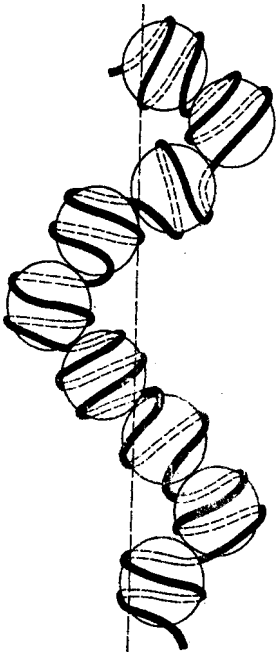

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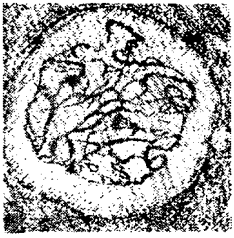

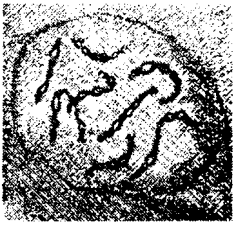

MEDICAL BIOLOGY

O.-Y.L. BEKISH

MEDICAL BIOLOGY

Translation from Russian by A.A.Bobr.

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Б 42 Medical biology: Textbook for students of higher educational establishments. Vitebsk : VSMU Press, 2003 - 346.p., 163 pic., 9 tab.
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In this textbook, the main divisions and aims of biology are described accordinary to life organization levels. The questions of human reproduction, bioethical aspects of genetics, tissue and organs transplantation, ability to have poison by living beings as ecological phenomena are considered. The material of textbook is backed by contemporary findings of medical-biological sciences. The interactions of different parts of biology are shown.

The textbook corresponds with typical educational plan and program, proved by Ministry of health care of republic of Belarus. It is designed for students of higher medical educational establishments.

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PREFACE.

Contemporary biology rapidly accumulates knowledge about fundamental and systemic mechanisms of living. 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 isn't only historical. Even now, in every day routine a man faces the biological aspects of his being. Human beings change the nature, but in the same time, the nature changes human beings. The pattern of these relationships reflects state of human health.

The content of this book corresponds with new program of medical biology and general genetics for students of higher educational establishments, which was proved by Ministry of Health Care of Republic of Belarus in 1997. Considering this, author decided to paid attention to medical aspect of material. Human studying is performed accordinary with life organization levels. It allows showing close relationship between biology and medical disciplines.

"Molecular – genetic life organization level" part is devoted to studying 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 life organization level" part analyzes cell as an open system with substances, information and energy flows. The particular attention is paid to cell theory value for medicine. The problems of cells proliferation are also discussed.

"Ontogenetic life organization level" part is directed on studying processes of living organisms reproduction, human reproduction, ethical and juridical aspects of human reproduction disturbances. Principles of heredity and diversity are written noting specific features of human being. Studying of developmental biology is directed to understanding of general principles of human ontogenesis, genetic, cellular, and systemic homeostasis mechanisms, bioethical aspects of tissues and organs' transplantation.

In "Population-Species life organization level" the features of humankind populations' structure, genetic polymorphism of humankind populations and genetical aspects of predisposition to various somatic diseases were described. The

problem of genetic load and its value for humankind were considered.

The "Biospheral life organization level" is devoted to anthropoecological problems, in particular, to differentiation of humankind into adaptive types. The biological and social aspects of human adaptation to living conditions were considered. The conditions "predpathology – pathology - compensation", as possible conditions of human being were discussed. The ecological aspects of parasitism were considered. The ability to have poison is discussed as ecological phenomena. The questions of etiology, pathogenesis and clinical pictures of poisoning were considered.

Suggested structure of material provides reaching the main aim of medical biology course – studying a human being as biosocial being with accent on its biological features. They are most important for formation of fundamental knowledge basement of students.

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

1.1. The biology as a natural science about the life.

The biology – is a science, which studies life as a special form of matter being having its own laws of existence and development. The subject of biology study is live organisms and their natural communities. Biology is a natural science as astronomy, physics, chemistry, geology and other sciences are. It is a complex science. It includes more than 50 disciplines. There are following among them:

- Morphological disciplines (anatomy, histology) describing 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 necessary condition for modern medicine progress.

1.2. The essence of life. The life organization levels.

What is a life? Many scientists have tried to answer this question. And it is still an aim of contemporary biology. Many hypothesis and thesis were generated to give an appropriate answer. However, everyone needs to have in mind that each theory, each hypothesis is a reflection of life position of definite scientist. For example, Karl Linney (1707-1778) suggested many new principles in biology (new biology nomenclature which is in use until now), but being a very faithful he accepted the world creation by god.

The contemporary view on life suggests that 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. One of most successful was given by J. Bernar: "Life is a function of proteins and nucleic acids interaction on Earth".

All modern views on a life origination based on two following statements: 1) Life weren't brought to Earth from outspace; 2) The living organisms weren't self originated.

In 1924 A.I. Oparin was first to consider all theoretical points about life origination. In his book "The origin of life", he presented the main principles

about life origin on Earth, about its evolutionary development. These principles were proved in following years. The process of life origination has three stages:

1) chemical – primary formation of simple organic substances on Earth.
2) prebiological – abiological synthesis of main organic substances.
3) biological – origination and evolution of simple biological systems.

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. V.M. Goldansky (born in 1923) suggested following definition of life: "The life is a form of polymer bodies (systems) being which are able to self replication in conditions of constant exchange of energy and substance with environment". The others 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 main signs of live, which can be described in following.

Discretion and integrity. The organic world is integral and discrete in a same time. It is integral because it is a system of related units. It is a 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 integral system.

Structural organization. Life mater is built out of same substances as inorganic matter. However, molecules of life matter are more complex. It is because of special order on a molecular level. The structural organization is a proper feature of life on an all level of its organization. The hereditary information is encoded by genes, but none gene act successfully outside of genotype. The integrity of proteins and nucleic acids provides life being on Earth.

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

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

Heredity and diversity. They are the important features of life connected with traits 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 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 which were absent in parents. If structure of nucleic acid have been changed, the new traits appeared from that can lead to organism die or to better adaptation to environmental conditions. The diversity gives matter for new species formation and evolution.

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

Irritability. It is a property of life, which provides contacts of organism with environment and surrounding organisms. In monocellular organisms, it is presented by taxises, in plants – by tropisms, in higher animals – by reflexes. With help of this, organisms selectively react on stimuli; they can get from environment necessary substances. Consequently, the metabolic exchange is closely related with it. The irritability is connected with chemical nature of life substrate.

Internal regulation and homeostasis. Each organism, being an open system, keeps main parameters of internal environment on a same level. It keeps homeostasis. Homeostasis is supported with help 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 study life processes on different levels. These levels are called life organization levels. There is a list of them.

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

Cellular level. Elementary structure of this level is a cell. Elementary event is cell division and cell development. On this level all organisms look kind of similar. The genetic information is realized in particular proteins on this level too. Protists cellular level coincides with organism level. This level dominated in Archey Era.

Ontogenetic level. Elementary structures are organisms. Elementary events are ontogenesis, differentiation and still unknown mechanism that direct all that processes. On this level, there is variety of life forms. Earth is inhabited by more than 3 millions species. Each species consist of organisms. Each organism presents elementary life unit. Nervous and humoral regulation provides constant state of internal environment and homeostasis. There is no life outside of organism.

Population level. Elementary structures are populations of any life species. Elementary event is directed changes in their genofond. Such changes lead to formation of new adaptation to changing nature. Accumulated adaptations and

adjustments result in new species formation on a base of natural selection. Population is 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, which are elementary events on this level.

Biospheral level. Elementary units on this level are biogeocenosis, whereas elementary evens are biogeocenosis upgrade to next level, to next well-balanced state. Biogeocenos is open system for 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 faces us a problem of environment protection.

Life matter on an Earth is presented by organisms. Each organism consists of lower organization levels and at the same time, it is a part of 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 molecular-genetic level, the discrete elements of prokaryotes, non-cellular life forms and eukaryotes are similar. Life 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 cellular level, we can say that cell of different organisms more similar than differ from each other. However, on 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 place among natural sciences.

In XX century, the biology became statistically based. The genetics, biophysics, molecular biology and others use mathematics calculation in their research. These researches pushed biology on a leading place among natural science. On a modern stage of humankind being, biology facilitates in formation of new agricultural biogeocenosis, which made a great impact on natural production. Now biology regulates relation of them with natural biogeocenosis. Agricultural biogeocenosis have to provide food supply for growing human population. In addition, we have to keep gentle balance in main biosphere processes to survive here on Earth. Not so far in a future, we can face food and oxygen deficiency, if contemporary population growth will be preserved for several decades. To fight it we have to limit reproductive strategy and discover new agricultural methods with higher outcome. The nature gives us all what we need to survive here. Negative ecological impact has feedback to a human. Humans will face changes in their genofond, stimulated by their industrial pattern of being.

1.4 The biology role in doctors training.

The biology is theoretic basement of medicine, that why it is important to study biology for future doctor. Morphological, biochemical, genetical and physiological disciplines give a basement 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.

Doctor's mind is formed on a base of cytology, genetics, molecular biology, anthropology, ecology and evolution theory. Doctors should keep in mind the consequences of industrial impact on environment. It is important to know cell pathology, especially proliferate cell ability, genetics, especially human hereditary diseases, ontogenesis, especially concept about defects of development, ecology, especially concept about adjustment disorders, parasitology, poisonous plants, animals and fungi.

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

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

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

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 firstly discovered by F. Miescher in 1869. However, scientists began to pay attention to the nucleic acids as a place of hereditary information storage only after J. Watson and F. Crick's works (1953). 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 transmitting 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 tree elements: an organic base, a phosphate group, a 5-carbon sugar. The base is bound to first carbon atom in the sugar and phosphate group is bound to fifth carbon atom in the sugar. Third atom of sugar always has a hydroxyl (-OH) group.

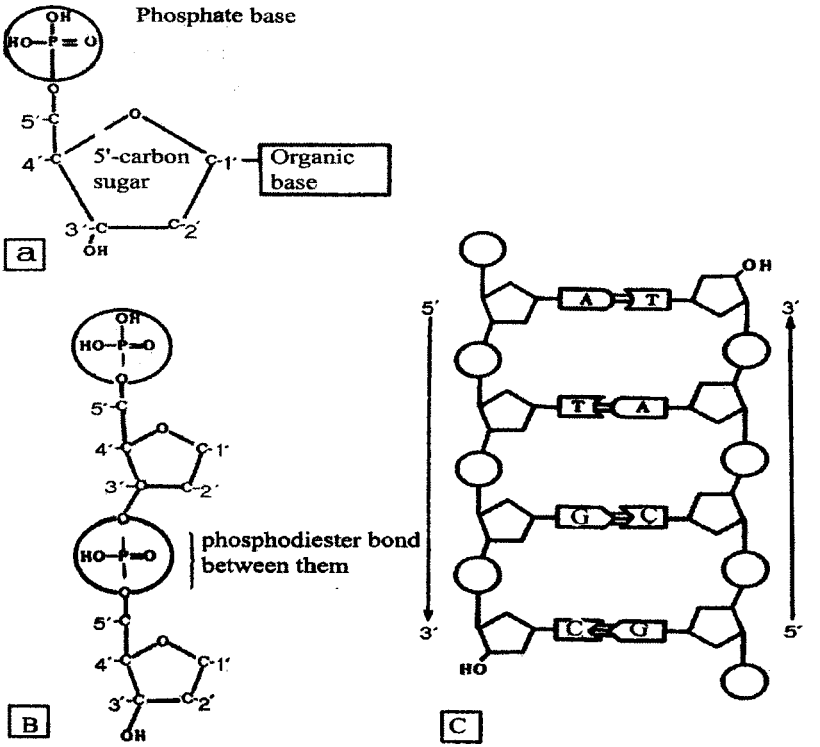
The nucleotide linkage in the nucleic acid molecule is provided by phosphodiester bond between phosphate group of one nucleotide and hydroxyl group of another. Further linking can occur in the same way, since two-unit polymer still has a free 5' - phosphate group at one end and a free 3'- hydroxyl group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

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

1. The proportion of A always equals that of T and C similarly equal to G; A=T, G=C.
2. From the above rule, it follows that 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 6-ketogroupes

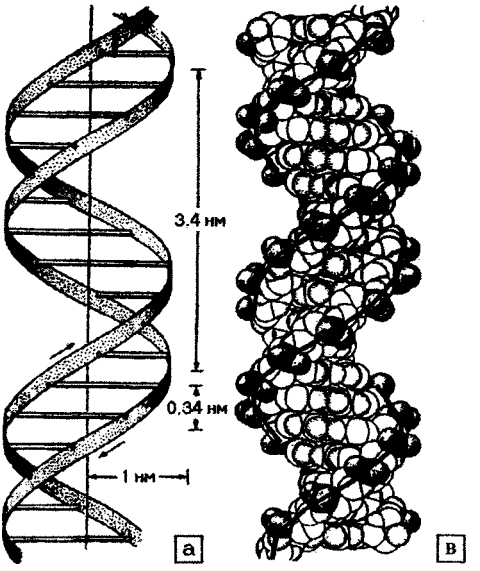
(A+C=G+T).

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



Pic 2.1 The structure of nucleic acids: a - nucleotide structure, b- nucleotide linkage to polymer chain, c- scheme of DNA molecule structure. (by V.N. Yarygin, 1997)

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. (Pic 2.2) This allowed them to explain physical, chemical and biological properties of DNA. With help of x-ray analysis, it was shown that diameter DNA helix is 2 nm, and made a complete spiral turn every 3.4 nanometers. Each complete spiral turn include 10 nucleotide pairs. The main principles of DNA structure was formulated in following statements:

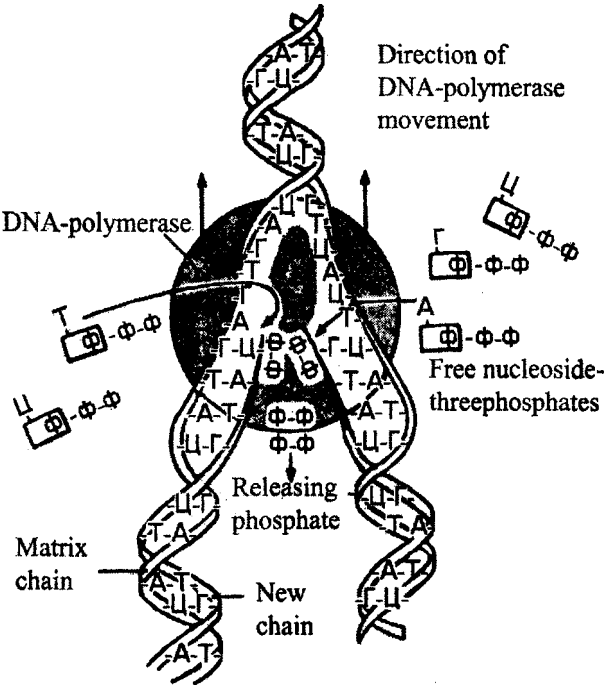


Pic 2.2 The J. Watson and F.Crick DNA model. a - scheme of double helix, b - tree-dimenitional model of DNA

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 and overwise.
2. Each nucleoside is in the plane, which has a right angle with helix axis.
3. Two chains are bounded to each other with help of hydrogen bonds between bases.
4. The pair's linkage is very specific. There is only two possible pair A:T and G:C.
5. The sequence of pairs in one chain may vary in wide range but the sequence of pairs in the second chain has to be complementary to it. Thus, the pair sequence in one chain defines the complementary sequence in the other chain.

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

In the DNA, structure it can be distinguished a primary structure - a poly



Pic 2.3. The DNA molecule replication (N. Green et al., 1990).

nucleotide chain, a secondary structure - two complementary to each other antiparallel polynucleotide chains, bounded by hydrogen bonds, and third structure - tree dimenitional spiral with characteristics described above. (Pic 2.2)

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

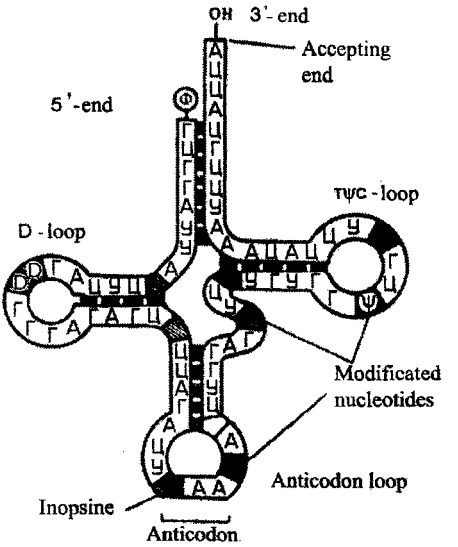
replication may occur at the different or same time. The ability of DNA polymerase to add nucleotides only in direction from 3' to 5' means that the process of replication in two DNA strands should be different. On a one matrix, the replication of DNA occurs continuously from 3' end to 5' end. On another matrix, the process of replication performed by short fragments. Then the short fragment of DNA are 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 distribution of mother DNA in the molecules is different. After conservative replication, the half of daughter DNA molecules is made from new material and second from old one. After semiconservative and dispersive replication, each of daughter DNA molecules has a half made from new material and a half from old one. However, the semiconservative and dispersive replication can be distinguished after daughter molecules replication. If it is a semiconservative replication 50% of daughter molecules of second generation will be made from half of new material and half of old material. The other 50% will be made from only new material. If it is dispersive replication, all molecules of second generation will be made from 25% of old material and 75% will be made from new material.

The RNA molecule is single strand. It is consist of such nucleotides as adenine, guanine, cytosine and uracil instead of thymine. While helix like folding some complementary regions can bind to each other making spiral. There are exist three RNA types: matrix RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA).

All types of RNA (except viruses RNA) are made on DNA matrix by transcription. Firstly, a long precursor is made than it subject to processing. The more short RNA is made after processing. The primary transcript and intermediate products of RNA synthesis are known as pro-RNA. It became shorter with help of cutting end sequences and some of fragments from the middle of chain. Then 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 this RNA is no more than 75-85. The molecular weight is 25 -28.000 Daltons. The tRNA presents 10% from the all cellular RNAs. These RNA are not bound to any particles. While realization of genetic information each of tRNA bind and transfer specific amino acid. The complementary bindings of pairs make a "clover leaf-like" structure (pic 2.4). In this structure, there are four parts, which carry out different functions. The first is accepting part, made by two complementary bounded terminal parts. It is consist of 7 base pairs. The 3' end of this part is a little bit longer. It form a single strand



Pic 2.4. The structure of transfer RNA molecule (R.W. Holley et al., 1965 with changes).

region which is ended by CCA fragment with free -OH group. To this end, amino acids are attached. Three other parts are complementary bounded nucleotide sequences, which are ended by non-complementary loops. The middle part of the loop consist of 5 nucleotides and contain in it own structure anticodon (three nucleotides which are complementary to mRNA codon, which code the amino acids, transported by this tRNA).

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

Ribosome RNA. There are three types of rRNA. 5S-RNA consists of 120-121 nucleotides and has a molecular weight around 40000 Daltons. It is associated with the large subunit of the ribosome. The molecule contains 3-4 bounded spiral regions and probably has a secondary structure in form of cloverleaf. 5.8S-RNA

consists of 130-160 nucleotides and has a molecular weight around 55000 Daltons. It is bounded in the ribosome with rRNA. It contains many modified bases. rRNA presents 85% of all cell RNA. It may be light (rRNA1), including 1600- 2000 nucleotides and having a molecular weight around 700000 Daltons and heavy (rRNA2), including 3200- 5200 nucleotides and having a molecular weight around 1700000 Daltons. The light RNA is in the small ribosome subunit and heavy RNA is in the large ribosome subunit.

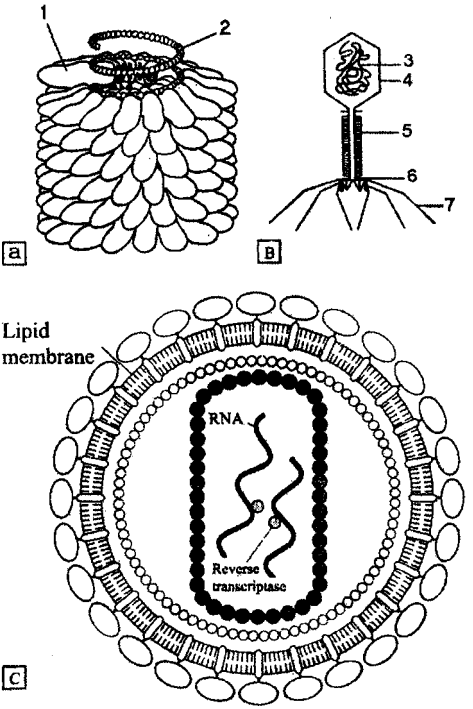
The ribosome RNAs are not only structural elements of ribosomes. They also provide binding of mRNA special sequence. By this is the start point of translation and reading frame states. In addition, rRNA provides interaction of tRNA and ribosome.

Messenger or matrix RNA. It presents 5% of total cell RNA. It consists of 300-3000 nucleotides and has a molecular weight until 10*7 Daltons. The size of molecule depends on required information. It is single stranded, but may have complementary bounded regions. The regions have information surrounded by non-informational regions. The leader sequence to start translation on a 5' end and terminal sequence on a 3' end to terminate it. The synthesis of mRNA starts from recognizing of promoter site on DNA by RNA polymerase. The strands of DNA separate from each other and on a one of them, the RNA transcription starts. The linkage of nucleotides is performed according with 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 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 terminator has a name - transcripton.

2.2 The organization of hereditary material of non-cellular forms, prokaryotes and eukaryotes.

The non-cellular life forms are viruses and bacteriaphages (pic 2.5). Viruses - are non-cellular life forms, which are able to enter to special live cells and reproduce itself 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 to RNA-containing and DNA-containing. A nucleic acid serves as storage of hereditary information.

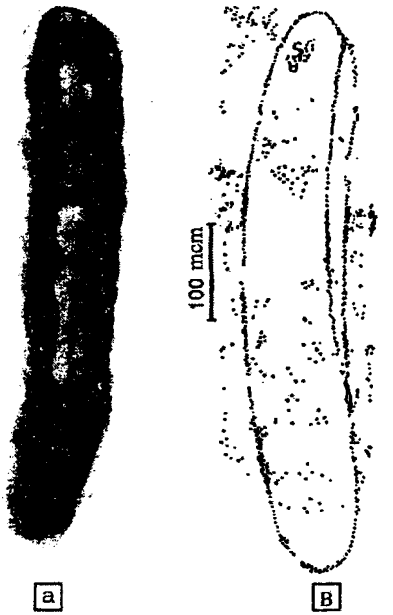
All viruses are divided into simple or complex. The simple viruses consist of nucleic acids and protein coat (capsid). The complex viruses may also have



Pic 2.5. The scheme of non-cellular forms structure. A – tobacco mosaic virus (1 – protein coat, 2 – RNA molecule); B – bacteriaphag T4 (3 – DNA, 4 – head, 5 – tail, 6 – base plate, 7 – tail fibers); C - HIV (human immunodeficiency virus) (K. Swenson, P. Webster, 1980 and R. Gallo 1987).

lipoprotein membrane, carbohydrates and non-structural proteins. The size of viruses may vary from 15 to 2000 nanometers. 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 stranded RNA and single stranded DNA. The RNAs as usual are 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 (pic 2.6). The E.coli has a DNA of 1mm long. It has 4x10*6 nucleotide pairs, making around 4000 genes. The 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

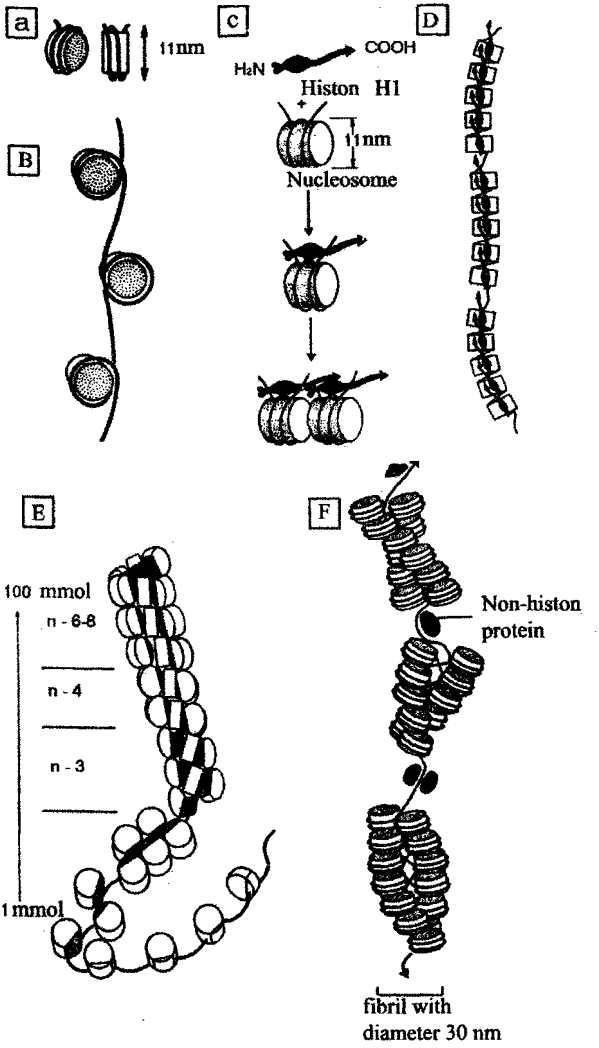


Pic 2.6. Escherichia coli. A – general view (lighter part present DNA); B – autoradiogram of circle chromosome. DNA is marked by tritium. On a left side, the replication beginning is visible. (S.M. Gershenzon 1979).

less stable as chromatin of eukaryotes.

The genetic material of eukaryotes in interphase nucleus is presented by chromatin. When cell divides by mitosis, the chromatin is spiralized to chromosomes. Besides DNA, chromatin contains many different proteins. Most of them are histons. The histons are proteins with positive charge and molecular weight 10000-20000 Daltons. They have 5 classes: H1, H2A, H2B, H3, and H4. The H1 contain a lot of lysine, H3 - arginine, H4 - arginine and glycin. The others, so called non-histon proteins, are in a small amount. According to common point of view, chromatin is presented by spiraling strings. There are following levels of chromatin folding (pic 2.7).

The nucleosome string. This level of chromatin organization is provided by four types of histon proteins: H2A, H2B, H3, H4. They form a proteins 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 proteins core. One core is covered by 146 nucleotide pairs of DNA. The cores are connected with each other



Pic 2.7. Molecular organization of chromosome:

a – free nucleosome; b - nucleosome string; c – nucleosome connection by histon; d – chain of nucleosome groups divided by free DNA regions; e – dependence of DNA spiralization from NaCl concentration (100 mmol NaCl correspond to 6-8 nucleosomes on one turn of helix, the lower concentration corresponds to lower nucleosomes number); f - interphase chromonemm (V.N. Yarygin, 1997 and F. Fogel, A. Motulsky, 1989).

by linker DNA. The linker may be 15 to 100 nucleotides long. It depends on cell type. In experiments in vivo, it is shown that 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 decreasing, each spiral turn has 3-4 nucleosomes. With help of nucleosome, chromatin organization the double helix of DNA with diameter 2nm and average length 5 cm achieve a diameter 10-11 nm and length 2cm.

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

Interphase chromonemm. This level of chromatin folding is provided by folding of 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. The one loop contain from 20000 to 80000 nucleotide pairs. After such folding, interphase chromonemm has the diameter 100-200 nm. The regions of interphase chromonemm undergoing further folding makes a 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 heterochromatin

The constitutive heterochromatin is in the telomere regions and regions near the centromere and along some internal fragments. It is believed constitutive heterochromatin to provide keeping of total nucleus shape, attaching chromatin to karyolemm, participating in chromosome recognition during meiosis, making an intervals between genes.

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

Metaphase chromosome. In the beginning of mitosis, chromatin condenses to chromosomes. Chromosomes become visible. The mitotic superspiralization makes process of chromosome movement easier.

The chromosome DNA consist of more than 10*8 nuclcotide 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. It is 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 the 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 makes constitutive heterochromatin. There is around 75% of chromatin non-participating in transcription. This is 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. The genetic code was discovered by M. Nierenberg and H.G.Corana in 1965. For this discovering, they and R.Holly received a 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:

Table 2.1. Messenger RNA codons.

1st letter	2nd letter				3rd letter
	U	C	A	G	
U	PHENYLALANINE	SERINE	TYROSINE	CYSTEINE	U
	PHENYLALANINE	SERINE	TYROSINE	CYSTEINE	C
	LEUCINE	SERINE	STOP	STOP	A
	LEUCINE	SERINE	STOP	TRYPTOPHAN	G
C	LEUCINE	PROLINE	HISTIDINE	ARGININE	U
	LEUCINE	PROLINE	HISTIDINE	ARGININE	C
	LEUCINE	PROLINE	GLUTAMINE	ARGININE	A
	LEUCINE	PROLINE	GLUTAMINE	ARGININE	G
A	ISOLEUCINE	THREONINE	ASPARAGINE	SERINE	U
	ISOLEUCINE	THREONINE	ASPARAGINE	SERINE	C
	ISOLEUCINE	THREONINE	LYSINE	ARGININE	A
	START-METIONINE	THREONINE	LYSINE	ARGININE	G
G	VALINE	ALANINE	ASPARTIC ACID	GLYCINE	U
	VALINE	ALANINE	ASPARTIC ACID	GLYCINE	C
	VALINE	ALANINE	GLUTAMIC ACID	GLYCINE	A
	VALINE	ALANINE	GLUTAMIC ACID	GLYCINE	G

1. The genetic code has 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 nucleotides are the same, 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. Studying of DNA structure tightly connected with gene function has assisted in dissolving many questions: How genes reproduce itself? What is the nature of mutations? How genes determine proteins structure? However, all the questions dissolved with help of DNA decoding, have brought a new giant problems. The functioning of DNA in details is not clear yet. Discovering DNA structure exited a new wave of biological researches and formation of new theories.

CHAPTER 3. CELL BIOLOGY AND PHYSIOLOGY.

3.1 The cytology as a science. Cell theory, its value for medicine.

The division of biology that study cell structure and functions is called cytology. The cell's discovery is connected with the names of great scientists such as R. Hooke (1635-1703, M. Malpigi (1628-1694), N. Gru (1641-1712) etc. They were first to describe cell structure of many plants. A. Laevenhook (1632-1723) was a first exploring animal cell and cells of protozoa. These researchers paid a lot of attention to cell membrane structure. Only Y. Purkinje (1787-1869) firstly concluded a nucleus being in a chicken egg and presence of fluid substance inside of the cell. He gave a name to this substance - protoplasm. In 1831 English botanists R. Brown (1773- 1858) and in 1836 Check scientists G. Valentin (1810-1883) were the first to find nucleuses in animal and plant cells. In 1838 German botanists M. Shleiden (1804-1881) concluded that nucleus is most important pert of the cell and it is connected with new cells formation. As you can see from above, the cell discovering wasn't a work of one scientist. It was a collective work during two centuries.

In 1839 German zoologist T. Schwan reported principles of cell theory, such as:

1. A cell is a main structural unit of all animal and plant organisms.
2. The growth, development and differentiation of animal and plant tissues are due to cell formation.
3. A cell in appropriate limits is an individum, and organism is sum of them.
4. New cells appear from cytoblastemm.

The first three conclusions of T. Schwann are still correct. The fourth one isn't.

Further development of cell theory is connected with a name of German scientist P. Virchow (1821-1902), who published his work "The cellular pathology" in 1858. P. Virchow was a first describing pathological process by materialistic way. He showed the connection of the pathological events with changes in cell structure. He corrected the fourth T. Schwann thesis and suggested a new one: Omnis cellula e cellula - each cell is from cell. And today we still know only one way of cell appearance - by cell division. However, it might be considered that on early stages of life development cell appeared from non-cellular structures. The P. Virchow conclusion that there is no life outside of the cell is still correct. But others his conclusions weren't proved by further science development. In particular, P. Virchow intensively developed incorrect conclusion of T.
Schwann about organism as a cell sum, from which it might be interfered that

pathological process of organism is a sum of pathological processes in particular cells. P. Virchow and his fellows didn't recognized the differences between part and total, observing organism without it historical development and environment. Assessing the P. Virchow's "The cellular pathology" in general, it may be pointed that it was an important sign in a history of biology and medicine. And after slight correction, it made a basement for contemporary views to organism cell structure.

The formation of cell theory was completed on a base of new findings acquired from modern cell researches. Main statements of cell theory are:

1. All organisms are composed of one ore more cells, within which the life processes of metabolism and heredity occur.
2. Cells are the smallest living things, the basic unit of organization of all organisms.
3. Cells arise only by division of previously existing cell.
4. Cells of multicellular organisms are specialized in function and form tissues.
5. Cells of specialized tissues form organs.

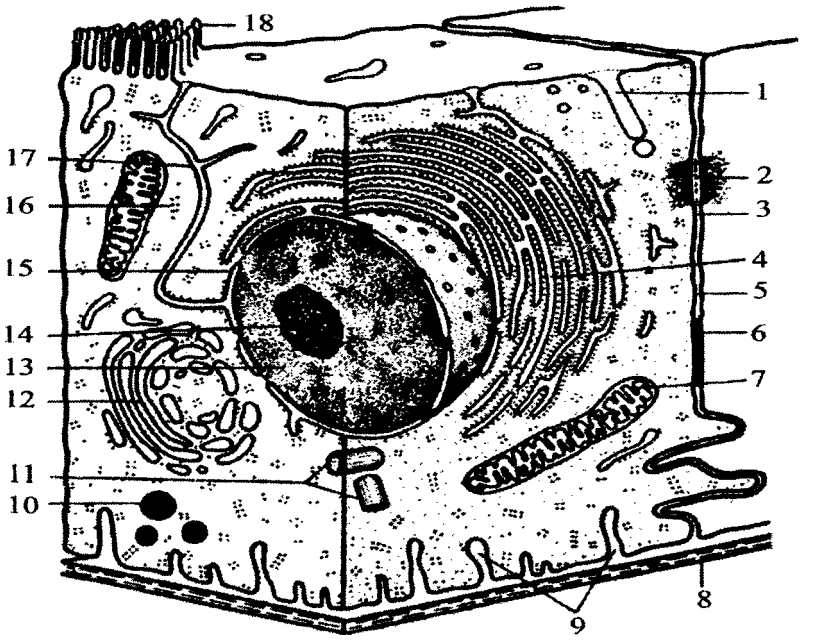
The cell theory is a great generalization of XIX century. The creation of cell theory had a great value for development of materialistic view on life in all branches of biology and medicine.

3.2 The cell biology.

All life matter is represented by monocellular organisms and multicellular organisms.

A cell is a smallest structure, which has all properties of life matter and can maintain all this properties by itself and also give these properties to next generations. A cell is elementary structural functional genetic unit of all live organisms, providing exchange of energy and substances, reproduction, growth and development, irritability and movement, heredity and diversity, homeostasis. The structural elements of eukaryotic cell are cell membrane, cytoplasm and nucleus.

The cell membrane separates protoplasm of a cell from outside environment and at the same time, it regulates ions and substance passing inside and outside of the cell. According to contemporary findings plasma membrane consist of phospholipids bilayer. 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 binds with hydrophilic parts of phospholipids, hydrophobic regions of protein binds with hydrophobic parts of phospholipids. Beside that, an animal cell has glycocalyx outside of phospholipids bilayer with width 10-20 nm, presented by glycolipids and glycoproteins. A plant cell has cell wall, which is made of cellulose. The inner cell membranes, which form organelles, have a same structural principle, without glycocalyx (pic 3.2). The cortical layer of cytoplasm lies close to inner cell



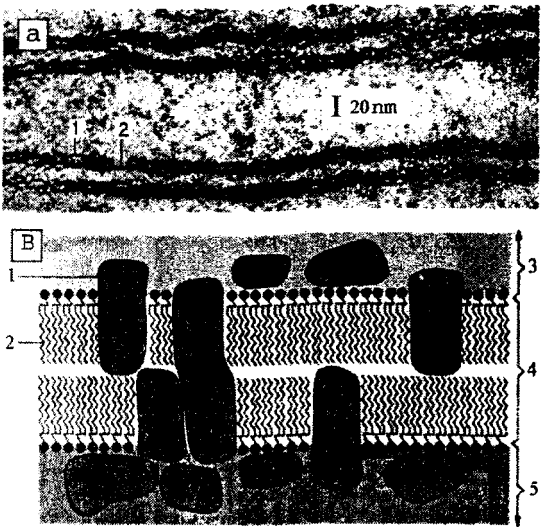
Pic 3.1. The scheme of animal cell structure:

1 – pinocytosis canals; 2 – desmosome; 3 – intercellular gap; 4 – rough endoplasmic reticulum; 5 – cell membrane; 6 – tight junction; 7 – mitochondrion; 8 – basement membrane; 9 – basal lacunas; 10 – lysosomes; 11 – centrioles; 12 – Golgi complex; 13 – chromatin; 14 – nucleolus; 15 – nuclear envelope with pores; 16 – ribosomes; 17 – smooth endoplasmic reticulum; 18 – vilia (by E. Hadorn, R. Vener, 1989).

membrane surface. It has a lot of microtubules and microfilaments, containing contractive proteins.

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

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 fluid condition to gel condition and back. The compounds of cytoplasm are soluble proteins, such as glycolisis enzyme, ATPases etc, amino acids, lipids carbohydrates. Microtubules

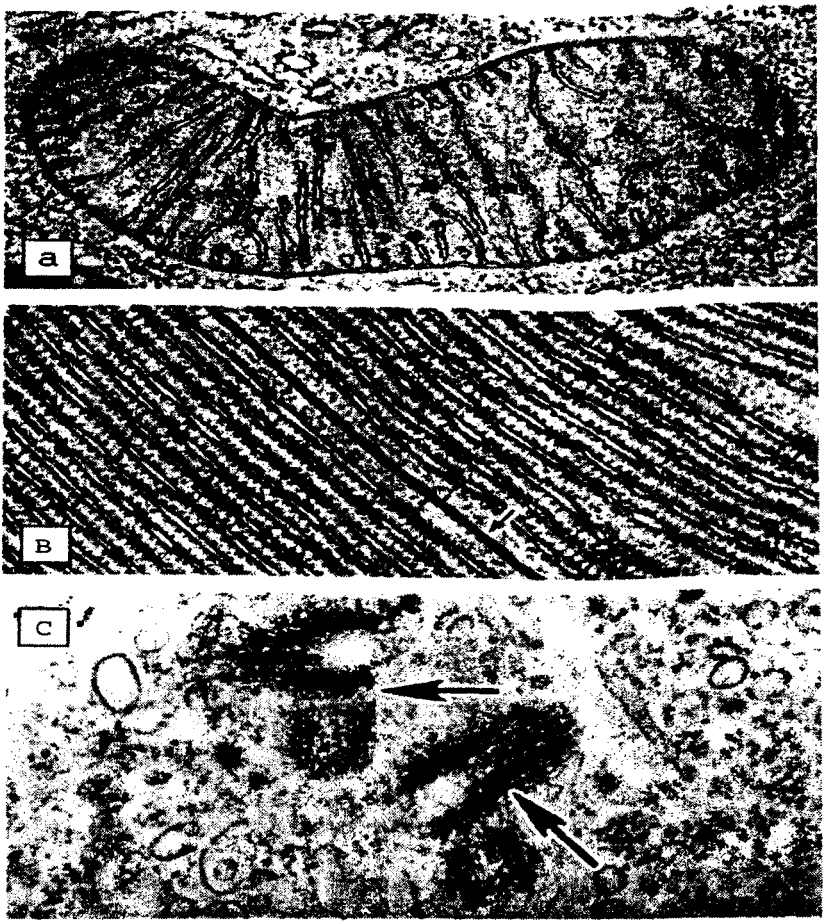


Pic 3.2. The electronic microscope photo (A) and scheme (B) of plasmalemm:
A :1 - three layer elementary membranes, 2 – intercellular gap. B: 1 – protein molecule, 2 – phospholipids molecule, 3 - – intercellular gap, 4 – phospholipids bilayer, 5 – intracellular space (by E. Hadorn, R. Vener, 1989).

are made from matrix proteins. Functionally, cytoplasm is internal cell environment - the place for intracellular metabolism performing.

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

The endoplasmic reticulum. The endoplasmic reticulum, weaving sheets through the interior of the cell, creates the serious of 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 travels to



Pic 3.3 The electronic microscope photo of mitochondrion (a), rough EPR (b), and centrosome (c) (in Biology Science an inquiry into life, 1980).

vesicle forming system, called complex Golgi. In the endoplasmic reticulum of liver cells occur detoxications of harmful and toxic substances. 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 structures with diameter 15-35 nm. Each ribosome consists of small subunit and large subunit. They merge in the presence of mRNA. If there are several ribosomes merged by one mRNA, such structure called polysome. The polysomes may stay free in cytoplasm or

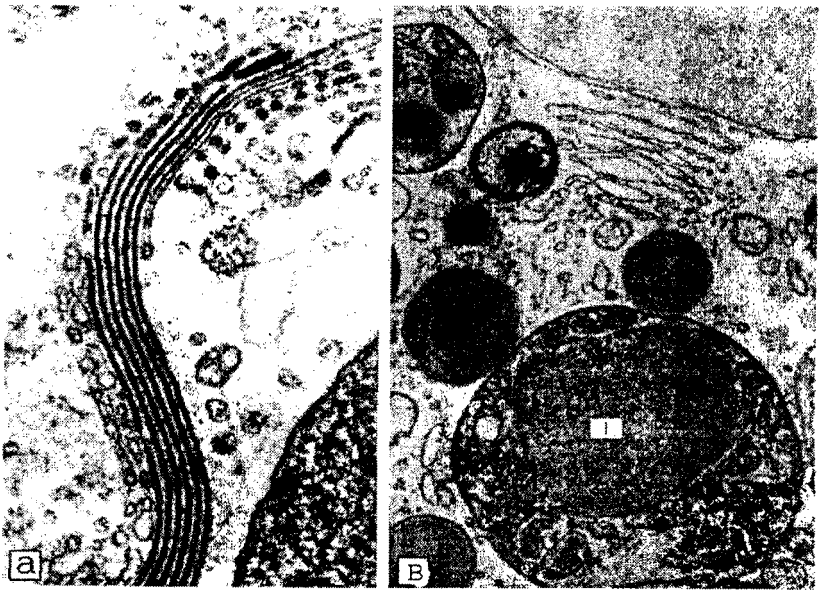
attach to endoplasmic reticulum membranes. They are the place of active protein synthesis. They allow making proteins in large amounts. If they spread in cytoplasm, they make proteins for internal use. If they attached to endoplasmic reticulum membranes, they make proteins for external use (examples are milk synthesis and digestion enzymes synthesis).

The Golgi complex, named in honor of Italian scientist who described it first, is visible in light microscope as differentiated region of cytoplasm situated 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 are 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 complex Golgi function is concentration and condensing of internally produced substances for further excretion from a cell. It is stated that in complex Golgi glycolipids, glycoproteins, yolk granules and lysosomes are formed.

The lysosomes (from Greek - lysis - dissolving) are sphere shaped vesicles with diameter 0.2 - 0.4 mcm, containing set of acid hydrolases enzymes. They help to catalyze reaction of nucleic acids, proteins, lipids and carbohydrates splitting. A lysosome is surrounded by one layer biological membrane, sometimes it may be a protein fibrils 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 protests bodies and phagocytes are probably made of merged lysosomes. There are primary (inactive) lysosomes and secondary lysosomes. Secondary lysosomes are activated primary lysosome, and in these lysosomes, a process of digestion takes place. Secondary lysosomes may be subdivided 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 group of vesicle shaped cell organelles with diameter 0.1 - 1.5 mcm. 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 one liver cell.

The mitocondria (from Greek - mitos - thread, chondros - corpuscule) - are round shape or stab shape structures of 5 - 10 mcm. long and 0.5 mcm. width. The mitochondria number is varied from 150 to 1500 per cell or even several hundreds thousands in female sex cells. The mitochondrion coat is 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 surround internal mitochondrion matrix. There are apparatus of protein biosynthesis in it. It is presented by circular, closed DNA molecule without histons, ribosomes, tRNA, enzymes of DNA replication, tran



Pic 3.4. The electronic microscope photo of Golgi complex (a) and lysosome (b). (in Biology Science an inquiry into life, 1980).

scription and translation. The main function of mitochondria is to obtain energy by oxidative phosphorilation of chemical substances and to store it in ATP form. Mitochondria take part in a steroid hormone and some amino acid synthesis.

The plastids - are the group of organelles existing in plants. The plastid body is bounded by two membranes that resemble those in mitochondria. An internal plastid membrane lies in close association with one another; by fusing their peripheries, two adjacent membranes form a disk shaped close compartment, called tilakoid.Plastids contain stacks of such tilakoids. Each stack, called granum, may contain several dozen tilakoids and a plastid may contain hundreds or more grana. According to tilakoid pigment plastids may be divided to chloroplast, chromoplasts and leucoplasts.

Green plant cells usually contain chloroplasts. They perform photosynthesis. The photosynthesis provides formation of mono-, di-, and polysugars. Having its own circle DNA and ribosomes chloroplasts may perform a protein biosynthesis. Like mitochondria, all plastids come from division of existing plastids. In early stages of development, plastids look like mitochondria. It may be due to their similar function. Mitochondria perform energy transformation from dissimilation processes, and chloroplasts perform photosynthesis to transform sun energy to energy of chemical bond. Mitochondria apparently originated as endosymbi

Pic 3.5. The electronic microscope photo of chloroplast (by H.T.Arnott, 1964).

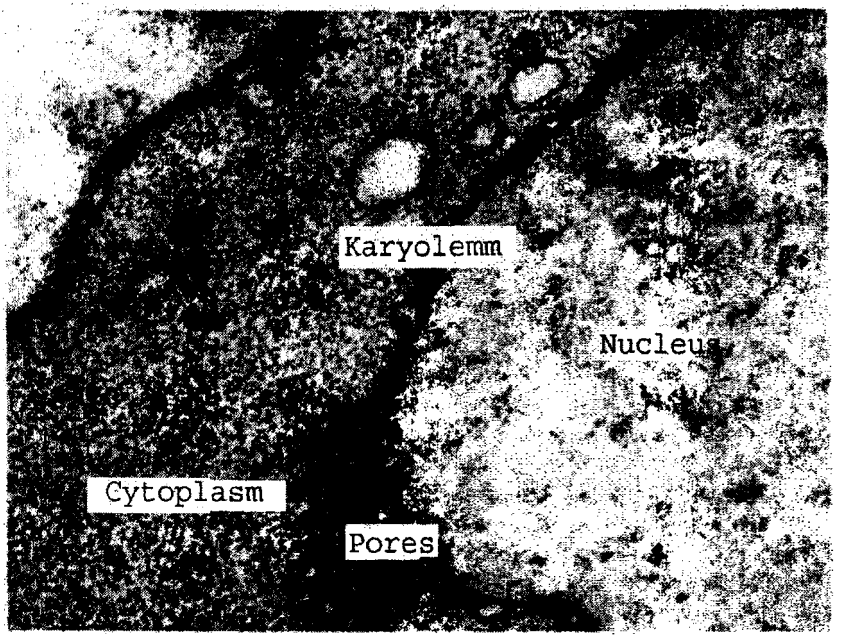
otic aerobic bacteria, whereas chloroplasts seem to be originated as endosimbiotic aerobic photosynthetic bacteria.

The cell center - is a good visible organelle, consisting of one or two small centrioles and radiated sphere surrounding them. With help of electronic microscope it was revealed that each centurion is small cylindrical body of 0.3 - 0.5 mcm. long and with a diameter 0.15 mcm (pic 3.3).The walls of cylinder are made of nine parallel tubules. Cell center works actively during mitosis. Centrioles come to a cell poles. Spindles are attached to them. During mitosis, chromosomes move, by spindle, toward centrioles on different poles. General purpose organelles also include microtubules and microfilaments.

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

The inclusions - are temporal cytoplasmic structures, related with cellular metabolism. The cell's functional state provides their appearance or dissolving.

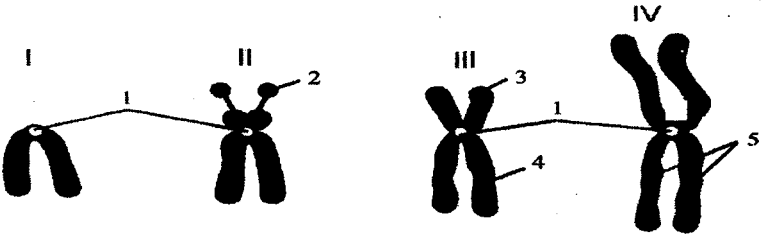
There are these following types of inclusions: trophical (carbohydrates, proteins, lipids), secretoral (secrete granules in glands), pigment (melanin, lipofuscin, hemoglobin etc.) and excretory (uric acid etc.).



Pic . 3.6 . The electronic microscope photo of cell nucleus (in Biology Science an inquiry into life, 1980).

The nucleus. It is a constant component of all living cells. There are two different nuclear states. One is mitotic, another is interphase. Such division was made because of different nucleus activity and appearance during these periods of cell cycle. Previously, it was believed that interphase nucleus was inactive. But now it has been proven an adverse statement, it is very active during interphase. All plastic processes occur during interphase. Different cells have different nucleuses. But commonly nucleus has a sphere or ellipsoid shape. The shape of nucleus depends on cell shape containing it and it may vary in wide range. Nucleus sizes vary no only between different cell types but also within one cell type. Cells of internal organs may have a polymorphism in sizes or volumes. The functional cell state may have an influence to nucleus size. It is stated that functional nucleus enlargement may be considered as a criteria of 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.

The karyolemm - is a good visible in a light microscope. But structure that is more definite may be revealed only by electronic microscope. The karyolemm is



Pic 3.7. The chromosomes' shapes:
I – telocentric; II- acrocentric; III – submetacentric; IV – metacentric (1 – centromere; 2 – satellite, 3 – short arm, 4 – long arm). (by Yarygin, 1997).

made of two biological membranes, each having 0.006-0.009 mcm. of width. The space between them is called perinuclear space. It has a width 0.01-0.02 mcm. The external membrane extends to membranes of endoplasmic reticulum. The nuclear envelope is semipermeable. In some regions, membranes of karyolemm fuses together to make a pore in a nuclear envelope. These pores have a diameter 0.08-0.09 mcm. Pores aren't just holes in envelope. They contain substance with moderate electronic density. Pores contain a protein structure, which is called pore complex. It regulates a substance flow through nuclear pore.

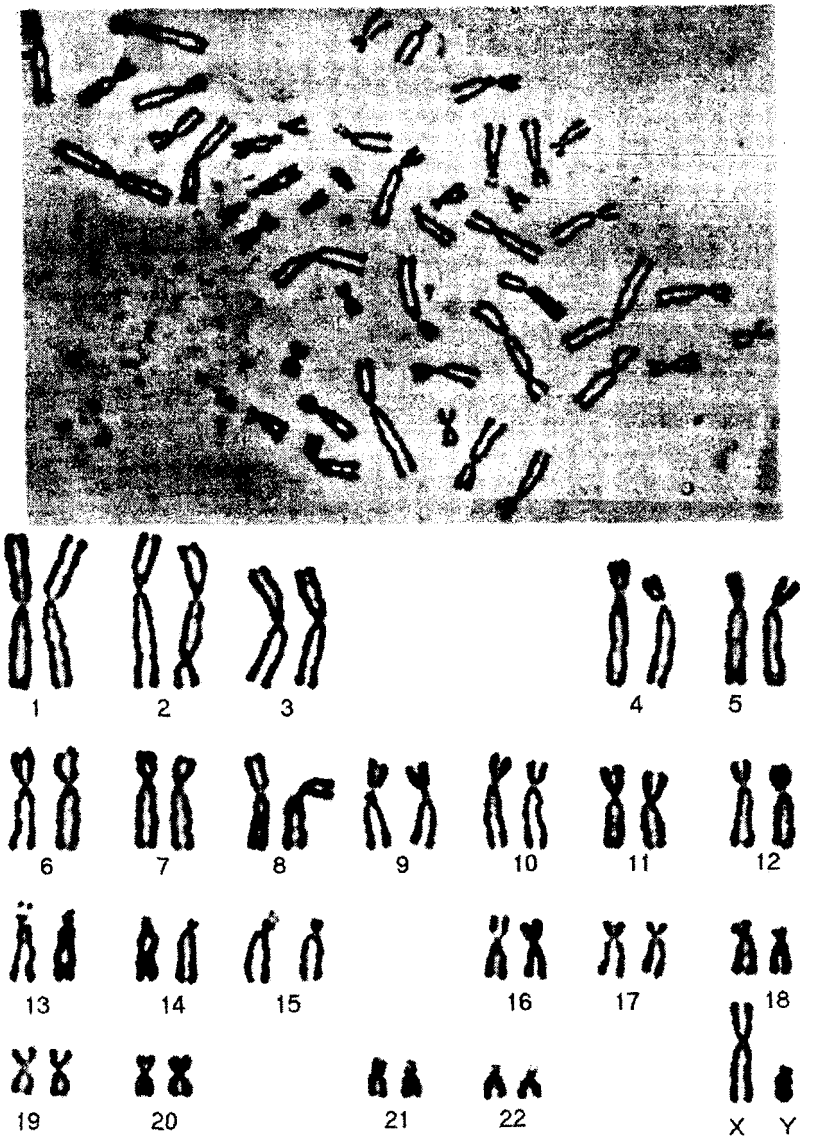
Nuclear pores extend to protein layer underlying nuclear envelope (lamina densa). It shows a complex mechanism of regulation of nuclear/cytoplasmic relations. It is possible that close connection of lamina densa and karyolemm helps to bring an

order in interphase chromosome localization. The function of nuclear envelope is separation of eukaryotic cell hereditary information from cytoplasm and regulation of nuclear/cytoplasmic relations.

The nucleoplasm. It makes 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 genetic apparatus. Also it has fibrillar proteins and may give a support to nucleus structures.

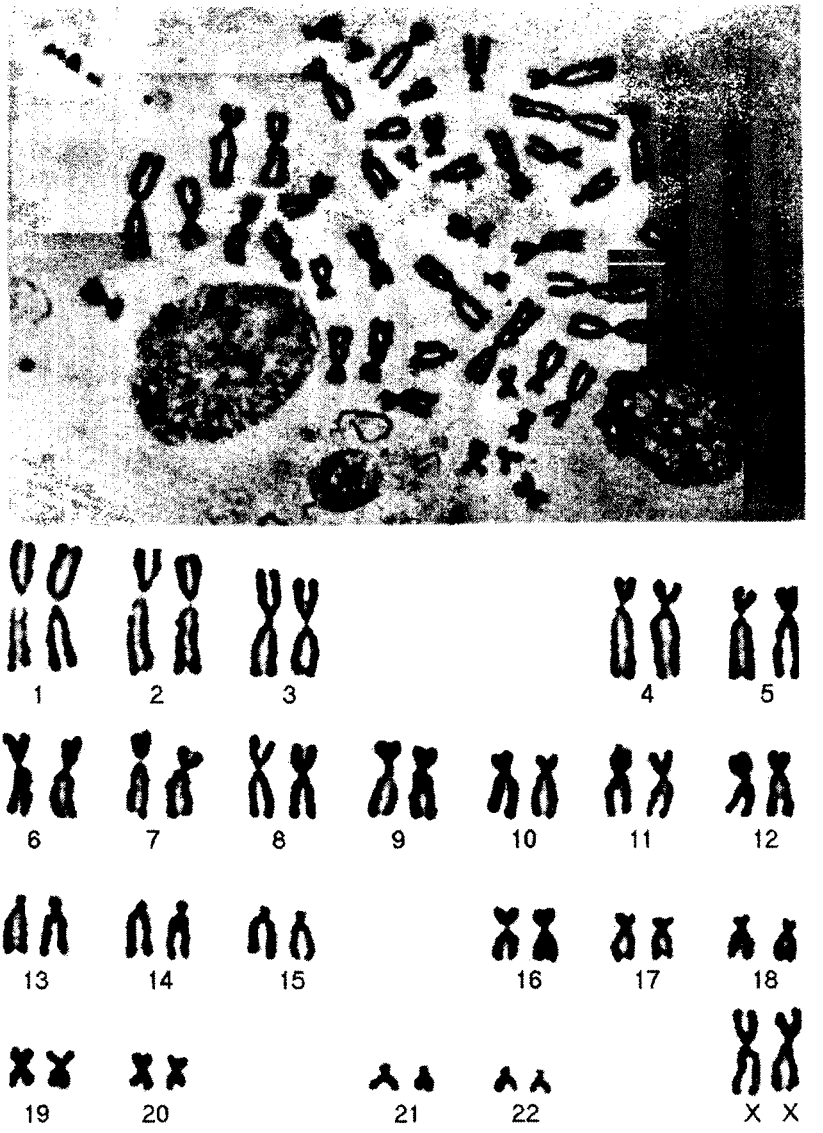
The nucleolus. It is a structural component of interphase nucleus. It is dissolved in prophase and it is newly formatted in telophase. It is formed from special thread like structures of proteins and giant molecules of RNA precursors. Them mature RNA is made from such precursors. Genes, which are responsible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

The chromatin is the interphase form of hereditary information being. It's organization was described above in chapter 2.2.

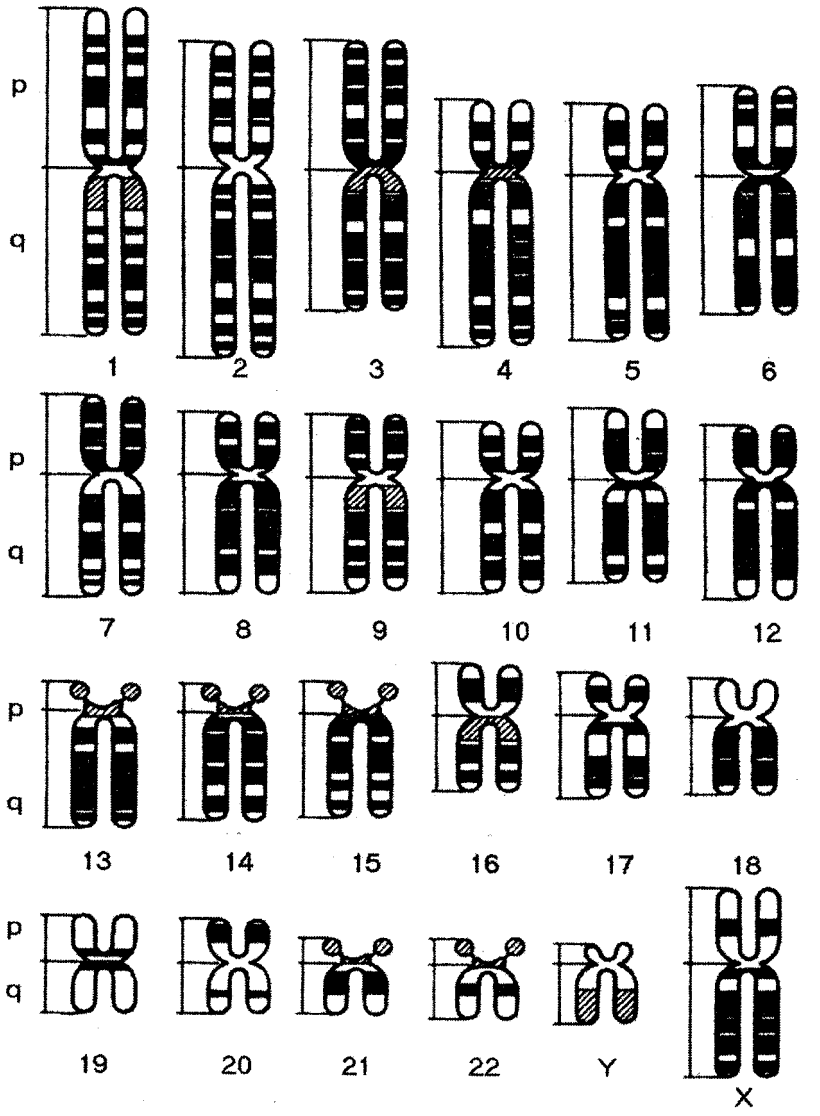


Pic 3.8. Male karyotype.

Upper part is metaphase plate; lower part – idiogramm (in Biology Science an inquiry into life, 1980).



Pic 3.9. Female karyotype:
Upper part is metaphase plate; lower part – idiogramm (in Biology Science an inquiry into life, 1980).



Pic 3.10. The chromosome segmentation accordinary Paris nomenclature: positive segments G and Q – light; negative segments R – dark; variable regions are crossed (by Paris Conference 1971).

The chromosomes - are components of cell nucleus, which are good visible during mitosis. They have a complex structure, ability to replicate itself and transmit hereditary information to offspring. The chromosomes usually look like straight or curved stabs (pic 3.7). Each chromosome contains two chromatids. Chromosome shape may be defined by primary and secondary strip position. In place of primary stripe, there is a chromosome region without DNA. Inside of it, there is a special structure - centromere (kynetochore). The spindle is attached to this structure. The centromere divide chromosome on two arms. Accordinary centromere position and arm length it may distinguished following chromosome types: metacentric (with equal arms), submetacentric (arms slightly different), acrocentric (arms significantly different) and telocentric (without one arm). Chromosome arms are appointed the Latin letters, "q" for long arm and "p" for short arm. The percentage ratio of small arm length to total chromosome length is considered as centromere index. If centromere index is about 50%, it is a metacentric chromosome. If centromere index is less then 50% it is submetacentric chromosome. If centromere index is around zero, it is acrocentric chromosome. Some chromosomes have a secondary strip, which divides a chromosome satellite from main chromosome part. Chromosome satellite is pointed by letter "S". Chromosomes strictly follow such rules as: rule of constant chromosome number, i.d. somatic cells of every species have their own chromosome number (drosophila has 8, human - 46), rule of chromosome pairs (chromosome which make a pair are homologues chromosome), Ascaris lumbricoideus has only 1 pair, human has 23, rule of individuality - non homologues chromosomes differ from each other, rule of continuity - an ability of chromosomes to autoreproduction.

Table 3.1 The human karyotype chromosomes characteristics.

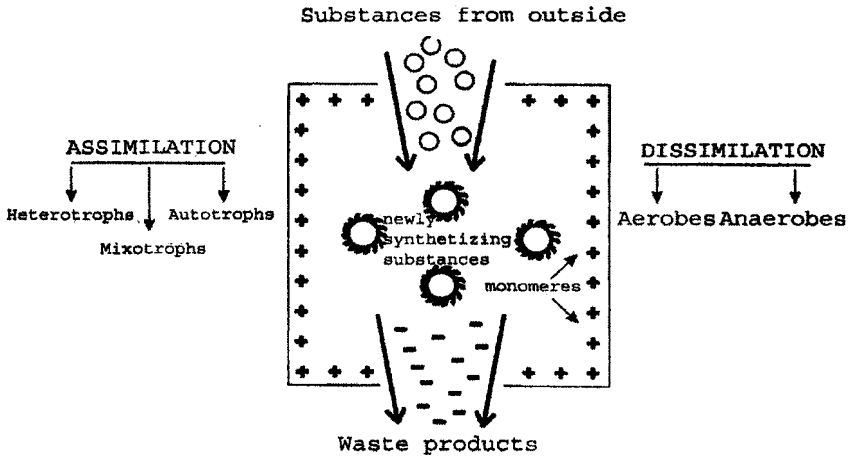
Chromosomes groups	Chromosomes characteristics	Chromosome pairs
A (I)	Biggest metacentric	1-3
B (II)	Big submetacentric	4-5
C (III)	Middle metacentric and submetacentric	6-12,X
D (IV)	Middle acrocentric	13-15
E (V)	Small submetacentric	16-18
F (VI)	Small metacentric	19-20
G (VII)	Small acrocentric	21-22,Y

All features of somatic cell chromosomes structure taken together make a karyotype. This term was firstly introduced by Russian scientist G.A. Levitansky (1878 - 1942) in 1924. Normal human karyotype includes 46 chromosomes (23 pair in a diploid set). 44 from them are somatic chromosomes and 2 are sex chromosomes (pic 3.8 and 3.9). List of chromosomes placed accordinary size

decreasing is called idiogramm. The term "idiogramm" and listing principle was suggested by cytologist S.G. Navashin (1857-1930) in 1921. Chromosomes are divided by size and by centromere position accordinary Denver's classification (1960). In the same year, K. Pattaw suggested to divide chromosomes to 7 groups, pointing each group by Latin alphabet letter (table 3.1). 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 was developed in Paris (pic 3.10).

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. On a level of organism and on a level of a cell it may be distinguished external and internal substance exchange. An external exchange in organism - is exchange with external environment that means incoming of food substances and outcoming of waste substances. An internal exchange in organism occurs by assimilation and dissimilation. Accordinary with assimilation type organisms may be divided on heterotrophic, mixotrophic and autotrophic; accordinary with dissimilation type organisms may be divided on aerobic and anaerobic.



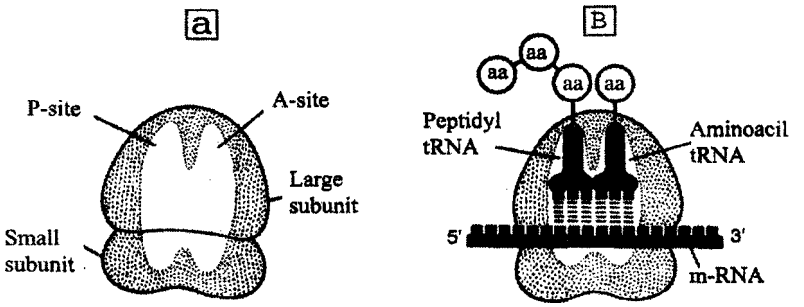
Pic 3.11. The cell as self-regulating system.

Energy is defined as the ability to bring about change, or, more generally, as the capacity to do work. Accordinary to exchange type with environment living systems may be divided on: isolated - without any exchange, adiabatic - there is no substance exchange, but there is energy one, excluding heat energy, closed - there is no substance exchange, but there is energy one in any form, open - any exchange is possible. The energy flow of organism is presented by cellular energy producing processes such as photosynthesis, chemosynthesis, fermentation and respiration. During photosynthesis in plant cells, the sun's energy is converted to energy of chemical bonds of ATP and NADP.H2. Then this energy is used in a plastic processes. During chemosynthesis the transformation of one type of chemical bond to another occurs. So, nitrificating bacteria oxidize ammonium to nitrites and then to nitrates; sulfur bacteria oxidize H2S 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. During fermentation, products dissimilate to organic substance still having a lot of energy in its bonds. So, that is why the energy outcome from fermentation is small. This process occurs in hyaloplasm. The major role in energy exchange in heterotrophic organisms is respiration. With 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 synthesis of ATP. The ATP synthesis occurs on inner membrane and crysts of mitochondrion, 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 providing cell energy supplyment. The products of glycolisis (pyruvates) come to mitochondrion. There they ARE subject to oxidation linked with ADP phosphorilation to ATP. From systems converting energy of ATP to mechanical work, the mechanical-chemical system of muscle is studied better than anything. It consists of contractive proteins actine and myosin and adenosintriphosphatase enzyme, splitting ATP with energy liberating. Energy supplying mechanisms of cell are very effective. The coefficient of useful action of chloroplast and mitochondrion are 25% and 45-60% subsequently. It is more than steam engine (8%) and internal combustion engine (17%) have.

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 outcome from organism. THE organism serves as a transmitter of these signals (internal information). The information cannot be defined neither as matter nor as energy. But material or energy transmitters carry it. During hormone regulation hormone can get to any part of an organism but only some of them are



Pic 3.12. The tRNA and ribosome binding;
A – unloaded ribosome;B – loaded ribosome: aa – amino acids (by V.N. Yarygin 1997).

able to accept it. For example, thyrotropic hormone of anterior pituitary acts only on thyroid gland. During nervous regulation, the information parameter is impulse rate (number of impulses per time unit). A cell accepts external information flow from intercellular matrix with help of receptors on a cell surface.

The information flow in an organism is performed with help of brain cortex and endocrine glands. In a cell, internal information is written in DNA. In internal information flow nucleus and cytoplasm DNA, mRNA, cytoplasm apparatus of translation takes part. The internal information flow provides the heredity of species signs from generation to generation. In eukaryotic cell, the genomes of chloroplasts and mitochondria also take part in internal information flow.

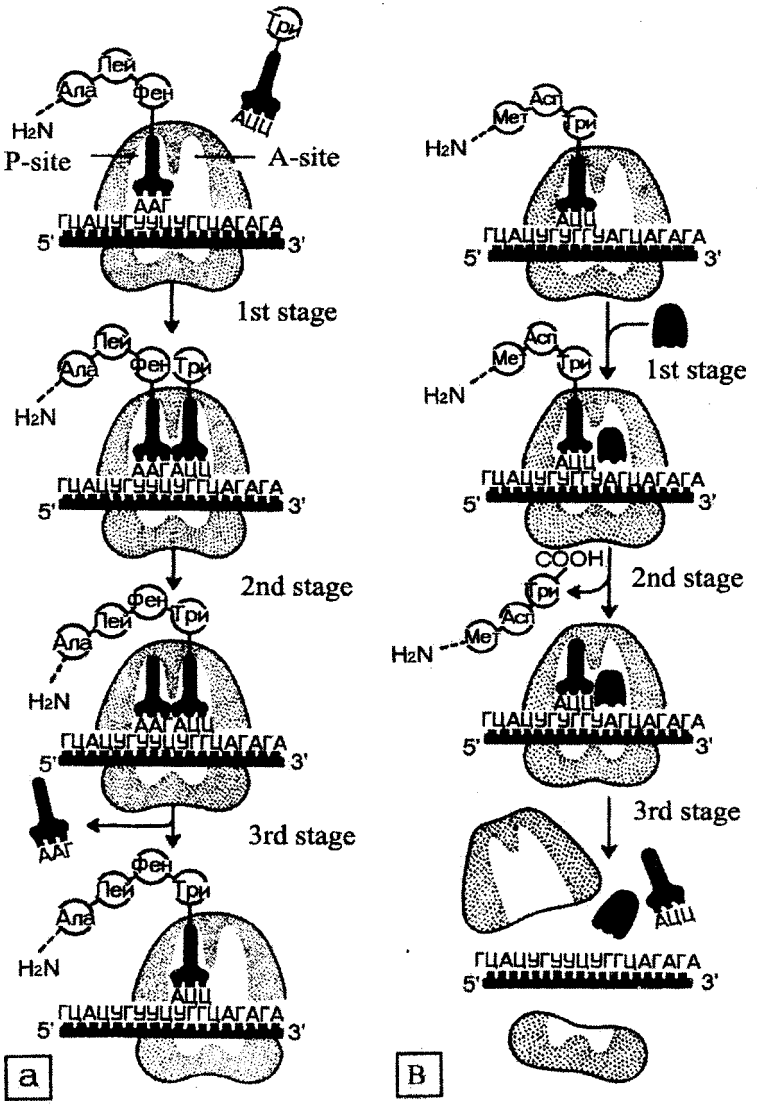
"Living matter" or "living state" - is, firstly, not a structure. It is a process. The living structures aren't stable; they are always under destroying and rebuilding. This renewing (the substance flow) occurs with different speed. The measure to determine substance flow is period of renewing. It is a time required to change half molecules of substance to new molecules. The substance flow is characterized by 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 may be concluded in following.

1. Amino acid activation by specific enzyme in a presence of ATP following to aminoaciladenilat formation.

2. Attachment of activated amino acid to specific tRNA liberating AMP.

3. Binding of aminoacil-tRNA (tRNA with amino acid) to ribosome. Then, incorporation of amino acids to protein liberating tRNA.

In the ribosomes, there are two furrows, one for growing polypeptide chain, second for mRNA. Also in ribosome, there are two sites for tRNA binding. A-site is for tRNA carrying amino acid, P-site for tRNA carrying polypeptide chain.



Pic 3.13. The elongation (a) and termination (b) of protein synthesis (by V.N. Yarygin 1997)

There are three phases in translation: initiation, elongation and termination of polypeptide synthesis (pic 3.13).

The initiation phase. It provides the beginning of protein synthesis. During this phase occurs merging of two previously separated rRNA subunits on definite mRNA site and attachment to it first aminoacil-tRNA. In a mRNA molecule near the-end is a complementary site to rRNA sequence of small subunit. The mRNA binds with small ribosome subunit to put 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 small ribosome subunit. When initiation phase is over, initiation factors leave ribosome subunit.

The elongation phase. It is a sequence of cyclic repeating events. During this phase occur specific recognizing of next codon in A-site by aminoacil-tRNA and complementary binding of codon and anticodon. While this binding, a transported amino acid is in the A-site nearby previously incorporated in 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's 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 codon-terminator appears at on A-site of ribosome.

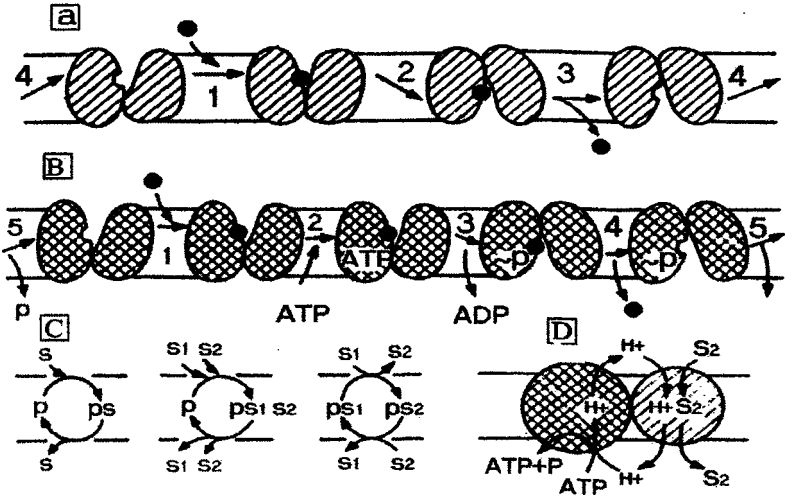
The termination phase. It is also called finishing of polypeptide chain synthesis. It start from encounting one of codon-terminators. There is no tRNA, which is able to bind with this codon. Instead of tRNA this codon is recognized by special release factor. The molecule of water is bounded to terminal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

A cell as open biological system has a substance exchange with external environment. A passive transport occur due to kinetic energy, however for active transport the metabolic energy is needed.

The plamolemm selectively regulate substance exchange.

While free transport molecules or ions pass through membrane passively at the original state. During a transport with transmitters, they pass through 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



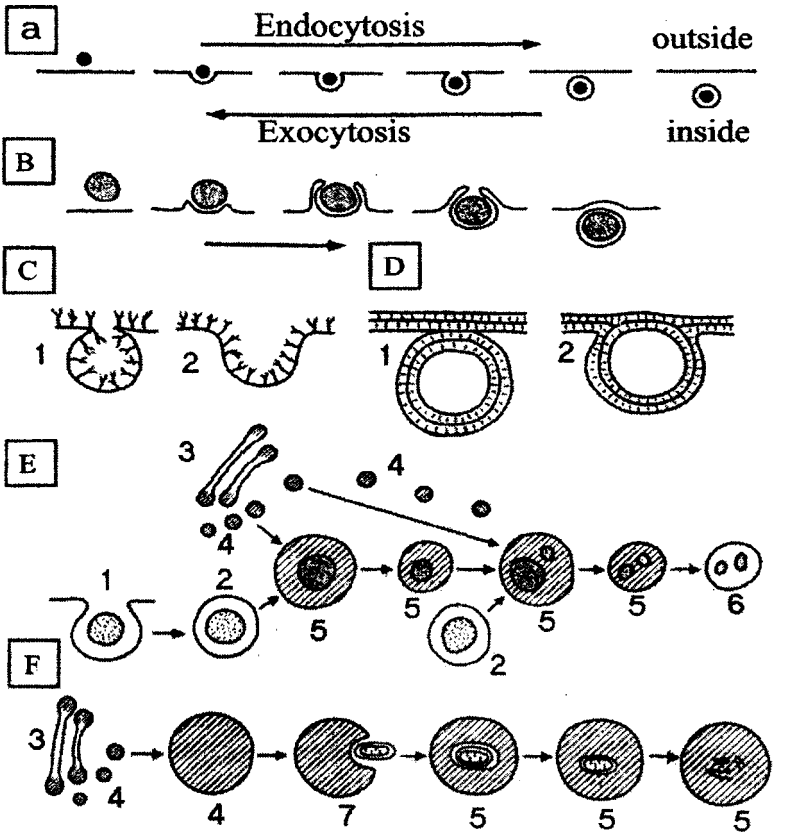
Pic 3.14. The transport of substances through plasma membrane:

A – catalyzing membrane passing: 1 – substrate attachment, 2 – conformation shift, 3 – substrate release, 4 – conformation shift (substrate is black, transport proteins are crossed). B – active transport: 1 – substrate attachment, 2 – ATP bounding, 3 – ATP hydrolysis, giving up ADP and energy, 4 – substrate release, 5 – conformation shift. C – different types of catalyzing passing: S – unique substrate, S1 and S2 two substrates of one transport protein. D – "proton pump", on a right side is parallel passing of second substrate S2 (from Kompendum der allegemeinen biologe editedby G. Elisabeth et al., 1982)

for cellular respiration, and carbon dioxide formed as a result of respiration, in 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 membrane occurs less actively because membrane lipids serve as a barrier, limitating diffusion.

According to a two ways theory, or theory of lipid filter, the lipid soluble molecules can diffuse directly through lipid bilayer. The rest of substances may pass only through slight imperfections in the sheet of lipid molecules. They passing speed of bigger particles depend on not only their molecular weight but also on their solubility. The water diffusion through semipermeable membrane is called osmosis. During this process occur free water concentrations decreasing 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 leads to increasing animal cell volume. For example, erythrocytes in a clear water increase in volume until the cell burst. In a plant, cell hypotonic conditions lead only to slight increasing cell in 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



Pic 3.15.The endocytosis, exocytosis and lysosome functions:

A – endo- and exocytosis; B – simple phagocytosis; C – exocytosis of Golgi vesicle; D – two phases of exocytosis (1 – membrane and vesicle still not fused, 2 – lipid bilayers fusion); E – heterophagocytosis, F - autophagocytosis (1 – endocytosis, 2 – endocytosis vesicle, 3 – Golgi complex, 4,5 – primary and secondary lysosomes; 6 – residual bodies, 7 – organelle consumption; regions with lysosome enzymes are crossed)./(from Kompendum der allegemeinen biologe editedby G. Elisabeth et al., 1982)

membrane. There are different transporters with different mechanism of action and different specificy to substrate (pic 3.14).

The passive transport with transport protein according to concentration gradient is called catalyzed transport or facilitated diffusion. By this way sugars, amino acids and other substances pass through membrane (pic 3.14a).

The coupled transport is a specific case of facilitated diffusion. Some trans-

porters carry two different substrates together in one direction or in controversial directions.

The active transport - it is transport of molecules and ions across membrane against concentration gradient driven by the expenditure of chemical energy. There is energy requirement because a substance has to move against its natural intention to diffuse in controversial direction. The transport ATPases - are transport proteins, which is able to degrade ATP liberating energy. This process may be considered as an engine of active transport. By this way, protons (proton pump) and ions (ion pump) enter to a cell. For example, a secretion of HCl in mammalian stomach and wide spread sodium-potassium pump, transporting K+ inside and Na+ outside of a cell, use active transport. The unbalanced states - the electrochemical potentials - are made on a surface of a cell with help of proton and ion pumps. They are used for performing parallel (or antiparallel) transport and they carry different molecules against their concentration gradient. Examples are transportation Na+ and sugar in animal cells in the same direction and same transportation of H+ and sugar in a plant cells.

The active transport may be performed by endocytosis and exocytosis.

The endocytosis - is a membrane vesicles formation by membrane invagination while consumption of soluble substances (pinocytosis) and solid substances (phagocytosis) (pic 3.15).Such vesicles are called pinosomes or phagosomes. Using endocytosis ovicell consume yolk proteins, leucocytes engulf foreign substances and immunoglobulines, a cell of renal tubules adsorb proteins from primary urine.

The exocytosis - is a process that is controversial to endocytosis. Different vesicles from Golgi complex fuse with plasma membrane and eject contains. Them vesicle membrane may stay as a part of plasmolemm or come back to cytoplasm in a form of a vesicle. Today the data were received that lysosomes takes part in removing whole cell or their organelles from an organism. That means that lysosomes perform autophagocytosis processes.

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 organism growth, development and regeneration. The time between cell formation by mother cell division and it own division or death is called cell cycle. For cell of an undividing cell populations the cell cycle is time between cell formation by mother cell division and it own death. The mitotic cycle is obvious component of cell cycle. The mitotic cycle is a time between two cell divisions and all processes that occur during this time. The mitotic cycle of growing population may be divided to two big periods: the period between divisions - an interphase, when cell grow, perform it function, and get prepare PI to divide; and cell division - mitosis. There IS cell

growth, DNA replication, duplication chromatid number, producing of mitotic spindle proteins, energy producing and storage during interphase.

The interphase may be divided to three periods.

Postmitotic or presynthetic period, period G1. During this period cells grow, produce RNA, proteins, store energy, but they don't make DNA. In presynthetic period cell nucleus contain diploid chromosome number, each chromosome contain only one chromatid. Chromosomes are despirilized. If we mention that DNA amount in 23 chromosomes is C, so the DNA amount in G1 is 2C.

Synthetic period, S period. During this period DNA replication occur. Each chromosome receives second chromatid. As a result of this amount of DNA after S period is 4C and chromosome number is diploid, each chromosome contain 2 chromatids.

Postsynthetic or premitotic period, period G2. During this period there is producing mitotic apparatus proteins and producing and storing energy for further mitosis. The next step is mitosis. The initial signal of mitosis start is changing of nucleus/cytoplasm ratio.

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

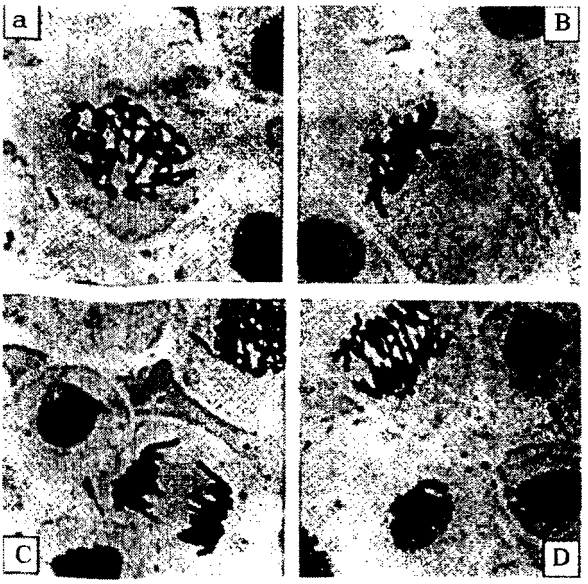
There are two types of cell divisions: indirect division (mitosis) and direct division (amitosis). The mitosis consists of mitosis itself, meiosis, endomitosis and polyteny. The amitosis is divided by shape (equal, non-equal, multiply, without citotomy) and by type (generative, reactive, degenerative).

The first to describe mitosis phases was I.D.Chistiakov in 1874. The detailed description of plant cell mitosis was made by E. Strassbourger (1876-1879) and animal cell mitosis by V.Fleming (1882).

3.4.1 The mitosis.

The mitosis (from Greek "mitos" - thread) - is unique type of animal and plant cell division, during which cell pass a range following changes leading to two daughter cell formation with diploid chromosome number and 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 (pic 3.16).

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



Pic 3.16. The mitosis in cells of onion root:
A – prophase; B – metaphase: C – late metaphase; D – early anaphase and late telophase (by O. Necasu et al., 1969).

width. There is diploid chromosome number in a nucleus.
Each chromosome consists of two chromatids, the DNA amount is 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, bounded to chromosome centromere.

The prometaphase. The cell cytoplasm has a small viscosity. Embedded in cytoplasm, chromosomes moves toward 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 good visible, that's why chromosome counting is performed at this stage. Each chromosome splits along itself on two chromatid. The nucleus characteristic is 2n - 2chromatids - 4C.

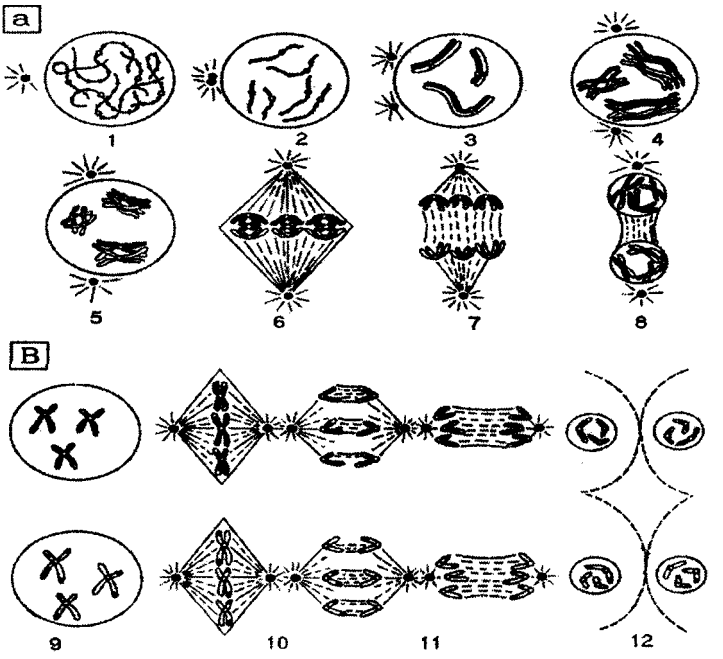
The anaphase. During this stage occurs chromatid movement toward cell poles. Such chromatid become a sister chromosomes. The spindle threads contract and pull chromosomes to cell poles. There are very active processes in cytoplasm, which is look like boiling fluid, while microphotographing. There are two chromosomes set at the end of movement on a cell poles. Each has diploid chromosome number, 2n, 1 chromatid, 2C DNA amount.

The telophase. The daughter chromosomes despiralize, loose good visible state. They are surrounded by new nucleus coat. The nucleolus is formed. The cell center looses its activity. The cytotomy (the cell cleavage) begins. The nucleus characteristics are 2n, 1 chromatid, 2C DNA amount.

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

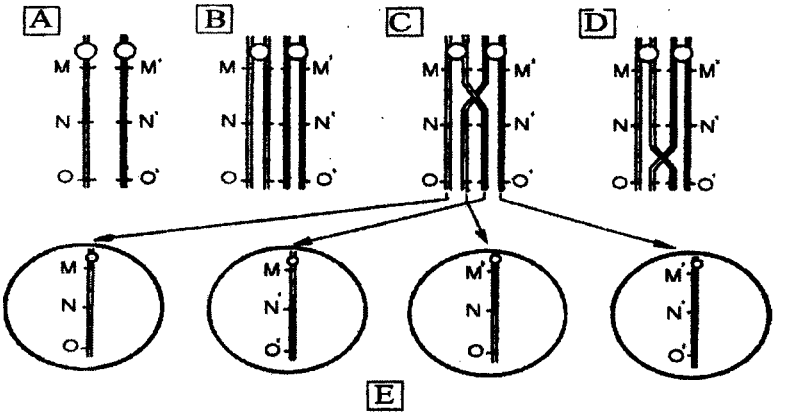
3.4.2 The meiosis.

This type of division appeared as a special mitosis form providing sexual reproduction of organisms. As meiosis result, 4 haploid cells are formed from one somatic cell with diploid chromosome number. The meiosis has two following divisions: the first - reducing division, which decreases chromosome number in half (meiosis I), the second - equalizing division when a cell save their haploid



Pic 3.17. The Meiosis scheme:

A – meiosis I (1 – leptomenn; 2 – zygonemm; 3 – pahynemm; 4 – diplonemm; 5 – diakinesis; 6 – metaphase I; 7 – anaphase I; 8 – telophase I); B – meiosis II (9 – interphase; 10 – metaphase II; 11 – anaphase II; 12 – telophase II) (by D.G. Harnden, 1974).



Pic 3.18. The scheme of crossing over:

A – couple of homologous chromosomes with three heterozygous locuses; B – stage of four chromatids; C,D – crossing over between two chromatids; E – four types of combinations in gamete after crossing over (by K. Shtern, 1965).

chromosomes set (meiosis II) (pic 3.17). The most complicate is meiosis I. It has elongated prophase consisting of five stages.

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

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

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 have been 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

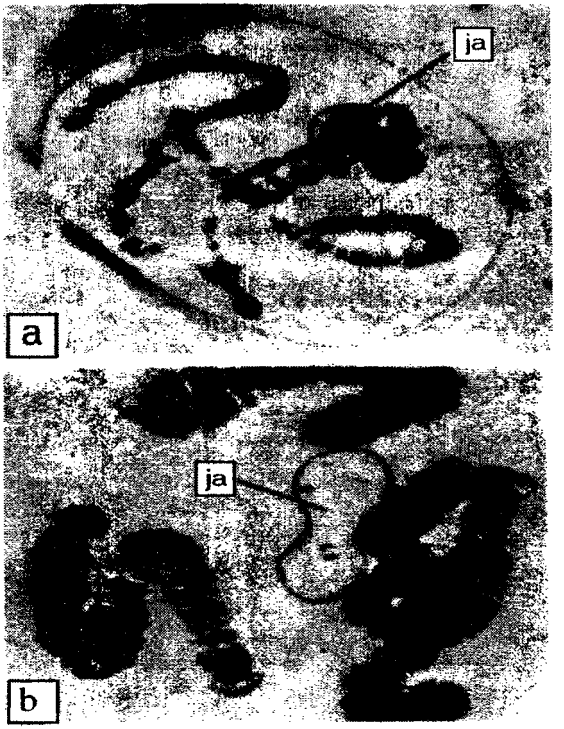
poles.

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

Between meiosis I and meiosis II is a short time period called interkinesis. During which chromosomes uncoils. 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 are moved to cell poles. In telophase II a cell containing haploid chromosome set, 1 chromatid and DNA amount 1C, are formed. Their destiny may be different: to be used for zygote formation or to die.

3.4.3 The endomitosis and polyteny.

The endomitosis - is one of mitosis type. During endomitosis occur only chromosome replication but it is not following by cell division. As result of this, the chromosome number in a cell is multiplied, sometimes in more than ten times.



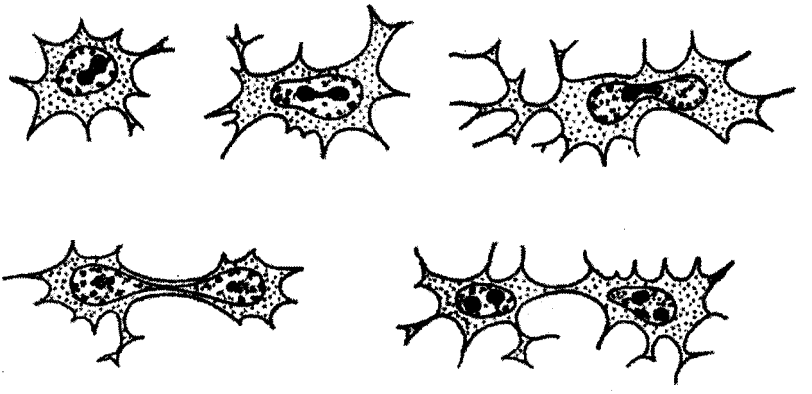
Pic 3.19. The polytenic chromosomes in nucleuses of salivary gland cells of Drosophila: a – chromatin in the nucleus; b – enlarged chromosomes with nucleolus (ja) (by O.Necasu et al., 1969).

The endomitosis occurs in intensively working 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 chromonemms reproducing in chromosomes without increasing chromosome number. The number of them might be increased in many times (in 1000 and more). The chromosomes grow until giant sizes because of DNA amount increasing. The polyteny was firstly described by A. Balbiani in 1881. The 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 (pic 3.19). The polyteny occurs in some insects, infusoris and some plants. In a drosophila, salivary gland cells the ploidity of chromosomes reach 1024. The polyteny is used for chromosome mapping and revealing chromosome changes.

3.4.4. The amitosis.

The amitosis (from Greek, a- negative, mitos - thread) or direct division of cell is nucleus division without chromosome spiralization and assembling mitotic apparatus. In 1841 R.Remark was first to describe amitosis. During direct division, firstly, nucleolus is divided into two parts, and then such division occurs with nucleus and cytoplasm (pic 3.20). 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 having many nucleuses are created (amitosis without cytotomy).



Pic 3.20. The amitosis: stages of division of synovial mouse cell (by P.B. Gofman-Kadoshnikov, 1966).

There are several factors that may lead to amitosis. According to these factors, amitosis may be divided to three types: generative, reactive and degenerative (Zhilkin L.N., 1966).

The generative amitosis may occur while highly spetialized cell division. It is in infusoria while macronucleus division, in some mammalian cells (liver cells, epidermis cells).

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

The degenerative amitosis may occur only in aging cells. It is presented by nucleus fragmentation and it has no any 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, leading to tissue growth. Contemporary, cells of animal tissues may be divided into three main groups: labile, stable and static.

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

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

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

The process of wound healing connected with cell division. The value of proliferation is determined by tissue ability to division. None wound may be healed without cell division. And operating surgeon has to consider the ability of the cell and tissues to reproducing (proliferation).

3.4.6The mechanisms providing cell division.

A pioneer in studying of reasons and controlling factors, which are responsible for cell division, was A.G. Gurvich (1874-1954). He pushed forward the hypothesis about influence of special mitotic rays on division process. L. Y. Bliaher (1954) and I.A. Utkin (1959) showed an important role of neurohumoral regulation of mitotic activity. It was stated that epinephrine secretion suppress mitotic activity, but thyroid hormones activate mitosis. Removal of the adrenal gland leads to switching off effect of mitosis suppression. It was stated that there are many reasons

leading to mitotic divisions. It was proved that all synthetic processes in a cell preparing to division are controlled by its genetic material. The genes controlling this process are in different chromosomes. F. Jacob and J. Monod (1961) suggested a hypothesis of gene activity regulation in prokaryotes. This hypothesis may be used today and for explanation of eukaryotes gene activity.

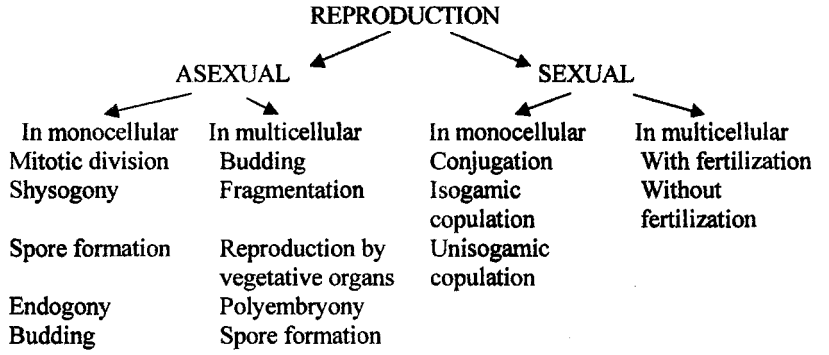
The cell biology is very important for understanding ontogenetic life organization level. It is still needed to make completely examination of all structural cell components, to understand reasons of determination, differentiation and synchronization of cellular reproduction, to clear mechanisms of controlling, regulation and integration of cell and its organelles. Thus, answering this question is important for

CHAPTER 4. ORGANISMS REPRODUCTION.

4.1 The classification of reproduction types.

The ability to reproduce itself is one of the main features of life systems. On molecular level, reproduction process is determined by nucleic acids duplication ability. On ontogenetic level, self reproduction is performed in different forms: from simple division of protists to sexual reproduction of animals and plants, which is very complicate process in structural and functional aspects.

The reproduction - is ability of organisms to produce new organisms similar to them; and ability of organism to produce offsprings. One's being is supported by cell reproduction; and species being is supported by organism's reproduction. The reproduction is necessary condition of species being and generation's continuity in it. Although, the reproduction ways in worlds of plants and animals are very diverse, but they may be divided into two general types: asexual and sexual.



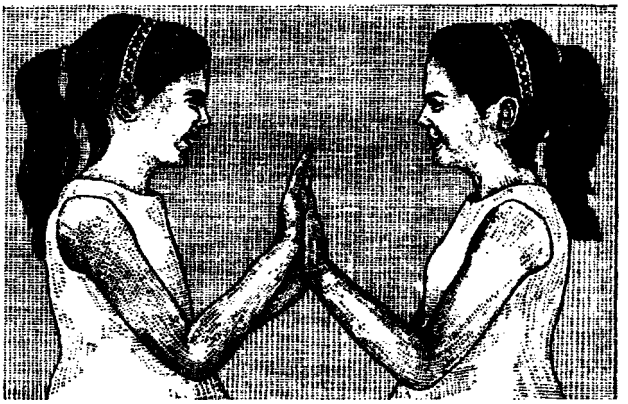
4.2 The asexual reproduction.

The asexual reproduction is a reproduction in which only one parent organism takes part. As result of its division or budding one or several new organisms are formed. These organisms are identical in genotype to parent organism. During asexual reproduction, the somatic cell sets a new organism. There is no special reproductive cells formation.

Protists (ameba, flagellata, and infusoria), bacteria, cianobacteria and some green algae have asexual reproduction in form of binary fission, plasmodiums –

in form of shysogony, some fungi – in form of budding. A toxoplasm has an internal budding so called endogony. Between multicellular animals the sponges, hydras have asexual reproduction in form of budding; flatworms and annelids have asexual reproduction in form of fragmentation (body cleavage on several parts).

Multicellular plants have vegetative organs for asexual reproduction such as root, shoot, leaf, tuber, bulb and others.



Pic 4.1. The monozygous twins (by S.Sinnot, L.Dunn, Th.Dobzhansky, 1958).

As particular case of asexual reproduction, vertebrates have polyembryony. It was described by I.I.Mechnicov. He observed medusa blastula splitting and further development of entire organism from each cellular conjugate. Humans also have such way of reproduction. It leads to twins development (pic 4.1).

The spore formation is a type of asexual reproduction, which is characterized by special cell formation. A spore (from a Greek. spora – a seed) – is one of life cycle stages using for reproduction. It is consist of cell, appeared from mitosis or meiosis. It is covered by coat, which defends it from harmful external conditions. Protists, algae, fungi, mosses, ferns and whisk ferns have a spore formation. Bacteria also produce spores, but their spores serve for surviving in inappropriate conditions, not for reproduction. Some higher plants have a spore formation as a way of reproduction.

The asexual reproduction is typical for animals with low level of structural and physiological organization. Among them, there are many human parasites. Their asexual reproduction serves not only for increasing organism's number, but also facilitates to take a new areas for living and to survive in an inappropriate conditions.

4.3 The sexual reproduction.

The sexual reproduction means a development of offspring from fertilized ovicell – zygota, i.e. fused male and female sex cells. While sexual reproduction the continuity between generations is performed by special sex cells – gametes (from Greek "gamos" - marriage). Such cells have a haploid chromosome set and they are formed in meiosis. These cells are spermatozoa and ovicells.

The sexual reproduction now dominates in animal and plant world. It has some advantages over asexual reproduction.

1. A higher reproduction coefficient is reached, i.e. it gives more new organism germs.
2. A full renewing of genome occurs. It happens because of mother and farther genetic information fusion. Such process is a permanent source of hereditary diversity. It extends an adaptation ability of species in abiotic and biotic conditions and provides a success in survivement competition.

The basement of sexual reproduction is sexual process. The essence of it is a fusion of genetic material of parents to genetic material of offspring.

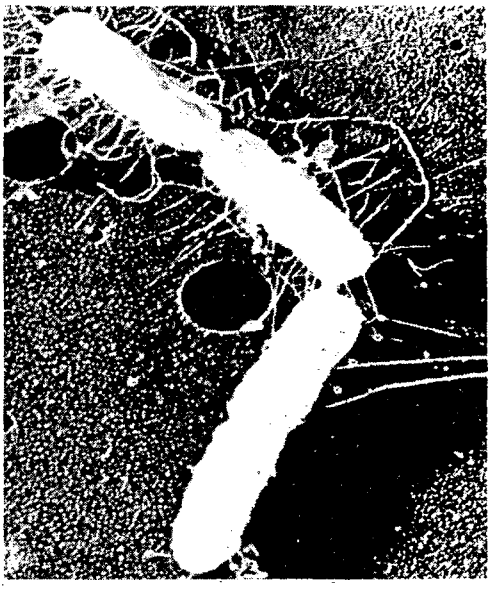
The sexual reproduction of multicellular organisms, including a human, is characterized by three external morphological features.

1. A source for new organism formation is special cells of parent organism – gametes.
2. There are two types of sex cells: male and female. Commonly they are produced by different individuals, excluding genuine hermaphroditism cases. Sex cells differ from each other by morphological and physiological properties, i.e. they have sex differentiation (specialization).
3. The fusion of two gametes, male and female, is needed for new organism formation.

Eukaryotes have three main types of sexual reproduction. They have been formed during their evolution. They are conjugation, copulation and irregular types of sexual reproduction.

The conjugation (from Latin "conucatio" - fusion) – is a form of sexual process, providing increasing genetic variability, having no sex cell formation. It occurs in prokaryotes (enterobacteria, pseudomonads etc.), protists (infusoria), algae (ulotrix and others), and fungies (pic 4.2). During conjugation two organisms temporarily unites for genetic information exchange. As result of this, organisms genetically different from parents appear. Then they perform asexual reproduction.

The copulation (from Latin "copulatio" - joining) – is a process of sex cell fusion, in which cells are almost same (isogamy) or different (anisogamy). Isogamy occurs in monocellular algae, lower fungies, flagellatae. Anisogamy occurs in



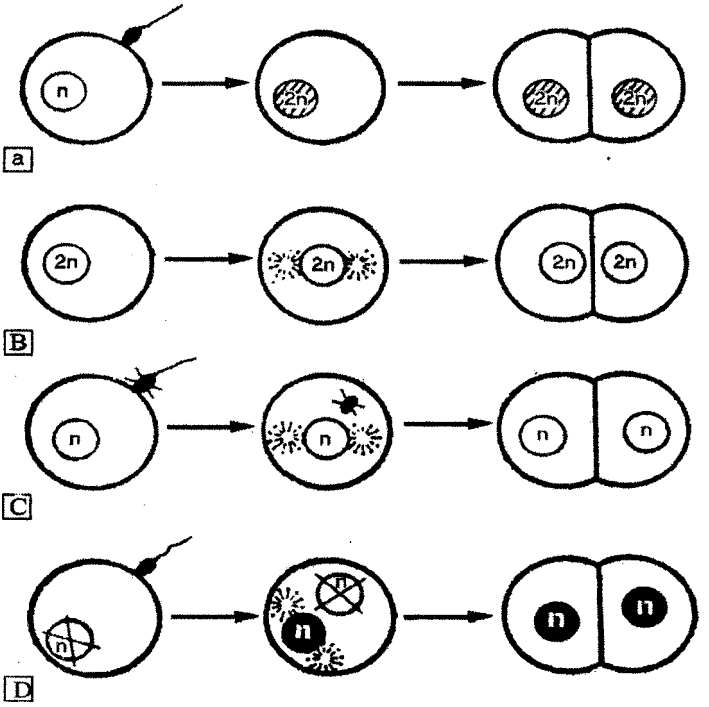
Pic 4.2.The electronic microscope photo of bacteria conjugation (by N.P. Dubinin, 1976).

chlamidomonas and plasmodiums. If gametes are very different from each other (oogamy), the term fertilization may be used for pointing their fusion. Humans and higher vertebrates have an oogamic copulation.

The irregular types of sexual reproduction are parthenogenesis, ginogenesis and androgenesis.

Parthenogenesis (from Greek "parthenos" - virgin) – is a process of embryo development from unfertilized ovum (pic 4.3 b). A natural parthenogenesis was described by Sh. Bone in XVIII century. It may occur in lower crustacea, some insects (bees) and birds (turkey). Parthenogenesis might be stimulated artificially, through ovicell activation by different factors. The artificial parthenogenesis was firstly described by A.A. Tichomirov. It may be distinguished somatic (diploid) and generative (haploid) parthenogenesis. In somatic parthenogenesis, an ovicell is not subject to reducing division (meiosis). Moreover, even if it is subject to it, two newly formed haploid nucleuses are fused to one, restoring diploid chromosome set. In generative parthenogenesis, an embryo is developed from haploid ovicell. Plant parthenogenesis is called apomixis.

Ginogenesis (from Greek "ginos" - female) – is a type of sexual reproduction, when sperm serves only like activators of ovicell development, and fertilization doesn't occur (pic 4.3c). Only female genetic material is used for embryo devel



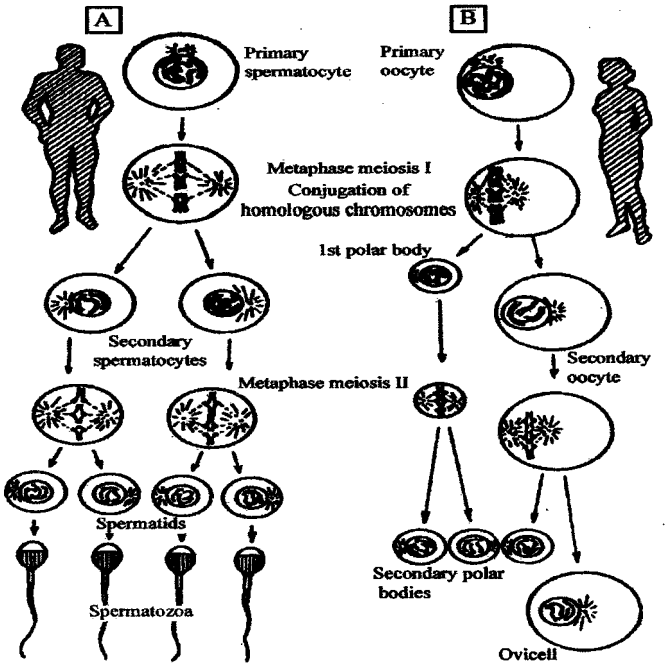
Pic. 4.3. The types of sexual reproduction:

A – usual fertilization; B – parthenogenesis; C – ginogenesis; D – androgenesis (by M.E. Lobanov, 1967).

opment. Ginogenesis occurs in some nematodes, amphibians and in some angiosperm plants.

Androgenesis (from Greek "andros" - male) – is a type of sexual reproduction when embryo development is performed from male nucleuses and female cytoplasm (pic 4.3d). It may take place in such cases when female nucleus has died before fertilization occurs. If only one sperm enters ovicell, there is development of haploid embryo. As usually, such embryos are weak. It may survive better if diploid chromosome set is restored. If there is a polyspermy, the fusion of two male nucleuses may occur. Androgenesis occurs in silkworm, some wasp species, corn and tobacco-plant.

Androgenesis and ginogenesis are used for studying heredity principles, nucleus- cytoplasm interactions, for getting strictly homozygote organisms and animals of same sex.

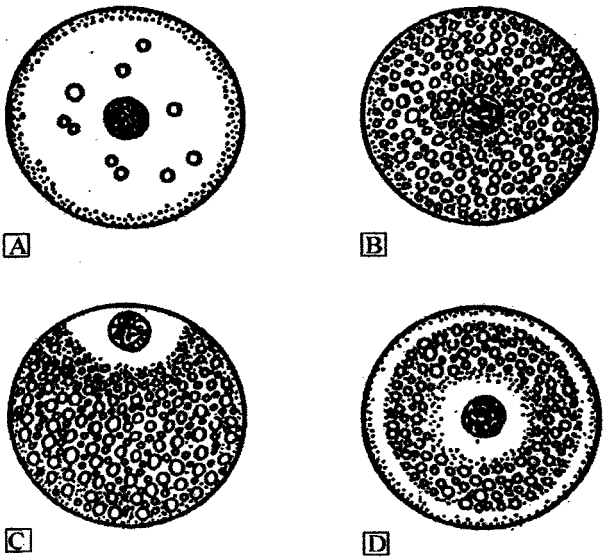


Pic 4.4. The spermatozoa (A) and ovicells (B) formation in human (by N.P.Dubinin, 1976).

4.3.1 The gametogenesis. The features of gametes structure.

The gametogenesis is a process of sex cell formation. All cells of a body, somatic and reproductive, have their origin from embryonic cells. During embryonal development 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 (pic 4.4).

The spermatogenesis. During a first period (period of reproduction) cells of sexual germ are presented by spermatogonia. It is small round shape cells with a small amount of cytoplasm, dividing very actively. They are subject to division almost all life long, from childhood to eldely. At puberty onset, the part of spermatogonia stops their division and they are changed to spermatozoa. A growth period is characterized by reproduction termination and spermatogonia are changed to primary spermatocyte. They grow, increasing their size in four times. They lie

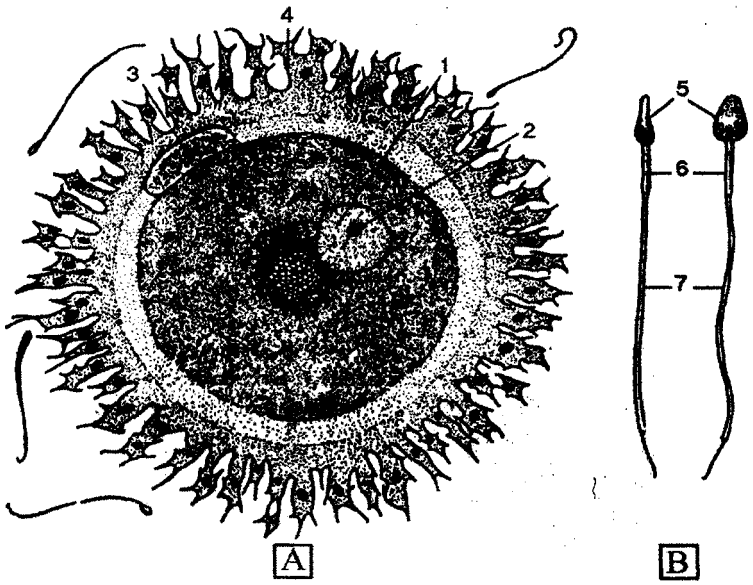


Pic. 4.5. The ovicells' types:
A – alecitinal, B – isolecitinal, C – telolecitinal, D – centrolecitinal (by B.N. Tokin, 1966).

in semineferous tubules closer to duct. During maturation period a meiosis division is performed. As result of this primary spermatocytes are changed to secondary spermatocytes and then to spermatids. Secondary spermatocytes are in two times less in volume than primary spermatocytes.

However, spermatids are in four times less in volume than primary spermatocytes. They lie closer to duct lumen than primary spermatocytes. During period of formation, the spermatids are changed to spermatozoids

The oogenesis. Oogonia have a reproduction period only during embryonic development. At the end of this period, oogonia stop reproducing and are changed to primary oocyte. They are preserved in ovarium until puberty. At the puberty onset, the growth period starts in selected oocytes. It may be distinguished "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 maturation period two irregular meiosis divisions occur. Primary oocyte gives up the secondary oocyte and the first polar body. Then secondary oocyte gives up second polar body and after that, it becomes mature



Pic. 4.6. The human ovicell (A) and spermatozoon (B) (x2000);
1 – nucleus, 2 – nucleolus, 3 – polar body, 4 – corona radiate, 5 – head, 6 – neck, 7 – tail (by K. Villy, V. Detier, 1971).

ovicell. The first polar body may be divided to two polar bodies. This irregular division may be explained by expediency of yolk and cytoplasm preservation for ovicell.

Thus, the main differences of oogenesis from spermatogenesis may be concluded in following: 1) the reproduction period of oogonia is terminated after birth; 2) The oogenesis growth period is longer and have subdivisions to "small growth" and "large growth". Oocyte becomes bigger than spermatocyte; 3) Primary oocyte may give only one full gamete, whereas spermatocyte gives four; 4). In oogenesis period of formation is almost absent.

The sex cells, which were formed in gametogenesis, have a following structure.

Ovicells – are oval, big, immobile cell which are in hundreds or even millions times bigger than spermatozoa. Many animals have ovicell without centrosome, unable to be divided.

There are several ovum types according to yolk amount and distribution. Isolecitinal ovicells (primary and secondary) have a satisfactory amount equally distributed yolk, with nucleus in central of a cell. Polylecitinal ovicells (centrolecitinal and telolecitinal) have excessive amount of yolk. Alecitinal ovicells

have very little equally distributed yolk. The ovicells of mammalians and flat-worms are alecitinal. However, some researchers consider mammalian ovicell to be isolecitinal as many mollusks, lanceolate ovicells are. In telolecitinal ovicell yolk is distributed irregular. It is very little yolk near animal pole of such ovicell. A large amount of yolk is on vegetative pole of ovicell. The examples of such ovicells are ovicells of amphibia, reptilia and birds. Centrolecitinal ovicell has a large amount equally distributed yolk. However, near cell membrane there is a cytoplasm layer without yolk. The nucleus of such cells also is surrounded by the same cytoplasm layer. Arthropods have ovicells of this structure.

The ovicell is protected by coats (pic 4.6a). There are primary coat produced by ovicell itself, secondary coat, produced by follicular cells, tertiary coats that surround ovicell while it moves in uterine tube.

All animals have primary coat. It also called yolk coat. Humans and mammalians have it as an internal part of dense coat. The external part of dense coat is produced by follicular cell and it is secondary coat. Microvilia of ovum enter to the dense coat from inside and microvilia of follicular cells enter from outside. On a high power magnification, it is looked striated and that why called radiated coat "corona radiata" or shining coat "zona pellucida". The dense coat contains primary and secondary coats.

Tertiary coats are well developed in reptilians, birds, amphibians and cartilaginous fishes. These coats have no cellular structure. They are produced by uterine tube mucosa to defend ovum from different harmful influences. Those animals that live on a land use such coat for water and food storage for embryo.

Spermatozoa – are a small, mobile cell with nutritive substances storage reduced to minimum. A sperm has head, neck and tail. In the head there is a nucleus surrounded by thin cytoplasm layer. There is acrosome on a top of the head. Acrosome is derived from complex Golgi. It is consist of compact mass and membrane. It contains active substances facilitating ovum coats penetration by sperm. There are two centrioles, proximal and distal in a sperm neck. Distal centriole forms axis thread of a tail. Proximal one takes part in cell division after fertilization. Tail is an organ of movement. The core of a tail is axial thread. It is surrounded by mitochondria (in a main part) providing energy for movement.

A sperm brings centrosome to ovicell while fertilization. The cytoplasm of sperm head has liquid-crystal state, which defend it from harmful environmental influences. Sperm has high nucleus/cytoplasm ratio corresponding to it main task – to bring genetic material to ovicell. Acrosome enzymes help to dissolve ovicell coat.

4.3.2 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 system of reflexes and is performed by special copulation organs.

It is believed that gametes secret special substances – hamons, which provide their interaction on a distance. Ovicell produce ginohamon I and II, sperm produce androhamon I and II. Ginohamon I is non-protein structure with low molecular weight, stimulating sperm movement and increasing probability of sperm and ovicell contact. An antagonist of ginohamon I is androhamon I with similar chemical structure. It suppresses sperm movement and preserves them from preliminary energy waste. Ginohamons II (fertilysins) are proteins or glycoproteins. They totally block sperm movement facilitating sperm attachment to ovicell membrane. Androhamone II helps to dissolve ovicell coats. The methods of artificial insemination of fishes and farm animals were suggested by scientists V.P.Vrasskiy and I.I.Ivanov. The artificial insemination of human was permitted in USSR in 1987.

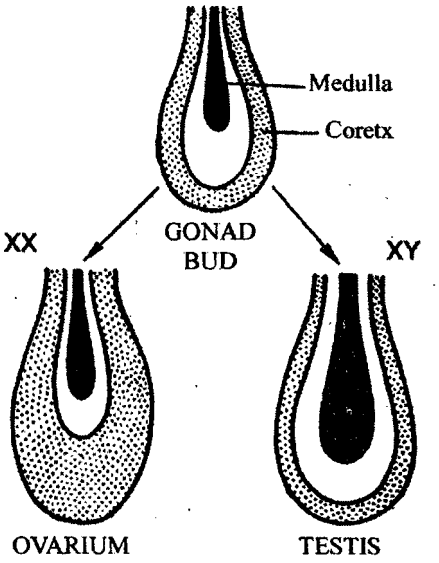
Fertilization is a process of two gametes fusion resulting in zygota formation. Fertilization consists of three stages: penetration, activation and fusion.

The sperm and ovicell meeting is provided by unspecific factors facilitating their merging such as excessive sperm production, large sizes of ovum, secretion of hamons.

The acrosome reaction occurs at the moment of sperm and ovicell touching. The liberated acrosome enzymes help to dissolve ovum coats. It allows fusing sperm and ovum cell membranes. Then cytoplasms of sperm and ovum fuse. The sperm nucleus and centriol come to 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 ovum and change membrane charge. Then cortical reaction occurs. The contents of cortical granules assist dense coat exfoliation. It is become more solid and impermeable for sperms. It is called fertilization coat. The amphibians and bony fishes have cytoplasm changes called cytoplasm segregation. Activation is finished by protein synthesis start.

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



Pic. 4.7. The scheme of gonad differentiation in ontogenesis (by M.E. Lobashov, 1967 with changes).

4.3.3 The hermaphroditism. The formation of sex dimorphism.

When organisms had become multicellular, they received a possibility to form gametes of two types in one organism at the same time, i.d. they were hermaphrodits. It is less possible that multicellular organisms at first had different sexes. Indeed, there are many hermaphrodits between plants, flatworms, annelids, mollusks. In spite of producing both types of sex cells, the self-fertilization is untypical for them. Usually it happens because of asynchronic maturation of male and female gametes.

Even human may have true hermaphroditism. It appeares as a disturbance of embryogenesis when all body cell have same chromosome set – XX or XY. However, some human hermaphrodits have mosaic distribution of chromosomes in somatic cells. Some cells have XX, some XY.

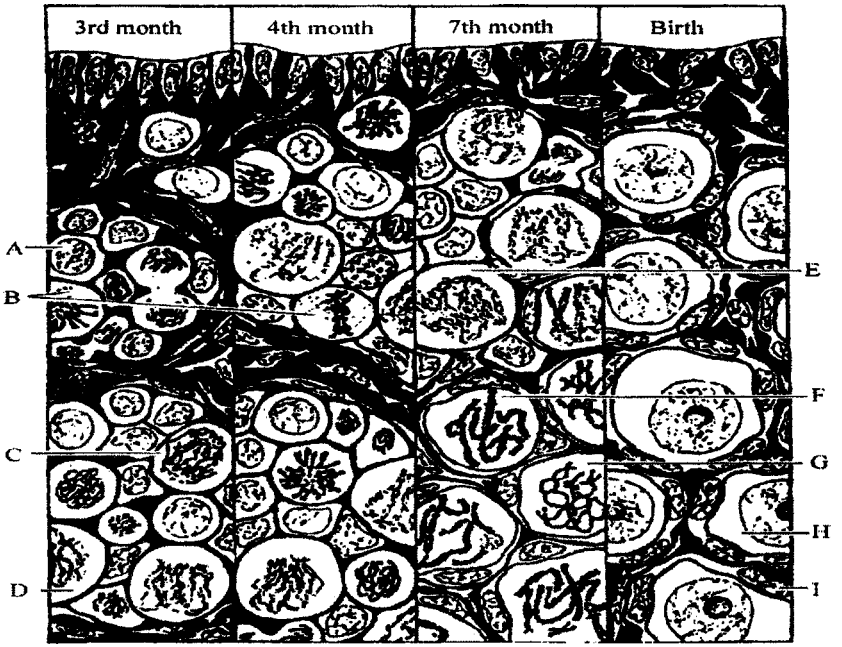
A human and mammalian gonad is developed from a bisexual germ. It cortex (outlayer) has a properties to form ovarium, but medulla (inner layer) has a properties to form testis. If organism has genotype XX, the cortex is developed better than medulla, forming ovarium. If organism has genotype XY, the medulla is developed better than cortex, forming testis. Accordinary to those facts M. Chartman (1936) assumed a concept about organism's bisexuality

The formation of sex dimorphism was closely connected with eukaryotes appearance. This process was related with increasing gametes sizes and with formation of big and small gametes, with appearance of anizogamy as copulation type, with sperm production in large amount. The next step was a specialization of organisms on that which produce mostly spermatozoa and that which produce mostly ovicells.

CHAPTER 5. HUMAN REPRODUCTION.

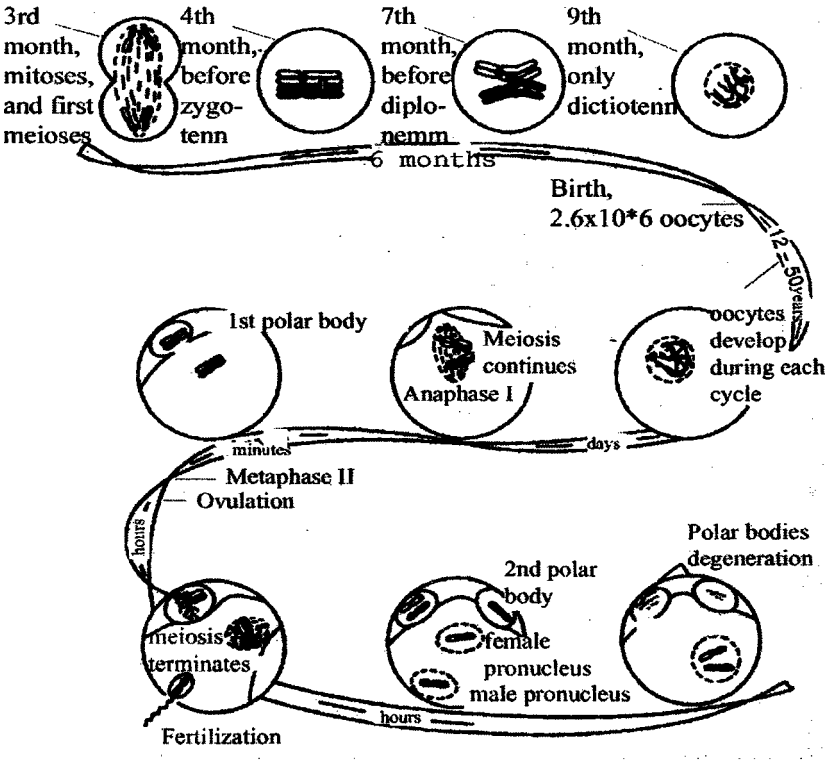
5.1 The features of human spermatogenesis and oogenesis. Their regulation by hormones.

When an embryo has reached a size 20 mm, specific sex features of female become evident. The primary sex cells, incorporated in gonad germ, proliferate and are subject to differentiation to ovogonia in ovariums of embryo at 2nd month of development. At the end of 3rd month in deep layer of female gonad, it may be distinguished a differentiated oocytes in prophase of meiosis I. At 7th month, the histological differentiation of ovarium is very active. So, at 9 month there are 200000-400000 oocytes in an each embryo ovarium. Some investigators state that there are about 1 million oocytes (pic 5.1). Oocytes are surrounded by follicular cell monolayer and form primary follicule. After birth, oocytes are preserved until puberty in diplonemm of meiosis prophase I. When puberty has been reached, the oocytes continue their meiosis. First meiosis division has done before ovula



Pic. 5.1. The oogenesis in human female embryo:

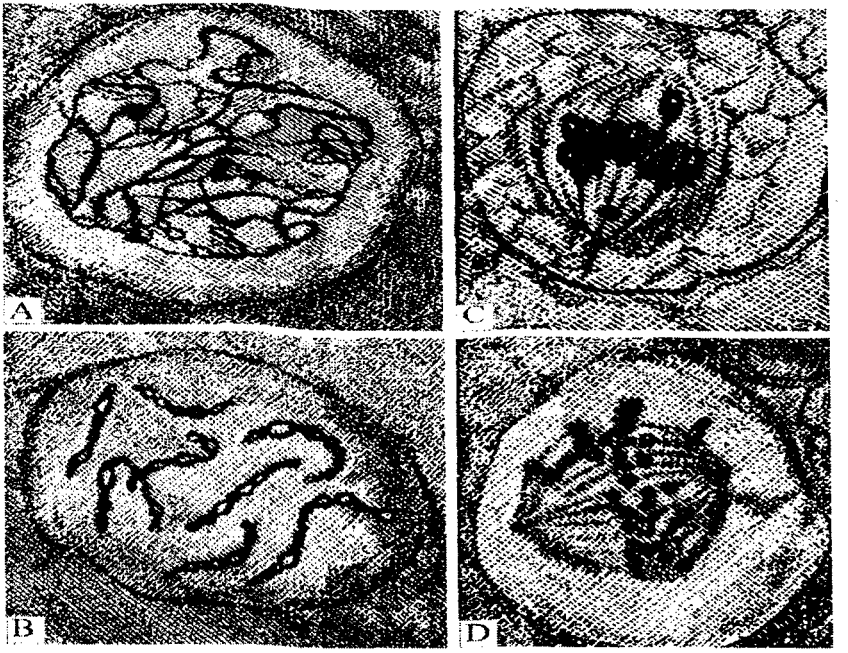
A – interphase; B – metaphase; C – anaphase; D – leptonemm; E – zygonemm; F – pahynemm; G – diplonemm; H – diakinesis; I – oocyte surrounding cell (by S.Ohno, 1962).



Pic. 5.2. The scheme of vogenesis in female organism (by K.Bresch, M.Hausman, 1972).

tion (liberating of ovicell from follicule). This division is very unequal. Secondary oocyte gets the most of cytoplasm, whereas a polar body gets a minimum. The second meiotic division does not occur until fertilization and result in production of 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 (pic 5.2).

Now it is apparent that regular follicule growth, ovulation and regression is regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) of pituitary gland. Growing follicules produce estrogens (estradiol) which may act on pituitary hormone production. It is stated that follicule growth mostly depends on FSH, but ovicell maturation and ovulation mostly depends on LH. The hormone mechanism integrates two different, evolutionary unconnected processes as follicule growth and ovulation. This allows providing fully differentiated ga



Pic. 5.3. The meiosis in human spermatogenesis:

A – zygonemm (conjugation of homologous chromosomes); B – pahynemm; C – metaphase I; D – anaphase II (by B.Severinghause, 1942).

metes for fertilization. To trigger meiotic division it is necessary to have a small amount of LH. But to perform ovulation we need to have a peak of LH concentration. So, in some cases, ovicell has done meiotic division, but LH concentration isn't enough to perform ovulation. At this situation an intrafollicular aging of ovum occurs. The properties of ooplasm are changed, which is mainly concerned for cortical layer and for spindle apparatus. This cause an ovum death, loosing fertilization ability, or formation of zygote with unbalanced chromosome set. This resulting in embryo death and formation of embryo with chromosome defects (such as Dawn syndrome). It is believed that intrafollicular ovicell aging is connected with seasonal disturbances in neurohornonal regulation pattern.

A male primary sex cell is subject to differentiation to spermatogonia when a male embryo has reached a size 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 male's gametes formation continues throughout all life. A process of sperm

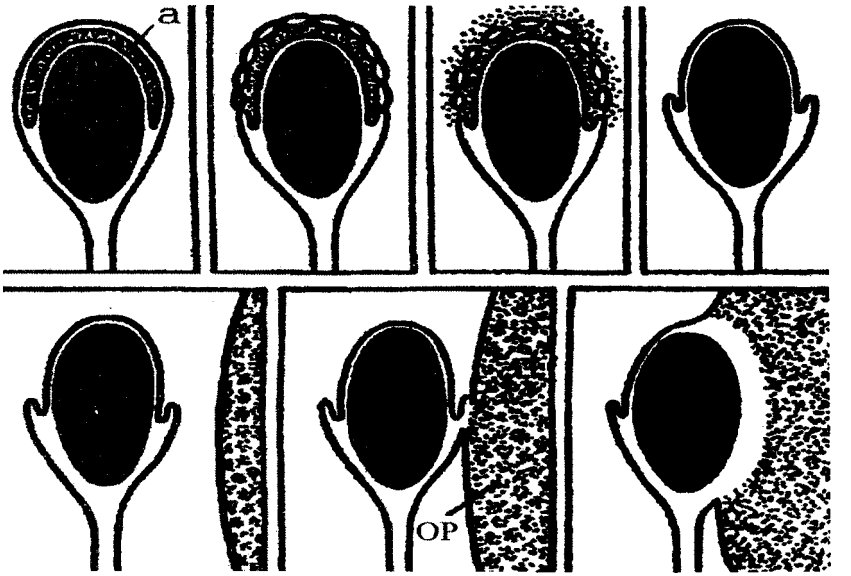
formation takes about 70 days. Each day 10*7 spermatozoa are produced per 1 gram of testis weight. The epithelium of semineferous tubules consist of external layer of germinative epithelial cells and six inner layers corresponding spermatozoa formation stages. The division of germinative cell gives a rise to many spermatogonia, which increase in size and become primary spermatocytes. Primary spermatocytes are subject to meiosis I forming secondary spermatocytes. They becomes spermatids after meiosis II (pic 5.3).There are Sertoli cell in-between developing lines of cell. They perform nutrition for developing cells and they also secrete a fluid that helps spermatozoa to move inside of the 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. To produce spermatozoa successfully it is necessary to have both testosterone and FSH. Whereas a development and maintenance of male secondary sexual characteristics requires only testosterone.

5.2. The human fertilization.

Ovum and sperm have a limited life span and that why a limited ability for fertilization. A liberated from follicle human ovum preserves fertilization ability during 24 hours, whereas spermatozoa are still active during 4 days if placed in female sexual ways. However, 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 sperm number plays an important role in fertilization.

During human ovulation, an ovum is liberated from ovarium. It is surrounded by layer of follicular cells, which is bounded to each other by proteoglycans. In such complicated dressing ovum is unavailable for sperm penetration. It should be liberated from "corona radiata". One sperm cannot dissolve such coat. They need to work all together to dissolve it. From a great number of spermatozoa attacking ovum only one can enter it. Ovum membrane bulges out making an acception hill toward sperm, permitting a sperm nucleus to enter the cytoplasm of the egg. Only this nucleus will fuse with ovum nucleus. If any other sperm would enter the ovum cytoplasm, it will be destroyed in cytoplasm.

When sperm has touched ovum, it perform acrosome reaction. It is liberation of enclosed in acrosome enzymes, such as hyaluronidase, protease, and enzyme dissolving follicular cells attachments. During this reaction, a sperm plasmolemm and external acrosome membrane touch each other in many sites. Then, they pro



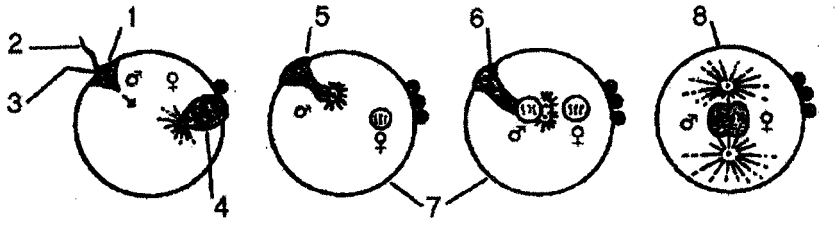
Pic. 5.4. The acrosome reaction and first stages of sperm and ovicell membrane fusing in mammalians:

A – acrosome, OP – ooplasm, nucleus is black (by C.R.Austin, 1972).

duce holes in these sites. The enzymes are liberated through these holes. Apparently, sperm pass zona pellucida with help of proteolytic enzyme. Then, it touches ovum plasmolemm by head side and ovum membrane incorporates sperm membrane.

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

The human spermatozoa penetrate ovicell, which is in maturation period. 10 hours after penetration oocyte eliminate primary polar body and 24 hours later secondary polar body (pic 5.5). Right after sperm penetration, the ovicell performs cortical reaction. It helps to make impermeable coat for other sperms. At the same time, the other sperms surrounding ovum loose their directed activity, although keeping their mobility. After that the ovum changes its metabolic activity, such as increasing membrane permeability, increasing of warm producing,



Pic. 5.5. The scheme of following stages of sperm and ovicell fusing in human during fertilization:

1 – sperm head, 2 – sperm tail, 3 – accepting hill, 4 – second meiosis division, 5 – entering way, 6 – nucleuses getting closer to each other, 7 – formation of polar bodies, 8 – nucleuses fusing (by K. Villy, V.Detier, 1971).

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

Humans have similar rhythms of reproductive activity as animals do. Such rhythms were formed according to environmental factors influences. It is known that menstrual cycles have a same length as moon cycles, although a direct connection between them is lost. Today around 10% of menstrual cycles of healthy women are without ovulation. The interchange of ovulatory and anovulatory cycles depends on activity of neuroendocrine system. Thus, a birth rate statistics in Western Europe, Australia and USA showed that birth rate curve have 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 during spring and autumn months.

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 ovulation and fertilization, to overmaturation of female and male gametes. The influence of this factor is proved by higher rate of chromosome defects in human embryo on early stage of development and by wide spectrum and higher rate of "spontaneous" development defects in humans than in animals.

5.3. The critical periods in human development.

An important aspect, concerning mechanisms of reproductive process defects, is that influence of harmful factors is different in different ontogenesis stages. P.G. Svetlov suggested a concept about critical periods of human development based on pathological findings. The most vulnerable periods of embryo structures forming usually coincide with the first stages of some organs formation, occurring mainly in a first 9 weeks of development. Hence, P.G. Svetlov suggested

providing health care for women at that time (elimination of harmful factors, creating less intensive work schedule, providing additionary vacations and so on). However and today these suggestions aren't used in health care. In his last work, P.G. Svetlov assumed that gametogenesis also has critical periods. It was shown that ovicell especially sensitive to harmful factors influence in a preovulatory period of sex cycle. During this period alcohol and range of others substances cause more defects. That means that we have to concern not only about early pregnancy stages care but also about preserving of preovulatory period of sex cycle.

5.4. The biological sex determination in a human.

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

The formation of this system start from genetic sex determination by chromosomes set (pic 5.6). The genetic sex determines gonad (or genuine) sex, identificated by main sign of sex – histological structure of sexual gland. It is genuine because it is allows to determine gamete sex, i.d. ability of sexual gland to produce spermatozoa or ova. Gonads show an individual role in reproduction process. Also gonad sex determines hormonal sex – 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). Morphological sex means features of structure and development of internal and external sexual organs, and also secondary sexual characteristics. It is important to note that a term "sex" is composed from many related to each other biological, social and psychological components. *Sex – is a union of organism's signs and properties providing participating in reproduction and hereditary information transmission through making gametes.*

The biological sex differentiation is programmed by genetic sex chromosome set in zygote after gamete nucleuses fusion (pic 5.7).

It was pointed above that embryonic gonad is bisexual. Formation of primary gonads occurs on 5th week of embryonic development. The genetic sex is determined by sex chromosome (X or Y) of sperm. The X chromosome has a gene of testicular feminization (Xtfm), normal allele of which is responsible for receptor synthesis for androgens. Since, male and female organism has at least one X

chromosome. That means that both sexes have such receptor. Y chromosome has a gene, which is responsible for synthesis H-Y antigens, which stimulate differentiation of sexual folds' cells to semeniferous tubules and intersticial cell. If individual has genotype Xtfm Xtfm, the ovarium will be formed from primary gonad cortex. If individual has genotype Xtfm Yh-Y, the testis will be formed from primary gonad medulla.

At 10th week of 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 (gonad's sex) may be determined by generative elements state: primary follicules with oocyte I in ovariums and semeniferous tubules with spermatozoa in testis.

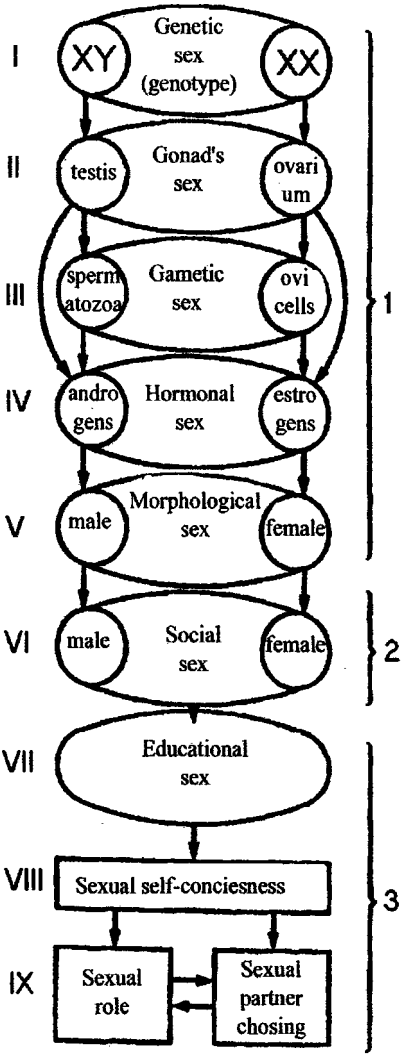
A hormonal gonad function is producing sex hormone in their intermediate tissues (teca cell in ovarium and Leidig cell in testis). Both ovarium and testis produce main sex hormones: testosterone, estrogen, progesterone, but in different ratio. Ovariums mostly produce estrogens and after ovulation progesterone.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

Tissues of potential female reproductive system are not activated and they don't develop. In an embryo with sex chromosome set XX the absence of testosterone allows reproductive system to develop female pattern. On a 10-12th week of embryonic development the internal sex organs are formed. Until differentiation period, both male and female embryo has a rests of pronephros urethra, which are a precursors of sexual organs of both sexes.

So called Muller's canals are precursors of female sex organs – uterine tubes, uterus, and upper part of vagina. So called Wolf's ducts are precursors of male reproductive organs – epididymis, vas defferens, seminal vesicles.

After 12th week of development in case of having satisfactory concentration of testosterone, there is musculinisation of external sex organs in a male embryo. It is done in 20th week. There is atrophy of vagina appendix, formation of scrotum suture (scrotum formation), enlargement corpus cavernosa of penis and formation of cavernose part of urethra.

In puberty, the definite level of estrogens provides formation of female sexual characteristics – feminization (female body constitution, mammal glands formation, hymen, vagina and uterus enlargement). Androgens provide male skeleton type, good muscular development, development of larynx cartilages, voice muta



Pic.5.6. The human sex formation:
1 – physical determinants of sex, 2 – intermediate determinant, 3 – social-psycological determinants (by G.S. Vasilchikov, 1990).

tion, scrotum and penis enlargement, 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.

5.5. The human hermaphroditism. The transsexualism.

Individuals of both sexes might be hermaphrodits since primary gonads have generative elements of both sexes. They may have separated or combined gonads. A testis, as usually, is underdeveloped and has no maturated spermatozoa. An ovarium (or part of it) is more developed. Follicules may develop and have ovulation. Karyotype is usually 46XX, rather 46XY, less possible 46XY/XX. In a foreign literature, it was described 146 true hermaphrodies, in national only 20. False hermafroditism is more common. It includes all pathological forms of sexual development. The secondary sexual characteristics may be formed as in female pattern as in male pattern. It is necessary to distinguish transsexualism, fetishism, transvestism and other abnormalities of human sexual behavior from hermafroditism.

Transsexuals – are peoples with normally developed sex (male or female), which doesn't satisfy them because of their psychological dominant. They want

to change it by surgery to controversial. The population transsexualism rate varies from 1 in 37000 to 1 in 100000. The average age of patients on a first doctor's appointment is 23-24 years for males and 25 years for females.

Fetishism – is a worship of fetish, a subject representating sexual partner. As a subject, people may use underwear, clothes, parfume and so on. Only men have fetishism.

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

Only very expressed transsexualism may be treated by surgery. In case of fetishism and transvestism, the other kinds of psychological treatment are performed.

5.6. 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. It was stated that pre-natal human mortality rate is highest at 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 early pre-natal human mortality rate is closely related with changes in ovicell occurred before leaving follicule, i.d. proembryonic defects in ontogenesis.

The contemporary reproductive strategy must to include such important element as prevention of hereditary defects. It includes firstly pre-natal diagnostic of hereditary defects on early development stages among pregnant women of so called "risk group". If embryo has exposed hereditary defect, the pregnancy may be interrupted on early stages. Thus, we can prevent birth of disabled child. Today we can use biomedical science achievements such as chromosome mapping, biochemical testing and very sensitive ultrasonic devices, to do so.

In recent years new prospective methods to fight human sterility are developed. It is closely connected with reproductive strategy. These methods are artificial insemination, in vitro fertilization, embryo placement to uterine tubes, ovicell and embryo donorship, "substitutive motherhood". The birth of Louise Brown, first child, which was born as result of artificial insemination, gives a hope to all sterile couples all over the world. The number of such couples is 10% from whole world population. If there is a high risk to have a child with hereditary defects, it is possible to perform in vitro fertilization with predinplantational embryo diagnostics, such as cytogenetic and biochemical diagnostics. Following placement of only healthy embryo to uterine tubes guarantee a healthy offspring development. Methods of "new reproductive strategy" allow changing gametes with defects to healthy gametes obtained from donor. These works are actual for today.

5.7. The bioethics. The ethical and justice aspects of interventions in human reproduction.

Bioethics – is a science studying ethical (i.d. moral), justice and social problems connected with medicine and biology development. The main field of bioethics study is ethical problems as consequences of biomedical researches and their usage in artificial fertilization, transplantology, gene engineering etc. 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 Hippocrates Oath, a doctor promises, "not to do any harm for a patient". That why bioethics has a tight relation with deontology and medical ethics. The deontology is a union of ethical rules of doctor and patient contact. In 1987, European Bioethics Expert Committee suggested a list of recommendation for artificial human reproduction. As it was mentioned by them, it is necessary to have a law regulation of "substitutive motherhood", a ban on gametes and embryo trade. That woman should be considered as mother who has delivered child. Now in general, the artificial fertilization for science purposes is prohibited. Now, there is a ban on in vitro embryo growing more than 14 days.

All aspects of surgery performing for transsexual patients require justice reglamentation. There are many bioethicals problems connected with human cloning possibility.

Thus, the contemporary reproductive strategy is based not only on modern biomedical science achievements. It has to include all aspects of human being such as ethical problems, social relations and legislation.

CHAPTER 6. GENETICS AS A SCIENCE. GENE LEVEL OF HEREDITARY MATERIAL ORGANIZATION.

6.1 The 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 suggested by English scientists W.Batson in 1906 (from Greek 'geneticos' – related with birth).

Heredity – is an organism's property to transmit their traits and development features in line of following generations. Because of heredity, many species having been preserved unchanged during hundreds millions years (opossum, latimeria, gatteria). In sexual reproduction, a material basement of heredity is sperms and ovicells, in asexual reproduction – single somatic cells.

While studying heredity, we need to distinguish a term "herediting". Herediting is principles of hereditary traits transmittion process from one organism generation to another while reproduction. During sexual reproduction, herediting is performed through the sex cells, during asexual through the somatic cell division. The analysis of herediting principles is an important method to study heredity patterns.

Embryonic cell don't carry all traits of adult individual. It carries only material for those traits, which may give these features in a future. This material of future traits development is called genes. *The gene is a unit of heredity, determining one elementary trait, whether it is related with protein structure or elementary organism reaction. The genotype is integrity of all organism genes. The phenotype is integrity of all organism traits.* It mast be concerned that terms genotype and phenotype commonly are used in a narrow meaning. They may be related with such traits, which are interested for researcher at this moment.

The diversity – it is a variety of individual or group traits and properties. The diversity is a reflection of unstable preserving of individual hereditary information. It includes a gene changing and gene combinating and changes in gene expression throughout individual development. Thus, heredity and diversity are two fundamental properties of life matter. That dialectic union provides organisms evolution on Earth.

The genetics studies heredity and diversity in four aspects.

Firstly, it studies a problem of genetic information storage. It makes clear the material place of genetic information storage and the ways of genetic information coding.

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

Thirdly, it analyzes a problem of genetic information realization. It studies how genetic information may be realized in definite traits of developing organism,

in correspondence with external environment impacts.

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

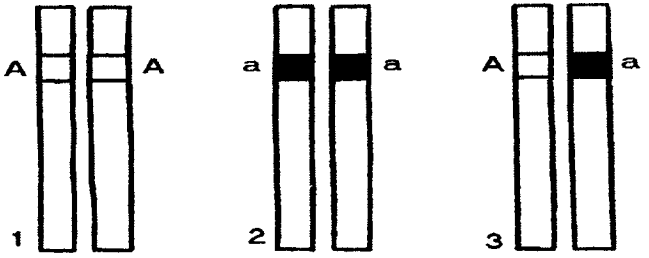
The history of genetics starts from 1900. This is a year of rediscovering Mendel's Laws of heredity by G. De Fris, K. Correns, A. Chermack. The first stage of genetics development covers the period between 1900 and 1912. It was a period of Mendel Laws of heredity recognition. The second stage of genetics development covers the period between 1912 and 1925. It was a time of accepting Morgan's chromosomal theory of inheritance. The third stage of genetics development (1925-1940) was characterized by discovering of artificial mutagenesis and by studying of 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 of genetic events on molecular level.

6.2 Gene level of hereditary information organization.

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

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

G. Mendel suggested gene pointing by Latin alphabet letters. Genes, which encode development of alternative traits, are called allelic genes. Allelic genes situate in homologues locuses of homologues chromosomes. Each gene may have two conditions: dominant and recessive. Dominant gene is that dictates the appearance of heterozygotes. One allele is said to be dominant if an individual who is heterozygous for that allele has a same appearance as an individual who is homozygous for it. Recessive gene is whose phenotype effect is masked in heterozygotes by presence of a dominant gene. A dominant allele is pointed by capital letter of Latin alphabet (A), and recessive allele is pointed by small letters (a). Organisms having similar alleles of one gene for example both dominate (AA) or both recessive (aa) are called homozygotes. Organisms having different alleles of one gene for example one dominate and other recessive (Aa) are called heterozygotes (pic 6.1). If an organism has only one allele of gene (like in male X



Pic. 6.1. The scheme of allelic genes localization in homologous chromosomes:
1 – dominant homozygote; 2- recessive homozygote; 3 – heterozygote.

chromosome), it is called hemizygote.

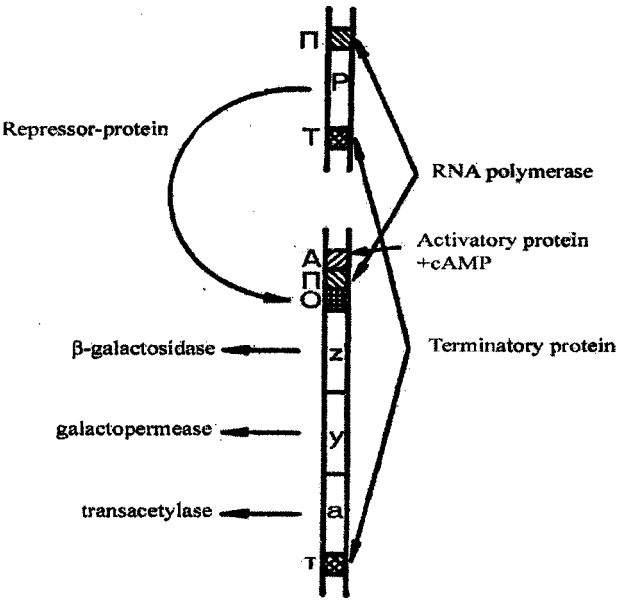
We see that last decade molecular genetics success changes old statements about gene. Today we may say that the gene – is a region of genomic nucleic acid, which is characterized by specific nucleotide sequence and which presents function unit different from other genes. Now it is stated that gene has a smaller divisions. It was discovered by American genetics S. Benzer. He studied a fine structure of E.coli T4 bacteriophag genes. He founded a gene to be divided into many parts during crossing over. Later, the same gene structure for eukaryotes was showed. The minimal unit of mutation is muton; the minimal unit of recombination is recon. Minimal size of them is one nucleotide pair.

Until 70th years of 20th century, it was believed gene to consist of unseparated DNA region. However, in 1977 it was shown that some adenovirus genes exist in a form of fragments instead of unseparated DNA region. These fragments may be exons (having useful information) and introns (without it). Introns are removed during gene expression (process of realization genetic information). Then, exons are bounded together by their ends. Such removing of unuseful information was named gene splicing (it was described above in chapter 2.1). It is performed with 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, gene of human β -globulin contains three exons and two introns; gene of stable region of heavy chain of human immunoglobulin contains 4 exons and 4 introns. So it is said, gene to have a mosaic structure. Mosaic 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 isn't 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 during evolution. It was shown that intron mutations might break splicing process, terminate protein biosynthesis and change protein structure.

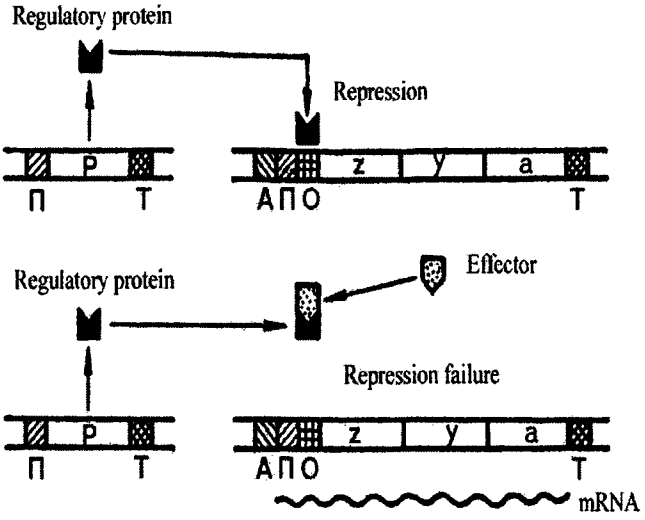
The term "gene" was firstly used for pointing some hereditary intends to form some phenotypic traits. In 1944 J. Beadle and A. Tatum pushed forward the hypothesis: one gene – one enzyme. Their idea since has been modified. Now, we know that many proteins are composed of several kinds of polypeptide chains, each specified by 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 a nucleotide sequences not only having hereditary information but also controlling gene expression and replication.

6.3 The gene expression and repression.

The genetic mechanisms of gene expression were studied by French scientists F. Jacob and J. Monod in 1961. The main statement of their discovery is that the genes may be of two kinds. One is structural genes, which encode information about macromolecules made by cell. Second is regulatory genes (or acceptory genes), which don't encode polypeptide chain, but they regulate working of structural genes with help of different proteins attached to them.



Pic. 6.2. The structure of lactose operon of E.coli:
П – promoter; P – regulating gene; A – region for activating protein attachment; O – operator, T – terminator, z,y,a, - structural genes (by S.M.Gershenzon, 1979).



Pic. 6.3. The repression (upper scheme) and induction (lower scheme) of lac-operone of E.coli (by M.S.Gershenzon, 1979).

Operon – is a cluster of functionally related genes transcribed onto a single mRNA molecule in bacterial cell. It is consist 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. This operon is responsible for synthesis of protein that bacteria use to obtain energy from the sugar lactose. Operon is started from CAP site. It is a site for CAP-protein binding. CAP is an activator protein, which facilitates the unwinding of DNA duplex and so enables the polymerase to bind the nearby promoter. CAP protein need to be activated by existed in a cell cAMP. Next to CAP site is promoter. Promoter is nucleotide sequence recognizable by RNA polymerase. RNA polymerase binds promoter and then moves along operon transcribing it. Next to promoter is operator. It is consist of 21 nucleotide pairs. It is a place for regulatory protein binding, which may suppress transcription. Next is a group of structural proteins. Operon is terminated by terminator. It is a short DNA region, which works as a stop signal for transcription (pic 6.2). The main regulation of lac-operon working is performed by regulatory protein, which is encoded by regulator gene (pic 6.3). This protein continuously persists in a cell in 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 promoter and so

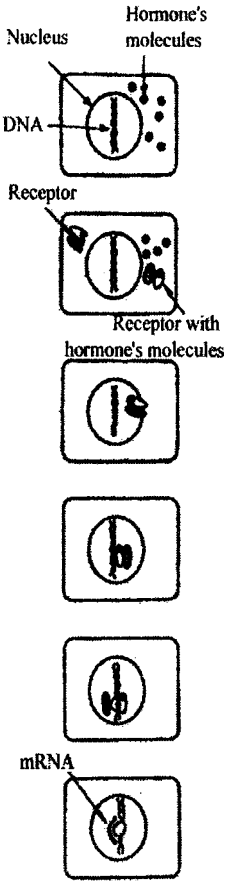
The table 6.1 The operon working regulation types. (by S.M.Gershinzon 1979)

Direction of regulation	Character of regulation	
	Negative regulation	Positive regulation
Induction	Effector breaks regulatory protein binding to operator. Structural genes are transcribed	Effector enables regulatory protein to bind operator. Structural genes are transcribed
Repression	Effector enables regulatory protein to bind operator. Structural genes are not transcribed	Effector breaks regulatory protein binding to operator. Structural genes are not transcribed

blocks the transcription of the 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 operator site. Here, lactose works as an effector – a small substance that changes protein properties while binding with it. When operator is liberated from repression, RNA polymerase may moves along gene transcribing it. This starts a producing of all enzymes needed to lactose proceeding. That means gene induction. Thus, the regulation of lac-operon is performed by repressive protein binding to operator, which represses transcription. Induction occurs only when operator is free from repressive protein. This regulation type is called negative protein synthesis induction.

A negative repression has a similar mechanism. Negative repression is a regulatory protein binding to operator, which suppresses transcription. The differences in these two types are in following. During negative induction, an effector breaks regulatory protein binding to operator, whereas during negative repression effector enables regulatory protein to bind operator. An example of negative repression is the working of E.coli operon, which is responsible for tryptophan synthesis. The regulator gene, which is not a part of tryptophan operon, always makes a regulatory protein. If cell use all tryptophan for its needs, regulatory protein doesn't bind operator site. But if it is an excess of tryptophan in a cell, tryptophan binds regulatory protein modifying it structure. Modified protein enables to bind 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 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 regulatory protein, which binds with operon and activates its transcription.



Pic. 6. 4. The regulation of transcription by steroid hormones (by S.M.Gershenzon, 1979).

Arabinose is the effector.

During positive repression, the regulatory protein, encoded by 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 table 6.1 summarizes main features of different type's genetic regulation of operon.

The eukaryotes gene regulation has been studied less than prokaryotes gene regulation. It is due to 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. Firstly, almost all eukaryotic genes contain only one structural gene, instead of several structural genes in bacterial operon. Secondary, 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. Thirdly, eukaryotes have a group simultaneous genes repression in whole nucleus, in whole chromosome or in significant region of it. It is mostly performed by histon proteins, which are a structural component of chromosomes. An example of it is full total repression of gene activity during spermatogenesis. Fourthly, the gene expression of eukaryotes may be regulated by steroid hormones (pic. 6.4). The target cells have special receptor proteins. These receptors are encoded by testicular feminization gene of X-chromosome. Binding of the receptor to hormone leads to complex formation. This complex activates expression of definite gene. Fifthly, eukaryotes' genes may change their activity during ontogenesis.

The example of different gene expression in ontogenesis is a genetic control of human hemoglobin synthesis. It is known that hemoglobin molecule contains four polypeptide chains: two identical α-chains and two identical β-chains. The adult hemoglobin (HbA) is differed from embryo hemoglobin (HbF). The differences are related with β-chains. In embryo's hemoglobin there is no β-chain. It is

replaced by γ-chain. However, in an adult blood we may find an HbA2 in small amount. The β-chain in this hemoglobin is replaced by σ-chain. All three types of normal human hemoglobins are encoded by separate locuses. The locus $^{\alpha}$ A is responsible for a-chain synthesis. It is active throughout all life. The locus β A is responsible for polypeptide chains synthesis in HbA. It becomes activated only after birth. The locus γ F is responsible for polypeptide chains synthesis in HbF. It works actively during embryonic development. The locus γ A2 is responsible for polypeptide chains synthesis in HbA2. It is active throughout the life after birth.

Each of hemoglobin genes (α A β A, γ F, γ A2) is a structural gene because it is responsible for primary structure of polypeptide chain.

We see different kinds of hemoglobins that arise from different gene combinations. It is clear that working of structural genes is under supervision of regulatory genes. It is become evident from a fact of HbF exchange to HbA after birth. Here we see the working of special gene – "switch gene", which suppress activity of γF gene and activate βA gene. As result of this, embryo hemoglobin is exchanged to adult one. We may suppose that this simultaneous switching of gene activity may be due to action of gene operator of both γ F and βA genes.

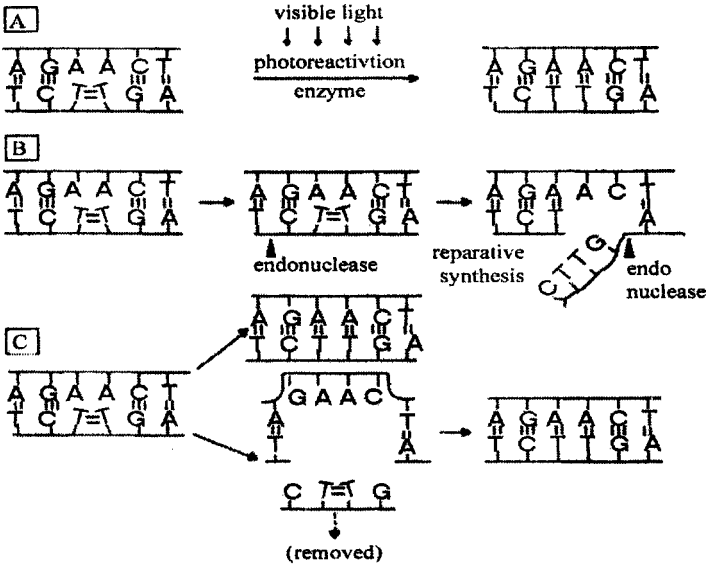
Table 6.2. The human hemoglobins' characteristics

Type of Hb	Polypeptide chains	Gene locuses
HbA	2α, 2β	$\alpha^A \beta^A$
HbA2	2α, 2σ	$\alpha^A \sigma^{A2}$
HbF	2α, 2γ	$\alpha^A \gamma^F$

6.4 DNA reparation.

Some damage of DNA may occur due to action of different agents or during protein biosynthesis. Many of those damages are corrected by special reparative enzymes. Reparation (from Latin – reparatio – to recover) – is a process of restoring natural DNA structure, which has been damaged during protein biosynthesis or due to harmful influences of external agents, having presented in all organism cells. The reparation process is based on fact that DNA molecule contains two complementary chains. So if one of them has been damaged, it may be repaired corresponding to other chain.

The DNA reparation was discovered in bacteria subjected 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 a one strand. The resulting cross-link between adjacent bases of the DNA strand is called a pyrimidine dimer. However, it was shown that cells subjected to ultraviolet radiation survive better while plac-



Pic. 6.5. The DNA reparation:
A – phtopeactivation, B – "dark" reparation, C – postreplicative reparation (by F.Fogel, A.Motulsky, 1989).

ing on light than in darkness. It was stated that here occur photoreactivation or light reparation. The pyrimidine dimers are replaced by special enzyme, which become activated by action of visible light (pic 6.5a).

Later it was founded that cells may replace damaged regions of DNA without light exposure (dark reparation). We may observe dark reparation when cell recovering from ionizing radiation exposure, chemical impact or from other factors. It has several stages involving several enzymes. The first enzyme (endonuclease) recognizes damaged region and cuts DNA strand around it. The second enzyme (endo- or exonuclease) makes a second cut on DNA strand. The third enzyme cuts off damaged nucleotides. The fourth enzyme (DNA polymerase) makes a new strand of DNA corresponded to undamaged one. The fifth enzyme (ligase) glues the ends of DNA strands (pic 6.5b).

The postreplicative reparation is performed by recombination (fragments exchange) between two newly made DNA molecules (pic 6.5c). It is useful when pyrimidine dimers have not been removed by light reparation.

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

Working together replication and reparation enzymes provide a small level of DNA molecule mistakes.

6.5 The statements of gene theory.

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

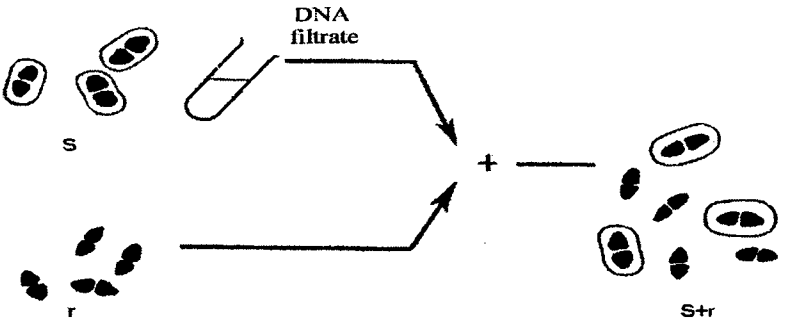
1. The gene has definite locus in chromosome.
2. The gene is a part of genomic nucleic acid. The number of nucleotides in genes is not same.
3. There is mutation and recombination inside of a gene.
4. There are structural and functional genes.
5. The structural genes encode the macromolecules structure (such as proteins, tRNA, rRNA).
6. The functional genes control the structural genes activity.
7. The triplet's line in gene corresponds with amino acids line in polypeptide.
8. Genes are able to reparation.
9. The genotype on being discrete acts as integrated unit.

6.6 The genetic engineering.

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

To give to an organism a new hereditary property we need to insert an appropriate gene (or group of genes) and to obtain functioning of this gene in particular cells. So we need to set it to regulatory system. The solving of this task may be divided into three stages: 1) obtaining genetic material (genes); 2) inserting genetic material to new organism; 3) setting of inserted genes to genetic cell apparatus and their fixation in it. Let's look all these stages through.

The obtaining genetic material. The genetic material may be obtained by 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 big circular DNA molecule and in small circular DNA fragments containing just several genes. These small fragments are called plasmids. The plasmids using gave a strong impact to a genetic engineering development. We may get a gene by different way, but commonly we use special enzymes such



Pic. 6.6. The transformation of bacteria of "r' culture to "S" cultureunder influence of DNA filtrate of "S" culture (by F.Kaudewitz, 1959).

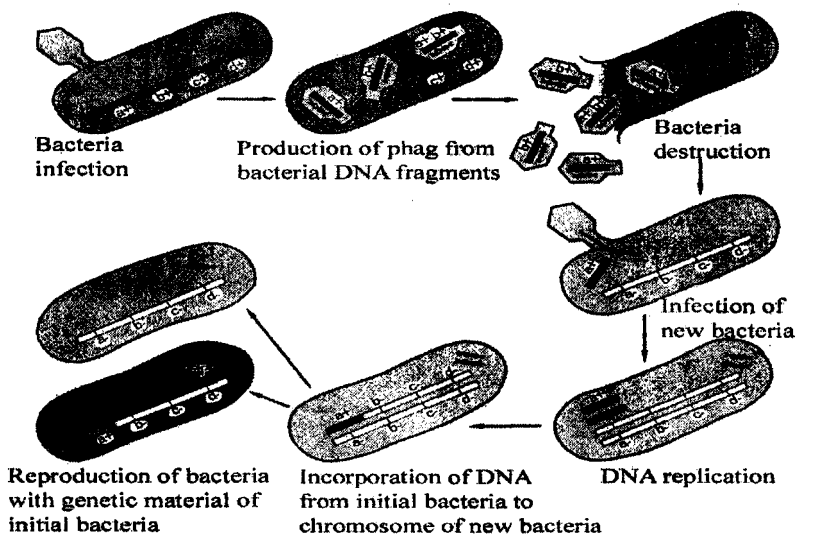
as restriction endonucleases and ligases. The restriction endonucleases are molecular "seizures" for fragment to be cut. The ligases are sealing enzymes. They can join cut strands back together. So may use these enzymes for DNA fragments elongation, DNA regions removing.

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

The transformation (from Latin transformation - rebuilding) – is changing of hereditary material by incame foreign DNA fragment. It is a one of genetic information exchange ways in prokaryotes. It was firstly observed by F. Griffit in 1928. In transformation, the inserted DNA fragments will be transmitted to all offsprings of next generations (pic 6.6).

The transduction (from Latin transduction – getting new localization) – is a way of transmitting of genetic material from one bacterial cell (donor) to another (recipient) by using moderate bacteriophag. It was discovered by J. Lederberg and N. Cinder in 1952 while analyzing a changing in genetic material in some bacteria (shigells, salmonells etc.). When the prophag being induced, the small part of bacterial DNA incorporates to phag's genome. Bacteriophag, carrying bacterial DNA, is called transducting phag. When new cell is infected by such phag, the DNA region inserts to cell genome. It is natural and wide spread between bacteria process of getting genetic recombination. That why it is widely used in genetic engineering of bacteria (pic 6.7).

The conjugation – is a process of genetic information exchange in bacteria during contact period. Information is transmitted from donor ("male" cell) to recipient ("female" cell). The conjugation is regulated by F-plasmids (fertility factors). One having F-plasmid is considered as donor. Another without it is considered as recipient. The size of exchanged material is determined by time of contact. As result of this, we have a cell with its own chromosome and with frag-



Pic. 6.7. The bacterial transduction (Biological Science an inquiry into life, 1980).

ment of another one. This cell has a recombination of these genes. The cell from which material has been taken stays unchanged. Its genetic material is restored by DNA reduplication (pic 4.2).

The setting of inserted genes to genetic cell apparatus. The genes inserted to foreign cells cannot be reproduced. However, we may cope with this problem, if genes will be inserted to a structure, which has excellent apparatus of reproducing. Such structures are called vectors. It is a main device for all genetic manipulations. It is a structure, which is able to bring a foreign gene to a cell and to provide gene replication in a new cell. Plasmids, bacteriaphages, viruses and cosmids are widely 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. 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 mosaic gene structure, decoding of gene structure, 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 producing of vaccines and serums; synthesis of hormones,

vitamins, enzymes; diagnostics of human genetic defects on early stages of embryo development; genetic surgery (replacement of damaged gene by normal one) and so on.

6.7 The bioethical aspects of genetic engineering.

In 1984, the European Committee of genetic engineering recommended 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 mast to be prohibited. The works of chimeras and hybrids producing with help animal or human genetic material must to be banned. Only somatic cells may be used for therapeutic aims. The using of sex cells for genetic therapy will be possible, when advantages of such treatment over somatic cells genetic therapy will be proved.

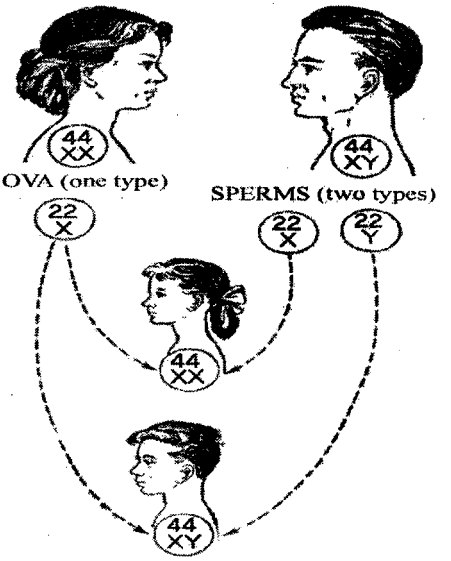
CHAPTER 7. CHROMOSOME AND GENOME LEVEL OF HEREDITARY MATERIAL ORGANIZATION IN PORKARYOTES AND EUKARYOTES.

The chromosomes play an important role in herediting. It was proved by discovering chromosome sex determination, groups of gene linking, genetic and cytological chromosome mapping. These facts were summarized in chromosome theory of inheritance.

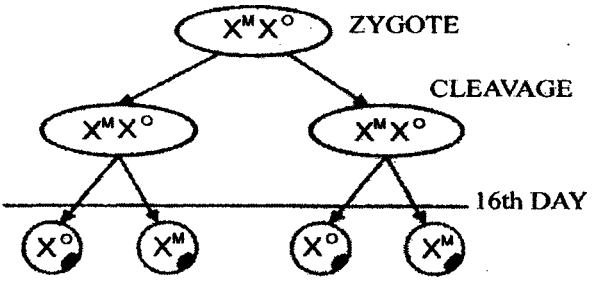
The chromosome level of hereditary material organization is characterized by chromosome structure. The chromosome of non cellular live forms is presented in a form of naked DNA chain (or RNA chain in some viruses). The chromosome of the prokaryotes is a naked circular DNA molecule. The chromosome of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

7.1 The sex genetics.

A large contribution to sex genetics studying was made by American scientist C. Mac-Klang in 1901-1902. He proved that the X-chromosome determines



Pic. 7.1. The sex herediting in human (by N.P. Dubinin, 1963).



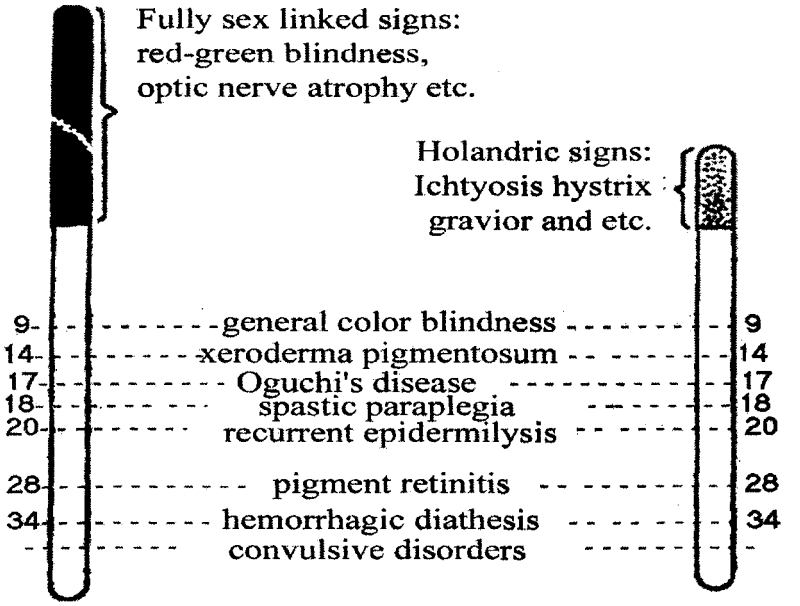
Pic. 7.2. The scheme of the X-chromosome inactivation in female embryo (X_m – mother's chromosome, Xo – father's chromosome) (by R.G. Zayats et al., 1998).

the sex of the Protentor bug. In 1959, female organisms with the chromosome set "XO" were discovered. It was concluded that the Y-chromosome determined male sex.

The organism containing same sex chromosomes is called homogametic. The organism containing different sex chromosomes is called heterogametic. The sex of future child depends on sex chromosome combination in the zygote (pic. 7.1). 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 humans) 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 heterogametic organism.

But sex may be determined also by a chromosome balance, so called "sex index". Balance sex theory was suggested by K. Bridgess and R. Goldshtein in 1911. They sated that male and female sex of Drosophilla is determined by ratio of sex chromosomes to autosomes, instead of sex chromosomes combination. The genes of female organism are mostly located in X-chromosomes, whereas male organism genes are mostly located in autosomes. If ratio is X:A=1, it is female organism. If ratio is X:2A=0.5, it is male organism. If it is intermediate ratio (from 1 to 0.5), it is intersex organism. Increased ratio (3X:2A=1.5) leads to overmatured female formation. Decreased ratio (X:3A=0.33) leads to overmatured male formation.

The balance sex theory may be used in humans. 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, the ovarium, uterus tubes, uterus underdevelopment is founded. If patients have three X-chromosomes (XXX:44A), the secondary sex signs expression may be broke. Normal male sex chromosomes to autosomes balance is XY:44A. The patients with Kleinfelter syndrome (XXY:44A) have unexpressed secondary sex sings, gynecomasty, and failed spermatogenesis.



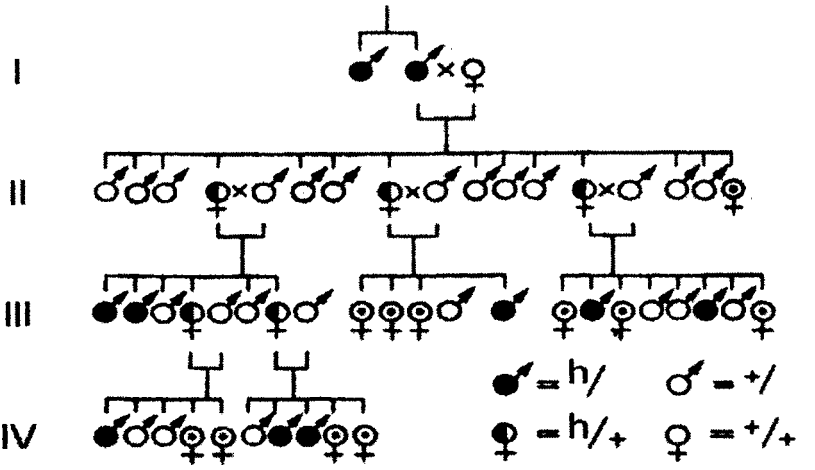
Pic. 7.3. The genes mapping for those. which linked with X- and Y-chromosomes: black segment represent genes, which are fully linked with X-chromosome, grey segment – fully linked with Y-chromosome, white segments – partially sex linked genes (by J. Neal, W. Shell, 1958).

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 haven't. This structure was named in a name of M. Barr - Barr's body or sex chromatin. Later it was founded that Barr's body is inactivated X-chromosome. During first 16 days of embryo

development both X-chromosomes work very actively, perhaps producing a double number of products encoded in X-chromosome. This fact is used for explanation of higher survival rate of female's embryo.

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

The traits, which are controlled by genes of sex chromosomes, are called sex linked. Sex linkage was demonstrated by T. Morgan on an example of eye color heredity in Drosophila melanogaster. So it was stated trait transmission from father to daughters and from mother to sons. More than 60 human genetic sex linked diseases have been identified. Most of them are recessive. Genes, which are on sex chromosomes. may be divided into 3 groups (pic 7.3 and 7.4).



Pic. 7.4. The pedigree of family with sex linked hemophilia A hereditng:
I-IV – generations (by E. Hardon, R. Vener, 1958).

Genes, which are in homologues regions of sex chromosomes, was 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 non-homologues to Y-chromosome, was 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 non-homologues to X-chromosome, was named holandric genes (from Greek holos - whole; andros - male). There are diseases connected with holandric genes. They are hypertrichosis of ear, ichtiosis, syndactilia and others.

7.2 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. Consequently, every organism has limited trait group numbers for independent assortment. This number is limited by chromosome number. On the other side, it is evident that organism's traits are very numerous, but the chromosome number is limited and small in compare to them.

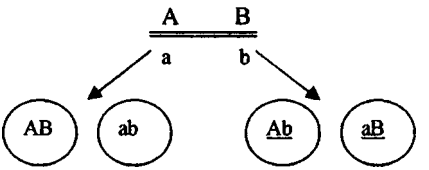
So we may conclude that each chromosome has many genes. If it is correct, we may state that third Mendel's rule (of independent assortment) related only to chromosome assortment. Studying traits combinations according to the third rule, Morgan discovered that in some cases there were no new combinations between

genes. That means it was a full gene linkage. He obtained the ratio 1:1. In some other cases, he obtained ratios different from classical Mendel's ratio. So he suggested calling this gene heredity, limiting independent assortment, 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 reproductive cell formation. It provides 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 evolutionary role of combinative diversity. We may find crossing over analyzing postbreeding traits assortment. When genes are in different chromosomes, we may write diheterozygote genotype as $\frac{A}{a}\ \frac{B}{b}$

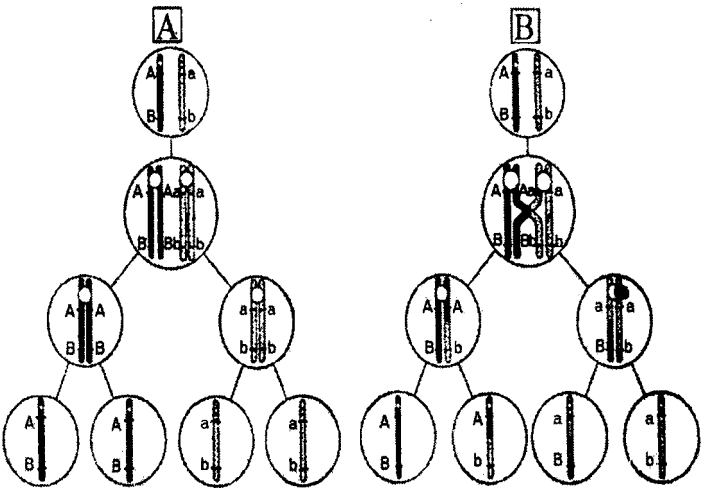
When genes are in a same pair of homologues chromosomes, we may write genotype as $\frac{A\ \ B}{a\ \ b}$

The gametes, which were subject to crossing over, are called crossed over gametes. So those which weren't in crossing over are called non crossed over gametes (pic 7.5). AB/ab = AB and ab (non crossed over gametes) + Ab and aB (crossed over gametes).



Accordingly, organisms, from crossed over gametes, are called crossed over organisms. And organisms, from non crossed over gametes, are called non crossed over or non recombinant organisms. We can confirm previous statements in Morgan's classic experiment demonstrating the chromosomal basis of gene linkage in Drosophila. He examined such traits as body color and wing length, which are localized on one chromosome (pic 7.6). You may see results of such breeding on a picture 7.6.

Assumed all of this T. Morgan formulated the thesis: genes, which are located in one chromosome, are linked, and this linkage as strong as close they are to each other. This rule was named Morgan's rule, after Tomas Hunt Morgan. It is hard to study gene linkage in a human. But anyway, we may list some examples of human



Pic. 7.5. The scheme of two pair allelic genes splitting, which are localized in one chromosome pair:
1 – without crossing over, 2 – with crossing over in meiosis (by K. Shtern, 1965).

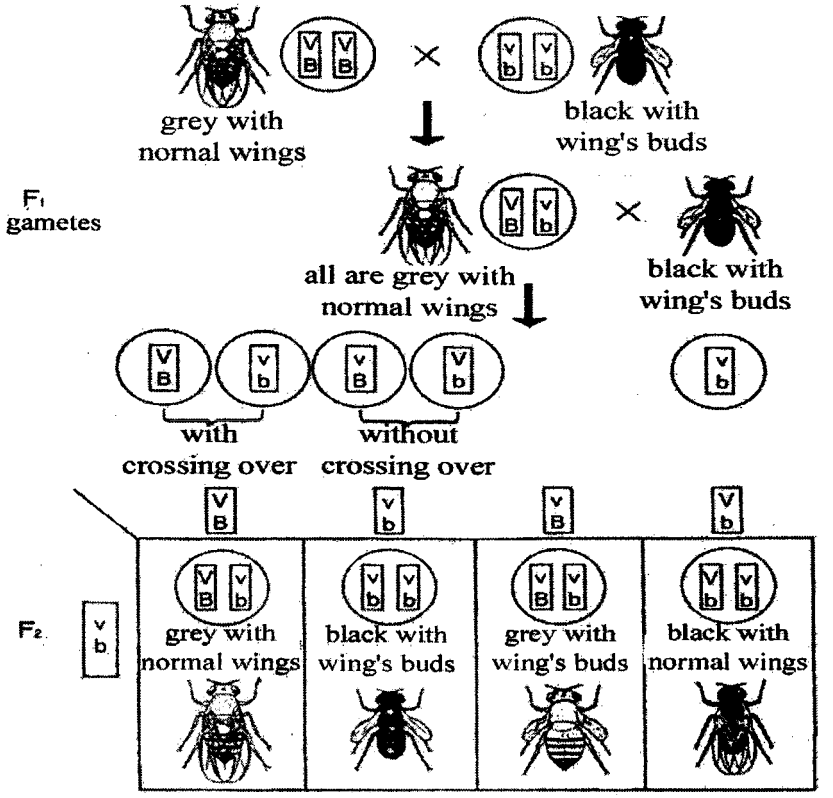
gene linkage.

Gene linkage of A, B, C, D/DR locuses of HLA system responsible for histo-compatibility antigen synthesis in 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 a genes responsible for A and B antigens excretion with saliva. Gene linkage of polydactilia genes and cataract genes. X-chromosome gene linkage of hemophilia genes and colour-blindness genes; and also colour-blindness genes and muscular Duchene dystrophy.

It was suggested that distance between genes are 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, after Thomas Hunt Morgan. To measure gene distance in testcross we may use the following formula.

$$X=(a+b)/n \times 100\%$$

Here X is a distance between genes, a is a number of individuals in first crossed over group, b is a number of individuals of second crossed over group, n

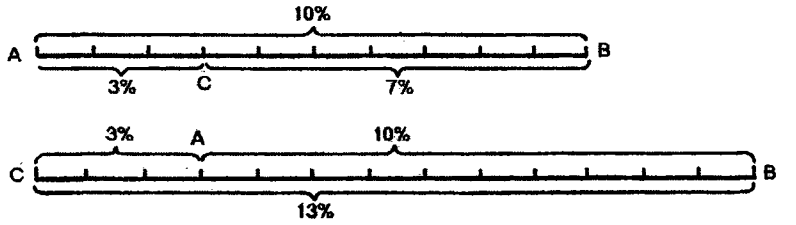


Pic. 7.6. The herediting of linked traits in Drosophila (Th. Morgan's experiment).

is total hybrids number, 100 is a coefficient for percentage measurement.

7.3 The chromosome maps.

Above we stated that distance between genes corresponds with crossing over percentage. So we can prove that conclusions by assessment gene distance between genes A and B and at the same time between genes B and C (pic 7.7). So if we have distance between A and B 10% and distance between A and C 3% of crossing over, we may conclude that the gene is either between genes A and B or on a side of them (gene A is between B and C). So if the distance between B and C is 7% of crossing over, that means genes are in a range A,B,C (pic 7.7, upper



Pic. 7.7. The scheme of genetic chromosome mapping.

scheme) So if the distance between B and C is 13% of crossing over, that means genes are in the range C,A,B (pic 7.7, lower scheme). Thus, chromosome gene localization is linear and distance between them is related with crossing over frequency. But this thesis is good enough only for closely placed genes. For genes which are far from each other that rule appear to have some imperfections. The genes, placed in one chromosome, are linked and they make one linkage group. Number of linkage groups equals to haploid chromosome set.

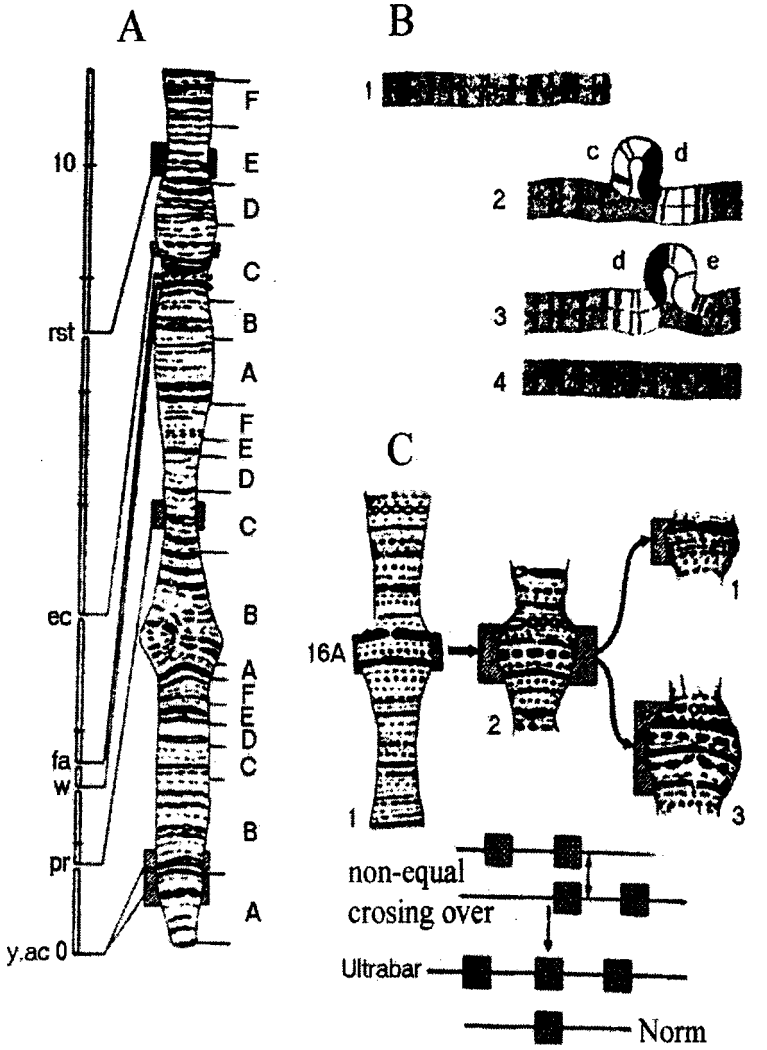
Thus, frequencies with which crossing over occurs in crosses can be used to construct a genetic map, in which distance is measured in terms of frequency of recombination. The genetic map - is a conditional line with pointed genes according their relative distance in centiMorgans. Some organisms, which were studied more actively than others, have genetic maps of all chromosomes (drosophila, corn, and so on) (pic 7.8).

Having determined linear chromosome discontinuity, scientists faced the necessity to make a cytological map and to compare them with genetic maps. The cytological map - is a chromosome map, where gene localization and gene distance is defined in chromosome. The construction of cytological maps is based on chromosome aberration analysis (translocatons) and differentiated staining of polutenic chromosomes (pic 7.8). For today, we have made and compared cytological maps of Drosophila chromosomes. It proves linear gene arrangement in chromosomes. All 23 human chromosomes have been mapped for today, but these maps don't include all human genes. So that work still needs to be done. The most detailed map was made for first chromosome (20 genes were placed).

7.4 The statements of chromosome theory of inheritance.

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

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



Pic. 7.8. The genetic and cytological chromosome maps (by N.N.Orlov 1968):

A – genetic map of Drosophila X-chromosome and corresponding part of X-chromosome from Drosophila salivary gland. B – gene localization with help of deletions method: 1 – part of two conjugated chromosomes of Drosophila salivary gland, 2 – deletion I, 3 – deletion II, 4 – localization if gene d resulting from those deletions; C – locus BAR in X-chromosome from Drosophila salivary gland: 1 – norm, 2 – double region 16A of BAR mutant, 3 – triple region 16A of ULTRABAR mutant.

2. Each gene has a definite locus in chromosome. There is a linear gene arrangement in chromosomes.
3. There is allelic gene exchange between homologues chromosomes.
4. The distance between genes is closely related with crossing over percentage between them.

7.5 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 is consisted of structural genes only. In the bacterial genome most of the genes are unique. That means they are in chromosome only in one copy. 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 1000 structural genes in E.coli. Such genes contain only about 1-1.5 millions of nucleotide pairs.

It is clear that only way is to suggest that the rest of nucleotides are in DNA regions with undiscovered function. The DNA spiralization in prokaryotes is less than in eukaryotes.

The eukaryotes genome has more complicate organization. It contains larger numbers of genes, and larger amounts of DNA in the chromosomes. It has a complicated gene activity controlling system which is related with cells and tissue differentiation in ontogenesis. The more complicated in evolutionary plan an organism is, the larger amount of DNA it contains. Eukaryotes also have excessive genes. So the human genome contains 3 billons nucleotide pairs, which is enough to make more than 2 millions structural genes. Conversely, different assessments of the human genome have from 50000 to 100000 structural genes. This is in 20-40 times less than possible. More than half of the genome consists of unique genes, which are not repeated. The bull calf has 55% of such genes, human 64%, drosophila 70%.

To discover human genome sequence an international research program was designed. The research under this program is performed in many countries such as USA, Japan, EU, Russia and other. All research programs related with human genome are coordinated by HuGO council of UNESCO. The human genome contains 3 billions nucleotide pairs. To write it in a form of letters require 2 millions sheets of paper. It requires a long time (at least 10 years) and huge funding (3

billions dollars, 1 dollar per one "letter"). The program "Human Genome" has aim to dissolve the following problems:

1. To determine human DNA structure, that means to determine all nucleotide sequences.
2. To explain physiological value of genetic texts, that means to explain the relationships between genetic sequences and physiological and hereditary traits.
3. To study molecular basis of hereditary diseases, their prenatal diagnostics, preventive measures; to study hereditary nature of allergy, immune defects, cancer, susceptibility to cardiovascular diseases, psychiatry, endocrine and other diseases.
4. To defend human genome from mutation preventing rise of genetic load (ecology aspect of program).
5. To find the ways of bacteria, plants and animal evolution.

Completing "Human Genome" program will help science and medicine to find defect genes and to start treating of hereditary diseases controlled by those genes. It also will facilitate understanding of ovum development to mature organisms. It also will help to dissolve problem of drug intolerance. It will allow constructing drugs without side effects; creating genetic library, which will help to understand events not only in human but also in all life creatures such as bacteria, plants and animals. It will allow determining all genes structure and determining correspondence between genes and traits.

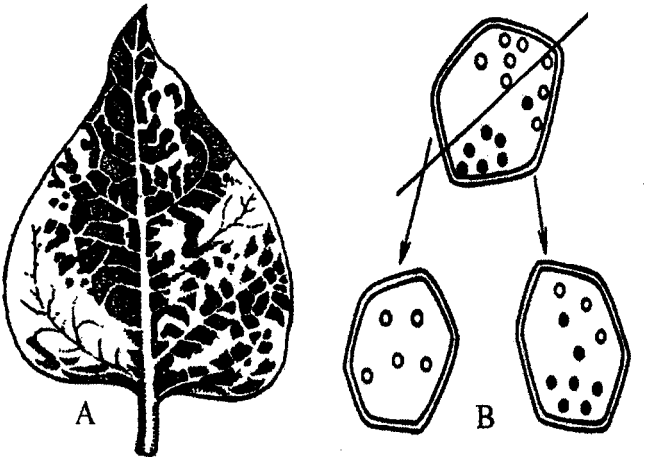
However, determining genome structure of every person may lead to discrimination. Some people may be discharged from job on a base of this analysis. So that means we need to create new justice documents to prevent it.

7.6 The cytoplasmic material of heredity.

The chromosome theory of inheritance state 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 mitochondrion 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. First to describe cytoplasmic inheritance were German genetics E.Baur and K.Korrens. They did it on example variegated leaf inheritance in some plants.

All hereditary factors localized in cytoplasm are termed plasmotype or plasmon. The unit of cytoplasmic hereditary material same to gene are called plasmogene. It was stated that plastids (plastid's DNA) and mitochondria (mitochondrion's DNA) have their own DNA. They are able to self reproduction.



Pic. 7.9 The cytoplasmic material of hereditіng:

A – the leaf of small tortoise-shell plant; B – thescheme of occasional distribution of green and white plastids in cell division (by C.Correns, 1906 and M.E. Lobanov, 1967).

And they are responsible for transmitting cytoplasmic hereditary information. Plastids are self-reproduced organelles of plant cells. They may be inherited by descends only through cytoplasm of mother organism cells. In yeast mitochondria it was detected the genes responsible for respiratory enzymes synthesis. It was shown that these genes are placed in circle DNA molecule of plasmids.

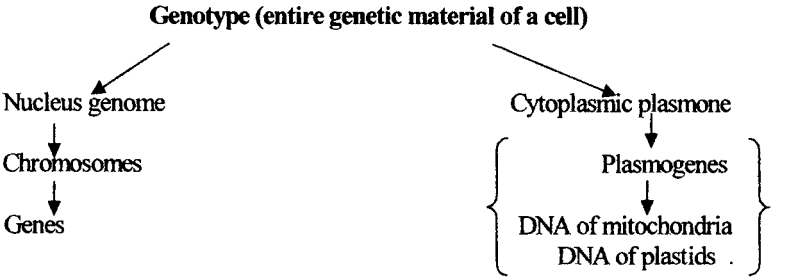
In bacterial cells there are three types of plasmids: containing sex factor F, factor R and factor col - colicinogenic. The bacteria containing F factor are males. They form cytoplasmic bridge toward female cells. Through that bridge, the factor is transmitted to recipient cell during conjugation. That cell becomes male. R factor is responsible for bacteria tolerance to some antibiotics action. The plasmid with 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 still unknown factors.

7.7 The system of cellular genetic apparatus.

The system of cellular genetic apparatus includes nucleus genome and cyto-

plasmic genome. The apparatus is discrete. This apparatus is presented by chromosomes and their genes in nucleus and by plasmogenes of organelles in the cytoplasm.

The scheme of cell genetic apparatus



CHAPTER 8. THE PRINCIPLES OF TRAITES HEREDITING DURING REALIZATION OF GENOTYPE TO PHENOTYPE.

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

If a trait expression is controlled by only one gene, it is monogenic heredity. If a trait expression is controlled by several genes, it is polygenic heredity. Since gene may be placed in autosomes or in sexual chromosomes. Accordingly, it may be distinguished two variants of heredity – autosomal, and linked with X-chromosome or Y-chromosome. And also due to character of gene expression it can be distinguished dominant and recessive hereditary. The heredity linked with sexual chromosomes and linked heredity at all was described in a chapter 7.1 and 7.2.

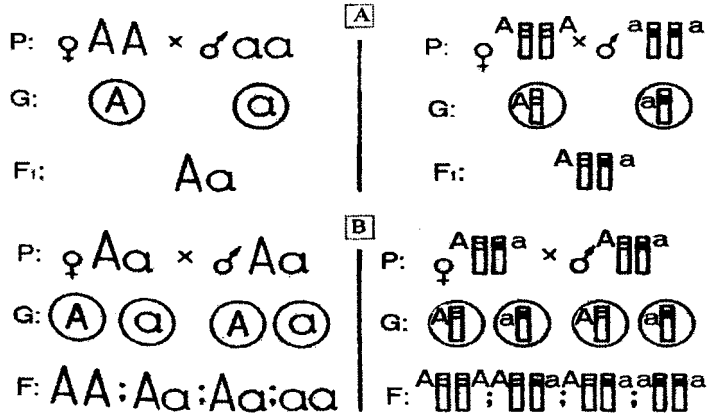
8.1 The monogenic herediting.

As it was said above, monogenic heredity is heredity of traits controlled by one gene. The main principles of monogenic heredities were discovered by G. Mendel; perhaps by his hybridologic method. The essence of such a method is in 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 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 it is necessary to know some useful signs. The female organism is placed on a first place; male is placed on a second. Crossing is pointed by letter "x". Parents are putted on a first line and are pointed as "P" generation (from Latin parentis - parent). The gametes, which are produced by parents, are putted in second line. The offspring are putted in a third line. They are labeled as the F1 generation (from Latin *filia* - daughter). Index is used for representing generation number. The hybrids of F1 have only one trait expressed. Second one is suppressed. This is an essence of First Law of Heredity. It can be formulated by this way: *In a cross between homozygous-dominant ane homozygous-recessive individuals, all of the F1 progeny will be heterozygous; they will all*



Pic. 8.1. The scheme of crossing and cytological basements of First (A) and Second Mendel's Laws.

resemble the homozygous dominant parent in their phenotype. The First Law was also named as Law of dominating (pic 8.1a).

Having analyzed F2 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 (pic8.1b). The outcome of such cross can be illustrated by a Punnett square, suggested by English geneticist Reginald Crundall Punnett.

To explain results of 2nd Mendel's Law W. Batson suggested a thesis of "gametes purity". It can be formulated by 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 "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 a testcross. It is because of 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 homozygous dominant individual. If it will be 1:1 ratio among offsprings, it is heterozygous dominant individual.

It was founded in monohybrid crosses that numerous traits have a phenotypic ratio in F2 generation 3:1. 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. Analyzing hybrids of F2 generation, it was founded that independent assortment of different traits occurs. Such

event was named Third Law of Heredity. *It states that genes located on different chromosomes assort independently of one another*. To make cross scheme easy to write we may use so called phenotypic radical – it is dominant genes of organism, which determines it phenotype. For Third Law it will be the following: 9A-B-: 3A-bb: 3aaB-: 1aabb.

Each trait pair gives phenotypic ratio 3:1 in F2, which is provided by independent assortment of homologues chromosomes in meiosis. In polyhybrid cross, the acquired ratio of hybrids in F2 can be described by formula (3+1)*n, where "n" - is 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 while fertilization.
3. The same survival rate of zygotes of any genotype.
4. Full trait expression independently from development conditions.
5. Gene location on different chromosomes in dihybrid and polyhybrid crosses.
6. The same probability of all kinds of gamete formation on a 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 provides independent assortment of chromosomes during gametes formation. That means 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 long period of time. During such period many environmental factors may act on gametes and developing organisms. That's why some deviations may occur in real traits ratio. Pointed above conditions bring an element of probability to such ratio. Therefore, to analyze it, we need to use several statistic methods which allow to prove inherited theoretical ratio principle or to deny it. One of them is X2-method. Using it, we can determine is it deviation occasional or regular.

Analyzing patterns of heredity in garden pea Mendel worked with several traits pairs. But human has thousands of traits which follow Mendel's Laws of Heredity. They are hair color, ear color, nose shape, teeth shape, finger shape, and so on. The definite knowledge of traits and their description are the aims of medical genetics. Many hereditary diseases follow Mendel's Laws of Heredity. Among them are achondroplasia, diabetes insipidus, albinism, pancreas fibrosis, syndactilia, glaucoma, hemophilia, and so on. In 1970 American geneticists V. Mac Quisic was first to publish catalog of hereditary human traits. Since, it has being updated

every year. Thus, if in 1958 it was known only 412 hereditary human traits, in 1978 – 2511, in 1981 – 3217.

8.2 The polygenic heredity.

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

The human height is determined by interaction of three allelic gene pairs, using principle of cumulative polymeria: A and a, B and b, C and c. Individuals with genotype aabbcc have a smallest height (around 150 cm), but individuals with genotype AABBCC have highest height (around 180 cm). Heterozygous height will depend on dominant genes number.

There are four dominant genes P1, P2, P3 and P4, which are presented in double dose. They are responsible for the integuments pigmentation intensity. If all genes in genotype are dominant, skin pigmentation is maximal like in native Africans (P1P1P2P2P3P3P4P4). If all genes are recessive, skin pigmentation is minimal like in European Caucasians (p1p1p2p2p3p3p4p4). Mulatto's pigmentation depends on dominant genes number.

Polygenic heredities are directed by following rules:

- Variations of quantitative traits depend on 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 genetic control.
- The amplitude of traits variation corresponds with polygenes number in species genotype. The more polygenes are in genotype, the larger amplitude of traits variation the species has.

8.3 The genetic factors value in phenotype formation.

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

under direction of many factors.

Among genetic factors affecting phenotype formation are interactions of genes from one allele (dominance, recessing, incomplete dominance, codominance) and from different alleles (dominant and recessive epistasis, hypostasis, complementarity), from many alleles, pleiotropic gene action, gene dose.

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

The incomplete dominance occurs when recessive allele is not fully suppressed. Some human and animal traits are subject to such 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 reduced 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 heterozygous organism. Such event was named codominance. It can be traced by assessing proteins, which are encoded by both of the genes. If both proteins are present in a 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 codominant pattern of inheritance.

The modified proportions may be due to interaction of non allelic genes. It can be 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 usually leads to new traits formation, which were absent in parents.

In dominance, one gene is suppressed by another from same allele: A>a, B>b and so on. However, there is another type of interaction when one gene is suppressed by another from different allele: C>D, A>b, c>d and so on. Such 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 also called gene supressors. There are dominant and recessive epistases accordinary to epistatic genes.

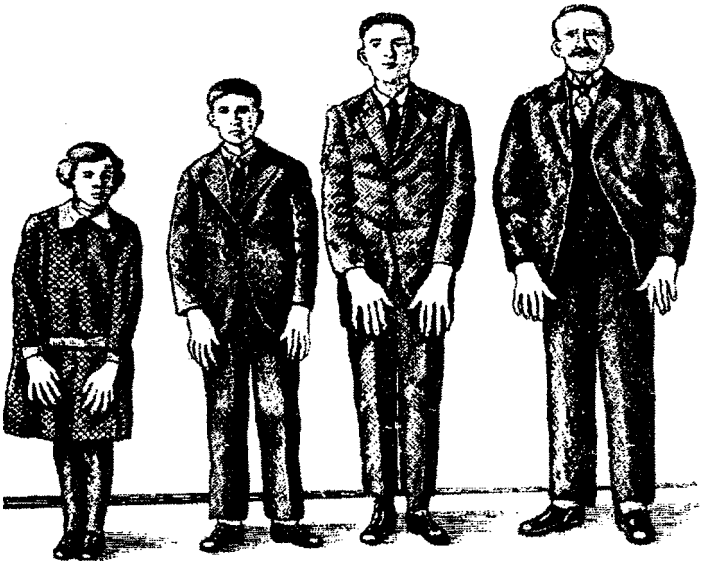
The recessive epistasis can be studied on example of human "Bombey phenomenon". If a person has dominant allele of blood group (A or B), these alleles

aren't expressed. As result of this person have I blood group. Such effect is explained by suppression effect of "Bombay phenomenon" gene in 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).

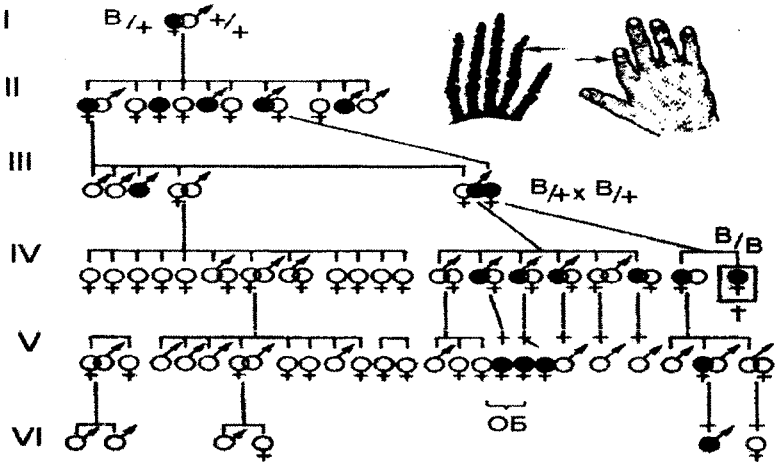
The table 8.1 The human ABO blood groups.

Blood group	Gene	Genotype	Agglutinogens	Agglutinines
I	I^0	I^0I^0	-	αβ
II	I^A	I^AI^A, I^AI^0	A	β
III	I^B	I^BI^B, I^BI^0	B	α
IV	I^A,I^B	I^AI^B	AB	-

All what 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 a1, a2, a3, a4 and so on. 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. The existence of ABO blood system was suggested by K.Landshteiner in 1900. He observed that blood coagulation occur in



Pic. 8.2. The arachnodactilia in Marphan's syndrome(by E.Verschuer, 1938)



Pic. 8.3. The herediting of dominant brachidactilia gene in human:
Black circles are heterozygotes (Bb), light circles are recessive homozygotes (bb), BB – lethal dominant homozygote (by O.Mohr, C.Wreidt, 1919).

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, б and в. In a population, there are all four blood groups (Table 8.1): A (having antigen A and antibody в), B (having antigen B and antibody б), AB (Having both A and B antigens and none antibody), and O (having only antibodies б and в without antigens). Group AB always has heterozygous genotype (IaIb). Group A may be homozygous (IaIa) or heterozygous (IaIo) in genotype. The same to B blood group. Group O always has homozygous recessive genotype (IoIo). Also genes of human HLA histocompatibility system, which are localized in 6th chromosome, are multiple genes (Pic. 14.1).

Often, 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. Primary pleiotropic gene expresses its effects simultaneously. For example, Marphan's syndrome is encoded by one gene (pic 8.2). It has following traits: big height, thin fingers (arachnodactilia), eye lens dislocation, heart defect, high catecholamine level in blood. Another example is sickle cell anemia. The mutation in normal allele leads to defective hemoglobin formation. The erythrocytes loose their ability to transport oxygen and acquire sphere shape. Homozygote dies right after birth, but heterozygotes survive and are more resistant to malaria. The dominant mutation causing brahidactilia (short fingers) in homozygous state leads to embryo death before delivery (pic 8.3).

The gene mutation causing Hartnep's disease leads to breaking tryptophan

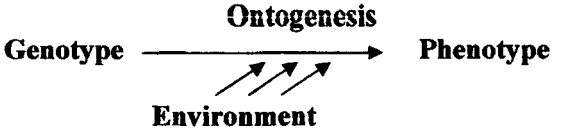
amino acid absorption in small intestine and reabsorbtion in kidney tubules. That result in simultaneous damage of two organs. In secondary pleiotropic gene action, we may see one gene effect that causes expression of several others. In particular, abnormal hemoglobin s in homozygous state leads to sickle cell anemia, which in turn leads to secondary phenotypic traits as malaria tolerance, anemia, hepatolienar syndrome, affection of heart and brain.

The gene action depends on gene dose. Normally each trait is controlled by two allelic genes, which may be homoallelic (dosage 2) or heteroallelic (dosage 1). In some cases gene dosage may be more than 2 (trisomia) or even less than 1 (monosomia). Gene dose is necessary for normal organism formation. For example, in female inactivation of one X-chromosome occurs after 16 days of embryonic development.

It is more complicated to determine variant of heredity in case of genocopies – are the cases when same trait is developed under control of different genes. For example, phenilketonuria is developed either with deficiency of dehydropteridinreductase or with deficiency dehydropholatereductase.

8.4 The environmental factors influence on realization of genotype to phenotype.

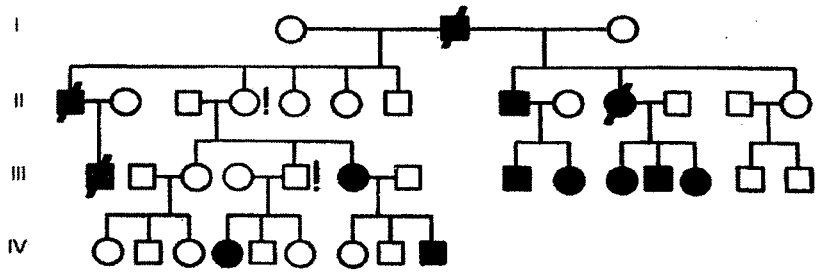
All organisms have an adaptation to environmental factors which act during centuries such as gravitation, magnetic field, sun radiation and so on and which act locally such as food deficiency, freezing, overheating, noise and etc. That's why human has a high level of adaptation to environmental factors. It is caused by gene ability to determine not only a definite trait but also limits of its variation. It leads to less dependence of organism from environment, to increasing complicity of genetic apparatus and gene controlling system. Realization of gene in phenotype occurs in proper environmental condition, which may be illustrated in following scheme.



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 condition of gene expression

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

One trait controlled by one gene may be expressed in one individual and be absent in another. Such event is called penetrance of gene. The penetrance is measured by calculating percentage of individuals having mutant phenotype in



Pic. 8.4. The gene penetrance in "blue sclera" syndrome:
black symbols are individuals with blue sclera; oblique line – frequent fractures; ! – absence of penetrance; I-IV – generations (by J.Bell et al., 1928).

population, which is homozygous on this gene. The complete penetrance (100%) means that every individual express 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 (pic 8.4).

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 genotype interaction and different reaction of 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, which are look like genotype determined, but really having induced by environmental factors are called phenocopies. Thus, child rachitis may be due to low consumption of vitamin D or due to hereditary defect. Eye cataract, which is caused by German measles during pregnancy, looks like eye cataract due to gene defect.

Phenotype is formed also with help of environment and ontogenesis. So, tendency to presbyopia is inherited. But with lens accommodation some sight correction occurs. However, in elderly 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 development.

CHAPTER 9. DIVERSITY.

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

It can be distinguished two variants of diversity: genotypic and phenotypic. The genotypic (hereditary) diversity can be combinative and mutational. The phenotypic diversity can be ontogenetic and modificational.

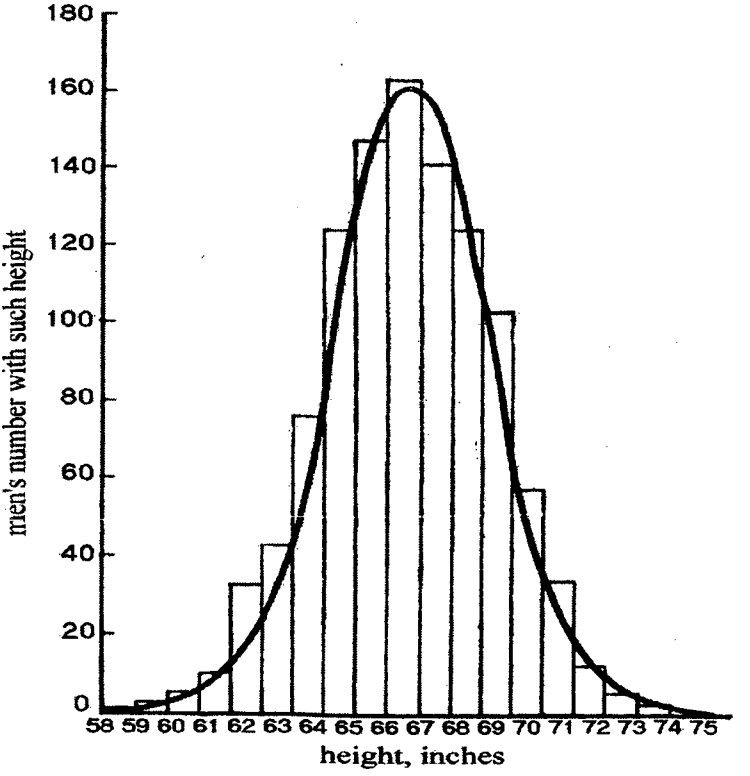
9.1 The phenotypic diversity.

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

9.1.1 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 a main difference from 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 humans are 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 genetic ones, don't follow such pattern. The level of phenotype changes in genetic mutation don't correspond with intensity and duration of environmental effect.

Each trait of humans are formed in genotype and phenotype interaction. And variations of traits are limited. They are limited by material matter of heredity structures, which are in appropriate limits called norm of reaction. The norm of reaction – are the limits of modificational diversity of organism. In a human we may observe a full range of traits starting from completely determined by genotype (ABO blood groups, iris color etc.) to determined with strong help of



Pic. 9.1. The curve of normal distribution of men by height (K.Willy, 1964).

environment (human height) and finishing by almost fully determined by environment (weight).

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 19th century, A.Veismann refuted arguments of J.B. Lamark. He cut off rat's tails in 22 generations but in spite of this, rats in 23rd generation had tails.

9.1.2 The ontogenetic diversity.

During ontogenesis many physiological, morphological, biochemical and other organism properties are being changed. Their time and place of appearance in phenotype are strictly determined by genotype. The ontogenetic diversity is

diversity showing normal development changes in organism or its cells during individual development. You can recall the examples in your own individual development. The main difference from genotypic diversity is that organisms have the same genotype throughout all individual development. From a variety of mechanisms controlling ontogenetic diversity the main 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, development of secondary sex signs, grey hair, loosing of skin elastics, and the increased rate of bone fractures in elderly.

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

To treat properly, the doctor needs to know the mechanisms of ontogenetic diversity and their role in development of some hereditary human diseases. For example, phenilketonuria is hereditary effect, which may be evaluated right after birth. It is related with intolerance to one amino acid. If the patients are treated well in the first years of life they can fight with disease by themselves after puberty. But if the patients aren't treated they develop irreversible changes in the brain.

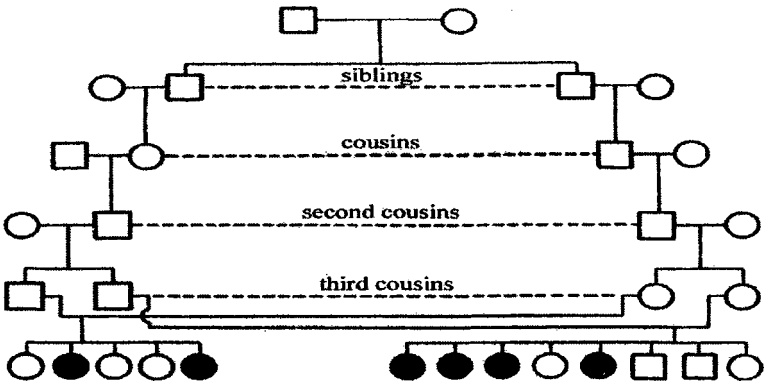
9.2 The genotypic diversity.

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

9.2.1 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 new trait formation. Combinative diversity is inherited according to Mendel's Laws. On gene expression in combinative diversity, the following factors may have some influence such as interaction of allelic and non-allelic genes: pleiotropic gene action, gene linkage, gene expressivity, penetrance, and so on. The wide traits variety is provided by combinative diversity.

Concerning human, combinative diversity is observed in crosses that have



Pic. 9.2. The inbreeding of two related families resulted in amavrotic idioty (by T.Sjogren,1931).

already been made. The family crosses systems may be of two types: inbreeding and outbreeding.

The inbreeding – is crosses between relatives. The level of inbreeding depends on 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 diversity of each line will decrease. The inbreeding often leads to an offspring's degeneration. It was pointed in ancient times. All tribe taboo and inbreeding bans tell us about that. The human inbreeding in majority of cases is harmful (pic 9.2). The family relation among parents increases risk of hereditary defects in offspring.

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

9.2.2 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 allelic gene position, changing of gene structure, changing in chromosome

number and state, changing of cytoplasmic DNA containing structures. First to summarize material about mutation was H. de Fris. He published "The mutational theory" in 1901. The main statements of that theory are in following:

1. Mutations appear 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.

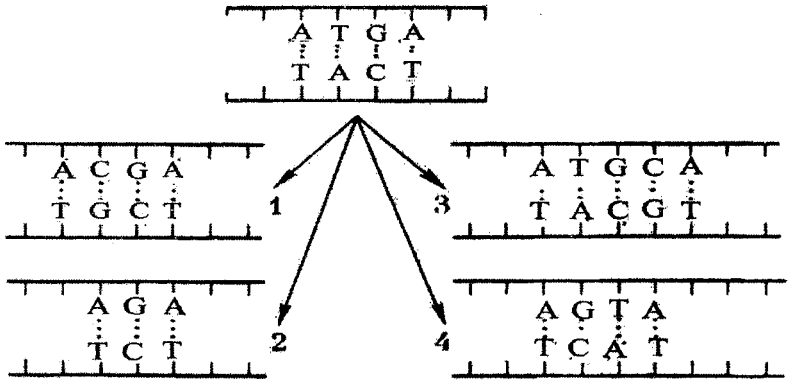
All mutations are divided on groups. The mutation classification helps to study and describe them. It is made according mutation causing factors and cells subjected to mutation.

The table 9.1 The classification of mutation.

Classifying factor	Mutations' names
According mutated cells	1 – generative 2 – somatic
According genotype change	1 - gene mutation 2 - chromosome aberrations 3 - interchromosome aberrations (translocations) 4 - genome mutations 5 - cytoplasmic mutations
According adaptive significance	1 – useful 2 – harmful 3 – neutral
According reason of mutation	1 – spontaneous 2 - induced

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 in particular individual. If mutation is recessive, it may take several generations to express it 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 be subject to mutation 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 normal cell



Pic. 9.3. The local gene mutation:

1 – the bases' pair interchange in DNA molecule, 2 – deletion of one bases' pair, 3 – insertion of one bases' pair, 4 – mislocalization of one bases' pair inside of the gene (by N.P.Dubinin, 1976).

phenotype to cancer one is based on somatic cell mutation.

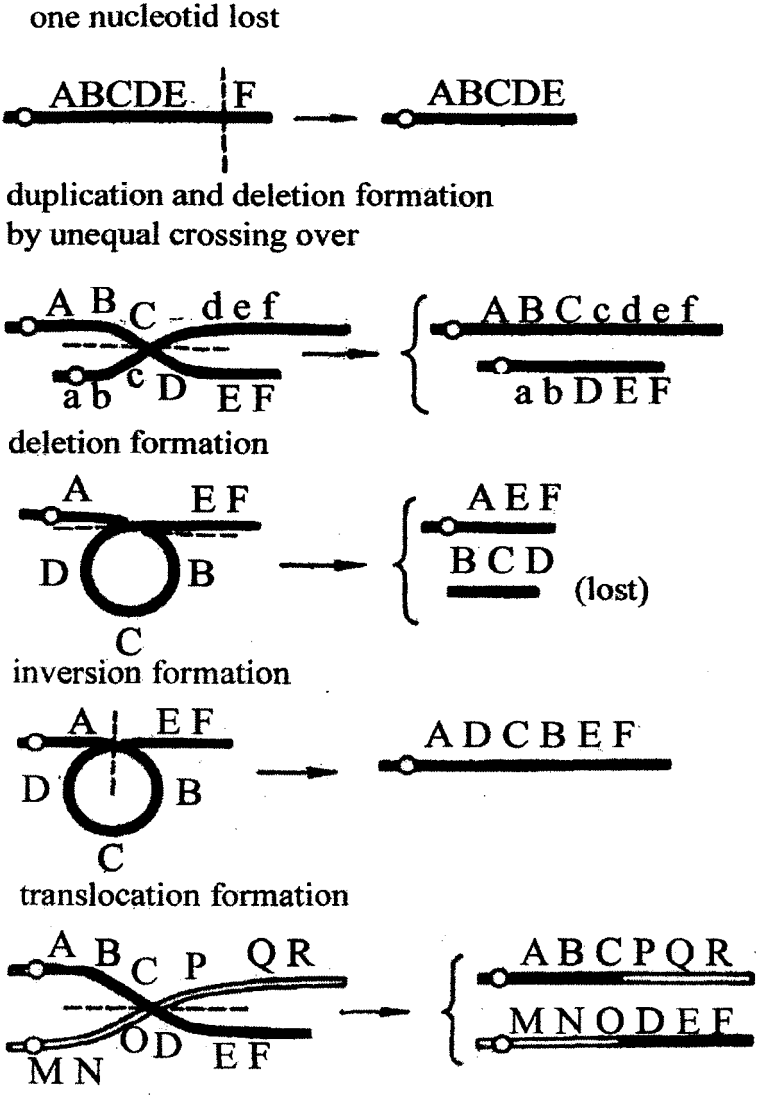
Gene or point mutations are alteration involving only one or few nucleotides in the coding sequence. They may be as dominant as recessive one. The examples are vitamin B resistant rachitis, metabolic exchange imbalance of phenylalanine amino acid. In general all point mutation have one of following mechanisms:

1. Nucleotide pair exchange in DNA molecule
2. Deletion of nucleotide pair (or group of pairs) in DNA molecule
3. Insertion of nucleotide pair (or group of pairs) to DNA molecule
4. Translocation of nucleotide sequence inside of the gene

All these alterations lead to three classes of gene mutation: missence mutation, nonsence mutation and frameshift mutation. The small changes in gene structure may cause reading frameshift. They in turn cause big ultimate changes in protein structure and function.

Missence mutations appear when several nucleotides inside of codon have been changed. It is possible shift of one purine base to another purine (A-G) or of one pyrimidine base to another pyrimidine (C-T). It results in codon changing (transition). But shift of one purine base to purimidine one is also possible and called transversion. Missence mutation results in one amino acid exchange in protein chain (abnormal hemoglobins). The physiological properties of protein have been changed which makes a field for natural selection. This is a main class of point mutation. It is 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 of the gene. It terminates transcription resulting in failure of protein synthesis. The causes of nonsence mutation are the same as for



Pic. 9.4. The mechanisms of main types of chromosomes' aberrations formation (by S.M.Gershenzon,1979).

missence mutation.

Frameshift mutations are caused by nucleotide deletions and insertions. When they occur, they lead to the creation of genetic message that is out of synchrony with the normal reading pattern, three- base increments being displaced one or two positions.

Chromosome aberrations or rearrangements are referred 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 arm deletion, duplication of some chromosome regions, chromosome region inversion. 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 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 Dawn syndrome.

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

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

Anueploidy is changing in number of several or one chromosome. In human, it was observed trisomy of 21st, 13th and 18th chromosomes, monosomy of X-chromosome and others. Aneuploidy leads to decreasing survival ability of organism.

Cytoplasmic mutations are mutations in DNA of cytoplasmic organelles. These mutations are stable. They are transmitted to next generation (for example, lost of cytochrome oxidase in yeast mitochondria). Examples of human cytoplasmic mutations are that which cause some types of myopathy, anencephalitis, Olbright osteitis, Spina bifida.

Accordingly adaptive significance mutations may be divided to harmful, useful and neutral. But that classification is conditional. There is a very slight difference between useful and lethal mutation because of 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, Edvards-Smith and Pattaw syndromes. There is no useful mutation among human. Neutral mutations have no influence on organism survival. Usually they are cosmetic defects (polydactilia, mosaic color of iris and so on). Semilethal mutations decrease organism survival and may cause death (hemophilia, Duchenne dystrophy, Dawn syndrome etc.).

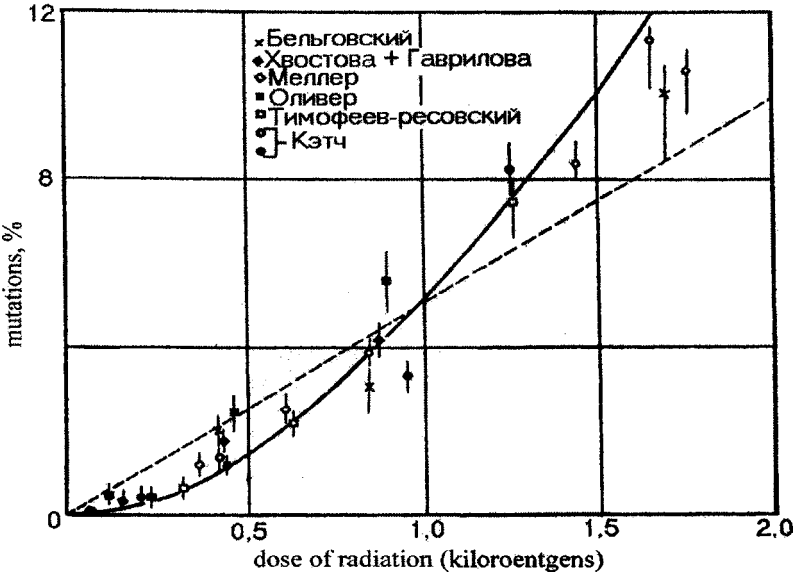
Mutations, which appear in natural conditions, are called spontaneous mutations. The mutational process mainly is characterized by mutational rate. Each species has definite mutational rate. Some species have high mutational rate, some species have low one.

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*10^-5, for hemophilia is 3.2*10^-5. Particular gene is subject to mutation very rare, but total gene number in genotype is huge and that's why general mutation rates are high. In some species there are special genes – genes mutators. Such genes significantly increase mutational rate. They were 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 were induced by external and internal environmental factors. Such factors are called mutagens. These factors lead to mutation induction over spontaneous mutational rate. All mutagens may be divided to three types: physical, chemical and biological.

Among physical factors most important is ionizing radiation. Ionizing radiation may be electromagnetic or wavelike (X-ray, gamma rays, cosmic rays) and corpuscular (в-bodies, electrons, positrons, protons, neutrons, б-bodies). 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



Pic. 9.5. The dependence of chromosome's aberration formation from radiation dosage (dotted line – hypothetic values, continuous line – real values) (by N.V. Tymofeev-Ressovskiy, K.G. Zymmer, 1947).

for human and to millions Roentgens for bacteria and viruses. Ionizing radiation primary damages nucleus of the cell. It was shown that nucleus in 100000 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. The mutational rate strictly corresponds with radiation dose. The higher radiation dose acquired, the higher mutational rate is (pic 9.5). The strong mutagen is UV radiation. It mutative effect depends on its wavelength. It doesn't cause ejection of electrons from outer shells, but it activates them for different chemical reactions. It is less active than ionizing radiation.

Significantly weaker factor is temperature. The increasing of temperature on 10 degrees leads to increasing of mutation rate in 3-5 times. But this factor is more important for lower organisms.

Chemical mutagens include various substances. The list of them is updated every year. They are divided into several groups. The first group includes (alcyling) substances, which are strongest mutagens (dimethylsulfat, iprit, ethilenimin, nitrozalcyl-, nitromethyl- and nitrozoethylcarbamide etc.). Many of them are carcinogens. The second group is nitrogen bases analogs (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, and formaldehyde).Chemical mutagens can induce point mutation and chromosomal mutations as well.

Biological mutagens are presented by viruses, bacteria, helminthes and their metabolites. It was found that animal and plant viruses induce mutations in Drosophila. It is possible that mutagen element in viruses is nucleic acid. Bacteria can induce chromosome and chromatide ruptures. Bacterial endonucleases may activate formation of 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. That why, it is important to protect humankind from mutagens. Everyone should follow the rules while working with isotopes, X-rays containing devices. Some protection can be reached by consumption of mutation protective drugs (cysteine, chinacrin, some sulfanilamides etc.).Each organism has system of DNA repair. If this system is less efficient in the repair of DNA damage caused by expose to sunlight or other sources of UV radiation, affected individuals have xeroderma pigmentosum. Those who have this disease develop extensive malignant skin tumors after expose to 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 mutational process it is important to study induced mutations, mutagens, mechanisms of DNA repair.

CHAPTER 10. HUMAN GENETICS.

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

10.1 The methods of human genetics studying.

Human genetics studies traits inheritance in human. To study such inheritance, it was discovered and was successfully applied several methods. Nevertheless, none from them is universal. Let's look them through.

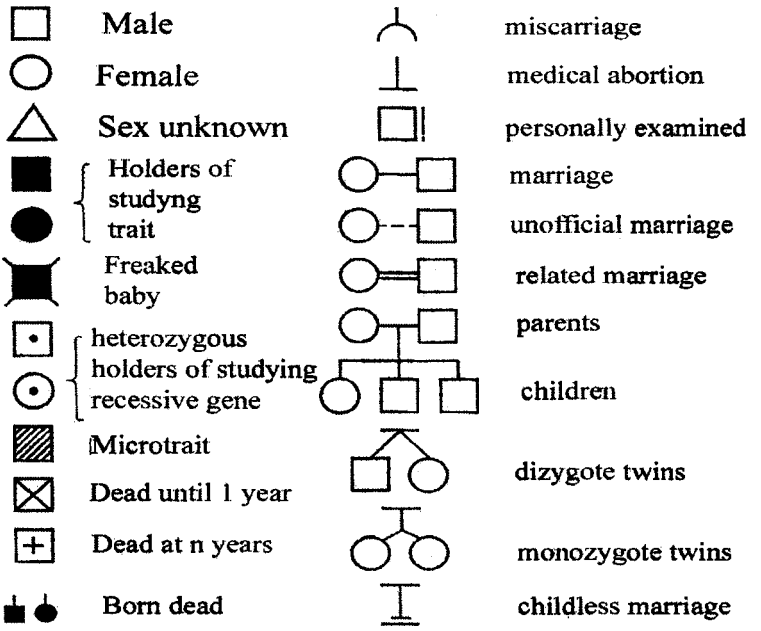
10.1.1 The pedigree analysis.

To study how a human traits are inherited, investigators look at the results of crosses that have already been made – they studied family histories, called pedigree. This methods may be applied if it is known direct parents of individual which is studied (he is called poband) or if it is known children of such individual. To make pedigree specific signs are used (pic 10.1). They were suggested by G. Ust in 1931. We analyze pedigree to determine 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. The trait occurs in horizontal and vertical lines of pedigree as well. The child may be affected, if anyone from parents is affected too. However, it is important to remember about incomplete penetrance of dominant gene. Some diseases develop 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 (pic 10.2a).

In the autosomal recessive pattern of inheritance, the mutated trait appears only in homozygous state in individuals of both sexes. If parents are healthy, but they are heterozygotes, you can expect that 25% of offsprings will have disease. The trait occurs in horizontal line of pedigree not in every generation. If parents are both recessive for trait, all offsprings will have such trait. The examples are albinism, phenyketonuria, diabetes mellitus, and red hair (pic 10.2b).

In the X-chromosome linked dominant pattern of inheritance, the mutated



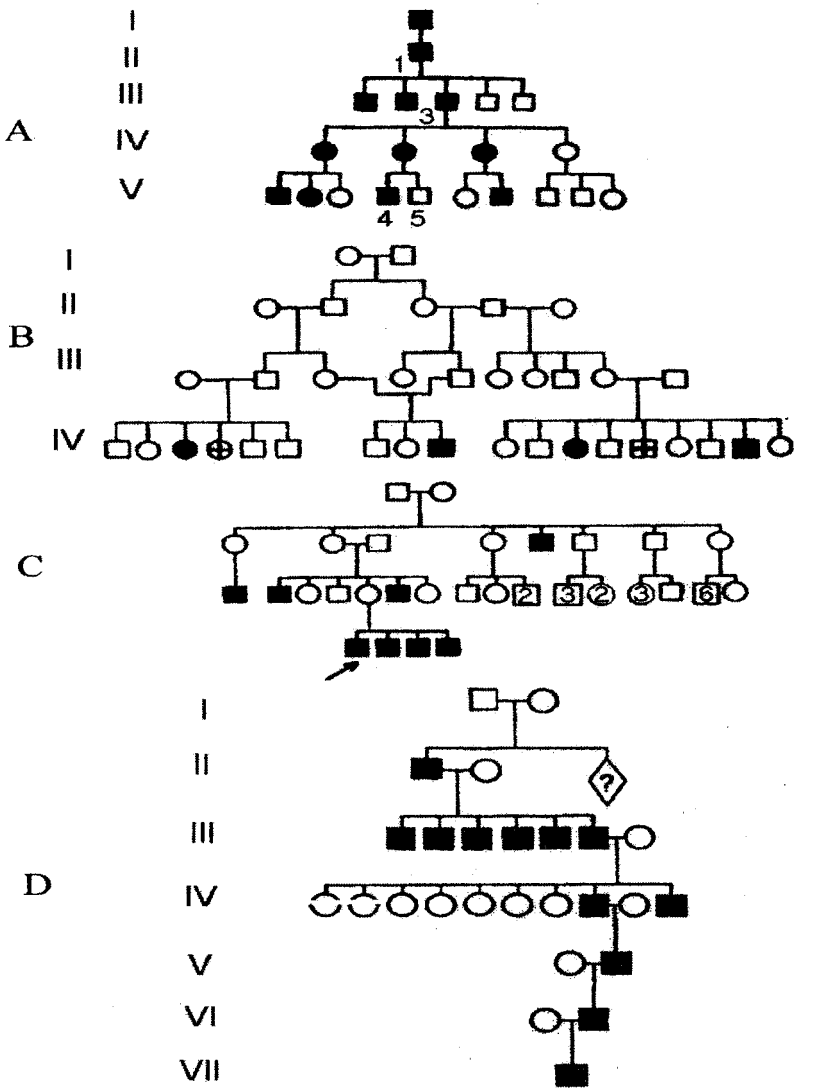
Pic 10.1. The genetic symbols for pedigree (by.G.Ust, 1931 with changes).

trait appears in individuals of both sexes. The trait occurs in horizontal and vertical lines of pedigree as well. Inbreeding increases probability of ill childbirth. Female express such trait more often, because they may get trait from mother and father as well. The follicular keratosis, pigment dermatosis are inherited according X-linked dominant pattern of inheritance.

In the X-chromosome linked recessive pattern of inheritance, the mutated trait appears mainly in males. In a family, there are half of males suffered from disease and half of females having gene in heterozygous state. If the male have such trait, he inherited it from mother line of pedigree. The most common diseases having such pattern of inheritance are hemophilia A, muscular Duchenne dystrophy, daltonism (pic 10.2 c).

In the Y-chromosome linked pattern of inheritance, the mutated trait appears only in males. The syndactilia, hypertrychosis of cochlea are inherited Accordinary such pattern. The ability to develop male gonads is holandric trait, located in Y-chromosome (pic 10.2d).

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

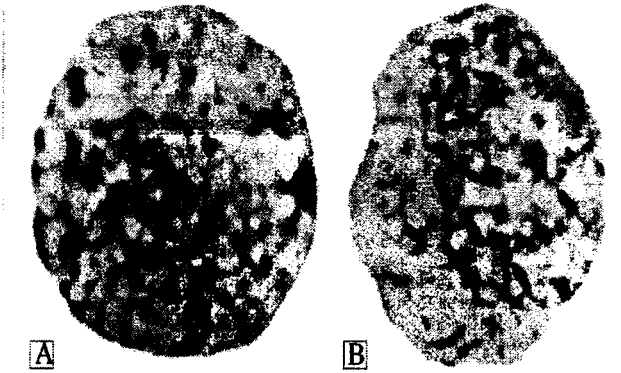


Pic 10.2. The types of human inheriting:

A – autosomal dominant (pedigree of white curl); B – autosonal recessive (pedigree of phenylketonuria); C – X-linked recessive inheriting (pedigree of Duchene's muscle dystrophy); D – Y-linked inheriting (pedigree of "man- porcupine"); I-VII – generations (by K.Shtern, 1965).

10.1.2 The cytogenetic method.

It is usually called cytological analysis of 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 phenotype effect. It is based on chromosome microscoping. Chromosomes are studied in metaphase of mitosis in fibroblasts and lymphocytes, which are cultivated in artificial conditions. The luminescent microscoping also may be used. In this case, we need to stain chromosomes by fluorochrom. Chromosomes are classified according Denver classification. This method allows determining diseases related with changes in chromosome set and shape. It is also used for chromosome mapping.



Pic. 10.3. The female chromatin-positive (A) and male chromatin-negative (B) nucleuses (by E.F. Davidenkova, 1965).

The method is kind of complicated. The lymphocytes grow in a culture. They are stimulated to division by phytohemaglutinin. In metaphase, spindle proteins are destroyed by colhicin. After that, chromosomes are available for observation for long time. Using this method J. Tiyo and A.Levann in 1956 stated that human karyotype has 46 chromosomes.

In 1969 T. Casperson discovered the method of chromosome staining. It made possible to distinguish chromosomes accordinary their segments staining. The aneuploidity, chromosome aberrations, translocations, polyploidity may be revealed with help of this method. Among aneuploidities we can determine excessive X- and Y-chromosome, trisomy in 13th, 18th, 21st chromosome. We may determine deletion of 5th chromosome ("cats scream" syndrom), of 18th (mental retardation, deformation of skeleton) and of X-chromosome. The deletion of short arm of X-

chromosome is referred as partial monosomy in X-chromosome. The most common translocation is translocation of 21st chromosome on 15th, 13th, 14th chromosome in females and on 22nd chromosome in males.

If there are defects in sex chromosome set, we can determine them easily. For such purpose evaluation of sex chromatin in somatic cells are used. The most common material for that is buccal epithelium (pic 10.3). Sex chromatin (Barr's body) – is condensated second X-chromosome in female cells. It is inactivated on 16 day of embryogenesis. It looks like heterochromatin body nearby nucleus membrane. It is revealed on preparations stained by aceto-orsein. 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 such formula: Barr's bodies' number plus one. For example, if woman has one Barr's body that means she has two X-chromosomes (1+1); if there is no Barr body in female cell that means she has one X-chromosome (0+1); if man hasn't 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 determined in 20-40% of male cells.

The express-methods for sex chromatin determining are used for hereditary, related with changing in sex chromosome set, diseases diagnostic, sex determining in hermaphrodites, transsexuals, and in forensic medicine.

10.1.3 The statistic method.

The method is based on demographic statistics data and mathematic analysis of them. Using Hardy-Weinberg principle, we can calculate rate of defect gene staying in heterozygous state in human populations (see chapter 17.1).

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

Such method also is useful in understanding dynamic genetic assortment in populations. Different populations have a different genetic structure. For example, let's look through gene assortment for genes of ABO blood group system. Thus, in India and China the concentration of allele Ib is highest. This concentration falls down to east and to west from those countries. Among Native Americans and Australians there isn't Ib allele. At the same time, Native Americans and Australians have highest concentration of Io allele. The allele Ia is expressed very 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 primary affects people with blood group A. That lead to higher mortality

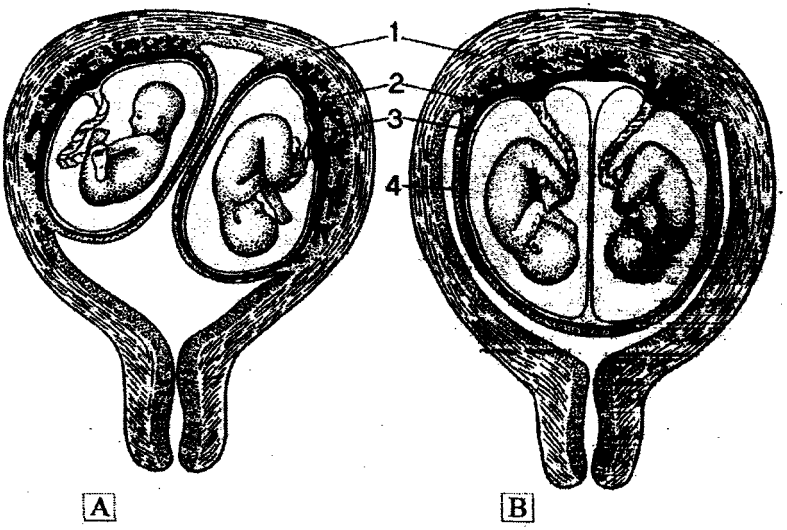
among them and elimination Ia allele from population. The places where smallpox was wide spread (India, America, Arabic countries) have a low Ia allele rate among population. In the pointed above regions allele Ib became most frequent.

The data acquired with help of population statistics are used for planning health care funds, required drugs and required specialists number.

10.1.4. The twins' method.

The method's idea was suggested by F. Galton in 1876, and was developed by G. Simens in 1924. The method is based on studying of traits of twins having same sex, which are changed by environmental condition. Twins are two or more delivered at the same time individuals in animals usually having only one (cow, horse, and human). Twins, who develop from one fertilized ovum, are called monozygote twins (pic 4.1). Twins, who develop from two different fertilized by different sperms ova, are called heterozygote twins (pic 10.4). Heterozygote twins may have different sex. The most common situation is having two twins, but it is possible but rare to have three, four, five and even more twins. Twins rate in population is around 1%. One fourth of them are monozygote. But monozygote rate in different population is different. For instance, in mongoloid race it is 60%, in other races it is around 30%.

Pic. 10.4. The dizygote non-identical twins (brother is albino, whereas sister is pigmented) (by S.Sinnot, L.Dunn, Th.Dobzhansky, 1958).



Pic. 10.5. The twins:
A – dizygote twins with independent coats; B – monozygote twins with common placenta; 1 – uterus wall; 2 – chorion vilia; 3 – amnion; 4 – smooth chorion (by E.L.Potter, 1948).

Both types of twins are used for genetic research. By this way, we can understand both influences of different environmental conditions on same genotypes and influences of same environmental conditions on different genotypes. If studied trait is expressed in both twins, it is called concordance. If studied trait is expressed only in one twin, it is called discordance. Comparing level of traits concordance in different twins' groups, we can determine the impact of genotype and environment to phenotype formation. Such method is not presented in routine doctor's job, but it is important to remember about twins' concordance in disease development.

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

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

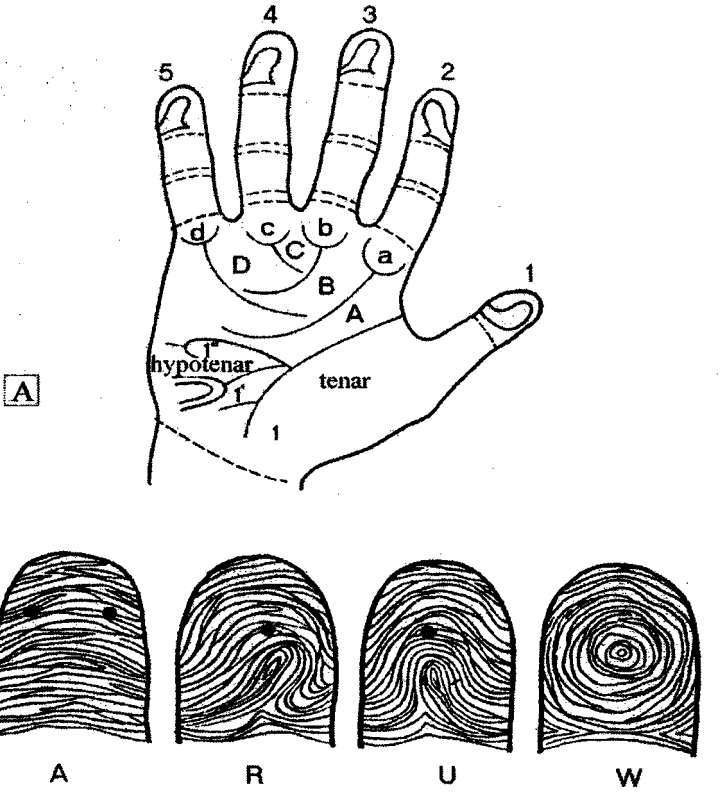
Where Cmz is percentage of concordated pairs of monozygote twins, Cdz is percentage of concordated pairs of dizygote twins.

With help of twins' method, we can study the following:

- The role of environment in disease development.
- The definite factors enhancing environment impact.
- The correlation between traits and functions.

10.1.5 The dermatogliphic method.

The dermatogliphic is a branch of genetics studying hereditary patterns of fingerprints, handprints and footprints of human. The first to suggest such studying was F. Galton in 1892 (pic 10.6). The fingerprints are individual. The process of papillary picture formation occurs in 3-6 month of embryo development. It is based on epidermal and dermal differentiation and on growth and movement of



Pic. 10.6. The human skin hand folds (A) and papillary pictures (B):
A – arches, R – radial loop, U – ulnar loop, W – helix (by G.D.Berdyshev, I.F.Kriviruchko, 1979).

cell complexes.

Genes responsible for fingerprints type formation participate in derma saturation by water. So, gene A determine arch appearance on water saturated finger; gene W determine appearance of helix on significantly saturated finger pillow; gene L determine appearance of arch on fingers with directed water distribution. It was stated that ulnar loops are more common in first and fourth finger, where radial loops are more common in third finger. In fourth and fifth fingers normally there are no radial loops. Helixes are more common in first and fourth fingers; arches in second and third. Arches are expressed very rare. On a left hand usually ulnar loops and arches are. On a right hand usually radial helixes and loops are. In a literature, it is stated that females have higher arches rate and loops rate and lower helixes rate in compare with males. The frequency rate for radial loops is 0.2-10%, for ulnar loops is 25-75%.

The dermatoglifics is widely used in hereditary disease diagnostics. Some inherited diseases have specific dermatoglific features (such as trisomy in 13^{th}, 18^{th}, 21^{st} chromosome pair). The analysis of fingerprints may be used for diagnostics. The changes in flexor hand lines occur in individuals with Schereshevsky-Terner syndrome. It was described the specific features in fingerprints for myasthenia gravis, schizophrenia and others diseases.

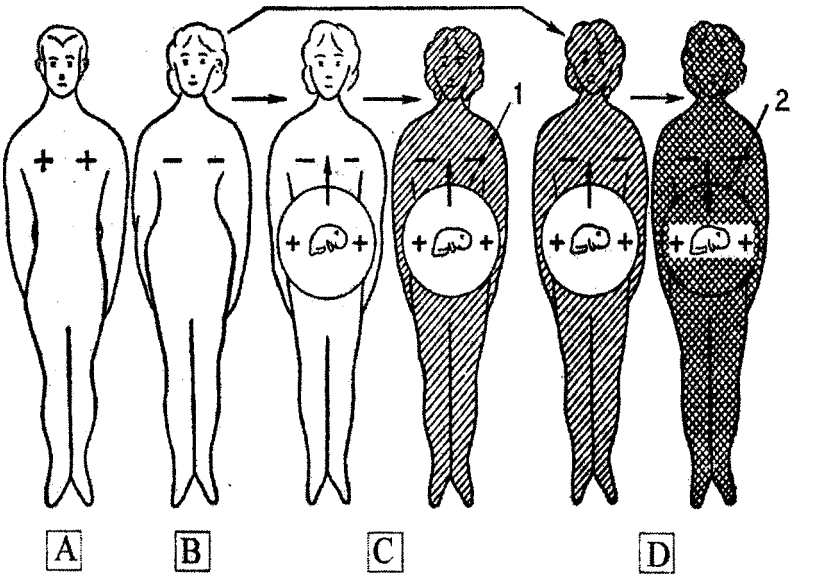
The fingerprints' studying has a wide distribution in forensic surveys.

10.1.6 The immunological methods.

Such methods are based on studying antigens of human cells and fluids (blood, saliva, stomach juice). Most common are erythrocyte antigens, leukocyte antigens, blood proteins. Different erythrocyte antigens form different blood group: ABO, Rh, MN, Luis, Lutheran, Daffi

Blood group determining is important for blood transfusion. Also it was stated a correlation between having a blood group and having a disease: stomach cancer more frequent among people with blood group A, whereas peptic ulcer is more frequent among people with blood group O.

It was shown by K. Landsteiner and I. Levin that human erythrocytes have antigen similar to rhesus monkey. It resulted in discovering new blood group – Rh-group. The Rhesus factor is inherited dominantly in homozygote and heterozygote state as well. Only 15% of Europeans have Rhesus negative blood group. If Rhesus negative mother has Rhesus positive embryo, it may lead to a potentially fatal condition called erythroblastosis fetalis. If mother is homozygous in recessive allele and father is homozygous in dominant allele, the child inherits fathers Rh-factor (pic 10.7). During first pregnancy, Rh-positive erythrocytes of embryo stimulate antibodies formation in mother's organism. However, child is not affected by them because of low concentration of them. However, during second pregnancy,



Pic. 10.7. The Rh-factor inheriting in human and erythroblastosis fetalis:

A – father is Rhesus positive (Rh+); B – mother is Rhesus negative (Rh-); C – first pregnancy, Rh+ antigene cause antibodies formation, baby can be normal (oblique crossing - 1); D – second pregnancy, erythroblastosis fetalis, bady dies (2) (by N.P.Dubinin, 1976).

the antibodies concentration becomes critical and erythroblastosis fetalis is developed. Next pregnancies will have more and more severe erythroblastosis.

10.1.7 The biochemical methods.

Contemporary families have a few children. Its make using of pedigree analysis very complicate. Therefore, biochemical methods of evaluation of different enzymes activity and interesting chemical substances are widely used. Thus, we can check different stages of metabolic pathways and reveal crucial defected points in them.

The biochemical methods are applied for diagnostics hereditary metabolic exchange diseases. They are determined on a 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 by 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 desease, hemochromatosis) and so on. Taking into account polymorphism of hereditary exchange diseases, biochemical method is crucial in its diagnostics.

10.1.8 The ontogenetic method.

The ontogenetic method is the studying gene expression during development. There are two periods of human development: antenatal (before birth) and postnatal. Postnatal is divided to morphogenetic and postmorphogenetic. In morphogenetic period, there are last stages of brain cortex and different organ's systems formation. Gradually, the immune system is formed. In morphogenetic period, gene activity can be of two types: switching on and switching off, activation and suppression of gene action. In postmorphogenetic period, there is formation of secondary sex signs. Only several genes are activated (which responsible for secondary sex signs) during this period. The gene repression is presented wider. The genes, which are responsible for r-globulin synthesis, melanin synthesis, connective tissue matrix synthesis, are repressed. Such repression occurs on a level of transcription and translation. But main is gene activity activation and suppression. The heterozygote state gene expression may be changed, thus, phenylketonuria gene may affect a human mind in heterozygote state. Men while aging express changing in voice, body's shape, in mind (become more impressive, crying). Women acquire harder voice, new character and, unfortunately, changing in body's shape.

It is known that some hereditary diseases may be expressed not only in homozygous state, but also in heterozygous state as implicit forms. Therefore, developing of new methods of diagnostics such disease expression are in great importance today. So, the individual having heterozygous phenylketonuria allele can be determined by intravenous phenylalanine injection following by evaluating of its level in blood. Normally the phenylalanine level stays the same, but in individual having heterozygous phenylketonuria allele the phenylalanine level increases. Very often heterozygotes have intermediate enzymes activity. Now it was developed the methods to determine heterozygous allele state for more than 40 hereditary diseases. Such diagnostics is important for in time treating and for assessment the risk of having child with such defect. Such diagnostics performed for cripple child parents and siblings is necessary for prognosis his offspring genotype. Recognizing of individuals having heterozygous defect allele can be performed by different ways. First one is thoroughly examination of patient looking for microsymptons. Thus, heterozygotes for anoftalmia have decreased eye size; heterozygotes for Duchenne muscular dystrophy have increased level of creatinphosphokinase in blood. Second one is load tests. We have described it for phenylketonuria above. The same tests can be performed for assessment essencial

hyperlipidemia and disaccharidase insufficiency. Third one is cells and tissue microscoping. So, the "foam" lipid loaded cells are founded in lipidosis's heterozygotes, cells reached in glycogen are founded in glycogenolisis's heterozygotes. Fourth one is direct evaluation of enzyme activity, suffered from mutation. It is possible in hemophilia, galactosemia, glucose-6-phosphatase insufficiency.

In addition, ontogenetic method is used to determine mechanism of disease development on different ontogenetic stages, which is important for further treatment and preventive measures. Method includes biochemical, immunological and cytogenetic methods. In particular, we may determine on early stage of development a phenylketonuria, galactosemia, vitamin-D-resistant rachitis and so on; and on later stages of development – alkaptonuria, diabetes mellitus etc.

10.1.9 The methods of somatic cells genetics.

Such methods are based on studying cell culture of somatic cell. In a cell culture, the traits are expressed independently from environmental conditions and can be studied in clear state. Now using modern technologies, we can get generation line from one cell. It was stated that somatic cells may join together and form new cells. The cells from one organism as well as from other organisms may be joined. It results in hybrid formation. Hybrid cells have properties of precursor cells. They are used for studying immunological, biochemical, and cytological trait transmission.

The advantage of this method is getting genes in clear state, "per ce". Also we can get as many cells as needed for cytological, biochemical and immunological analysis. In hybrid cells we can perform analysis of gene linkage and gene localization, discover mechanisms of gene activity, gene interactions, gene mutations and so on.

10.1.10 The molecular-genetic methods.

The molecular-genetic methods help to describe changes in structure and functions of nucleic acids. Its include methods of gene extraction, gene synthesis, in vitro gene activity studying, gene transfection. It really pushed forward researches of human heredity and nature of hereditary diseases. Genetic engineering methods are real devices for treatment of hereditary diseases. It allows receiving primary human gene product and further using of it for 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 for genetic diseases treatment.

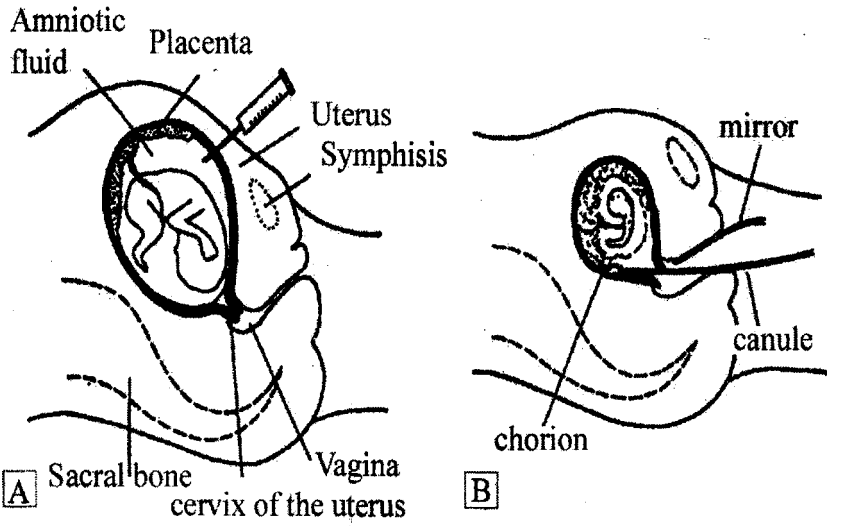
10.2 The prenatal diagnostics of hereditary diseases.

All methods of prenatal diagnostics can be divided to biological and physical.

The physical methods are X-ray examination of embryo, ultrasonic examination and fetoscopia. X-ray examination gives diagnosis of hereditary defects only in last third of pregnancy. The anencephalia, spinal cord hernia and hydrocephaly are good visible in X-rays. The variant of X-ray examination is fetographia. This is a method when contrast substance is injected to amnion cavity. This method allows diagnosing alimentary canal athresy, urinary system defects. The fetoscopy gives a real visible image of embryo, but it has many side effects and is used very rare. Many defects of nervous system are determined with help ultrasonic examination. Also it helps to evaluate defects of kidney such as polycystosis.

The biological methods are amniocentesis and chorionopexia (pic 10.8).

The amniocentesis is performed on 14-16th week of development when amount of amniotic fluid is sufficient and when there is a time to cancel pregnancy. 15-20 ml of amniotic fluid are taken and centrifuged. The supernatant is used for biochemical and immunological methods, whereas cell detritus is used for cytogenetic methods. Now it is possible to determine sex of embryo, all chromosome abnormalities, more than 60 hereditary diseases, intolerance to Rh-antigen, he-



Pic. 10.8. The prenatal diagnostics of hereditary diseases:
A – amniocentesis; B – chorionopexia (by F.Fogel, A.Motulsky, 1990).

moglobinopathy, enzymopathy, immunodeficiency syndromes with help of amniocentesis.

The same investigations are conducted while chorionopexia is performed. This method has several advantages over amniocentesis. It may be performed on earlier stage of development (6-7th week) and it excludes penetration of amniotic space. The material for investigation is chorion particles, taken from cervical canal of pregnant woman.

10.3 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. It was calculated that among 5 billions Earth inhabitants, there are 10 millions which may be affected by different hereditary diseases such as diseases of nervous system (schizophrenia, epilepsy), endocrine system (cretinism), blood (hemophilia), metabolism (phenylketonuria, albinism) and so on. The understanding causes of them allow treating them well. Using human genetics achievements, the genetic counseling service have been designed. The best worlds about human genetics value were said by I.P.Pavlov in 1935. "The life requires using of Mendel's Laws of inheritance. The genetic principles have been studied enough to start using them intensively. Our doctors should know Laws of inheritance as ABC. The realization of knowledge about inheritance can relieve mankind from grief and sorrow."

CHAPTER 11. HUMAN HEREDITARY DISEASES.

11.1 The classification of human hereditary diseases.

These days, we see a decreasing rate of infectionous diseases, but at the same time hereditary disease rate are increasing. More than 3000 prevalently hereditary diseases have been registered. In the world more than 1.5 millions 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. In the Republic of Belarus, 30-40% of patients in children's hospitals have hereditary diseases. Among children dying in the first year, 30% have a hereditary defect.

HEREDITARY DISEASES

The diseases of metabolic exchange	The chromosome diseases	The cytoplasmic diseases
1. Amino acid metabolism 2. Lipid metabolism 3. Carbohydrate metabolism 4. Steroid metabolism 5. Purine metabolism 6. Blood coagulation system 7. Hemoglobinopathy 8. Mineral exchange	1. Related with changing in number and structure of sex chromosomes 2. Related with changing in number and structure of autochromosomes	1 Some miopathies 2 Anencephaly 3 Skeleton defects (Albrights osteitis, Spina bifida etc.)

V.P. Ephroimson (1968) suggested dividing human hereditary diseases into five groups according the etiological role of inheritance and the environment.

1. Diseases expressed in patients with particular genotype independently from environmental conditions (chondrodystrophy, hemophilia, Huntington disease, xeroderma pigmentosum etc.).

2. Diseases expressed in patient with particular genotype, but in special environmental conditions (gout).

3. Diseases expressed in patient with different genotypes, but rate and severity depending on genotype and environment (essential hypertension, peptic ulcer).

4. Diseases expressed in patient with any genotype, but rate and severity depend on genotype (tuberculosis, caries).

5. Diseases completely dependant on environmental conditions.

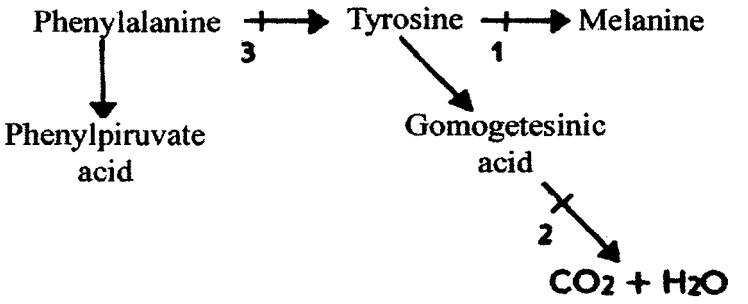
This classification is mostly theoretical, but it reflects common views that expression of many hereditary diseases depends on physiological organism states and relationships of organisms with environmental factors.

Levels of damage, of all hereditary diseases can be divided into three groups: diseases of metabolic exchange, chromosomal diseases, and cytoplasmic diseases.

11.2 The diseases of metabolic exchange.

Normally, genes control steps of different metabolic pathways. 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't work at all, the metabolic precursors of reaction controlled by the enzyme are accumulated in the tissue. These accumulated substances suppress activity of surrounded cells. This mechanism occurs in phenylketonuria, galactosemia, and alkaptonuria. On the other side, absence of the metabolite can cause a range of hereditary defects as hereditary cretinism, adrenohenital syndrome and so on. The pathology process also may occur on a level of renal tubules. The accumulated substance can be excreted improperly or not fully. According to imbalanced exchange it can be distinguished following types of metabolic exchange diseases.

Diseases of amino acid exchange. The most common example of this type is phenylalanine misbalance (pic 11.1).



Pic. 11.1. The scheme of human phenylalanine exchange:

1-3 – the points of metabolism blocking by mutations; 1 – albinism, 2 – alkaptonuria, 3 – phenylketonuria (by M.E. Lobanov, 1967).

Phenylketonuria - is an autosomal recessive disease. It is caused by deficiency of phenylalaninhydrxylase enzyme. This enzyme converts phenylalanine to tyrosine. When it is blocked, phenylalanine is converted to phenylpyruvate and excreted with the urine. The rate of this disease in Europe is 1:10000. The signs of disease are irritability, convulsions, mental retardation, microcephaly, loss of pigmentation of skin, hair, and the iris. If newborns suffering from this disease are feed 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 test is used. It gives green color to urine when it is positive. The express-tests are used to evaluate phenylketonuria right after 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. Thus, melanocytes loose their ability to produce melanin pigment. The signs of the disease are absence of melanin in skin, hair, and eyes. The eyes look of red color because of visible blood capillaries. The rate of this disease is about 1:20000.

Alkaptonuria - Is a recessive abnormality, having a rate of about 3-5:1000000. . 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 with added Milon's reactive (containing ions of Hg) which prove the presence of tyrosine in the urine.

Diseases of lipid exchange. This hereditary disease group includes familiar lipidoses characterized by 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 disease is bad transparency of plasma over erythrocyte in erythrocyte sedimentation reaction. The important addition 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 diet reduced in fat (fat consumption around 30-60g per day). The syndrome is caused by different mechanisms. Among them is suppressed chylomicron removal from 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 arthrosclerosis develop very

fast. The common sign is xantoms and xantelasms on the skin and tendons. It is an incomplete dominant disease with rate 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 was firstly described by E. Tay in 1881 and L. Sach in 1896. The second name of disease is Tay-Sach disease. Affected children appear normal at birth and do not usually develop the symptoms until about eight months, at which time signs of mental deterioration become evident. Within a year if birth affected children are blind; they rarely live past their fifth year. Among other signs are defects of parenchymal organs (liver, kidney), skin. Tay-Sach disease is rare in most human populations. However, Tay-Sach disease has a high incidence among Jews of Central and Eastern Europe. Many parents were relatives, which can prove theory about local reproduction of singular mutation. Individuals 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 result, the lysosomes fill with gangliosids, swell, and eventually burst, releasing oxidative enzymes that kill the brain cell. There is no known cure for this condition. The rate of disease is 1:300000 in usual 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 increased glucose blood level. The abnormal gene is wide spread (about 4-5% of homozygotes), but has a small penetrance (about 20%). 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 autoimmune destruction of Lanherhans insuli, which produce insulin. All cells of the body need insulin to get glucose from a blood. If there is no insulin, cells suffer from glucose deficiency, in spite of high level of glucose in blood. The one way to treat such diabetes is to eject insulin continuously throughout the life.

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

Diseases of steroids exchange. Main disease from this group is adrenohenital syndrome. Its rate is 1:5000 - 1:67000, whereas heterozygous rate is about 1:35 - 1:128. It is an autosomal recessive disease. It is expressed in a form of hermafroditism 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, we can find many androgenic 17-ketosteroids. 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 early puberty development and early bone growth zone closure. The late onset is connected rather with adrenal cancer than with adrenohenital 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 increased level of it in an organism. During gout, uric acid concentration reach 5-16 mg%. It is provided by enhanced uric acid synthesis and decreased removing through kidneys. The gene nonpenetration in women makes genetic analysis more complicate.

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

Hemophilia A - is a sex linked disease. Only men suffer from this disease. It is caused by defect of VIII coagulation factor (antihemophilic protein). 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 patient is 16-22 years. It is believed that there are 125000 patients suffering from hemophilia A in the world. In spite of each generation gene removing, the disease rate stays constant. The lost mutations are refilled by new ones. The origination of new mutations of hemophilia A occur with 1.3-4.2*10*-5 rate. 28% of hemophilia cases are sporadic caused by new originated mutations, whereas 72% of hemophilia cases are inherited from previous generation.

Hemophilia B - is sex linked disease too. Only men suffer from this disease. It is caused by defect of IX coagulation factor. Clinical signs 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's 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 WHO data, the birth rate of hemophilia A child is 1:10000, whereas the birth rate of hemophilia B child is in 10 times less. But patients with hemophilia A die more often in early postnatal period. That's why, hemophilia B occurs in population only in 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 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, it is revealed two different hemoglobins moving with different speed. One is normal hemoglobin A, and the second is the mutant.

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 very rare. But in homozygous individuals the hemoglobin S is abundant. Erythrocytes most of the time stay in a sickle shape and that why they are removed by spleen from 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 individual for T hemoglobin (dominant allele of talasemia) have no clinical signs as heterozygous individuals for hemoglobin S. But the homozygous state causes very severe erythroblastic anemia (Mediteranean 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 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) became very spread in populations, especially in some geographic zones. It was found that gene S is wide spread among native Africans and their descendents in America; gene C - among population of Guinea Gulf; gene E - among population of South-East Asia; gene D - in West India; gene T - among population of Italia, Greece, Bengali, South-East Asia and South China. The heterozygous individuals are more resistant to Plasmodium vivax invasion.

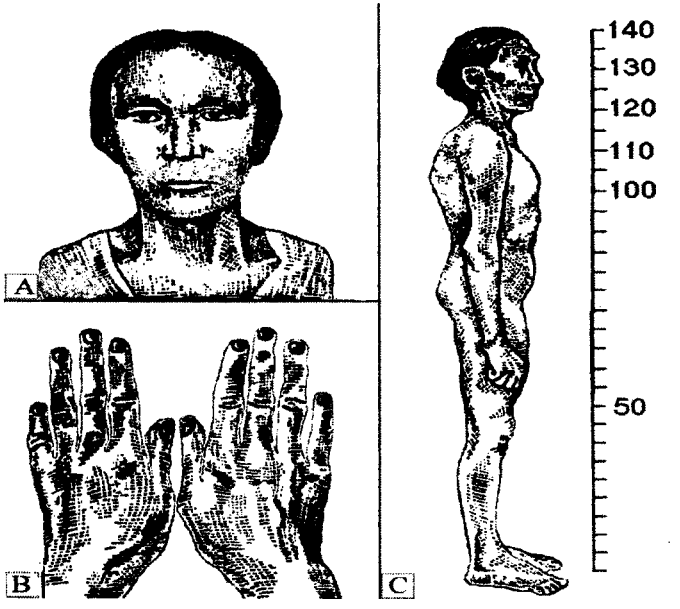
Diseases of ions exchange. There are hepatolenticular degeneration (Wilson disease) and hemochromotosis in this group.

Wilson disease is autosome recessive disease. During this disease, ions of cuprum infiltrate liver, brain, kidney, 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 kidney. Pathogenesis of disease is still not clear. Half of the patients were born in families of close relatives who were affected. Heterozygotes show decreased incorporation of Cu64 isotope to cerulloplasmine.

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

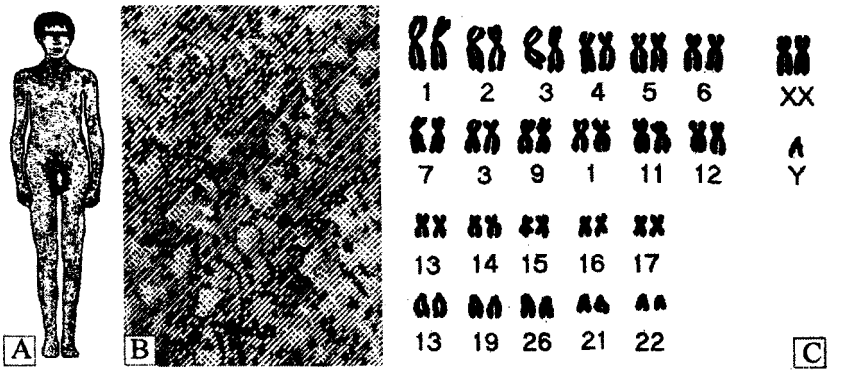
1.3 The human chromosome diseases.

Using of the cytogenetic method makes it possible to separate groups of diseases related with imbalance in 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



Pic. 11.2. The X-trysomy syndrome:

A – abnormalities in facial skeleton, B – shortness of second phalange of little finger, C – expressed kyphosis in thoracic part of spinal column (by E.F. Davidenkova, 1965).

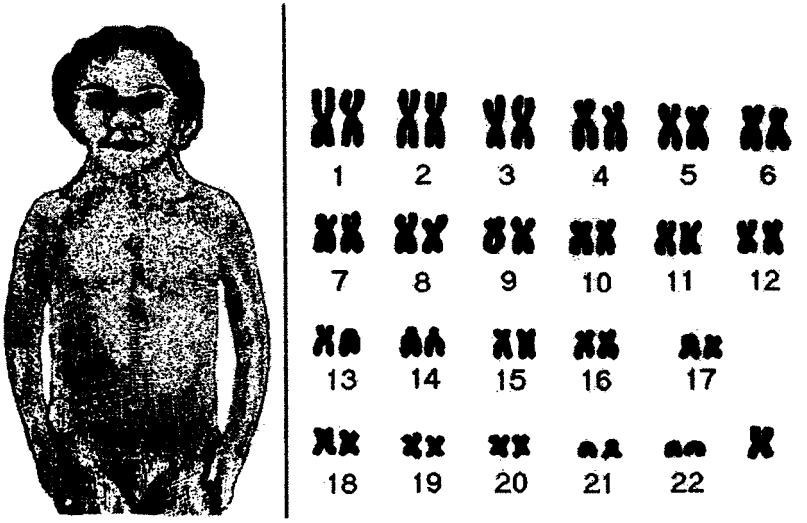


Pic. 11.3. The Kleinefelter's syndrome (A) with typical testis histology (B) and idiogramm (C)(by M.L.Barr,1948, E. Bergemann,1962).

related with chromosomes separation in meiosis. The deviance in sex chromosomes is not lethal, but they often lead to decreased fertility and some development abnormalities.

There are the following human sex chromosome diseases.

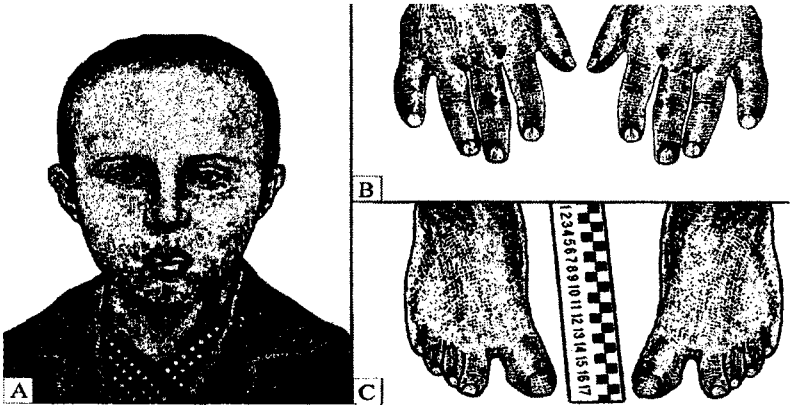
Additional Y-chromosome has less severe effects on phenotype. There is no special sign to distinguish person having additional Y-chromosome. It is known



Pic. 11.4. The Turner's syndrome:
The girl with syndrome and her chromosome set (by O.Lelong et al., 1963).

that part of them develop pattern of antisocial development. The most of men having additional Y-chromosome are fertile. It makes genetic analysis of them more complicated.

Additional X-chromosome in women. It gives a wide phenotypical polymorphism. It occurs with rate 1.4:1000 girls. Diagnostic feature is having two sex chromatin bodies in buccal epithelium cells. The most of individuals having genotype 47, XXX express normal physical and mental phenotype without any deviations in reproductive system. But some of them may have pathological changes in

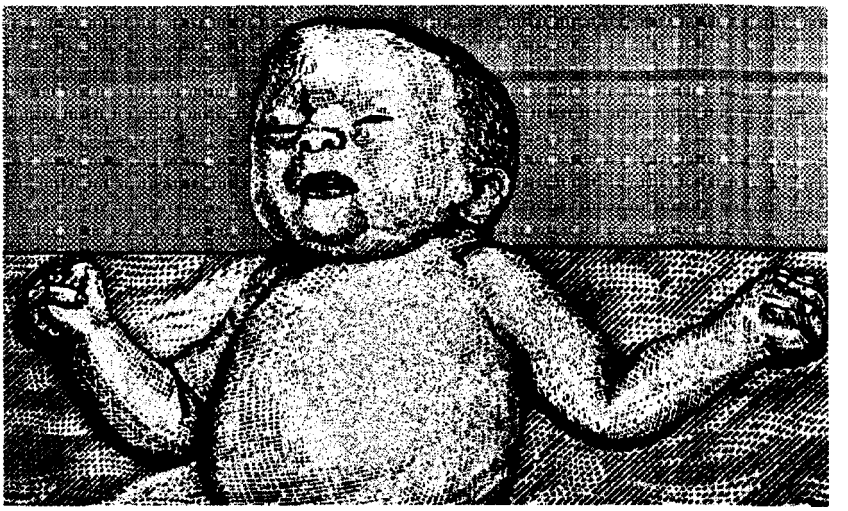


Pic. 11.5. The Down syndrome:

A – patient of 13 years old; B – small finger deviation; C – big gap between I and II finger of foot (by E.F. Davidenkova, 1965).

reproductive system such as secondary anemia, dismenorrhea, early climax. Intellectual development is normal or on a lowest limit of normal condition. It was founded that there is a higher rate of schizophrenia 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). It gives a wide phenotypical polymorphism. It occurs in about 1 out 500 male births. The typical feature is a having of sex chromatin in nucleus of buccal epithelial cells. It becomes evident in puberty. The clinical signs mainly concerns 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 is founded in perinatal kid's deaths 10 times more often than in survived children (pic 11.3).



Pic. 11.6. The child having three chromosomes from 16-18 group (by J. Edwards et al., 1960).

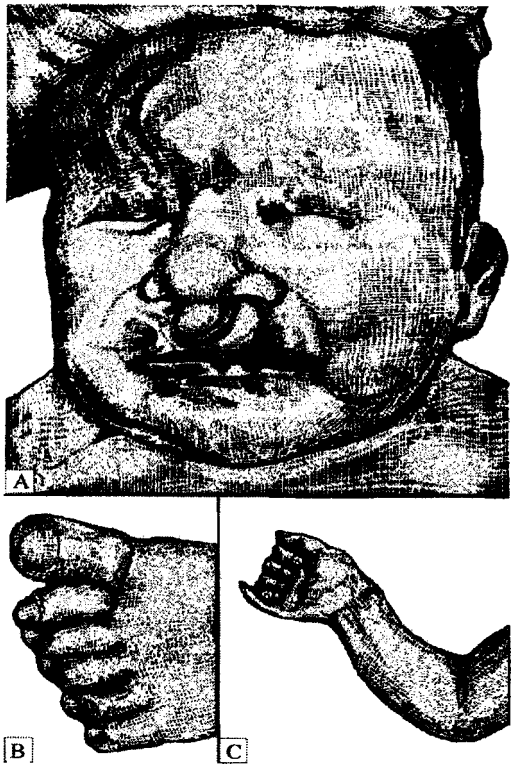
Absence of X-chromosome in women (Turner's syndrome). It occurs roughly once in every 5000 female births. Such individuals have no sex chromatin in nucleus of buccal epithelial cells. It results in a sterile female of short stature, a webbed neck, disk shaped thorax, and immature sex organs that do not undergo puberty changes. Sometimes they have defects of color perception. Such embryos are subjected to high prenatal mortality, that why their population rate is small (pic 11.4).

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

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

Among autosomal set changes there are following which are most common.

Trisomy 21 (Down syndrome). The individuals having the syndrome have decreased size of scalp, small in stature, poor muscle tone, big gap between I and II finger of foot, immatured sex organs, mental retardation (pic 11.5). The mental retardation pathogenesis of trisomy 21 includes central nervous system immaturation, in particular, the insufficient myelinization of nervous fibers. About half 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 then the age of mothers having normal children. The life span of such individuals is about 21-24 years.



Pic. 11.7. The child having three chromosomes from 13-15 group (by K. Pattaw et al., 1960).

Trisomy 18 (Edward's syndrome). It is third in rate after trisomy 21 and 13. Individuals have severe prenatal immaturation and numerous defects 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 (pic 10.6).

Trisomy 13 (Pattaw's syndrome). Its rate is 1:5000 - 1:7000. The trisomic 13 individuals die in early childhood. More than 90% die in first year of life. Individuals have defects of brain and scalp (pic 10.7). The second group of defects is defects in finger number - polydactilia, especially hexodactilia (having 6 fingers). 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 (by Lasuc G.I. 1979). Some embryos with trisomy 13 are subjected to high prenatal mortality, that why 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 "cat"s scream" syndrome. The child's scream songs like a cat's scream. Other symptoms are larynx immaturation, microcefalia, mental retardation, poor muscle tone, low ear's position, and underdeveloped sexual characteristics. Deletion of long or short arm of 18 chromosome leads to face defects, skeletal defects, internal defects, microcephalia, mental retardation and other abnormalities.

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

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

11.4 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 mother's 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 12. THE PRINCIPLES OF EMBRYONIC DEVELOPMENT.

12.1 The ontogenesis, its types and periods.

Individual development or ontogenesis - is a process of organism development from it's 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 got name 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. Sh.Bonne, L. Spallaciani, and others stayed with the preformism position. The controversial point of view was suggested by Aristotle. He believed that new embryos developed from homogenous, unstructuralizated matter. Later, such views got name epigenesis. With help of K.Wolf (1734-1794) the epigenesis concept won and facilitated embryology development.

K.Bar (1792-1876) 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 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 genotype. There are two types of ontogenesis: direct and indirect.

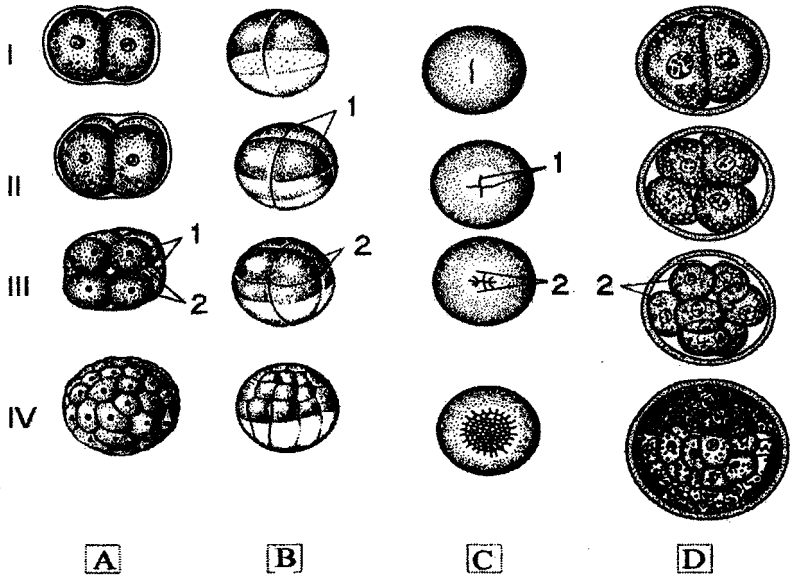
The indirect development. The species having such ontogenesis have several intermediate development stages before maturation. Species may have simple or complete metamorphosis. In simple metamorphosis, the wing, if present, develops externally during the juvenile stages; ordinary no resting stage exists before last molt. The juvenile stages are called nymphs and they are morphologically quite similar to (imago –I don't know this word). For complete metamorphosis, the wings develop internally during the juvenile stages and appear externally during only the resting stage the immediately precedes the final molt. The juvenile stages are called larva and pupa and they are morphologically different from imago.

The direct development. The species having such ontogenesis deliver a baby similar to adult organism. This ontogenesis occurs in species whose ova are rich in yolk (fish, birds, reptilians). The exception is the Mammalians. The have ova 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.

12.2 The characteristics of embryonic development.

The embryonic period starts from 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



Pic.12.1. The cleavage of chordates with different ovum type:
A – lancelet, B – frog, C – bird, D – mammalian; I – two blastomeres, II – four blastomeres, III – three blastomeres, IV – morula; 1 – cleavage grooves, 2 – blastomeres (by N.Yarygin, 1997 with changes).

called an embryo before formation of the main tissue stems, and is called a fetus after that.

Prozygote period – is the period that precedes zygote development. It was discussed in chapter 4.

Zygote period - it is monocellular stage of new organism development. It is formed as 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 synthesis starts on a matrix of mRNA made in oogenesis.

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 influences by presence of yolk. It can be holoblastic (symmetrical and asymmetrical) and meroblastic (discoidal and superficial) (pic 12.1).

The symmetrical holoblastic cleavage is in isolecital eggs (in aquatic vertebrates such as lancelets and agnaphants). The cleavage occurs throughout whole the egg. After fertilization, the zygote divides into two cells, which are called blazoners. Then, both cells divide 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 eggs of Amphibia. First two divisions are same as symmetrical division. The cleavage occurs throughout the whole egg too. But yolk-rich cells divide more slowly than those which are poor in yolk. It results in formation of two poles: apical (poor in yolk) and vegetative (rich in yolk). Blastomeres are different in size. Those, which are on apical pole, are smaller than those that are on vegetative pole.

Mammalians and human have little yolk in ovum. They have holoblastic asymmetrical cleavage. Each blastomere has it own rhythm of division. That's 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 shape of disc.

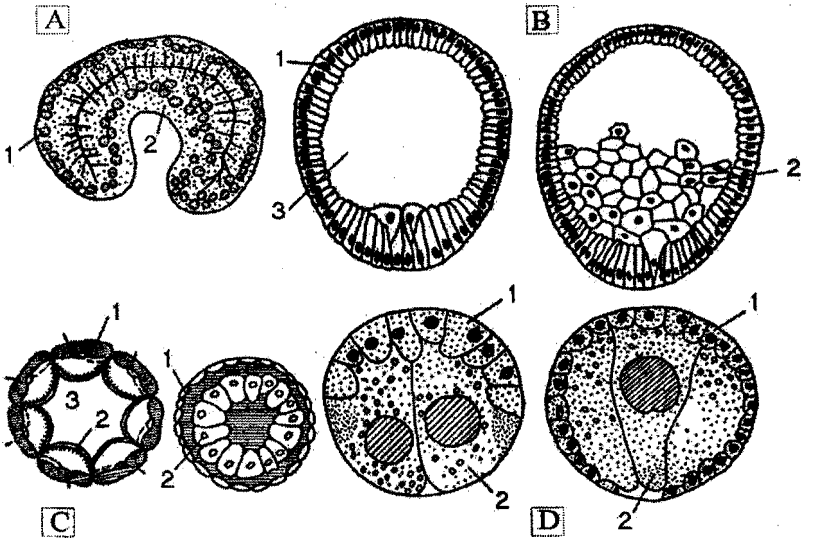
In discoidal meroblastic cleavage, cleavage occurs only in a tiny disc of polar cytoplasm, called blastodisc, which lie astride the large bulk of yolk material. It occurs in the polylecitinal eggs of some mollusks, reptiles, birds and some fish.

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

In spite of different patterns of cleavage in different organisms, all are terminated by the formation of a blastula. It is one of the signs showing similar origin of life and parallelism in evolutionary development of structures. At the end of the cleavage, blastomeres are separated by 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.

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.

Invagination occurs in animals having isolecital eggs. The vegetative pole



Pic. 12.2. The gastrula's types:

A – invagination gastrula, B – immigration gastrula, C – delamination gastrula, D – epibolia gastrula; 1 – ectoderm, 2 – entoderm, 3 – blastocoel (by B.N.Tokin,1966).

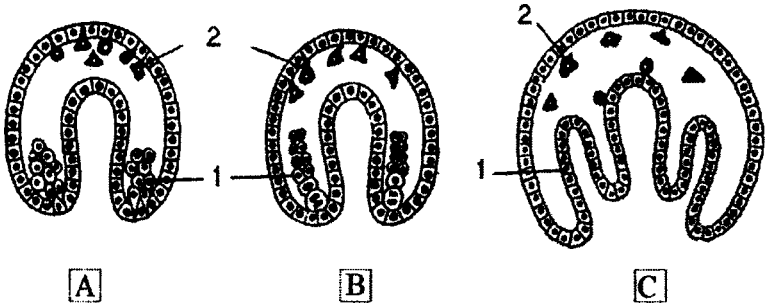
of blastula invaginates inside. Opposite poles almost touch each other. This decrease volume of blastocoel to minimum and it looks like narrow rime. It results in formation of two-layer embryo. The external layer is called primary ectoderm; the internal layer is called primary entoderm. The invagination form primary intestine (archenteron) or gastrocoel. The opening on one end called blastopore.

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

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 these layers upon being formed surround the gastrocoel.

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

Delamination occurs in Cnidarians. It is gastrulation by splitting. During



Pic. 12.3. The ways of mesoderm formation:

A – by cell migration from blastopore lips, B – by cell migration from two teloblasts; C – by mesodermal engulfs invagination; 1 – bud of mesoblast, 2 – mesenhyme bud (by V.Shimkevich,1925).

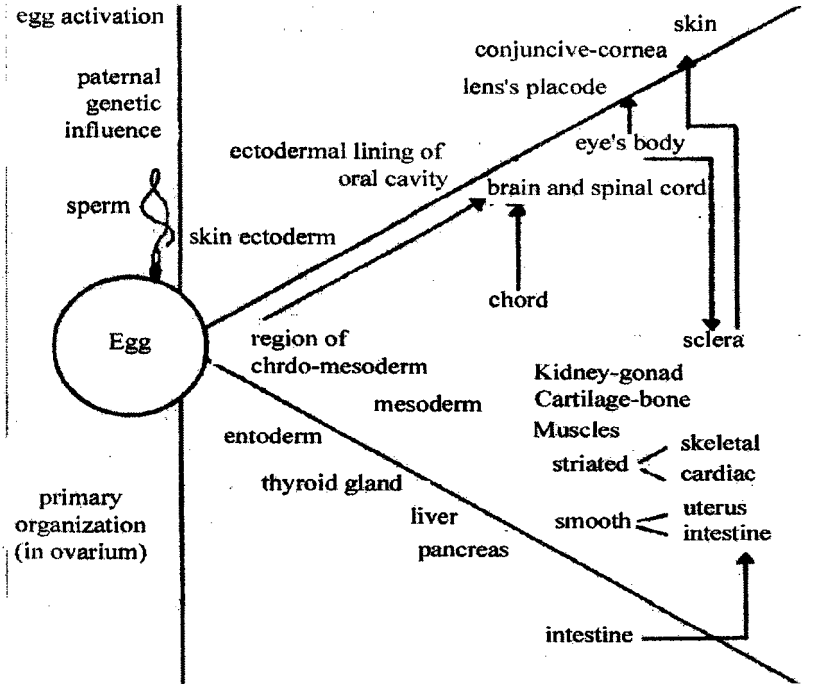
delaminations cells of blastoderm is divided parallel to blastoderm surface. Thus, inner layer underlying ectoderm is made. It was also described by I.I.Mechnicov.

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

All more complicated animals also develop a third layer called the mesoderm. It is situated between the previous two. 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 (from Greek "thelos" - end) and second is enterocoelic (fro Greek "enteros" - internal, "koiloma" - coel). The first is typical to Protostomia, whereas 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 secondary coel.

The enterocoelic way. It happens when groups of cells in the form of paired vesicles start to be separated from the primary intestine or primary coel. The coel of these vesicles become secondary coelom, which can be segmented. The coelomic vesicles are formed symmetrically from both sides of intestine. The wall of sack looking toward intestine called splanchnopleure, whereas a second one looking toward ectoderm called somatopleure. Thus, the cavities, having very important morphological and functional value, are formed. During 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 cardiovascular system. Gastrocoel becomes a coel of small in-

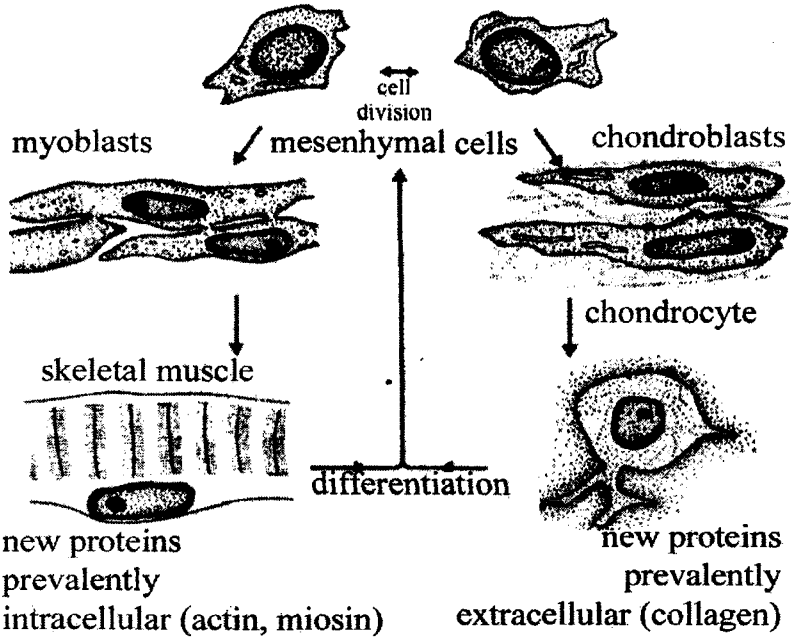


Pic. 12.4. The scheme of vertebrates' cells differentiation (by B.H.Willier, 1980).

testine. In enterocoelic way, the gastrocoel also gives coelom.

The organs and system formation is a 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 layer generate formation of all organs of developing embryo (pic 12.4).Ectoderm give 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 (pic 12.5).

The beginning of organogenesis is called neurulation. Neurulation is the formation of the nervous tube. At the same time secondary intestine and chord are formed. On either side of the developing chord, segmented blocks of tissue form. First, spinal ectoderm induced by chord becomes nervous plate. Then, a layer of



Pic. 12.5. The differentiation of unspecialized mesodermal cells to cells of two types – muscle cells and cartilage cells (by C.H.Waddington,1966).

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 embryo's back. The canal inside the tube called neurocoel (pic 12.8).

Mesoderm separates to dorsal and ventral regions. Dorsal regions are segmented and presented by somites. Ventral part is called side lamina and it connects with somites with help of intermediate mesoderm.

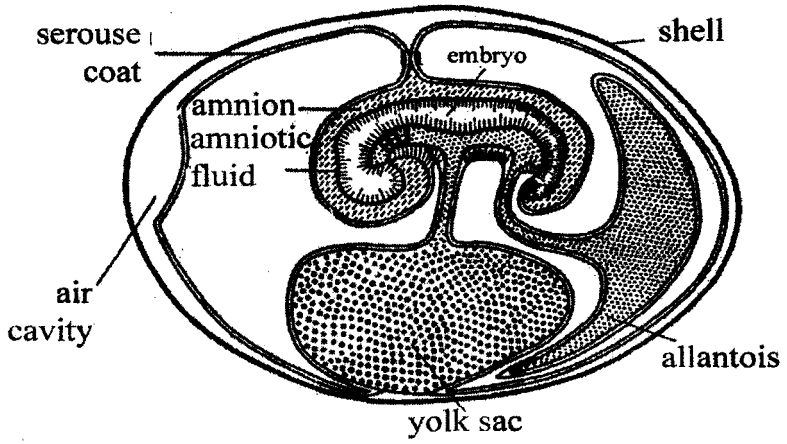
The ventromedial part of somites called sclerotome on being induced by neural tube and chord give rise to vertebrae, bones and cartilages. The intermediate part of somites called myotome give rise to all skeletal muscles. The external dorsolateral pert of somites called dermatome give rise to skin derma. Intermediate mesoderm called nephrotome gives rise to excretory organs and to sexual glands. The primary sex cells separate from other embryonic cells in early 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.

12.3 The provisional organs and their role in mother-fetus relationships.

Some provisional organs are made from embryo material. Most primitive is the *yolk sack*. It first appears in fish embryos. It has endodermal origin. It is membrane with many vessels, which surrounds yolk storage. It serves for transmitting nutrition from yolk to embryo. It is of great importance for reptilians, and birds, because their eggs contain much yolk. The mammalian embryo also forms yolk sack, but it not so important. In reptilian, bird, and mammalian embryos, new three provisional organs for defense and embryo nutrition were made. They are amnion, chorion, and allantois (pic 12.6).

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

Chorion develops from the external layer of the primary body fold. In reptilian and bird eggs the chorion touches the egg's shell, whereas in mammalian embryo it touches uterine mucosa. It forms external villi, incorporated into uterus wall. These villi together 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 embryo to provide sufficient supply for it.



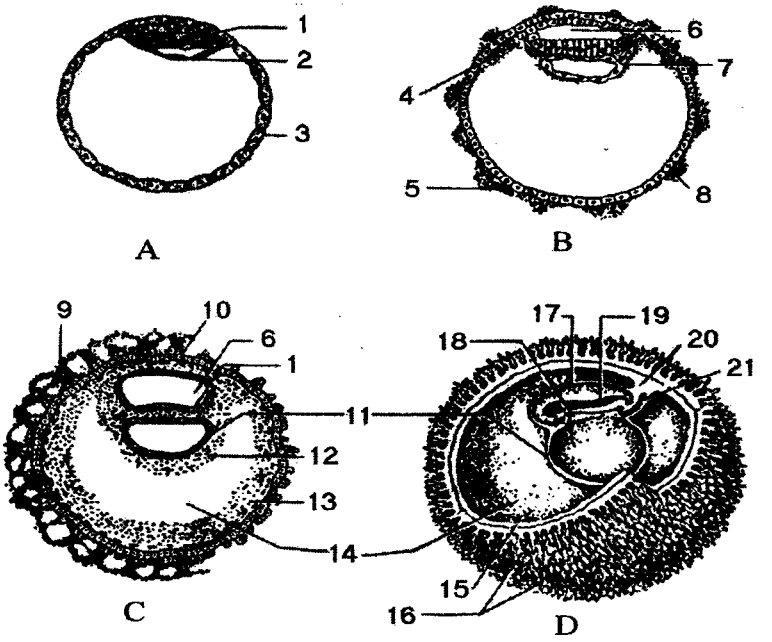
Pic. 12.6. The provisional organs of amniotes on example of bird's embryo (by V.Shimkevich,1922).

Allantois (from Greek "allantoides" - sausage shaped) 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. Embryos can take oxygen through this membrane and give off carbon dioxide and metabolic waste products.

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

12.4 The course of human development.

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

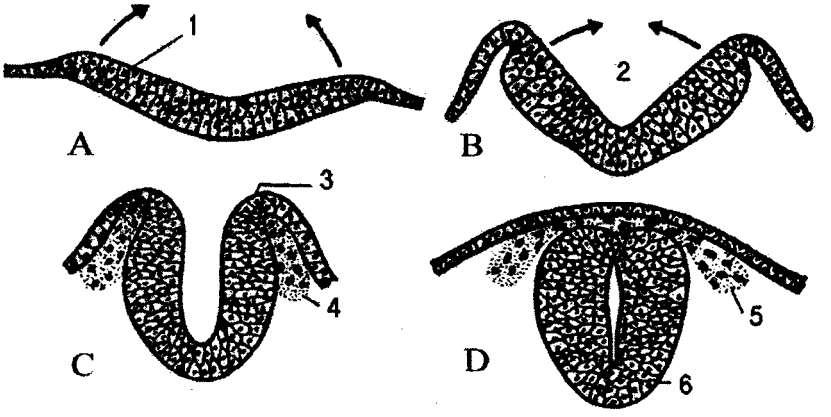


Pic. 12.7. The human embryo's structure from 10th to 20th days of development (A-D):

1 – ectoderm, 2 – entoderm, 3 – trophoblast ectoderm, 4 – mesoderm, 5 – cellular trophoblast, 6 – amniotic cavity, 7 – yolk sac, 8 – syncitium, 9 – syncitial trophoblast, 10 – cytotrophoblast, 11 – yolk sac entoderm, 12 – visceral mesoderm, 13 – somatic mesoderm, 14 – non-embryonic coel, 15 – chorion mesoderm, 16 – chorion vilia, 17 – amnion ectoderm, 18 – anterior gut, 19 – embryo disk, 20 – fetus leg, 21 – allantois (by K. Villy, V. Detier, 1974).

The human cleavage has it own properties. The first division is asymmetrical. Each blastomere has it own rhythm of division. That's why, the stages of 2, 3,5,7,9 blastomeres can be observed. On the 3rd day, the group of blastomeres, called morula, is formed. On the 4th day, blastomeres start to produce fluid in side to 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. Embryoblast situated near only one pole of the morula. Further, throphoblast gives rise to chorion, whereas embryoblast gives rise to embryo (pic 12.7)

Then, 3 to 6 day later, the embryo reaches the uterus, attaches to the uttering lining, or endometrium, and penetrates into the tissue of the lining. Cells of throphobalst reproduce very actively and produce enzymes dissolving uterus lining. The trophoblast is divided into two layers: internal (cytotrophoblast) and (internal external?) (syncitiotrophoblast). At the same time the embryoblast rapidly grows. In the embryoblast gastrulation occurs. Primary entoderm forms yolk sack on the 9th day of development. Primary ectoderm preserves to form secondaty endoderm, ectoderm and mesoderm. Formation of secondary ectoderm, entoderm and mesoderm occurs on 15th day of development in second phase of gastrulation. The second phase of gastrulation begins at 14 - 15 day of development. It is performed by cell migration and partial invagination. The cells of primary ectoderm reproduce itself very intensive. 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 primary strip. Then these cells migrate in between two layers and form a third layer

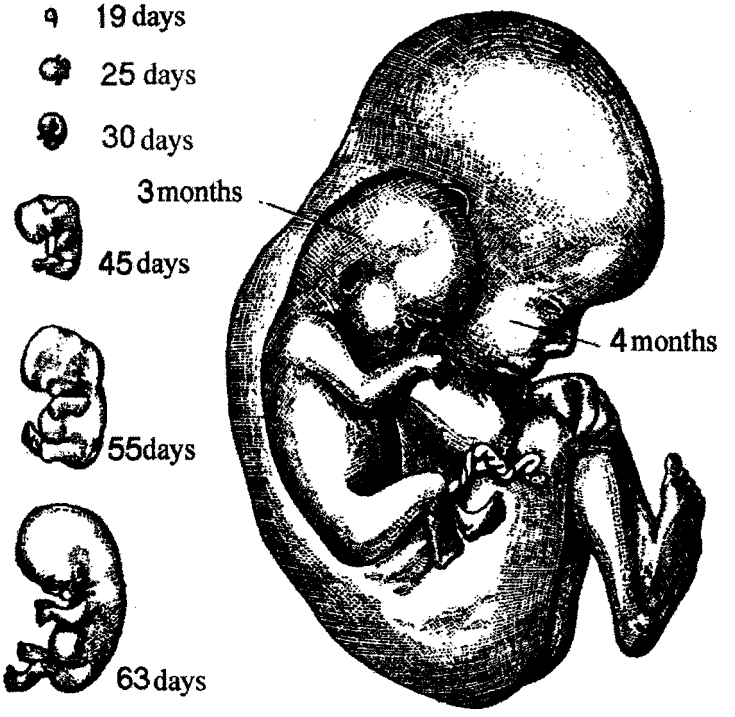


Pic. 12.8. The nervous tube formation in human embryo on following stages (A-D):
1 – nervous plate, 2 – neural groove, 3 – neural fold, 4 – neural crest, 5 – nervous ganglion bud, 6 – nervous tube (by K.Villy, V. Detier,1974).

- mesoderm. Part of the primary strip material migrate to the endoderm layer and slide the cells of primary endoderm to a side position. There, primary endoderm cell take part in the 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 above chord, the nervous plate is formed. Then, a layer of ectodermal cells situated 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 chord. From both sides of chord, the somites are created (Pic 12.8).

In the fourth week organogenesis occurs. The eyes form. The tubular heart develops its four chambers and begins to pulsate. The arms and legs buds have begun to form. Embryo is about 7.5 mm of length. The main visceral arches form. In 6th week of development, embryo has 12 mm of length. Five brain subdivi-



Pic. 12.9. The human embryo and fetus on different stages of development (by K. Villy, V. Detier, 1974)

sions becomes clearly visible. Thymus and parathyroid gland form. 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 provisional organs development also has specific features of a human. The beginning of amnion and chorion development occurs on 7-8 day.

The chorion forms from trophoblast. The syncitiotrophoblast touching uterus lining dissolve it. At the end of the 2nd week, the primary villi of chorion form 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 form inside of secondary villi which becoming tertiary villi. When tertiary villi have been formed, the region of chorion and uterus contact is called the placenta.

The amnion forms from primary ectoderm. For a while, the amniotic cavity is surrounded by 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 forms from primary entoderm. Then, the primary yolk sack falls down and is replaced by secondary yolk sack on the 13th day.

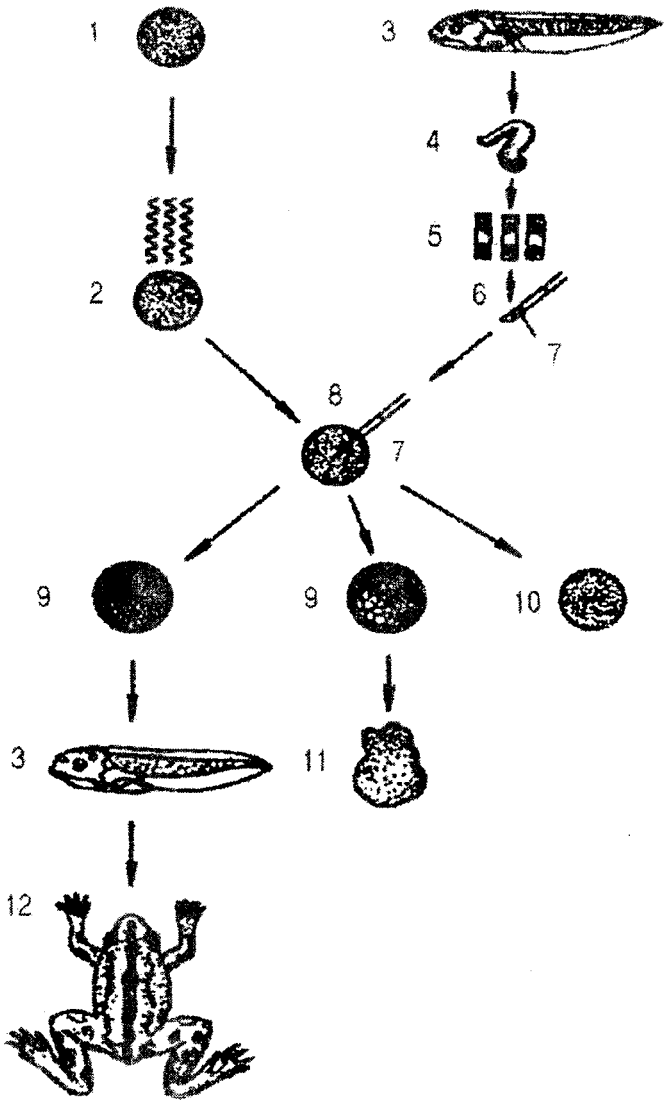
Allantois forms as pocket of intestine. The allantois mesoderm fuses with chorion mesoderm, bringing blood vessels in it.

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

12.5 The gene controling 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 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. In the first stage, the genes regulating ontogenes process aquired information for activation or repression from external factors, surrounding cells, hormones and etc. In the second stage, the information is taken from genes in the processes of transcription and translation. It results in synthesis



Pic. 12.10. The frog development from ovum with nucleus replaced by tadpole's intestine nucleus:

1 – non-fertilized egg, 2 – UV radiation, 3 – tadpole, 4 – tadpole's intestine, 5 – intestine cells, 6 – micropipette, 7 – donor-nucleus; 8 – recipient nucleus; 9 – blastula, 10 – division failure, 11 – abnormal embryo, 12 – mature frog (by D. Gerdon,1966).

of different polypeptids. They may be proteins regulating extracellular metabolic processes, reproduction rate, cell migration, gene activity and so on. On 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 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's and father's genomes are completely repressed in this stage.

In amphibians, if two first blastomeres have been separated, they can develop two new organisms. That means that they are of the same value or totipotent (omniopotent). In tritone, the totipotentness of cells are preserved to the 16 blastomers stage, in 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 the formation of the different structures of the human body from almost homogenous mass. But in spite of differentiation, cells keep all hereditary information, which is proved in J. Gerdon experiments in 1964-1966 (pic 12.10). The scientist has taken nucleuses from skin cells and intestine cells and put them into frog ova, without nucleuses. Many of them develop to new frogs. The same method was used to select Dolli sheep in England. If the same methods will be used in 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 embryo consist of 1000 blastomeres; tRNA synthesis starts in the end of blastula stage; rRNA starts only in gastrula .

In mouse embyogenesis, the synthesis of mRNA, tRNA, rRNA starts earlier, on a stage of 2-4 blastomeres. However, it also follows a plan determined by information aquired from mother 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 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 doesn't exceed 10-20%, but it consists of different genes. All structural genes of eukaryotes can be divided into three groups:

1. Genes are actively working in all organism cells. Its genes are coding enzymes of metabolic exchange, common macromolecules.
2. Genes are actively working only in tissues of one type. For example; genes are coding myosin in muscular tissues, and collagen in connective tissues.

3. Genes which are needed to perform special function in specialized cell, like hemoglobin synthesis in erythroblasts, hormone synthesis in endocrine cells, digestive enzymes synthesis in alimentary canal, and so on. So, 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.

12.6 The embryonic induction.

In animals, the stem cell populations separate from each other and then they give rise to different tissues and organs. This is a time of embryonic induction setting. Embryonic induction means that one tissue or group of cells can have influence on development of another. Such phenomenon was discovered by G. Speerman and G. Mangold in 1924. The first inductor is cells of dorsal part of blastopore that induce differentiation of ectoderm cells and nervous tube, which in turn induce chord formation on dorsal part of endoderm. The chord induces formation of alimentary canal from 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 switching on and off specific genes blocks in surrounding cells.

12.7 The critical periods in embryogenesis.

Study of animal development resulted in discovery of so called "critical periods of embryogenesis". The term is used to point to the period when the embryo is very sensitive to various harmful influences, which can result in developmental defects. An organism's sensitivity varies in different embryogenesis stages. In some periods, the embryo is more sensitive to chemicals; in others, embryo is more sensitive to temperature changes. Critical periods are characterized by increased metabolism and respiration, and decreased 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. Implantation is the first critical period in Mammalians. It is characterized by new nutritive and gases exchange conditions, which require new adjustments. The next critical period is placentation.

In human development, the following critical periods were founded 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 pregnant woman.

12.8 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 in general result of genetic information realization, in particular environmental conditions. The mammalian embryo development 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 pregnant woman can cause severe developmental defects in embryo. If one endocrine gland worked inappropriate in mother, the same gland function may fail in the embryo. The excess of some hormones can cause defects in development. For example, when hydrocortisol is injected into pregnant rats on 12 day of pregnancy, all newborn have a defect of facial structure, but all other organs develop successfully. That shows that hormone action is selective. Also during the first and second month of pregnancy, a mother contracting rubella (German measles) can upset organogenesis in the developing embryo. Most spontaneous abortions occur in this time.

The physiological state of the mother's organism has direct influence on offspring health. It is needed to point out to doctors of gynecological ambulance.

Today, modern man undergos influence from various chemical, physical, biological and psycological factors. Such influences on pregnant mother 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, protoza (toxoplasma), and viruses (German measles). Some drugs have teratogenic effect too. In 1960s, for example, many pregnant women took the tranquilizer tialidomide to minimize discomfort associated with early pregnancy. Unfortunately, this drug had not been adequately tested. It interferes with fetus limb bud development, and its widespread use resulted in many deformed babies. There are some more drugs having similar effect on embryogenesis. The X-rays and other ionizing radiation have strong teratogenic effect on embryo development. Doctors have to keep it in mind while prescribing different diagnostic procedures, drugs and physiotherapy, especially in early stages of pregnancy.

12.9 The correlations in ontogenesis. The ontogenesis as a holistic process.

Organisms develop as whole system together with environmental conditions.

There are a range of factors determening organism development.

Genetic factors provide determination of development. That's why chicken zygote develops to mature chicken, and human zygote develops to mature chicken, in spite of environmental factors. The ooplasm segeregation leads to the formation of different cell types in an embryo. Then, the embryonic induction starts. The different cell populations 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 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. I.I.Shmalgausen (1884-1963) distinguished three correlation types - genomic, morphogenetic, and functional.

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

The 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 and so on). Also we may say that same processes occur during embryonic formation of various organs from same buds. For example, in mammalians from gills arches the jaws, larynx cartilages, processes styloideus and auricular bones are formed.

The functional correlations - are correlations between organ's parts which is functionally dependent. For example, correlations 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 gonad development.

For different organs, there are different correlation types. New correlations appear during ontogenesis. That leads to new differentiations. In other word we can conclude that new correlation appear as result of interactions of differentiated parts. And these interactions lead to next level of differentiation. So, organism's parts develop all together.

CHAPTER 13. POSTNATAL ONTOGENESIS. AGING AND DEATH OF ORGANISM.

13.1 The postnatal ontogenesis, its periods.

The postnatal ontogenesis is a period between organism's birth and death. It has three periods: prereproductive, reproductive and postreproductive.

The prereproductive period is also called growth period. During this period, the organogenesis and intensive growth take place. In the beginning of this period, the organs have been sufficiently differentiated to allow organism surviving outside of mother's organism. The alimentary canal, respiratory pathways and sense organs start to perform their function right after the birth. Whereas nervous system, circulatory and excretory systems have already started to work in fetus. The individual and species traits are completely formed during prereproductive period. Human prereproductive period is also called juvenile period (from Latin «juvenilis» - young). According to the ontogenesis type, this period occurs differently.

In direct organogenesis, newborns differ from adults only by sizes, proportions and organs differentiation level. The same is in a human. A newborn has skeleton, muscles, central nervous system and internal organs, which need to be developed.

In indirect organogenesis, larvae are subject to metamorphosis. The metamorphosis occurs in cnidarians, annelids, mollusks, arthropods and amphibians.

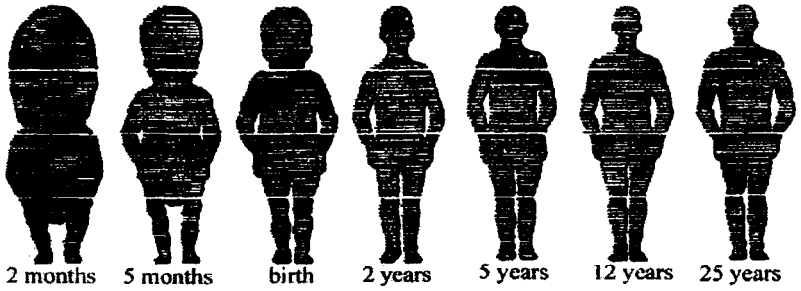
The reproductive system is differentiated as last one. When it has been differentiated, the reproductive period starts. During this period organism can reproduce itself. It lasts for several days in some species (silkworm), or for many years in others (mammalians).

The next period is postreproductive period or period of aging. Aging is terminal period of ontogenesis.

13.2 The organism's growth.

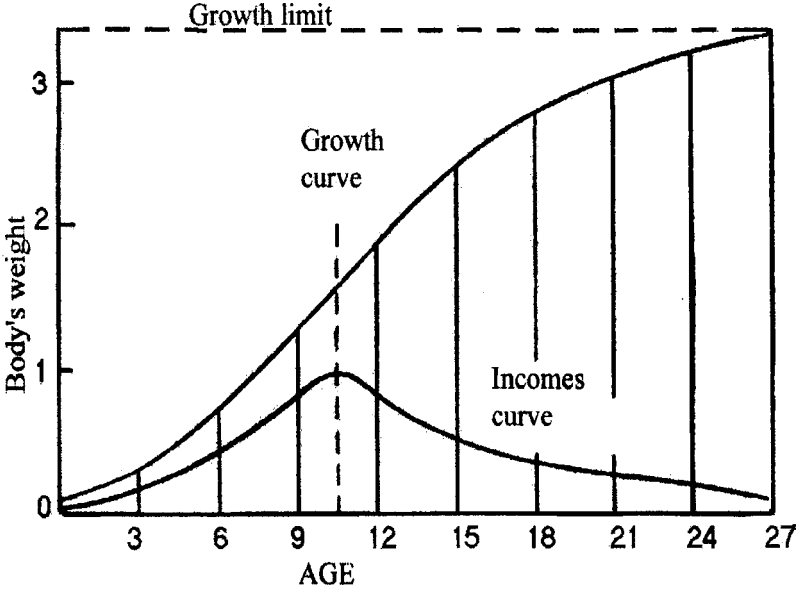
Every living creature has growth during development. The growth - is increasing of linear body sizes, which characterizing by increasing of cell number and cell sizes. Body's weight increase until the assimilation rate is over the dissimilation rate. According their growth pattern, all animals can be divided into two groups: with determined growth and undetermined growth. The birds, insects and mammalians refer to first group, whereas mollusks, fishes, amphibians and reptilians refer to second group.

The growth is increasing of length and weight. The most intensive growth of human occurs on first year of life, when body's length elongates on 23-25 cm. On



Pic 13.1 The changes in body's shape and body's proportions in ontogenesis (by H.B.Glass,1943).

second year, the growth rate decreases, but it is still high. A baby gives 10-11 cm in tall. On third year, a baby gives 8 cm in tall. From 4 to 7 years, a baby becomes taller on 5-7 cm annually. From 11-12 years in girls and from 13-14 years in boys to 16-17 years, there is last surge of growth. They grow on 7-8 cm annually. The same pattern is for body's weight increasing (pic 13.1).



Pic. 13.2. The scheme of growth and growth incomes of an organism (by P.B. Gofman-Kadoshnikov, 1966).

The growth curve for most of animals has S shape (pic 13.2). It has two arms corresponding growth phases. The first (left) arm gently slops in beginning and than rapidly rises up. This is the phase of increasing incomes. The second (right) arm has controversial pattern. It is the phase of decreasing incomes. To explain this, Ch. Maynot and I.I.Shmalgausen suggested hypothesis of growth and differentiation dependence. The embryonic and low differentiated tissues grow faster than high differentiated tissues. During aging, the number of low differentiated tissues significantly decreases. This leads to growth rate falling. It is emphased by mathematic formula.

Cv*t=const

Where Cv is growth rate intensively and t is age. The product of Cv to t is constant value.

13.3 The influence of external and internal factors on organism's growth.

There are many external and internal factors, which act on animal and human growth. To have normal development, organism should have adequate food and vitamin supply. The food has to contain necessary amount of proteins, carbohydrates, fats and minerals. Light is also very important factor in development because it provides conversion of vitamin D to active form. Vitamins are also external factors. They can be divided into two groups: watersoluble (vitamins C, P, PP, B group) and lipidsoluble (A, D, E, and K). Vitamin A is a part of rodopsin – pigment of vision. It also participates in skin epithelium development and organism growth regulation. Vitamin D regulates calcium and phosphate exchange. Vitamin K participates in blood clotting, whereas vitamin E accelerates gametogenesis. Vitamin C and vitamin P make blood vessel wall more resistant. Vitamins B1 and B6 accelerate processes in nervous system. Vitamins B2 and PP provide normal development of mucous, skin and eye conjunctive. Vitamin B12 plays important role in hemopoiesis.

From endogenic factors, hormones are most important.

The pituitary is a central endocrine gland. Its hormones regulate work of peripheral endocrine glands (thyroid, adrenal, testis and ovarium). There are three lobes in pituitary: anterior, posterior and intermediate. They produce trope hormones (from Greek "tropos" – more expressive) and usual hormones as well. The trope hormones regulate functioning of other glands; among them are thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone and luteinizing hormone. It also produces somatotropin (growth hormone), which enhance protein synthesis providing cell growth. If child has inherited pattern of low somatotropin production, he is pituitary dwarf. If child has inherited pattern of high somatotropin production, he will have gigantism.

That means he will be extremely tall. If such pattern has been changed in adult, he will have acromegaly. It is enlargement of terminals of the body, such as limbs, nose and so on. The intermediate lobe produces melanotropin, which regulate melanin production in skin. The posterior pituitary produce (or actually store and release) vasopressin (also called antidiuretic hormone, ADH), which regulate diuresis and blood pressure, and oxytocin, stimulating contraction of uterus and ejection of milk.

Thyroid hormones (thyroxin and threiodthyronin) accelerate oxidative processes occurring in mitochondria. Without adequate thyroxin, growth is retarded. Children with underactive thyroid glands are not able to carry out the carbohydrate breakdown and protein synthesis at normal rates, a condition called cretinism, which results in stunted growth. Mental retardation is also seen because thyroxin is needed for normal development of CNS. Adults with too little of this hormone also have showed metabolism, affecting their mental performance. Hyperfunction of thyroid in adults results in thyriotoxicosis. It is characterized by increased metabolism, labile emotional status, accelerated pulse and other signs.

The parathyroid glands produce parathyroid hormone. It regulates calcium and phosphate exchange. The parathyroid hormone excess results in bone destruction and frequent spontaneous fractures. The deficiency in parathyroid hormone leads to low calcium blood level, titanic muscle contractions and retardation of teeth development.

The adrenal cortex produces aldosterone, cortisol and other glucocorticosteroids, regulating mineral, carbohydrate and fat exchange, blood pressure. The adrenal medulla produces adrenaline and noradrenalin, which regulate vessel tonus.

Islets of Langerhans of pancreas produce insulin and glucagone regulating carbohydrate exchange.

The Leidig cells of testis produce testosterone, which control spermatogenesis regulation and formation of secondary sexual signs. The teca-cells of ovarium produce estrogen and progesterone. They regulate ovulation, oogenesis, pregnancy and secondary sexual signs formation.

There are many factors having harmful effects on human organism. The most spread is alcohol and drug consumption. Alcohol very easy penetrates placenta barrier and comes to fetus circulation. The alcohol concentration in fetus blood can reach 70-80% of mother concentration. In some cases it results in spontaneous aborts or in child death right after birth. If child survive, he can have alcoholic fetus syndrome. The light form of this syndrome is characterized by mental and physical retardation, microcephalia and so on. The middle and severe form of this syndrome is also associated with development defects and different psychiatric pathology. Alcohol leads to preliminary aging and death.

The drugs consumption leads to preliminary aging and death too. It is very

dangerous when drugs are taken during the puberty, when all reproductive functions set. Human can became drug addicted even after one or two drug injections. The treatment of such people is very complicate task.

13.4 The acceleration.

In the last 100-150 years the acceleration of child growth and development occurs. It starts even in embryonic development. In postnatal period, the growth stops in 16-17 years old girls and in 18-19 years old boys. The adults of next generation are taller than adults of previous generation are. It is because of growth acceleration in puberty. There are many theories explaining acceleration: Earth magnetic field changing, heterosis or human migration theory, urbanization, feeding improvement and so on. Probably, acceleration is result of many factors. In accelerated boys, the rate of chest volume increasing overlap the rate of body's growth. The heart, muscles, some other tissues and organs grow slowly than others. Such temporal disharmony is typical for puberty. However, in accelerated organism, it has more severe expression. The doctors, teachers and coaches have to have it in mind. So, pregnant women 16-18 years old have more complicated labors. We face consequences of acceleration in our life. We need to think about it while buildings, furniture and computer designing.

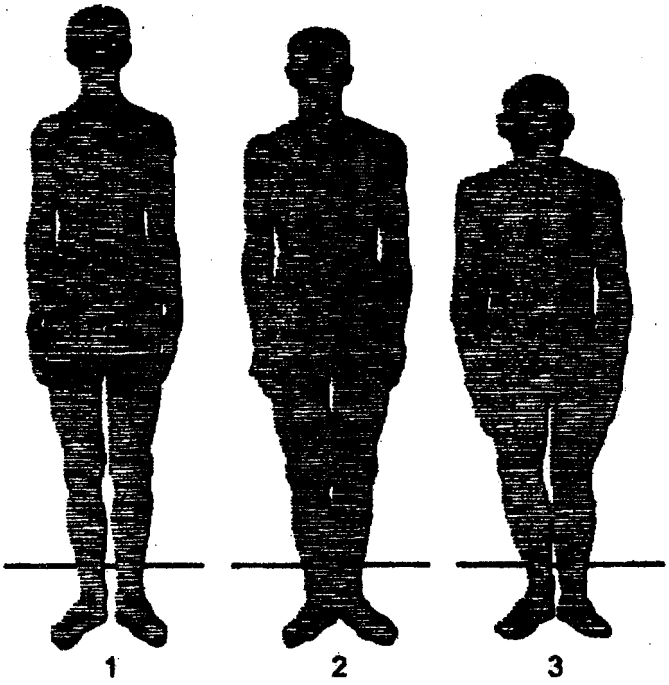
The problem of acceleration can be solved with help of specialists in different fields of knowledge, by analyzing many factors.

13.5 The human constitution.

The human constitution can be summarized in following. It is a sum of morphological, functional and behavior signs have been formed as result of genotype realization in particular environment.

To evaluate human constitution it was suggested many classifications. In 30's years of XX century, the German psychiatrist E. Cretchmer suggested three morphological types: leptosomic, picnic and athletic. The leptosomic type has following features: all body's diameters and perimeters are less than average, narrow shoulders, thin arms, and long chest. The picnic type has big internal cavities, big head, body's diameters and perimeters are more than average. The picnic has short, strong stature, short, massive neck, relatively short limbs. This type is formed after 30 years of age. The athletic type has massive skeleton, good muscle development, wide shoulders, and narrow pelvis, big foots and hands. E. Cretchmer showed correlation between patient constitution and emotional status.

M.V.Chernoruckiy in 1927 suggested astenic, normostenic and hyperstenic types in classification. Astenics have low diaphragm position, drop-shaped heart, long lungs, and arterial pressure with tendency to decreasing, increased metabo-



Pic.13.3. the types of human constitution:
1 – astenic, 2 – normostenic, 3 – hyperstenic (by M.V.Chernoruckiy, 1927)

lism. Hyperstenics have high diaphragm position, high volume stomach, long intestine, relatively big heart and arterial pressure with tendency to increasing. They also have tendency to obesity. Normostenic is moderate type with good proportions (pic 13.3).

W.Sheldon (1940) suggested classifying human constitution accordinary three embryonic layers. There are three types in his classification: ectomorphic, mesomorphic and endomorphic. Also he suggested the evaluation scale for each element of constitution type. The degree 1 corresponds to lowest expression of sign, whereas degree 7 corresponds to maximal expression. The extreme ectomorphic type (1-1-7) coincides with astenic type description. The extreme mesomorphe type (1-7-1) coincides with athletic type description. The extreme endomorphic type (7-1-1) coincides with hyperstenic description.

W.Sheldon pushed forward the idea, which was suggested by E. Cretchmer, about the connections between human constitution and type of character. The ectomorphic component of character has such features as restraint, reticence and resistance to alcohol action. The mesomorphs are confident in stature, extraverts.

Alcohol may cause their aggressive behavior. The endomorphs are relaxed in stature, emotionally expressive; they tend to share their problems and so on. All that schemes also contain additional features (variants in head, neck, limbs constitution and so on).

From early beginning, the concept about human constitution included a part about different liability to diseases among people of different types. Many investigators stated that schizophrenia was observed with higher rate in individuals of ectomorphic type, whereas maniac-depressive psychosis was observed with higher rate in individuals of endomorphic and mesmorphic types.

It was pointed that leptosomic individuals suffer from tuberculosis more frequent than others. They also have higher rate of neurosis, arterial hypotension, gastritis, peptic ulcers.

Mesomorphs usually have diseases of cardiovascular system. They have excessive weight relatively to their height, so that can have some influence on atherosclerosis development. Their children can have same problems with cardiovascular system.

Endomorphs have higher rate of some endocrine diseases, diseases of metabolic exchange, arterial hypertension and atherosclerosis.

At the same time, pointed above correlations are not obvious. They do not occur in every person. However, there is no doubt that modern man health is significantly conditioned by social environment.

13.6 The organism aging. The role of biological and social factors in aging.

The gerontology is a science that study principles of aging. But even if you are not specialist gerontologists, you can approximately evaluate age of a man by his appearance. Deep wrinkles, flabby skin, grey hair are common signs of elder. But statistically, the deviance in such parameters as arterial pressure, heart beating rate, electrocardiography, electroencephalography, glucose blood level and others is minimal. So, we face paradoxes, which was pointed by Democritus (about 470-460 B.D.). He wrote, "Aging is failure of whole body, whereas all its parts preserve safe". It has deep biological science. There are many adaptation mechanisms, which are involved during aging to keep main body's parameters constant. They fight against extinction of metabolism and rapid failure in functions. Therefore, during aging, we can see the systems, which still work actively. Aging is unavoidable process, which increases year by year, leading to decreasing of adaptation ability and increasing of death probability. Aging results from limitation of self regulation mechanism, in particular gene activity regulation mechanisms.

There is WHO classification determining the age. Elders are people having 60-74 years of age, old are people having more than 75 years of age, and long-

livers are those who have more than 90. But this division is conditional. It is possible to be aged in 50 tears, whereas some people are active having more than 70 years. S.P. Botkin and I.I.Mechnikov suggested hypothesis about preliminary and physiological aging. It is nonsense to evaluate every disease as aging. However, preliminary aging is conditioned by factors which cause strong and deep disturbances in metabolism. Theoretically, preliminary aging should be termed as non-correspondence in genetic program of development and its realization.

Medical health care is a strong factor of social defense during aging. There is a branch of medicine, which provides health care and conducts medical researches for elders. It is called geriatry (from Greek "geron" – elder, and "iateria" - treatment).

13.6.1 The hypotheses of aging.

There are more than 500 different theories to explain mechanisms of aging. But most of them lost their importance for today. Modern gerontology tries to discover all chain of processes resulting in aging.

Gonads removing do not result in increasing of life span. It was proved by many castration experiments. From the other side, gonads grafting or injection of sex hormones extracts also do not result in life span increasing. That means there is no direct dependence of life span from degree of developing and functioning of sexual glands. The relationships between them are very complicate involving many other endogenic factors. If we will change only one factor, it is not successive to increase life span.

I.I.Mechnikov considered that life span depends on following some rules. He listed all those rules in a concept about normal life and gave a name to this "orthobiosis" (from Greek "orthos" – correct, "bios" - life). The rules of orthobiosis concerned about the following: to obey the rules of social and occupational hygiene, rational diet with necessary intake of sour milk products to provide intestine environment where pathological bacteria can't reproduce. However, this theory as many others concerned about only one side of aging.

The majority of investigators agree that aging results from changes in genetic apparatus and defects of protein biosynthesis. Modern theories state that aging is directed by genetic apparatus. During ontogenesis, many changes in genetic apparatus occur. This changes lead to decreasing of their self-renewing activity and activity of protein producing systems. The number of histon proteins in old cell more than in young one. They bound DNA molecule tighter (G.D.Berdyshev 1972). The free radical damage of DNA is also considered as important factor of aging. Free radicals are chemical atoms having uncoupled electron on outer shell. Such radicals as H, OH, OOH, are very active in chemical reactions. So, they can damage DNA and cell membranes.

Some investigators relate starting changes of organism aging with changing of DNA, RNA, enzymes properties. The hypothesis of this branch considers that main reason of aging is macromolecules wearing off which lead to total organism failure. This hypothesis suggests that speed of aging depends on genetic inherited factors and life conditions.

Accordinary genetic or program hypothesis, aging is controlled directly by genetic material. Some hypotheses assume that there are biological watches in organism. They can switch on and off activity of different genes which control aging. It is believed that thymus is such "watch". It terminates its functioning in adult starting aging processes.

There is no universal aging theory, but we can assume that elements of theories listed above will be incorporated in a new synthetic theory. We need to keep in mind that aging rate greatly depends on social factors.

13.6.2 The organism death. Euthanasia.

The terminal period of life is death. Death is unavoidable event. It results from all previous ontogenesis. Death results from many reasons. Accidents may cause preliminary death in any ontogenesis period. The multicellular organisms have death occurring at one way. The metabolism becomes disordered; body becomes dead and it is digested by bacteria.

The monocellular organisms have death occurring at two ways: accidental death and division of cell. There is no dead body after cell division. And some scientists suggested considering monocellular organisms as potentially immortal (A.Veisman 1895). Such concept is shared from religious and mystical ideas about immortal soul. According mystical view, death is caused by separation of soul from the body. The biology denied such view. It proved that aging is an idle, consistent process. After death of whole organism, the parts of it still live for some time. They die in the line (brain cells – liver cells – heart cells – peripheral organs).

Modern science has tried to define the term "death". It was suggested by Russian scientists V.A.Negovsky to distinguish clinical and biological death. *The clinical death is failure of heart beating, absence of breathing and reflex reactions.* It is a first and reversible stage of dieing. During clinical death, all organs can survive for 3-5 minutes because their metabolism still goes on. *Biological death is irreversible process. It starts when brain cortex cells start to die. It follows by dieing of cells of all other organs. The metabolism is disordered. The autolysis of cell and tissues occurs.*

If anyone is in clinical death condition, we can return him to a life. The complex of such treatment is called reanimation. In the clinics, there are special units of reanimation and emergency care.

Euthanasia (from Greek "eu" – good, "thanatos" - death) is closely related with death. It is a death resulting from patient will. But in general, it is not corresponds with Hippocrates Oath, in which doctor promises to treat patient until patient's last moment of life. Formally, it is right thinking. But we can't ignore the fact, that fight for a patients life is appreciate until we have a hope to help him. When last chance to help is lost, we face a problem of charity in its highest sense. It is euthanasia. The euthanasia can be of two types: passive and active. Passive euthanasia is canceling of patient's treating, switching off all life maintaining apparatuses. Active euthanasia is injection of drugs which terminate his life by most comfortable way. Today, there is only one country, where euthanasia is legal. There are some juridical attempts to change the laws in USA. Here, in Belarus, the questions about euthanasia are only under theoretical discussion.

CHAPTER 14. ONTOGENETIC HOMEOSTASIS.

14.1 The general patterns of homeostasis.

The preserving organism as a whole system is a main and most common biological law. It is provided by reproduction in vertical line of generations, and by homeostasis throughout organism life. *Homeostasis is a maintaining a relatively stable internal physiological environment in organism, involving some form of feedback self-regulation.* This term was suggested by V.Cannon in 1929. Homeostasis provides freedom from the influences of unprogrammed disturbances that might upset the delicate balance required to produce complex organized tissues. However, if that influences overlap normal limits for a long time, the organism can adapt to them not only by maintaining stable environment, but also by changing activity of several system to cope with it better. For example, it accelerates heart beating and breathing rate while hard muscular work. The homeostasis reactions can be directed on maintaining stable internal environment condition, limitation of harmful substances impact, designing the new forms of optimal interactions of organism with environment in changing conditions. That means that term homeostasis is not only maintaining steady state of main functional constants, but also it includes adaptation.

The main components of homeostasis were determined by C.Bernar (1813-1878) and V.Cannon (1871-1945) and were updated accordinary new findings later. These components can be classified on three groups:

1. Substances providing cell needs (proteins, fats, carbohydrates, ions, oxygen, hormones).
2. Surrounding factors, affecting cell activity (osmotic pressure, temperature, pH).
3. Mechanisms, providing structural and functional integrity (heredity, diversity, regeneration, immunity).

To study these regulating principles, the new science was created by N. Viner (1894-1964). It is called cybernetics. The cybernetics is a science about optimal direction of complex processes occurring in nature, industry and society, as well. Using cybernetics terminology, we can assume that organism is complex directed system with interactions of many variables of internal and external environment. The general principle of system working is in following. Incoming variables comes to the system where they are transformed accordinary with system functions to outgoing variables. The functional dependence of outgoing variables from incoming variables is described by system behavior law.

In biology, the incoming variables can be reasons, stimuli, irritation, whereas outgoing variables can be consequence, effect, reaction and so on. The self-regulation processes are based on biological feedback. There are positive and

negative feedbacks. The negative feedback decrease influence of incoming signal on outgoing signal. The positive feedback act controversy; it enhance influence of incoming signal on system response. The negative feedback helps to keep steady state condition. The positive feedback pushes system away from initial state. However, positive feedback also can work as self-regulating mechanism. All self-regulation systems work in this way: when constants are shifted from basal level, they switch on systems to correct it. That principle was described by P.K.Anohin in 1935, as an effect of reverse afferentation, which is needed for adaptive reactions.

There are following levels of homeostasis: genetic, cellular and systemic.

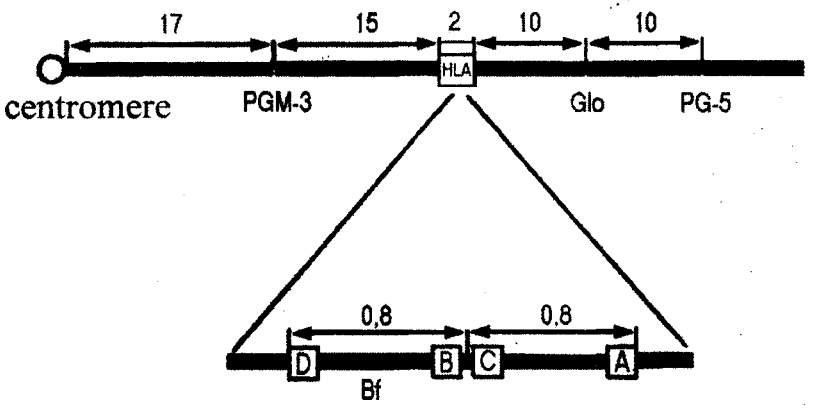
14.2 The genetic mechanisms of homeostasis. The transplantation as an example of homeostasis gene controlling.

Starting from primary gene products, there is a connection "one structural gene – one polypeptide chain". Gene regulatory mechanisms determinate homeostasis processes, such as protein synthesis, DNA reparation, gene expression and repression, preserving diploid chromosome set in eukaryotes somatic cell nucleus, gene control of expression blood groups ABO, Daffi, Lutheran, Rh-factor, human histocompatibility complex and so on.

From genetic point of view, we can distinguish elementary and systemic homeostasis events. The example of elementary event is human histocompatibility, which prevents transplants rejection. The transplantation is placing of tissue or organ from one individual to another. The tissue or organ, which is transplanted, called transplant. The organism from which tissue or organ have been taken is called donor; the organism to which tissue or organ are transplanted is called recipient. There are autotransplantation, syngenic transplantation, allotransplantation and xenotransplantation. In autotransplantation, donor and recipient are the same person. Syngenic transplantation is performed only for monozygote twins. In allotransplantation, donor and recipient are individuals of same species. The successful allotransplantation can be performed only with determining genes of histocompatibility complex. In xenotransplantation, donor and recipient are individuals of different species.

The transplantation immunity determines the success of transplantation. All cells are marked with "self-markers" on their surfaces to prevent the attack of one's own cells by immune system. These are called histocompatibility antigens. The combination of these antigens is unique for each individual as a fingerprint. Only identical twins have the same self-makers. The more closely related individual are to one another, the more likely they are to possess some common self-antigens. This is a reason that tissue transplants are more likely to succeed if the donor and recipient are matched with respect to these antigens.

The major human histocompatibility system is a HLA system (Human



Pic. 14.1. The genes of human histocompatibility (by J.Dausset,1975).

Leukocyte Antigen). This name was given because histocompatibility antigens express and are revealed better on leukocyte surface. The genes, which control this system, are in 6th chromosome and are presented by six locus's A, B, C, D1, D2 and R (pic 14.1). This complex of linked genes has length 2 morganids. The structural plan of main histocompatibility system is similar in all animals. In 1975, the WHO Histocompatibility Nomenclature Committee and World Immunological Societies Union accepted universal terminology for genetic description of HLA system. The antigens, which were internationally approved, are named HLA-A1, HLA-A2 and so on. Those, which just have been discovered, are pointed with index W (work).

The antigens are divided into two groups, which are controlled by closely linked genes. The first group antigens are revealed on leukocytes by serum complement-dependent reaction. Therefore, they are called SD-antigens (Serum Defined). The second group antigens are revealed on leukocytes by method of mixed leukocytes cultures. Therefore, they are called LD-antigens (Leukocyte Defined). SD-antigens are controlled by three sublocuses of sixth chromosome: HLA-A, HLA-B, HLA-C. LD-antigens are controlled by sublocus D of sixth chromosome. Each gene, controlling human HLA-antigens, has many alleles. Thus, sublocus HLA-A has 19 alleles, sublocus HLA-B has 20 alleles, sublocus HLA-C has 5 alleles, sublocus HLA-D has 6 alleles. By this way, it has been revealed about 50 antigens. It is believed that such genetic polymorphism is due to similar origin of some genes from others and due to close relationship of these genes.

The probability to find HLA identical donor among non relatives is from 1:4000 to 1:7000 (by G.V. Petrov, 1976). It is very important to find donor and recipient having similar HLA-antigens. The survival rate of transplanted kidney identical in all 4 HLA-antigens is 70% during two years. The survival rate of

transplant matching only in three antigens is around 60%. If only two antigens are matched, kidney survives only in 45% of cases. If only one is similar to donor, it survives only in 30% of cases. So, to perform successful transplantation, the special centers network has to be created. It should perform human typing on HLA-antigens. It also should select appropriate pairs "donor-recipient" throughout the world. The example of such system is "Eurotransplant" system in Netherlands.

There were two scientists, who made a great impact on discovering immunity. They are I.I. Mechnikov, who discovered phagocytosis, and P. Erlich, who discovered humoral immunity. Both of them were awarded by Nobel Prize in 1908.

K. Landsteiner's discovery of blood groups pushed forward the researches in the field of immunogenetics. There are 14 isoantigenic systems on human erythrocytes including more than 70 antigens.

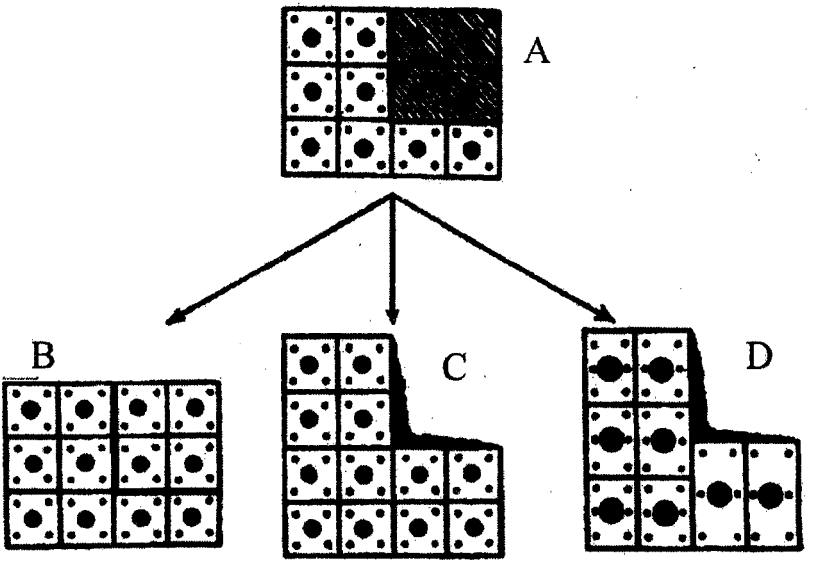
Bacteria, viruses, Protists, helminthes and even mutated cells of human carry foreign information, which need to be recognized by immune system. All of them are antigens. And immune system produces antibodies to recognize and to destroy them. As it was mentioned by F. Bernet (1961), the main function of immune system is recognition of "self" and "foreign", i.d. maintaining of steady state of internal environment.

14.3 The cellular mechanisms of homeostasis.

The cellular mechanisms of homeostasis are directed to replace dieing parts of tissues and organs. The example of this is regeneration. *Regeneration (from Latin "regeneratio" - repair) is an ability of the cells, tissues and organs to replace died and lost parts directed on restoring functional activity.* This process occurs on all levels of life matter organization: cell protein renewing, cell organelles renewing, cell renewing and so on. The studying of regeneration is very important for medicine. Medicine every day faces events, which is closely connected with regeneration starting from scratch healing to events that are more complex as nerve regeneration, bone remodeling and so on. All animal types have regeneration. Mammalians can have molecular regeneration (renewing of different molecules), intracellular regeneration (regeneration of cell organelles), and cellular regeneration (cell division).

All human tissues and organs can be divided into three type's accordinary their ability to regenerate.

1. Tissues and organs, which can give cellular regeneration (bones, loose irregular connective tissue, bone marrow, endothelium, mesothelium, linings of alimentary canal, respiratory pathways, urinary pathways).
2. Tissues and organs, which can give both cellular and intracellular regenerations (liver, kidney, lungs, smooth and skeletal muscle tissue, autonomic nervous system, pancreas, endocrine system).



Pic. 14.2. The scheme of different form of reparative regeneration in mammalians:
A – tissue damage, B – complete regeneration, C – regeneratory hypertrophy, D – intracellular regeneration (by D.S.Sarkisov et al.,1975).

3. Tissues and organs, which can give only intracellular regeneration (myocardium, cells of central nervous system).

During evolution, the two types of regeneration have been formed: physiological and reparative.

Physiological regeneration occurs in normal condition. The purpose of it is to replace deteriorated cells and tissues. It is very spread evens. It is occur in all live organisms: bacteria, plants, animals and human. We may consider as physiological regeneration the erythrocyte and leukocyte replacement, teeth's replacement in childhood, hair growth, and postmenstrual processes in uterus. There are special cells to perform this type of regeneration. They are called cambial cells. They are not differentiated cells preserving for further regeneration. For example, cells of basal layer of skin are cambial cells for skin epidermis regeneration.

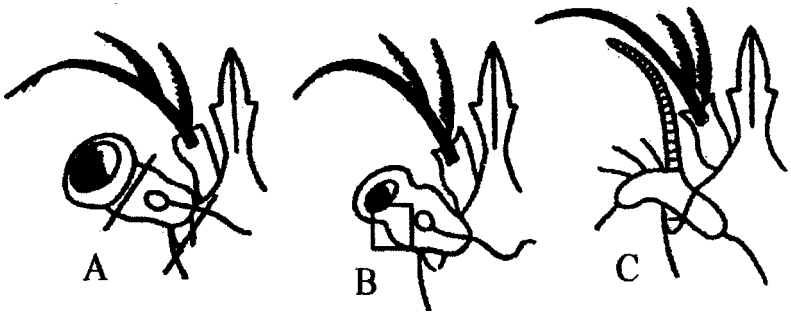
Physiological regeneration maintains structural homeostasis and provides possibilities for organs to work. The cell renewing by cell division is called proliferation. The proliferation rate is calculated by mitosis count in 1000 cells. There are two phases in physiological regeneration: destroying and restoring. In the first phase cells die. Their parts stimulate proliferation of other cells and thus provide second phase.

Reparative regeneration occurs in pathological condition. The purpose of it is to replace dieing and lost parts after injury. It occurs in wound healing, bone fracture healing, damaged organs restore. All injuries, mechanical, chemical, radioactive and so on, results in reparative regeneration. Reparative regeneration also occurs during disease recovering. Also it occurs in autotomia cases. Autotomia is condition when animal, for example lizard, loses part of its tail, if it is catch by predator. In vertebrates, the reparative regeneration can be of three types (pic 14.2):

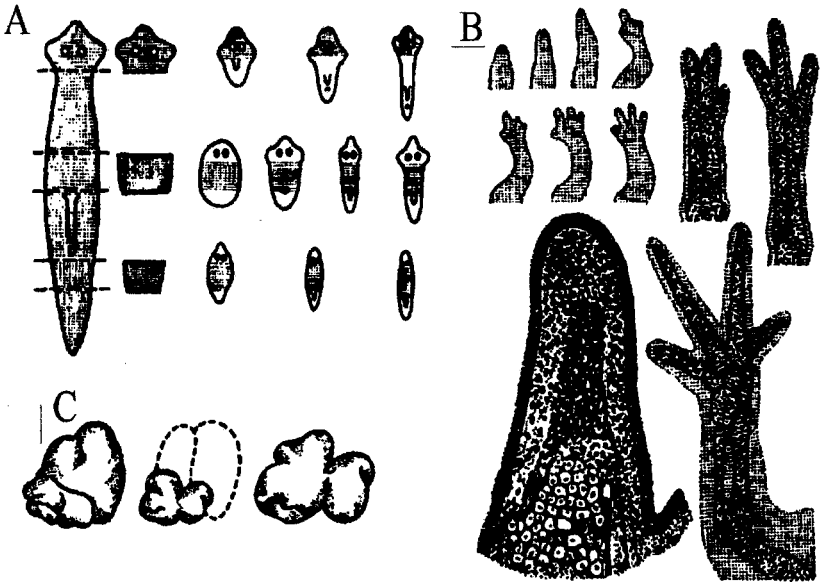
1. Complete regeneration, when regenerated structures are the same as before injury.
2. Regeneratory hypertrophy, when lost part is replaced by scar, but rest of the organ enlarges its sizes to perform the same function as before regeneration.
3. Intracellular compensative hyperplasia of organelles. The lost part is replaced by scar. In the rest of the organ cells, the organelles divide and grow to enable cells perform function, as it was before injury. The cell number doesn't increase.

The reparative regeneration can be of two types: typical (holomorphosis) and atypical (heteromorphosis) (pic 14.3). In typical regeneration, the regenerated organ is the same as was before injury. The example is regeneration of acsolotle limb after amputation. In atypical regeneration, the regenerated organs differ from uninjured one. For example, if crayfish eye has been removed with underling nervous ganglion, the new limb grows on place of eye. The studying of heteromorphosis is important for discovering factors, which direct regeneration. It can give a possibility to direct regeneration of lost organs in a future.

There are many ways of organs replacement: morpholaxis, epimorphosis, endomorphosis and compensative hypertrophy.



Pic.14.2. The typical and atypical regeneration in crayfish:
A – the eye before operation (two levels of amputation are showed), B – the regenerated eye, if nerve ganglion was preserved (holomorphosis), C – the segmented appendage, if nerve ganglion was removed (heteromorphosis) (by P.B. Gofman-Kadoshnikov, 1966).



Pic. 14.4. The ways of reparative regeneration:

A – morpholaxis (any part of planaria flat worm can give rise for entire body), B – epimorphosis (following stages of triton limb regeneration), C – endomorphosis (compensative hypertrophy of liver after removing its part); (by L.D. Liozner, 1962).

Morpholaxis – is the regeneration by remodeling of regenerating region. In the beginning, the size of new individual or repaired organ is smaller, but later it acquires normal size. The morpholaxis occurs in echinoderms, flat worms and others organisms (pic 14.4a).

Epimorphosis – is a growth of new organ from amputation wound surface. The examples are regeneration of tail in lizard, limb of acsolotle, the skeletal muscle regeneration with removed part. In young acsolotles the limb can regenerate in three weeks, whereas in adults in one-two month. Epimorphosis doesn't always result in formation of same organ as was before. Such regeneration is atypical (pic 14.4b).

Endomorphosis or regenerative hypertrophy – it is enlargement of rest part of the organ. Here, there is no a growth of new organ from amputation wound surface. The example is liver regeneration in mammalians. If part of liver has been removed, the surface of the wound is healed by scar. The cells in survived part proliferate very active to replace the volume and function of lost part. But, the organ's shape does not restore (pic 14.4c).

Compensative hypertrophy – is changes in one organ if other organ from the

same system has been lost. The example is hypertrophy of one kidney if another has been removed.

The reparative regeneration widely occurs in a human body. The bone restores very well from the fractures. You even can elongate the bone by gradually shifting away its broken parts. The tendon also regenerates. The peripheral nerves can regenerate by elongating their terminals. This regeneration can be facilitated by sewing together proximal and distal part of nerve.

It was stated that liver, spleen and pancreas regeneration in mammalians occurs by endomorphosis way. It can be used for normalization of organs functioning. If one part of the liver is affected by disease, we can remove it. Another part will take the functions of the removed part. In coupled organs (kidney, lung, testis and others), the compensative hypertrophy takes place, if one of them have been lost. Thus, if one lung has been removed, the remaining lung enlarges in size and takes function of both lungs. The epimorphosis occurs in blood vessels and urinary pathways regeneration.

14.4 The systemic mechanisms of homeostasis.

The systemic mechanisms of homeostasis are provided by main regulatory systems; nervous, endocrine and immune. The nervous system has its own features: fast response, short time reaction, effect is localized in the place where signal have been directed. The nervous homeostasis regulation is controlled by central nervous system. Coming to cells, nervous impulses can change the membrane charge; regulate chemical processes, control anabolism and catabolism of biological active substances. Moreover, the brain carries out endocrine function. It is known more than 50 neurohormones. The most of them are produced in hypothalamus (vasopressin, oxytocin, releasing factors and so on). At the same time, hypothalamus is a main center of autonomous nervous system controlling functions of internal organs by parasympathetic and sympathetic parts. The autonomic nervous system takes your temperature, monitors your blood pressure, and sees to it that your food is properly digested. Most physiological conditions are maintained within relatively narrow bounds, a condition referred to as homeostasis.

From homeostasis and adaptation view, the nervous system is a main organizer of all body's processes. I.P. Pavlov considered that all adaptation processes are regulated by reflex arcs. There are many levels of homeostatic regulation, which are closely related with each other. The first level is homeostatic systems of cellular and tissue levels. The second level is peripheral nervous regulatory processes such as local reflexes. The next level is processes regulated with involving central nervous system and numerous feedbacks. On the top of this pyramid is brain cortex and processes regulated by our conciseness.

In the complex multicellular organism, the connections between cells are

provided by endocrine system. Each gland in this system acts on other glands and receive information from them too. It is well-balanced negative feedback between gland secretory activity and hormone concentration in the blood. The higher concentration of hormone in a blood, the more gland secretion is suppressed.

The endocrine glands can be central and peripheral. The anterior pituitary is a central gland, all others are peripheral. It is because anterior pituitary hormones regulate secretion pattern of peripheral glands. However, hormone of peripheral glands can act on anterior pituitary suppressing its function. The hormonal regulation is performed through blood stream. Then, released hormones are transmitted to target cells, where they act (pic 6.4). The effect is long time. The endocrine glands are regulated by hypothalamus, which control pituitary.

Thus, in hypothalamus the nervous and endocrine centers are integrated into neuroendocrine system. Many other substances, except hormones, are involved in endocrine regulation. They are catecholamines and their precursors, histamine, prostaglandins, kinins and others. The reactions providing homeostasis involve many endocrine glands. The effect is transmitted from gland to gland as in chain.

Continuous changing of environment provides homeostasis throughout the life. If organism has grown in steady state conditions, he doesn't survive in natural conditions.

14.5 The aging and homeostasis.

During aging, different homeostatic defects occur on different levels of organism organization. On molecular-genetic level, the number of histon proteins in cell increases. They bound DNA molecule tighter. The internucleosome regions become less available to nuclease enzymes. The DNA-polymerase becomes less active; it leads to decreasing of replication rate. The proteins, which repair DNA, become less active too. It results in DNA structure damage, failure of transcription and translation, appearing abnormal proteins. The processes of gene expression and repression are deteriorated. The number of mutated genes increases. The frequency of chromosomes aberrations increases with age starting from 75. On cellular level homeostatic defects result from changes of membrane systems, osmotic pressure of cell, electrical charge, disturbances of external and internal cellular exchange, metabolic defects, defects of cell division and so on. There are also defects in systemic homeostasis mechanisms. Among them, there are brain cortex atrophy, deterioration of endocrine function and others.

To evaluate homeostasis in elderly, we need to note two very important things.

1. All homeostatic values have very complicate regulation. Same level of metabolism and functioning has different base in different life periods. For example, arterial pressure increasing may occur in young and elder as well. However, in young organism, this level is provided by

hard heart working, whereas in elder organism, it is provided by vessels tonus.

2. The basement level for many function is similar as for young as for elder organism. At the same time, the range of adaptation, rate of adaptation and adaptation potential are less than in young organism. The functional workload helps to reveal them. Thus, after workload the arterial pressure, pulse rate, breathing rate comes back to normal value slowly than in young. That means that adaptation mechanisms in elders are insufficient to cope with workload.

14.6 The biological rhythms and homeostasis.

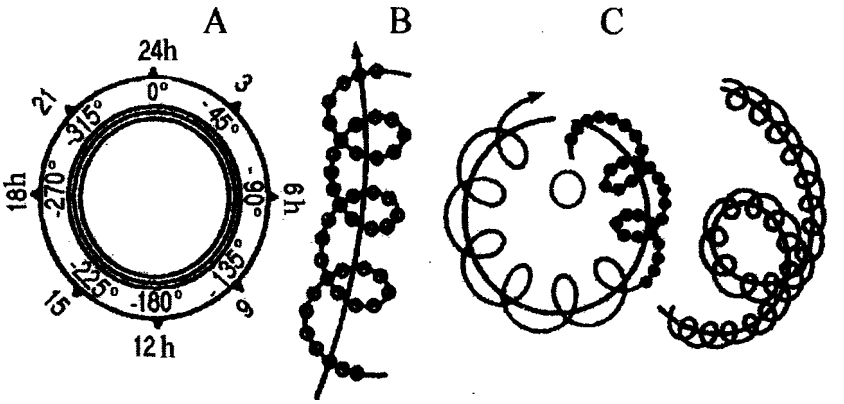
All life processes are rhythmical. They have different period of repeating, like day, month, year etc. There are close relationships between influence of natural factors on organism and its adaptation. There are natural rhythms. It is the repeating events in nature. The rhythms, which are traced in live organisms, are called biorhythms. They are regular quantity and quality changes of some biological processes, occurring on different life organization levels: cell, tissue, organism and population. The number of dividing cells is different in different time of the day. This observation results in discovering of daily rhythms. The science, which studies rhythms, is called chronobiology (from Greek "chronos" - time). It describes the daily mitotic rhythms, which is very important for medicine. There are also monthly and yearly rhythms of tissue and cell renewing (pic 14.5). The example of monthly rhythm is menstrual rhythm in women; the example of yearly rhythm is changing of reproductive ability of man throughout the year.

The one of the most common rhythm in nervous system is rhythm of dream and wake. This is a fundamental rhythm of all higher animals providing working of all body's systems. The internal environment has it own rhythms of changing. They are controlled by endocrine system. By the way, all cells have their own daily rhythm.

The biorhythms corresponding with natural rhythms are called "ecological" rhythms or "adaptive" rhythms. They are yearly, monthly, seasonal, ebb's and flow's rhythms, daily rhythms.

Accordinary stage of dependence from external conditions, biological rhythms are divided into exogenic and endogenic. The exogenic rhythms depend on rhythms of geological, physical and natural factors (photoperiodization, temperature, atmosphere pressure, gravitation and so on). The endogenic rhythms occur in constant external conditions. They are daily rhythms of main physiological constants (mitotic rate, hormone secretion and so on).

The modern man doesn't need to strictly follow natural biorhythms. The feeding and drug treatment can modulate any rhythmic situations. However, if some-



Pic.14.5. The organism's biological rhythms:
A – daily, B – monthly, C – yearly rhythms (by V.N. Kaznacheev, 1980).

one recovers from disease ignoring natural biorhythms, it is one of conditions to make disease chronic. The development of chronic disease can be presented as contradiction between biological and social part of human. Generally, humankind comes to era of chronical pathology of any etiology.

The analysis of biorhythms in general evolutionary view facilitates to study biological mechanism of human homeostasis more deeply. It also helps to design new effective drugs to increase human resistant to harmful effects.

So, the homeostasis is a big problem for contemporary biology and medicine, because it is not means only maintaining of steady state of internal environment. The mechanisms supporting homeostasis can change organism's properties. The disease itself also is a problem of homeostasis, the relative failure of its mechanism to protect and recover organism. The working schedules and other hygienic procedures have to be designed on a basis of homeostatic patterns. However, salvation of these problems waits us in a future.

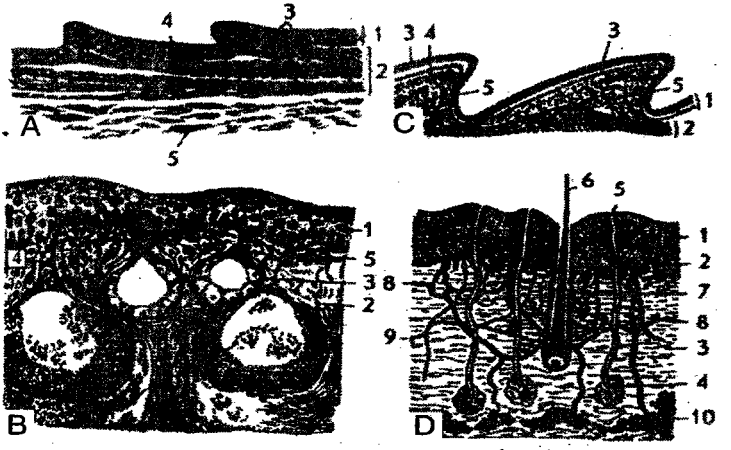
CHAPTER 15. COMPARATIVE AMATOMY OF VERTEBRATES.

The comparative anatomy data allows tracing evolutionary development of the same organ. The comparative anatomy is of big interest not only for biologists, but for doctors too. Human has animal origin. The complex structures, which doctors deal with, have a long history of development. On a base of this knowledge, doctors can correctly understand the ways of hereditary defects formation and reserve regenerative potential of the organ. Having in mind for the specifics of medical university, we present the material in short form with special emphasis on human features.

The material is presented by systems, but it is necessary to keep in mind that organism works as whole system.

15.1 The integuments.

All chordates have two layers of integuments: epidermis originated from ectoderm and derma originated from mesoderm. The main evolutionary directions



Pic. 15.1. The mammalian integuments:

A – of bony fish (1 – epidermis; 2 – corium; 3 – mucose glands; 4 – bony scales; 5 - muscles); B – of amphibians (1 – multilayer epithelia; 2 – corium; 3 – mucose gland; 4 – glands duct; 5 – pigment cells); C – of reptilians (1 – epidermis, 2 – corium; 3 – stratum corneum; 4 – pigment cells; 5 – skin ossification regions); D – of mammalians (1 – external keratinizing layer of epidermis, Malpigian layer, 3 – corium, 4 – sweat gland, 5 – sweat gland duct opening, 6 – a hair, 7 – sebaceous gland, 8 – blood vessel, 9 – skin nerves, 10 – adipose tissue), (by R. Wiederscheim, 1909).

were at first, changing of epidermis layers number from simple, one-layer epithelia to multilayer epithelia, at second, changing the epidermis/derma ratio to derma prevalence side.

Amphibians and fishes have skin with the following features: multilayer epidermis with abundant mucous monocellular or multicellular glands, derma with dense rows of collagen fibers, placed by layer – longitudinate and vertical (pic 15.1a,b).

Reptilians, Birds, and Mammalians have performed the great aromorphosis – developing of dry keratinized epidermis. This was very important to adapt them for being on land. Their epidermis has two layers: growing and keratinized. Reptilians and Birds have no glands in the skin in contrast to Mammalians (exceptions are special glands – hip glands of lizard, musky gland of crocodile and so on). The mammalian's skin is rich in gland (sweat, milk and others). The keratinized layer makes skin appendages: scales, feathers, nails and claws. Keep in mind that fish's scales have mesodermal origin and bonelike structure (pic 15.1c,d).

The inherited defects of integument in humans are excessive keratinizing of skin, lack of sweat glands, hemangiomes, teleangioextasia.

15.2 The skeleton.

Chordates were the first to develop anaxial skeleton (chord). In vertebrates, chord is changed to a cartilaginous or bony skeleton. It has three parts: axial skeleton, skull skeleton, and appendicular skeleton.

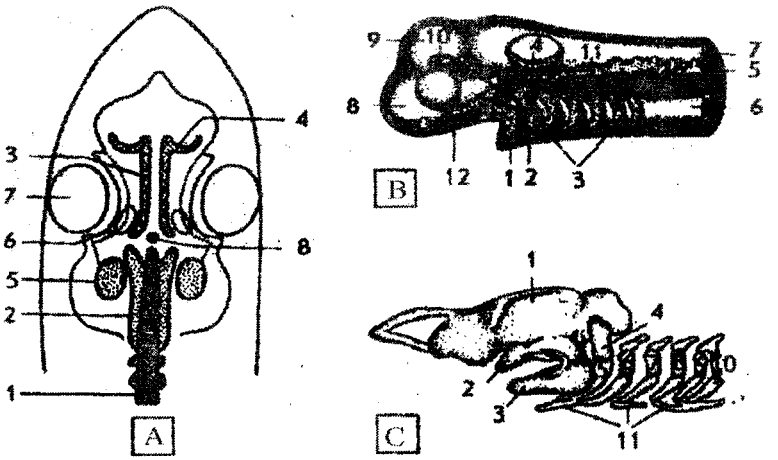
The axial skeleton. During evolution, it has the following tendencies of changing.

The first tendency is to give more strength to skeleton. It was performed by following change of chord to cartilage and then to a bony skeleton (in subphylum Cephalochordata – chord, in fishes – cartilaginous and bony skeleton).

The second tendency is to divide the axial skeleton into subdivisions (in fishes – body's and tail segments, in amphibians – cervical, body's, sacral and tail segments, in reptilians and mammalians – cervical, thoracic, lumbar, sacral, and tail segments).

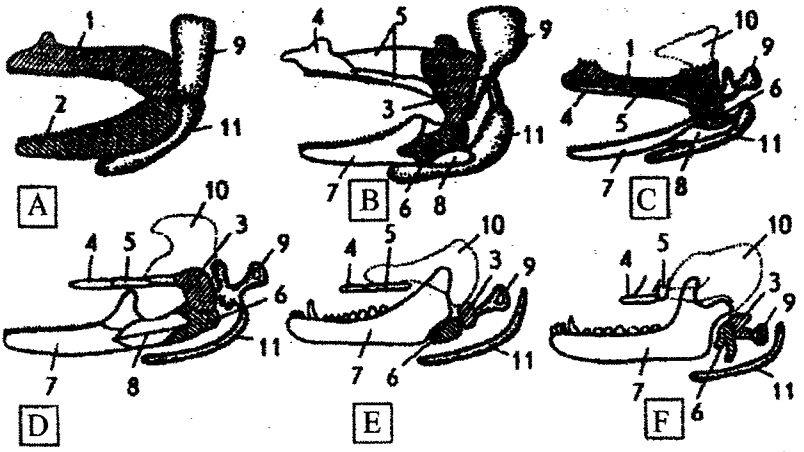
There are several features of axial skeleton, which have been formed during human evolution. They are the physiological curves of vertebral column, changing of rib cage shape – flattening in dorsoventral direction, and widening in the lateral direction.

The skull skeleton. Of the skull's 28 bones, 8 form the cranium that encases the brain; the rest are facial. Earlier in evolution, they were called, subsequently neurocranium and visceral skull, which gave support to respiratory organs of lower vertebrates. The formation of neurocranium is due to merging of three cartilage pairs: parachordal, trabecular, and ophthalmic (pic 15.2a). The visceral skeleton is founded as apparatus that supports respiratory pathways and the beginning of



Pic 15.2. The cartilaginous foundations for axis cranium (A) and cartilaginous cranium in shark embryo (B) and adult individual (C);

A:1 – chord, 2 – parachordalia, 3 – trabecules, 4 – olfactory capsules, 5 – hearing capsule, 6- ophthalmic cartilages, 7 – eye, 8 – pituitary, B: 1 – jaw's arch, 2 – hyoideus arch, 3 – 3rd-6th gill arches, 4 - hearing capsule, 5 – chord, 6 – gut, 7 – spinal cord, 8 – forebrain, 9 – midbrain, 10 – ophthalmic cartilages, 11 – parahordalia; C – 1 – axial cranium, 2 – palatine square cartilage, 3 – lower cartilage of 1st arch, 4 – hyomandibular cartilage, 5 – hyoid, 6 – 10 – gill's arches, 11 – copula (by I.I. Shmalgausen, 1947 with changes).

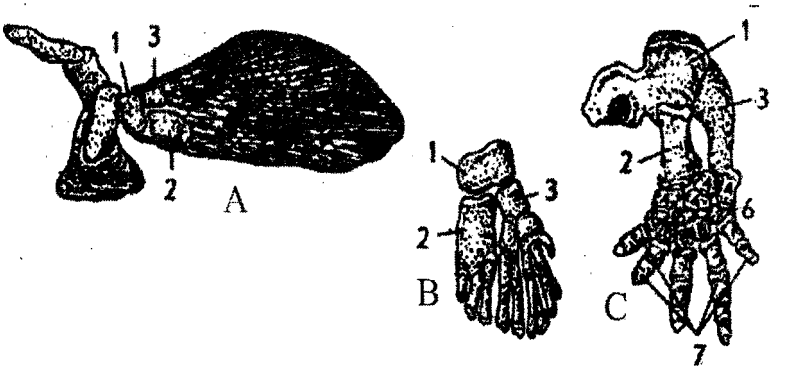


Pic. 15.3.The changes in two first visceral gill arches:

A – shark, B – bony fish, C – amphibian, D – reptilian, E – teriodont, F – mammalian. 1 - palatine square cartilage, 2 – lower cartilage of jaw's arch; 3 – square bone (incus in mammalians), 4 – palatine bone, 5 – sphenoid bone, 6 – malleus and its precursors; 7 – dental bone, 8 – angular bone, 9 – hyomandibular cartilage (stapes in mammalians), 10 - scales bone, 11 – hyoid (by I.I. Shmalgausen, 1947).

the alimentary canal. It is differentiated into jaw's arch (to catch food), hyoid arch (to bind with cranium) and gill arches (to fixate gills). The visceral skull is developed well only in cartilaginous fishes (pic 15.2 b,c).

It is reduced in land animals: the upper part of jaw's arch bounds with cranium, the hyoid arch gives the bones of inner ear, the rests of gill arches changes to larynx cartilages (pic 15.3). The facial skeleton is newly formed structure.



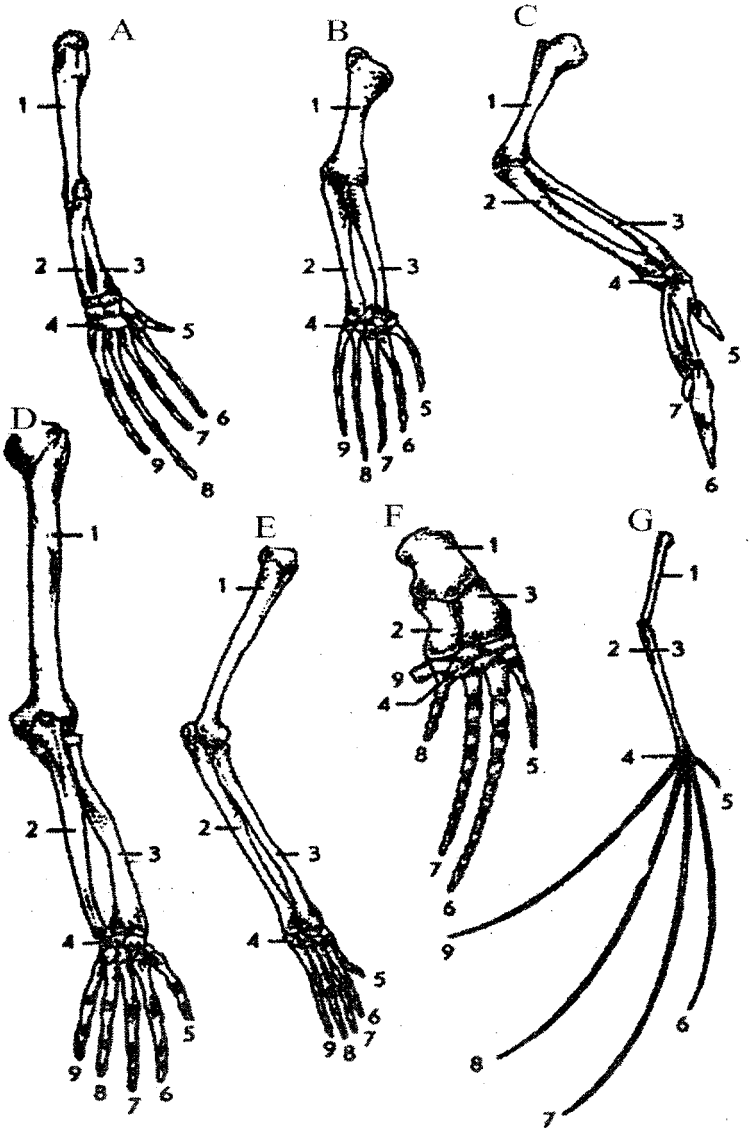
Pic. 15.4 The scheme of paired fin of Crossopterygii fish and stegocephal:
A – thoracic girdle of Crossopterygii fish; B – internal skeleton of fin; C – the skeleton of anterior limb of stegocephal. 1 – homologous element to humerus, 2 – homologous element to radius, 3 – homologous element to ulna, 4 – bones of proximal wrist, 5 – bones of distal wrist, 7 – fingers phalanges. (by I.I. Shmalgausen, 1947)

During human evolution, the skull acquired several features, such as enlargement of neurocranium (it became taller, instead of flat), changing of facial/ cranium ratio in a favor of cranium, the chin formation connected with development of speech.

The appendicular skeleton. There are paired (upper and lower limb) and unpaired (tail and back fins in fishes) limbs. The skeleton of paired limbs forms pectoral and pelvic girdle to support them (pic 15.4). The all limbs of land animals are made according to one scheme (pic 15.5). The bones of the pectoral girdle and upper limb correspond with bones of the pelvic girdle and lower limb: scapula - huckle-bone, coracoid – sciatic bone, procoraoid – pubic bone, humerus – femur, ulna and radius – tibia and fibula, hand bones – foot bones.

During human development, the appendicular skeleton has been changed in the following ways. The pelvis was enlarged because of shifting of centre of gravity. The thumb opposes the others. The foot forms the arch; that serves as damper while walking.

Among inherited defects of spinal column the most common are changing in vertebra number (increasing or decreasing), knitting of vertebra's body and processes, arches disjunction, atlas assimilation, scoliosis. There are defects of chest development such as ribs underdevelopment, development of cervical ribs, addi-



Pic. 15.5. The skeleton of anterior limbs of different vertebrates:
A – frog, B – lizard, C – bird, D – human, E – cat, F – whale, G – bat; 1 – humerus, 2 – ulna, 3 – radius, 4 – wrist bones, 5 – 9 – fingers phalages. (by K. Willy, V. Detier, 1974).

tional ribs, splitting of sternum. There are defects of limbs development such as cranial-clavicular disostosis, synostosis of ulna and radius, or tibia and fibula, hemypodia (limb underdevelopment), ectropodia (limbs reduction to bud size), apodia (absent of limb accompanied by pelvis bone underdevelopment), arachnodactilia, brachidactilia, plydactilia, syndactilia, flat-foot, club-foot and so on.

Among skull defect the common are cleft palate, harelip, craniostenosis (preliminary suture closure), microgenia (underdevelopment of lower jaw), micrognatia (underdevelopment of upper jaw), exoencephalia (absence ofcranium bones). The teeth development defects are adentia (absence of teethes), diastema (teeth development in unusual place), and bite defects.

15.3 The brain.

The brains of vertebrates have three principal divisions: the hindbrain, the midbrain, and the forebrain. Each part of the brain was developed from separated bud.

The forebrain bud (prosencephalon) divides into two parts. The anterior part forms anterior part of brain or telencephalon, which in most of veretebartes differentiates to big hemispheres. The posterior part of forebrain bud gives diencephalon. The midbrain bud gives rise to mesencephalon. The hindbrain bud also divides into two parts

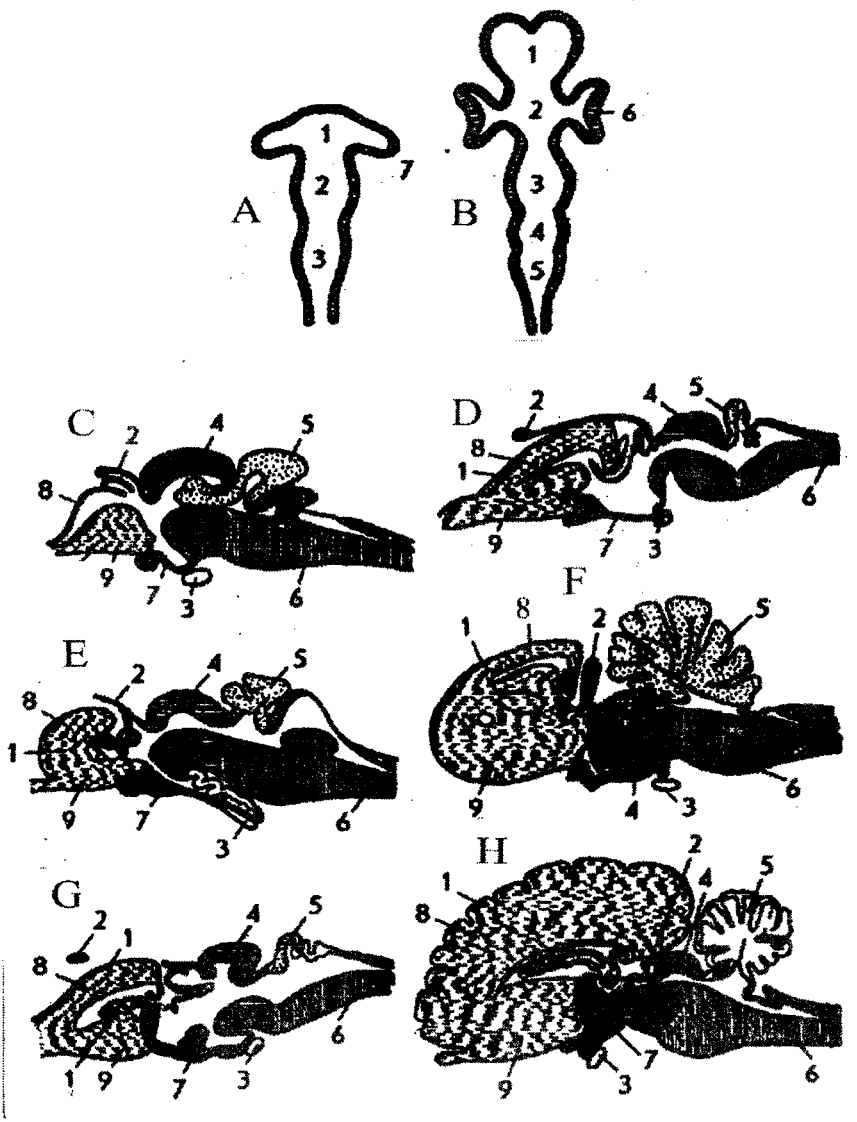
The anterior part of it gives rise for cerebellum or metencephalon. Whereas posterior part differentiates to myelincephalon or medulla oblongata which extends to spinal cord (pic 15.6 a,b).

During brain development, the internal cavities of brains are formed. They are called brain ventricles. The cavity of telencephalon is two lateral ventricles. The cavity of diencephalon is third ventricle. The cavity of medulla oblongata is fourth ventricle. The cavity in the mesencephalon is Silvii's aqueduct.

In every brain part, there are cloak (palium) and basis. The cloak is formed from that brain parts, which lies above ventricles, whereas basis is under the ventricles. The brain matter isn't homogeneous. The darker regions are grey matter, whereas whiter regions are white matter. The white matter is formed by processes of neurons. The myelin sheets of them are rich in lipids having white color. The gray matter is presented by cell bodies of neurons in between gliocytes. The layer of gray matter on a surface of any brain part has a name cortex.

Thus, the vertebrate's brain consists of 5 divisions. They are placed in same sequence. But the degree of their development differs within vertebrata subphylum. All these differences are due to phylogenesis. There are three types of brain: ichtiopsydic (from greek "ichtios" - fish), zauropsydic (from Greek "sauros" - pangolin), and mammalians.

The fishes and amphibian have ichtiopsydic brain type (pic 15.6 c,d,e).



Pic. 15.6. The brain of mammalians:

A – stage of three brain buds; B – stage of five brain buds (1 – forebrain, 2 – diencephalon, 3 – midbrain, 4 – cerebellum, 5 – medulla oblongata, 6 – eye's goblet, 7 – eye's vesicle), C – bony fish, D - cramp-fish, E – frog, F – reptilian, G – bird, H – mammalian (1 – forebrain, 2 – epiphysis, 3 – pituitary, 4 – midbrain, 5 – cerebellum, 6 – medulla oblongata, 7 – diencephalon, 8 – brain cloak, 9 – striated bodies), (by F.F. Talysin, 1947 with changes).

The fish brain has a primitive structure. It is small and has little forebrain. The telencephalon is not divided into hemispheres. The cloak of telencephalon is narrow and without cell bodies. The cells are in the basis where they form two striated bodies. There are two olfactory bulbs ahead of the brain. In general, the fish's telencephalon is only olfactory center. The diencephalon is covered by telencephalon and mesencephalon. It has an offshoot going down of cloak, called epiphysis. The offshoot of basis called pituitary. The mesencephalon is most developed brain division in fishes. It is an optic center containing two optic lobes. It has a cortex. It is a highest division of fish's brain collecting all impulses from the body. Here the responses are also designed. The cerebellum of fish is well developed. Therefore, they have different movements. The medulla oblongata has visceral lobes, which are very developed. It is because of good development of taste organ. There are 10 pairs of cranial nerves leaving brain.

The amphibian brain has several progressive changes in compare with fish's brain. In is due to living on land. The total brain volume and development of telencephalon have been increased. The telencephalon is divided into two hemispheres. The cloak of telencephalon is still narrow. The striated bodies are still in the basis. The olfactory bulbs are significantly separated from forebrain. The telencephalon is still only olfactory center. The diencephalon is good observed from outside. The cloak makes epiphysis, whereas basis makes pituitary. The mesencephalon has less size than in fishes. The mesencephalon hemispheres are well developed. It is the leading division of central nervous system analyzing all information. It is still important as optic center. The cerebellum is less developed than in fishes because the body's position is more stable. It looks like bolster near anterior part of medulla oblongata. The medulla oblongata has no cloak and serves as a place for cranial nerves leaving (III-X).

The birds and reptilians have zauropsydic brain type (pic 15.6 f,g).

The reptilians have further brain enlargement. The telencephalon becomes the most developed brain division. It is due to striated bodies' enlargement. The cloak of telencephalon is still narrow. On the surface of the cloak, the layer of brain cells appears forming primary cortex (archicortex) of primitive structure. The telencephalon becomes dominant part of brain. In the diencephalon, there is dorsal appendage of special structure. It is developed mainly in lizards and it takes a function of organ of vision. The mesencephalon decreases in size and loose its dominant role in the brain. It also becomes less important as optic center. The cerebellum develops better than in amphibians. The medulla oblongata makes a curve in vertical plane. The 11 pairs of cranial nerves leave the brain.

The bird's brain continues increasing in volume. The telencephalon covers all others parts because of its size, excluding cerebellum. The increasing of telencephalon is due to further increasing of striated bodies. The cortex has no further development and even degrades. The telencephalon cortex looses its lateral parts.

The diencephalon is small, epiphysis is small too, and pituitary is developed well. In mesencephalon, the optic lobes are developed very well. It is due to the very important role of vision in bird's life. The cerebellum rises greatly and develops vermix and lateral lobes. The cerebellum development connected with development ability to fly. The 12 pairs of cranial nerves leave the brain.

The mammalians have mammalian brain type (pic 15.6 h).

Here is also increasing of brain volume but due to development of brain cortex. On a surface of cortex, the layer of gray matter appears. The mammalian cortex differs from reptilian cortex. It is a new formation carrying out many functions, instead of only olfactory function in reptilians. It is called neocortex. In lower mammalians, the surface of cortex is plain, whereas in higher mammalians it forms brain convolutions increasing its surface. The cortex becomes dominant brain division. The olfactory lobes are developed well. The diencephalon has epiphysis and pituitary. The mesencephalon is less in size. It has two groves dividing it into four optic hills. The anterior hills are connected with optic receptors, whereas posterior hills are connected with hearing receptors. The cerebellum develops greatly. It has a very complicate internal and external structure. The medulla oblongata develops bolsters and pyramids. The 12 pairs of cranial nerves leave the brain.

The defects of human brain development are anencephaly (underdevelopment of forebrain), microcephalia (general underdevelopment of brain), hydrocephaly (excess of cerebrospinal fluid), underdevelopment of brain lobes, cranial hernias.

15.4 The digestive system.

The general organization of the digestive tract is the same in all vertebrates, although different elements are emphasized in different groups. Specializations among the digestive system of different kinds of vertebrates reflect differences in the way these animals live. The differentiation is directed to teeth differentiation, alimentary canal differentiation, separation of digestive glands and increasing of absorption surface in the intestine.

The fishes develop large pharynx with gill slits. In the mouth there are numerous teethes. The stomach is small. The intestine develops villi and folds of mucous. The liver is relatively bigger than in others vertebrates. The pancreas and swim bladder develop from intestine invaginations.

The amphibians develop small one line teethes and salivary glands. The stomach and intestine are well separated. The terminal part of intestine is called cloaca. The liver is well developed too.

The reptiles still have teeth similar to each other. The snakes have part of salivary glands producing poisons. The bud of caecum is formed in the border of

small and large intestine.

The birds, because of flying, loose jaws and teeth. They develop a beak. Many birds develop gizzards, which are often filled with grit that acts in a place of molars to break up food. The stomach has glandular and muscular parts. Birds have a convoluted small intestine by means of which they prolong the process of digestion and aid absorption of digestion products. The terminal part of the intestine is cloaca too.

The mammalians have heterodont teeth system. They have molars, premolars, canines, and incisors. During development, the gill chambers are formed from the sidewall of the pharynx. The first gill chamber gives rise to the auditory tube and middle ear. The second gives rise to the tonsil sinus. The third and fourth chambers give rise to thyroid and parathyroid gland. The stomach contains glands of different types. The large intestine is much bigger than in others vertebrates. The rectum and vermiform appendices and rectum have been made. The intestine is terminated by anus.

The defects of digestive system development are athresy of esophagus, macro and microesophagus, gastroptosis (lower positioning of stomach), Merckell's diverticulum, situs viscerus inversum, neck fistulas.

15.5 The respiratory system.

The feature of the respiratory system of chordates is close embryonic, phylogenetic, and functionally with the digestive system. The close relations are determined by topographical and dynamic coordinations in phylogenesis and morphogenetic and ergontic correlations in ontogenesis.

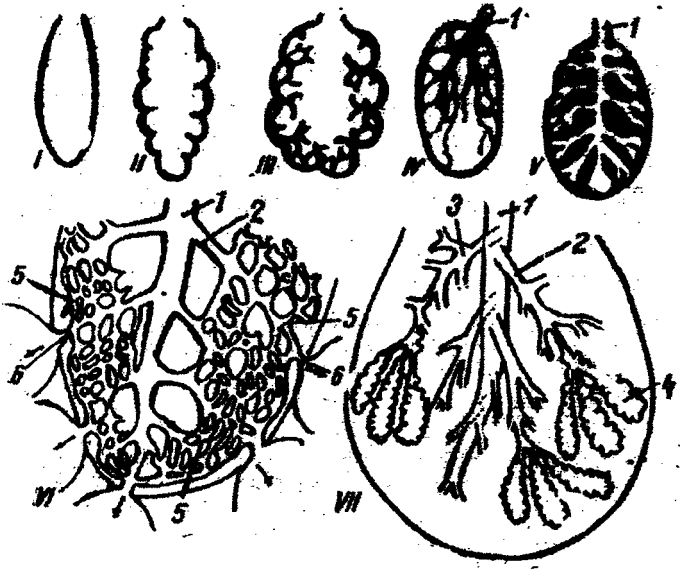
The main direction of respiratory system differentiation is changing of gill breathing to lung breathing. It leads to more complicate differentiation of respiratory pathways an increasing of respiratory lung surface.

Gills were firstly developed in fishes as folds of mucous on gill arches. They are supplied by venous blood by gill's arteries. The swim bladder was formed as outpocketings of pharynx. It performs a hydrostatic function, balancing of body in water. The first to make swim bladder were lobe-finned fishes.

Amphibians were derived from lobe-finned fishes. On a stage of tadpole, amphibians have gills, but in adults there are no gills. The adult amphibians have lungs. The gill's arches being changed incorporate to larynx cartilages. The lungs start directly from larynx and have a small surface. The gases exchange is performed through the lungs and skin surface as well (pic 15.7 a,b,c,d).

The reptilians have upper (nose cavity) and lower (larynx, trachea, bronchi) respiratory pathways. The lungs of reptilians have small cell structure and therefore they have larger respiratory surface (pic 15.7 e).

The lungs in bird look like spongy bodies connected by bronchi, instead of sacs like shapes in reptilians (pic 15.7 f). Bronchi enter each lung from the ante-



Pic. 15.7. The scheme of lung structure invertebrates:

I,II – amphibians with tail, III – tailless amphibian, IV – scale amphibian, V – crocodile, VI – bird, VII – mammalian (1 – bronchi, 2,3 – ventral and dorsal bronchi's branches, 4,5 – lung alveoli, 6 – connection of lungs with air sacs) (by F.F. Talysin, 1947).

rior part and tend to go backward. They leave lungs entering the air sacs. The air sacs are placed throughout the body even entering the bone cavities.

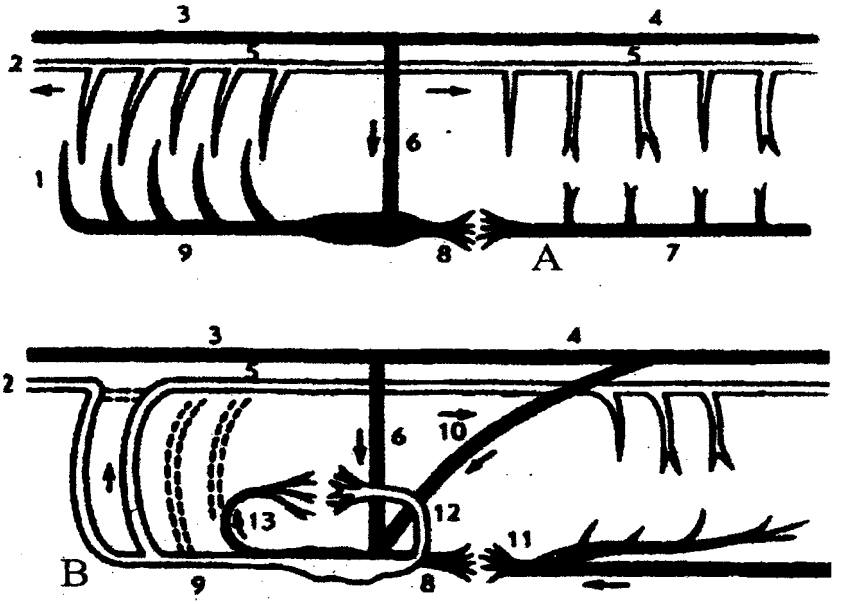
In mammalians, we observe good branching of bronchi forming bronchial tree with bronchi of second, third and fourth grade. The last are terminated by alveoli. The chest is separated from abdomen by diaphragm, which is greatly involved in the breathing (pic 15.7 g).

The human hereditary defects of respiratory system are preserving of gill's slits, athresia of trachea, tracheal-esophagus fistula, agenesia (absence) and hypoplasia (underdevelopment) of lung or its lobe, additional lobes or lung, lungs cyst.

15.6 The circulatory system.

The circulatory system of vertebrates has similar organization as the circulatory system of lower chordates and even annelids. It is consist of ventral and dorsal vessels, which have anastomosis in the intestine wall and body's wall.

The main tendencies in circulatory system development are following: separation of heart, vessel differentiation to blood and lymphatic vessels, formation of double circulatory system, development of structures which separate arterial and

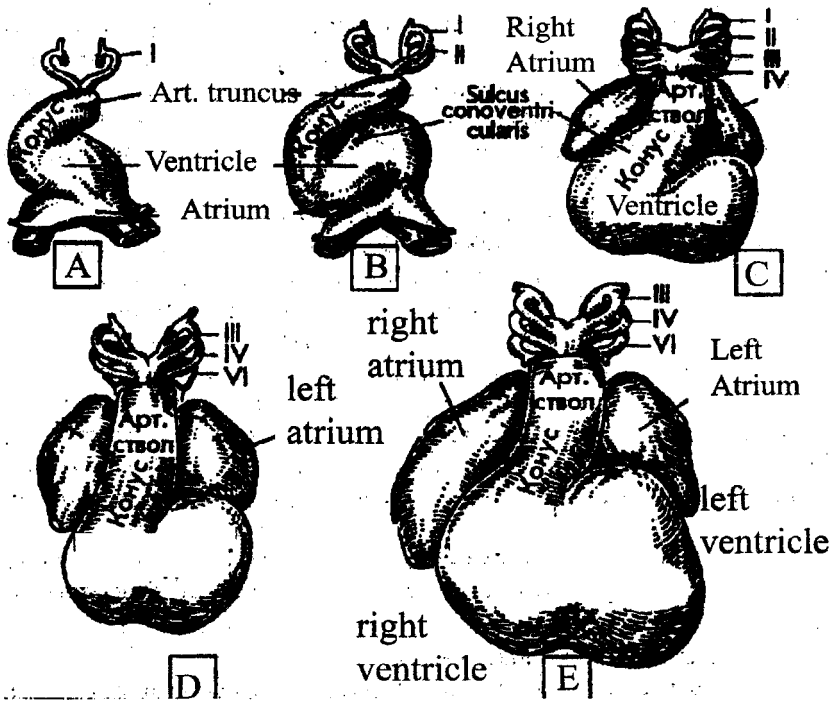


Pic. 15.8.The structure of circulatory system of water (A) and land (B) vertebrates:
1 – gill arteries, 2 – carotid artery, 3 – anterior cardinal vena, 4 – posterior cardinal vena, 5 – dorsal aorta, 6 – Cuvier's duct, 7 – subintestinal vena, 8 – hepatic vena, 9 – ventral aorta, 10 – inferior vena cava, 11 – vena porta, 12 – lung vena, 13 – lung artery (by F.F. Talysin, 1947 with changes).

venous circulation.

The lower vertebrates (fishes) have simple circulation (pic 15.8 a). Their circulatory system is almost same to the lanceolate circulatory system. The progressive improvement is appearance of two chambers heart consisting of atrium and ventricle. The fish's heart pumps only venous (nonaerated) blood. It is delivered to heart by cardinal veins to sinus venous, then to the atrium, ventricle, and by aorta to gill's arteries. The blood is oxygenated in the gills. The gill's arteries are branched entering the gill. It increase surface of gases exchange. The fishes have portal systems of liver and kidneys.

In land animals, the arterial (aerated) as well as venous (nonaerated) blood enters the heart. It is because of the formation of double circulation: the pulmonary circulation, in which blood travels from the heart to the lungs and back, the systemic circulation, in which blood travels from the heart to the rest of the body and back. Amphibians and reptilians have mixing blood in the heart, whereas birds and mammalians have developed separation of circulation pathways and have arterial and venous blood separated from each other in the heart. For all land animals, there is typical replacement of gill's arteries by aorta arches, and cardinal



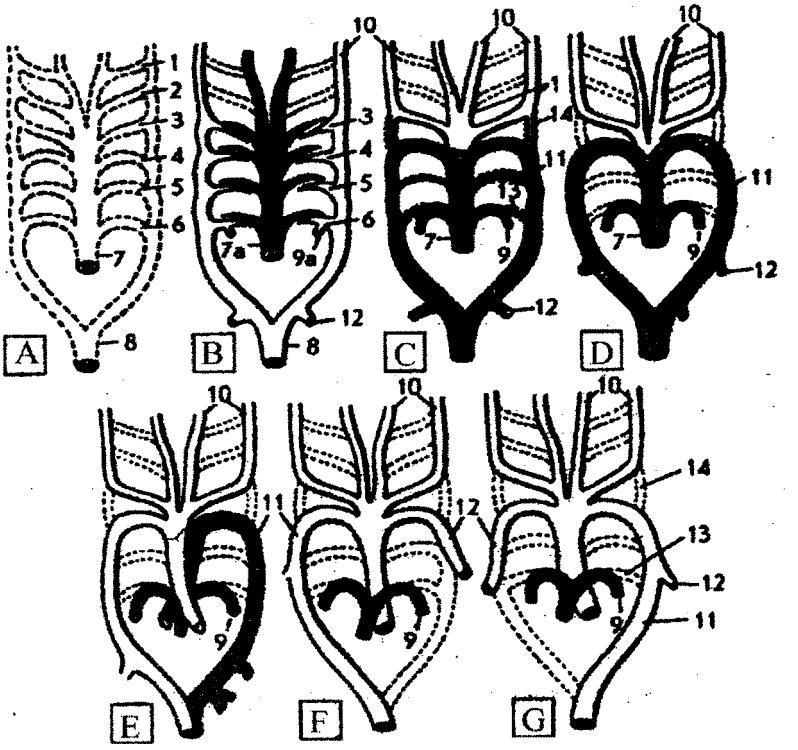
Pic 15.9. Curving of heart tube and formation of heart chambers in human embryo (anterior view):

Embryo length is 2.08 mm(A), 3 mm(B), 5.2 mm(C), 6 mm(D), 8.8 mm(E), I-VI are gill arteries.(by V.N. Yarygin, 1984).

veins by lower vena cava. The rest of cardinal veins in human body are veins azygous and hemiazygous. The veins of head merge to upper vena cava. Because of active locomotion, the limbs vessels are developed very well. The portal system of kidney is replaced by system of excretory products filtration.

In embryogenesis, the heart is originated from strait tube, which curves further to S-shaped tube (pic 15.9). The posterior part of bud moves too dorsal side and form atrium. The anterior part stays on ventral side and forms ventricle with wide muscular wall. The part of the tube behind the atrium forms sinus venous. In lower vertebrates, ahead the ventricle the conus arteriosus is formed.

In front of the heart the ventral aorta is formed. It gives off the paired vessels – arterial arches. These arches surround the pharynx and join on a dorsal side of it to dorsal aorta. They also send ahead the carotid arteries for head supply. The number of arterial arches in vertebrates isn't big. Thus, fishes have 6-7 arches,



Pic 15.10. The transformation of aortic arches of vertebrates:

A – embryonic bud, B – fish, C – amphibian with tail, D – frog, E – reptilian, F – bird, G – mammalian. 1 – 6 – 1st – 6th aortic arches, 7 – aortic trunks, 8 – dorsal aorta, 9 – lung artery, 10 - carotid artery, 11 – aortic arches, 12 – subclavicular artery, 13 – Botalli duct, 14 – carotid duct. (by I.I. Shmalgausen, 1947, with changes).

whereas in land animals 6 arches are founded (pic 15.10 a). The first two pairs are partially reduced in all vertebrates. The rest of them form maxillaries artery and sublingualis artery. Next arterial arches are divided into incoming and outcoming gill's arteries (pic 15.10 b). In land animals, the arterial arches' pairs from third to sixth are subject to several changes. The third pair looses connection with dorsal aorta and gives rise to carotid arteries. The fourth arch is significantly developed and forms arches of dorsal aorta. In amphibians and reptilians these arches are symmetrical (pic 15.10 c,d,e). In birds, the left arch is reduced, whereas the right subject to further development (pic 15.10 f). In mammalians, the right arch is reduced, whereas the left subject to further development (pic 15.10 g). The fifth pair of arches is reduced too. The sixth forms pulmonary arteries and looses connection with dorsal aorta. In the embryo of land animals, the pulmonary arteries

are connected with the aorta by a narrow duct, which is called the Botalli duct. It is preserved in adult reptilians and amphibians. In humans, it is closed right after birth. But if it stays open, it can results in heart defect formation.

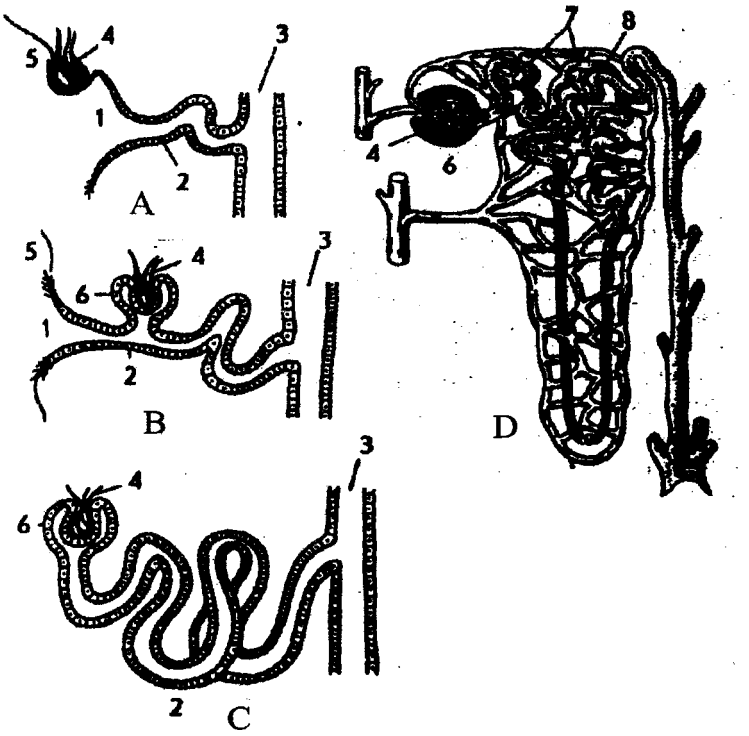
There are many abnormalities of circulatory system development in human. The most common are heart septa defects that result in formation of three chambers or two chamber heart. Among vessels abnormalities, the most important are deviation of aorta formation and big vessel formation that are derivates of gill's arches. The most common is failure of Botalli duct obliteration. Sometimes, there is no reduction of right fourth arterial arch. It results in formation of two aortal arches and so called "arterial circle". It becomes narrower with age and requires surgery. In normal human embryogenesis, there is only one trunk leaving ventricles, which further is divided into aorta and pulmonary artery. In 2.1% of cases such division hasn't been performed. It results in body's supply by mixed blood. The transposition of aorta and pulmonary artery can occur if that septa have been place improperly. In this case aorta leave right ventricle, whereas pulmonary artery – right. One of most severe heart defects of human is Fallo triad (pulmonary artery stenosis, defect in interventricular septa, hypertrophy of right ventricle). It also can be accompanied by aorta dextraposition, and called Fallo tetrad. Fallo pentad also includes defect of interauricular septa.

15.7 The excretory system.

The evolution of the excretory system includes changing of nephiidia in lower chordates to kidneys, made of numerous excretory canals, and subsequent changing of different kidney's kinds in vertebrates' embryonic development. These kinds are in the following line: prekidney or pronephros, primary kidney or mesonephros and secondary kidney or metanephros. The typical feature is the close relationships between the excretory system and blood. During phylogenesis, the nephron number increases, they become longer, and convoluted. The line of excretory organs changing, pointed above, reflects evolution of excretory system. Let's discuss the structure of each kidney.

The prekidney or pronephros has the most primitive structure (pic 15.11 a). It is found in all vertebrates in early stages of embryogenesis in the anterior part of the body. It consists of 6-12 funnels (nephrostoms) with excretory canals. The neprostom has villi on its border and opens to body's cavity. The funnels leave by straight excretory canals entering a common duct – ureter of pronephros. It extends along the whole body and enters cloaca. The funnel of nephrostom and excretory canal are a pronephros structural unit, called a nephron. It has no direct connection with circulatory system. Therefore, the waste products come to it through coelomic fluid. In human embryo, it has no functional significance.

The primary kidney or mesonephros is founded after formation of proneph-



Pic 15.11. The nephron evolution:

A – pronephros, B – mesonephros, C – metanephros, D – human kidney; 1 – nephrostom, 2 – excretory canal, 3 – ureter, 4 - glomerulus of vessels, 5 – coelom, 6 – capsule of primary glomerulus, 7 – proximal convolute tubes, 8 – distal convolute tubes, 9 – nephron loop (by I.I. Shmalgasen, 1947 with changes).

ros in body's segments. The nephron of primary kidney also starts with funnel opening to coelom. The excretory canal leaves the funnel entering the ureter. The progressive changing is formation of the Bowman's capsule on dorsal part of excretory canal. The glomerulus of vessels enters this capsule. This glomerulus and Bowman's capsule form Malpigian corpuscle. The direct connection between circulatory and excretory systems appears. At the same time, the excretory canal elongates and is divided into divisions. In the excretory canal the processes of reabsorbing of glucose, water, and other substances occur. The primary urine becomes concentrated. The number of nephrons in primary kidney is significantly higher than in pronephros. The nephron's canals firstly enter the pronephros ureter. Later, this cnal divides into two canals. One of them, save its connection with pronephros (called Muller's canal). The second becomes independent ureter of primary kidney (Wolf's canal). The primary kidney works throughout the life in

amphibians and fishes. In reptilians, birds and mammalians, it exists only in embryonic development.

The secondary kidney or metanephros. In reptilians, birds and mammalians there is a third bud of kidney development. It lies behind the body's kidney and is called secondary kidney (pic 15.11 c,d). The nephron of secondary kidney has no funnel. It looses its connection with coelom. It starts directly from Malpigian corpuscle. The vessels glomerules are bigger than in mesonephros. Each primary nephron of secondary kidney divides into several new nephrons. Therefore, the number of nephrons significantly increases. The secondary kidney is a main excretory organ in reptilians, birds and mammalians. The defects of human excretory system development are aplasia (absence), hypoplasia (underdevelopment) and distopy (mislocalization) of kidney; doubling of kidneys, joining of kidneys; hydroureter (extension and fluid excess in ureter); ureter mouth ectopy (abnormal localization); entering uterus to urethra, aplasia and doubling of urine bladder; diverticulum and cysts of urine bladder; opening of urethra on upper (epispadia) and lower (hypospadia) surface of penis; doubling, stenosis and diverticulum of urethra.

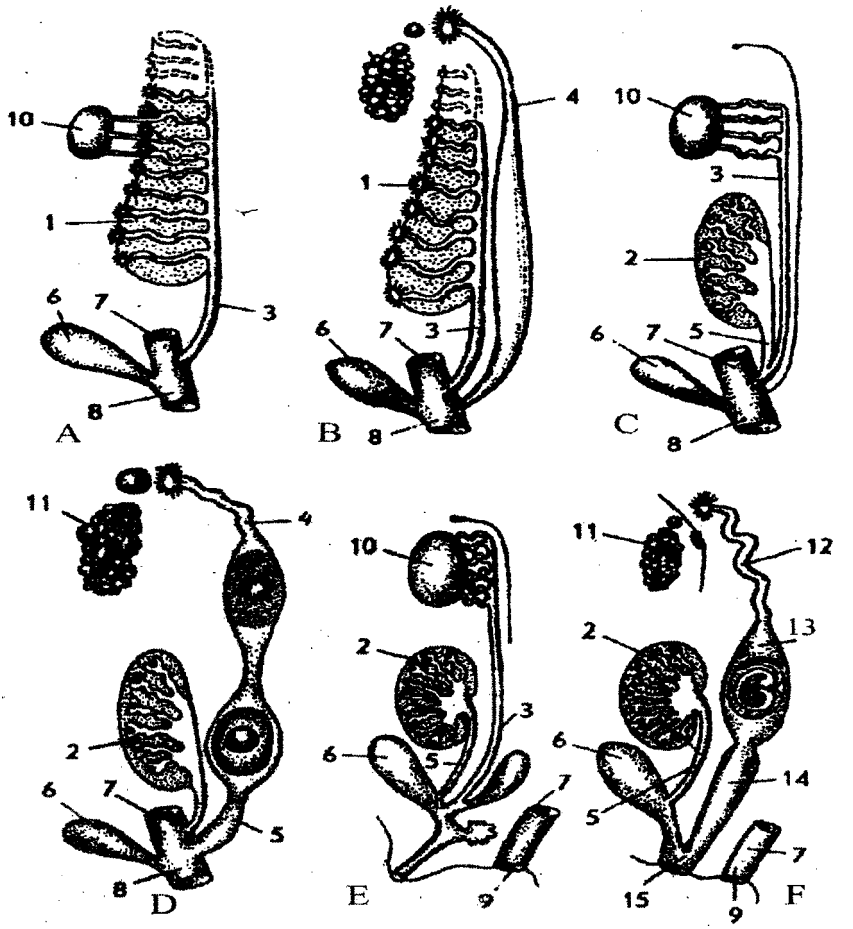
15.8 The reproductive system.

The sexual glands of all vertebrates are founded as paired folds of nephrogonotom of somite. The primary sex cells are separated right after gastrulation. They move to sexual folds. The gonad, which has been formed, is indifferent. It can develop testis and ovarium as well. The indifferentation of vertebrate's gonad is called primary hermaphroditism. The disturbances in gonad differentiation can result in ovotestis. Children, having ovotestis, show the signs of hermaphroditism in external sex organs.

The vertebrates with poicilotermic temperature regulation have reproductive organs inside the body. Whereas, mammalian's testis moves along inguinal canal to scrotum. Scrotum serves as cooler for testis. It is believed that reduced temperature is better for sex cell formation.

The excretory system of vertebrates has close relation with reproductive system. In fishes' and amphibians' females (pic 15.12 b), the pronephros ureter (Muller's canal) changes to oviduct. The dissimilation products are excreted through primary kidney and its ureter (Wolf's canal). The fishes and amphibians males (pic 15.12 a) reduce all system of pronephros with Muller's canal. At the same time, the connection between testis and primary kidney is formed. The epithelial lining of body's walls gives rise to threads connecting primary kidney and testis. The male sex cells are ejected through deferens tubes to kidney and than they comes along ureter to outside.

The females of reptilians and birds (pic 15.12 d,f) develop oviduct from pro-



Pic 15.12 The evolution of urinary and reproductive system of vertebrates:

A male and B – female of some fishes and amphibians, C – male and D – female of reptilians and birds, E – male and F – female of mammalians (1 – mesonephros, 2 – metanephros, 3 - Wolf's canal, 4 - Muller's canal, 5 – ureter, 6 – urine bladder, 7 – posterior part of intestine, 8 – cloaca, 9 – anus, 10 – testis, 11 – ovarium, 12 – oviduct, 13 – uterus, 14 – vagina, 15 – urinary sinus) (by E.I. Lukin, 1989).

nephros ureter (Muller's canal). The males reduce all structures of pronephros (pic 15.12 c,e). Only some canals from anterior part of pronephros are preserved to form epididymis. The Wolf's canal transforms to sperm evacuating canal. It looses function of urine excretion because of formation of secondary kidney.

In reptilian's and bird's oviducts there is differentiation to departments. The anterior part produces protein shell, whereas posterior part produces leather-like

(in reptilians) and impregnated with calcium (in birds) shell.

Mammalians deliver live babies. Therefore, the structure of the oviducts becomes more complicate. The oviducts are divided into three parts: uterine tubes, uterus and vagina. The animals having placenta have a joining of distal oviducts parts. So, as result of this they can face several types of sexual ways organization. The rodents develop double uterus. The predators can develop two-horn uterus. The primates have simple uterus.

The defects of reproduction system development in women are double uterus with one or two vaginas, two-horn and one-horn uterus, athresia of vagina, agenesia and hypoplasia of ovariums, hermaphroditism. The men can develop anarchism (absence of testis), cryptorchism (testis positioning out of scrotum), phymosis (narrowing of foreskin), absence or doubling of prostate and penis, testis ectopy, hydrocoele

THE POPULATION-SPECIES LIVE ORGANIZATION LEVEL.

CHAPTER 16. STRUCTURE OF HUMANKIND POPULATIONS.

16.1 The population, its ecological and genetical characteristics.

All species are presented in the nature by their populations. The population is a real thing, the same as cell, individual and biosphere is.

A population consists of the individuals of given species that occur together at one place and during long time (large number of generations). Population is separated from other populations by one or another kind of isolation. Within a population the particular level of panmixing occurs. Panmixing is ability to mate with any individual in population. If there are some limitations of free mating in population, such population is called non-panmixing.

A population is an elementary evolutionary unit. Species, group of populations have their own evolutionary fate, but they aren't elementary evolutionary units. The population is a whole structure in ecological, genetic and morphophysiological aspect. Individuals, families can't be elementary evolutionary units. Individuals are not subject to evolution. Only groups of individuals are able to do so. And the population is a smallest group which is subject to evolution.

The population has ecological and genetical characteristics as well. The main ecological characteristics are the following: size of population, number of individuals, area of living, age and sex structure, population dynamics. Genetically, population has to be divided equally to same sex groups. But individuals of different sex have different ability to survive. Therefore, the secondary and thirdly sex distribution in population differ from genetical one. In human population, the secondary distribution right after birth is 100 girls on 106 boys. But in the age group 16-18 years, it becomes equal because of higher boy's mortality. In the age group 50 years, the distribution is following: 85 men to 100 women; in 80 years, 50 men to 100 women.

Each individual, having general species characteristics, have its own traits and genetical features. *All genetical information of population (that means full gene set of all individuals) is called population genefond.* Of course, the main principles of inheriting are used to study population genetics, such as Mendel's Laws of herediting, independent assortment of gametes while fertilization and so on. The first to evolve studying of population genetics was V. Yogansen (1903). He described the effect of selection in genotype mixture. At the same time, he showed that the selection doesn't work in clear lines (among offsprings of one self-reproducing individual). The differences between individuals in population may be due to their genotype differences as well as influences of external

environment. The differences between individuals in the line are only due to influences of external environment.

The works of S.S. Chetverikov were in great importance. He was first to design methods of genetic analysis of population and to assume concept about genetical structure of population. He showed that all evolutionary events occur in population, which is rich in mutations.

At the same time in population, there are individuals with dominant and recessive traits. The question appears: why recessive genes are not replaced by dominant genes? For example, if "brown eyes" is dominant trait (A), why the number of individuals with blue eyes (a) doesn't decrease? The solution to the puzzle of why genetic variation persists was developed independently and published almost simultaneously in 1908 by G.H. Hardy, an English mathematician, and G. Weinberg, a German physician. They pointed out that in the large population in which there is random mating and in the absence of the forces that change the proportion of the alleles in the given locus, the original proportion of genotypes will remain constant from generation to generation. Dominant alleles do not in fact replace recessive ones. Because their proportion does not change, the genotypes are said to be in Hardy-Weinberg equilibrium.

In algebraic terms, the Hardy-Weinberg principle is written as an equation. Its form is what is known as binomial expansion. For dominant gene "A", the concentration is pointed by "p", whereas for recessive gene "a", the concentration is pointed by "q". The resulting equation looks like this.

$$p^2 AA + 2\ pqAa + q^2 aa$$

Where p is frequency of one allele and q is frequency of another. Because there are only two alleles, p and q must equal 1. Thus, the Hardy-Weinberg rule states that in a large population mating at the random and in the absence of the forces that would change the proportion of the different alleles in the given locus, the process of sexual reproduction (meiosis and fertilization) alone will not change their proportions.

This rule can work only in appropriate conditions such as:

1. The population should be very large.
2. All individuals have to mate independently and randomly.
3. The homozygous and heterozygous individuals have to have same survival rate, same ability to reproduction, and not subject to selection.
4. The mutations (direct and reverse) have to occur at the same rate.

The allele distribution is based on allele frequency in population. If we know frequency of recessive gene, we can calculate the frequency of dominant gene according the Hardy-Weinberg rule. Conversely, if we know frequency of dominant gene, we can calculate frequency of recessive one, frequency of heterozygotes and so on.

The Hardy-Weinberg rule can be named as law of equality of gene frequencies in panmixing populations. This equality preserves until any factor will change allele frequency. The new breeding, which occurs in population with changed frequencies of alleles, is called stabilizing breeding.

16.2 The features of humankind population structure.

The population structure of humankind is very diverse. It was divided into many particular populations. Therefore, the humankind isn't great panmixing population. It is a mixture of many very different populations. Among then, it can be as open population, where people can mate with representatives of other populations as closed populations, where people can mate only inside of the population. All of them have a very different rate or reproduction. There are dems and isolates.

The dem (from Greel "demos" - people) – is local relatively isolated group of close relatives with random mating. It stable can exist during life of several generations. The particular dems of population can differ one from another by several traits. They have higher level of panmixing in compare with population.

The isolates – are populations or groups of populations, which are isolated from other populations of the same species. They have very limited exchange of individuals. The example is parses. It is a tribe of peoples, who worship to fire. They lived in 12^{th} century in the Baku region. Then, they were forced by Muslims to migrate to India. They still believe in Fire God and allow marriages only between close relatives.

Dems and isolates have very low population income. The rate of marriages between close relatives is around 80-90%. It facilitates expression of rare pathological genes, which have been preserved in heterozygous state. These genes become homozygous and cause hereditary diseases. These races are becoming extinct.

16.3 The influence of elementary evolutional factors on human population.

Many factors can alter allele frequencies. Only four, alter the proportions of homozygotes and heterozygotes enough to produce significant deviations from the proportions predicted by the Hardy-Weinberg principle. These are mutations, isolation, genetic drift, and natural selection. All of them occur and in human populations too.

16.3.1 The mutations.

Mutations are the material for evolutionary selection. In general mutation rate of one gene is about $10^{-4} – 10^{-8}$. The number of genes in one genotype is about

thousands. So, we may conclude than general mutation rate in one individual is significant. Also, it is needed to note the reverse mutation of the gene. The mutations can be evaluated by relative frequency changing of one gene to another gene frequency. The very important factor, which enhances expression of mutated genes, is combinative diversity. It allows spreading of mutated genes throughout the population. The spontaneous mutation process leads to formation of different mutations. The mutational process has no any specific direction that means mutations can occur in any gene and in any form. The evolutional value of mutations is that they maintain high level of heterozygotes in population.

The prevalence of heterozygotes over recessive homozygotes in population is very significant. Most of the pathological mutations are recessive. So, that prevalence preserves their expression. The dominant mutations are expressed better. Therefore, among described mutations, the number of dominant and codominant pathological mutations is higher than recessive. Thus, in 1978 it was counted that human has 1489 autosome-dominant genes, 1117 autosome recesive and 205 sex linked genes.

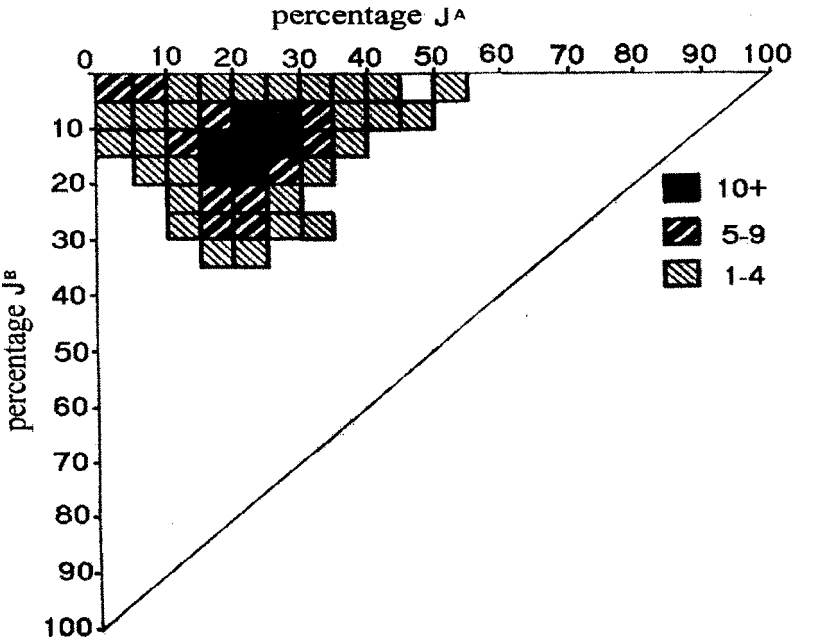
16.3.2 The isolation.

The isolation is appearance of any barriers breaking panmixing. The isolation value is limitation of free mating, which lead to stating differences between populations and separate parts of the species. In human populations the factors increasing inbreeding rate are distance and customs. They encourage people to mate within one village or within one group of villages. If the population level in this population is stable for several generations and the numbers of offsprings are different, it increases the probability of close related marriages with all consequences of it. It is more possible in small villages separated from others by distance and natural barriers (mountains, big rivers and so on). The same effect may be if in the population there is race, caste, religious and professional segregation. The custom to look for a wife among cousins and nieces results in the same effect.

The urbanization of last decades rapidly decreases the rate of close related marriages. It breaks the isolation factors. However, urbanization does not always results in decreasing of inbreeding. Some population groups come to the city together. They preserve close related marriages. Also, the important factor is that birth rate in cities is low. The cities' population is always fulfilled by rural population, which has origin from close related marriages.

16.3.3 The genetic drift.

The Hardy-Weinberg Rule doesn't work in small populations. In the small



Pic.16.1. The blood group allele frequency polymorphism, Ia,Ib,Io (by A.Brues,1954).

populations as times goes by the number of heterozygotes (Aa) decrease, whereas the number of homozygotes (AA, aa) increase. The first to study this event were S. Right and R. Fisher in 1927. This event was called genetic drift. The deep understanding of it was made perhaps N.P.Dubinin and D.D.Romashov in 1932.

It was stated that in the small populations with high inbreeding rate, the level of heterozygotes falls down. The population becomes genetically more similar. That can result in accumulation of defect traits and elimination of individuals with these traits from population without natural selection. The accumulation of lethal genes may results in population extinction.

The genetic drift is a random change in the frequency of alleles in the locus. The genetic drift occurs only in small populations. It can be of two types: as differences between generations of the population, and as differences between two related population at the same time but in different places.

Most of human populations have polymorphism in ABO blood groups that means they contain all three alleles of it (Pic. 16.1). In majority of human populations, the frequency of allele Ia is around 15-30%, allele Ib 5-20%. At the same

time, the frequency of these alleles in the Eskimo population in Alaska and Greenland is 30% and 6% respectively; in a small tribe in Tula (Greenland), the frequency of allele Ia is 9%. In Labrador's isolates, the allele Ib is absent. Thus, among Cherokee Indians the frequency of Ia is 80%, whereas among Indians of Utah State it is 2%.

16.3.4 The natural selection.

As Darwin pointed out, some individuals leave behind more progeny than others, and the rate at which they do so is affected by their inherited characteristics. We describe the result of this process as selection. Darwin argued that the more successful reproduction of particular genotypes, which is how he defined the selection, is the primary force that shapes the pattern of the life on earth. The selection of these genotypes, however, is indirect: selection acts directly on phenotype. The phenotype is determined by the interaction of the genotype and the environment, and the linkage between the particular alleles and the particular characteristics of the phenotype is less direct for some features than for others.

It is believed that the frequencies of particular genes in human population are subject for selection, especially if they live in the environment that has been changed not so far ago. It can be stated by evaluation of reasons of spontaneous aborts and perinatal mortality. Accordinary to N.P.Kuleshov findings (1978), more than 42% of spontaneous aborts are due to chromosome abnormalities. In the first third of pregnancy, this number reaches 70 % in second – 30 %, in third – 4 %. Among babies that were delivered dead the 6% have chromosomal abnormalities. The perinatal mortality in 6.2% of cases is due to chromosome pathology too.

The selection affects the ability to make impact to next generation. It is provided by two ways: selection of individuals, which can't survive until puberty, selection of genetic factors that affect reproduction.

16.4 The genetic polymorphism of human populations.

The polymorphism is the presence in a population of more than one allele of a gene at the frequency greater than that of newly arising mutations. The polymorphism is a universal event in a life. J. Holdein (1892-1964) called the human species as most polymorphic species on Earth. Almost all human traits are polymorphic. Genetic polymorphism arises in population by fixing of mutation in population. It is classified into three groups: genes, chromosomal and genomic.

The genes polymorphism is due to existing of two or more alleles of gene. It like ability to taste phenltiocarbamide is provided by dominant allele (TT, Tt), whereas failure to do so is provided by recessive allele (tt). The blood group ABO is provided by three alleles. The polymorphism in many alleles can be inherited

by human even on prehuman stage of evolution; in particular, Rh-facor polymorphism occurs in Rhesus monkey too.

The chromosomal polymorphism is related with chromosome aberrations. The examples are deletion of short arm of 4th chromosome (Wolf-Hirshhorn syndrome), deletion of short arm of 5th chromosom (syndrome of "cat's scream").

The genomic polymorphism is presented by changing in chromosome set. The examples are Terner syndrome (XO), Kleinfelter syndrome (XXY), Dawn syndrome (21st chromosome trisomy).

The relationships of polymorphism and selection and polymorphism origin gave us following types of polymorphism: transitional, neutral and balanced.

The transitional polymorphism is explained as replacement of one allele by another in one locus. The new allele in new conditions becomes more important and replaces initial one. It isn't stable polymorphism because earlier or later the new gene will completely replace initial allele and population will be monomorphic by new allele. The rate of such processes can not be evaluated during life of one generation.

In neutral polymorphism, the spontaneous changing of gene frequencies occurs. It is due to occasional processes (genetic drift, founder principle and so on). In general, it concerns traits, which have no big adaptive effects. The evolution of these groups is neutral, because genes are changed by genetic drift.

The balanced polymorphism – is polymorphism provided by selection against both homozygotes in favor of heterozygotes. The recessive genotype is eliminated more than dominant one. The differences in elimination rate of those genotypes maintain stable being of both alleles in population with specific rate for each. The most studied systems are system of hemoglobin selection by malaria (selection of abnormal hemoglobins affected by talasemia, with defect of glucose-6-phosphate-dehydrogenase). The stability of these polymorphisms disappears because of success of fight against malaria. Such balanced polymorphism becomes transitional. However, elimination of pathological genes from population requires time.

The big amount of discovered polymorphic systems in human with significant alleles number shows that almost every person have unique gene set. Thus, we can say about biochemical, immunological personal features of individual. It is very important in medicine and especially in forensic investigation.

16.5 The genetic load. Its medical value.

Findings of S.S.Chetvericov, N.V.Timopheev-Resovskiy, N.P.Dubinin and V.G.Dobgansky in 30s years of 20 century showed that lethal mutations can be accumulated in populations in recessive form. They defined it as genetic load. The genetic load is relative decreasing individual's ability to survive in compare with optimal genotype.

Human has same laws of population and mutational genetics as others species have. It is correct for genetic load too. This statement is backed by high frequency of hereditary diseases. Among them there are many, which are provided by recessive gene. In this case, it is possible that healthy parents will have cripple child. It is calculated that there are about 100 hereditary diseases, which affect about 4% of newborns.

The volume of genetic load is calculated by analyzing of close related marriages. The offspring of such marriages express genetic load in form of high prenatal mortality. Thus, in France the number of dead newborn among close relatives is from 26 to 50 in 1000 newborns, whereas the same index for non-relatives is from 19 to 21 in 1000 newborns. The genetic load isn't only mutations that have came to homozygous state, but also as all mutation spectrum that decreases adaptive properties of individuals. There are three types of genetic load in populations: mutational, balanced, and substitutional.

The mutational load arises because of repeated mutations. Its volume is evaluated as mutation rate in all locuses, which give negative changes.

The balanced load arises when selection acts in different directions on homozygotes and heterozygotes (Hbs gene).

The substitutional load arises when environmental conditions have been changed. The allele, which provided adaptation in previous conditions, becomes negative. It is replaced by new adaptive allele. It causes transitional polymorphism and expression of genetic load by initial allele.

The problem of genetic load becomes more and more important. The number of inherited defects increases. The knowledge of genetics and biology is necessary for clinical medicine. These problems are in great importance for anthropology to understand further evolution of human. Today it is very important to study problem of genetic load in close connection with environment pollution and its effect on genetic load.

THE BIOSPHERAL LIFE ORGANIZATION LEVEL.

CHAPTER 17. THE ECOLOGY. THE ANTHROPOECOLOGY.

17.1 The ecology, it aims and value.

Life on Earth cannot exist in a form of separate populations. It exists as community of organisms of different species, where all species related to each other. Ecology studies these relations on a biospheral life organization level. The term "ecology" was suggested by A.Gekkel in 1866. However, as independent science, ecology was founded at the beginning of 20th century.

Ecology – is a science, which studies a close network of relationships between organisms' communities and environment, a structure, dynamics and historical development of communities – ecosystems, biogeocenoses and biosphere. Ecology is a system of biological disciplines, which study life on higher organization levels. That means that ecology studies relationships of populations and species within species and relationships of them with environment. Ecology studies the influence of communities on their environment too. Ecology has to regulate using of natural resources, to forecast weather changes, to prevent biosphere damage by human, to safe human environment. The subject of ecological study is: physiology and behavior of individuals in natural environment, birth rate, mortality, migration, relationships within species, interspecies relationships, and energy and substance cycles.

17.2 The biological systems studing by ecology.

The closest relations occur between individuals, which inhabit the particular region of environment with similar conditions. Such regions were called biotopes (from Greek "bios" – life, "topos" - place). The community of organisms that inhabit biotope for a long time is called biocenosis. Biocenosis can include thousand species, but majority of them play a minor role in it. Several main species regulate life in it. In land biocenosis, the regulating factor is plants. Concerning close relationships of biocenosis with abiotic environment, A.Tensley suggested the term "ecosystem" in 1935.

Ecosystem – is complex association of plants, animals, fungi, and microorganisms that interact with their nonliving environment in such a way as to regulate a flow of energy through them and the cycling of nutrients within them. Ecosystems have no limited volume. It can exist in the water drop and ocean as well. To make ecosystem description more comfortable it is divided into following elements.

1. Inorganic substances, incorporated into exchange;

2. Organic substances (proteins, fats, carbohydrates and so on), which connect biotic and abiotic parts;
3. Climate (temperature and other physical factors);
4. Producents – autotrophic organisms, mainly green plants, which is able to create food from inorganic substances;
5. Macroconsuments – heterotrophic organisms, mainly animals, which eat other organisms or organic substances;
6. Microconsuments – heterotrophic organisms, mainly fungi and bacteria, which destroy and degrade dead organisms, adsorb some products of degradation and release inorganic and organic substances for further usage by producents. Producents, macro- and microconsuments are biomass of ecosystem.

The geographic localization of main world ecosystems correlates with climate and land zone. Ecosystem is recognized by main plant community that inhabits it. The most expressive picture of ecosystem can be observed on a plane flight from one pole to another. The main world ecosystems are tundra, taiga, temperate deciduous forest, tropical forest, grassland, desert, mountains, oceans and so on. It is important to note that pathogenic organism, transmitter, and recipients are the parts of particular ecosystem, such as taiga, grassland and so on. All these parts and relations are presented in centers of transmissional diseases. They have been appeared during evolution without any human influence.

Biocenosis and biotope taken together make biogeocenosis. Biogeocenosis is limited in territory, internally similar system of functionally related organisms and nonliving environment, which has particular energy state, type and rate of substance and information exchange (V.Sukachev 1940). The main part of biogeocenosis is biocenosis. Biocenoses differ from each other by species' composition. The main property of them is interaction of populations. The ecological influence of one population extends throughout the biocenosis in all directions, but the more chains have been passed, the less intensive influence is. The indexes of structure and functioning of biocenosis are species composition, number of trophic levels, primary production, and intension of substance and energy flow.

The most stable is biogeocenoses, which have high species variety, existence of non-spetializated species, slight separation from neighboring systems and big biomass.

The biggest ecosystem is biosphere. It includes all life creatures of Earth, which interact with physical environment of Earth. This system takes energy of the sun and maintains stable equilibrium. The term "biosphere" was suggested by Austrian geologist E. Zuss (1875) considering one Earth layer.

Further development of concept about biosphere is connected with name of Russian scientists V.I.Vernadsky. He used this term firstly in 1911. He suggested that biosphere contains four main components: living substance – all living

organisms; biogenic substance – all substance which is made by living organisms (atmospheric gases, bituminous coal, lime and so on); stagnant substance – is made without organisms (volcano, meteors); biostagnant substance – is result of collaboration of organisms and abiogenic processes (wind, water and so on). The terms "living substance" and "stagnant substance" which were used by him are not very successful. They are reflection of initial author's view on processes of life development and evolution. Now following terms are in use: community of organisms, living shell of earth, life film, and Earth biomass. In spite of "stagnant substance" the following terms are used: mineral elements, inorganic substance, abiogenic substance. The higher border of biosphere is about 15-20 kilometers over land surface. The lower border is limited by organic sedimentations on the oceans bottom (more than 10 kilometers of depth).

Today biosphere is considered as a region where the life exists on the Earth. It includes all organisms and their rests, parts of lithosphere, hydrosphere, and atmosphere, which have been changed by living organism and which are the place of their living now.

17.3 The anthropoecology.

The rapid industrialization of modern society brought two new terms to ecology: "human ecology" and "ecology of society". *Human ecology is defined as a science that studies principles of environment and society interactions and methods of conservancy.*

The subject of human ecology is studying of principles of environment and society interactions, principles of population growth, health care, and improvement of physical and psychical abilities of Homo sapiens. It gives possibilities to study general, fundamental principles of preserving health in all human populations, concerning all climates, geographical, social and industrial conditions. Human ecology studies the principles of existing and development of anthropoecologycal systems, which are communities of people having dynamic exchange with environment to satisfy the requirements.

The communities of people differ from each other by social structure and industry development. In anthropoecological system, the relationships between humans and nature can be of two types. At first, there are changes in biological and social indexes of an individual and a whole society, directed to adopt the natural conditions. From the other side, there are changes in a nature to satisfy human requirements. The general result of interactions in anthropoecological systems is individual and group adoption of humans to live in different environments, with different natural, industrial and cultural conditions. Human receives a full adoption, including physical, emotional, ecological, and industrial.

Since ancient ages, humans change their environment. They facilitated for-

mation of new ecosystems, such as agrocenoses and city's ecosystem.

Agrocenosis (from Greek "agros" - field) is a community of organisms that inhabit agricultural territories. In natural biocenoses, the plants component is created historically, whereas in agrocenoses the plant component is created by human. Usually, it is presented by one agricultural species of plants with satellite weed. Human suppresses other species, which can grow on this territory, to provide better conditions for selected one. There is no natural succession. The species change occurs only by human will.

The intensive agriculture results in changing of natural biocenoses to agrocenoses, which become more important in regulation gases balance in atmosphere.

The city as ecological system differs from other ecological systems by following features:

1. It has more intensive metabolism on a square unit because of using energy of fuel and electricity.
2. The substances (metals, plastics and so on) are exchanged mostly between outside and inside, lesser than within the system.
3. It has higher outcome of waste products. Many of them cannot be recycled at all and they are more toxic than their natural precursors.

City cannot survive without fuel and electricity supply. The land under the cities now is about 5% of total Earth territory. However, the influence of cities on a surrounding environment is significant. City is not only consumer of oxygen and water; it is also big producer of pollution. City does not produce food by itself, it does not recycle the water and inorganic materials, and it does not enrich air by oxygen. So, it can't be considered as ecosystem. To consider a city as biocenosis, we have to include all environments that provide city's life.

The city's conditions are specific. Here it is easier to find a job, to get a health care, to provide food supply. But at the same time, here, in the cities, the consequences of nature changing are most expressive. Air pollution results in smog, fog and acid precipitation. In the summer period the temperature rapidly rise up, which lead to increasing mortality form cardiovascular diseases. There is negative impact on human health from overpopulation of cities, land pollution, water pollution. Cities have a low birth rate. Population income results from migration of rural population.

17.3.1 The ecological diversity and human adaptive types.

People live in very different natural conditions. And people by themselves differ from each other in different aspects (like bodies' proportions, biochemical and physiological parameters). So, we can say that there is biological diversity of human. The division of human population to Caucasians, Negroid, Asians and so

on shows their particular features. However, it does it not perfectly with many mistakes. The list of race characteristics obscures the fact that all races have their own diversity. The limits of diversity of such traits as growth, weight, skin pigmentation very often overlap each other in different populations. The term "race" is very often in use for description cultural, but not biological race features (like "Aryan" race). It can result in racist concepts. So, therefore concerning human biological diversity, it is more correct to study diversity of human populations which inhabit different geographic zones.

The human biological diversity concerns different anthropomorphic measurements such as length of arms, body, shoulders width, skull volume and so on. The herediting of such traits depends on many genes. It was proved that individual height differences are due to gene action. But it is very difficult to explain these correlations for human populations.

Thus, many findings show that average human height in industrialized countries has been significantly enlarged since beginning of 20th century. But this enlargement is mostly related with better environmental conditions (food supply) than with ethnic segregation and differentiated migration.

Humans have very diverse fingerprints pictures (look at chapter 10.1.5). In different population there are different tendency of fingerprint pictures. For example, Bushmen have prevalently arches with small expression of picture, whereas Chinese and Native Americans have prevalently helixes with high expression of picture. It was noted that Europeans and Africans have prevalently loops. The fingerprints pictures are under genetic control, but there isn't still good scheme which explain its herediting.

Human populations have high biochemical diversity. It is strictly follow genetic laws. It concerns different abnormal hemoglobins, glucose-6-phosphatedehydrogenase and other enzymes, herediting of ABO and Rh-factor blood groups. (Look at chapters 10.1.6, 10.1.7 and 17.4).

Living in different geographic zones results in ecological diversity of different human populations. Such diversity is presented not only physiological adaptations but also in features of body's constitution. It proves that adaptive human types have a long history of formation.

Adaptive type – is norm of biological reaction of human on environment conditions. It provides good balance between them and it is expressed in a form of morphophysiological features of population. It includes complex of biological, immune, biochemical features providing better adaptation to particular environment. They don't depend on race or ethnic origin of population. There are following human adaptive types: arctic, tropical, temperate climate zone inhabitants, mountaineer, peoples of deserts and others.

The arctic type was formed in cold arctic climate with prevalence of animal food. The people of this type have increased self-warming, strong muscles and

skeleton, big chest, high hemoglobin level, high cholesterol and protein level in blood, high concentration of minerals in bone matrix, increased ability to oxidize fats. They have lower arterial pressure in compare with inhabitants of temperate climate.

The tropical type was formed in warm and wet climate with lack of animal proteins in the food. The people of this type have long body, smaller muscles with long limb bones. The chest volume is less than in arctic type. The have more intensive sweating, higher metabolism, higher fat synthesis, low cholesterol concentration, increased arterial pressure. The ATP concentration is relatively lower. In this type, there are tallest and shortest tribes.

The adaptive type of temperate climate inhabitants. It stays on intermediate position between arctic and tropical types. It is hard to determine ecological factors, which facilitated formation of it because of most part of the population live in cities.

The mountaineers. It was formed under hypoxic conditions. They have high metabolism, relative elongation of skeletal bones, enlargement of chest, increasing of oxygen-binding capacity of blood because of increased erythrocyte number. The arterial pressure is lower.

The desert inhabitants. They have low metabolism, high hemoglobin level, which is resulted from dehydratation and water lost in desert conditions. They have low level of skeleton mineralization.

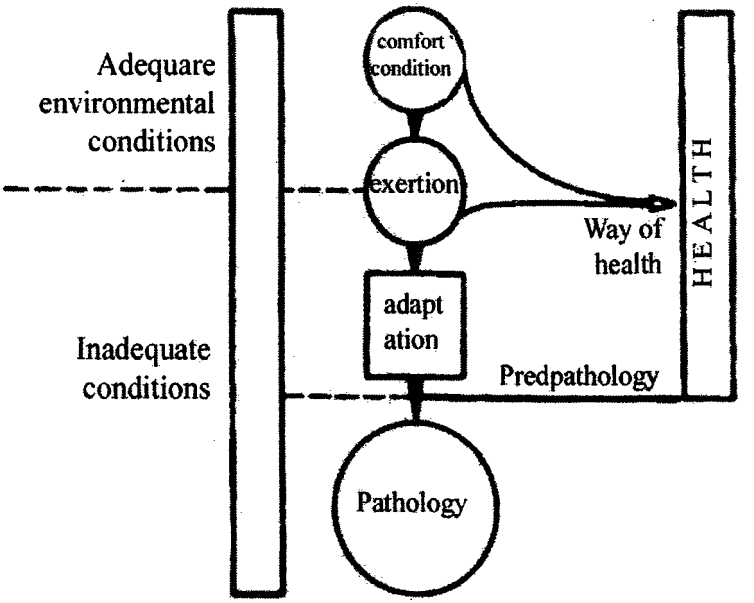
The existence of adaptive types shows significant ecological diversity of mankind. Therefore, human was able to settle many geographic regions of the Earth.

17.3.2 The biological and social aspects of adaptation to environmental conditions.

Adaptation is a fundamental property of life matter. Therefore, the term "health norm" is defined as "optimal state of life system with maximal adaptation". The mechanisms of adaptation to various environmental conditions are result of long evolution. The adequate external conditions are those that coincide with phenotypical properties of organism at the particular moment of it being. The inadequate conditions are those that don't coincide with phenotypical properties of

Table 17.1 **The ratio between bodies mass (kg) and volume (m^2) among different population (by J. Wayner, 1979).**

French	38
Albanians	37
Arabs	36
Somalia	35
Mexicans	35
Citizens of Andaman Islands	32



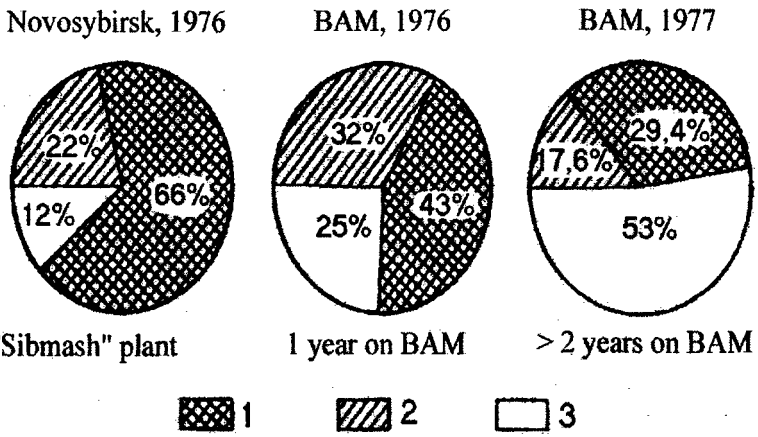
Pic.17.1. The possible states of biosystem (by V.P.Kaznacheev,1980).

organism as a biosystem. Living in inadequate conditions requires additional adaptational efforts. Evaluating the organism state in different external conditions, we can found several organisms conditions: physiological, stress condition, adaptation and pathological (pic 17.1). The phenomena of adaptation can be referred to separate category of events. It is result of evolutionary and historical development.

In every environment, where humans live, there is particular climate. Effective adaptation to climate is necessary to perform comfort condition, to do the job

Table 17.2 **The biological parameters of adaptation of Europeans and Asians who are in the same arid climate conditions (by J. Wayner, 1979).**

Parameter	Asians	Europeans
Mass (kg)	55	80
Square of body's surface, (m^2)	1.6	2.0
Energy expenditure for 1 kg.	4	4
Releasing warm, kDj/m^2 *h	137	160
Evaporating warm, kDj/m^2 *h	165	195
Sweat quantity, g/h	440	650



Pic.17.2. The population structure of BAM's builders:
1 – "mixt" 2 – "sprinter", 3 – "stayer' (by V.P.Kaznacheev,1980).

well, which requires extremely concentration or physical efforts, for normal growth and development. One of the important features of climate adaptation is adaptation to temperature shifts. The immediate physiological reaction on overheating is increasing heat lost by organism. It is performed by circulatory system and by perspiration. Although, the total number of sweat glands differs from on man to another, there is no significant difference in this trait when whole races were compared.

It is important to compare different body types from the climate adaptation point of view. In the line from temperate climate to arid climate, the ratio between bodies mass and volume decreases (Table 17.1).

In the table 17.2 there are some parameters of adaptation of Europeans and Asians who are in the same arid climate conditions.

It is clear from table 17.2 that sweating rate in native Asians less than in adopted Europeans. It is due to lower mass and lower square of body's surface. They have equal energy expenditure during one hour (4 calories), but the releasing and evaporating warm is different in these groups, in particular, Asians loose less energy than Europeans.

The modern humankind generally escapes natural selection. However, it is become clear that human as a species, have been insufficiently adopted to long negative environment influences. Such long negative environment influences are common in our modern life. It is possible that this is one of the reasons of chronic diseases of modern man. Another reason is closely related with biological rhythms. During illness, a man modulates his biological rhythms by special feeding, treat-

ment pattern and so on. It results in desynchronisation and development of chronic disease.

Now, the social mechanisms of adaptation are in great importance. Organizing his own activity, a man can direct processes of biological and physiological adaptation. It can be used in Health Care System. Adaptations show the different levels of ecological relationships between humans. We can note individual level, population level and global level of relations within species.

17.3.3 The health as a category of anthropoecology.

All aspects of human adaptation are directed to save individual health, as well as, health of whole population.

The definition of health was firstly given by WHO (World Health Organization, Geneve, 1968): "The health is a condition of full physical, spiritual and social well-being, and not only absence of diseases of physical defects".

The more detailed definition was given by academic B.D. Petrakov (1971): "The health is a condition of social, biogenetic, psycophysiological and physical well-being, when all organism systems work together to balance with social and natural environment; there are no diseases, physical defects and any pathological conditions".

Academic V.P. Kaznacheev (1980) gave both definitions for "individual health" and for "population health", where he pointed out all social, psycophysiological, biogenetic criteria and concerned about life span of individual and transmitting of information between generations.

Individual health can be defined as a process of preserving and development of psychological, biological and physical functions, with optimal ability to work, with optimal social activity and maximal life span.

Population health is a process of social and historical development of psycophysiological and biological activity of population, transmitting of information between generations, improvement environment condition and enlargement of living territory.

The individual life, as well as and population life is a process of adaptation formation. The health isn't only absence of diseases of physical defects, but also physical, spiritual and social harmony of man. It includes good, kind relationships with people, nature and with himself. Trying to treat diseases, modern medicine has not succeeded in giving health. Treated man always has consequences of disease and treatment. Anthropoecology suggests saving health of healthy men. Medicine does not pay enough attention to that. To solve these questions, it was suggested a new science "valeology" by I.P. Brechman in 1980. It studies basements of saving human health. The main factors of health are rational life style, rational diet, liquidation of harmful habits, active movement.

CHAPTER 18. THE ECOLOGICAL BASIS OF PARASITISM.

18.1 Parasitism as a form of ecological relationships in nature.

Organisms live on Earth with close relations with each other. To maintain their lives they need food. It can be either species of animals or plants. Organisms have to defend themselves from predators and have organs to fight with rivals. The following relationships have been formed during evolution: food chains, competition, antibiosis, symbiosis.

Food chains - are relationships connected with feeding, energy transmitting from the general source (sun energy) through line of organisms, to the organisms of higher levels. Energy lost from level to level is around 80-90%. Therefore, such chains do not exceed 4-5 steps. In these relationships, organisms of higher level eat organisms of lower one.

Competition - is a form of relationships between organisms of one or different species which live in the same environmental conditions. For example, plants compete with one another for light, mineral substances, land. Plants with bigger crowns get more light than others, thus they grow better, suppressing others. If a plant has better roots, it can survive better than others during drought. The competitive relationships can occur in plants and animal species, which live in the same conditions.

Antibiosis - it is a relationship where an organism suppresses life activity of others by releasing special substances - antibiotics. I.I. Mechnicov stated that such relationships exist between putrefactive and lactate bacteria in intestine. Pennicillum fungi produce special substance - penicillin, which suppress growth of bacteria. Phitocydes - antibiotics of plant - were discivered by B.P. Tokin in 1928. There are several plants producing phitoncydes: onion, garlic, pine, cedar and others. In the pine and cedar forests, there are almost no bacteria in the air.

Symbiosis relationships - are those in which two or more kinds of organisms live together in often elaborate relation. There are three kinds of symbiosis: mutualism, commensalism, and parasitism.

Mutualism is kind of symbiosis which is useful for both organisms. The examples of such relationships can be lichen (fungi and algae), and hermit-crab and actinia.

Commensalism – is a kind of symbiosis where one organism receives benefit

but the second doesn't receive benefit or harm. It can be when one organism uses another as place for living without any harm for them. The barnacles can settle on a whale's back. It gives them opportunity to move with him and to have access to fresh sources of plankton on which they feed. They do not in anyway harm to whale.

Parasitism - is kind of symbiosis when one organism (parasite) uses another (host) as a source of food and place for living. It is harmful for host, but in most cases, it is not lethal. There are many forms of parasitism. There are facultative and obligatory; temporal and permanent; truth and false, ectoparassitism and endoparasitism. Parasitism is very wide spread in nature. It is exist in all types of animals. It is especially abundant in Protozoa, flat worms, nematodes, and arthropods. According to V.A. Dogel's findings, there are more than 60-65000 parasitic species. Such wide distribution of parasitism allows speculation that it appeared in many animal groups independently during evolution.

Parasitism is studied by parasitology. Parasitology is a division of biology that studies parasites, their biology and ecology, their relationships with host and environment, diseases caused by them, and methods of treatment of parasitological diseases. Parasitology as a science concerns many questions of general biology. It also studies the formation of morphological and functional adjustments of parasites to their life and origin of these adjustments. Parasitology is very important in studying human, animal, and plant diseases that are caused by parasites. Accordingly, there is medical parasitology, veterinary parasitology, and phytoparasitology.

Medical parasitology studies the biology and ecology of human parasites, diseases caused by them, methods of diagnostics, treatment, and prevention of these diseases. It includes medical protozoology, helmintology and arachnoenthomology. Medical protozoology studies pathogenic protozoa, which cause human diseases. Medical helmintology studies flat worms and nematodes, which cause human diseases. Medical arachnoenthomology studies arthropods as transmitting agents, natural reservoir and causative organisms. Medical parasitology is used to solve following problems:

- Studying of morphology, biology, ecology, and the systematics of human parasites.
- Discovering the ways how parasites act on the human organism (and overwise) to understand mechanisms of diseases caused by them.
- Suggesting new ways of treatment and preventing of diseases caused by parasites.

To solve these problems, the methods of many other biological disciplines such as anatomy, zoology, cytology, histology, genetics, physiology, ecology, pathology, and hygiene are used.

18.2 The characteristics of parasites.

Parasites are such organisms, which use other organisms as sources of food and environment, giving off completely or partially the function of relationships with environment to their hosts (V.A. Dogel 1947). All parasites are divided into two big subdivisions: ectoparasites and endoparasites. Ectoparasites are animals that live on surface of the body. Mainly they are arthropods. Ectoparaistes can be permanent (having all life cycle on a body), like louses, and temporal (which are on surface only during feeding), like mosquitoes. Endoparasites, accordinary their localization can be classified to intercellular parasites (which live inside of a cell), like plasmodium malariae; tissue parasites (which live in tissues), like Enthamoeba histolytica, trypanosomes, fillaria and so on; organs parasites (which affect various organs), like Opistorhus fellineus, and others; and cavity's parasites (which settle different bodies cavities such as pleural cavity, abdominal cavity an so on), like Taenia soleum, Ascaris lumbricoideus, Enterobius vermicularis and others. All endoparisites are permanent parasites.

Each parasite should have at least one host. Parasites having only one host are called monoxenic or monohost parasites. For example, Hymenolepis nana and Enterobius vermicularis live only in human. The majority of monoxenic helminthes need the fertilized ova to be evacuated to external environment. The parasites that need two or more host during their life cycle called heteroxenic or multihost parasites (Plasmodium, Taenia soleum and others).

K.I. Skriabin and R.S. Schults (1931) suggested epidemiologic classification of endoparisites. All helminthes are divided into geohelminthes, biohelminthes and contact helminthes. Geohelminthes are worm in which development of invasive larva occurs in a soil. Human invasion occur through unwashed vegetables, fruits (Ascaris lumbricoideus, Trichocephlus trichiurus) or through the skin while close contact with soil (Necator americanus, Ancylostoma duodenale). Biohelminthes are parasites obligatory having several host to complete their life cycle (all Trematodes, Cestoides, Fillaria and so on). Contact hemlines are parasites that can have their full life cycle in one organism, without leaving an organism (Hymenolepis nana, Enterobius vermicularis).

18.3 Parasites host.

The parasite host - is an organism, in which parasites permanently or temporally live and reproduce by a sexual or asexual way. The host changes occur

because of different life stages in the parasite. Larval stages are developed in one organism, whereas mature parasites live in another. There is one more reason to change a host. It is the way of changing generations which are reproduced by a sexual or asexual way.

The host where the parasite becomes mature and performs sexual reproduction is called the definite host. Thus, the human organism is definite host for many cestodes and trematodes.

The host where parasite's larvae live and can perform asexual reproduction is called an intermediate host. The human is an intermediate host for plasmodiums, and Echinococcus granulosus.

For some parasites, it is necessary to have two intermediate hosts to complete their life cycle. Second intermediate host called additional host. Thus, Opisthorhis felineus have two intermediate hosts: one is mollusk Bithynia leachi, additional - some fishes.

The hosts where parasites have optimal life and reproduction are called obligate hosts. Thus, the human is an obligate host for Ascaris lumbricoideus, Ancylostoma duodenale, and others.

The host where parasite can live, but it is not fully adapted is called the facultative host. For example, a human can be an obligate host for Diphyllobothrium latum. However, this cestod can live in fox, but in this case, it has lesser size and lives no longer than two month. So, fox is facultative host for Diphyllobothrium latum.

Organisms where parasites reserve for a time without developing are called reservoir host. Reservoir hosts accumulate parasite and facilitate the spread to others. For example, a pike can eat additional host of Diphyllobothrium latum. Thus, it accumulates larva of Diphyllobothrium latum in its tissues, preserving them for definitive host.

18.4 The ways of parasite invasion into human body.

There are different ways for parasites to enter the human body: through mouth, skin, blood, placenta, and so on.

The oral way of invasion is the most common. By eating fruits and vegetables a human can swallow larva of helminthes and cysts of protozoa. In some cases, it can be accompanied by interintestinal and transplacental ways.

Interintestinal ways of invasion takes place when all stages of helminth development occur in the intestine without leaving the organism. This way is typical for Hymenolepis nana and Strongyloides stercoralis.

Transplacental way means that invasional stages of parasite development can enter the developing embryo through placenta from his mother. It is very common during Toxoplasma invasion. It can result in development of inherited

toxoplasmosis. It was describe that this way can occur during malaria, visceral leishmaniasis, ancylostomosis.

Transdermal way - is invasion of parasite through undamaged skin. It is typical for shystosomes, fillaria-shaped larva of ancylostoma and others.

The contact way is transmittion of parasites directly from affected man to healthy one or through medical instruments, linen and others, which were in use by affected individual. This way is typical for Trichmonas vaginalis, louses.

The transmittional way of invasion is performed by sanguivorous insects. There are two variants of this way: *inoculation and contamination*. During *inoculation*, parasite is actively entered the blood of human or animal. It is due to active destruction of integuments by transmitter. During *contamination*, a parasite is placed on the undamaged skin. But human can rub it in because of itching. Both contamination and inoculation can be specific and mechanical. In *specific inoculation*, parasites actively reproduce themselves in transmitter and then they are entered into the host. It occurs during malaria, leishmaniasis and so on. *Mechanical inoculation* can also be called occasional. The parasite stays in the oral cavity without reproducing. It waits for the appropriate moment to enter a host. When a transmitter bites someone, parasites go to the tissues of the bitten animal. Thus, biting flies transmit exciter of anthrax. Specific contamination occurs in those cases when the parasite is reproduced in the intestine of transmitter. Then, it is ejected with feces to the skin, where it is rubbed in by human. It is typical for Provachek' rickettsia and for plague while louse biting. During mechanical contamination, houseflies can transmit cysts of protozoa and helminthes ova on the food staffs.

There is also a transovarial way of invasion. It is very important in nature to preserve parasites in the generation line. Thus, the female can transmit parasites to her offspring through sex cells. Such a way of transmittion is typical for exciter of taiga's encephalitis. Ixodes can preserve this parasite during 12 generations. Argasides can preserve exciter of relapsing fever for three generation.

18.5 The relationships in the system "parasite-host". Parasitocenosis.

The parasite and its host make a system of interrelated individuals "parasite-host". Such systems live in particular environment conditions. Parasites affect hosts by causing disease. This ability of parasite to make harm for the host is called pathogeny. The host organism is an external environment for parasite. Some harmful external effects such as overheating, overcooling, fasting, fatigue, and adding some social factors in human, can result in stirring up activity of parasites. For example, commensial forms of amoeba can be changed to pathogenic one in those conditions. The final result of "host-parasite" relationships depend on particular conditions, specific species features and individual features of this couple.

It is possible for several parasite species to settle one host. Their relationships can make pathogenic effect worse or, opposite, make it less severe.

The community of parasites living in the host organism in particular organs called parasitocenosis. Such term was suggested by E.N. Pavlovsky. It stated the relationships between protozoa, helminthes, and bacteria, which inhabit human intestine. It is important for a doctor because knowledge of these relationships can increase effect of treatment.

18.6 Diseases caused by parasites, their classification.

Medical parasitology studies diseases caused by animal exciters. The diseases caused by pathogenic protozoa, helminthes and arthropods are called invasions. In comparison, diseases caused by bacteria are called infections.

A person invaded by parasites can be a source of contamination of the parasite to others and to himself. Invasion of self is called autoinvasion. The example of autoinvasion is Enterobius vermicularis. Individuals can bring larva of his worm back to mouth if child rub itching places in perianal area. Repeated invasion by parasites of the person who already suffered from this parasite are called reinvasion. The source of invasion is carriers of parasites - ill animals and human. For example, a person who suffers from trichocephalosis, diphyllobothriosis, ascaridosis, or other helminthosises can give up helminthes ova with their feces. Individuals who have suffered from amoebiasis, liambliosis can spray out cysts of amoeba and lamblia with feces, thus facilitating invasion of others.

An international nomenclature of invasion exciters has been created. The name of the diseases consist of the zoological name of exciter plus suffix "asis" or "osis", like amoeba - amoebiasis, leishmania - leishmaniasis.

Diseases that are transmitted by sanguivorous insects are called transmissive diseases. Among them are invasional (malaria, leishmaniasis, trypanosomosis) and infectional (spotted fever, relapsing fever, plague) diseases as well. There are obligate-transmissive and facultative-transmissive diseases. Obligate-transmissive diseases have to be transmitted by sanguivorous insects, like malaria exciters and leishmania exciters are transmitted by mosquitoes. Facultative-transmissive diseases can be transmitted also by other ways (orally, in contact). Thus, plague exciter can be transmitted through louse bite, and also through air while contact with ill person.

According to "parasite-host" relationships all invasions are divided into two groups: zoonoses and anthroponoses. Zoonoses are diseases, which can occur in animal and the human body as well (leishmaniasis, trypanosomosis, plague etc.). Anthroponoses are diseases, which can occur, only in human body (malaria, amebiasis, ascaridosis etc.).

18.7 The concept about natural regions of parasite diseases.

There is a special group of parasite diseases that have natural geographic regions, where it is preserved for centuries. It is a group of infectional or invasional diseases, which can exist in one region for a long time without any human influence. This concept was suggested by E.N. Pavlovsky on example skin leishmaniasis and encephalitis. He gave the following definition of this event: "it is event, when exciter, transmitter and reservoir-animals exist in natural conditions for many generations without any human influence in preexisting evolution and nowadays".

The natural region of parasite disease - is a territory with particular ecosystem, which include, at first, organisms - exciters of disease, at second, organisms - hosts of parasites, at third, organisms - transmitters, carrying out disease from ill individual to healthy one.

The exciters of such diseases can be pathogenic viruses, bacteria, protozoa, or helminthes. The natural reservoir of exciter is organism in which exciter can be preserved for a long time and be transmitted directly or indirectly (with help of transmitter) to healthy organism.

The transmitters of such diseases can be ticks, mosquitoes, flies, louses, and others providing exciter circulation in the region. There are specific (obligatory) and facultative transmitters. In the organism of specific transmitter, the parasite can perform some stages of development and give up offspring. The transmitter becomes able to transmit invasion very soon. For example, mosquitoes are specific transmitters for leishmania, whereas malaria mosquitoes are specific transmitter for malaria.

In the organism of facultative transmitter organism can not reproduce. So, it is very often that the transmitter hasn't a sufficient amount of parasite to infect the host. For example, specific transmitter for spring-summer encephalitis is Ixodes persulcatus, but it also can be transmitted by another tick Boophylus calcaratus, which is facultative transmitter for it.

Such regions of diseases can be in wild nature and in area of human living (synanthropic regions). The formation of synanthropic (from Greek "syn" - together, and "anthropos" - human) regions is provided by some agricultural animals. They can be reservoirs of parasites and they live together with human. Among them are sheep, dogs, mousse, goats and others. The following protozoa diseases were considered as having natural regions: leishmaniasis, toxoplasmosis, trypanosomosis. There are also helminth diseases which havenatural regions. Among them are opistorchosis, diphyllobothriosis, aleolococcosis, filliariosis and othes. Many virus and bacterial diseases also have natural regions.

This concept, suggested by E.N. Pavlovsky, allows designing of new methods of preventing parasite diseases. It is generally recognized worldwide.

CHAPTER 19. MEDICAL PROTOZOOLOGY.

19.1 Protists, their characteristics and classification.

Medical protozoology studies biology and ecology of representatives of kingdom Monocytozoa, which are exciters of human and animal diseases. In addition, it studies epidemiology, pathogenesis, clinical picture, treatment and preventive measures against such diseases.

Unicellular organisms have very small sizes. Their body is only one cell having all general components of cell: membrane, nucleus and cytoplasm. Cellular membrane consists of three layers. In many cases, under cellular membrane there is thin layer of fibrils. Taken together with cellular membrane it makes pellicle. Fibrils can contract and therefore the cell can change shape and slightly move. Cytoplasm, as usually, is divided into two parts: external one – ectoplasm, which is presented by colloid gel, and internal one – endoplasm, which is presented by colloid sol. All cellular organelles are presented in endoplasm, such as endoplasmic reticulum, mitochondria, Golgi complex. Some species have contractive vacuoles regulating osmotic pressure.

There are special organelles of movement: cilia and flagella. Each flagella (or cilia) consist of fibril's bunches covered by cell membrane. One fibril's bunch stays in the center of this structure forming central axis. Flagella have two fibril's bunches in the central axis, whereas cilia have only one. Unicellular organisms usually have a few flagella (1-4), whereas they can have thousands of cilia.

Majority of Protists has one nucleus, but there are species having many nucleuses. There are one or several nucleoluses in karyotype, or endosoma – structure in the central of the nucleus with the same functions as nucleoluses. During mitosis, unicellular organisms form a spindle of division. Nucleoluses disappear, whereas endosoma preserves during all time of division. Majority of unicellular organisms has no more than six chromosomes.

A cell of Protists, while active working period, is called trophozoite. It can get nutrition by two ways. First, some nutritive substances can diffuse through cell membrane or they can be transported by active membrane transport. Second, cell can use phagocytosis and pinocytosis to catch nutrients. They get energy from oxidation of carbohydrates and store it in a form of ATP.

Some species (amoeba, lamblia and others) can transform itself into resistant form – cyst. It is stable, covered by special shell, form of life cycle. All metabolic processes in cyst go on very slowly. This form is needed to cope with inappropriate external conditions.

Unicellular organisms have both sexual and asexual reproduction. In asexual reproduction, a cell is divided into two daughter cells. The pathogenic Sporozo-

ans have multiply division – schizogonia, sporogonia. Sexual reproduction occurs in Sporozoans (oogamic copulation) and in Ciliates (conjugation).

Several species have alternation of sexual and asexual reproduction phases. It is more common among parasites having several hosts during life cycle. They form special propagative stages. In some cases, propagative stages help to survive in harmful external conditions (like amoeba cysts), in other cases, they are inside of the cell and are transmitted to the host with help of transmitter (like gametocytes of plasmodiums).

Cysts, oocysts, sporozoites of unicellular organisms are invasional for human. Only trophozoites make pathogenic effect on human metabolism. In some cases, invasional and pathogenic phase can be the same (trophozoites). This occurs in trichomonas vaginalis.

International committee of Protists systematics suggested (in 1980) to subdivide Monocytozoa kingdom into 7 phyla: Sarcomastigophora, Labyrinthula, Apicomplexa, Microsporidia, Acestosporozoa, Microsporidia, Ciliata. Human parasites are in the three phyla: Sarcomastigophora (classes Sarcodina and Zoomastigota), Apicomplexa (class Sporozoa) and Ciliata (class Ciliata).

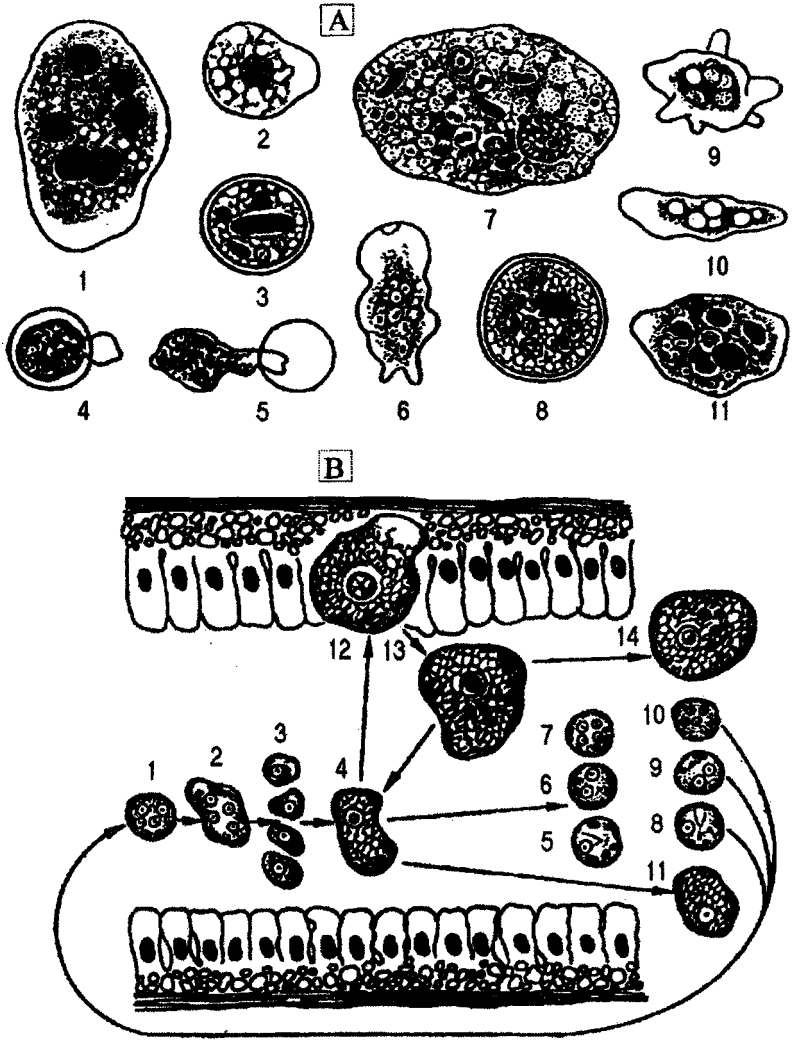
19.2 Pathogenic organisms from Sarcodina class.

Class Sarcodina is simplest class of unicellular organisms. Body is presented by cell. They usually have one nucleus, but some forms have many nucleuses. Movement and phagocytosis are performed with help of pseudopods. The pseudopods are flowing projections of cytoplasm that extend and pull the amoeba forward or engulf food particles. The have only asexual reproduction (mitosis). In harmful conditions, they form cysts. The Sarcodina comprise about 10000 species. Entamoeba hystolytica, limax amoebas are pathogenic for human. Entamoeba coli and Entamoeba gingivales may live as saprophytes in the human body without any harmful influence.

Entamoeba hystolytica – is the cause of amoebic dysentery. It was discovered by Russian doctor R.A. Lesh in 1875, in the faeces of patient suffered from blood dysentery.

In the life cycle, there are two stages – vegetative (trophozoit) and rest stage (cyst). Accordinary external condition, they can transform one to another. The trophozoite can exist in four forms: tissue form (to 40 mcm in size), big vegetative form (forma magna), intestinal lumen form (forma minuta) and predcyst form.

The transmittion of the dysentery amoeba from man to man takes place by the cyst form. The cysts pass with contaminated food and water by the stomach and intestinal canal. Often also, a house fly acts as a vector, because it seeks out human excreta, takes up the cysts from these and can again pass out in its faeces cysts which are still infective. Cysts can survive in flies' intestine for 48-72 hours.



Pic.19.1. The human parasitic amoebae and development cycle of Entamoeba hystolytica:

A: 1-6 - Entamoeba hystolytica (1 – big vegetative form with swallowed erythrocytes; 2 – small vegetative form; 3 – cyst; 4-6 – cyst leaving); 7 - Entamoeba coli (vegetative form), 8 – its cyst, 9-11 - Entamoeba gingivalis; B: 1-2 – cyst entered alimentary canal, 3 – metacystic amoebae, 4 – forma minuta, 5-10 – cysts, which are excreted with faeces, 11,12 – forma magna, 13-14 – big vegetative form in the intestine lumen (by E.N. Pavlovsky, 1951).

Cysts also can be transmitted through house staff (linen, plates and dishes, toys and so on).

The life cycle of Entamoeba hystolytica is complicate. In the lumen of large intestine, they loose their resistant shell. Than, the parasite divides into eight small cells, which are transformed into vegetative forms. They can turn back to the cyst form and come out. They also can be transformed to big vegetative form. These forms enter intestine wall and form ulcers. Getting deeper, they make tissue forms. Tissue forms can enter blood stream and travel throughout the organism. They may cause abscesses in the liver, lungs and in the other organs. In the faeces of patient, it can be found the trophozoites and cysts as well.

Entamoeba hystolytica is a worldwide disease, but it more often settles regions inbetween latitude 30 North and latitude 20 South. Amoebiasis is common in Middle Asia, Transcaucasia, Africa, Latin America, and South Asia. In Europe, it occurs very rare.

Laboratory findings are based on microscopic diagnostics of faeces smears, abscesses pus, ulcers biopsy. We need to find tissue and big vegetative form of amoeba to prove diagnosis. If only cysts and minuta forms have been found, it is not enough to prove diagnosis. Immunological tests (reaction of indirect hemagglutination, enzyme linked immunoassay) are used as additional methods of diagnostics. In complicate cases, doctors use biological test (rat infection by doubt material).

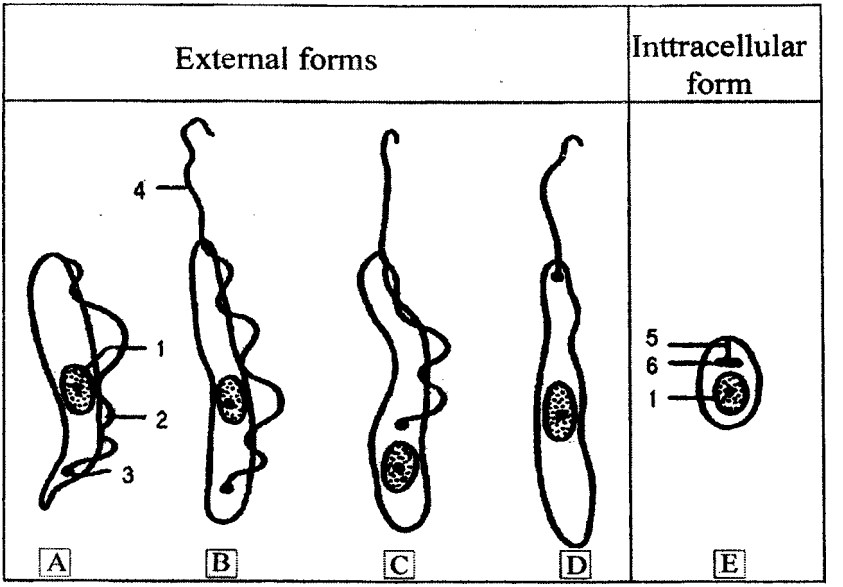
The preventive measures against amoebiasis are directed to follow personal hygiene rules and general cleanliness (washing vegetables and fruits, washing hands before eating, keeping foodstuffs away from houseflies). Social measures are diagnostics and treating of ill patient and carriers of cysts, reducing flies population, prevent wasting of land and water by faeces of ill patient.

Entamoeba coli. Morphologically it is the same as Entamoeba hystolytica. It forms vegetative form and cyst. However, it has no proteolytic enzymes and does not penetrate intestine wall. Cyst is about 13-25 mcm in size and has 8 nucleuses. It has not pathogenic effect for human.

Entamoeba gingivales. It lives on teethes surface and in teethes affected by caries. Body sizes are about 6-60 mcm. It eats bacteria and leucocytes. Its pathogenic effect is not clear.

Limax group amoebas. Since 1966, it became clear that some amoebas living out of organism have pathogenic effect on a human. They are grouped to one group Limax. They are very wide spread: in dung, soil, animal body. Representatives of two genus's (Naegleria and Acanthamoeba) are pathogenic for human.

The representatives of **Naegleria** genus are very virulent. They may cause meningoencephalitis and, sometimes, general failure of internal organs. They have amoeba-shaped, flagella's, and cyst forms.



Pic.19.2. The stages of life cycle of Zoomastigota with kynetoplast:
A – metacyclic (invasional) form, B – tripomastigota, C – epimastigota, D – promastigota, E – amastigota (by R.Night,1985 with changes).

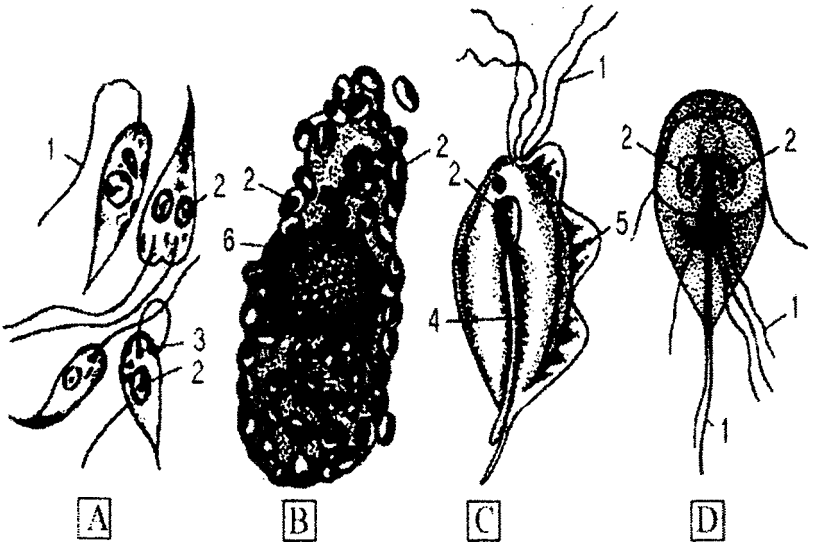
The representatives of Acanthamoeba genus are less virulent. They affect upper respiratory pathways, rarely brain and other organs. They have amoeba-shaped and cyst forms. Cysts have double shell with one or two pores with covers.

A human can be infected by Limax group amoebas while swimming in open pools and pounds with silt bottom.

19.3 Pathogenic organisms from Zoomastigota class.

Representatives of class Zoomastigota have stable shaped body. On anterior part of the cell, there is nucleus with karyosome in the center. They move with help of flagella. Flagellas are fixed to the cell membrane by kynetosoma. It is a special structure placed right under cell membrane. All Zoomastigota are divided into two groups: those who have kynetoplast (tripanosoma and leishmania) and those who have not (lamblia and trichomonads). Kynetoplast is a special mitochondrion-like structure.

In life cycle of Zoomastigota with kynetoplast, there are following development stages (pic 19.2): *tripomastigota* – it has undulating membrane with free flagella, kynetoplast is placed in the posterior part; *epimastigota* – it has it has undulating membrane with free flagella, kynetoplast is placed in front of the



Pic. 19.3. The Zoomastigota which are human parasites:
A – Leishmania tropica (promastigota); B - Leishmania tropica (amastigota); C – Trichomonas vaginalis (vegetative form); D – Lamblia intestinalis (vegetative form); 1 – flagella, 2 – nucleus, 3 – kynetoplast, 4 – axostyl , 5 – undulating membrane, 6 – nucleus of tissue's cell, which is affected by Leishmania tissue forms (by E.N. Pavlovsky,1959).

nucleus; *promastigota* – it has only free flagella, kynetoplast is shifted to anterior part of the cell; *amastigota* – it has sphere shape, very short flagella, under light microscope only nucleus and big kynetoplast are visible. In life cycle of Zoomastigota without kynetoplast, there are only two stages: cyst and vegetative form, or only vegetative form (pic 19.3). They eat food through special invagination of membrane (cystom) or through micropores placed over whole membrane.

They reproduce themselves by bilateral division, starting from anterior pole of the cell. The class includes more than eight thousands of species. Many of them are human parasites

The exciters of African trypanasomosis (Sleeping Sickness) (Trypanasoma brucei gambiense and Trypanasoma brucei rhodesiense). The most common symptoms of it are irregular fever, lymphadenitis, transient local oedema and erythema, psychological and nervous disturbances, increasing cachexia, in the terminal stages and overwhelming desire to sleep.

Trypanasoma brucei gambiense was found in blood in 1902 and in spinal fluid in 1903. Human is definite host for it, whereas pigs are additional host for it. The transmission of the disease from man to man is effected by a bite of the tsetse fly of the genus Glossina (Glossina palpalis, Glossina tachinoides). Trypanasoma

brucei rhodesiense was described in 1909-1912. The main host of it is forest antelope, whereas additional hosts are different forest animals, farm animals and human. It is transmitted by flies Glossina morsitans, Glossina pallidipes and others.

Both parasite types are morphologically similar. They have curved body that is narrower on the both ends. They have flagella and undulating membrane. Body's length is around 15-40 mcm., width – from 1.4 to 2 mcm.

There are two stages in the life cycle of trypanasoma. It has tripomastigota stage in a human and epimastigota stage in the vector organism (tsetse fly). Trypanasoma brucei gambiense naturally occur in Central Africa (Gambia, Cameroon, Uganda, Nigeria, Zaire and Angola). Trypanasoma brucei rhodesiense naturally occur in countries of East and South Africa (Ethiopia, Uganda, Kenya, Tanzania, Zimbabwe and Botswana). There are only sporadic cases of infection by Trypanasoma rhodesiense, prevalently in hunters, tourists and so on.

Parasites live in human organism and cause cyclic changes in patient state. It is due to following mechanisms. Human immune system on being activated kills many of parasites. Those who have survived become shorter and change their antigenic appearance. At this stage patient feels better. However, short trypanosomes may get back their initial shape in the vector organism. They again become invasive for human. Such changes may occur many times.

The patients who suffer from sleeping sickness have irregular fever, lymphadenitis, transient local oedema and erythema, psychological and nervous disturbances and overwhelming desire to sleep. Without treatment, a patient can survive for 5-7 years.

The transmission of the disease from man to man is effected by a bite of the tsetse fly of the genus Glossina (Glossina palpalis, Glossina tachinoides). The transmittion also can be performed during blood transfusion.

Laboratory diagnostics is based on microscoping of material of lymph nodes, spinal fluid, bone marrow, peripheral blood taken during fever period. Among immunological methods, the reaction of complement binding and the immune fluorescent reaction are most useful.

Effective preventive measure is lomidin treatment (once in 6 months 4mg/kg in intramuscular injections) in the trypanosomiasis gambiense regions. Chemical preventive treatment for trypanosomiasis rhodesiense is not effective. Social preventive measures are treatment of ill people, avoiding tsetse biting. It is also includes regular medical examination of population in trypanosomiasis regions, decreasing flies population, making forest-free barriers around villages.

The exciter of American trypanosomiasis (Chagas's disease) (Trypanasoma cruzi). It is the disease, which have natural region of distribution. First to describe the exciter of this disease was G. Chagas in 1907. Body's length is about 15-20 mcm. The body is curved and has undulating membrane with free flagella, which is 1/3 of total body's length.

During life cycle, it has stages of tripomastigota and amastigota in the organisms of humans and mammalians (armadillo, opossum, fox, anteater and guinea-pig). They are natural reservoirs of disease. It also has epimastigota stage in the bugs of Ttriatoma, Panstrongylus genera. When trypanosomes enter human tissues, they loose flagella and become amastigota. It is oval with diameter about two mcm. In affected cells, amastigota forms pseudocysts. Than, amastigota become tripomastigota. They are S-shaped having undulating membrane with free flagella. Tripomastigota enter the blood stream, where it preserves without reproduction. The bugs suck the blood with tripomastigota. In bug's intestine tripomastigota becomes epimastigota. Epimastigota stage is a stage of active reproduction. After 10-30 days of being in bug's intestine, epimastigota form invasive tripomastigota, which are ejected with faeces.

Pic.19.4. The South American leishmaniasis (by Manson-Bahr, 1993).

The acute stage of the disease is accompanied by fever, diarrhea and lymphadenitis. In the chronic stages, a characteristic myocarditis occurs; mega-oesophagitis and megacolon may also be seen. Disease prevalently affects small children. In older children, it often has chronic form.

Disease is limited to South and Central America between latitude 42 North and latitude 43 South. It is common in Brasilia, Argentine, Venezuela, Bolivia, Guatemala, Columbia, Honduras, Paraguay, Uruguay, Ecuador, Chili, Costa-Rica and Panama.

The way of human infection is specific contamination. Trypanosomes on being placed on human skin with bug faeces are rubbed into the wounded skin in the bite place. It is possible to be infected by trypanosomes while blood transfusion and through placenta.

Laboratory diagnostics is based on microscoping of material of spinal fluid, bone marrow, peripheral blood. Specific immunological method is the reaction of complement binding with cardiac muscle antigen of ill animals. Skin allergic probe with specific antigen is also used.

The main preventive measures are decreasing of bug population, blood donor examination to prevent transmission during blood transfusion.

The exciter of cutaneous leishmaniasis (Oriental sore) (Leishmania tropica). It was described by P.F. Borovsky in 1898. The parasite life cycle has two stages: amastigota – in human, mammalian body, and promastigota – in mosquitoes of Phlebotomus genus (pic 19.3a,b).

Amastigota is oval with size 3-5x1-3 mcm. It is placed in skin cells and lymphatic nodes. Promastigota has a spindle shape with size 10-20x4-6 mcm. It also has flagella coming out from kynetoplast.

There are two types of Leishmania tropica: Leishmania tropica major and Leishmania tropica minor. The first one is cause of rural skin leishmaniasis with acute necrotic forms. The second one is cause of urban skin leishmaniasis with late onset.

Typical clinical sign of skin leishmaniasis is formation of oval, non-healing ulcers on the skin. After healing, we can see the coarse scars. Immunity against this disease preserves all live long.

Rural form of skin leishmaniasis occurs in North and West Africa and Asia. Urban form of skin leishmaniasis occurs in Middle East, North and West Africa and West India.

The transmission can occur only through mosquitoes bite (specific inoculation). Mosquitoes suck blood from ill man or animal and than becomes infective after 6-8 days.

Laboratory diagnostics is based on light microscoping of material taken from ulcers. To get material following procedures have to be completed. You should take skin fold with ulcer to break blood supply. Than, you should cut and remove piece of epidermis by scalpel and scrape off some detritus in the bottom of the ulcer. Acquired material is stained on the table glass. Part of material is streaked onto plates with NNN-agar medium to prove diagnosis in further.

To prevent disease it is useful to use repellents and make vaccination by live culture of Leishmania tropica major. Social preventive measures can be summarized in following: revealing and treatment of ill people, dressing ulcers by bandages to prevent mosquitos' bites.

The exciter of cutaneous leishmaniasis of the New World (Leishmania mexicana, Leishmania brazilienzis, Leishmania peruviana). All these exciters have amastigota stage and promastigota stage in the life cycle.

This disease has natural regions of distribution. The natural reservoir for it is different species of wild rats, mice, monkeys and others animals of tropical forests. The vectors are mosquitoes from Lutzomya and Psychodopygus genera.

Leishmania affect skin, in 10-20% of cases mouth, nose, throat, larynx mucosa. It also may affect mucosa of reproductive organs (pic.19.4).

It occurs in all countries of Latin America and in south states of USA.

The way of infection is transmission (specific inoculation).

Laboratory diagnostics is the same as for skin leishmaniasis of Old World. Some serologic reactions (immunofluorescent reaction, ELISA, allergic skin probes) are used for diagnostics.

Preventive measures are directed to revealing and treatment of ill people, prevent mosquitoes biting, decreasing population of vectors.

The exciters of visceral leishmaniasis (Kala-Azar). They are presented by three species: **L. donovani donovani** – is exciter of India's leishmaniasis, **L. donovani infantum** – is exciter of Mediterranean leishmaniasis, **L. donovani archibaldi** – is exciter of East African leishmaniasis.

Morphologically they are the same as all other Leishmania species.

They have two stages in the life cycle: amastigota – in the human, mammalian organism, and promastigota in the vector organism (different mosquito species of Phlebotomus genus). India's leishmaniasis is localized in East states of India, Pakistan, Bangladesh, and Nepal. Mediterranean leishmaniasis is often in Greece, Spain, Portugal, France, former Yugoslavia republics, Middle East, North-West China, and Latin America. Sporadically it occurs in Middle Asia and Transcaucasia. East African leishmaniasis is often in Sudan, Kenya, Somali, Ethiopia, Uganda, and Chad.

Children under 12 years of age are affected by this disease more often than adults are. Visceral leishmaniasis accompanied by irregular fever and marked enlargement of spleen and liver, leading gradually to severe anemia and, when untreated, to death.

The way of infection is transmission (specific inoculation while mosquito biting). The source of invasion in India's leishmaniasis is ill man, in Mediterranean leishmaniasis are ill dogs, foxes, jackals and gophers, in East African leishmaniasis is ill man and desert rodents. It was described that occasionally disease can be transmitted during blood transfusion.

Laboratory diagnostics is based on light microscoping of material taken from bone marrow, lymphatic nodes, spleen and liver. Part of material is streaked onto plates with NNN-agar medium to get parasite culture. Some serologic reactions (immunofluorescent reaction, ELISA) are used for diagnostics.

Preventive measures are directed to revealing and treatment of ill people, prevent mosquitoes biting, dogs treating.

Trichomonas vaginalis – is exciter of urogenital trichomoniasis. It can survive only in human organism.

Body's shape is oval or spindle. The length is from 10 to 30 mcm. Nucleus is oval and is placed in anterior part of the cell (pic 19.3c). In front of the nucleus, there are place for attachment of four flagella and undulating membrane. A tubular axostyle passes aside from the nucleus and along the entire body of the trichomonad; in the posterior end, it protrudes in the form of a long spindle-like

process or a tail. It can get nutrition with help of osmotic diffusion of it also can swallow some bacteria and erythrocytes through barely visible cytostom at the anterior end of the body. It can live only in a form of trophozoite. It is a world spread parasite.

Trichomonad lives in vagina and in cervix of the uterus in women, and in urethra, urine bladder and prostate in men. About 20-40% of women and 15% of men are infected by trichomonad. Trichomonad affects urogenital epithelia. It causes formation of inflammatory regions and epithelia desquamation. Men recover from disease in a month without treatment, whereas women suffer from it for several years.

Trchomonad's infection occurs after puberty. The way of trichmonad transmission is sexual contact.

Laboratory diagnostics is based on microscoping trichomonads in native smears from vagina, urethra and cervix of the uterus. Trchomonads can be cultivated in the nutrient media.

Preventive measures are revealing and treating of ill people, educational programs concerning safe sex.

Trichomomas hominis (Intestinal trichomonad). It is oval with the anterior rounded and posterior sharpened end of the body. It is from 5 to 15 mcm long. Nucleus is placed in anterior part of the cell. In front of the nucleus, the flagella and axial thread of undulating membrane branch off from several blepharoplasts. It reproduces by simple division. It inhabits human large intestine. The parasite enters human body through mouth with unclean foodstuffs. Does intestine trichomonad has pathogenic effect or no, is still unclear.

Lamblia intestinales – is exciter of human lambliasis. It was discibed by D.R. Lamble in 1859.

It lives in human intestine. It has two forms: vegetative and cyst. Parasite is 10-25 mcm long and 8-12 mcm wide. The vegetative form resembles a split pear and has two symmetrical halves. Four pairs of flagella are attached to blepharoplasts. The cytoplasm also contains characteristic para-basal body. The anterior part has a sucking disk by which it attaches itself to the intestinal membrane. They reproduce by simple division Oval cysts are surrounded by a thick membrane. The mature cyst has four nucleuses. Cysts formation occurs in distal part of an intestine. Cysts can survive in the external environment for several weeks (pic.19.3,d).

Lamblia can live in the intestine without any harm for host. People who have such lamblia are carriers of them. However, it is more common that lamblia causes inflammatory processes in large intestine. They can affect processes of wall digestion and absorbtion.

Lamblia intestinales is found in all parts of the world, but especially in the tropics and it is commoner in children than in adults. It is related with insufficient

skills of children to keep everything clean. One carrier or ill man can give up more than 10 millions of cyst per day.

The way if invasion is oral. Cysts can get into food by contamination of food as result of faulty disposal of human excreta and of general uncleanliness. Swallowed parasite leaves the cyst in duodenum. Each cyst can give up two trophozoits.

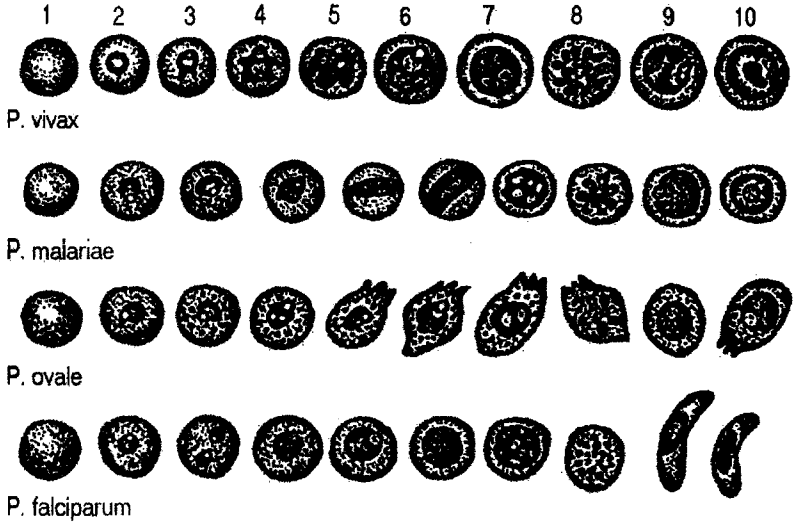
Diagnostics is performed by microscoping of duodenal fluid for trophozoits. The faeces is examined for cysts and trophozoits (while diarrhea).

Preventive measures are directed to follow personal hygiene rules, to kill vectors. It is especially important for places where children congregate. Social preventive measures are directed to avoid faeces disposal of environment.

19.4 Pathogenic organisms from Sporozoa class.

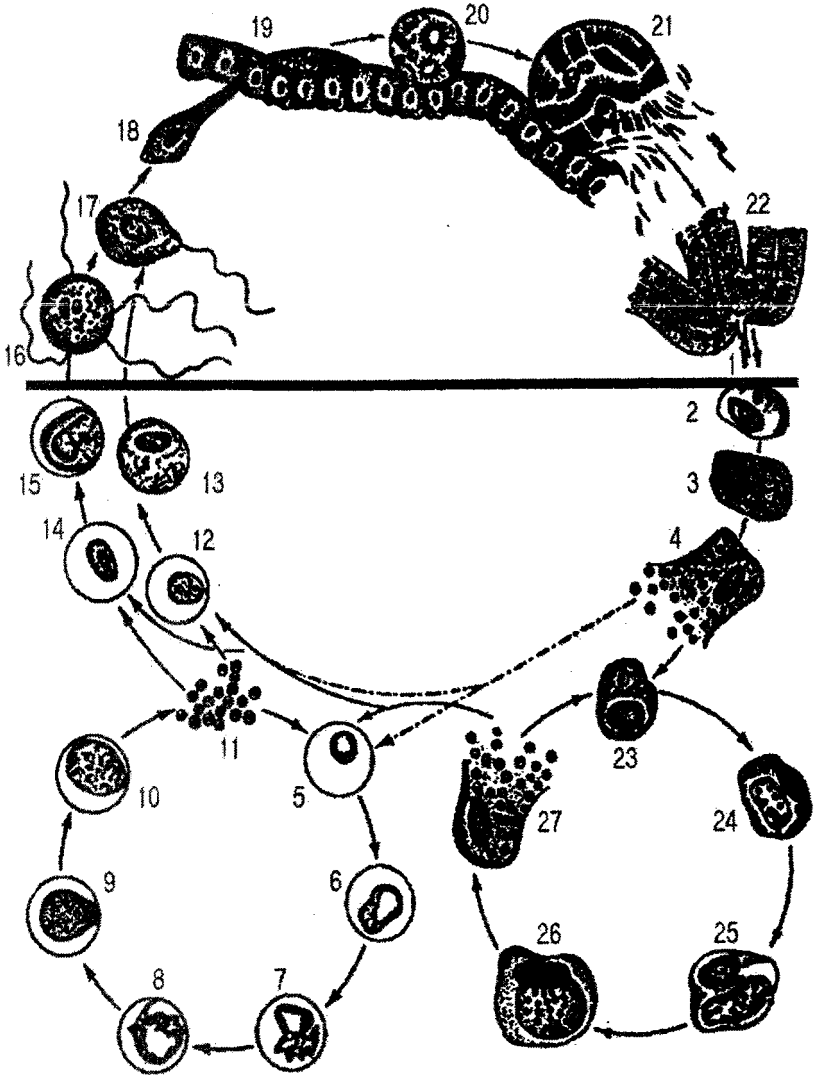
In the Sporozoa class there are ony intercellular parasites having two types of asexual reproduction (schizogonia, sporogonia) and sexual reproduction. Main human parasites are representatives of Plasmidium, Toxoplasma, Pneumocyst, Cryptosporidium genera.

The exciters of malaria are referred to Plasmodium genus. There are four species in this genus: **Plasmodium vivax (Grassi and Feletti, 1890)** – is exciter



Pic.19.5. The exciters of human malaria:

1 – erythrocyte, 2 – early trophozoite stage, 3-4 – older trophozoite stage, 5-6 – early schizont stage, 7 – older schizont stage, 8 – merulation, 9 – female gamont, 10 male gamont (by N.A.Demina,1968).



Pic.19.6. The cycle of Plasmodium malariae development:

1 – sporozoite, 2,3,4 – tissue schyzogony, 5 – merosoit entering to erythrocyte, 6-10 – erythrocytic schysogony, 11 – merozoit release to blood plasma, 12-15 – gamonts formation, 16 – male ganonts formation, 17 – fusion of male and female gamonts, 18 – ookynete, 19,20 – oocyst growth, 21 – sporozoites enter mosquito's salivary glands, 22-27 – paraerythrocytic schysogony (by Sh.D.Moshkovsky, 1968).

of "tertian" malaria; **Plasmodium malariae (Laveran, 1881)** – is exciter of "quartan" malaria; **Plasmodium ovale (Stephens, 1922)** – is a cause of malaria, which is morphologically similar to P.malariae, but has develop periodicity as P.vivax; **Plasmodium falciparum (Welch, 1897)** – is exciter of tropical malaria (pic 19.5). Human is an intermediate host for Plasmodium, whereas mosquito is definite host. All four exciters have similar life cycles (pic 19.6). In a human organism the following stages can be seen: asexual reproduction in liver cells (tissue schizogony or exo-erythrocytic schyzogony), than development in erythrocytes (erythrocytic schyzogony), and formation of gametocytes (immature gametes). Gametogony and sporogony occur in mosquito organism.

The exo-erythrocytic schyzogony starts right after mosquito bite. The sporozoites enter the capillary vessels of the skin with salivary juice from the mosquito and, at first, enter the general circulation. After approximately a hour, the injected sporozoites are taken up by the parenchymal liver cells in which they divide and multiply to form liver schizonts containing several hundreds of merozoites and reaching a size of 25 to 40 mcm in about 7 days. P.falciparum can make more than 30 thousands of merozoits from one schizont. Othes species can form about 15 thousands of merozoits from one schizont. Duration of this phase is for P.vivax – 8 days, for P.falciparum – 5-6 days, for P.malariae – 13-16 days, for p>ovale – 9 days. The liver cells are ruptured by over population of merozoits. Thus merozoits are liberated from liver cells and enter blood stream.

The erythrocytic schyzogony. On the erythrocyte membrane, there are antigens to which tissue merozoits are attached. In this place, erythrocytes membrane engulfs to enable parasite enter erythrocyte. Merozoit, which has entered erythrocyte, called erythrocitic trophozoite. It has four stages of development:

1. – Stage of young trophozoite. It starts 2-3 hours after merozoit entering. Parasite develop vacuole which shift cytoplasm with nucleus to the periphery. Therefore, this stage also called young ring stage.
2. – Stage of older trophozoite. The parasite grow in sizes, the nucleus becomes bigger. It expresses pseudopods, which enable it to move. In the erythrocyte cytoplasm, many small granules appear.
3. – Stage of young schizont. It continues enlarging in sizes. The granules of red pigment appear in parasite cytoplasm. Vacuole disappears. Nucleus starts to divide into several parts. Chromatin is irregular in shape.
4. – Stage of older schizont. The nucleus division is completed. It results in merozoits formation. They are 1.5 mcm in diameter. The pigment granules surround them.

When older schizonts have been formed, they rupture affected erythrocytes and liberate from them. Clinically, it results in fever attacks. It occurs repeatedly in P.vivax ("tertian" fever), in P.ovale (like "tertian") and in P.falciparum (tropica)

every 48 hours, in p>malaria ("quartan" fever) every 72 hours. Merozoits affect new erythrocytes. The reproduction cycle starts once again. After several days of erythrocitic schyzogony onset, part of merozoits transforms to male and female gamonts. From this moment, a man becomes infective. Mature male gamont has light blue cytoplasm and big nucleus diffusely stained. Mature female gamont has dark blue cytoplasm, compact, good stained nucleus. Gamonts have large amount of pigment. Gamonts become mature during tree days. Only in P.falciparum it takes 9 days. Gamonts of P.falciparum are sickle shaped. They can stay in a blood for three weeks. Gamonts of other species disappear earlier.

Gametogony takes place in mosquito's stomach. 15 minutes after swallowing, male gamonts loose erythrocyte shell and form 6-8 active gametes on a periphery of the cell. Gametes can move. They look like flagella. This process was called exflagellation. Female gamonts also present female gametes on a periphery of the cell. Male and female gametes fuse forming zygote. It becomes elongated. It called ookinete. Ookinete penetrate stomach wall and get under basement membrane. It looses ability to move, forms dense shell. This stage called oocyst. Oocyst is subjected to meiosis division.

Next stage is sporogonia. It is a cell after second meiosis division of oocyst. Nucleus and cytoplasm divides rapidly into many parts. They form more than 10000 daughter cells (sporozoites). Sporozoites reach mosquito's salivary glad with lymph flow, when oocyst shell has been ruptured. Now the mosquito can infect someone. Duration of sporogonia depends on weather conditions and on plasmodium type.

The distribution of malaria on the Earth is mosaic. P.vivax is most spread. It can be found almost everywhere between latitude 63 North and latitude 40 South. Natural habitat of P.malaria and P.falciparum is almost the same. The exciter of malaria tropica causes 985 of total malaria deaths. The exciter of malaria quartan is more spread in Africa. It is also common in Oceania islands (New Guinea, Philippines, and Thailand).

Malaria is severe disease. The most striking symptom of disease is the periodic fever. The merozoit liberation from erythrocytes is accompanied by liberation of many toxic products. This lead to rapid temperature rising, fatigue and headache. Attack of disease can last for 6 to12 hours. The interval between attacks of the fever is 48 hour in tertian malaria, and 72 hours in quartan malaria. The number of attacks can be 10 to 15. Than, they fail because of formation of specific immunity. However, parasites still preserve in blood. Such man is dangerous as carrier of disease.

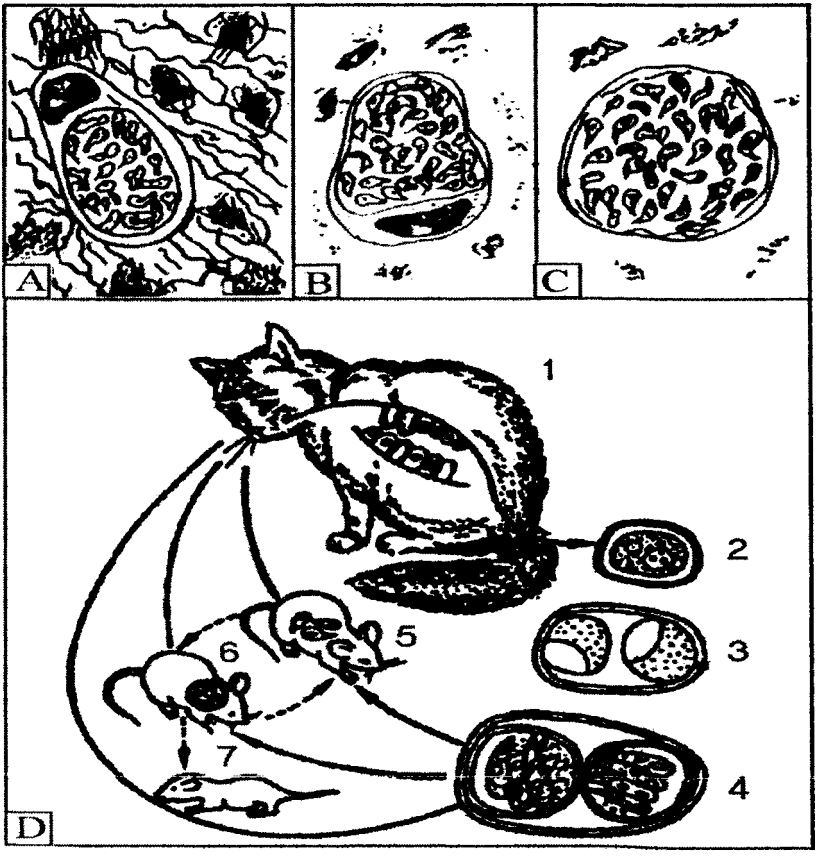
The way of plasmodium invasion is transmissional. Nevertheless, it is possible to get infected after blood transfusion and through placenta.

Laboratory diagnostics is based on microscoping of blood preparation (smear or "thick drop") stained with Giemsa. Plasmodium has specific appearance in blood smear. Some serological methods are used for malaria diagnostics, such as

indirect immunofluorescence, indirect hemagglutination and others.

Individual preventive measures include chemical prophylactic treatment (suppressive therapy) and avoiding of mosquito biting. Several plasmodiocidic drugs can be used for chemical prophylactic treatment (chlorohin, fansydar, metakelfin, daraclor and so on). It is useful to use window nets to avoid mosquito entering into the houses. Repellents are also useful. Efforts to eradicate malaria have focused on elimination of the mosquito vector and on development of drugs to poison the parasite once they have entered the human body.

Toxoplasma gondii – is obligate intracellular parasite. It is cause of toxoplasmosis of human and animals. S.Nicolle in 1908 discovered it and classified it



Pic.19.7.The toxoplasm and its life cycle:

A – tissue cysts in muscle fiber, B – in macrophage, C – in brain smear (by A.Ya.Lysenko, M.B.Lavdovskaya, 1992), D – life cycle of toxoplasm (1 – development in cat's intestine, 2-4 – oocysts, 5,6 – proliferative stages in mouse, 7 – newborn mouse, which was infected through placenta) (by D.K. Frenkel, 1974).

as independent genus Toxoplasma. Parasite develops with the host change (pic 19.7). Final hosts domestic cats and some wild representatives of that family (ocelot, bobcat, and Bengali tiger). Invasion cannot survive in the nature without cats. Intermediate hosts are domestic and wild mice, rats, rabbits, sheep, pigs, cows, some birds and human.

Shape of toxoplasma depends on development stage. Thus, on trophzoit stage, it has either semilunar or arch shape, and about 4-7x2-4 mcm of size. One end of causative agent is sharpened, the other, somewhat rounded. Cell is covered by shell having internal and external membranes. Cytoplasm is mostly homogenous with small granules. There are mitochondria, endoplasmic reticulum, Golgi complex, ribosomes and so on.

Trophozoites can reproduce itself by both sexual and asexual way. Asexual way is schyzogonia with merozoites formation. Sexual way occurs when part of merozoites transforms into sex cell (micro- and macrogametes). Microgametes and macrogametes fuse forming oocyst (20-100 mcm of size). They are surrounded by thick shell. Oocysts are excreted with faeces to the environment, where they can preserve for a long time. When conditions become appropriate, each oocyst forms two sporocyst with four sporozoites in each. Such oocyst becomes invasional. In the intermediate host, the life cycle occurs mostly in a same way. Sporozoites penetrate epithelial cells of intestine. Than, they live and divides in it forming trophozoites.

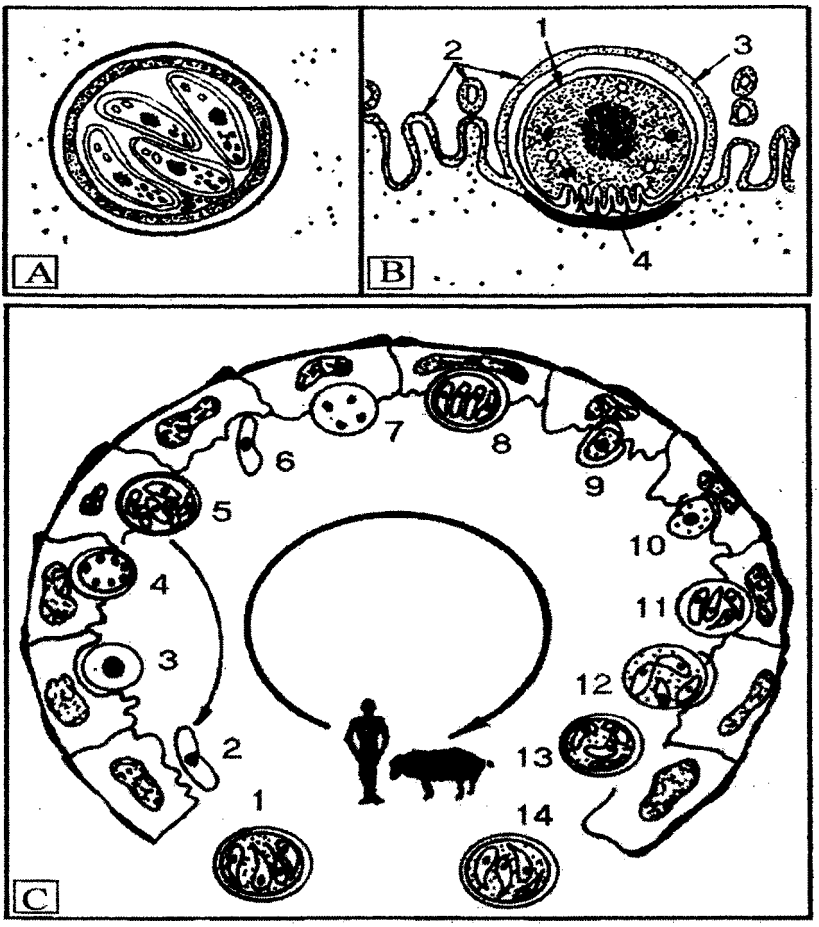
Trophozoites can divide many times. Than, they can travel with blood flow to any tissue of intermediate host. In the tissue, they can form tissue cysts. It is latent invasional form of parasite. They are placed in brain, heart, muscles, and eyes. They can survive for years.

Human toxoplasma invasion very rare results in acute disease with fever, lymph node enlargement. Adults are mostly asymptomatic carriers of disease. But in some cases, toxoplasmosis becomes acute affecting nervous tissue, eyes, heart and so on. It is very dangerous when toxoplasmosis occurs in pregnant woman. It can result in various defects formation in embryo, such as hydrocephaly, microcephaly and so on. It also can result in mental retardation.

Toxoplasmas are found in man all over the world in the regions where definite hosts live. There are anthropic regions of toxoplasmosis (source of invasion is domestic and household animals and rodents) and natural regions (source of invasion is wild animals).

A human can be infected from animals during flaying animals, while eating rough meat, during contacts with cats even through air. Human also can infect embryo through placenta. There were noted sporadic cases of invasion during blood transfusion and organs transplantation.

More valuable for diagnostics is serological examination, which includes complement-fixation reaction, indirect hemagglutination, ELISA (enzyme linked



Pic.19.8. The Cryptosporidium parvum and its life cycle:

A – oocyst, B – trophozoite (1 – coat, 2 – microvilia, 3 – parasitetrophic vacuole, 4 – feeding organelle), C – life cycle scheme (1 – oocyst, 2 – sporozoites, 3 – trophozoite, 4 – dividing schizont, 5 – mature schizont with merozoites, 6 – merozoites, 7 - dividing schizont II, 8 – mature schizont II, 9-13 gameto- and sporogony, 14 – invasional cyst) (by A.Ya.Lysenko, M.B.Lavdovskaya, 1992).

immunosorbent assay) and so on. Parasitological method is revealing of parasite during microscoping stained blood smears, spinal fluid, and material from lymph nodes.

The preventive measures are directed to break the chain of parasite transmitting. It includes avoiding faeces disposal in children areas, following personal

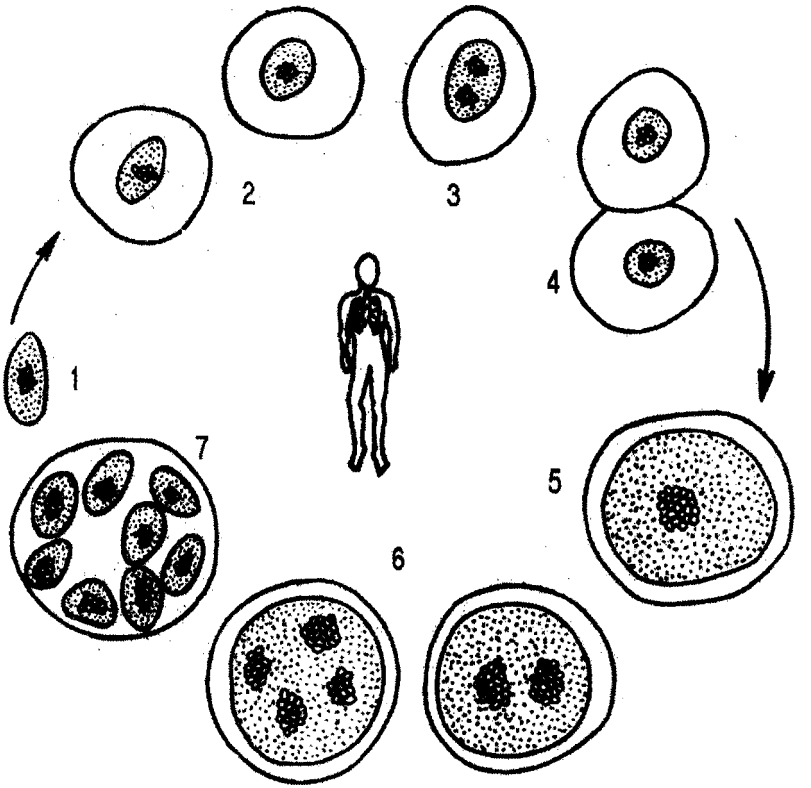
hygiene rules, following rules of animals flaying. It is very important to prevent toxoplasmosis in pregnant women.

Cryptosporidium parvum. It is a small cell, which infects external layer of intestine epithelia. It has interchange of sexual and asexual reproduction (Pic.19.8).

The source of human invasion is domestic animals (calves, piglets, lambs, dogs, cats and others). The susceptibility to this disease is small.

Clinical signs of cryptosporidiosis are gastroenteritis, diarrhea, fatigue and weight lost.

Diagnostics is based on faeces microscoping. Ziehl-Neelsen stain is used to found oocyst in faeces. Oocysts become red when have been stained in this stain. Inside of oocyst, the small sporozoites are visible.



Pic.19.9. The life cycle of Pneumocystis carinii:
1 – sporozoites, 2- trophozoite, 3,4 – trophozoite division, 5,6 – sporogony stages, 7 – cyst with eight sporozoites (by A.Ya.Lysenko, M.B.Lavdovskaya, 1992).

Preventive measures include keeping general cleanliness.

Pneumocystis carinii. It has trophozoite of irregular oval shape. It size is about 1 to 5 mcm. It as founded in lung alveoli of human and animals. It was not found any signs of sexual reproduction (Pic.19.9).

A human is infected through air. He inhales trophozoites. In lungs, trophozoites inhabit alveolar epithelia. Here, they divide by simple division. Then, they enlarge in size forming cyst with 2-8 sporozoites. When sporocyst wall is ruptured, sporozoites get off and start new cycle of reproduction.

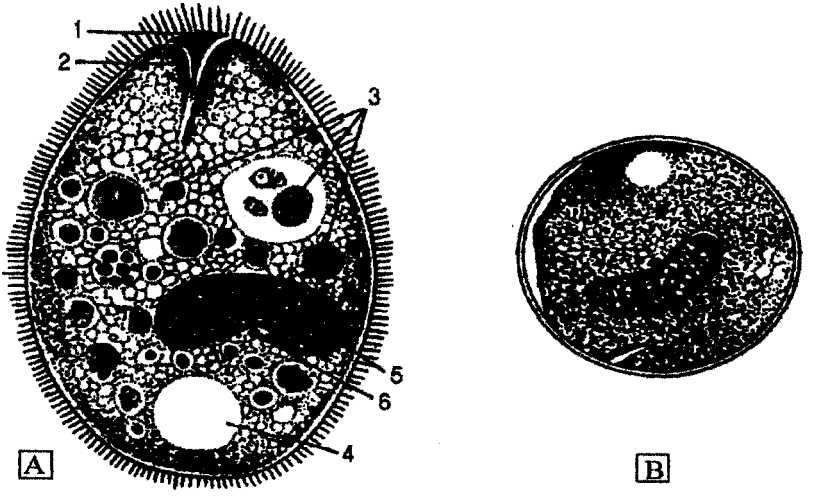
It is interesting, that most common cause of death among VIH-infected people is pneumocystosis.

To make correct diagosis, the specific genetic probes of PCR (polymerase chain reaction) are used.

As preventive measure, the vaccination by recombinant vaccine is used for VIH-infected people.

19.5 Pathogenic organisms from Cilliata class

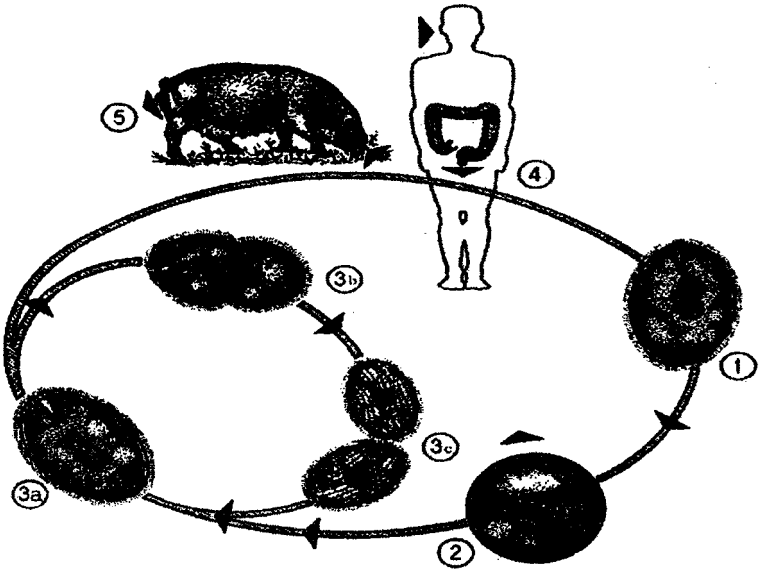
The Ciliates can live alone and parasite in intestine of some vertebrates and invertebrates. Most of them feature large number of cilia. They have cytostom at anterior cell end. Waste products are removed through cytoproct (anal pore). In cytoplasm, there are many contractile vacuoles and two nucleuses: big (vegeta-



Pic.19.10. The Balantidium coli, vegetative form (a), cyst (B):
1 – cytostom, 2 – cytopharynx, 3 – digestive vacuole, 4 – excretory vacuole, 5 – macronucleus, 6 – micronucleus (by G.V. Epshtein, 1934).

tive) and small (generative). There are both types of reproduction: asexual (simple division) and sexual (conjugation). They have trophozoite and cyst stages in the live cycle.

Balantidium coli. It is only one of Ciliates, who can infect a man. It is a cause of balantidiasis of human and animals. It was discovered by Sweden scientists N. Malmsten in 1857.



Pic.19.11. The life cycle of Balantidium coli:

1 – vegetative form, 2 – cyst, 3 – parasite reproducing, 4 – living in large intestine of human being, 5 – a pig, as a reservoir host (by G.Piekarsky, 1962).

Trophozoite is oval. It is 70-150 mcm long and 40-50 mcm wide (pic 19.10). Macronucleus has beanlike shape and is close connected with micronucleus. Trophozoites live in large intestine attached to mucosa. They eat bacteria, food particles, erythrocytes, leukocytes. Cysts are formed in intestinal lumen. They are oval with diameter 45-65 mcm. They are resistant outside of organism to various harmful factors. In a new host, cyst leaves shell in small intestine. Than, it attaches mucosa in the large intestine (pic 19.11).

Balantidium can produce hyaluronidase enzyme. It helps to penetrate intestine wall causing ulcers formation. Clinical sign of disease is acute diarrhea with blood and pus. Sometimes, intestine wall perforation may occur. Balantidium may enter blood stream and travel to liver, lungs and other organs. There it causes

formation of abscesses.

It is found in all continents where pigs are involved in agriculture.

The way of invasion is oral through food and water contaminated by cysts. Butchers and other men who work with pigs are infected more often.

Laboratory diagnostics is based on microscoping faeces for trophozoites and cysts. Faeces should be fresh and warmed to 30-35 degrees centigrade. Sometimes, balamtidium can be cultivated onto nutritive medium.

Preventive measures are based on following personal hygiene rules and keeping all pig farms as clean as possible. It is important to reveal and treat ill people and symptomless carriers.

CHAPTER 20. MEDICAL HELMINTHOLOGY.

Medical helminthology – is a division of medical parasitology that studies parasite worms as exciters of human diseases. Diseases, which are caused by helminthes, called helminthoses. Human can be a host for more than 250 species of worms. More than half of them are flatworm, the rest of them are nematodes.

Today, helnimthoses are most spread parasite diseases in a world. Therefore, mach attention is pair to them. Accordinary data of WHO Helminthosis Committee (report №227) "...parasite worms in general affect health of whole mankind". Helminthes can live in any tissues and organs of human body. However, intestine is most common place of their living. Paragonimus westermani and Echinococcus granulosus can inhabit lungs. Almoust all trematodes can inhabit liver. Brain can be a place for tapeworm cysts storage. Muscles are the place for Trichinella spiralis larvae preserving.

Clinical picture of helminthoses is very complicate. It is due to parasite action on host, as well as, host action on parasite. It is incorrect to discus helminthoses as only parasite action on host, or only host action on parasite invasion. All clinical signs are the consequences of these interactions. The expression of clinical signs depends on number of parasites affecting the host. However, it is so particular in each case.

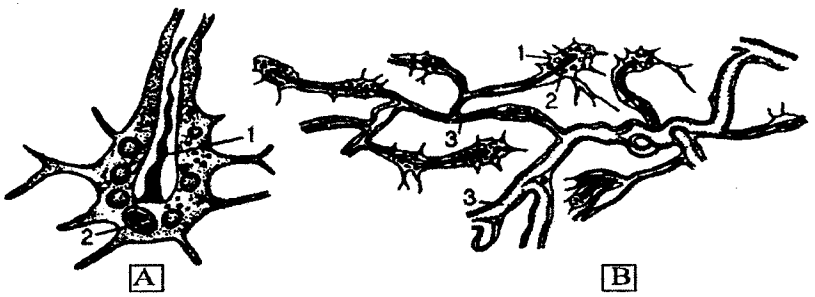
20.1 Phylum Plathelminthes.

Flatworms are very spread in nature. There are more than 7300 species in this phylum. They live in sea, ponds, land. Many of them are parasites.

Flatworms develop from three embryo layers. They have bilateral symmetry of body. Body is flat in dorso-ventral direction. There is no coelom. Internal organs is suspended in loose connective tissue – parenchyma. Musculo-cutaneus sack consists of external layer – tegument (multinucleus unicellular structure) and three muscular layers (longitudinal, cross and oblique).

Many flatworms have gut with only one opening. The gut is branched and it extends throughout the body. It divides into anterior, middle and posterior part. Undigested particles are eliminated through the mouth. Tapeworms lack digestive system. They adsorb their food directly through their body walls.

Flatworms do have excretory system, which consists of a network of fine tubules that runs throughout the body. Cilia line the hollow centers of the bulblike flame cells, which are located on side branches of the tubules. By doing so, cilia move water with the substances to be excreted into a system of tubules and then to exit pores located between epidermal cells. Flame cells were named because of the flickering movements of the tuft of cilia within them (pic 20.1).



Pic.20.1. The excretory organs of flatworms:
A – terminal cell (1 – cilia, 2 – cell's nucleus); B – structure of terminal branches of protonephridia (1 – terminal cells, 2 – cilia, 3 – excretory canalss) (by P.B.Gofman-Kaadoshnikov,1966).

Flatworms lack respiratory system. They uptake oxygen through whole body surface.

Flatworms lack circulatory system. However, flatworms have thin bodies and highly branched digestive cavities, which facilitate diffusion of oxygen and food.

Nervous system is presented by two longitudinal nerve cords and two swelling at the anterior end.

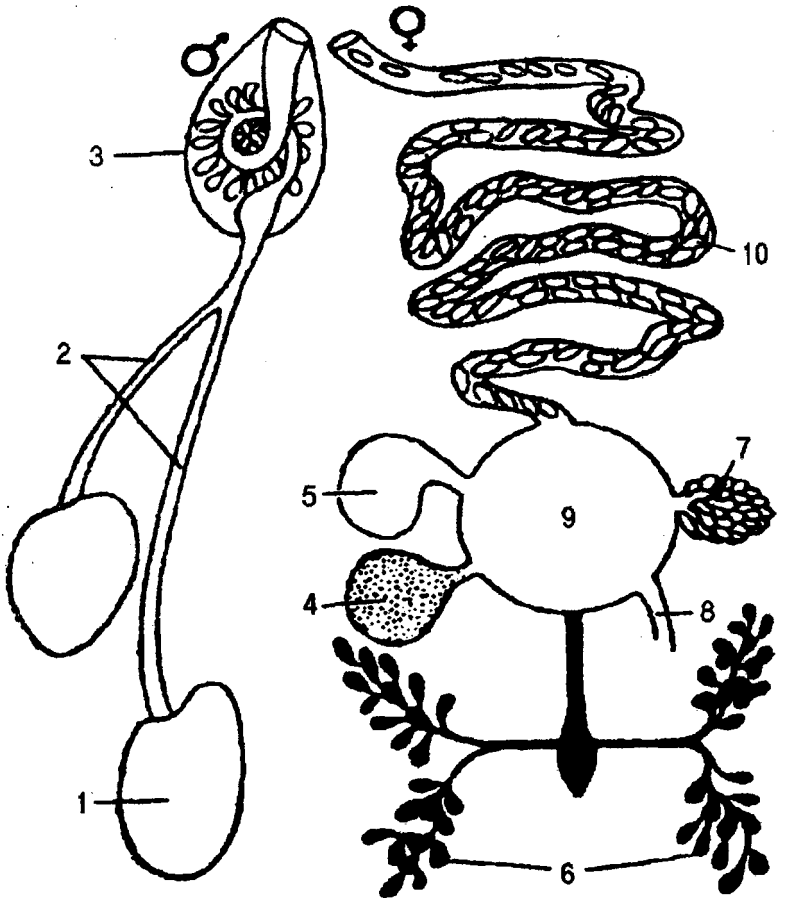
Flatworms are hermaphroditic, excluding blood flukes (Schistosomas).

Phylum has three classes: Class Tutbellaria, Class Trematoda and class Cestoidea. Class Tutbellaria has no medical importance. Accordinary epidemiological classification, flatworms are biohelminthes (all Trematodes, Diphyllobothrium latum, Tania soleum, Echinococcus granulosus) and contact helminthes (Hymenolepis nana).

20.1.1 Pathogenic representatives of Class Trematoda.

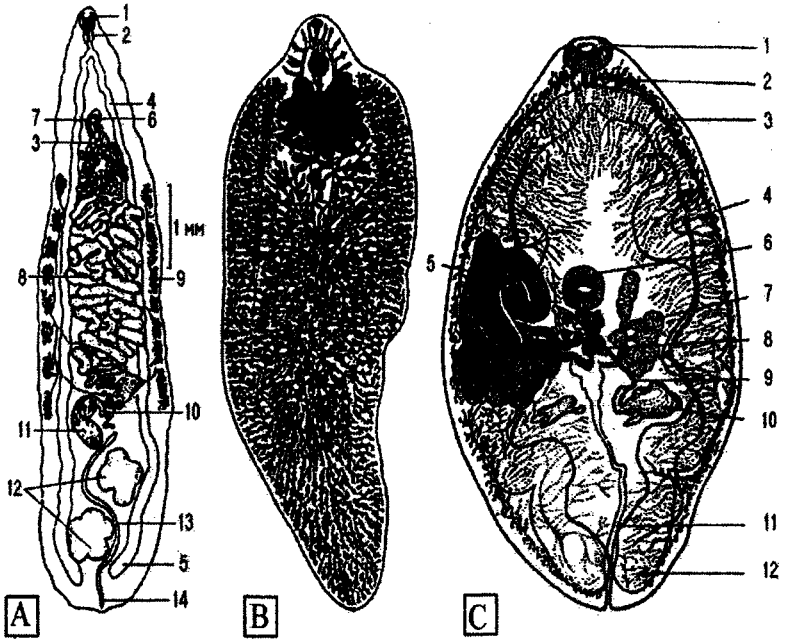
Class Trematoda includes parasites only. Body has a leaf-shape. There are strong organs of attachment: sucker, small anchors, hooks covering whole body. They help to attach to the host. They were formed after a long period of adjusting to parasite being. All Trematodes are hermaphroditic (pic 20.2). Male reproductive system is presented by two testicles and two sperm ducts, which fusing form one duct. This duct passes through male copulatory organ – cyrrus. Femal reproductive system is presented by ovary and oviducts. Ovicells travel to special chamber of female reproductive system – ootype. During copulation, cyrrus erect and enter vagina of other worm. Sperm cells leave cyrrus entering accepting chamber. Additional structures of female reproductive system are Mellis's bodies. There is also Laurerov chanal, which enter ootype. Their function is not clear.

Flukes – are biohelminthes, having interchange of reproduction strategies, host change and generation alternation. Adult stage (marita) inhabit organism of



Pic.20.2.The structure of hermaphroditic reproductive system of flukes:
1 – testis, 2 – sperm duct, 3 – cyrrus, 4 – ovarium, 5 – accepting chamber, 6 – yolk bodies, 7 – Mellis's bodies, 8 - Laurerov chanal, 9 – ootype, 10 – uterus (by K.I.Skryabin, R.S.Schults,1929).

vertebrates. Its ova need to be placed into water to continue development. First stage larva, called miracidium, leaves the ovum. It can be ingested by snail. Within the snail, it transforms to sporocyst. Within the sporocyst rediae are produced, which are elongated, nonciliated larvae. This larva continues growing within the snail, giving rise to the several individuals of the tadpolelike next larva stage, the cercariae. The cercariae, which are produced within the snail, escape into the water,



Pic.20.3. The trematodes – human parasites:

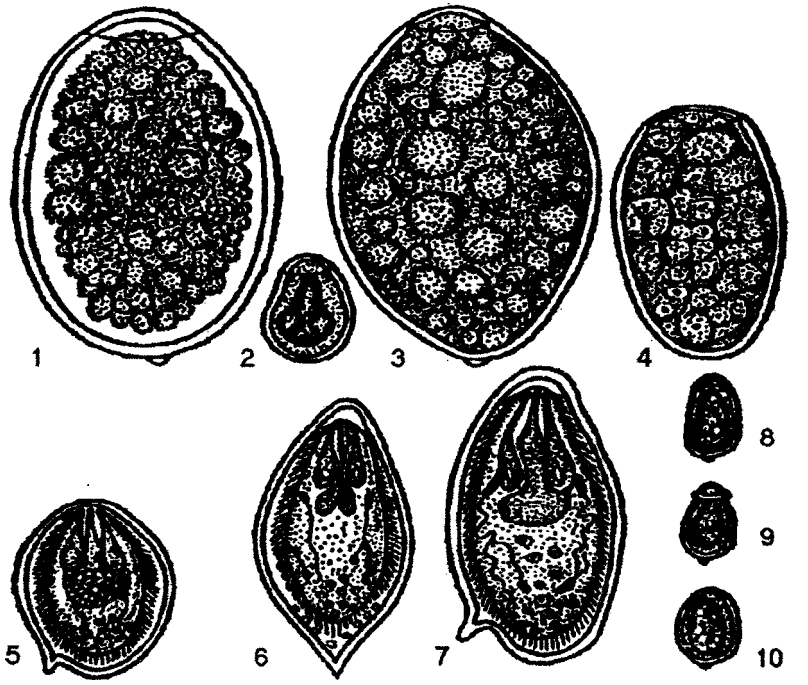
A – Opisthorchis felineus, B – Fasciola hepatica:(1,3 – oral and viserl suckers, 2 – pharynx, 4,5 – intestinal branches, 6 – female sexual opening, 7 – male sexual opening, 11 – accepting chamber, 12 – testis, 13 – canal of excretory system, 14 – excretory pore) (by K.I.Skryabin, R.S.Schults,1929); C – Paragonimus westermani (1 – oral sucker, 2 – pharynx, 3 – gut, 4 – nervous cord, 5 – uterus, 6 – visceral sucker, 7 – ovarium, 8 – Mellis's body, 9 – ductus deferens, 10 – testis, 11 – excretory canal, 12 – yolk bodies) (by P.B. Gofman-Kadoshnikov,1966 and A.A.Slusarev,1970).

where they swim about. They look for definite or second intermediate host. If they look for definite host, they can transform to cyst stage – adolescariae. They are located on the pondweed and can be ingested by animals. Second group looks for second intermediate host. Having found it, they bore into the muscles or under the scales, loose their tails and transforms to metacercariae. Intermediate hosts are usually fishes. Having entered final host, invasional stages of flukes travel throughout the body looking for an organ where they will live until the end.

We will discuss most important representatives of this class.

Large liver fluke (Fasciola hepatica) – an exciter of fascioliasis (pic 20.3b). This fluke is about 20-40 mm in size and it lives in the bile ducts of its hosts, where it can live for many years. It is distributed over all parts of the world.

Adult stage has leaf-shaped bogy. There are mouth and ventral suckers. Its uterus is highly branched, but it is not big. It is located behind ventral sucker.



Pic.20.4. The eggs of trematodes:

1 – liver fluke, 2 – smaller liver fluke, 3 - Fasciolopsis buski, 4 – Paragonimus westermani, 5 – Japanese fluke, 6 – urogenital fluke, 7 - intestinal fluke, 8 – opisthorchis felineus, 9 – Clonorchis sinensis, 10 – metagonimus (by U.A.Berezantsevu and E.G.Avtushenko, 1976).

There is ovarium behind the uterus surrounded by yolk bodies. The testicles are in the central part of the body. Eggs of Fasciola hepatica have a regular oval, somewhat elongated form, a thin yellow membrane, an operculum on one end and flat knob on the other. Eggs measure 125-150 by 62-81 mcm (pic 20.4,1).

The egg starts to develop in water. The miracidium leaves the ovum. It can be ingested by snails (genera Glaba, Radix, Lymnaea). Within the snail, it transforms to sporocyst. Within the sporocyst rediae are produced, which are elongated, nonciliated larvae, with mouth, pharynx and alimentary tube. This larva continues growing within the snail, giving rise to the several individuals of the tadpolelike next larva stage, the cercariae. The cercariae, which are produced within the snail, escape into the water, where they swim about. They have all organs as mature form has. Than, they transform to cyst stage – adolescariae. They are located on the pondweed and can be ingested by animals. In the intestine of final host,

adolescariae leave defense shells and bore through intestine wall to the bile ducts. In the bile ducts, they grow and become mature after 3-4 month after invasion.

Fascioles can plug up bile ducts, causing mechanical jaundice. Parasite antigens are strong. They may cause acute allergic reactions. They affect bile ducts; they also make wound on their walls. Massive invasion can result in liver cirrhosis.

The way of invasion is oral with pond water and water plants.

Laboratory diagnostics is based on faeces examination for eggs. Some transitional eggs can be revealed in healthy people after eating liver of ill animals. So, patient that need to be examined have to escape liver from diet. Some serological tests are used fro diagnostics, such as immunofluorescent, indirect hemagglutination, latex-agglutination, complement-fixation.

Preventive measures are directed to avoid using pond water for drinking, to wash vegetables before eating and so on. Social preventive measures are treating ill animals and people, pastures interchange, health care eduction.

Fasciola gigantica (Giant liver fluke). It is also exciter of fasioliasis. Its georraphical distribution is Uzbekistan, South-East Asia, Hawaii lands.

It is bigger in size than fasciola hepatica (up to 75mm). Eggs sizes are 37-162 x 87-112 mcm. It is more severe for man because of larger sizes. Development cycle, diagnostics and preventive measures are the same.

Fasciolopsis buski (The giant intestinal fluke) – is exciter of fasciolopsiasis. It has 70 mm long. It has thick body, two unbranched digestive tube. Eggs are about 130-140 x 80-85 mcm (pic 20.4,3).

Adult forms live in the small intestine of human and pigs. The intermediate host is snails from Segmentina genus. Adolescariae are located on pondweed. After invasion, parasite does not migrate.

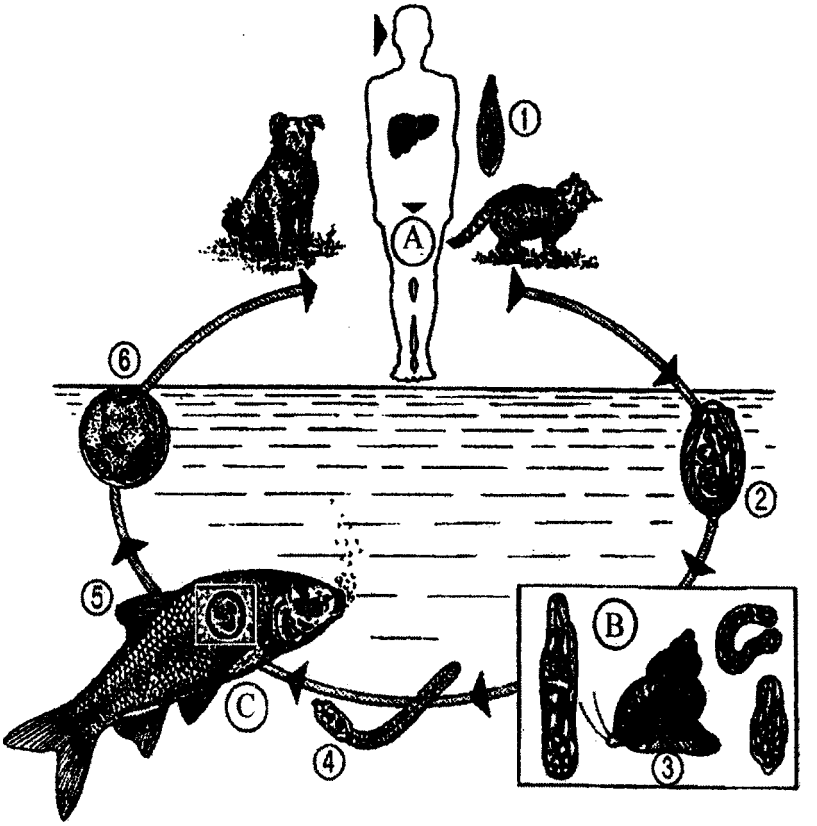
Main clinical signs are due to disturbances of digestion, absorption, secretion and motility in alimentary canal.

Geographical distribution is Central and South China, South Asia.

Way of invasion is oral. Diagnostics and preventive measures are the same as for Fasciola hepatica.

Opisthorchis felineus (the cat liver fluke) – is a cause of opisthorchiasis. It was firstly described by K.N. Vinogradov in 1891 in Siberia (pic 20.3a). Parasite body has 13 mm long; digestive canal has two unbranched tubes. In the centre of the body, there is branched uterus. There is oval ovarium behind it. Two rosette-shaped testicles are at the terminal part of the body. Eggs measure 26-30 by 10-15 mcm, they are slightly elongated, asymmetrical in shape and have smooth thin light yellow membrane. On the anterior pole of the egg there is a hardly noticealble knob.

The intermediate host is mollusk Bithinia leachi. In the mollusk intestine, miracidium leave the egg, travel to liver and transform to sporocyst. Last one give



Pic.20.5.The life cycle of Opisthorchis felineus and Clonorchis sinensis:
A – definite host, B – intermediate host, C – additional host; 1 – marita, 2 – egg, 3 – mollusk of Bythinia genus, 4 – cercariae, 5,6 – metacercariae (by G.Piekarsky,1962).

rise to rediae. Rediae divide and transform to cercariae. They have mouth and ventral suckers, digestive tubes and tail. The cercariae, which are produced within the snail, escape into the water, where they swim about. If they encounter the fish of the family Cyprinidae – the family that includes carp and gold-fish – they bore into the muscles or under the scales lose their tails, and transform into metacercariae within the cysts in the muscle tissue. Thus, fishes are second intermediate host for this fluke. If a human or other mammal eats raw infected fish, the cysts dissolve in the intestine and young flukes migrate to the bile ducts or pancreatic duct, where the mature (pic 20.5).

The acute stage of opisthorchosiasis is witnessed by signs of acute allergosis with high pyrexia and eosionophilic leucocytosis. In the chronic stage, the symptoms of pancreatitis, cholecystitis, hepatitis are common.

The opisthorchosiasis is biohelminthosis. It can be found in West Siberia, along Volga, Don, Dnepr, Dnestr, North Donets, Pripiat, Neman rivers.

To make correct diagnosis, it is needed to examine duodenal fluid and faeces of ill man. In faeces, the eggs can be found. In some cases, the serologic reactions are useful. The examples are indirect hemagglutination, ELISA and so on.

Personal preventive measures are directed to quit such food habit as eating uncooked or improperly cooked fish. The social preventive measures are directed to health care education, checking out fish, which is for sale and so on.

Opisthorchis viverrini – is a cause of opisthorchosiasis viverrini. Body has 10 mm long. Parasite testicles have big lobes. Eggs are small with slightly visible bulges on the poles. Final hosts are wild predators from cats and dogs families, and human. Intermediate host is mollusk of Bithynia genus. Adult organism lives in bile ducts and pancreatic ducts.

In the acute phase, the fever, skin rashes, bronchitis occur. In chronic phase, the symptoms of pancreatitis, cholecystitis, and hepatitis are common.

Geographic distribution is Thailand, Laos, Taiwan, and India.

Human invasion occurs at the same way as by Opisthorchis felineus. Laboratory diagnostics and preventive measures are also the same.

Clonorchis sinensis (the Chinese liver fluke) – is a cause of clonorchiasis. . Body has sizes about 10-20 x 1-4.5mm. The anterior end is widened and it has sucker. Testicles branch and are in the terminal part of the body. Eggs look like Opisthorchis's eggs. They can survive in water for three months. Eggs measure 26-30 by 10-15 mcm (pic 20.4,9).

First intermediate host is mollusk of Bithynia genus; second is fish of the family Cyprinidae. Final hosts are humans and eating fish animals (pic 20.5).

Clonorchiasis is biohelminthosis, zoonosis. It can be found in China, Korea, Vietnam, and Japan.

Pathogenesis, clinical picture, laboratory diagnostics and preventive measures are similar to opisthorchosiasis.

Paragonimus westermani (The lung fluke) – is exciter of human paragonimiasis. Parasite body is oval. When it is alive, it is reddish-brown and resembles a coffee bean. It size is about 7.5-16 mm. Eggs measure 80-110 by 50-60 mcm. The golden-brown eggs have an operculum (pic 20.4,4).

Lung fluke has two intermediate hosts: the first is mollusks of Oncomelania genus, the second is crabs and shrimps. In the first host, the cercariae develop. In the second host, the metacercariae develop. Definite hosts, such as human, pig, cat, dog, otter, mink, can be infected while eating fresh crabs and shrimps (pic 20.3,C).

Adult parasite lives in lungs. Young parasite migrates to lungs from intestine through abdominal cavity, diaphragm and pleura. Migration is accompanied by allergic reactions. Fluke localization in lungs results in focal pneumonia.

The paragonimiasis is desease with strict natural regional distribution. It occurs in tropics of Old and New World, along Amur river, in Japan and South China.

Invasion way is oral with fresh, uncooked crabs or shrimps.

Diagnostics is based on examination of sputum and faeces for the eggs. In some cases, the serologic reactions are useful. The examples are indirect hemagglutination, ELISA and so on.

Personally, you have to avoid eating of fresh crabs and shrimps. Society has to care about health care education in affected regions.

Dicrocoellium lanceolatum (The smaller liver fluke) – is an exciter of dicrocoeliasis. It lives in bile ducts of farm animals. It occurs in human body very rare.

It sizes about 10 mm long. It has lancet shape. The digestive canal has two unbranched tubes. There are two oval testicles. They are located behind ventral sucker. There is ovarium behind them, surrounded by yolk bodies, uterus and sperm accepting chamber. Eggs of Dicrocoellium lanceolatum have a regular oval, a thin yellow membrane, an operculum on one end. Eggs measure 38-45 by 25-30 mcm (pic 20.4,2).

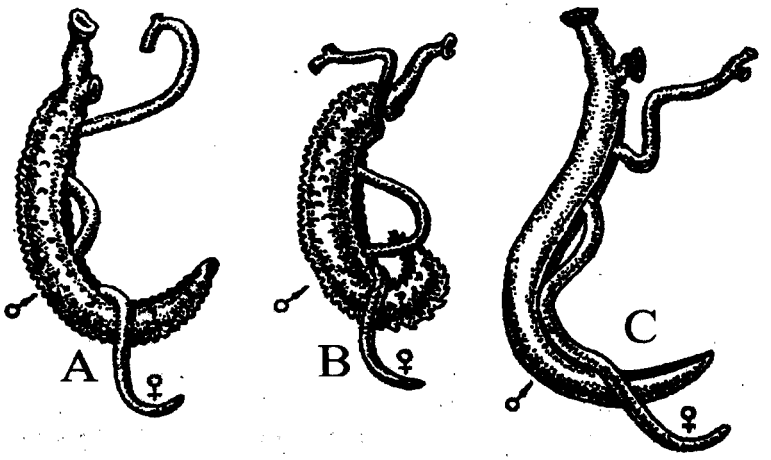
Eggs are escaped from final host with faeces. Than, it need to be ingested by first intermediate host – mollusk from Zebrina or Helicera genera.). Within the snail liver, it transforms to first range sporocyst. Than, it transforms to a second range sporocyst. This larva continues growing within the snail, giving rise to the several individuals of the tadpolelike next larva stage, the cercariae. The cercariae travel to mollusk's lungs. There they congregate and make congregated cysts. Those cysts escape onto plants. Here, they can be ingested by second intermediate host – ants of Formica genus. In ants, cercariae leave defense shell and transform to metacercariae. Human and animal invasion occurs with occasional swallowing of ants with weed.

Clinical picture of dicrocoeliasis is similar to fascioliasis. It is spread worldwide.

Diagnostics is based on examination of faeces for the eggs.

Personally, you have to avoid eating of ants with weed. Society has to care about health care education in affected regions, treating of ill animals, pastures sanitary regulations.

Blood flukes of Schistosoma genus. They are causes of schistosomiasis. In this group, there are organisms of both sexes living in human blood. Males have flat body, whereas females have tread-like body. Matured females are in ginecoform canal on ventral side of male organism. Suckers are small. They are on anterior end of parasite.



Pic.20.6. The blood flukes (by C.Belding,1942).
A - Schistosoma haematobium; B - Schistosoma mansoni; C - Schistosoma japonicum.

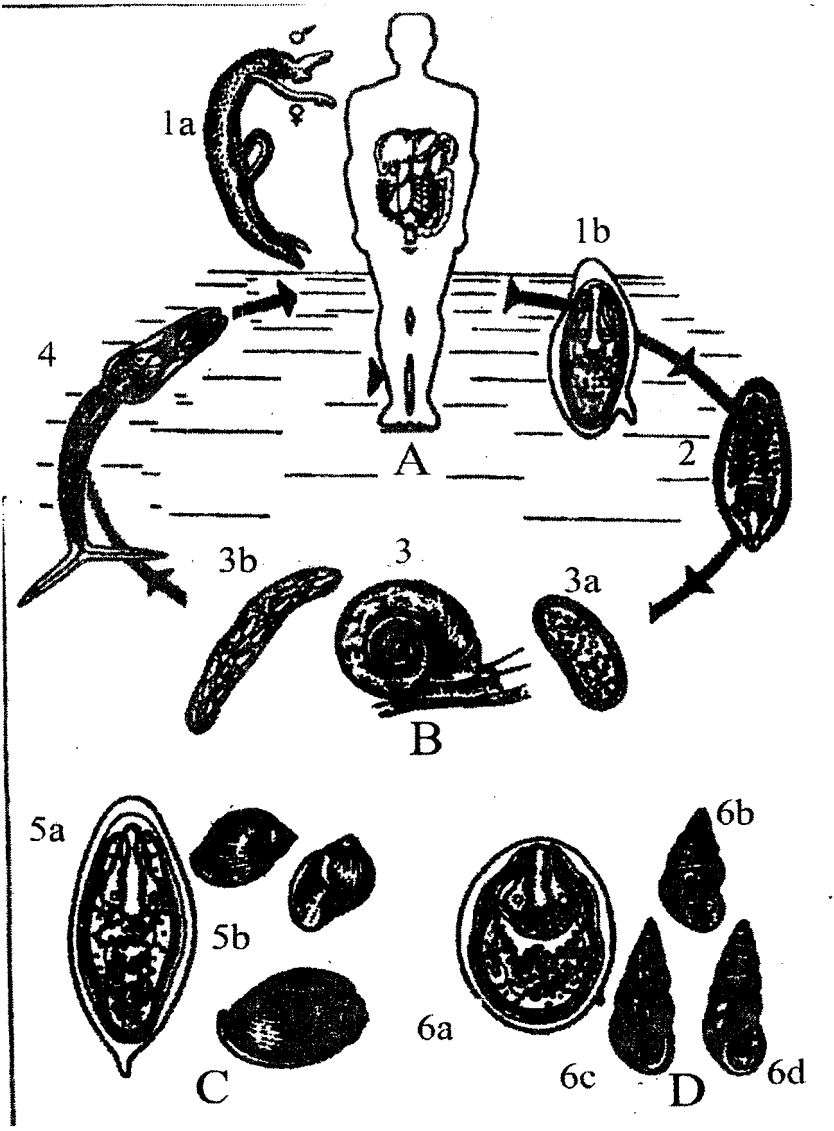
Geographical distribution of Schistosomas is tropical latitudes of Asia, Africa and America.

Definite host for them is human. Intermediate hosts are tropical mollusks. Miracidium leaves egg in the water. Than it enters a snail, where it transforms to sporocyst of first and second range and, finally, to cercariae. Cercariae escape intermediate host to swim in the water. Swimming in the water, they bore under the human skin. It is possible when people swim, work in rice field or on irrigative system. Wearing cannot prevent parasite invasion. On the invasion site, there are skin eruptions, rashes, itching. It is cercariosis. Entered schistosomas travel with lymph and blood to right part of heart, lungs, mesenteric veins, urinary veins.

There are several species of schistosomas, which are most common in a human (pic 20.6).

Schistosoma haematobium – it is exciter of urogenital schistosomiasis. It lives in large veins of intestine and urogenital system. The male is about 15 mm long, the female – 20 mm. Parasite surface is rough. Eggs are oval, measure 112-170 by 40-70 mcm. They have transparent yellow membrane with protrusion in the form of a spine on one pole (pic 20.4,6). Female deliver 200-300 eggs per day. The intermediate hosts are mollusks of Bullinus, Planorbis or Planorbarius genera. The final hosts are humans and monkeys (pic 20.7). Eggs use their protrusion to bore ureter or urinary bladder wall. Then, they escape body with urine. Eggs become active to do so only at noon.

Patients suffering from urogenital chistosomiasis have blood in the urine,



Pic.20.7. The life cycle of schistosoma:

A – definite host;1a – copulating male and female, 1b – invasional egg, 2 – miracidium, 4 – cercariae; B – intermediate host (3a – sporocyst of I range, 3b – sporocyst of II range, 3 – mollusk of Planorbis genus);C: 5a – egg of Schistosoma haemotobium, 5b – mollusks of Bullinus genus; D: 6a – egg of S.japonicum; 6b – mollusk of Schistosoma genus, 6c – mollusk of Oncomelania genus, 6d – mollusk of Katayama genus (by G. Piekarsky,1962).

pain in lower abdomen, urolithiasis. It was noted that urine bladder cancer occurs in ten times more often in the regions where schistosomiasis is wide spread.

The urogenital schistosomiasis can be found in Middle East, Africa, India, on the islands in Indian Ocean.

Schistosoma mansoni - it is exciter of intestinal schistosomiasis. The male is about 6-13 mm long, the female – 7-17 mm. Eggs are oval, measure 144-175 by 45-68 mcm. They have transparent yellow membrane with protrusion in the form of a spine on a side. Female deliver 100-300 eggs per day. The final hosts are humans, farm animals, dogs. The intermediate hosts are mollusks of Physopsis, Planorbis or Biomphallaria genera (pic 20.7).

In human, they inhabit mesenteric and portal veins. Patiens have symptoms of colitis, portal venous congestion, cirrhosis, diarrhea with blood.

The intestinal schistosomiasis can be found in North, Ecvatorial, South-East Africa, South-West Asia, Brasilia, Venezuela.

Schistosoma japonicum – it is exciter of Japanese schistosomiasis. It lives in large veins of intestine. The male is about 9.5-17.8 mm long, the female – 15-20 mm. Parasite surface is rough with small protrusions. Eggs are more oval than in previous species, measure 70-100 by 50-65 mcm. They have very small protrusion in the form of a spine on a side. Female deliver 1500-3500 eggs per day. The final hosts are humans, ungulate animals, dogs and rodents. The intermediate hosts are mollusks of Oncomelanis genus.

Clinical symptoms are similar to intestinal schistosomiasis, but they have particular features. The chronic stage of invasion starts earlier, 25-30 days after invasion. Severe dermatitis occurs more often. Number of eosinophils in blood smear can reach 80%. Massive invasion leads to massive affection of lungs, liver, kidneys. Acute invasion may result in allergic brain affection. Prognosis is negative, if treatment was started late.

The Japanese schistosomiasis can be found in South Japan, South China, Philippines.

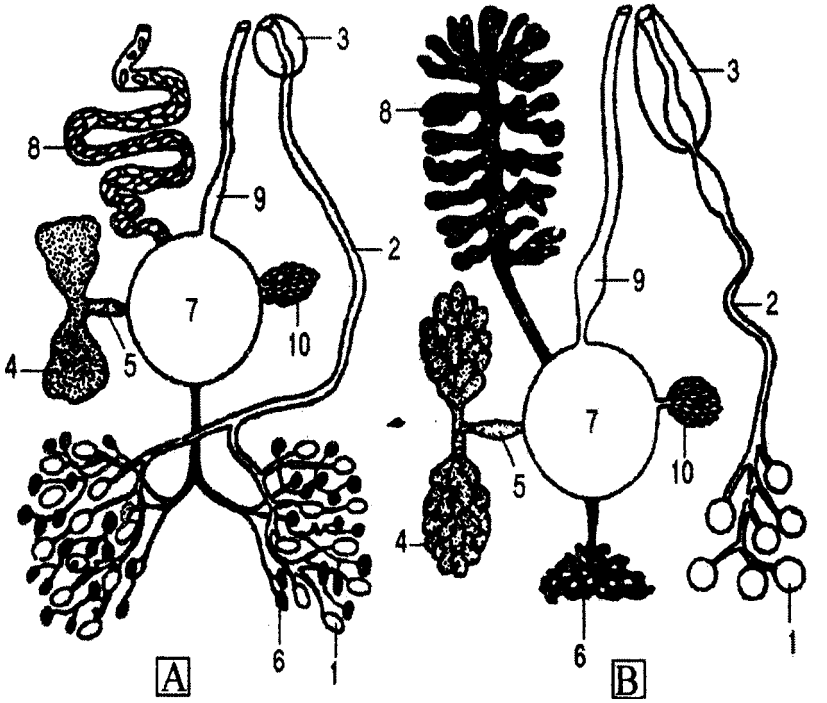
The way of invasion is transdermal way for all types of schistosomiasis.

Diagnostics is based on examination of urine and faeces for the eggs. In some cases, the serologic reactions are useful. The examples are indirect hemagglutination, immunofruorescent test, ELISA and so on.

Personal preventive measures are to avoid swimming in suspicious ponds, where can be schistosoma cercariae. Social preventive measures are directed on treating ill people, elimination ponds disposal by human faeces, health care education.

20.1.2 Pathogenic representatives of Class Cestoda.

Tapeworms, as flukes, are parasite of vertebrate animals. They have tape-like structure (strobila). The strobila is divided into many proglottids. On the anterior



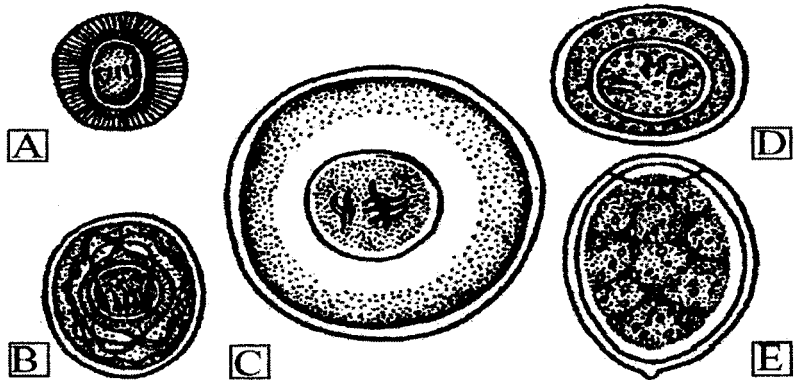
Pic.20.8. The structure of Cestodes's reproductive system:
A and B different kinds of tapeworms; 1 – testis, 2 – sperm duct, 3 – cyrrus, 4 – ovarium, 5 – oviduct, 6 – yolk body, 7 – ootype, 8 – uterus, 9 – vagina, 10 – Mellis's body (by K.I.Skriabin, R.S.Schults,1929).

end, there is a head or scolex with attachment organs (suckers, bothriae and hooks). Next to the scolex is neck with young, growing segments. In the middle part of the body the segments are hermaphroditic, in the posterior part they are mature with dilated uterus filled with ova. These ova, each surrounded by a shell, emerge from the proglottids through either the pore or the ruptured body wall, leave their host with the faeces, and are deposited on the leaves, in water or in other places from which they can be picked up by another animal.

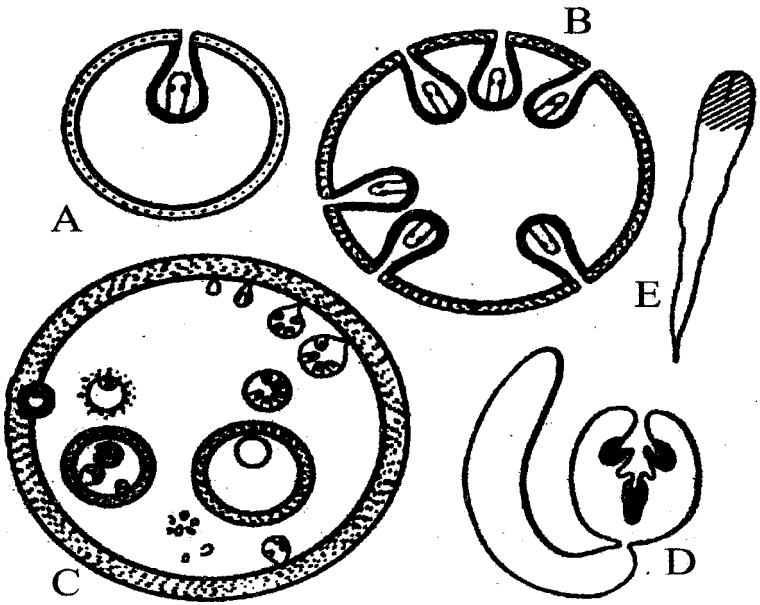
Body is covered by tegument, which is morphologically similar to that in flukes, but functionally to the vertebrate's intestine mucosa. It contains antiproteolytic enzyme, which prevent it from digestion in intestine.

Cestodes lack digestive system; they adsorb nutrients through entire body surface.

They lack respiratory system too. Because of oxygen lack environment, metabolic processes are based on simple fermentation.



Pic.20.9. The eggs of cestodes:
A – of teneids, B – of Heminolepis nana, C – rat's tapeworm, D – of dippilidum, E – Diphyllobothrium latum (by U.A. Berazantsev and E.G.Abtushenko,1976).



Pic.20.10. The structure of cestodes' larvae:
A – cysticercus, B – cenur, , C – echinococcus, D – cysticercoid E – plerocercoid (by E.N.Pavlovsky,1951).

Excretory system is presented by protonephrids. Main protonephridic trunks are on a both sides of the body.

Nervous system is presented by scolex ganglion and two nervous cords, which extend throughout the body.

Reprodactive system is well developed in mature proglottids. It is presented by ovarium, yolk body, vagina, underdeveloped uterus, testicles, ductus deferens, cyrrus (pic 20.8). They have cross insemination.

Cycle of development starts from egg passing out of the human with the faeces (pic 20.9). It contains embryos, which can start to develop in intermediate host digestive system. It has hooks. It burrows the walls of the intestine and ultimately reaches the muscles, liver, lungs by the way of blood and lymph vessels.

There, it transforms to larva. Larvae of different Cestodes have different structure. There are five types of Cestodes larvae (pic 20.10):

1. The cysticercus. It has sphere shape with head pushed inside. Head has suckers. There is fluid within the sphere. The head can come out in some conditions.
2. The cenur – it is a sphere with several pushed inside heads.
3. The cysticercoid – it has a sphere with a head pushed inside and tail coming out of sphere.
4. The echinococcus – it is a big mother sphere with many daughter spheres inside. There are scolexes in the daughter spheres. Sphere's cavity is filled by metabolic parasite wastes.
5. The plerocercoid – it has worm-like shape. On the anterior end, there are two attachment grooves (bothriae).

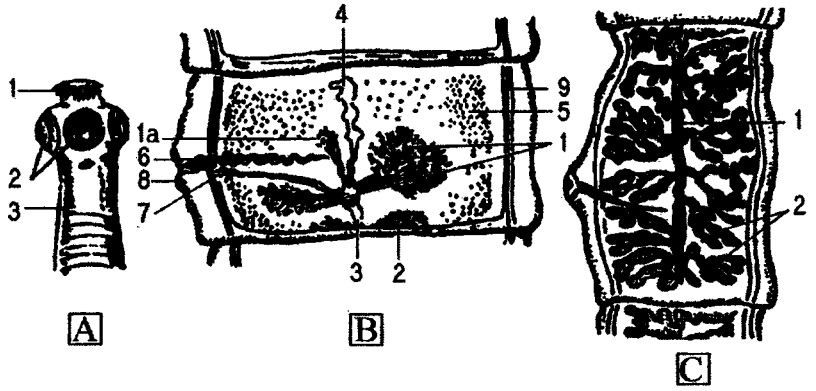
Entered final host, larva matures with help of digestive enzymes. The head comes out and attaches to the intestine wall. The sphere is destroyed. Definite hosts can be infected through eating meat of intermediate hosts with larvae. Final hosts, as well as, intermediate hosts are vertebrates.

Diseases, which are caused by tapeworms, are called cestodiases. They are zoonosis biohelminthoses and contact anthroponosis helminthoses (hymenolepiasis).

We will discuss main representatives of Cestoda Class, which are human parasites.

Taenia soleum (The pork tapeworm) – is a cause of teniasis. Mature form lives in the human intestine, whereas larva stages live in muscles, eyes, brain of a human. It can be found worldwide.

Parasite can be 3 meters long. There are four suckers and a crown of hooklets on the scolex (pic 20.11). In hermaphroditic proglottids, the ovarium has three lobes. In mature proglottids, the uterus branches into 7-12 side branches. Eggs are oval and have three shells. The external one exists only in uterus. Second is formed by onchosphere. It is golden brown in color, thick and rough. Third, the internal one, surrounds onchosphere. It is thin. Eggs measure 20-44 by 28-38 mcm (pic



Pic.20.11. The Taenia soleum:

A – scolex (1 – crown of hooklets, 2 – suckers, 3 - neck); B – hermaphroditic segment (1 – ovarium, 1a – third lobe of ovarium, 2 – yolk body, 3 – ootype, 4 – uterus, 5 – testis, 6 – sperm duct, 7 – vagina, 8 – sexual cloaca, 9 – excretory canal); C – mature segment (1 – main canal of uterus, 2 – side branches) (by A.A.Slusarev,1970).

20.9,1).

The final host is a human. The intermediate hosts are pigs and very rare human (pic 20.11). A pig becomes infected while eating food contaminated by human faeces with parasite proglottids. In the stomach, onchospheres leaves proglottids and travel to muscles. Two month later, they transform to cysticercus.

The eating of uncooked, infected pork may lead to infection with tapeworms. In the intestine, the cysticercus pulls out scolex and attaches to intestine wall. Than, cysticercus begins to produce proglottids. It becomes mature after 2-3 months after invasion.

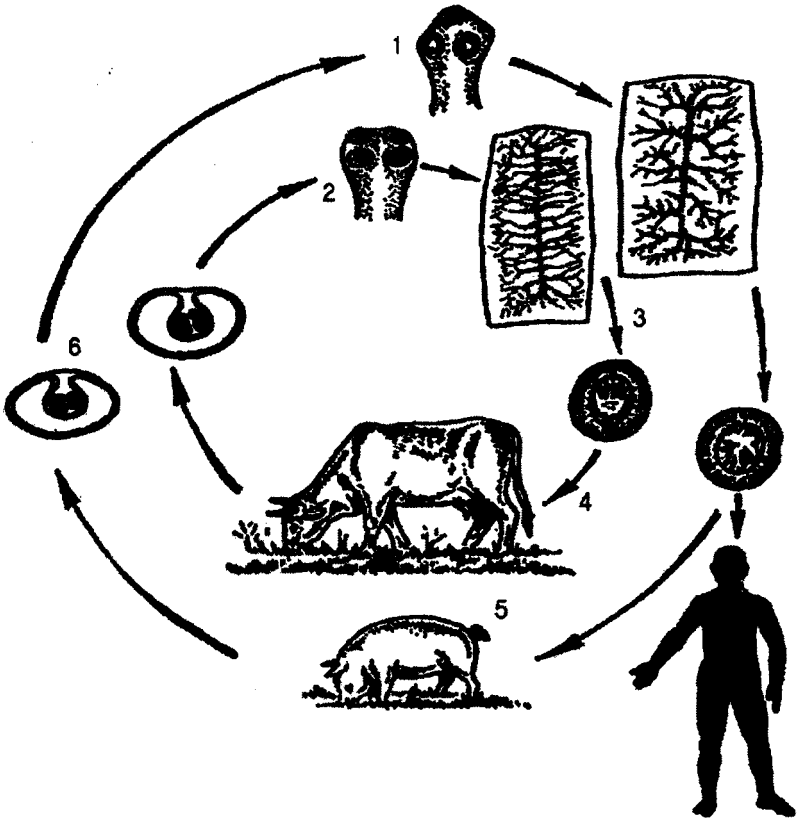
Pathogenic action is due to mechanical damage and nutrients lost. The digestive disorders, anemia, fatigue occur.

Having vomiting, patients with teniasis may push tapeworm proglottids back to the stomach. Thus, they release oncosperes, which can burrow stomach wall and travel to muscles, brain and eyes by the way of blood and lymph vessels. Therefore, they may cause cysticercosis of brain and eyes – the severe disease of human.

Diagnostics is based on examination of faeces for the mature proglottids. It is important to count number of side branches of uterus. Among serologic methods, the indirect hemagglutination test and ELISA are used.

Preventive measures include the escape of uncooked pork eating. It is also important to set government food inspection of suspicious meat and to reveal and treat ill patients.

Taeniarhynhus saginatus (The beef tapeworm) – it is exciter of teniarhynchiasis. Mature form lives in the human intestine. It can be found

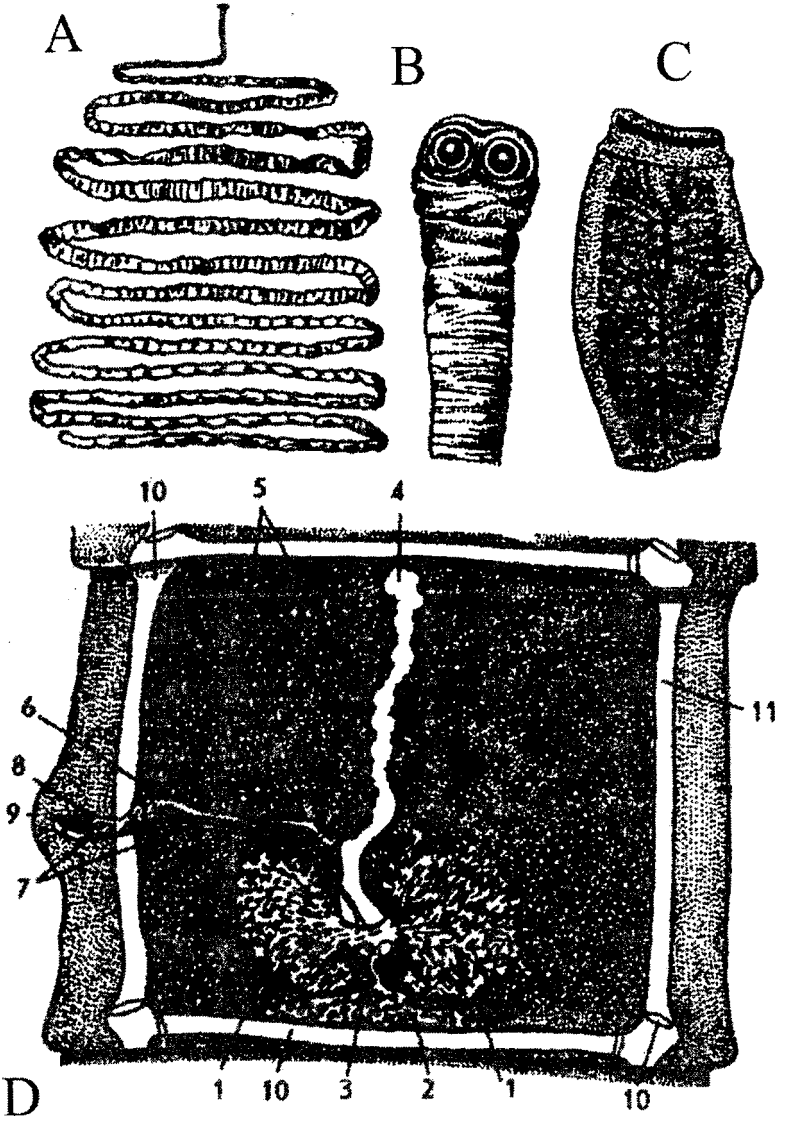


Pic.20.12. The life cycle of Taenia soleum (1) and Taeniarhynchus saginatus (2): 3 – mature segments, 4 – eggs, 5 – intermediate hosts, 6 – measles (by G.Piekarsky, 1962 with changes).

worldwide (pic 20.13).

Parasite can be 4-10 meters long. There are four suckers on the scolex. In hermaphroditic proglottids, the ovarium has two lobes and uterus does not branch. They have square shape. In mature proglottids, the uterus branches into 17-34 side branches. They are extremely long. Eggs are similar to Taenia soleum. Thus, there are no differences in egg shape; all of them are called "teneid's eggs". In one mature proglottid, it can be more than 175 thousands of eggs. One mature Taeniarhynhus saginatus can deliver about 2500 proglottids per year.

The final host is a human. The intermediate hosts are cows (pic 20.12). Mature proglottids are exerted with faeces by groups of five-six proglottids. A cow



Pic.20.13. Taeniarhynchus saginatus:

A – mature parasite, B – scolex, C – hermaphroditic segment, D – mature segment; 1 – ovarium, 2 – yolk body, 3 – Mellis's body, 4 – uterus, 5 – testis, 6 – sperm duct, 7 – vagina, 8 – cyrrus, 9 – sexual cloaca, 10 – excretory canals, 11 – nerve cord (by A.A.Slusarev,1970).

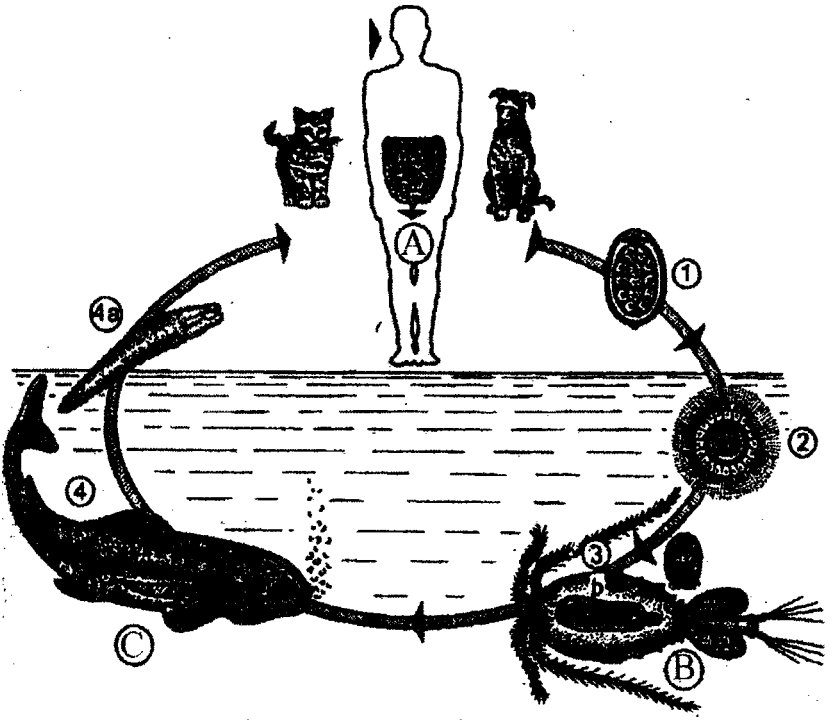
may ingest these proglottids. In the muscles, the cysticercus is formed. The development cycle is similar to Taenia soleum. It is important to note that proglottids can pass out and actively crawl over the body and on the linen. It may attract patient attention. Have eaten infected meat, a human becomes infected. The head pulls out of the cysticercus and attaches to the intestine wall.

Clinically, teniarhynchiasis is similar to teniasis. However, there is no cysticercus formation in the brain and muscles.

Diagnostics is based on examination of faeces for the mature proglottids. It is important to count number of side branches of uterus

Preventive measures include escape of uncooked beef eating. It is also important to set government food inspection of suspicious meat and to reveal and treat ill patients.

Diphyllobothrium latum (The fish tapeworm) – is exciter of diphyllobothriasis. Mature form lives in the human intestine. It can be found in regions with many rivers, lakes and ponds.



Pic.20.14. The life cycle of Diphyllobothrium latum:

A – definite host, B – intermediate host, C – additional host; 1 – invasional eggs, 2- coracidium, 3a – young larva with hooks, 3b – procercoid, 4,4a – plerocercoid (by G.Piekarsky,1962).

Mature worm have strobila 7-10 meters long. There are attachment grooves (bothriae) on the scolex. They help to attach to intestine vilia. Strobila has about 4000 of proglottids. Immature proglottids are short. Mature proglottid is more wide than tall. Uterus has helixes, which form rosette. It opens on anterior side of proglottid. There are many eggs in faeces. Eggs are oval, brown in color, with operculum on the one pole. Eggs measure 70-83 by 50-54 mcm (pic 20.9,5).

Final hosts are human and animals eating fish (cats, dogs, foxes, bears). There are two intermediate hosts: the first is small Crustacean (Copepoda), the second is fish (pic 20.14). If eggs reach water, they hatch into coracidium. Coracidium is ciliated larva. It has three hooks pairs. Coracidium need to be ingested by small Crustacean. In its intestine, the coracidium lose cilia and transforms to procercoid. The procercoid is elongated larva with six hooks on the posterior part of the body. If small Crustacean is ingested by fish, the procercoid travels to muscles and transforms to plerocercoid. In the organism of big predatory fishes, plerocercoids can accumulate. That means that they are reservoir hosts.

Parasite eats host food. It can selectively adsorb vitamin B12 causing B12 deficiency anemia. It also causes nutrients lost. It can damage intestine mucosa. Group of parasites can cause intestinal congestion.

Peoples can be infected while eating uncooked fish or fresh caviar.

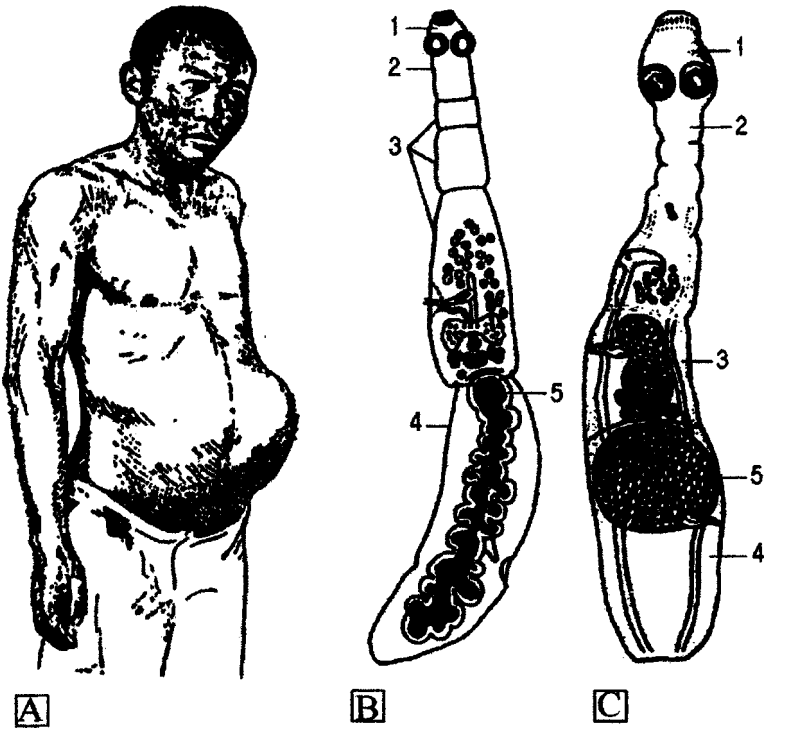
Diagnostics is based on examination of faeces for the eggs.

Preventive measures include the escape of uncooked fish eating. It is also important to set government food inspection of suspicious fish and to reveal and treat ill patients.

Echinococcus granulosus (The dog tapeworm) – is exciter of echinococciasis. It is zoonosis biohelmithosis. In a human, it occurs in larva stage. It can be found worldwide.

Mature organism is about 2-6 mm long. Strobila has three-four segments (pic 20.15,b). There are four suckers and proboscis with two crowns of hooklets on the scolex. Next to last segment is hermaphroditic. The last one is mature with uterus containing about 5000 eggs with onchospheres. Eggs look like Tenia soleum eggs.

The final hosts are dogs, wolves, jackals. The intermediate hosts are cows, pigs, camels and human. Parasite eggs are in the faeces of final hosts. Furthermore, mature segments can crawl out of intestine and leave eggs on the hair. A human is infected by swallowed eggs. In the intestine, onchospheres leave egg. It burrows the walls of the intestine and ultimately reaches the muscles, liver, and lungs by the way of blood and lymph vessels. There it transforms to larva. The walls of larva include external capsule and internal parenchymal shell. On the internal parenchymal shell, the daughter vesicles are formed. In these vesicles, there are scolices. Human is a deadlock branch for Echinococcus granulosus. Final hosts eat affected organs of animals. Thus, they become infected.



Pic.20.15. The Echinococcus granulosus:

A – patient with liver echinococciasis, B - Echinococcus multilocularis, C – Alveolococcus multilocularis; 1 – head, 2 – neck, 3 – hermaphroditic segment, 4 – mature segment, 5 – uterus with eggs (by E.N.Pavlovsky, 1951 with changes).

Clinically, Echinococcus invasion affect liver functions (pic 20.15,a), lung functions and some other organs. Rupture of Echinococcus vesicle leads to internal organs insemination by daughter scolices. It results in anaphylactic shock development and sudden death.

Laboratory diagnostics is based on serologic reactions: immunofluorescent test, indirect hemagglutination, latex-agglutination test, ELISA and others.

Personal preventive measures are in following personal hygiene (washing hands after contact with dog and before meal). Social preventive measures are based on treating of ill dogs, veterinary control of meat for dogs.

Alveolococcus multilocularis – is exciter of alveolar echinococciasis. It is zoonosis biohelmithosis. In a human, it occurs in larva stage. It can be found worldwide, but rare than Echinococcus.

Mature stage of parasite is similar to Echinococcus (pic 20.15,c). Distinguishable features are number of hooklets and uterus of sphere shape.

The final hosts are dogs, wolves, foxes. The intermediate hosts are mice, and very rare – human. Human is a deadlock branch for it. Larva stage is rough vesicle with smaller vesicles inside. They are without fluid. Each vesicle has small parasite scolex. It can grow outside to surrounding tissue. It destroys surrounding tissue. The liver and lungs are commonly affected. The metastases to CNS and lymph nodes may occur. It is more malignant than echinococciasis.

Diagnosis has to be proved by serological tests.

Personal preventive measures are in following personal hygiene (washing hands after contact with dog and before meal). Social preventive measures are based on treating of ill dogs, veterinary control of meat for dogs, sanitary control of flaying enterprises.

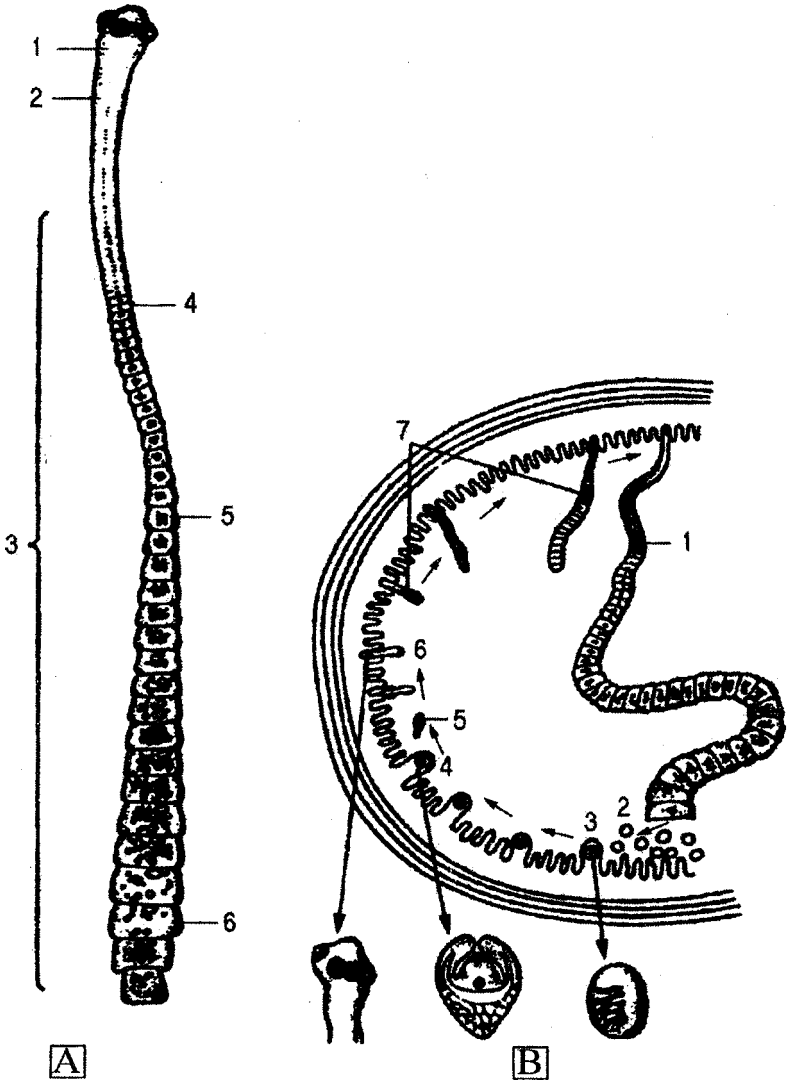
Hymenolepis nana (The dwarf tapeworm) – is a cause of hymenolepiasis. It is contact anthroponosis. It can be found worldwide especially in countries with arid climate. Children are always more infected than adults are.

Mature organism is about 1-5 cm long. Strobila has 200 and more segments (pic 20.16). There are four suckers and proboscis with crown of hooklets on the scolex. Scolex is pear-shaped. Eggs are elongated with transparent membranes. Eggs measure 45 by 37 mcm. They have onchosphere with six hookers within (pic 20.9,2).

Human is final and intermediate host, as well. Swallowed eggs release onchospheres. The onchospheres borrow intestine wall and attach to it. Here, the cystecercoids are formed. Several days after, the intestinal vilia is destroyed by parasite. They fall into the intestine lumen. Within about 2 to 3 weeks, it becomes adult tapeworm. Up to 1500 parasite can be in the intestine at the same time. After 4 weeks, the first egg can be found in the stool. Life span of parasite is 1-2 months. Eggs can be preserved in the intestine. Thus, they can develop again without leaving the organism. It is called autoinvasion. In this way a very heavy infection may be aquired, especially in children. However, most of the eggs pass out of the organism. The eggs of parasite need to be ingested by cockchafer of Tenebrio genus. Within it the cystecercoids are formed. Ivasion occurs by eating improperly baked dough. In the human intestine, the cystecercoids give rise to mature parasites.

Affected children suffer from intestine vilia lost, stomachache, fatigue, headache, irritability.

Peoples are infected by eating contaminated food by parasite eggs. Contact infection with this worm from man to man is possible, because the mature eggs can develop further well without intermediate host. It is especially possible when hands are contaminated by eggs. And these eggs can come in to the organism with various foodstuffs. There are no eggs on vegetables, fruits and in water. So, none can be infected by eating these food and drinking water.



Pic.20.16. Hymenolepis nana:

A – mature parasite (1 – scolex, 2 – neck, 3 – strobilla, 4 – immature proglottid, 5 – hermaphroditic proglottid, 6 – mature proglottid); B – cycle of development in human intestine (1 – mature parasite, 2 – egg 3- oncosphere, 4 – cysticercoids, 5 – cystecercoid in intestinal lumen, 6 – scolex attachment to intestinal wall, 7 – strobilla growth) (by E.N. Pavlovsky, 1951 with changes).

Diagnostics is based on examination of faeces for the eggs. Among serologic methods, the indirect hemagglutination test and ELISA are used.

Personal preventive measures are in following personal hygiene (washing hands after contact with dog and before meal). Social preventive measures are based on sanitary procedures in children establishments, health care education among children.

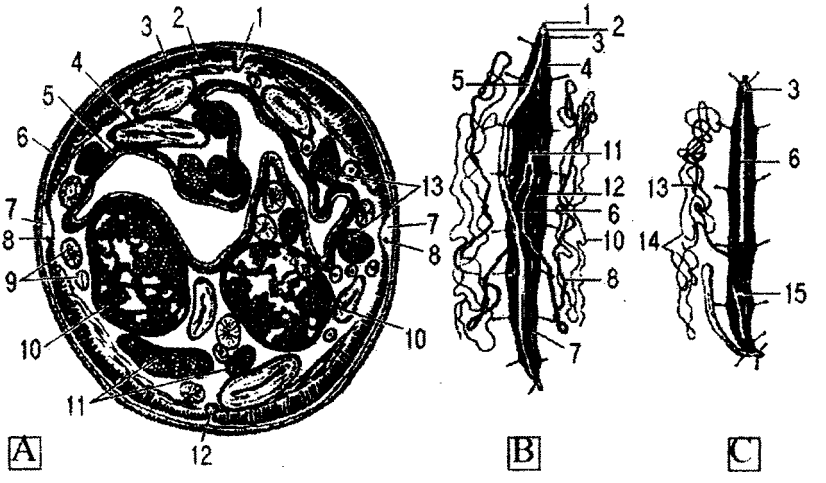
20.2 Phylum Nemathelminthes.

The nematodes, eelworms, and roundworms comprise a large phylum, Nematoda, with some 500 thousands recognized species. The members of this phylum are ubiquitous. They live in water, in land, in animals.

Nemathelminthes are bilaterally symmetrical, cylindrical, unsegmented worms. They develop from three embryonic layers. They have primary body cavity, external cuticle with underlying muscles, organs systems (digestive, excretory, nervous, reproductive), two sexes, terminal part of digestive system with anus.

There are several classes in Nemathelminthes phylum. However, only one of them has medical importance. It is Nematoda Class.

The morphology of this Class is similar to whole phylum (pic 20.17). They are covered by flexible, thick cuticle, which is molted as they grow. Their muscles



Pic.20.17. The structure of round worms:

A – cross section of Ascaris (1,7,12 – dorsal, lateral and visceral bolsters of hypoderm, 2,3 – muscular cells, 4,9 – ovarium, 5 – gut, 6 – cuticle, 8 – excretorycanal, 10 – uterus, 11,13 - oviduct); B and C – internal structure of female and male (1 – lips, 2 – nervous circle, 3 – pharynx, 4 – phagocytic cells, 5 – esophagus, 6 – middle gut, 7,12 – lateral and visceral bolsters of hypoderm , 8 – oviduct, 9 – uterus, 10 – ovarium, 11 – vagina, 13 – sperm duct, 14 – testis, 15 – ductus defferens) (by A.A. Slusarev,1970).

constitute a layer beneath the epidermis and extend along the length of the worm, rather than encircling the its body. These longitudinate muscles pull both against the cuticle and against the pseudocoel. Digestive system is made of anterior, middle and posterior intestine. The excretory system is made of protonephridiums. Their number is small. Gases exchange occurs through entire parasite surface. Parasites metabolic processes are based on simple fermentation because of lack of oxygen. Nervous system is presented parapharyngeal nerve circle and nerve cord extended from it. These cords are connected by commisuras. Sense organs are presented by touch feeling cells and by cells percepting chemicals. Reproductive organs have tubular shape. In female they are coupled, in male aren't. Male reproductive system is presented by testicles and sperm duct that enter terminal intestine. Female reproductive system includes couple of ovaries, couple of oviducts, couple of uteri, and common vagina that opens on the ventral side of the body. All internal organs are in the primary body cavity filled by fluid. It facilitates gases and metabolites exchange and forms hydrostatic skeleton.

Reproduction is only sexual. Fertilized egg starts to develop in uterus. However, larva formation in the geohelminthes can occurs only outside with oxygen access. The biohelminthes deliver living worms. The larva molts several times. In development cycle of majority of Nematodes there is no host interchange.

Accordinary development cycle features, nematodes are divided into geohelminthes (Ascaris lumbricoideus, Trichocephalus trichirus, Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis), biohelminthes (Trichinella siralis, Dracunculus medinensis, Filariidae, Wucheria bancrofti and others) and contact helminthes (Enterobius vermicularis).

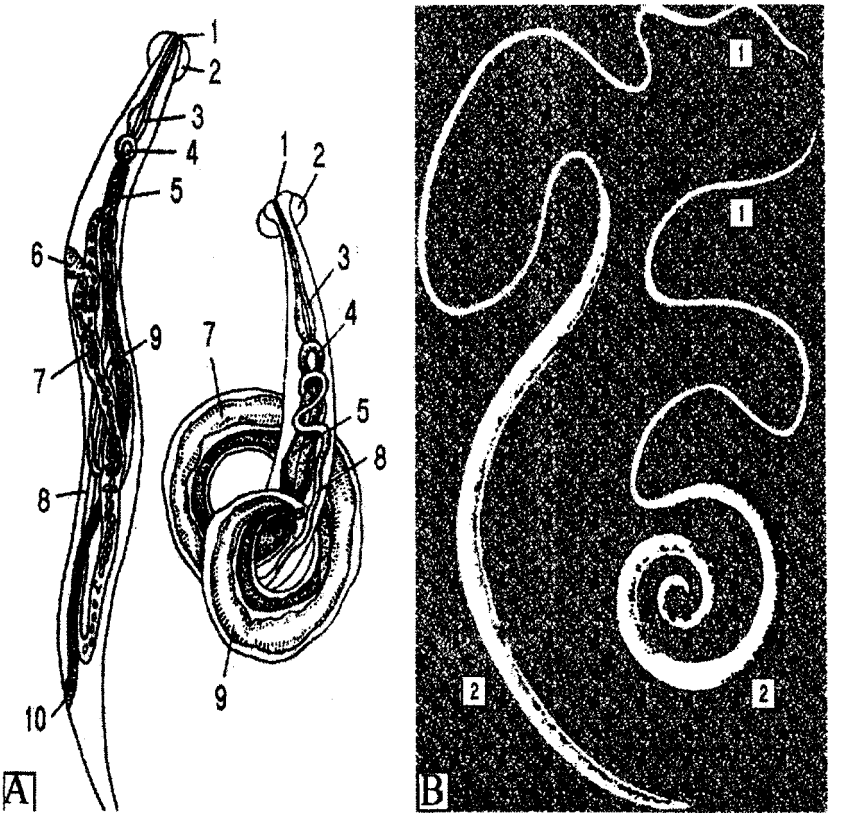
20.2.1 Human geohelminthes of Nematoda Class.

Trichocephalus trichirus (The whipworm) – is a cause of trichocephaliasis. It is anthroponosis geohelminthosis. Mature form lives in caecum, yet, other portions of intestinal tract may also become infected in cases of massive invasion. It can be found almost worldwide.

Trichocephalus trichirus is a round helminth with the tread-like anterior end, which is longer than the posterior end. In the anterior end, there is only esophagus.In the posterior end, there is intestine and reproductive system. Eggs have barrel shape with thick cuticle of brown color. There are two colorless "plugs" on the poles. Eggs measure 50-54 by 22-23 mcm. One mature female Trichocephalus trichirus can deliver about 60000 eggs per day (pic 20.19,5).

Trichocephalus trichirus sucks the blood. The anterior end burrows intestine mucosa.

Trichocephalus trichirus is only human parasite. Eggs escape into external environment. They develop in the soil during 20-25 days with temperature about



Pic.22.18. Trichocephalus trichirus and Enterobius vermicularis:

A – male and female of Enterobius vermicularis (1 – mouth, 2 – vesicle, 3 – esophagus, 4 – bulbus, 5 – midgut, 6 – vagina opening, 7-9 – parts of reproductive system, 10 - anus); B – male and female of Trichocephalus trichirus (1 – anterior end, 2 – posterior end) (by N.B. Gofman-Kadoshnicov,1966).

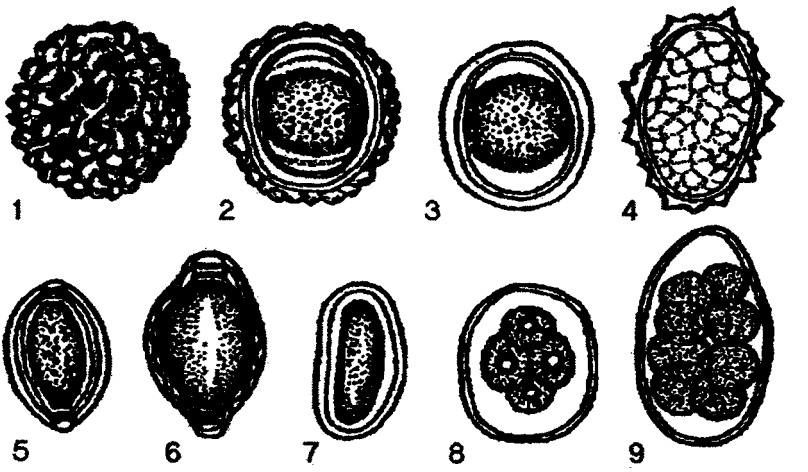
25-30 centigrade. If invasional egg comes into human intestine, it loses its shells and mature. Life span of Trichocephalus trichirus is about 5-6 years.

Human becomes infected by eating contaminated vegetables, berries or drinking water.

Pathogenic action of Trichocephalus trichirus is anemia development and psychological disturbances because of acute stomach ache. They may penetrate intestine wall and cause peritonitis. Trichocephalus trichirus may cause appendicitis.

Diagnostics is based on faeces examination for eggs.

Personal preventive measure is to follow personal hygiene rules. Social preventive measures are health care education.



Pic.20.19. The nematodes' eggs:
1,2,3 – of Ascaris, 4 – of Ascaris (unfertilized), 5 – of Trichocephalus trichirus, 6 – of tominx, 7 – of Enterobius vermicularis, 8 – of ancylostomids, 9 – of trichostrongylid (by U.A. Berezantsev and E.G.Avtushenko,1976).

Ascaris lumbricoideus (The large intestinal roundworm) – is a cause of ascariasis, which is anthroponosis geohelminthosis. Mature form lives in the small intestine. It can be found worldwide.

Mature female is about 40 cm long, whereas male is only about 15-25 cm. It has cylindrical body. The tail end of male worms is curved ventrally. Fertilized egg is oval and has a thick multi-layer membrane, with the external membrane of the egg being yellow-brown in color and covered with large trabecules. In the central part of the egg, there is a circle blastomere. Eggs measure 50-70 by 40-50 mcm (pic 20.19,1). Unfertilized eggs are markedly elongated; the external membrane of the egg is dark yellow, thin, trabecular. The eggs are filled with yolk cells. They measure 50-100 by 40-50 mcm (pic 20.19,4). One mature female Ascaris lumbricoideus can deliver about 240000 eggs per day.

Ascaris lumbricoideus is only human parasite. Eggs escape into external environment. They develop in the soil during 16-18 days with temperature about 13-36 centigrade (optimal is 24-30 centigrade). The terms can be changed, if temperature has been deviated from optimum.

Human becomes infected by eating contaminated vegetables, berries. If invasional egg comes into human intestine, it loses its shells and bores intestine wall. Then, it travels to lungs by blood vessels. Then, the larva moves up along respiratory pathways. Reaching the pharynx, it can be swallowed again. This migration lasts for two weeks. Repeatedly entered intestine, the larva becomes ma-

ture. It takes 2-2.5 months. Life span of Ascaris lumbricoideus is about a year. Ascaris lumbricoideus does not attach to the intestine wall. They are fixated just by pushing out intestine walls by their ends. They are very mobile. Sometimes they can enter bile ducts, pancreatic ducts, esophagus and even respiratory pathways.

Patients, who suffer from ascariasis, have following symptoms: headache, fatigue, dizziness. Ascaris can cause intestinal congregation and mechanical jaundice.

Migrating larvae are the cause of allergic reactions, especially in lungs, referred as pneumonia with massive eosinophilic infiltration.

Early diagnostics can be made of a stage of migrating larvae (sputum examination, serological reactions, revealing Lefler's infiltration during X-ray examination). Intestinal ascariasis diagnosis depends upon the demonstrationof the ova in the patient stool.

Personal preventive measures are to follow personal hygiene rules. Social preventive measures are health care education, treatment of ill patients, decreasing flies population as mechanical vectors of eggs.

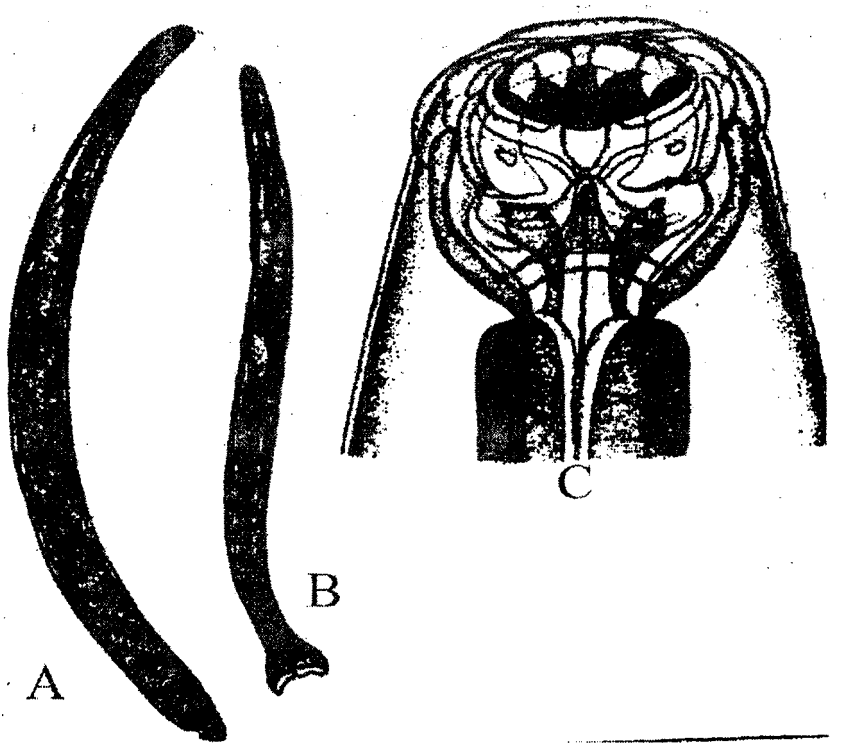
Ancylostoma duodenale, and Necator americanus – are exciters of ancylostomiases, which are anthroponosis geohelminthoses. Both parasites can be found in tropics and subtropics.

Both parasites live in the duodenum and proximal parts of small intestine. They are similar in structure. They cause same clinical symptoms. In general, they are called ancylostomids. Males are about 8-11 mm long, females – 10-18 mm long. Body is red-yellow in color. The anterior end is narrower than posterior one. The anterior end is curved dorsally and includes buccal capsule. In Ancylostoma duodenale, it has four cuticular teethes, whereas in Necator americanus, it has two crescentic cutting plates. They catch small region of intestine by buccal capsule and suck the blood. The posterior end is wider. It contains bursa copulatrix, which is different in Ancylostoma and Necator.

Ancylostoma duodenale eggs are colorless, oval, having dull poles, covered by transparent membrane. In the central part of the egg, there are two to four circle blastomeres. Eggs measure 56-60 by 34-40 mcm. If eggs are in the faeces for more than a day during warm season, they can divide and form larvae, called rabitiform larvae. Necator americanus eggs are the same. One mature female delivers about 10000 eggs per day (pic 20.19,8).

The rabitiform larvae are invasional. The anterior intestine has esophages and round bulbus with crescentic cutting plates. Larva eats rotted organic substances. It molts twice. After second molt, cuticle delaminates but not comes off. So, larva preserves like in the shell. At this time, anterior intestine is rebuilt to cylindrical form. The lava becomes invasional and are called filariform larva.

The human can be infected by two ways: orally and through undamaged



Pic.20.20. Ancylostoma duodenale:
A – female, B – male, C – head (there are teethes in oral capsule) (by P.B.Gofman-Kadoshnikov, 1966 with changes).

skin. But, larvae prevalently enter the body through the mouth. If they have come through the mouth, they do not migrate. They just catch intestine wall and start maturing. It takes 4-5 weeks to mature for Ancylostoma duodenale larvae, and 8-10 weeks for Necator americanus larvae. The mature Ancylostoma duodenale life span is 1-3 years, rare 5-6 years. The mature Necator americanus life span is 10-15 years.

The transdermal invasion is possible if larvae bore undamaged skin while working with soil. It is a main way for Necator americanus, but it is possible for Ancylostoma duodenale too. Bored under the skin, the larvae travel to lung with blood flow. Than, they crawl along respiratory tree to the pharynx. In the pharynx, they are swallowed. Thus, they finally reach intestine. Necator americanus females start to produce eggs 6 week after transdermal invasion, whereas Ancylostoma duodenale females – 6-8 months after transdermal invasion.

Patients complain on stomachache, digestion disturbances, fatigue, headache,

emaciation, memory shortening. Children development becomes slower. All of these are due to blood lost.

Laboratory diagnostics is based on faeces examination for eggs and larvae. Serological tests, such as immunofluorescens test, indirect hemagglutination, ELISA, are also used.

Personal preventive measures are in following personal hygiene (washing hands after contact with dog and before meal). In the ancylostomiasis regions, everyone has to wear shoes while walking on the land. Social preventive measures are based on treating of ill patients, sanitary control of construction projects of towns and villages for sewage system, health care education.

Strongyloides stercoralis (The dwarf treadworm) – is a cause of strongyloidiasis, which is anthroponosis geohelminthosis. Mature form lives in the small intestine. It can be found in regions of temperate climate, but extremely often in tropics and subtropics. It has complicate life cycle with alternation of parasitic and free living stages.

Parasitic females are 2.2 mm long with cylindric esophagus without dilatations. Freeliving females are less (1 mm) with esophagus having dilatation called bulbus. Parasitic and free-living males are similar to each other. Body's length is about 0.7 mm. Esophagus has bulbus.

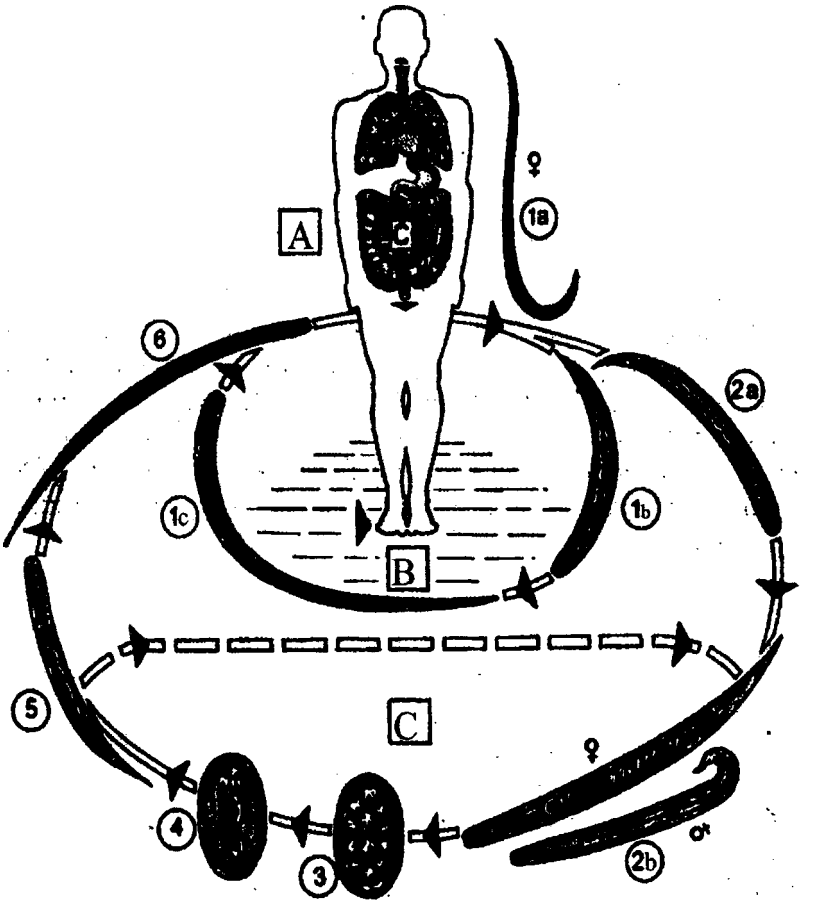
Eggs measure 5-5.8 by 3-3.4 mcm. In these, rhabditiform larvae develop and emerge from the eggs. These larvae are about 2.5 by 1.6 mcm. They may have two ways of development (pic 20.21).

1. *Direct development.* The rhabditiform larvae escape the intestine and live in the soil for a while. During this living, they grow, molt twice and become the infective, so-called filariform larvae. They can enter human body through mouth with contaminated food and, which is more often, transdermaly (through undamaged skin). If they have entered transdermaly, they migrate as Ancylostoma duodenale larvae (through blood, lungs, pharynx and esophagus). When they have got to the intestine, they start to mature. It takes about two weeks. Then, mature organism copulates. 17 days after copulation, females enter intestine wall and start to produce eggs. Mature female can deliver about 50 eggs per day.

2. *Indirect development.* The rhabditiform larvae escape the intestine and live in the soil. There, they transforms to mature female and male organisms. They produce rhabditiform larvae again. They become filariform larvae, as in direct development.

The rhabditiform larvae can developp into filariform larvae even in the intestine of the same human being and these immediately penetrate the intestinal wall, enter the blood vessels and perform migration through the lungs until they reach intestine where they mature. This is called autoinvasion.

Patients with strongyloidiasis suffer from digestion disturbances, emaciation. On the early stage, the allergic reactions (fever, skin irritation, bronchitis) are



Pic.20.21. The life cycle of Strongyloides stercoralis:

A – intestinal development, B – direct development, C – indirect development; 1a – mature worm, 1b - rhabditiform larva, 1c - filariform larva, 2a - rhabditiform larva in faeces, 2b – free living generation, 3 – egg, 4 – egg with larva, 5 - rhabditiform larva, 6 - filariform larva (by G.Piekarsky, 1962).

observed.

Laboratory diagnostics is based on faeces and duodenal fluid examination for eggs and larvae. In migration stage, larvae can be revealed in the sputum. Serological tests, such as immunofluorescens test, indirect hemagglutination, ELISA, are also used.

Preventive measures are the same as for Ancylostoma duodenale invasion.

20.2.2 Human contact helminthes of Nematoda Class.

Enterobius vermicularis (The pinworm) – is a cause of enterobiasis, which is contact anthroponosis helminthosis. Mature form inhabits lower small intestine. It can be found worldwide.

Parasitic females are 10 mm long, whereas males are 2-5 mm long (pic 20.20,a). The posterior end of female is curved spirally. They eat intestinal contents. Eggs are asymmetrically oval with one side curved outside and the other flat. The membrane is multilayer, smooth, and colorless. Inside of the eggs, there is embryo on different stages of development. Eggs measure 50-60 by 20-30 mcm (pic 20.21,7).

Fertilized females come out of intestine usually at nighttime. They pass out anus and lay their eggs in peryanal region. They may lay about 10-12 thousands of eggs during 15-45 minutes. Eggs cause inching. Eggs become mature during 6-7 hour. Eggs can get to the hand while scratching. The eggs also can be transferred to the toys, linen and other staff. If eggs are swallowed, they quickly give a rise to mature organism. The life span of mature Enterobius vermicularis is about a month. Children are especially affected. They usually have autoinvasion.

The patients with enterobiasis have troubled sleep, tiredness. Pupils lose ability to study well. Sometimes, Enterobius vermicularis can cause appendicitis.

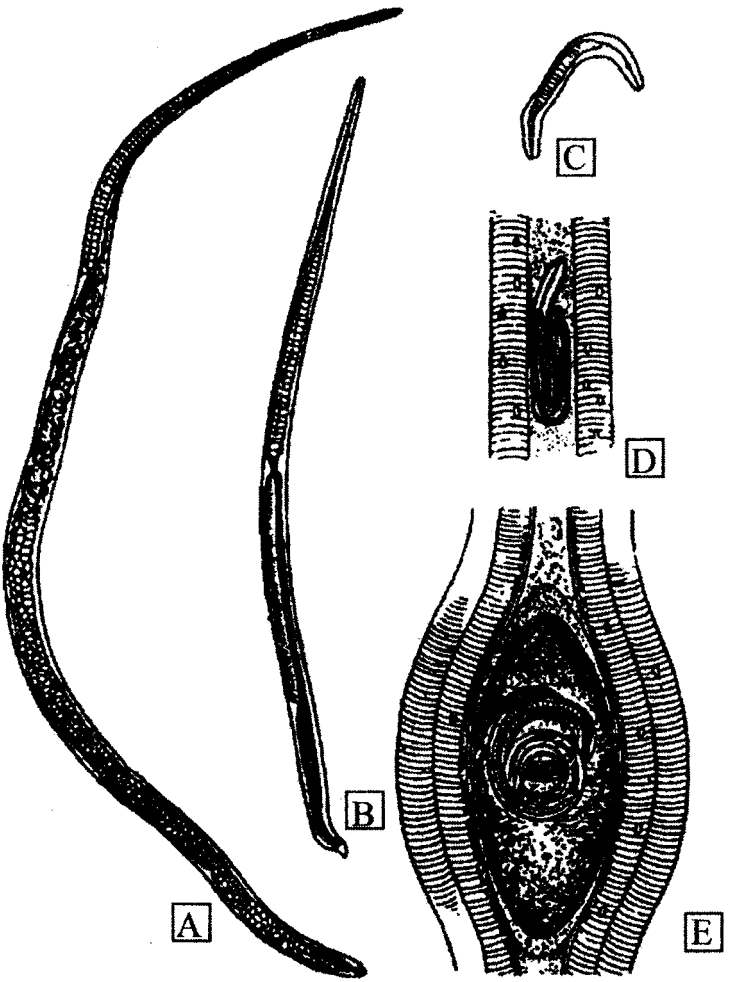
Laboratory diagnostics is based on anal folds scrape or adhesive tape smear examination for eggs and revealing living Enterobius vermicularis crawling out of anus. As a rule, there are no eggs in the faeces.

Personal preventive measures is to follow personal hygiene rules, especially by children. The pants should be worn. The cotton tampon should be placed over anus. Thus, crawling Enterobius vermicularis lays eggs in the tampon and does not cause inching. Social preventive measures include treatment of ill patients, regularly rooms tidying up, separation of ill and health children.

20.2.3. Human biohelminthes of Nematoda Class.

Trichinella spiralis (The trichina worm) - is a cause of trichinellasis, which is zoonosis biohelminthosis. Mature trchinells lie in the small intestine of animals and human being. Trichinella spiralis larvae are incapsulated in striated muscles. It can be found worldwide.

Parasitic females are 2.6-3.6 mm long, whereas males are 1.4-1.6 mm long (pic 20.22). The parasite hosts are predatory mammalians and human. Any animal, where Trichinella spiralis lives, is both final and intermediate host. Mature parasites live in the hosts intestine for 1,5 to 2 months. Males die after copulation. Females produce 1,5-2 thousands of alive larvae for their life. Larvae burrow



Pic.20.22. Trichinella spiralis:

A – female, B – male, C,D – non-encapsulated larvae in muscles, E – encapsulated larva (by P.B.Gofman-Kadoshnikov,1966).

intestine wall and enter the blood vessels. They travel throughout of organism by blood vessels, but enter only striated muscles (diaphragm, tongue muscles, masseter, deltoideus, gastrocnemius, intercostal muscles and other). The size of migrating larva is 100 by 6 mcm. The maximal length of larva in muscles is 1mm. The period of migration lasts for 2 to 6 weeks. Entering muscles, the larva is curved

spirally and is covered by shell. The shells are apt to adsorb calcium. In calcinated capsule, the larvae can survive for years.

To mature, the larvae should enter intestine of the other host. Fox example, infected rat can be eaten by pigs, dogs, foxes. The capsules are digested by digestive enzymes. The larvae are released and they mature in 2-3 day.

A human being can be infected by eating infected pork or meat of wild animals (bears, wild boar and etc.).

The clinical signs of trichinellasis are fever, headache and muscle ache, oedemata, marked eosinophilia, fatigue, digestive disturbances. The degree of clinical signs expression depends on number of swallowed parasites ranged from asymptomatic to death.

Diagnostics is based on history of disease, general examination, muscle biopsy results, immunological tests (immunofluorescent test, indirect hemaglutination, ELISA and others).

The preventive measures include obligatory microscoping of killed animals muscles for Trichinella spiralis larvae. It also includes strong termal cooking of suspicious meat. The veterinary inspection of pork and wild meat should be made on farms, meatpacking plants, and markets.

Dracunculus medinensis (The Medina worm) – is a cause of dracunculiasis of human and animals. It lives in skin derma layer near joints prevalently in lower limbs. It occurs in countries with tropic and subtropic climate (tropical Africa, India, Iran, Pakistan and so on).

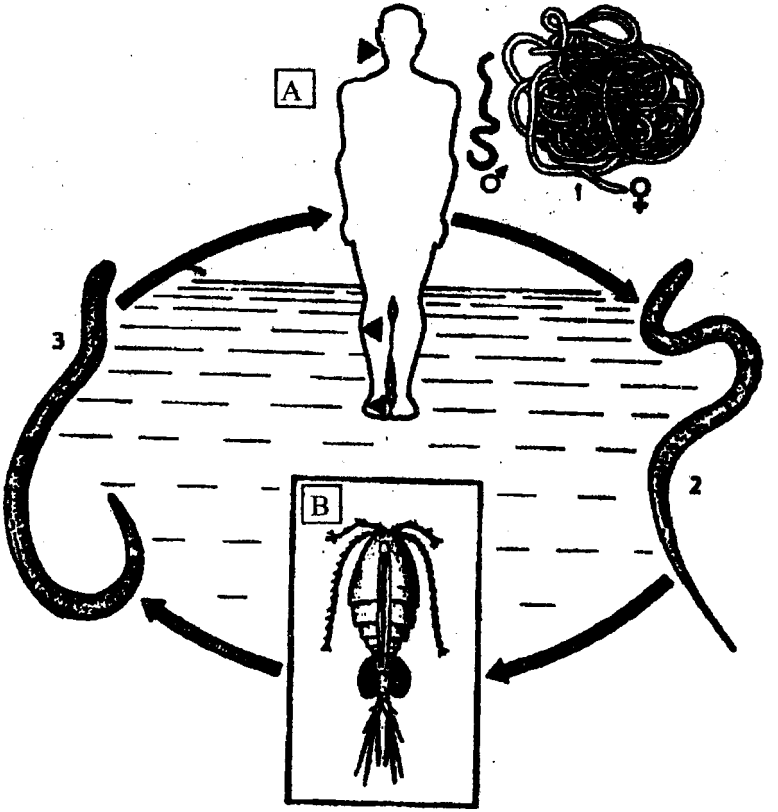
Thread-like mature female worm is up to 1.5 m. long and 1-2 mm. board – the males are only up to 2 cm. long.

The final hosts of the Medina worm are humans, monkeys, dogs, cats, wild animals. The intermediate host is small Crustacean (Copepoda). Living in human derma, Medina worm makes a thread-like roller. Near anterior female parasite end, the dracunculema (vesicle with diameter 2-7 cm filled by serum fluid) is formed. If human being touches the water, it causes severe itching. When vesicle is ruptured, the female parasite pushes out the head and lays larvae. Larvae measure 500-750 by 15-25mcm. Larvae are swallowed by intermediate host - small Crustacean (Copepoda). Within it, they transforms to invasional stage, microfilaria. The small crustacean can be swallowed with the water. In the intestine, microfilaria bores the intestine wall and enters the blood vessels by which they travel to the skin derma. In the derma they mature for a year (pic 20.23). The parasite can be loclized atypically: under the stomach serum layer, under meninges.

The typical symptoms are itching, allergic reactions on migrating larvae, tissue ulcers, which can be accompanied by secondary infection.

Diagnostics is based on skin examination for parasite. If parasite is localized atypically, it may require serological tests.

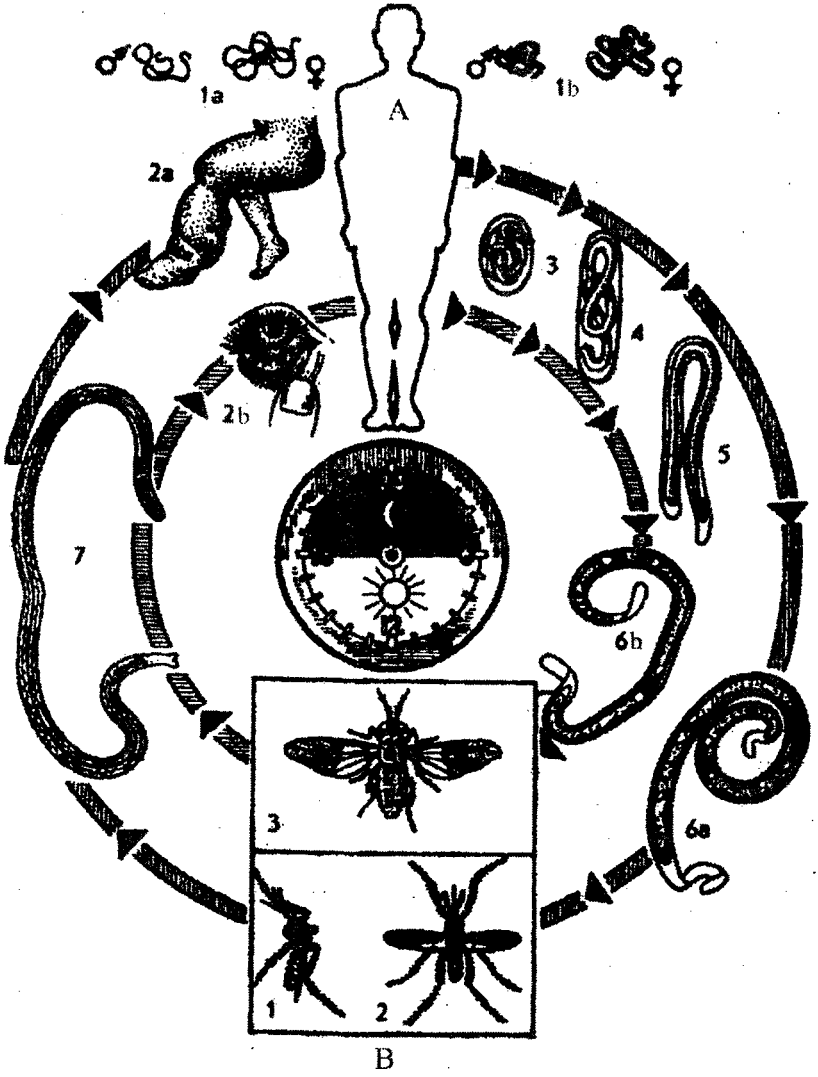
Personal preventive measures are to boil water in the dracunculiasis regions.



Pic.20.23. The life cycle of Dracunculus medinensis:
A – definite host; B – intermediate host (Cyclopus); 1 – mature helminth, 2 – free living larva, 3 – metacyclic larva (by G.Piekarsky,1962).

Social preventive measures are to provide clean, fresh water supply in the dracunculiasis regions and to treat ill people.

Nematodes of Filariidae family – are exciters of filiariasis, which are biohelminthoses with transmissive way of invasion. All parasites of this group are common in tropics. Their development requires host interchange. The final hosts are human and some other mammalian species. The intermediate hosts are sanguivorous representatives of Diptera family of insects (mosquitoes, gadflies, greases). The larva activity follows the daily rhythm. In species, which larvae are transmitted by mosquitoes, the larvae appear in blood at night. In species, which larvae are transmitted by gadflies, the larvae appear in blood at noon. It depends



Pic20.24. The life cycles of Filariidae family:

Brugia malayi and Wuchereria bancrofti (external circle) and Loa loa (internal circle):

A – definite host (1a,1b – mature helminthes, 2a – elephantiasis due to invasion of Brugia malayi and Wuchereria bancrofti, 2b – Loa loa migration to conjunctiva; 3-5 – stages of microfillaria development in human being, 6a – microfillaria of Brugia malayi and Wuchereria bancrofti in blood, 7 – larva from intermediate host); B – intermediate hosts: 1,2 – mosquitoes from Aedes genus for Brugia malayi and Wuchereria bancrofti, 3 – gadfly of Chisops genus for Loa loa (by G.Pickarsky,1962).

on vector activity. In the vector body, the larvae develop in muscles and fat body. They molt twice. Than, they becomes mature and travel to oral apparatus. When intermediate host sucks the blood of final host, the larvae enter the body of final host. Than, they travel by blood and lymph vessels throughout the body.

It is known several Filaria species, which are pathogenic for a human being and differ one from another.

Wuchereria bancrofti – is exciter of wuchereriasis.

The mature female is up to 80-100 mm. long; the males are only up to 40 mm. long. The final host is a human being; the intermediate hosts are mosquitoes of Anopheles, Culex, Aedes, Mansonia genera. Such mosquitoes attack a human being at night. In the transmitter organism, larvae develop to invasional stage during 8-35 days. Then, it moves to the mosquito proboscis. The mosquito bites the human being and enters invasional larvae to the blood. They mature for 3-18 months (pic 20.24 – external circle). Mature helminthes live in the lymph nodes and vessels. Their life span is 3-4 years, but sometimes it can reach up to 20 years. The females deliver microfilaria (127-320 by 7-10 mcm.), which migrate from deep vessels to superficial accordinary the daily rhythm.

Symptoms of disease are fever, skin eruption, oedemata. Late, after 2-7 years, the veins and lymphatic vessels are dilated by them and elephantiasis is developed (lymphatic edema of legs, sex organs, mammary glands).

Wuchereriasis is spread in West and Central Africa, South-East Asia, on Caribbean islands.

Brugia malayi – is exiter of brugiasis. The mature female is up to 55 mm. long; the males are only up to 20 mm. long. The females deliver microfilaria about 200-260 by 5-6 mcm. of size. The final host is a human being, monkeys, dogs, cats; the intermediate hosts are mosquitoes of Anopheles, Aedes, Mansonia genera.

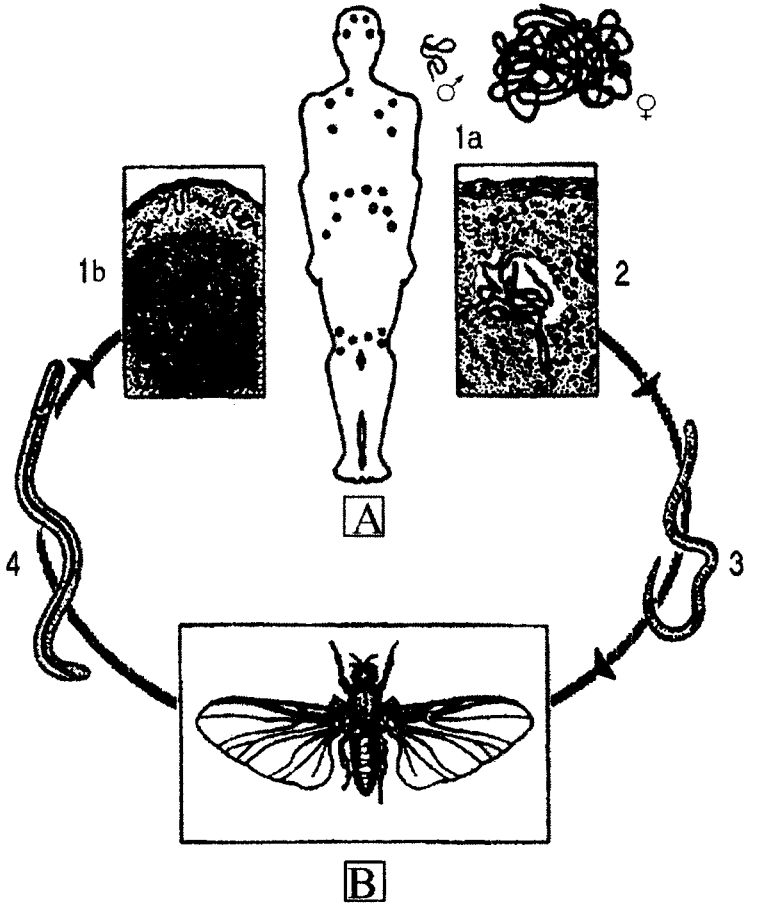
The development cycle and caused diseas is similar to wuchereriasis. Invasional larvae mature for 8-9 days (pic 20.24 – external circle).

Symptoms are similar to wuchereriasis. The difference is that elephantiasis affects upper and lower limbs, but very rare sex organs.

Brugiasis is spread in Asia (India, China, Korea, Vietnam, Thailand, Indonezia, Philppines, Malaysia).

Loa loa – the exciter of loasis. It is white, transparent worm. The mature female is up to 50-70 mm. long; the males are only up to 30-34 mm. long. The females deliver living larvae about 250-360 by 6-8 mcm. of size. Mature helminthes live in the skin derma, under the eye conjunctiva, in-between serous membranes. The human being is a final host. The intermediate host and vector is gadflies of Chysops genus. In gadflies, the microfilarias become mature for 7-10 days (pic 20.24 – internal circle).

The pathogenic action is due to allergic reaction on helminth antigens and



Pic.20.25. The life cycle of Onchocerca volvulus:

A – definite host; B – intermediate host (Simulium damnosun); 1a – mature male and female, 1b – section through onchocercosiasis node, 2 – microfillaria, migrating to derma, 3 – micrifillaria in blood, 4 – meacyclic microfillaria from intermediate host (by G.Piekarsky,1962).

due to mechanical wounding of tissue by crawling parasites. If they have come to the eye, they can cause conjunctivitis, edema of optic disc, paresis of eye moving muscles.

The loasis is common in tropical forests of West and Central Africa.

Onchocerca volvulus – the exciter of onchocercasis, which is transmissive transdermal biohelminthosis. The mature female is up to 30-50 mm. long; the

males are only up to 19-42 mm. long. The females deliver microfilariae about 285-386 by 9 mcm. of size. The final host is a human being. The mature organisms give birth to microfilariae. They travel to skin, eyes, lymph nodes. The intermediate host is gnat of Simulum genus (pic 20.25). Biting ill man, the gnat sucks microfilariae. They develop in the gnat for 6-12 days. When infected gnat with invasional microfilariae bites a human being, the microfilariae come under the skin. Than, they travel to lymphatic system, muscles aponeuroses, fat tissue, where they mature during 18 months. The life span of mature oraganism is up to 20 years.

The leading symptoms of onchocercasis are skin itching resulting in dermatitis and formation of dense connective nodes (onchocercoma) of different size (from 0.4-0.5 to 3-5 cm in diameter).The common place of connective nodes localization is head, neck, shoulders. The severest complication of onchocercasis is eyes affection resulting in blindness.

It is wide spread in Africa and in some states of tropical America.

The onchocercasis is most important medical and social problem of developing countries. Only in Africa, 20 millions of people are affected by onchocercasis each year.

Dipetalonema perstans – is the exciter of dipetalonemasis. The mature female is up to 70-80 mm. long; the males are only up to 40-50 mm. long. The females deliver either very long microfilariae about 160-200 by 5-6 mcm. of size or short microfilariae about 90-110 by 4 mcm. of size. The final host is a human being. The intermediate host and vector is greases of Culicoides genus.

Biting ill man, the grease sucks microfilariae. They develop in the grease for 7-10 days. When infected grease with invasional microfilariae bites a human being, the microfilariae come to the human organism.

Mature parasites are in the small intestine mesentery, liver, pericardium. The larvae are in the heart lumen, lung vessels, spleen vessels. They may cause lymph congregation, lymph vessels dilatation in affected organs. This disease is spread in Africa, Central and South America.

Mansonella ozzardi – is the exciter of mansonellasis. The mature female is up to 65-81 mm. long; the males are only up to 38 mm. long. The females deliver either microfilariae about 173-240 by 4-5 mcm. of. The final host is a human being, in which mature filariae live in the mesentery and under serous membranes of abdominal cavity. The intermediate host and vector is greases of Culicoides genus.

This disease is spread in South America and islands of West-India.

Diagnostics of filariases are based on examination of blood smear or "thick drop" preparations for microfilariae. Serological tests are important. The following are in common usage: immunofluorescent, indirect hemagglutination, ELISA. Of course, it is important to have in mind clinical signs.

Personal preventive measure is to avoid sanguivorous insects biting. Social preventive measures are to reveal and treat ill patients and to fight against vectors.

20.3 The helminthes, which only migrate in the human being (larva migrans).

In the human organism, the some parasite larvae can live. However, human being is not natural host for them. Such parasites can live, migrate but they not mature. Larvae have antigens, which cause local and general allergic reaction in human body. There are cutaneous and visceral forms of larva migrans.

The exciters of cutaneous form of larva migrans can be trematodes, which affect swimming birds (Schistosomatidae), and unusual for human nematodes (Ancylostoma caninum, A. brziliense, Strongyloideus mioplami). If a human become infected by tremotodes, the pustular skin elements, nettle-rashes, itching, dermatitis, sometimes fever, fatigue appear. 1-3 days after, the pustular elements transform to crusts. 1-2 week after invasion, the man recover. If a man is infected by nematoda larvae, it results in allergic dermatitis, which erases along larva's way with speed 1-5 mm per day. For diagnostics, we can use skin scratches for larvae revealing and we can find transient eosinophil rise in the blood smear.

The exciters of visceral form of larva migrans can be cestodes larvae (Diphyllobothrium erinacei europei, Tanea solium, of Multiceps genus and others) and nematodes larvae (of Toxocara, Anisakis, Angiostrongylus and others genera).

Sparagasis – is chronic helminthosis, zoonosis. Typical feature of it is infiltrate formation under the skin. It is caused by larva of Diphyllobothrium erinacei europei. The mature helminthes are 250 by 1.2 cm long, whereas the larvae (plerocercoids) are 1-60 cm by 2-3 mm. long. The eggs escape to ponds. They have host interchange during development. The final hosts are – cats, dogs, foxes, wolves; the intermediate hosts are cyclops and frogs, snakes, birds. The cyclops ingests eggs. Within cyclops plerocercoid develops. It continues development in frog or snake, which have swallowed cyclops. A human being can be infected by drinking water with cyclops, by eating frog meat or by healing wound with help of frog meat. The sparangosis occurs in Japan, East Africa, South America, USA, Russia, sporadically in Belarus.

Cystecercosis – is chronic biohelminthosis, zoonosis. It is charectirized by development of cysticercus of Taenia soleum in different human tissues (brain,eye bulbus, muscles and etc.). Symptoms results from cysticercus localization in the body. While brain localization, the symptoms of local brain function failure occur. Diagnostics is possible with help of computer tomography, ultrasonic examination and with help of immunological methods such as immunofluorescent test, indirect hemagglutination, ELISA. It can be found worldwide.

Cenurosiasis – is chronic biohelminthosis, zoonosis. Mature helminthes of Multiceps genus live in wolves, jackals, foxes. The intermediate hosts are farm animals, pigs, sometimes, human being. In the intestine helminths onchospheres release larvae – cenurs. Such larvae travel to brain, spinal cord, eye and other organs. 4-5 months after invasion, a human being note fatigue, headache, signs of cerebral hypertension, epileptiformed convulsions. Diagnostics is possible with help of computer tomography, ultrasonic examination etc. It can be found worldwide.

Toxocarasis - is biohelminthosis, zoonosis, which is caused by migration of Toxocara genus larvae. Childrens of age from 1 to 4 are prevalently affected. The disease is accompanied with fever, dry coughing, asthma attacks. In the liver bioptats, the eosiniphilic granulems are revealed. Diagnostics is possible with help of immunological methods such as immunofluorescent test, indirect hemagglutination, ELISA. It can be found worldwide.

Anisakiasis - is biohelminthosis, zoonosis, which is caused by Anisakis (herring worms), Phlocanema (cod worms) genera larvae. Human being can be infected by eating meat of those infected fishes (they are intermediate hosts of these trematodes). Clinical signs of disease are acute allergic reaction, formation of parasitic granulemes in the intestine wall that can cause intestine congregation and stomach pain. Diagnosis is based on anamnesis, and clinical picture. It can be found worldwide.

Angioslrongyliasis - is biohelminthosis, zoonosis, which is caused by nematodes of Angioslrongylus renera. They normally affect rodents. The larvae affect brain, spinal cord, eye. Human being can be infected by eating uncooked mollusks and shrimps (they are intermediate hosts of these nematodes). It is spread on shore of tropical seas, lakes, rivers.

20.4 The pathogenic influence of parasites on human organism.

The majority of parasite diseases have no specific features. They express as complex of symptoms peculiar to many parasite diseases and many infections, as well. The pathogenic influence of parasites is diverse. It includes the following: nutrients lost, local damage, helminthes action as stress agents, changing immunity balance, influence on infectional diseases. The hereditary factors are very important in realization helminthes pathogenic action.

We will discuss different mechanisms of helminthes pathogenesis.

20.4.1 The nutrients lost during invasion.

Helminthes enter human body on larva stage. Eating human nutrients (such as carbohydrates, proteins, fats, vitamins), they mature. For example, plerocer-

coid of Diphyllobothrium latum is about 3 cm, whereas mature worm is about 10-12 meters long; the Ascaris lumbricoideus larva measures by micrometers, whereas mature worm is up to 25-40 cm. Many flatworms and roundworms accumulate vitamins (C, B1, B12, A and others) in their bodies in concentration mach more than in the host tissues.

Many helminths eat blood, lymph and other tissues of organism. Thus, one Ancylostoma duodenale can suck from 0,08 to 0.34 ml of blood. Trichocephalus trichirus also suck blood. The significant blood lost occurs through wounds of intestine which resulted from helminthes cuticular teethes, suckers, hookers action. Migrating larvae of Ascaris lumbricoideus, Ancylostoma duodenale, Necator americanus and others can cause mechanical vessel rapture. Ancylostomides produce anticoagulants that make blood lost worse.

The helminthes can cause refectory increasing of salivation in ascariasis, trichocephaliasis, which leads to important enzymes lost.

The list of this group factors shows that pathogenic effect of helminth depends on functional condition of host organism and on number of active parasites. For example, the factors that need to be pointed out on assessing for B12 deficiency anemia in diphyllobothriasis are amount of B12 receiving with food, level of gastromucoprotein production, food assimilation in the intestine, B12 storage in the liver. Finally, the number and sizes of parasites adsorbing this vitamin are also important.

20.4.2 The helminthes local damage.

The helminthes are foreign bodies for human being. Therefore, wherever they live, they mechanically and chemically affect surrounding organs and tissues.

Firstly, helminthes give mechanical pressure to the surrounding organs, which may results in duct, cavities, vessels, respiratory pathways congregation. In turn, it leads to organ atrophy. For example, echinococcus vesicle cause liver tissue atrophy, and cysticercus of Taenia soleum cause brain atrophy.

Secondly, helminthes damage surrounding organs by hooker, suckers, cuticular teethes or while migration. Thus, Taenia soleum and Teniarinchus saginatus affect intestine wall; flukes (cat liver, Chinese liver, lung, and large liver flukes) – affect parenchyma of organs where they live. Trichocephalus trichirus damage intestine mucosa by borrowing.

Thirdly, helminthes irritate mechanical and chemical interoreceptors. Thus, they can affect functioning of organs and organ's systems through CNS reflex arcs. It also affects CNS functioning itself (troubled sleep, irritability and so on). It is well known that children with ascoridiasis have troubled sleep. Couple ascarids can cause spastic intestinal congregation. Children suffering from

hymenolepiasis have mentally retardation.

Fourthly, helminthes can cause local damage of CNS, if they are localized in the brain or spinal cord. These focuses can affect functioning of different organs and systems. For example, if cysticercus of Taenia soleum is localized in hypothalamus, the fever, drowse, hemopoiesis changes (increasing of erythrocyes and leukocytes level in blood) are observed.

Fifthly, waste metabolic products of parasite, accompanied with chronic mechanical and allergic irritation in some cases may cause proliferation or metaplasy of host cells: connective tissue growing, changing epithelial type of mucosal lining, cyst and capsule formation over the parasite. It was proved that there is a relation between chronic helminthoses with chronic inflammatory reactions and cancer grow. For example, chonic invasion by cat liver fluke leads to liver cancer formation.

20.4.3 The helminthes as stress agents.

The helminthes and, especially, their migrating larvae, are strongest irritators (stress agents), causing activation of adrenal-pituitary system. This system is greatly involved into defense reactions of infected organism.

There are different external stimuli that can cause complex of nonspecific reactions, called by H. Selier "general adaptation syndrome". There are three stages in developing this reaction. During first alarm stage, there is irritation of receptors, enhanced adrenalin output, increased blood glucose level, accelerated heart rate, increased blood pressure. During second resistant stage, there is hypothalamus release liberins, which activate anterior pituitary to make ACTH (Adreocorticotropic hormone). It, in turn, stimulates adrenal cortex to produce hormones, which increase organism resistance to stress agents. During third depletion stage, which occurs only than stress irritation is over strong, the adrenal cortex is not able to give up necessary amount of hormone. It can result in death. The general adaptation syndrome is normal physiological reaction against disease.

During first two weeks of invasion, the level of ACTH and adrenal cortex hormones increases as reflection of parasite invasion. Later, because of continuous irritation of adrenal-pituitary system, the level of such hormone decreases. This system is significantly activated in trichineliasis, opistorchiasis, ascariasis and other invasions. Because of this, it was suggested treatment of trichineliasis by glucocorticosteroids as replacement therapy and pathogenic therapy, as well.

20.4.4 The role of hereditary factors on invasional process.

The hereditary factors of hosts are very important in development of invasional

process. It is a consequence of the works performed in 70-80's years of XX century. These works were performed on laboratory animals (mousse, rats) of different lines with experimental trichineliasis, trichocephaliasis, hymenolepiasis, opistorchiasis and others invasions.

There is genetical resistance to helminth invasion in different human groups. Thus, the majority of people suffering from trichocephaliasis, ascariasis, strongyloidiasis, enterobiasis and Manson schistosomiasis have A blood group. Overwise, the majority of people suffering from hymenolepiasis have blood groups O and B. Peoples with blood group O are predisposed to onchocercosis. Noting this, we can suppose that agglutinins б and в play role of natural antiinfectional defense agents.

It is known that HLA system plays an important role in histocompatibility. It controls immune response on different antigens, antigen recognition, and regulation of different cells participating in immune response. It was stated that many disease have associations with different alleles of HLA system. In particular for parasites, it was showed such relationships for Japanese schistosomiasis (Kojima S, et al, 1984). The immune response on external stimuli, as parasites are, is controlled by HLA-DR and HLA-DQ locuses. It is possible that helminth resistance is controlled by other locuses different to HLA locuses.

It was shown that metabolites of bacteria and viruses have strong mutagenic effect. However, the question about such effect for parasite metabolites was not answered until recently. The first investigation of this problem was performed by I.I. Iliynskih in 1981 for opisthorchiasis. It was stated that during opisthorchiasis the number of cells with chromosome aberration, chromosome raptures and alteration of chromosome set number in bone marrow increases. In acute phase of opisthorchiasis, starting from 15th day, the number of heteroploid cells with cytogenetic defects increases. The chronic phase of invasion is accompanied with rapid rise of such defects and increasing severity if them. In primary infected patient, the level of damaged cells is increased, but not too high. In repeatedly infected patients, the level of such cell is significantly raised.

Author stated that Trichinella spiralis, Trichocephalus trichirus, Ascaris lumbricoideus invasion cause cytogenetic defects in the human blood leukocytes. The level of this defects correlates with migration stage of larvae. Helminth invasion cause indirect influence on host organism. While therapy of trichinelliasis by mebendasol, it was observed increased allergic predisposition, increased rate of chromosome mutations. Using of anti-inflammatory drugs suppresses allergic reactions and therefore decreases rate of chromosome mutations.

Helminthes cannot directly contact with cell nucleus apparatus. They do it through their metabolites transported by blood, lymph, tissue fluid.

Since, number of people who suffer from helminthoses reaches hundreds millions, it is important to remember that it can facilitate genetic load growing in

human populations. Fast studying of mutagenic helminth influence of human genotype can result in admitting reasons of immune disturbances in ill organism. It also will help to design new methods of helminth invasions treatment.

The studying of genetic factors of ecological pair "parasite-host" is important for understanding processes of invasional processes, helminthosis preventive measures, ecological relationships of Homo sapience.

20.4.5 The changes in immune homeostasis of human with helminth invasion.

Parasites cause a wide spectrum of allergic reactions in the human body. The nature and mechanisms of these reactions are unique. They are often different from reaction caused by viruses and bacteria. It is due to specific morphological and biological helminthes features. Such features are big size of helminthes, intercellular localization in the body (instead of intracellular localization of bacteria), complex structure with different functions, complex development with many stages occurring in many parts of the body, differences in metabolism and in antigenic properties of larvae on different development stages. Concerning all of this, the immune response in parasite invasion is slight during simple invasion, it depends on number of parasites in infected organism, it has short period of duration, it has different pattern on different stages of invasion development.

Helminthes tissues and metabolites are antigens. They may be of two types: endogenic and exogenic. The endogenic antigens are close related with parasite structure. They become available for immune system only after parasite death in tissues. There are many similar antigens in close related parasites. Therefore, it makes serological diagnostics of such parasites very complicate because of cross-reactions. The exogenic antigens are substances, which are excreted normally throughout whole parasite life.

In spite of frequent literature reports, there are no toxins of parasites. They are not toxic for human being (look to chapter 22.3.1). The substances, which were suggested as toxins, are parasite metabolites without specifics.

Helminthes excrete products of their metabolism, which are exogenic antigens. They may have various influences on organism. D.Y. Krisheblat (in 1958) suggested dividing them into histolysins, antienzymes, trophogons and tilakogens. The histolysins digest human tissues providing conditions for parasites moving and larvae delivering. The helminthes antienzymes act as supressors of host ezymes. It helps them to survive in the intestine. It suppresses their phagocytosis by macrophages, and suppresses blood clotting. The tropogons cause nutrients income to the place of parasite being. The tilakogens provides connective tissue growth around helminth. The histolysins, antienzymes, trophogons and tilakogens are proteins and strong antigens for host immune system. The second source of strong exogenic antigens is substances, which are produces during larva molting.

The expression of immune reaction in helminthosis is determined by helminthes antigen quantity and by way of its representation for immune system. The main part of parasite antigens comes into macrophages. The exclusion is antigens connected with membranes; they may cause activation of B-lymphocytes directly, without macrophages. In majority of cases, B-lymphocytes are activated with help of macrophages. Activated B-lymphocytes undergo to blast-transformation reaction and start to produces lines of B-lymphocytes making immunoglobulines of all types against parasite antigens. This immunity is not permanent. The cases of permanent immunity against parasites are unknown. The time of parasite living within host body is determined by life span of parasite. Typically, mature parasites are not sensitive to the action of immune system.

Helminthoses can cause hypersensitive reactions of all four types. The mixed reactions also take place, especially after parasite death in the tissues. It explains the side effects of tissue helminthoses therapy.

First type. IgE-induced immediate hypersensitivity develops on the surface of mast cells while complex IgE-antigen of helminth interacts with cell receptor. Mast cells release histamine, serotonine, slow reacting anafilaxy substance and anafilactic factor of eosinophil chemotaxis. The cytoplasmic kinines become activated too. The typical reactions of this type are local or general anafilactic reaction, which develop after echinococcus cyst rapture, and during skin allergic tests.

In the opistorchiasis, strongyloidiasis, trichinelliasis pathogenesis, the reactions of first type play leading role. Thus accordinary authors findings, in trichinelliasis there is increasing of tissue free histamine level, decreasing of bounded with tissue proteins level of amine, suppressing of hystaminepexic ability of tissue proteins, increasing activity of hystidinedecarboxilase enzyme, decreasing activity of histaminases in tissues and increasing histamine excretion with urine. The increasing of tissue free histamine level is due to dual mechanism: histamine release from tissue storage (it is proved by raised degranulation of mast cells) and decreasing of bounded with tissue proteins level of amine, suppressing of hystaminepexic ability of tissue proteins from one side, and increased production of histamine due to activation of hystidinedecarboxilase enzyme from another. The strength of histamine system deviations correlates with level of disease severity. Thus, in light trichenilliasis there is slight increasing tissue free histamine level, slight suppression of histaminase activity and coming back to normal values at the end of seventh week. In trichenilliasis of middle severity, system is in subcompensated state. In severe trichenilliasis, the system of histamine is in the decompensated state.

Helminthoses, the trichenilliasis, the strongyloidiasis, the opisthorhiasis in particular, have typical overexpressed hypereosinophilic reaction. The system "mast cell – IgE – eosinophil" developed evolutionary. It play an important role in immunity, providing parasite destruction.

Second type. Complement-dependent cytological reactions develop as result of antybody-antigen interaction of the surface of organism cell, which cause complement activation resulting in cells destroy. It occurs rare in helminthoses. The immunologically determined erythrocyte lysis occurs in schistosomiases.

Third type. It is reactions of immune complexes. They are due to formation of immune complexes "antigen-antibody" either in tissue (typical Artus phenomen) or in blood. It results in inflammation, edema, neutrophil infiltration and damage of affected tissues of host. In helminthoses, these reactions are accompanied by eosiniphilic infiltration. Eosinophils have chemotaxis to immune complexes. Artus phenomen may develop during allergic skin test for helminthes antigen. This mechanism is partially responsible for development acute lymph node reaction during lymph fillariasis, trichenellic myositis, lung affection while ascaris larvae migration. The typical feature of reactions of this type is pulmonary eosinophily. Circulating immune complexes can result in development of glomerulonephritis in schistosomosis, laoasis, trichinelliasis.

Fourth type. Cellular slowed reactions connected with specific sensibilized T-lymphocytes, which are accumulated in affected region. They release lymphokines, which attract macrophages. This results in granulema formation. The slowed skin reactions on injected parasite antigen are connected with this type of reactions. As tuberculin reactions, they may occur in trichinelliasis, echinococciasis, parogoniasis, and other helminthoses. Nevertheless, they are rare used for diagnostics. They provide granulema formation around schistosoma eggs in urinary pathays walls, intestinal walls, and inflammatory changes in trichinelliasis, filliariases.

Nervous system also takes part in regulation immune homeostasis by adrenergic and cholinergic mechanisms. Sympathetic and parasympathetic systems act on parasite biology, as well as, on formation of hypersensitivity of various types, especially immediate one, in tissue helminthoses. These systems are involved due to host organism sensitization by helminthes antigens.

Eicosanoids are also involved in development of hypersensitive reactions of first, third and fourth types. It is believed that they facilitate helminthes escape from host intestine, formation inflammatory reaction around parasite larvae. They also determine level of allergy expression during parasite invasions.

The expression of pathological and immunological processes depends on how many parasites infect host organism. The more parasites enter the host organism, the more larvae will be delivered, the more severe disease will be. However, this dependence has upper limit, exceeding which there is no such relationships between parasites number and severity of disease.

In human helminthoses, the immune response suppression may occur. There are conditions of primary and secondary immunodeficiency conditions. The pri-

mary immunodeficiency is inherited condition. It is due to inherited defects of regulating genes resulting in T-lymphocytes or B-lymphocytes functions failure. The secondary immunodeficiency is defect of immune system acquired during the life. It can be due to helminth presence. It can be specific and unspecific. It can be due to massive release of antigen after helminth death resulting from treatment. In addition, it can be due to immunosuppressive therapy of helminthoses. Parasites can release immunosuppressive substances causing immunodeficiency (eicosanoids, corticosteroids). Such phenomenon was observed in trichineliasis, schistosomiasis, ascariasis and other invasions.

20.4.6 The helminth influence on infectional diseases development.

The fact, that invasions have influence on infection development, was strictly proved. Wounding skin and mucosa, parasites make appropriate conditions for bacteria to enter the body. Migrating larvae can spread bacteria throughout the organism. Bacteria, which are placed in the place of helminth invasion, may complicate local reactions on parasite invasion. Helminthes may affect defense mechanisms of host and cause general immunodeficiency condition.

Helminthes make infections development more complicate due to development of immunodeficiency condition. In endemic regions, where ascariasis, trichinelliasis, opistorchiasis, schistosomiasis are spread, the scarlet fever, the typhoid, the dysentery, the tuberculosis have longer, complicated duration. Children, who infected by helminthes, lack in producing immunity on vaccination.

CHAPTER 21. MEDICAL ARACHNOENTHOMOLOGY.

The arachnoenthomology is division of medical parasitology, which studies representatives of Arthropoda phylum as ectoparasite, endoparasites and vectors of human disease exciters.

Arthropoda – is most successive phyla of all living animals in term of number of individuals and species, total mass and complete occupation of terrestrial habitats.

Arthropods have the following features of structure: heteronomic segmentation of the body, which is expressed as different structure and functions of different segments; segment fusing into body's parts (head, thorax, abdomen); appearance of segmented limbs; muscle separation and appearance of striated muscles; external chitin skeleton, protecting body from external influences and serving as a place of muscles attachment; mixed coelomic cavity, resulting from fusing of primary and secondary coelomic cavity in embryogenesis; having organs systems (digestive, respiratory, excretory, circulatory, endocrine, reproductive).

The phylum Arthropoda has three subphyla: Branchiata, Chelicerata, Tracheata. In each of them, there is only one class, which is important for medicine – Crustacea, Arachnida, and Insecta.

The Crustaceans are not as important for medicine as Arachnidans and Insects. They can be only intermediate hosts for Diphyllobothrium latum, Dracunculus medinensis, Paragonimus westermani. Therefore, in the name of the division there are names of Arachnidans and Insects only.

Pathogenic influence of arthropoda on human being is due to their value as intermediate hosts of helminthes; human poisoning agents; vectors of diseases; parasites of human being. Arthropoda can transmitte invasion by specific and mechanical inoculation and contamination.

21.1 The Arachnida class.

The Arachnidans – are Arthropoda, which were adapted to survive on the land. They have organs of air respiration. Two anterior parts fuse to one – cephalothorax. It connected with body by thin stem or fuse with it.

The body is covered by cuticle of chitin and hypoderm, which has cellular structure. The appendages of hypoderm – silk glands and poison gland – are localized in chelicerae base. The Arachnidans have 6 pairs of limbs, from which two anterior pairs (chelicerae and pedipalps) are adapted to catching and pounding of food. The rest four pairs are for locomotion.

The digestive system is adapted to eat fluid food. The pharynx has a function of sucking.

The respiratory system is presented by leaf-shaped lungs, which open out-

side by stigma (special openning). Lungs of Arachnidans are homologous of Crustacean gills. The tracheae are tubes, which highly branch and come to every organ and tissue where the gases exchange takes place.

The excretory system is presented by modificated metanephridia. Many species form special Malpigian tubules, which are slender projections of the digestive tract. These are attached at the junction of the midgut and hindgut. They excrete dissimilation products to the hindgut.

The circulatory system is open. It is most complicate in scorpions and spiders, which have lung. The principle component of circulatory system is longitudinate vessel, which is called the hearth. The vessels branch off this central vessel and bring blood to the organs. The blood is returned back to the heart by lacunas. The mites have reduced blood vessels and, sometimes, the heart.

The central nervous system of the arthropod is a double chain of segmented ganglia running along the animal ventral surface. This chain gives up peripheral nerves. The forms, having some segments fused, can fuse and nervous segments too. The Arachnidan typical feature is 1-6 pairs of simple ears.

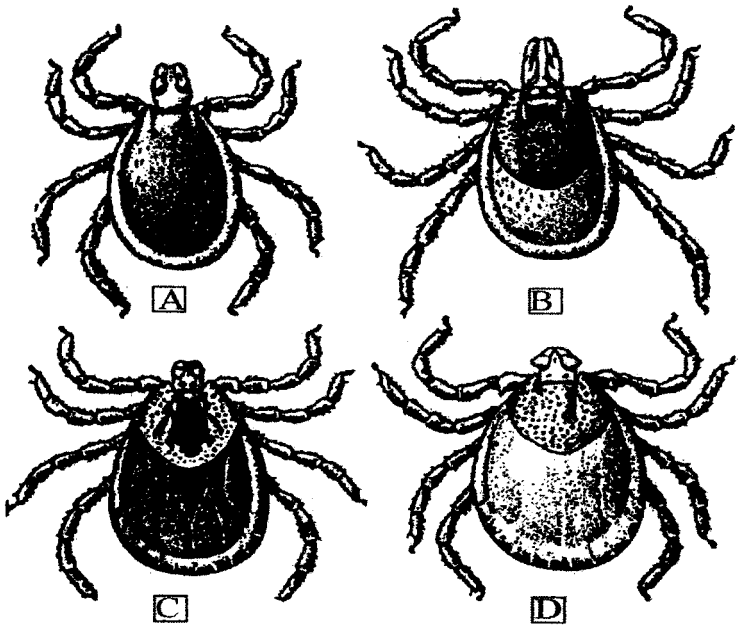
The Arachnidans are animals having two sexes. The female ovarium is in the abdomen, whereas oviducts fuse to the single duct, which open in the anterior part of the abdomen. The male testicles are also in the abdomen and sperm ducts fuse to the single duct, which open on the abdomen surface. The sexual dimorphism is much expressed. Some species deliver living offsprings.

The development can be direct or with metamorphosis.

In the Arachnida Class, the mites (Acari order) have the most important medical value. The Order Acari, the mites, is the largest – in term of number of species – and most diverse of the arachnids. Many of them are sanguivorous. They may parasite on birds, mammalians and human being. They can be vectors of transmissive diseases. The important families of Order Acari are Ixodidae, Argasidae, Trombiculidae, Gamasoidae, Sarcoptidae, Demodecidae, and Tyroglyphidae.

21.1.1 The mites as vectors of transmissive diseases.

The representatives of Ixodidae family. They are ectoparasites of mammalians and human being. They live in the forests and bushes. The typical feature of them is fusing of cephalothorax and abdomen to the one unit. The oral organs include upper jaw and modificated lower jaw. Lower jaw may unite with lower lip to form proboscis with hooklets. This proboscis is for biting and fixation in the host body. The proboscis is on anterior body's surface or on lower anterior surface. The oral organs and surrounding tissues were incorrectly called "small head". The mites have two sexes. They have good expressed sex dimorphism. In males, the dorsal shield covers entire back, whereas in females it covers only neck. The oral apparatus is visible from dorsal side. The body's sides are scal-



Pic.21.1. The representatives of Ixodidae family:
A,B – male and female of Ixodes persulcatus; C – female of Dermacentor pictus; D – female of Haemaphysalis concinna (by D.V. Vinogradov-Volzhinsky,1977).

loped. As a rule, the mites have eyes. There are special hooklets and suckering pillows on limbs to be attached to the host organism. On being attached to the host, the mites can suck the blood for several days. The females can enlarge their sizes in 3-4 times while sucking. The females are very fertile. They can lay up to 17 thousands eggs. The development is presented by simple metamorphois (egg-larva-nymph-imago). Nymphs have no sexual opening. The transformation to next stage connected with blood feeding. The Ixodidae family includes the following genera: Ixodes, Dermatocentor, Hyalomma and others. The typical representatives of Ixodes genus are dog and taiga mite. The typical representative of Dermatocentor genus is pasture mites (pic 21.1).

The dog mite (Ixodes ricinus) has oval body, with shield on the dorsal surface. In males, it covers entire back, whereas in females it covers only neck. The males are brown colored with size up to 2.5 mm long. Hungry female is also brown in color with size up to 4 mm long. The replete female is yellow-red in color and is up to 11 mm long. They live in forests and bushes in Europe. The dog mite support rabbit fever circulation among rodents. It also can transmitte this

exciter to human being. It is also vector for West-European encephalitis virus.

The taiga mite (Ixodes persulcatus) is externally similar to the dog mite. It occurs in the taiga forests of Europe and Asia. It lives as parasite on many species of birds and mammalians. It supports circulation of taiga encephalitis virus among wild animals (chipmunk, hedgehog, mouse). This virus can be transmitted by transovarial way (between generations).

The mites of Dermatocentor genus have eyes, dorsal shield with enamel picture. It occurs in Transbaikalia, West Siberia, and European part of Russia. The larvae and nymphs attack only small animals, whereas mature mites can attack big animals and human being. The Dermatocentor pictus and Dermatocentor marginatus are vectors of rabbit fever exciter. The Dermatocentor nuttali is vector of Omsk's hemorrhagic fever virus and spotted Rocky Mountains fever virus.

The mites of Hyalomma genus – are big Ixodes mites (more than 5 mm long). They have eyes. The typical feature is very thick and long legs. They live in steppe regions and in tropical montains of South Europe. They can be vectors for Crimean-Congo fever virus.

The representatives of Argasidae family. They lack of dorsal shield. The oral apparatus is visible from ventral side. As usually, they have no eyes. There is almost no sex dimorphism. There are no accessories for attachment on the host. The time of blood sucking is about 3-30 minutes. They may fast for a long time. The places of preferable living are caves, burrows, sheds. The geographical distribution is countries with arid climate (Middle Asia, India, Iran, Afghanistan, Transcaucasia). The life span is about 20 years.

The village mite (Ornithodorus papillipes) – is typical representative of Argasidae. It is vector and reservoir of relapsing fever exciter (Borreliia sogdiana) in natural and anthropourgic regions. The way of transmittion is specific inoculation or transovarial (fro 1-2 generation). The exciters can enter the human being either while biting or through undamaged skin from mites' excrements. They occur in Middle Asia, West China, India, Iran, Iraq, Syria, Afghanistan, Israel, Jordan, Lebanon, south states of USA, Venezuela, Columbia, Mexico, Guatemala, and Panama. The disease signs are fever, inflammatory events in respiratory system, affection of CNS, which disappear 2.5-4 months after infection.

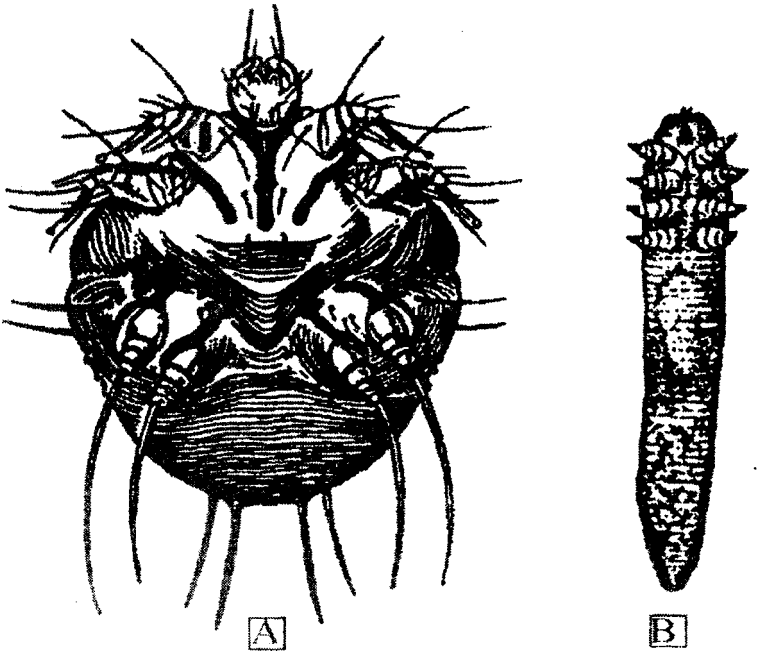
The representatives of Trombiculidae family – are ectoprasites, which are yellow or red colored. They are spread worldwide. The larvae need blood to develop well. Falling from the tree to the human leg, they start to crawl up to inguinal region. They start to feed there. They dissolve skin by their saliva and cause dermatitis. After feeding, the larvae fall down to the land and continue development. The larvae of Trombicula acamushi can transmitte rickettsia of tsutsugamushi fever, which occurs in Far East, Japan, India, Pakistan, China and other countries.

The representatives of Gamasoidae family – are yellow-brown in color. They have body 0.2-0.5 mm to 1.5-2.5 mm long. The body is covered by long

setae. The development occurs by simple metamorphosis (egg-larva-nymph-imago). The females lay eggs in burrows and nests of host, and on host itself. The hosts are rats, mice, hens, pigeons, swallows, martins. The Bdellonyssus bacoti and Dermanissus galinae can attack human being and transmitte excites of virus diseases (rickettsia of rat spotted fever, Qu-fever viruses, smallpox-like rickttsiasis, San-Lui encephalitis). The biting of such mites can cause dermatitis.

21.1.2 The mites as parasites of human skin.

The itch-mites are skin parasites of many mammalians species, including human. They are exciters of scabies. The mites gnaw canals in the human epidermis, where the female can lay eggs. They eat tissue fluid and epidermis cells. When they crawl along their canals, they irritate nerve endings causing severe inching. The human being can be infected by contact with infected man in baths, through clothes and linens. The human can be infected by horses, sheep's, goats, dog's inch-mites. They cause typical skin damage by they can survive on the human skin for a long time.



Pic.21.2. The mites which are parasite of human skin:
A - Sarcoptes scabiei, B - Demodex folliculorum (A – by E.P. Pavlovsky,1935, B – by C. Berleze,1909).

The exciter of human scabies is Sarcoptes scabiei. It is spread worldwide. The body is oval and covered by setae. The female is up to 0.4 mm long, whereas male is about 0.3 mm long (pic 21.2a). The limbs are shortened and they have 6 segments. The oral apparatus is adapted to gnawing in human skin. They gnaw 2-3 mm canal every day. In these canals, the female lays eggs (up to 20 for a life). The development occurs by simple metamorphosis (egg-larva-nymph-imago) in 12-14 days. The life span of mature mite is 2 months. The infection occurs only while direct contact with infected man. The fertilized females are transmitted. Human can be attacked by dog's, cat's mites, but they can not gnaw canals in the epidermis of human being.

The diagnostics is based on revealing of mites while microscoping in drop of 50% glycerin solution. The diagnosis can by suspected on the base of typical dermatologic picture.

The personal preventive measure is in following personal hygiene rules. The social preventive measures are treatment of ill, disinsection of wearing, health care education.

The Demodecidae mites. These are small mites with worm-like body. The dorsal shield is only on the anterior part of the back. The limbs are short with two hooks on the end. They inhabit oil-bags and hair follicles of human being and mammalians. They are very fertile. They cause demodecoses.

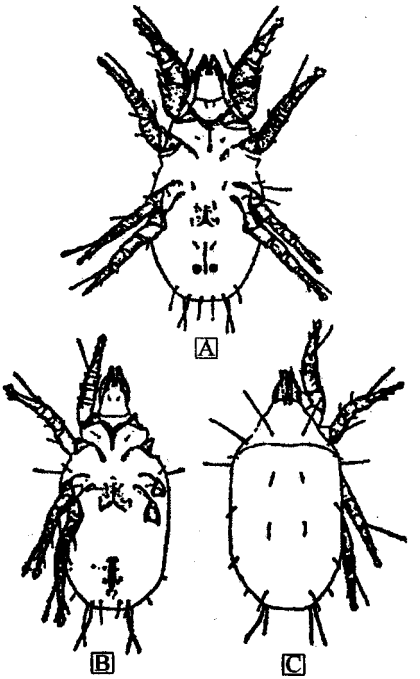
The Demodex folliculorum – is small (female up to 0.38 mm; male up to 0.3 mm) worm-like skin parasite of human being. It causes demodecosis (pic 21.2,b). The mites inhabit oil-bags and hair follicles of face, neck, shoulders. They direct head downward. They are by groups of 4 individuals. They may occur in healthy people without any symptoms of disease. In impaired men, they can cause duct congregation. It leads to formation of acne with pus. If secondary infection accompanies demodecosis, it can result in purulent pustules formation. The way of transmission is direct contact with infected man and through using clothes of infected man.

The diagnostics is based on revealing of mites while microscoping in drop of 50% glycerin solution.

The personal preventive measure is in following personal hygiene rules and treating diseases, which make organism weaker. The social preventive measures are treatment of ill, disinsection of wearing, health care education.

21.1.3 The mites as inhabitant of human dwelling.

The representatives of Tyroglyphidae family – are small (0.4-0.7mm) eyeless mites. The jaws are nipper-like, lower-jaw palpus has three segments. The oral apparatus is of gnawing type. Thecephalothorax is divided from abdomen by



Pic.23.3. The mites which are parasites of hman dwelling:
A – flour mite, B,C, - cheese mite (by E.N.Pavlovsky,1951).

incision. They can actively move looking for food. They eat food storage – grain, fishes, flour, cheese, meat, dry vegetables and fruits. The food infected by such mites can cause irritation in digestive tract. It also can be allergic. The mites can bite a human being causing grain itching dermatitis. Entering respiratory pathways with dust, they can cause acaridosis of respiratory system. The representatives of this family are Tyroglyphus farinae and Tyroglyphus siro.

The mites of Dermatophagoides genus are very interesting. They live in pillows, mattress, carpet and furniture. They are up to 0.1 mm long. In one gram of domestic dust, there are about 100-500 individuals of Dermatophagoides pteronyssinus. The 45-85% of patients with asthma have allergic reactions on antigens of this mite.

The fight against domestic mites includes decreasing humidity and temperature in storage buildings. It also includes wet cleaning of house and using syntetic furniture, pillows, mattresses, in which mites cannot live.

21.2 The Insecta Class.

They are highest invertebrate. They have highest number of species. Their body divides into head, thorax and abdomen. There have sense organs – antennae and eyes – on the head. There is also complicate oral apparatus. Its structure depends on type of the feeding. The thorax has three segments, each of them carry one pair of legs. Beside that, the second and third segments can carry two wings. The abdomen includes 6-12 segments.

The body is covered by cuticle of chitin and hypoderm, which has cellular structure. The appendages of hypoderm are different glands (smelling, vex, molting). The muscles are striated.

The digestive system starts from mouth. It continues by mouth cavity, in which ducts of salivary gland open. The anterior part of the intestine has dilatation, called craw. The digestion and absorption occurs in the middle intestine. The posterior intestine opens outside by anus.

The respiratory organs are presented by tracheae, which deliver air to all organs.

The excretory organs are Malpigian tubules and "yellow body" (accumulation kidney). The Malpigian tubules are slender projections of the digestive tract. These are attached at the junction of the midgut and hindgut. They excrete dissimilation products to the hindgut. The dissimilation products are crystals of uric acid.

The circulatory system is not well developed. It has no function of oxygen transportation. It is open. The heart and aorta are on the dorsal side.

The nervous system is a double chain of segmented ganglia running along the animal ventral surface. It starts from suprapharyngeal-paired ganglion. The nerve ganglia of neighbor segments can fuse. The eyes are compound, but they can be simple too. The organs of balance, taste, smell and, sometimes, hearing are present.

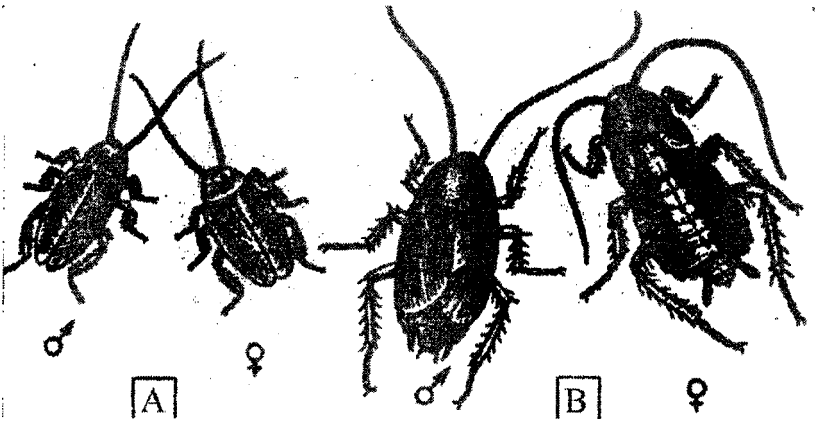
The insects have two sexes. The development occurs by simple or complete metamorphosis.

The medical value of insects is big. It is due to pain from biting, local allergic reactions, possibility of infection of bitted places, transmitting various diseases. The insects can cause crop failure, abolish storages and therefore cause humans starvation.

The Insecta Class includes 34 orders. Among them, the Blattoidea, the Hemiptera, the Anoplura, the Aphaniptera, the Diptera have a medical value.

21.2.1 The Blattoidea Order.

They are most ancient insects. They are known from Carbon period. They are



Pic.21.4. The cockroaches – inhabitants of human dwelling:
A – black, B – red cockroach (by E.N. Pavlovsky,1951).

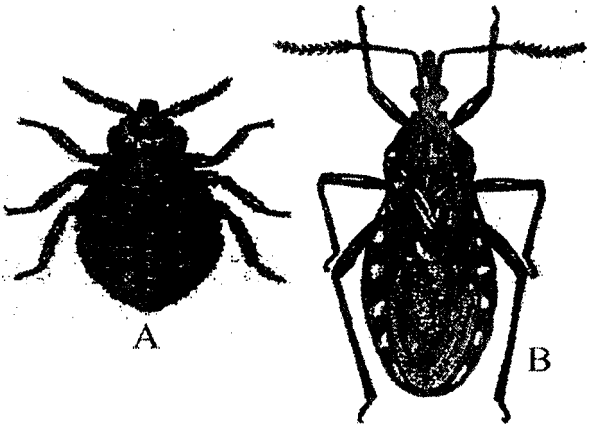
domestic parasites. They spoil foodstuffs, causing economic damage. It is known about 3.5 thousands of species in this Order (pic 21.4). In the human dwelling, the Blatta orientalis (black cockroach), Blatta germanica (red cockroach), Polyphaga saussurei (Egypt's cockroach), Periplaneta Americana (American cockroach) occur. They are active at nighttime. They are mechanical vectors of different infections and invasions. They can infect foodstuffs by bringing infection on their legs. Thus, the exciters of diphtheria, typhoid, cholera, cysts of protozoa, helminthes eggs can be transmitted. The bacteria of typhoid and dysentery can survive in the cockroach gut for 2-4 days.

There are several methods of killing cockroaches. The most effective is poisoned bait. The intensive disinsection only decrease their number. It is due to having special valves, which close tracheae in presence of poisons. In addition, they have wide genetical polymorphism and good ability to adapt in any situation.

21.2.2 The Hemiptera Order.

The chinches have wings containing a lot of chitin in the anterior part; and transparent in the distal part. The piercing-sucking oral apparatus forms two canals. One of them is for sucking fluid food; the other is for excretion of salivary glands secret. There are about 40 thousands species of chinches. Only representatives of Cimicidae and Reduviidae families have medical value (pic 21.5).

Bed-chinch (Cimex lectularis) is world spread. It is most adapted to parasite being. The body is flat; the wings are reduced. They can fast for several months. They attack human being at night. They have rest at daytime. In tropics, the C. rotundatus permanently inhabit human dwelling. It is smaller, darker, with narrow



Pic.21.5. The parasitic chinches;
A – bed chinch, B – kissing chinch (A – by V.I. Beklemeshev,1949, B – by A.Y.Lysenko, 1974).

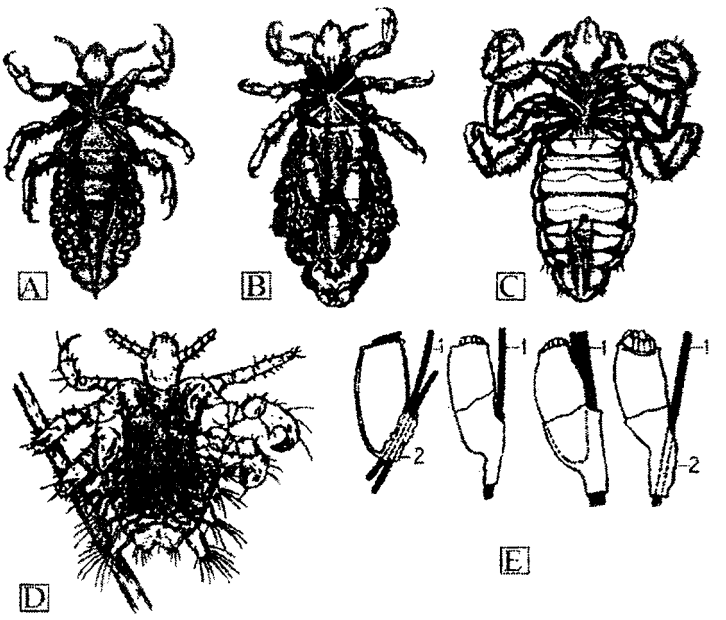
anterior part of the back. Bed-chinch sucks blood throughout whole life. The role in transmitting exciters of diseases was not proved. Human being can be attacked by pigeon's, swallow's and bat's chinches.

The kissing chinches are spread in South and Central America. They can fly. They are sanguivorous on all development stages. They bite painless. They bite prevalently near the lips, therefore they was named "kissing chinches". Hey are specific vectors of Chagas's disease exciters. Living in the burrow of wild rats, armadillos, ant-eaters, opossums, they get infected by Trypanasoma cruzi. 5-15 days later, they start to excrete exciters with faeces. After biting a human being, the chinch turns backward and lay faeces on the wound. The specific contamination occurs. The chinches of Triatoma infestans and Panstrongylus megistus are also important in transmitting trypanosomiasis.

21.2.3 The Anoplura Order.

The louses are wingless, sanguivorous insects. They are permanent parasites of human and animals. They have big epidemiological importance. The human parasites are two species: Pediculus humanus (human louse) and Phtirus pubis (pubic louse). The species Pediculus humanus has two subspecies: Pediculus humanus capitis – the head louse, Pediculus humanus humanus – body louse. The body louse has life span about 50 days, head louse about 40 days, pubic louse about 30 days.

The louses have two sexes. The fertilized female lays about 6-14 eggs per day. During whole life, females of head and body louses lay about 140-150 eggs, whereas female of pubic louse lays only 30 eggs. They have simple metamorpho-



Pic.21.6. The louses – human parasiyes:
A,B – male and female of head louse, C – body's louse, D – female of pubic louse, E – eggs of louses (1 – a hair, 2 – gluing mass) (by E.N. Pavlovsky,1951).

sis: egg-three nymphs-imago. It takes 25-30 days to complete all these stages. The louses suck blood on all development stages. They can fast no long than 10 days. Biting, the louses put saliva on the wound. It causes inching and skin pigmentation. The louses living on human body was called pediculiasis. The complication of it can be disease of vagrants or plica polonica. It is a disease of haired skin of head. It results in formation of purulent wound under the cap of twisted, coherent hairs. The disease caused by pubic louse is called phtiriasis.

The head and body louse can transmitte exciter of spotted fever (Rickettsia provaczeka). The presence of rickettsia in the patient blood was proved by O.O.Mochutkovsky through conducting experiment on himself. The rickettsias reproduce in the louse intestine and escape it with faeces. They can enter human being by two ways. The first, when human being licks blood after biting (specific inoculation). The second, when human being rubs exciters into the wound (specific contamination).

The head and body louse can transmitte exciter of louse relapsing fever (Borrelia recurentic). The exciter enters the louse with human blood. Than, its travel to the coelom. The human cannot be infected while louse biting. It is possible only

when louse is rubbed into the skin by human himself (specific contamination). It was proved by doctor G.N.Minch in Odessa.

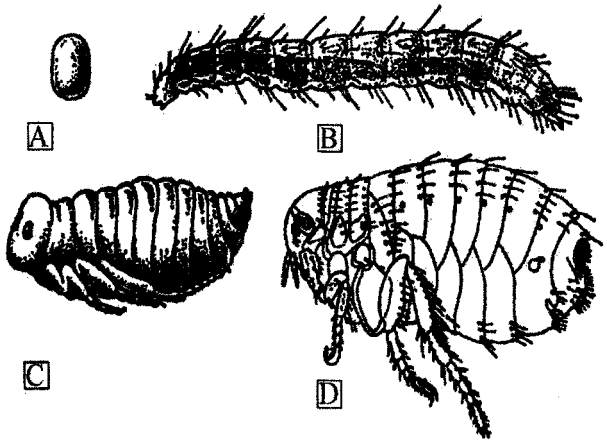
The role of pubic louse in transmitting exciters of diseases was not proved.

The fight against louses is based on strict following personal hygiene rules (washing, ironing of clothes). There are special shampoo and ointments to kill louses. To kill eggs, the hair should be cut shortly.

21.2.4 The Aphaniptera Order.

The fleas are wingless, sanguivorous ectoparasites of human and animals, and birds. The body is flattened from the sides. The oral apparatus is of piecing-sucking type. The third pair of legs is a jumping leg (pic 21.7). The female lays about 450 eggs in floor splits and rodent burrows. The eggs give rise to larvae, which are feed by degrading organics. The larvae are subject to complete metamorphosis (egg-larva-pupa-imago). The development may take from 20 days to 1 year. It depends on environment temperature. The life span of fleas is from 2 to 5 years.

The most common are Pulex irritans (human flea), Xenopsilla cheopis, Ceratophyllus fasciatus and others (rodent flea). The fleas suck human, rat blood and also they can easily suck blood of other animals. The rat flea lives in the rat burrow, whereas human flea lives in floor splits, under wallpapers. The rodent fleas are specific vectors for plague. Entered flea's stomach, the plague bacteria start to reproduce. They full fill all space of the stomach. This condition is called "plague



Pic.21.7. The human flea:
A – egg, B – larva, C – pupa, D – mature female flea (by D.V.Vinogradov-Volzhinsky,1977).

block". Biting a human being or animal, the flea eructates bacteria from the stomach to the wound. Thus, the exciters enter the blood. If there are no natural host around, the rodent flea can attack a human being and infect him by plague bacteria. In addition, it was stated that tularemia, endemic rat typhoid, brucelliasis are transmitted by fleas. They can be intermediate host in development cycle of rat dwarf tapeworm.

The fight against fleas is directed to the keeping cleanliness of the dwelling. It is recommended to use insecticides and different rodent killing drugs. The repellents are used for individual prophylactic.

21.2.5 The Diptera Order.

This order has largest number of species among insects (more than 80 thousands of species). The typical feature of them is absence of second pair of wing. Thy are reduced to balancers. It is mace-shaped appendages, which work as hygroscopic apparatus while flying. They have complete metamorphosis (egg-larva-pupa-imago). In many species, the female have suck blood to perform full development of eggs in ovarium. The males feed plant's nectar. The exclusions are males of tsetse fly and autumn biting fly.

Accordinary to the antennae length, the representatives of Diptera Order is divided into two suborders: with long antennae and with short antennae. The first includes Culicidae, Phlebotomidae, Simuliidae, Ceratopogonidae families. The second includes Tabanidae, Muscidae, Sarcophagidae and others.

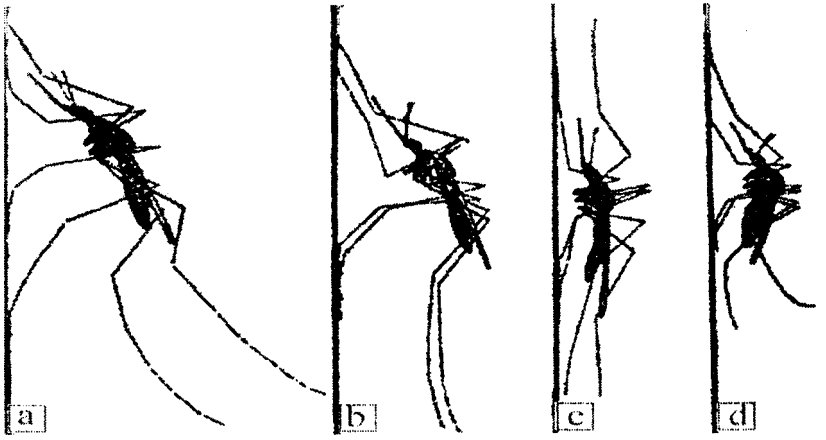
The Culicidae (mosquitoes). They are sanguivorous insects. The thin proboscis of females can pierce to capillaries. Many species suck blood at twilight, at night or at sunrise. The larvae develop in water. They breathe through tubes from the surface of the water. In this family, there are three important genera – Anopheles, Culex, and Aedes. They are spread worldwide.

The eggs of Anopheles mosquitoes differ from eggs of Culex and Aedes Mosquitoes. The Anopheles mosquitoes lay eggs separately on the water surface. Each egg has a curved inward belt. It also has swimming chambers. The Culex eggs have no belt and chambers. They lay eggs by groups on water surface. The Aedes lay eggs on wet land near intermittent rivers and ponds by groups or separately.

The Anopheles larvae have one pair of breathing openings on next to last segment. They lay horizontally in the water. The Culex and Aedes larvae have breathing tubes on next to last segment. They lay at an angle to the water surface.

The Anopheles pupa has breathing tubes of conical shape, whereas Culex pupa has cylindrical.

The mature mosquitoes have differences in head appendages structure, wings color, and landing pattern. The Anopheles females have lower jaw palpus as long



Pic.21.8. The mosquitoes' landing on vertical surface:
A – Anopheles maculipennis (normal), B,C – the same during winter, D – Culex pipiens (normal) (by E.N. Pavlovsky,1951).

as proboscis is. The Culex females have lower jaw palpus which smaller than proboscis in 4 times. The Anopheles males have lower jaw palpus with mace-shaped bulge on the end. It is as long as proboscis is. The Culex males have lower jaw palpus longer than proboscis and without mace-shaped bulge on the end. The Anopheles mosquitoes have dark spots on the wing, which are absent in Culex. Landing on the skin, the Anopheles mosquitoes keep their body at the angle to the skin surface. They direct their abdomen outward. The Culex mosquitoes keep their body parallel to the skin or directed to the skin.

The mosquitoes of Anopheles genus are definite hosts and specific vectors for malaria exciters. They transmitte it to the human being by specific inoculation. The oral apparatus of female is of piecing-sucking type (because of blood sucking), whereas oral apparatus of male is of sucking type (feeding by nectar). The Anopheles mosquitoes live near human dwelling. They start to fly at twilight. The female sucks blood after fertilization. It is needed for eggs development. The sucking time is 0.5-2 minutes. Then, the females fly to the dark places. There, they stay for 2-12 days digesting food. At spring and summer, the eggs are formed. Then, females fly to the nearest pond and lay eggs on the water surface. At autumn, the blood is used for fat body formation to survive at winter. It can spend a winter in vaults and basements. At spring, these females lay the eggs. Later, after blood sucking, the spring and summer females lay their eggs. After laying the eggs, the females fly searching new food. They can lay eggs several times during one season. In tropics, the Anopheles mosquitoes are specific vectors for exciters of lymphatic filiariasis (Wuchereria bancrofti, Brugia malai).

The Culex mosquitoes are specific vectors for exciter of Japanese encephalitis,

West Nil encephalitis, wuchereriasis and brugiasis.

The Aedes mosquitoes maintain circulation of yellow fever virus, Japanese encephalitis virus, exciters of lymphatic filiariasis (Wuchereria bancrofti, Brugia malai) in the nature.

For individual protection from mosquitoes biting, the repellents and mechanical devices (nets) are used. The fight against mosquitoes is directed to interrupting life cycle on a stage of water larvae. For this purpose, the wild pond should be filled up by sand. It is possible to use insecticides to kill larvae in small pond with high concentration of larvae. The biological methods are also effective. Thus, in Transcaucasia, it was successful rearing of gambusia fishes, which eat mosquito larvae. It results in decreasing mosquito population in several times.

The Phlebotomidae (mosquitoes). They are small (1.2-3.7 mm long), sanguivorous insects with golden-brown or grey color of body. The thorax engulfs outside. The wing and body is covered by setae. They lay eggs in rodent burrows, where is high humidity and many organics. The larvae develop two months. Then, they transform to pupa for 10-12 days. The pupa gives rise to imago.

They are twilight insects. They are very active during several hours after sunset. They fly near the land with many landings. If wind rise over two meters per second, they cancel flying. The geographical distribution is between 50 north latitude and 40 south latitude. They are found in Kazakhstan, Uzbekistan, Kyrgyzstan, Turkmenistan, Crimea, Caucasus, South Ukraine and Moldavia. They live in villages (in farm buildings where is conditions for arthropods development), as well as, in rural areas (rodent burrows, caves, tree hollows).

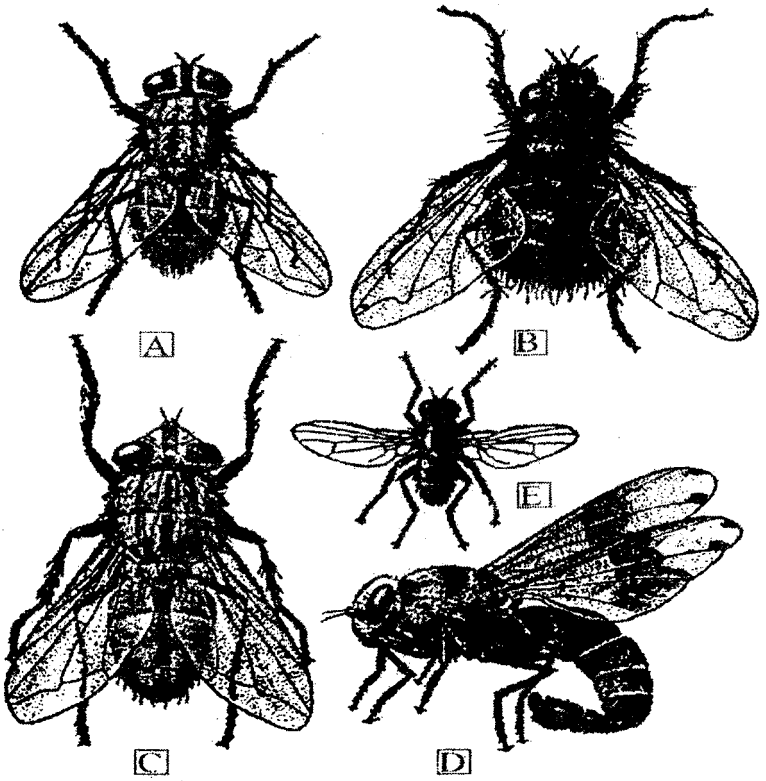
The mosquito's biting is very painful. It causes itching with inflammatory reaction. If a human being was bitted many times, he can have troubled sleep, risen temperature, and fatigue. Such type of mosquitoes is specific vectors for exciters of leishmaniasis and phlebotomic fever. The virus of phlebotomic fever is transmitted by transovarial way.

For individual protection, the repellents and nets are applied. The fighting against mosquitoes is performed with help of insecticides.

The Simuliidae (gnats). They are small insects (2-5 mm long). They resemble flies. The oral apparatus is short. It is designed for skin piercing and licking the blood. The wings are transparent without spots. The limbs are short and thick. They occur near rivers and stream with rapid current and clear water, where they lay their eggs. The larvae do not apt to move. 2-3 weeks after, the pupa is formed. A week after this, the pupa releases imago. Only females suck the blood.

They are ectoparasites of animals and human being. Attacking them, the gnats are very troublesome (crawl over the body and under the clothes, enter the nose and ears). They can transmitte exciters of tularemia and anthrax. They are very important as vectors of onchocercosis exciters in tropical Africa and America.

For individual protection, the repellents and nets are applied. The mechani-



Pic.21.9. The domestic flies:
A – house fly, B – blue meat fly, C - Wolfart's fly, D – gastric gadfly of horse, E – cheese fly (by D.V.Vinogradov-Volzhynsky,1977).

cal cleaning of rapid current zones of rivers is also in use.

The Ceratopogonidae (greases). They are small (1-2.5 mm long) insects with dark colored body. The small part of them are ectoparasites of birds, mammalians and human being. They can be found worldwide, except Arctic zone. They have complete development. They have spotted wings, long antennae, and piecing-sucking type of oral apparatus. They develop in ponds and in wet land. The development of egg to imago stage takes about a month. Many species develop in shallow water of shoreline.

The greases attack human near places of their development at calm weather. They cannot fly if wind is more than 2 meters per second. The acute inflammatory reaction with severe itching develops after greases biting. In tropics of America

and Africa, the greases can be the vectors of filiariases (Acanthocheilonema perstans, Mansonella ozardi). In China, the Japanese encephalitis virus was found in greases. It Russia, the virus of lymphocyte choriomemingitis and bacteria of tularemia were also found in greases.

To fight against greases, the personal protection tools are most effective.

The Tabanidae (gadflies). They are large flies (6-30 mm long). The oral apparatus has features of both piercing-sucking type and licking type. The body is covered by thin setae. The females lay their eggs on coast plants. The larvae develop in wet silt. The larvae are predators. The cycle of development lasts for an year. They are spread worldwide.

They are ectoparasites of human being and animals. They can attack a human being in taiga, on the coast of forest rivers, in steppes, and in other natural zones. They like to land on wet skin after swimming. To satisfy, they need to suck about 100-200 mg of blood. Therefore, they make a big wound and secrete saliva to it. The saliva is very toxic. It causes immediate defense reaction of host. Thus, gadfly needs to go to another host. This phenomenon called "interrupted feeding". The gadflies are vectors of tularemia bacteria, anthrax bacteria, and, in some countries, of loalasis parasites (Loa loa).

To fight against greases, the personal protection tools are most effective.

The Muscidae (real flies). They are insects with small antennae. The sizes can vary from 6-8 mm to 18 mm (pic 21.9,a,b,c). They have completed metamorphosis. The exception is tsetse flies. They deliver one larvae, which immediately transforms to pupa. 3 weeks after, the imago appears. Flies develop in the savage areas, in the rotted fruits and vegetables. The typical representatives of Muscidae are house fly (Musca domestica), market fly (Musca sorbens), biting fly (Stomoxys calcitrans) and tsetse flies (Glossina palpalis, Glossina morsitans).

The flies are inspecific, mechanical vectors for exciters of alimentary infections (dysentery, typhoid, cholera), of tuberculosis, diphtheria and also of helminthes eggs and protozoa cysts. The biting fly and tsetse fly are sanguivorous (both male and female). The biting fly can participate in spreading of zoonosis infections (tularemia, plague, anthrax, brucllíasis). The tsetse flies are specific vectors for exciters of African trypanosomiasis.

The Sarcophagidae (grey meat flies). They are presented by grey meat fly, Wolfart's fly and by othes species (pic 21.9,c). They are large (9-24 mm long) flies, which deliver living larvae. They have typical lines and chess picture on the back. The larvae can move inside the organism. The pupa formation occurs in external environment. The mature form lives outside of organism. They can be found worldwide. The development of them occurs in animals cadavers or, rare, in human excrements.

The larvae of Wolfart's fly develop in wounds, in lumen of animals and human. They cause severe damage of internal organs. The gery meat flies can be vectors

for exciters of alimentary infections. The larvae are cause of myiasis.

To fight against greases, the personal protection tools (repellents) are most effective.

The gadflies of Gastrophilidae, Hypodermatidae and Oestridae families. These are the flies whose larvae develop in the organs and tissues of animals and human being. The mature flies live several days. They do not feed. The larvae are obligatory parasites. There are three families of gadflies: Gastrophilidae, Hypodermatidae and Oestridae.

The females of Gastrophilidae flies lay eggs on the horses hair (pic 21.9,d), from where the horse lick them and swallow. They live in the stomach. 12 months after, the larvae escape the gut with faeces. The pupa formation occurs in the land. Human beng can be infected after contact with horses. The larvae penetrate the skin and migrate, causing severe inching. It was called "crawling disease". The treatment is only surgical.

The females of Hypodermatidae flies lay eggs into the skin of farm animals, deer. The tumour is formed around the place of biting. Human being can be infected very rare. It causes furuncle formation on haired skin of head, on shoulder. The treatment is only surgical.

The females of Oestridae flies deliver living larvae. The females spray larvae into the nose of seep and gouts. The human can be infected on pasture. The larvae can be spread to conjunctive, nostrils, eyes. The eyes myiasis can be external (larvae are under conjunctive or in tear bag) or internal (in eye bulbus). The treatment is only surgical.

CHAPTER 22. POISONOUS LIVING ORGANISMS AND THEIR ECOLOGICAL VALUE.

There are many species of plants, fungi and animals, which are poisonous. However, ability to have poison is universal event in nature. It is an important mechanism of struggle for existence. Poisons of living organisms are used in ecological relationships between species. The substances, which take part in this relationships giving benefit to organism that produce them, are called allomans. They include poisons of plants (phytotoxins), poisons of fungi (mycotoxines), and poisons of animals (zootoxines).

The ecological view on this problem allows understanding of ecological relationships of organism with poison. It also helps to understand relations between toxin type and features of species being in the nature. In spite of big efforts in zoo- myco- and phytotoxines studying, there are very few toxins, which were studied experimentally. Plants, in compare with animals, use poisons only for defense from animals that can eat them. The traditional view on poisonous plants concerns only plants, which are poisonous for human being. Many of then are medical herbs. However, really, there are many plants, which are poisonous for insects, animals, but they are good for human. Even approximate list of herbs with insecticide properties includes more than 1000 species. Many of them are not well studied.

22.1 The poisonous fungi.

The fungi are a distant kingdom of organisms, comprising more than 80000 named species. In Belarus, there are about 1000 species of higher fungi.

Poisoning by poisonous metabolites of fungi occurs by eating, drugs treating (ergot) and folk medicine methods treating (toadstool, death-cup).

Morphologically all fungi are divided into macromycetes and micromycetes. The macromycetes are group of higher fungi with different systematics, whereas micromycetes are the group of all other fungi with microscopical sizes.

In spite of common mention that macromycetes are more poisonous than micromycetes, reality shows that it is incorrect. The micromycetes are more toxic and they can cause severest alimentary poisonings.

The most famous among micromycetes is aspergilus genus. They produce aflotoxines (table 22.1). Human being becomes poisoned by eating contaminated foodstuffs. The main signs of poisoning are fatigue, appetite lost, failure in movement coordination, convulsions, paresis, body weight lost and others. The specific symptoms of acute aflotoxicosis are multiply hemorrhages, oedema, and in some cases, jaundice and blood clotting failure.

The micromycetes from Fuzarium genus produce more than 40 mycotoxines

Table 22.1 The characteristics of misromycetes mycotoxines. (b.N.Orlov et. al. 1990).

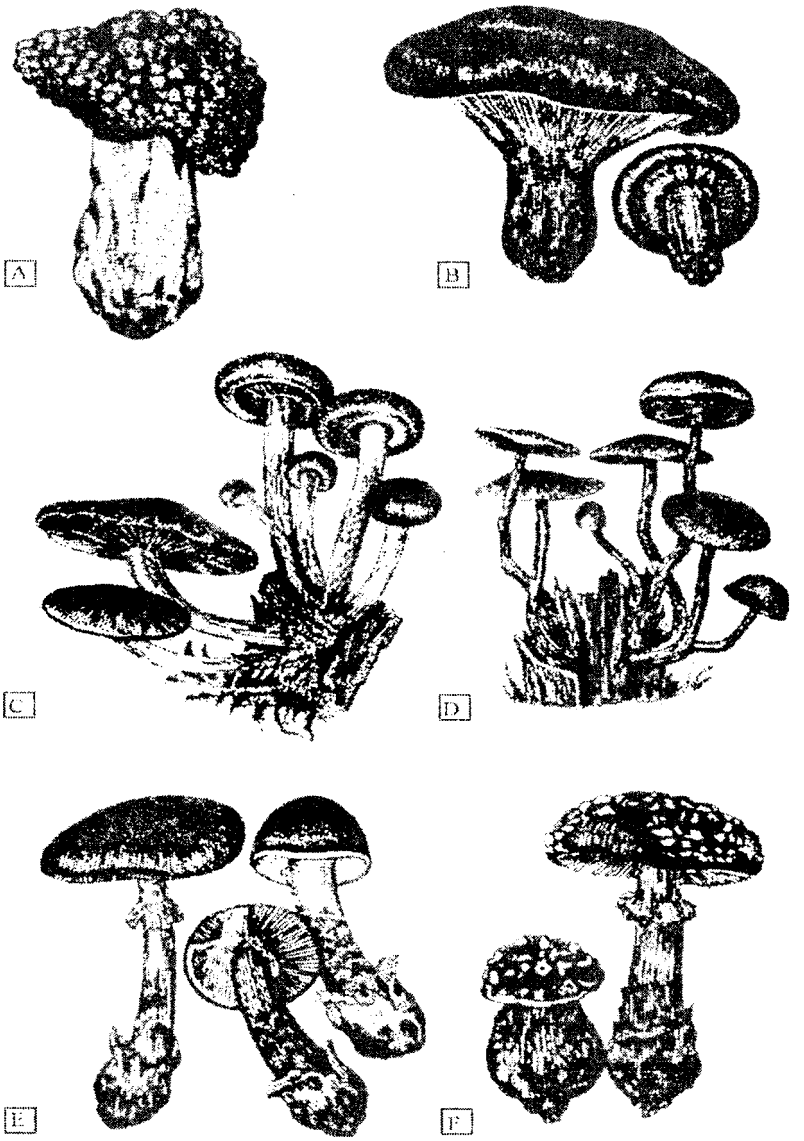
Producing organisms	Mycotoxines	Natural substrates	Pattern of toxic action
Aspergilus flavus, Aspergilus parasiticus	Aflotoxines B1,B2,G1,G2	Peanuts, corn, cottonseeds, nuts, vegetables, forage.	Hepatotoxic and hepatocanceroge nic, mutagenic, teratogenic, immunosuppress ive.
Aspergilus ochraceus, Penicillum viridicatum	Ochrotoxines B,C.	Wheat, coffee beans, cheeses, forage.	Nephrotoxic, teratogenic.
Penicillum patulum and others	Patulin	Fruits, vegetables, juices, jam.	Neurotoxic, mutagenic, teratogenic,
Fusarium grminaerum and others	Trychocetin mycotoxines	Wheat, forage, hay.	Neurotoxic, hemorrhagic, leucopenia, immunosuppress ive, dermatotoxic
Fusarium grminaerum	Zearalenon	Corn, barley, whet, forage, sorghum.	Estrogenic, teratogenic.
Claviceps purpurea	Ergotoxines	Wheat	Neurotoxic

referred to sexviterpens. The typical is poisoning by "tipsy bread". It is bread contaminated by Fuzarium graminearum. 30-60 minutes after eating this bread, the vomiting, stomach pain, diarrhea, fatigue and bare walking are observed. A day after, the severe headache and dizziness are observed. If "tipsy bread" is taken routinely, the emaciation, vision lost, psychological disorders appear.

The ergot fungi (Claviceps) affect more than 150 species of agricultural and wild crop plants. The ergot produces mycotoxines: ergotamine, ergosin and others. They are exposed on the sclerocilia of ergot. The poisoning occurs if flour is contaminated by ergot sclerocilia. If the concentration of sclerocilia exceeds 2%, it may cause massive poisoning. The main symptoms can be expressed in two forms: gangrene form and convulsion form.

First aid in mycotoxin poisoning is in gastric lavage by 2% $NaHCO_3$ with carbon adsorbent. The treatment by laxative drugs is also helpful.

The preventive measures against mycotoxicoses include inspection of food-



Pic.22.1. The poisonous macromycetes:

A – Gyromitra esculenta, B – Paxillus involutus, C – Hypholom sublaterium, D – Hypholoma falsciculare, E – toad-stool, F – death-cup (by B.A.Orlov et al.,1990).

stuffs state, elimination of contaminated foodstuffs. It is important to note that mycotoxines are very stable substances. They cannot be inactivated by thermal cooking.

The macromycetes, traditionally, is divided to eatable, relatively eatable, almost uneatable and poisonous.

There is a group of fungi among eatable, which are poisonous until cooking preparation. They are morels and other mushrooms (pic 22.1 a,b). The Paxillus involutus contains dangerous toxins, including muscarin. It accumulates carcinogenic substances and special protein antigens, which change blood composition. The Paxillus involutus mushrooms gathering is prohibited by sanitary laws.

The relatively eatable fungi – are satanic mushroom, grey dung mushroom. They are eatable only after specific sanitary preparation.

The poisonous fungi are toadstool, death-cup and others (pic 22.1, c,d,e,f). In the toadstool body, there are two groups of mycotoxines: amanitines – more poisonous but slowly acting, and phalloidines. They affect prevalently liver cell damaging EPR and nucleuses of hepatocytes. The death-cups contain muscarin, muscaridin, choline, betain and other. They are toxic mainly due to muscarin and muscaridin action on M-cholinorecptors of autonomic nervous system

First aid in mycotoxin poisoning is in gastric lavage by 2% $NaHCO_3$ with carbon adsorbent. The treatment by laxative drugs and potassium permanganate solution are also helpful. The artificial breathing should be applied if needed.

To avoid harmful effect on digestive tract and liver cells it is suggested to satisfactory cook fungi before eating. The preparation of fungi foodstuffs without thermal cooking is unfavorable. It is prohibited to trade mushrooms of different kinds in one set. The problem of mushroom poisoning is very important. The human being can be poisoned by eating old mushrooms, where poison can be formed as result of degradation processes in mushrooms. Fungi can accumulate dust substances and salts of heavy metals. Thus, it is harmful to gather mushrooms near highways.

22.2 The poisonous plants.

Today, plants are considered as poisonous if they produce even in small amounts phytotoxines, which are poisonous for human and animals. However, this definition is relatively conditional. Thus, clover during mild winter (with January isotherm over +5 centigrade) accumulates in young shoots significant amount of cyanogenic glycosides. Thus, clover protects itself form snails, which can eat shoots early in spring. At summer, massive growth makes unimportant small shoots lost by snails. Therefore, there is no need in toxic defense.

Since ancient times, the plant's poisons were used in folk medicine. Modern

pharmacologists advise to use them carefully because off side effects, especially when they are overdosed.

There are about 1000 species of poisonous plants. They are mostly Angiosperms. Mainly they are plants of countries with arid climate and highlands. The flora of arid regions includes about 70% of total poisonous plants number.

There are different classifications of poisonous plants based on poison compound or poison action. There are poisonous plants with subdivision extremely poisonous plants and conditionally poisonous plants (they are toxic only in particular living places, after inappropriate storage, affected by fungi or microorganisms). The poisonous plants are crystal tea ledum (Ledum palustre), hemlock, May lily of the valley, poison- buttercup, corn poppy and others.

The group of extremely poisonous plants includes black henbane, belladonna, jimson weed, water hemlock, weed-elder, daphne and others.

22.2.1 The poisonous organs of plants.

Phytotoxines can be concentrated in whole plant or in specific organs. Thus, in seed-lobes of many Rosacaes there is amigdalin, which gives a taste of "bitter almond". The amigdalin degrades to prussic acid. The presence of prussic acid preserves young shoot of cherry, almond, prune, peach and apricot from eating by animals. The amigdalin also is in fruits of bird cherry tree, apple tree, cherry-laurel tree, rowan-tree and others.

The seasonal poison accumulation is due to different functioning of different plant organs during year cycle. In the storage underground organs, the maximum amount of poison maintains during winter rest, whereas in shoots the maximum in reached during flowering. Some plants have poisonous immature seed and fruits. However, the majority of fruits are toxic after maturation.

The same plants can be toxic for one species and harmless for other species. Thus, belladonna and jimson weed are very toxic for human being, but they are harmless for rodents, hens and other species. Nevertheless, they are toxic for chickens and ducks. The poisonous fruits of May lily of the valley are not toxic for foxes. The foxes eat them to escape helminthes.

The poisonous plants are common reason of animal and human poisoning. It particular concerns children, who like to eat "beautiful" fruits, roots, bulbs and shoots. The form of such poisoning is overdosing of herb drugs. The inhalation of poisonous evaporations of several plants (crystal tea ledum) may also cause poisoning. The plants can cause skin irritation, in form of allergic reactions, while direct contact (nettle, spurge, spurge-flax, rue). Sometime poisoning can occur by eating honey contaminated by pollen of poisonous plants (crystal tea ledum, cherry-laurel tree, spurge-flax) or by eating milk and meat of animals, which have ate poisonous plants (buttercup, yew, poppy).

22.2.2 The poisonous substance and their mechanisms of action.

The plants poisons are referred to several groups accordinary to chemical nature.

Alkaloids – are nitrogen containing organic bases with heterocyclic structure. They act selectively to different organ systems. Thus, they can be used for treatment of different disorders. The alkaloids are colorless crystals, bitter on taste, almost insoluble in water, but good soluble in organic solvents (ether, chloroform, benzyl). The salts of alkaloids are good soluble in water and almost insoluble in organic solvents. The most common alkaloids are nicotine, morphine, ephedrine, colchicum and others.

Organic acids plays very important role in substances exchange in plants. They are used in amino acids, saponins, alkaloids, steroids synthesis. There are following groups of organic acids: aliphatic, aromatic, acyclic. The most common among aliphatic acids are formic acid, acetic acid, isovalerianic acid. They smell foxy. The apple acid and lemon acid are present in all plants. The most common among aromatic acids are benzoic acid (compound of ether oils and balsams), gallic acid (compound of tannins) and caffeic acid. The acyclic acids are presented by chinic acid, which is in the blackberry, cranberry, coffee.

Lipids are group of various substances, which are dissolved in organic solvents. It includes fats, phospholipids, sterols, vexes and others. Oils are divides into three groups: nondrying oils (olive oil, almond oil, castor oil), semidrying oils (sunflower oil, corn oil, cotton oil) and drying oils (linseed-oil, hempseed oil). The non drying oils are used for preparation of injectional solutions of sexual steroids and other lipidsoluble drugs, and as laxative drugs. The semidrying oils are used for preparation of different ointments; corn oil is used for atherosclerosis prophylactics. The drying oils are used for preparation of ointments for burns treatment. They are also substrate for prostaglandins synthesis.

Terpenoids are oxygen-containing derivates of terpins, which consist of isoprene units (C_5H_8). They are connected by "head to tail" way. Terpenoids of ether oils have spasmolitic and aseptic properties. The ether oils are often used as expectorant drug. They have anticancer and cytotoxic effect. The cucurbicines has anticancer effect; they are in the form of glycosides in plants of Cucurbitaceae, Cruciferae families.

Heart (steroid) glycosides are derivates of cyclopentanperhydrophenartren. They are divided into two groups: cardenolids and bufadienolids. The heart glycosides have cordiotonic effect; they raise excitability and contractibility of myocardium. However, they are heart poisons if they are overdosed. The cardenolids and bufadienolids occur in animals; they can be compound of frog poison.

Saponines are steroids with 27 carbon atoms in a molecule. The water solutions of saponins make stable foam. They have bitter taste, which cause irritation

of mucosa and reflex excitement of vomit apparatus. They are not absorbed in alimentary canal. However, if they appear in the blood, it results in CNS paralysis and erythrocytes hemolysis.

Flavanoids are phenol derivate. They have similar structure $C_6 - C_3 - C_6$ they are white (kachetins), yellow (flavons), orange (chalcons) and vilolet (antoyans) crystals. The majority of flavonids occur in a glycoside form. They have wide spectrum of biological action (antioxidant, anticancer, antispasmodic, hypotensive, estrogenic effects).

Tannins are big polyphenol molecules. They are present in many plants, especially in dicotyledons. In tanning process, the tannins interact with collagen molecules. It gives collagen proteins a property to resist moist and microorganism influence. Tannins have bonding and bactericide effects.

Coumarins are oxygen containing heterocyclic substances. They are derivates of benzol-$^{\alpha}$-pyrron. They are found very often in plants (more than 200 substances). Coumarins have antispasmodic, anticoagulant, vasodilatative and photosensitizing effects. Dicoumarin is antagonist of vitamin K.

Anthraquinones are group of anthracene derivates. The representatives of this group are anthraquinone and its reduced derivates. Many of them increase gut peristaltics, therefore, they have laxative effect. Some of anthracene derivates can reduce blood hemoglobin level and affect liver and kidney functions.

22.2.3 The poisonous algae.

The poisonous compounds of algae were found recently in representatives of dynophyta algae, gold algae, green algae and cyan bacteria. The cyan bacteria can produce and accumulate algotoxines. It was stated that the reason of the massive poisoning on shore is feed chains with phytoplankton as starting chain. The algotoxines are accumulated in water ecosystem. The second chain is mollusks and fishes. The next chain is animals and human. The water resources contamination by algotoxins is dangerous. The poisoning can occur even while swimming at florescence period.

The poisoning by cyan bacteria has many clinical forms. In alimentary form, the vomiting, stomachache, intestine spasms, diarrhea, headache, muscle and joints pain are observed. In dermato-allergic form, the dermatitis, itching, hyperemia of eye conjunctive, allergic reactions of respiratory tree are observed.

If skin was in contact with cyan bacteria, it should be washed thoroughly. To avoid such poisoning, the water boiling, filtration and sanitary water inspection are recommended.

22.2.4 The poisonous higher plants.

The major part of poisonous plants is Angiosperms. There are poisonous

mosses, liverworts, hornworts, Gymnosperms and Angiosperms.

Lycophyta representatives (lycopods) are evergreen perennial weeds or bushes. The Licopodium silago has medical value. It is evergreen perennial weed with height about 10-20 cm. The overground part of the plant is poisonous. It contains toxic alkaloids: selagine, clavatin, lipocodin, nicotine, which have neurotropic effect. The selagine contracts pupils, in toxic doses it can cause vomiting, decreasing of muscular tonus, suppressing of breathing. The poisoning occurs by eating or chewing weed. The main symptoms of poisoning are vomiting, headache, fatigue, tongue numbness. It severe cases, it is possible that the heart arrhythmia and syncope condition appear. First aid is stomach lavage, carbon adsorbent prescription. In case of vomiting – ice pieces swallowing.

Sphenophyta representatives (horsetails) are perennial spore weeds. The shoots are high, straight, segmented, solid, green or brown with ribs on a side. Spore strips are on a top of main shoot. In CIS, there are 15 species of horsetails. The entire plant is poisonous. It contains toxic alkaloids (palustrine), saponins (ecvizetotine), flavonic glycosides. Their action appears 40-87 days after poisonoing. The signs of poisoning are pupils' dilatation, unmotivated aggression, and muscles paralyses. The farm animals can suffer from horsetail poisoning in form of alimentary disorders, fatigue and weight lost. First aid is elimination of contaminated hay.

Pterophyta representatives (ferns) are most ancient group of higher plants. It is known about 10 species of poisonous ferns. The Dryopteris filixmas has medical value. It is big plant with height anout 40-100 cm. It has thick lignificated root. This root is poisonous. It contains filixic and flavospidinic acids, aspidinol and albasidin. The extracts of dried root possess antihelminth effect. It paralyzes tapeworms. The poisoning occurs when the root extract was overdosed. The symptoms of poisoning are vomiting, headache, fatigue, stomachache, dizziness, vision disorders. In acute intoxication the jaundice and atrophy of optic nerve appear. First aid is stomach lavage, carbon adsorbent prescription, salt laxative prescription.

Gymnosperms with toxic effects are in Gnetales and Coniferophyta classes.

The Gnetales are diclinous, leafless, evergreen, small bushes with ribes on young shoots. They contain poisonous alkaloids – ephedrine and pseudoephedrine. The ephedrine excites α and β adrenoreceptors, increase noradrenakine release fron synapses. It is known about 20 species of Gnetales. The typical representative is Ephedra distachia. The symptoms of poisoning are vomiting, enhanced perspiration, skin eruption, anuria, general neural excitation, arterial pressure raising, breathing disorders.

First aid in poisoning is in gastric lavage by 2% $NaHCO_3$ with carbon adsorbent. The treatment by laxative drugs and potassium permanganate solution are also helpful.

The Coniferophyta (pine, spruce, silver fir, larch, juniper) are worldwide plants. It is typical for them to have terpenoids in all body parts. The terpenoid resin have phytoncidic (bacteriocidic, protistcidic) effect. The Coniferophyta resin is a mixture of resin acids – abietinic, L-pimaric, D-pimaric. A human being can be affected while working with wood. The symptoms of poisoning are vomiting, severe salivation, stomachaches, diarrhea, and frequent urination.

First aid in poisoning is in gastric lavage by 2% $NaHCO_3$ with carbon adsorbent. The treatment by laxative drugs and potassium permanganate solution are also helpful.the skin washing is helpful in external affection.

The Angiosperms is most numerous group of plants. It includes about 400 species of poisonous plants.

Umberlliferae family.

Cicuta virosa – all parts of plant are poisonous, especially root (pic 22.2,c). The main toxin is cytotoxins. It is absorbed very fast from digestive tract. It affects central nervous system, causes convulsions. 15-20 minutes after poisoning, the headache, vomiting and stomachache develop. The death can result from breathing failure accompanied with acute heart failure.

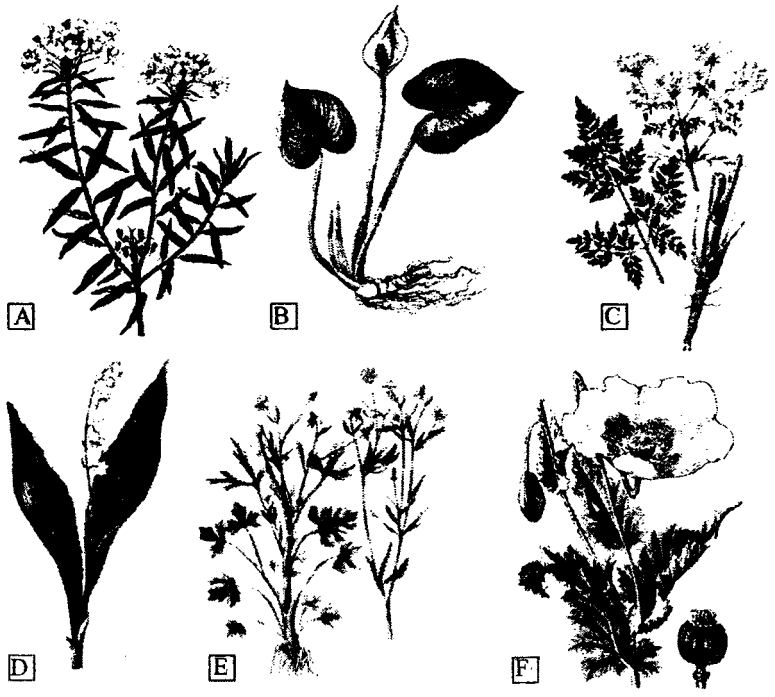
Conium maculatum – is high diseasonal plant with unpleasant mouse smell. All parts of plant are poisonous, especially immature fruits. It contains alkaloids: coniine, conhydrine. The human being can be poisoned by eating shoots and fruits. The signs of poisoning are vomiting, dizziness, excessive salivation, defects in swallowing, speech. The general excitation is accompanied by convulsions and leads to suppression of CNS.

Solanacae family.

Solanum nigrum – is semibush with crawling long shoots (pic 22.2,f). The shoots, leafs and immature fruits are poisonous. It contains alkaloid – soladine. Solanine irritates mucosa of digestive tract and suppresses CNS. The human being can be poisoned by eating immature fruits.

Datura stramoncum - all parts of plant are poisonous, including seeds (pic 22.2,d). It contains tropanic alkaloids: atropine, hyoscyamine, and scopolamine. The signs of poisoning are defects in swallowing, diarrhea with blood, CNS function disorders.

Hyoscyamus niger – is a tall (up to 1 meter), diseasonal plant with big leafs (pic 22.2,b). All parts of plant are poisonous, including seeds. A honey from these flowers is also poisonous.) It contains alkaloids: atropine, hyoscyamine, and scopolamine. The human being can be poisoned by eating immature fruits or by overdosing drugs, which made of this plant. The clinical picture of poisoning is acute psychosis with hallucinations.



Pic.22.2.The extremely poisonous plants:
A – Belladonna, B - Datura stramoncum, C – Dophne mezerium, D - Colchicum autumnale. E - Hyoscyamus niger, F - Cicuta virosa

Papaveracae family.

Papaver somniferum - all parts of plant are poisonous (pic 22.2,e). The maximum of poisonous substances are in immature boxes (fruit). It contains more than 20 alkaloids: morphine, codeine, papaverine, protopine and others. The morphine is narcotic analgesics. However, if taken routinely, it may cause addiction.

Chelidonium maius – it contains alkaloids: sangvinorine, cheleritine, chelidonine, which have small narcotic effect and antiseptic effect. The sangvinorine in toxic doses can cause convulsions.

Ranunculaceae family.

Ranunculus scleratus – the over land part of the plant is poisonous. It contains lactones (ranunculine, protoanemonine) and phlavonoids (cempferol, cvercetine).

The juice of this plant can cause severe irritation of skin and mucosa. In severe cases, the CNS damage occurs (convulsions, conciseness lost).

Cruciferae family.

Erysimum cheiranthoideus - the over land part of the plant is poisonous.. It is toxic due to having following glycosides – erysimine, ertcanoside and others. These glycosides enhance excitation and contractibility of myocardium, decrease conductivity. In light form of disease, the extrasystoles occur. In severe cases, the vomiting, shortness of breath, bradicardia followed by tachycardia.

Leguminosae family.

Melilotus officinalis – is tall, two-seasonal plant. It has small, complex, branched on three parts leafs. The over land part of the plant is poisonous. It contains aromatic lactone – cumarin. If hay subjects to fermentation, the dicumarine forms. It has anticoagulation (anticlotting) effect.

Fumariaceae family.

Corydalis cava – the plant tubers are poisonous. It contains alkaloids: bulbocapnine, bicuculine, coricovine and others. The bulbocapnine affect CNS, causing sleepiness in small doses, catalepsy up to 18 hours in average doses, convulsions resulting in death in large doses.

Thymelaeaceae family.

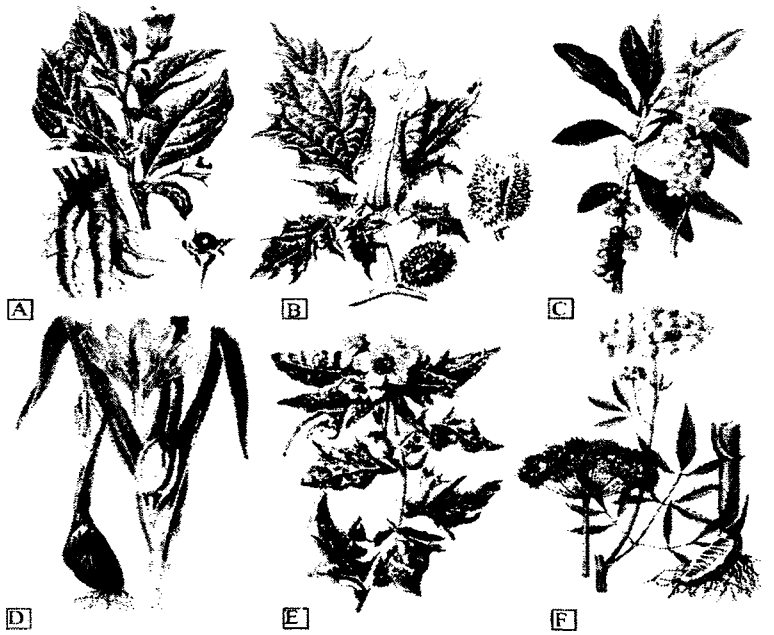
Dophne mezereum – the cortex, leafs, flowers and fruits are poisonous. It contains alkaloids liserine, daphnine, daphnitine. The liserine is local irritator. The daphnine is antivitamine K, causing defects in blood clotting.

Cannabinaceae family.

Cannabis sativa is diclinous plant with poisonous seeds, fruits and young tops of female individuals. It contains cannabinol, cannabidinol etc. The human being can be poisoned by eating or by smoking cannabis drugs (hashish, marijuana). If it is taken routinely, the psychiatry disorders and degradation of personality occurs.

Ericaceae family.

Ledum palustre - .the over land part of the plant is poisonous. It sprays out



Pic.22.3. The poisonous plants:
A - Ledum palustre, B - Calla palustris, C – Conium maculatum, D - Conrallaria majalis, E - Ranunculus scleratus,F – Papaver somniferum

poisonous ether oil with ledol, cymol and others. The human being can be poisoned by eating or by inhaling ether oil vapor, or through skin and mucosa. Clinical signs are sleepiness, vomiting, fatigue, increased sweating, decreased arterial pressure level, tachycardia, in severe cases – shortness of breathing and asphyxia.

Araceae family.

Calla palustris. It has thick root and big leafs on thick leafstalks. The entire plant is poisonous, especially roots and berries. It contains saponine-like substance and aron-like evaporating substances. Children become poisoned by eating berries. The vomiting, salivation, diarrhea, shortness of breathing, tachycardia and convulsions may occur.

Euphorbiaceae family.

Euphorbia waldsteinii – is tall (40-80 cm), multiseasonal plant with white,

acrid juice. The entire plant is poisonous, especially roots. It contains titerpenoids (euphol, euphorbol), diterpenoids and flavonoids. If putted on skin, juice cause skin irritation, inflammation and abscesses. It is very dangerous for eyes. If taken orally, it can cause death.

Compositae family.

Tanacetum vulgare - is tall multiseasonal plant. The over land part of the plant is poisonous, especially inflorescences. It spays ether oils, in which there are terpens ketons and tuyons. If it is inhaled, it may cause vomiting and diarrhea. If it is taken orally, it may cause kidney affection and CNS disturbances (hyperreflexia following by depression).

Liliaceae family.

Conrallaria majalis. The over land part of the plant is poisonous. It contains soponine, convallarine and heart glycosides. The human being can be poisoned by eating fruits or by preparations overdosing, which is made of this plant.

Colchicum autumnale – is multiseasonal plant with beautiful flowers. It is up to 15 cm tall. Leafs are long, shining, thick. Flowers are big and violet. The entire plant is poisonous, especially seeds and .tubers. It contains alkaloids colchicine, cocholine and others. 3-6 hour after taking in, the poisoning develops. The signs of poisoning are vomiting, diarrhea, oligouria, arrhythmic pulse. The convulsions development, body's temperature fall and shortness of breathing are also possible.

Veratum Lobelianum – is tall (70-80 cm), multiseasonal plant with many leafs. Flowers are plain. The entire plant is poisonous, especially roots. It contains alkaloids yervine, germine and others. . The human being can be poisoned by eating roots and leafs. First signs are tickleness in throat, in eyes, in nose, excessive salivation, crying, running nose, vomiting, diarrhea. It can be followed by heart failure.

First aid is immediate stomach lavage to remove all parts of the plant. Accordinary to plant type, it can be performed with activated carbon absorbent, 1% solution of potassium permanganate, 0.5% solution of tannin and others. The laxative drugs are prescribed. The artificial respiration can be applied if needed. A poisoned man has to be delivered to toxicological department of nearest hospital.

22.2.5. The rational using and protection of poisonous plants.

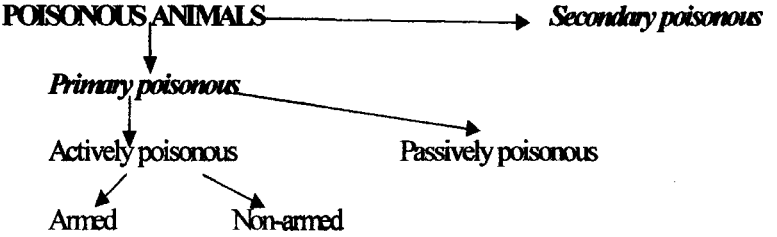
The fight against natural bushes of poisonous plants is not a best way to cope with them. Many of them are in The Red Book. Many of them can be valuable

drugs substrate. But all of them are components of natural ecosystems. Due to harmful human influence, the populations and areas of poisonous plants decrease. Sometimes, it is needed to set special areas to plant poisonous plants. The question about rational way of poisonous plants using is very important and actual.

22.3 The poisonous animals.

There are about 5 thousands species of poisonous animals worldwide. They live in water and on the land, as well. They are more often in countries with tropical and subtropical climate. They are relatively poisonous. That means that poison play a specific role in interspecies relationships. It can be poisonous for one species and non-poisonous for another. The poisonous substances can be used to frighten away predators, to hide running away, to lure females.

Accordinary to having special devices for producing and injection of poison, the classification of poisonous animals was suggested.



Primary poisonous are animals who produce poison in special glands or having poisonous metabolites. The ability to have poison is specific sign of the species and occurs in all individuals of the species. The primary poisonous animals are dinoflagellates, cnidarians, some species of spiders, scorpions and others.

Actively poisonous animals have specific apparatus for poison. Armed animals have specific device to wound preys and to inject poison into its internal environment. It is most effective way to poison. Many poisonous cnidarians, mollusks, arthropods, fishes, reptilians are armed poisonous animals. Non-armed aimals have no such device. They produce poison by skin (as amphibians do) or by anal glands (as some insects do). They poison preys when they touch their skin. The poison is absorbed from the skin, the effectively it acts.

Passively poisonous animals produce poisons and accumulate them in different organs and tissues, as mollusks, insects and aphibians from Caudata Order.

Secondary poisonous are such animals that can accumulate exogenous poisons. They may be toxic only when they are ate (some mollusks accumulating dinoflagellates poison; insects accumulating poison of poisonous plants).

Passively and secondary poisonous animals are dangerous only if they are feed. The main difference between them is that in passively poisonous animals,

the poison preserves continuously throughout the life, whereas in secondary poisonous animals, it appears only sporadically.

It is still not clear, how poisons appeared in animals. It is believed that on early stages of evolution, the poisons are only metabolites, which were excreted into external environment or were accumulated in the body. Then, evolution directed development to appearance of special organs, which produce poison. At first, it was due to increasing of defense properties of ectoderm (cnidarians, amphibians). Then, it was due to development of endocrine and exocrine glands. Thus, Hymenoptera, poisonous apparatus is closely connected with reproductive system, whereas in mollusks and snakes, it is connected with digestive system. At the same time, many fishes preserve poison accumulation in many tissues and organs.

22.3.1 The characteristics of animals' poisons.

The animals' poisons are natural biologically active substances. They very selectively interact with biological structures. They called zootoxins. The science, which studies them, is called zootoxinology. It borders the following disciplines: molecular biology, zoology, physiology, pharmacology, pathology.

Zootoxinology is ancient science. The emblem of the medicine is cup winded round by snake. It was designed in ancient Greece. In ancient Greece, the healing gopd Aesculapius and health god Hygia were painted with snakes. The big contribution was made by Avicenna (980-1037), E.N. Pavlovsky (1884-1965), N.A. hologkovsky (1858-1921), F.F. Talysin (1903-1976), S.V. Pigulevsky (1899-1974) and others.

Zootoxins are very different chemically. They may include aliphatic and heterocyclic compounds, alkaloids, steroids, non-enzymatic polypeptides, and enzymes. They are "genuine toxins", which not exist in recipient organism. Another group of toxins is substances, which exist in recipient organism. They are acetylcholine, catecholamine, indol derivates, enzymes and their inhibitors.

The toxicity is most important characteristics of toxins. It is ability of chemical substance to induce tissue and organ damage. It may result in failure of main organism functions and death.

Accordinary to physiological effect, the zootoxins are divided into neurotoxins (affecting prevalently nervous system), cytotoxines (damaging tissue cells), hemorrhagines (affecting blood clotting), hemolysins (causing erythrocyte lysis).

There is correlation between chemical nature of poison and structure of poisonous apparatus. Thus, the majority of poisons are mixture of proteins and enzymes (poisons of cnidarians, spiders, scorpions, snakes). They are active only if they were injected parenteraly, because they can be digested by digestive enzymes if were taken orally. Therefore, animals with such poisons have specific apparatus

to pierce and wound their preys. From the other side, animals with poisons which are active if were taken orally, have no so particular apparatus.

Predators as usually have better poisonous apparatus (snakes, spiders, scorpions). It is due to their life pattern. In general, the poisons of predators are neurotoxins. They are needed to affect nervous system. This makes prey immobile. Animals without specific poisonous apparatus use poisons for defense (frogs, ants).

Poison, which entered the organism, is distributed in the body irregularly. It is due to various membranes (plasma membranes, capillaries walls) and different barriers (hematoencephalic, placental). The speed of membrane diffusion determines speed of poison action. Zootoxins affect organs and systems selectively, that means that they affect target-cells. Zootoxins action may have local and resorptive character.

The clinical picture of poisoning depends on several factors. First is poison chemical composition (prevalence of one component will determine clinical picture). Second is place of poisoning. The more close to CNS organism was bitted, the more toxic action toxin has. Third is season. After molting or winter sleeping, the poison of animals is more toxic. Fourth is psychological state of affected man. Patients with labile nervous system state express more severe picture of poisoning.

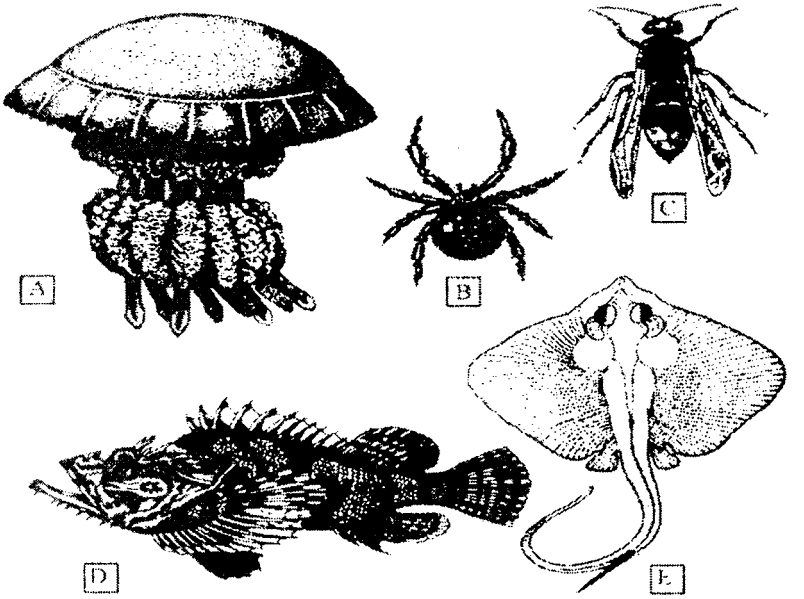
22.3.2 The poisonous Protists.

The most common poisonous Protists are dinoflagellates. Their poison consists of neurotoxin and hemolysin. The massive reproduction of dinoflagellates results in event called "red flood". It lead to massive death of sea animals. Some fishes and mollusks can survive, but they become contaminated by poison. Thus, such fishes and mollusks become poisonous too. They can be found in Pacific Ocean near North American coast, in Atlantic Ocean near Canada, Britain Islands, Europe, tropical American coasts. Human being can be poisoned by eating contaminated mollusks (mussels). The clinical picture shows affection of nervous system (numbness of tongue, lips, fingers, heart and respiratory failure that can result in death).

The plankton and eatable mollusks should be inspected to avoid massive poisoning. The contaminated mollusks can be neutralized by oxygen. After 72 hours exposition, the toxicity is reduced on 50-70%. Then, they can be used as a food.

22.3.3 The poisonous Cnidarians.

The poisonous animals occur in all classes of this phylum. In Hydrozoa class,



Pic.22.4. The poisonous animals:
A – jelly fish, B – karakurt spider, C – Easten wasp, D – sea ruff fish, E – sea electric skate (by S.V.Pigulevsky,1966,1975).

the "cross" jellyfish (Goniomus) and Portuguese man-of-war (Physalia utriculus) are poisonous. The first live in Pacific Ocean, second in tropical and subtropical zones of oceans. In Scyphozoa class, the cubomedusas (chironix, chiropsalmus), diskomedusas (cyanea, pelagia, hriazora), corneomedusas (rhysostoma, stomopholus) are poisomous. The first and second medusas live in warm seas of Indian, Pacific and Atlantic oceans. The third lives in Black sea and Sea of Azov (pic 22.4a). In Anthozoa class, gogronaria, actinia, madrepoores corals are poisonous. The first lives in Arctic and Antarctic seas. Others live in warm seas worldwide. The typical feature of cnidarians is cnidocytes with poisons. This poison consists of cytotoxins, neurotoxins. Neurotoxins specifically interact with ion canals (especially in actinia). The nematocyst is discharged from cnidocyte and affect target. The human being can contact with cnidarians while swimming, diving, fishing. This contact results in allergic vesicle formation, which is accompanied by severe itching. It is due to dermatotoxins action. Therefore, such cnidarians are called "sea nettle" or "sea bee". The diskomedusas are most toxic. Their poisons also cause muscles affection, tissue necrosis, heart rate disorders, short time deafness and dumbness, excitation, hallucinations. The cnidarian's poisons are

used in experimentally neurophysiology for antiserum preparation.

The preventive measures are in using diving wearing, awareness while swimming and fishing. The poison dermatitis is best cured by alkaline ointments. The poisoned man should treated accordinary to symptoms, which he has.

22.3.4 The poisonous mollusks.

Humans use mollusks as a food. Moreover, this tendency apt to increase. Therefore, we need to keep in mind the toxicity of mollusks. Among mollusks there are actively and passively poisonous animals as well.

Among actively poisonous mollusks are textile conus (live in tropical seas of Indian and Pacific oceans), terebra, octopus, amplisia and other inhabitants of warm seas. The primary poisonous mollusks have attacking apparatus (proboscis with stinging teethes) and poison glands. Inside each tooth, there is canal for poison evacuation. The main compound of poison is neurotoxin. It affects nervous system, central and peripheral as well. The bitted place is very painful. Pain can stay fro 4 weeks. It is accompanied by edema and hyperemia. The toxin affects neural synapses causing muscles convulsion, especially in respiratory muscles. It makes breathing and swallowing harder. The symptoms of general intoxication are also present (headache, vomiting, fever).

The secondary poisonous mollusks are acmea, Virginia oyster (North America), arca, modiolus, mussel (Mediterranean Sea, Atlantic Ocean), spondilus, wolsella (Indian and Pacific Oceans). They very easy absorb poisons, pathogenic organisms, dinoflagellates. In many countries, they can absorb waste products of industrial enterprises, which damp their sewage system into the sea. They can be contaminated by bacteria and spray out different infections.

To avoid poisoning by mollusks, everyone should be aware with wild poisonous mollusks. It is important to design and build modern sewage system with multilevel cleaning system. It will prevent dumping of waste products and bacteria into the sea. It will break pathological cycle of bacterial circulation.

22.3.5 The poisonous arthropods.

The Arthropoda Phylum is most numerous on The Earth. It is spread worldwide. Therefore, it includes many species of poisonous animals. They are in Arachnida and Insecta classes. The Diplopoda class (millipedes) is presented only by poisonous animals.

Aranea Order (spiders). The poisonous spiders can be divided into the spiders with nerotropic effect of poison and with hematotropic effect of poison.

In the first group, there are birdeaters (simple, scareness, thinleg). They are spread in Africa and Latin America. The poison apparatus is presented by poison

glands and by chelicerae. It is very aggressive spiders. They often bite legs and arm of human being. After biting, pain goes away quite soon. The symptoms of general intoxication develop (fatigue, fever, uncoordinated motions). The poison is excreted from organism. Death cases occur very rare.

In the second group, there are tarantulas, karakurts.

The karakurts are in South Europe, Kazakhstan, Middle Asia, Arabia, North and West Africa (pic 22.4,b). The poison glands are on cephalothorax. Their ducts open in chelicerae. The main compounds of poison are neurotoxin and hemorrhagin. The bitted place aches and develops edema. Then, joints, muscles, bones start to pain too. 1-2 hours after, the poison reaches important brain centers. Patient cannot walk. He has pain attacks at any exertion. The vomiting, accelerated heart beating and dizziness develop. It is accompanied by general excitation, urination and defecation disturbances. The lethal rate is 2-4%.

The tarantulas are in Europe, Asia, America. The poison glands are on cephalothorax and partially in chelicerae, which are wounding apparatus. The main compounds of poison are cutotoxin and hemolysin. Bitted place ache. The vesicle, edema, hyperemia develop on a bitted place. The hemorrhagic vesicles exfoliate the skin. Then, skin and derma necrosis develops. The lethal cases are very rare.

The Scorpiones Order. This order includes more than 550 species. The sting is located on terminal part of the body, which is slender toward the end. The main compounds of poison are hemorrhagin, hemolysin, and small amount of neurotoxin. The scorpions stings human beings prevalently in dwellings. The stung place aches and develops edema. The lymphangiitis and hyperemia develop on a stung place. Then, the symptoms of general intoxication develop (fatigue, fever, uncoordinated motions, vomiting, headache, muscle convulsions). The liver, kidneys and heart are most affected. The erythrocytes hemolysis occurs. The lethal cases happen.

Poisonous insects. They are in different classes of Insecta Phylum (pic 22.4,c). The bee's poison is presented by enzymes, non-enzymatic peptides, and biological amines. The main compounds are neurotoxins. The bee's and wasp's poisons are very allergic. This makes clinical picture of poisoning worse.

The bees and bumblebees are representatives of Apidae family.

The honey bees are used by man from ancient times. The working bees have poisonous apparatus to defend family from enemies. The poison compounds are enzymes (phospholipase A_2, hyaluronidase, MCD-peptid), biological amines (serotonine, histamine, catecholamines). The chemical composition of poison changes during bee aging. The biting of even one bee is painful. The massive biting can result in death. The clinical picture depends on biting number, localization of bitted places, functional organism state. The most expressive are local symptoms (pain. edema). If biting was massive, the internal organs damage can occur, especially kidneys. 0.5-2% of people have allergic reactions of bee sting. First aid is sting removing, washing of bitted place by alcohol containing

solutions and by liquid ammonia solution. In severe cases, the emergency medical care should be called.

Bumblebees are large insects. They are covered by setae. They are black, red-yellow or yellow in color. The chemical compounds of bumblebee's poison are not completely studied. It is known that it contain phospholipases A and B, histamine, acetylcholine, serotonine. The bumblebee sting has same symptoms as bee sting.

The wasps and hornet are representatives of Vespidae family.

The hornets make their nests from paper of their own production. The hornet Vespa crabo is found in Belarus widely. It is 35 mm in size. The head is yellow, whereas thorax is black and abdomen is yellow with black spots in terminal part. The poison compounds are phospholipase A_2, hyaluronidase, biological amines. The hornet sting cause local (pain, edema, inflamation) and general symptoms (headache, dizziness, accelerated heart beating, fever). The hornet beating may cause severe allergic reactions, which require desensitization treatment.

The simple wasp is an insect. The female is about 15-25 mm long, male 13-17 mm long. Its color is black with yellow strips. It makes paper nests. They gnaw deep inside of apple, pear and other fruits. Thus, a human being can swallow them with fruits. The pharynx and tongue sting is very dangerous and can result in death. The wasps of Vespidae family very often visit human dwellings. It makes possible contact with them. The wasps' sting is long, curved, with notches on the end. It is much bigger than bees' sting. The poison compounds are phospholipase A and B, hyaluronidase, serotonine, histamine, catecholamines, kinins. The wasps' poison has prevalently hemotropic action, whereas bees' poison is neurotropic. After stinging, a human feel acute pain. The inflammatory reaction appears around stung place. In some cases, the edema develops. The treatment is prescribed accordinary symptoms. It is good to cool stung place, if it is in oral cavity.

The ants are representatives of Formicidae family. They are worldwide. The typical representative is red forest ant. The female and male sizes are 9-11 mm long, working ant size is 5-9 mm long. They make ant hills with underground galleries. The forest ants are predators. The poisonous organs are different. Some have sting, some haven't. They just spray poison around. In stingless ants the main compound of poison is formic acid. The treatment of poisoning is prescribed accordinary symptoms.

Poisonous millipedes are separate class of Arthropoda phylum. All species produce toxins. The giant tropical millipedes are most dangerous for human being (giant Ceylon scolopendra, Crimea and Aral scolopendrae). In millipedes poison the acetylcholine, serotonine, histamine and proteolitic enzymes were found. It breaks synaptic transmittion.

The preventive measures include personal defense and using of special serums (antikarakurt, antiscorpion) and antidote using.

22.3.6 The poisonous fishes.

There are many species of poisonous fishes. They can be actively poisonous, passively poisonous and secondary poisonous.

The actively poisonous fishes are perches, skates, samara fish, sheat-fishes, Synanceja verrucosa, dragon-fishes and others (pic 22.4,d,e). They have poison glands and tools to damage prey with canals for poison. The clinical picture of poisoning depends on particular poison properties. Thus, if divers are bitted by skate, the acute pain, fatigue, consciousness lost, convulsions and breathing disorders develop. The dragon-fish poison cause necrosis of tissues of bitted region. If human being is affected by samara fish's poison, it causes edema, hyperemia and lymphangiitis of affected region. 10-15 minutes after, the symptoms of general intoxication is added to clinical picture (arterial pressure fall, muscle paralysis, heart failure). The bitted regions pains for a long time during recovering.

The majority of fishes are passively poisonous (fuga-fish, hedgehog-fish, conger eel, and moray). They have poisons in internal organs, skin, muscles and so on. Many of them are poisonous only seasonally. The most important compounds of passively poisonous fish poisons are tetrodontoxin (close to dinoflagellates toxin), sigdatoxin (stimulates permeability increasion of nerve cell membranes), hallucinogens (causing hallicinations).

The secondary poisonous are very limited number of species. Their meat become poisonous, if it was contaminated by bacterial or dinoflagellates poisons. The tunny-fish meat becomes poisonous insome sesons, but the reason of this is not clear.

The preventive measures are in using diving wearing, awareness while swimming and fishing. It is important to follow sanitary instruction while working on fish plants. The poisoned man should treated accordinary to symptoms, which he has. To avoid poisoning by passively poisonous fishes, it is important to know their features and know how to cook them properly.

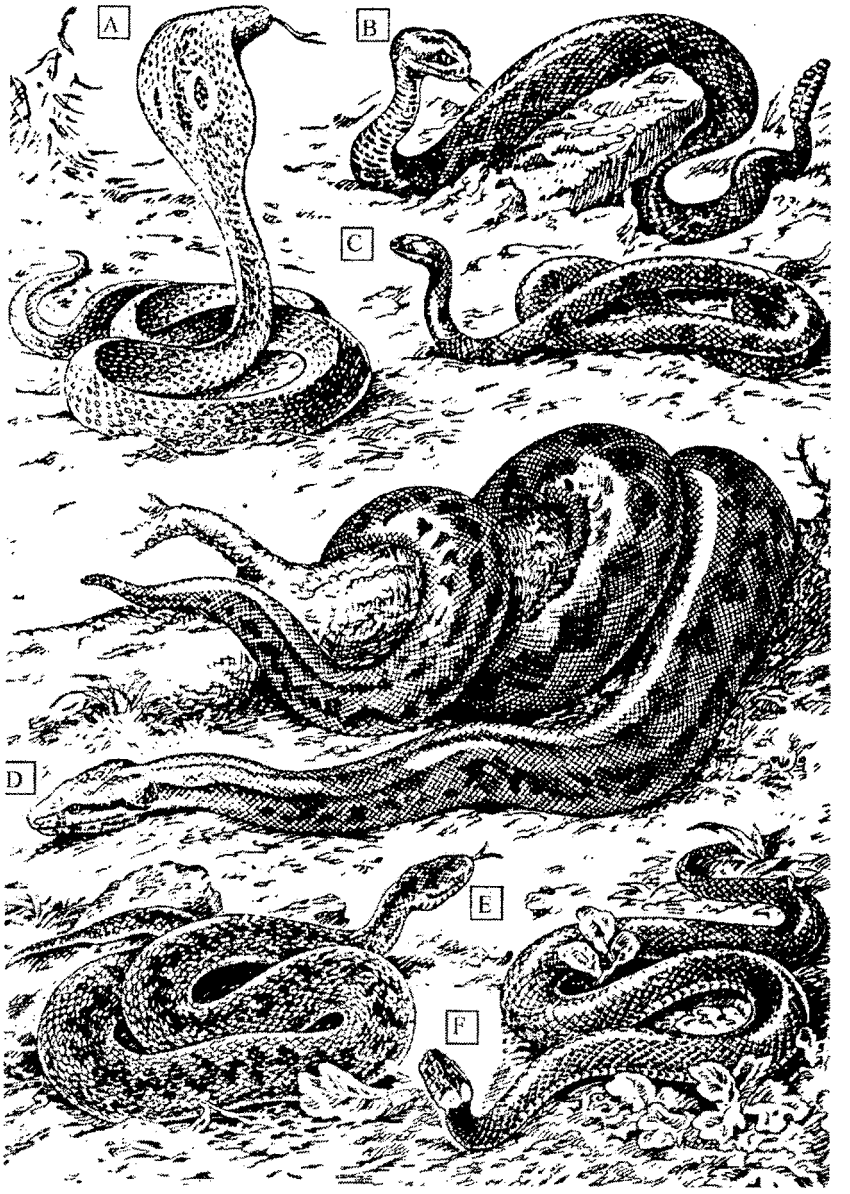
22.3.7 The Poisonous Amphibians.

There are only passively poisonous animals among Amphibians. The skin glands are for respiration as well as for defense due to their poisonous secrete. It compounds are highly toxic substances (brachotoxin), anesthetic substances, biological amines, cardiotonic steroids, hemolytic proteins.

Some salamander species, California triton and grey frog are poisonous. The skin toxin of amphibians is for killing predators that trying to catch them.

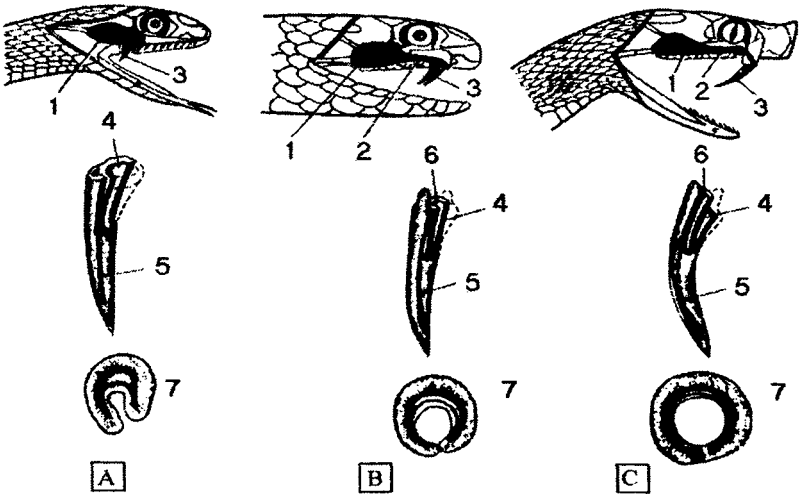
22.3.8 The poisonous Reptilians.

The big group of Reptilians is actively poisonous armed animals (pic 22.5).



Pic.22.5.The snakes:

A – cobra, B – rattlesnake, C – corals aspid, D – boa, E – viper, F – grass snake (by F.f.Talysin,1963).



Pic.22.6. The structure of poisonous snake's apparatus:

A – grass-snakes; B – aspids, C – vipers; 1 – poisonous gland, 2 – gland duct, 3 – poisonous teethes, 4 – drainage cavity of poisonous teeth, 5 – groove for poison, 6 – canal in poisonous teeth, 7 – cross section of poisonous teeth (by B.N. Orlov et al.,1990).

The poisonous apparatus of snakes consist of glands, ducts and poison conducting teethes. Accordinary to structure of poison conducting teethes, the snakes are divided into three groups (pic 22.6): tooth with furrow located on posterior part of jaw (Opisthoglypha), tooth with furrow located on a top of jaw (Proteroglypha), tooth with canal, located on a top of jaw (Solenoglypha).

The snakes having tooth with furrow located on posterior part of jaw are grass snakes. The typical representatives of them are tigroid grass-snake, African bumelang, African boiga, gery tree snake and others.

The snakes having tooth with furrow located on a top of jaw are in two families: Aspidae and Marine snakes' family. The Aspidae are king's cobra, which is biggest snake in the world (up to 5.5 meters long), Indian and Middle Asian cobras, Australian taypan and others. The marine snakes are two-colored pelamide, spiral and striped flippertail, enhydrina and others. They occur only in Indian and Pacific oceans.

The snakes having tooth with canal, located on a top of jaw are in two fami-

lies: adders' family and Lachesis family. The adders are simple adder, sand efa, gurza and others. The Lachesis snakes are found in South and East Asia, in North and South America. In Asia, the lancehead snakes are common. In America, botrops and rattlesnakes are common.

About 1 million people is bitted by snakes per year, mainly in tropics and subtropics.

Snakes poison is a complex of biologically active substances. It is different in representatives of different families. The aspids and marine snakes poison includes neurotoxins, which break impulse synaptic transmission in chilonergic synapses. It cause death as result of breathing failure and CNS failure. The adders and rattlesnakes poison contain hemorrhagins, hemolysins, cytotoxins. It cause big hemorrhagic edemas, resulting from increased capillaries permeability and blood clotting failure. It leads to massive necroses. In rattlesnakes poison there is neurotoxin also, which makes clinical picture more severe

The warmer is outside; the more toxic is snake poisoning. The snakes 6-9 months of age have most toxic poison. The toxicity of poison increases in ten times after molting. The level of poisoning depends on many factors, such as snake size, snake sex, amount of injected poison, deepness of bite, skin properties of affected man, worn clothes. The children and women have more severe poisoning. The general and local signs depend on snake species.

The preventive measures of snake poisoning include awareness while contact with snakes, using of monovalent ("Anticobra") and polyvalent ("Antigurza") serums, using antidotes.

22.3.9 The wildlife protection and using of poisonous animals.

The wildlife protection is conducted in two directions. First is protection of useful species, which are the sources of valuable drugs (snakes, bees), pollinators of plants (bumblebees, hornets), predators killing harmful insects (frogs, ants, spiders, wasps). Second is protection of species, which provide stable being of biogeocenoses and ecosystems, which enable then to cope with any external influences.

In many countries of the world, the state forests are founded. They preserve wild nature. It is important to explain people the value of wild nature. Moreover, the poisonous animals can be used rationally. It concerns snakes and others, whose drugs are used in medicine. Long experience of scientists of special centers for poisonous animals reproduction shows that, if everything is set well, there is no need to catch wild animals.

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