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MEDICAL BIOLOGY AND GENERAL GENETICS

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В учебном пособии отражены разделы биологии, имеющие значение в медицинском образовании врача. Материал изложен в соответствии с уровнями организации живого – молекулярно-генетическим, клеточным, онтогенетическим, популяционно-видовым и биосферно-биогеоценотическим. Освещены вопросы репродукции человека, биоэтические аспекты генетики, трансплантации тканей и органов человека. Отражены вопросы сравнительной анатомии человека, ядовитости живых организмов. Материал учебника изложен с учетом достижений медико-биологических наук, показана взаимосвязь отдельных ее областей.

Учебное пособие соответствует типовому учебному плану и программе, утвержденных Министерством образования Республики Беларусь (2016).

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PREFACE

Contemporary biology rapidly accumulates the knowledge about fundamental and systemic mechanisms of living beings. The social value and relation with individual's life of contemporary biology increase. A human being becomes a target for modern biological research. Human being is related to wild nature. This relation is not only historical. Even now, in every day routine a man faces the biological aspects of his being. Human beings change the nature, but at the same time, the nature changes human beings. The pattern of these relationships reflects a state of human health.

The content of this book corresponds to a new program of medical biology and general genetics for students of higher educational institutions, proved by Ministry of Health Care of the Republic of Belarus in 2016. Considering this, the authors decided to pay attention to the medical aspect of the material. The study is performed according to with life organization levels. It shows showing close relationship between biology and medical disciplines.

"Molecular - genetic level of life organization" is devoted to study of genetic material of non-cellular forms, prokaryotes and eukaryotes, of nucleic acids characteristics, of processes of nucleic acids synthesis, of hereditary information coding.

"Cellular level of life organization" analyzes cells as an open system with substances, information and energy flows. The problems of cells proliferation are discussed.

"Ontogenetic level of life organization" is directed at studying the processes of living organisms reproduction, human reproduction, ethical and juridical aspects of human reproduction disturbances. The principles of heredity and diversity are covered noting specific features of human beings. Studying of the developmental biology is directed at understanding general principles of human ontogenesis, genetic, cellular, and systemic homeostasis mechanisms, bioethical aspects of transplantation of tissues and organs.

In "Population-species level of life organization" the features of humankind populations' structure, genetic polymorphism of humankind populations and genetical aspects of predisposition to various somatic diseases are described. The problem of genetic load and its value for humankind are considered.

The "Biospheral level of life organization" is devoted to anthropo-ecological problems, in particular, to differentiation of humankind into adaptive types. The biological and social aspects of human adaptation to

living conditions are considered. The ecological aspects of parasitism are considered. The causative agents of parasitic diseases are described as etiological factors in medical pathology. The problems of etiology, pathogenesis and clinical pictures of poisoning are considered.

The main task of the biology course is to study a human being as a biosocial with an accent on its biological features whicha are most important for formation of fundamental knowledge in students in studying medical and biological disciplines.

Authors

CHAPTER 1. THE ROLE OF BIOLOGY IN A SYSTEM OF MEDICAL EDUCATION

1.1. BIOLOGY AS A NATURAL SCIENCE ABOUT LIFE

Biology is a science, which studies life as a special form of matter movement, its laws of existence and development. The subject of biology studies living organisms and their natural communities. Biology is a natural science as well as astronomy, physics, chemistry, geology and other sciences. It is a complex science. It includes more than 50 disciplines, among them are:

- morphological disciplines (anatomy, histology) describing an organism structure;
- physiological disciplines (cell physiology, plant physiology, animal physiology);
- general biological disciplines (cytology, genetics, evolution, etc.);
- ecological disciplines (biogeography, parasitology);
- bordering disciplines (biochemistry, biophysics, anthropology, molecular biology, space biology, etc.).

Biology is a leading natural science. The high level of biological research is a necessary condition for modern medicine progress.

1.2. THE ESSENCE OF LIFE. THE LIFE ORGANIZATION LEVELS

The life substrate is a complex of substances. These substances are from two biopolymer classes: proteins and nucleic acids. There were several efforts to determine life based on this statement. Life is a function of proteins and nucleic acids interaction on the Earth. All modern views on a life origination are based on two following statements: life was not brought to the Earth from outspace; the living organisms were not self originated. The main feature of life is reproduction and renewing of protein bodies. It is based on DNA self-replication and transmitting genetic information to a new cell. Life is a form of polymer system beings which are able to self replication under conditions of constant exchange of energy and substance with environment. The other fundamental features of life are: self-renewing on a base of substance and energy exchange, self-reproduction providing relations between generations, self-regulation based on information, energy and substance flow. These features provide the main signs of living.

Discretion and integrity. The organic world is integral and discrete at the same time. It is integral because it is a system of related units. It is discrete because it consists of separated units – organisms. Each organism

consists of cells, they in turn consist of organelles, but all of them work together as an integral system.

Structural organization. Living matter is built out of the same substances as an inorganic matter. However, molecules of a living matter are more complex. It is because of a special order on a molecular level. The structural organization is a proper feature of life at all levels of its organization. The hereditary information is encoded by genes, but no gene acts successfully outside the genotype. The integrity of proteins and nucleic acids provides a living matter on the Earth.

Substance and energy exchange. The main property of life is a metabolic exchange. Each organism can be presented as an open system supporting constant substance and energy exchange with the environment. In living organisms, substance exchange leads to repairing lost parts. The structure of a living matter reproduces itself with the help of DNA information. Living organisms are in integrity with the environment, whereas all physical, chemical and biological properties of the environment provide conditions for all living processes.

Reproduction. It provides a living matter. Each species consist of individuals having their own life span. With the help of reproduction, life span of species is much longer than that of individuals. The reproduction of species provides biosphere being.

Heredity and diversity. They are important features of life connected with inheriting and ability of these traits to be changed in different environmental conditions. The heredity provides material succession between generations. Traits, which are inherited, provide adaptation to the environment. The storage and transmitting hereditary information is a function of nucleic acids. The diversity is a feature opposite to heredity. It provides origination of new traits, absent in parents. If the structure of nucleic acid has been changed, new traits which appeared can lead organism to die or to adapt to environmental conditions. The diversity gives living matter for new species formation and evolution.

Growth and development. It is a property of organism to grow and develop by cell divisions and differentiation. An organism grows and develops puberty, which allows it to reproduct. The organisms inherit only possibility to develop traits. This possibility is realized during individual development (ontogenesis).

Irritability. It is a property of life, which provides contacts of organism with the environment and surrounding organisms. In monocellular organisms, it is presented by taxises, in plants - by tropisms, in higher animals - by reflexes. With the help of this, organisms selectively react on stimuli; they can get necessary substances from the environment. A metabolic exchange

is closely related with it. The irritability is connected with the chemical nature of life substrate.

Internal regulation and homeostasis. Each organism, being an open system, keeps up the main parameters of the internal environment on at the same level. It keeps up homeostasis. Homeostasis is supported with the help of neurohumoral regulation. The self-regulation in biological systems is based on negative feedback. Thus, such processes as inheritance, metabolism, reproduction and so on are regulated.

Modern biology studies life processes on different levels. These levels are called life organization levels.

Molecular-genetic level. Central regulating systems – codes of hereditary information, transmitted from generation to generation are elementary structures of this level. Codon reproducing and protein synthesis on a gene matrix are elementary events. DNA reduplication preserves genetic information, placed in genes, for the next generation.

Cellular level. Cell is the elementary structure of this level. Cell division and cell development are elementary events. All organisms look like similar on this level. The genetic information is realized in particular proteins on this level as well. Protists cellular level coincides with an organism level. This level was dominated in Achaean era.

Ontogenetic level. Organisms are elementary structures. Ontogenesis, differentiation and still unknown mechanism that direct all these processes are elementary events. On this level, there is a variety of living organims. The Earth is inhabited by more than 3 million species. Each species consist of organisms. Each organism presents an elementary life unit. The nervous and humoral regulation provides a constant state of internal environment and homeostasis. There is no life outside the organism.

Population level. Populations of any life species are elementary structures. Directed changes in their genofond is an elementary event. Such changes lead to the formation of a new adaptation to change nature. Accumulated adaptations and adjustments result in new species formation on a base of natural selection. Population is an open genetic system because of possibilities of interpopulation breading. The elementary evolutionary factors act on population genofond, which results in evolutionary significant changes in genofond. It is an elementary event on this level.

Biospheral level. Biogeocenosis are elementary units on this level. Biogeocenosis upgrade to the next level, the next well-balanced state are elementary events. Biogeocenos is an open system for the energy flow and substance flow as well. All biogeocenosis even different in structure are united to one complex, called biosphere. Biosphere is a perpetually-sealed envelope, so that we face a problem of environment protection.

Living matter on the Earth is presented by organisms. Each organism consists of lower organization levels and at the same time, it is a part of a higher organization level. It needs to be pointed that structural elements on lower levels are quite similar, at the same time, they become more different with increasing complicity. On a molecular-genetic level, the discrete elements of prokaryotes, non-cellular living organisms and eukaryotes are similar. Living matter for all of them is presented by four similar organic bases, connected with five-atom sugar and phosphate, forming nucleic acids, and by 20 amino acids. On a cellular level, we can say that a cell of different organisms is more similar than different from each other. However, on an organism level we can observe a large variety among organisms. This variety results from different combinations of lower level units. These combinations provide new structural features.

1.3. THE BIOLOGY ROLE IN DOCTORS TRAINING

Biology is theoretic essentials of medicine, that is why it is important for future doctors to study biology. Morphological, biochemical, genetical and physiological disciplines are essential for pathology. Such practical branches of medicine as therapy and surgery are based on anatomy, physiology and biochemistry. Epidemiology is based on achievements of ecology, zoology, parasitology, microbiology and virology. Biology also gives a specific view on life processes.

Knowledge on cytology, genetics, molecular biology, anthropology, ecology and evolution theory is essential to a future doctor. Doctors should keep in mind the consequences of industrial impact on the environment. It is important to know the cell pathology (proliferate cell ability), genetics (human hereditary diseases), ontogenesis (concepts of defects development), ecology (concepts of adjustment disorders), parasitology, poisonous plants, animals and fungi.

Modern advances in medicine were made on essentials of biology. For instance, L. Pasteur's discovery about bacterial essential of fermentation resulted in the formulation of the main aseptic and antiseptic principles. Modern concepts of immunity resulted in the discovery of phagocytosis formulated by I.I. Mechnikov (1845-1916). Mendel Laws of inheritance resulted in the formulation of chromosome theory of inheritance. That is why I.V. Davidovsky (1897-1968) said that theoretical medicine was mainly a general biology.

Human health depends on an environment state. Biology helps to make a new science based on the view on human relations with nature, on using natural resources, on environment protection, on preventive measures against parasite and infection diseases.

MOLECULAR-GENETIC LEVEL OF LIFE ORGANIZATION

CHAPTER 2. THE NUCLEIC ACIDS AND THEIR ROLE IN LIVING ORGANISMS

2.1. THE STRUCTURE OF NUCLEIC ACIDS

The studying of molecular-genetic life organization is connected with the studying of structure and functions of nucleic acids. Nucleic acids are macromolecules. They were first discovered by F. Miescher in 1869. Scientists began to pay attention to the nucleic acids as a place of hereditary information storage after J. Watson and F. Crick's works (1953). The nucleic acid exists in two forms: desoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the storage of genetic information. It is in the nucleus chromosomes, in the mitochondria, in the chloroplasts of eukaryotic cells, in prokaryotic cells, in many viruses. RNA serves for transmiton and realization of hereditary information in prokaryotic and eukaryotic cells. In many viruses RNA work as a primary storage of hereditary information. Nucleic acids are composed from nucleotide subunits. The nucleotide subunit is composed of three elements: an organic base, a phosphate group, a 5-carbon sugar (Fig. 2.1). The base is bound to the first carbon atom in the sugar and phosphate group is bound to the fifth carbon atom in the sugar. The third atom of the sugar always has a hydroxyl (-OH) group.

The nucleotide linkage in the nucleic acid molecule is provided by phosphodiester bond between a phosphate group of one nucleotide and hydroxyl group of another nucleotide. Further linking can occur in the same way, since two-unit polymer still has a free 5' - phosphate group at one end and a free 3'- hydroxyl group at the other end. This linking occurs with the help of polymerase enzyme. A new nucleotide can be attached to the chain only to 3' hydroxyl group of the polymer. A nucleotide without phosphate group is named nucleoside. Organic bases are purine – adenine and guanine or pyrimidine – thymine, cytosine and uracil. DNA consists of $2x10^9$ and more nucleotides (Fig. 2.1).

Analyzing DNA of different origin, E. Chargaff in 1949-1955 developed the principles of DNA composition. Chargaff results are commonly referred to as Chargaff rules:

1. The proportion of A always equals to T and C similarly equal to G; A=T, G=C.

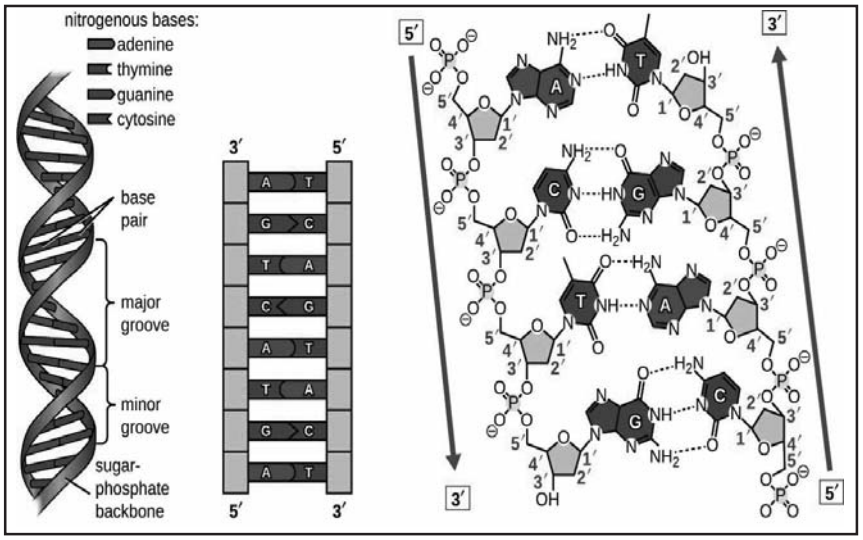


Fig. 2.1. Chemical structure of DNA (by Raven & Jones).

2. There is always an equal proportion of purines (A and G) and pyrimidines (C and T).

3. The number of bases with 6-aminogroupes equal to number of bases with 6-ketogroupes (A+C=G+T).

4. The ratio of such bases as A+T/G+C is species-specific value.

These findings served as a key for DNA structures discovery. J. Watson, F. Crick made a 3-dimenitional model of DNA in form of double helix (Fig. 2.2). This allowed them to explain physical, chemical and biological properties of DNA. With the help of x-ray analysis, it was shown that diameter DNA helix is 2 nm, and made a complete spiral turn every 3.4 nm. Each complete spiral turn includes 10 nucleotide pairs. The main principles of DNA structure was formulated in the following statements:

1. Each DNA molecule consists of two long antiparallel polynucleotide chains, making double helix. The antiparallelity of polynucleotide chains is provided by linkage of 5' end of one chain to 3' end of the other.

2. Each nucleoside is in the plane, which has a right angle with helix axis.

3. Two chains are bounded to each other with the help of hydrogen bonds between the bases.

4. The pairs linkage is very specific. There are only two possible pairs A: T and G:C.

5. The sequence of pairs in one chain may vary in a wide range but the sequence of pairs in the second chain has to be complementary to it. Thus,

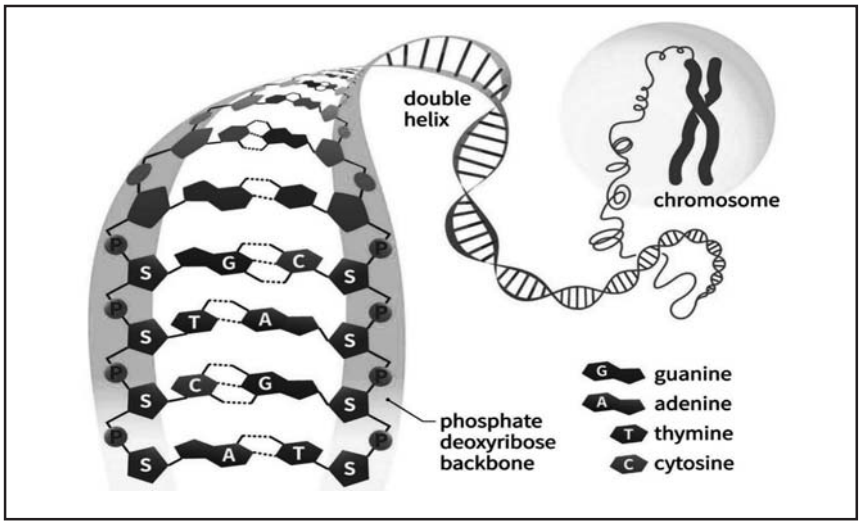


Fig. 2.2. Double helix structure of DNA (by Raven & Jones).

the pair sequence in one chain defines the complementary sequence in the other chain.

For discovering the DNA dimenitional model, J. Watson, F. Crick and M. Wilkins were awarded a Nobel Prize in 1962.

It can be distinguished a primary DNA structure - a polynucleotide chain, a secondary DNA as structure - two complementary to each other antiparallel polynucleotide chains, bounded by hydrogen bonds, and third DNA structure - three dimenitional spiral with characteristics described above.

A DNA molecule is able to replication. This is a very complicated process. First, the double stranded DNA molecule separates at one end with the help of heliase enzyme. Each strand becomes a matrix for new complementary strand synthesis. As a result, two DNA molecules are formed with the same structure. The regions of DNA despiralizing by heliase enzyme are called replication forks (Fig. 2.3). At these regions, with the help of DNA polymerase enzyme DNA of two new molecules is synthesized. The replication fork moves along mother spiral during a replication process. The DNA fragment from the point of replication starts to the point of replication end forms a replication unit - a replicon. The eukaryotic cells have a large number of replicons. That is how the replication of DNA of eukaryotic chromosomes starts at several points. In the different replicons, replication may occur at the different or the same time. The ability of DNA polymerase to add nucleotides only in the direction from 3'

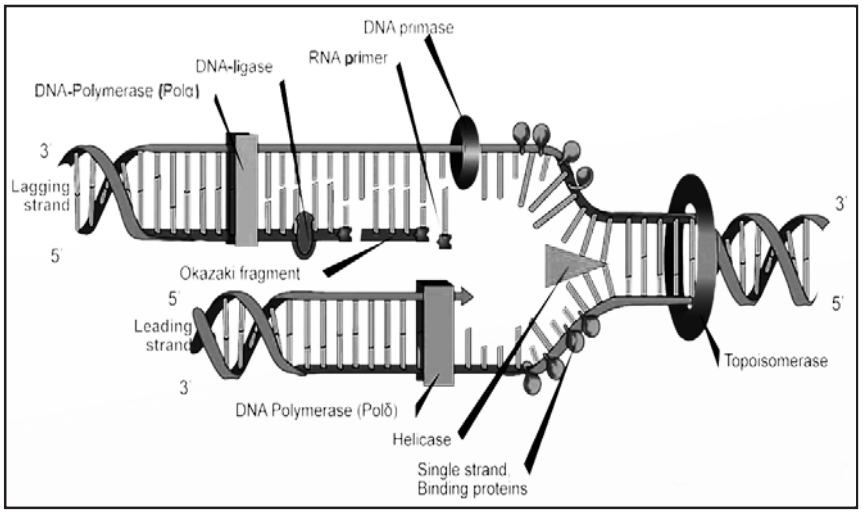


Fig. 2.3. Function of the replication fork of DNA (by study.com).

to 5' means that the process of replication in two DNA strands should be different. On one matrix, the replication of DNA occurs continuously from 3' end to 5' end. On another matrix, the process of replication is performed by short fragments. Then the short fragment of DNA is added to the growing chain in the 3' to 5' direction DNA polymerase jumps ahead to fill in another gap. These fragments are called an Okazaki fragments.

Three types of DNA replication can be distinguished: conservative, semiconservative, dispersive. All these types allow making a daughter DNA consisting of the same amount of mother DNA and newly formed. Only the distribution of a mother DNA in the molecules is different. Half of daughter DNA molecules is made from new material and the second half from the old one after the conservative replication. Each of the daughter DNA molecules has a half made from new material and a half from the old one after the semiconservative and dispersive replication. The semiconservative and dispersive replication can be distinguished after the daughter molecules replication. At a semiconservative replication 50% of daughter molecules of the second generation will be made from half of new material and half of old material. The other 50% will be made just from new material. At a dispersive replication, all molecules of the second generation will be made from 25% of old material and 75% will be made from new material.

The RNA molecule is a single strand. It consists of such nucleotides as adenine, guanine, cytosine and uracil instead of the thymine. Some

complementary regions can be bind to each other making a spiral. There are three RNA types: matrix RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA).

All types of RNA (except viruses RNA) are made by transcription on the DNA matrix. The primary transcript is made to processing. The short RNA is made after processing. The primary transcript and intermediate products of RNA synthesis are known as pro-RNA. It became shorter with the help of cutting end sequences and some of fragments from the middle of the chain. Then the rest of the fragments is subject to splicing, that means its binding. Also a new terminal sequences are bounded and some of nucleotides are subject to methylation and hydroxylization.

Transfer RNA. The number of nucleotides in tRNA is no more than 75-85. The molecular weight is 25,000 -28,000 daltons. The tRNA presents 10% from all cellular RNAs. tRNA are not bound to any particles. Each of tRNA bind and transfer specific amino acid. The complementary bindings of pairs make a “clover leaf-like” structure. There are four parts which carry out different functions. The first is an accepting part, made by two complementary bounded terminal parts. It consists of 7 base pairs. The 3' end of this part is a little bit longer. It forms a single strand region which is ended by CCA fragment with free -OH group. Amino acids are attached to this end. Three other parts are complementary bounded nucleotide sequences, which are ended by non-complementary loops. The middle part of the loop consists of 5 nucleotides and contains anticodon in its own structure (three nucleotides which are complementary to mRNA codon, which code the amino acids, transported by the tRNA).

The different types of tRNA are characterized by a stable nucleotide sequence and more often consist of 76 nucleotides. Varying numbers of nucleotides are connected to changing the number in an additional loop. The primary tRNA structure as a sequence of nucleotides forms a secondary tRNA structure in a “clover leaf-like” form. The secondary structure forms the third structure, characterized by two double helixes. There are several tRNA types able to bind with same codons. As a result there are around 40 types of tRNA in the cytoplasm in spite of 61 by codon number of this. This quantity is enough to provide transportation of 20 different amino acids to a place of protein construction in the ribosome.

Ribosome RNA. rRNA presents 85% of all cell RNA. It may be light ($rRNA_1$), including 1,600-2,000 nucleotides and having a molecular weight around 700,000 daltons and heavy ($rRNA_2$), including 3,200-5,200 nucleotides and having a molecular weight around 1,700,000 daltons. The light RNA is in the small ribosome subunit and heavy RNA is in the large ribosome subunit. The ribosome RNAs are not only structural elements of

ribosomes. They also provide binding of mRNA in a special sequence. It is the starting point of translation and reading the frame states. rRNA provides an interaction of tRNA and ribosome.

Matrix RNA. It presents 5% of total cell RNA. It consists of 300-3,000 nucleotides and has a molecular weight up to 10^4 daltons. The size of the molecule depends on required information. It is single stranded. mRNA may have complementary bounded regions. The regions have information surrounded by non-informational regions. The synthesis of mRNA starts from recognizing promoter site on DNA by RNA polymerase. The strands of DNA are separated from each other and on one of them, the RNA transcription starts. The linkage of nucleotides is performed according to its complementarity to DNA nucleotides. The RNA polymerase can make polynucleotide only in one direction from 5' to 3' end. That is why only one strand of DNA can serve as a matrix for RNA synthesis. This strand is called codogenic strand. As the RNA polymerase moves along the strand into the gene, encountering each DNA nucleotide in turn, it adds the corresponding complementary RNA nucleotide to the growing RNA strand. When the enzyme arrives at the special stop the signal at the far edge of the gene, which is called terminator, it disengages from RNA and releases the newly assembled RNA chain. The fragment of DNA molecule including promoter, transcribed sequence and a terminator form has a transcription unit - a transcripton.

2.2. THE ORGANIZATION OF HEREDITARY MATERIAL OF NON-CELLULAR FORMS, PROKARYOTES AND EUKARYOTES

The non-cellular life forms are viruses and bacteriaphages. Viruses are non-cellular life forms, which are able to inpour into special live cells and reproduce themself only inside of these cells. Bacteriaphages are viruses of bacteria. There is only one type of nucleic acid in the viruses (DNA or RNA). By this, viruses can be divided into RNA-containing and DNA-containing. Nucleic acids is a place for hereditary information. All viruses are divided into simple or complex. The simple viruses consist of nucleic acids and protein coat (capsid). The complex viruses may also have lipoprotein membrane, carbohydrates and non-structural proteins. The size of viruses may vary from 15 to 2,000 nm. The molecular weight of viruses DNA is around $200x10^6$ daltons and viruses RNA is from 10^6 to $15x10^6$ daltons. The nucleic acids vary in shape. There may be single-strand RNA and double-strand DNA as well as double-strand RNA and single-strand DNA. The RNAs are usually linear. Some viruses may have a set of RNA fragments, each carrying part of necessary information for virus reproduction.

The genetic material of bacteria is organized as a single, circular molecule of DNA. The Echerichia coli has a DNA of 1mm long. It has $4x10^6$ nucleotide pairs, making around 4,000 genes. Most of prokaryote DNA (95%) is actively transcribed in any moment of time. There are no histons providing nucleosome organization of genetic material. The DNA molecule of prokaryotes folds in a form of loops. Then it binds some histons to form nucleotide. The nucleotide is less stable than chromatin of eukaryotes. The genetic material of eukaryotes in interphase nucleus is presented by chromatin. Chromatin is a substance of chromosomes which contain a complex of DNA, RNA and proteins. When the cell divides by mitosis, the chromatin is spiralized to chromosomes. Besides DNA, the chromatin contains many different proteins. Most of them are histons. The histons are proteins with a positive charge and molecular weight 10,000-20,000 Daltons. They have 5 classes: H1, H2A, H2B, H3, and H4. The H1 contains a lot of lysine, H3 - arginine, H4 - arginine and glycin. The others, so called non-histon proteins, are in a small amount. According to a common point of view, the chromatin is presented by spiraling strings. There are the following levels of chromatin folding.

The nucleosome string (Fig. 2.4). This level of chromatin organization is provided by four types of histon proteins: H2A, H2B, H3, H4. They form

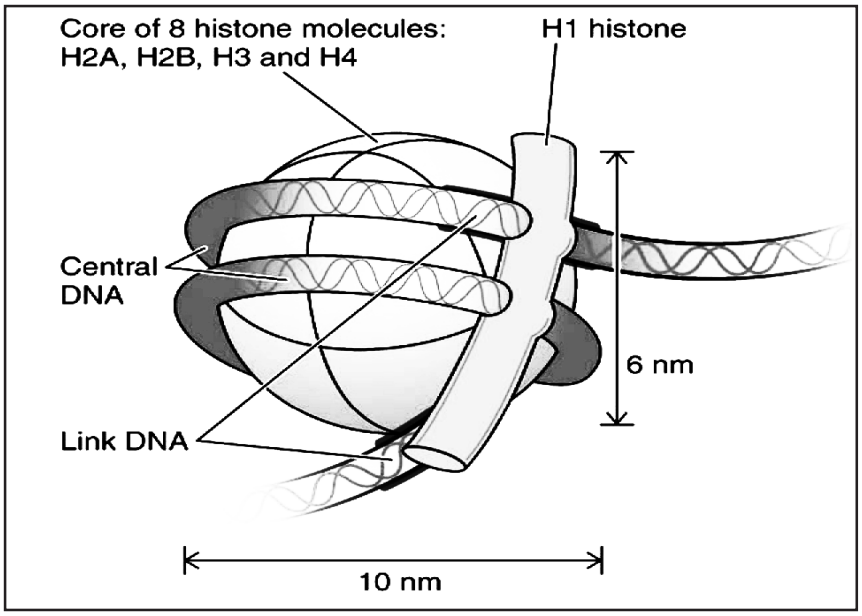


Fig. 2.4. Schematic representation of a nucleosome (by Bruce Alberts et al.).

a protein bodies, which look like a puck, - the cores. The cores are formed from 8 histons (2 of each type). The DNA molecule spirally turns over a proteins core. One core is covered by 146 nucleotide pairs of DNA. The cores are connected with each other by linker DNA. The linker may be 15 to 100 nucleotides long. It depends on a cell type. In experiments in vivo, it is shown that the structure of nucleosome string depends on the NaCl concentration. So, if the concentration is 100 mmol, one spiral turn has 7-8 nucleosomes. If the concentration decreases, each spiral turn has 3-4 nucleosomes. As the result of the nucleosomal chromatin organization the double helix of DNA with the 2 nm diameter and the average 5cm - length achieves the 10-11 nm diameter and the length 2 cm.

Chromatin fibril (Fig. 2.5). The next chromatin folding is provided by H1 histon protein. It is bounded with the linker DNA and is put nucleosomes close to each other. Such chromatin fibril, so called elementary febrile, has the 20-30 nm diameter and 1.2 mm length.

Interphase chromonemm. This level of chromatin folding is provided by folding chromatin fibrils to loops. The non-histon proteins take part in this process. They merge pointed regions making the loop with the fragments of chromatin fibril in it. One loop contains from 20,000 to 80,000 nucleotide pairs. After such folding, interphase chromonemm has the diameter of 100-200 nm. The regions of interphase chromonemm undergoing further folding makes structural blocks, which can be visible in the interphase nucleus as chromatin particles. There are euchromatin regions and heterochromatin regions, according to their functional activity. The euchromatin regions have a less tight folding because of active transcription processes. The heterochromatin regions have a tighter folding because of lack of transcription processes. There is constitutive and facultative hetero-chromatin.

The *constitutive heterochromatin* is contained in paracentromeric and telomere regions and along some internal fragments. It is believed that constitutive heterochromatin maintains the total nucleus structure, binds the chromatin to karyolemm, participates in mutual recognition of chromosomes during meiosis, making intervals between genes.

The *facultative heterochromatin* is informative. It contains genes and may be changed to euchromatin. The example of a facultative chromatin is a sex chromatin body, which is developed in the cells of organisms with homogametic sex. Also, the facultative chromatin formation occurs during the processes of the cell differentiation, serves as a shutdown mechanism of activity of several genes which is not necessary in the cell of such specialization.

Metaphase chromosome. Chromatin condenses to chromosomes at

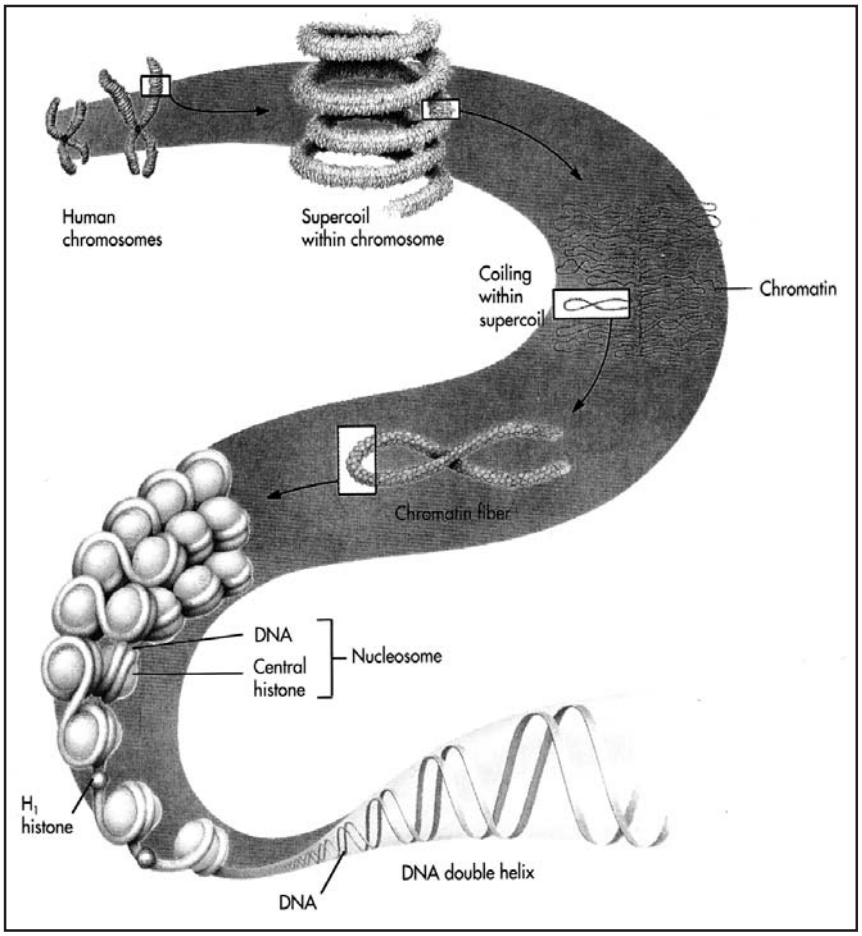


Fig. 2.5. Levels of chromosomal organization (by Raven & Jones).

the beginning of mitosis. Chromosomes become visible. The mitotic superspiralization makes a process of chromosome movement easier.

The chromosome DNA consists of more than 10^8 nucleotide pairs, which form information blocks - genes, placed linearly. They represent 25% of total DNA.

The gene is a functional unit of DNA, containing information for protein or RNA synthesis. There are spacers between genes. They are non-informative regions of DNA of different length. The excessive genes are presented by a large amount of identical copies, for example genes for

tRNA and rRNA. In the DNA, there are sequences of the same nucleotides. They may be moderate and highly repeating. The moderate repeating sequences are 300 nucleotide pairs of length and usually they are the spacers and excessive genes. The highly repeating sequences make constitutive heterochromatin. Around 75% of chromatin does not participate in transcription since it corresponds to highly repeating sequences and nontranscribed spacers.

2.3. THE GENETIC INFORMATION CODING

The genetic information is coded in DNA. In 1954 G.Gamov suggested that coding of information in DNA has to be performed by several nucleotide sequences. To code 20 amino acids having only four nucleotide types only triplet code can be used. In this code, each amino acid is coded by 3 nucleotides (Fig. 2.6). M. Nierenberg and H.G.Corana discovered the genetic code in 1965. For this discovery, they and R.Holly were awarded the Nobel Prize in 1968. The results of their works are most important in molecular biology for understanding life processes. The genetic code has such postulates:

1) The genetic code has a triplet structure. The triplet of mRNA is called codon.

2) In the genetic code in most cases, one amino acid corresponds to several codons of mRNA. In a codon for one amino acid, the first two

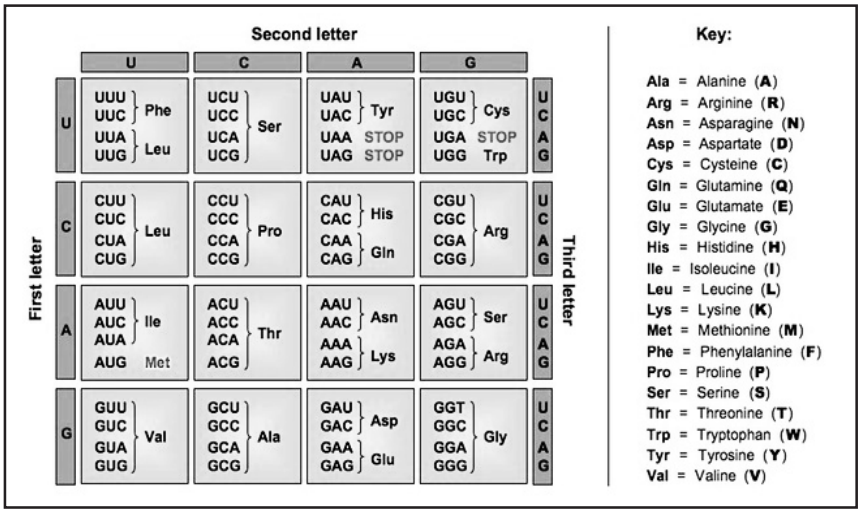


Fig. 2.6. Genetic codes table.

nucleotides are the same with the third varying.

3) The nucleotide sequence is recognized only in one direction, triplet by triplet.

4) AUG - is a start codon.

5) UAG, UAA, UGA - are stop codons.

6) The genetic code is universal for all organisms.

The structure of DNA, material storage of heredity, is a key to understanding the chemistry of life.

CELLULAR LIFE ORGANIZATION LEVEL

CHAPTER 3. CELL BIOLOGY AND MORPHOLOGY

3.1. THE CYTOLOGY AS A SCIENCE

Cytology is a branch of biology which deals with the study of structural and functional organization of the cell as the unit of living matter. The subject of cytology is the cell of unicellular (bacteria, protists, algae, fungi), as well as multicellular organisms (animals, plants, fungi) organisms. Cytology studies the structure and function of cells, their chemical composition, the relationship with each other in a multicellular organism, reproduction and development, adaptations to the environment.

3.2. THE CELL MORPHOLOGY

All living matter is represented by monocellular organisms and multicellular organisms. It is usually divided into two superkingdoms: prokaryotes and eukaryotes. Superkingdom prokaryotes include two kingdoms - archeobacteria and bacteria (including blue-green algae). Superkingdom eukaryotes include kingdoms - Fungi, Plants and Animals. Prokaryotic cells do not have nuclei. They do not separate from the rest of the cytoplasm of the DNA structure. As part of the cytoplasm of prokaryotic cells are no special structures - organelles. Prokaryotes are smaller than eukaryotes (0,5-5 μm) organized structurally simpler and probably they represent a more ancient group of organisms. Cells of eukaryotic organisms are larger (13 μm). They have a nucleus and intracellular binding structure - organelles allocated in their cytoplasm.

A cell is the smallest structure which has all properties of living matter and can maintain all those properties by itself and also give these properties to the next generations. A cell is an elementary structural functional genetic unit of all living organisms, providing exchange of energy and substances, reproduction, growth and development, irritability and movement, heredity and diversity, homeostasis.

The structural elements of the eukaryotic cell are cell membrane, cytoplasm and nucleus (Fig. 3.1).

The cell membrane (cytolemma, plasma membrane) separates protoplasm of a cell from outside environment and at the same time, it regulates ions and substance passing inside and outside the cell. According to the contemporary findings a plasma membrane consists of phospholipid

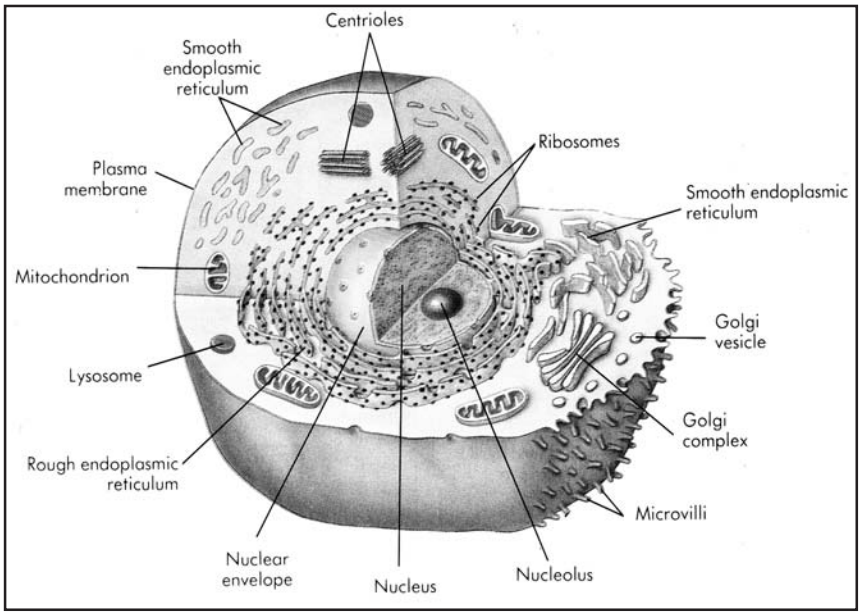


Fig. 3.1. The structural elements of the eukaryotic cell (by Raven & Jones).

bilayer (Fig. 3.2). The hydrophobic nonpolar surfaces look toward each other, and polar hydrophilic surfaces look outside of membrane. There are proteins incorporated into membrane. The hydrophilic parts of the proteins bind with hydrophilic parts of phospholipids, hydrophobic regions of protein bind with hydrophobic parts of phospholipids. Besides, an animal cell has glycocalyx outside the phospholipids bilayer with width 10-20 nm, presented by glycolipids and glycoproteins. A plant cell has a cell wall which is made of cellulose. The inner cell membranes which form organelles, have the same structural principle, without glycocalyx. The cortical layer of cytoplasm lies close to the inner cell membrane surface. It has a lot of microtubules and microfilaments containing contractive proteins.

The plasmalemm performs the following functions: separation, defense, transportation, regulation of chemical balance inside the cell. There are receptors in the plasmolemm which are able to recognize biological active substances. A cell can percept outside signals and react to changes in the environment or in the organism state with the help of receptors.

The cytoplasm is presented by semifluid matrix with several organelles and inclusions. The matrix is a main substance of the cell. The colloid features, viscosity, elastic properties, internal movement depends on it. The cytoplasm matrix is a very complex colloid system which is able to change

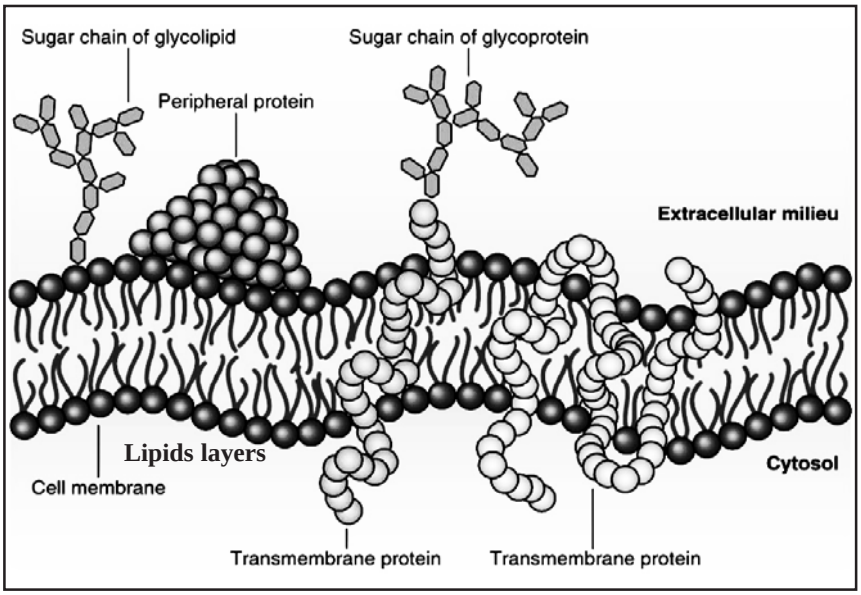


Fig. 3.2. Structure of cell membrane (by Bruce Alberts et al.).

fluid condition to gel condition and back. The compounds of cytoplasm are soluble proteins, such as glycolisis enzyme, ATPases, amino acids, lipids, carbohydrates. Microtubules are made from matrix proteins. Functionally, cytoplasm is an internal cell environment (the place for intracellular metabolism performing).

The organelles are stable, highly differentiated cytoplasm bodies, carrying out certain functions. They can be distinguished organelles of a special and general purpose. Organelles of general purpose (endoplasmic reticulum, ribosomes, complex Golgi, lysosomes, mitochondria and centrosome) are present in all cell types. The organelles of special purpose (myofibrils, neurofilaments, vilia, cilia, flagella, microtubules and microfilaments) are of certain cell types. According to its structure, organelles are divided into organelles derived from membranes (lysosomes, complex Golgi, endoplasmic reticulum) and non-membrane organelles (ribosomes, centrosome, microtubules and microfilaments).

The endoplasmic reticulum. The endoplasmic reticulum weave sheets through the interior of the cell, creates the channels and interconnections between its membranes that isolates some spaces as membrane-enclosed sacs called vesicles. The membranes may be rough and smooth. The rough endoplasmic reticulum has ribosomes attached to its membrane. The rough

endoplasmic reticulum produces proteins for external use, as a secretion of secretary cells. The most active regions of protein synthesis are called ergastoplasm. The channels of smooth endoplasmic reticulum contain enzymes that provide carbohydrate, steroids and lipid synthesis. When the synthesis is complete, substances move to vesicle forming system, called complex Golgi. The detoxications of harmful and toxic substances occur in the endoplasmic reticulum of liver cells. In the channels and vesicles of smooth endoplasmic reticulum of striated muscle, the calcium ions participating in muscle contraction are stored.

The ribosomes are round shape ribonucleoprotein particles with 15-35 nm in diameter. Each ribosome consists of a small and large subunits. They merge in the presence of mRNA. If there are several ribosomes merged by one mRNA, such structure is called polysome. The polysomes may stay free in cytoplasm or attach to endoplasmic reticulum membranes. They are the place of active protein synthesis. They allow making proteins in large amounts. If they spread in cytoplasm, they make proteins for internal use. If they are attached to endoplasmic reticulum membranes, they make proteins for external use (examples are milk synthesis and digestion enzymes synthesis).

The Golgi complex is named in honor of the Italian scientist who was the first to describe it. It is visible in a light microscope as a differentiated region of cytoplasm is placed near the nucleus. It is formed from flattened stacks of membranes. On a side of stacks there are folds called cisternae. In the plant cells complex Golgi is made from small bodies named dictiosome. Dictiosome is a deck of small disk shaped vesicles. Vesicles are separated from sides of dictiosome. It is believed that the main function of the Golgi complex is concentration and condensing of internally produced substances for further excretion from a cell. It is stated that glycolipids, glycoproteins, yolk granules and lysosomes are formed in the Golgi complex.

The lysosomes are globe-shaped vesicles with the diameter 0.2 - 0.4 mcm, containing a set of acid hydrolases enzymes. They help to catalyze the reaction of nucleic acids, proteins, lipids and carbohydrates splitting. A lysosome is surrounded by one layer biological membrane, sometimes covered by fibrous protein layer over its surface. Lysosome enzymes also help to digest aged cell structures or even completely died cell. The lysosome damage and its enzyme liberation lead to total cytoplasm dissolving. Digestive vacuoles in bodies of protists and phagocytes are probably made of merged lysosomes. There are primary (inactive) lysosomes and secondary lysosomes. The secondary lysosomes are activated from primary lysosome, and in these lysosomes, a process of digestion takes place. The secondary lysosomes may be subdivided in to heterolysosomes (phagolysosomes) and

autolysosomes (cytolysosomes). Heterolysosomes digest substances obtained by phagocytosis and pinocytosis. Autolysosomes digest internal cell structures, which are not able to perform its functions any more.

The microbodies are a group of vesicle shaped cell organelles with the 0.1 - 1.5 μm diameter. They are surrounded by one layer biological membrane. Peroxisomes are referred to this group. They contain catalase enzyme which catalyze hydrogen peroxide degradation. There are around 70 to 100 peroxisomes in a liver cell.

The mitochondria are round-shaped or stab shape structures of 5 -10 mcm long and 0.5 μm width. The mitochondria number is varied from 150 to 1500 per cell or even several hundred thousand in female sex cells. The mitochondrion coat consists of two biological membranes. The inner membrane makes an internal leaf shaped invaginations that is called cristae, or tubular shaped invaginations which is called tubules. The inner membrane surrounds internal mitochondrion matrix. There are apparatus of protein biosynthesis in it. It is presented by circular, closed DNA molecule without histones, ribosomes, tRNA, enzymes of DNA replication, transcription and translation. The main function of mitochondria is to obtain energy by oxidative phosphorilation of chemical substances and to store it in the ATP form. Mitochondria take part in a steroid hormone and some amino acid synthesis.

*The cell center i*s a good visible organelle which consists of one or two small centrioles and radiated sphere surround them. With the help of an electronic microscope it was revealed that each centurion is a small cylindrical body of 0.3 - 0.5 μm long and with 0.15 μm in diameter. The walls of cylinder are made of nine parallel tubules. The cell center works actively during mitosis. Centrioles come to cell poles. Spindles are attached to them. Within the period of mitosis, chromosomes move, by spindle, toward centrioles on different poles. The general purpose organelles also include microtubules and microfilaments.

Microtubules are organelles of different length with 24 nm in diameter. They are structural elements of flagella, cilia, centriole, spindle. They also may stay free in cytoplasm carrying out a support function and providing cell shape. Microfilaments are long thin organelles spread through all cell cytoplasm. They provide cell movement and form a cell frame and take part in intracellular organelles movement.

The inclusions are temporal cytoplasmic structures, related with cellular metabolism. The cells functional state provides their appearance or dissolving. There are the following types of inclusions: trophical (carbohydrates, proteins, lipids), secretoral (secrete granules in glands), pigment (melanin, lipofuscin, hemoglobin, etc.) and excretory (uric acid).

The nucleus. It is a constant component of all living cells. There are two different nuclear states. One is mitotic, the other is interphase. Such a division was made because of different nucleus activity and appearance during these periods of a cell cycle. Previously, it was believed that the interphase nucleus was inactive. But now it has been proven an adverse statement, it is very active within the period of the interphase. All plastic processes occur during the interphase. Different cells have different nucleus. But commonly a nucleus has a sphere or an ellipsoid shape. The shape of nucleus depends on a cell shape containing it and it may vary in a wide range. Nucleus sizes vary not only between different cell types but also within one cell type. The cells of internal organs may have a polymorphism in sizes or volumes. The functional cell state may have an influence on nucleus size. It is stated that functional nucleus enlargement may be considered as a criteria of the increased cell activity. The ratio between nucleus and cytoplasm volume is called as nucleus/cytoplasm ratio. It may serve as an indicator of cell activity and may be a factor of cell division. The nucleus consists of karyolemm (nuclear envelope), nucleoplasm, nucleolus and chromatin (Fig. 3.3).

The karyolemm is easy visible in a light microscope. But the structure that is more definite may be revealed only by an electronic microscope. The karyolemm is made of two biological membranes, each having 0.006-0.009 μm. The space between them is called perinuclear space. It has the width 0.01-0.02 μm. The external membrane extends to membranes of endoplasmic reticulum. The nuclear envelope is semipermeable. In some

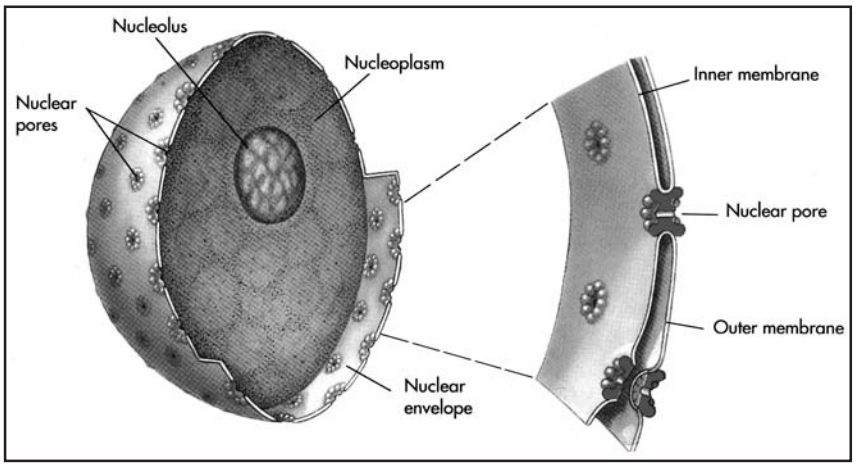


Fig. 3.3. Structure of nucleus (by Raven & Jones).

regions, membranes of karyolemm fuses together to make a pore in a nuclear envelope. These pores have the diameter of 0.08-0.09 μm. Pores are not just holes in envelope. They contain a substance with a moderate electronic density. Pores contain a protein structure, which is called a pore complex. It regulates a substance flow through a nuclear pore. Nuclear pores extend to a protein layer underlying a nuclear envelope (lamina densa). It shows a complex mechanism of regulation of nuclear/cytoplasmic relations. It is possible that close connection of lamina densa and karyolemm helps to bring an order in interphase chromosome localization. The function of the nuclear envelope is separation of eukaryotic cell hereditary information from cytoplasm and regulation of nuclear/cytoplasmic relations.

The nucleoplasm forms an internal environment of a nucleus. It has proteins as a main part of it. It plays an important role in providing normal functioning of the genetic apparatus. Also, it has fibrillar proteins and may give a support to nucleus structures.

The nucleolus. It is a structural component of interphase nucleus. It is dissolved in prophase and it is newly formatted in the telophase. It is formed from special threadlike structures of proteins and giant molecules of RNA precursors. Mature RNA is made from such precursors. The genes in different regions of different chromosomes are responsible for RNA synthesis. They are called nucleolus organizers. Merging into one structure, these regions form nucleolus. In mitotic chromosomes these regions are seen as secondary strips.

The chromatin is the interphase form of hereditary information. Its organization was described in Chapter 2.2.

The chromosomes are components of the cell nucleus which are well visible in the course of the mitosis. They have a complex structure, ability for self-replication and transmit hereditary information to offspring (Fig. 3.4). The chromosomes usually look like straight or curved stabs. Each chromosome contains of two chromatids. The shape of chromosome may be defined by primary and secondary strangulation. There is a chromosome region without DNA in a place of a primary strangulation. There is a special structure centromere (kynetochore) inside it. The spindle is attached to the structure. The centromere divides chromosome in two arms (Fig. 3.5). The chromosomes may be distinguished by the following types accordinary centromere position and arm length: metacentric (with equal arms), submetacentric (arms are slightly different), acrocentric (arms are significantly different) and telocentric (without one arm). Chromosome arms are designated with Latin letters, “q” for a long arm and “p” for a short arm. The percentage ratio of a small arm length to total chromosome length is considered a centromere index. If the centromere index is about 50%, it

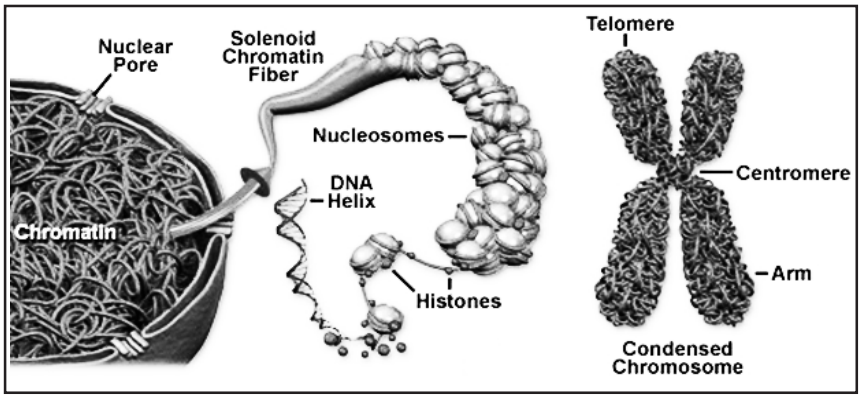


Fig. 3.4. Chromatin and condensed chromosome structure (by Raven & Jones).

is a metacentric chromosome. If the centromere index is less than 50% it is a submetacentric chromosome. If the centromere index is around zero, it is an acrocentric chromosome. Some chromosomes have a secondary strangulation which divides a chromosome satellite from the main chromosome part. Chromosome satellite is pointed by the letter "S".

Chromosomes strictly follow such rules as: the rule of constant chromosome number, i.e. somatic cells of every species have their own chromosome number (drosophila has 8, human - 46); the rule of chromosome pairs (chromosome which make a pair are homologues chromosome), Ascaris lumbricoideus has only 1 pair, human has 23; the rule of individuality - nonhomologues chromosomes differ from each other; the rule of continuity - an ability of chromosomes to autoreproduction.

All features of somatic cell chromosomes structure make a karyotype.

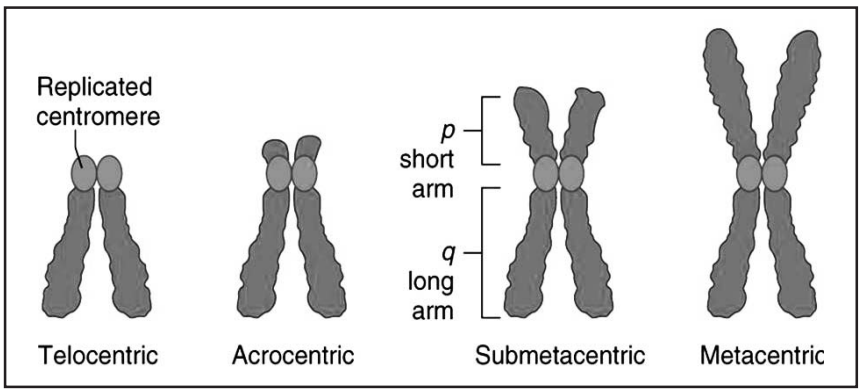


Fig. 3.5. Chromosome types (by Raven & Jones).

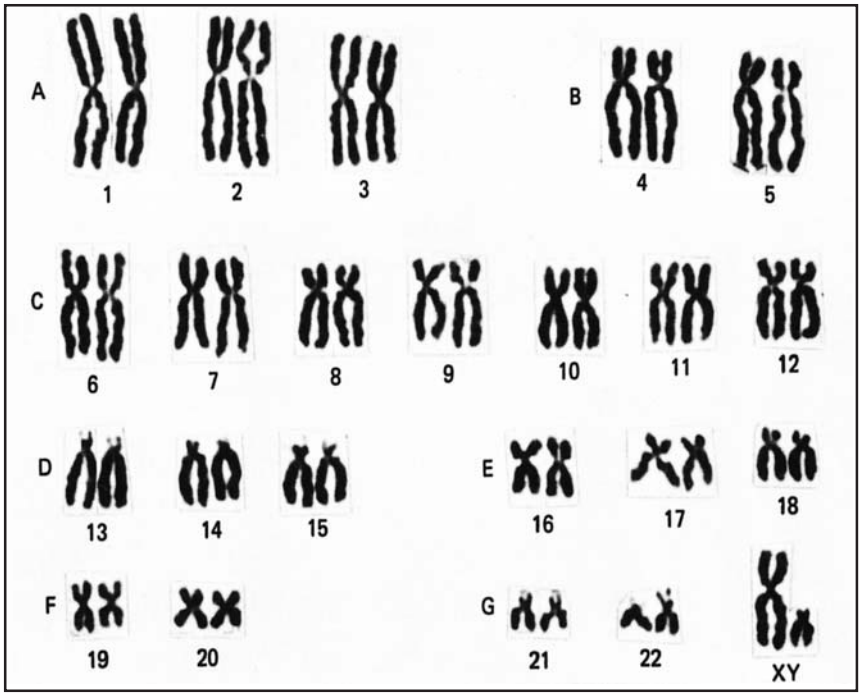


Fig. 3.6. Human male karyotype (by mun.ca).

A normal human karyotype includes 46 chromosomes (23 pairs in a diploid set), 44 of which are somatic chromosomes and 2 are sex chromosomes (Fig. 3.6).

The ideogram is pairwise position of chromosomes placed according to size decreasing. Chromosomes are divided by size and by centromere position accordining to Denver's classification (1960). The same year, K. Pattaw suggested dividing chromosomes in to 7 groups, pointing each group by the Latin alphabet letter (Fig. 3.7).

Later the classification was updated on a base of new findings achieved by selected metaphase chromosome regions staining and chromosome mapping. The localization of specifically stained region is unique for each non-homologues chromosome. It allows making a "chemical chromosome maps". Using selective chromosome staining in 1971 the human linear chromosome maps were developed in Paris.

Group	Size and centromere position	Ideogram number	Number in Diploid cell
A or I	Large; Metacentric/Submetacentric	1 – 3	6
B or II	Large; Submetacentric	4, 5	4
C or III	Medium; Submetacentric	6 – 12 and X	15 (male) 16 (female)
D or IV	Medium; Acrocentric	13 – 15	6
E or V	Small; Metacentric/Submetacentric	16 – 18	6
F or VI	Small; Metacentric	19 – 20	4
G or VII	Smallest; Acrocentric	21, 22 and Y	5 (male) 4 (female)

Fig. 3.7. Characteristics of human karyotype chromosomes.

3.3. THE ORGANIZATION OF INFORMATION, ENERGY AND SUBSTANCE FLOW IN A CELL

A cell is an open self-regulating system which has an information, energy and substance flow. External and internal substance exchange can be distinguished on a level of organism and a cell. An external exchange in the organism is an exchange with the external environment that means the incoming of food substances and outcoming of waste substances. An internal exchange in the organism occurs by assimilation and dissimilation. According to an assimilation type the organisms may be divided into heterotrophic, mixotrophic and autotrophic; according to dissimilation type, organisms may be divided into aerobic and anaerobic.

The energy flow. Energy means the ability to make external action, or more generally, the capacity to do work. The energy flow of the organism is presented by cellular energy producing such processes as photosynthesis, chemosynthesis, fermentation and respiration. In the course of the photosynthesis in plant cells, the suns energy is converted into energy of the chemical bonds of ATP and $NADP.H_2$. Then this energy is used in a plastic processes. Within the period of chemosynthesis the transformation of one type of the chemical bond in to another occurs. Nitrificating bacteria oxidize ammonium to nitrites and then to nitrates; sulfur bacteria oxidize H_2S to sulfic acid; ferrobacteria oxidize iron ions. The energy liberating from oxidation is used for carbon dioxide reduction to organic substances.

In the heterotrophic organism cells, the energy flow is provided by respiration and fermentation processes. Products dissimilate to organic substance still having a lot of energy in its bonds during fermentation. So, that is why the energy outcome from the fermentation is small. This process occurs in hyaloplasm. The respiration has the major role in energy exchange in heterotrophic organisms. With the help of this process such low energy substance as glucose, fatty acids; amino acids are dissimilated to carbon

dioxide. The energy liberating from oxidation of these substances is used for ATP synthesis.

The ATP synthesis occured in inner membrane and crysts of mitochondria containing enzymes of citric acid cycle. The energy of ATP converts to some work type - chemical, mechanical, regulating, osmotic, and electric.

Anaerobic glycolisis is a less effective process in supplying the cell vital activity with energy. The products of glycolisis (pyruvates) come to mitochondria. There they are subject to oxidation linked with ADP phosphorilation to ATP. From the systems converting the ATP chemical bonud energy into mechanical work, the mechanical-chemical system of muscle is better studied. It consists of contractive proteins actine and myosin and adenosintri-phosphatase enzyme, splitting the ATP with energy release. Mechanisms for supplying the cell with the energy are very effective. The efficiency coefficients of chloroplast and mitochondrion are 25% and 45-60% subsequently. It is more than a steam engine (8%) and internal combustion engine (17%).

The information flow. Each cell as each organism has an information exchange (information flow). Cells and organisms receive information about their environment - about light, food, sexual partner, enemy, etc. (external information). The other information flow always outcomes from the organism. The organism serves as a transmitter of these signals (internal information). The material or energy transmitters carry it. In the course of the hormone regulation the hormone can get to any part of an organism but only some of them are able to accept it. For example, thyrotropic hormone of anterior pituitary acts only on the thyroid gland. Within the period of the nervous regulation, the impulse rate (the number of impulses per time unit) surves as the information parameter. A cell accepts an external information flow from intercellular matrix with the help of receptors on a cell surface.

The information flow in an organism is performed by the brain cortex and endocrine glands. Internal information in a cell is recorded into DNA. Nucleus and cytoplasm DNA, mRNA, cytoplasm apparatus of translation take part in an internal information flow. The internal information flow provides the heredity of species characters from generation to generation. In eukaryotic cell, the genomes of chloroplasts and mitochondria also take part in an internal information flow.

The substance flow. "Living matter" or "living state" is not a structure, but a process. The living structures are not stable; they are constantly destroyed and rebuilt. This renewing (the substance flow) occurs with different speeds. The measure to determine a substance flow is a period

of renewing, i.e. the time when the half molecules of the substance is changed into new ones. The substance flow is characterized by a plastic exchange in a cell - photosynthesis, chemosynthesis, protein biosynthesis, etc. All three types of RNA take part in protein biosynthesis. The sequence of polypeptide chain synthesis processes is made in following ways.

1. The amino acid is activated by specific enzyme in a presence of ATP following way to aminoaciladenilat formation.

2. Activated amino acid binding with specific tRNA.

3. Aminoacil-tRNA (tRNA with amino acid) binding with ribosomes and incorporating of amino acids into protein with tRNA release.

There are two furrows in the ribosomes, one for holding the growing polypeptide chain, the other for mRNA. There are two sites for tRNA binding (A-site is for tRNA carrying amino acid, P-site for tRNA carrying polypeptide chain).

There are three phases in ***translation***: initiation, elongation and termination of polypeptide synthesis.

The initiation phase provides the beginning of protein synthesis (Fig. 3.8). Two previously separated rRNA subunits are united on a definite mRNA site and the first aminoacil-tRNA is attached to it during this phase. In a mRNA molecule near its 5-end there is a site complementary to rRNA of a small ribosome subunit. The mRNA binds with the small ribosome subunit to place the start codon (AUG) in P-site. When the first aminoacil-tRNA is positioned over the first AUG codon sequence of mRNA, the large ribosomal subunit binds, forming the A and P sites, and polypeptide synthesis begins. There is aminoacil-tRNA in the P-site, but A-site contains next mRNA codon. The initiation processes are catalyzed by initiation factors. These factors bind with a small ribosome subunit. When the initiation phase is over, the initiation factors leave the ribosome subunit.

The elongation phase. It is a sequence of cyclic repeating events. Specific recognizing of the next codon in A-site by the aminoacil-tRNA and complementary binding of a codon and anticodon occur in the course

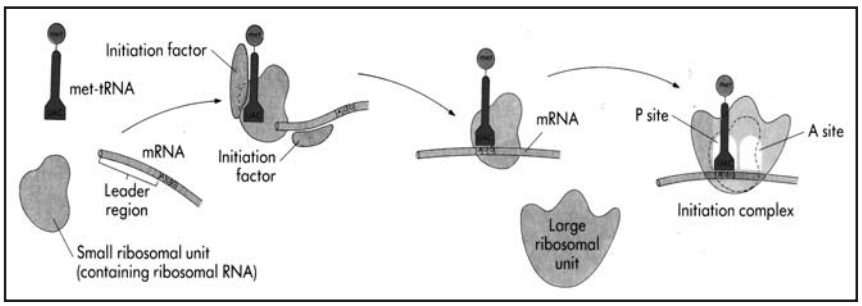


Fig. 3.8. The initiation phase (by Raven & Jones).

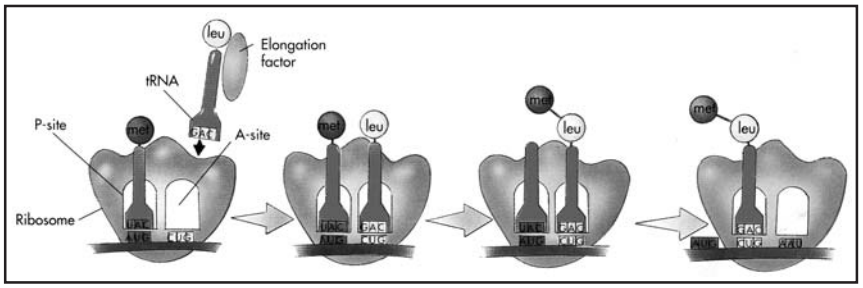


Fig. 3.9. The elongation phase (by Raven & Jones).

of this phase (Fig. 3.9). Transported amino acid is in the A-site nearby previously incorporated in the protein structure amino acid in the P-site. Then two amino acids undergo a chemical reaction in which previously incorporated in protein structure amino acid is released from its tRNA and it is attached instead by a peptide bond to incoming amino acid. The abandoned tRNA falls from its site on the ribosome, leaving that site vacant. Then ribosome moves along mRNA molecule a distance corresponding three nucleotides. This movement reposition growing chain and exposes the next codon to tRNA. Then subsequent tRNA recognizes the next codon bringing a new amino acid to the polypeptide chain. The actions listed above have been repeated until the codon-terminator appears at on A-site of ribosome.

The termination phase. It is also called termination of polypeptide chain synthesis (Fig. 3.10). It starts from encounting one of codon-terminators. There is no tRNA, which is able to bind with this codon. Instead of tRNA this codon is recognized by a special release factor. The molecule of water is bounded to terminal amino acid and the protein chain is released from the ribosome. After that, the ribosome breaks in two sub-units.

The passive transport. A cell as an open biological system has a

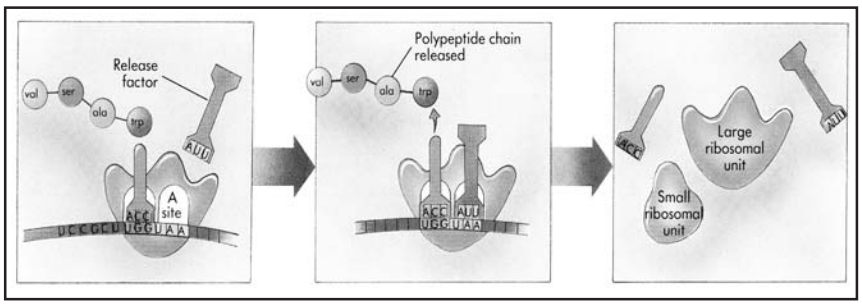


Fig 3.10. The termination phase (by Raven & Jones).

substance exchange with the external environment. A passive transport occurs to kinetic energy, however for an active transport the metabolic energy is needed.The plasmolemm selectively regulate the substance exchange. While free transport molecules or ions pass through membrane passively at the original state. They pass through the membrane bounded with membrane transmitters.

Diffusion is a net movement of molecules to regions of lower concentration as a result of random spontaneous molecular motions. Gases, as oxygen consumpted solutions are subject to active diffusion through membranes. They move from the regions of higher concentration to the regions of lower concentration by diffuse gradient. Diffusion through the membrane occurs less actively because membrane lipids serve as a barrier, limitating diffusion.

There is a theory of lipid filter (the lipid soluble molecules can diffuse directly through a lipid bilayer). The rest of substances may pass only through slight imperfections in the sheet of lipid molecules. The passage velocity of bigger particles depends not only on their molecular weight but on solubility. The water diffusion through semipermeable membrane is called osmosis. During this process the free water concentrations decreases in a cell which may be explained by solutant (dissolved molecules) influence and by action of structured components (macromolecules, cell wall capillaries, etc.). Osmotic water consumption causes the increase of a cell volume. For example, erythrocytes in clear water increase in volume until the cell bursts. In a plant cell hypotonic conditions lead only to a slight increase of a cell volume. The osmotic water consumption leads to creation of high turgor pressure in a vacuole, which acts conversely to that consumption.

The plasmolemm contains transport proteins, which carry substrates through the membrane. There are different transports with a different mechanism of action and different specificy to substrate.

The passive transport with transport protein according to concentration gradient is called catalyzed transport or facilitated diffusion. Sugars, amino acids and other substances pass through membrane by this way.

The coupled transport is a specific case of facilitated diffusion. Some transporters carry two different substrates together in one direction or in controversial directions.

The active transport is a transport of molecules and ions across the membrane against concentration gradient driven by the expenditure of chemical energy. The energy is required because the substance has to move against its natural intention to diffuse in opposite direction. The transport ATPases are transport proteins, which are able to degrade ATP

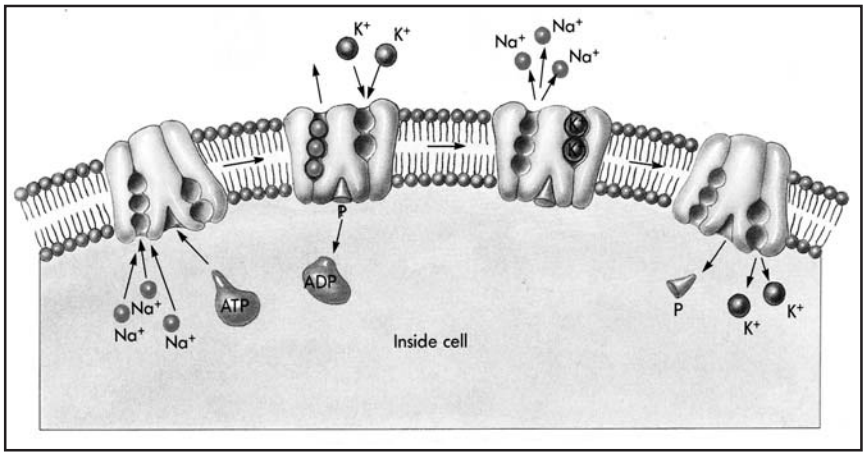


Fig. 3.11. The sodium-potassim pump (by Raven & Jones).

with energy release. This process may be considered as an engine of active transport. Protons (proton pump) and ions (ion pump) enter a cell in this way. For example, a HC1 secretion in mammalian stomach and wide spread sodium-potassium pump, transporting K^+ inside and Na^+ outside a cell use active transport (Fig. 3.11). The unbalanced states - the electrochemical potentials - are made on a surface of a cell with the help of proton and ion pumps. They are used for parallel (or antiparallel) transporting and carry different molecules against their concentration gradient. For example, transportation of Na^+ and sugar in animal cells in the same direction and same transportation of H^+ and sugar in plant cells.

The active transport may be performed by endocytosis and exocytosis.

The endocytosis is a membrane vesicles formation by membrane invagination in absorbing of soluble substances (pinocytosis) and solid substances (phagocytosis). Such vesicles are called pinosomes or phagosomes (Fig. 3.12). Using endocytosis the ovicells absorb yolk proteins, leucocytes absorb foreign substances and immunoglobulines, a cell of renal tubules adsorb proteins from primary urine.

The exocytosis is a process controversial to endocytosis. Different vesicles from the Golgi complex fuse with plasma membrane ejecting its contents outward. Furthermore the vesicle membrane may stay as a part of plasmolemm or return to cytoplasm in a form of a vesicle. Today the data were received that lysosomes take part in removing the whole cell or their organelles from an organism. That means that lysosomes perform autophagocytosis processes.

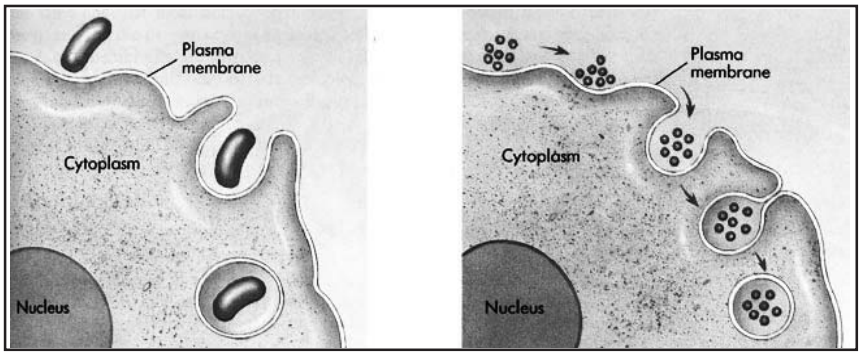


Fig. 3.12. Endocytosis, phagocytosis in left, pinocytosis in right (by Raven & Jones).

3.4. THE CELL PHYSIOLOGY

One of the main biological properties of the cell as an elementary life system is its ability to self-reproduce. Cell reproduction provides the organism growth, development and regeneration. The time between the cell formation by division of a mother cell and its own division or death is called a cell cycle. For the cell of an undividing cell populations the cell cycle is the time between cell formation by mother cell division and its own death. The mitotic cycle is an obvious component of a cell cycle. The mitotic cycle is the time between two cell divisions and all processes that occur during the time. The mitotic cycle of growing population may be divided into two large periods: the period between the divisions - an interphase. This time the cell grows, performs its function and gets prepared to divide; and the cell division - a mitosis. There is a cell growth, DNA replication, duplication chromatid number, producing mitotic spindle proteins, energy producing and storage during the interphase.

The interphase may be divided into the three periods.

1. Postmitotic or presynthetic period (G_1). During this period cells grow, produce RNA, proteins, store energy, but they do not make DNA. In the presynthetic period the cell nucleus contain diploid chromosome number, each chromosome contains only one chromatid. Chromosomes are despirilized. If the DNA number contained in 23 chromosomes is C, than G_1 contains 2C DNA.

2. Synthetic period, S period. During this period mitotic apparatus proteins are produced and the energy for further mitosis is produced and stored. As a result of this amount of DNA after S period is 4C and

chromosome number is diploid, each chromosome contains 2 chromatids.

3. Postsynthetic or premitotic period, period G_2. During this period mitotic apparatus proteins are produced and the energy for further mitosis is produced and stored. The next step is mitosis. The initial signal of mitosis start is changing of nucleus/cytoplasm ratio.

The integrity of the processes to prepare the cell for division and mitotic division itself is a mitotic cycle of the cell. If daughter cells immediately begin to prepare for the next division, their mitotic cycle and cell cycle are the same. In other cases the daughter cell are subject to differentiation and carry out different functions. Their cell cycle results in a cell death.

There are two types of cell divisions: indirect division (mitosis) and direct division (amitosis). The mitosis consists of mitosis itself, meiosis, endomitosis and polyteny. The amitosis is divided by shape (equal, non-equal, multiply, without citotomy) and by type (generative, reactive, degenerative).

3.4.1. THE MITOSIS

The mitosis is a unique type of an animal and plant cell division, during which all cells undergo a range of sequential changes leading to two daughter cell formations with diploid chromosome number and a full range of genes which are necessary for all individual hereditary properties development. The mitosis is subdivided into five phases: prophase, prometaphase, metaphase, anaphase and telophase (Fig. 3.13).

The prophase. In the cell coming into division, chromosomes condensate and become visible by a light microscope. In early prophase a centriole is divided into two parts and each part moves to opposite cell pole. At the same time the condensation process continues. It results in chromosome

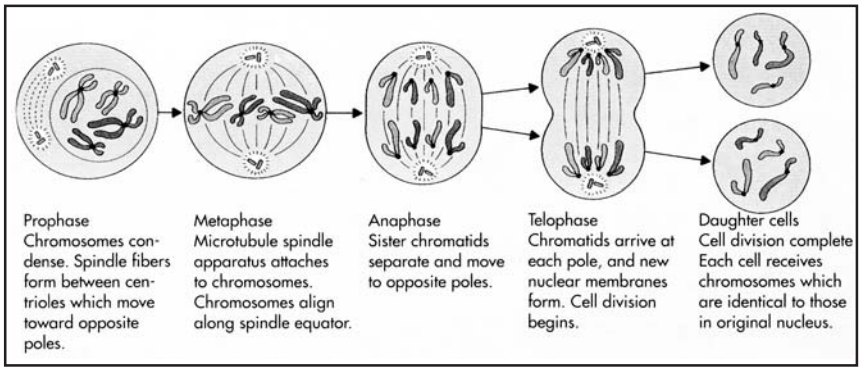


Fig. 3.13. Mitosis (by Raven & Jones).

shortage and its increased width. There is a diploid chromosome set in a nucleus. Each chromosome consists of two chromatids, the DNA amount is equal 4C. Between centriols a radiate figure is formed. The nucleolus dissolves under the lysosomes action. The division spindle is made of two tubules types. The first one is polar, connecting both centriols, the second one is chromosomal, bound to chromosome centromere.

The prometaphase. The cell cytoplasm has a small viscosity. Chromosomes moves toward a cell center. The nucleus coat is dissolved.

The metaphase. It begins when the pairs of sister chromatids align in the center of the cell. They are well visible, that is why chromosomes are counted at this stage. Each chromosome splits along itself on two chromatids. The nucleus characteristic is 2n - 2chromatids - 4C.

The anaphase. Chromatids movement toward cell poles during this stage. Such chromatids become sister chromosomes. The spindle threads contract and pull chromosomes to the cell poles. There are very active processes in cytoplasm. There are two chromosome set at the end of the movement on cell poles. Each has diploid chromosome number, 2n, 1 chromatid, 2C DNA amount.

The telophase. The daughter chromosomes are despiralized, lose a well visible state. They are surrounded by a new nucleus coat. The nucleolus is formed. The cell center loses its activity. The cytotomy (the cell cleavage) begins. The nucleus characteristic is 2n, 1 chromatid, 2C DNA amount.

The mitotic cycle duration is different. It may vary from several minutes to hundreds of hours. It depends on a tissue type, a physiological organism state and environmental factors (temperature, light, chemicals, etc.).

3.4.2. THE MEIOSIS

This type of division appeared as a special mitosis form providing sexual reproduction of organisms. Four haploid cells are formed from one somatic cell with diploid chromosome number as a result of meiosis (Fig. 3.14). The meiosis has two divisions: the first - reducing division which decreases chromosome number in half (meiosis I), the second - equalizing division when a cell keep their haploid chromosomes set (meiosis II). The meiosis I is the most complicate. It has an elongated prophase consisting of five stages.

The leptonemm. It is characterized by an increasing of a nucleus volume. The diploid chromosome set becomes well visible. The chromosomes are thin, each containing two chromatids.

The zygonemm. There is a chromosome conjugation. The homologous pairs of chromosomes line up side by side and then they exactly join, each

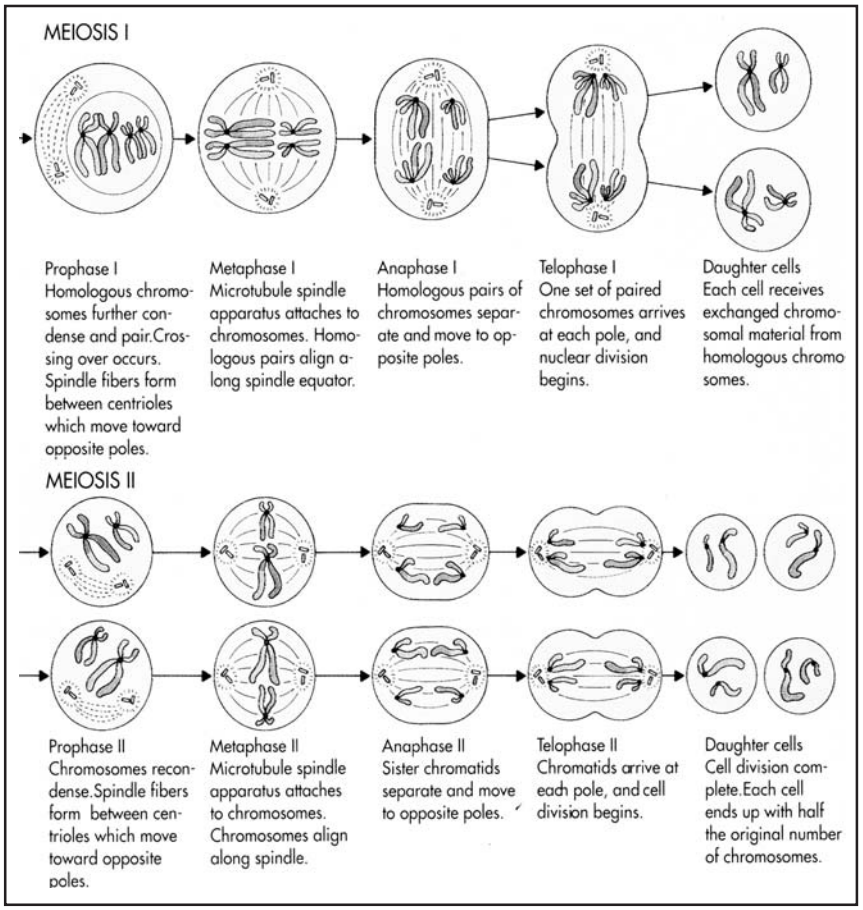


Fig. 3.14. Meiosis (by Raven & Jones).

gene located directly across from its corresponding sister on the homologous chromosome.

The pahynemm. It is very long. The conjugated chromosomes lie very tight to each other, forming bivalents. The bivalent consists of 4 chromatids. At this stage the crossing-over process occurs. The homologous chromosomes exchange some fragments that lead to genetic information exchange. It is one of mechanism of combinational diversity.

The diplonemm. The chromosomes start to coil. The chromosomes of bivalent begin to move apart. This movement starts from centromeres.

The points at which portions of chromosomes are exchanged can often be seen under the light microscope as an x-shape structure known as a chiasm.

The diakinesis. The chromosomes continue to coil. They become short and wide. The nucleus coat dissolves.

The metaphase I. The homologous chromosomes are by pair at the cell equator.

The anaphase I. The homologous chromosomes start to move toward cell poles.

The telophase I. The two cell containing haploid chromosome set, 2 chromatids and DNA amount 2C are formed.

Between meiosis I and meiosis II there is a short time interval called interkinesis. During this period chromosomes are despiralized. The meiosis II occurs as a usual mitosis. The only differences are that there is a haploid chromosome set on equator in metaphase II and in anaphase II chromatids move to the cell poles. In telophase II a cell containing haploid chromosome set, 1 chromatid and DNA amount 1C, are formed. Their destiny may be different: either they are used for zygote formation or die.

3.4.3. THE ENDOMITOSIS AND POLYTENY

The endomitosis is one of mitosis kinds. After chromosome replicatation the cell is not divided. The chromosome number is multiplied in the cell, sometimes in ten times more as a result of this.

The endomitosis occurs in intensively functioning cells: in tissues of nematodes, insects, in some plants. It is assumed that endomitosis appeared in evolution as a variant of mitosis.

The polyteny is reproduction of chromonemms in chromosomes without increasing chromosome number. The number of them might be increased in many times (in 1,000 and more). The chromosomes become of giant sizes since the DNA amount is increased. The polyteny was firstly described by A. Balbiani in 1881. All phases of mitotic cycle are lost except chromonemm reproduction. If we stain these chromosomes, we can see dark strips (disks) across the chromosome. They appear because of irregular chromosome spiralization. The polyteny occurs in some insects and some plants. In salivary gland cells of a drosophila, the ploidity of chromosomes reach 1,024. The polyteny is used for chromosome mapping and revealing chromosome changes.

3.4.4. THE AMITOSIS

The amitosis is direct division of a cell which means the nucleus division without chromosome spiralization and assembling mitotic apparatus.In

1841 R.Remark was the first to describe amitosis. During the direct division, firstly, nucleolus is divided into two parts, and then such a division occurs with the nucleus and cytoplasm. The nucleus may be divided into two equal parts (equal amitosis) or into two non equal parts (non equal amitosis), or into several parts (fragmentation, plasmodium shysogony). Sometimes the cytoplasm is not divided and then cells with many nucleuses are created (amitosis without cytotomy).

There are several factors that may lead to amitosis. According to these factors, amitosis may be divided into three types: generative, reactive and degenerative.

The generative amitosis may occur in dividing of highly specialized cells. It is observed in infusoria during macronucleus division, in some mammalian cells (liver cells, epidermis cells).

The reactive amitosis may occur while cells undergo some harmful impacts or during metabolism disbalancing (fasting, tissue denervation, disturbances in nucleic acids exchange). As usual it has no cytotomy. It leads to a multinuclear cell formation. It might be considered as a compensatory organism reaction resulting in increasing of metabolic surface between the nucleus and the cytoplasm.

The degenerative amitosis may occur only in aging cells. It is presented by the nucleus fragmentation and it has no connection to cell reproduction. The appearance of degenerative amitosis form is a sigh of necrobiotic processes.

3.4.5. THE CELL PROLIFERATION

The proliferation is an increasing of cell number by mitosis which leads to tissue growth. The cells of animal tissues may be divided into three main groups: labile, stable and static.

Labile cells are able to renew themself fast and easy during organism life (blood cells, epithelial cells, cells of alimentary channel mucosa).

Stable cells are cells of the liver, pancreas, salivary glands, etc. They have a limited ability to reproduction. This ability appears only during reparation of damaged organ.

Static cells are cells of the myocardium and nervous tissue. They are not subject to division or subject to division in extraordinary conditions.

The process of wound healing is due to division. The value of proliferation is determined by the ability of tissue division. No wound may be healed without a cell division. And an operating surgeon has to consider the ability of the cell and tissues to reproduction (proliferation).

3.4.6. THE MECHANISMS PROVIDING CELL DIVISION

The mechanisms of cell division were discovered by L. Hartwell, T. Hunt and P. Nourse (Nobel Prize in 2001). For the first time the key molecules have been identified that regulate the cell cycle in eukaryotes. The specific class of genes was discovered controlling the cell cycle itself. The key regulator of the cell cycle - cyclin-dependent kinase (CDK) was identified.

The mechanism of the action of this gene determines the chemical phosphorylation of other proteins with which it conducts the cells through the whole cycle inherent to them. Simultaneously special cyclin proteins were discovered that regulate the function of cycline-dependent kinase. These cyclins are periodically supressed at each cell division which is extremely important for the control of the cell cycle. Among the genes responsible for the fission process, a CDK 28 gene was isolated, which controls the first step in the process of passing G_1 - cell cycle phase. This gene was named as “start”. The particular gene CDK 2A plays a key role in the cell cycle control. It corresponds to the “starting” gene controlling the transition from step G_1 to step S. Gene cdc 2 controls various phases of the cell cycle. It has been named CDK 1 (cyclin - dependent kinase 1) which encodes a protein belonging to the group of the so-called cyclin-dependent kinases in a human. Their activation is in a direct connection with the reverse process of phosphorylation. The essence is that the phosphate groups are attached to the protein or split off from it. Six different CDK molecules were found in a human.

Proteins cyclins are normal proteins that are formed and destroyed during each cell cycle. They are such named because the level of these proteins in the cell cycle oscillates with a certain frequency. Proteins-cyclins are bound with CDK-molecules, thus regulating CDK activity and selecting the proteins for subsequent phosphorylation. Throughout the cell cycle CDK- number of molecules does not change, however, due to the regulatory function of the cyclins the activity of CDK molecules undergo certain changes. Dicsovering the mechanisms of a cell division is important for understanding the development of chromosomal instability in cancer cells. Such changes in chromosome structure are the result of violations of the control over of a cell cycle. The genes encoding CDK-molecules and cyclins can function as oncogenes. During a cell cycle CDK molecules and cyclins act together with the products of tumor suppressor genes. The increase of CDK-molecules and cyclins is detected in humans with brain tumors, breast cancer.

3.4. THE CELL DEATH

Cell death of individual cells or entire groups consistently occurs in multicellular organisms, the cause of which may be different. They are divided into two categories: necrosis and apoptosis which is often referred to as programmed cell death.

3.4.1. NECROSIS

Necrosis is type of a cell death associated with impaired intracellular homeostasis as a result of violations of the permeability of cell membranes. It leads to changes in concentration of ions in the cell, irreversible changes in the mitochondria and cessation of all vital functions, including the synthesis of macromolecules. Necrosis causes damage to the plasma membrane, inhibition of the activity of membrane pumps under the action of many poisons, irreversible changes in energy due to lack of oxygen and poisoning of mitochondrial enzymes. The cell swells due to its watering, increase of Na^+ and Ca_2^+ ion concentration in the cytoplasm, acidification of the cytoplasm, swelling and vacuolar membrane components gap termination of protein synthesis in the cytoplasm, liberation of lysosomal hydrolases and cell lysis occur in cytoplasm. The cell nuclei initially compact (pyknosis of nuclei), but as the nucleus is swelled and its membrane is ruptured, the boundary layer breaks up into small masses (karyorrhexis), then the karyolysis comes - nucleus is dissolved. Large groups of cells are exposed to death and areas of necrosis are attacked by white blood cells.

3.4.2. APOPTOSIS

During the development of organisms and their functioning in adult state the part of cells constantly die without physical or chemical damage, this is a sort of “causeless” death which is observed at all stages of ontogenesis. “Spontaneous” cell death occurs in the adult organism. Blood cells, skin epidermis, the cells of small intestine, the follicular cells of the ovary after ovulation die. Cell death is regulated by cell to cell interactions in different ways. Cells in multicellular organism need signals to stay alive. In their absence, the “suicide” program or a programmed death are developed. At the same time the cell can receive signals which trigger processes in the target cells leading to the death of apoptotic type. The “apoptosis” term was introduced in studying the liver cell death at partial ligation of the portal vein.

The process begins with the fact that the neighboring cells lose contact, specific chromatin condensation occurs in the nucleus. Morphological signs of apoptosis-meteorological consist in reducing the size, cell atrophy,

compaction and fragmentation of chromatin usually adjacent to the nuclear membrane. These changes are the earliest manifestations of apoptosis, prior to degradation processes. Then in the nuclear membrane, invaginations are formed and chromatin fragments are discharged from the nucleus. The nucleus is fragmented into separate parts, then the cell itself is fragmented into individual corpuscules delimited by the plasma membrane - apoptotic bodies.

Apoptosis is a process leading not to dissolution of the cell (lysis) but its fragmentation, disintegration. Apoptotic bodies are phagocytosed by macrophages or adjacent normal cells. At the same time an inflammatory response is not developed. The death process is similar both during embryonic development in adulthood, and in pathological processes. Apoptosis can be triggered by a number of external factors (radiation, toxic effect of certain enzymes, inhibitors of cell metabolism, effects of parasites metabolites). Irreversible damage to DNA causes the apoptosis.

The biological role of apoptosis is of great importance. It is removal of modified or pathological cells, particularly mutated or infected by viruses. Apoptosis is a genetically programmed cell death, governed by specific genes. As in any biological system, such regulation is done by antagonistic principle - stimulates apoptosis gene p53, inhibits - gene bcl 2. The protein controlled by a p53 gene has the ability to block the cell division and to launch apoptosis mechanism. Such a mechanism is found in tumor cells in 55-70% of cancer patients. Elective cell death is no less important for morphogenesis than other cellular processes. It is found that a cell death has three levels of regulation: genetic control, cell-to-cell interactions and organismal level.

ONTOGENETIC LIFE ORGANIZATION LEVEL

CHAPTER 4. MAMMALIAN AND HUMAN REPRODUCTION

4.1. THE CLASSIFICATION OF REPRODUCTION TYPES

The ability to reproduce itself is one of the main features of life systems. On a molecular level, the reproduction process is determined by the ability of nucleic acids duplication. On an ontogenetic level self reproduction is performed in different forms: from a simple division of protists to sexual reproduction of animals and plants (Fig. 4.1), which is a very complicated

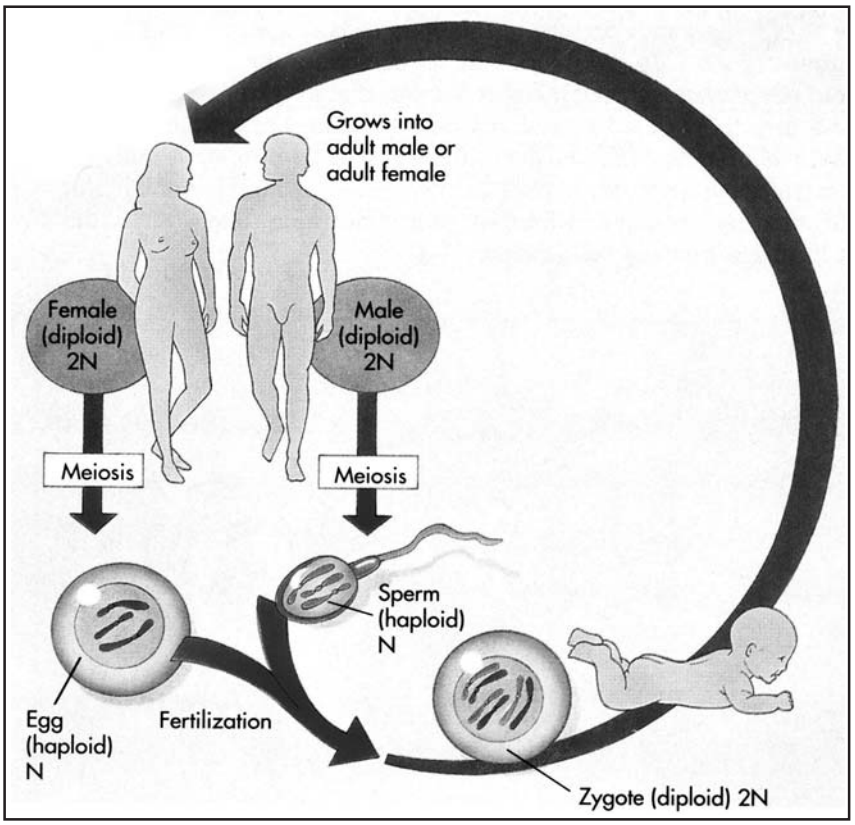


Fig. 4.1. Sexual reproduction of human (by Raven & Jones).

process in structural and functional aspects.

The reproduction is the ability of organisms to produce new organisms similar to them; and the ability of an organism to produce offsprings. Individual being is supported by a cell reproduction; and species being is supported by organisms reproduction. The reproduction is a necessary condition of species being and continuity of successive generations in it. Although, the reproduction ways in worlds of plants and animals are very diverse, they may be generalized into two general types: asexual and sexual.

4.2. THE FEATURES OF HUMAN SPERMATOGENESIS AND OOGENESIS. THEIR REGULATION BY HORMONES.

The *gametogenesis* is a process of a sex cell formation. All cells of a body, somatic and reproductive have their origin from embryonic cells. At the process of embryonal development a group of cells separates from others. And after several divisions they form gonial cells (gonia). At the beginning they are the same, but later they subject to differentiation. In a male organism they differentiate to spermatogonia, in a female organism to oogonia. The gametogenesis has four periods: reproduction, growth, maturation and formation.

The main features of oogenesis. Oogonia has a reproduction period only in the course of an embryonic development. Oogonia stop division and changed to primary oocyte at the end of this period. They are preserved in ovarium until puberty. At the puberty onset, the growth period starts in selected oocytes. It may be distinguished into two periods: "small growth" (nucleus and cytoplasm volume increasing), and "large growth" (accumulation of yolk inclusions - proteins, fats, fats-like substances). There is a lot of yolk in amphibia, reptilia and birds ova, but there are a few yolks in lancelets, mammalian and human ova. The nucleus is changed to badly stained vesicle. Many animals loose centrosome. During a maturation period two irregular meiosis divisions occur. Primary oocyte gives up the secondary oocyte and the first polar body. Then the secondary oocyte gives up a second polar body and after that, it becomes mature ovicell. The first polar body may be divided into two polar bodies. This irregular division may be explained by expediency of yolk and cytoplasm preservation for ovicell.

Human oogenesis. When an embryo has reached the size of 20 mm, specific sex features of female become evident (Fig. 4.2). The primary sex cells, incorporated in gonad germ, proliferate and are differented in oogonia in ovaria of two-month-old embryo. At the end of the 3rd month in a deep layer of female gonad a differentiated oocytes in prophase of meiosis I are distinguished. By the 7th month, the histological differentiation of

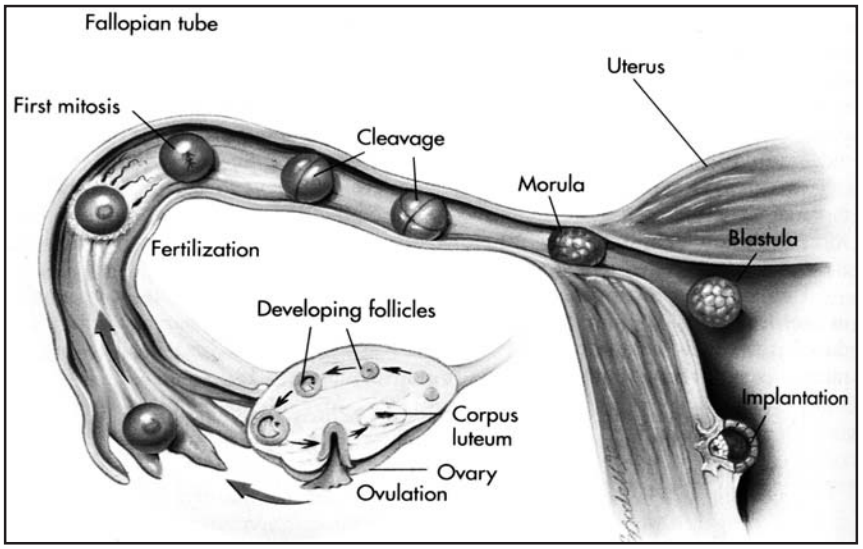


Fig. 4.2. Human oogenesis (by Raven & Jones).

ovarium is very active. So, by the 9-month there are 200,000-400,000 oocytes in each embryo ovarium. Some investigators state that there are about 1 million oocytes. Oocytes are surrounded by a follicular cell monolayer and form a primary follicle. After birth, oocytes are preserved until puberty in diplonemm of meiosis prophase I. When puberty has been reached, the oocytes continue their meiosis. The first meiosis division is done before ovulation (liberating of ovicell from follicle). This division is very unequal. The secondary oocyte gets the most of cytoplasm whereas a polar body gets the minimum. The second meiotic division does not occur until fertilization and result in the production of a second polar body and a single haploid egg nucleus. Both cells move into fallopian tube, where polar bodies are destroyed liberating nucleus substance into surrounding ovum environment.

Now it is apparent that regular follicle growth, ovulation and regression is regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) of pituitary gland (Fig. 4.3). Growing follicles produce estrogens (estradiol) which may act on pituitary hormone production. It is stated that follicle growth mostly depends on FSH, but ovicell maturation and ovulation mostly depends on LH. The hormone mechanism integrates two different, evolutionary unconnected processes such as follicle growth and ovulation. This enables providing fully differentiated gametes for fertilization. To trigger meiotic division, a small amount of LH is required. But to perform ovulation,

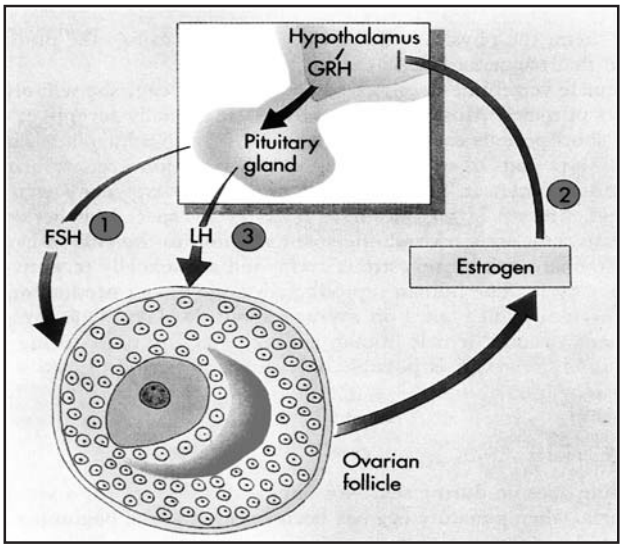


Fig. 4.3. Hormones regulation of human oogenesis (by Raven & Jones).

we need to have a peak of LH concentration. In some cases ovicell has done meiotic division, but LH concentration is not enough to perform ovulation. Then intrafollicular aging of ovum occurs. The properties of ooplasm are changed which is mainly concerned for cortical layer and for spindle apparatus. This causes an ovum death, loosing fertilization ability or formation of zygote with unbalanced chromosome set. This results in embryo death and formation of embryo with chromosome defects (such as Down syndrome). It is believed that intrafollicular ovicell aging is connected with seasonal disturbances in a neurohornonal regulation pattern.

The main features of spermatogenesis. In the course of the period of reproduction sexual cells are presented by spermatogonia. There are small round shape cells with a small amount of cytoplasm. They divide very actively. They are subject to division almost all lifelong from childhood to adult. At puberty onset, the part of spermatogonia stops their division and they are changed into spermatozoa. A growth period is characterized by a reproduction termination and spermatogonia are changed to a primary spermatocyte. They grow and four times increase their size. They lie in semineferous tubules closer to the duct. During the maturation period meiosis division is performed. As a result of this, primary spermatocytes are changed to secondary spermatocytes and then to spermatids. Secondary spermatocytes are two times less in volume than primary spermatocytes. However, spermatids are four times less in volume than primary

spermatocytes. They lie closer to tubule lumen than primary spermatocytes. During the period of the formation, spermatids are changed to spermatozoa.

Human spermatogenesis. A male primary sex cell is subject to differentiation to spermatogonia when a male embryo has reached the size of 15 mm. A specific sex signs formation in a male embryo starts earlier than in a female embryo. A period of primary spermatogonia formation is very short. During this period many mitotic abnormalities occur, such as failures in chromosomes moving. Many cells die at this stage. The process of males gametes formation continues throughout the whole life. A process of sperm formation takes about 70 days. Each day 10^{x7} spermatozoa are produced per 1 gram of testis weight. The epithelium of semineferous tubules consist of an external layer of germinative epithelial cells and six inner layers corresponding to spermatozoa formation stages. The division of germinative cell gives a rise to many spermatogonia which increase in size and become primary spermatocytes. Primary spermatocytes are subject to meiosis I to forme secondary spermatocytes. They become spermatids after meiosis II. There are Sertoli cells between developing lines of cells. They perform nutrition for developing cells and they also secrete a fluid that helps spermatozoa to move inside of tubules. In an inner layer, spermatozoa are formed from spermatids. A growth and reproduction of sperms is stimulated by follicle-stimulating hormone. A testosterone secretion is stimulated by luteinizing hormone. The testosterone is a main male androgenic hormone. It stimulates development and maintenance of male primary and secondary sexual characteristics. It is necessary to have both testosterone and FSH to produce spermatozoa successfully. Development and maintenance of male secondary sexual characteristics requires only testosterone.

Ovicells are oval, big, immobile hundreds or even millions times bigger than spermatozoa (Fig. 4.4). Many animals have ovicell without centrosome, unable to be divided. There are several ovum types according to yolk amount and distribution. The ovicells of mammalians and human are secondary isolecitinal. The ovicell is protected by coats. There are primary coat produced by ovicell itself and secondary coat, produced by follicular cells (Fig. 4.5). All animals have the primary coat (yolk coat). Human and mammalians have it as an internal part of a dense coat. The external part of a dense coat is produced by follicular cell and it is secondary coat. Microvilia of ovum enter the dense coat from inside and microvilia of follicular cells enter from outside. The dense coat contains primary and secondary coats.

Spermatozoa is a small, mobile cell with nutritive substances storage reduced to a minimum. A sperm has a head, neck and tail. In the head

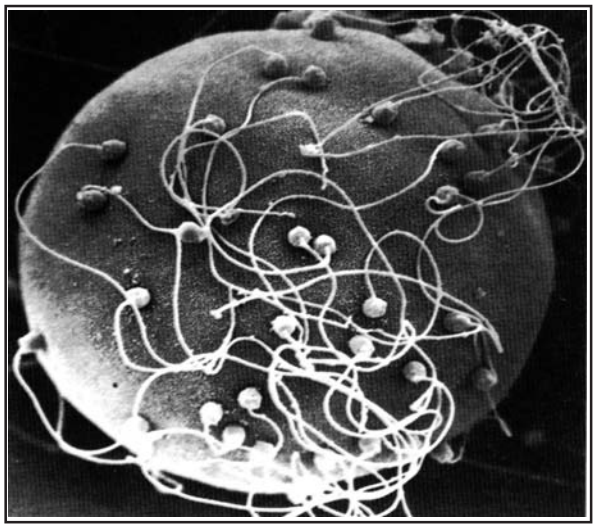


Fig. 4.4. Ovicell and sperms of human during fertilization (by V.P. Pishak).

there is a nucleus surrounded by thin cytoplasm layer. There is an acrosome on a top of the head. The acrosome is derived from the Golgi complex. It consists of a compact mass and a membrane. It contains active substances facilitating ovum coats penetration by sperm. There are two centrioles, proximal and distal in a sperm neck. The distal centriole forms axis thread of a tail. The proximal one takes part in a cell division after fertilization. A tail is an organ of movement. The core of a tail is an axial thread. It is

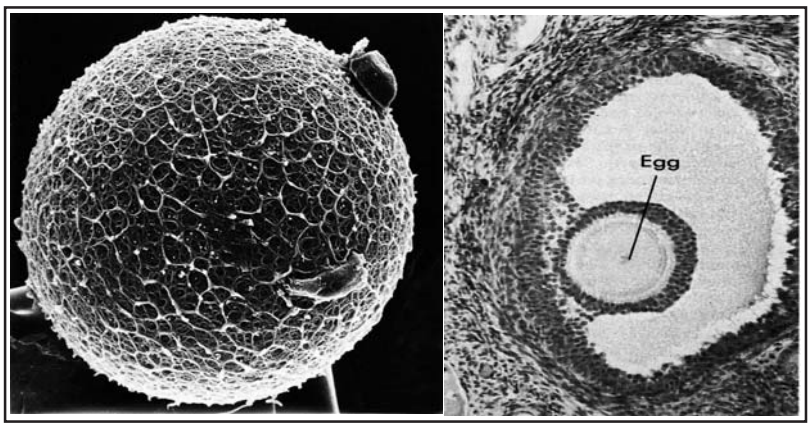


Fig. 4.5. Primary yolk coat (left) and secondary by follicary cells coat (right) of mammalian ovicell (by V.P. Pishak).

surrounded by a mitochondria (in a main part) providing energy for movement. A sperm brings centrosome to ovicell into fertilization. The cytoplasm of a sperm head has a liquid-crystal state. It protects sperm from the harmful environmental influences. The sperm has high nucleus/ cytoplasm ratio. The sperm transfers genetic material to ovicell. Acrosome enzymes help to dissolve an ovicell coat.

4.3. THE INSEMINATION. THE FERTILIZATION

Insemination is a condition providing sperm and ovum meeting. There are external (in fishes and amphibia) and internal (in reptilia, birds and mammalia) insemination. During external insemination sperms and ova are ejected to external environment. During internal insemination sperms are ejected directly to female sexual ways that provides gametes meeting in approximately stable conditions. Such insemination is provided by a system of reflexes and is performed by special copulation organs.

The gametes have special substances - hamons which provide their interaction on a distance. An ovicell produces a ginohamon I and II, a sperm produces androhamon I and II. Ginohamon I is - non-protein structure with low molecular weight, stimulating sperm movement and increasing probability of a sperm and ovicell contact. An antagonist of ginohamon I is androhamon I with a similar chemical structure. It suppresses a sperm movement and preserves them from a preliminary energy waste. Ginohamons II (fertilysins) are proteins or glycoproteins. They totally block a sperm movement facilitating sperm attachment to a ovicell membrane. Androhamone II helps to dissolve ovicell coats.

Fertilization is a process of two gametes fusion resulting in zygote formation. Fertilization consists of three stages: penetration, activation and fusion. The meeting of a sperm and ovicell is provided by unspecific factors facilitating their merging such as an excessive sperm production, large sizes of ovum, secretion of hamons. The acrosome reaction occurs at the moment of a sperm touching an ovicell. The liberated acrosome enzymes help to dissolve ovum coats. It enables fusing sperm and ovum cell membranes. Then cytoplasms of sperm and ovum merge. The sperm nucleus and centriol come to a ovum cytoplasm.

The ovicell activation is a series of events initiated by sperm penetration. The region of membrane which is made of sperm membrane, is permeable for sodium ions. They come in an ovum and change a membrane charge. Then cortical reaction occurs. The contents of cortical granules assist dense coat exfoliation. It is called a fertilization coat. The amphibians and bony fishes have cytoplasm changes called cytoplasm segregation. Activation is finished by a protein synthesis start.

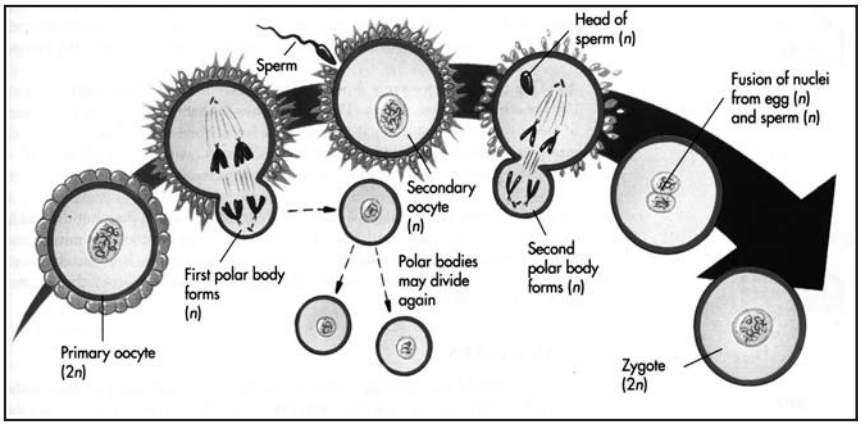


Fig. 4.6. Human fertilization (by Raven & Jones).

Many mammalians have ovicell at the time of sperm meeting at the diakinesis stage (Fig. 4.6). After fertilization, a meiosis block is removed. At the moment of meiosis termination in a ovicell a sperm nucleus appearance changes firstly to an interphase nucleus appearance, and than to prophase nucleus appearance. Such a nucleus with doubled DNA concentration and haploid chromosome set has a name "male pronuclei". The nucleus of ovicell after meiosis has a name "female pronuclei". It also has a DNA concentration 2C. Both pronucleuses merge and fuse. This is a moment of full gametes fusion resulting in zygote formation.

4.4. THE HUMAN FERTILIZATION

Ovum and sperm have a limited life span and a limited ability for fertilization. Human ovum retains the fertilization during 24 hours. The spermatozoa are still active during 4 days if placed in female genital tracts. They are able to fertilize ovum only in first 2 days. The speed of sperm movement varies between 1.5-3 mm/min. There are 350 millions of spermatozoa in an average human ejaculate. Only part of them reaches the oviduct to take part in fertilization. If a number of spermatozoa in men's ejaculate is less than 150 millions (or 60 millions per 1 ml) the probability of fertilization is very small. Generally, "useless" excess of a normal sperm number plays an important role in fertilization (Fig. 4.7).

During a human ovulation, an ovum is released from ovarium. It is surrounded by a layer of follicular cells which is bound to each other by proteoglycans. In such complicated dressing an ovum is unavailable for

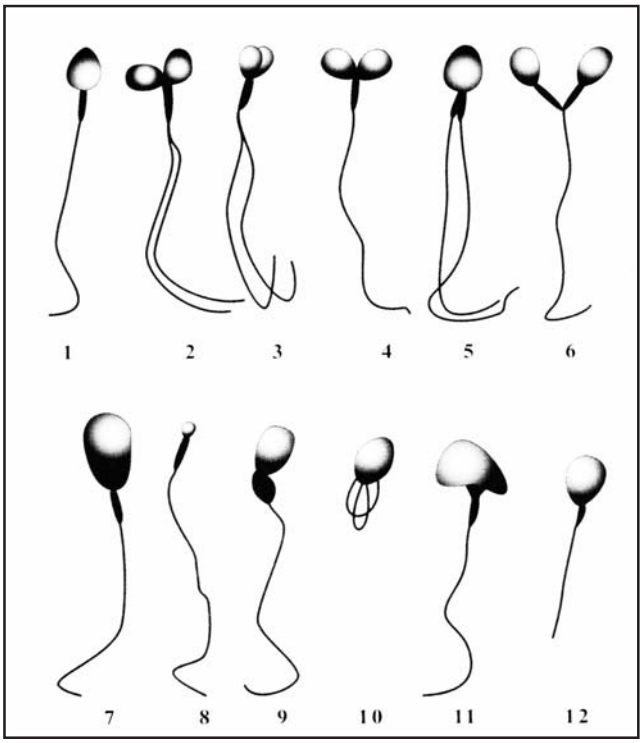


Fig .4.7. Normal (1) and abnormal (2-12) sperms of human (by V.P. Pishak).

sperm penetration. It should be released from a secondary cout of ovum. One sperm cannot dissolve such a coat. They need to work all together to dissolve it. From a great number of spermatozoa attacking a ovum only one can enter it. The ovum membrane bulges out making an acception hill toward a sperm, permitting a sperm nucleus to enter the cytoplasm of the egg. Only this nucleus will fuse with a ovum nucleus. If any other sperm would enter the ovum cytoplasm, it will be destroyed in cytoplasm.

When a sperm comes in contact with an ovum, it performs an acrosome reaction (Fig. 4.8). This is the liberation of enzymes enclosed in acrosome - hyaluronidase, protease and enzyme binding follicular cells. During this reaction, a sperm plasmolemm and external acrosome membrane stick together in many sites. Then, they produce holes in these sites. The enzymes are liberated through these holes. The sperm pass a secondary cout of ovum with the use of proteolytic enzyme. Then, it touches a ovum plasmolemm by a head side and ovum membrane incorporates a sperm

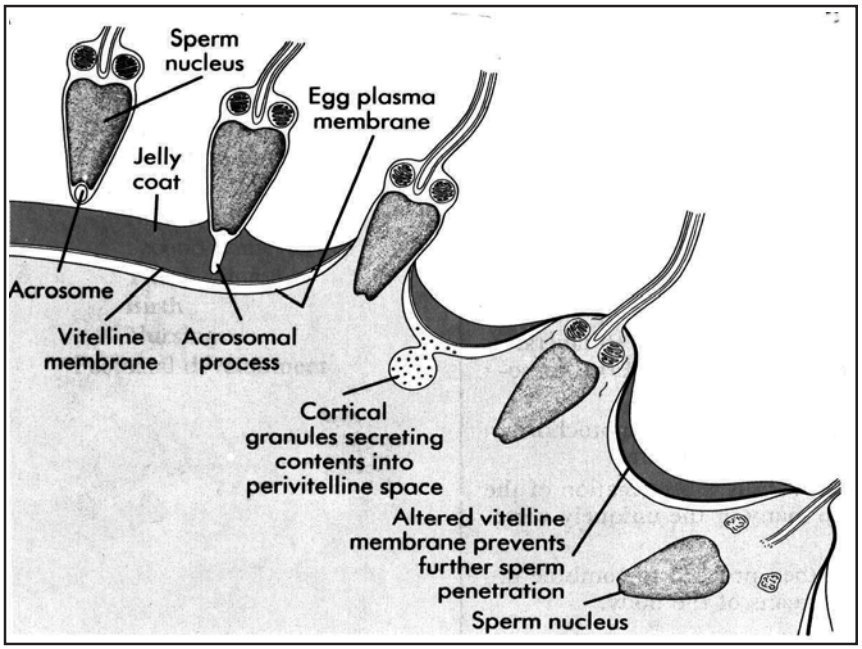


Fig. 4.8. Acrosome reaction of human sperm (by Raven & Jones).

membrane.

Mammalian spermatozoa which have just entered female sexual ways, are unable to perform a acrosome reaction. To receive these properties, they need to be subject to capacitation in oviducts. During capacitation a sperm becomes activated under an influence of female sexual ways mucosa. It takes different time in different species. In rats, it lasts for 3 hours, in rabbits for 5 hours, in human for 7 hours. In contrast to a majority of animals, human sperm head keeps it primary orientation in ooplasm and moves to female nucleus without turning. Gradually, a sperm nucleus changes to male pronucleus. Its chromatin becomes more dispersed.

The human spermatozoa penetrate a ovicell which is in maturation period. Oocyte eliminates a primary polar body 10 hours after penetration and a secondary polar body 24 hours later. Right after a sperm penetration, the ovicell performs a cortical reaction. It helps to make a impermeable coat for other sperms. At the same time, other sperms surrounding ovum loose their directed activity, although keeping their mobility. After that a ovum changes its metabolic activity, such as an increasing membrane permeability, the increasing of warm producing, the accelerating of oxidation-reduction

reactions rate in more than 70 times, activation of protein synthesis, activation of lipid and carbohydrate exchange.

The human has the same rhythms of reproductive activity as animals. Such rhythms were formed according to influences of environmental factors. It is known that menstrual cycles have the same length as moon cycles, although a direct connection between them is lost. Around 10% of menstrual cycles are without ovulation in healthy women today. The interchange of ovulatory and anovulatory cycles depends on activity of neuroendocrine system. A birth rate statistics in Western Europe, Australia and USA showed that a birth rate curve has a following structure. It has a wide peak during winter, spring recession, slight summer raise and significant decrease during autumn. Hence, human copulation, similar to other mammalian, occurs more often in spring and autumn months.

The strong social and cultural factor invasion to human biology has led to sexual intercourse act estrangement from reproductive purposes. It serves as a source of getting pleasure. It leads to disynchronisation of ovulation and fertilization, to overmaturation of female and male gametes. The influence of this factor is proved by a higher rate of chromosome defects in human embryo in early stages of the development and by wide spectrum and higher rate of "spontaneous" development defects in humans than in animals.

4.5. THE BIOLOGICAL SEX DETERMINATION IN A HUMAN

The division of mankind into two sexes assumes every individual to have a full correspondence of a anatomical body plan, a structure of sexual organs, body's proportions (growth, shoulder/pelvis width ratio, distribution of adipose tissue and so on), sexual realization (feeling oneself as representative of a definite sex), and at least adequate direction of a sexual drive and appropriate stereotypes of sexual behavior.

The formation of this system starts from a genetic sex determination by chromosomes set. The genetic sex determines gonad sex, identificated by a main sign of sex a histological structure of sexual gland. It is gonad because its determined gamete sex, i.e. the ability of sexual gland to produce spermatozoa or ovicell. Gonads show an individual role in reproduction process. Also the gonad sex determines the hormonal sex. It is the ability of sexual gland to produce specific sex hormones (during embryonic development only testis are hormone active, whereas in puberty both ovarium and testis are hormone active). Then, the level and dominating directions of hormonal action determine morphological (or somatic) sex (phenotype). The morphological sex means features of structure and development of internal and external sexual organs as well as secondary

sexual characteristics. It is important to note that the term "sex" is composed from many related to each other biological, social and psychological components. Sex is a union of organisms signs and properties providing participating in reproduction and hereditary information transmission through gametes production.

The biological sex differentiation is programmed by a genetic sex chromosome set in zygote after gamete nucleus fusion.

The embryonic gonad is bisexual. Formation of primary gonads occurs under the 5th week of embryonic development. The genetic sex is determined by sex chromosome (X or Y) of the sperm. The X chromosome has a gene of testicular feminization (Tfm), normal allele of which is responsible for receptor synthesis for androgens. The male and female organism has at least one X chromosome. That means that both sexes have such a receptor. Y chromosome has a sex determining region (SRY), which is responsible for formation of a male sex signs. It stimulates differentiation of sexual cells to semeniferous tubules and intersticial cell. If an individual has a genotype $X^{Tfm}X^{Tfm}$, the ovarium will be formed from primary gonad cortex. If an individual has genotype $X^{Tfm}Y^{sry}$, the testis will be formed from primary gonad medulla.

At the 10th week of the development the sex of embryo may be determined by two criteria: sex chromosome set and histological structure of sex glands. The sex of mature gonad (gonads sex) may be determined by a generative elements state: primary follicules with oocyte I in ovariums and semeniferous tubules with spermatozoa in testis.

A hormonal gonad function is to produce sex hormone in their intermediate tissues (teca cell in ovarium and Leidig cell in testis). Both ovarium and testis produce the main sex hormones: testosterone, estrogen, progesterone, but in a different ratio. Ovariums mostly produce estrogens and after ovulation progesterone. Testis mostly produces testosterone. The typical for ovarium and testis features of sex steroid biosynthesis form hormonal sex. It is a sexual steroid ratio and their properties, characterizing each sex. Testosterone released into the embryo blood interacts with androgen receptors in target cells of a potential reproductive system. Then complex testosterone-receptor passes into a nucleus, where it activates genes responsible for tissue growth and development. Testosterone stimulates the development of only those tissues, which give rise for male reproductive system. That is why, male is developed from embryo with sex chromosome set - XY.

Tissues of a potential female reproductive system are not activated and not developed. In an embryo with sex chromosome set XX the absence of testosterone allows a reproductive system to develop a female pattern.

The internal sex organs are formed on the 10th-12th week of the embryonic development. Until the differentiation period, both a male and a female embryo have rests of pronephros urethra which are precursors of sexual organs of both sexes. The Muller's canal is a basis of female sex organs (uterine tubes, uterus, and upper part of vagina). Wolfian ducts are a basis of male reproductive organs (epididymis, seminal ducts, seminal vesicles).

After 12th weeks of the development in case of having satisfactory concentration of testosterone, there is musculinisation of external sex organs in a male embryo. It is terminated on a 20th week. There is an atrophy of a vagina appendix, a formation of scrotum suture (scrotum formation), an increase of cavernous dody of penis and a formation of cavernous part of urethra.

In puberty, the definite level of estrogens provides a formation of female sexual characters - feminization (female body constitution, mammal glands formation, hymen, vagina and uterus enlargement). Androgens define a male skeleton type, a good muscular development, a development of larynx cartilages, a male type of hair distribution. The synchronization of ovarial cycle (follicule development, ovulation, corpus luteum formation) and pituitary hormone regulation setting also occurs in puberty. Males have stable pituitary regulation.

4.6. THE HUMAN HERMAPHRODITISM. THE TRANSSEXUALISM

Individuals of both sexes might be hermaphrodites since primary gonads have generative elements of both sexes. They may have separated or combined gonads. Testes, as usually, are underdeveloped and have no maturated spermatozoa. An ovarium (or its part) is more developed. Follicules may develop and have ovulation. Karyotype is usually 46XX, rather 46XY, less possible 46XY/XX.

The false hermaphroditism is more common. It includes all pathological forms of sexual development. The secondary sexual characteristics may be formed both in a female pattern and in a male pattern.

It is necessary to distinguish transsexualism, fetishism, transvestism and other abnormalities of human sexual behavior from hermaphroditism.

Transsexuals are people with normally developed sex (male or female) which does not satisfy them because of their psychological dominant. They want to change it surgically to controversial. The population transsexualism rate varies from 1 in 37,000 to 1 in 100,000. The average age of patients at the first doctors appointment is 23-24 years for males and 25 years for females.

Fetishism is a worship of fetish, a subject representating a sexual partner.

As a subject, people may use underwear, clothes, parfume.

Transvestism is a case when an individual picks up clothes of a controversial sex for getting pleasure and satisfaction.

Only expressed transsexualism may be treated by surgery.

In case of fetishism and transvestism, the other kinds of psychological treatment are performed.

4.7. THE CONTEMPORARY REPRODUCTIVE STRATEGY OF HUMANKIND

The main purpose of contemporary reproductive strategy is removing harmful factors breaking normal gametes formation, fertilization and early stages of development. As it has been stated the prenatal human mortality rate is the highest at the first week after fertilization; 16% of gametes are not able to fertilization at all; 42% of embryo dies right after fertilization. It is believed that an early prenatal human mortality rate is closely related with changes in an ovicell occurred before leaving the follicle, i.e. proembryonic defects in ontogenesis.

The contemporary reproductive strategy in Europe should include such an important element as a prevention of hereditary defects. It includes firstly prenatal diagnostic of hereditary defects of a early development stages among pregnant women. If a hereditary defect is detected in an embryo, the pregnancy may be interrupted on early stages. We can prevent the birth of a disabled child. Today we can use biomedical science achievements such as chromosome mapping, biochemical testing and very sensitive ultrasonic devices.

In recent years new prospective methods to fight human sterility have been developed. It is closely connected with a reproductive strategy. These methods are artificial insemination, in vitro fertilization, embryo placement to uterine tubes, ovicell and embryo donorship, "surrogate mother". If there is a high risk to have a child with hereditary defects, it is possible to perform in vitro fertilization with preinplantational embryo diagnostics, such as cytogenetic and biochemical diagnostics. The following placement of the only healthy embryo to uterine tubes guarantee a healthy offspring development. The methods of "new reproductive strategy" allow changing gametes with defects to healthy gametes obtained from a donor. These works are actual for today.

Artificial insemination is the injection of an another sperm with genetic material in the female genital tract for pregnancy. There are following artificial insemination methods used depending on the way of injection of sperm: vaginal; interservical; uterine method; transabdominal (introduction of sperm together with one or two eggs in the fallopian tube funnel). The

artificial insemination of husband sperm applied under a restriction of the urethra lumen, impotence, the absence of ejaculation with oligospermia (decrease sperm counts). The artificial insemination by the sperm of donor implemented with asospermia or oligospermia in husband (absence of sperm or low count of sperm) with morphological changes and impaired sperm motility, incompatibility spouses Rh, presence of hereditary diseases in man. The pregnancy occurs in 10-15% of cases with artificial insemination.

In Vitro Fertilization (IVF) is the main method of treatment of all forms of infertility in which sperm fertilizes the ovum in a test tube. The zygote is injected in to the uterus of a barren woman or a surrogate mother. Luisa Braun is the first child who was born in 1978 as a result of in vitro fertilization. IVF is effective in cases where the fallopian tubes are removed, disrupted their permeability, a husband has asospermia or oligospermia. After the ovulation ovum is surgically removed from the ovary and is transferred to the nutrient medium in the embryology laboratory. Sperm and ovum are fertilized in special solutions with the use of modern medical equipment. After 2-4 days the embryos are ready for preimplantation diagnosis. Doctors can check an embryo consisting of only 4-8 cells using modern genetic techniques. This method of diagnosis revealed chromosomal and gene diseases such as Down syndrome, hemophilia and others. In addition, using preimplatation diagnostics can determine a future sex of a child. The embryo transfer to the uterus (implantation of the embryo) is the simple a procedure of the whole method. With a special flexible catheter 2-3 fertilized eggs are transferred into the uterus. IVF pregnancy occurs in 30-35% of cases. 20 pregnancies delivery results in birth of 18 children. When the average favorable outcome of the procedure (pregnancy), are frequent cases where fertilization of the tubes leads to multiple pregnancies: conceived double or triple as in an attempt IVF involving several eggs.

Egg donation is anonymous, altruistic and selfless transfer of eggs from one completely healthy woman pass to the other sick woman.

The procedure of *sperm donation* is used if men's sperm is not produced in the testicles, there are serious diseases that can transfer the potential father-child inheritance. Donors often use the services of women who have no sexual partner. Very high requirements are made to the donors of sperm. Firstly, donors can only be men aged 20 to 40 years of age. Second, the donors should have their own healthy children without a hereditary disease. Doctors must examine the donor by on infectious and sexually transmitted diseases. It is nessary to make the semen analysis: its performance should be above average values (and a lot of high-grade motile sperm - more than 1/3 of the total). After the man provided a sperm sample, it is been freezed and six months later the donor takes all the tests again. If

the disease is detected, the genetic material can be used for a artificial insemination.

Surrogacy is an assisted reproductive technology. Three people are involved in the conception and birth of a child in a surrogacy maternity: 1) genetic father - a person providing his sperm for fertilization and consonants after the birth of a child to take over his father duties; 2) the genetic mother - the person who has submitted an egg for fertilization and consonants after the birth of a child to take the mother responsibilities; 3) the surrogate mother - a woman of childbearing age, to agree on a fee or free of charge to bear and give birth to a child from genetic parents, and does not aspire to the role of the child mother. In some cases (infertility of a future foster mother or its complete absence, as well as if a child will be brought up by a single parent or a gay couple), the surrogate mother can also be a genetic mother. Genetic parents may take the role as legal parents after the birth of a child. In most cases, surrogacy is used to overcome infertility in couples in which a woman is not able to bear a child for medical reasons. Surrogacy is only possible using IVF.

4.8. THE BIOETHICS. THE ETHICAL AND JUSTICE ASPECTS OF INTERVENTIONS IN HUMAN REPRODUCTION

Bioethics is a science studying ethical (i.e. moral), justice and social problems connected with medicine and biology development. The main field of bioethics study are ethical problems as consequences of biomedical researches and their use in artificial fertilization, transplantology, gene engineering. The main bioethic aim is to defend humankind and society from negative consequences of biomedical science achievements. For this purpose, the ethic rules may be used such as laws or any other lawful documents.

Even in the Hippocrates Oath, a doctor promises, “not to do any harm for a patient”. That is why bioethics has a tight relation with deontology and medical ethics. The deontology is a union of ethical rules of a doctor and patient contact. In 1987, the European Bioethics Expert Committee suggested a list of recommendations for a artificial human reproduction. It is necessary to have a law regulation of “surrogate mother”, a ban on gametes and embryo trade. The woman should be considered as mother who has born a child.

The artificial fertilization is prohibited for science purposes. There is a ban on in vitro embryo growing more than 14 days.

All aspects of a surgery performed for transsexual patients require justice reglamentation. Many bioethicals problems have arisen lately connected with a human cloning possibility.

The contemporary reproductive strategy is based not just on modern biomedical science achievements. It has to include all aspects of human (ethical problems, social relations and legislation).

CHAPTER 5. GENETICS AS A SCIENCE. GENE LEVEL OF HEREDITARY MATERIAL ORGANIZATION.

5.1. GENETICS, ITS SUBJECT, AIMS, STAGES OF DEVELOPMENT

Genetics is a science about principles of heredity and diversity of organisms and about methods to direct them. The term "genetics" was introduced by English scientists W.Batson in 1906 (from the Greek "geneticos" – related to birth).

Heredity is a property of an organism to transmit traits and development features in line of following generations. Many species have been preserved unchanged for hundreds of millions of years (opossum, latimeria, gatteria). In a sexual reproduction a material basement of heredity are sperm and ovicell, in asexual reproduction – single somatic cells.

Inheritance is a way of hereditary traits transmittion process from one organism generation to another at reproduction. Inheritance is performed through the sex cells in the course of sexual reproduction and through the somatic cell division in the course of asexual reproduction. The analysis of herediting principles is an important method to study heredity patterns.

Embryonic cells do not carry all traits of an adult individual. It carries only material for traits which may give these features in future. This material of future traits development is called a gene.

The gene is a unit of heredity which determins one elementary trait. It is related with a protein structure or a elementary organism reaction. The genotype is integrity of all organism genes. The phenotype is integrity of all organism traits. The genotype and phenotype terms are commonly used in a narrow meaning. They may be related with traits which are interesting for researchers at this moment.

The diversity is a variety of individual or group traits and properties. The diversity is a reflection of unstable preserving an individual hereditary information. It includes gene changing and gene combinating and changes in gene expression throughout an individual development. Heredity and

diversity are two fundamental properties of life matter. That dialectic union provides organisms evolution on the Earth.

Genetics studies heredity and diversity in four aspects.

First, it studies a problem of genetic information storage. It studies the place of genetic information storage and ways of genetic information coding.

Second, it studies a problem of genetic information transmitting and the principles of the transmitting from cell to cell, from generation to generation.

Third, it analyzes a problem of genetic information realization. It studies how genetic information may be realized in definite traits of a developing organism, in correspondence with external environment impacts.

Fourth, it considers the problem of genetic information changing. It discovers the types and reasons of changing and mechanisms of its appearance.

The history of genetics starts since 1900. That was a year of rediscovering Mendel's Laws of heredity by G. De Fris, K. Correns, A. Chermack. The first stage of genetics development covers the period between 1900 and 1912. It was a period of Mendel Laws of heredity recognition. The second stage of genetics development covers the period between 1912 and 1925. It was a period of accepting Morgan's chromosomal theory of inheritance. The third stage of genetics development (1925-1940) was characterized by discovering artificial mutagenesis and by studying genetic processes of evolution. In the fourth stage of genetics development (1940-1953) some works about genetic control of physiological and biochemical traits appeared. And the firth stage of genetics development (from 1953 to nowadays) is characterized by studying genetic events at a molecular level.

5.2. GENE LEVEL OF HEREDITARY INFORMATION ORGANIZATION

The molecular genetics is a part of genetics which studies molecular bases of heredity. It was founded in 40-50s years of the 20th century using newly appeared ideas and devices in physics and chemistry. We may distinguish such levels of hereditary information organization as gene, chromosome and genome in prokaryotes and eukaryotes on the basis of molecular genetics.

A gene level of hereditary information organization is closely connected with a success of chromosomal theory of inheritance. At the first quarter of the 20th century scientists mentioned that the gene is a material part of heredity which lies in chromosome. It is able to self-reproduction. It is a minimal unit of recombination, mutation and genetic function.

G. Mendel suggested gene pointing by the Latin alphabet letters. Genes

which encode a development of alternative traits are called allelic genes. Allelic genes are located in homologues loci of homologues chromosomes. Each gene may have two conditions: dominant and recessive. The dominant gene determines the appearance of heterozygotus. One allele is said to be dominant if an individual who is heterozygous for that allele has a appearance as an individual who is homozygous. The recessive gene is masked in heterozygotes by presence of a dominant gene in a phenotype.

A dominant allele is pointed with a capital letter of the Latin alphabet (A) and a recessive allele is pointed with a small letter (a). Organisms which have similar alleles of one gene for example both dominate (AA) or both recessive (aa) are called homozygotus. Organisms which have different alleles of one gene, for example, one dominate and other recessive (Aa) are called heterozygotus. If an organism has only one allele of the gene (like in male X chromosome)it is called hemizygotus.

Today we may say that a gene is a region of genomic nucleic acid which is characterized by specific nucleotide sequence and presents a function unit different from other genes. Now it is stated that a gene has smaller divisions. It was discovered by the American genetics S. Benzer. He studied a fine structure of E.coli T4 bacteriophage genes. The gene can be divided into many parts while crossing-over. Later, the same gene structure for eukaryotes was determined. The minimal unit of mutation is muton; the minimal unit of recombination is recon. The minimal size of them is one nucleotide pair.

Until 70s years of the 20th century, it was believed that a gene consists of unseparated DNA region (Fig. 5.1). In 1977 it was shown that some adenovirus genes exist in the form of fragments instead of unseparated

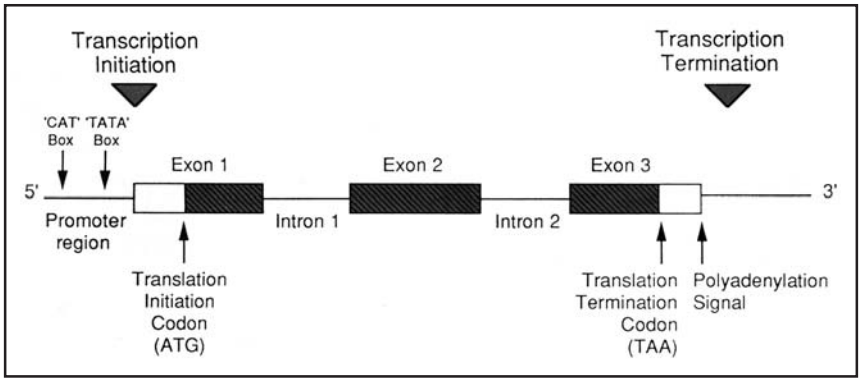


Fig. 5.1. Structure of eucaryotic gene (by Robert F. Mueller et al.).

DNA region. These fragments may be exons (having useful information) and introns (without it). Introns are removed during gene expression (process of genetic information realization). Then, exons are bounded together by their ends. Such removing of unuseful information was named gene splicing (Fig. 5.2). It is performed with the help of special enzymes – revertases. In the beginning, this event seemed to be ridiculous, but later it appeared to be wide spread, especially in birds and mammalians. For example, the gene of human globulin contains three exons and two introns; the gene of stable region of a heavy chain of human immunoglobulin contains 4 exons and 4 introns. So it is said, that a gene has a intron-exon structure. The intron-exon gene nucleotide sequence firstly is copied to pro-mRNA molecule. It is a precursor of mature mRNA. Then, pro-mRNA is subject to gradually processing and splicing. And only after that it is ready to further transcription. The explanation for introns being is not still cleared. It is possible that exons will be bonded by different ways during splicing to form new proteins. Also it may be that introns serve as a material for new genes development

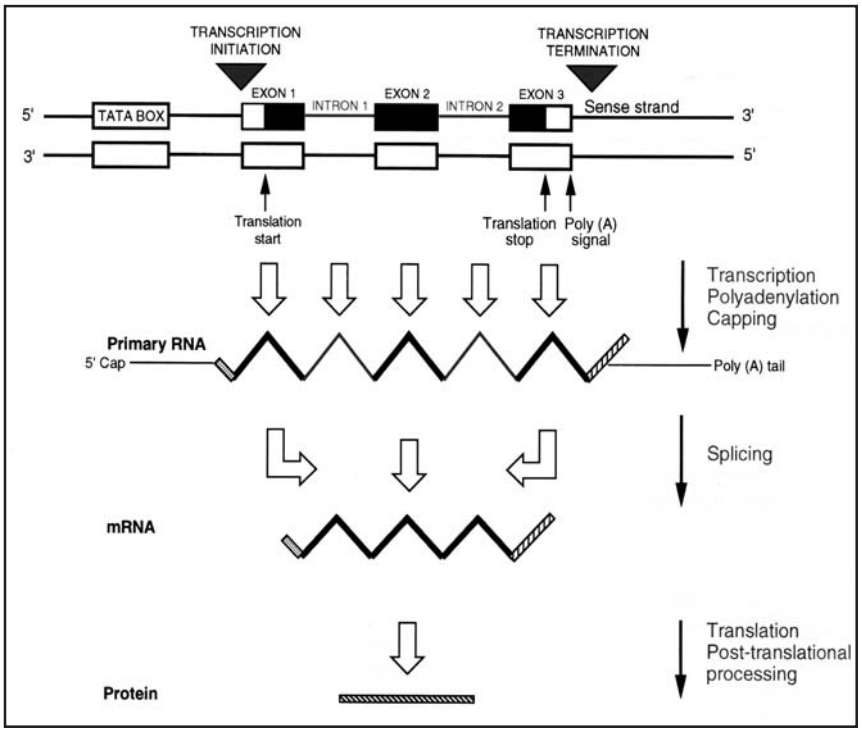


Fig. 5.2. Proceccing and splicing at mRNA synthesis (by Robert F. Mueller et al.).

during an evolution. It was shown that intron mutations might break a splicing process, terminate protein biosynthesis and change a protein structure. The term "gene" was firstly used for pointing some hereditary intends to form some phenotypic traits. In 1944 J. Beadle and A. Tatum proposed the hypothesis: one gene - one enzyme. Their idea has been modified. Many proteins are composed of several kinds of polypeptide chains, each specified by a separate gene. The modern restatement of Beadle and Tatum proposal would be that one gene specifies one polypeptide. The DNA molecule may perform several functions. It has nucleotide sequences not only having hereditary information but also controlling gene expression and replication.

5.3. THE GENE EXPRESSION AND REPRESSION

The genetic mechanisms of gene expression were studied by the French scientists F. Jacob and J. Monod in 1961. The main statement of their discovery is that genes may be of two kinds. The first one is a structural gene which encodes information about macromolecules made by a cell. Second is a regulatory gene which does not encode polypeptide chain, but they regulate the worke of structural genes with the help of different proteins attached to them.

Operon is a cluster of functionally related genes transcribed onto a single mRNA molecule in a bacterial cell. It consists of structural genes and regulatory genes related to them. It represents a regulatory unit of gene expression. The structure and functioning of operons were studied on example of lac-operon of E. coli (Fig. 5.3). This operon is responsible for a synthesis of protein that bacteria use to obtain energy from the sugar lactose. Operon starts from a CAP site. It is a site for CAP-protein binding. CAP is

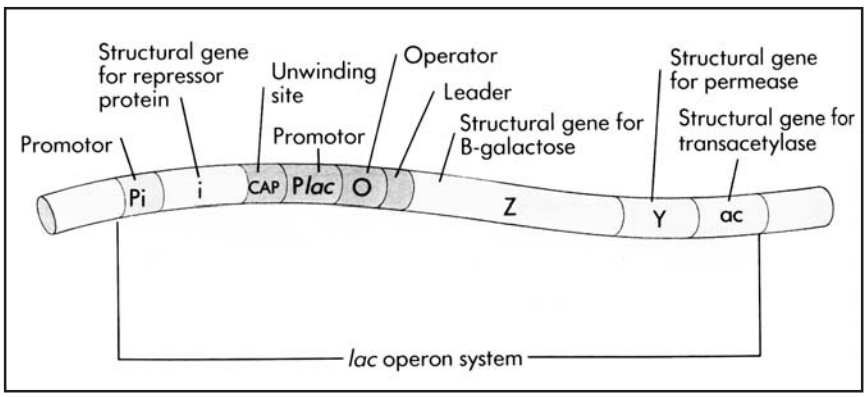
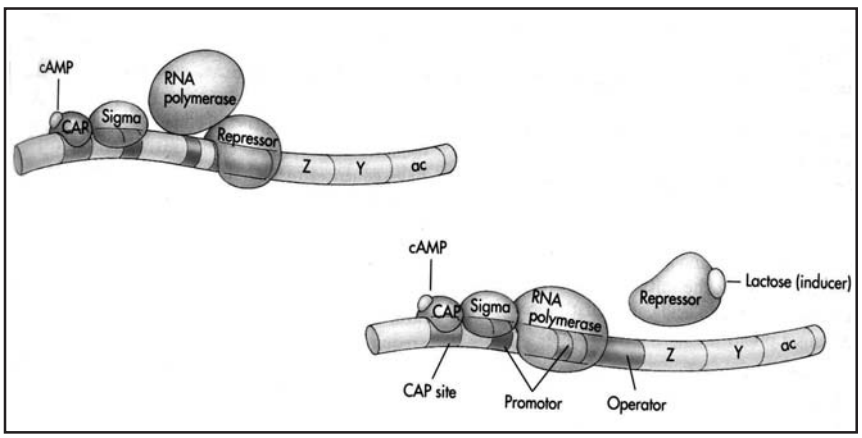


Fig. 5.3. Structure of lac operon system (by Raven & Jones).

an activator protein which facilitates the unwinding of DNA duplex and so enables the polymerase to bind the nearby promotor. Next to a CAP site is a promotor. The promotor is nucleotide sequence recognizable by RNA polymerase. RNA polymerase binds the promotor and then moves along the operon transcribing it. Next to a promotor there is an operator consistsing of 21 nucleotide pairs. It is a place for repressor protein binding, which may suppress transcription. Next is a group of structural proteins. Operon is terminated by the terminator. It is a short DNA region which works as a stop signal for transcription.

The main regulation of lac-operon operation is performed by a repressor protein which is encoded by the regulator gene (Fig. 5.4). This protein is continuously synthezied in a cell in a very small amount. There are no more than 10 molecules of such protein in cytoplasm at the same time. This protein may bind the operator site of operon. Binding the repressor protein to the operator prevents binding of the polymerase to the promotor and so blocks the transcription of structural genes of the operon. The synthesis of encoded enzymes fails. During lactose incoming the repressor protein binds lactose and it changes its structure. The repressor protein fails to bind an operator site. Lactose works as an effector (a small substance that changes protein properties while binding with it). When an operator is liberated from repression, RNA polymerase may move along gene transcribing it. This produces all enzymes nessesery to lactose proceeding. That means a gene induction. The regulation of lac-operon is performed by repressor protein binding to an operator which represses transcription. Induction occurs only when an operator is free from repressive protein. This regulation type is called negative protein synthesis induction.



Fig, 5.4. Work of lac-operon system (by Raven & Jones).

A negative repression has a similar mechanism. The negative repression is a repressor protein binding to an operator which suppresses transcription. During negative induction an effector breaks repressor protein binding to an operator, whereas during negative repression an effector enables repressor protein to bind an operator. An example of a negative repression is the work of E.coli operon which is responsible for tryptophan synthesis. The regulator gene which is not a part of a tryptophan operon, always makes a repressor protein. It needs if a cell uses all tryptophan, repressor protein does not bind operator site. But if there is an excess of tryptophan in a cell, tryptophan binds repressor protein modifying it structure. Modified protein enables to bind an operator and suppress transcription of structural genes. Thus the tryptophan synthesis is terminated.

There is also a positive regulation of protein synthesis. The regulatory gene product activates an operon transcription instead of repressing it. We may see this way of gene regulation in catabolic E.coli operon which is responsible for producing enzymes for the arabinose sugar usage. The regulator gene produces a repressor protein, which binds with operon and activates its transcription. The arabinose is the effector.

During a positive repression, the regulatory protein, encoded by a regulator gene and activating operon transcription, fully or partially is suppressed by effector. This scheme may be useful for explaining tryptophan synthesis operon working in E.coli.

The eukaryotes gene regulation has been studied less than prokaryotes gene regulation. It is due to a complex gene structure, gene placing in chromosomes, nucleus having and cell differentiation. But it is possible that mechanisms of eukaryote gene regulation are similar to prokaryote one. But they have significant differences. *First*, almost all eukaryotic genes contain only one structural gene, instead of several structural genes in bacterial operon. *Second*, in eukaryotes the genes which are responsible for different steps of one biochemical pathway, are spread throughout genome. Bacteria generally have them localized in one operon. *Third*, eukaryotes have a simultaneous group genes supression in a whole nucleus, in whole chromosome or in significant region of it. It is mostly performed by histon proteins, which are structural components of chromosomes. An example of it is a full total repression of gene activity during spermatogenesis. *Fourth*, the gene expression of eukaryotes may be regulated by steroid hormones. The target cells have special receptor proteins. These receptors are encoded by testicular feminization gene of X-chromosome. The receptor binding to a hormone forms the complex which activates expression of a definite gene. *Fifth*, eukaryotes genes may change their activity in course of ontogenesis.

The example of different gene expression in ontogenesis is a genetic control of human hemoglobin synthesis (Table 5.1). It is known that hemoglobin molecule contains four polypeptide chains: two identical б -chains and two identical в-chains. The adult hemoglobin (Hb^A) differe from embryo hemoglobin (Hb^F). The differences are related with в-chains. In embryo hemoglobin there is no в-chain. It is replaced by г-chain. In an adult blood we may find an Hb^{A2} in small amount. The в-chain in this hemoglobin is replaced by sigma-chain. All three types of normal human hemoglobins (Hb^A, Hb^{A2}, Hb^F) are encoded by separate locuses. The locus $в^A$ is responsible for в-chain synthesis. It is active throughout all life. The locus $в^A$ is responsible for polypeptide chains synthesis in Hb^A. It becomes activated only after birth. The locus $г^F$ is responsible for polypeptide chains synthesis in Hb^F. It works actively in course of embryonic development. The locus a^{A2} is responsible for polypeptide chains synthesis in Hb^{A2}. It is active throughout the life after birth.

Table 5.1. **Characteristic of human hemoglobins**

Kinds of Нв	Polypeptide chains	Gene locuses
НвА	2α, 2β	α^A, β^A
$НвА_2$	2α, 2σ	α^A, σ^{A2}
НвF	2α, 2γ	α^A, γ^F

Each of hemoglobin genes is a structural gene because it is responsible for a primary structure of a polypeptide chain.

We see different kinds of hemoglobins that arise from different gene combinations. It is clear that structural genes operation is under supervision of regulatory genes. It becomes evident from the fact of Hb^F exchange to Hb^A after birth. Here we see the function of special gene - “switch gene” which suppresses activity of $г^F$ gene and activate $в^A$ gene. As a result of this, embryo hemoglobin is exchanged to an adult one. We may suppose that this simultaneous switching of a gene activity may be due to an action of a gene operator of both $в^A$ and a^{A2}genes.

5.4. DNA REPARATION

Some damage of DNA may occur due to an action of different agents or during protein biosynthesis. Many of those damages are corrected by special reparative enzymes. Reparation is a process of restoring a natural

DNA structure which has been damaged during a protein biosynthesis or due to harmful influences of external agents, having presented in all organism cells. The reparation process is based on the fact that a DNA molecule contains two complementary chains. So if one of them has been damaged, it may be repaired corresponding to the other chain.

The DNA reparation was discovered in bacteria exposed to ultraviolet radiation. The pyrimidine bases in DNA adsorb ultraviolet radiation. This changes the structure of these bases. Now they are able to make a covalent bond between two pyrimidine bases placed together on one strand. The resulting cross-link between adjacent bases of the DNA strand is called a pyrimidine dimer. It was shown that cells exposed to ultraviolet radiation survive better in the light than in darkness. It was stated that here photoreactivation or light reparation occured. The pyrimidine dimers are replaced by special enzyme which activated by action of a visible light.

Later it was found that cells may replace damaged regions of DNA without a visible light (dark reparation). We may observe dark reparation when a cell is recovered from ionizing radiation, chemical impact or from other factors (Fig. 5.5). It has several stages involving various enzymes. The first enzyme (endonuclease) recognizes a damaged region and cuts a DNA strand around it. The second enzyme (endo- or exonuclease) makes a second cut on a DNA strand. The third enzyme cuts off damaged nucleotides. The fourth enzyme (DNA polymerase) makes a new strand of DNA corresponding to an undamaged one. The fifth enzyme (ligase) connects the ends of DNA strands.

The postreplicative reparation is performed by recombination (fragments exchange) between two newly made DNA molecules. It is useful when pyrimidine dimers have not been removed by light reparation.

If the reparation cannot successfully repair a high number of DNA defects, the cell blocks DNA replication to prevent defects transmission to next cell generation.

Combined actions of replication and reparation enzymes ensure a small level of DNA molecule mistakes.

5.5. THE STATEMENTS OF GENE THEORY

The findings listed above allow formulating the gene theory. Its statements are the following.

1. The gene has a definite locus in chromosome.
2. The gene is a part of genomic nucleic acid. The number of nucleotides in genes is not the same.
3. Mutation and recombination takes place inside a gene.

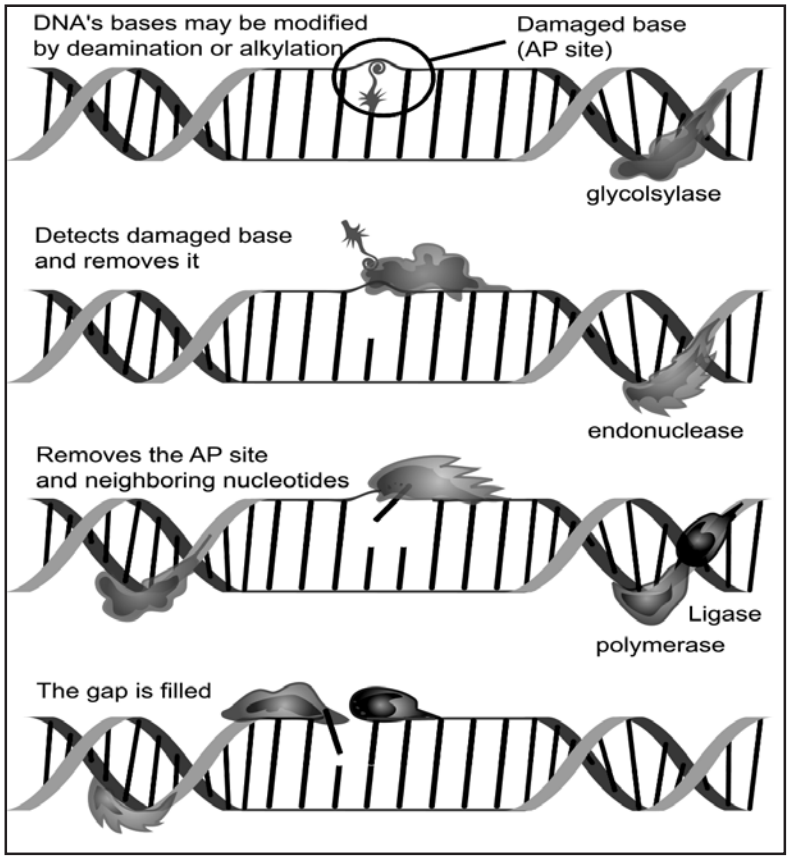


Fig. 5.5. Dark reparation of DNA (by Raven & Jones).

4. There are structural and regulatory genes.

5. The structural genes encode the macromolecules structure (such as proteins, tRNA, rRNA).

6. The functional genes control the structural genes activity.

7. The triplet's line in a gene corresponds with amino acids line in polypeptide.

8. Genes are able to reparation.

9. The genotype being discrete acts as an integrated unit.

5.6. THE GENETIC ENGINEERING

The genetic engineering has an application in practical field among all molecular genetics branches. The genetic engineering is a complex of methods for delivering genes from one organism to another or it is a technology of directed construction of new biological organisms. The genetic engineering includes following operations: gene synthesis outside an organism, cleavage of genes and genetic structures, directed gene recombination, copying and reproducing of obtained or newly synthesized gene, transport and insertion of such genes into genome subjected to modification, experimental composition of genes in one cell.

We need to insert an appropriate gene (or group of genes) and to obtain functioning of this gene in particular cells to give to an organism a new hereditary property. So we need to set it to a regulatory system. To solve this task, the process may be divided into three stages: 1) obtaining genetic material (genes); 2) inserting genetic material to a new organism; 3) setting of inserted genes to a genetic cell apparatus and their fixation in it.

The obtaining genetic material. The genetic material may be obtained by a gene cleavage from donor cells or by its synthesis. We may get genes in chemical reactions or from rRNA using reverse transcriptase. Bacteria have genetic information stored in a big circular DNA molecule and in small circular DNA fragments containing just several genes. These small fragments are called plasmids. The use of plasmids gave a strong impact to a genetic engineering development. We may get a gene by different ways, but commonly we use special enzymes such as restriction endonucleases and ligases. The restriction endonucleases are molecular for a fragment to be cut. The ligases are sealing enzymes. They can join cut strands back together. So they may use these enzymes for DNA fragments elongation, DNA regions removing.

The inserting genetic material to a new organism. We may use transformation, transduction, conjugation and somatic cells hybridization for this purpose.

The transformation means changing of a hereditary material by penetrating in it of a foreign DNA fragment. It is a one of ways of genetic information exchange in prokaryotes. It was firstly observed by F. Griffit in 1928 (Fig. 5.6). In a transformation the inserted DNA fragments will be transmitted to all offsprings of next generations.

The transduction is a way of transmitting genetic material from one bacterial cell (donor) to another (recipient) by using moderate bacteriophage. It was discovered by J. Lederberg and N. Cinder in 1952 while analyzing a changing in genetic material in some bacteria (shigells, salmonells, etc.).

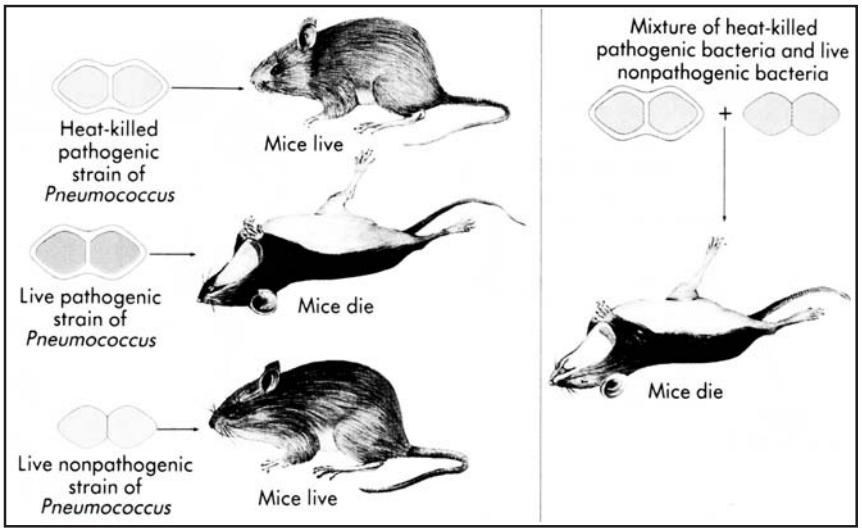


Fig. 5.6. Griffits experience by finding of transformation in bacteries (by Raven & Jones).

When the bacteriophag being induced, the small part of bacterial DNA incorporates to a bacteriophag genome (Fig. 5.7). Bacteriophag carrying bacterial DNA is called a transducting bacteriophag. When a new cell is infected by such bacteriophag, the DNA region inserts to a cell genome. It is natural and wide spread between a bacteria process of getting genetic recombination. It is widely used in genetic engineering of bacteria.

The conjugation is a process of genetic information exchange in bacteria during a contact period. Information is transmitted from a donor ("male" cell) to a recipient ("female" cell). The conjugation is regulated by F-plasmids (fertility factors). One having F-plasmid is considered as a donor. Another bacteria without F-plasmid is considered as a recipient. The size of exchanged material is determined by the time of contact. As result of this, we have a cell with its own chromosome and with fragment of another one. This cell has a recombination of these genes. The cell stays unchanged from which material has been taken. Its genetic material is restored by DNA reduplication.

The setting of inserted genes to a genetic cell apparatus. The genes inserted to foreign cells cannot be reproduced. Such structures are called vectors. It is the main device for all genetic manipulations. It is a structure which is able to bring a another gene to a cell and to provide gene replication in a new cell. Plasmids, bacteriaphages, viruses and cosmids are widely

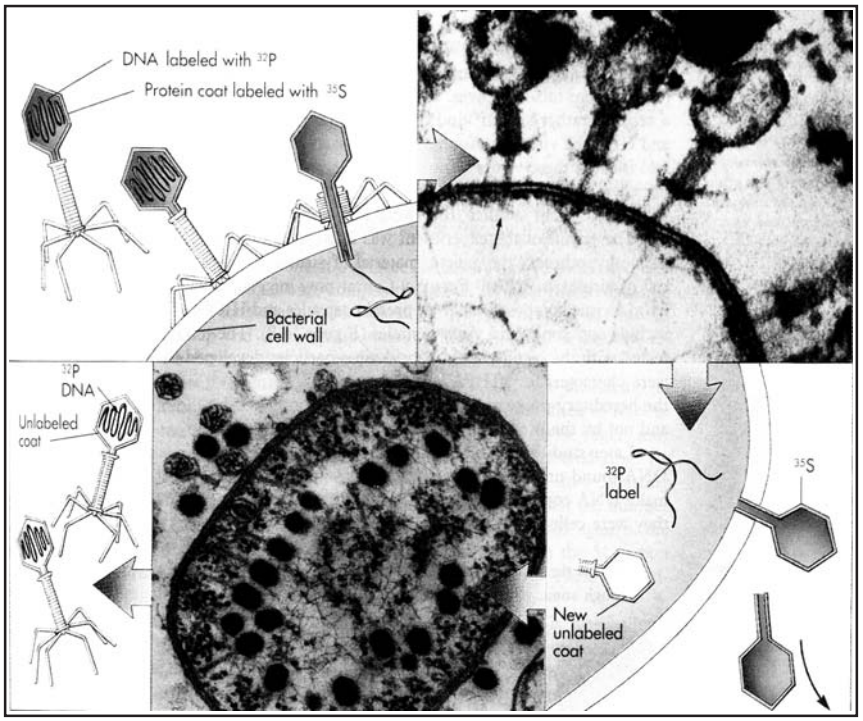


Fig. 5.7. Transduction in bacteries with bacteriophages use (by Raven & Jones).

used as vectors. Cosmids are vectors obtained by bacteriophag and plasmid fragment fusing. Plasmids are vectors which are independent from the main DNA molecule. They may be reproduced by themselves (Fig. 5.8). We may get vectors with 35-40 nucleotide length of insertion by using plasmids. Different viruses are used as vectors for animals and human.

The development of genetic engineering has facilitated in discovering many fundamental biological problems such as a mosaic gene structure, decoding of a gene structure, a chemical gene synthesis and so on. The genetic engineering is a theoretical base for biotechnology. It is a directed production of necessary products and materials by using biological objects and processes. The biotechnology is used for microbiological production of vaccines and serums (Fig. 5.9); synthesis of hormones, vitamins, enzymes; diagnostics of human genetic defects on early stages of embryo development; genetic surgery (replacement of a damaged gene by a normal one).

According to the WHO the definition of "Genetically modified organisms (GMOs) are organisms (plants, animals or microorganisms), whose genetic

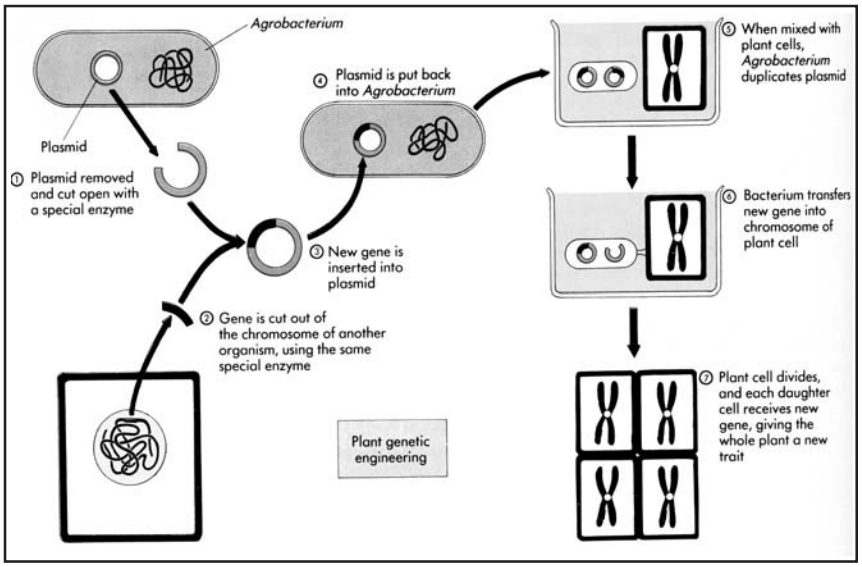


Fig. 5.8. Process of agrodacteria construction with methods of genetic engineering use (by Raven & Jones).

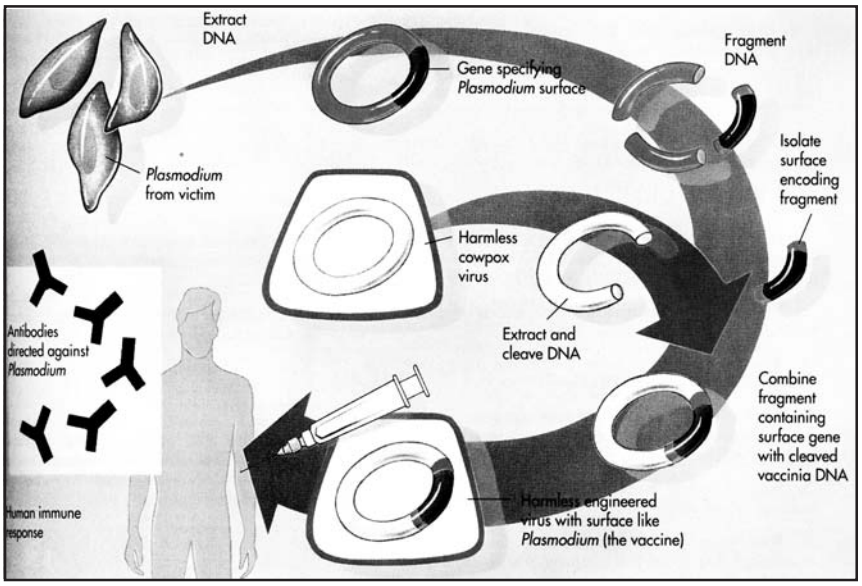


Fig. 5.9. Process of malaria vaccine construction with methods of genetic engineering use (by Raven & Jones).

material (DNA) has been altered. Such changes would have been impossible in nature as a result of breeding or natural recombination". Genetically modified product (GMO) is a food whose raw material and other derivatives were prepared from genetically modified organisms or GMO. Food and Agriculture Organization of the United Nations (FAO) whose work is aimed at solving the problem of hunger in the world, the question of creation of transgenic varieties of plants or other organisms as an integral part of agricultural biotechnology. Direct transfer of genes for useful traits is a natural extension of work on animal and plant breeding, breeders have expanded opportunities in terms of handling the process of creating new varieties and expand its capabilities, in particular the transfer of useful traits between non-interbreeding species, transgenic soybeans, corn, cotton and others. The cheaper culture is more productive in the cultivation in some cases.

The main stages of GMO creating: obtaining isolated gene; introduction of a gene into the vector for transfer into the organism; gene transfer vector in a modifiable organism; transformation of cells of an organism; selection of genetically modified organisms and the elimination of those that were not successfully modified.

2,833 permits were granted in 36 countries for the use of genetically modified crops in 2013. The total market allowed 27 genetically modified crops (336 varieties). The main crops are soybeans, corn, cotton and potatoes. Genetically modified crops occupied overwhelming majority of areas. It is culture with resistant to herbicides, insect pests or acculturations with combinations of these properties. WHO finds it impossible to approve of the danger or safety of GMF, but offers to carry out a separate assessment in each case, as different GMO contain different genes. WHO proved to the absence of high-risk products from GMO in comparison with products derived from organisms derived by conventional methods. As a result of 130 research projects in North America and Europe for over 25 years and carried out with the participation of more than 500 independent research groups have shown that GMOs are no longer dangerous to humans than organisms obtained using traditional plant breeding techniques.

5.7. THE BIOETHICAL ASPECTS OF GENETIC ENGINEERING

The European Committee of genetic engineering recommends to supervise all experiments of DNA recombination by genetic engineering council of state, where such experiments take place. Such recommendation was made for canceling experiments, which might be harmful for humankind

or environment. Most of the experiments connected with human genetic material cloning must be prohibited. The works in producing of chimeras and hybrids using animal or human genetic material must be banned. Only somatic cells may be used for therapeutic aims. The use of sex cells for genetic therapy will be possible, when advantages of such treatment over somatic cells genetic therapy will be proved.

CHAPTER 6. CHROMOSOME AND GENOME LEVELS OF HEREDITARY MATERIAL ORGANIZATION IN PROKARYOTES AND EUKARYOTES

Chromosomes play an important role in inheretance. Sex determination groups of genes, genetic and cytological chromosome mapping was proved by discovering chromosome. These facts were summarized in chromosome theory of inheritance.

The chromosome level of hereditary material organization is characterized by a chromosome structure. The chromosome of non cellular live forms is presented in a form of a naked DNA chain (or RNA chain in some viruses). The chromosome of the prokaryotes is a naked circular DNA molecule. The chromosome of the eukaryotes is a complex of DNA with histone proteins.

6.1. THE SEX GENETICS

A large contribution to sex genetics study was made by the American scientist C. Mac-Klang in 1901-1902. He proved that X-chromosome determines the sex of the Protentor bug. In 1959, female organisms with the chromosome set ‘’XO” were discovered. It was concluded that the Y-chromosome determine a male sex.

The organism containing same sex chromosomes is called homogametic. The organism containing different sex chromosomes is called heterogametic. The sex of a future child depends on a sex chromosome combination in the zygote (Fig. 6.1). There are four variants of chromosome sex determination in animals by female homogamete or heterogamete. The female homogameting may have following variants: XX, XY (in mammalian and human) and XX, XO (in bugs). The female heterogameting may have following variants: ZW, ZZ (in butterflies) and ZO, ZZ (in birds). The sex is determined by a heterogametic organism.

But a sex may be determined by a chromosome balance, so called “sex index”. The balance sex theory was suggested by K. Bridgess and R. Goldshtein in 1911. They noted that male and female sex of Drosophilla

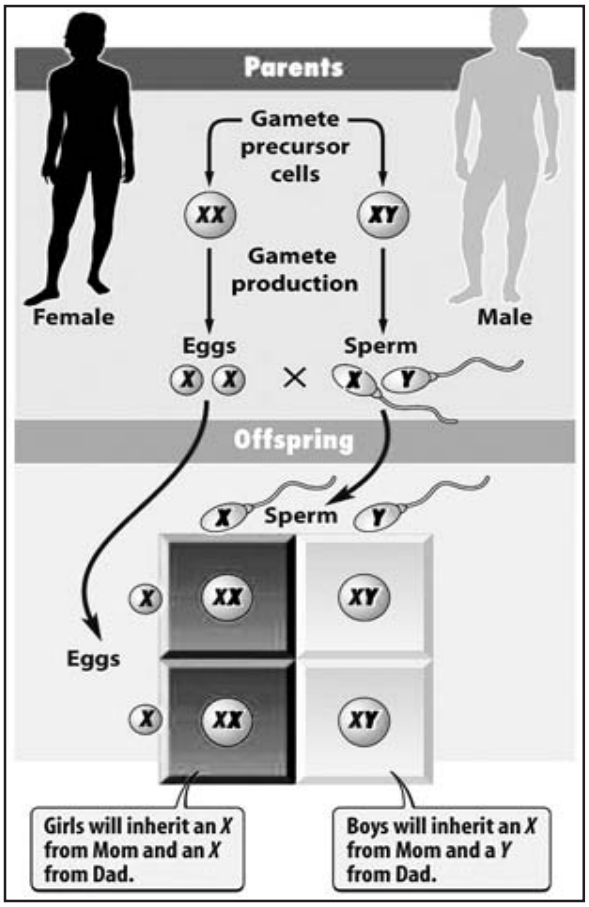


Fig. 6.1. Inheritance of sex in human (by W.W. Norton et al.).

is determined by the ratio of sex chromosomes to autosomes, instead of the sex chromosomes combination. The genes of a female organism are mostly located in X-chromosomes, whereas male organism genes are mostly located in autosomes. If the ratio is X:A=1, it is a female organism. If the ratio is X:2A=0.5, it is a male organism. In case of an intermediate ratio (from 1 to 0.5), it is an intersex organism. The increased ratio (3X:2A= 1.5) leads to overmatured female formation. The decreased ratio (X:3A=0.33) leads to overmatured male formation.

The balance sex theory may be applied for a human. The normal female sex chromosomes to autosomes balance is XX:44A. If such balance is

XO:44A which is observed in patients with Shereshevsky-Terner syndrome, then the underdevelopment of ovarium, uterus tubes, uterus is observed. The secondary sex characters are underdeveloped if patients have three X-chromosomes (XXX:44A). Normal male sex chromosomes to autosomes balance is XY:44A. The patients with Kleinfelter syndrome (XXY:44A) have unexpressed secondary sex characters, gynecomasty and failed spermatogenesis is observed.

In 1949, M. Barr and G. Bertram showed that female nervous cells have a body of well stained chromatin in a nucleus which male nervous cells do not have. This structure was named Barr's body or sex chromatin. The Barr's body is an inactivated X-chromosome. During first 16 days of embryo development two X-chromosomes work very actively in each female cell, producing a double number of products encoded in X-chromosome. This fact is used to explain the higher survival rate of female's embryo.

The inactivation of one X-chromosome takes place between 10-19 days of embryonic development. Once inactivated X-chromosome preserve such a structure in a line of somatic cells generations.

The traits which are controlled by genes of sex chromosomes are called sex-linked genes. Sex linkage was demonstrated by T. Morgan on an example of eye color heredity in a Drosophila melanogaster. The trait transmission was stated from a father to daughters and from a mother to sons. More than 60 human genetic sex-linked diseases have been identified. Most of them are recessive. Genes, which are in sex chromosomes, may be divided into 3 groups.

Genes which are in homologues regions of sex chromosomes, were named partially sex-linked. There are diseases connected with partially sex linked genes. They are total colorless blindness, pigment xeroderm and others.

Genes which are in X-chromosome region for which the non-homologues is absent in Y-chromosome were named fully sex-linked. There are diseases connected with fully sex-linked genes. They are muscular Dushene dystrophy, hemophilia and others.

Genes which are in Y-chromosome region for which the non-homologues is absent in to X-chromosome were named holandric genes. There are diseases connected with holandric genes. They are hypertrichosis of ear, ichtiosis, syndactilia and others.

6.2. THE GENE LINKAGE. THE MORGAN'S RULE

We may conclude from the principles of genetic analysis that independent

trait combinations may occur only if genes responsible for such traits are on different chromosome pairs. Every organism has a limited gene group numbers for independent assortment. This number is limited by a chromosome number. On the other hand, it is evident that organism's traits are very numerous, but the chromosome number is limited and small.

So we may conclude that each chromosome has many genes. If it is correct, we may state that a third Mendel's rule (of independent inheritance) relateы only to chromosome number. Studying traits combinations according to the third rule, Morgan discovered that in some cases there were no new combinations between genes. That means it was a full gene linkage. He obtained the ratio 1:1. In some other cases he obtained a ratios different from a classical Mendel's ratio. So he suggested calling this gene heredity, limiting independent inheritance, as gene linkage. The studies of Morgan's researching group showed that there is regular gene exchange between homologous chromosomes. The process of gene exchange is called crossing-over. It occurs in meiosis during sex cell formation. It provides a combinations of genes, which are localized in one chromosome. The cells of animals, plants and bacteria have crossing-over. The exceptions are drosophila males and silkworms females.

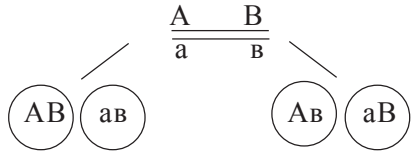
Crossing-over provides gene recombination and by this it increases an evolutionary role of combinative diversity. We may find crossing-over analyzing postbreeding traits combination. When genes are in different chromosome pairs, we may write diheterozygote genotype as

$$\frac{A}{a} \quad \frac{B}{b}$$

When genes are in the same pair of homologues chromosomes, we may write genotype as:

$$\frac{A \quad B}{a \quad b}$$

The gametes, which were subject to crossing-over, are called crossoved gametes, and those not exposed to crossing-over are called non-crossoved



non-crossoved gametes crossoved gametes

gametes.

Organisms from crossover gametes are called crossover organisms.

Organisms, from noncrossover gametes are called non-crossover or non-recombinant organisms. We can confirm a previous statement in Morgan's classic experiment demonstrating the chromosomes of gene linkage in Drosophila. Morgan's examined such traits as body color and wing length which are localized in one chromosome.

Assumed all of this T. Morgan formulated the thesis: genes which are located in one chromosome are linked, and the strength of linkage is more when distance between genes is less. This rule was named Morgan's rule. We may list some examples of human gene linkage.

Gene linkage of A, B, C, D/DR loci of HLA system responsible for histocompatibility antigen synthesis in the 6th chromosome. Gene linkage of ABO blood group genes and genes of nail defects in one chromosome. Gene linkage of Rh-factor gene and gene responsible for oval erythrocyte shape. Gene linkage in 3rd chromosome locus of Lutheran blood group and locus which has genes responsible for A and B antigens excretion with saliva. Gene linkage of polydactyl genes and cataract genes. X-chromosome gene linkage of hemophilia genes and color-blindness genes: and also color-blindness genes and muscular Duchene dystrophy.

Morgan suggested that a distance between genes is related with crossing-over percentage between them. One unit of gene distance was defined as 1% of crossing-over between genes and was called one centimorgan. To measure gene distance in testcross we may use the following formula.

$$X = \frac{a + в}{n} \cdot 100,$$

Where X - is a distance between genes, a - is a number of individuals in first crossoved group, b - is a number of individuals of second crossoved group, n - total hybrids number, 100 is a coefficient for percentage measurement.

6.3. THE CHROMOSOME MAPS

The distance between genes corresponds to the crossing-over percentage. Correctness of these considerations can be checked by determining the frequency of crossing between genes A and B and independently of it between B and C genes (Fig. 6.2). So if we have a distance between A and B in 10% and a distance between A and C is 3% of crossing-over we may conclude that the gene is either between genes A and B or in opposite side (gene A is between B and C). So if the distance between B and C is 7% of crossing-over that means that genes are in the range A, B, C. So if the distance between B and C is 13% of crossing-over, that means the genes are in the range C, A, B. Chromosome gene

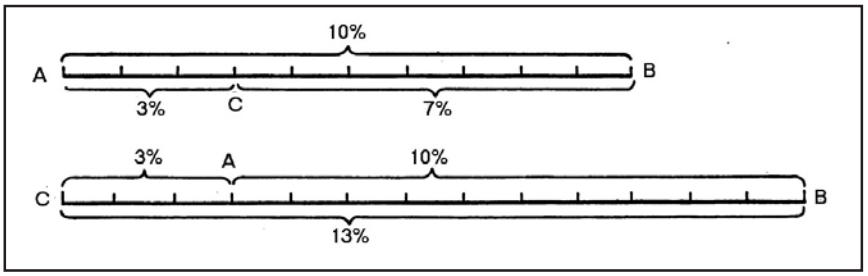


Fig. 6.2. Scheme of genetic map construction.

localization is linear and distance between them is related with crossing-over frequency. But this thesis is typical only for closely placed genes. For genes which are far from each other that rule appears to have some imperfections. Genes which placed in one chromosome are linked and they make one linkage group. The number of linkage groups is equal to haploid chromosome set.

Frequencies with which crossing-over occurs in crosses can be used to construct a genetic map in which distance is measured in terms of frequency of recombination. The genetic map is a conditional line with pointed genes according with relative distance in centimorgans. Some organisms which were studied more actively than others, have genetic maps of all chromosomes (drosophila, corn, human).

Having determined a linear chromosome discontinuity, scientists faced the necessity to make a cytological map and to compare them with genetic maps (Fig. 6.3). The cytological map is a chromosome map, where a gene localization and a gene distance is defined in chromosome. The construction of cytological maps is based on chromosome aberration analysis (translocatons) and differentiated staining of chromosomes. Scintiests have made and compared cytological maps of some mammalian. All 23 human chromosomes have been mapped for today.

6.4. THE STATEMENTS OF CHROMOSOME THEORY OF INHERITANCE

Assuming all above, we may formulate the base points of chromosome theory of inheritance.

1. Genes are in chromosomes. Each chromosome is a gene linkage group. The number of linkage groups is equal to the haploid chromosome set.

2. Each gene has a definite locus in chromosome. There is a linear gene

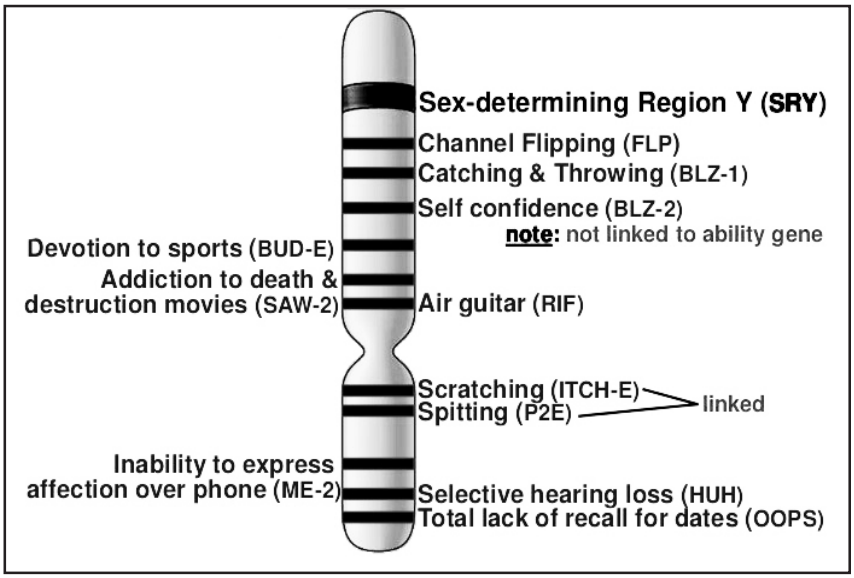


Fig. 6.3. Cytology map of Y chromosome in human (by Raven & Jones).

arrangement in chromosomes.

3. There is a allele gene exchange between homologues chromosomes.

4. The distance between genes is closely related with crossing-over percentage between them.

6.5. THE GENOME LEVEL OF HEREDITARY MATERIAL ORGANIZATION

The organization of hereditary material presented by nucleic acids and the principles of genetic information coding in prokaryotes and eukaryotes shows the similar origin of them.

The genome is an assemblage of all haploid chromosome set genes of definite species. The genome level of hereditary material organization has specific features in prokaryotes and eukaryotes.

The virus genomic nucleic acid consists only of structural genes, in the bacteria genome most of the genes are unique. That means they are in chromosome only in singular number. Only exclusion is genes which encode rRNA and tRNA. These genes are repeated in bacterial genome several times. It is interesting to note a discrepancy between nucleotide number and gene number in bacteria genome. It was stated that DNA of E. coli contain 3.8 millions of nucleotide pairs. At the same time it was found

around 1,000 structural genes in E. coli. Such genes contain only about l.5 millions of nucleotide pairs. It is clear that the only way to suggest that the rest of nucleotides DNA are in regions which function is not clear. The DNA spiralization in prokaryotes is less than in eukaryotes.

The eukaryotes genome has a more complicated organization. It contains larger numbers of genes, and larger amounts of DNA in chromosomes. It has a complicated gene activity controlling system which relates to differentiation of cells and tissue in ontogenesis. The more evolutionary complicated organism is the larger amount of DNA it contains. Eukaryotes also have excessive genes. More than half of the genome consists of unique genes, which are not repeated. The calf has 55% of such unique genes, a human - 64%, drosophila - 70%.

The nucleus of each human somatic cell consists of 23 pairs of chromosomes: each chromosome has one DNA molecule. The length of all 46 molecules in a human cell is almost 2 m, the number of base pairs is 6.4 billion, sufficient to form 4 mln of structural genes. But the genome of a human consists of 35 thousand of structural genes (i.e. 100 times less than it could be encoded by the genome).

Redundancy of genome (C-value) is no correlation between the physical size and complexity of the genome of organisms. The amount of DNA in the haploid genome is indicated by the Latin symbol C, since it is constant within a species of organisms. In 1978, T. Cavalier-Smith said that a small part of genome sequences of nucleotides are transcribed in eukaryotes (3% of the genome in human). Such considerable redundancy of noncoding nucleotide sequences and the variability of DNA amount in close species are named C-value. It is assumed that the redundancy of the genome is the genetic information extra protection against the damaging effects of chemical mutagens, particularly needed in multicellular organisms to prevent the accumulation of genetic load in dividing somatic cells during ontogenesis. Probably one of the ways to achieve this is inclusion into the genome of eukaryotic sequences redundant nucleotides. Perhaps among the excess nucleotide sequences are repressed in evolution of genes or expanding growth of probability of survival of organisms under changed environmental conditions.

In 1990, a special international program “Human Genome” (“Human Genome Project”) was established to study the human genome - one of the most daring, expensive and potency important projects in the history of civilization. To solve this problem the International Consortium was organized, bringing together 20 laboratories and hundreds of scientists around the world. The human genome consists of 6.4 billion nucleotide pairs, the

recording of which was deciphered in 2005. The program "Human Genome" was aimed at achieving the following main objectives:

- establishment of the human genome DNA structure, i.e., determining the sequence of nucleotides;
- locate all the genes of an organism and determine their functional significance.

As the result of the program "Human Genome" has been established that a human has 31,780 protein coding genes. It has been shown that a typical human gene consists of approximately 28,000 base pairs and has 8 exons, its coding sequence is 1340 base pairs to encode 447 amino acids. The number of encoding proteins genes in human genome was only 2-fold more the same genes in the genome of the worm, flies, plants. In general, the proportion of genes encoding proteins accounted for 2% of the genome; for regions coding the RNA - about 20% of genome, repetitive sequences occupy more than 50% of the genome. Scentists identified 320 genes of all common and 170 rare genetic disorders, 30 recessive and 100 dominant oncogenes. 1400 genes were separated involved in the development of hereditary diseases.

6.6. THE CYTOPLASMIC MATERIAL OF HEREDITY

The chromosome theory of inheritance states that main part of heredity information is in a nucleus, but it is also possible that part of information is in cytoplasmic organelles such as mitochondria and chloroplast. Such forms of hereditary are not directed by Mendel's Laws.

Plants and animals ova have cytoplasm which is rich in cell organelles, but sperm has very few organelles. So that means that traits which are encoded in cytoplasmic genes are inherited in mother line of pedigree. The first who described cytoplasmic inheritance were German genetics E.Baur and K.F.Correns. They described it on an example of variegated leaf inheritance in some plants.

All hereditary factors localized in cytoplasm are termed *plasmotype* or *plasmon*. The unit of cytoplasmic hereditary is called plasmogene. It was stated that plastids (plastids DNA) and mitochondria (mitochondrions DNA) have their own DNA. They are responsible for transmitting cytoplasmic hereditary information at reproduction.

Plastids are self-reproduced organelles of plant cells. They may be inherited by descends only through cytoplasm of mother organism cells. The genes responsible for respiratory enzymes synthesis were detected in yeast mitochondria. It has been shown that these genes are placed in circle DNA molecule of plasmids.

In bacterial cells there are three types of plasmids: containing the sex factor F, factor R and factor Col - colicinogenic.

The bacteria containing the F factor are male. They form cytoplasmic bridge toward female cells. Through that bridge, the factor is transmitted to a recipient cell during conjugation. That cell becomes male.

The R factor is responsible for bacteria tolerance to some antibiotics action. The plasmid with the R factor may be transmitted to other cell during conjugation and play an important role in changing bacteria hereditary properties. Colicinogenic plasmids contain special genes which encode special proteins – colicins. Such proteins may kill bacteria of same species without this factor. The material for cytoplasmic inheritance is genes of plasmids, mitochondria and some any still unknown factors.

The system of cellular genetic apparatus includes nucleus genome and cytoplasmic genome. The apparatus is discrete. This apparatus is presented by chromosomes and their genes in nucleus and by plasmogenes of organelles in the cytoplasm.

CHAPTER 7. THE PRINCIPLES OF TRAITES INHERITANCE DURING REALIZATION OF GENOTYPE TO PHENOTYPE

Heredity is the method of transmitting of hereditary information from generation to generation through gametes in sexual reproducing and through somatic cells during asexual reproducing.

If a trait expression is controlled by only one gene it is a monogenic inheritance. If a trait expression is controlled by several genes, it is a polygenic inheritance. Genes may be placed in autosomes or in sexual chromosomes. Accordingly, there are two variants of heredity - autosomal and linked with X-chromosome or Y-chromosome. Dominant and recessive inheritance can be distinguished based on the character of gene expression.

7.1. THE MONOGENIC INHERITANCE

Monogenic inheritance heredity of traits is controlled by one gene. The main principles of monogenic inheritance were discovered by G. Mendel due to his hybridologic method. The essence of such a method is in the following:

1. We need to conduct analysis of alternative, contrast trait pairs in several generations of parents having these contrast traits. In each generation, we need to count only definite trait pair ignoring other differences between crossed organisms.

2. We need to count hybrids in line of the following generation.

3. We need to use personal analysis of offspring for each hybrid organism.

The cross in which parents are analyzed by one alternative traits pair is called monohybrid cross, by two pairs – dihybrid cross and by many pairs – polyhybrid cross.

To write a scheme of cross is necessary to know some useful signs. The female organism is placed on the first place and the male is placed on a second. Crossing is pointed by the letter "x". Parents are put on the first line and are pointed as "P" generation. The gametes produced by parents are put in the second line. The offsprings are put in a third line. They are labeled as the F_1 generation. The index is used for representing a generation number. The hybrids of F_1 have only one trait expressed. The second one is suppressed. This is an essence of First Law of Heredity. It can be formulated as follows: in a cross between homozygous-dominant and homozygous-recessive individuals, all of the F_1 progeny will be heterozygous; they will all resemble the homozygous dominant parent in their phenotype. The First Law was also named as Law of Dominating.

After analyzing of F_2 generation hybrids Mendel formulated Second Law of Heredity or Law of Segregation: in crossing two heterozygous individuals analyzed by one alternative traits pair, we can predict phenotypic ratio 3:1 and genotypic ratio 1:2:1. The outcome of such cross can be illustrated by a Punnett square, suggested by the English geneticist R.C.Punnett.

To explain the results of 2nd Mendel's Law W.Batson suggested a thesis of "gametes purity". It can be formulated in this way: genes in gametes of hybrids are discrete (pure) and not blended. Such thesis and Mendel's Laws are the best illustration of philosophic categories of "cause and effect". The cause why traits are not blended is that genes for these traits are in different homologues chromosomes. These chromosomes in meiosis come to different gametes.

To analyze a genotype of individual with dominant phenotype, we can use testcross. This is because an individual with dominant phenotype may be either homozygous or heterozygous. In a testcross, analyzing individuals are crossed with homozygous recessive one. If all offspring are the same, it is a homozygous dominant individual. If a ratio among offsprings is 1:1, this is a heterozygous dominant individual.

Numerous traits have a phenotypic ratio in F_2 generation 3:1 in monohybrid crosses. To perform dihybrid cross, Mendel took homozygous organisms having two pairs of alternative traits. The hybrids of first generation look similar to their dominant parents. The independent assortment of different traits occurs in hybrids of F_2 generation. This

conclusion was named Third Law of Heredity. It states that genes located on different chromosomes assort independently of one another. To make the cross scheme easy to write, similar phenotypes sometimes are defined as phenotypic radical. It is dominant genes of an organism, which determines it phenotype. Under the Third Law it will be as follows: 9A-B-: 3A-bb: 3aaB-: laabb (Fig. 7.1).

Each trait pair gives a phenotypic ratio 3:1 in F_2 which is provided by independent assortment of homologues chromosomes in meiosis. In polyhybrid cross, the acquired ratio of hybrids in F_2 can be described with a formula (3+l) n, where "n" is a number of alternative traits pairs.

As every natural law, Mendel's laws may work only in definite conditions, which are:

1. The same probability of all kinds of gamete formation by all hybrids while monohybrids cross.
2. The same probability of all possible gametes combinations at fertilization.
3. The same survival rate of zygotes of any genotype.
4. Full trait expression independently from development conditions.

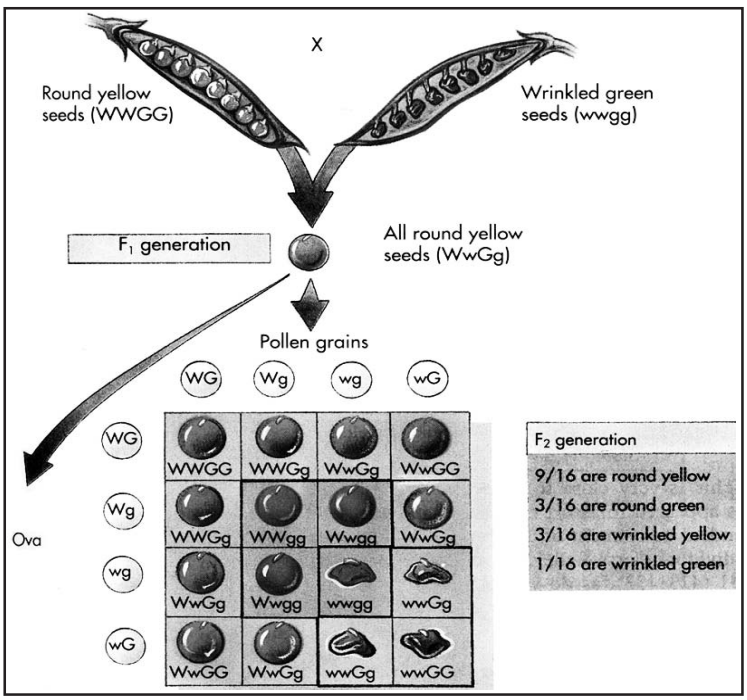


Fig. 7.1. Third law of G. Mendel.

5. Gene location in different chromosomes in dihybrid and polyhybrid crosses.

6. The same probability of all kinds of gamete formation on the basis of independent assortment of non homologous chromosomes in meiosis while dihybrid and polyhibryd cross.

As it was said above the main mechanism providing traits splitting in hybrid's generation is meiosis. It ensures independent assortment of chromosomes during a gametes formation. It means that splitting occurs in haploid gametes, on a level of genes and chromosomes, but it is analyzed in diploid organisms on a level of traits. These two moments are divided by a long period of time. During such a period many environmental factors may act on gametes and developing organisms. That is why some deviations may occur in real traits ratio. Conditions pointed above create an element of probability to such a ratio. We need to use several statistic methods to analyze it which allows proving inherited theoretical ratio principle or to deny it. One of them is X_2-method which can be used to determine whether this deviation is occasional or regular.

Analyzing patterns of heredity in a garden pea Mendel worked with several traits pairs. But a human has thousands of traits which comply with Mendel's Laws of Heredity. They are hair color, ear color, nose shape, teeth shape, finger shape. The definite knowledge of traits and their description are the aims of medical genetics. Many hereditary diseases are inherited according to Mendel's Laws of Heredity. Achondroplasia, diabetes melitus, albinism, pancreas fibrosis, syndactilia, glaucoma, hemophilia are among them. In 1970 the American geneticist V.MacQuisic was the first to publish a catalog of hereditary human traits. Since that, it has been updated. More than 4,000 hereditary human traits were known in 2000 year.

7.2. THE POLYGENIC INHERITANCE

All previously discussed types of gene relation were alternative traits. Such traits as weight, pigmentation level, etc., are hard to divide on phenotypic classes. They are often called quantitative traits. Each of them is formatted under the influence of several genes or polygenes. This event was named polygenic heredity or polymeria. Such genes are called polymeric genes. All polymeric genes act similarly in a trait development. For example, in corn and oats the seeds color is determined by several genes. The level of trait expression depends on a number of dominant polymeric genes that means on gene dose.

The human height is determined by interaction of three allelic gene pairs, using the principle of cumulative polymeria: A and a, B and b, C and

c. Individuals with genotype aabbcc have the smallest height (around 150 cm), but individuals with genotype AABBCC have the highest height (around 180 cm). Heterozygous height will depend on a dominant genes number.

There are four dominant genes P_1, P_2, P_3 and P_4 which are presented in double dose. They are responsible for the integuments pigmentation intensity. If all genes in a genotype are dominant, skin pigmentation is maximal similar to native Africans ($P_1P_1P_2P_2P_3P_3P_4P_4$). If all genes are recessive, skin pigmentation is minimal similar to European Caucasians ($p_1p_1p_2p_2p_3p_3p_4p_4$). Mulatto's pigmentation depends on a dominant genes number.

Polygenic heredities comply with following rules:

Variations of quantitative traits depend on a dominant genes number of polymeric genes.

The measurement of traits diversity is amplitude of traits variation. The limits of variation of quantitative traits are under a genetic control.

The amplitude of traits variation corresponds to polygenes number in species genotype. The more polygenes are in genotype, the larger amplitude of traits variation the species has.

7.3. THE GENETIC FACTORS VALUE IN PHENOTYPE FORMATION

The formation of phenotype is a complicated process which takes time. The phenotype is the observable expression of trait (affecting an individual's structure, physiology or behavior) that results of the biological activity of the DNA molecules. It is the realized expression of a genotype. Genes provide only a possibility of traits expression. It depends on genetic factors, environmental factors and individual development. That means that a formation of a phenotype is under direction of many factors.

Among genetic factors affecting a phenotype formation is interactions of allele genes (dominance, recession, incomplete dominance, codominance) and from non-allele genes (dominant and recessive epistasis, hypostasis, complementarity), from multiple alleles, a pleiotropic gene action, a gene dose.

The dominance is the interaction when one dominant allele (A) is expressed independently from other recessive alleles (a). Heterozygotes (Aa) phenotypicaly are the same as homozygotes (AA). This allele is dominant in a heterozygous organism. The example is eyes color inheritance. Heterozygous organisms have brown eyes. Brown eyes color is dominant, blue eyes is recessive.

The incomplete dominance occurs when a recessive allele is not fully suppressed. Some human and animal traits are subject to such a gene interaction. In incomplete dominance the heterozygous individuals express

neither dominated phenotype nor recessive phenotype. Heterozygous individuals express an intermediate phenotype with slight deviance to dominant or recessive one. The example of incomplete dominance in human is inheritance of anophtalmia (aa) and normal eyes development (AA). Heterozygous individuals (Aa) have small eye size. The similar examples are inheritance of sickle cell anemia, acatalasia (absence of catalase enzyme) and others.

Alleles of one gene may work together in a heterozygous organism. It was named codominance. It can be traced by assessing proteins which are encoded by both of the genes. If both proteins are present in blood, it is a codominance. This method is used in genetic counseling to determine heterozygous individuals having recessive alleles of hereditary diseases. The IV (AB) blood group has a codominant pattern of inheritance.

The modified proportions may be due to an interaction of non-allele genes. It can be of two types complementary and epistasis (dominant and recessive).

The complementary or accessory genes are the genes which can give a new trait when they are both in genotype (A-B-). If they are along (aaB- or A-bb) they encode only usual traits. In human complementary interaction occurs in heredity of normal hearing and deafness. Complementary is usually leads to new traits formation, which were absent in parents.

In dominance, one gene is suppressed by another from the same allele: A>a, B>b. However, there is another type of interaction when one gene is suppressed by another from different allele: A>b, c>d. The event was named epistasis. The gene suppressing expression of another gene is called epistatic gene. The gene, which is suppressed by epistatic gene, is called hypostatic. Epistatic genes are also called gene supressors. There are dominant and recessive epistases accordinary to epistatic genes.

The recessive epistasis can be studied on example of a "Bombay phenomenon" in human. If a person has a dominant allele of blood group (A or B), these alleles are not expressed. As result of this a person has I blood group. It is explained by a suppression effect of "Bombay phenomenon" gene in a recessive homozygous state (hh). In cross of diheterozygotes of these genes we will have 25% of persons having I blood group, because of their homozygous genotype in H gene (hh).

All that was said above is correct if one locus of homologous chromosomes has only two alleles: A and a, B and b. But really we may have modified genes having several alleles such as a^1, a^2, a^3, a^4. Such alleles are called multiple alleles. Almost all genes that have been studied exhibit several different alleles. The alleles that determine the human ABO blood group, for example, comprise three common alleles (Tab. 7.1). The

existence of ABO blood system was suggested by K.Landshteiner in 1900. He observed that blood coagulation occurs in some cases blood mixture, but in some does not. In blood transfusion, it can lead to death. It was stated that erythrocytes contain two antigens A and B, whereas plasma contain two antibodies. In a population, there are all four blood groups: A (having antigen A and antibody β), B (having antigen B and antibody α), AB (having both A and B antigens and none antibody), and O (having only antibodies β and α without antigens). Group AB always has heterozygous genotype (I^AI^B). Group A may be homozygous (I^AI^A) or heterozygous (I^AI^o) in genotype. The same is to B blood group. Group O always has homozygous recessive genotype (I^oI^o). Also genes of human HLA histocompatibility system which are localized in 6th chromosome, are multiple genes.

Table 7.1. Blood groups on system ABO.

Blood group	Gene	Genotype	Antigens	Antibodies
I (O)	I^O	I^O I^O	-	α, β
II (A)	I^A	I^A I^A, I^A I^O	A	β
III (B)	I^B	I^B I^B, I^B I^O	B	α
IV (AB)	I^A, I^B	I^A I^B	A, B	-

The Rh blood group system is one of thirty-five known human blood group systems. It is the second most important blood group system, after the ABO blood group system. The terms Rh factor, Rh positive and Rh negative refer that to the Rh(D) antigen.

The MN blood group in humans is under the control of a pair of co-dominant alleles, L^M and L^N. Most people in the population are M/M. In fact, they tend to possess the opposite genotype (N/N).The MN blood group system is under control of an autosomal locus found on chromosome 4, with two alleles designated L^M and L^N.

An individual allele will have more than one effect on phenotype. Such an allele is said to be pleiotropic. The pleiotropic gene action may be primary and secondary. The primary pleiotropic gene expresses its effects simultaneously. For example, Marphan's syndrome is encoded by one gene. It has following traits: big height, thin fingers (arachnodactily), eye lens dislocation, heart defect, high catecholamine level in blood (Fig. 7.2). Another example is sickle cell anemia (Fig. 7.3). The mutation in normal allele leads to a defective hemoglobin formation. The erythrocytes lose their ability to transport oxygen and acquire a sphere shape. Homozygote dies right after birth, but heterozygotes survive and are more resistant to malaria. The

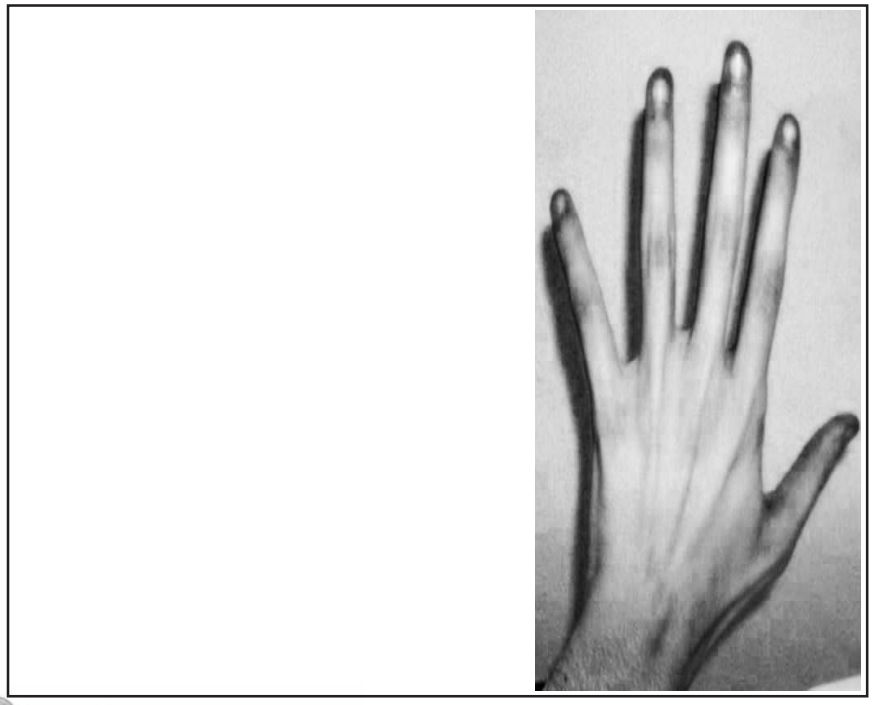


Fig. 7.2. Marfan syndrome symptoms (on left) and arachnodactilia (on right).

hidactily (short fingers) in homozygous state
livery. The gene mutation causing Hartnep's
ohan amino acid absorption in small intestine
ules. That results in a simultaneous damage

ne action, we may see one gene effect that
hers. In particular, abnormal hemoglobin s
sickle cell anemia, which in turn leads to
s malaria tolerance, anemia, hepatolienar
nd brain.

ı gene dose. Normally, each trait is controlled
y be homoallelic (dosage 2) or heteroallelic
gene dosage may be more than 2 (trisomia)
a). The gene dose is necessary for a normal
xample, in female inactivation of one X-
ays of embryonic development.

determine a variant of heredity in case of

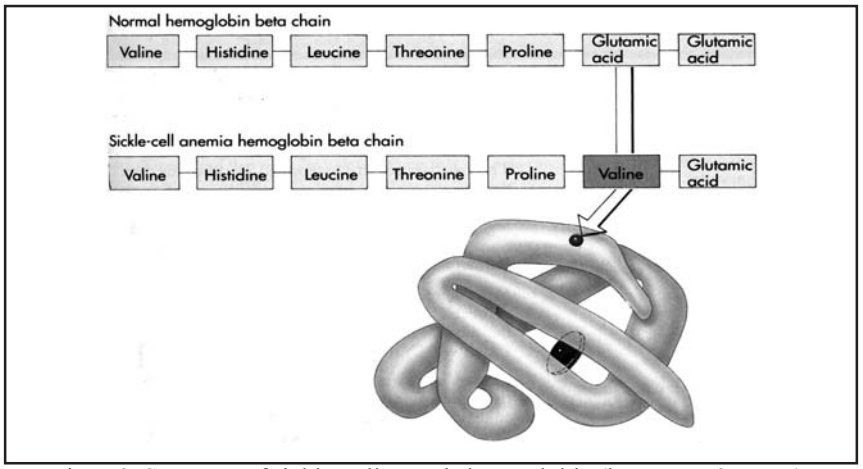


Fig. 7.3. Structure of sickle-cell anemia hemoglobin (by Raven & Jones).

genocopies. It is a case when the same trait is developed under control of different genes. For example, phenilketonuria is developed either with deficiency of dehydropteridinreductase or with deficiency dehydropholate-reductase.

7.4 THE ENVIRONMENTAL FACTORS INFLUENCE ON REALIZATION OF GENOTYPE TO PHENOTYPE

All organisms have an adaptation to environmental factors which act in the course of centuries such as gravitation, magnetic field, sun radiation and so on. Such factors as food deficiency, freezing, overheating, noise, etc., act only for a short time and locally. That is why a human has a high level of adaptation to environmental factors. It is caused by a gene ability to determine not only a definite trait but also limits of its variation. It made the organism to be less dependent from environment, but increased the complicity of genetic apparatus and gene controlling system. The realization of a gene in a phenotype occurs in a proper environmental condition.

The expressing of gene effects has particular characteristics as long as one gene in different organisms may be expressed by different ways. It is caused by different environment conditions of gene expression.

The level of a phenotypic gene expression is called the expressivity of gene. For example, we may observe different grades of polydactyl manifestation.

Trait controlled by gene may be expressed in one individual and be absent in another. Such event is called the penetrance of a gene. The penetrance is measured by calculating the percentage of individuals having

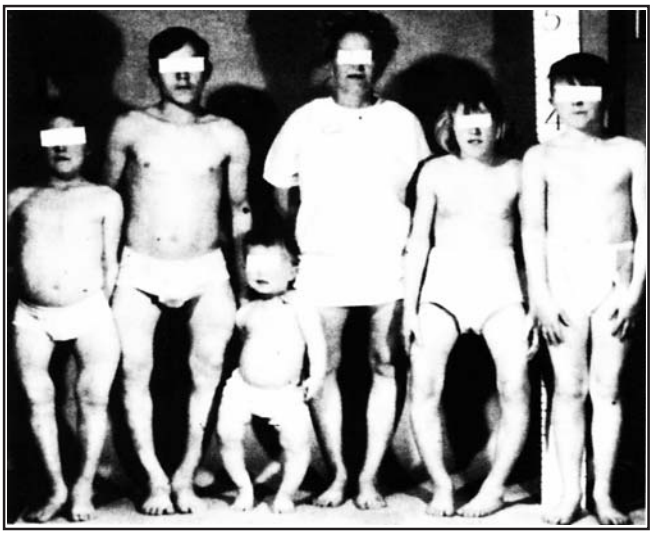


Fig. 7.4. D-resisnant rachitis (example of phenocopies).

mutant phenotype in population, which is homozygous of this gene. The complete penetrance (100%) means that every individual expresses the trait, the incomplete penetrance (30-40%) means that only part of individuals express the trait. For example, Colombo (the defect of eye) is inherited dominantly with penetrance around 50%, amniotrophyc sclerosis has the same inheritance. The syndrome of blue sclera (thin blue external eye coat, otosclerosis, deafness and frequent bone fractures) give 100% penetrance for blue sclera, 63% for frequent bone fractures and 60 % for deafness. All three symptoms are expressed in 44% of individuals.

The terms “penetrance” and “expressivity” is more often referred to autosome dominant traits. The autosome recessive traits are expressed only in homozygotes with complete penetrance and high expressivity. The expressivity and penetrance are determined by a genotype interaction and a different reaction of the genotype to environmental condition.

The trait formation is determined by not only existence of specific gene in genotype. In some cases, the trait may be formed only by specific combination of external factors. The phenotype changes similar to changes of genotype nature but induced by environmental factors are called phenocopies. Thus, child rachitis may be due to low consumption of vitamin D or due to a hereditary defect (Fig. 7.4). Eye cataract which is caused by German measles during pregnancy, looks like eye cataract due to the gene defect.

The phenotype is also formed with the help of environment and

ontogenesis. But with lens accommodation some slight correction occurs. In elderly people accommodation fails and it leads to presbyopia. The accommodation failure may be explained by working conditions.

We may state that phenotype formation depends on many factors. This principle shows a dialectic unity of genetic and environmental factors in a development.

CHAPTER 8. DIVERSITY

Besides heredity, genetics studies diversity as well. Diversity is the ability of an organism to change their traits, getting new ones or loosing old ones. The reason of diversity may be a variety of genotypes or variety of environmental condition determining a trait expression. Diversity provides traits and properties variety in different individuals.

Two variants of diversity can be distinguished: they are genotypic and phenotypic. The genotypic (hereditary) diversity can be combinative and mutational. The phenotypic diversity can be ontogenetic and modificational.

8.1. THE PHENOTYPIC DIVERSITY

The phenotypic diversity shows phenotype changes under the environmental condition, which not change a genotype, but level of it expression is determined by a genotype.

8.1.1. THE MODIFICATIONAL DIVERSITY

The modificational diversity describes the individual's changes caused by environmental factors. To understand the relative impact of genotype and the environment in phenotype formation, we need to investigate modification appearing under some environmental conditions. The examples are skin pigmentation of UV light, weight varying due to diet imbalance, effects of low vitamin intake, and so on. The modification diversity reaction is understandable and has only one direction to change. That means that the same environmental effect causes the same organism reaction in organisms. This is the main difference of mutations, which have strait direction in changes. Each mutagen may cause different effects. And different mutagens may cause the same mutation. The most common modification in mammals and human was modifications related to weight varying due to diet misbalance. The level of modification expression corresponds with intensity and duration of environmental effect. The mutations, especially the genetic ones, do not follow such pattern. The level of phenotype changes in genetic mutation do not correspond to with an intensity and duration of the environmental effect.

Each trait of a human is formed in a genotype and a phenotype interaction. And variations of traits are limited. They are limited by material matter of

heredity structures, which are in appropriate limits called the norm of reaction. The norm of a reaction is the limits of modificational diversity of an organism. In a human we may observe a full range of traits starting from completely determined by the genotype (ABO blood groups, iris color, etc.) to traits influenced by the environmental factors (human height) and finally to traits strongly dependent on environmental conditions (weight, level of muscular development).

The modifications, in spite of mutations, are not inherited. Nevertheless, for a long time in biology the incorrect thesis of J.B. Lamark was supported. He suggested that modification might be inherited. In the end of the 19th century, A. Veismann refused arguments of J.B. Lamark. He cut off rats tails in 22 generations but in spite of this, rats in 23rd generation had tails.

8.1.2. THE ONTOGENETIC DIVERSITY

In the course of ontogenesis many physiological, morphological, biochemical and other organism properties change. Their time and place of appearance in a phenotype is strictly determined by a genotype. The ontogenetic diversity is diversity that shows normal development changes in an organism or its cells withing the period of an individual development. You can recall the examples from your individual development. The main difference from a genotypic diversity is that organisms have the same genotype throughout all individual development. Main mechanisms of controlling ontogenetic diversity are the following: different gene activity, different activity of endocrine glands, different relation between processes of growth and differentiation in different periods of life. The examples are milk-teeth exchange, the development of secondary sex characters, grey hair, skin elasticity deterioration, and the increased rate of bone fractures in elderly.

The ontogenetic diversity plays a definite role in development of some hereditary diseases. A range of hereditary defects appears in embryo (polydactilia, syndactilia, achondrodisplasia, amavrotic idioty). Some diseases are developed in childhood or puberty. And very few are developed in elderly. For example, family Friedreich's ataxia is developed in a child of 6-12-years old, cerebellum ataxia – in young men of 20-30-years old, alcaptonuria – around 30-years old, diabetes mellitus type II – after the age of 40, gout – only in men of 40-years and older.

To treat properly, the doctor needs to know the mechanisms of ontogenetic diversity and their role in a development of some hereditary human diseases. For example, phenilketonuria is a hereditary effect, which may be evaluated right after the birth. It is related with intolerance to one amino acid. If patients are treated well in the first years of life they can

fight the disease by themselves after puberty. But if the patients aren't treated properly, irreversible changes are developed in their brains.

8.2. THE GENOTYPIC DIVERSITY

The diversity, which involves changes in a genotype due to mutations or gene combinations, is called genotypic diversity. It may be of two types: mutational and combinative.

8.2.1. THE COMBINATIVE DIVERSITY

The combinative diversity is the formation of new allele combinations due to crossing-over in meiosis and gene recombination. New gene combinations and interaction between them may cause a new trait formation. The combinative diversity is inherited according to Mendel's Laws.

Some factors may have influence on a gene expression at a combinative diversity. They are interaction of allelic and non-allelic genes: pleiotropic gene action, gene linkage, gene expressivity, penetrance. This wide traits variety is provided by a combinative diversity.

The combinative diversity in human is observed in a system of marriages. The family crosses systems may be of two types: inbreeding and outbreeding.

The inbreeding is mariage between relatives. The level of inbreeding depends on a level of familiarity. The closest inbreeding is a marriage between sisters and brothers or between parents and kids. The less close inbreeding is between uncles and cousins. The first consequence of inbreeding is an increasing number of homozygous defect allele's distribution. Such increases rise with every new generation. The second consequence of inbreeding is population splitting to several independent lines. The diversity of inbreeded population will rise, but a diversity of each line will decrease. The inbreeding often leads to an offspring's degeneration. It was pointed out in ancient times. All tribe taboo and inbreeding bans tell us about that. The human inbreeding in a majority of cases is harmful. The family relation among parents increases a risk of hereditary defects in offspring.

The outbreeding is mariage between unrelated individuals. The unrelated individuals are those who have no relatives in 6 or more generations. Outbreeding is the controversial crosses system. It raises a heterozygote level in population, combines alleles of parents. Homozygous defect alleles are suppressed dominant alleles. All genes are combined more often so it increases the combinative diversity.

8.2.2. THE MUTATIONAL DIVERSITY

The diversity with rapid, strong changes of trait is called mutational. Mutations are occasional, stable changes of genetic cell apparatus. They

may include changing allele gene position, changing of gene structure, changing in chromosome number and state, changing of cytoplasmic DNA containing structures. The first who summarized material about mutation was H. de Fris. He published "The mutational theory" in 1901. The main statements of that theory are as follows:

1. Mutations appears suddenly.
2. New forms are stable.
3. Mutations are changes in quality.
4. Mutations may be harmful and usable.
5. The same mutations may appear repeatedly.

All mutations are divided into groups. It was built on the basis of factors that cause mutations and type of mutated cells. There are two types of mutated cells: generative, somatic. By the character of genotype change mutations can be: gene mutations (point); chromosomal abberations, translocations, genomic mutations, cytoplasmic mutations. By adaptive type mutations can be: useful, neutral, harmful (lethal, semi-lethal). By the cause of mutation: spontaneous, induced.

Generative mutations (mutations in sex cells), may be revealed only if affected cells take part in new organism formation. If mutation is dominant, it may be expressed even in a particular individual. If mutation is recessive, it may take several generations to be expressed in phenotype. The examples of human generative mutation are foot pemphigus, cataract and brachiphalangia. The example of recessive human generative mutation is cases of hemophilia in some families.

Somatic mutations (mutations in somatic cells) may be transmitted to the next generation only during asexual reproduction. Somatic cell may mutate during embryogenesis. The earlier a mutation has appeared in embryogenesis, the more sever consequences of that mutation will have. The example of human somatic mutation is vitiligo (white depigmented spots on a skin with depigmented hairs). The research of somatic mutation is very important in understanding cancer causes. It was suggested that transformation of a normal cell phenotype to cancer one is based on somatic cell mutation.

Gene or point mutations are the alteration involving only one or few nucleotides in the coding sequence. They may be as dominant as a recessive one. The examples are vitamin-D-resistant rachitis, metabolic exchange imbalance of phenylalanine amino acid. In general, all point mutation have one of following mechanisms:

a) nucleotide pair exchange in DNA molecule;
b) deletion of nucleotide pair (or group of pairs) in DNA molecule;
c) insertion of nucleotide pair (or group of pairs) to DNA molecule;

d) translocation of nucleotide sequence inside of the gene.

All these alterations lead to three classes of gene mutation: missense mutation, nonsense mutation and frameshift mutation (Fig. 8.1). The small changes in a gene structure may cause the reading of frameshift. They in turn cause big ultimate changes in a protein structure and function.

Missence mutations appear when several nucleotides inside of a codon are changed. It is possible to change of one purine base to another purine (A-G) or one pyrimidine base to another pyrimidine (C-T). It results in codon changing (transition). But a change of one purine base to pyrimidine one is also possible and called *transversion*. Missence-mutation results in one amino acid exchange in protein chain (abnormal hemoglobin's). The physiological properties of protein are changed which makes a field for natural selection. This is a main class of point mutation caused by UV radiation, chemical mutagens, ionizing radiation and so on.

Nonsence mutations are a kind of missence mutation. They result in terminal codon appearance inside the gene. It terminates a transcription resulting in failure of protein synthesis. The causes of nonsence mutation are the same as for missense mutation.

Frameshift mutations are caused by nucleotide deletions and insertions. When they occur, they lead to the creation of genetic message that is out

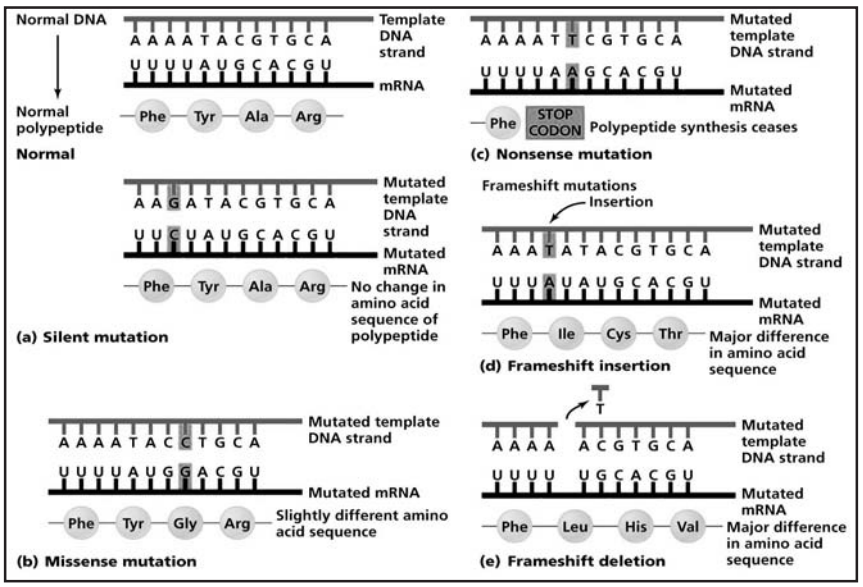


Fig. 8.1. The main classes of gene mutations (by Pearson Education).

of synchrony with the normal reading pattern, three- base increments being displaced to one or two positions.

Chromosome aberrations or rearrangements are referred to as mutations, because they result in cell properties changing and changing of properties of next generations of the cell. There are following types of aberrations: chromosome region deletion, duplication of some chromosome regions, chromosome region inversion (Fig. 8.2). They are caused by crossing-over failure resulting in chromosome structure rearrangement. The more common are deletion of short arm of 4th chromosome (Wolf-Hirshhorn syndrome), of 5th chromosome ("cat's scream" syndrome), of 9th chromosome and X-chromosome, deletion of long arm 13th chromosome (Orbelli syndrome), deletion of long and short arms of 18th chromosome and 21st chromosome.

Interchromosomal aberrations are related with a regional exchange between nonhomologous chromosomes. They are also called translocations. The lack of chromosome telomeres results in chromosome insufficiency in meiosis. That leads to conjugation of another chromosome fragments to the chromosome. The most often translocation is translocation of 21st pair to 13th and 22nd chromosome pairs. That phenotypically is expressed as Down syndrome.

Genome mutation involves all cell genome in a mutation process. The imbalance in chromosome set may be caused by increasing or decreasing of haploid chromosome set or by increasing or decreasing of particular chromosome in number. The organisms with increased chromosome number of haploid chromosome set are called polyploid. An individual that has gained or lost a whole chromosome is called aneuploid.

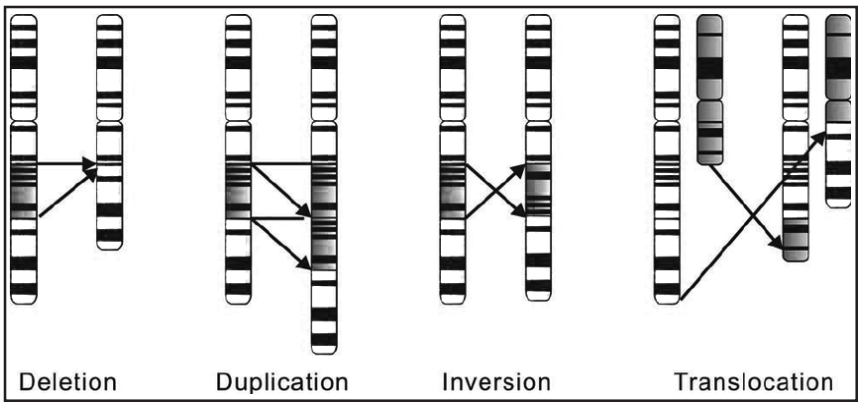


Fig. 8.2. The mechanisms of main types of chromosomes aberration formation.

The polyploidy is a genome mutation where all diploid set of chromosome is multiplied. There are triploid cells (3n), tetraploid cell (4n), etc. Polyploidy results in cell sizes enlargement, increasing fertility. It is more common in plants and rare in animals (infusoria, amphibian). The polyploidy of leucocytes in leucosis was described in human.

The aneuploidy is the change in number of several or one chromosome. D-trisomy syndrome of 21st, 13th and 18th chromosomes, monosomy of X-chromosome and others was observed in human. The aneuploidy leads to decreasing of survival ability of an organism.

Cytoplasmic mutations are mutations in DNA of cytoplasmic organelles. These mutations are stable and transmitted to a next generation (for example, lost of cytochrome oxidase in yeast mitochondria). Examples of human cytoplasmic mutations are some types of myopathy, anencephalia, Olbright osteitis, Spina bifida. Mutations may be divided on harmful, useful and neutral accordinaly adaptive significance. But that classification is conditional. There is a very slight difference between useful and lethal mutation because of a gene expression. The examples of human lethal and sublethal mutations are epiloya (syndrome which characterized by pathological skin growth, mental retardation, epilepsy, tumor of heart and kidney), inherited ichtiosis, amavrotic idioty (brain degeneration and color blindness), talasemia and brachidactilia in homozygotes, Edwards and Patau syndromes. There is no useful mutation among human. Neutral mutations have no influence on an organism survival. Usually they are cosmetic defects (polydactilia, mosaic color of iris). Semilethal mutations decrease an organism survival and may cause death (hemophilia, Duchenne dystrophy, Down syndrome, etc.).

Mutations, which appear in natural conditions, are called spontaneous mutations. The mutational process is mainly characterized by mutational rate. Each species has a definite mutational rate. Some species have a high mutational rate, some species have a low one.

General features of mutational process and mutational rate are concluded in following statements.

- different genes of one organism have different mutational rate (there are stable and unstable genes).
- similar genes in different genotypes have a similar mutational rate.

In human population mutational rate for talasemia is 4×10^{-4}, for albinism is $2{,}8 \times 10^{-5}$, for hemophilia is $3{,}2 \times 10^{-5}$. The particular gene mutates very rare, but total gene number in genotype is huge and that's why the general mutation rates are high. In some species there are special genes – genes mutators. In some species there are special genes – genes mutators. Such genes significantly increase a mutational rate. They are found in Drosophila,

corn, E. coli, yeasts and other organisms. It is believed that gene mutators change properties of DNA polymerase, which cause massive mutations. Induced mutations are mutations, which are induced by external and internal environmental factors. Such factors are called mutagens. These factors lead to a mutation induction over a spontaneous mutational rate. All mutagens may be divided into three types: physical, chemical and biological.

Among physical factors the most important is ionizing radiation. Ionizing radiation may be electromagnetic or wavelike (X-ray, gamma rays, cosmic rays) and corpuscular (electrons, positrons, protons, neutrons). When such radiation reaches a cell, it is absorbed by the atoms that it encounters, imparting the energy to the electrons of their outer shells and causing these electrons to be ejected from the atoms. The ejected electrons leave behind ionized atoms with unpaired electrons, each called a free radical. Most of the free radicals in a cell are produced from water molecules. Free radicals are a highly reactive chemically, reacting violently with other molecules, including DNA. Different animals have a different sensitivity to ionizing radiation: lethal dose (LD) vary from 700 roentgens for human and to millions roentgens for bacteria and viruses. Ionizing radiation primary damages nucleus of the cell. It was shown that nucleus in 100,000 times more sensitive than cytoplasm. The immature sex cells are more sensitive than mature ones. The main damage is exposed in chromosome DNA. It is presented by point mutations and chromosome aberrations (Fig. 8.3). The mutational rate strictly corresponds with a radiation dose. The higher radiation dose acquired, the higher mutational rate is. The strong mutagen is UV radiation. Its mutative effect depends on its wavelength. Its does not cause ejection of electrons from outer shells, but it activates them for different chemical reactions. It is less active than ionizing radiation. The temperature is the significantly weaker factor. The increasing of temperature by 10 degrees leads to the increasing of a mutation rate in 3-5 times. But this factor is more important for lower organisms.

Chemical mutagens include various substances which list is updated every year. They are divided into several groups. The first group includes alcyling substances, which are the strongest mutagens (dimethylsulfat, iprit, ethilenimin, etc.). Many of them are carcinogens. The second group is analogues of nitrogen bases (5-bromuracil, 5- bromdesoxyuracil, 8-azoguanin, 2-aminopurine, etc.). The third group is acrydil stains (acrydil yellow, prophlavin). The fourth group is substances form all other chemical groups (hydroxylamine, different peroxides, uretan, formaldehyde). Chemical mutagens can induce point mutation and chromosomal mutations as well.

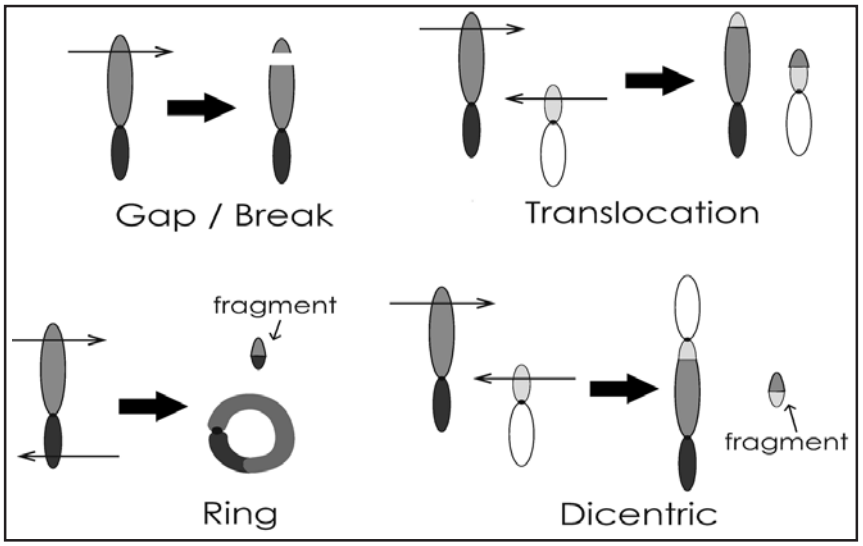


Fig. 8.3. Types of chromosome aberration after ionizing radiation influence.

Biological mutagens are presented by viruses, bacteria, helminthes and their metabolites. It was proved that animal and plant viruses induce mutations in Drosophila. It is possible that a mutagen element in viruses is nucleic acid. Bacteria can induce chromosome and chromatid aberrations. Bacterial endonucleases may activate formation of a thymine dimer. The metabolites of helminthes, probably, break crossing over and chromosome movement in anaphase of mitosis and meiosis.

It becomes clear that all mutagens are universal. They can cause mutation in all life forms. For all known mutagens, there is no lower limit of their action. Mutations cause numerous defects and inherited diseases. It is important to protect humankind from mutagens. Everyone should follow the rules while working with isotopes, X-ray equipment. Some protection can be reached by the consumption of mutation protective drugs (cysteine, chinacrin, some sulfanilamides, etc.). Each organism has a system of DNA repair. If this system is less efficient in the repair of DNA damage caused by expose to a sunlight or other sources of UV radiation, affected individuals have xeroderma pigmentosum. Those who have this disease develop extensive malignant skin tumors after the expose to the sunlight. Xeroderma pigmentosum is caused by mutation affecting genes responsible for DNA repair enzymes. This group of diseases also includes Bloom syndrome and teleangioectasia. Thus, for understanding the mutational process it is important to study induced mutations, mutagens, mechanisms of DNA repair.

CHAPTER 9. HUMAN GENETICS

It is hard to study a human genetics. The main difficulties are failure of directed breeding, a late puberty, a small number of offsprings. The negative moment is also social segregation, which retards realization of human abilities. In spite of all difficulties listed above, some success was achieved in this field. Many traits were mapped and described. But features of mental and creative activity depend on many factors, including social, that it is hard to analyze them. But it is stated that they have hereditary nature ones.

9.1. THE METHODS OF HUMAN GENETICS STUDYING

Human genetics study traits inheritance in a human. Several methods were discovered and was successfully applied to study such inheritance. Nevertheless, all methods are not universal.

9.1.1. THE PEDIGREE ANALYSIS

To study how human traits are inherited, investigators look at the results of crosses that have already been made - they studied family histories, called pedigree. This method may be applied if direct parents of an individual under study (poband) are known or if childrens of such individual are known. Specific signs are used to make pedigree (Fig. 9.1). We analyze a pedigree to determine a pattern of inheritance.

There are several patterns of inheritance.

In the *autosomal dominant* pattern of inheritance, the mutated trait appears in heterozygous state in individuals of both sexes (Fig. 9.2). The trait occurs in horizontal and vertical lines of a pedigree as well. The child may be affected, if anyone from parents is affected too. It is important to remember about incomplete penetrance of dominant gene. Some diseases are manifested only after achieving particular age. For instance, Hantington's chorea appears only in individual over 35 years of age. The sparkles, brachidactilia, cataract are inherited according the autosomal dominant pattern of inheritance.

In the *autosomal recessive* pattern of inheritance, the mutated trait appears only in homozygous state in individuals of both sexes (Fig. 9.2). If parents are healthy, but they are heterozygotes, you can expect that 25% of offsprings will have a disease. The trait occurs not in every generation in a horizontal line of a pedigree. If parents are both recessive for trait, all offsprings will have such trait. The examples are albinism, phenyketonuria, diabetes mellitus, and red hair.

In the *X-chromosome linked dominant* pattern of inheritance, the mutated trait appears in individuals of both sexes (Fig. 9.2). The trait occurs

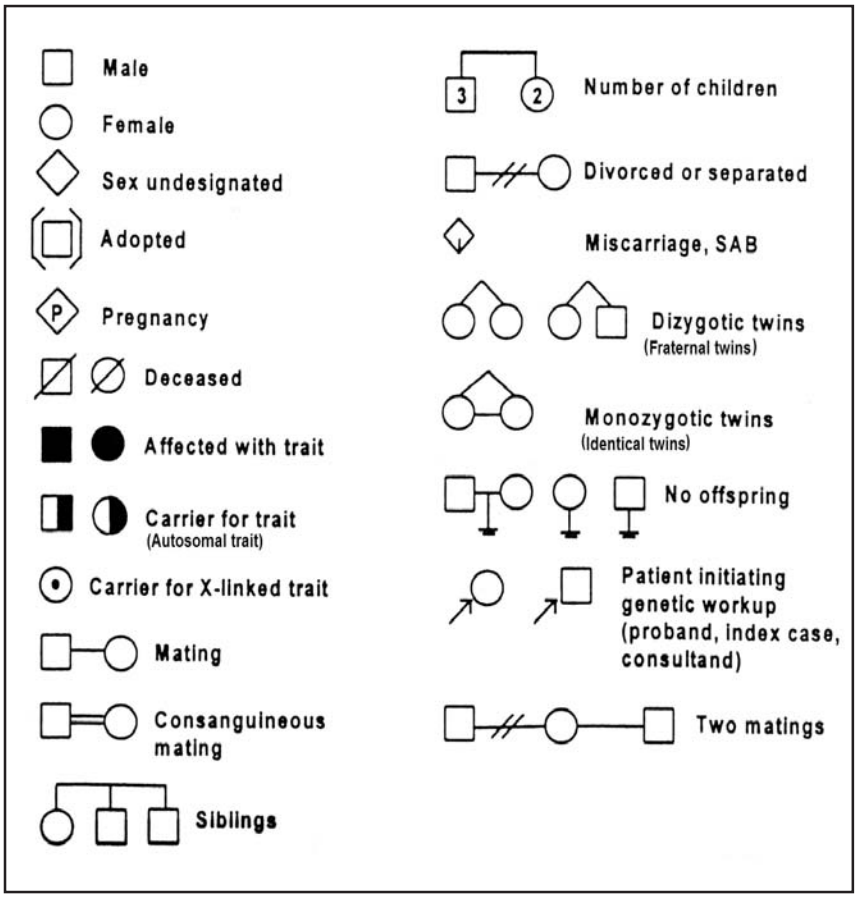


Fig. 9.1. Symbols of pedigree analysis.

in horizontal and vertical lines of pedigree as well. Inbreeding increases probability of sick newborns. Such trait is expressed more often in female, because they may get a trait from mother and father as well. The follicular keratosis, pigment dermatosis are inherited according a X-linked dominant pattern of inheritance.

In the *X-chromosome linked recessive* pattern of inheritance, the mutated trait appears mainly in males (Fig. 9.2). In a family, the half of males is sick from a disease and half of female has a gene in heterozygous state. If the male has such a trait, he inherits it from a mother line of pedigree. The most common diseases having such a pattern of inheritance are hemophilia A, muscular Duchenne dystrophy, daltonism.

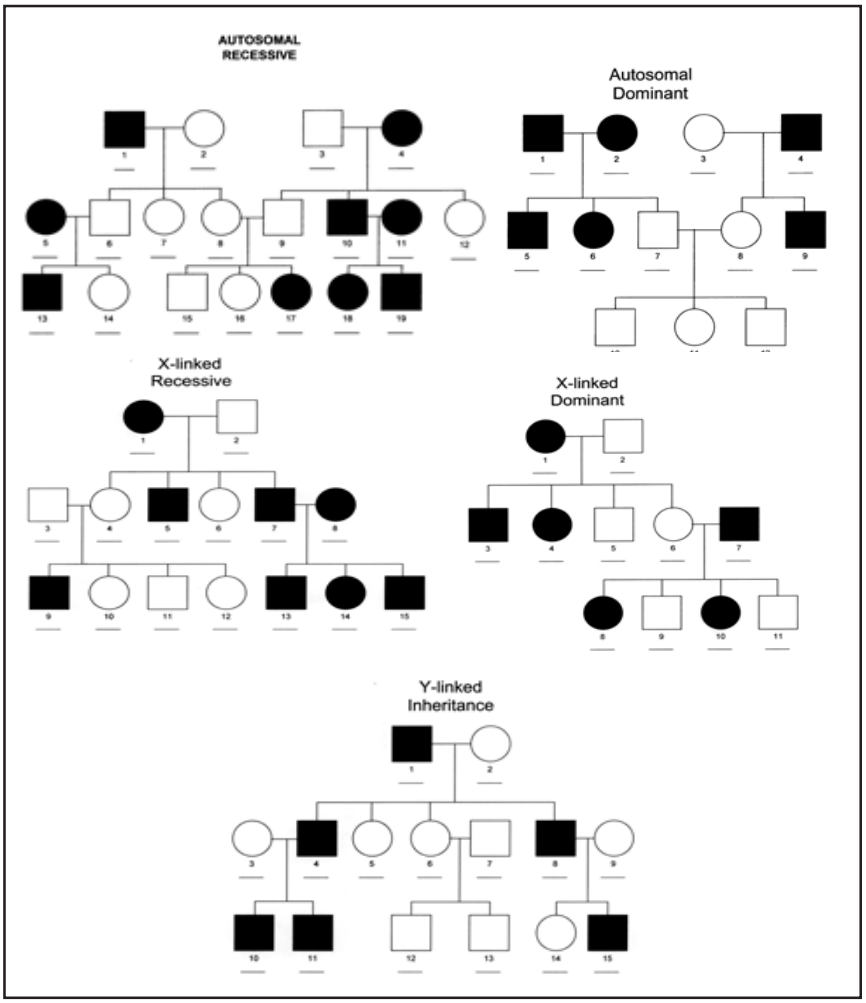


Fig. 9.2. Types of pedigree in human.

In the *Y-chromosome linked* pattern of inheritance, the mutated trait appears only in males (Fig. 9.2). The syndactilia, hypertrychosis of cochlea are inherited according to such pattern. The ability to develop male gonads is holandric trait, located in Y-chromosome.

The pedigree analysis allows determining the heterozygous state of a defected gene and probability to have a child with hereditary defect. The method is used for determining hereditary diseases in genetic counseling.

9.1.2. THE CYTOGENETIC METHOD

This method is usually called cytological analysis of a human karyotype in normal and pathological conditions. The term "cytogenetic" can be used, only if cytological analysis is combined with pedigree analysis and it is possible to link cytological pictures with a phenotype effect.

It is based on chromosome microscoping. Chromosomes are studied in a metaphase of mitosis in fibroblasts and lymphocytes, which are cultivated in artificial conditions (Fig. 9.3). The luminescent microscoping may also be used. In this case, we need to stain chromosomes by fluorochrom. Chromosomes are classified according to the Denver classification. This method allows determining hereditary diseases related with changes in chromosome structure and number. It is also used for chromosome mapping.

This method is quite complicated and is based on growing of lymphocyte cells in breeding ground. They are stimulated by dividing of phytohemaglutinin cells. In metaphase, spindle proteins are destroyed by colhicin. After that, chromosomes are available for observation for long time. In 1956, J.

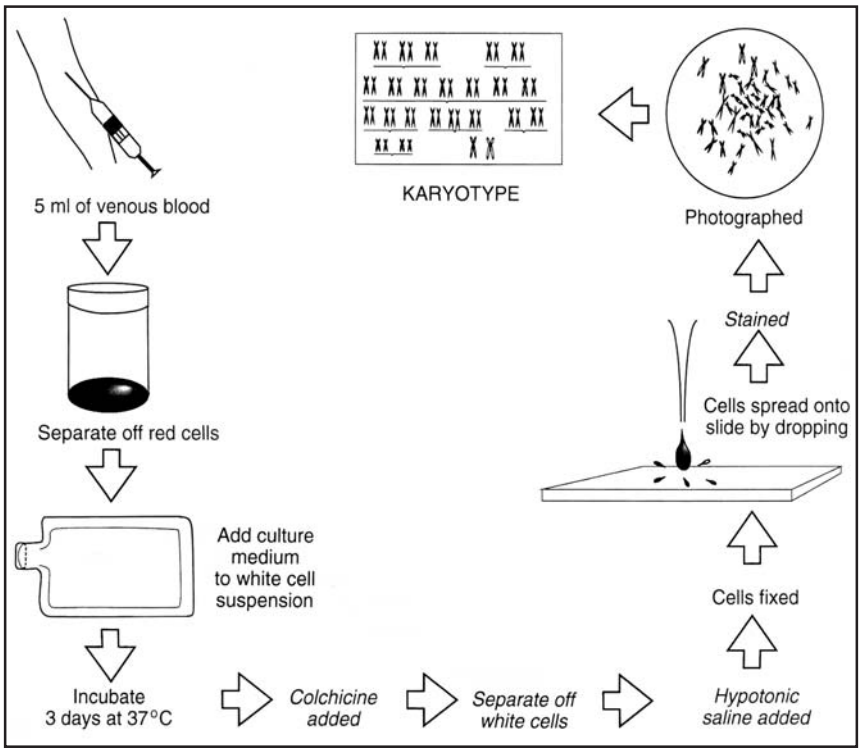


Fig. 9.3. Structure of cytogenetic method.

Tiyo and A.Levann used this method to state that a human karyotype has 46 chromosomes.

The method of chromosome staining made it possible to distinguish the chromosomes according to their segments staining. The aneuploidity, chromosome aberrations, translocations, polyploidity may be revealed using this method. Among aneuploidities we can determine excessive X-and Y-chromosome, trisomy in 13th, 18th, 21st chromosome. We may determine deletion of the 5th chromosome (a "cats scream" syndrom), the 18th (mental retardation, deformation of skeleton) and of X-chromosome. The deletion of a short arm of X-chromosome is referred to as partial monosomy in X-chromosome. The most common translocation is translocation of the 21st chromosome to the 15th, 13th, 14th chromosome in females and to the 22-d chromosome in males.

If defects apply to a sex chromosome set, it can be determined easily. For such purpose the evaluation of sex chromatin in somatic cells is used. The most common material for that is buccal epithelium. Sex chromatin (Barr's body) is a condensed second X-chromosome in female cells. It is inactivated on the 16th day of embryogenesis and looks like heterochromatin body nearby nucleus membrane. It is revealed on preparations stained by acetoorsein. Normally, Barr's bodies are determined in 20-40% of female cells and in 1-3% of male cells. Number of X-chromosomes is calculated according to such formula: Barr's bodies number plus one. For example, if a woman has one Barr's body that means she has two X-chromosomes (1+1); if there is no Barr body in a female cell that means she has one X-chromosome (0+1); if a man has not Barr's body that means he has sex chromosomes set like that - XY (0+1).

In somatic cells, in particular in buccal epithelium, it is possible to determine Y-chromatin. Slides need to be stained by akrychin followed by ultraviolet microscoping. Y-chromatin is intensively stained body in a nucleus, usually near nucleolus. Normally, Y-chromatin is contained in 20-40% of male cells.

The express-methods to determine a sex chromatin are used for studying the change in sex chromosome set, diseases diagnostic, for determining the sex in hermaphrodites, transsexuals and in forensic medicine.

9.1.3. THE STATISTIC METHOD

The method is based on demographic statistics data and mathematic analysis of them. Using Hardy-Weinberg principle, we can calculate a rate of a defect gene staying in heterozygous state in human population.

The population statistic method is widely used for health care management. It allows calculating necessary amount of drugs, medical devices, etc.

The method is also useful in understanding dynamic genetic assortment in population. Different populations have a different genetic structure. For example, let us look through a gene assortment for genes of the ABO blood group system. Thus, in India and China the concentration of allele I^b is the highest. This concentration falls down to east and to west from those countries. Among Native Americans and Australians there is not I^b allele. At the same time, Native Americans and Australians have the highest concentration of l^o allele. The allele l^a is expressed rare in Native Americans, Indians, Arabs and Western Europeans. It was suggested that such distribution was made because of epidemics of plague and smallpox. The smallpox affects people with the A blood group at first. That leads to a higher mortality among them and elimination I^a allele from the population. The places where smallpox was wide spread (India, America, Arabic countries) have a low of l^a allele rate among population. In the pointed above regions allele I^b became most frequent. The data acquired with the help of the population statistics are used for planning health care funds, required drugs and required specialists number.

9.1.4. THE TWINS METHOD

The method idea was suggested by F. Gallon in 1876, and was developed by G. Simens in 1924. The method is based on studying the traits of twins having the same sex, which are changed by the environmental condition. Twins are two or more delivered at the same time individuals in mamalian usually have only one (cow, horse, human). Twins, born from one fertilized ovum, are called monozygote twins. Twins, born from two different, fertilized by different sperms ova, are called heterozygote twins. Heterozygote twins may have a different sex. The most common situation is twins, but it is possible but rare to have triples, quadruplets, even quintuplets. The twins's rate in population is around 1%. The quarter of them is monozygote. But a monozygote rate in different population varies. For instance, in mongoloid race it is 60%, in other races it is around 30%.

Both types of twins are used for a genetic research. In this way, we can understand both influences of different environmental conditions on same genotypes and influences of same environmental conditions on different genotypes. If the studied trait is expressed in both twins, it is called concordant twins. If the studied trait is expressed only in one twin, it is called discordant twins. By comparing the level of traits concordance in different twins' groups, we can determine the impact of a genotype and environment to a phenotype formation. The method is not presented in doctors practice, but it is important to remember about twins concordance in disease development.

Twins method is based on comparative study of traits concordance. It allows listing hereditary diseases, determining a role of environment in disease development. For these purposes, the coefficients of inheritance (H) and environment impact (E) are used. They are calculated by Holtzinger's formula:

$$Í = \frac{Ñ_{MZ} - C_{DZ}}{100 - C_{DZ}} 100;\ Å = 100 - Í\ ,$$

C_{MZ} is percentage of concordated pairs of monozygote twins, C_{DZ} is percentage of concordated pairs of dizygote twins.

Using twins method, we can study the following: the role of environment in disease development; definite factors enhancing or weakning the environment impact; correlation between characters and functions.

9.1.5. THE BIOCHEMICAL METHODS

Since the present families have a few children, it is complicated to use pedigree analysis. Therefore, biochemical methods of evaluation of different enzymes activity and interesting chemical substances are widely used. We can check different stages of metabolic pathways and reveal crucial defected points in them.

The biochemical methods are applied for diagnostics of hereditary metabolic exchange diseases. They are determined on three levels: molecular (protein structure and quantity assessment), cellular (evaluation of defect enzymes) and organism (searching for intermediate metabolites). The following diseases can be determined with biochemical methods: hemoglobinopathy, failure in amino acid exchange (phenylketonuria, alkaptonuria), in carbohydrate exchange (diabetes mellitus, galactosemia, fructoseuria), in lipids exchange (hypercholesterinemia, amavrotic idioty), in minerals exchange (Konovalov-Wilson disease, hemochromatosis). Taking into account polymorphism of hereditary exchange diseases, biochemical method is crucial in its diagnostics.

9.1.6. THE MOLECULAR-GENETIC METHODS

The molecular-genetic methods describe changes in structure and functions of nucleic acids. It includes methods of gene extraction, gene synthesis, in vitro gene activity studying, gene transfection. It has really pushed forward researches of human heredity and a nature of hereditary diseases. Genetic engineering methods are real devices for treatment of

hereditary diseases. It allows receiving primary a human gene product and using it further in patients with deficiency.

The reverse DNA transcription on mRNA matrix has resulted in discovering DNA probe. Such DNA probes facilitate localization of mutant genes in a cell.

Further gene engineering development will result in new approaches in treatment of genetic diseases.

9.2. THE PRENATAL DIAGNOSTICS OF HEREDITARY DISEASES

Prenatal diagnosis is aimed to solve biological and ethical problems before birth to prevent the birth of a child with pathology, not amenable to treatment by interruption of pregnancy with woman's consent. Prenatal diagnosis is possible to establish the diagnosis of chromosomal diseases, the majority of congenital malformations fermentopathy. Some of them can be detected in almost any stage of pregnancy (chromosomal disease), another part - after the 12th week (reducing defects limb atresia, anencephaly) of pregnancy, and some - only in the second half of pregnancy (diseases of heart, kidney).

Indications for a prenatal diagnosis are: the presence of hereditary diseases in the family; women's age of 35 and over, 45-years old men and older; a history of spontaneous abortion in pregnant women in early pregnancy, stillbirths of unknown origin, children with multiple malformations and chromosomal abnormality; the existence of structural chromosome aberrations (translocations and inversions) in one of parents; heterozygosis of both parents on the same pair of alleles in pathology with an autosomal recessive mode of inheritance.

Indirect and direct methods for prenatal diagnosis are applied. In indirect methods, the obstetric-gynecologic methods are used to examine a pregnant woman, blood serum is tested for alpha-fetoprotein. Direct methods are used for a fetus. The direct non-invasive methods include ultrasonography. The direct invasive (with integrated tissue disorders) is chorionic villus sampling and amniocentesis. The identification of alpha-fetoprotein is made by radioimmunoassay in the amniotic fluid and blood serum of a pregnant women. The high content of alpha fetoprotein helps to diagnose some severe fetal malformation - open neural tube defects, anencephaly, congenital defects. The increase of alpha-fetoprotein in maternal serum indicates the malformations in the fetus.

Ultrasonography is the use of ultrasound to obtain images of the fetus and its membranes. By all accounts, the method is safe, so the duration of the study is not limited and, if necessary, it can be used repeatedly.

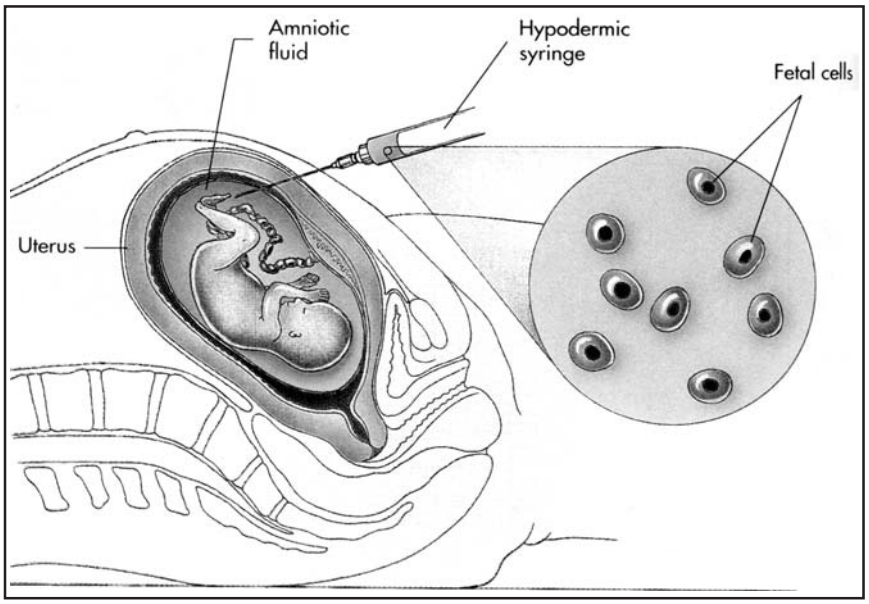


Fig. 9.4. Amniocentesis (by Raven & Jones).

Ultrasound does not penetrate through the bone and the hollow bodies filled with air. Starting from the 5th week of pregnancy, one can get a picture of the embryo membranes and on the 7th week – embryo itself. By the end of 6th week of pregnancy, embryo heart activity can be registered. In the first two months of pregnancy the ultrasound is not able to detect fetal anomalies, but can determine its viability. From the 12th week, the "nuchal folds" measurement or NT are the diagnostic value to determine fetal chromosomal aberrations (fluid accumulation on the rear surface of the neck between the tissue covering the spine and skin). Using software programs, the probability of a child with Down syndrome can be calculated based on "nuchal folds" length. In the 2nd trimester ultrasonic diagnostic capabilities are significantly increased. On 12-20th week of pregnancy, a twin pregnancy, the placenta localization, anencephaly, bone defects and neural tube closure, atresia of the gastrointestinal tract can be diagnosed. The probability of birth of a sick child is the ratio 1:360 and higher used in invasive prenatal diagnosis.

Chorionic villus sampling is carried out on 6-7th week and eliminates interference in the amniotic space. The material for the study are pieces of chorionic taken under ultrasound control by transabdominal access or through the cervical canal of the uterus of a pregnant woman transcervically. The chorion villi biopsy is performed under aseptic conditions transcervically

using 1.6 mm plastic catheter via the cervical canal, transabdominal using a special spinal needle through the abdominal wall. The aspiration of chorionic villi is taken in a syringe pre-filled with saline (20-30 ml). The received material is examined by biochemical and cytogenetic methods.

The amniocentesis is performed om 14-16th weeks of gestation, when the amount of amniotic fluid is already large enough when the decrease of its volume on 15-20 ml is not so important for a fetus or when the pregnancy can be terminated (Fig. 9.4). The obtained amniotic fluid is centrifuged and depending on the purpose of study the supernatant is used for biochemical, immunological methods or cell suspension for cytogenetic techniques. The sex of the fetus can be determined by amniocentesis. The amnicentesis is important for diagnise of X-linked diseases, all chromosomal diseases, more than 60 hereditary metabolic diseases of the fetus and the mother incompatibility of erythrocyte antigens, hemoglobinopathies, erythrocytic enzimopathies, immuno-deficiency states. Under unfavorable prognosis of having a baby with genetic or morphological pathology, proved by methods of prenatal diagnosis, women are advised to terminate their pregnancy.

9.3. THE HUMAN GENETICS VALUE FOR MEDICINE

The value of human genetics is huge. It gives methods of hereditary disease diagnostics. It is important not only in theoretical aspect for understanding evolutional and developmental processes, but also in practical too. There are 10 million who may be affected by different hereditary diseases such as diseases of nervous system (schizophrenia, epilepsy), endocrine system (cretinism), blood (hemophilia), metabolism (phenylketonuria, albinism). Using human genetics achievements, the genetic counseling service have been designed.

CHAPTER 10. HUMAN HEREDITARY DISEASES

10.1. THE CLASSIFICATION OF HUMAN HEREDITARY DISEASES

The decreasing rate of infections is diseases observed now, but at the same time hereditary disease rate are increasing. More than 3,000 prevalently hereditary diseases have been registered. In the world more than 1.5 million children are born with hereditary diseases each year. Around 10% of them die in the first year of life. In countries with good developed health care, they represent 15-20% of the total number of hospitalized patients. All hereditary diseases can be divided into three groups: diseases of metabolic exchange, chromosomal diseases, and cytoplasmic diseases.

10.2. THE DISEASES OF METABOLIC EXCHANGE

Normally, genes control different metabolic stages. The gene mutation may cause decreased enzyme activity or even failure in function. There are many diseases caused by failure of one metabolic step. This group of diseases is called diseases of metabolic exchange. When enzymes can not work at all, the metabolic precursors of a reaction controlled by the enzyme are accumulated in the tissue. These accumulated substances suppress an activity of surrounded cells. This mechanism occurs in phenylketonuria, galactosemia, and alkaptonuria. On the other hand, absence of the metabolite can cause a range of hereditary defects as hereditary cretinism, adrenohenital syndrome. The pathology process may also occur on a level of renal tubules. The accumulated substance can be excreted improperly or no fully. Following types of metabolic exchange diseases can be distinguished according to an imbalanced exchange.

Diseases of amino acid exchange. The most common example of this type is phenylalanine misbalance (Fig. 10.1).

Phenylketonuria is an autosomal recessive disease. It is caused by deficiency of phenylalaninhydorxylase enzyme. This enzyme converts phenylalanine to tyrosine. When it is blocked, phenylalanine is converted to

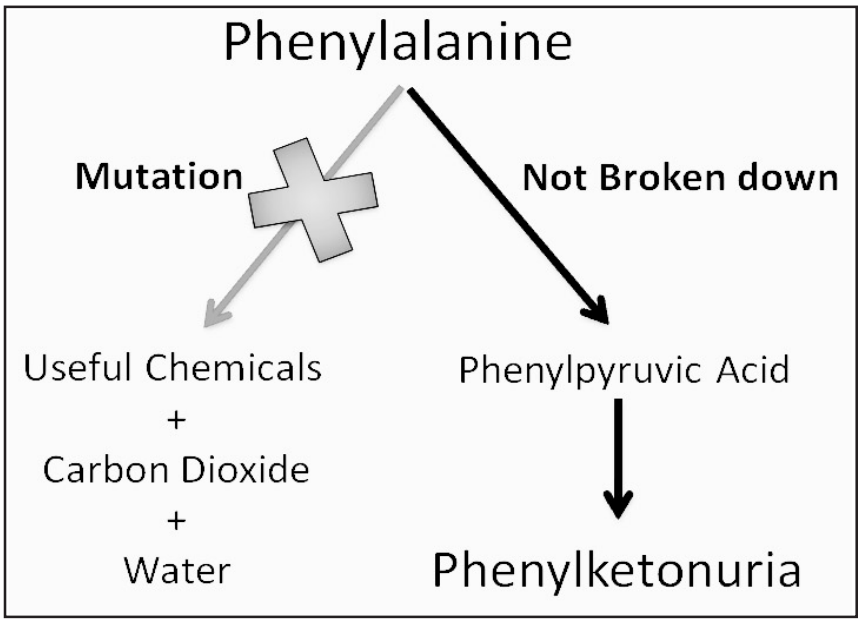


Fig. 10.1. The scheme of human phenylalanine exchange.

phenylpyruvate and excreted with the urine. The rate of this disease in Europe is 1:10,000. The signs of a disease are irritability, convulsions, mental retardation, microcephaly, loss of pigmentation of skin, hair, and the iris. If newborns suffering from this disease are fed as usual newborns, they express all those signs in few months. But if we give them a diet without phenylalanine, they develop as usual children without any signs of mental retardation. To evaluate phenylketonuria, the 10% $FeCl_3$ test is used. It stains the urine into green when it is positive. The express-tests are used to evaluate phenylketonuria right after a delivery.

Total albinism is an autosomal recessive disease. It is caused by a defect of the gene controlling the enzyme, which converts tyrosine to melanin. Melanocytes loose their ability to produce melanin pigment. The signs of the disease are absence of melanin in the skin, hair, and eyes. Eyes are red because of visible blood capillaries. The rate of this disease is about 1:20,000.

Alkaptonuria is a recessive abnormality, having a rate of about 3-5:1,000,000. It is caused by a deficiency of homogentistic acid oxidase enzyme. Signs of the disease are special staining of cartilages and arthritis in elderly. There are diagnostic signs such as fast changing in color to dark in urine with added bases and changing in color to red if Milon's reactive is added (containing ions of Hg) which proves the presence of tyrosine in the urine.

Diseases of lipid exchange. This hereditary disease group includes familiar lipidoses characterized by a excessive level of lipids in the blood and by excessive intracellular storage. The first group includes essential familiar hyperlipidemia and essential familiar hypercholesterolemia. The second group includes gangliosidoses (Tay-Sach disease), sphignomielose (Nyman-Pick disease), and cerebrosidose (Goshen disease).

The essential familiar hyperlipidemia is characterized by excessive levels of glycerids and chylomicrons and dispersed lipopropeins in blood, especially after fatty food intake. The first sign of a disease is bad transparency of plasma over erythrocyte in an erythrocyte sedimentation reaction. The important additional signs are xantoms, acute stomach pain with tachycardia, vomiting. These signs are also observed in patients with acute abdomen inflammation processes. The incorrect diagnosing leads to unnecessary surgical examination. The proper therapy for such patients is a low-fat diet (fat consumption around 30-60 g per day). The syndrome is caused by different mechanisms. Among them is suppressed chylomicron removal from a blood and glycerin metabolism block. It is possible that in many cases it is inherited dominantly.

The essential familiar hypercholesterolemia is characterized by excessive levels of cholesterol and phospholipids in blood. The atherosclerosis is developed very fast. The common signs are xantoms and xantelasms on the skin and tendons. It is an incomplete dominant disease with a rate of 1:500. Today, one real way of treatment is an appropriate diet containing a few of cholesterol rich compounds. Instead of fat of milk and eggs, it is better to use vegetable oil.

Infantile amavrotic idioty (Tei-Sax disease) was described by E. Tei in 1881 and L. Sax in 1896. The affected children appear normal at birth and the symptoms are not usually developed until eight months, when signs of mental deterioration become evident. Within a year if a birth affected the children become blind. Among other signs are defects of skin and parenchymal organs (liver, kidney). Tei-Sax disease is rare in most human populations. However, Tei-Sax disease has a high incidence among Jews of Central and Eastern Europe. Many parents were relatives, which can prove a theory about local reproduction of singular mutation. Individual homozygous for the allele lack an enzyme necessary to break down a special class of lipids called gangliosids, which occur within the lysosomes of the brain cells. As a result, the lysosomes fill gangliosids, swell, and eventually burst, releasing oxidative enzymes that kill the brain cell. The medical cure for this condition is not known. The rate of disease is 1:300,000 in population.

Diseases of carbohydrate exchange. Among the diseases are diabetes mellitus, pentoseuria, fructoseuria, glycogenoses, galactosemia, and hyperbilirubinemia.

Diabetes mellitus is an autosomal recessive disease with an increased glucose blood level. The abnormal gene is wide spread (about 4-5% of homozygotes), but has a small penetrance (about 20%). The total number of patient is about 1.2-1.3% of population, whereas gluoseuria is evaluated in 2.7%.

There are two types of diabetes mellitus. The first one develops mainly in young people. It is caused by an autoimmune destruction of Langerhans islets, which produce insulin. All cells of the body need insulin to get glucose from the blood. If there is no insulin, cells suffer from a glucose deficiency, in spite of a high level of glucose in the blood. The method of treatment is injections of insulin.

Diabetes with late onset is called diabetes of the second type. It often occurs in obese people with atherosclerosis. It is caused by a small glucose consumption by tissues because of insulin receptors breakdown. It is treated well by sulfanilecarbamide preparations. The diabetes is diagnosed through checking a blood glucose level and an urine glucose level.

Diseases of steroids exchange. The main disease from this group is adrenogenital syndrome. Its rate is 1:5,000 - 1:67,000, whereas heterozygous rate is about 1:35 -1:128. It is an autosomal recessive disease. It is expressed in a form of hermaphroditism in females and as preliminary virilization in males. Commonly it is because of hereditary hyperplasia of adrenal gland caused by inherited defects of steroid hormone biosynthesis. In the urine of such patients, many androgenic 17-ketosteroids are found. The natural sex of a patient is determined by evaluating sex chromatin of buccal epithelium. Clinical signs may be presented by virilization only and accompanied with adrenal failure and electrolyte imbalance. In many cases, virilization is accompanied with high blood pressure. Both males and females have an early puberty development and early arrest of bone growth. The late onset is connected rather with adrenal cancer than with adrenogenital syndrome.

Diseases of purine exchange. It is gout. It is an autosomal recessive disease with incomplete penetrance (about 20%) in males and complete nonpenetrance in females. The disease develops exclusively in aged men as urate salts infiltrations in tissues. Such infiltration causes inflammatory reactions. The kidneys suffer from gout very often and kidney failure is a main cause of death of these people. Approximately 1-2% of people have hereditary asymptomatic pattern of disease, with suppressed uric acid exchange and an increased level of it in an organism. During gout, uric acid concentration makes 5-16 mg%. It is due to enhanced uric acid synthesis and decreased removing through kidneys. The gene has no nonpenetration in women.

Diseases of blood clotting system. They are represented by hemophilias A, B and C.

Hemophilia A is a sex linked recessive disease. Only men suffer from this disease. It is caused by the defect of VIII coagulation factor (antihemophilic protein). The clinical sign of hemophilia is hemorrhage. The hemorrhage in hemophilia is caused by innocent reasons and it may last for hours. The symptoms become evident in early childhood. An average life span of a patient is 16-22 years.

Hemophilia B is sex linked recessive disease as well. Only men suffer from this disease. It is caused by the defect of IX coagulation factor. Clinical signs are similar to hemophilia A. The genes, which are responsible for hemophilia A and B, are localized in different X-chromosome regions. The IX factor concentration in a patient blood is about 2-6% from normal value. An average life span of patient having hemophilia B is 22 years. The rate of sporadic cases is about 9%.

According to the WHO data, the child birth rate with hemophilia A is

1:10,000, whereas the birth rate of hemophilia B is 10 times less. But patients with hemophilia A die more often in early postnatal period. That is why, hemophilia B occurs in a population only 5 times less than hemophilia A.

Hemophilia C or Willebrand disease is an autosomal dominant disease. It is caused by rare changes in antihemophilic protein structure (factor VIII) and decreasing activity of the factor preventing vessels wall damage. Patients have less ability to stop hemorrhage (women have especially long and abundant menses). Sometimes, a blood transfusion is required to treat those patients.

Defects in hemoglobin structure. Abnormal hemoglobins are evaluated mostly by electrophoresis. If hemoglobins of heterozygous individual are subjected to electrophoresis. Two different hemoglobins move with different speed. One is normal hemoglobin A, and the second is abnormal.

The most important is *hemoglobin S*. Erythrocytes containing hemoglobin S become "sickled" in shape. In heterozygous individuals having Ss genotype the concentration of hemoglobin S is small, and erythrocytes express sickle shape. But in homozygous individuals the hemoglobin S is abundant. Erythrocytes mostly stay in a sickle shape and they are removed by spleen from the blood. Sickle cell erythrocytes cause thrombosis, they are subject to massive hemolysis. That leads to homozygous death in early childhood, whereas heterozygous are clinically normal.

Heterozygous individuals for *hemoglobin T* (dominant allele of talasemia) have no clinical signs as heterozygous individuals for hemoglobin S. But the homozygous state causes very severe erythroblastic anemia. Its clinical symptoms are spleen and liver enlargement, bone changes caused by compensative hyperplasia of bone marrow. Erythrocytes are produced smaller in shape with less amount of hemoglobin and they have decreased life span. If the patient has talasemia, he produces hemoglobin F throughout the life.

In spite of lethal phenotype, genes S and T (and some other genes encoding defect hemoglobins C, D, E) spread widely among populations of some specific geographic zones. It was found that gene S is widly spread among native Africans and their descendents in America; gene C – among the population of the Guinea Gulf; gene E – among the population of South-East Asia; gene D – among the population in West India; gene T – among the population of Italia, Greece, Bengali, South-East Asia and South China. The heterozygous individuals are more resistant to Plasmodium vivax invasion.

Diseases of ions exchange. There are hepatolenticular degeneration (Wilson disease) and hemochromotosis in this group.

Wilson disease is an autosome recessive disease. During this disease, ions of cuprum infiltrate the liver, the brain, the kidney, the cornea tissues. Also, the excessive excretion of cuprum ions is evaluated, whereas the blood level of cuprum ions is low. The cerulloplasmine level is also small. The reabsorbtion of amino acids, glucose, uric acid and phosphate salts is failed in the kidney. Pathogenesis of the disease is not clear yet. Half of the patients were born in families of close relatives who were affected. Heterozygotes show decreased incorporation of Cu^{64} isotope to cerulloplasmine.

Hemochromatosis is the disease of ferrum storage with everyday 2-4mg income. It is characterized by an excessive amount of hemosiderin in the liver, heart, endocrine glands and tissue reaction to those infiltrations. Clinically, hemochromatosis has the following signs as the liver cirrhosis, hand skin pigmentation, diabetes mellitus in men over 35 years of age. It is rarely expressed in women. It is probably due to lost of ferrum during lactation, pregnancy and menses. It is inherited dominantly with incomplete penetrance. However, some variants with an early onset may have a recessive pattern of inheritance. Heterozygous individuals have an increased skin pigmentation, high ferrum blood level and an increased ferrum absorption from intestine.

10.3. THE HUMAN CHROMOSOME DISEASES

Using the cytogenetic method makes it possible to separate groups of diseases related with imbalance in a chromosome number and structure as well. They are called Human chromosome diseases. Statistically, it was determined that 0,7 % of newborns have chromosomal diseases. Deviance in chromosome number is related with chromosomes separation in meiosis. The deviance in sex chromosomes is not lethal, but it often leads to a decreased fertility and some development abnormalities.

There are the following human ***sex chromosome diseases***.

Additional Y-chromosome causes less severe effects on a phenotype. There is no special sign to distinguish a person having additional Y-chromosome. It is known that part of them develop a pattern of antisocial behaviour. The most of men having additional Y-chromosome are fertile. It makes genetic analysis of mutations more complicated.

Additional X-chromosome in women. It gives a wide phenotypical polymorphism. Its rate is 1.4:1,000 in girls. Diagnostic feature is two sex chromatin bodies in buccal epithelium cells. The most individuals having karyotype 44 + XXX express normal physical and mental phenotype without any deviations in the reproductive system. But some of them may have pathological changes in the reproductive system such as secondary anemia,

dismenorrhea, early climax. The intellectual development is normal or on a lowest limit of a normal condition. It is proved that the higher rate of schizophrenia is among X-chromosome trisomic women. In rare cases, such as X-chromosome polysomy, the deviations are more expressed.

Additional X-chromosome in men (Kleinefelter's syndrome) gives a wide phenotypical polymorphism. It occurs in about 1 out of 500 male births. The typical feature has a sex chromatin in the nucleus of buccal epithelial cells. It becomes evident in puberty. The clinical signs are mainly manifested in insufficient development of male secondary sexual characteristics. They are tall, with long limbs, with sclerotic degeneration of semeniferous tubules and, in some cases with diminished mental capacity. The XXY-complex does not lead to perinatal death. However, the XXY-complex occurs in perinatal kid's deaths 10 times more often than in survived children.

Absence of X-chromosome in women (Turner's syndrome) occurs roughly once in every 5,000 female births. Such individuals have no sex chromatin in the nucleus of buccal epithelial cells. It results in a sterile female of short stature, a webbed neck, disk shaped thorax, and immature sex organs that do not undergo puberty changes. Sometimes they have defects of color perception. Such embryos are subjected to high prenatal mortality, that is why their population rate is small.

Absence of X-chromosome in men. Such zygote is unviable and fails to develop further. The humans cannot survive without any of the genes on the X-chromosome.

Sex chromosome aberrations. The most common is deletion of a short arm of X-chromosome. It leads to a formation of phenotype similar as X-chromosome monosomy.

Among ***autosomal changes*** there are the following which are most common.

Trisomy 21 (Down syndrome). The individuals having the Down syndrome have a decreased size of scalp, small in stature, poor muscle tone, big gap between I and II finger of foot, immatured sex organs, mental retardation (Fig. 10.2). The mental retardation pathogenesis of trisomy 21 includes central nervous system immaturation, in particular, the insufficient myelinization of a nervous fibers. About half of patients have heart defects and defects of big vessels. The Down syndrome rate is about one out of 700-800 births. The average age of mothers having children with Down syndrome is on average 6-8 years older than the age of mothers having normal children. The life span of such individuals is about 21-24 years.

Trisomy 18 (Edward's syndrome). It is third in a rate after trisomy 21 and 13. Individuals have severe prenatal immaturation and numerous defects

Fig. 10.2. Karyotype and photo of patients with Down syndrome.

of skeletal system, in particular, facial part of scalp. The internal defects are defects of interventriculum septum of heart, defects of aortic valve and pulmonary artery valve, cryptorchysm in males. They also have severe mental retardation, abnormal bending of joints and prevalating length of index finger over middle one, low ear's position and small lower jaw. With a good treatment they can survive till one year of age.

Trisomy 13 (Patau syndrome). Its rate is 1:5,000 - 1:7,000. The trisomic 13 causes early death. More than 90% children die in the first year of life. Individuals have defects of the brain and the scalp. The second group of defects is defects in a finger number as polydactilia. They also have abnormal bending of joints, defects of heart septa, incomplete intestine turn, abnormalities in inner reproductive organs in both sex children, typical changes in pancreas. Some embryos with trisomy 13 have high prenatal mortality, that their population rate is small.

Autosome aberrations. The most common are deletions of 5th and 18th chromosomes. Deletion of 5th chromosome short arm was described by J.Lejen as "cats scream" syndrome. The child's scream sounds like a cat's scream. Other symptoms are larynx immaturation, microcefalia, mental retardation, poor muscle tone, low ears' position, and underdeveloped sexual characteristics. Deletion of long or short arm of 18th chromosome leads to face defects, skeletal defects, internal defects, microcephalia, mental retardation and other abnormalities.

Different translocations cause the development of different chromosome diseases. They can be of such variants: translocation of 21 chromosomes to 15 chromosomes results in Down syndrome, translocation of 21 chromosomes to 13, 14 and 22 chromosome.

The rate of chromosome abnormalities increases with mother age, starting from 35.

10.4. THE CYTOPLASMIC DISEASES

It is necessary to point diseases related to changes in mitochondrial DNA. There are very few of them. They can be transmitted only by mothers line. There are some inherited myopathies with abnormal mitochondria, Albright osteitis, Olier osteochomdromatosis. It is possible that spina bifida and anencefalia have cytoplasmic pattern of inheritance.

CHAPTER 11. THE PRINCIPLES OF EMBRYONIC DEVELOPMENT.

11.1. THE ONTOGENESIS, ITS TYPES AND PERIODS

Individual development or ontogenesis is a process of organism development from its origination to death. In sexual reproduction, the life of a new individual starts with zygote formation. Even in ancient times, there were two controversial views on the principles of individual development. Hippocrates believed that there is small, but completely developed organism in ovum or in mother's body. Later, such views were named preformism. In XVII century, the first researchers, who used microscope, believed that the embryo is already formed in ovum (ovism) or in sperm (animalculism). During development, the embryo only grows and enlarges in size. The controversial point of view was suggested by Aristotle. He believed that new embryos were developed from homogenous, unstructura-lizated matter. Later, such views were named epigenesis. Owing to K. Wolf the epigenesis concept won and facilitated embryology development.

K.Bar showed that both preformism and epigenesis are incorrect. He

presented ontogenesis neither as premade structures growth nor as new organs formation from homogenous matter, but as restructurization, remodeling of structures, which corresponds with a modern view.

Individual development is encoded in the genotype. The genotype determines where, when, and how genes will work. The ontogenesis is a reflection of species history fixed in a genotype. There are two types of ontogenesis: direct and indirect.

The indirect development. The species having such ontogenesis have several intermediate development stages before maturation. Species may have simple or complete metamorphosis (Fig. 11.1). In simple metamorphosis, the wing, if present, develops externally during the juvenile stages; ordinary no resting stage exists before last molt. The juvenile stages are called nymphs and they are morphologically quite similar to imago. For complete metamorphosis, the wings are developed internally during the juvenile stages and appear externally during only the resting stage immediately precedes the final molt. The juvenile stages are called larva

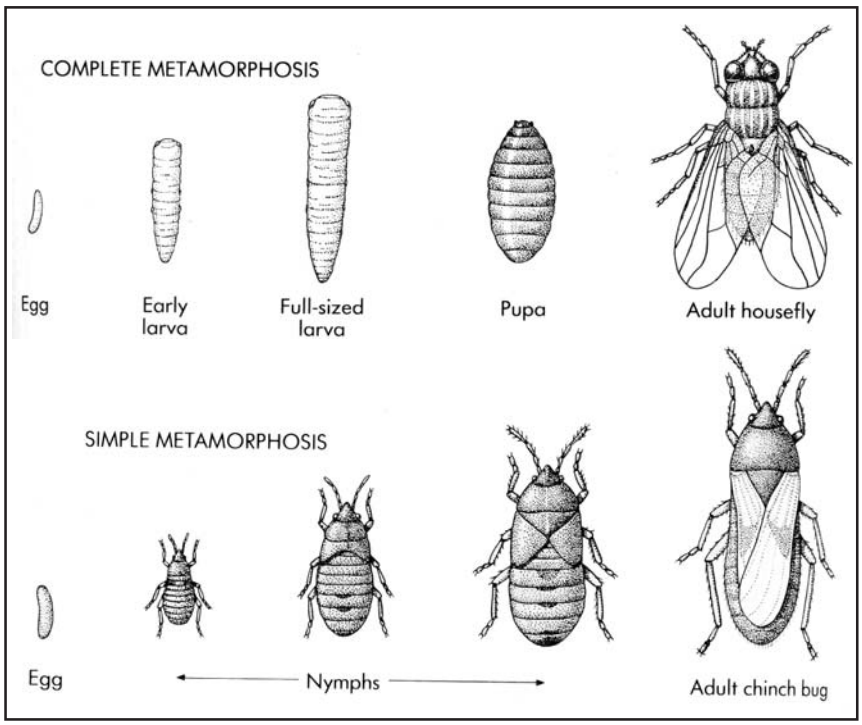


Fig. 11.1. The complete and simple metamorphosis (by Scott & Foresman).

and pupa and they are morphologically different from imago.

The direct development. The species having such ontogenesis has a baby similar to adult organism. This ontogenesis occurs in species whose ovum is rich in yolk (fish, birds, reptilians). The exception is the Mammalians. They have ovum poor in yolk, but they have direct ontogenesis. It is because the embryo is supplied by the mother organism through the placenta. The embryo has provisional organs such as the amnion, chorion, yolk sack, and allantois.

Ontogenesis has two periods: embryonic and postembryonic.

11.2. THE CHARACTERISTICS OF EMBRYONIC DEVELOPMENT

The embryonic period starts from the zygote formation and terminates by birth. The embryonic development includes the following periods: prozygote, zygote, cleavage, gastrulation, tissue and organ formation. The mammalian embryo is called an embryo before a formation of the main tissue stems and it is called a fetus after that.

The prozygote period is the period that precedes zygote development. It was discussed in chapter 4.

The zygote period is a monocellular stage of a new organism development. It is formed as the result of sperm and ovum fusion. It was revealed that significant cytoplasm movement in zygotes of Amphibia, Reptilia and Mammalia occurs. Such movements determine regions of further organs and tissue formation (ooplasmatic segregation). The zygote also expresses bilateral symmetry. In the zygote, the protein is synthesed on a matrix of mRNA made in oogenesis.

The cleavage is a rapid division of the zygote into a larger and larger number of smaller and smaller cells. The pattern of cleavage is greatly influenced by the presence of yolk. It can be holoblastic (symmetrical and asymmetrical) and meroblastic (discoidal and superficial).

The symmetrical holoblastic cleavage is in isolecital eggs (in aquatic vertebrates such as lancelets and agnaphants). The cleavage occurs throughout the whole the egg. After fertilization, the zygote is divided into two cells, which are called blastomers. Then, both cells are divided again forming four blastomers. Repeatedly, it increases cell numbers in such line: 2, 4, 8, 16, 32 and so on.

The asymmetrical holoblastic cleavage is typical in the telolecital egg of Amphibia (Fig. 11.2). First two divisions are the same as symmetrical division. The cleavage occurs throughout the whole egg as well. But yolk-rich cells are divided more slowly than those which are poor in yolk. It results in formation of two poles: apical (poor in yolk) and vegetative (rich

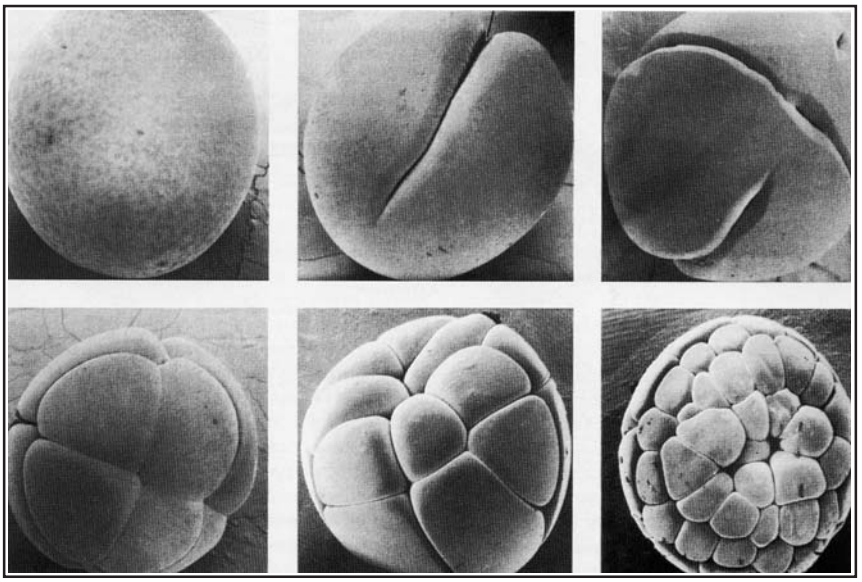


Fig. 11.2. The asymmetrical holoblastic cleavage of frog egg.

in yolk). Blastomeres are different in size. Those, which are on an apical pole, are smaller than those that are on a vegetative pole.

Mammalians and humans have little yolk in ovum. They have holoblastic asymmetrical cleavage.

Each blastomere has its own rhythm of division. That is why, the stages of 2, 3, 5, 7, 9 blastomeres can be observed. Some blastomeres are lighter and are placed externally. They give a rise to trophoblast. The cells of the trophoblast can dissolve tissues, perhaps that the embryo can be implanted in the uterine wall. Then, trophoblast cells are separated from embryoblast (darker cells staying internaly) and make a vesicle. The embryoblast cells are placed on the inner surface of the trophoblasts in a shape of disc.

In the discoidal meroblastic cleavage, cleavage occurs only in a tiny disc of polar cytoplasm, called blastodisc, which lie astride the large bulk of yolk material. It occurs in the polylecitinal eggs of some mollusks, reptiles, birds and some fish.

The superficial cleavage occurs in centrolecitinal eggs of Arthropoda. The cleavage starts from nucleus cleavage placed centrally in cytoplasm. The nucleuses move outward to a regions poor in yolk. The bordering cytoplasm is spited to blastomeres. It results in a formation of one layer of blastomeres surrounding yolk material.

In spite of specifics of cleavage in different organisms, all organisms

are terminated by the formation of a blastula. It is one of features showing similar origin of life and parallelism in evolutionary development of structures. At the end of the cleavage, blastomeres are separated by a fluid. This fluid localized centrally makes a primary space – blastocoel. Cells of blastula wall are called blastoderm. Starting from blastula, blastomeres are commonly called embryonic cells. All animal species have a blastula stage.

The gastrulation is the process of two-layer embryo formation. After blastula, all animals start to form layers of embryo. There are four types of gastrulation: invagination, immigration, epibolia and delamination.

The invagination occurs in animals having isolecital eggs (Fig. 11.3). The vegetative pole of blastula invaginates inside. Opposite poles almost touch each other. This decrease a volume of blastocoel to minimum and it looks like narrow rime. It results in a formation of two-layer embryo. The external layer is called primary ectoderm. The internal layer is called primary entoderm. The invagination forms the primary intestine or gastrocoel. The opening one end is called blastopore.

Destiny of the blastopore is different. In mollusks, arthropoda, and worms

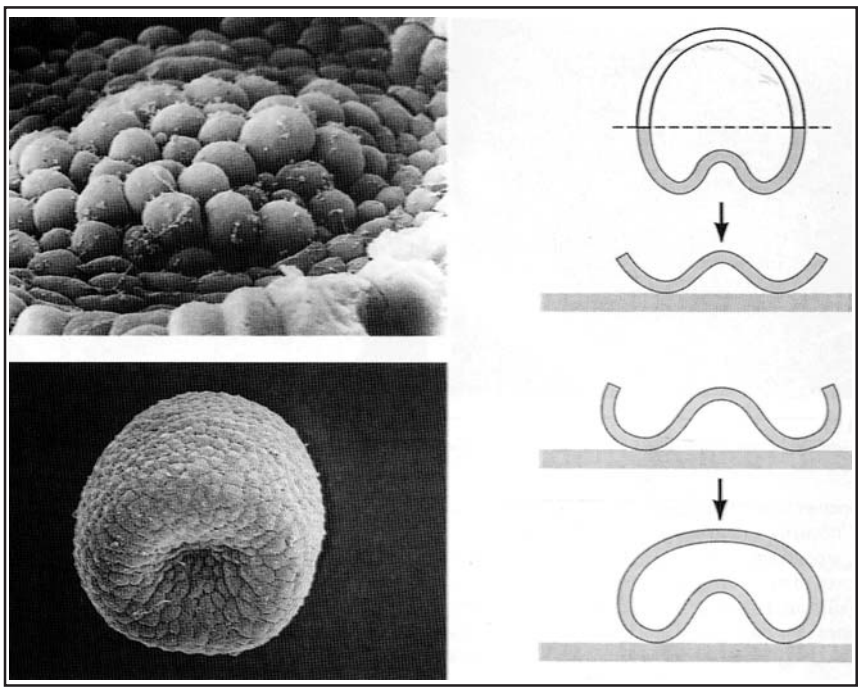


Fig. 11.3. The invagination gastrula (by Raven & Jones).

it is transformed into the definitive mouth of the adult organism. Such animals are called protostomia. In animals having a chorda the blastopore is transformed to an anal canal, whereas the mouth is made on the opposite side the result of complicate processes (invagination of ectoderm and fusion with primary intestine). Such animals are called deuterostomia.

The immigration was described by I.I. Mechnikov in the embryo of medusa. Some cells of blastoderm migrate to the blastocoel and form a second layer. Both layers are formed surround the gastrocoel.

The epibolia occurs in animals having big eggs rich in yolk (reptilian, birds). Small cells of an animal pole are divided quickly than a cell of the vegetative pole, which is rich in yolk. Cells of animal pole grow over vegetative pole cells becoming an external layer. The cells of the vegetative pole become an internal layer.

The delamination occurs in Cnidarians by splitting. During delamination the cells of blastoderm are divided parallel to a blastoderm surface. Thus, inner layer underlying ectoderm is made.

It is important to note that mixed forms of gastrulation may occur as well. For example, amphibians have the invagination, the epibolia and the immigration. Only Cnidarians and Sponges terminate their development at a two-layer stage.

In all more complicated animals a third layer called the mesoderm is also developed. Mesoderm is of two different kinds: mesenhyme and mesoblast. Mesenchyme is presented by cells immigrated from both ectoderm and endoderm layers. It is spread in the embryo between all the other structures. Mesoblast is formed later. There are two ways for mesoblast formation. One is teloblastic and second is enterocoelic. The first is typical to Protostomia, whereas a second is typical to Deuterostomia.

The teloblastic way. It happens when cell groups start to proliferate and migrate inward from both blastopore sides. Then, these groups fill all space between first two layers. Then, cells make a secondary cavity.

The enterocoelic way. It happens when groups of cells in the form of paired vesicles start to separate from the primary intestine or primary coel. The coel of these vesicles become a secondary coelom, which can be segmented. The coelomic vesicles are formed symmetrically from both sides of intestine. The splanchnopleure is the wall of sack looking toward intestine. The somatopleure is a second one looking toward ectoderm. The cavities, which have very important morphological and functional value, are formed. During a formation of the gastrocoel and coelom the volume of the blastocoel significantly decreases. Finally, it transforms to narrow rimes in between intestine wall and coelom. Further, they become spaces of the cardiovascular system. Gastrocoel becomes a coel of small intestine.

In an enterocoelic way, the gastrocoel also gives coelom.

Formation of organs and systems is main aim of embryonic period. Embryonic layers contact with each other and this provides connections between different cell groups. Such connections have a great impact on further cell development. They can stimulate each other to develop different signs. Such relations are called embryonic induction. The material of three embryonic layers generate formation of all organs of a developing embryo. Ectoderm gives rise to interguments (external epithelia, skin glands, teethes). A part of ectoderm deeper inside gives rise to the nervous system. Endoderm gives rise to the intestines with digestive glands, and lining of respiratory glands. Mesoderm forms all muscular tissues, all types of connective tissues, cartilage, bone, excretory organs, peritoneum, blood, part of ovary and the testis tissue. The beginning of organogenesis is called neurulation. Neurulation is formation of the nervous tube. At the same time a secondary intestine and chord are formed. On either side of the developing chord, segmented blocks of tissue are formed. First, spinal ectoderm induced by chord becomes a nervous plate. Then, a layer of ectodermal cells situated above the chord invaginates inward, forming a long groove – neural groove. The edges of this groove then moves toward each other and fuse, creating a long hollow tube, the neural tube, which runs beneath the surface of the embryos back. The canal inside the tube called neurocoel.

Mesoderm is separated into dorsal and ventral regions. Dorsal regions are segmented and presented by somites. The ventral part is called a side lamina. Somites are connected with a side lamina by the intermediate mesoderm.

The ventromedial part of somites (sclerotomes) induced by neural tube and chord forms vertebrae, bones and cartilages. The intermediate part of somites called myotome forms all skeletal muscles. The external dorsolateral pert of somites called dermatome forms skin derma. Intermediate mesoderm called nephrotome forms excretory organs and to sexual glands. The primary sex cells are separated from other embryonic cells in early stage of development. The mammalians sex cells are supplied by nutrition better than any other cell of the body. Primary sex cells migrate to a place of their definite localization and incorporate in sex glands.

11.3. THE PROVISIONAL ORGANS AND THEIR ROLE IN MOTHER-FETUS RELATIONSHIP

Some provisional organs are made from embryo material. The most primitive is the yolk sack. It first appears in fish embryos. It has endodermal origin. It is a membrane with many vessels, which surrounds yolk storage. It serves for transmitting nutrition from yolk to an embryo. It is of great

importance for reptilians, and birds, because their eggs contain much yolk. The mammalian embryo also forms the yolk sack, but it has no functions for embryo. New three provisional organs were formed for defense and embryo nutrition in reptilian, bird and mammalian embryos. They are amnion, chorion and allantois (Fig. 11.4).

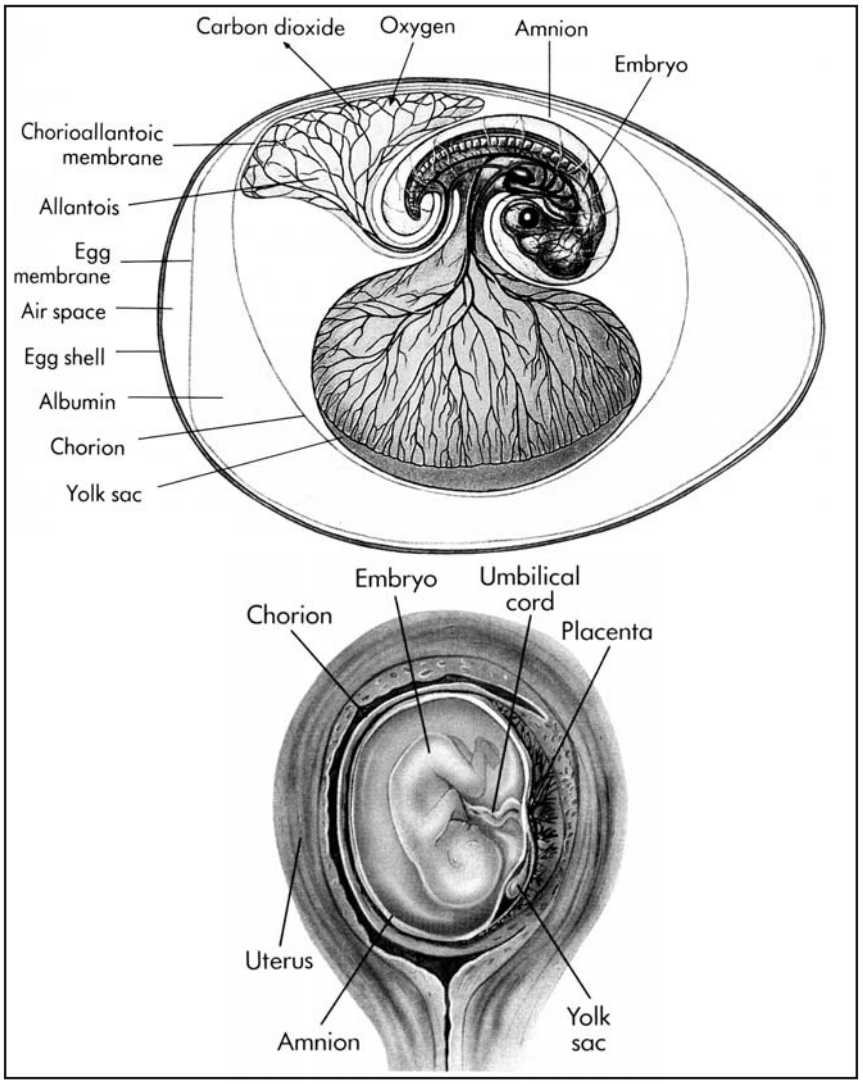


Fig. 11.4. The provisional organs of amniotes on example of birds embryo (up) and human embryo (down) (by Raven & Jones).

Amnion is developed from the internal layer of the primary body fold. The space between the amnion and embryo is called the amniotic cavity. It is filled with fluid secreted by the amnion and embryo. Amniotic fluid prevents embryo water loss, serves as defense pillow, and provides conditions for embryo movements.

Chorion is developed from the external layer of the primary body fold. In reptilian and bird eggs the chorion touches the eggs shell, whereas in mammalian embryo it touches uterine mucosa. It forms external villi, incorporated into uterus wall. These villi with uterine tissue form the placenta. The placenta provides water and food supply for the embryo. Also, it helps to excrete waste products of the embryo. It grows together with an embryo to provide sufficient supply for it.

Allantois is a diverticulum of intestine. It grows between amnion and chorion. In reptilians and birds, the allantois serves as a place of nitrogen waste products storage. The allantois fuses with the chorion making an allantois-chorion membrane which is rich in vessels. Embryo can take oxygen through this membrane and give off carbon dioxide and metabolic waste products.

The human have a small allantois. It contains vessels coming to the placenta. The yolk sack has no specific function in a human embryo. During development, an embryo, allantois and yolk sack grow and merge forming an umbilical cord. The umbilical cord contains vessels, allantois, and yolk sack. It connects the fetus with the placenta.

11.4. THE COURSE OF HUMAN DEVELOPMENT

The human prenatal development has three periods: primary (1st week of development), embryonic (2-8 week of development) and fetal (from 8 week to birth).

The human cleavage has its own properties (Fig. 11.5). The first division is asymmetrical. Each blastomere has its own rhythm of division. That is why, the stages of 2, 3, 5, 7, 9 blastomeres can be observed. On the 3rd day, the group of blastomeres is formed. It is a morula. On the 4th day, blastomeres start to produce fluid inside of morula. Thus, they are moved outward on periphery. This fluid forms a primary coel - blastocoel. The cells placed on the periphery are called throphoblast. The group of cells situated inside the morula is called an embryoblast. The embryoblast is located near only one pole of the morula. Further, throphoblast gives rise to chorion, whereas embryoblast gives rise to an embryo.

The embryo reaches the uterus, attaches to the uttering lining, or endometrium and penetrates into the tissue of the lining of 3 to 6 day later. Cells of throphoblast are reproduced very actively and produce enzymes

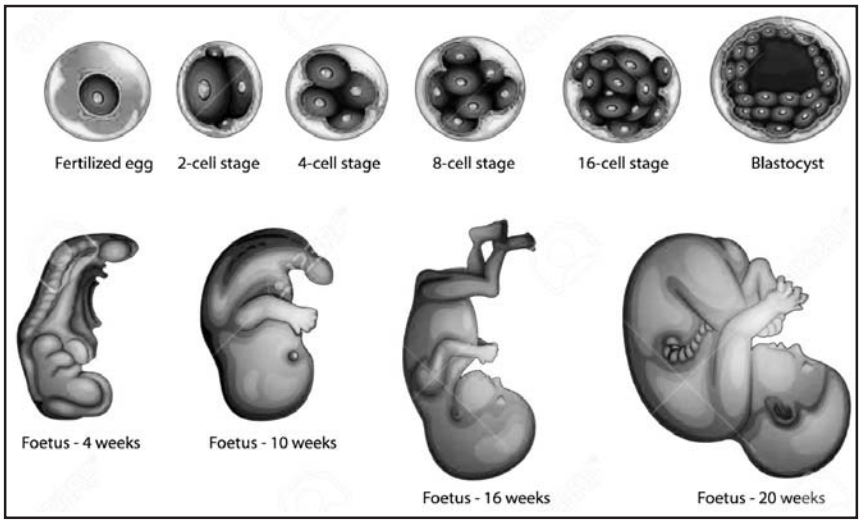


Fig. 11.5. Human embryonic and foetal development (by shutterstock.com).

dissolving an uterus lining. The trophoblast is divided into two layers: internal (cytotrophoblast) and external (syncitiotrophoblast). At the same time the embryoblast rapidly grows. Gastrulation occurs in the embryoblast. The primary entoderm forms the yolk sack on the 9th day of development. Primary ectoderm preserves to form a secondaty enctoderm, entoderm and mesoderm. The formation of a secondary ectoderm, entoderm and mesoderm occurs on 15th day of development in a second phase of gastrulation. The second phase of a gastrulation begins on 14 -15th day of development. It is performed by a cell migration and partial invagination. The cells of a primary ectoderm reproduce themself very fast. And then they start to move form the side of embryo disc to its end. Afterward they move in the central part of the disc and form a primary strip. Then these cells migrate between two layers and form a third layer mesoderm. Part of the primary strip material migrates to the endoderm layer and slides the cell of primary endoderm to a side position. There, primary endoderm cells take part in formation of a yolk sac. As a result of gastrulation we have a 3 layer embryo with ectoderm, mesoderm and endoderm.

At the end of the 3rd week the nervous plate is formed above a chord. Then, a layer of ectodermal cells located above the chord invaginates inward, forming a long groove - neural groove. The edges of this groove then move toward each other and fuse, creating a long hollow tube, the neural tube, which runs beneath the surface of the embryos back. The cell

line under nervous tube forms a chord. From both sides of a chord, the somites are created.

In the fourth week the organogenesis occurs. The eyes are formed. The tubular heart develops its four chambers and begins to pulsate. The arms and legs buds begin to form. The embryo is about 7.5 mm in length. The main visceral arches are formed. In 6th week of development, the embryo is 12 mm in length. Five brain subdivisions become clearly visible. Thymus and parathyroid gland are formed. The histogenesis of the alimentary canal and sex gonad differentiation occur. Between the 6th and 8th week of development the embryo expresses general features of a face. The head gets round in shape. The neck becomes clearly visible. Buds of the external ear and nose are formed. Eyes move from the sides upward and get closer together. Legs and arms become clearly differentiated with good distinguishable fingers. The tail is almost unseen. The big hemispheres start to grow. At the end of 8th week the embrionic period of development terminates. Almost all main organ systems have differentiated. The embryo is about 40 mm of length and 5g of weight.

The development of human provisional organs also has specific features. The beginning of amnion and chorion development occurs on 7-8th day.

The chorion forms from trophoblast. The syncitiotrophoblast touching an uterine lining dissolves it. At the end of the 2nd week, the primary villi of chorion are formed from cytotrophoblast. In the 3rd week of development, the mesodermal mesenhyme grows inside the primary villi, forming secondary villi. At the end of 3rd week, the vessels are formed inside of secondary villi which become tertiary villi. When tertiary villi have been formed, the region of chorion and uterus contact is called the placenta. The amnion is formed from primary ectoderm. For a while, the amniotic cavity is surrounded by an amnion cell and partially by trophoblast. Then, sides of amnion grow toward each other and fuse. After that, the amnion cavity is surrounded only by amnion cells. The yolk sack is formed from primary entoderm. Then, the primary yolk sack falls down and is replaced by secondary yolk sack on the 13th day. Allantois is formed as pocket of intestine. The allantois mesoderm fuses with chorion mesoderm, bringing blood vessels in it.

From the 9th week, the fetal period starts. It is characterized by intensive growth, further structures differentiation and starting of functioning. It terminates by birth.

11.5. THE GENE CONTROLLING OF EMBRYONIC DEVELOPMENT

Molecular-genetic processes determining first stages of ontogenesis in

non-vertebrate and vertebrate animals are similar. They start in prezygotic period. The basement of ontogenetic process is hereditary information inherited from parents. The realization of this information depends on an influence of external factors.

All multicellular organisms have a general scheme of ontogenetic processes consisting of three stages: information for gene expression, information from genes and information from proteins. On the first stage, the genes regulating ontogenes process acquire information for activation or repression from external factors, surrounding cells, hormones, etc. On the second stage, the information is taken from genes in the processes of transcription and translation. It results in synthesis of different polypeptids. They may be proteins regulating extracellular metabolic processes, reproduction rate, cell migration, gene activity. On the third stage, the information from the proteins is used for tissues and organs formation.

During oogenesis, the ovum produces rRNA, ribosomes, and those mRNA which will be needed after fertilization for the first stages of embryo development.

After fertilization, cleavage occurs. In the first stages, it is regulated only by information contained in the ovum. Active protein synthesis takes place, provided by ribosomes and RNAs from the ovum. Thus, mother and father genomes are completely repressed in this stage.

In amphibians, if two first blastomeres have been separated, they can develop two new organisms (Fig. 11.6). That means they are of the same value or totipotent (omniopotent). In tritone, the totipotentness of cells is preserved to the 16 blastomers stage, in a rabbit till 4 blastomeres stage. The same can be observed in human blastomeres. It is proved by birth of two, four and even seven monozygous twins.

In the blastula stage, the embryo cells loose there totipotentness. The differentiation starts. It is formation of different structures of the human body from almost homogenous mass. But in spite of differentiation, the cells keep all hereditary information, which is proved in J. Gerdon experiments in 1964-1966. The scientist took nucleuses from skin cells and intestine cells and put them into a frog ovum, without nucleuses. Many of them developed into new frogs. The same method was used to select Dolli sheep in England. If the same methods are used in a human, it gives us the possibility to get copies of geneticaly identical twins.

In frog embryogenesis, mRNA synthesis canceled in ovum starts again in the middle of blastula stage, when the embryo consist of 1,000 blastomeres; tRNA synthesis starts in the end of blastula stage; rRNA starts only in gastrula.

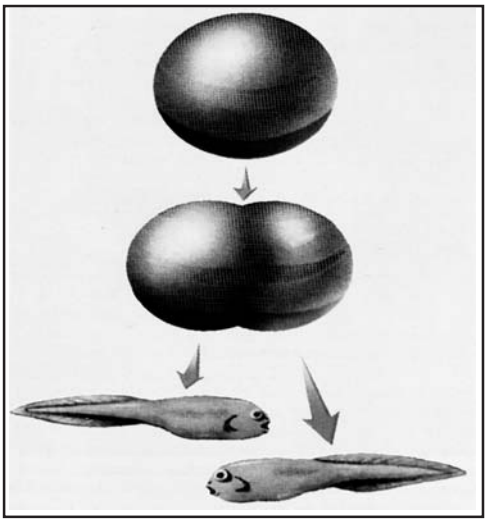


Fig. 11.6. The totipotent of frog zygote.

In mouse embyogenesis, the synthesis of mRNA, tRNA, rRNA starts earlier on the stage of 2-4 blastomeres. However, it also follows a plan determined by information acquired from a female through the ovum cytoplasm.

In the first embryogenesis stages till late blastula, only the part of genetic information concerning general metabolic processes is active. Then, tissue specific genes become activated that means the embryonic cell differentiation starts.

In differentiated cells, most of the cells are depressed. The number of active working cells is different form cell to cell. It does not exceed 10-20%, but it consists of different genes. All structural genes of eukaryotes can be divided into three groups:

1. Genes actively working in all organism cells. These genes code enzymes of metabolic exchange, common macromolecules.

2. Genes actively working only in tissues of one type. These genes code myosin in muscular tissues, and collagen in connective tissues.

3. Genes needed to perform special function by specialized cells, like hemoglobin synthesis in erythroblasts, hormone synthesis in endocrine cells, digestive enzymes synthesis in alimentary canal. Cells which are very close in structure and origin may differ in some gene activity. For example, properties of cartilage in intervertebral discs differ from properties of cartilage of joints surface lining.

11.6. THE EMBRYONIC INDUCTION

In animals, the stem cell populations are separated from each other and then they give rise to different tissues and organs. This is a period of embryonic induction setting. Embryonic induction means that one tissue or group of cells can have influence on development of other cells. Such phenomenon was discovered by G. Speerman and G. Mangold in 1924. The first inductor is cells of a dorsal part of blastopore that induce differentiation of ectoderm cells and nervous tube, which in turn induce a chord formation on a dorsal part of an endoderm. The chord induces formation of an alimentary canal from the cells of ventral part of endoderm (secondary inductors). The mechanism of induction is concluded in formation of specific substanses which migrate to surrounding tissues to change their properties. The nature of inducters is unclear. The modern view is that inductors are chemicals which switch on and off specific genes blocks in surrounding cells.

11.7. THE CRITICAL PERIODS IN EMBRYOGENESIS

The study of animal development resulted in discovery of the so-called "critical periods of embryogenesis". The term is used to point the period when the embryo is very sensitive to various harmful influences, which can result in developmental defects. Organism's sensitivity varies in different embryogenesis stages. In some periods, the embryo is more sensitive to chemicals, in others an embryo is more sensitive to temperature changes. Critical periods are characterized by the increased metabolism and respiration and decreased of growth rate. There are critical periods in development of the whole organism and critical periods in development of particular organs. The critical periods coinside with active morphological differentiation and with the begining of the next developmental stage.

As for human development, the following critical periods were defined by P.G. Svetlov: implantation (6-7 day of development), placentation (end of 2nd week of development), and perinatal period (labor). In critical periods, all environmental conditions of embryo are changed and all systems are restructured (changing in respiration pattern, in circulation, in nutrition). Studies of critical embryogenesis periods show the importance of preventive measures against harmful habits for a pregnant woman.

11.8. THE ENVIRONMENTAL FACTORS ROLE IN EMBRYOGENESIS

The embryo development occurs with constant interaction between hereditary and external factors. It results in phenotype formation, which is the result of genetic information realization, in particular environmental

conditions. The development of a mammalian embryo occurs in relatively constant condition, but this does not exclude influences of external factors on development, especially in modern ecological conditions. It was stated that metabolic imbalance, vitamin deficiency, infections, and endocrine pathology in a pregnant woman can cause severe developmental defects in embryo. If one endocrine gland worked inappropriate in a mother, the same gland function may fail in the embryo. The excess of some hormones can cause defects in development. For example, when hydrocortisol was injected into pregnant rats on 12th day of pregnancy, all newborns had a defect of facial structure, but all other organs developed successfully. That shows that a hormone action is selective. The woman contracting rubella (German measles) can upset organogenesis in the developing embryo during the first and second month of pregnancy. Most spontaneous abortions occur in this time.

The physiological state of the female organism has direct influence on offspring health. This must be considered by the doctors of gynecological ambulance.

Today, a modern man undergoes influence from various chemical, physical, biological and psycological factors. Such influences on a pregnant woman organism can result in development defects in embryo or even to prenatal death. Teratogenic (from Greek “teratos” - moron) effect can have chinin, alcohol, coffee, different toxins, protozoa (toxoplasma), and viruses (German measles). Some drugs have teratogenic effect. For example, many pregnant women took the tranquilizer talidomide to minimize discomfort associated with early pregnancy. Unfortunately, this drug has not been adequately tested. It interferes with fetus limb bud development, and its widespread use resulted in many deformed newborns. There are some more drugs having a similar effect on embryogenesis. The X-rays and other ionizing radiation have a strong teratogenic effect on an embryo development. Doctors have to keep it in mind while prescribing different diagnostic procedures, drugs and physiotherapy, especially on early stages of pregnancy.

11.9. THE CORRELATIONS IN ONTOGENESIS. THE ONTOGENESIS AS A HOLISTIC PROCESS

Organism is developed as a whole system together with environmental conditions. The range of factors can determine organism development. Genetic factors provide determination of development. That is why chicken zygote develops to mature chicken and human zygote develops to mature chicken, in spite of environmental factors. The ooplasm segeregation leads to formation of different cell types in an embryo. Then, the embryonic

induction starts. The different population cells interact with each other stimulating growth and differentiation. In this stage, ontogenesis is directed by cell to cell interactions.

Some factors can be very harmful for an embryo development. They can be physical (temperature changing, ionizing radiation), chemical (drugs), and biological (infections and invasions) nature. They can disturb embryogenesis even in small doses.

The organs structure and function are closely connected. That means that physiological events have a morphological basis. The organism is not a mosaic of parts, organs or traits. The organism development, as a holistic system, is provided by complicated system of connections or correlations. They are three correlation types – genomic, morphogenetic and functional.

Genomic correlations are provided by a whole genome. They are directed by genes and by biochemical processes in cells. The mechanisms of such correlations are the gene genotype balance, gene linkage, gene interactions and the pleiotropic gene action. Thus, genomic systems regulating cell proliferation and cell death regulate the body proportions in male and female organism.

Morphogenetic correlations are interactions between two or more morphogenetic processes. The example is embryonic induction (chord and nervous tube interactions, eye's lens induction of cornea formation). Same processes occur during embryonic formation of various organs from same buds. For example, in mammals from gills arches the jaws, larynx cartilages, processes styloideus and auricular bones are formed.

Functional correlations are correlations between organ parts which is functionally dependent. For example: the correlation between nervous centers, nerves and peripheral organs development; the correlation between muscle, nerves and vessels growth in the developing arm; the correlation between secondary sex signs and a gonad development.

For different organs, there are different correlation types. New correlations appear during ontogenesis. That leads to new differentiations. The new correlations appear as result of interactions of differentiated parts. These interactions lead to next level of differentiation. Organism is developed all together.

CHAPTER 12. POSTNATAL ONTOGENESIS. AGING AND DEATH OF ORGANISM

12.1. POSTNATAL ONTOGENESIS

The postnatal ontogenesis or a period of postnatal development is the stage of ontogenesis which begins when an embryo exits the egg shells or birth and ends with a death of the organism. Postnatal ontogenesis is divided into three periods: prereproductive, reproductive and postreproductive.

The prereproductive period is also called the period of growth and morphogenesis. It is characterized by the continuation of the early fetal life organogenesis and the increase of a body size. By the beginning of this period, the body can exist and develop outside the female or outside of egg shells. From this point begins the function digestive tract, the respiratory system and sense organs. The nervous, circulatory and excretory systems begin to function even in the embryo. During the prereproductive period a final shape specific and individual characteristics of the organism and the individual achieves the characteristic dimensions. The prereproductive period is called juvenile. This period depends on the type of ontogenesis proceeds differently in the direct and indirect development. In the direct development of neonates differ from adult sizes by shapes, underdevelopment of a number of organs and body proportions. The larva undergoes of the transformation or the metamorphosis in the indirect development.

The reproductive period or the period of maturity is characterized by the completion of the formation of the reproductive system and the start of reproduction. The duration of this period in some species (silkworm) lasts several days, while others for many years (mammals, man).

The postreproductive period or the aging period occurs after the reproductive period. The old age is naturally and inevitably coming the final period of ontogenesis. The onset of old age is associated with the aging of the organism. These concepts should be strictly differentiated. Aging is a cause of the onset of old age that is, old age is a consequence of the aging process.

12.2. THE GROWTH OF THE ORGANISM

The development of any living organisms in ontogenesis is characterized by growth. The height is a quantitative trait characterized by an increase in the number of cells and accumulation of extracellular mass formations, the linear dimensions of the body. The body weight increases as long as the speed of the assimilation rate is higher in comparison of the dissimilation rate. All living organisms can be divided into two groups by the nature of

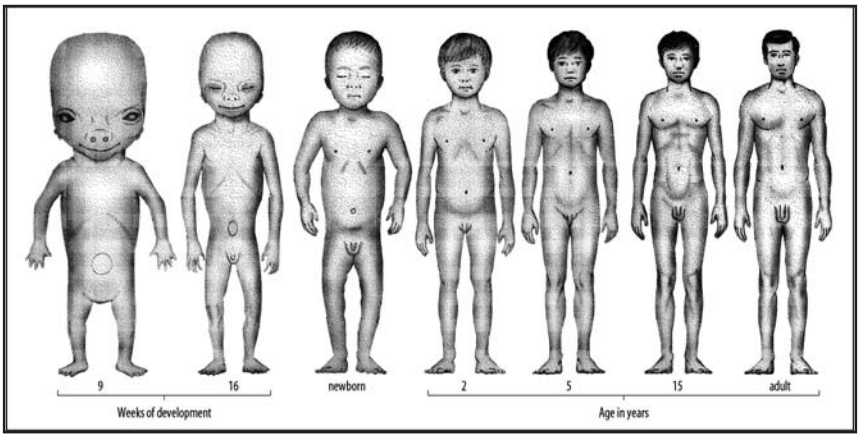


Fig. 12.1. Changes of body forms and proportional in human ontogenesis.

the growth: with certain and uncertain growth. The first group includes insects, birds, mammals; the second one – molluscs, crustaceans, fish, amphibians, reptiles. The increase of body corresponds to the increase in a length and a weight.

The most intensive growth in humans occurs in the first year of life (Fig. 12.1), when a child body increases by 23-25 cm in length. In the second year the growth rate slows down, but remains high (10-11 cm), in the third year – 8 cm. At 4-7 years a child grows by 5-7 cm. 11-12 years in girls and 13-14 years in boys to 16-17 years (7-8 cm per year) the growth burst is observed.

12.3. INFLUENCE OF EXTERNAL AND INTERNAL FACTORS OF ENVIRONMENT ON THE GROWTH OF ORGANISMS

The growth process in humans and animals depends on many exogenous and endogenous factors. Good nutrition is needed for the normal development of the body. Food should include the necessary proteins, fats, carbohydrates, minerals. The role of light is determined by its participation in the synthesis of calciferol in a body (vitamin D_2) and the pigment melanin in the skin. Therefore, the light can be considered as an important factor in the growth and a development. Exogenous factors affecting the growth and a development of the organism also include vitamins, which depend on the solubility. They are divided into lipid-soluble (vitamins A, D, E, K) and water-soluble (vitamins C, P, PP, group B).

Vitamin A is a part of the visual pigment rhodopsin, and thus affects the visual acuity, as well as on the development of skin epithelium, the

conjunctiva and growth of the organism. Vitamin D_2 regulates the exchange of calcium and phosphorus. Vitamin K is involved in the clotting process and vitamin E influence on gametogenesis. Vitamin C has an effect on the strength of the vascular wall and the growth of the organism, vitamin P – on capillary permeability and resistance; B_1 and B_6 vitamins – the nervous system; vitamins B_2 and PP – the normal development of the mucous membranes, conjunctiva, skin; vitamin B_{12} – in the process of hematopoiesis.

The great importance is related to hormones. The pituitary gland is the central endocrine glands that control the operation of the hormones of peripheral endocrine glands (thyroid, adrenal gland, the islets of Langerhans of the pancreas, testes and ovaries). The pituitary is distinguished by anterior, intermedial and posterior lobes which produce except tropic, own hormones (Fig. 12.2). Tropic hormones of the anterior pituitary include thyroid-stimulating hormone, which regulates thyroid function, adrenocorticotropic – adrenal gland, follicle-stimulating and luteinizing hormones – gonads. The anterior lobe of pituitary secretes its own growth hormone (GH), which affects protein synthesis, which provides increased cell proliferation, increase in linear dimensions and weight of the body. If the decline in growth hormone production is observed in a child, then the pituitary dwarfism

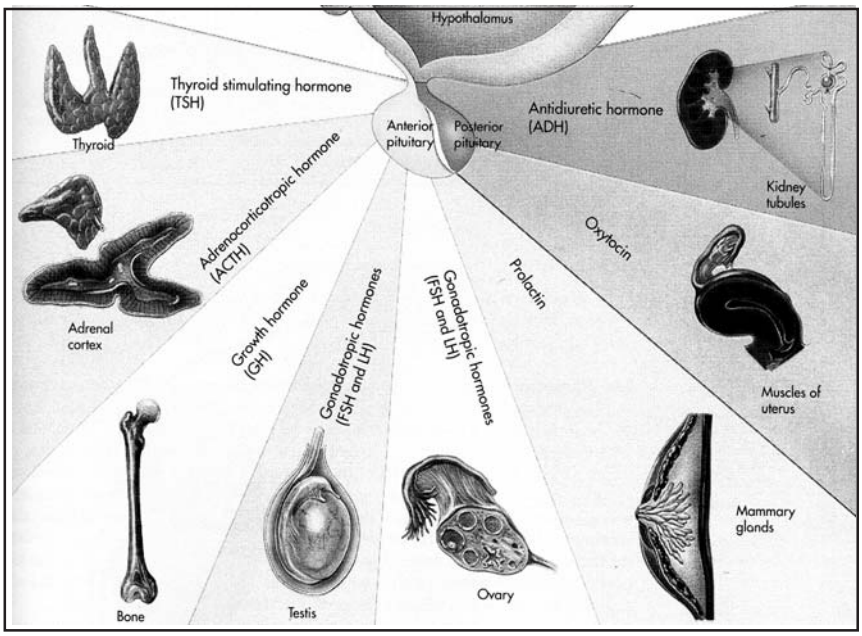


Fig. 12.2. The main hormones of human hypophysis (by Raven & Jones).

is developed. With the increased secretion of growth hormone there is a gigantism. Acromegaly (overgrowth of bones of hands, feet and face) is developed if growth hormone secretion is enhanced in an adult. The intermedial lobe of the pituitary produces melanotropin, which regulates the synthesis of melanin in skin cells. The posterior lobe of the pituitary accumulates two hormones of hypothalamus. The vasopressin ensures the regulation of blood pressure and urine output. The oxytocin stimulates the contraction of smooth muscles of the uterus.

Thyroid hormones (thyroxine, 3-iodothyronine) increase the oxidative processes in the mitochondria. At insufficiency of thyroid function, the cretinism is developed in a child, characterized by mental retardation, delayed growth and sexual development, a violation of body proportions, since long bones are developed short and thick. The hyperthyroidism in the adult leads to disease – hyperthyreotoxicosis, characterized by increased metabolism, goggle-eyed, lability of the nervous system and other features.

Parathyroid glands produce parathyroid hormone that affects the metabolism of calcium and phosphorus and their elimination from the human body. Excess parathyroid hormone in the body leads to the destruction of bone, fractures may be spontaneous, but its lack causes the decrease of the calcium content in the blood, tetany, delaying development of teeth.

The adrenal cortex produces aldosterone, corticosterone and glucocorticoids, which regulate diuresis, blood pressure, mineral and carbohydrate exchanges. The medulla secretes adrenaline and noradrenaline, which ensure the regulation of a vascular tone.

The islets of Langerhans of the pancreas secrete insulin and glucagon antagonist, providing regulation of carbohydrate metabolism. Leydig cells of the testes produce testosterone, through which the regulation of spermatogenesis are ensured and secondary sexual characteristics are formed.

Ovarian cells secrete estrol, estradiol and progesterone, which ensure oogenesis, ovulation and the formation of secondary sexual characteristics.

Alcohol and drugs are the factors that have a detrimental effect on the human body. The ethanol readily penetrates from the mother through the placenta to the fetus. The content of blood alcohol fetus and its metabolism products may reach 70-80% of the amount of alcohol in the blood of pregnant women. In some cases, pregnant women who drink alcohol, have spontaneous abortion, stillbirth or death shortly after birth. The complex of specific losses arising in the fetus is alcohol intoxication (alcohol embryopathy). In moderate and severe stages of alcohol embryopathy numerous physical defects and deformities are added, as well as various mental pathology. Alcohol is a cause of premature aging and reduces the length of human life.

12.4 ACCELERATION

The acceleration is observed at the stage of fetal development. The postnatal growth in girls is ceased to 16-17 years and in young men - to 18-19 years. In adults, growth is increased in comparison with previous generations, mainly due to its acceleration at puberty. There are many hypotheses about the causes of acceleration (change in the magnetic field of the Earth, the theory of heterosis, or migration of people, improve nutrition, urbanization, etc.). The acceleration of the process is rather the result of many factors. In the younger generation accelerated growth of breast circumference and transverse dimensions of the body are behind the body length. The size of the heart, muscles and other organs and tissues increase slowly. This temporary disharmony is the peculiar organism of teenagers. Due to the acceleration it is somewhat deeper. Doctors, teachers, sports coaches should keep it in mind. The external physical development may be a lag in formation of various organs, systems, functions. So, in 16-18-year-old pregnant women, not to mention the 14-15-year-olds, a high percentage of various complications of pregnancy and fetal malformations are recorded. The effect of acceleration intrudes into everyday life. For example, increasing the length of the body must be considered when designing the height of ceilings in the rooms, furniture, layout controls, etc. The acceleration problem can be solved as a result of the joint efforts of specialists in various fields of knowledge, painstaking analysis of a variety of factors.

12.5. CONSTITUTION

The constitution is the special features of the characteristics of growth of the organism.

M.V. Chernorutski proposed to distinguish asthenic, normostenic, hypersthenic types of a body. Astenics have the low position of the diaphragm, heart elongated drop shaped, elongated lungs, blood pressure tends to decrease, the metabolism slightly increased. Hypersthenics have the high position of diaphragm, voluminous stomach, long intestine, heart relatively large, blood pressure tends to increase, dominated by the processes of assimilation, there is a tendency to obesity. Normostenic is moderately well-fed, is proportional to the type of development.

E. Kretschmer identified three morphological types: leptosomic, pyknic and athletic. The leptosomic type is characterized by a slight development in width, all diameters and circumferences below the average body, narrow shoulders, thin arms, the chest is long and narrow. People of the endomorph type are characterized by large dimensions of the internal cavities of the head, chest, abdomen, the relative prevalence of the perimeters and

diameters. The picnic type has a dense shape, short neck, a massive, relatively short limbs. This type is formed at a mature age, after 30 years. In humans there is an athletic type of massive rough skeleton, good muscle development, broad shoulders, the pelvis is relatively narrow, big feet and hands. E. Kretschmer showed a difference in the manifestation of the emotional sphere, depending on a body type in patients.

The classification of W. Sheldon is based on the theory of development of all body systems of the three germ layers. He singled out ectomorphic, mesomorphic and endomorphic types of a constitution (Fig. 12.3), for which characteristics he introduced the evaluation scores for each component of the tissue (1 to 7). Score 1 corresponds to the lowest severity component, the score 7 – maximum severity. The deadline ectomorphic option (1-1-7) matches the description of an asthenic type. The deadline mesomorphic option (1-7-1) matches the description of a muscular type. Deadline endomorphic option (7-1-1) is characterized by the round-spherical shape, a tendency to obesity, the prevalence of body anteroposterior dimensions of the cross. W. Sheldon in his work further developed E. Kretschmer's idea about connection of a body type and temperament. The ectomorphic type is characterized by emotional restraint, reticence, greater resistance to the action of alcohol. Mesomorphs are characterized by confidence in movements and posture, extroversion. Alcohol can cause violent

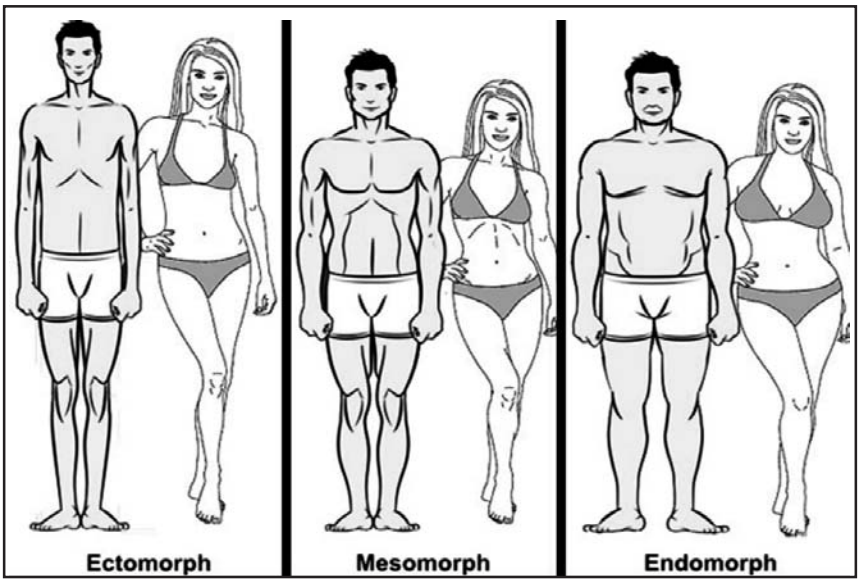


Fig. 12.3. Classification of human body forms by W.Sheldon.

manifestations in them. Endomorphs have relaxed posture, ease of communication and expression of feelings, smooth change of mood, desire for people in difficult periods of life.

Already at the very origins of constitution the concept was developed in a close connection with the doctrine of "predisposition" of the organism to certain diseases. Many researchers have noted the great frequency of schizophrenia at high ectomorphic development component and depressive psychosis - at elevated values of endogenous and mesomorphy components.

Leptosoms have a higher frequency in by tuberculosis. They are characterized by irritability and reactivity, increased incidence of neurosis, vegetative dystonia, hypotension, gastritis, gastric and duodenal ulcers. Mesomorphs have the predisposition to diseases of the cardiovascular system (coronary sclerosis, heart attacks). The etiology of heart attacks more likely to occur with respect to the excess growth of weight. Children of mesomorphic type have also an increased frequency of functional disorders of the cardiovascular system. However, these trends are not always detected. At the same time there is no doubt that modern man physical and mental health is largely due to the social environment. The constitution substantially eliminates the possible effect of natural selection within the species Homo sapiens.

12.6. AGING. ROLE OF BIOLOGICAL AND SOCIAL FACTORS IN THE AGING

Gerontology is the special biological discipline which studies tbe laws of aging. Deep wrinkles, loose skin, drooping corners of the mouth, gray-haired temples are typical external signs of age. However, if to hold a special study, it appears that the difference in indicators such as blood pressure, the frequency of heart rate, electrocardiogram, electroencephalogram, blood glucose, gastric analysis of the data will be minimal. With aging, due to the regulatory process, there are adaptive mechanisms. They resist to fading and sharing functions, promote their preservation or oppose a drastic change. That is why at a certain stage of aging, despite some obvious structural changes may persist for an optimal level of activity of a number of systems. Aging is inevitably and naturally increased with time, developing long before the old age a multi-unit biological process will inevitably lead to reduction in adaptive capacities of the organism, increasing the likelihood of death.

Aging is the result of self-limiting mechanisms that reduce their potential at the primary changes in the regulation of the genetic apparatus. According to the classification adopted today humans are divided on elderly people aged 60-74 years, old – over 75 years, long-lived – over 90 years. This

division is conditional. It is possible to grow old in 50 years. It is possible to be in a good health and in working capacity in 70 years. Having started the movement in respect to the same pace, people come to the finish line at different times. I. Mechnikov and others spoke of existence of physiological and premature aging. It is absurd to consider any bad health as premature aging. Obviously, premature aging is determined by those factors that are the most profound and lasting change course and for fundamental metabolic processes in cells associated with its primary and most important structures. In purely theoretical terms premature aging should be defined as the degree of non-compliance of the genetic program of the individual development with its concrete implementation. Numerous examples show that physiological aging is associated with vigorous activity. Examples of centenarians show that physiological aging cannot be considered necessarily as a heavy and burdensome period of life.

Geriatrics is special research science to provide medical care for the aging. This is the section of clinical medicine dealing with diseases especially in elderly and senile and develop methods for their treatment and prevention.

12.6.1. HYPOTHESIS OF AGING

There are a 500 hypotheses about the aging process, most of which is of historical interest only. Today gerontology seeks to uncover the initial changes and subsequent chain of cause-and-effect relationships that lead to profound disturbances of the body work. Removal of the gonads in human, as evidenced by numerous examples of castration, do not increase human lifespan. Attempts by scientists to achieve rejuvenation by introducing extracts of the sex glands, gonads, or by transplanting their duct ligation ended unsuccessfully. I. Mechnikov believed that life expectancy depends on compliance with certain conditions, which he joined in the doctrine of a normal life and called orthobiosis.

The orthobiosis concept involves hygiene rules, hardworking moderate life, a balanced diet, including eating dairy products to create an unfavorable environment for bacterial putrefaction. This theory, like many others, explained only one cause of aging. Most researchers agree that the primary mechanisms of aging are associated with shifts in the genetic apparatus, in violation of the protein biosynthesis. Many modern theories suggest that aging is a consequence of primary changes occurring in the genetic apparatus of cells.

Quantitative and qualitative changes take place in nucleoprotein complexes in ontogenesis, which lead to a change in the intensity of their self-renewal and reduce the activity of proteinsynthesis systems. Increase

of histone content, their relations to DNA are more durable and the content of non-histone proteins decreases is observed in old age.

Free radicals (chemical species having the unpaired electron in an outer orbit) influnce on increase of the genetic damage. Radicals such as -H, -OH, -OOH, are extremely reactive and can damage the DNA molecule and the cell membrane.

Some researchers link the initial changes of aging with changes in biological properties of macromolecules; RNA, DNA, chromatin proteins, enzymes. Some hypotheses explain the fundamental principle of aging in an increasing deterioration with age structures in the range of macromolecules to the body as a whole, resulting in the state not compatible with life. Aging structure hypothesis includes genetic predisposition, conditions and way of life, from which the rate of aging depends

According to genetic or software hypotheses aging is under direct genetic control, which is carried out by means of special genes. It is associated with the presence of specific genetic programs.

Some software hypothesis are based on assumption that the body biological clock functions in accordance with the age-related changes which occur. The role of "hours" is given to the thymus, terminating operation during the transition of the body into mature age.

A major role in recent years is the hypothesis of existence of telomerase – an enzyme shortening the length of specific areas of chromosomes (telomeres). Telomerase activity and telomere shortening leads to organism aging.

Unified theory of aging has not yet been created, but it can be assumed that many of the elements of the particular theories will be included in future synthetic theory of aging. The intensity of the aging process is caused not only by biological factors, but also a social, which largely depends on the duration of human life and the pace of aging.

12.6.2. DEATH OF THE ORGANISM. EUTHANASIA

The final stage in the life of an organism is the negation of life, or death of the individual. Death is a natural phenomenon. It is prepared by the whole course of ontogenesis. Death always finds its expression in the form in some or other chance. Death of a human, even at ones old age occurs due to various reasons. Random reasons can cause premature death in at any period of ontogenesis. In multicellular organisms death always appears in the same form. Ordered exchange is replaced by erratic exchange, which decomposes under the influence of microorganisms. In unicellular organisms there are two forms of ontogenesis completion: death from accidental causes the formation of a corpse and the natural conclusion

of ontogenesis division. The idea of immortality of unicellular organisms is borrowed from religious and mystical ideas of the immortal soul. According to religious beliefs, death is an instantaneous act, caused by the separation of the soul from the body. Biology completely refused this view. The death is slowly and consistently commit process.

There are clinical and biological deaths. Clinical death is characterized by cessation of the heart rate, breathing and lack of reflexes. This is the first and still reversible stage of dying. At the moment of clinical death, all organs and tissues remain alive, their metabolism remained orderly. Its duration is 3-5 minutes. Biological death is an irreversible process, which starts with the death of the cerebral cortex cells and subsequent death of cells of all tissues and organs. Biological death is characterized by disordered chemical reactions in cells, tissue autolysis and decomposition. Doctors can recover organism in the state of clinical death, applying mechanical ventilation, cardiac massage, the use of special drugs. Currently, methods of revitalizing the human body have been successfully used in the clinic (resuscitation) which created a special intensive care unit.

The concept of "euthanasia" is closely related to the concept "death"– a voluntary withdrawal from life through or with the assistance of a doctor. Euthanasia is essentially contrary to doctor's commandments, who taking the Hippocratic oath, vows to treat a patient until the last moment of ones life. The shape of this thought is true. However, we have no right to ignore the fact that the struggle for the life of the patient is valid as long as there is hope, that his salvation is possible.

The euthanasia can be done in two ways: passive and active. Passive euthanasia means the termination of the patient's treatment or disconnecting him from the life-sustaining equipment. Active euthanasia means the introduction of solution to cease patient's life under conditions of maximum physical and psychological comfort. At present, the only country that uses euthanasia is the Netherlands and some states of the USA. In other countries, euthanasia issues are just discussed in the theoretical aspect.

CHAPTER 13. ONTOGENETIC HOMEOSTASIS

13.1. GENERAL LAWS OF HOMEOSTASIS

Homeostasis as an open living system exists because of the preservation of its integrity. Preserving the integrity of the individual structural properties of the organism is one of the most common biological laws. This law provides a number of generations in the vertical playback mechanisms and throughout an individual's life – homeostasis mechanisms.

Homeostasis is relative dynamic constancy of composition and properties of the internal environment and the sustainability of basic physiological functions of the body. Homeostasis is the genetically-fixed adaptive property of the organism to the usual environmental conditions. These conditions can go beyond the "norm" for short or long time. In such cases, adaptation phenomena are characterized not only by the restoration of usual properties of the internal environment, but also a short-term change in the function (increased heart rhythm and increase the frequency of respiratory movements with enhanced muscle activity). Homeostatic reactions can be used to maintain steady state levels, to eliminate or limit the action of harmful factors on development or maintenance of optimal forms of interaction between organism and environment in the changed conditions of its existence. All these processes determine the adaptation. The concept of homeostasis is not only the known constancy of various physiological constants of the body, but also includes the processes of adaptation and coordination of physiological processes that ensure the unity of the body not only in norm, but also in changed conditions of its existence. Main components of homeostasis can be divided into three groups: A. Substances which provide cell needs (proteins, fats, carbohydrates, sodium chloride, calcium and other inorganic substances, oxygen, hormones). B. Ambient factors affecting the cellular activity (osmotic pressure, temperature, concentration of hydrogen ions). C. Mechanisms for structural and functional unity (heredity, regeneration, immunobiological reactivity).

The principle of regulation has been so widespread that it has arisen in the study of a special science of the general patterns of management processes and regulation called cybernetics. Cybernetics is the science of purposeful and optimal control of complex processes occurring in nature, in human society, or in the industry. Using the terminology of cybernetics, we can say that a living organism is a complex controlled system, in which constantly many variables of external and internal environment interact. Common to all systems is the presence of certain input variables converted in it in accordance with its functions in output variables. The dependence

of output variables from input is defined by the law of the system behavior.

In biology, the input variables are characterized by concepts: reason, stimulus and a weekend – consequence, effect, response, reaction, etc. The main role in the processes of self-regulation plays feedback, i.e. the effect of the output signal on the system control. There are negative (-) and positive (+) feedbacks. The negative feedback reduces the effect of input influence on the output value. The positive feedback, on the contrary, increases the effect of the input signal. The negative feedback helps to restore the original level, whereas a positive relationship often takes the system further away from the initial state. However, the positive communication can be the basis of self-regulation. All kinds of self-operate have same principle: self-deflection on the ground level serves as a stimulus to activate the mechanisms correcting the violation. There are the following levels of homeostasis mechanisms: genetic, cellular and systemic.

13.2. GENETIC MECHANISMS OF HOMEOSTASIS

13.2.1 TRANSPLANTATION OF ORGANS AND TISSUES

The transplantation as a manifestation of the gene control mechanisms of regulation of gene expressed homeostasis in the fact that all the processes of homeostasis are genetically determined. In particular, these are process of matrix synthesis, repair of genetic material, expression and repression of genes, conservation of diploid state of somatic cells in eukaryotic, gene controls of synthesis of the blood group antigens under AB0 system, Daffi, Luteran, MN, Rh-factor, tissue compatibility. From a genetic point of view, one can distinguish between elementary and systemic manifestations of homeostasis. An example of elementary manifestations of homeostasis can be histocompatibility of tissues and organs, which determines the possibility of transplantation of tissues or organs.

Transplanted portion is called a graft. The body which gives the tissue or organ transplant is called a donor. The body to which a graft is transplanted is called recipient. There are autotransplantation, syngenic transplantation, allotransplantation (homotransplantation) and xenotransplantation (heterotransplantation). The autotransplantation is a case when the donor and the recipient is one organism. The syngenic transplantation is carried out in identical twins. The allotransplantation is a case when a donor and recipient are different individuals of the same species. Successful allotransplantation in human can be in selection of donors and recipients using histocompatibility of genes. The xenotransplantation is a case when a donor and a recipient are different species of organisms. Success of

transplantation depends on transplantation immunity which determines the immunological reaction (tissue incompatibility with homo- and heterotransplantation). Transplantation immunity is determined by the genetic constitution of the donor and recipient. Tissue incompatibility genes are the genes responsible for the synthesis of antigens, causing the reaction to transplanted tissue. The study of genetics of human histocompatibility antigens is of great scientific and practical importance, since it allows the selection of compatible donors and recipients for the transplant of organs and tissues and to solve other problems. The system of HLA (Human lymphocyte antigen) is the main genetic histocompatibility system in a human. This name is given because histocompatibility antigens are detected on the surface of leukocytes and are detected by antiserum to these cells. HLA system is in the sixth chromosome and represented loci A, B, C, D (DP, DQ, DR sites). This set of linked genes has a length of 2 map units (Fig. 13.1). The main histocompatibility system genetic structure in different animals and in a human is the same. In 1975, the nomenclature committee of WHO and the International Union of Immunological Societies histocompatibility adopted a common terminology to describe the genetic loci and alleles of HLA system.

System HLA antigens is divided into two groups which are controlled by closely linked genes. The antigens of the first group are identified in leukocytes serological methods via complement-dependent lymphocytotoxic test and is called the SD-antigens (serum defined). They are controlled by three loci HLA-A, HLA-B, HLA-C. Antigens of HLA system of the second

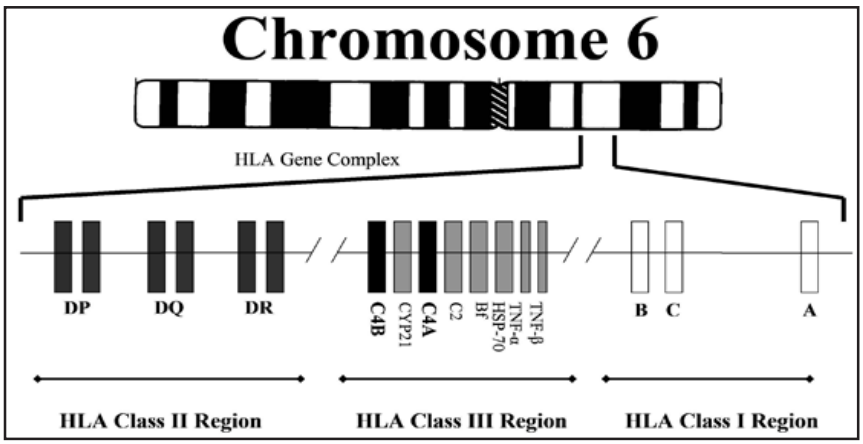


Fig. 13.1. Structure of HLA system.

group are determined by the method of mixed cultures of lymphocytes and designated LD - antigens (lymphocyte defined). LD-antigens controll sublocus HLA-D of sixth chromosome.

Each of the genes controlling human HLA-antigens, has a large number of alleles. Sublocus HLA-A has 23 alleles, sublocus HLA-B – 49 alleles, sublocus HLA-C – 8 alleles, sublocus HLA-D – 44 alleles.

Among unrelated parties the possibility to find HLA-identical donor is ranged from 1: 4,000 to 1: 7,000. The identity of a donor and recipient on HLA system antigens is important for organ and tissue transplants. Transplantation of kidney, identical to 4 antigens HLA system provides its engraftment to 70% within two years, while transplantation graft identical in 3 out of 4 antigens – 60%, in 2 – 45% and in 1– 30% of cases. Donor selection system for organ transplants must be made in special centers, equipped with powerful computers. An example of such an organization is a "Eurotransplantat" in the Netherlands. In some countries, tens of thousands of people were typed using the HLA-system. 14 isoantigens systems are described in human erythrocytes, including more than 70 different antigens, the study of which led to emergence of immunogenetics. Another genetic information is bacteria, viruses, protozoa, helminthes, arthropods, including modified cells of the organism. All these factors are antigens, substances which when administered to an organism form antibodies or other form of immune response. The main importance of the immune system is in recognition of "own" and "another", in maintaining a constant internal environment – homeostasis.

13.2.2. MORAL, ETHICAL AND LEGAL ASPECTS OF TRANSPLANTATION OF TISSUES AND ORGAN

Donors for transplants are mainly in intensive care units of hospitals. Potential donors are patients with severe brain damage whithout cells activity or patients with biological death. The body of these patients is alive. In order for them, the determination of death is necessary to carry out for a possible remove of organs.

In public health organizations doctors carry out a statement of patient's death in the cases: the patient has a cardiac activity; patients underwent mechanical ventilation; there are preliminary data on total and irreversible loss of brain function in patients. The structure of the consultation for stating patient's death includes physicians with experience in this specialty for at least 5 years, including: the physician and resuscitator; neurologist or neurosurgeon; other medical specialists to conduct additional research. Medical specialists involved in removing and transplantation of human

organs and tissues cannot be included in the structure of the consultation for ascertaining of a death.

In transplantation, there are two types of donors - living and deceased. The living donor is a person who gave a voluntary consent in the prescribed manner on remove of human organs and tissues to be transplanted to the recipient. The deceased donor is a person which organs and tissuses are remove after the death for transplantation to the recipient. Living donors can not be in following cases: persons are not husband (wife) or close-relatives; minors; incapacitated person; persons suffering from mental illness or having a disease dangerous to life and health of the recipient; pregnant women; children left without parental care.

Removing of organs from a deceased donor is not allowed if: a person has expressed disagreement on removal of his organs for transplantation after death; authorities submitted a statement of disagreement on removal of organs for transplantation, written by husband (wife), close relatives or legal representative of a deceased donor.

Commercialization of organc and tissues donation to obtain illegal profits by saling donor's organs or tissue to recipients in the public and private health facilities. Purchase and sale of organs is prohibited in all over the world.

13.2.3. PRESERVATIONS OF TISSUE AND ORGANS

Preservations of organs and tissues are methods of influence on the whole organism isolated from the part physical, chemical, biological factors that allow to maintain its vitality and full function for considerable time of existence outside the body. Preserving organs and tissues is a subsidiary undertaking and the stage of transplantation of organs and tissues.

For example after the cessation of a blood circulation, the brain dies after 5-6 minutes, the liver - 20-30 minutes, kidneys - 40-60 minutes, the heart - 60 minutes and the limb may remain viable under these conditions for 4-6 hours. The preservation of organs and tissues is an important part of transplantation. It solves the problem of reliable and long-term preservation of organs for hospitals.

To decrease the ischemic damage 3 groups of methods of isolated organs and tissues are used:

1. Methods of biological perfusion providing for maintaining the initial level of metabolic activity in the organs by perfusion of blood in the normothermic mode or close to it (t = 34-38 °C).

2. Methods of hypothermic preservation of organs and tissues that are based on providing a reduced but adequate graft metabolic activity by

keeping it at t = 8-12 °C (hypothermic perfusion) or t = 2-4 °C (cold without perfusion pharmaco-preservation).

3. The method of deep cooling (cryopreservation) based on conditions ensuring the fullest reversible termination metabolic activity in transplants (tissue sections, cell suspension) by storing them at temperatures below 0 °C (frozen storage).

Separation preserving organs and tissues or agency has stocks of preserved transplants (organs and tissues), typed on immunologic compatibility factors, and their exchange with other medical institutions both within the country and abroad, called banks of tissues and organs. Preservations allows procure organs and tissues, to stockpile tissue grafts in a bank to be used as necessary to produce grafts exchanged between medical institutions, selecting the most appropriate for the immunological compatibility to the recipient, who is sometimes for many hundreds of kilometers from the receiving transplant. The following organs and tissues used for preservation: heart, blood vessels, lungs, trachea, liver, kidney, endocrine glands, intestines, limbs, teeth, bone marrow, joints, the stem cells, blood, skin, bone, cartilage, fascia, cornea, sclera, pleura, pericardium, peritoneum, heart valves, nerves, tendons, muscle wall of the bladder, urethra.

Stem cells are undifferentiated (immature) cells are able to self-renew and form new stem cells divide through mitosis and differentiate into cells of various organs and tissues. In the human body these kinds of cells more than 220. The stem cells remain and function in the adult organism, so the renovation and restoration of tissues and organs can be carried out. The number of stem cells is decrease with aging. Human stem cells are transplanted for therapeutic purposes. For example, hematopoietic stem cell transplantation is performed for the recovery process of hematopoiesis in the treatment of blood cancers.

13.3. CELLULAR MECHANISMS OF HOMEOSTASIS

Cellular mechanisms of homeostasis are used on restoring of natural dead cells of our tissues and organs if their integrity is violated. These phenomena include regeneration. Regeneration is the process of updating the structural elements of the body and restores them after the amount of damage, aimed at ensuring the necessary degree of functional activity. The regeneration process is evident at all levels of organization of living matter: the updated cell proteins, components of cellular organelles, whole organelles and cells themselves. The study of phenomena of regeneration is of great interest for medicine, for healing of any, even the smallest scratches, not to mention the complex phenomena such as the restoration

of organ function after a nerve damage or fracture, belongs to that group of phenomena. The task of medicine is to master the process of restoring the lost parts, learn how to manage the regeneration process. The phenomenon of regeneration is well expressed by the representatives of all types of animals. In mammals, the regeneration can be carried out in the form of the molecular regeneration (various levels of renovation molecules), organells (increasing the number of organelles and hyperplasia of nuclear apparatus) and cellular regeneration (cell division).

Depending on the characteristics of regeneration reactions in the tissues and organs of mammals, they can be grouped into three categories:

1) tissues and organs, which are characterized by cellular regeneration (bone, loose connective tissue, hematopoietic system, endothelium, mesothelium, mucous membrane of the gastrointestinal tract, respiratory tract and the urogenital system);

2) tissue and organs, which are characterized by cellular and intracellular regeneration (liver, kidneys, lungs, smooth and skeletal muscle, autonomic nervous system, pancreas, endocrine system);

3) tissues which are characterized by primarily (myocardium) or exclusively (central nervous system ganglion cells), the intracellular regeneration.

There are two types of regeneration: physiological and reparative.

Physiological regeneration is a recovery process that occurs after the wear and tear and the loss of elements of an organism in its natural life. It is a universal phenomenon, inherent in all living organisms: microorganisms, plants, animals and human. The physiological regeneration are dead and renewal of blood cells, hair change, the replacement of milk teeth permanent, reduction processes in the womans uterus after menstruation. Ñambial cells are the least differentiated and the least specialized cells. They are involves in the process of physiological regeneration. Cambial cells of the skin cells of the epidermis are the basal layer.

External and internal factors are influenced on physiological regeneration. The decrease in the atmospheric pressure causes an increase in the number of red blood cells. Their number is influenced by physical activity, food intake, light baths, etc. The following examples are the influence of internal factors on physiological regeneration. Denervation of the limb changes the function of bone marrow, which affects the decrease in the number of red blood cells. Cyclic update lining of the uterus is closely related to the secretion of female sex hormones.

Physiological regeneration supports the structural homeostasis and provides the ability to perform their functions. It is manifestation of the most important properties of life - self-renewal. The proliferative

regeneration is replacement of cells number by their division. The intensity of proliferation is judged by the number of mitosis, falling to one thousand cells counted. Two phases are distinguished in physiological regeneration: destructive and restorative. The resulting decomposition products of the first phase in the cell stimulate proliferation of other cells, and by this the second phase is provided.

The reparative regeneration is restoration of organs and tissues, the lost of injury or damage to the body. The reparative regeneration is the basis of healing, fusion of bone fractures, recovering of deleted or damaged organs. The reparative regeneration occurs not only after mechanical injury, but also after burns, chemical and radiation damage tissues. It includes the restoration of reparative regeneration occurring after the destruction of tissues caused by various diseases and recovery autotomy, when the animal, such as a lizard, separates a part of the tail.

In vertebrates, reparative regeneration may occur in following forms:

a) complete recovery, when the recovery of original structure of tissue from damages is observed;

b) regenerative hypertrophy, when a scar is formed on site of damage, and regeneration is deployed in the rest of the body, which mass is increased and is closer to the original as a result of cell division;

c) intracellular compensatory hyperplasia of ultrastructures, when a scar is formed on site of injury, and restoration of the original mass of functioning structures occurs primarily or exclusively due to hyperplasia of ultrastructures in survived cells, the number of which is not increased, but each cell value is increased.

Recovery of lost organs and tissues is made in following ways: morphallaxis, epimorphosis, endomorphosis, compensatory hypertrophy, regeneration induction.

The morphallaxis is regeneration through adjustment of the regenerating area. At the same time there is a regrouping of remaining parts of the body. The new individual size or reduced first body is less than the original, but further it increases. Morphallaxis is observed in regeneration of hydra, planarians, sea squirts and other organisms.

The epimorphosis is regeneration, which consists in regrowth of a new body from the amputation surface. Examples of epimorphosis can serve regeneration of limbs or tail in a triton or axolotl, regeneration of skeletal muscle by removing its portion. The limb of young larvae of axolotl can regenerate for 3 weeks, in adult newts – for one, two months.

The endomorphosis or regenerative hypertrophy is a phenomenon in which the growth of the wound does not occur, and the growing body

tissue residue. An example is liver regeneration in mammals. If a liver is injured its removed distant part is never recovered, the wounded surface heals. Inside the remaining portion, the cell division is increased and further the original weight and volume is restored, but not the form of the organ. The liver function also returns to normal.

The compensatory hypertrophy is a change in one of the organs in violation of the other, relating to the same body system. An example of compensatory hypertrophy may be an increase in the amount of one of the kidneys if the other is removed.

The regeneration induction is a case when remains of dead tissues promote the restoration of new ones. The extirplated bones are well recovered good due to periosteum residues. The restore of significant areas of bone may occur by gradual moving apart its fragments. Peripheral nerves can regenerate through the regrowth of nerve fibers of the central end. Regeneration promotes cross-linking of the peripheral and central nerve segments.

It was established that in mammals the regeneration of internal organs (the liver, pancreas, spleen) is an endomorphosis type. Endomorphosis can be used to normalize the function of abnormal organs. On paired organs (kidneys, lungs, ovaries, etc.) the loss of one of them or part of it comes compensatory hypertrophy of the intact organ. Vessel walls, urinary tracts which grow from the wounded surfaceis is restored by epimorphosis.

The physiological regeneration reflects the essence of life is a continuous breakdown and protein synthesis, cell renewal, while reparative regeneration occurs as the body's reaction to the violation of the physiological and is essentially a physiological regeneration in the patient.

13.4. SYSTEM MECHANISMS OF HOMEOSTASIS

The system mechanisms are ensured by interoperability of major regulatory systems: nervous, endocrine and immune.

The special feature of the nervous regulation is the speed of response, the manifestation of the effect directly in the place where the signal is received, the short duration of reaction. The nervous regulation of homeostasis is controlled and coordinated by the central nervous system. Nerve impulses, entering the cells, tissues and organs, invoke not only the excitation and inhibition, but also direct, rearrange chemical processes, regulate anabolism and catabolism of biologically active substances. It was found that the brain is inherent in endocrine function.

Currently there are more than 50 neurohormones, the greatest number was found in the hypothalamus (vasopressin, oxytocin, and statins group

liberins regulating pituitary function, etc.). At the same time the hypothalamus is the top center of the autonomic nervous system that controls the functions of the internal organs of sympathetic and parasympathetic divisions. Examples of systemic manifestations of homeostasis can be the constant of temperature and blood pressure. Elementary and systemic manifestations of homeostasis can be regarded as normal genotype response to changes in environmental conditions.

From the standpoint of homeostasis and adaptation, the nervous system is the main organizer of all body processes. Between different levels of homeostatic regulation there is a clear hierarchical subordination in the system of regulation of internal processes of the body. The most primary level consists of homeostatic systems of cellular and tissue levels. Secondary level is peripheral nerve regulatory processes such as local reflexes. The next located is the closed systems of self-regulation of certain physiological functions with a variety of channels of «feedback» mediated by the central nervous system. The top of this pyramid is occupied by the cerebral cortex.

In complex multicellular organism, both direct and backward linkages are made not only by nervous, but also by hormonal (endocrine) regulation. Each of the gland part of the endocrine system affects the other organs of the system and, in turn, is influenced by the latter.

The basic principle of homeostasis in the endocrine system can be formulated as maintaining the balance between the tension of the secretory activity of glands and its concentration of hormone in the circulating blood. For example, when the amount of thyroid hormone is abnormally high, the functional activity of the gland itself is weakened, and vice versa.

Endocrine glands can be divided into two groups. Anterior lobe of the pituitary is considered the central and other endocrine glands are peripheral. This division is based on the fact that the anterior lobe of the pituitary produces tropic hormones that activate some peripheral endocrine glands. In turn, the hormones of peripheral endocrine glands act on the anterior pituitary, inhibiting the secretion of tropic hormones.

Regulatory mechanisms are implemented by endocrine hormones secreted into the fluid connective tissue of the body (blood, lymph) with subsequent effects on target cells having hormone-sensitive receptors present on the cell membrane, or target organs. This effect is of long-term action.

The regulation of the endocrine glands is carried out mainly through the hypothalamus and under the control of the pituitary gland (anterior lobe) on the principle of direct and negative feedback. Thus, hypothalamic neural and endocrine cells are integrated into the neuroendocrine system.

Besides hormones, other highly active biological substances (catecholamines, their precursors and reaction products of: acetylcholine, histamine, serotonin, prostaglandins, kinins etc.) are involved in the humoral regulation of homeostasis.

Reactions providing homeostasis cannot be limited to any single endocrine gland and capture, more or less, all glands. The resulting reaction becomes a chain and spreads to other effectors. The physiological significance of hormones is to regulate other functions of the body, and the chain reaction must be expressed maximally. Constant violations of the internal environment of the body help to maintain its homeostasis during a long life.

13.5. AGING AND HOMEOSTASIS

There are disorders of homeostasis at all levels of the organization of the body during aging. At the molecular-genetic level with aging in the chromosomes is of an increase in the content of histones, becoming stronger connection with a DNA, reducing the number of acidic proteins. DNA segments that connect nucleosomes become less accessible to nucleases. By reducing the activity of the DNA polymerase rate of DNA replication is reduced. Decreased activity of repair enzymes results in damage to the DNA structure and, consequently, disruption of processes of transcription and translation, the appearance of abnormal proteins. Processes of expression and repression of genes are broken. The number of mutated genes increases with aging. In people older than 75 years an increased frequency of chromosome aberrations is observed. At the cellular level homeostasis defects during the aging are expressed in changes of membrane systems, osmotic properties of a cell, an electrical potential, exchange between the cells and the liquid medium inside the body, metabolism, disorders of cell division processes, etc. Aging causes changes in systemic homeostasis mechanisms. Atrophic processes in the cerebral cortex, the extinction of the function of the endocrine system are responsible for violation of homeostasis.

Assessing homeostasis in old age, two important facts must be noted.

1. All homeostatic quantities are difficult-regulated. One and the same exchange and function level at different ages has unequal internal process. The blood pressure in young and old people is not significantly different. However, in young people it is supported by the increase of the heart work, and in old people - due to the high vascular tone.

2. Baseline number of functions in different age periods differs insignificantly. However, the reliability, the potential, the range of functions

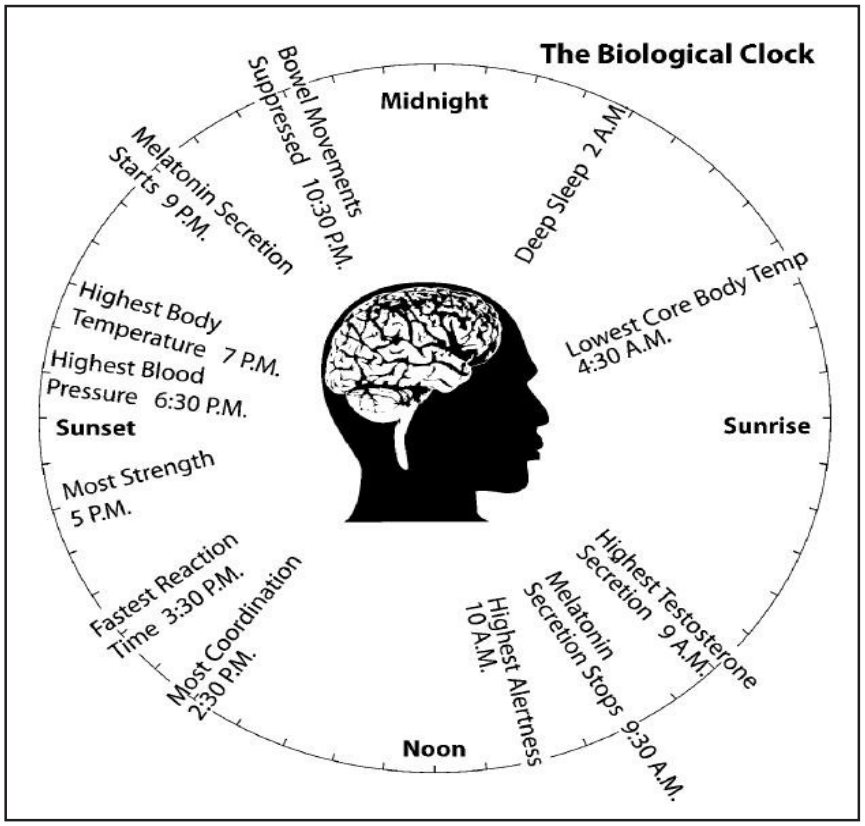


Fig. 13.2. Daily biological rythm of human.

in aging falls significantly. So after exercise in the elderly blood pressure, heart rate, heart activity, oxygen consumption slowly comes back to initial value than that in a young man. Consequently, the adaptive mechanisms that occur during aging are already insufficient to maintain the exchange rate and functions at different loads.

13.6. BIOLOGICAL RHYTHMS AND HOMEOSTASIS

All vital processes in the body are subject to a strict rhythm: daily, monthly, yearly, etc. It was found that the problems of the influence of solar and geophysical factors on human adaptation processes are closely connected with the problems of biorhythmology. The main symptom of rhythmic processes is their frequency. Rhythms, recorded live in the world,

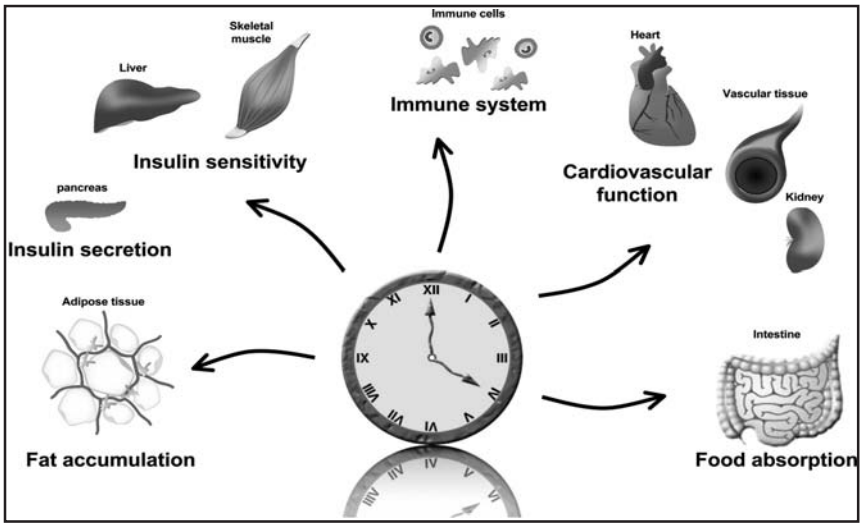


Fig. 13.3. Daily biological rythm of basic processis in human.

are known as biological or biorhythms. They can be characterized as a regular quantitative and associated qualitative change of some features of the biological processes taking place at different levels of organization of life: cellular, tissue, organism and population. The number of dividing cells differ at different times of the day which resulted in discovery of daily rhythms of cell divisions. *Chronobiology* studies the mechanisms of regulation of circadian rhythms, mitotic activity which has implications for medicine. Existence of daily periodicity of biological processes indicates the adjustability of the physiological regeneration of the body (Fig. 13.2, 13.3). In addition to daily, there are monthly and annual cycles of renewal of tissues and organs. Examples of monthly rhythms may serve menstrual cycles, per annum – change of fertility in human, depending on the season. Rhythm of the nervous system determines the rhythm stimulation and inhibition, in particular, sleeping and waking. This fundamental rhythm of higher organisms provides the activities of all systems. Biological rhythms that match the duration of corresponding geophysical cycles are called "environmental" or "adaptive". These cycles are year, seasonal, monthly and daily variations. The modern man is relieved from the need to maintain strict nature-inspired rhythms. His food, medicines can mimic almost any rhythmological situation. Chronic disease process is a manifestation of the so-called chronopathology. The occurrence of chronic pathological

processes may be the result of biological and social contradictions in a human. In fact, humanity is entering a period of chronic diseases regardless of their etiological and pathogenic characteristics.

Chronobiological analysis of patterns in the general biological evolutionary terms contributes to a better understanding of biological mechanisms of human homeostasis and purposeful use of effective tools that enhance the body's resistance to extreme factors. Qualitative change in the properties of an organism and its reactivity is associated with mechanisms of homeostasis. The disease in its biological nature is also a problem of homeostasis, a violation of its mechanisms and recovery pathways. Effective methods of hygiene and rational therapy are developed on the basis of laws of homeostasis.

CHAPTER 14. COMPARATIVE ANATOMY

Comparative anatomy of vertebrates is a part of anatomy which studies the structure of the same organ systems in different animals. On the basis of comparative similarities it establishes the historic ties and common origin of different groups of animals, allows tracking successive transformations of the same organ in the process of its development and to understand the main direction of the evolutionary process.

Comparative anatomy combines the study of adult forms with comparative study of bodies at the stages of embryonic development. Human is a creature of an animal origin. The knowledge about historical development of the basic systems of vertebrate organs for medical professionals, including professionals in the field of dentistry is important. The knowledge about the comparative anatomy of vertebrate organ systems allows a doctor to distinguish congenital malformation of the violations caused by the teratogenic factors, to identify the ways of forming deformities, to develop rational ways of operative elimination of defects, to use various tissues of fetal origin in conducting transplantation (midgut intestine is endodermal origin, back intestine is ectodermal origin).

14.1. SKIN COVERINGS

The skin covering the body has two components in chordates: epidermis of ectodermal origin and dermis of mesodermal origin. The main directions of evolution of the skin are: change of mucosal epithelium on the dry corneum; change in the ratio between the dermis and the epidermis in the predominance of the dermis; gland differentiation and development of epidermal derivatives. In anamniotes a skin structure is characterized by following features: multilayered epidermis with many mucous cells,

functioning as single-celled or multicellular glands; dermis with dense rows of collagen and elastic fibers which are located right in alternating layers - longitudinal and vertical. The largest aromorphosis is observed in amniotes by replacing mucosal epithelium on dry corneum covering. This transformation has been an important tool in the process of evolution and dispersal to the land. In reptiles and birds glands are absent in the skin (except for a small number of special purpose glands - femoral gland in lizards, musk gland of a crocodile, and the oil gland of birds). The skin of mammals has many glands (sweaty, greasy, milky). Due to the stratum corneum the derivatives are formed in amniotes - horny plates, scales, feathers, claws, nails. The fish scales are not epithelial but of mesodermal origin.

Malformations of the skin in a human are: local body hypertrichosis; absence of sweat glands; increase in the number of nipples; increase in the number of mammary glands; hemangioma (benign skin vascular tumors); capillary dilation.

14.2. SKELETON

Axial skeleton (chord) first appears in chordates. In vertebrates, it is replaced with a cartilage or bone skeleton and differentiated into three divisions: axial skeleton, skeleton of a skull and skeleton of limbs.

The axial skeleton in the process of evolution has undergone a number of changes that can be reduced to two major ways: 1) strengthening of the axial skeleton, resulting in replacement of the chord into cartilaginous skeleton in the process of evolution and subsequent replacement of the cartilaginous skeleton into bone (in cyclostomes - chord; in fishes - cartilaginous, osteochondral or bone skeleton); 2) differentiation of the axial skeleton in the parts (in fishes - truncal, tail; in amphibians - the neck, truncal, sacral, caudate; in reptiles, mammals - cervical, thoracic, lumbar, sacral, caudate).

Characteristic changes in the axial skeleton in the process of anthropogenesis include: formation of the spine bends; changing the shape of the chest in dorsoventral flattening and expansion in the lateral directions.

Among ontophilogenetic-caused defects of the spine in a human the reduction or increase in the number of vertebrae is observed more often, the fusion of bodies or processes of vertebrae, the non-fusion of spinal vertebraes (spina bifida or spinal canal defect), the cleft of arches, the assimilation of the atlas (fusion I cervical vertebra with the occipital bone), scoliosis, violation of the caudal spine reduction (persistence of the tail). Among malformations of chest ribs are hypoplasia, the presence of cervical ribs, spare ribs, sternum splitting or hernia.

The skeleton of skull is composed of two parts: cranial - neurocranium serving as a receptacle for the brain; visceral skull – splanchnocranium giving support to respiratory lower vertebrates (gill slits). The formation of cranium is due to accretion of three pairs of cartilage near chord - parachordal, trabecular and ophthalmic.

The visceral skeleton is an apparatus that strengthens the gill system, covering the front part of the digestive tube and differentiated into maxillary arch (for food capture), the hyoid arch (for attachment to the skull) and gill arches (for attaching the gill). In terrestrial vertebrates, the visceral skeleton is reduced: the top of the arc of the jaw fuses with the bottom of the skull; from the hyoid arch bones of the inner ear are formed and remnants of gill arches are transformed into cartilage of the larynx and the skeleton of the tongue. The facial skeleton is a new structure.

In the process of anthropogenesis the skull has undergone the following changes: intensive development of neurocranium; changing in parameters (higher rather than flattened); change in relationship between the facial and brain parts towards the reduction of facial; appearance of a chin protrusion in connection with the development of speech.

Among skull malformations a cleft palate, cleft lip, development only one auditory ossicles, column craniostenosis (premature fusion of the skull bones), underdevelopment of the lower jaw, underdevelopment of the upper jaw, exencephaly (underdevelopment of bones of the skull) occur.

Malformations of tooth development are absence or underdevelopment of teeth, diastema (presence of a wide crevice between teeth), development of teeth in an unusual place, malocclusion, identical dental system (teeth of one species, usually the incisors).

The skeleton of limbs. There are pairs (front and rear) and unpaired (fins - dorsal, caudal) limbs. The paired limb skeleton consists of zones that serve as a support for the limb. The basis of the structure of terrestrial vertebrate limbs is a common scheme, common to the front and rear limbs. Three major bones of the shoulder girdle and free upper limb bones match the pelvis and lower extremity: shoulder blade - the ilium; coracoid - ischium; procoracoid - pubic bone; humerus - the femur; radius and ulna - small and tibia; hand bones - the bones of the foot.

Changes in the limbs of the skeleton in the process of anthropogenesis are characterized by the following features: the center of gravity is shifted (gravity vector passes through promontorium) which leads to expansion of the pelvis; the thumb of the hand is opposed to the others. The arch of the foot is developed performing the role of shock absorber during walking.

Among limb malformations, the traumatic clavicular dysostosis, Sprengel's disease (violation of heterotopia belt upper extremities from

the cervical region to the level of 1-2 thoracic vertebra or innate high standing shoulder blade), synostosis (fusion) of bones of the forearm or lower leg, hemipodia (hypoplasia of limbs having the appearance of the stump), ectropodia (reduction of limbs to the rudiments size), apodia (missing limbs while hypoplasia of the pelvis), arachnodactyly, polydactyly, syndactyly, flat feet, clubfoot, splitting hands and feet are the most common.

14.3. BRAIN

Brain formation in all vertebrates begins with formation of three cysts or cerebral vesicles on the front end of the neural tube. They are: anterior (prosencephalon), middle (mesencephalon) and posterior (rhombencephalon). The anterior brain cyst is divided by the transverse constriction into two divisions. The first of them forms the anterior part of the brain (telencephalon) which in most vertebrates forms the so-called cerebral hemispheres. The intermediate brain (diencephalon) is developed from the back of the anterior cerebral cyst. Middle cerebral cyct is not completely divided and converted into the midbrain (mesencephalon). The posterior brain cyst is also divided into two parts: the hindbrain or cerebellum (metencephalon) is formed in the anterior part; the medulla oblongata (myelencephalon) is formed from the posterior part, which goes into the spinal cord without a sharp boundary.

In the process of formation of five brains vesicles the cavity of neural tube forms a series of extensions, which are called brain ventricles. The cavity is called the forebrain lateral ventricles, intermediate - third ventricle, the medulla oblongata - the fourth ventricle, midbrain - sylvie canal, which connects the 3rd and 4th ventricles. The hindbrain has not a cavity.

Each brain region has the mantle and the basis. The mantle consists of brain parts, lying above the ventricles, the basis is under the ventricles. The substance of the brain is not uniform. Dark areas are the gray matter, brigh areas are the white matter. The white matter is accumulation processes of nerve cells to the myelin sheath which is rich in lipids, giving a whitish color. The grey matter is a cluster of nerve cells between the elements of neuroglia. The cortex is a layer of gray matter on the surface of the mantle of any part of the brain. All vertebrates brain consists of five units arranged in the same sequence. However, the degree of their development varies among representatives of different classes. These differences are due to phylogenesis. There are three brain types: ichtiopsidic, zauropsidic and mammal.

The main areas of the brain evolution are: the change of expansion of the anterior end of the neural tube in the brain; differentiation of the brain into parts and development of brain ventricles; displacement of the

regulating center of neural activity in mesencephalic bottom forebrain and then forebrain cortex; the archiocortex appearance and change it to the neocortex; an increase in brain volume and cortical surface due to the development of the gyrus; increased number of pairs of cranial nerves.

Ontophilogenetic-caused defects of the central neural system include malformations of the spinal cord, brain and impaired differentiation of the cortex.

The defects of the spinal cord are amyelia (absence of the spinal cord), which is usually associated with anencephaly (hypoplasia of the forebrain), hydromieliya (hydropsy of the spinal cord), diplomieliya (doubling of the spinal cord in the cervical or lumbar enlargement).

Defects of brain development include cysts, anencephaly (hypoplasia of the forebrain) prozencephaly (non-separation of the hemispheres of the forebrain with hypoplasia of the cortex), microcephaly (general underdevelopment of the brain), complete or partial macrocephaly, hydrocephaly (hydropsy of the brain, caused by congestion of cerebrospinal fluid in the ventricles of the brain or the subarachnoid area), the underdevelopment of the frontal lobes or some parts of the brain, brain herniation.

Among defects of cortex differentiation the agyria (lack of gyri), oligogyriya with pachygyria (small-honors thickened gyri) which are accompanied by a simplification of the histological structure of the cortex, polygyria (large number of small and abnormally located gyri) are distinguished. In children with developed brain disabilities the mental retardation and disorders of may reflexes are detected. Most children die within the first year of life.

14.4. DIGESTIVE SYSTEM

In vertebrates, the digestive system is represented by anterior, middle and posterior intestine, which degree of differentiation is different in representatives of different classes. The intestinal tube is divided into sections, the jaw apparatus is improved. There is a differentiation of teeth on incisors, canines and molars. Vertebrate alimentary canal complication is expressed in isolation of oral cavity, differentiation of an intestinal tube on the throat, esophagus, stomach, small and large intestine, as well as isolation of glands - salivary, pancreatic, liver and increase of surface absorption in the intestine. The fish with the advent of jaws have numerous teeth. The stomach of most fish is poorly developed, on the inner surface of the intestinal tube folds the mucous membranes are formed, the villi appear. The liver is relatively larger than those of other vertebrates. The pancreas, as well as the swim bladder is developed from the outgrowths of the intestines. Amphibians have small single-row teeth in the jaws.

Becoming landliving animals they have salivary glands. They have well isolated stomach, small and large intestine, ending in the cloaca, the well expressed liver. In reptiles the teeth remain homogeneous. The salivary glands in snakes have transformed in poisonous. Since birds are able to fly, jaws and teeth disappeared, and they have a horny beak instead. In esophagus of most birds there is a sacciform enlargement – a goiter. Bird's stomach is divided into glandular and muscular parts. The intestines of birds are long, thin, two blind spikes and relatively short colon. The last one is cloaca.

The heterodontic dentition is formed in mammals (incisors, canines and molars appear). When the outer part of digestive tube is formed, four gill pockets are developed on pharyngeal side walls on each side. Different organs are developed: from the first - the eustachian tube and middle ear, from the second - tonsillar sinus, from the third and fourth - the parathyroid glands and thymus.

The mammalian stomach contains digestive gland of different types. The length of colon is increased sharply compared to other classes. The cecum and appendix appears. Intestinal tube ends with the anus, except the egg-laying types with cloaca.

Malformations of the digestive system in a human are cell aplasia (cessation of development of new tissue elements of the body), narrowing and atresia (absence of clearance) of the esophagus, micro- and macroesofagus, gastroptosis (ptosis of the stomach), Meckel diverticulum (formation of colon diverticulum), Hirschsprung's disease (multiple colon adhesions), hernias (subphrenic, inguinal, femoral), the opposite arrangement of the internal organs, the short mesentery. Sometimes in case of rudiments of gill slits, congenital fistulas and cysts of the neck are saved.

14.5. RESPIRATORY SYSTEM

Feature of organization of the respiratory system in chordate is phylogenetic, embryonic and functional relationship with the digestive. The close connection of the two systems in the phylogeny is determined by their topographical, dynamic coordinations in ontogenesis (example of ergontic morphogenetic correlation).

The main directions of evolution of vertebrates are following: the respiratory system is reduced to a change of gill respiration in the skin-lung and pulmonary; appearance and differentiation of respiratory tracts, increasing of the respiratory surface of lungs.

The gills as specialized respiratory organs appear for the first time in fish in the form of thin folds of mucous membrane lying on the gill arches.

They are supplied by the venous blood via gill arteries. Due to the protrusion of the ventral side of the pharynx a swim bladder is formed, performing the hydrostatic function, balancing the fish body in the water. Swimbladder has first formed in crossopterygii fishs. In amphibians, related in origin with the crossopterygii fish, the gills function at larval stage, and at adult level the lungs are formed. Their gill arches, being reduced, become a part of cartilage of the larynx. The lungs start directly from the larynx, because their respiratory surface is low, the gas exchange to a greater extent occurs through the skin. Reptiles have the upper respiratory tract (not completely delineated by oral nasal cavity), the lower - larynx, trachea, bronchi. The lungs in reptiles are fine mesh, have large respiratory surface. Lungs in birds are spongy bodies, filled with ramifications of the bronchi, and not the bags, like in reptiles. The bronchi are included in each lung on the ventral side and continue to the rear end of the lung and go further to the cavity of the thin-walled air bag belly. Air bags are located not only in the abdominal cavity, but grow in all parts of the body, penetrating into its ramifications and bones.

Mammals have the complicated bronchial tree, bronchi of the second, third and fourth orders, and bronchioles appear. Alveoli are in ramifications of the latter. Thoracic cavity is separated from the abdominal diaphragm which plays an important role in the breathing act.

Malformations of the respiratory system in a human may preserve as gill slits, atresia of the trachea, tracheo-esophageal fistula, agenesis (absence) or hypoplasia (underdevelopment) of the share or the whole lung, bronchus hypoplasia or an additional share of the lung, lung cysts.

14.6. CIRCULATORY SYSTEM

In vertebrates, the circulatory system is based on the same type as the circulatory system of the lower chord and even earthworms. It is based on ventral and dorsal vessels connected by anastomoses in the intestinal wall and the walls of the body.

Main ways in evolution of vertebrates are the following: the circulatory system includes the separation of a vessel muscle - the heart; the vascular differentiation in the blood and lymph; the appearance of the second circulation; the development of tools to distinguish arterial and venous blood currents.

Lower vertebrates (fish) are characterized by a single circulation. Their circulatory system almost completely repeats the scheme of the circulatory system of Amphioxus. Differences of progressive character are the two-chamber heart consisting of the atrium and ventricle. The heart of fish contains only venous blood that comes from the blood vessels on the venous bodies into the venous sinus and then into the atrium and ventricle of the

abdominal aorta artery in the gill where it is oxidized. Gill arteries, unlike Amphioxus vessels, fall into the capillaries and thereby increase the respiratory surface. In addition to the portal system of the liver, the fish has the portal system of kidneys. It is formed by the cardinal veins which fall into a network of capillaries in kidneys.

Both venous and arterial blood flows in the heart of terrestrial vertebrates due to formation of the second pulmonary circulation, resulting in the mixed blood in the heart of amphibians and reptiles. Only in birds and mammals due to formation of a four-chambered heart the blood currents are separated. In all land animals, the system of vessels with gill capillaries is replaced by arcs of the aorta and cardinal veins are gradually replaced by rear hollow veins. In reptiles and mammals, the secondary special vessels remain from cardiac veins. Venous blood vessels of the head are combined in front vena cava. A gate venous of kidneys gradually is replaced by intrarenal filtration of blood degradation products and mammalians do not have kidney portal system.

During embryogenesis, the heart is put into a straight tube which is bent and then increases in rear shaped, thin-walled half germ is dorsally displaced, moves forward and forms an atrium. The front part is on the ventral side and forms the ventricle which muscle wall is severely thickened. A tube division behind the atrium forms the venous sinus, ahead of the ventricle in lower vertebrates the muscular tube (arterial cone) is developed.

Ahead of the heart the unpaired abdominal aorta is developed from which the paired vessels (arterial arc) run along the gill partitions. These arcs cover the throat and are connected on its dorsal side in the dorsal aorta, giving forward to the carotid arteries. The number of arcs arterial vertebrate is small and corresponds to the number of visceral arcs. In cyclostomes - from 5 to 15 pairs, in fishes - 6-7 pairs, in terrestrial vertebrates - 6 pairs of arterial arches. The first two pairs of arcs in all vertebrates are subject to a partial reduction, are stored in the form of the jaw and hyoid arteries. Following arterial arcs in the fish are divided into afferent and efferent brachial arteries. In terrestrial vertebrates, 3-6 arterial arcs experience a series of transformations. The third pair of arcs loses connection with the dorsal aorta and enters the carotid arteries. The fourth pair of arcs is significantly developed and gives rise to actual arcs (or roots) of a dorsal aorta. In amphibians and reptiles these arcs are developed symmetrically. In birds the left arch is atrophied, and only the right remains in adulthood. In mammals, only the left aortic arch is preserved. The fifth pair of arcs is reduced (only in salamanders it is saved as a small duct). The sixth pair of arcs forms a pulmonary artery and loses contact with the aortic arch. Embryonic bond of pulmonary arteries with aortic arch is called

the arterial duct and is preserved in adulthood in tailed amphibians, some reptiles, and sometimes in human.

Abnormalities of the cardiovascular system in human are divided into three main groups: heart disease; vices major vessels; associated malformations.

Congenital heart defects are the most common as defects (patent) of the atrial septal (frequency of 1 per 1,000 live births), interventricular septum (Tolochinova-Roge's disease), leading to the emergence of a 3-chamber and very rarely 2-chamber of the heart, heart valves. Also acardia (no heart), dextrocardia (the location of the heart on the right), fibroelastosis endocardial (growth of connective tissue rich in elastic fibers) occur.

Congenital heart defects include three types of ectopia of the heart: neck (localization of the heart in the neck area, which leads to the death of a child after birth); abdominal (the location of the heart in the epigastric area or in one of the kidneys, if the heart is formed by the normal patients reach old age); extrasternal (heart location out of the chest, urgent surgery is necessary).

Among vascular disorders the most important clinical abnormalities are disorders in development of aorta and large vessels, which are derived from the gill arches. The most frequently the patent arterial duct is observed (the distal segment of the left artery of VI gill arch that connects the pulmonary artery to the aortic arch). In the embryonic period, when the lungs do not function, such connection is necessary. In adults, it leads to serious violations. Sometimes in a human embryo, the reduction of the right artery of IV gill arch and the aortic root to the right does not occur. As a result, two aortic archs are developed spanning the trachea and esophagus in the "aortic annulus" which gradually shrinks with age, resulting in impaired swallowing, and surgical intervention is required. In embryogenesis in a human, only one truncus arteriosus comes from a ventricle, which is further divided by a spiral pulmonary into artery and aorta. The septum is not developed in 2.1% and therefore the truncus arteriosus is survived in post-embryonic period, resulting in a flow of mixed blood circulatory system.

Severe combined congenital heart disease and blood vessels in human are: the triad of Fallot - valve pulmonary stenosis, atrial septal defect, right ventricular hypertrophy determines 2.5% of all cases of heart disease; tetrad of Fallot – stenosis of the pulmonary trunk, high ventricular septal defect with diametr of 2 cm, dextraposition of aorta, the fourth acquired component - right ventricular hypertrophy, the frequency of 0.7 cases per 1,000 live birth, a poor prognosis, children die at an early age, or live up to 20-30 years; pentad Fallot - the atrial septal defect is attached to tetralogy.

14.7. EXCRETORY SYSTEM

Evolution of the excretory system in chordates is expressed in transition from nephridium lower chord to the special organs - the kidneys, consisting of a large number of excretory tubules connected by the common excretory duct, and succession of three types of kidney in the embryonic period in vertebrates - pronephros or head kidney, trunk or primary kidney (mesonrphros) and pelvic kidney or secondary (metanephros). The direct communication with the excretory system of the blood is established, increase in the number of nephrons, their differentiation into sections, increasing the length of the excretory tubules ensuring increased filtration and readsorbtion function of the kidneys. The change of excretory organs in embryonic period reflects the stages of evolution of the excretory system. Each tab corresponds to a fetal stage of historical development of vertebrates and has some innovative features. Let us consider the structure of each kidney.

Pronephros or head kidney is the most primitive structure. It is laid in all vertebrates in the very early stages of embryonic development at the head end of the body and consists of 6-12 metamerically located funnels (nephrostomy) with extending away from them excretory tubules. Nephrostome on the edge has cilium and opens into the body cavity. From the funnel direct excretory ducts deviate, that fall into a common excretory duct – the pronephros ureter. The ureter is growing along the spine and opens into the cloaca. Funnel nephrostomy with excretory canaliculus is a structural pronephros unit - nephron which is inadequate in the absence of a direct link between the circulatory and excretory systems. These dissimilation products from the blood do not come directly into the kidney, and the first in the coelomic fluid. In modern vertebrate, the pronephros operates only in the early stages of embryonic development. In a human embryo the pronephros has no function value.

Primary or mesonephros is laid after the formation of the head kidney in the trunk of the body segments. Nephron of a primary kidney also begins with funnel opening in general. From the funnel, the excretory tubule diverges which flows into the ureter. Progressive change is the appearance on the dorsal side of the excretory tubule of a blind outgrowth in the form of a double-walled bowl in the structure of the nephron - Shymlanskaya-Bowman's capsules into which a vascular glomerulus grows in, forming together with the capsule a Malpighian body. A direct relationship between the circulatory and excretory systems occurs. The excretory tubule is elongated and differentiated into departments. The processes of back sunction of glucose, water and other substances take place in the tubule, i.e. the concentration of primary urine occurs. The number of nephrons in

the primary kidney compared to pronephros is increased markedly, the metameric structure is lost, but the excretion surface is greatly increased. Tubules in the nephrons of primary buds first open into the ureter pronephros. Later, the channel is split longitudinally into two channels. One of them remains bound with the pronephros (Muller duct) and the other becomes an independent primary kidney ureter (Wolf duct). Primary kidney functions in lower vertebrates - fish, amphibians - throughout life. In higher vertebrates - reptiles, birds, mammals - it is stored only in the embryonic period.

Secondary or pelvic kidney (metanephros). In higher vertebrates amniotes in embryonic development, exept the head and trunk kidney, a third tab is formed in the segments of the body lying behind the body kidney, called a secondary or pelvic kidney. A pelvic kidney nephron has a funnel, dur to which the communication with the celom is completely lost. Nephron starts right from the capsule Shymlansky - Bowman's surrounding a vascular glomerulus, in other words with Malpighian corpuscles. Vascular glomeruli are larger than in the mesonephros. From each of the initial nephron by budding several secondary are formed, and therefore the number of nephrons is increased and the total excretory surface is inhanced. The main excretion body in reptiles, birds and mammals during the entire life is a secondary kidney.

Ontophilogenetical caused malformations of excretory system in human are the following: aplasia (absence), hypoplasia (decrease) dystopia (offset) of kidney; wandering kidney; kidney fusion (horseshoe); a doubling of the kidneys; absence or doubling of the ureter; narrowing of the ureter; hydroureter (expansion and edema of the ureter); ectopia mouths (abnormal falling into the bladder); confluence of the ureter in the urethra; aplasia or a doubling of the bladder; diverticula and cysts of the bladder; the location of the urethral opening on the top (epispadias) or bottom (hypospadias) of the penis; doubling stenosis, urethral diverticula.

14.8. REPRODUCTIVE SYSTEM AND ITS RELATION TO THE EXCRETORY

Gonads in all vertebrates are developed as a pair of folds of nephrogonotoma in somite legs. Primary sex cells are isolated from embryos already at the stage of gastrulation. They actively move in the sex folds. The resulting gonad is indifferent. It may be developed in future in the testis, or in the ovary, depending on organism genotype. Indifference of developing gonads of vertebrates is called primary hermaphroditism. Violation of gonadal differentiation in a human can lead to emergence of ovotestis. In children with ovotestis, the signs of hermaphroditism and vulva are detected.

In cold-blooded vertebrates the gonads are in the abdominal cavity, whereas in mammalian testes move through the inguinal canal into the scrotum where the temperature is always lower. It is assumed that the low temperature is more favorable for spermatogenesis in mammals. The excretory system of vertebrates is characterized by a close relationship with the reproductive system, which is caused by phylogenetically. In females, the ureter anamniotes pronephros (Mullerian duct) is converted into the oviduct and dissimilation products are displayed on their own through a primary kidney and its ureter (Wolffian duct). In males the anamniotes in embryogenesis the complete reduction of pronephros occurs, i.e. not only the excretory tubules disappear, but the ureter as well (Mullerian duct). At the same time there is a connection between testis and a primary kidney. From the epithelium lining the wall of the body cavity, strands are formed connecting the tubules of a primary kidney and seminiferous tubules. Male sex cells through the seminiferous tubules enter the kidney and via the ureter (Wolffian duct) are exctracted out, which is therefore called the urogenital duct.

In amniote females, like in anamniotes, an oviduct is developed from the pronephros remnants and its ureter (Mullerian duct). In male amniote, the pronephros and its ureter is completely reduced. Ducts of front part of the primary kidney in males are saved and together with a part of mesonephros duct are converted into an appendage of the testis - epididymis, and the ureter of a primary kidney turns in the seminal duct (Wolffian duct). It looses the urine excretion function in connection with formation of a secondary kidney, unlike anamniotes males.

Differentiation into sections is observed in reptiles and birds in the oviducts. The front part of turtles, crocodiles and birds evolves protein. The rear part produces leathery (in reptiles) or soaked with lime (in birds) shell. In mammals, due to the live-birth function the differentiation of oviduct becomes more difficult. Oviducts are divided into 3 sections: fallopian tubes, uterus and vagina. In placental the fusion of distal oviduct at different levels occurs. As a result, double uterus (rodents), two-horned uterus (carnivores, artiodactyls, etc.) or only the uterus (some bats, prosimians, people) may develop.

Ontophylogenetical malformations of the reproductive system in women are: double uterus with one or two vaginas; two- and one-horned uterus; atresia and narrowing of the vagina; agenesis and hypoplasia of the ovaries; hermaphroditism. In men anorchia (no eggs), cryptorchidism (testicle location is not in the scrotum), phimosis (narrowing of the foreskin), or the absence of a doubling of the prostate and penis, ectopia testis and prostate, hydrocele (hydrocele) may be developed.

POPULATION-SPECIFIC LEVEL OF LIVING

CHAPTER 15. POPULATION STRUCTURE OF HUMANKIND

15.1. POPULATION. ITS ECOLOGICAL AND GENETIC CHARACTERISTICS

Population is a set of individuals of one species, which live in certain area for a long time (a large number of generations) within some degree of panmixia and which is separated from adjacent the same set of individuals varying degrees of pressure isolation.

The panmixing population is an organism of one species with free interbreeding. The non panmixing population is an organism of one species with some limitations for interbreeding. Restrictions of marital relationship in humankind populations are religion, social and property status.

The population can be characterized by ecological and genetic factors. Ecological characteristics of population are number of individuals, age and sex structure and population dynamics. Genetic characteristics of gender split provide primary sex ratio 1: 1. Due to varying viability of a male and a female, the primary relationship is markedly different from the secondary and tertiary relations. The secondary sex ratio in humankind populations is of 100 girls to 106 boys for the age 16-18 years. Its a result of increased male mortality ratio. The tertiary sex ratio in humankind populations is 85 males per 100 females for the age 50 years. There are 50 men per 100 women for the age of 80 years.

The gene pool of the population is all the genetic information of the population. It is a complete set of genes that has formed in the course of its evolution. Individuals with both dominant and recessive trait may be in the population at the same time. The recessive gene is not reduced by the dominant. For example, the number of blue-eyed people are not reduced by an action of the dominant brown-eye gene.

In 1908 G.Hardy (mathematician) and W.Weinberg (doctor) obtained a mathematical phenomen of not reduced receccive genes in populations. For example: if we take the infinitely large population, wihout selection, mutation and mixing with other populations, consisting of blue-eyed (a) and brown-eyed (A) people, then the frequency of homozygotes and heterozygotes remains constant for the first (AA x aa) and the second stages of panmixia (AA x aa x Aa). The total concentration is $pA + qa = 1$

if the concentration of the dominant gene "A" is p and the concentration of the recessive allele "a" is q. The combination of spermatozoa and ovum in panmixing population (pA + qa) (pA + qa) gives the distribution of genotypes of the formula: $p^2AA + 2pqAa + q2aa$.

This expression is Newton binomial formula: $(p + q)^2$. The Hardy-Weinberg law says that in panmixing large population with no selection, mutation and mixing of populations, there is a consistency in distribution of homozygotes and heterozygotes.

The Hardy-Weinberg law expresses the probable distribution of genotypes in any freely interbreeding population. But its appearance is possible under the following conditions:

1. The population must have the large number of individuals.
2. All the individuals in the population must be able to interbreed freely.
3. Homozygous and heterozygous individuals for this pair of alleles must be equally fertile, viable and not subjected to selection.
4. Direct and inverse mutations must occur with the same frequency.

The distribution of alleles in an infinitely large population with free interbreeding and the absence of selection and mutations of genes is based on gene concentration presenting in the population. The gene concentration is relative frequency in the population. The frequency of a dominant gene can be determined if the frequency of recessive genes is known, using the Hardy-Weinberg law. The frequency of heterozygous with abnormal gene and probability of occurrence of hereditary diseases can determined if the concentration of a recessive gene is know in population.

15.2. FEATURES OF HUMANKIND POPULATION STRUCTURE

Humankind in the earliest stages of its history was divided into many populations with different sizes. It is not a single panmixing population. Humankind popullation has the following characteristics: very numerous in marital relations; very unevenly breeding; large human populations include more than 4 thousand people. Small populations are divided into dems and isolates.

Dem is a relatively isolated local self-sustaining group of closely related individuals which exists sustainably for a few generations. Dems have the following characteristics: include not more than 100 individuals; there are 1-2 generations; more range of panmixia; have an enhanced degree of inbreeding as compared to populations. Examples of dems are mountainous areas, small religious sect, families with many children.

Isolates are groups of people spacely isolated from other isolates or subpopulations or there is a very limited exchange of individuals between

them. Isolates include up to 1500 individuals. There are multiple generations which have an increased panmixia degree compared to populations, minor exchanges among individuals are possible. An example of an isolate can serve Parses - fire-worshiper tribe that lived up to the XII century in the district of Baku and then moved under muslim pressure in India. Parses worship the god of fire even today and maintain sectarian closely related marriages. Examples of isolates are major religious sects (Baptists, Pentecostals, Old Believers, Jehovah's Witnesses, etc.); peoples living in other countries (Tatars, Jews, Poles, etc.).

Dems and isolates are characterized by a low natural increase, the rate of closely marriages is 80-90%. Even in rare recessive alleles, the heterozygote number in dems and isolates is quite high and contributes to the transfer of recessive genes of pathological states from heterozygous in homozygous. These facts lead to the emergence of a hereditary disease, reduction of viability or even to extinction of the population.

15.3. INFLUENCE OF ELEMENTARY EVOLUTIONARY FACTORS ON HUMAN POPULATIONS

The main developmental factors determining the structure of the gene pool of the population are mutation process, isolation, genetic drift, selection, acting in human populations.

15.3.1. MUTATIONS

Mutation is an elementary evolutionary material. The process of occurrence of mutations is a permanent elementary evolutionary factor exerting pressure on populations of living organisms. The frequency of spontaneous mutations is within the range 10^{-4} - 10^{-8}. The overall incidence of mutations per generation reaches significant values because the total number of genes in the genotype reaches tens of thousands. There are both direct and reverse mutations of the same gene. The pressure of the mutation process can be determined by changing the frequency of one allele in relation to the other. Combinative variability is an extremely powerful factor in enhancing the pressure of the mutation process in populations. Among monogenic inherited features, dominant and codominant mutations exceed recessive mutations in number.

15.3.2. ISOLATION

Isolation is the occurrence of any barrier that violate panmixia. Isolation barrier factors increase inbreeding in human populations. There are following isolation barrier factors in human populations: distance factors, customs, initiating marriages within a village or marriages within nearby villages;

racial, religious, caste, property and professional isolations.

The ongoing urbanization in recent decades, along with breaking the isolation of factors causes a sharp drop in frequency of consanguineous marriages and the fall of birth rate of mutant homozygotes. Urbanization does not always reduce inbreeding.

15.3.3. GENETIC DRIFT

The Hardy-Weinberg law is not applied in small isolated populations. It is based on statistical regularities that do not play a role in small populations. There is a segregation of heterozygotes (Aa) and accumulation of homozygotes (AA, aa) in them. S.Wright and R.Fischer studied this phenomenon and called it as genetic drift.

In small, intercrossed populations the heterozygosity is decreased and genetic homogeneity is increased. This phenomenon can lead to accumulation of certain adverse symptoms and subsequent elimination of the population regardless of their selection. The accumulation of lethal genes could lead to extinction of the population.

The genetic drift is a change in the genetic structure of populations as a result of any accidental causes. The genetic drift is manifested only in a small number of population in two forms: differences between successive generations of the same population observed over time and differences between both existing related populations observed in area.

Most human populations are polymorphic of blood groups AB0, so they contain all three alleles. In most populations on Earth allele I^A frequency varies between 15% and 30%, and alleles I^B - between 5% and 20%. At the same time, the frequencies of these alleles in the population of Greenland and Alaska Eskimos is 30% and 6%, while in the small tribe northern Eskimos (300 men), Tula (Greenland) gene frequency I^A is only 9%. The I^B gene is absent in Labrador isolates. Sharp deviations in blood types in different tribes of Indians are detected. So, blood group I^A gene is observed in Blackfeet Indian tribe in 80%, and in the Indians of Utah - 2%.

The high degree of reproductive isolation of indigenous human populations over several generations creates the conditions for a genetic drift. An example of genetic drift actions in human populations is an “effect of ancestor”. It occurs when a few families break away from the parent population and create a new population in another territory. This population usually maintains a high level of marital isolation that contributes to the consolidation of its gene pool one allele and the elimination of others. As a result, the frequency of rare allele of genes becomes very high. For example, Mennonite sect that supports inbreeding lives in Pennsylvania state (USA). Three couples based sect in America in 1770. This isolate has a high

concentration of the gene, which determines dwarfism with polydactyly in homozygotes. About 13% of those isolates were heterozygous for that gene. In other groups of Mennonites living in the United States, the disease is not detected.

The isolation and genetic drift has led to a high incidence of child cystinosis in France homogentisuria in the Czech Republic and Slovakia. Genetic drift clearly occurs at setting of new settlements when the population as a separate random sample is extracted from a large population and colonizes a new area.

In population genetics, gene flow (also known as gene migration or allele flow) is the transfer of genetic variation from one population to another. If the rate of gene flow is high enough, then two populations are considered to have equivalent genetic diversity and therefore effectively be a single population. It has been shown that it takes only "One migrant per generation" to prevent populations from diverging due to drift. Gene flow is an important mechanism for transferring genetic diversity among populations. Migrants change the distribution of genetic diversity within the populations, by modifying the allele frequencies (the proportion of members carrying a particular variant of a gene). High rates of gene flow can reduce the genetic differentiation between the two groups, increasing homogeneity. For this reason, gene flow has been thought to constrain speciation by combining the gene pools of the groups, thus preventing the development of differences in genetic variation that would have led to full speciation. In some cases migration may also result in the addition of novel genetic variants to the gene pool of a species or population.

A population bottleneck or genetic bottleneck is a sharp reduction in the size of a population due to environmental events (such as famines, earthquakes, floods, fires, disease, or droughts) or human activities (such as genocide). Such events can reduce the variation in the gene pool of a population; thereafter, a smaller population, with a smaller genetic diversity, remains to pass on genes to future generations of offspring through sexual reproduction.

15.3.4. NATURAL SELECTION

C. Darwin defined the natural selection as preservation of individuals with useful and destruction of harmful individual deviations - "survival of the fittest." This formula does not reflect sufficiently some important genetic consequences of selection. Differential reproduction of animals is important in the process of natural selection. The main significance in the evolution is not survival of the species, but the contribution of each individual in a population gene pool. The individual that leaves more offspring has a large

part of population gene pool. Only success in breeding of different species can serve as an objective genetic-evolutionary criterion for natural selection.

Natural selection is a differential reproduction of different genotypes. There is every reason to believe that the frequency of some genes in human populations is changing under the influence of selection, especially in populations that live in the environment which has recently undergone major changes. The confirmation of selection in human populations can serve factors to detect causes of spontaneous abortion and perinatal mortality in a human. More than 42% of spontaneous abortions occur due to the lethal effects of chromosomal abnormalities. At different stages of pregnancy during the first trimester of 2-4 weeks this figure rises to 70% in the second - 30%, in the third trimester (20-27 weeks) - 4% of a chromosomal etiology as the cause of spontaneous abortion. Among stillborn 6% has lethal chromosomal abnormalities. Perinatal mortality in 6.2% of cases is caused by a chromosomal abnormality.

The selection action ensures the ability of a body to contribute to the genetic profile of future generations. This is achieved in two ways: selection for survival, when all depends on survivability of organisms before reproduction, and selection of genetic factors affecting reproduction.

The special situation occurs when the selection acts by increasing the survival rate of heterozygous individuals under full excision of negative homozygous form before reproduction. This form of selection is called counter-selection. It is clear that heterozygotes (Aa) are more viable than each of homozygotes (AA, aa) separately. Phenomenon of the counter-selection can be described on the example of sickle-cell anemia in a human. Individuals who are homozygous in the gene HB^S (HB^S HB^S) suffer from malaria while heterozygotes (HB^A HB^S) are quite healthy although their red blood cells contain hemoglobin HB^A and HB^S. The frequency of such heterozygotes in West Africa is about 40%, whereas among African Americans - only 9%. Holders of genotype HB^A and HB^S are resistant for falciparum malaria pathogen which is especially important for children from 6 months up to 5 years. Children have passive immunity obtained from the mother up to 6 months and after 5 years they develop active immunity against the parasite. The presence of HB^S among African Americans indicates on their origin from areas of high concentration of heterozygotes.

15.4. GENETIC POLYMORPHISM OF HUMAN POPULATIONS

Polymorphism is any of a variety of forms of the same species of organisms. Polymorphism is the most universal phenomenon of life. A human is the most polymorphic species on Earth. Human almost has all polymorphic

traits (eye color, hair, shape of nose and skull, blood, etc.). Polymorphism may be the result from intra discrete variability of hereditary character which can be determined by standard reactions. Genetic polymorphism occurs due to insertion of different mutations in the population gene pool. It is classified as gene, chromosome and genome.

The gene polymorphism is the presence of two or more alleles. For example, the ability of people to taste phenylthiourea is determined by a dominant allele (TT, Tt), homozygous recessive (tt) - do not feel. Inheritance of blood groups is determined by three alleles - A, B, O. Polymorphism of the human Rh (Rh + and Rh-), which was originally detected in monkeys rhesus monkey.

The chromosomal polymorphism is associated with chromosomal aberrations. For example, deletion of the short arm of chromosome 4 (Wolf-Hirschhorn syndrome), deletion of the short arm of chromosome 5 (syndrome of "cat cry").

The genomic polymorphism is due to a change in the number of chromosomes in the karyotype. For example, the monosomy XO (Turner syndrome), the presence of additional X-chromosome in male - XXY (Clinfelter syndrome), the trisomy in the 21st pair of autosomes (Down syndrome).

Polymorphic genetic systems under their alleged systems include three groups of polymorphisms: transient, neutral, balanced.

*The transient polymorphism i*s due to a change of genetic composition of population under the studied locus. One new allele in changed conditions of the environment becomes more favorable and replaces the "source." Such polymorphism may not be stable because due to natural selection sooner or later the "original" allele will be displaced by a new one, and the population will be monomorphic under the "new" allele. The speed of this process can not be seen withing a single generation.

The neutral polymorphism is due to random stochastic processes (genetic drift), resulting in random variations of gene allele frequencies. For example, the occurrence of differences in adaptive-indifferent characteristics (adherent or free earlobe). Changes in gene frequencies of these features are carried out by the mechanism of genetic drift, which explains their evolution neutral type.

The balanced polymorphism is due to a complex balance between selection against both homozygotes in favour to heterozygotes. Recessive genotype undergoes the stronger elimination than dominant genotype. The differences in elimination of these two genotypes speed maintain constant, stable equilibrium existance in both alleles of the population with its own frequency. This explains the stableness of this polymorphism.

Systems of balanced polymorphism are studied more extensively, which are associated with selection on malaria - abnormal hemoglobin, thalassemia, deficiency of erythrocyte enzyme of glucose-6-phosphate dehydrogenase. The stability of these polymorphisms disappears due to success in fighting malaria. Balanced polymorphism is transformed into transient.

A large number of polymorphic systems discovered in a human lately with a large number of alleles leads to the fact that almost every person has a unique set of genes, suggesting the biochemical and immunological identity of the individual. It is of great importance in medical practice, especially in forensics. Genetic predisposition is multifactorial in nature and is defined by plurality of genes with a predominant effect of one or more. To establish these genes biochemical and immunological methods of anthropogenetics are used. More than 130 polymorphic gene loci encoding polymorphic proteins are described in our days. These are enzyme proteins, antigens, transport proteins, etc.

There are numerous reports on association of the disease with immunological markers (antigens of the AB0 blood group and system of HLA). People with blood group II (A) are prone to cancer of the stomach, colon, ovary, cervix, rheumatism, coronary heart disease, thromboembolism, etc. People with I blood group (O) are prone to diseases of gastric ulcer and duodenum ulcer, etc. Associations of HLA system antigens indicate on hereditary predisposition: to chronic hepatitis, rheumatoid arthritis, hyperthyroidism, multiple sclerosis - in people with group antigens DR.; to psoriatic arthritis, ankylosing spondylitis - antigens B-27; to youthful diabetes - antigens B-15; to diabetes - B-6 antigens.

15.5. GENETIC LOAD, ITS MEDICAL VALUE

Genetic load is relative decline in vitality of individual in population compared to optimal genotype. Human obeys to all same laws of mutation and population genetics as all other organisms. The facts of a wide distribution in human of congenital hereditary diseases prove it. Many of diseases are among them caused by presence of recessive genes. In this case, a child with abnormalities is born in apparently healthy parents. There are many different inherited diseases that affect each generation, about 4% of newborns. The volume of the genetic load is studied by analyzing the consequences of consanguineous marriages. Descendants from the marriage of relatives are influenced by genetic load in the form of a high percentage of stillbirths and a high mortality rate up to a year or more. According to observations made in France, stillbirths in related marriages constitute from 26 to 50 per 1,000 live births, whereas non-relatives - from 19 to 21 per 1,000 live births. Genetic load is understood not only as lethal

mutations (passing in the homozygous state) but also the entire spectrum of mutations that lowering the adaptive properties of individuals. There are three types of population genetic load distinguish: mutation, balanced, substitutional (transition).

The mutational load arises due to repeated mutations. Its volume is determined by the frequency of mutations in all the locuses that give negative changes.

The balanced load occurs when the selection in different directions acts on homozygotes and heterozygotes (HB^s).

The substitutional load occurs during changes in environmental conditions when allele previously providing adaptive rate becomes negative. Under these conditions, the frequencies of both alleles - an old one, which lost adaptive value, and a new one are still high. This causes a significant manifestation of polymorphism and genetic load due to the old allele.

The problem of genetic load in a human is essential to modern medicine, since hereditary diseases become more dangerous in human diseases. Knowledge of genetics of congenital disease, the degree among population, geography of disease genes is necessary for practical medicine. These issues are extremely important for anthropology, for understanding of future human biological evolution. The issue of genetic load in a human is of particular importance in protecting the environment against pollution.

BIOSPHERE-BIOGEOCENOTIC LEVEL OF LIFE ORGANIZATION

CHAPTER 16. FUNDAMENTALS OF ECOLOGY. ANTHROPOECOLOGY

16.1. ECOLOGY AND ITS AIMS AND VALUE

The ecology is a biological science that studies interaction of population with the environment, structure, dynamics and historical development of communities - biogeocenosis, ecosystems and biosphere as a whole.

The ecology can be defined as a system of scientific disciplines studying life on underorganismal level of the organization. This means that the ecology studies the laws of interaction and relationship of individuals and populations or species complex (communities) with each other and with inorganic environmental conditions. Ecology deals with interaction of organisms with the environment which leads to development, reproduction and survival of individuals, structure and dynamics of populations and communities and their role in ecosystems processes. Ecology studies the impact of organisms and their complexes on their environment, it creates a scientific basis for rational exploitation of biological resources, forecasting changes in nature under the human influence and managing the processes occurring in the biosphere, preservation of the human environment.

Subjects of ecology are the following: physiology and behavior of individual organisms in their natural habitat, fertility, mortality, migration, intrarelationships; interspecies relationships, energy flows and the cycling of matter.

16.2. ANTHROPOECOLOGY

Anthropoecology is the science that studies the general laws of interaction between society and environment as well as practical problems of its protection. The subject of human ecology is to study patterns of interaction of human population with environmental factors. Environment regulates population development, saving and health development, improving the physical and mental capabilities of Homo sapiens. This approach makes it possible to study the most common, basic health preservation and development patterns of population, taking into account the specifics of climate and geographic and socio-industrial conditions. Human ecology studies the laws of existence and development of anthropoecological

systems, which represent a community of people who are in a dynamic interaction with the environment and supplying their needs.

Community of people differs in production of wealth and the structure of socioeconomic relations. During the existence of anthropoecological systems the interaction of people and environment is carried out in two directions. Firstly, biological and social indicators of individuals and society are changed as a whole to meet the requirements applicable to a human. Secondly, the environment is self-reconstructed to meet human requirements. The overall result of biological and social processes in anthropoecological system is individual and group adaptation of human societies to live in habitats differed in natural conditions, forms of management and culture. As a result, a human adapts to conditions of life physiologically, environmentally, technically and emotionally.

There are three levels of human interaction with the environment - individual, group and global. The individual level characterizes the interaction of each human with environment. On the group level the interaction of human population with the environment is studied, and on the global level – the whole humankind. Examples of global human-environment interaction are decrease of the ozone layer, reduce of non-renewable natural resources, pollution of the oceans, humankind growth.

The human after separating from the animal world, immediately began to affect actively on the environment, which ultimately caused the formation of ecosystems under human activities. These man-made ecosystems can be considered as agrocenosis and cities as a living environment of people (urbocenosis).

The agrocenosis are a set of organisms that live in agricultural lands used for planting crops. In natural biocenoses the complex of plant component comprising variety of species is made historically in natural biocenoses, while in agrocenoses the vegetation is created by a human. A city as a human-made ecological system differs from the natural ecological systems by following features:

- more intensive metabolism per unit area through the use of energy fuels and electricity;
- involvement of substances in migration (metals, plastics, etc.) not only within the system, as on inlet and outlet thereof;
- a powerful stream of waste which is generally more toxic than the natural raw materials from which they were derived.

The land area occupied by cities at present does not exceed 5% of the total Earth area. But the impact of cities on the environment is enormous. The city may affect the surrounding biogeocenoses not only as a consumer

of oxygen and organic matter, but also as a powerful polluter. The city does not produce food itself, does not enrich the air with oxygen, does not return water and inorganic materials in the material cycle. So the city cannot be considered as ecological system. In order to treat the city as a biocenosis it is necessary to expand its borders considering those invironment which determine its livelihood. Living conditions in the cities are unique. It is easier to solve the problem of employment, food supply, health care there. Industrial emissions cause increased cloud cover, heat exchange, fog formation, formation of smog. In summer, the temperature rises sharply, and the mortality rate among people who suffer from chronic cardiovascular disease increases. High population density, contamination of soil, water and air negatively affects the human. The city has a low birth rate and population growth is mainly due to arriving of people from rural areas.

16.2.1. ENVIRONMENTAL VARIABILITY AND ADAPTABILITY OF THE HUMAN TYPES

People live on Earth in various environmental conditions, different regions with various biogeographic characteristics. People differ from each other in various aspects (dut to ratio of parts of the body sizes, to many biochemical and physiological features), i.e. various aspects of a human biological diversity. People are divided on mongoloids, caucasians, negroid. Limits of variability of quantitative traits like height, skin color, hair which are characterized by a continuous distribution in different populations, are often overlapped. The term “race” is often used incorrectly by mixing biological and cultural aspects (“german” race) if we speak about the differences between people. Such incorrect concepts easily lead to racist doctrines.

Biological variability in human deals with different anthropometric indicators: body length, hands shoulder width, the size of cranium, etc. Inheritance of anthropometric characteristics depends on many genes. It is proved that individual differences in growth are really genetic. There are considerable difficulties in interpretation of these correlations for human populations. Numerous data indicate that the average height of an adult in the XX-th century in economically developed countries has increased significantly. These differences are more related to environmental conditions (nutrition) rather than the ethnic separation or differential migration.

The zonal character of geographic variation of many vital morphological and functional features of a person indicates on environmental variability of existence of people. The variability is manifested not only in physiological

characteristics but also in characters of body structure, which confirms the long history of formation of adaptive types of people.

The adaptive type is a norm of human biological response to environmental conditions, providing a state of relative equilibrium with environment and is expressed in a complex of morphological and physiological characteristics of population. It is a morphological and functional complex, biochemical, immunological traits that determine the best human biological adaptation to environment. Adaptive types do not depend on a race or ethnicity of population. There are the following basic adaptive types of people: arctic, tropical, mild climate zone, mountain, desert.

The arctic type was formed under the influence of cold climate and animal food. An increase in heat production, a relatively strong development of the musculoskeletal system, large size of the chest, a high hemoglobin level, high mineral content in bones, high blood proteins, level of cholesterol, increased ability to oxidize fat are typical for this type of people. Arterial pressure is lower.

The tropical type was formed under the hot and humid climate, the low content of animal protein in the food. The tallest and smallest tribes live there. The tropical type is characterized by elongated shape of the body, reduced body weight with increased length of limbs, reduced chest circumference. More intense sweating, increased indicators of basal metabolism and fat synthesis, decreased blood cholesterol concentration, increased blood pressure, lowered level of metabolism and lowered concentration of ATP are typical for tropical type.

The adaptive type of mild climate zone is located between the Arctic and tropical types. To define environmental factors that determined the formation of this type is difficult, since most of population lives in cities.

The adaptive type of high mountain regions is formed under the influence of hypoxia. This type is characterisated by increased level of basal metabolism, skeletal bone elongation, chest expansion, increased oxygen capacity in blood by increasing the number of erythrocytes, hemoglobin content and relative ease of its transition into oxyhemoglobin. Blood pressure is lowered.

The adaptive type of deserts is characterized by reduced basal metabolism, increased level of hemoglobin due to dehydration and changes of blood concentration in desert conditions. Low level of mineralization of the skeleton is typical for population of extratropical deserts.

The presence of adaptive types indicates on large environmental variability of man, which is probably a consequence of settlement of people across the globe.

16.2.2. BIOLOGICAL AND SOCIAL ASPECTS OF ADAPTATION OF THE POPULATION TO LIVING CONDITIONS

Adaptation is one of the fundamental qualities of living matter. It is essential to all known forms of life. The concept of "normal health" is defined "as the optimal state of a living system that ensures maximum adaptability". Adaptation property of living systems is a level of individual health of a living creature.

Adaptation mechanisms of the biological system to appropriate environmental conditions are the result of long evolution and ontogenesis. Activity of a human body in inadequate environmental conditions requires extra adaptation mechanisms. The effective adaptation of human organism to the environment is necessary to ensure the comfort of state, to perform physical work without fatigue, to do various kinds of skilled work, requiring attention and to ensure normal conditions of growth and development. Efficiency of adaptation depends on the degree of homeothermy disorders.

Adaptation to the climate depends on differences in the nature of a body between different populations. In transition from mild to hot climates the ratio of body weight to surface area decreases. Perspiration in indigenous population is less than that of acclimatized Europeans due to less weight and smaller body surface area. For the same energy consumption per kilogram of weight per one hour (4 calories), the amount of heat generated per unit body surface by convection, and evaporation, in these groups is significantly different, namely, in the Asian group it is significantly lower than in European. When a person appears in extreme conditions his process of adaptation will depend on individual properties of constitution. Different constitutional types of people react differently to external influences during the early years of the adaptive process.

16.2.3. HEALTH AS A CATEGORY OF ANTHROPOECOLOGY

All biological and social aspects of human adaptation aimed at maintaining the health of the individual and population, which belong to different levels of social organization. Determination of the individual's health was first given in the Constitution of the World Health Organization: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

A more complete definition of health was done by professor B.D. Petrakov. He thought that "Health is a state of complete social, biogenetic, psychophysiological and physical well-being in which the human body systems are dynamically mutually balanced with social and natural environment. It is a condition wihtout disease and physical defects."

V.P.Kaznacheev introduced the terms “individual health” and “population health” which reflect not only social, physiological, biogenetic criteria but also the duration of the active life of an individual and the succession between generations. The health of a person is the process of preservation and development of mental, physical and biological features, best work capacity and social activity with a maximum of active lifespan.

Health of population is the process of social and historical development of psychophysiological and biological life of the population, succession of generations at ever increasing rate of social production, improved conditions of population during development of new territories. Life of the individual, as well as population in the environment is the developing process of adaptations. Health is not the absence of disease, but physical, social, psychological harmony of human, friendly, peaceful relations with people, with nature and himself. The main aim of modern medicine is enhancement of health and treatment of diseases. But the cure of diseases does not always bring health. Aftersensation of diseases, and the treatment itself remains in a human. Medicine needs to be engaged in protection of health not only sick but healthy people from the point of anthropoecology.

Valeology (lat.- valeo - long live, to be healthy) is a new medical science which develops the basis for protecting a wellness of a human health. The major health factors are the rational life, elimination of bad habits, active movement, physiologically balanced diet.

16.2.4. ANTHROPOCENOLOGY

Anthropocenology is a section of human ecology which studies the relationship of communities with the environment. The aim is to develop recommendations on the rational use of natural resources, the recommendations on the use of fertilizers.

Humankind has always been closely connected with the biosphere, because it is a habitat. The possible human existence is due to the biosphere. A human gets everything necessary for life (food, air, water, clothes) from the biosphere.

Natural resources are all sources of mineral raw materials, energy, flora and fauna which are used by people to ensure their livelihoods. Natural resources are divided into non-returnable and returnable.

Non-returnable natural resources include almost all minerals. It is known that the minerals are formed in the Earth crust for million years. But mineral deposits are used by human withing decades. Mineral wealth concentrated in the Earth crust, according to some types of raw materials is already on the verge of total exhaustion. Most of deposits of mineral

raw materials can be exhausted in one or two centuries. To renew these losses in natural conditions tens of millions of years are required.

Returnable resources consist of microorganisms, plant and animal. Plants produce organic matter and are the source of creation of Earth biosphere and the ultimate source to satisfy physiological, nutritional needs of man. Normal breathing air composition is maintained during photosynthesis. Natural vegetable raw materials are used in many industries and in agriculture. Forested land surface is involved in ensuring the fight against wind and water erosion, protection of crops and orchards against destructive actions of hot winds, regulation of water balance, creation of recreation areas for the public. According to the Food and Agriculture Organization of the United Nations (FAO), about 26 million km^2 of meadows and pastures (18.6% of the Earth) produce food. Some kinds of plants are used in medicine, as food and aromatic agents.

Humankind has been cutting down the forest intensively. Forest area is stabilized now in Europe, but the cutting is carried out in Africa, South America. In some areas there is a change of plant types: a cedar, beech, pine, spruce are cut down and replaced by less valuable species.

Animals are an integral part of each natural complex. Freshwater and marine animals are important as a source of protein production. The annual catch of fish, crustaceans, mollusks in the world exceeds 40 million tons, hunting provides about 1 million tons of meat per year.

Many animal species are vanished. The Red Book proves the fact of killing or being under the threat of extinction of plants and animals. Therefore, the conservation, restoration and sustainable use of biological resources is important for human.

Anthropocenology is a biology science which solves problems of an individual defense at work with toxic, poisonous substances. It became actual after the humenkind developed biological methods to fight winged insects.

Anthropocenology is actual for protecting a person working with radioactive isotopes, in collection and storage of radioactive isotopes, in decontamination of polluted areas. This problem is greatly increased after the accident on the Chernobyl nuclear power station. As a result, there was a problem not only to protect the population from radionuclides and human health, especially the younger children, but also the decontamination of agricultural land and settlements. Decontamination activities in areas affected by radioactive contaminations are carried out in case they reduce pollution levels to normal state. These works should be carried out in conjunction with other protective measures to reduce the level of

contamination and the resulting radiation dose of population. The decision to conduct decontamination work should be based on comparing of estimated costs with the expected benefit. Decontamination should be carried out by specialized state-owned enterprises on the basis of design and estimate documentation, and followed by land improvements.

Anthropocenology should focus its efforts on development of environmental awareness in population. This part is important for extensive educational work with the use of all media (radio, television, internet). Educators, teachers of secondary, vocational and higher education institutions should make the formation of ecological consciousness and thinking. A special responsibility rests with the healthcare professionals who need to own all the available information on environmental situation to provide specialized medical care. It is necessary to educate the population to measures of safe living in areas contaminated by radiation. Radiation literacy in the family should be implemented through the school, and radio-ecological education of children.

CHAPTER 17. GENERAL MATTERS OF MEDICAL PARASITOLOGY

17.1. PARASITISM. ITS KINDS.

Parasitism is a form of co-existence of two genetically dissimilar organisms of different species where one organism (the parasite) uses another (the host) as a source of food and environment, causing it harm, but not destroying it.

Forms of parasitism are diverse. Obligate (constantly occurring, mandatory) and facultative (possibly, optional), temporary and permanent, true and false, ectoparasitism and endoparasitism are distinguished.

Parasitism is widespread in nature. It is found almost in all types of animal kingdom. Especially a lot of species of parasites are available in protozoa, flat and round worms, arthropods. There are about 60-65 thousand of them.

Parasitology is a biological discipline that studies the biology and ecology of parasites, their relationship between hosts and environment, as well as diseases caused by them and measures to fight them in humans, animals and plants.

Parasitology is divided on medical parasitology, veterinary parasitology and phytoparasitology.

17.2 ORIGIN OF PARASITISM

Transition to a parasitic way of life in different groups of animals was in various ways. Most of ectoparasites originated from free-living arthropods and other animals. Bloodsucking diptera, bedbugs, ticks, fleas, lice do not differ much from the predatory insects. Many bloodsucking diptera eat not only blood, but also plant juices. Males of mosquitoes, black flies, biting midges, mosquitoes, horseflies do not drink blood at all. Males and females of flask and tsetse flies feed on blood.

Some endoparasites descended from ectoparasites, but they lay eggs on feathers. Transition to endoparasitism also occurred on changing of instinct in choosing a place of oviposition. Wolfartic flies ancestors lay eggs not in decaying organic matter but on suppurating wounded surfaces. The precursors of skin and gastric gadflies stick eggs to the hair of animals, and the ancient abdominal gadflies acquired the ability to jet larvae in animal's nostrils, or in human eyes. Intestinal endoparasites could originate as a result of the systematic introduction of cysts or eggs in digestive system of potential hosts. The possibility of this way of parasitism is evidenced by the presence of ability for a number of generations to exist in external environment as free individuals (strongiloidy) in some facultative parasites. Most of blood parasites of vertebrates previously lived in the gut of arthropods. When the latter began feeding on blood the intestinal parasites fell into the circulatory system of a vertebrate and gradually adapted to living in it, having retained the ability to grow in the gut of arthropods (trypanosomes, leishmania, plasmodium). The emergence of parasitism became possible only after the Earth was inhabited by a large number and variety of animals, greatly differing in size. For the first time the parasitism has widespread due to different groups of free-living worms. Further evolution of parasitism has been associated with the appearance of vertebrates. Complex cycles of parasites gradually began to form where the vertebrates mainly acted as definitive hosts. Human parasites evolved with the evolution of its host. Some of them remained the connection with former hosts, many have become strictly human-specific.

17.3. THE OBJECT AND PURPOSE OF MEDICAL PARASITOLOGY. CLASSIFICATION OF PARASITIC DISEASES.

Medical parasitology studies biology and ecology of human parasites, diseases, caused by them, methods of diagnosis, treatment and prevention, as well as scientific basis of dealing with them.

Medical parasitology includes medical protozoology, helminthology and arachnoentomology. Medical protozoology studies pathogenic protozoa in

human. Medical helminthology studies the role of helminthes of flat and round worm types as human pathogens. Medical arachno-entomology studies the role of arthropods (mainly ticks and insects) as vectors of human pathogens, their natural reservoirs and pathogens. Medical parasitology solves three main objectives:

1) to study morphology, biology, ecology and taxonomy of human parasites;

2) to investigate the influence of parasites on a human body, mechanisms of parasite patogenic action;

3) to develop methods of diagnosis, treatment, prevention and eradication of parasitic diseases.

To solve these problems, medical parasitology uses the methods of various biological disciplines (anatomy, zoology, cytology, histology, genetics, physiology, pathological anatomy, ecology, population statistics). Human diseases caused by pathogenic protozoa, helminthes and arthropods are called invasive. Infectious diseases are diseases caused by pathogenic microbes, viruses or spirochetes.

Invasion is infection of organism by parasite.

Autoinvasion is a case when a human or animal infected by a parasite can be a source of infection not only for others but for itrself. Example of autoinvasion is a reinfection with pinworms. The sick child may infect himself again if the eggs of parasite are located under his nails.

Re-invasion is a reinfection of a human or animal by parasites by which he waw previously infested. The source of invasion is parasite carriers (the sick animal, human). For example, a person who suffers from ascariasis, trichocephalesis, diphyllobothriasis or other helminths defecates of invasion eggs together with faeces into the environment. Individuals who recovered from amoebiasis can excrete feaces of dysentery amoeba cysts, giardia infection in the environment and infect the others.

The unified nomenclature of parasitic diseases is adopted today which are designated by the zoological name of pathogen for which the generic name of a parasite is added the suffix “is” or “es” (amoeba - amebiasis, leishmania - leishmaniasis, fasciola - fasciolosis).

Transmissive is diseases caused by blood-sucking arthropods. Depending on the role of a disease carrier of the exciter, the obligate and facultative transmissive diseases are distinguished.

Obligate transmissive diseases can be transmitted by blood-sucking arthropods as specific carriers. For example, malaria exciter is transmitted by a malaria mosquito (female), leishmania exciter are transmitted by the mosquitoes.

Facultative transmissive diseases can be transmitted not only by blood-sucking vectors, but also by other way (oral, pin). The pathogen of plague can be transmitted to a human through the bite of rodent fleas and by droplets in contact with a patient when removing skins from diseased animals.

Parasitic diseases are divided into two major groups due to relationship developed between parasite and host: zoonoses and anthropono-ses.

Zoonoses are diseases the exciters of which can parasitize in both animals and human (leishmaniasis, trypanosomiasis, balantidiasis, taiga encephalitis, swine etc.).

Anthroponoses are diseases, which exciters can parasitize only in human (malaria, amoebiasis, trichomoniasis, ascariasis, enterobiasis, etc.).

17.4. PARASITES AND THEIR CHARACTERISTICS

Parasites are organisms that use other living organisms as a food source and habitat, placing at the same time partially or fully on their hosts the task of regulation of their relationship with the environment. The host organism is habitat of first order for a parasite. The external environment in which a host lives, acts on a parasite only indirectly via the host organism and is a second order. Parasites, depending on the habitat, are divided into two large groups: ectoparasites and endoparasites.

Ectoparasites are animals living on a host body (mainly arthropods). Ectoparasites can be constant (for example, lice) if the entire life cycle is spent on skins of an animal or human body, temporal (mites, mosquitoes, flies, etc.), which are on the host body only to suck blood.

Endoparasites are animals that live in the tissues and organs of the host. By location in a human or animal, they are classified into intracellular (leishmania, plasmodium, toxoplasma); tissue (dysenteric ameba, trypanosomes, balantidiums, schistosomes, filaria, guinea worm, larvae of trichinella, scabies mites, etc.); intraorgan (opisthorchis, klonorchis, fasciola, paragonimus, etc.) and cavitary (porcine and bovine tapeworms, broad tapeworm, ascaris, pinworm, hookworm, whipworm, etc.). All endoparasites are permanent parasites of a human.

Monoxenic are parasites developed only in one host body. For example, a dwarf tapeworm, pinworm is parasitic only in a human. Most of monoxenic helminthes (ascaris, whipworm, hookworm, etc.) for a complete cycle of development need to exit the fertilized eggs from the host into the environment.

Heteroxenic are parasites that commit the development cycle changing the hosts (malarial plasmodia, porcine and bovine tapeworm, trematodes, trichinella, filaria, etc.). In accordance with the level of specialization obligate, facultative and false parasites are identified.

Obligate parasites are organisms in which a parasitic lifestyle is mandatory, species-specific form of existence (roundworm, whipworm, filaria, trichinella, lice, fleas, ticks, etc.). *Facultative parasites* are organisms with free lifestyle and become parasitic only by altering conditions of existence in the external environment (Strongyloides stercoralis). *False parasites* are free-living organisms which can exist for some time in fly faeses.

All helminthes are divided into geohelminthes, biohelminthes and contact helminthes. Biohelminthes are parasitic worms whose life cycles depend on a change of a host (all trematodes, cestodes, filaria, trichinella, etc.). Geohelminthes are parasitic worms which infective larvae are developed from a fertilized egg in the soil. A human is infected through unwashed vegetables, fruits containing invasive eggs (roundworm, whipworm) or via larvae in direct contact with the soil (hookworm, American hookworm). Contact helminthes are parasitic worms, the cycle of which may completely pass in a body without departing into external environment (dwarf tapeworm, threadworm).

17.5. HOST OF PARASITE

Host of parasite is an organism in which a parasite lives temporarily or permanently and is reproduced by sexual or asexual way. The parasites life cycle consist of stages of change the host. The larval stages are usually developed in the body of one species. The mature stages are developed in the body of another species.

The final or definitive host is an organism in which a parasite reaches sexual maturity and is reproduced in sexual way. The human body is the final host of most species of cestodes, trematodes, nematodes.

The intermediate host is an organism which inhabits the larval stage of the parasite and only asexual reproduction of a parasite is possible. Human is an intermediate host for the malaria parasites, tapeworm, alveococcus and others. To complete the development cycle for some parasites (opistorchis, paragonimus, tapeworms, etc.) but two (or more) intermediate hosts are needed.

The second intermediate host is called optional. Opisthorchis has two intermediate hosts (first is clam Bithynia leachi, second - many species of fish).

The obligative host is an organism in which a parasite is provided with best survival rate, rapid growth and highest fertility. Man is an obligate host for dysentery amoeba, roundworm, hookworm and other parasites.

The optional host is an organism in which a parasite can live, but not fully adapted. For example, a human is an obligate host for the tapeworm

wide. Cestodes may parasitize in the fox body but their size does not reach big length and life does not exceed two months.

The reservoir host is an organism in which a parasite is not developed, but only accumulated in invasive stage. The reservoir host accumulates larval stages of pathogen and transfers invasion.

17.6. WAYS OF ENTRY PARASITES IN THE HOST ORGANISM

Various parasites can penetrate into the human body in different ways: through a mouth, skin, blood, placenta, etc. There are the following ways of human infection.

The oral way is the most common. Through a mouth a person can swallow cysts of protists, larvae of worms with contaminated vegetables, fruits, meat. In some cases, the oral way of infection may be added with intracolonic or transplacental infection.

Percutaneous way of infection when infective larvae penetrate through intact skin (schistosome cercariae, filariform ancylostoma larvae).

Contact way of infection is caused by direct transmission of the exciter from an invaded to healthy person or by contact with dirty underwear, medical instruments, etc. It is observed during infection of Trichomonas vaginalis (sexual contact), scabies mites, lice.

Intraenteric way occurs during the development of the infective helminth larvae from the fertilized egg in intestinal villi without exiting into the environment, and then from an adult parasite. This way of infection is observed in a dwarf tapeworm, intestinal ugritsy.

Transplacental way occurs when invasive stages of a parasite penetrate through the placenta of a pregnant woman into the fetus. It is observed in parasitism of toxoplasma and leads to development of congenital toxoplasmosis. Transplacental infection of the fetus is observed in pregnant women with malaria, sleeping sickness, visceral leishmaniasis (kala-azar), hookworm.

Transmissive way is carried by arthropods. There are two ways - inoculation and contamination.

In the inoculation way a parasite is actively introduced into human or animal blood with saliva through vector mouth if host skin is damaged.

The contamination is a way when a parasite is laid by a bloodsucker on a host undamaged skin. A host can actively inject the exciter by scratching itchy areas of skin. Inoculation and contamination can be of two types: specific and mechanical. *Specific inoculation* is characterized by intensive growth of the exiciter in the body of the vector, and then it is

injected into a human or mammal. It is observed in malaria, leishmaniasis, trypanosomiasis.

Mechanical inoculation occurs when the pathogen reaches the mouthparts of the vector, survived there for some time, but is not reproduced, and then is entered into the wound by sucking blood. So a stable-fly inoculates the exciter of anthrax.

Specific contamination is observed when the parasite is reproduced in the intestines of the vector, and then excreted in feces, with spitting the food on skin and then is rubbed by a man while combing. In *mechanical contamination* the vectors (flies) can bring on food cysts protists, helminthes eggs, pathogenic bacteria of intestinal infections (dysentery, typhoid, etc.).

Transovarial transmission occurs when a female transfers the exciter to their offspring through the germ cells. This is observed in ticks in transmission and preservation of the pathogen taiga encephalitis in twelve generations. Transovarial transmission of spirochetes of tick-borne relapsing fever is described in argasids in three generations.

17.7. RELATIONS IN THE SYSTEM PARASITE-HOST. PARASITOCENOSES.

A parasite and host comprise interconnected elements of a "host-parasite" single biological system which reside in various specific environmental conditions. Parasite usually has an adverse effect on a host which causes disease. The property of the parasite to have pathogenic effects on the host is designated as pathogenicity. The host organism is an external environment for the parasite. Adverse changes in physiological state of the host (cooling, hyperthermia, starvation, overwork, etc.) and for a human - the negative impact of various social factors that contribute to enhanced parasites. For example, a commensal form of a dysenteric ameba under the above conditions is transformed into pathogens that causes amoebiasis. The final result of interaction of parasite and host depends on their specific features, specific environmental conditions, individual characteristics of given parasite and host. Several species of parasites may live in a host at the same time. When interacting with one another, they can both enhance and impair the combined negative effects. The group of parasites living in a host organism, in its individual organs, is named parasitocenoses. The term "parasitocenoses" was proposed by E.N.Pavlovsky. It is a relationship between the protozoa, helminthes and intestinal bacteria human. Knowledge of elationship within parasitocenosis is important for doctors because it allows them to increase the effectiveness of treatment.

17.8. THE CONCEPT ABOUT NATURAL REGIONS OF PARASITE DISEASES

Among parasitic diseases there is a special group of natural focal diseases - infectious and parasitic diseases that may exist for a long time in certain areas, regardless a person. The doctrine of natural focal of transmissible disease in a human was developed by E.N. Pavlovsky.

He gave the following definition of natural foci: "This phenomenon, when the exciter, its specific vector and animals - reservoirs of the pathogen during the change of their generations exist for an unlimited time in the nature not dependent on a human as in the course of its past evolution, and in its present period. "Natural foci of disease are the territory with its specific biocoenosis which includes: firstly, the causative organism of disease; secondly, host-pathogens which are donors of blood-sucking arthropods; thirdly, organisms-vectors of pathogens from animal to a healthy patient (recipient). Activators of natural focal transmissible diseases can be pathogenic viruses, bacteria, protozoa and helminthes. Natural reservoir of the activator is animals (vertebrates and arthropods). In their bodies the causative agent can be continuously maintained and transferred directly from it or by a vector (if this is an infested vertebrate containing an exciter in its blood) to a healthy organism.

Vectors of natural focal transmissible diseases may be ticks, mosquitoes, flies, gnats, midges, horse flies, lice, fleas which circulate the causative agent in the hearth. Specific (obligate, true) and optional vectors are distinguished. In the body of the specific vectors a causative pathogen develops and is reproduced. The vector is able to infect the host of the recipient in a relatively short period of time. For example, mosquitoes are specific vectors for leishmania, mosquitoes of the family Anopheles - for malaria parasites, or kissing bugs – for the pathogen for American trypanosomiasis. In the body of an optional vector a causative pathogen can also be reproduced. Natural foci of transmissible diseases can be both in the wild nature and in the area of human activity (synanthropic foci). Formation of synanthropic foci is due to the fact that some species of mammals and birds (goats, sheep, dogs, rodents, sparrows, swallows, etc.) are vectors of pathogens of natural focal disease and live near a human. Among protozoan diseases the natural foci is detected, except leishmaniasis, at toxoplasmosis, trypanosomiasis (African and American). Among helminthes, opisthorchis, paragonimiasis, schistosomiasis, alveococcosis, filariasis relate to natural focal invasions. Natural focal character is also set for many viral and bacterial diseases (spring-summer encephalitis, rabies, tick-borne relapsing fever, swine, etc.).

17.9. PREVENTION OF PARASITIC DISEASES

Arrangement of prevention of parasitic diseases can only be based on thorough knowledge of the fauna of pathogenic parasites of a human, their biology and ecology, as well as vectors and working conditions and human life as an object of invasion. It is necessary to take into account the ways of transmission of infection, pathogenic effect of parasites on human and back impact of a human on the parasite, as well as sensitivity of parasites and their hosts to various measures of exposure and response. The basis for prevention of parasitic and infectious diseases is biological, chemopreventive and immunological methods that can not only prevent the development of disease, but also to improve human health and many animals against parasitic diseases.

Biological methods are based on strict consideration of the parasite life cycle and are focused on its break, creating conditions to violate the development of a parasite. These include biothermal disinfection of feces against protozoan cysts and helminthes eggs, plowing and grazing land reclamation, drainage of water basins, protection of water basins against feces, etc. All these activities are aimed to destruct parasite or individual stages of life cycle, intermediate hosts and vectors.

Chemoprevention is aimed at destruction and prevenditng of reproduction of invasive and pathogenic forms of a parasite. In particular, chemotherapy has been used successfully to prevent malaria, trichinosis and other invasions in a man. Chemoprevention is widely used in veterinary medicine to prevent parasitic diseases in farm animals. Treatment of parasitic diseases solves the problem of destruction of invasion of pathogens in a body of a sick person or animal or to decrease their biological effect. A set of measures aimed at expulsion of worms from the body, their destruction inside or in the environment was named deworming in 1925 by K.I. Scriabin. It it effective against those helminthes, which pathogens live in the definitive host for a long time, but the larval stage is short.

Immunoprevention is based on passive immunization, related to introduction into the organism of antibodies against a particular pathogen or attenuated pathogen culture to create immunity. It is widely used for prevention of infectious diseases. Issues of immunization invasions are still under development stage. There are currently actively conducted researchs to develop vaccines based on genetically engineered against malaria pathogens, trypanosomiasis, leishmaniasis, schistosomiasis and other parasitic diseases.

CHAPTER 18. MEDICAL PROTOZOOLOGY

18.1. PROTISTS, THEIR CHARACTERISTICS AND CLASSIFICATION

Medical protozoology studies biology, ecology, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment and prevention of representatives of monocytozoa kingdom which cause human disease. Protozoans are microscopic in size. Their body is a one cell consisting of outer membrane, cytoplasm and nucleus. Their membrane has a three-layer structure. A thin shell consists of fibrils which with the plasma of membrane forms a pellicle. Fibrils can be reduced, so that the cell can change its shape, and to move smoothly. Cytoplasm is usually divided into an outer transparent portion - ectoplasm which is a colloidal gel, and inner - endoplasm which is a colloidal sol. There are important cell organelles in endoplasm: the endoplasmic reticulum, mitochondria, Golgi complex. There are also contractile vacuoles in some species which regulates water-salt balance. Special movement organelles are cilia and flagella which are formed by the threadlike outgrowths of ectoplasm. Each flagellum (cilium) consists of a bundle of fibrils surrounded by a cell membrane. Peripheral fibrils, plunging into the cytoplasm, form a basal grain (blepharoplast). A protists cell has generally few flagella (1-4), while the number of cilia can reach several thousand in one individual. Most protists have one nucleus, but there are multinuclear forms. Karyoplasm may have one or several nucleoli or special formation (endosome) in the center of the nucleus instead. During mitosis, the mitotic spindle is formed, the nucleoli disappear and endosome is saved. Most parasitic protists have six or fewer chromosomes in the nucleus.

Trophozoites are protist cells during the active life. The nutrition of trophozoite can be done in two ways. Firstly, the nutrient penetrates through the membrane by diffusion or by active membrane transport. Second, nutrition is supplied by phagocytosis and pinocytosis. Vacuoles are formed around nutrients caught in cell. The energy is stored in the form of ATP due to glycolysis and oxidative phosphorylation (three carboxylic acid cycle in protists having mitochondria). Certain species of protists (amoeba, giardia, balantidiums etc.) in contacting with the external medium are capable to form resistant forms - cyst, a simple fixed lifecycle form coated with a dense membrane. The cyst metabolic processes are reduced, although the nuclear may be devided and spare nutrients are spent. Protists are reproduced asexually and sexually. In asexual reproduction the cell is divided by mitosis into two cells. Schizogony, sporogony are multiple division in

Sporozoa. The sexual process occurs in Sporozoa (oogamic copulation) and Ciliophora (conjugation). The asexual and sexual reproduction is observed in some protists alternation. This is typical for a parasite which life cycle extends nearly to the change of a host and formation of special propagative stages. Propagative stage in some cases ensures overliving in the external environment (cysts of dysenteric amoeba, giardia, toxoplasma oocysts). Propagative stage in others is located intracellularly and transmitted to the recipient by a vector (gametocytes of malaria plasmodium). Cysts, oocysts, sporozoites are infective stages for a human. Trophozoites are pathogenic stage for a human. In some cases, invasive and pathogenic stages may be only trophozoites (for example, Trichomonas vaginalis). Human parasites are found in three phyla of protists: Sarcomastigophora (Sarcodina and Zoomastigota classes), Apicomplexa (Sporozoa class) and Ciliophora (Ciliata class).

18.2. PHYLUM SARCODINA

Sarcodina are the most simply organized protists class. The cytoplasm restricted by an outer membrane is the body. Usually there is a single nucleus, but there are sometimes multinuclear forms. The movement and phagocytosis is made by pseudopodia which are formed in places of transition of ectoplasmic gel into sol. Their reproduction type is asexual (mitosis). Cysts are formed under unfavorable conditions. The class includes about 10 thousand species. Dysentery amoeba, as well as non-pathogenic oral and intestinal amoeba can parasitize in a human body.

DYSENTERIC AMOEBA (Entamoeba histolytica) is a causative pathogen of amebiasis, anthroponotic human disease manifested mainly in patients with ulcerative lesions of the large intestine, as well as development of abscesses in the liver and in other organs.

The life cycle of a parasite has two stages - the vegetative (trophozoite) and the cyst. They can transfer into each other depending on conditions of existence. Trophozoite in a human body can exist in four forms: tissue, large vegetative (forma magna), luminal (forma minuta) and precyst.

The tissue form is a form of pathogenic amoeba of 20-25 μm. It parasites in the colon mucosa and on histological sections of affected areas of the intestine wall. It may occur in liquid feces in ulcers decay.

The large vegetative form is pathogenic amoeba of 20-60 μm. They are found in freshly isolated liquid faeces of patients with acute amoebiasis. It often contains red blood cells at different stages of digestion. It is often called a red blood cells hog (or hematophagous erythrophage).

The luminal form resides in the lumen of the upper small intestine, the size of 15-20 μm. It is found in freshly extracted liquid feces from convalescent patients and patients with chronic amoebiasis.

The precystic form resembles a luminal of 12-20 μm. Cysts are nonmotile, coated with membrane, transparent, round shape, size of 8-15 μm.

The cycle of development. A human is infected with amoebiasis orally by swallowing the parasite cysts with food (Fig. 18.1). Less common factors to transmit dysentery amoeba cysts may be household items (linen, dishes, toys, door handles). Amoeba cysts are spread by synanthropic flies, cockroaches less. Cysts can survive in the intestine for 48-72 hours. In the lumen of the colon the cyst loses shell, and the parasite is divided into eight small cells which transformed into the vegetative forms. They can be re-

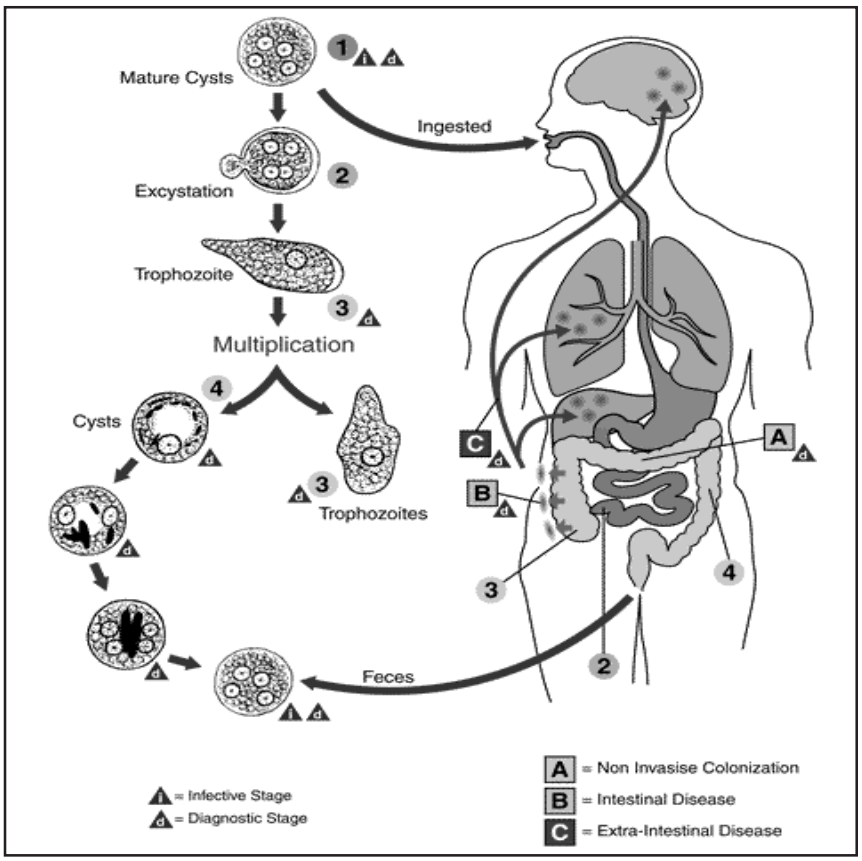


Fig. 18.1. The cycle of development of Entamoeba histolytica (by DPDx and CDC).

encysted and excreted outside. When existent conditions deteriorate, small vegetative forms are converted into large, penetrate into in the lining of the intestinal wall and cause formation of ulcers. They are transformed into tissue foms which can enter the bloodstream and spread throughout the body, causing the formation of abscesses in the liver, lungs and other organs. Trophozoites and cysts are found in feces of a patient.

Pathogenic action, symptoms. There are invasive amoebiasis and asymptomatic carriage. Under the clinical course the intestinal (amebic dysentery) and extra-intestinal amoebiasis are distinguished. In 90% of cases the E. histolytica infection is followed by asymptomatic carrier state. In acute intestinal amoebiasis the incubation period ranges from several days to several months. Fulminant amoebic colitis is developed which causes fatal case as a result of perforations of colon wall and peritonitis. Over time the disease passes to the chronic phase which without specific treatment may last up to 10 years or more. Extra-intestinal amoebiasis is manifistated in developing of the amoebic abscesses which can be formed in any organ. Abscess has a semifluid mass consisting of decayed tissue, lymphocytes, red blood cells and elements of connective tissue. In intestinal amoebiasis perforation, amoebic appendicitis, intestinal obstruction (resulting in scarring), rectal prolapse, intestinal bleeding may be developed.

Epidemiology. The source of infection is a person who excretes mature cysts of amoebas. Typically, this is a form of healthy carriers of luminal amoebae. The cysts remain viable under the action of disinfectants (chlorine, ozone) in concentrations normally used on waterclean stations. Therefore cysts can spread via drinking water. The mechanism of infection of amoebiasis is fecal-oral. Ways of infectionare through water, nutritional and contact. Amoebiasis cases are recorded everywhere but more often in tropical and subtropical zones.

Methods of diseases diagnosing. Clinicaly amoebiasis can be determined by detecting in patient's fecea of tissue forms of dysentery amoeba and/or large vegetative. They need to be distinguished from other dysentery amoebas that live in the human gut. There are serological study methods (immunosorbent assay - ELISA, indirect immunofluorescence - IIFT) for amoebiasis diagnostic.

Prevention. Measures for prevention of human infection with cysts of dysenteric amoebae are focused on personal hygiene (washing with boiled water of fruits, vegetables, washing hands before eating, after the toilet, drinking boiled water, protecting food from flies, cockroaches). Social prevention is aimed at detecting and treatment of patients and cyst-contaminators, eradication of flies, to prevent contamination of water and soil by patients faeces with amebiasis.

18.3. PHYPLUM ZOOMASTIGOTA

Type Flagellates combines protists in which one or two flagella surve as organelle movement, which is an outgrowth of the cytoplasm containing inside 9 pairs of microtubules coated with plasma membrane. A basal body and blefaroplast containing proteins and RNA are the base of the flagellum. All parasitic forms do not have contractile vacuole. Reproduction is asexual (longitudinal division in half). The following stages are distinguished in the life cycle of flagellate with kinetoplasts:

- tripomastigote has undulating membrane with free flagellum, kinetoplasts located at the rare end of the body;
- epimastigote has undulating membrane with a free flagellum, kinetoplasts located in front of the nucleus;
- promastigote has only free flagellum, kinetoplasts shifted to the front end of the cell;
- amastigote has a spherical or oval shape, the flagellum is very short, under the light microscopy the nucleus and large kinetoplasts can only be seen in the cell.

The medical importance has the Leishmania family (the exciter of human leishmaniasis), Trypanosoma family (exciter of human trypanosomiasis), Trichomonas family (the exciter of human trichomoniasis) and Lamblia family (the exciter of human giardiasis).

PATHOGENIC CUTANEOUS LEISHMANIASIS (anthroponotic - Leishmania tropica, zoonotic - L. major, the New World - L. mexicana mexicana). Anthroponotic cutaneous leishmaniasis is common in the Middle East, Africa and India. Zoonotic cutaneous leishmaniasis occurs in Africa and Asia, Turkmenistan, Uzbekistan. Cutaneous leishmaniasis of the New World is registered in all the countries of Latin America and the southern areas of the US.

The morphology of the parasite. Amastigote is an oval of size 3-5x1-3 μm and is localized in the skin, lymph nodes. Promastigote of fusiform shape is 10-20x4-6 μm, at the front end of the body they have a flagellum extending from kinetoplasts.

The cycle of the parasite runs in two stages: amastigote - in human, mammals and promastigote in the body of mosquitoes of family Phlebotomus. The way of human infection by exciters of cutaneous leishmaniasis is only transmissive through the bite of mosquitoes (specific inoculation). Mosquitoes feeding on blood of a sick human or animal is invaded by the parasite and after 6-8 days it becomes contagious.

Pathogenic action, symptoms. Anthroponosic and zoonotic cutaneous leishmaniasis is characterized by formation of rounded, long non-healing ulcers on exposed parts of the body (of the face, extremities). In the nasal

mucosa and oral cavity the small nodules are formed passing into polypous growths. After healing the scars remains on a body and a patient obtains immunity for entire live. Cutaneous leishmaniasis of the New World is characterized by deeper skin lesions in 10-20% of cases, the mucous membranes of the nose, mouth, pharynx, larynx, and at least - the genitals with the development of the destructive inflammatory changes.

Epidemiology. The source of infection is a sick human. An additional reservoir of L. tropica is the sick dog, L. major - rodents and L. mexicana mexicana - different species of wild rats, mice, monkeys, sloth. Transmitting agent is mosquitoes. The disease occurs throughout the year. Anthroponotic type of cutaneous leishmaniasis occurs mainly in towns and cities. The disease is sporadic, mostly children are sick and among the newcomers - people of all ages.

Methods of diagnosing diseases. Medical history of patients staying in an endemic area has a great importance. Material for microscopic examination should be taken from the edge of a defeated part or infiltrate. Fixed slide stained on Romanovsky-Gimsa method is examined in the usual way. In case of ulcers or granulomas the material is taken from the marginal infiltration. Laboratory diagnosis is based on detection of amastigote of Leishmania in the material obtained from the bottom of the ulcers and infiltration. Some of the material is inoculated on medium NNN-agar which allows obtaining accurate diagnosis of Leishmania culture. Serological methods are also used.

Prevention. It is recommended to use repellents. Social prevention is aimed at the identification and treatment of patients, the imposition on leishmanioms (ulcers) dressings to prevent infection of mosquitoes. Measures are being taken to destroy of mosquitoes.

PATHOGENIC OF VISCERAL LEISHMANIASIS (L. donovani). The disease is known as Kala Azar.

The morphology of the parasite. The parasite does not differ from other species of Leishmania according to morphological characteristics.

The cycle of development. In a life cycle pathogens undergo amastigote stage in a human, mammals and promastigote in the body of vector (different species of mosquitoes of family Phlebotomus). The infection way is transmissive, by specific inoculation through mosquitoe vectors. The source of infection in the Indian leishmaniasis is a sick man, while in the Mediterranean-Central Asian - sick dogs, jackals, foxes, squirrels and in East Africa - a sick man and rodents. Cases of transmission of exciter are known through blood transfusions.

Pathogenic action, symptoms. Children under 12-years old are more commonly infected. The disease is followed by a non-periodic fever,

enlargement of the spleen and liver, decrease of erythrocytes in the blood. If untreated, the disease ends in death. The incubation period lasts from 3 weeks to 12 months. The disease begins gradually. At the active stage of the disease the fever is marked, spleen, liver and lymph nodes are enlarged. Digestive tract function (diarrhea) is debilitated. Hypersplenomegaly can lead to splenic infarction. The recover patients have resistant for parasite and long-lasting immunity.

Epidemiology. Kala Azar is anthroponosis. The source of infection is a sick human. The highest morbidity is registered among 5-9-year-old children. Vectors are the mosquitoes Ph. argentipes. Indian visceral leishmaniasis is observed in eastern states of India, Pakistan, Bangladesh, Nepal. Mediterranean-Central Asian visceral leishmaniasis is recorded in Greece, Spain, Portugal, France, Yugoslavia, the Middle East, in the north-western China, in a number of countries in Latin America, sporadically – in the Central Asia and Transcaucasia. East African visceral leishmaniasis occurs in Sudan, Kenya, Somalia, Ethiopia, Uganda, Chad.

Methods of diagnosing diseases. The Leishmania is detected in bone marrow from the sternum, lymph nodes, spleen and liver. To obtain parasite culture, the material is planted on NNN-agar medium. For serodiagnosis the indirect immunofluorescence reaction and the reaction of enzyme-labeled antibodies with an antigen from Leishmania is used.

Prevention of visceral leishmaniasis is aimed at early detection and treatment, the fight against mosquitoes, protecting people from their attacks, treatment of sick dogs.

PATHOGENIC OF AFRICAN TRYPANOSOMIASIS (Trypanosoma gambiense, T. rhodesiense) is a transmissive disease which is characterized by fever, rash presence (exanthema), lymphadenitis, cachexia and development of lethargy in later stages of disease. Human is the main host for T. gambiense. Forest antelope is the definitive host for T. rhodesiense. An additional host for the Gambian type are pigs, and for the Rhodesian type - wild animals, cattle and human. The vectors are the tsetse fly (Glossina palpalis, G. morsitans).

The morphology of the parasite. The body is curved and narrowed at both ends, is provided with a flagellum and undulating membrane. The body length is 15-40 μm, width - 1.4-2 μm.

The cycle of development. In the life cycle the trypanosome undergo tripomastigoty stage in the human body and epimastigote in the vector body (tse-tse fly). Infected tsetse flies attack hourses during daylight and are able to transmit trypanosomes throughout life.

Pathogenic action, symptoms. A patient with trypanosomiasis has muscle weakness, exhaustion, depression, drowsiness. Sleeping sickness

without treatment takes 5-7 years and usually ends in death of the patient. There are 2 stages of the disease: haemolymphatic and meningoencephalitic (terminal or sleeping sickness). The haemolymphatic stage occurs within 1-3 weeks after infestation, and is associated with the proliferation of trypanosomes through the body from places of initial insertion. The meningoencephalitic stage develops after a few months or years, and is characterized by lesions of the central nervous system. In the terminal phase the mental disorder is enhanced, there are convulsions, incontinence of urine and stool. The disease results in death with symptoms of cachexia and cerebral coma.

Clinic of Rhodesian sleeping sickness is more acute and severe. The incubation period is shorter than that of the Gambian form. The fever period is longer. Weakness and wasting rapidly grows. Heart diseases are more severe.

Epidemiology. The Gambian form of trypanosomiasis is predominantly anthroponoses. It occurs in West and Central Africa. Rhodesian form of a sleeping sickness is a typical zoonotic disease. The main reservoir of infection in nature is forest antelope. The disease occurs in the countries of Eastern and Southern Africa. Mixed infections caused by T. gambiense and T. rhodesiense cases are identified in refugee camps because of the intensive migration of people caused by social conflict.

Methods of diagnosing diseases. The laboratory diagnosis is based on detection of trypanosomes in smears of punctuate of lymph nodes, cerebrospinal fluid, bone marrow, peripheral blood, taken during febrile illness, as well as immunological diagnostic methods.

Prevention. Personal chemoprophylaxis is effective in foci of trypanosomiasis. The methods of prevention are detection and treatment, protection of the population from biting tse-tse flies, population survey and identification of patients in the initial stage of the disease, elimination of flies.

AMERICAN TRYPANOSOMIASIS (Trypanosoma cruzi) or Chagas disease is transmissive disease characterized by natural foci.

The morphology of the parasite. Pathogen was first described by G. Chagas in 1907. The length of the parasite in human blood is 15-20 μm. The parasite body is of S-shape. Free flagellum is about 1/3 of the body length.

The cycle of development. The life cycle of trypanosomes includes stages of tripomastigoty and amastigote in human and mammalian organism (armadillo, opossum, anteater, fox, guinea pig, etc.). It is a natural reservoir of exicter. Bugs of family Triatoma, Panstrongylus are the vector of disease.

It has epimastigote stage of parasite. Trypanosomes after penetrating into tissue cells of a human, mammals lose the flagella and are transformed into amastigote with an oval shape and size about 2 μm in diameter. Pseudocysts are formed in infected cells. Subsequently amastigote are transformed into tripomastigoty which are characterized by S-shaped, undulating membrane with a free flagellum. Tripomastigoty enter the blood, but do not multiply. Bugs with blood sucking swallow parasites in the intestines, where tripomastigoty are transformed into epimastigote. The latter are reproduced by dividing extracellularly. After 10-30 days invasive tripomastigoty appear in the rectum of a bug and then are excreted with faeces.

Pathogenic action, clinic. Pathogenic action is expressed in developing of myocarditis, hemorrhages in the meninges, meningoencephalia. The disease affects mainly young children. At older ages, the disease becomes chronic. Human infection with the pathogen occurs as a specific type of contamination. Trypanosomes, trapped on the surface of the body with feces bugs, penetrate through the damaged skin, mucosa in the bite area. Infection with trypanosomes is possible in blood transfusion and transplacental during pregnancy. At the site of initial penetration, the trypanosomes are phagocytosed by macrophages and rapidly multiply in them. Furuncle infiltrations are formed after 7-14 days of infection in some patients. On 4-6th week after infection the hematogenous dissemination of parasites occurs with generalization of the process. Pseudocysts may form in the cells of all tissues in intestinal smooth muscles. Malaise, headache, chills appear, the body temperature rises to 38-40^{0}C. Acute stage lasts for 4-6 weeks. Disorders of the peripheral nervous system are followed by convulsions, paralysis. In the terminal stage, the disease is often complicated by meningoencephalitis.

Epidemiology. The disease is common in all countries of America, the most frequently is recorded in Brazil, Argentina, Venezuela, Bolivia, Guatemala, Colombia, Honduras, Paraguay, Uruguay, Ecuador, Chile, Costa Rica, Panama. The number of patients is 18 mln. including 200 thousand of new cases annually.

Methods of diagnosing diseases. The Chagas disease is detected in endemic areas on clinical symptoms (heart failure, furuncle infiltrations). The laboratory diagnosis is based on detection of trypanosomes in smears of blood, cerebrospinal fluid. The complement fixation with an antigen of cardiac muscle of infested animals is applied for serological diagnosis. Intradermal test is also used for a specific antigen. The patient can be

infected by T. cruzi in alimentary way (mother's milk), by blood transfusions, by amniotic fluid.

Prevention is based on eradication measures against bugs vector, elimination of conditions for bugs to attack a human, survey of donors to prevent the transmission of trypanosomes in blood transfusion.

UROGENITAL TRICHOMONADS (Trichomonas vaginalis) is the exciter of urogenital trichomoniasis. A parasite is only in the human body (in female – in urethra, vagina and other parts of the reproductive system, and in male - the urethra, prostate and epididymis).

The morphology of the parasite. The body shape is oval or spindle-shaped, body size is 4-32x2-14 μm. The nucleus is the oval, located at the front end of the extended body. The parasite has 4 available flagellum from the front core and undulating membrane. The body is penetrated by the supporting rod (aksostil) consisting of microtubule and ending in a pointed tip at the rear end of the body. The parasite feeds on solute dissolved in the vaginal secretions substance. It is reproduced by dividing in two, sometimes in four individual cells. The parasite exists in the vegetative form (trophozoite). It occurs everywhere.

The cycle of development. Trichomonads live in the vagina and cervix of women, in the urethra, the bladder, and the prostate gland of a mail. Women are infected in 20-40% of cases, men - 15% of cases. Trichomonads closely contacting the epithelium of the genitourinary system, causes the appearance of fine inflammatory foci beneath the epithelial layer, and peeling of the surface mucosal cells. Disease in men and women proceeds a few years.

Pathogenic action, clinic. The incubation period of urogenetal trichomoniasis is 7-10 days, but sometimes varies from 3-4 days to 1 month or more. There are three forms of disease: acute, chronic, vector of trichomonads. The acute form of the disease is characterized by development of the vagina lining hyperemia, frothy appearance of gray-yellow in color with blood, itching and burning in the vulva, pain during sexual intercourse. In symptomatic form of infestation in men, trichomonas cause recurrent mycotic urethritis. Important is the ability of T. vaginalis to phagos quote gonococci, chlamydia, resulting in difficulties of treatment and there is a possibility of recurrence of gonorrhea. Among the examined individual parasites the detection frequency ranges from 0.5 to 80%. In human, trichomoniasis is sexually transmitted disease.

Epidemiology. The source of infection is a sick human. The excicter infection is a sexual way. According to WHO, more than 333 million of patients with trichomoniasis are recorded annually in the world. Prevalence of the disease among women reaches 30-50%. The level of male incidence

varies from 6 to 10%, and in patients with gonorrhea - up to 19%, infertility - from 4 to 10%.

Methods of diagnosing diseases. Diagnosis is based on detection of Trichomonas in smears from the vagina, urethra and cervix. Native and stained preparations are studied.

Prevention is based on identification and treatment of patients with trichomoniasis, carrying out health education and educational work among the population. Individual prevention is to use condoms.

GIARDIA (Lamblia intenstinalis) is the exciter of human giardiasis. It lives in the lumen of the small intestine. Giardiasis can be in the form of latent parasite contamination and manifest forms of affecting mainly the small intenstine.

The morphology of the parasite. The life cycle consists of two stages: vegetative (trophozoite) and cyst. Trophozoite is pear-shaped with a pointed rear end, 10-25 μm in length and 8-12 μm in width with a thickness 3 μm. Parasite has two nucleus, two discs located on the front side of the ventral surface, and four pairs of symmetrically arranged flagella. Parasite attaches by the disk to epithelial cells of the villi and crypts of the duodenum and small intestine. Trophozoites do not penetrate the epithelial cells, but discs form grooves on micro-cells villous surface. The parasites are multiplied by binary fission. Cysts are oval with size of 8-12 x 7-10 μm. The mature cyst has 4 nucleus. Cysta are formed in the distal small intestine and colon. Cysts are stable in the environment for several weeks.

The cycle of development. The way of infection is oral (Fig. 18.2). Cysts are ingested by eating unwashed vegetables, fruits, the water from random sources. When ingested the parasite is excystated in the duodenum where two trophozoites are produced from each cyst. The main source of infection is a person infected with giardia. The mechanism of transmission of the causative agent is fecal-oral. Cysts are transmitted by water where parasites remain alive for 3 months at a temperature of 4-20^0 C. The water contact way of infection is observed in infant school. Children under the age of 9 years are more exposed to Giardia infection. Boys are infected in 2-3 times more often than girls. Giardia can occur in healthy individuals (asymptomatic carriage), but often cause inflammation in the small intestine. A large number of Giardia covering broad surface of the intestinal wall disrupts absorption processes and wall digestion.

Pathogenic action, symptoms. Nutrient absorption and enzyme activity is disturbed (invertase, lactase) leading to increased fermentation processes. Symptomatic invasion is manifested in symptoms of lesions of the gastrointestinal tract. Patients are worried about nausea, burping when eating, heartburn, loss of appetite, cramping abdominal pain.

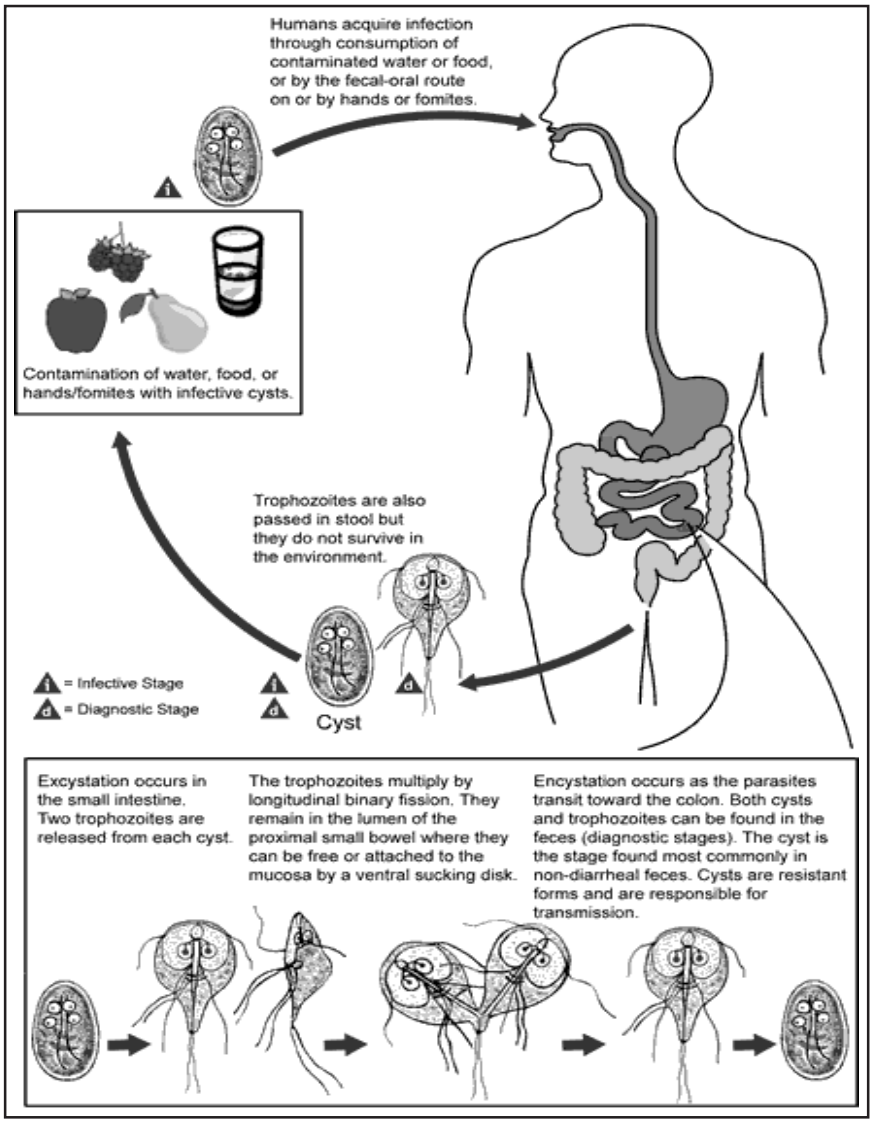


Fig. 18.2. The cycle of development of Lamblia intestinalis (by DPDx and CDC).

Epidemiology. Giardiasis is widespread and in many countries it is one of the most common intestinal parasitosis of a human. Average infestation is of up to 10%. Children are infected up to 40-50%.

Methods of diagnosing diseases. Laboratory diagnosis is made by microscopy of duodenal contents, where only trophozoites are detected, and fresh fecal in which smear cysts and trophozoites (liquid stool) are detected. Giardia vegetative forms can be detected in liquid feces during diarrhea. Slides with smear prepared from feces stained with Lugol solution are examined to detect cysts.

Prevention is based on strict observance of rules of personal hygiene, eradication of mechanical vectors (flies, cockroaches), especially in childrens establishments. Social prevention is aimed at preventing the environment, water, food from fecal contamination, and also carrying out sanitation.

18.4. PHYLUM SPOROZOA

The Sporozoa phylum includes more than 4000 species. Sporozoa consists of exclusively intracellular parasitic which life cycle includes two kinds of asexual reproduction (schizogony and sporogony) and a sexual process. The major parasites of human are the families Cryptosporidium, Pneumocystis, Toxoplasma, Plasmodium. Sporozoans are characterized by specific cellular ultrastructures. All sporozoans are parasites. Due to living in a specific environment of a host organism the sporozoans lost a number of organelles in the course of evolution. In many species, the processes of reproduction have been intensified. Asexual reproduction often alternates with sexually. The life cycle of many Sporozoa terminates in one host. Their distribution among hosts population is associated with the release into the environment in which they are experiencing in the form of sporulated oocysts, surrounded by dense protective sheath. Heteroxenic Sporozoea which are developed with a change of hosts are transmitted from one host to another without departing from the outside. In these kinds the sporules are not formed in life cycle. These species are distributed by transmitting sporozoites, gamonts or tissue cysts.

Sporozoa is very widespread and parasitize in representatives of almost all classes of multicellular animals. They live primarily in the host cell and throughout its life impair their function, causing severe disease.

CRYPTOSPORIDIA (Cryptosporidium parvum) is intestinal coccidia that damages the top layer of the intestinal epithelium. In a human sexual and asexual reproduction occurs simultaneously. Cryptosporidium cause cryptosporidiosis in a human - protozoan disease, occurring with lesions of the mucous membranes of the digestive system and is manifested in profuse diarrhea, loss of body weight. It is often observed in severe form in individuals with immunodeficiency and poses a real threat to the lives of HIV-infected people. The source of infection for human is domestic animals

(calves, piglets, dogs, cats, etc.). The oocysts are resistant in the environment.

The morphology of the parasite. C. parvum is the only species of cryptosporidia pathogenic to a human. Oocysts have ovoid, ellipsoid or spherical forms, covered by bilayer membrane. Diameter of oocysts ranges from 2.5 to 7 μm. There are 4 sporozoites inside the oocyst.

The cycle of Cryptosporidium includes triad processes specific for Sporozoa: merogony, gametogony and sporogony. It ends with one host. Merogony begins after a multiple growth of sporozoites which are transformed into vegetative forms - trophozoites. The nucleus is divided into several parts, forming the multi-nucleated cell – a meront (schizont). Meront splits into 8 merozoites that enter into the lumen of the intestine and attach themselves to the surface of epithelial cells, are rounded and give rise to a new cycle of asexual reproduction. Three days after infection the merozoites start sexual reproduction - gametogony. *Gametogony* begins after merozoites penetrate into the host cells which give rise to gamont which are developed intracellularly. In the process of development the gamonts turn into mature gametes. There is oogamy in Cryptosporidium. As the result of fusion of micro- and macrogametes the zygote is formed, around which the oocyst coated with dense shell is formed. *Sporogonia* in Cryptosporidium occurs in the host organism. Inside the oocysts the sporozoites are formed (sporulation). Most of sporulated oocysts (oocysts walled) leave the host organism along with feces. Some (thick-walled oocysts) release sporozoites in the intestines of the host which can give rise to new cycles of merogony (autosuperinvasion). A host is infected when the oocysts is ingested. In its digestive tract, sporozoites leave the oocyst and are attached to the epithelial cells of the stomach or small intestine.

Pathogenic action, symptoms. Cryptosporidium causes malabsorption and fluid filtration the watery diarrhea is developed in the intestine up to 10 times or more a day, causing dehydration and weight loss. Diarrhea is followed by cramping abdominal pain, fever (up to 38° C). Diarrhea can cause a loss of up to 15-17 liters of liquid per day. The disease is one of the first places among the AIDS-related infections.

Epidemiology. The main source of infection is a human or many kinds of animals. The mechanism of infection is faecal-oral. The water and dirty hands can be factors to transfer this disease (including swimming pools). Cryptosporidiosis is observed in different climatic zones on all continents. The highest incidence occurs in developing countries with a hot climate and low sanitary culture.

Methods of diagnosing diseases. The diagnosis of cryptosporidiosis is set upon detection of Cryptosporidium oocysts in smears of patient's

fecal or bronchial-alveolar lavage, stained by Ziehl-Nielsen, safranin by Kester or azur eosin by Romanowsky-Giemsa. NRIF and IFA methods, PCR diagnostics are applied as well.

Prevention. Non-specific preventive measures are carried out in the same way as in other enteric infections. Since Cryptosporidium oocysts can penetrate through the conventional filters, filtration systems are recommended at the water-purifying stations, hindering particle of 1 micron or less size. Prevention is based on cleaning, mechanical removal of sewage, manure.

PNEUMOCYSTIS (Pneumocystis carinii) is conditionally pathogenic intracellular parasite with a strong tropism for the lung tissue. Pneumocystosis is opportunistic infection causing death in patients with various immunodeficiency conditions, including HIV infection. The cycle of development can be carried in the lumen of the alveoli, but in case of immunodeficiency in a host is able to destroy the cells of many tissues. Mature parasite cysts trapped in human lungs have an oval or circular shape with a diameter of 7-10 μm. There are 8 sporozoites inside them. When the cyst bursts, the sporozoites reach the alveoli and are transformed into small mononuclear haploid trophozoites of 1-1.5 μm size. Trophozoites merge to form diploid individuals who for some time are reproduced by dividing in two. Then sporogony comes and 8 sporozoites are formed during mitotic division. A new host is infected by cysts and sporozoites that enter into the environment with droplets of mucus by a coughing patient.

Pathogenic action, symptoms. The disease is manifested in people with primary or secondary immunodeficiencies. Alveoli are gradually filled with foamy exudate. Alveoli walls are damaged, the thickness of which increases by 15-20 times. Weakness, headaches, fever, sweating, cough with frothy sputum are manifested in pneumocystis. Retrosternal pain aggravated by inhalation occurs. Breathing becomes shallow, dyspnea increases. In auscultation during catarrhal symptoms dry and moist rales are heard.

Epidemiology. The source of infection is a human especially with AIDS. The transmission mechanism is aerogenic. The transmission path is airborne. There is possibility of transmission of the causative agent from a mother to a fetus via placenta. Children mostly suffer from it. The most severe disease occurs in infants. Pneumocystis infestation is widespread. Most often it occurs in European countries.

Methods of diagnosing diseases. Identification of a causative agent is carried by microscopic examination of fluid of broncho-alveolar lavage and transbronchial biopsy samples taken during bronchoscopy. PCR method is applied successfully.

Prevention. Patients should be isolated. Wet cleaning and disinfection is made in hospital wards after discharge. Hospital wards for babies are disinfected periodically by ultraviolet irradiation.

TOXOPLASMA (Toxoplasma gondii) is an obligate intracellular parasite, the causative agent of toxoplasmosis in animals and human. The toxoplasmosis is the protozoan zoonoses. The parasite develops with the change of hosts. Definitive hosts are domestic cats and some wild feline (lynx, tiger, lion, etc.). Intermediate hosts are the mice and rats, sheep, pigs, rabbits, cattle, some species of birds, as well as people.

The morphology of the parasite. T. gondii is an obligate intracellular parasite, exists in three forms: trophozoite, merozoite and oocyst. Trophozoites have size of 4-7x2-4 μm, shaped like a crescent with a rounded rear end, and are formed by multiplication of sporozoites in the epithelial cells of final and intermediate hosts. Merozoites are elongated of 5-8x1-2 μm, their nucleus is considerably displaced to the rear end of the body which is located within cells. Oocysts have rounded-oval shape, the size of 9-11x10-14 μm. Each mature oocyst contains 2 sporocysts. The oocysts are formed as a result of the sexual process which occurs in epithelial cells of the intestine of final hosts.

The development cycle of Toxoplasma includes stages of schizogony and gametogony (Fig. 18.3). Schizogony occurs in the body of intermediate and final hosts. Host cells are destroyed as a result of the accumulation of parasites and released trophozoites penetrate in adjacent cells. Trophozoites are hematogenically and lymphogenous spread to various organs. They completely disappear from the blood, penetrating into cells, where trophozoites are transformed into merozoites. Toxoplasma enter the final host organism by ingesting intermediate host tissues containing pseudocysts Toxoplasma (tissue cysts), or due to accidental ingestion of oocysts from the environment. In the intestine, the cyst shell is destroyed and merozoites penetrate into skin cells, which multiply schizogony. As a result, the merozoites are formed. Part of merozoites penetrating into enterocytes gives rise to male and female gametes (gamont) which, after their transformation exit the lumen of the enterocytes. Male gamonts are divided repeatedly to form microgamete. Macrogametes are formed from female gamonts. As the result of the fusion of microgametes and macrogametes the immature oocysts is formed which with faeces enter into the environment. Sporogony (maturation oocysts) lasts from 2 days to 3 weeks and occurs in the environment at a sufficient humidity and temperature from 4 to 37^{0}C. The oocyst forms two sporocysts each forming 4 sporozonta. Mature oocysts are highly resistant to unfavorable factors and can survive in the environment up to 1.5 years.

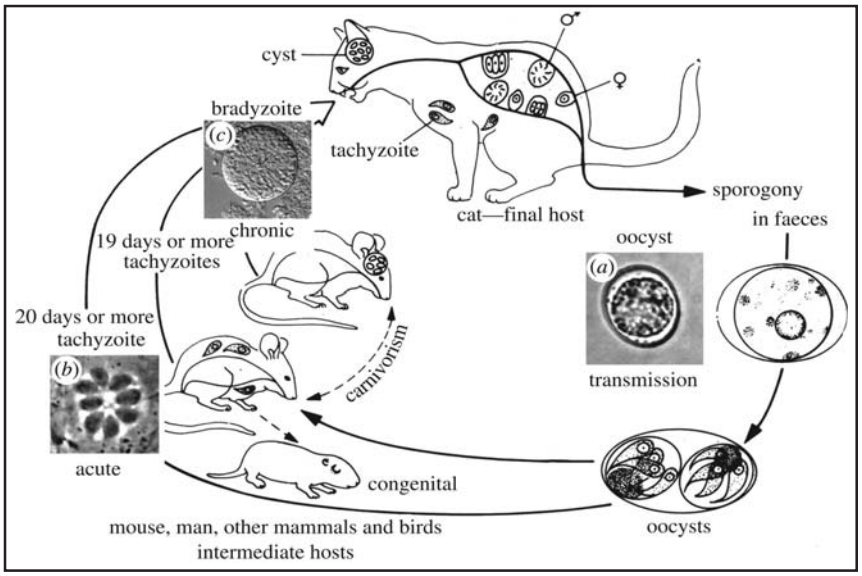


Fig. 18.3. The cycle of development of Toxoplasma gondii.

Pathogenic action, symptoms. Toxoplasma in epithelial cells of the small intestine causes their death. They are able to get into the brain, striated muscles, liver, etc. and cause the development of local inflammatory reactions, as well as the formation of specific granulomas. The disease is asymptomatic or nonspecific symptoms of intoxication (fever up to 37.5^{0}C, weakness, headache, loss of appetite). In congenital toxoplasmosis features of the course depend on the mother time of infection during pregnancy. Fetal death occurs with infection in the first trimester of pregnancy. Severe damages of CNS, eyes, hydrocephalus, malformation of the fetus occurs with the infection in the second or third trimester of pregnancy. Toxoplasmosis is severe disease in patients with impaired immunity (HIV infection, prolonged use of immunosuppressive drugs). The specific "parasite sepsis" or necrotizing meningoencephalitis, often with fatal consequences may develop as a result of constantly increasing parasitaemia.

Epidemiology. The sources of infection are both intermediate and definitive hosts of Toxoplasma. Oocysts may stand definitive in hosts for 1-3 weeks and may persist alive in the soil up to 1.5 years. They are able to overwinter, to endure thawing and freezing. Cats become infected by eating rats and mice containing cysts of Toxoplasma. The oral way of infection is main for a human. The leading factors of transmission are

meat products, fresh fruits and vegetables, unpasteurized milk and dairy products, etc. Younger children are easily infected by contact with cats. Women are frequently infected during testing of ground beef. The recipient may be infected by the transplant organ from an infected donor at trasplantation. Transplacental fetal infection can occur when a mother is infected during pregnancy. In repeated pregnancies the trans-placental transmission of pathogens is not observed. Toxoplasmosis is found worldwide. The level of invasion in different countries varies from 5-10 to 50-80%.

Methods of diagnosing diseases are based on results of serological tests (ELISA). Disease can be determined in a patient with Toxoplasma infection (presence of specific IgG). Upon detection of IgM, exceeding the threshold of sensitivity of reaction in two or more times, it is possible to ascertain the presence of acute stage of acquired and congenital toxoplasmosis in a patient. To diagnose toxoplasmosis in AIDS patients, direct methods to detect a causative agent are widely used (blood microscopy, cerebrospinal fluid, biopsies of lymph nodes, brain tissue and bronchoalveolar lavage fluid).

Prevention. In order to prevent congenital toxoplasmosis, all women planning a pregnancy should be examined in presence of specific antibodies to Toxoplasma in blood (IgM and IgG). At negative results the following rules must be observed for the whole period of pregnancy: avoid any contact with cats; wash hands thoroughly after contact with the earth and raw meat; do not eat raw or half-baked meat dishes, as well as not to carry out a tasting of minced meat; thoroughly wash vegetables, fruits and vegetable greens, pour over with boiling water; every three months to carry out serological screening for toxoplasmosis. Distruction of rodents, flies and cockroaches is of important value, which may be mechanical vectors of oocysts.

MALARIA is a group of anthroponotic protozoan vector-borne human diseases which pathogens are transmitted by female mosquitoes of the Anopheles family. It is characterized by advantageous damage of erythrocytes, liver cells, and manifested by fever, anemia, and hepatosplenomegaly. In humans the malaria is provoked by 4 species of parasites: Plasmodium vivax - the causative agent of a three-day malaria, P. ovale - the causative agent of the three-day malaria (or oval-malaria), P. falciparum - the causative agent of tropical malaria, P. malariae - the causative agent of a four-day malaria.

The cycle of development. Development of parasites occurs with the change of hosts and alternating forms of parasites reproduced sexually and asexually (Fig. 18.4). A definitive host of parasites are females of

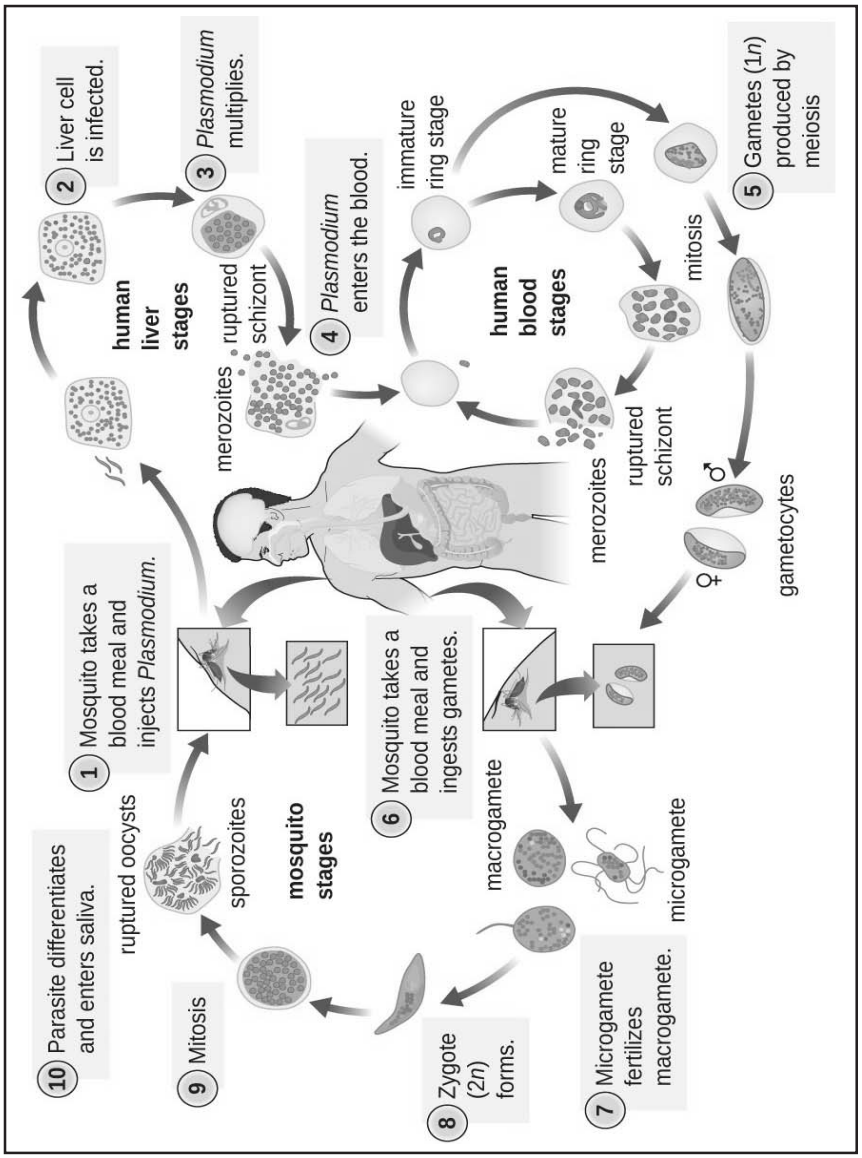


Fig. 18.4. The cycle of development of malaria plasmodium (by Lumen Learning).

Anopheles mosquitoes in which there is sexual reproduction of parasites and an intermediate host is the person, in which body which Plasmodium

are reproduce asexually (schizogony). *Exoerythrocytic schizogony*: sporozoites penetrate into the human while the infected Anopheles mosquito female sucks his blood. After 15-45 minutes, they enter the liver and actively penetrate into hepatocytes. From that moment, the pre-erythrocytic tissue schizogony begins. Its duration of different species of parasites can be from 6 days to several months and even years. In hepatocytes, the sporozoites are trnansformed into tissue trophozoites. Nuclei of trophozoites are divided many times forming the large number of tissue merozoites. Merozoites move in the blood stream after destruction of infected hepatocytes. Tissue merozoites actively penetrate into the red blood cells where erythrocyte schizogony occurs. Malarial plasmodia undergo 5 successive stages during the erythrocytic schizogony (Fig. 18.5):

- young (early) trophozoite - the initial stage. This stage is characterized by the larger size and presence of the central vacuole than in the merozoite which gives a ring shape to the parasite;

- developing trophozoite - nucleus and cytoplasm of parasite gradually increases in size, the central vacuole is shortened, and the granules of malarial pigment appear;

- mature (late) trophozoite – nuclei of large size, cytoplasma occupies the most part of erythrocyte, the central vacuole is weakly expressed or

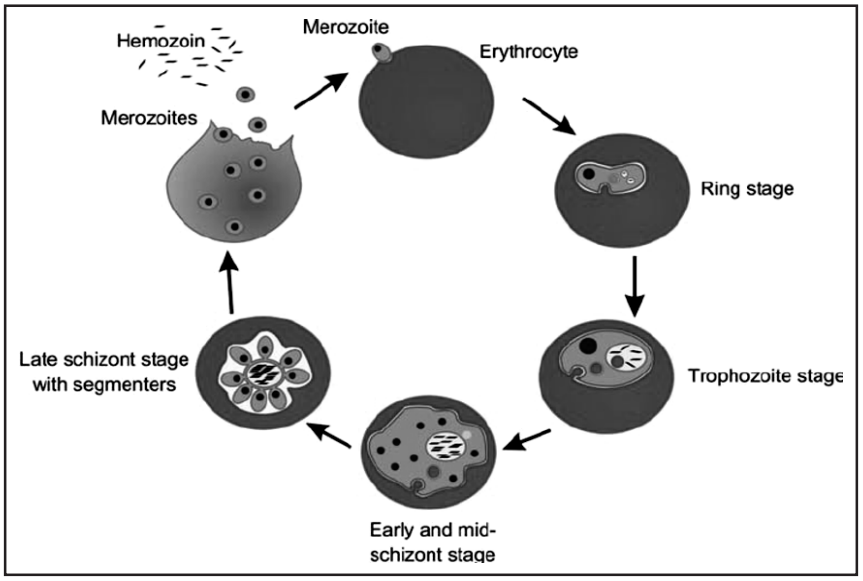


Fig. 18.5. The erythrocytes shizogonia of malaria plasmodium (by Researchgate.net).

absent, the pigment is easily visible;

- developing (early) schizont - the number of nuclei increases, the pigment grains are concentrated in individual clusters;

- mature (late) schizont - accumulation of individual nuclei around which the areas of fragmented cytoplasm are segregated. This process is called merulation - formation of merozoites inside the erythrocyte. Each species of plasmodium have characteristic manner. Piles of pigment remain between Merozoites, number and arrangement of which is specific to each species of causative agents.

After the erythrocyte membrane is destroyed, merozoites pass into the bloodstream. Much of them die as a result of interaction with the host immune factors, and others actively penetrate into the erythrocytes, and the erythrocytic schizogony cycle repeats. The duration of this cycle is determined by the genotype of parasites and pathogens (for a three-day, three-day type and falciparum malaria to 48 hours and for causative agents of four-day malaria - 72 hours). Completion of each subsequent cycle of erythrocytic development causes a progressive increase in the number of circulating parasites.

Gametogony. After several cycles of erythrocytic schizogony some merozoites are transformed into immature sex cells - gametocytes (gamonts) which in the process of further differentiation form microgametocytes (male sex cells) and macrogametocytes (female sex cells). In patients blood the male and female gametocytes are formed in 3-5:1ratio. Female gametocytes reach functional maturity in red blood cells, mens' – upon entering the stomach of a mosquito. Gamonts of some parasites (P. falciparum) are able to circulate long in the peripheral blood.

Sporogonia. Parasites penetrate in the body of a female malaria mosquito with blood of infected patients. In mosquitos stomach asexual parasites die. Men microgametocytes are divided into several parts (exflagellation), forming 6-8 moving microgametes. Female gametocytes in erythrocytes are converted into female gametes. As a result of merger of male and female sex cells a mobile zygote is formed (ookinete), which actively penetrates through the wall of mosquitos stomach. Ookineta is encapsulated on the outer surface of the stomach. Sporozoites are formed in oocysts. After the oocyst is destroyed, parasitic cells are spread to organs and tissues of a female malaria mosquito with hemo-lymphatic current, where they accumulate in salivary glands. Depending on environmental conditions and biological characteristics of the carrier, a minimal sporogonic duration may be 6-8 days (for the causative agent of three-day malaria), and the maximum - to 1.5-2 months (for the causative agent of four-day malaria). P. vivax and P. ovale are similar in their development. The duration

of their tissue schizogony is respectively 6-9 and 9-10 days. From each sporozoite penetrated into the hepatocyte as a result of tissue schizogony, 10 thousand merozoites are developed and enter into the blood. P. falciparum are developed quickly in liver cells - within 5-7 days, moreover from each sporozoite can be formed around 30-40 thousand merozoites during exoerythrocytic schizogony which enter the blood. P. malariae is developed into liver cells for a long time. The tissue schizogony cycle lasts 14-16 days. The number of merozoites is formed by dividing each tissue schizont and does not exceed 10-15 thousand. Erythrocytic schizogony cycle is 72 hours which is significantly longer than that in other species of parasites. The level of parasitaemia in blood is usually much lower than for other forms of malaria. In most cases it does not exceed 5-10 thousand in 1 ml.

Pathogenic action, symptoms. Fever is one of the leading symptoms of disease, the attack of which reflects the reaction centers of thermoregulation due to entering the blood of pathologically altered erythrocyte protein, waste products of parasites and merozoites. To implement the malaria attack not only a sufficient number of parasites is necessary, but also allergic alteration of an organism as a result of repeated antigenic irritations of the immune system.

Characteristic symptoms of malaria are hepatosplenomegalia. Spleen and liver is increased due to blood supply and a significant increase in reaction of the reticuloendothelial system on breakdown products of erythrocytes and parasites toxins at the first acute attacks of the disease.

Malarial infestation is characterized by development of anemia, which severity depends on the level of parasitemia and duration of the disease. Anemia is aggravated by development of autoimmune processes - the formation of antibodies to red blood cells. Increased spleen leads to a hypersplenism syndrome, which causes the development of progressive-guide anemia, leukopenia and thrombocytopenia.

The mechanism of pathogenic effects of parasites associated with changes in erythrocyte properties plays a leading role in development of dangerous complications such as coma malaria and acute renal failure. The clinical picture is defined by symptoms of intoxication. After 4-6 months after undergoing the malaria the efficacy of specific immunity is decreased and re-infection is possible. Depending on the species of the causative agent, the clinical course of the disease and its complications, following forms of malaria are distinguished.

Vivax malaria. The incubation period can be short (12-14 days) or long-term (6-30 months), depending on characteristics of the strain pathogens. The three-day malaria is characterized by long and relatively

benign course. The initial period is manifested in malaise, weakness, headache, chilliness, aching in back and limbs. In most cases the typical attacks of malaria are preceded by the wrong type of fever (up to 38-39 ° C) which lasts for 2-3 days. Later, during the height of disease, temperature attacks are periodic: they occur in a day at the same time of day, usually between 11 and 16 hours. Patients feel cold, accompanied by shaking chills during the attack. The liver and spleen are increased already in the first week of illness. Anemia develops gradually, with progressive course its symptoms are recorded on 2-3rd week of illness. Leukocytosis is moderate in the peripheral blood. The erythrocyte sedimentation rate is increased. Temperature attacks are observed in the natural course of disease without ethiotrop treatment for 4-5 weeks. Symptoms are gradually reduced and their severity is spontaneously terminated.

Ovale malaria. The duration of a short incubation period is 12-16 days. The duration of incubation can last from 6 to 15 months or more. This form of malaria is a benign disease and often ends by spontaneous convalescence after completion of primary attacks. According to the clinical manifestations, the malaria-oval is similar to three-day malaria. Usually the disease continues about 2 years. In rare cases, late relapses can occur in 3-4 years after the initial relief of attacks of fever.

Falciparum malaria. The incubation period is from 25 to 30 days. The disease usually begins without prodromal phenomena and initial fever. Temperature attacks last about 13 hours with 2-day intervals. Four-day malaria can be complicated by development of nephrotic syndrome. It arises as a result of subsidence on a basal membrane of immune complexe cells formed by interaction of IgG and IgM with parasitic antigens and complement. In a complicated four-day malaria the prognosis is extremely unfavorable as malarial nephropathy is not treatable.

Tropical malaria. The incubation period is 8 to 12 days (average 10 days). In non-immune individuals the tropical malaria often occurs in severe form. Without timely treatment the death may occur in early days of the disease. The initial period of the disease is characterized by polymorphism of clinical manifestations. The first signs of the disease may be malaise, chilliness, sweating, headache, dizziness, loss of appetite, nausea, pains in back, bones and joints, loose stools. In most cases in non-immune individuals, the disease begins suddenly, the patient is excited, complains of general weakness, chills, headache, aches in muscles and joints. Increase of body temperature to 38°C is possible. Temperature attacks in tropical malaria are characterized by the lack of strict periodicity. They may begin at any time, but occur more frequently in the first half of a day. The decrease of body temperature is not accompanied by sweating.

Epidemiology. Malaria diseases on the territory of countries are formed by populations of causative agents (P. vivax, P. malariae, P. falciparum), vectors (mosquitoes of the Anopheles family) and the human populations. Malaria is transmissive invasion. There are also transplacental, transfusion and parenteral ways of infection. Transplacental fetal infection is rare. The most common infection occurs during childbirth. Malaria transmission to the fetus is possible in case of complete absence of immunity to the invasion in a mother. Transfusion way of parasite infection can occur through blood transfusions. Its probability depends on the number of parasites in the blood. Parenteral infection can occur in violation of the rules of asepsis and the use of not-steriled medical instruments. This way is particularly actual among drug users.

The source of infection is a sick person or a parasite, in which blood gametocytes are present. Gametocytes P. vivax, P. malariae, P. ovale appear in blood in the first days of illness, and their number grow after a few cycles of erythrocytic schizogony. Patients with tropical malaria in first days of illness are not sources of infection because in their peripheral blood the gametocytes begin to appear on 9-10-th day of the disease. In 2-3rd week their number increases. Sex cells can be maintained in the patient for a long time (up to two months) without specific treatment. The greatest epidemic danger of malaria parasites poses infected immigrants from highly endemic regions.

Most people are susceptible to infect to all species of malaria.

Methods of diagnosing diseases. Malaria diagnosis is established only on detection of malaria plasmodia in blood. Methods of malaria diagnostic are based on the study of thin smear of blood products and "thick drop". Thin blood smear comprises fixed erythrocytes arranged in one layer. In red blood cells plasmodium are well visualized, which makes it possible to properly set the species of the causative agent and its stage of development.

A mandatory element of parasitological diagnose serves the parasitaemia level. Number of parasites in 1 ml of blood is an important criterion in assessing the severity of disease. In typical cases, the disease pathogens of the three-day and four-day malaria microscopy can be detected in its initial period, when the clinical picture is dominated by symptoms of intoxication.

Detection of P. falciparum in blood often coincides with the beginning period of the disease. In uncomplicated malaria only young trophozoites and gametocytes are found in peripheral blood, since the development of schizonts occurs in capillaries of internal organs. With the high level of

parasitaemia Plasmodium parasites are observed in almost every field of view of the microscope. More than 30% of erythrocytes may be affected.

Prevention. The main in the system of anti-malaria activities is the timely detection and treatment of patients. Actively identifying sources of infection are carried out by cheking backyards or organized examination of persons belonging to the infection risk. The passive method is to survey the patients. Mosquito breeding places, their number, the daily-ness asset of attacks on human must be detected. Based on these data, timing and methods for combating malaria-transmitting mosquitoes in different stages of their development are determined.

Chemical, physical and biological methods are used to fight mosquitoes. To protect mosquito attacks, measures to prevent the entry of insects into living rooms and personal protective equipment are applyied.

Individual chemoprophylaxis is carried out for non-immune person, temporarily residing in endemic areas. The malaria situation in the region, the presence of individual intolerance of drugs, duration of stay of these persons in the endemic area is considerd at selecting a scheme of personal chemoprophylaxis.

18.5. PHYLUM CILIOPHORA

Ciliates are both free-living single-celled organisms and intestinal parasites of invertebrates and vertebrates. The surface of their body is covered with rows of cilia, providing a spiral forward motion. Food is swallowed by cytostome located on the front end of a cell. The decay products are removed through an anal pore. There are several contractile vacuoles and two nuclei in the cytoplasm of cells: big (vegetative) and small (generative). The reproduction is performed either by dividing or sexually (conjugation). In the life cycle they undergo cyst and trophozoite stages.

BALANTIDIUM COLI is the only one species of ciliophora, which parasites in human. The balantidiasis is zoonotic disease of human and animals (pigs, rats) characterized by general intoxication, debilitating diarrhea and exhaustion.

The morphology of the parasite, life cycle. Trophozoite is oval, length of 70-150 μm and a width of 40-50 μm. Macronucleus is bean-shaped, closely associated with the micronucleus of spherical shape. Trophozoites usually inhabit by attaching to the colon mucosa. Reproduction is by dividing of cells. They feed on bacteria, food particles, erythrocytes, leukocytes. Cysts are formed in the lumen of the intestine, have an oval or circular shape with diameter of 45-65 μm. Cysts is resistant in the external environment. In the body of a host the cyst is released from the small

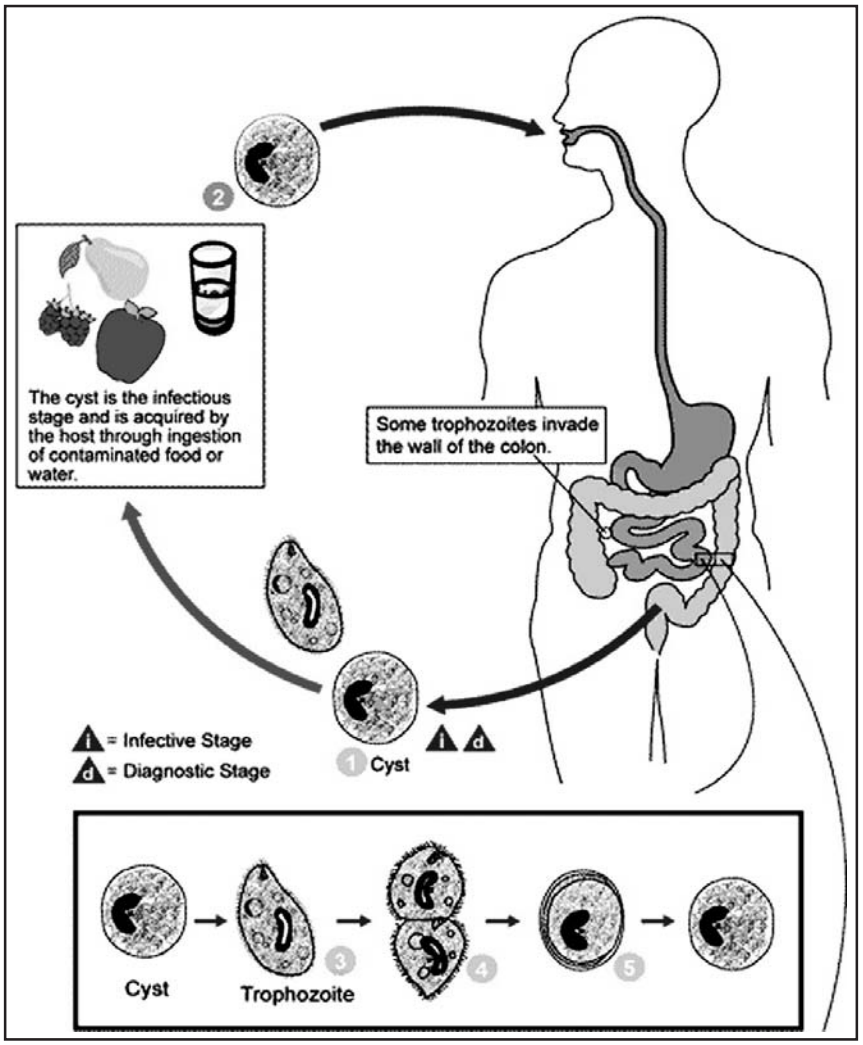


Fig. 18.6. The cycle of development of Balantidium coli (by DPDx and CDC).

intestine then enters the colon. Balantidium are able to produce the enzyme hyaluronidase. Disease is characterized by prolonged diarrhea with blood and pus, and sometimes intestinal wall is perforated with peritonitis. Balantidiums can enter the bloodstream and settle in the liver, lung and other organs, causing abscess there. Balantidiums live in the large intestine

of a human, pigs, rabbits, dogs, horses, cattle, sheep. Being in the intestine lumen of pigs and other animals, balantidiums form clusters ("colony"). Trophozoites feed on host components of food, intestinal microflora. The reproduction is a transverse division (mitosis) and sexually (conjugation). Conjugation occurs between the large and small forms of the parasites, but not between two individuals of the same size. Some balantidiums, gradually moving with faeces to the anus, are encysted in the environment to mature cysts, which, falling into the intestine of a new or the same host, give rise to a new generation of balantidiums. Cyst formation in the intenstine and excretionof cysts in patients with balanthidiasis are rare.

Pathogenic action, symptoms. Balantidiums can penetrate into the intestine tissue. The bacterial flora can penetrate into the gut tissue when the parasite invasion into the mucous membrane. In these cases, the pronounced inflammatory reaction occurs around trophozoites.

The most characteristic pathological change in the intestinal mucosa during balantidiasis is formation of ulcers. Ulcers size ranges from 1 mm to several centimeters. Groups of balantidiums are found around edges of the ulcer and contiguous healthy tissues.

Clinical manifestations range from mild, subclinical to very severe, accompanied by debilitating diarrhea, exhaustion, general prostration. Feces are abundant, often with a putrid odor, mixed with mucus and blood. The liver is enlarged and painful on palpation. Patients lose weight rapidly. The cachexia develops. They may die within 3-5 days of the onset of symptoms.

The acute form may become chronic in which exacerbation with impaired gut function and moderate symptoms of intoxication from 7 to 30 days is changed into periods of relative improvement lasting for 3-6 months.

The dissemination process of balantidiums can occur in other parts of the intestine, mesenteric nodes, liver, lungs and the urogenital tract at chronic stage of diseases.

Epidemiology. The main source of infection is a pig. The human as a source of infection is insignificant. Balantidiums are found in human quite rare. The disease occurs in clinically pronounced form, in which the liquid stool extracts only vegetative forms that quickly die in the environment. Ways of infection are through water and food. Method of infection is oral via food and water contaminated by cysts. Most often people working in pig farms and meat processing plants become infected. It is believed that the duration of incubation period is about 10-15 days. Balantidiasis is found on all continents where swine breeding is developed. Cysts of the parasite can survive in swine stables up to 104 days, in soil - up to 244 days. Sporadic cases of balantidiasis are registered in all countries of the world, especially in warm and wet regions where in centers of rural residents the balantidiums infestation may reach 1-9%, and in some cases - 28%.

Methods of diagnosing diseases. Diagnosis of balantidiasis is established on data of epidemiological, clinical and instrumental examination methods. Laboratory diagnosis is based on detection in slides feces of trophozoites and cysts of the parasite. Faeces must be fresh and warmed up to 30-35^0 C. Cultivation method is used in some cases. Smears of freshly prepared liquid feces or material taken from the edge of ulcers are examined to detect vegetative forms. Slides are studied at low (80x) and then at large (400x) magnification, preferably at a heating stage at 37° C.

Prevention and control measures are to prevent environmental pollution with faeces of pigs and people, observing hygienic rules for construction and operation of pigsties, as well as following rules of personal hygiene. Early detection and treatment of patients with balanthidiasis is important.

CHAPTER 19. MEDICAL HELMINTHOLOGY

The human can host more than 250 species of helminthes. About half of them belong to flatworms, and others - to roundworms. The great attention is paid to the problem of helminthes invasions. Helminthes invasions today are perhaps the most common parasitic diseases in human. According to the WHO Committee of Experts on helminthes (Report 277) «... parasitic worms adversely affect essentially on the state of health of population of the world». Helminthes can parasitize in all organs and tissues of living organisms. Human intestine is the most frequent place of worms. Lungs are a place of parasitism of lung fluke, tapeworm. Almost all flukes parasitize in the liver (opisthorchis, clonorchis, fasciola, etc.). Larva of tapeworm parasitize in the brain (cysticercus, echinococcus, etc.). Muscles are a main place for trichinella larvae. The clinical picture of human helminthes infections is the result of very complex interacted processes of influence of a parasite and host. It is a mistake to consider the clinical picture of helminthes infections as a unilateral impact of the parasite on a host, or, conversely, a host to the parasite, because the basis of both clinical and pathogenic effects on relations between a host and parasite, forming a system of mutual influence. Intensity of action of pathogenic helminths and its nature is largely dependent on the species of parasite which penetrate into the body and deposit therein as well as on characteristics of their localization in each individual case.

19.1. PHYLUM FLATWORMS (PLATHELMINTHES).

Flatworms are widely available in nature. There are about 7300 species. They are found in fresh and marine waters, soil. Many species have parasitic way of life.

Flatworms are developed for three germ layers, and have bilateral symmetry of the body that is flattened in the dorsoventral direction. The body cavity is absent. The internal organs are located in loose connective tissue (parenchyma). Skin and muscle sack consists of a cover tissue - tegument (acellular multinucleus structure) and three layers of muscles - longitudinal, transverse and oblique.

The digestive system is available only in Tutbellaria and Trematodes, represented by front and midgut that ends blindly. Undigested remains are released through the mouth. The digestive system in tapeworms is missing. The nutrition carried out by the entire body surface.

The excretory system is represented by branching protonephridia that start in the back of the parenchyma cells of star-shaped, called the final or terminal cells. They are tubules with a bunch of cilia wavering like a candle flame. Terminal cells open into the tubules. The latter go into ducts of larger lumen incorporating with the external environment by excretory pores.

Respiratory system in flatworms is absent. They breathe through the body surface or are anaerobic. The circulatory system in flatworms is not available. Partially a highly branched intestine performs this function instead of flukes, from which branches nutrients are transported through interstitial fluid to tissues.

The nervous system is represented by a peripharyngeal nerve ring and nerve trunks extending from them. Flatworms are hermaphrodites except blood flukes. This type is divided into three classes: Tutbellaria, Trematoda and Cestoidea.

Flukes and tapeworms have medical importance. According to epidemiological classification representatives of flatworms are biohelminths (all flukes, tapeworms, Echinococcus, Alveococcus) and contact (dwarf tapeworm) helminths.

19.1.1. CLASS TREMATODA

This class includes only the parasitic representatives. The body is shape. Due to parasitism, they have strong organs of attachment - suction cups, small spines – covering the entire body and helping to attach the host. Flukes are hermaphrodites. Male reproductive system is represented by two testes and spermoduct which when combined form an ejaculatory duct extending through the body of the male copulatory - cirrus. Female reproductive system is represented by the ovary and sexual ducts. Eggs via oviduct enter the ootype (the central chamber of female reproductive system). Cirrus protrudes outwards and is inserted into the vagina of another worm, so that the sperm reach the seminal receptacle. Additional organ of

the female reproductive system are vitellaria with ducts, Mehlis' gland. Laurer's duct and ducts of Melissa cells go into in ootype also.

In the life cycle of trematodes, alternation of reproduction ways, change of hosts and alternation of generations are observed. Adult stage (marita) resides in the vertebrate organism. Eggs have to get into the water for further development. The ciliary larva (miracidia) comes out from the egg which must be ingested by an intermediate host (gastropod snail). In the latter the larva turns into sporocysts. The redia is a new generation of larva which is developed parthenogenetically from embryonic cells. Subsequent larval generation (cercaria) is formed parthenogenetically inside redia from embryonic cells. Cercaria leaves in the body of snail and swim freely searching for the main or second intermediate host. While searching for a main host, cercarias are encysted on plants and transformed into adolescaria and can then be swallowed by herbivores. Cercarias can actively penetrate through intact human skin. The cercarias penetrate into the muscles of the second intermediate host and became metacercaria (infective stage for the first host). The larvae migrate in tissues after penetration of infective stages of flukes in the body of a final host. The larvae find the place in a final host in which they reach sexual maturity and will live until death.

LIVER FLUKE (Fasciola hepatica) is a causative agent of fascioliasis, biohelminthosis which is characterized by a chronic disease affecting the liver and biliary tract. Parasite lives in the bile ducts of the liver, gall bladder, sometimes in the pancreas. Fascioliasis occurs worldwide.

The morphology of the parasite. Marita of fasciola has a length of 3-5 cm, leaf-shaped body, the front end is retracted in beak-shaped way. There are oral and ventral suckers on the body. Multilobed uterus is small, located behind the ventral sucker. The ovary is behind the uterus, multilayer yolk glands are located in lateral, average body part is occupied by the testes. Eggs are large, yellow-brown in color, oval in shape, the cover is easily distinguishable on one of the pole, sizes of - 125-150 x 62-81 μm.

The cycle of development. The egg begins to grow when in water from which the larva comes out - miracidium penetrating actively into the intermediate host body. It is a small snail Galba truncatula (Fig. 19.1). In the body of the snail the miracidia resets ciliary cover and transforms to the next stage - sporocyst. A new larval generation - redia is developed by parthenogenesis. They have the mouth, pharynx, the digestive tube. Redia is also divided by parthenogenesis to form the next generation of larvae - cercaria, who already have bodies that are typical for an adult fluke. Cercaria leave the mollusk, actively move in water, attach themself to plant stems and turn into a new larval stage of spherical shape - adolescaria

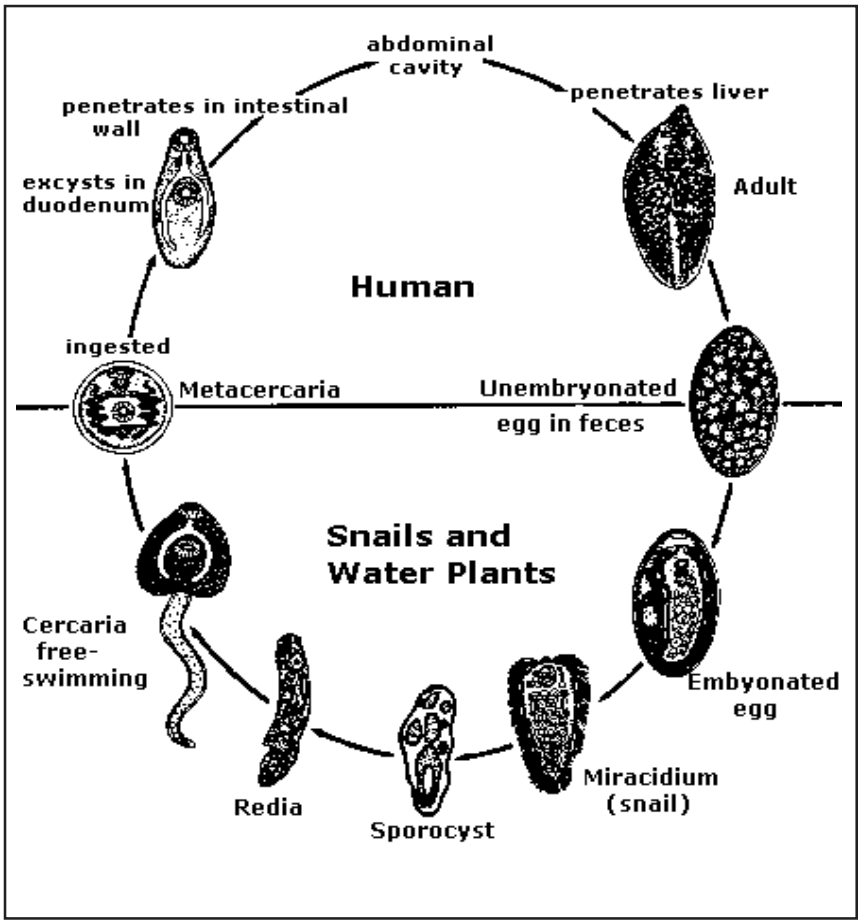


Fig. 19.1. The cycle of development of Fasciola hepatica (by DPDx and CDC).

(metacercaria). The latter is ingested by a definitive host. In the intestine of the final host adolescaria come out of the shells and go into the abdominal cavity, and then migrate to the liver bile ducts, where in 3-4 months they become mature and start producing eggs.

Pathogenic action, symptoms. In migration period the young fasciola injure the intestinal mucosa and, penetrating into the blood vessels, disrupt blood flow in the liver. The functions of the gastrointestinal tract, cardiovascular, respiratory, central nervous and reticuloendothelial systems are violated. A dramatic shortage of vitamin A and other antioxydant vitamins

occurs, allergization is developed. The incubation period at fascioliasis lasts 1-8 weeks. There are acute and chronic periods of the disease. In the acute (migration) stage the allergic myocarditis is developed, signs of liver lesion are more pronounced, eosinophilia leukosytosis is clearly detected. After 3-6 months of infection symptoms typical to the chronic disease appear. Liver is increased again, disorders of stool, anemia, hepatitis and malnutrition occur.

Epidemiology. The main source of infection is cattle. Fasciola eggs in ponds and winter pastures are stored up to 2 years. Adolescaria at 100% relative humidity endure temperature fluctuations in the range from -18 to + 42^{0}C. Under relative humidity of 25-30%, they are killed by 36^{0}C. A person is infected by eating plants (watercress water, wild onion, sorrel), drinking water from reservoirs or swimming therein contaminated by adolescaria, by eating garden vegetables (lettuce, onions), watered from such infected sources.

Methods of diseases diagnosing. The laboratory diagnosis is based on detectying Fasciola eggs in feces. Transient eggs can also be found in healthy people after eating of the liver of infected animals. Given the above, the liver must be excluded from the diet of a patient to avoid fascioliasis. In addition, for the diagnosis of fascioliasis serological tests are used.

Prevention. Personal preventive measures are to avoid drinking polluted water, to wash thoroughly raw vegetables. Measures of public prophylaxis are based on treatment of sick animals and people, changing pastures, health educators.

CATS FLUKE (Opisthorchis felineus) is the causative agent of opisthorchiasis, biohelminthosis characterized by damage of the hepatobiliary system and pancreas.

The morphology of the parasite. The body of parasite reaches a length of 13 mm; intestinal tube has two unbranched stems, which stretch along the sides to the rear end. It ends blindly. Multilobed uterus is in the middle part of the body, followed by a rounded ovary. Two testis are located at the rear of the body. Feline fluke egg is oval-shaped, yellow in color, the front end has a cover. Sizes of eggs are 26-30 x 10-15 μm.

The cycle of development. The egg should get into fresh water, where it is ingested by the intermediate host - snail Bithinia leachi, in which hindgut the miracidia comes out of the egg, penetrates into the liver and converts into sporocysts (Fig. 19.2). The latter has a sacciform body filled with sex cells, which are divided into parthenogenetic and give the second generation, called redia.

Redias are divided by parthenogenetic way and provide third generation, called cercariae. They have oral and ventral suckers, biramous intestine and tail.

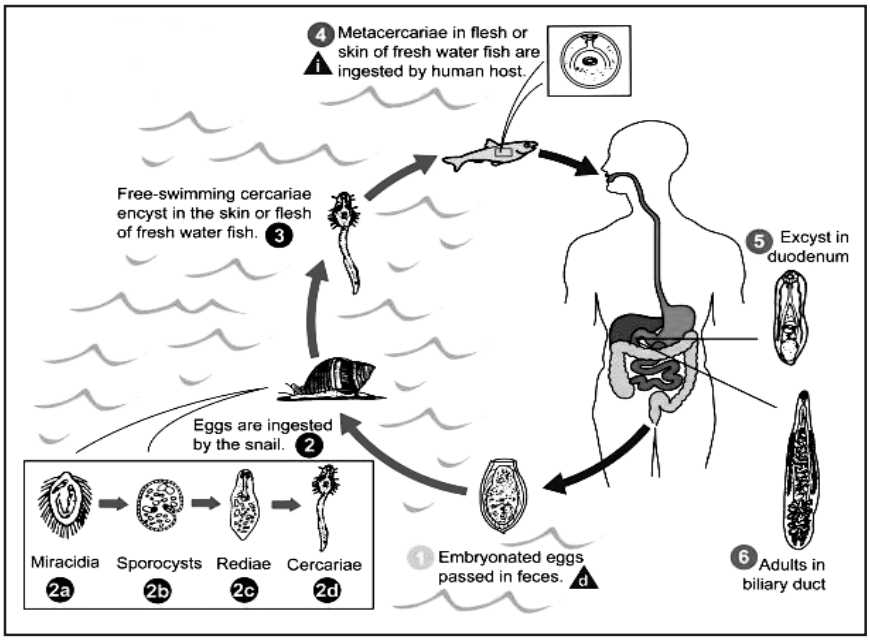


Fig. 19.2. The cycle of development of Opisthorchis felineus (by DPDx and CDC).

Cercariae come out from the body of the snail, swim freely in the water, and actively penetrate into the carp body, its muscles. Here they are developed into metacercaria. Fish are second intermediate host of opisthorchis.

Wild and domestic fish-eating mammals, as well as people become infected by eating fresh, frozen, dried or not enough cooking fish. Young flukes are released in the intestine of man and penetrate into the pancreas or liver.

Pathogenic action, symptoms. The disease occurs in the acute phase with significant allergic symptoms. Chronic stage of the disease is manifested by damaging the hepatobiliary system. Patients complain of a feeling of heaviness, fullness in the epigastric region, in right upper quadrant. Decreased appetite, nausea, vomiting, frequent dyspepsia. Long duration of infestations can lead to formation of chronic hepatitis syndrome and subsequently - to development of cirrhosis and even liver cancer (hepatocellular carcinoma). In patients with chronic opisthorchiasis chronic the gastritis, duodenitis is often developed, up to formation of ulcers.

Epidemiology. Opisthorchiasis - biohelminthosis, zoonosis, spread in the Western Siberia, the Volga-Kama basin, in basins of the rivers Don, Dnieper, Dniester, the Northern Donets and in Belarus - in the basins of the Neman, the Pripyat.

Methods of diagnosing diseases. Opisthorchiasis diagnosis is based on epidemiological history, eating fresh, frozen, not well cooked or fried fish of a family carp. For serological diagnosis of opisthorchiasis, the immunological test systems are applied based on enzyme immunoassay and indirect hemagglutination. However, they do not provide a basis for establishing a definitive diagnosis and require parasitological confirmation which is set upon detection of feline fluke eggs in duodenal contents or feces, which begin to excrete out no earlier than 4 - 6 weeks after infection.

Prevention. Personal prevention of opisthorchiasis is aimed to not eating raw, dried fish; social prevention - on health education, strict sanitary control over the sale of fish and its cooking.

PULMONARY FLUKE (Paragonimus westermani) is the causative agent of paragonimiasis, biohelminthosis manifested of the respiratory system damages.

The morphology of the parasite. Trematodes body has an ovoid shape, it may resemble an orange seed, coated with spines, in length reaches from 7.5 to 16 mm. Eggs golden-brown color, size 80-110 x 50-60 μm, there is a flat cover.

The cycle of development. Pulmonary fluke develops with the change of two intermediate hosts: the first - snail of the Oncomelania family, where the larval is developed in the egg - cercaria, which leaves the snail and penetrates into the second intermediate host (crabs, crayfish, shrimp). There parasite reaches the infective stage - metacercaria whose final host may become infected (Fig. 19.3). The final host is a man, pig, cat, dog, otter, mink. The adult parasites settle in the lungs, migrating from the intestine through the abdomen, diaphragm and pleura. The migration of parasite is accompanied by allergic reactions. The localization of the parasite in the lungs leads to a focal pneumonia.

Epidemiology. Paragonimosis is a natural focal disease, occurring in the Amur region and in some parts of Japan, South China. The way of infection is orally in areas where people eat raw shellfish.

Methods of diagnosing diseases. Diagnosis of paragonimosis is carried out by studying the sputum and feces, where helminthes eggs can be detected, as well as by immunological reactions (indirect hemagglutination immunoassay).

Prevention. Personal prevention is based on the principle: not to eat raw crabs, shrimp, crawfish. Public prevention based on health education.

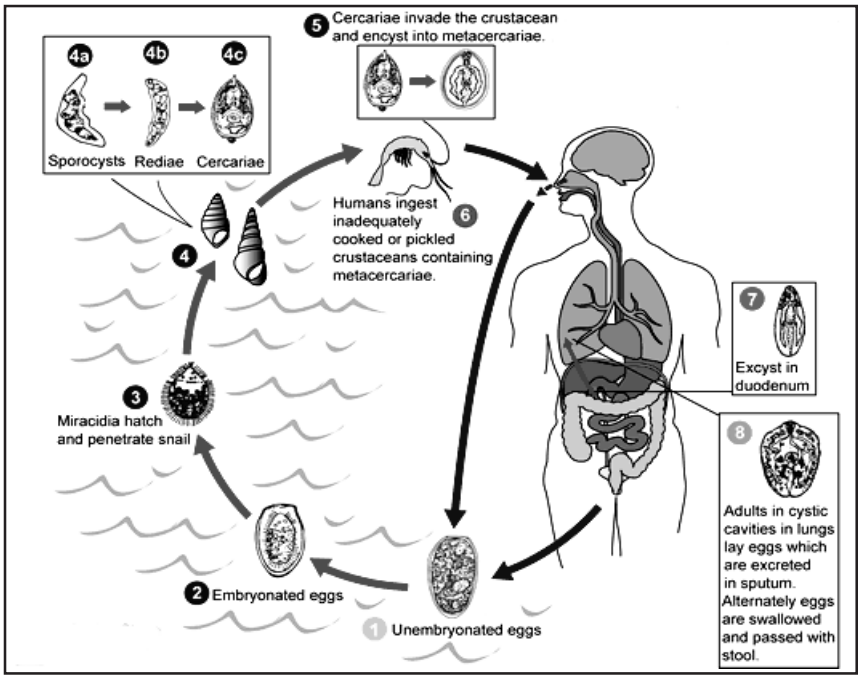


Fig. 19.3. The cycle of development of Paragonimus westermani (by DPDx and CDC).

BLOOD FLUKES or schistosomes, the causative agent of schistosomiasis. This family includes dioecious organisms that live in blood vessels of the human body. Wide body is typical for males. Cord body is typical for females. Females are placed in the gynaecophoric channel on the ventral side of the male at puberty. Male body is wider and shorter than in females. Suckers are small and located on the front end of the body. Schistosoma parasites live in the tropics of Asia, Africa and America.

The cycle of development. A human is a final host for the schistosome, and intermediate - some species of freshwater snails in the tropics (Fig. 19.4). From the egg, which fell into the water, a miracidia comes out, which then undergoes stages of sporocysts of first and second order and a cercaria is developed in a snail. Cercariae, leaving the intermediate host, swim in water and actively penetrate into human skin when swiming or working in water in rice fields, irrigation systems. Clothing does not prevent the penetration of cercariae in a human body. At the site of penetration skin lesions occur - swimmer's itch, manifested as rash, itching. Penetrated into the human the cercariae through the lymphatic

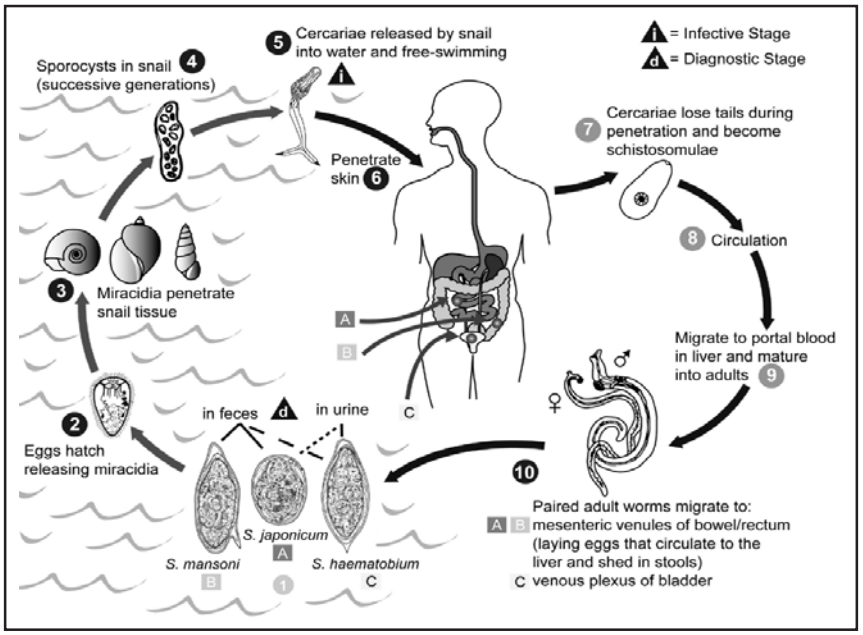


Fig. 19.4. The cycle of development of schistosomes (by DPDx and CDC).

and blood vessels enter the right part of heart, then in lungs and then into the veins of the mesentery, bowel walls and the urogenital system.

Cercariosis shistosomatid dermatitis. Causative agents of cutaneous Larva migrans are parasitic flukes of Schistosomatidae family. The final host is waterfowl birds. If a man is infected with cercariae of birds trematodes, on the penetration site of a parasite into human skin the pustular elements, urticaria, pruritus (cercariosis shistosomatid dermatitis) appear, often with fever and general malaise symptoms. After 1-3 days the pustular (containing pus) cells are transformed into crusts, and after 1-2 weeks a patient is recovered.

There are several species of schistosomes, three of which are the most common parasites in human.

Schistosoma haematobium is the the causative agent of urogenital schistosomiasis. Large veins of the abdominal cavity and urogenital system are infested. In male up to 15 mm, female - 20 mm. The body surface is finely uneven. Eggs are oval with a terminal spine, have a yellowish-brown transparent shell. Sizes of eggs are 112-170 x 40-70 µm. The female produces 20-300 eggs per day. Intermediate hosts are snails of Bullinus, Planorbis families. The final host is a human. Eggs via spike destroy the

wall of blood vessels and then they enter the ureter or bladder and urine output to the external environment. Parasite eggs get into the urine only during the hottest time of a day. Blood in the urine, pain in the suprapubic area, often formation of stones in the urinary tract is observed in patients with urinary schistosomiasis. The bladder cancer occurs 10 times more often in foci of urinary schistosomiasis. Urogenital schistosomiasis is found in the Middle East, Africa, Indian Ocean islands, there are small pockets of India.

Schistosoma mansoni is the causative agent of intestinal schistosomiasis. Size of a male is 6-13 mm in length. Size of a female is 7 to 17 mm. Eggs are yellowish brown shell with a spike on the side. Size of eggs is 144-175 x 45-68 μm. The female produces about 100-300 eggs per day. Definitive hosts are people, cattle, dogs; intermediate hosts are snails of Planorbis, Physopsis, Biomphallaria families. In man the parasites inhabit the mesenteric veins of the colon and liver portal vein system. Phenomena colitis, diarrhea mixed with blood is observed in a patient, polyposis colon cancer, symptoms of venous stasis and liver cirrhosis are possible. Intestinal schistosomiasis is found in Northern, Equatorial, Southeast Africa, Southwest Asia, Brazil and Venezuela.

Schistosoma japonicum is Japanese schistosomiasis causative agent. It parasitizes in blood vessels of the intestines. Therefore clinic corresponds to that described with intestinal schistosomiasis. A male size of 9,5-17,8 mm, and a female - 15-20 mm in length. The cuticle is covered with small spikes. Dimensions of eggs are 70-100 x 50-65 μm. Eggs are more rounded than the species described above; a spike is located on the lateral surface, has a very small size. The female produces about 1500-3500 eggs per day. Intermediate hosts are snails of the Oncomelania family. Final hosts are human, hoofed animals, dogs, rodents. The clinical symptoms are largely similar to that for intestinal schistosomiasis, however, it has its own characteristics. Chronic infestation stage occurs before - after 25-30 days from the date of infection of cercariae. Common dermatitis is detected more frequently. The number of eosinophils can reach 80%. Massive penetration of S. japonicum eggs leads to more frequent lesions of the liver, lung, kidney. In the acute phase of infection the diffuse brain lesions of allergic nature may be developed. Prognosis is always unfavorable with late treatment. Japanese schistosomiasis is common in southern Japan, southern China, the Philippines.

Methods of diagnosing diseases. Diagnosis of human schistosomiasis is based on finding the parasite eggs in the urine or in patient's feces, and serological methods via - immunofluorescence, indirect hemagglutination, enzyme-labeled antibodies.

Prevention. Personal preventive measures are directed on prohibition of swiming and to contact with the water, which can be of various species of schistosome cercariae. Public prevention involves treatment of patients, protection of water bodies from contamination by human faeces and health education.

19.1.2. CLASS CESTOIDEA

Cestodes are parasites of vertebrates. The adult worms consist of three parts, the head, neck and trunk. They are characterized by tape-like trunk (strobila). Strobila usually is divided into multiple segments (proglottides). At the front end of the worm is a head (scolex), with attached organs - cup-like suckers, hooks, sucking grooves (bothria). Behind the head is a non-segmented neck, from which the young immature segments with undifferentiated organ systems. Hermaphrodite proglottides are located in the middle part of the body. In this part male and female reproductive system is developed. There are mature segments that contain eggs filled the uterus and the rudiments of other organs at the end of strobila. Mature proglottides are gradually detached and removed to the outside. New young proglottides are formed from the neck of parasite.

The worm body is covered outside with skin-muscular sack, which surface layer (tegument) is morphologically similar to that of flukes. Tegument of cestodes produces antiproteolitic enzymes that protect the parasite from being digested in guts of a host. The digestive system is absent. Cestodes eat by the whole body surface. The respiratory system is absent, too. Since tapeworms live in an oxygen-free environment, bioenergetics processes occur as fermentation type. The excretory system is protonephridia type. The main trunks of protonephridia are located on sides of the body. The nervous system is represented by ganglion located in scolex and two major side shafts extending from the ganglion which extend along the entire body. The reproductive system is formed in hermaphroditic proglottides. It includes the ovary, vitellarium, vagina, ootype, underdeveloped uterus, testes, ejaculatory duct and copulatory organ - cirrus. Insemination is cross.

The cycle of tapeworms is associated with the majority releasing invasive eggs. It contains the larva with hooks - oncosphere that can be developed in the intermediate host in contact with its digestive system. Oncosphere via hooks penetrates through the intestinal wall into the blood or lymphatic vessels and migrates throughout the body, settling in the liver, lung, muscle, where while growing is transformed into larvae. Larvae structure is different and characteristic for each species of cestodes. Six types of Larvae are distinguished: 1. Cysticercus - bubble-like form, filled with fluid inside with invaginated one head. The head can turn inside out.

2. Coenurus - bubble-like form with invaginated several heads. 3. Cysticercoid - inflated with an invaginated head at the back end which is the tail appendage. 4. Larvocyst echinococcus - a big bubble-like form with maternal and bubbles inside. In the past scolexes is developed. Bladder cavity is filled with liquid containing waste products of the parasite. 5. Larvocyst alveococcus - conglomerate of a large number of small, bubble-like form on the outer surface of which bud daughter vesicles. Larvocyst tends to grow into the adjacent tissue. 6. Perocercoids - a worm-like shape at the front end of his body has two grooves - bothria. Larva in the final host, under the influence of digestive enzymes is transformed into adult. Head is turned inside out and attached to the intestinal wall and bubble breaks. Final hosts are usually infected by eating intermediate hosts in the body which are larvas. Those and others are mostly vertebrates. Diseases caused by tapeworms are called cestodosis. This zoonotic biohelminthes and contact anthroponotic helminthes (hymenolepiasis). Let us consider the most important representatives of the class Cestoidea, which are parasitic in humans.

PORK TAPEWORM (Taenia solium) is a causative agent of taeniasis, biohelminthosis main clinical manifestation is dysfunction of the gastrointestinal tract. In the sexually mature parasite in the small intestine, and in the stage of the larva - in the muscles of eyes, in the human brain. It is widespread.

The morphology of the parasite. The parasite reaches a 3 m length. In the head there are four cup-like suckers and 22-32 hooks. The hermaphroditic segments ovary has 3 lobes. The mature segments uterus constitutes 7-12 pairs of lateral offshoots. Eggs are rounded, with three membranes. The first shell is only available when the egg is in the uterus. The second shell (embryonal) is formed in oncospheres. It is thick, radially striated, dark brown in color. The third inner (thin egg membranes) covers directly oncospheres. Size of eggs is 28-44 x 28-38 μm.

The cycle of development. A final host of the parasite is a human. Intermediate hosts are pigs, occasionally people (Fig. 19.5). Infection of pig occurs by eating food, which can be mature segments of tapeworm. In the stomach of a pig the egg oncospheres out that the blood vessels penetrate into the muscles, where it is transformed into cysticercus in two months (Cysticercus cellulosae), having a diameter of 5-8 mm, and in parenchymal organs - 1.5 cm. Life expectancy at cysticercus pigs 3-6 years, after which they shrivel and die petrified.

Human infection occurs by eating raw or undercooked pork. Cysticercus, turn a scolex, is fixed to the villi of the mucous membrane and begin to grow segments. After two or three months the helminthes reaches puberty. After 2-3 months of infection by tapeworm the segments

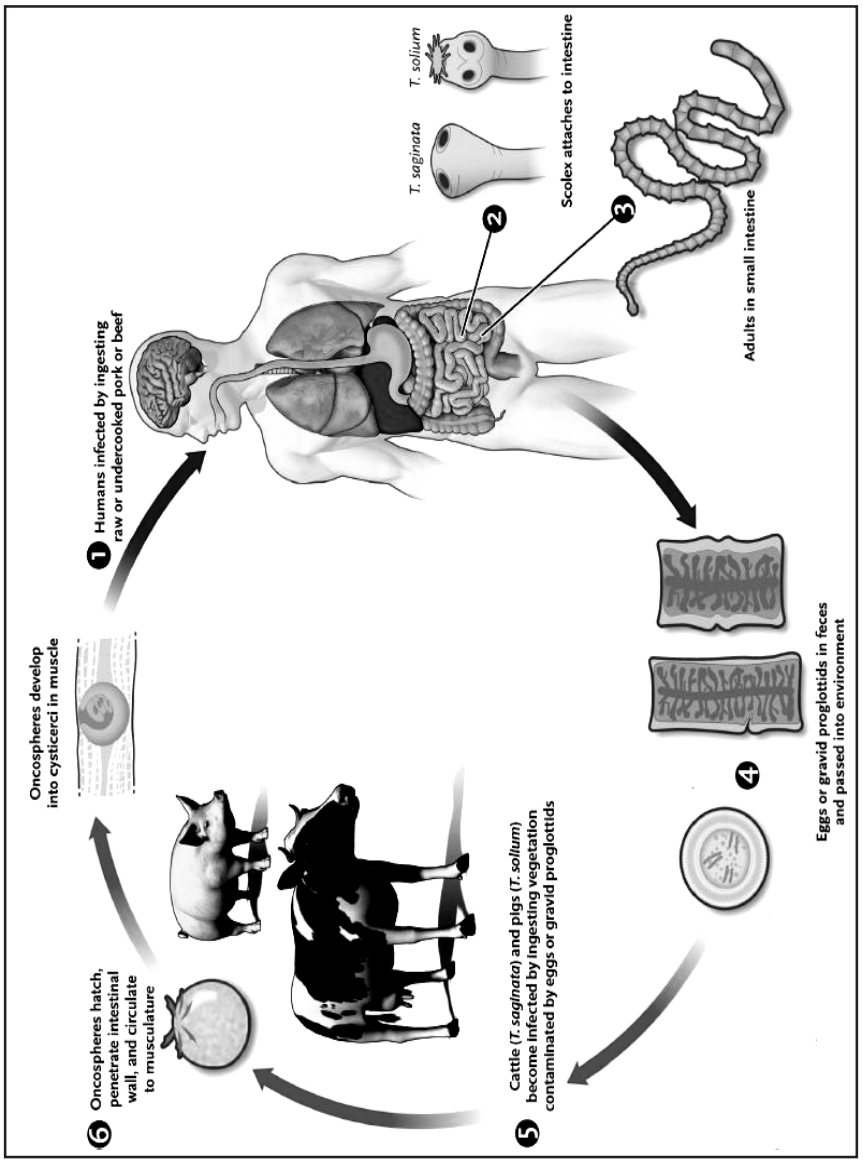


Fig. 19.5. The cycle of development of Taenia solium and Taeniarhynhus saginatus (by DPDx and CDC).

begin to separate from the mature eggs. Since faeces allocated bits strobila predominantly are composed of 5-6 segments. The lifespan of the pork tapeworm in the human is a few years.

Pathogenic action, symptoms. Pathogenic effects caused by mechanical action, loss of food of the host organism. Indigestion, anemia, general weakness observed at teniasis.

Cysticercosis. Mature proglottids of pork tapeworm possibly penetrate in the stomach in patients with taeniasis. Oncosphere is released by digestion. It penetrates through the stomach wall into the blood and lymphatic vessels and accumulates in muscle, eye, brain to form there cysticercus. Cerebral and eyes cysticercosis is a heavy human disease. Symptoms of central nervous system lesions are developed with the localization of parasite larva in the brain. Diagnosis is possible by applying the computer tomography, ultrasound scans of the brain, as well as via immunological reactions. It occurs worldwide.

Methods of diagnosing diseases. Taeniasis diagnosis is made by finding mature tapeworm proglottids in human faeces. Be sure to take into account the number of lateral branches of the uterus in the mature segment. Immunological methods are applied for cysticercosis of brain (reaction indirect immunofluorescence hemagglutsinatsii, enzyme-labeled antibodies).

Prevention. Personal prevention is not to eat raw and half-baked pork, and the public is to coordinate work of sanitary and veterinary services (examination of pork on slaughterhouses and markets), identification and treatment of patient teniasis.

BEEF TAPEWORM (Taeniarhynhus saginatus) is a causative agent of taeniarhynchosis, biohelminthosis with chronic, characterized by gastrointestinal disorders. It parasitizes in the small intestine of human. It is widespread.

The morphology of the parasite. The parasite reaches a length of 4-10 m. There are only 4 suckers in the head. Hermaphrodite segments are of square shape. The uterus is not branched, ovary has two lobes. Mature segments are highly elongated. The uterus is branched, the number of its lateral branches reaches 17-34 pairs. Eggs are the same as in the armed tapeworm. They do not have specific features, so the diagnosis is indicated by family of parasite (taeniids eggs). The number of eggs in each of the mature proglottides reaches 175 thousand. Beef tapeworm allocates about 2500 mature proglottids during the year.

The cycle of development. The main host is a human, an intermediate host is a cattle (Fig. 19.5). Mature segments are excreted in faeces by groups of 5-6. A cow swallowing such segments is an intermediate host of the parasite. Larvas are forms in muscles (cysticercus). The disease is similar to taeniasis. It should be remembered that proglottides are able to actively crawl out of the anus and crawl over the body and underwear. Topically measled meat in the stomach under the influence of the human

digestive juices is turned head. It is attached to the villias of the intenstine and the parasite begins to grow.

Pathogenic action, symptoms. The disease is similar to taeniasis. The pathogenic effect of the parasite is due to the action of its suckers and movable elements strobila which damage mucosal irritate bowel receptors and affect the motor and secretory function of the gastrointestinal tract in general. The sensitization of host organism by parasite metabolism products is important. Patients complain of nausea, sometimes vomiting, heartburn, change in appetite, feeling of heaviness and pain in the abdomen, bloating, unstable faeces, segments of the parasite crawling out from the anus at night. Often there is decreased secretion of gastric juice. Blockage of the bowel tangles taeniids can lead to symptoms of bowel obstruction. Sometimes in taeniarhynchosis symptoms of duodenal ulcer or biliary colic are observed. Measled stage is not developed in the human body.

Methods of diagnosing diseases. The question about the excretion of parasite segments is the most common method for mass population survey. When taeniarhynchosis segments usually come out during the day, making active movements, and continue for some time to move through the body, causing a sensation of pins and something sticky and cold. Since actively moving segments leave eggs on the perianal skin folds, it is used for the diagnosis of perianal scrape.

Prevention. Personal prevention is based on principle of non-use of untested raw beef in food. Social prevention is to make patients to pass a mandatory veterinary examination in beef slaughterhouses, markets, to protect pastures from contamination with human faeces, as well as to conduct health education.

FISH TAPEWORM (Diphyllobothrium latum) is a causative agent of diphyllobothriasis, biohelminthosis with a chronic course and a violation of the upper digestive tract functions, and in a severe case - development of anemia. Small intestine of a human is infested. It meets foci confined to areas with a large number of ponds.

The morphology of the parasite. Mature parasite has strobila 10-12 m and more. Scolex has the sucking grooves (bothrias), which are used to fix to the villi. Strobila consists of a large number of segments (up to 4000). Immature segments are short, and mature - in width than in length. The mature segments are located in the posterior part. Uterus has the form of loops, which form the socket having a discharge hole disposed at the front edge of proglottids. The feacus has a lot of eggs. Eggs are oval yellow-brown color, a cover is visible at a pole. Eggs size is 70-83 x 50-54 μm.

The cycle of development. The final host is a human and fish-eating mammal (cat, dog, fox, bear). Intermediate hosts: first – crustacean cyclops, second - the fish (Fig. 19.6). Eggs with faeces should pass into

the water, where after 3-5 weeks a larva is released from the egg covered with cilia – coracidium. It is equipped with three pairs of hooks. Coracidium is swallowed by the final intermediate host - lower crustaceans (or cyclop diaptomids). In the intestine crustacean coracidium loses cilia penetrates into the body cavity and is turned into procercoid (larva has elongated body with 6 hooks on the rear end of the body). A second host is a fish and in its muscles the procercoid turns into the next stage - plerocercoid. In the large predatory fish plerocercoids are accumulated, and they act as reservoir hosts.

Pathogenic action, clinic. The parasite feeds on host digested food. It is able to selectively absorb vitamin B_{12}. Pernicious anemia may be developed in a patient. D. latum infringes the intestinal mucosa by sucking grooves, which leads to tissue necrosis. Strobiles of few worms can cause intestinal obstruction. Human infection occurs by eating fish.

Methods of diagnosing diseases. Diagnosis is based on detection of tapeworm eggs in patient's faeces.

Prevention. Personal prevention is to eliminate a bad-cooked fish from the diet. Social prevention is based on health education, detection and

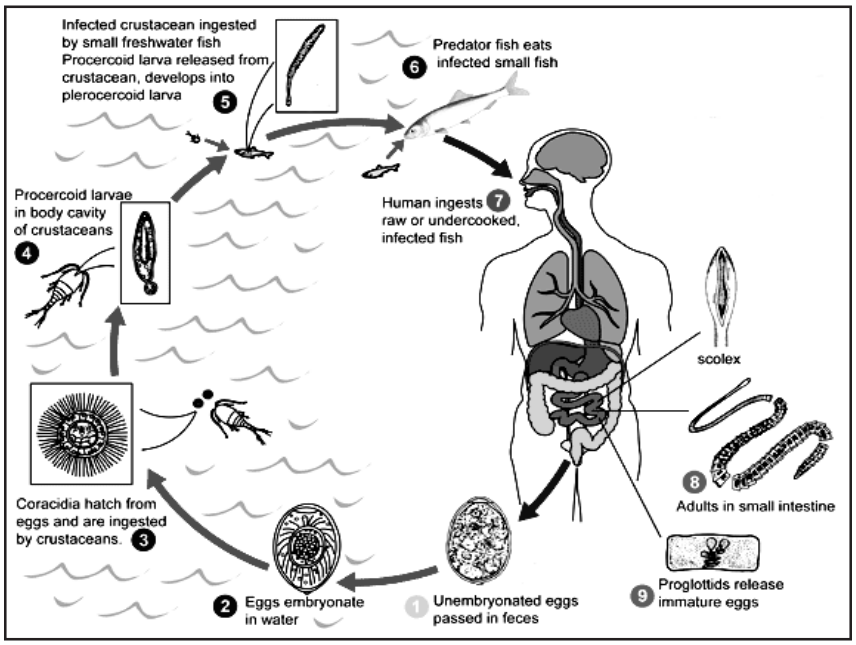


Fig. 19.6. The cycle of development of Diphyllobothrium latum (by DPDx and CDC).

treatment of patients with diphyllobothriasis, preventing fecal contamination of the environment.

DOG TAPEWORM (Echinococcus granulosus) is a causative agent of zoonotic biohelminthosis. Parasite lives at larval stage in a human. It is distributed around the world.

The morphology of the parasite. Sexually mature form of Echinococcus strobila is 2-6 mm in length, which consists of three or four segments. There are four suckers on the scolex and proboscis with two groups of hooks. The penultimate segment is immature and the last segment is mature, whose uterus contains up to 5 thousand eggs of developed oncospheres. Eggs in shape and size are similar to the eggs of taeniids.

The cycle of development. Definitive hosts may be a dog, wolf, jackal, and intermediate hosts are large and small cattle, pigs, camels and people (Fig. 19.7). The feces of final hosts have eggs of parasites. In addition, the mature tapeworm segments can crawl out of the anus and leave the eggs in the coat of animal. The human is infected by eggs orally. In the intestine oncosphere is developed from eggs and penetrates into the blood vessels and through the blood stream it is stored in various organs, where it is converted into larva. Larva bladder wall comprises an outer

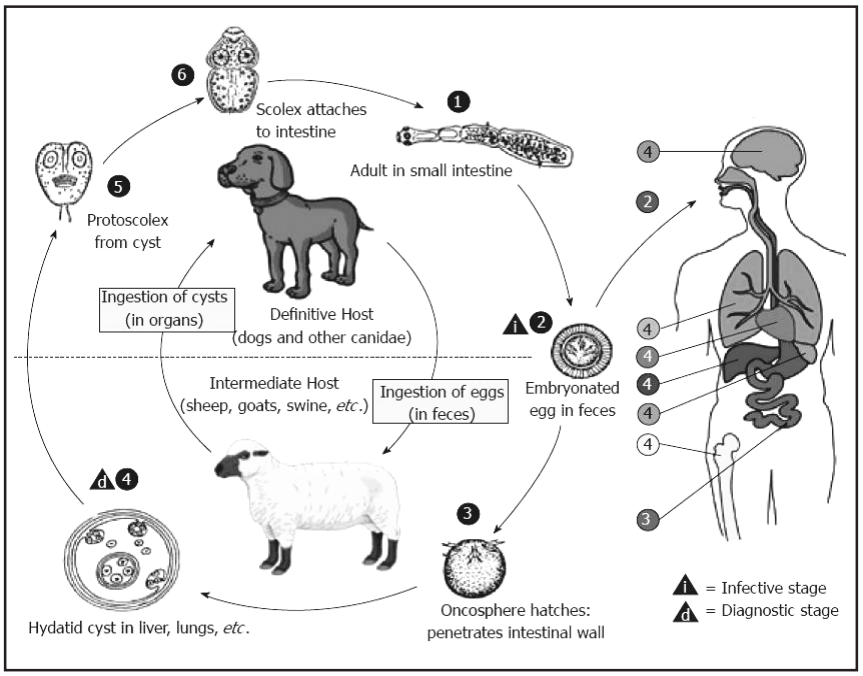


Fig. 19.7. The cycle of development of Echinococcus granulosus (by DPDx and CDC).

layered capsule and an inner parenchymal capsule shell in which blisters are formed. They are scolexes. Human for echinococcus is blind branch. The final host is infecteded by eating the affected organs of animals, and swallowing scolexes.

Pathogenic action, clinic. Echinococcus pathogenic effects on a human body is associated with impaired liver function, lung and other organs affected, which parasitized by larvas. Rupture echinococcus bubble leads to colonization of internal organs of the abdominal cavity wall subsidiary scolex, anaphylactic shock and death of a patient.

Methods of diagnosing diseases. Currently enzyme immunoassay method is widely used. It gives positive results in 90% or more cases with a liver disease and about 60% – by echinococcosis lungs. Sometimes the indirect hemagglutination and lateksagglyutination also is used.

Prevention. Personal prevention consists in observing the rules of personal hygiene (washing hands before eating, after contact with dogs). Social prevention is based on eradication of stray dogs, the treatment of work and the ban to feed a family dog with organs of animals infected with echinococcosis.

DWARF TAPEWORM (Hymenolepis nana) is a causative agent of hymenolepiasis, contact helminthiasis of human and some rodents characterized by disorders of digestive tract functions. It is ubiquitous, and affects mainly children.

The morphology of the parasite. Strobila of dwarf tapeworm is 1-5 cm, in which there are 200 or more segments. Scolex is pear-shaped, it has four suckers and proboscis with hooks. Eggs are of ellipsoid shape with transparent colorless shells. Sizes of eggs are 45 x 37 μm.

The cycle of development. Human for a dwarf tapeworm is both a final and intermediate host. If swallowed, the dwarf tapeworm eggs in the small intestine turn into oncospheres that are introduced into the villi. Here cysticercoids is developed. After a few days the affected villi are destroyed and cysticercoid falls into the bowel lumen. 14-15 days, they reach sexual maturity. At the same time, in human 1500 of dwarf tapeworms may parasitize. The lifespan of the parasite is 1-2 months. Parasite eggs are not released into the environment (autoinvasion), quickly reaching maturity even in the intestine (intracolonic route of infection). In such cases, the infestation takes hard for a long period. If the dwarf tapeworm eggs, highlight the body of a patient with feces fall into the digestive system. Cysticercoid is developed. If a beetle is swallowed with uncooked bread, adult parasites are developed from cysticercoids in the human gut.

Pathogenic action, clinic. Infested children have the destruction of a large number of the villi intestine, pain in abdomen, complaints of general weakness, fatigue, headaches; children become moody and irritable.

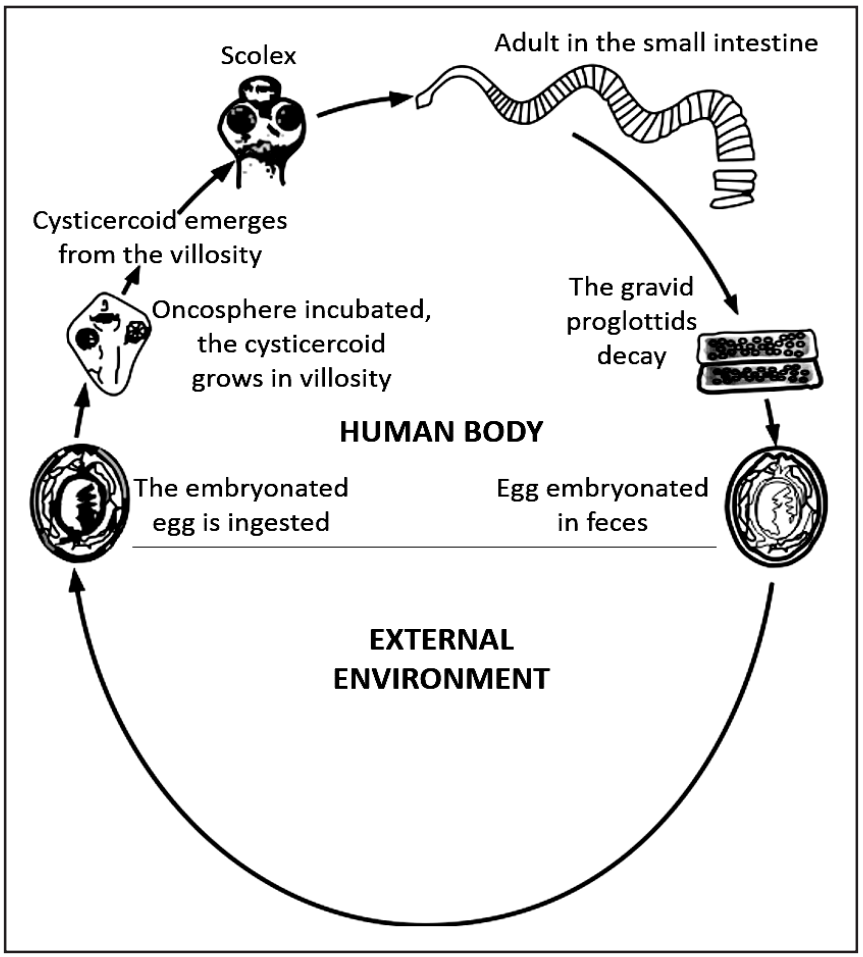


Fig. 19.8. The cycle of development of Hymenolepis nana (by flickr.com).

Infection occurs by ingestion of eggs through the mouth, where they come from contaminated hands.

Methods of diagnosing diseases. Diagnosis is based on detecting eggs in patients feces.

Prevention. The personal prevention is based on observing the rules of personal hygiene, instilling hygienic habits for children (washing hands before eating, after using the toilet). Public prevention includes health education among parents, workers of children's institutions, disinfection of toys, household items, treatment of patients with preventive examinations in childrens groups.

19.2. PHYLUM NEMATHELMINTHES

There are described more than 500,000 of species. They live in different environments: in water (freshwater, marine), soil, decaying organic matter. Many species have parasitic way of life.

The body of roundworms is elongated fusiform or filiform having more or less circular shape in cross section. They are characterized by development from three germ layers, the presence of primary body cavity and skin-muscle sac bilateral symmetry, the presence of organ systems (digestive, excretory, nervous, reproductive), dioecious and appearance of the third posterior division of the digestive system with the anus.

Taxonomically phylum Roundworms are divided into several classes, of which only one class Nematoda has medical value.

The structure of this class basically corresponds to the general phylum. Skin and muscle bag consists of multilayer cuticle, hypodermis and one layer of longitudinal smooth muscle. Cuticle performs primarily defensive function. Muscles are arranged in the form of four longitudinal bands. The digestive system is formed by the anterior, middle and posterior intestine. Excretory system is protonephridial type. The number of secretory cells is low. Gas exchange takes place through the body cover, and in parasites - by type of fermentation. The nervous system is composed of peripharyngeal ring from which nerve trunks extend, connected to each other by commissures. Senses are presented by tactile cells and chemical sense cells. Genitals are tubular structure, in females - paired, in male - unpaired. Male reproductive system is represented by testis, vas deferens, ejaculatory duct, which opens into the hindgut. Female reproductive system includes two ovaries and two oviducts, two uteri, connecting to the common vagina, which opens to the outside on the ventral side. All the internal organs are located in the primary body cavity filled with liquid, which gives firmness to a body and provide a metabolism between organs.

Reproduction is only sexual. The fertilized egg starts to develop in the uterus, but formation of larvae at geohelminthes occurs in the environment under air oxygen. In biohelminthes live birth is observed. The larva molts several times in the process of growth and development, at the same time it is released from the old cuticle and replaced by a new one. Typically that in most species there is no change of hosts in the life cycle of parasitic nematodes.

Given the characteristics of the parasitic nematode life cycle is divided into geohelminthes (whipworm, roundworm, strongyloides, toxocara) biohelminthes (trichinella, dirofilaria) and contact helminths (pinworm).

19.2.1. GEOHELMINTHES OF CLASS NEMATODA

WHIPWORM (Trichocephalus trichiurus) is a causative agent of trichocephalesis, anthroponotic geohelminthosis manifested by dyspeptic syndrome and neurotic phenomena. Sexually mature worms are localized in the cecum and in the upper part of the colon. It occurs almost worldwide.

The morphology of the parasite. Whipworm is 3-5 cm in length. The front end has elongated body with the esophagus only. The back of the body is thickened with intestine and reproductive system. Eggs are barrel shaped with thick shell of yellow-brown color. Size of egg is 50-54 x 22-23 μm.

Female of parasite extracts about 60 thousand eggs daily.

The cycle of development. Whipworm feeds on blood of host (Fig. 19.9). It parasites only in human. Eggs with feces are extracted into the environment and developed in the soil for about 20-25 days at ambient temperature 25-30^0 C. The larva is released from the egg membranes in the intestine of human and is developed into mature individuals after infection by invasive eggs. The period of whipworm life is 5-6 years. Human is infected by eating contaminated eggs vegetables, berries and water.

Pathogenic action, symptoms. Pathogenic action of whipworm is expressed in development of anemia, nervous disorders. Patients feel the abdominal pain. Violation of the integrity of the gut wall opens the way for secondary infections. Whipworm can cause inflammation of the appendix. Dryness of mucous membranes, brittle nails, dermatitis, convulsions appear with long-term signs of vitamin A deficiency during the disease. Children with trichocephalosis have physical and mental development, underweight and stunting.

Methods of diagnosing diseases. Diagnosis is based on detecting in patient's feces of whipworm eggs. As whipworm females lay relatively few eggs, parasitological diagnosis must use the methods of enrichment.

Prevention. Personal prevention is based on keeping the rules of personal hygiene, and public - on health education.

HUMAN ROUNDWORM (Ascaris lumbricoides) is a causative agent of ascariasis, anthroponotic geohelminthosis which migration phase is characterized by allergic symptoms (eosinophilic pulmonary infiltrates, urticaria etc.) And in the intestinal - dyspeptic symptoms with possible severe complications. Sexually mature worm is localized in the small intestine. It occurs almost worldwide.

The morphology of the parasite. The mature female reaches a length up to 40 cm, and the male - 15-25 cm. They have cylindrical body, tapering towards the ends. The male's posterior end of the body has spirally-like form on the ventral side. Fertilized eggs are oval with a thick multi-layer

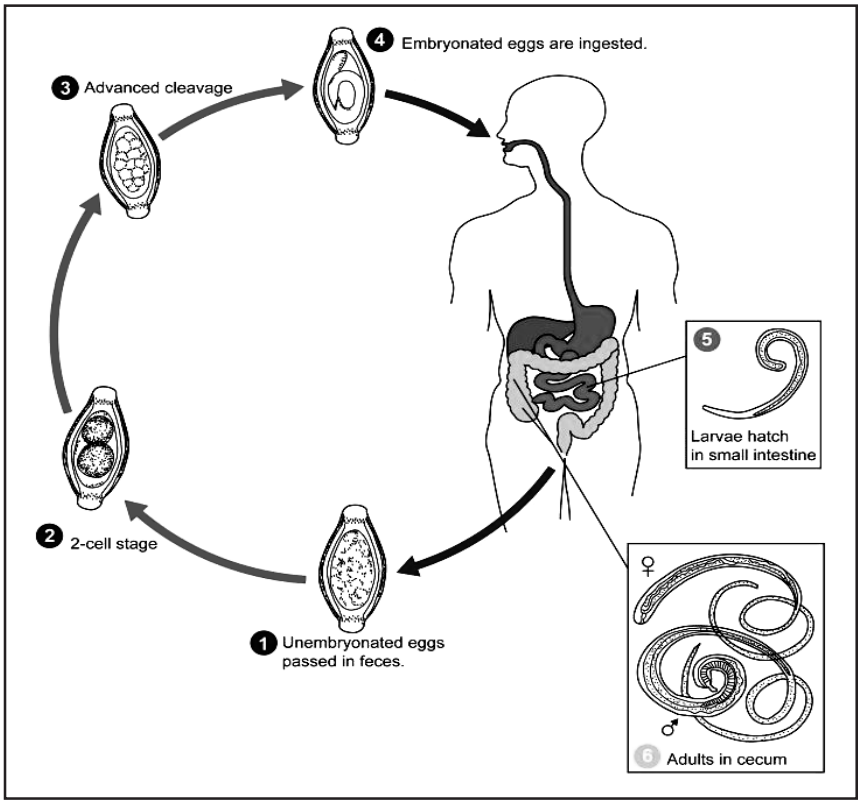


Fig. 19.9. The cycle of development of Trichocephalus trichiurus (by DPDx and CDC).

coating. The outer protein shell is yellow-brown color. Inside the egg there is spherical blastomere, which occupies a central position. Egg size is 50-70 x 40-50 μm. Unfertilized eggs are highly elongated. Their outer protein coat is thin with some sharply protruding mounds of dark yellow color. Such eggs are filled with yolk polygonal cells. Size of unfertilized egg is 50-100 x 40-50 μm. The roundworm female lays daily up to 240 thousand eggs.

The cycle of development. A human parasite ascaris lives only in man (Fig. 19.10). The fertilized eggs with feces are extracted. In the external environment a development occurs at a temperature from 13^0 to 36^0C, the optimum temperature - 24^0-30^0C, in which the duration of larval

development is 16-18 days. Infective roundworm egg is swallowed by man with unwashed vegetables or berries. In the intestine a larva is released from the egg, which penetrates into the wall of the intestine into the blood vessel, and with a flow of venous blood through the liver, right part of heart into the lungs. There, the larvae penetrate into the pulmonary alveoli, bronchi and trachea, where rises in the larynx and is swallowed with the saliva again. The migration lasts about two weeks. Once again in the human intestine, the larvae in 2-2.5 months turns into a sexually mature form. The duration of its life is for about a year. In the intestine, roundworm are not attached, but are held resting with their ends against the intestinal wall. Therefore, they are very mobile, can sometimes penetrate into the liver passages, ducts of pancreas, uterus, ovaries, stomach, and even through the esophagus and larynx into the airways.

Pathogenic action, clinic. Headache, weakness, dizziness, decrease in memory is observed in patients with ascariasis. Ascaris can cause intenstine obstruction. Migrating larvae of ascaris cause allergic reactions, especially in the lung tissue of the type of bronchopneumonia with pronounced eosinophilic infiltration.

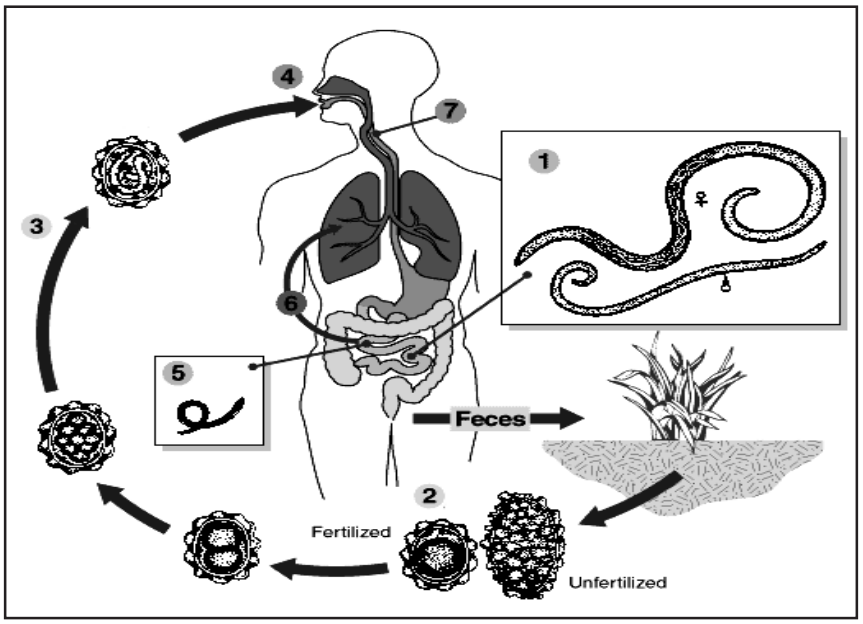


Fig. 19.10. The cycle of development of Ascaris lumbricoides.

Methods of diagnosing diseases. Early detection can be set at a migratory larvae level (sputum, immunological reaction, detection migrative infiltration at fluoroscopy). Intestinal ascariasis is diagnosed on detected helminthes eggs in patient's faeces.

Prevention. Personal prevention is based on observing the rules of personal hygiene (washing vegetables, fruits and berries before eating, washing hands before eating). Public prevention involves treatment of patients, improvement of toilets, avoiding the use of fresh human faeces as fertilizer, elimination of flies as mechanical carriers of ascaris eggs, sanitary and educational work.

TOXOCAROSIS (Toxocara canis, T. cati) is geohelminthiasis, zoonotic disease. Toxocariasis is an illness of humans caused by larvae (immature worms) of either the dog (T. canis) or cat roundworms (T. cati). Toxocariasis is often called visceral larva migrans (VLM). Depending on geographic location, degree of eosinophilia, eye and/or pulmonary signs the terms ocular larva migrans are applied to toxocariasis.

The morphology of the parasite. Both species produce eggs that are brown and pitted. T. canis eggs measure 75-90 μm and are spherical in shape, whereas the eggs of T. cati are 65-70 μm in diameter and oblong. At second stage the larvae are hatched from these eggs and are approximately 0.5 mm long and 0.02 mm wide. Adult T. canis are found only in dogs and the males are 4–6 cm in length, with a curved posterior end.

Females can be as long as 15 cm, with the vulva stretching one third of their bodylength. T. cati adult females are approximately 10 cm long, while males are typically 6 cm or less. The T. cati adults only occur in cats and male T. cati are curved at the posterior end.

The cycle of development. Cats and dogs can become infected with Toxocara through the ingestion of eggs or by transmission of the larvae from a mother to her offspring. Larvae hatch eggs in intestines of a cat or dog host. Larvae enter the bloodstream and migrate to the lungs, where they are coughed up and swallowed. The larvae mature into adults within the small intestine of a cat or dog, where mating and egg laying occurs. Eggs are passed in feces and only become infective after several weeks outside of a host.

On second stage the larvae also hatch in the small intestine of an accidental host, such as a human, after ingestion of infective eggs. The larvae will then migrate through the organs and tissues of the accidental host, most commonly through lungs, liver, eyes, and brain. From the second stage the larvae cannot mature in accidental hosts, after this period of migration, Toxocara larvae will encyst as second stage larvae.

Pathogenic action, symptoms. Physiological reactions to Toxocara infection depend on the hosts immune response and the parasitic load. Most cases of Toxocara infection are asymptomatic, especially in adults. When symptoms do occur, they are the result of migration of second stage Toxocara larvae through the body. High parasitic loads or repeated infection can lead to VLM. VLM is primarily diagnosed in young children, because they are more prone to exposure and ingestion of infective eggs. Toxocara infection commonly resolves itself within weeks, but chronic eosinophilia may result. In VLM, larvae migration incites inflammation of internal organs and sometimes the central nervous system. Patients can present with pallor, fatigue, weight loss, anorexia, fever, headache, rash, cough, asthma, chest tightness, increased irritability, abdominal pain, nausea, and vomiting. Sometimes the subcutaneous migration tracks of the larvae can be seen. Severe cases have occurred in people who are hypersensitive to allergens; in rare cases, epilepsy, inflammation of the heart, pleural effusion, respiratory failure, and death have resulted from VLM. Ocular larva migrans is rare compared with VLM. Toxocara damage in the eye is permanent and can result in blindness.

Methods of diagnosing diseases. Finding Toxocara larvae within a patient is the only definitive diagnosis for toxocariasis; however, biopsies to look for second stage larvae in humans are generally not very effective. Serological testing is more commonly used to diagnose Toxocara infection. Serological tests are dependent on the number of larvae within the patient, and are unfortunately not very specific.

Prevention. Actively involving veterinarians and pet owners is important for controlling the transmission of Toxocara from pets to humans. Pet feces should be picked up and disposed of or buried, as they may contain Toxocara eggs. Practicing this measure in public areas, such as parks and beaches, is especially essential for decreasing transmission. Hand washing before eating and after playing with pets, as well as after handling dirt will reduce the chances of ingesting with Toxocara eggs. Washing all fruits and vegetables, keeping pets out of gardens and thoroughly cooking meats can also prevent transmission. Finally, teaching children not to place nonfood items, especially dirt, in their mouths will drastically reduce the chances of infection.

STRONGYLOIDES STERCORALIS is a causative agent of strongyloidiasis, anthroponotic geohelminthiasis. It is localized in the small intestine. The disease occurs in mild climate regions, but is particularly widespread in tropical and subtropical areas with humid climate. It has a complex life cycle with alternation of parasitic and free-living organisms.

The morphology of the parasite. Parasitic females reach a length of 2.2 mm. and have a cylindrical esophagus without extensions. Female

are less (1 mm). Their esophagus form extension (bulb). Males as a parasitic or free-living hardly differ. The body is of 0.7 mm. Esophageal structure is similar to the structure of it in females.

The cycle of development. Eggs of a parasitic female reach 5-5,8 x 3-3.4 μm. Hatched rhabditiform larvae are even smaller (2.5 x 1.6 mm). Their development is made in two phases (Fig. 19.11).

1. Direct development. Rabditform larvae in the soil after a short period of feeding, growth, and two moults are transformed into invasive (filariform) larvae that do not feed. The latter can get into the human intestine through the mouth, and after 2 weeks turn into adult parasites, or, more often, infection occurs per undamaged skin. In the latter case, the larvae migrate like the larvae of Ascaris and reach the intestine through the respiratory tract, larynx, esophagus. Some larvae in this stage reach sexual maturity in the lungs. Copulation occurs before female penetrate into the intestinal wall, whereupon after 17 days and more females begin to lay eggs.

2. Indirect development. Rabditform larvae turn into free-living males and females in soil. They are produced into rabditform larvae. The latters turn into filariform as by direct development.

Sometimes (notably in constipation) the parasite life cycle can be completed without departing in the soil of rabditform larvae. The rabditform larvae stay for long in the lower part of the colon, where they turn into filariform larvae. The filariform larvae penetrate through the intestinal mucosa into the blood, lungs, the gut and are developed into adults. Autosuperinvasion occurs in such a way.

Pathogenic action, clinic. Itching, erythematous and papular rash is observed on the skin of feet and fingers in a place penetrated by the larvae. Swelling, extending to the back surface of feet and hands appears, and pains in joints of fingers after a few hours. Allergic symptoms may occur (hypereosinophilia up to 30-60%) when larvae migrate in infested patients. Leukocytosis is manifested also.

Intestinal stage is developed within 4-5 weeks after infection and is characterized by symptoms of digestive system, allergic reactions and astenonevrotic syndrome. Liquid feces, sometimes with admixture of mucus and blood, quickens to 20 or more times per day. The stools have putrid odor and contain many remnants of undigested food, mucus and blood. Depending on prevalence of various symptoms the intestinal, neuro-allergic and mixed forms of strongyloidiasis are distinguished. Strongyloidiasis proceeds heavily among AIDS patients.

Methods of diagnosing diseases. Diagnosis is based on detection of larvae (less eggs) in duodenal contents and feces. In migration phase, it

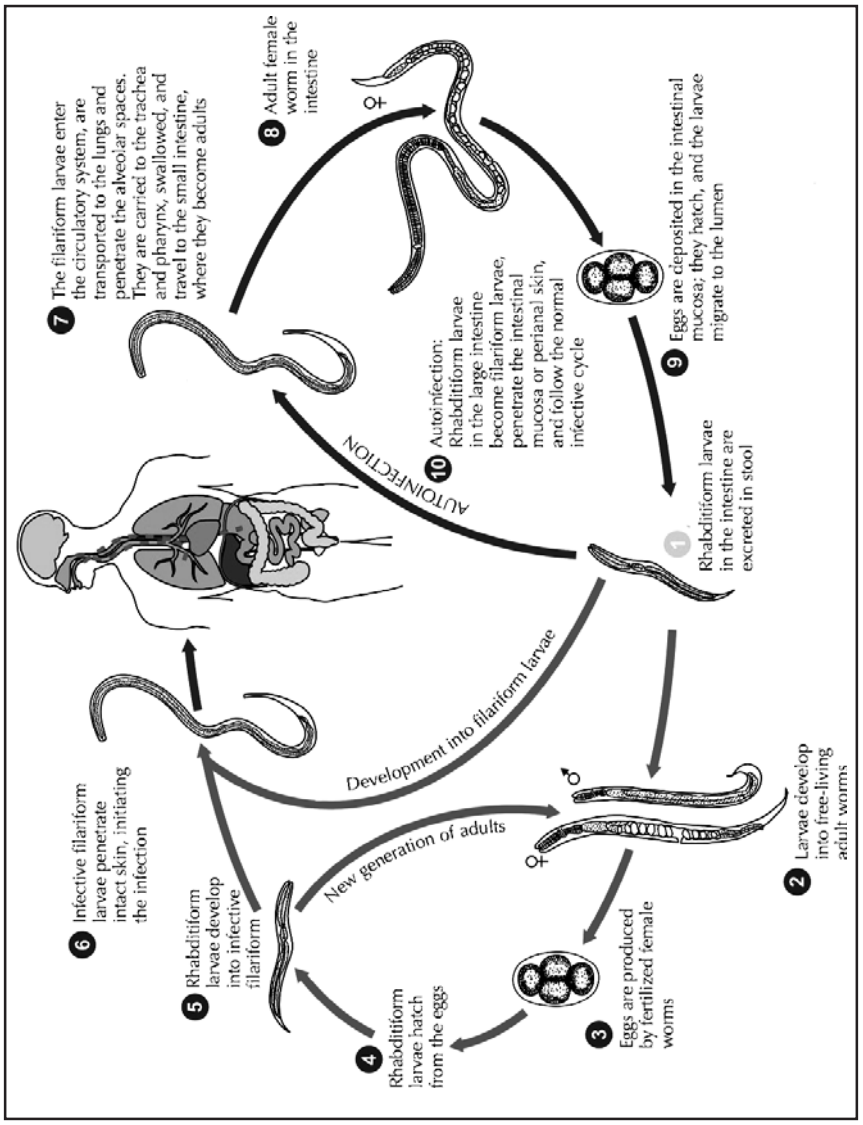


Fig. 19.11. The cycle of development of Strongyloides stercoralis (by CMAJ).

is possible to identify the larvae and adult parasites in sputum. Immunofluorescence and indirect hemagglutination reactions can be used.

Prevention. Prevention strongyloidiasis is the same as in ascaris.

19.2.2. CONTACT HELMINTHES OF CLASS NEMATODA

PINWORM (Enterobius vermicularis) is a causative agent of enterobiosis, contact helminthiasis occurring with perianal itch, dyspeptic disorders and neurotic reactions, observed more frequently in children. It parasites in the lower small intestine and is spread worldwide.

The morphology of the parasite. Pinworms female reaches a length of 10 mm, male - 2.5 mm. The posterior end of the male body has a spirally-like form. Pinworms feed on the contents of the intestine. Pinworm eggs are oval-shaped asymmetrical, one side is bulging, the other is flattened, a shell is smooth, colorless, multilayered. Inside the egg an embryo is at different developmental stages. Size of eggs is 50-60 x 20-30 μm.

The cycle of development. The fertilized females come out from the intestine through the anus usually at night. They lay 10-12 thousand eggs on perianal skin folds within 15-45 minutes (Fig. 19.12). The patients feel the intense itching. Laid eggs mature in 6-7 hours. By scratching itchy

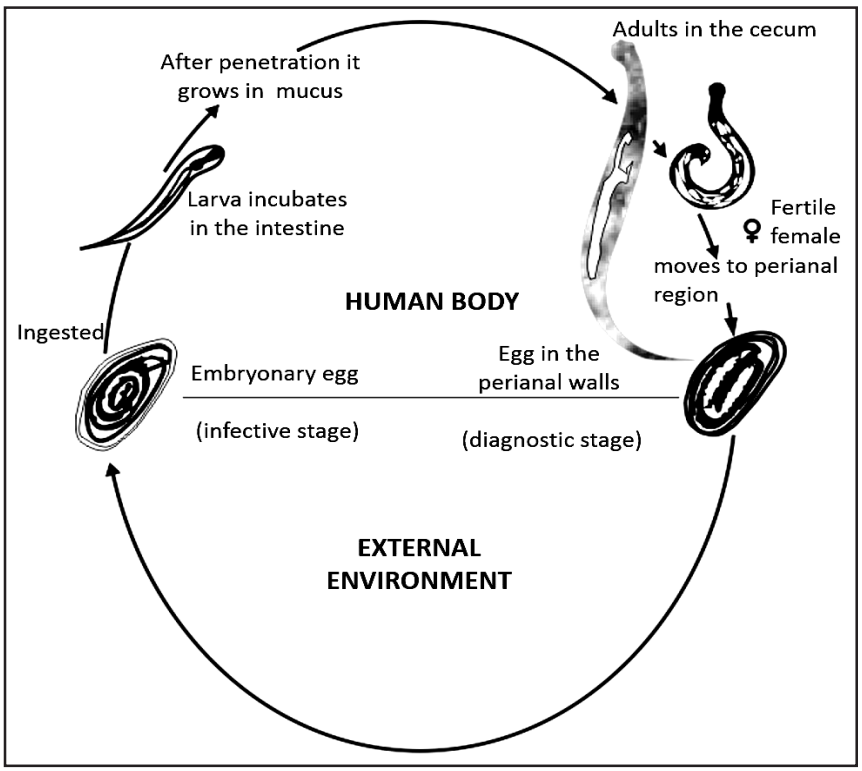


Fig. 19.12. The cycle of development of Enterobius vermicularus.

places the eggs get into his arms, clothes, toys. Adult parasites are rapidly developed in the gut if a patient ingests infective eggs. The life duration of parasite is about 1 month. It affects mainly children, suffering from autoinvasion.

Pathogenic action, symptoms. Patients with enterobiasis have restless sleep, deteriorating health, reduced working capacity, sometimes nervous disorders. Penetrated in the appendix, the pinworms can cause appendicitis.

Methods of diagnosing diseases. The diagnosis is made when the eggs are scraped from perianal folds or prints on adhesive tape, and scraped from the anus. In patients' feces pinworms and their eggs are often absent.

Prevention. Personal prevention is based on instilling hygienic rules to children. Sick children have to wear panties at night and adults infected with pinworms have to apply a dry wool swab to the anus. Pinworms lay eggs intoe the swab and do not cause itching. Public prevention involves treatment of patients, systematic wet cleaning, sterilizing linen and toys.

19.2.3. BIOHELMINTHES OF CLASS NEMATODA

TRICHINELLA (Trichinella spiralis) is a causative agent of trichinosis, zoonotic biohelminthosis. Mature Trichinella are localized between the villi of the small intestine of animals and human. Trichinella larvae live in striated muscle. Trichinosis is widespread.

Morphology and life cycle of the parasite. Female Trichinella reaches length 2.6-3.6 mm, a male - 1.4-1.6 mm. Hosts of the parasite may be a variety of carnivorous and omnivorous mammals, including a human. Trichinella has both final and intermediate host in one organism. Sexually mature parasites live in the small intestine of a host for 1.5-2 months. After copulation males die and females during their life hatch 1,5-2 thousand live larvae, and then also die. Larvae perforate the intestinal wall and are carried by blood flow throughout the body, but are deposited only in striated muscle (diaphragm, chewing, deltoid, calf, intercostals muscles). Larva migrans has the size of 10 x 6 μm. The length of muscle larvae is 1 mm. Migration period lasts from 2 to 6 weeks. After penetration into the muscle fibers, the larva is turned spirally, 2-3 weeks later it is capsulated and after one year can undergo calcification. In a calcified capsule the larva can remain viable for many years. For transformation into adult forms they need to get into the intenstine of another host. For example, a pig, boar, dog, cat can eat the trichinous rodent. Capsules with larvae of parasite are dissolved under the action of digestive enzymes. Larvae reach sexual maturity within 2-3 days. A person becomes infected by eating pork or meat of a wild animal (boar, brown and white bear, etc.).

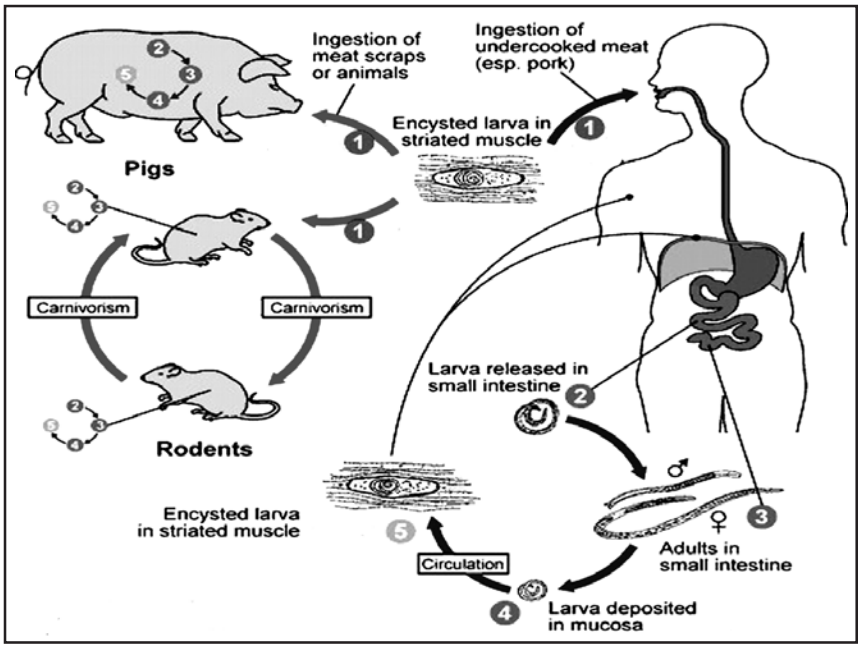


Fig. 19.13. The cycle of development of Trichinella spiralis (by DPDx and CDC).

Pathogenic action, clinic. The clinical picture of trichinosis is characterized by three major syndromes - fever, muscle swelling, and is accompanied by blood hypereosinophilia. Fever is one of the most constant symptoms of trichinosis. Swelling of face and eyelids combined with conjunctivitis is constant clinical sign. Swellings appear suddenly, grow for 3-5 days and remain for 1-3 weeks. Myalgia gradually increases with fever. Patients complain of pain in eyes, the occipital, intercostal muscles, the muscles of limbs. Eosinophilia of blood is the most constant and earliest symptom and is manifested already in the incubation period. Eosinophilia is usually 20-25%, but can reach 80% and above. The incubation period lasts from 5 to 40 days. The duration of incubation is observed in lung and abortive forms of trichinosis, in moderate form is 2-3 weeks, but in severe forms - 6-8 days.

Methods of diagnosing diseases. Main elements of the clinical diagnosis of trichinosis are the anamnestic data (eating the meat without a veterinary control) and the presence of typical symptoms of diseases.

Meat of wild or domestic animals is examined for presence of larvae Trichinella. The methods of compressor trichinelloscope or artificial

digestion are used. The indirect hemagglutination and enzyme immunoassay used for serological diagnosis. If the source of infection is not identified, a biopsy of the deltoid or gastrocnemius muscle is made (not earlier than 9-10-th day of illness). Biopsy is examined under a microscope at low magnification for the presence of Trichinella larvae.

Prevention. Personal prevention involves the obligatory trichinelloscope of meat of slaughtered animals (pigs, boar, bear) before use, careful thermal processing of pork and wild animals. Public sanitary prevention includes veterinary control in pig farms, binding trichinelloscope of pig carcasses in meat processing plants, pork.

DIROFILARIASIS (Dirofilaria immitis, D. repens, D. tenuis) Dirofilaria are long, thin parasitic roundworms that infect a variety of mammals. Infection is transmitted by mosquito bites. There are many species of Dirofilaria, but human infection is caused most commonly by three species, D. immitis, D. repens, and D. tenuis. The main natural hosts for these three species are dogs and wild canids, such as foxes and wolves (D. immitis and D. repens) and raccoons (D. tenuis).

The morphology of the parasite. D. immitis adult females are usually 230-310 mm long by 350 μm wide, D. repens – 100-170 mm long by 460-650 μm wide, D. tenuis – 80-130 mm long by 260-360 μm wide. D. immitis males are usually 120-190 mm long by 300 μm wide, D. repens – 50-70 mm long by 370-450 μm wide, D. tenuis – 40-50 mm long by 190-260 μm wide. Adults can live for 5 – 10 years.

The cycle of development. The definitive mammalian hosts for Dirofilaria are primarily domestic dogs, wild canids (such as wolves and foxes), and raccoons. In these hosts, sexually mature worms produce microfilariae that circulate in the blood and are ingested by mosquitoes sucking the blood. In mosquitoes, the microfilariae develop into larvae that migrate to the proboscis (the long, tubular part of the mouth of mosquito that punctures the skin), where they are ready to infect another host while sucking the blood. Several types of mosquitoes are capable of transmitting Dirofilaria infection, including Aedes, Anopheles, and Mansonia. Humans and a wide range of other mammals are accidental hosts that play no role in transmission of Dirofilaria. In these hosts, Dirofilaria larvae can develop into adult worms but the worms remain sexually immature and no microfilariae are produced.

Pathogenic action, symptoms. Human infections with D. immitis can result in areas of inflammation induced by dying adult worms in pulmonary arteries that appear as coin lesions on chest x-rays. Coin lesions can also be caused by cancer and other serious diseases, and a coin lesion discovered accidentally on a chest x-ray usually leads to an invasive

procedure to learn the cause. Most human cases of pulmonary dirofilariasis are diagnosed from samples taken during these procedures. Most reported cases of D. immitis infection in humans have been in persons with no symptoms. People with symptoms can have cough (including coughing up blood), chest pain, fever, and pleural effusion (excess fluid between the tissues that line the lungs and the chest cavity). Rarely, D. immitis worms have been found in humans outside the lungs, including the brain, eye, and testicle. When D. repens and D. tenuis infection is reported in humans, it is generally as the cause of nodules under the skin, but in some occasion, worms are found in the conjunctiva.

Epidemiology. Dirofilariasis is found throughout the world where Dirofilaria species are common. D. repens is the Dirofilaria species most commonly reported to cause dirofilariasis among humans in Europe. One or both of these species have been found to cause human dirofilariasis in other parts of the world.

Methods of diagnosing diseases. In humans, dirofilariasis is diagnosed most frequently by examining tissues in areas of inflammation in the lung obtained as part of the diagnostic investigation of coin lesions (small, round abnormalities) on chest x-rays or by examining tissues in nodules under the skin. Blood tests are not yet helpful in the diagnosis of dirofilariasis in humans.

Prevention. Dirofilariasis can be prevented by avoiding mosquito bites in areas where mosquitoes may be infected with Dirofilaria larvae. The risk of such mosquito bites can be reduced by leaving as little skin exposed as possible, by the use of insect repellent when exposed to mosquitoes, and by sleeping under an insecticide-treated bednet in areas where Dirofilaria-infected mosquitoes bite at night and have access to sleeping areas.

CHAPTER 20. MEDICAL ARACHNOENTOMOLOGY

Arachnoentomology is a section of medical parasitology, studying the value of arthropods as ectoparasites, exciters and vectors of diseases. Arthropods are the biggest phylum of animal (more than 1 million).

Arthropods are characterized by: heteronomous body, which is expressed in the fact that the segments have a different structure and different functions; merge the segments of the body sections (head, thorax, abdomen); separation of the muscles and the appearance of striated muscle; chitinous external skeleton that protects the body from external influences and is designed for attachment of muscles; body cavity - mixsocel formed by the fusion in embryogenesis of primary and secondary body cavities; the presence of organ systems (digestive, respiratory, excretory, circulatory,

nervous, endocrine and reproductive).

The phylum is divided into three subphylums: Branchiata, Chelicerata, Tracheata, in one of which the medical importance belongs to the classes - Cructacea, Arachnoidea and Insecta.

The value of small crustaceans (Cyclops act only as intermediate hosts for tapeworms wide, sparganum, guinea worm and crabs and crayfish - for lung fluke) is insignificant. The value of arachnids and insects is significant.

Pathogenic influence of arthropods on human health is determined by: the value of arthropods as the intermediate hosts of helminthes; toxic effect on humans; role as vectors of causative agents of infections and infestations; parasitism arthropods due to man. Transmission of pathogens and arthropod infestations to human is possible by specific or mechanical inoculation and contamination.

20.1. CLASS ARACHNIDA (ARACHNOIDEA)

Arachnids are arthropods, which are adapted to life on land. They are characterized by organs of the air breathing. Spider is characterized by the fusion of body segments, which form the cephalothorax and abdomen, and mites have lost even this division.

The body is covered with chitinous cuticle epidermis having a cellular structure. Arachnids are characterized by six pairs of limbs. The first two pairs (chelicera and palps) are adapted to capture and hash the food. The remaining four limbs are walking legs.

The digestive system is adapted to eat semi-fluid food, pharynx serves as a sucking organ.

Respiratory system is represented by leafy trachea or lungs, which are opened outwardly by special holes - stigmas. Lung of arachnids are homologous to the gills of crustaceans. Tracheae are branched tubes, which are suitable for all bodies, where gas exchange takes place.

The excretory system is represented by modified metanephridia. In many species, the special malpighian vessels are developed due to outgrowths of the intestinal tube between the middle and posterior intestine. Dissimilation products arrive in the hindgut.

The circulatory system is not closed. The most comlecated structure is in scorpions and spiders breathing by lungs. It consists of a pulsing heart lying on the back side and blood vessels departing from it. The blood flow returns to the heart through lacunae.

The nervous system has the form of the ventral nerve cord with lines of ganglia from which peripheral nerves extend. In forms, in which

individual segments are fused, nerve knots are combined as well. Spider is characterized by the presence of 1-6 pairs of simple eyes.

Arachnids are dioecious animals. The ovaries of females are located in the abdomen, and the fallopian tubes are merged into a single duct that opens in front of the abdomen. Testes of males also lie in the abdomen, and spermoducts extending from them merge and unclose with one hole on the lower side of the abdomen. Sexual dimorphism is pronounced. Some arachnids have live birth. Direct development or with metamorphosis is possible.

In the class of Arachnids the important medical value belongs to the ticks and mites (Acari). This is a large group of animals, many species of which are blood-sucking, parasitic on birds, mammals and man, acting as carriers of agents of transmissible diseases. An important family of Acari type is ticks (Ixodidae), Argasidae, Trombiculidae, Gamasoidae and itch (Sarcoptidae), Demodicidae, Tyroglyphidae mites.

20.1.1. TICKS AS VECTORS OF PATHOGENS VECTOR-BORNE DISEASES

Ixodidae ticks are ectoparasites of mammals and human who live in forests, in bushes. They are characterized by fusion of the cephalothorax and abdomen into one. Mouthparts complex is formed from a pair of the upper jaw, the lower jaw is strongly modified, which can grow together with the lower lip covered in spines proboscis, intended for puncturing the skin of a host and retenting the parasite. From the base of the proboscis segmented palps of different shapes depart. Proboscis lies at the front end of the body or on the lower front side thereof. A set of mouthparts and adjacent sheets is mistakenly called “head.”

Ticks are dioecious, they have well-marked sexual dimorphism. In males, the dorsal shield covers the entire back and in female it is small in size, has the form of a collar. Mouthparts are visible from the dorsal side and body edges are scalloped. They usually have eyes. For long-term fix to the host body the ticks have special claws and suction pads on the legs. Stuck to the host, ticks can suck blood for long (a few days), while females can grow in 3-4 times in size. The females are very fertile and can lay up to 17 thousand eggs in one time.

Development is accomplished by incomplete metamorphosis (egg - larva - nymph - adults). Nymphs have no genital opening. Transition from one larval stage to another is associated with blood nutrition. The Ixodidae family includes ticks Genus: Ixodes, Dermacentor, Hyalomma, etc. Typical representatives of the Genus Ixodes are Ixodes ricinus and I. persulcatus, and Genus Dermacentor - Dermacentor pictus, D. marginatus.

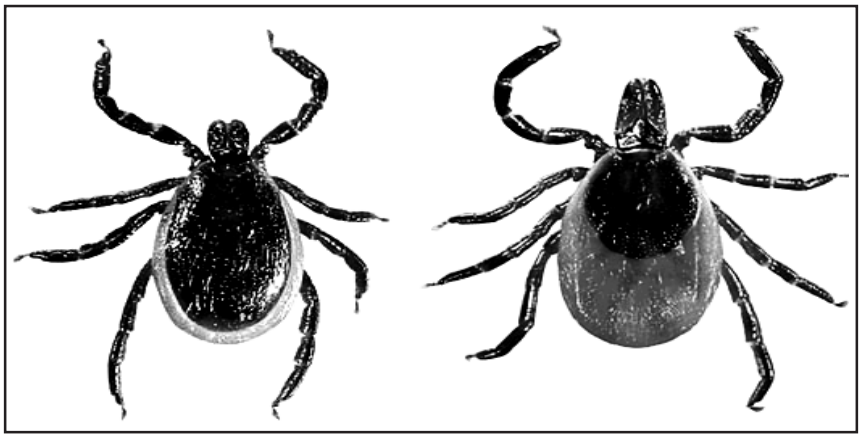


Fig. 20.1. Female and male of Wood tick
(by horse-canada.com).

Wood tick (Ixodes ricinus) has an oval body (Fig. 20.1), a scutum is on the dorsal side of the body which covers the entire dorsum in males and in females only the front part. Males are brown, 2.5 mm in length. A hungry female is brown, a well-fed one is of yellow-red color. A hungry female is 4 mm in length, a well-fed is 11 mm. They live in forests, scrubs in Europe. Dog tick supports tularemia foci among rodents and can transmit tick-borne encephalitis virus, Rickettsia Q fever and Lyme disease, tick-borne North Asian ricketsiosis.

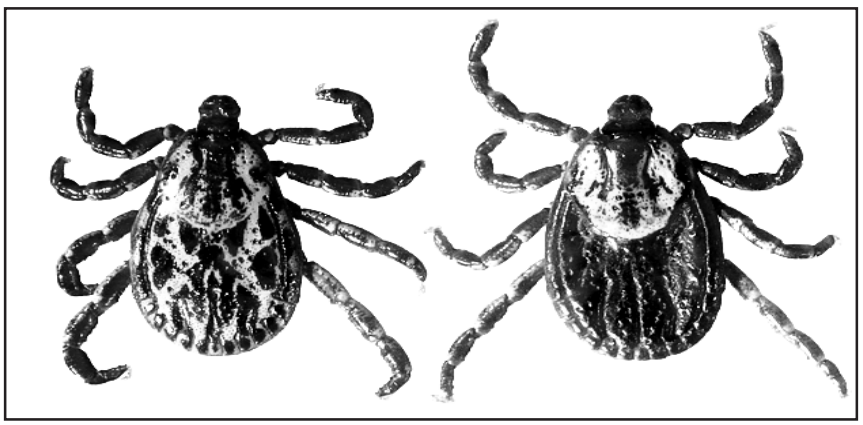


Fig. 20.2. Female and male of Dermacentor pictus
(by horse-canada.com).

Ixodes persulcatus is externally similar to a wood tick. It lives in forests (taiga) in Europe and Asia. It parasitizes on many species of mammals, birds. It supports in nature the circulation of a encephalitis virus, Lyme disease, tick-Northern-ricketsiosis. The virus of ticks can be transmitted transovarially.

Dermacentor mites have eyes, a dorsal shield is decorated with enamel pattern. They live in the European part of Russia, Western Siberia, the Trans-Baikal region. Larvae and nymph ticks feed only on small animals, and adults attack large animals and human.

Dermacentor pictus (Fig. 20.2), *D. marginatus* are vectors of the causative agent of tularemia, D. nuttalli – a vector of Omsk hemorrhagic fever virus, spotted fever of mountains.

Hyalomma ticks are large (5 mm). They have eyes. Very thick and long legs are typical feature of the tick structure. They live in steppes and mountains of the subtropical regions of Southern Europe. Hyalomma ticks of the genus are capable of transmitting the virus of Crimean hemorrhagic fever.

20.1.2. MITES AS PARASITES OF HUMAN SKIN

Itch mites are intraskin parasites of many species of mammals and human and cause scabies (Fig. 20.3). Mites bite through canals in the epidermis of the skin, in which the female lays eggs. Larvae and nymphs can be found in skin follicles. Itch mites feed on tissue fluid and epidermal cells. While moving in the skin the mite irritates nerve endings, causing unbearable itching. Infection of human appears with scabies patients in baths, through clothing, bedding. A human can be affected by itch mites from horses, sheep, goats, dogs and other animals. They cause the characteristic skin lesions.

The causative agent of human scabies is Sarcoptes scabiei. It is widespread. The body is oval in shape, covered with bristles. The female reaches a length of 0.4 mm, the male is 0.3 mm. Limbs are dramatically shortened, composed of 6 segments. Mouthpart is adapted for gnawing routes in the epidermis. Daily the mites burrow 2-3 mm canals where a female lays eggs (20 or more for life). The parasite is developed by incomplete metamorphosis (egg - larva - I nymph - II nymph - adults) for 12-14 days. The adult mites live up to 2 months. Infection occurs only in direct contact with a sick human, when newly fertilized females of the parasite are transferred. Itch mites of dogs, cats may also attack a human. They are not capable of forming canals in the epidermis.

Diagnosis is based on extraction of mites from the damaged skin and their microscopic investigation in a drop of 50% glycerol solution.

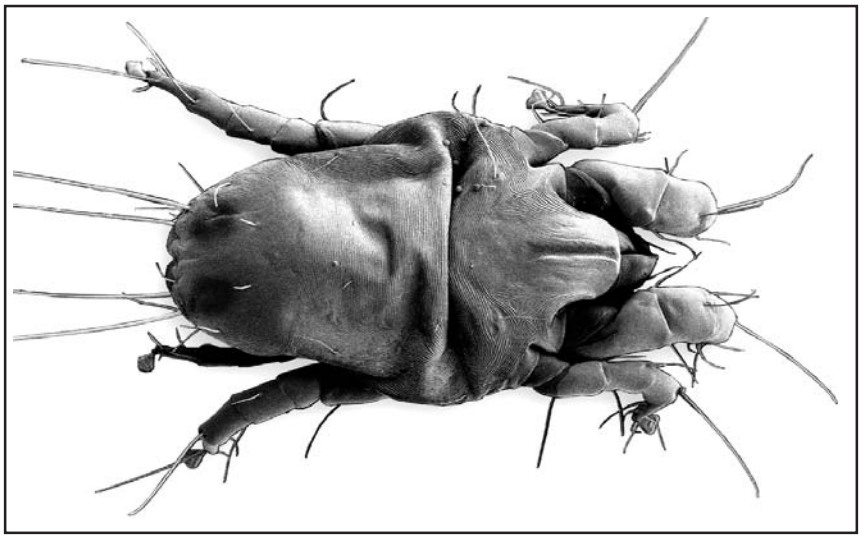


Fig. 20.3. Itch mite (by blogs.discovermagazine.com).

Personal prevention is based on keeping the rules of personal hygiene, to be careful when dealing with animals, and the public - on identification and treatment of patients, disinfection of their clothing, health sanitary work.

Follicli mites. It is small with an elongated worm-like body. Dorsal shield covers only a front portion of the back. Legs are short with two claws. They live in cavities and ducts of the sebaceous glands of the skin and hair bags of mammals and humans. The high fertility is typical for parasites.

Demodex folliculorum is small (female - 0.38 mm, male - 0.3 mm) intraskin wormlike human parasite that causes skin disease - demodecosis. Mites are found in sebaceous glands and hair follicles of the face, neck, shoulders, located with their head-end down, usually in groups of 4 organisms. Parasites may occur in completely healthy people without causing any symptoms. In weakened people the demodex are actively reproduced, causing clogging of the sebaceous glands, the appearance of pink acne with purulent contents. Purulent acne appears on the skin involving a secondary infection. Propagation of acne occurs in personal contact, common use of a towel and underwear. The diagnosis is made after studying under a microscope of contents of the pimple in a drop of glycerol on a microscope slide.

Personal prevention of demodecosis is based on compliance with the

Fig. 20.4. Demodex folliculorum (by morroccomethod.com).

rules of personal hygiene, the treatment of major diseases that weaken the body, and the public - on the identification and treatment of patients, health sanitary work.

20.1.3. MITES AS INHABITANTS HOUSING HUMAN

Tiroglyphic mites are small (0.4-0.7 mm) without eyes, mandibular palps are three-segmented, mouth apparatus of a biting type. Cephalothorax is separated by a notch from the abdomen. They are capable of active movements in searching for food. They eat food stocks - grain, flour, cheese, smoked meat and fish, dried vegetables and fruits, as well as epidermal scales exfoliated from human skin, mold spores. Food infected by Tiroglyphic mites can cause catarrhal phenomena in the gastrointestinal tract in human, and sometimes allergic phenomena. Ticks can bite a person causing grain itch, itch sellers of groceries and other options dermatitis. After penetrating in the respiratory tract with dust the tiroglyphic mites cause acaridosis of respiratory system. Members of this family are flour mite (Tyroglyphus farinae) and cheesy mite (Tyroglyphus siro).

Eradication of human inhabitants housing is to decrease the humidity and temperature in the premises where grain, flour, cheese and other food products are stored. The fight against household mites includes wet cleaning, to use furniture, cushions, mattresses made of synthetic materials, in which they can not settle.

20.2. CLASS INSECTA

These are higher invertebrates and most numerous in the number of species.

The body is divided into head, thorax and abdomen. Senses are on the head - antennae and eyes, mouthparts which structure is caused by nutrition method (chewing, sucking, piercing-sucking). Thorax consists of three segments, each of which carries one pair of legs. Furthermore, on the dorsal side of the second and third segments may carry a pair of wings. The abdomen consists of 6-12 segments.

Insects have a chitinous cover with hypodermis, which are derived from a variety of gland (odoriferous, wax, molting, etc.). Muscles are striated.

The digestive system begins with mouth. The ducts of the salivary glands open there. The front section of the intestine has an extension (goiter). The food is digested and absorbed in the midgut, which passes into the rear opened outwardly by anus.

The respiratory system has a trachea, which deliver air to all tissues and organs.

Excretory organs are malpighian tubules, fat body ("accumulation kidney"). Malpighian tubules are represented by numerous vessels flowing into the alimentary canal between the middle and rear intestines. Their lumen is filled with crystals of uric acid - a staple dissimilation in insects.

The circulatory system is underdeveloped and lacks the oxygen carrier function. It is not closed. The heart and aorta are arranged on the dorsal side.

The nervous system consists of the supra-oesophageal ganglion pair connected to the hypopharynx, along which body on abdominal side the chain of pair ganglia runs. Often there is a merger of ganglia of adjacent segments. Adult insects have facet eyes. There are also organs of equilibrium, taste, smell, and hearing.

Insects are dioecious animals. The development takes place with complete or incomplete metamorphosis.

The medical value of insects is due to: firstly, pain sensations causing by bites; secondly, local allergic reactions manifistated after bites; third, appearance of secondary bacterial infections in damaged skin; fourthly, the role of insects as vectors of infectious and parasitic, especially vector-borne diseases. Insects can destroy crops in fields, eat food stocks, and thereby deprive millions of people of food, condemning them to starvation.

The Class includes insects with medical importance: cockroaches, bugs, lice, fleas, diptera.

20.2.1. ORDER COCKROACHES (BLATTOIDEA)

These are house parasites, which spoil food causing the economic harm to human. There are about 3.5 thousand species. Black (Blatta orientalis), red (Blatta germanica), Egyptian (Polyphaga saussurei) and American (Periplaneta americana) cockroaches live in human housing. They are nocturnal, are mechanical carriers of various infections and infestations. Cockroaches can infect food, shifting diphtheria, typhoid fever, cholera, cysts, helminthes eggs on their feet or faeces. The typhoid, dysentery bacterias survive in the intestines of cockroaches within 2-4 days. To fight cockroaches the poisoned attractants are used. Intensive disinfestation only reduces their number, but does not eliminate completely. This is becasie the cockroaches have low sensitivity to toxic chemicals, the presence in the trachea of special valves closing in the presence of poisons in the air, a wide genetic polymorphism, high mobility and ability to prolonged starvation.

20.2.2. ORDER BUGS (HEMIPTERA)

The bugs have front wings heavily sclerotized in the proximal part, and in the distal - transparent. Piercing-sucking mouthpart forms two channels, one of which serves for sucking liquid food, and the other - to remove secretions of salivary glands. There are about 40 thousand of species of bugs.

The medical importance has the representatives of two families: Cimicidae (bedbugs-parasites) and Reduviidae (kissing bugs).

Bed bug (Cimex lectularius) is widely distributed in the world, the most adapted to parasitism (Fig. 20.5). The body is flattened in the dorsoventral direction, the wings are reduced. Bed bugs are able to fast for several months. Bugs attack a human at night and spend the day in shelters. In tropical countries, in human dwelling C. rotundatus constantly dwells, having a darker body color, smaller head size, narrow pronotum. Bed bug feeds on blood throughout the entire life cycle, its role in transfer of human pathogens has not been proved. Bugs of pigeons, swallows, bats can also attack a human.

Kissing bugs are common in South and Central America. They are able to fly and are blood-sucking insects at all stages of development. Their bites are painless. Places of bites are localized usually near the lips, for which are named “kissing”. They are a specific causative agent of Chagas disease vectors. Settling in burrows of forest rats, armadillos, anteaters, opossums and other animals, bugs become infected by Trypanosoma cruzi and in 5-15 days begin to excrete the pathogen with faeces. Attacking a human at night, the bug sucks the blood and turns into

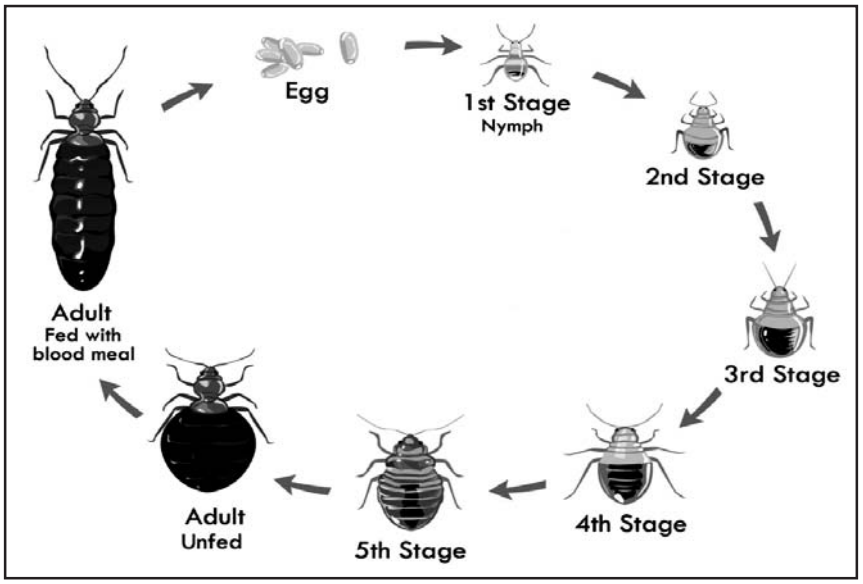


Fig. 20.5. The cycle of development of Bed bug (Cimex lectularius).

180^0 and then defecates on the bitten place. The way of infection is a specific contamination. Important in transmission of the causative agent of trypanosomiasis belongs to bugs of species Triatoma infenstans and Panstrongylus megistus.

20.2.3. ORDER LICE (ANOPLURA)

These are wingless, bloodsucking, permanent ectoparasites of human and animals which have epidemiological significance. In a human two species can parasitize: human - Pediculus humanus and pubic - Phtirus pubis (Fig. 20.6). Species of a human louse is represented by two subspecies: P. humanus capitis - head and P. humanus humanus. Body lice lives about 50, head - about 40, and pubic - to 30 days.

Lice are dioecious animals. Female after mating lays 6-14 eggs (nits) a day. The females of head and body lice lay up 140 to 150 eggs (nits) for all period of life (1.5 months), and pubic - up to 30 eggs (nits). The development with an incomplete metamorphosis: egg (nit) - 3 nymphal stages - mature organism. All metamorphosis completes in 25-30 days. Lice feed on the blood at all stages of development (2-3 times daily for 3-10 minutes), fasting is not more than 10 days. During eating the lice inject saliva to the wound, causing itching, skin pigmentation. Parasitizing of a head or body louse on human is called pediculosis, a complication which can be the disease of

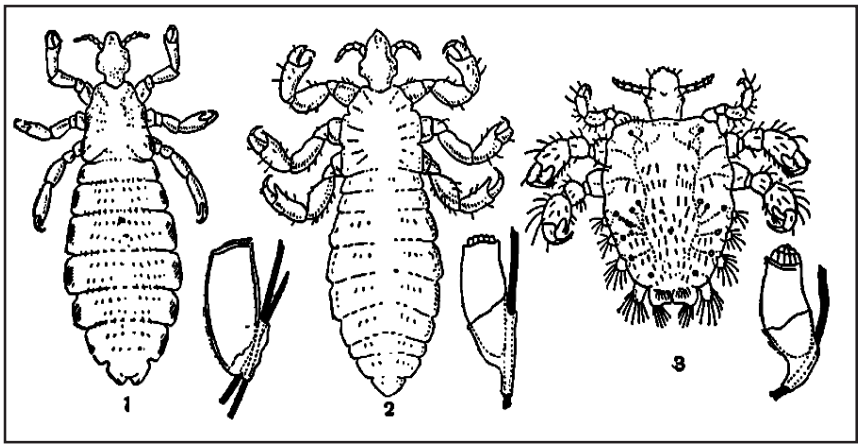


Fig. 20.6. Lice and its eggs:
1 - Pediculus humanus capitis; 2- Pediculus humanus humanus; 3 - Phtirus pubis.

vagrants or a mat (plica polonica) - pustular disease of the scalp, resulting in a hair cap, glued into a solid lump by serous. Disease caused by parasitizing on human of a pubic louse is called phtirioze. The head and body lice can carry the pathogen of typhus (Rickettsia provaczeka). The presence of Rickettsia in blood of patients was proved by O.O. Mochutkovsky on himself. Rickettsia are reproduced in the louce stomach and are excreted in feces. In the human the pathogen of a lousy typhus can enter in two ways: either by blood sucking (specific inoculation) or itching the skin by scratching and rubbing of the agent into the wound (specific contamination). Body and head lice can also be carriers of specific pathogen of the lousy relapsing fever (Borrelia recurentis). Pathogen enters the louse stomach with patient's blood and then into the body cavity. Louse's bite does not infect a healthy person. The causative agent is transmitted only when the louse is crushed and rubbed into the skin by specific contamination. The role of a pubic louse is not proven in transfer of infectious agents.

The fight against lice is based on thorough personal hygiene (washing in the bath, linen, underwear thermal treatment), special ointments, shampoos of chemicals destroying lice are used, short haircut to eradicate nits.

20.2.4. ORDER FLEAS (APHANIPTERA)

Fleas are wingless, blood-sucking ectoparasites of mammals, birds and humans. The body is flattened laterally. Mouthparts of a piercing-sucking type. They have no wings, the third pair of legs is jumping (Fig. 20.7). The

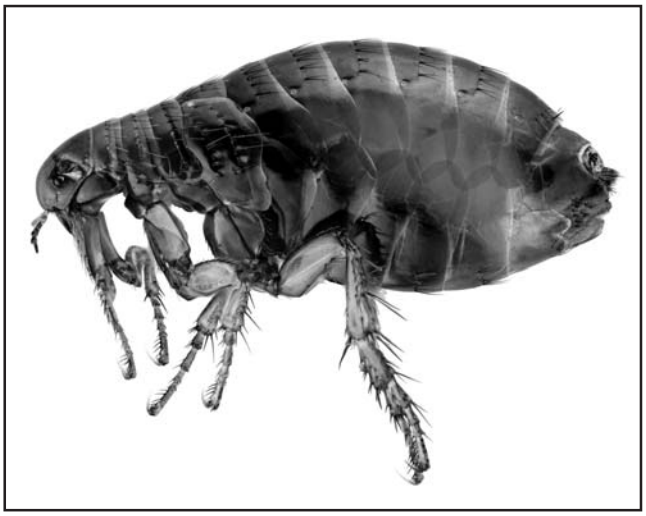


Fig. 20.7. Flea (by Do My Own Pest Control.com).

female lays up to 450 eggs in floor cracks, burrows of rodents. Wormlike larvae are developed from eggs that feed on decaying organic matter. Larvae pass several molts, then pupate and converted into mature organism (complete metamorphosis). Depending on the temperature of environment the development is from 20 days to 1 year. Fleas live from 2 to 5 years. Human flea is Pulex irritans, rodent fleas - Xenopsilla cheopis, Ceratophyllus fasciatus and other. Fleas feed on the blood of human, rat, and move easily to other animal species. A rat flea lives in burrows of rats, a human flea - in cracks of the floor, behind baseboards and wallpaper.

Fleas are a particular rodent vector of plague pathogen. Plague bacteria, once in the stomach of a flea begin to proliferate very rapidly, resulting in closing the lumen completely. This is called the plague unit. When feeding on a healthy animal or human, the flea punctures the skin, belches into the wound bacterial lump, so that a large amount of pathogens enters the bloodstream. In the absence of natural hosts the rodent fleas can attack a man and transmit the plague pathogen by biting. In addition, the transfer of tularemia, brucellosis and virus Omsk hemorrhagic fever, rickettsial flea epidemic typhus by fleas is proven. Fleas can be an intermediate host in development cycle of a rat dwarf tapeworm. The fight against fleas is aimed at maintaining of dwellings, outbuildings clean.

The use of insecticides and a variety of rodent control is recommended. For personal protection repellents are applied to impregnate clothing and linen.

20.2.5. ORDER DIPTERA

The most numerous order of insects (over 80 thousand species), which representatives have only one pair of wings, as the second is reduced and presented by halteres - clavate appendages, performing the role of the gyroscopic device during a flight. Development is carried out with complete metamorphosis (egg - larva - nymph - adults). In most species, the female should feed on blood, so that the next generation of eggs can fully develop in the ovaries. Males usually feed on the nectar of plants, except only males of tsetse flies and the stable fly, which feed on blood.

Mosquitoes (Culicidae) are blood-sucking insects. Thin female proboscis can penetrate directly in the capillaries. Mosquito larvae are developed in water receaving breathing oxygen through a siphon. It is attached to the surface of the water. In the mosquito family, there are three main famely - Anopheles, Culex, Aedes, spread worldwide (Fig. 20.8).

Eggs of Anopheles mosquitoes differ from Culex and Aedes eggs. Anopheles lay their eggs randomly on the water surface. Each egg is bordered by a concave belt and with swimming cameras. Eggs of Culex do not have chambers and are laid on water surfase by groops. Eggs of Aedes are laid on drying soil.

Larvae of Anopheles have one pair of breathing holes in the penultimate joint and placed horizontally on the water surface. Aedes and Culex larvae have respiratory siphon as the penultimate joint of the tube and are arranged angularly in the water, attaching a siphon. In the pupae Anopheles breathing tubes are conical shape, while the Culex - cylindrical.

Adult mosquitoes have differences in the structure of appendages of the head, the color of wings and landing. In the female Anopheles the palps are approximately equal in length to the proboscis, while in Culex - several times shorter than the proboscis. In Anopheles males the mandibular palps are club-shaped thickening at the end and the length is equal to the proboscis, while in Culex the club-shaped thickening misses, and palps are longer than the proboscis. Anophelex in the middle of the wing have dark spots, which Culex have no. Anopheles mosquitoes keep the abdomen raised at an angle to the surface when landing, whereas Culex mosquitoe's body is bent, the abdomen is inclined to the substrate or parallel to it.

Anopheles mosquitoes are the definitive hosts and vectors to specific malaria parasite - Plasmodium falciparum. Pathogen is transmitted to a human by a specific inoculation. Female's oral apparatus is of piercing-sucking type (blood supply), in a male - sucking mouthparts (feed on plant juices). Anopheles mosquitoes are found near human dwellings (non-residential construction, near water). Females begin to suck the blood after

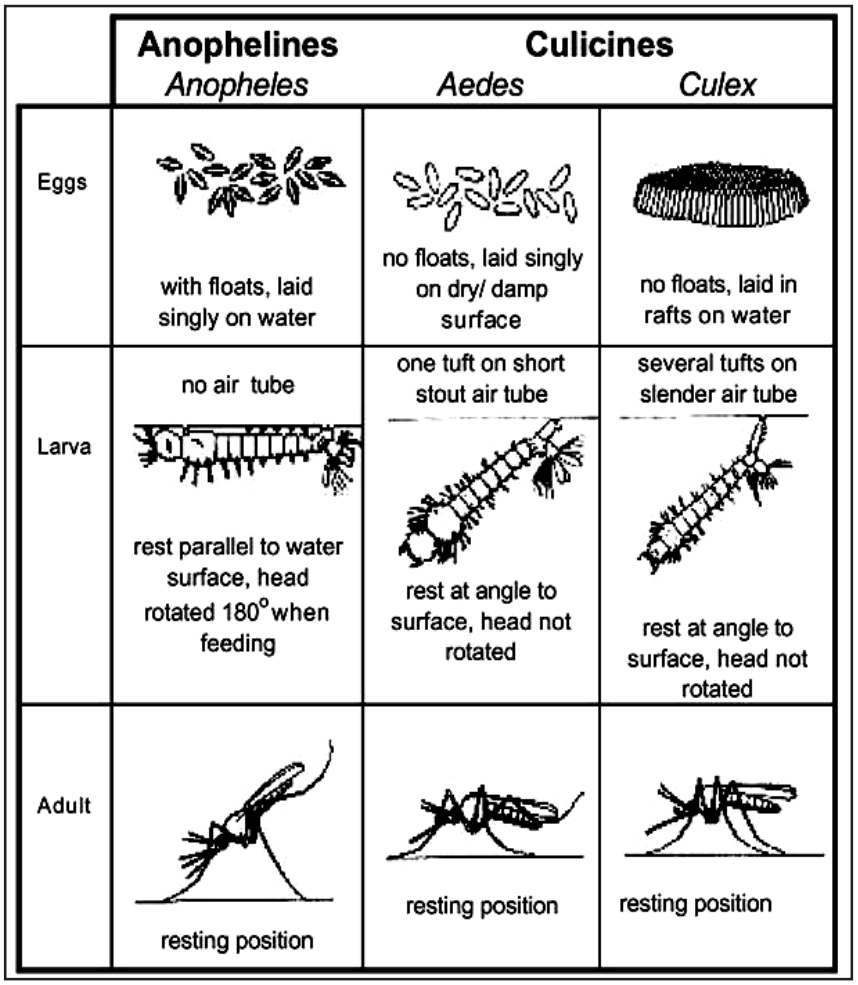


Fig. 20.8. The cycle of development of mosquitoes (Culicidae) (by telmeds.org).

mating since the eggs are not developed without blood. Time of sucking is 0.5-2 min, and then they fly to dark places to digest food for 2-12 days. In spring and summer after a single blood sucking the eggs are formed in the body. After eggs are matured the female migrates to the pool, laying eggs on the fly, or on aquatic plants. In autumn the blood in female is used to form fat, and eggs are not developed. This allows the female to spend the

winter in basements, cellars. In spring the females who survived the winter lay first generation of eggs. After sucking the blood spring and summer females lay eggs later. Having laid eggs, the females again fly in search of food (in one season may be several generations). Anopheles mosquitoes in tropical regions are also specific vectors of lymphatic filariasis (Wuchereria bancrofti, Brugia malayi). Culex mosquitoes are vectors of a specific Japanese encephalitis virus, West Nile, as well as pathogens of wuchereriasis and Brugia filariasis. Aedes mosquitoes maintain the circulation in natural foci of yellow fever virus, dengue fever, Haut-Nyong-Nyong fever, agents of filariasis (Brugia filariasis, wuchereriasis).

Repellents and mechanical devices are used for an individual protection against mosquito bites. Fighting mosquito is most effective in aquatic life stages - larvae and pupae, when pits and still water channels are filled with sand. Insecticides can be used to process separate reservoirs with a high content of larvae and pupae and crowded places with adult mosquito stages (animal houses, barns). Biological control measures in conjunction with irrigation and drainage are effective as well. So, in the Caucasus the number of mosquitoes was reduced due to reclamation and fish breeding eating mainly larvae of Diptera.

Black flies (Phlebotomidae) are small (1.2-3.7 mm) blood-sucking dipterous insects with yellowish, brownish or gray body color. They have strongly projecting thoracic hump, wings and body is covered with hair bristles. Black flies lay their eggs in burrows of rodents, where there is a lot of organic matter and high humidity. The larvae are developed about two months, and then pupate, then adult insects appear in 10-12 days. They eat in first hours after sunset. Black flies fly low over the ground with frequent landings. Black flie bites are painful, cause itching with a local inflammatory response. When multiple bites the people are deprived of sleep, the temperature may increase, overall health deteriorates. Black flies are specific vectors of leishmaniasis. The virus of pappataci fever is transmitted transovarially. Repellents and nets are used for personal protection. The fight against mosquitoes is conducted using insecticides.

House flies (Muscidae) are large insects which size is from 6-8 mm to 18 mm. The development comes with complete metamorphosis. House flies feed on leftovers, rotting fruits, vegetables, animal manure. Typical representatives of these flies are Musca domestica, Musca sorbens, Muscina stabulans, stable fly (Stomoxys calcitrans), tsetse fly (Glossina palpalis, G. morsitans). These flies act as non-specific, mechanical carriers of pathogens of gastrointestinal infections (dysentery, typhoid, cholera), tuberculosis, leprosy, diphtheria, and helminth eggs and protozoa cysts.

The stable fly, tsetse fly are blood-sucking (both female and male). The stable fly can participate in spreading of zoonotic infections (tularemia, plague, anthrax, brucellosis). Tsetse flies act as specific vectors of African trypanosomiasis pathogens.

Flesh fly (Sarcophagidae) is presented by the gray meat fly, wolfarth fly and other species. These are large (9-24 mm), viviparous insects with characteristic strips, checkers pattern, dark spots on their body. The larvae are capable to move within the body. Pupation occurs in the environment, and adult forms have free habit of life. A gray blowfly is developed on corpses of animals, less - in feces of humans. Larvae of a wolfarth fly are developed in wounds and cavities of animals and a human body causing severe damage to tissues and organs. Flesh flies can be carriers of gastrointestinal infections, and larvae are agents of myiasis. Repellents are used to prevent tissue myiasis.

CHAPTER 21. POISONOUS LIVING ORGANISMS AS AN ECOLOGICAL PHENOMENON

Among fungi, animals and plants that live on Earth, there are many species, which are called poisonous. However, toxicity as a universal phenomenon in nature should be considered more widely. It is one of the most important mechanisms in struggling for existence. Poisons produced by living organisms, are used by the latter in interspecific interactions. Substances involved in these interactions and benefit the body-producer, are called allomans. These include the toxins produced by fungi – mycotoxins, by plants - phytotoxins and by animals - zootoxins.

An ecological approach to the problem of toxicity is primarily a general biological approach, which allows to link together the features of biology of the species of animal or plant with the specific chemical structure and mechanism of action of toxins produced by them. Despite the advances in the study of myco-, phyto- and zootoxins the number of species studied experimentally toxins is small. In contrast to animals the vast number of plants uses alomancy solely to protect against phytophagous animals. The traditional view on poisonous plants is limited only species dangerous to human, domestic and farm animals. Poisonous species include a relatively small number of species, many of them are related to medicinal plants. In fact, the plants which are relatively harmless to a human, can become toxic to insects, birds or fish. Even a rough list of plants with insecticidal properties, has over 1,000 species, most of which is still poorly studied.

21.1. POISONOUS FUNGI

In nature, there are over 80 thousand fungi. Mushroom poisoning occurs due to toxic metabolites - mycotoxins which are ingested during a meal, the use of drugs (ergot) or self-medication (fly agaric, pale phalloides). Morphologically fungi are divided into micromycetes and macromycetes.

Macromycetes are a group of higher fungi, which differ in their taxonomic position, micromycetes are all other fungi that are microscopic in size. Despite the common misconception about the deadly poison of mainly macromycetes, toxicologically the most dangerous and numerous species composition are micromitcety causing severe food poisoning.

Among the best known microscopic fungi are aspergillus producing aflatoxins that selectively affect the liver and inhibit protein synthesis, causing the formation of necrosis. At an acute poisoning aflatoxin B_1 causes the development of necrotic lesions in myocardium, lung, kidney and spleen. Poisoning occurs by eating contaminated food. The main symptoms of poisoning are: lethargy, lack of appetite, loss of coordination of movements, convulsions, paresis, loss of body weight and other. Specific symptoms of acute aflatoxicosis are multiple hemorrhages, edema, dropsy, in a certain-ryh cases develop jaundice coagulopathy.

Micromycetes of Fuzarium order produce more than 40 mycotoxins belonging to the sesquiterpenes. Trichothecene mycotoxins inhibit protein synthesis and nucleic acid and damage lysosomes of epithelial and hematopoietic cells, causing their death. Typical is poisoning by “drunk bread”, which is caused by contamination of grain and flour by Fuzarium graminearum. After 30-60 min, vomiting, abdominal pain, diarrhea, weakness, a feeling of heaviness in the limbs, stiffness of gait occure. In a day severe headaches, dizziness are marked. Depletion, loss of vision, mental disorders are observed if “drunk bread” is consumed for long.

Fungi ergot affects more than 150 species of wild and crops of cereals. The ergot sclerotia contain mycotoxins of ergotamine ergozin et al., causing spasm of smooth muscle of blood vessels and the uterus, reduce the effect of epinephrine and serotonin, have the hallucinogenic effect, are capable of stimulating the respiratory center, to reduce blood pressure. Poisoning is caused by ingestion of ergot sclerotia, together with the grain and flour. The main symptoms of ergot poisoning can occur in 2 forms: gangrenous (“gangrene”) and convulsive (“evil cramps”). The main symptoms of poisoning with gangrenous form are: acute pain and burning sensation in the extremities; development of dry gangrene (up to rejection of soft tissue or whole limbs - in areas of articular joints). The main symptoms of poisoning during the most severe convulsive form are: mental

disorders arising in 2-3 weeks, in severe cases on a third day; nausea, vomiting, diarrhea, cramping, abdominal pain; insomnia, stupor, topical painful spasms alternated with epileptiform seizures. First aid in poisoning by mycotoxins includes gastric lavage suspension of activated charcoal in 2% sodium hydrogencarbonate solution, giving laxatives.

Prevention of mycotoxin provides monitoring over food products: withdrawal of food suspected in contamination with mycotoxins. Mycotoxins are chemically highly stable compounds and thermal treatment of products does not lead to their inactivation.

Macromycetes are divided into edible, conditionally edible, almost inedible and poisonous with subgroup of deadly poisonous.

Edible fungi can be eaten without any special cooking. Edible mushrooms are rich in vitamins (A, B_1, B_2, C, D and PP).

Conventionally edible are fungi that after proper cooking are suitable food. Gyromitra ordinary contains a gelvellov acid having hepatotrophic and hemolytic activities. Gelvellov acid can be easily neutralized at transition to the broth during brewing or prolonged drying (1.5-2 months). Fatal outcome after consuming the common line is observed in 30% of cases. Paxillus involutus slim contains a number of quite dangerous toxins, including muscarine, accumulating carcinogenic compounds and specific protein antigens that change the blood composition. Its picking is forbidden by sanitary regulations. Practically inedible mushrooms are not consumed.

Deadly poisonous mushrooms are pale toadstool, amanita, etc. In the body of pale toadstool 2 groups of mycotoxins are contained: amanitin - a poisonous, but slower acting, and phalloidin. The latter mainly influence on liver, hitting the endoplasmic reticulum and the cell nucleus hepatocytes, fallolizin causing lysis of hepatocytes and blood cells. Poisoning occurs when consuming the pale toadstool in food (normal taste). Heat treatment does not eliminate the toxic effect. After 1-2 days an uncontrollable vomiting, intestinal cramps, muscle aches, unquenchable thirst, choleriform diarrhea (often bloody) appear, jaundice and liver enlargement, pulse weak, thread may occur, blood pressure is lowered, a loss of consciousness. As a result of toxic hepatitis and acute cardiovascular disease fatal outcome happens in most cases.

Death-cup (red, pantherina) comprise muscarine muscaridine, choline, betaine and other poisons. Toxicity is mainly determined by the action of muscarine and muscaridine, stimulating M-cholinoreactive autonomic nervous system. Basic poisoning symptoms are developed after 30-40 minutes (less after 2 hours.): nausea, vomiting, abdominal pain, increased flux and salivation, lacrimation, dyspnea; constriction of the pupil; in severe

case - diarrhea, weakness, decreased blood pressure, heart rhythm disturbances, convulsions, collapse and comatose state is possible.

First aid in poisoning by macromicetes includes gastric lavage with activated charcoal, giving laxatives, assigning a 1% solution of potassium permanganate. In order to avoid a strong impact on the gastrointestinal tract and liver tissue by fungi and corrosive extractives consuming mushrooms without prior heat treatment is not recommended. Salting of fungi by cold method is undesirable. It is forbidden to trade salted mushrooms mixtured of different species. Human poisoning not only by poisonous, but also edible mushrooms becomes now of a first importance. This is due to the fact that a person can eat old edible mushrooms, in which toxic products can be formed by decomposition. Mushroom picking in bushes along roads with heavy traffic poses a risk to human. The edible fungi may accumulate heavy metals emitted with the exhaust gases of traffic.

21.2. POISONOUS PLANTS

Poisonous plants are those that produce phytotoxins, even in small quantities causing the death of human and animals. However, this definition contains a well-known measure of convention. For example, clover when growing only in a mild winter (January isotherm above + 5° C), accumulates in young shoots significant amounts of cyanogenic glycosides. Plant poisons have been used as therapeutic and preventive agents for many diseases for a long time. Current scientific pharmacopoeia recommends more cautiously relate to a curative action of phytotoxins, causing many side effects, especially in overdose. Poisonous plants consist of not more than 1,000 species among many species of flora, most of which are angiosperms. Mainly they are plants of southern regions and the highlands. Thus the arid flora comprises up to 70% of all births poisonous plants. There are different classifications of poisonous plants based on the specifics of composition or the toxic effect of biologically active substances. Among poisonous plants following are distinguished: definitely poisonous plants, with a subgroup of toxic, and conditionally poisonous (toxic only in certain localities or improper storage of raw materials, enzymatic action fungal microorganisms).

21.2.1. POISONOUS ORGANS OF PLANTS

Plant toxins can concentrate both in all parts of the plant, and in the specialized organs. There are also examples of narrow localization of phytotoxins. For example, many Rosaceae fruit cotyledons contain amygdalin giving them a bitter taste. When amygdalin is decayed, prussic acid with characteristic odor of “bitter almonds” is formed. Its presence in

cotyledons protects juvenile seedlings of almond, peach, apricot, plum, cherries from eating by animals. Amygdalin presents in fruits and bird cherry, laurel, apple, etc.

Seasonality of toxic substances is determined by operation characteristics of various plant organs during the annual cycle. In storage underground organs maximum toxins are concentrated in the winter period, and in above-ground parts - during flowering period. In some plants unripe fruits and seeds are poisonous (poppy, mustard, nightshade, alder buckthorn). But most of fruits is more toxic after ripening. The toxic properties of the same plants are different in effects on different groups of animals. Toxic to human belladonna is completely harmless to rodents, canines, hens, thrushes and other birds, but causes poisoning of ducks and chickens. Poisonous berries of a lily of the valley does not cause poisoning for foxes and are used by many canids to exempt from helminthes. Poisonous plants are the cause of human and animal poisoning. Notably the poisoning of children occurs by eating an attractive fruit, roots, bulbs, stems. As a special form the so-called drug poisoning should be considered if used incorrectly and overdose drugs from plants. Inhalation of poisonous plants causes the toxic effects. By direct contact with many plants the damage may occur to the skin and mucous membranes as strong allergic reactions. Sometimes poisoning by plant-based foods is associated with consumption of honey contaminated with poisonous pollen, as well as by milk and meat after eating by animals of toxic plants.

21.2.2. TOXIC SUBSTANCES AND THEIR MECHANISMS OF ACTION OF PLANT POISONS

There are different groups of poisones depending on chemical nature of the compounds. The most important of which are as follows.

Alkaloids are nitrogen-containing organic bases, in majority with a heterocyclic structure. The selectivity of action of alkaloids in various systems and organs of a man can allow them to be used as medicine. Alkaloids are usually colorless crystalline compounds, bitter taste and are practically insoluble in water but soluble in organic solvents (ether, chloroform, benzene). Salts of alkaloids, in contrast, are very soluble in water but not soluble in organic solvents. The most known alkaloids are nicotine, morphine, ephedrine, colchicine, etc.

Organic acids play a crucial role in metabolism of the plant. They are used in the synthesis of amino acids, saponin, alkaloids, steroids, etc. There are following group: aliphatic, alicyclic and aromatic organic acids. Among known aliphatic acids are formic, acetic, isovaleric having a pungent odor. Malic acid and citric acid are present in all plants. Out of aromatic

acids benzoic should be indicated, included in composition of essential oils, balms; gallic acid presented in tannins and caffeic acid. Acyclic and quinic acid are contained in blueberry, cranberry and coffee.

Lipids is a heterogeneous group of substances soluble in organic solvents. The composition of lipids is fat, phospholipids, sterols, waxes and other. Liquid oil is divided into three subgroups: non-drying (olive, almond, castor oil), semi-drying (sunflower, cottonseed, corn), and drying (flax, hemp). Non-drying oils are used for preparation of injectable solutions of sex hormones, camphor as laxatives. Semi-drying oils are used for preparation of ointments, oil extracts; corn oil is used for prevention of atherosclerosis. Drying oils are used for preparation of ointments for treatment of burns, the raw material for synthesis of prostaglandins. Terpenoids are oxygenated terpene derivatives, hydrocar-bons consisting of isoprenoid units (S5N8) associated usually as "head to tail".

Terpenoids of essential oils provide aseptic and antispasmodic action. Essential oils are often used as an expectorant. They have antitumor and cytotoxic effects. Antitumor activity is inherent to cucurbitacisn contained as glycosides in representatives of the family Cucurbitaceae and Cruciferae figwort.

Steroid (heart) glycosides are cyclopentanpergidro-fenantren derivatives. They are divided into 2 groups: cardenolides and bufadienolides. The largest number of plant species containing cardiac glycosides belongs to the family Ranunculaceae, Cruciferae, Liliaceae, figwort et al. Cardiac glycosides possess cardiotonic effect, increase myocardial contractility and excitability, but in large doses are cardiac poisons. Cardenolides and bufodienolidy are also found in animals and are part of the toad venom.

Saponins occur as steroids containing 27 carbon atoms per molecule. Aqueous solutions of saponins with shaking form a stable foam. Saponins have a bitter taste pungent, irritating the mucous membranes and reflex excitation of a vomiting center, increase the secretion of bronchi. Saponins are almost not absorbed in digestive tract, but getting into the blood, cause paralysis of the central nervous system, and hemolysis.

Flavonoids are phenolic compounds, combined by total composition structure C6 - C3 - C6. Flavonoids are white crystalline compounds of white (catechins) yellow (flavones), orange (chalcones), purple (anthocyanins) and other colors. Most flavonoids are found in a variety of glycosides and possess a wide spectrum of biological activities (antiradiation, antioxidant, anticancer, antispasmodic, hypotensive, estrogen, etc.).

Tannins are high-molecular polyphenols. They are found in many plants, especially in dicotyledons (bean, myrtle, Rosaceae). In the process of

tanning the chemical interaction of phenolic groups of tannins with collagen molecules occurs, resulting in proteins acquiring resistance to moisture and microorganisms. Tannins have astringent, bactericide and tanning effect.

Coumarins are oxygen-containing heterocyclic compounds, derivatives of benzene-alpha-pyrone. They are widely distributed in plants (more than 200 compounds). Coumarins have antispasmodic, anticoagulant, coronary vasodilating and photosensitizing effect. Bishydroxycoumarin - vitamin K antagonists.

Antrohinony are a group of anthracene derivatives, which are represented by antrohenonom or its reduced form. Many antroglycosides increase peristalsis of the large intestine that causes their laxative (senna leaves, bark and fruit of alder buckthorn). Some derivatives of antrohinonov cause a decrease in hemoglobin and red blood cells, disrupt the function of liver and kidneys.

21.2.3. POISONOUS HIGHER PLANTS

Among the representatives of the plant world the largest poisonous part refers to flowering plants. There are poisonous club mosses and horsetails, ferns, gymnosperms and angiosperms.

Club mosses are evergreen perennial herbs, rarely shrubs. The medical importance has moss Baranez (Licopodium silago) - evergreen herbaceous perennial of 10 - 20 cm height. Poisonous is aboveground part of the plant. It contains toxic alkaloids: selagin, klavatin, lipokodin, nicotine, which possess neurotropic activity. Selagin narrows the pupil, causes vomiting, muscle tone decreases, inhibits breathing in toxic doses. Poisoning occurs when eating grass (chewing by children). The main symptoms of poisoning include nausea, vomiting, headache, numbness language of gravity of the whole body. In severe cases, it may cause atrial cardiac arrhythmias, syncope. First aid for poisoning is gastric lavage, appointment of activated carbon, in vomiting - swallowing ice pieces.

Horsetails are spore perennial herbaceous plants. Stems are high, erect, jointed, ribbed, grooved, solid, green, or brown, hollow inside. Spore-bearing strips are placed more often on the top of the main shoot. Toxic is the whole plant, which may contain toxic alkaloids (palustrine), saponins (equivisetonin) flavone glucosides. Horsetails exert their effects after 40-87 days. Symptoms of poisoning: dilated pupils, increased aggressiveness, paresis and paralysis of muscles. In cattle eating horsetail the digestive disorders, general weakness, rapid emaciation are marked. First help is cessation of feeding on poor quality hay.

Ferns are the most ancient group of higher plants. There are about 10 types of toxic ferns. The medical importance has Dryopteris filixmas. This

is a plant of 40-100 cm height. Rhizome is toxic, which contains filiksovaya and flavospidinovaya acid, aspidinol, albaspidin. Extracts from the dried rhizomes have anthelmintic effect, paralyzing the tapeworms. The poisoning occurs resulting in drug overdose of a male fern and in self-medication. Symptoms of poisoning include nausea, vomiting, diarrhea, abdominal pain; headaches, dizziness, visual disturbances. With significant toxicity complications are possible such as jaundice, atrophy of the optic nerve. First aid for poisoning: gastric lavage with aqueous suspension of activated carbon, saline laxatives, hot drink.

Gymnosperms which have a toxic effect, are described in classes Gnetopsida and Pinopsida.

Gnetopsida are dioecious low leafless shrubs, shoots ribbed, evergreen. They contain toxic alkaloids - ephedrine, pseudoephedrine. Ephedrine stimulates the a- and â-adrenergic receptors, increases norepinephrine release from sympathetic nerve endings.

There are about 20 species of gnetalians, a typical representative is Ephedra distachia. Symptoms of poisoning: vomiting, sweating, skin rash, increased blood pressure, respiratory disorder. First aid for poisoning includes gastric lavage suspension of activated charcoal in 2% sodium hydrogen carbonate or 0.1% potassium permanganate solution.

Conifers (pine, spruce, fir, larch, juniper, etc.) are common in almost all natural regions. They are characterized by presence of terpene compounds (resins) in all parts of the plant. Resins of conifers have phytoncide value (bakteriotsidnoe, protistotsidnoe). Conifer resin is a solution of resin acids in the essential oil - abietic, L-pimaric, D-pimaric. Lesions of human by conifer resins may occur during mechanical and chemical processing of wood. Symptoms of poisoning include nausea, vomiting, severe salivation, abdominal pain, diarrhea, frequent urine. First aid for poisoning includes gastric lavage 0.2% potassium permanganate, giving laxatives, washing of the skin.

Angiosperms are the most numerous group, which includes toxic representatives having various effects on different groups of organisms. It contains more than 400 species of poisonous plants. Typical poisonous plants of the dicotyledonous and monocotyledonous class growing on the territory of our republic are as follows.

Cicuta virosa is entirely a poisonous plant, especially the rhizome. Toxic properties are due to cicutotoxin, which is rapidly absorbed from the digestive tract, giving a convulsive effect on the central nervous system. After 15-20 minutes of poisoning, headache, nausea, vomiting, abdominal pain appears. Death may occur from respiratory failure on background of acute cardiovascular insufficiency.

Conium maculatum is a high biennial (60-180 cm) with an unpleasant mouse odor. Toxic is the whole plant, but the most toxic substances are contained in unripe fruit. It contains alkaloids coniine, conydrine. Poisoning occurs with stalks in the mouth, by eating seeds. Nausea, salivation, dizziness, impaired swallowing and speech, skin blanching occurs. The excitation is accompanied by convulsions and passes into CNS depression.

Solanum nigrum is a shrub with a climbing long stem. Grass and unripe fruits are poisonous. It contains a poisonous alkaloid solanidin presented as glycoalkaloid solanine. Solanine has irritating effect on mucous digestive tract, inhibits the activity of CNS. Poisoning occurs when eating unripe fruit.

Datura stramoncum is completely a poisonous plant and its seeds. It contains tropane alkaloids atropine, hyoscyamine, scopolamine. The main poisoning symptoms: dry mouth, swallowing disorder, bloody diarrhea, dysfunction of the central nervous system.

Black henbane (Hyoscyamus niger) is a high biennial plant (1 m), with large sinuate-pinnatifid leaves. The whole plant and seeds are toxic. Toxic is honey collected from flowers of black henbane. It contains alkaloids: hyoscyamine (atropine), scopolamine. Poisoning occurs when eating oily seeds (by children), and an overdose of drugs, proceeding as acute psychosis with hallucinations

Papaver somniferum is completely a poisonous plant. Maximum poisonous substances are contained in immature boxes (latex). It contains more than 20 alkaloids - morphine, codeine, papaverine, protopine, etc. Morphine is a narcotic analgesic, has a strong analgesic effect, but when used repeatedly addiction is developed (drug addiction, morphinism). *Greater celandine* (Chelidonium maius) contains alkaloids sangvinorin, chelerythrine, chelidonine, which possess weak narcotic and bactericidal action. Sangvi-norin in toxic doses causes convulsions.

Beister Buttercup (Rahunculus scleratus) - aboveground portion of the plant is poisonous and comprises lactones (rahunculin, protoanemonin) and flavonoids (kaempferol, quercetin, etc.). The juice of the leaves can cause burning of the skin and mucous membranes. In severe cases, it can damage the central nervous system (tremor, convulsions, dizziness).

Cruciferous Erysimum cheiranthoides – the aboveground part of the plant is poisonous. Toxicity is due to steroid glycosides - erisimin, ericanosid, etc. Glycosides of jaundice enhance myocardial contractility and excitability, lower sinus automaton and conductivity. In mild poisoning form arrhythmia is observed, and in severe cases - nausea, vomiting, cyanosis, dyspnea, bradycardia followed by tachycardia, arrythmia.

Leguminous Melilotus officinalis is a high plant with small ternate leaves. The aboveground part of the plant is poisonous. It contains an aromatic lactone - coumarin. When the hay is decayed bishydroxycoumarin is formed having anticoagulant properties.

Cannabis sativa is a dioecious plant, in which young female tops, flowers and seeds are poisonous. It contains cannabinol, cannabidinol et al. The poisoning occurs by ingestion and smoking cannabis preparations (hashish, marijuana). With long-term use the mental disorders, dementia and degradation of an individual are developed.

Ledum palustre - the aboveground part of the plant is poisonous. Plant extracts toxic volatile oil, which comprises ledol, cymene, etc. Poisoning can occur when injesting rosemary, inhalation of essential oil vapors, as well as through skin and mucous membranes. There is a weakness, drowsiness, nausea, vomiting, sweating, lowering blood pressure, tachycardia. In severe cases, respiratory failure and suffocation occurs.

Euphorbia Valdstena is a high perennial (40-80 cm). The whole plant is toxic, but most - the roots. It contains triterpenoids (eufol, euforbol), diterpenoids and flavonoids. In contact with skin the milky sap causes severe inflammation, abscesses; it is dangerous if effects the eyes. If seeds are ingested, fatal outcome is possible.

Tanacetum vulgare is a high perennial (60-150 sm) with woody stems. The aboveground part of the plant and a maximum of inflorescences is poisonous. Plant extracts essential oils, which include bicyclic terpene ketones and thujone. When inhaled, it causes nausea, vomiting, diarrhea. When injested, kidney disease is marked, in CNS - hyperflexy followed by depression.

Conrallaria majalis - all plant and its fruit is poisonous. It contains saponin, konvallarin and cardiac glycosides: konvallamarin, konvallotoxin. Poisoning can occur by eating lily berries, overdosage of drugs.

Colchicum autumnale is a beautifully blooming perennial plant (15 cm). Leaves are broadly linear, long, shiny, fleshy. Flowers are purple-pink, large. The whole plant is toxic, but mostly tubers and seeds. It contains alkaloids colchicine, coholin. Poisoning is developed within 3-6 hours as nausea, vomiting, diarrhea, oliguria, heart arrhythmia. Possible cramps, low body temperature, breathing difficulty.

21.2.4. RATIONAL USE AND PROTECTION OF POISONOUS PLANTS

Poisonous plants can be valuable medicinal raw materials. Poisonous plants are useful components of the natural ecosystem. Catastrophic reduction of the gene pool of flora as a result of human impact forces to create special plantations for breeding of some poisonous plants. The

protection and management of the whole variety of poisonous plants is relevant and is of great economic importance.

21.3. POISONOUS ANIMALS

There are about 5 thousand species of poisonous animals. There are aquatic and terrestrial inhabitants, widely distributed around the world. Most often they are found in tropical and subtropical climates. Biological toxicity is not absolute but of relative character, since poisons are chemical factors involved in interspecies relationship. They can be used as a scare substance; as substance covering the escape (ink liquid cephalopods); as substances that serve as a lure to attract females, etc. Depending on special venom glands of animals, devices for removing poison and its injection into the victim, and other features their toxicological classification has been offered.

Primary-poisonous are animals that produce poisonous secret of special glands, or have toxic products of metabolism. Typically, the primary toxicity of poisonous animals is a specific character and occurs in all individuals of a given species. Primary-poisonous animals consist of dinoflagellates, coelenterates, some types of spiders, scorpions and others.

Active-poisonous animals have specialized apparatus.

Armed active-poisonous animals have a special wounding device that allows the poison secretion to be injected into victims body parenterally, that is, bypassing the digestive tract. These animals are many poisonous coelenterates, molluscs, arthropods, fish, reptiles.

Unarmed active-poisonous animals do not have a wounding device (amphibian skin glands, anal glands of insects). The toxic effect comes in contact with covers of a victim body.

In passively-poisonous animals the poisonous metabolites are produced in the body and are accumulated in various tissues and organs (digestive, genital), such as in fish, tailed amphibian, mollusks, insects.

Second-poisonous are animals accumulating exogenous poisons and exhibiting toxicity only when taking them for food (elasmobranch shellfish, which accumulate in the body the poison dinoflagellates, insects that feed on poisonous plants).

Passive-poisonous and secondary-poisonous animals are dangerous only for digestive tract.

21.3.1. FEATURES OF POISONS ANIMALS

Animal poisons are called zootoxins (Greek zoon -. animal, toxicon - poison). The zootoxinology is the science that studies the chemical nature and mechanisms of action of animal poisons in the body of an animal or human.

According to their chemical structure zootoxins are very diverse. Their composition can include aliphatic and heterocyclic compounds, alkaloids, steroids, non-enzymatic polypeptides, enzymatic proteins. These "true toxins" are not found in the recipient. Another group of zootoxin components are formed by chemicals occurring in the recipient. This is acetylcholine, histamine, catecholamines, indole derivatives, various enzymes and their inhibitors. In toxicometry of zootoxins the most important characteristic is their toxicity - a chemical property in minimum amount to cause pathological changes that lead to violation of fundamental processes of life of the organism and lead to its death. By the nature of physiological effects on the living organism the zootoxins are divided into: neurotoxins that act mainly on nervous system; cytotoxins, causing tissue damage cells; dermatoxins causing skin damage; hemorrhaging violating the permeability of blood vessels; hemolysin destructing red blood cells.

Human poisoning by animal poisons is influenced by many factors. Firstly, the composition of the venom. Predominance of one or another component will determine the clinical picture of poisoning: or the type of nervous system, soft tissue necrosis, vascular paralysis, hemolysis of erythrocytes, or combinations thereof. Second, the poisoning depends on place of damage. The closer the damage to the central nervous system, the harder the poisoning affect. Thirdly, depending on season of damage. After hibernation, molting the animal venom is more toxic. Fourthly, on a mental condition of a patient. In unbalanced patients with labile nervous system the poisoning is harder than in those with a stable nervous system.

21.3.2. POISONOUS COELENTERATES

In the hydroid class poisonous jellyfish Goniomus are considered, occurring in the waters of the Pacific Ocean and Physalia common in tropical and subtropical regions of the world ocean. Among Scyphozoa poisonous are jellyfish (hironex, hiropsalmus), semaeostomeae (cyanide, Pelagia, hrizaora) found in the warm waters of the Indian, Atlantic and Pacific Oceans and Rhizostoma jellyfish (rhizostoma, stomolofus) living in the Black and Azov seas. In the class of coral polyps are poisonous horn corals and gorgonian (found in the waters of the Arctic and Antarctic), sea anemones.

The characteristic feature of coelenterates is the presence of stinging cells in the vial containing the poison. Its composition contains both cytotoxins and neurotoxins, the latter is characterized by a high specificity interaction with ion channels (particularly in sea anemones). The isolation poison is associated with lightning ejection of the thread from the ampoule

stinging cells. A human contacts with poisonous coelenterates while swimming, in analysis of the trawl, in divers. In lesions the redness is observed in the form of strips to form fine bubbles, accompanied by strong itching and burning that is caused by effect dermatotoxin. Therefore enteric cavity is called “sea nettles”, “sea wasps”. Semaeostomeae is particularly toxic, since the shock can damage muscle, to develop necrosis of soft tissue, respiratory failure, cardiac rhythm, short-term deafness and dumbness, agitation, delirium, hallucinations. Coelenterates poisons are used in experimental neurophysiology, for preparing antisera.

Prevention of poisoning is based on the use of wetsuits, to be careful when swimming in water, the analysis of the trawl. For treatment of skin dermatitis lubrication ointments containing alkali are recommended and symptomatic treatment of common signs of poisoning.

21.3.3. POISONOUS ARTHROPODS

Phylum Arthropods are the most numerous and consist of number of species. They are found in the classes of arachnids (spiders, scorpions), insects (wasps, bees, ants). Centipedes class is fully represented by poisonous animals.

Order Spiders. Poisonous spiders can be divided into two groups - with neurotropic and hematotropic poisons.

The first group includes bird spiders, widespread in Africa and Latin America. Poison apparatus is presented by glands and injuring devices - chelicerae. Most often lower and upper limbs are bitten. After a bite, a sting pain quickly weakens and symptoms of intoxication are developed (fatigue, lethargy, drowsiness, uncoordinated movement). After some time, the poison is excreted, so fatalities are rare.

The second group includes tarantulas and karakurts. Karakurt can be found in Southern Europe, Kazakhstan, Central Asia, Arabia, North and West Africa. Poison glands are located in the cephalothorax, ducts open into chelicerae. The poison contains hemorragin and neurotoxin. On a bite site there is pain, swelling, burning sensation, and pains in joints, bones and muscles. In 1-2 hours, the poison reaches the vital centers of the brain. The patient can not stand on his feet, at the slightest stress pain attacks are exacerbated, nausea, palpitations, dyspnea, dizziness. This is combined with the general excitement, impaired urination and defecation. Lethality reaches 2-4%. Tarantulas are common in Europe, Asia and America. Poison glands located in the cephalothorax, partially in cheliceral. The poison has cytotoxin and hemolysin. On a bite site the swelling, redness, pain, hemorrhagic blisters, flaking the skin appear. Then necrosis of the skin and subcutaneous tissue is developed. Deaths are extremely rare.

Scorpions are represented over 550 species. Scorpion poison glands are located in the rear part of the body, ending with the anal blade containing poisonous stinger. The poison contains primarily hemorrhagin and hemolysin with a small amount of the neurotoxin. On a lesion site a sharp pain as if a red-hot pin prick, redness, swelling, lymphangitis appear. Then there are the symptoms of intoxication (fever, palpitations, shortness of breath, nausea, headache, cramps in fingers and toes), in more severe cases - a paralytic condition of muscles. Liver, kidney, heart are damaged. Hemolysis is observed. Fatal causes are able.

Poisonous insects are represented mainly by Hymenoptera: bees, bumblebees, wasps, hornets, ants, but are also found in beetles (Colorado potato beetle) and Lepidoptera. Poison of Hymenoptera contains the enzymatic proteins, non-enzymatic polypeptides, biogenic amines and others. It has mostly neurotoxins. Bee and wasps poison are potent allergens, which dramatically complicates the clinical picture of poisoning.

The family Apidae includes bees, bumblebees.

Honey bees from ancient times are used by human to produce honey and other bee products. Working bees have poisoning apparatus which serves to protect the family from predators. The poisonous composition includes enzymes - phospholipase A2, hyaluronidase, phosphatases, toxic polypeptides (melittin, alamin), biogenic amines (serotonin, histamine, catecholamines). The chemical composition of a poison varies with the age of a bee. Even one bee bite is very painful, and the massive bite can lead to death. The clinical picture of poisoning depends on number of bites, their location, a functional state of the organism. As a rule, the local symptoms of poisoning appear (pain, swelling). If massive doses of venom penetrate into the body the internal organs are damaged, especially kidneys. Allergic reactions to bee poison are observed in 0.5-2% of people. First aid is to remove the sting out of the skin, wash out the affected skin with a solution of ethanol and ammonia. In severe cases it is necessary to seek medical help.

Bumblebee (ground, meadow, field and others) are large insects, the body color can be black, red-yellow or yellow. The body is densely covered with hairs. The chemical composition of their venom has not been studied. It is known that phospholipase A and B, histamine, acetylcholine, serotonin are contained in poison. Bumblebee sting has symptoms similar with bee poisoning (pain, swelling).

The family Vespidae includes hornets, wasps.

Hornets are insects that build their nests from paper, made by themselves. In our country a hornet Vespa crabro is spread – a large and 35 mm long insect. The head is yellow, chest is black, abdomen in the rear

half is yellow, with black spots. The poison structure includes phospholipase, hyaluronidase, toxic polypeptides, biogenic amines. Hornet bites cause local (pain, swelling, inflammation) and common (headache, dizziness, palpitations, increased body temperature, and others.) symptoms of poisoning. Hornets bite causes allergic reactions that require desensitizing therapy. *Wasp* is an insect, a female reaches a length of 15-20 mm and a male - 13-17 mm. The body color is black with yellow pattern and sparse golden hairs. It builds paper nests. Wasp biting the tongue or throat is very dangerous, often causing death. Wasps of Vespidae family visit the home of a man and food stalls. This causes the frequent clashes of people and insects. Wasp's sting is long, saber-shaped curved and without notches, much larger than that of bees. The composition of poison includes phospholipase A and B, hyaluronidase, histamine, serotonin, wasp peptide, kinin protein. The poison is predominantly haemotropic, whereas in bees is neurotropic. Being bitten by a wasp, the person feels a burning pain, at the site of venom inoculation the inflammatory focus appear. *Ants* belong to the Formicidae family and are widespread in the world. A typical representative is a Formica rufa. Size of females and males is 9-11 mm. Forest ants are predators. Poisonous organs of ants are not the same in all species. In some they are equipped with a sting, the others do not have pricking devices. They just spurt poison from their glands. Int *formicids* and other ants lacking a sting a basic active venom is formic acid.

Prevention of Arthropod bites of poisonous comprises personal protection measures, and the use of special sera and use of antidots (heparin)

21.3.4. POISONOUS FISHES

Depending on presence of poisonous glands, apparatus for administration of poison fishes can be divided into active-poisonous, passive-poisonous and secondary-poisonous. Active-poisonous fishes include groupers, stingrays (sea cat, giant stingray, bracken, etc.). They have poison glands, tools to damage the victim tissue, through which the poison flows into the wound (thorn-rays, spikes). Poisones causes severe pain, weakness, loss of consciousness, convulsions and respiratory failure is developed. Upon contact with Scorpaenidae fish (Sebastien perch), hyperemia, edema, lymphangitis appear at the site of injury in a man. The burning pain is accompanied (in 10-15 minutes) by total poisoning symptoms (decrease of blood pressure, muscle paralysis, occurrence of cardiac and respiratory insufficiency). Most fishes of the world ocean refer to the passive-poisonous (fugu, toby, hedgehog-fish, conger, moray eel, etc.). Toxic substances are contained in their internal organs, muscles, skin, etc. Many of them are toxic only in certain seasons of a year.

The most important passive-poisonous fish include a variety of compounds: tetrodontoxin similar to acting mechanism of non-proteinaceous neurotoxins dinoflagellates; sigdatoxin increasing the permeability of nerve membranes; hallucinogens (mullet sultanok) causing hallucination.

Secondary-poisonous may be very few species of fish which meat infected with bacterial toxins becomes a cause of poisoning.

Prevention of poisoning by active-poisonous fish is based on keeping personal safety precautions while swimming, undoing the trail net, working on a fishing factory, etc. Prevention of passively-poisonous fish is determined by knowledge of their characteristics, improved cooking.

21.3.5. POISONOUS AMPHIBIANS

Among amphibians there are only passively venomous animals. Skin and mucous glands are not only for breathing but also for protection against predators, because their secretion may be toxic. Its composition contains highly toxic compounds (batrahtoxin), analgesic peptides (dermofins), biogenic amines, cardiotonic steroids, hemolytic proteins. Some species of salamanders, Californian newt, a toad are poisonous. The secretion of skin glands of amphibian serves to defeat predators when released into the digestive tract or on open mucosal surfaces.

21.3.6. POISONOUS REPTILES

Among the representatives of reptiles the large group of species is active-armed poisonous animals. Poisonous apparatus of snakes comprises gland, excretory ducts and poisonous conductive teeth. Depending on structural features of a poisonous tooth snakes are divided into three groups: back-grooved (groove tooth is located on the back of the jaw); antero-grooved (tooth groove is located on the front of the jaw); poisonous snakes with canal-teeth (tooth has a channel situated on front of a jaw). *Back-grooved snakes* include Water snakes family. Typical representatives are African Boomslang, African boiga and gray tree snake, cat snake, snake-arrow, etc. *Antero-grooved snakes* include two families: Aspids and Sea snakes. Aspids are king cobra, which is the largest venomous snake in the world (up to 5.5 m in length); Indian and Central Asian cobra; Australian Taipan; glandular snake and others. The sea snakes include bicolor bonito, skipjack and spiral hydrophis, engidrinu ringed laticauda and others. They are found only in the Indian and Pacific Oceans. Snakes with canal-teeth also include viper snake. The viper snakes are an adder, a sandy viper, lebetina viper, viper Cape and others.

Annually about 1 million people suffer from snake bites, mainly in tropical and subtropical zones. Snake venom is a complex set of biologically active substances, which differ in members of various families. The poison of

asps and sea snakes contain toxic polypeptides (neurotoxins), blocking synaptic transmission in cholinergic neuromuscular junctions, causing the death from respiratory failure on background of lesions of the central nervous system. The poison of vipers and rattlesnakes contains a large number of gemorraginy, hemolysin and cytotoxins. Therefore, as a result of poisoning extensive hemorrhagic edema are developed caused by increased vascular permeability and impaired blood clotting system, extensive necrosis. The poison of some rattlesnakes has also neurotoxin, which greatly complicates the clinic poisoning. The temperature factor is of great importance in the snake venom poisoning: in heat environment the poisoning is more severe. Maximum toxic poison of snakes is at the age of 6-9 months to 1 year. After molting the poison toxicity is increased by 10 times. The degree of poisoning also depends on the size, sex snakes, amount of injected venom, bite depth, skin characteristics, features of victim's clothing. Increasingly severe poisoning and death is seen in women and children. General and local symptoms of poisoning depend on specific features of snakes. Prevention of poisoning by snake venom includes: be careful in meeting and working with snakes; application of monovalent ("Antikobra") and multivalent ("Antigyurza") sera; application of safeners (heparin, etc.)

21.3.7. PROTECTION AND USE OF POISONOUS ANIMALS

Protection of poisonous animals is carried out in two ways. Firstly, the protection of species useful for a human, which are the source of toxic substances (snakes, bees); pollinating the plants (bumble bees); predators or parasites, eradicating harmful insects (ants, spiders, wasps). Secondly, the protection of species making up various biocenosis and ensuring, along with other animals, their stability and ability to withstand to various external effects. In many countries around the world, along with the introduction of legislation aimed at protecting flora and fauna, the network of landscape protection areas and wildlive areas are increased. In addition, poisonous animals must be used rationally. This applies to animals kept in the Serpentarium, which poisons are used in scientific research, in medicine. Snake venom is used for preparation of snake serum as a hemostatic agent, for treatment of heart disease, asthma, sciatica. Medicaments based on snake venom possess analgesic (based on their analgesic non-addictive), anti-inflammatory actions and are used in neuralgia, myositis, polyarthritis. Long-term experience of specialized centers for study and keeping the poisonous animals and obtaining their poisons proves that if correctly organized there is no need for frequent catching of poisonous animals.

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