar genes in different genotypes mutate with different frequency.

Each gene mutates in low rate but since the number of genes in genome is big the total mutation rate at all genes is high. So, the mutation rate in human population is: for thalassemia — 4×10^{-4}, for albinism — 2.8×10^{-5}, for hemophilia — 3.2×10^{-5}.

Special genes can have influence on frequency of spontaneous mutagenesis. ***Genes-mutators*** can sharply change the mutability of organism. Such genes are open at drosophila, corn, colon bacillus, yeast, and etc. It is supposed that genes-mutators change properties of DNA-polymerase which influence rusults to a mass mutation.

Physiological and biochemical condition of a cell have influence on spontaneous mutagenesis. So, it is shown, that during ageing and at long storage the frequency of mutations considerably increases. Among the possible reasons of spontaneous mutation, it is possible to note the accumulation of mutations in a genotype which block biosynthesis of substances. The excessive accumulation of predecessors of such substances can cause mutations. In spontaneous mutations of human the natural radiation can play the certain role. Due to natural radiation from 1/10 up to 1/4 of spontaneous mutations in human are arised.

Induced mutations arise under influence of special environmental agents. Any environmental agent that significantly increases the rate of mutation above the spontaneous rate is called a ***mutagen***. All agents of mutagenesis can be divided into three kinds: ***physical, chemical and biological.***

Ionizing radiation is the most important among physical agents. Ionizing radiation may be electromagnetic or wavelike (gamma-rays, X-rays, cosmic rays and etc.) and corpuscular (electrons, positrons, protons, and etc.).

Various animals are characterized by various sensitivity to ionizing radiations which changes from 700 ***p*** for human up to hundreds thousand and millions ***p*** for bacteria and viruses. Ionizing radiations cause first of all changes in the genetic apparatus of a cell. It is shown, that the nucleus of a cell in 100 thousand times is more sensitive to radiation, than cytoplasm. Much more sensitive to radiation the immature sex cells (spermatogonia) than mature (sperm). DNA of chromosomes is most sensitive to action of radiation. Changes are expressed in gene mutations and chromosome aberrations.

It is shown, that frequency of mutations depends on the doze of radiation and is directly proportional to a doze of an irradiation, i.e. at increase in a doze arises twice more mutations.

Ionizing radiations influence on the genetic apparatus not only direct but also indirectly. They cause radiolytic decomposition of water. Radicals arising at it (H, OH) have a damaging effect.

To strong physical mutagens belong the ultra-violet rays (length of a wave up to 400 nanometers) which do not ionize atoms but only raise their electronic shell. In a result, the chemical reactions which can result in mutation are developed in cells. Mutation rate increases with increase in length of a wave up to 240–280 nanometers (corresponds to a spectrum of DNA absorption). UV rays cause gene mutations and chromosome aberrations but in much smaller quantity than ionizing radiation.

The increased temperature is much weaker physical mutagen. Rise in temperature on 10ºC increases frequency of mutations in 3–5 times. There are only gene mutations at the lowest organisms. This factor does not influence on warm-blooded animals with a constant body temperature and on human.

Chemical mutagens are represented by set of various substances and their list continuously replenishes. Chemical mutagens can be divided on four groups:

1. Alkylating agents are chemicals that donate alkyl groups. These agents include methyl (CH3) and ethyl (CH3–CH2) groups, which are added to nucleotide bases by some chemicals. For example, ethylmethanesulfonate adds an ethyl group to guanine, producing 6-ethylguanine, which pairs with thymine. Sometimes these substances are supermutagens and cancerogens.

2. Base analogs, chemicals with structures similar to that of any of the four standard bases of DNA. DNA polymerases cannot distinguish these analogs from the standard bases; so, if base analogs are present during replication, they may be incorporated into newly synthesized DNA molecules. For example, 5-bromouracil (5BU) is an analog of thymine.

3. Intercalating agents, such as proflavin, acridine orange, ethidium bromide, and dioxin are about the same size as a nucleotide. They produce

mutations by sandwiching themselves (intercalating) between adjacent bases in DNA, distorting the three-dimensional structure of the helix and causing single-nucleotide insertions and deletions in replication.

4. Other chemical substances (hydroxylamin, different peroxides, uretan, formaldehyde).

Chemical mutagens can induce both gene and chromosome mutations. They can induce more gene mutations than ionizing radiations and UV-rays.

Biological mutagens are some kinds of *viruses, bacteria, fungi* and their metabolic products. It is shown, that all tested viruses of human, animals and plants induce mutations in drosophila. It is supposed, that molecules of DNA-viruses represent a mutagen element. Ability of viruses to cause mutation are found out in bacteria and actinomycetes.

Apparently, all mutagens, both physical and chemical, are universal, i.e. can cause mutations in any forms of a life. For all known mutagens there is no lower limit of their mutagen action.

Mutations cause congenital uglinesses and hereditary diseases of human. Therefore an essential problem is the protection of people from action of mutagens. It is very important to keep rules of safety from radiation in the nuclear industry, at work with isotopes and X-rays. The certain role can play antimutagens — the substances lowering effect of mutagenic actions (cystamine, chinacrine, the some sulfanilamides, derivatives of propionic and gallic acids).

4. DNA repair

Not all damages of the genetic apparatus caused by mutagens are realized as mutations. Many of them are corrected with the help of special reparing enzymes.

DNA repair — process of DNA structure restoration damaged at DNA replication or by physical and chemical agents. The repair mechanism is based on fact that each DNA molecule contains two full sets of the genetic information which are written in complimentary to each other polynucleotide chains. It provides preservation of the undistorted information in one chain even if another is damaged and correct defect on the base of intact chain.

Now it is known three mechanisms of reparation: ***photoreactivation, dark reparation, and post-replicative reparation.***

The photoreactivation consists in elimination of thymine dimers especially frequently arising in DNA under influence of UV rays with help of light. Replacement is carried out by special photoreactivation enzyme which molecule do not possesses affinity with intact DNA but identifies the thymine dimers and contacts with them right after their formations. This complex remains stable untill undergo to action of light. Light activates a molecule of enzyme; it is separated from the thymine dimers and simultaneously separates it on two separate thymines restoring the initial structure of DNA.

The dark reparation does not demand from light. It is capable to correct very various damages of DNA. The dark reparation proceeds in some stages at participation of several enzymes:

1. **Detection:** The damaged section of the DNA is recognized.
2. **Excision:** DNA repair endonucleases nick the phosphodiester backbone on one or both sides of the DNA damage.
3. **Polymerization:** DNA polymerase adds nucleotides to the newly exposed 3-OH group by using the other strand as a template and replacing damaged nucleotides.
4. **Ligation:** DNA ligase seals the nicks in the sugar–phosphate backbone.

Light and dark reparations are observed before replication of the damaged molecules. If replication of the damaged molecules occurs, affiliated molecules can undergo ***post-replicative reparations.*** The mechanism of it is not clear yet. It is supposed that gaps in defect DNA molecule can be built up with the fragments taken from intact DNA molecule.

The great significance has genetic differences in activity of repair enzymes. Among the best studied of the human DNA repair diseases is *xeroderma pigmentosum*, a rare autosomal recessive condition that includes abnormal skin pigmentation and acute sensitivity to sunlight.

The phenomenon of DNA repair is widespread from bacteria up to human and has great significance for preservation of the genetic information stability.

LECTURE 11

Theme: Bases of human genetics

Plan:

1. Human as specific object of the genetic analysis.
2. The methods of human genetics:
   - — the pedigree analysis;
   - — the cytogenetic method;
   - — the statistic method;
   - — the twins' method;
   - — the biochemical method;
   - — the dermatogliphic method;
   - — the immunological method;
   - — the ontogenetic method;
   - — the method of somatic cells genetics.
3. The methods of prenatal diagnostics.

1. Human as specific object of the genetic analysis

The human genetics studies phenomena of heredity and diversity in populations of people, features of inheritance of normal and pathological

attributes, dependence of diseases on genetic predisposition and factors of environment. A problem of medical genetics is revealing and prevention of hereditary diseases. The study of human inheritance requires special techniques — primarily because human biology and culture impose certain constraints on the geneticist. There are:

- Controlled mating is not possible.
- A long generation time.
- Human family size is generally small.

2. The methods of human genetics: the pedigree analysis; the cytogenetic method; the statistic method; the twins' method; the biochemical method; the dermatogliphic method; the immunological method; the ontogenetic method; the method of somatic cells genetics

1. The pedigree analysis

A pedigree is a pictorial representation of a family history, essentially a family tree that outlines the inheritance of one or more characteristics.

The pedigree analysis includes two stages:

1. Collection of information on family.
2. The draws a pedigree.

The person from whom the pedigree is initiated is called the **proband** and is usually designated by an arrow. The limited number of offspring in most human families means that it is usually impossible to discern clear Mendelian ratios in a single pedigree. Pedigree analysis requires a certain amount of genetic sleuthing, based on recognizing patterns associated with different modes of inheritance. There are: autosome-dominant, autosome-recessive, and sex linked.

Autosomal recessive traits normally appear with equal frequency in both sexes, and appear only when a person inherits two alleles for the trait, one from each parent. If the trait is uncommon, most parents carrying the allele are heterozygous and unaffected; consequently, the trait appears to skip generations. Frequently, a recessive allele may be passed for a number of generations without the trait appearing in a pedigree. Left-handedness, red hair, blue eyes, miopaty, diabetes, phenilketonuria are inherited in this type.

Autosomal dominant traits appear in both sexes with equal frequency, and both sexes are capable of transmitting these traits to their offspring. Every person with a dominant trait must inherit the allele from at least one parent; autosomal dominant traits therefore do not skip generations. Freckles, brachidactyly, cataract, fragility of bones, chondrodistrophy, polydactyly are inherited in this type.

X-linked recessive traits have a distinctive pattern of inheritance First, these traits appear more frequently in males, because males need inherit only a single copy of the allele to display the trait, whereas females must inherit two copies of the allele, one from each parent, to be affected. Second, because a male inherits his X chromosome from his mother, affected males are usually

born to unaffected mothers who carry an allele for the trait. Because the trait is passed from unaffected female to affected male to unaffected female, it tends to skip generations. Haemophilia, Duchen muscular dystrophy, and daltonism are inherited in this type.

X-linked dominant traits appear in males and females, although they often affect more females than males. As with X-linked recessive traits, a male inherits an X-linked dominant trait only from his mother — the trait is not passed from father to son. A female, on the other hand, inherits an X chromosome from both her mother and father; so females can receive an X-linked trait from either parent. Each child with an X-linked dominant trait must have an affected parent. X-linked dominant traits do not skip generations. Pigmentary dermatosis, keratosis, and brown enamel are inherited in this type.

Y-linked traits exhibit a specific, easily recognized pattern of inheritance. Only males are affected, and the trait is passed from father to son. If a man is affected, all his male offspring should also be affected. Syndactyly and hypertrichosis are inherited in this type.

2. The cytogenetic method.

The method is based on microscopic research of chromosomes and analysis of human karyotype in norm and pathology. For identification of chromosomes conduct the analysis of length of chromosomes and a ratio of their arm lengths (centromeric index). Then conduct karyotypic analysis on Denver classifications. This method allows establish human hereditary diseases, structure of chromosomes, translocation, and allows to build the genetic maps.

In 1969 T. Casperson has developed a method of chromosomes staining. It made possible to identify chromosomes on the base of stained segments distribution.

The aneuploidity, chromosome aberrations, translocations, and polyploidity may be revealed with help of this method.

If there is aneuploidity in sex chromosomes, it may be detected easily. For such purpose evaluation of sex chromatin in somatic sells is used. Sex chromatin (Barr's body) is condensed one of two X-chromosomes in female cells. The Barr's body has a disc form and it may be found in intherphase cell nucleus under the nuclear envelope.

In karyotype of the normal woman there are two X-chromosomes but one of them forms sex chromatin. The number of sex chromatin at human and mammals is less than the number of X-chromosomes by one. In the woman with karyotype XO — nucleus of cells do not contain the sex chromatin. In case of trisomy (XXX) — 2 Barr's bodies are formed.

In norm, chromatin-positive nuclei averaged 20–40% at women and 1–3% at men. In buccal epithelium it is possible to determine Y-chromatin. In norm, 20–90% of nuclei at man contain Y-chromatine.

3. The statistic method.

The method allows calculate frequency of heterozygotes in human populations having a pathological gene and distribution of gene and chromosome anomalies. The method is based on demographic statistics data and mathematic analysis of them using the Hardy-Weinberg principle.

For example: frequency of albinism (q^2) is equal to 1:20000 in a population, i. e. $q^2 = 1/20000$, means $q = \sqrt{1/20000} = 1/141$.

$p + q = 1$, it means $p = 1-q = 140/141$;

Frequency of heterozygotes is $2pq = 2 \times 140/141 \times 1/141 = 1/70$.

4. The twins' method.

The method is based on studying of attributes which changed under conditions of a life in twins. Twins come in two types: **dizygotic twins** develop from two eggs fertilized by two separate sperm and they have, on average, 50% of their genes in common; **monozygotic twins** develop from a single egg, fertilized by a single sperm, that splits into two embryos and they have 100% of their genes in common.

If both members of a twin pair have a trait, the twins are said to be **concordant**; if only one member of the pair has the trait, the twins are said to be **discordant**. **Concordance** is the percentage of twin pairs that are concordant for a trait.

Higher concordance in monozygotic twins compared with that in dizygotic twins indicates that genetic factors play a role in determining individual differences of a characteristic. Low concordance in monozygotic twins indicates that environmental factors play a significant role in the characteristic.

Twins method is based on comparing level of traits concordance using factors of a heredity (H) and influence of environment (E). They are calculated on the base of **Holtzinger equations**:

$$H = (Cmz - Cdz)/(100 - Cdz) \times 100, \quad E = 100 - H,$$

where: Cmz — concordance of monozygotic twins,

Cdz — concordance of dizygotic twins.

For example: concordance of monozygotic twins at schizophrenia is equal 70%, and concordance in dizygotic twins — 13%.

According with Holtzinger equations:

$H = 70 - 13/100 - 13 = 57/87 = 0{,}65$ (65%).

Hence, the genetic factors play a preferred role in schizophrenia manifestation — 65%, and influence of environment is only 35%.

With help of twins method may be studied the following:

1. A role of a heredity and environment in disease development.
2. The factors enhancing environment impact.
3. The correlation between traits and functions.

5. The biochemical methods.

The biochemical methods are applied for diagnostics of hereditary metabolic exchange diseases. On the base of biochemical method the enzyme activity and interesting chemical substances can be evaluated. We can check different stages of metabolic pathways and reveal crucial defects in them.

Metabolic exchange diseases can be detected on a three levels: molecular (protein structure and quantity assessment), cellular (evaluation of defect enzymes), and organism level (searching for intermediate metabolites).

On the base of biochemical methods the disorders of exchange of amino acids (phenylketonuria, alkaptonuria), carbohydrates (diabetes, galactosemia), lipids (idiotia), copper (Konovalov-Wilson's disease), and iron (hemochromatosis) can be detected.

6. The dermatogliphic methods.

Dermatogliphic — the section of the human genetics studying hereditary patterns of fingerprints, handprints and footprints. Skin patterns are strictly individual and genetically caused. Process of relief formation occurs within 3–6 months of intra-uterine development. The mechanism of formation of crests is connected with morphogenetic interrelations between epidermal and underlaing tissues.

The genes providing formation of skin patterns on finger-pad participate in regulation of saturation by liquid the epidermal and dermal layers.

The gene A — causes occurrence of an arch on a finger-pad, gene W- occurrence of a helix, gene L — occurrence of a loop. Thus, distinguish three basic patterns on finger-pads. Frequency of occurrence of patterns: arches — 6%, loops — about 60%, helix — 34%.

A hand relief is more complex. Skin patterns are hereditary caused and polygenic.

On formation of dermatogliphic patterns can have influence some damaging factors at early stages of embryogenesis (for example, intra-uterine action of a German measles virus gives a deviation in patterns similar to Down syndrom).

The dermatogliphic method is used in clinical genetics as additional confirmation of the diagnosis of chromosomal syndromes with change of karyotype.

7. The immunological methods.

Methods are based on studying antigens of human cells and organism fluids (blood, saliva, stomach juice). Most common are antigens of erythrocytes, leukocytes, and also blood proteins. Various kinds of erythrocyte antigens form different blood groups — AB0, the Rhesus factor and etc. The knowledge of blood groups is important for blood transfusion.

8. The ontogenetic method.

The ontogenetic methods allow study gene expression during development. The purpose of the ontogenetic methods is early detection and prevention of

hereditary diseases. The method is based on biochemical, cytogenetic and immunological methods.

Phenylketonuria, galactosemia, and vitamin B resistant rachitis become apparent in early stages of postnatal ontogenesis. Its timely diagnostics promotes the preventive actions and lowering of pathology. Such diseases as diabetes, padagra, alkaptonuria are shown at later stages of ontogenesis. The ontogenetic method has a special significance at studying activity of the genes which are heterozygotic condition. This allows reveal the recessive diseases linked to the X-chromosome. Heterozygotic conditions revealed with the help of studying of symptoms of disease (at anophtalmia — reduction of eyeballs); with the help of loading tests (the raised contents of phenylalanin in blood of patients with phenylketonuria); with the help of microscopic research of blood cells in tissues (accumulation of glycogen at glycogenosis); with the help of direct definition of gene activity.

9. The method of somatic cells genetics.

It is based on studying of a hereditary material in cell cultures of somatic cells. In this case, the traits are expressed independently from environment conditions. It is possible also to receive cell hybrids. It allows: to perform the analysis of gene linkage and their localization, establish the mechanisms of interaction of genes and regulation of activity of genes, discover gene mutations and so on.

3. Methods of prenatal diagnostics

Prenatal diagnostics is connected to tasks of prevention of a child birth with the incurable pathology. Now, it is possible to establish all chromosomal diseases, the majority of congenital malformations, and enzyme abnormalities which biochemical defect is known. The part from them can be established practically in any term of pregnancy (chromosomal diseases), a part — after 12 weeks of pregnancy (defects of limbs, anencephalia), and a part — only in second half of pregnancy (heart and kidney defects).

Common reasons for prenatal diagnostics:

1. A person knows of a genetic disease in the family.
2. A couple has given birth to a child with a genetic disease, birth defect, or chromosomal abnormality.
3. A couple has a child who is mentally retarded or a close relative is mentally retarded.
4. An older woman (mother age 35 or older) becomes pregnant or wants to become pregnant.
5. Husband and wife are closely related (e. g., first cousins).
6. A couple experiences difficulties achieving a successful pregnancy.
7. A pregnant woman is concerned about exposure to an environmental substance (ionizing radiation, drug, chemical, or virus) that causes birth defects.

8. Both parents are known carriers for a recessive genetic disease.

Now apply *indirect and direct methods* of prenatal diagnostics. At indirect methods, investigate a pregnant woman (for example the maternal blood tests). At direct methods, investigate a fetus. There are direct methods without surgical interventions, for example ultrasonography or ehography, and with disorder of integrity of tissues — chorionopexia, amniocentesis and fetoscopia.

Some genetic conditions can be detected by performing a *blood test on the mother*. For instance, α-fetoprotein is normally produced by the fetus during development and is present in the fetal blood, the amniotic fluid, and the mother's blood during pregnancy. The level of α-fetoprotein is significantly higher than normal when the fetus has a neural tube disorder or one of several other disorders. Some chromosome abnormalities produce lower-than-normal levels of α-fetoprotein. Measuring the amount of α-fetoprotein in the mother's blood gives an indication of these conditions. However, because other factors affect the amount of α-fetoprotein in maternal blood, a high or low level by itself does not necessarily indicate a problem.

Some genetic conditions can be detected through direct visualization of the fetus. Such visualization is most commonly done with *ultrasonography.* In this technique, high-frequency sound is beamed into the uterus; when the sound waves encounter dense tissue, they bounce back and are transformed into a picture. The size of the fetus can be determined, as can genetic conditions such as neural tube defects (defects in the development of the spinal column and the skull) and skeletal abnormalities.

Chorionopexia or chorionic villus sampling (CVS) can be performed between the 10th and 11th weeks of pregnancy. In CVS, a catheter — a soft plastic tube — with the use of ultrasound for guidance, is pushed through the cervix into the uterus. The tip of the tube is placed into contact with the chorion. Suction is then applied, and a small piece of the chorion is removed. The received piece of the chorion are used for cytogenetic, biochemical, and DNA analyses. CVS has a somewhat higher risk of complication than that of amniocentesis.

Amniocentesis. It is obtaining amniotic fluid and fetal cells for the subsequent analyses. A puncture can be performed on 15–17 week of pregnancy through abdominal wall under guidance of ultrasound. The received cells are used for cytogenetic, biochemical, and DNA analyses. Complications with amniocentesis (mostly miscarriage) are rare, arising in only about 1 in 400 procedures.

Fetoscopia is survey of a fetus with help of fibrooptic endoscope which is entered in amniotic cavity through a belly wall of uterus. The method allows examine the fetus, umbilical cord, placenta, and make byopsia. It is accompanied by high risk of interruption of pregnancy and has the limited application.

LECTURE 12

Theme: Hereditary diseases of human. Principles of genetic counseling

Plan:

1. Classification of hereditary diseases.
2. Diseases of metabolic exchange or gene diseases.
3. Chromosome diseases.
4. Cytoplasmic diseases.
5. Principles of genetic counseling.

1. Classification of hereditary diseases

Changes of the genetic characteristics of sex cells result in pathologies of progeny. They can concern changes of structure DNA — gene mutations, structures of chromosomes — chromosomal mutations, and amount of chromosomes — a genome mutation. All kinds of mutations cause hereditary diseases. The extensive range of diseases related with hereditary diseases: internal diseases, diseases of metabolism, blood, endocrine system, skin, eye, urinogenital, and nervous systems.

In case of gene mutations disease can be tracked with the help of pedigree method since mutant genes are transferred from parents to progeny. The majority of chromosomal anomalies, in particular aneuploidy, are characterized by the plural developmental anomalies, the lowered viability, mental degradation, barrenness and often are incompatible with a life. Thus, the majority of chromosomal mutations are not inherited, but in each generation they appear in a quantity (0,5–0,7%) basically as result of a new mutation in sex cells of healthy parents.

Distinguish monogene diseases at which genetic disorders are connected to a mutation in an individual locus of a chromosome, and polygenic — caused by cumulative action of mutations in several loci of chromosomes. In the second case the predisposition to disease is usual and disease is a result of interactions of genetic factors and environments.

The hereditary pathology is shown at different age: embryonic and postembryonic periods, in mature and even in elderly age.

It is necessary to distinguish concepts congenital and hereditary diseases. Sometimes they coincide, if hereditary disease is congenital, however in some cases such coincidence is not present. The congenital disease term speaks only about time of expression of disease, instead of about its reasons which can be as hereditary, and is not hereditary. For example, developmental anomalies of the facial skeleton (facial cleft), the skeleton of hands (poly- and syndactyly), some heart and internal diseases can arise both in case of gene mutations and as result of influence of harmful factors of environment during the critical periods of organ

development. Fetal hypoxia, avitaminosis, virus or parasite diseases of mother related with such factors at early stages of pregnancy (German measles, toxoplasmosis). Such copies of hereditary defects have name phenocopies and they are not inherited.

One of the important questions of hereditary pathology is the problem of individuality. «The basic, sometimes crucial importance among the internal reasons of diseases is factors of hereditary predisposition and individuality» (Davydovski I. V.).

Predisposition is shown in change of norm of reaction of an organism on action of factors of an environment. For example, at predisposed to diabetes, the norm of reaction to starch and sugar is changed.

Genetic individuality is shown in variations of organ structure, physiological functions, and biochemical reactions (variation of chemical composition of tissues, different types of excretion, different activity of enzymes). As a consequence, there are various reactions of organisms to influence of pathogenic factors. Influence of the same intensity for one person is pathogenic, for another — harmless. Any pathology, including hereditary, are caused by interaction of genetic factors and environments.

In many cases mutant allele causes predisposition to disease. So in case of padagra, penetrance of diseases is 10–20% at men. Disease is expressed at 30–50 years. Overeating, abusing of meat food and alcohol promotes development of diseases.

The phenomenon of predisposition is especially characteristic for polygene diseases: atherosclerosis, hypertension, schizophrenia, etc. At people predisposed to hereditary hypertensions the disease develops due to overstrain and conflicts but other people under influence of the same factors do not have disease.

In connection with above stated it is possible to divide hereditary diseases on 5 groups depending on ratio of roles of environment and genotype (Efroimson V. P., 1968).

1. The diseases expressed in individuals with a certain genotype independently from environmental conditions (chondrodystrophy, hemophilia, xeroderma pigmentosum, etc.).
2. The diseases expressed in individuals with a certain genotype and in presence of the certain factors of environment (podagra).
3. The diseases expressed in individuals with different genotypes but rate and severity depending on both a genotype and an environment (a duodenal ulcer disease).
4. The diseases expressed in individuals with different genotypes, but rate and severity depend on a genotype (tuberculosis).
5. The diseases completely dependent on environment.

Such classification reflects expression of hereditary diseases from a physiological condition of an organism and interaction with factors of environment.

Based on character of genotype damage the hereditary diseases classified on: diseases of metabolic exchange or gene diseases, chromosome diseases, and cytoplasmic diseases.

2. Diseases of metabolic exchange or gene diseases

Gene mutations at human are the reasons of many forms of hereditary pathology. The basic from of them: gene diseases, congenital developmental anomalies and diseases with hereditary predisposition.

Diseases with hereditary predisposition differ from monogene diseases that for their expression the action of the certain factors of environment is necessary.

Gene diseases are caused by two kinds of protein changes. The first group of diseases is connected with qualitative change of protein molecules, i. e. with presence of abnormal proteins (example — abnormal haemoglobins) which is caused by mutations of structural genes. Other group is characterized by quantitative changes of the protein contents in a cell that is connected to mutations of functional genes (disorder of regulation of gene activity). The accumulated substances as a result of change of activity of enzymes either are toxic or promote their formation.

Total frequency of gene diseases in a population is 2–4%. More than 3 000 of the hereditary diseases caused by genic mutations are described.

Gene diseases are classified on diseases of: aminoacid, lipid, and carbohydrate exchange, steroid exchange, blood clotting systems, incompatibility of mother and fetus on antigenes of blood groups (hemolytic anemia of newborns), hemoglobinopathy, and exchange of metals.

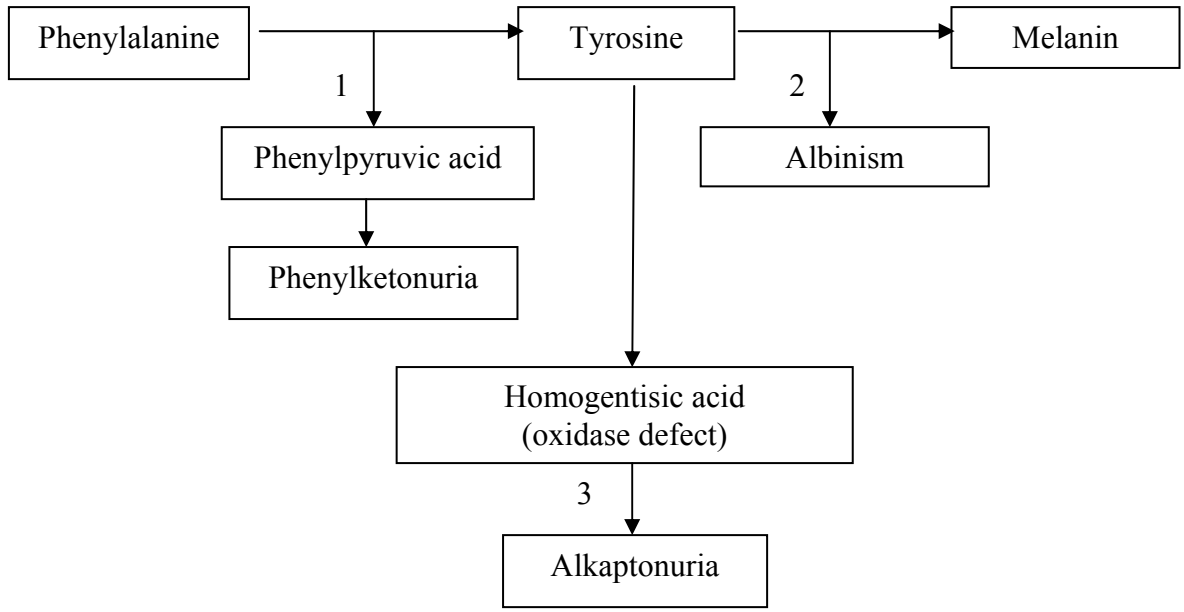
Diseases of amino acid exchange. Phenylketonuria and albinism are most frequent diseases.

Phenylketonuria is autosome-recessive disease. In Belarus, it meets with frequency 1:6000. It is caused by hereditary deficiency of enzyme phenylalanine hydroxylase that transform phenylalanine (PA) in tyrosine. In a case of absent of enzyme activity, PA does not turn in tyrosine and accumulated in blood serum as phenylpyruvic acids (PPA) which is released with urine and sweat (a «mouse» smell). PPA is neurotropic poison; in result, at child born with disease, hypererethism and supertension of muscles, convulsive epileptiform attacks, disorders of the high nervous activity, mental retardation, and microcephaly are observed. Disease is shown after a birth. To diagnostics apply the test with 10% solution of ferrous chloride ($FeCl_3$). A green colouring is developed after addition of ferrous chloride in urine. Effective method of treatment is dietotherapy — giving to the child a food with the low contents of phenylalanine. Treatment is necessary from the first weeks of a life and within first 7–10 years constantly keeps up contents of PA in blood. The brain of the adult person is steady against the high concentration of PPA.

Albinism is autosome-recessive disease with frequency from 1:5000 to 1:25000. It is caused by inability melanocytes to form melanin due to disorder of activity of enzyme tyrosinase. The eye-skin form is the most widespread (skin is milky-white, iris of eyes is light grey or light blue, pupil is red, body is sensitive to the UV rays, hair are very light).

Alkaptonuria is autosome-recessive disease with frequency 3–5:1 000 000. Disease is defect of oxidase which catalyses transformation of homogentisic acid in acetoacetic and fumaric acids. In result homogentisic acid is postponed in the connective tissue and pigmentation of ochre color (for example ochronosis of cartilage) is observed. Diagnostics: darkening of alkalized urine. Clinical expressions observed in the age of 40 years and older, also defects of backbone and joints are observed.

The scheme of disorders of phenylalanine-tyrosine metabolism in human



Diseases of carbohydrate exchange. The most often defects are disorders of lactose assimilation — galactosemia, fructose assimilation — fructosemia, pentose assimilation — pentosuria, and also glycogenosis, and diabetes.

Glycogenosis.

Diabetes is autosome-recessive widely distributed disease (about 4–5% of homozygotes) with 20% of penetrance. Frequency of diseases is 1,2–1,3%. It is characterized by the increased contents of sugar in blood. Diagnostics is based on definition of glucose in blood and urine, and also activity of insulin. The acute diabetes develops at insufficient formation of insulin B in insulin-producing cells of pancreas. Late developing disease is accompanied by fatness and atherosclerosis. Diabetes treated by sulfanilurea.

Galactosemia. Frequency of disease is 1:100000. In a basis of disease is deficiency of the enzyme which decomposes the galactose and its accumulation in different organs. There is disorder of glucose exchange in liver, kidneys, and

brain resulting to decrease in its contents in blood. Later amino acids (methionine, cysteine) are appearing in urine. Disease develops after a birth at milk feeding. Milk lactose is a source not metabolizing galactose. Symptoms of disease are: jaundice newborn, diarrhea, vomitting, gradual development of mental retardation, general dystrophy, and cataract. At urine analysis, galactose and proteins are found out. Early treatment by diet provides normal development. Absent of treatment gives destruction in the first months of a life from accompanying infections or hepatic deficiency; the cataract and mental retardation develop at survived children.

Disorders of lipid exchange. They are subdivided into 2 big groups: sphingolipidosis and disorder of exchange of the blood plasma lipids caused by diemyelinization of nervous fibres (multiple sclerosis).

All sphingolipidosis have autosome-recessive type of inheritance (infrequent can be linked with the X-chromosome). These are diseases of endocellular accumulation of sphingolipids (kind of glycolipids). It is caused by defect of enzymes catalysed their decomposition. For example: amaurotic familial idiocy (*the Tay-Sachs disease)* (frequency 1:5000). Children with Tay-Sachs disease appear healthy at birth but become listless and weak at about 6 months of age. Gradually, their physical and neurological conditions worsen, leading to blindness, deafness, and eventually death at 2 to 3 years of age. The disease results from the accumulation of a lipid called GM2 ganglioside in the brain. A normal component of brain cells, GM2 ganglioside is usually broken down by an enzyme called hexosaminidase A, but children with Tay-Sachs disease lack this enzyme. Excessive GM2 ganglioside accumulates in the brain, causing swelling and, ultimately, neurological symptoms. In the general population of North America, the frequency of Tay-Sachs disease is only about 1 person in 360,000. Among Ashkenazi Jews (descendants of Jewish people who settled in eastern and central Europe), the frequency is 100 times as great.

Disorder of lipid exchange in blood plasma is caused by disorders of enzymes or cell receptors. Lipids of plasma represent group of compounds basically of fat acids, triglycerides, cholesterols, and phospholipids. The real form of treatment is restriction of fat acids consumption with food.

Diseases of steroid exchange. Diseases are submitted by *adrenogenital syndrome* which is inherited as autosome-recessive disease with frequency 1:5000–1:67000. At girls, disease is shown in the form of pseudohermaphroditism, and at boys - premature virilization. The syndrome is caused by congenital adrenal hyperplasia and hereditary defect of biosynthesis of steroid hormones of cortex of adrenal glands because of reduction in activity of enzymes of synthesis of hormones. The initial sex is determined on the base of sex chromatine in cells of buccal epithelium.

Disorders of purine exchange. The gout (podagra) concerns to such diseases. This autosome-dominant disease have penetrance 20% at men and almost full nondevelopment at women. Illness develops in elderly age as

deposition of urates in organs and accompanied by inflammatory reactions. Approximately 1–2% of people have asymptomatic disorder of purine exchange.

Lesch-Nyhan syndrome develops almost exclusively in boys, and the trait is inherited as an X-linked recessive disorder; the presence of a defective gene on a male's single X chromosome causes the disease. In people who have Lesch-Nyhan syndrome, a mutation in the gene for enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) changes the amino acid sequence of the enzyme, rendering it nonfunctional. The result is that purines are not recycled; they accumulate and are converted into uric acid. High levels of uric acid produce the symptoms of the disease: blood in urine, high concentrations of uric acid in blood, and uncontrollable spasms in arms and legs. Male is mentally retarded and selfdestructively bit his fingers and lips.

Diseases of blood clotting system are represented by hemophilias A, B, and C. Hemophilia results from a genetic deficiency of blood clotting. When a blood vessel is severed, a complex cascade of reactions swings into action, eventually producing a protein called fibrin. Fibrin molecules stick together to form a clot, which stems the flow of blood. Hemophilia, marked by slow clotting and excessive bleeding, is the result if any one of the factors in the clotting cascade is missing or faulty. In those with hemophilia, life-threatening blood loss can occur with minor injuries, and spontaneous bleeding into joints erodes the bone with crippling consequences.

- Hemophilia A — is sex linked recessive disease. Male suffer from this disease in about 1000 times more frequent than female. It is results from abnormal or missing of blood clotting factor VIII. The gene is located in the long arm of the X-chromosome. Frequency of hemophilia A in Finland is $3{,}2\times10^{-5}$.
- Hemophilia B — is sex linked recessive disease. Male suffer from this disease in about 1000 times more frequent than female. It is results from abnormal or missing of blood clotting factor IX. The gene is located in the X-chromosome.
- Hemophilia C — is autosome-dominant disease. It caused by changes of blood clotting factor VIII and decreasing activity of factor preventing vessel walls damage.

Hemoglobinopathy are diseases related with disorder of structure of hemoglobin molecule. The most part of structural variants of Нв is the single replacement of amino acids due to substitution of one base pair in DNA molecule with change of triplet sence.

The most known form of anomaly hemoglobins is *the sicle-cell anemia* at which in 6-th position of the B-chain of hemoglobin the glutamic acid is replaced by valine (HbS). This causes the lowered solubility of hemoglobin and erythrocytes get the sicle form in homozygotes. In homozygotes develops

chronic hypoxia and anemia resulting in death due to hemolysis of erythrocytes and low ability of HbS to oxygen transfer. At heterozygotes (Ss), the content of hemoglobin S is insignificant.

Thalassemia is a mutation of a globin gene resulting in the reduced globin contents or to their full absence. The reason of L-thalassemia is full division of hemoglobin L-genes (in L chains). Genes of this kind are four, and from amount of absent genes the severity of disease depends. They are located in 16-th chromosome. At B-thalassemia there is a deficiency of B-globin synthesis. In a homozygous condition the gene is lethal (expressed as hemolytic anemia).

Diseases of metal exchange. To this group of diseases refer *hepatolenticular degeneration (Wilson disease).* It is autosome-recessive disease. During this disease, copper ions infiltrate liver, brain, kidney, and cornea tissues. Also the excessive excretion of copper ions is observed.

As result of gene mutation the deficiency of the enzyme inhibiting synthesis of ceruloplasmin which provides transport of copper in organism is develops. Ions of copper are part of some enzymes of mitochondria participating in reactions of oxidation. At ceruloplasmin deficiency the copper concentration in blood raises and there is its accumulation in organs. Disease is shown at school age. The increase of copper concentration in liver and spleen, disorder of their functions and also CNS, and decrease in amount of blood elements are observed. Then the cirrhosis, defeat of CNS, and mental degradation are develops. Diagnostics is based on measure of ceruloplasmin concentration in blood serum.

Hemochromatosis — is disease of iron ions exchange and storage. It is inherited dominantly with incomplete penetrance. It is shown by liver cirrhosis, pigmentation of skin, and diabetes at male after 35 years but it is rare at female.

3. Chromosome diseases

Chromosomal diseases name diseases caused by changes in number and structure of chromosomes. They can arise at different stages of organism development. If they arise in gametes of parents the anomalies will be in all cells of developed organism (a full mutant). If anomaly arises in process embryonic developments at zygote division, the karyotype of fetus will mosaic. Such mosaic is formed as follows. All blastomeres contain the identical set of chromosomes which is identical to a zygote set. At disorder of chromosome separation, the unequal amount of chromosomes (one blastomere with monosomy, another — with trisomy) gets in different blastomeres. At the subsequent divisions there are two cell lines (clones) preserving features of abnormal karyotype. The cells originating from normal blastomeres will have the constant karyotype. Such phenomenon have name the genetic mosaicism. Mosaic organisms can contain a several (2, 3, 4 and more) cellular clones with various karyotypes. Mosaicism can be in all or in single organs and organ

systems. At insignificant amount of abnormal cells the phenotypic manifestation can not be found out.

With chromosomal diseases 0.7% of all babies are born. Deviations of number of sex chromosomes and autosomes are connected to process of meiosis disorder. The majority of anomalies are incompatible with a life. The final diagnosis of chromosomal diseases is established by cytogenetic method.

Diseases caused by changes in number and structure of autosomes

The most common autosomal aneuploidy in humans is trisomy 21, also called *Down syndrome*. The incidence of Down syndrome in the United States is about 1 in 700 human births, although the incidence is higher among children born to older mothers. People with Down syndrome show variable degrees of mental retardation. Many people with Down syndrome also have characteristic facial features, some retardation of growth and development, and an increased incidence of heart defects, leukemia, and other abnormalities. About 4% of people with Down syndrome have 46 chromosomes, but some of them have an extra copy of part of chromosome 21 is attached to another chromosome through a translocation. This condition is termed *familial Down syndrome* because it has a tendency to run in families. The phenotypic characteristics of familial Down syndrome are the same as those for primary Down syndrome. Average life span is 25–36 years.

Trisomy 18, also known as *Edward syndrome*, arises with a frequency of approximately 1 in 8,000 live births. Babies with Edward syndrome are severely retarded and have low-set ears, a short neck, deformed feet, clenched fingers, heart problems, and other disabilities. Few live for more than a year after birth.

Trisomy 13 has a frequency of about 1 in 15,000 live births and produces features that are collectively known as *Patau syndrome*. Characteristics of this condition include severe mental retardation, a small head, sloping forehead, small eyes, cleft lip and palate, extra fingers and toes, and numerous other problems. About half of children with trisomy 13 die within the first month of life, and 95% die by the age of 3.

Diseases caused by changes in number of sex chromosomes

Anomalies of sex chromosomes are submitted more often by trisomy and monosomy. Both types of anomalies arise at merge of two kinds of gametes — normal and pathological.

Mechanism is submitted on the scheme

Egg	Sperm	Zygotes	Phenotype
In norm			
X	X	XX	The normal woman
X	Y	XY	The normal man
At nonseparation of chromosomes			
XX	X	XXX	Triplo X syndrome

0	X	X0	Turner syndrome
XX	Y	XXY	Klinefelter syndrome
0	Y	Y0	Lethal

The scheme shows that the reason of such anomalies is nonseparation of chromosomes during gametogenesis at one of parents or during early mitotic divisions of zygote.

Total frequency of chromosome anomalies is 2,6 on 1 000 newborns. Distinctive feature is mosaicism. Every possible combinations of various cell clones cause different clinical symptoms.

Persons with *Turner syndrome* have a single X chromosome in their cells. Persons who have Turner syndrome are female; they do not undergo puberty and their female secondary sex characteristics remain immature. This syndrome is seen in 1 of 3,000 female births. Affected women are frequently short and have a low hairline, a relatively broad chest, and folds of skin on the neck. Their intelligence is usually normal. Most women who have Turner syndrome are sterile.

Persons who have *Klinefelter syndrome*, which occurs with a frequency of about 1 in 1,000 male births, have cells with one or more Y chromosomes and multiple X chromosomes. Persons with this condition, though male, frequently have small testes, some breast enlargement, and reduced facial and pubic hair. They are often taller than normal and sterile; most have normal intelligence.

Syndrome XYY.

Original version of Klinefelter syndrome. Typic phenotypic manifestations: high growth (180–185 sm), aggressive behaviour, and oligophrenia. The low and average norm of intellectual development is observed. They are sterile. It is described for the first time in 1962 at phenotypically healthy men.

Triplo-X syndrome.

In about 1 in 1,000 female births, the child's cells possess three X chromosomes, a condition often referred to as triplo-X syndrome. These persons have no distinctive features other than a tendency to be tall and thin. Although a few are sterile, many are fertile. The incidence of mental retardation among triple-X females is slightly greater than in the general population, but most XXX females have normal intelligence.

Much rarer are women whose cells contain four or five X chromosomes. These women usually have normal female anatomy but are mentally retarded and have a number of physical problems.

Chromosomal reorganizations

More often meet deletions of 5-th and 18-th autosomes. At deletion a short arm of 5-th chromosome was described in 1963 as a *Cri-du-chat* syndrome. The name (French for «cry of the cat») derives from the peculiar, catlike cry of infants with this syndrome. Sharp hypoplasia of throats, microcephalia, mental retardation, muscular hypotonia is characteristic for the syndrom. Deletion of

long and short arms of 18-th chromosome is also accompanied by human disorders.

4. Cytoplasmic diseases

Cytoplasmic diseases are caused by mutations of mitochondrial DNA. Human mtDNA is a circular molecule encompassing 16,569 bp that encode two rRNAs, 22 tRNAs, and 13 proteins. The two nucleotide strands of the molecule differ in their base composition: the heavy (H) strand has more guanine nucleotides, whereas the light (L) strand has more cytosine nucleotides.

In recent years, a number of genetic diseases that result from mutations in mtDNA have been identified in human. There are some inherited myopaties with abnormal mitochondria, Albright osteitis, Olier osteochondromatosis, anencephalia, and spina bifida.

5. Principles of genetic counseling

The most effective approach to prevention of hereditary diseases is genetic counseling. For the first time such counseling has been organized at the end of 20th years of XX century by Russian geneticist and neuropathologist S. N. Davydenkov at Institute of nervous-psychiatric prevention in Moscow.

Genetic counseling is a relatively new field that provides information to patients and others who are concerned about hereditary conditions.

Genetic counseling often includes:

- interpreting a diagnosis of the condition;
- providing information about symptoms, treatment, and prognosis;
- helping the patient and family to understand the mode of inheritance;
- calculating probabilities that family members might transmit the condition to future generations;
- providing information about the risk for the disease;
- finally, genetic counseling tries to help the patient and family cope with the psychological and physical stress that may be associated with their disorder.

Clearly, all of these considerations cannot be handled by a single person; so most genetic counseling is done by a team that can include counselors, physicians, medical geneticists, and laboratory personnel.

Efficiency of counseling depends from:

- Accuracy of the diagnosis.
- Calculation precision of genetic risk for the disease.
- Understanding of genetic counseling value.

Genetic counseling includes 3 stages.

The *first stage* of genetic counseling usually begins with a diagnosis of the condition. Depending on accuracy of the diagnosis can be distinguished the next patients:

- which have suspicions on hereditary disease;

• which have established diagnosis, however, it give rise to doubts;
• which have right diagnosis.

The second stage include **calculating probabilities** that family members might transmit the disease to future generations:

• by theoretical calculations on the base of genetic laws;
• with the help of the empirical data for diseases with not clear mechanism.

The third stage of counseling is final. When the nature of the condition is known, a genetic counselor sits down with the patient and other family members and explains the diagnosis. The counselor helps the family interpret the genetic risks and explains various reproductive options that are available, including prenatal diagnosis, artificial insemination, and in vitro fertilization. A family's decision about future pregnancies frequently depends on the magnitude of the genetic risk, the severity and effects of the condition, the importance of having children, and religious and cultural views. The genetic counselor helps the family sort through these factors and facilitates their decision making.

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