MINISTRY OF HEALTH OF UKRAINE
POLTAVA STATE MEDICAL UNIVERSITY

Yeroshenko G.A., Klepets O.V., Perederii N.O., Vatsenko A.V., Ulanovska-Tsyba N.A., Riabushko O.B., Shevchenko K.V.

ORGANISMIC LEVEL OF LIFE ORGANIZATION. BASES OF HUMAN GENETICS

Poltava – 2021

MINISTRY OF HEALTH OF UKRAINE
POLTAVA STATE MEDICAL UNIVERSITY

Yeroshenko G.A., Klepets O.V., Kinash O.V., Perederii N.O., Vatsenko A.V., Ulanovska-Tsyba N.A., Riabushko O.B., Shevchenko K.V.

ORGANISMIC LEVEL OF LIFE ORGANIZATION. BASES OF HUMAN GENETICS

Training text-book
on Medical biology (module I part II)
for students of medical and dental specialties

Poltava – 2021

Composite authors:
Yeroshenko G.A., Klepets O.V., Kinash O.V., Perederii N.O., Vatsenko A.V., Ulanovska-Tsyba N.A., Riabushko O.B., Shevchenko K.V.

Reviewers:

L.Ya. Fedoniuk – the head of the Medical Biology department of the Ternopil National Medical University, doctor of medical sciences, professor.

A.Yu. Stepanenko – the head of the Histology, Citology and Embriology department of Kharkiv National Medical University, doctor of medical sciences, professor.

S.M. Bilash – the head of the Clinical Anatomy and Operative Surgery Department of Poltava State Medical University, doctor of biological sciences, professor

O.M. Bieliaieva – the head of the Foreign Languages with Latin and Medical Terminology Department of Poltava State Medical University, candidate of pedagogical sciences, associate professor.

Recommended by the Academic Board of the Poltava State Medical University as a training text-book for English-speaking students in speciality 221 Dentistry and 222 Medicine in a higher educational institutions of the Ministry of Health of Ukraine (dated 8 Desember 2021, minutes of the meeting № 3).

O64 Organismic level of life organisation. Bases of human genetics. Training text-book on Medical biology (module I, part II) for students of medical and dental specialties / G.A. Yeroshenko, O.V. Klepets, N.O. Perederii et al. – Poltava, 2021. – 119 p.

ISBN

Textbook for students of the internatonal faculty in the specialties 222 – Medicine, 221 – Dentistry.

The materials of the training text-book includes the tests of the 1st level (with one right answer), tests of the 2nd level – with the numerous choice of answers, typical tasks, in accordance with the Program of Medical biology for the students of medical and stomatological faculties of Higher Medical Educational Establishments of III–IV levels of accreditation, and also materials for self-preparation work.

Text-book will help students to master theoretical knowledge during audience classes and self-dependent preparation to the module control.

Methodical edition includes tests from the base of previous years tests of licensed examination «Krok-1» and tests which worked out by teachers of Medical biology departments that will help students to prepare effectively and pass module control as well as licensed examination.

UDC 575.856

The illustrations in this text-book are taken from the Internet.

TOPIC: Organismic level of organization of genetic information. Expression of the basic principles of inheritance on examples of Mendelian characters of humans.

Genetics: subject and tasks, stages of development, basic concepts and terms. Principles of hybridological analysis. Monohybrid crossing: the law of unit characters of first generation, law of segregation. Law of «cleanness of gametes». Cytological basis of the laws. Analysing crossing, its practical importance. Lethal genes. Deviation from the expected segregation. Di- and polyhybrid crossing: law of independent combining of characters, its cytologic meaning. Dominant and recessive types of inheritance of the normal and pathological human characters.

Bases of Genetics: terms and concepts

Genetics – is a branch of biology which studies the laws of heredity and variability.

Heredity – transmission of the characters, resemblances from one generation to another, ability to repeat the characters and properties by an organism and provide specific character of individual development and metabolism.

Variability – is the ability of living organisms to acquire new features in the process of individual development. These are raw materials for evolution.

Gene (W. Johansen, 1909) **–** is the basic physical and functional unit of heredity, which is responsible for the formation of a certain trait of an organism.

Alleles – the alternate forms or varieties of a gene. The alleles for a trait occupy the same locus or position on homologous chromosomes and thus govern the same trait. Because they are different, their action may result in different expressions of that trait.

Dominant allele (Latin: ***dominare* –** prevalence) – trait is expressed (marked with Capital letter – *A*).

Recessive allele (Latin: ***recessus* –** suppression) – trait is masked (marked with lowercase letter – *a*).

Homozygous organism – is an individual which has two identical alleles of the same gene. The homozygous individual receives these identical alleles from both parents.

1. the individuals have in genotype the same alleles (AA; aa; AAвв; ccDD).

2. the individuals give one sort of gamete.

Heterozygous organism – is an individual which has two different alleles of the same gene. The heterozygous individual receives different alleles from parents.

3. the individuals have in genotype different alleles (Aa, CcDd, AaBbCc).

4. the individuals give several sorts of gametes (**2^n, where *n* – number of traits with different alleles**).

Genotype – refers to the sum total of genes inherited from both the parents which provides individual development (ontogenesis) and formation of phenotype.

Phenotype – refers to the detectable or observable structural and functional characters by the genes interactions and factors of environment. It is determined by an individual's genotype and expressed genes, random genetic variation, and environmental influences.

Monohybrid inheritance is the inheritance of a single characteristic. The different forms of the characteristic are usually controlled by different alleles of the same gene.

Dihybrid is the crossing between individuals which differ in two characters. One allele pair determines each character.

Human genetics (Anthropogenetics) is the study of inheritance as it occurs in human beings.

Stages of development

Genetics	Anthropogenetics and medical genetics
Studying of inheritance and variation on the organismic level (first period of genetics development). Works: G. Mendel (1865); de Fries, Correns, Chermak (1900). Hybridological method. Laws of heredity.	Galton (1865) in his work: "Inheritance of the talent and characters is used **biometrical method** for the studying of human characters inheritance, Gerrod (1901**–**1902) – proved monogenic characters of alkaptonuria inheritance according to the Mendels laws.
Studying of heredity and variation peculiarities on the cellular levels (second stage). Works: Setton (1902**–**1903), Bovery (1902**–**1907), Morgan and others. Chromosomal theory of heredity (1911).	Bernstein (1924**–**1925) – established genetical basis of blood groups inheritance ABO system, proved presence of three genes of blood group system ABO.
Formulation of mutational theory and development **of population genetics** (third stage of genetics development). Works: de Fries (1901), Nadson, Meller (1925-1933), Vavylov (1920), Chetverikov (1925) and others.	1948**–**1949 – establishment of the causes of inheriting of some of molecular diseases; sickle-cell anemia, PKU, galactosemia (Polling and others); 1956**–**1959 – working on the methodic of human karyotype studying, development of clinical cytogenetics, chromosomal diseases.
Studying of inheritance and variation on the molecular level (forth stage). Works: Chargaff, Watson and Crick (1953) and others in molecular genetics development.	60**–**70 years of XX century – working of prenatal diagnostics of inherited disease and development of medical-genetic consulting. Gene and cellular engineering. Gene therapy.

Mendel's laws of inheritance

(achieved in 1865 by Gregor Mendel; confirmed in 1900 by de Fries, Correns and others)

The 1st law of Mendel:

the law of unit characters (universality of hybrids of the first generation)

At crossing of individuals, homozygous by alternative alleles, in their offspring the monotony by genotype and phenotype is observed.

Scheme

A – gene of yellow peas;
a – gene of green peas;
AA – genotype of homozygous yellow peas;
aa – genotype of homozygous green peas.

P: ♀**AA** × ♂ **aa**

G: **A** **a**

F_1: **Aa – heterozygous yellow peas**

The 2nd law of Mendel:

the law of segregation.

At crossing of heterozygous individuals in their offspring the splitting is observed in the ratio of three to one (3:1) by phenotype and 1:2:1 by genotype and individuals with recessive features appear, which make up no more than 1/4 of all

descendants.

Scheme

P : ♀Aa × ♂Aa
G: A A
a a

F2 : AA; Aa; Aa; aa

Segregation by phenotype – 3 : 1 (75% – with yellow peas; 25% – with green peas).

Segregation by genotype – 1 : 2 : 1 (25% homozygous with yellow peas; 50% – heterozygous with yellow peas; 25% – homozygous with green peas).

<u>The 3rd law of Mendel</u>:
the law of independent assortment

The alleles of two (or more) different genes get sorted into gametes independently of one another.

Scheme

A – gene of yellow peas;
a – gene of green peas;
B – gene of rounded peas;
в – gene of wrinkled peas;
AABB – genotype of homozygous yellow rounded peas;
aaвв – genotype of homozygous green wrinkled peas.

P : ♀ AABB ×♂ aaвв

G: AB aв

F_1: AaBв – diheterozygous yellow rounded peas

P: ♀AaBв x ♂ AaBв
G: AB Aв
Aв Aв
aB aB
aв aв

F2: Punnett square:

Gametes	**AB**	**Aв**	**aB**	**aв**
AB	**AABB** yellow rounded	**AABв** yellow rounded	**AaBB** yellow rounded	**AaBв** yellow rounded
Aв	**AABв** yellow rounded	**Aaвв** yellow wrinkled	**AaBв** yellow rounded	**Aaвв** yellow wrinkled
aB	**AaBB** yellow rounded	**AaBв** yellow rounded	**aaBB** green rounded	**aaBв** green rounded
Aв	**AaBв** yellow rounded	**Aaвв** yellow wrinkled	**aaBв** green rounded	**aaвв** green wrinkled

Segregation by phenotype – **9 : 3 : 3 : 1** [9/16 (56,25%) – yellow rounded; 3/16 (18,75%) – yellow wrinkled; 3/16 (18,75%) – green rounded; 1/16 (6,25%) – yellow wrinkled.

Segregation by genotype – **1 : 2 : 1 : 2 : 4 : 2 : 1 : 2 : 1.**

1s level tests

(one correct answer)

1. Phenylketonuria is inherited by autosomal-recession type. In family, where a mother and father are healthy, a sick boy was born (phenylketonuria). What genotypes of mother and father by these genes?

A. AA Aa
B. AA AA
C. Aa Aa
D. Aa aa
E. Aa AA.

2. Gene that determines the dark enamel of teeth for the humans is dominant and localized in autosomes. Husband is homozygous by dominant gene but his wife has a normal color of enamel of teeth. What biological law is the basis of inheritance of such sign for the children of this couples?

A. The law of unit characters
B. The law of segregation
C. The law of independent assortment
D. Phenomenon of linked inheritance
E. Phenomenon of sex-linked inheritance.

3. Children have analysed from one family. One of parent is homozygote by dominant gene of polydactyly and second – healthy (homozygote by recessive gene). In this case the following law has observed:

A. The law of unit characters
B. The law of segregation
C. The law of independent assortment
D. Phenomenon of linked inheritance
E. Law of «cleaness gametes».

4. Recessive gene of phenylketonuria is suspected in one parent. What risk of sick child birth in this family:

A. 0%
B. 25%
C. 50%
D. 75%
E. 100%.

5. Name a scientist which suggested to name a gene as discrete units of heredity :

A. T. Schwann
B. G. Mendel
C. T. Levitsky
D. T. Morgan
E. W. Johansen.

6. An area of chromosome where gene is located has named:

A. Triplet
B. Codon
C. Telomere
D. Locus
E. Anticodon.

7. Allele genes are:

A. Genes which are located in one chromosome

B. Genes which are located in non-homologous chromosomes
C. Genes which are located in the same loci of homologous chromosomes
D. Genes which determines polymeric traits
E. Genes inherited by Mendel laws.

8. Determine the correct definition of genotype:
A. Diploid chromosomes number
B. Haploid chromosomes number
C. Number of all genes
D. External features of an organism
E. Internal features of an organism.

9. Determine the correct definition of phenotype:
A. Diploid number of chromosomes in somatic cells
B. Haploid number of chromosomes in sexual cells
C. All genes of an organism
D. All features of an organisms which form during individual development by influence of environment
E. All genes in sexual chromosomes.

10. Define the amount of variants of sorts of gametes that produces diheterozygous individual in condition of location of genes in the different pairs of homological chromosomes:
A. 16
B. 8
C. 4
D. 6
E. 2.

11. Determine the Mendelian human trait:
A. Color of skin
B. Weight
C. Height
D. Arterial blood
E. Ability to use the right hand.

12. According to the second law of G. Mendel the correlation of phenotypes at crossing of two heterozygous individuals (complete dominance) will be:
A. 1 : 1
B. 1 : 2 : 1
C. 3 : 1
D. 1 : 1 : 1 : 1
E. 2 : 2.

13. According to the second law of G. Mendel the correlation of genotypes at crossing of two heterozygous individuals (complete dominance) will be:
A. 1 : 1
B. 1 : 2 : 1
C. 3 : 1
D. 1 : 1 : 1 : 1
E. 2 : 2.

14. Define the probability of child birth with the normal form and position of teeth in family, where a father and mother have large prominent teeth (dominant sign) and also they are heterozygotes:
A. 0 %
B. 100 %
C. 50 %
D. 75 %

E. 25 %.

15. Phenylketonuria has found in new-born child. The parents of this child are healthy and already have two healthy children. What possible genotypes of mother and father by gene that determines development of phenylketonuria?

A. AA AA
B. AA aa
C. Aa Aa
D. Aa aa
E. Aa AA.

16. A man has brown eyes (homozygote by dominant gene), but woman has blue eyes. For their children can be observed the law of:

A. The law of unit characters
B. The law of segregation
C. The law of independent assortment
D. Phenomenon of linked inheritance
E. Phenomenon of sex-linked inheritance.

2nd level tests:

1. What essence of the «law of cleanness of gametes»:

a) gamete is clean, contains genes in the homozygous state;
b) clean are gametes which have formed only by homozygous organisms;
c) gametes which form any organism are clean and contain information about possibility of development only one variant of every character.

2. At crossing of what organisms the segregation in posterity by genotype and phenotype will not take place in next generations:

a) at crossing of phenotypically similar organisms;
b) at crossing of organisms which are different by alternative traits;
c) at crossing of organisms which are homozygous by the same alleles;
d) at crossing of genotypically similar organisms.

3. Whether is possible to consider as alternative the following traits:

a) normal coagulation of blood and sickle-cell anemia;
b) normal metabolism of phenylalanine and phenylketonuria;
c) presence of dark pigment in a skin and its absence(albinism);
d) brown eyes and light hear;
e) short fingers on hands(brachydactylia) and high height;
f) dark and light enamel of teeth.

4. What is genotype? What determination is more exact:

a) totality of all nuclear genes of an organism;
b) totality of genes by which an organism has analyzed;
c) system of interactive genes of an organism.

5. What statements are characterize allelic genes:

a) genes in one chromosome;
b) genes in non-homological chromosomes;
c) genes in identical loci of homological chromosomes;
d) genes which determine alternative signs;
e) genes which determine non-alternative signs.

6. Non-allelic genes are localized in chromosomes:

a) in the homological areas of non-homological chromosomes;
b) on the different areas of homological chromosomes;
c) on different (non-homological) chromosomes;
d) on identical loci of homological chromosomes.

7. What is phenotype? What determination is more exact:

a) totality of external traits of organism, that is determined by a genotype;

b) totality of traits and properties which organism has analyzed;
c) totality of all traits and properties of an organism which are result of co-operation of genotype with an environment.

8. What organism is named homozygous:
a) organism where different alleles of gene in the somatic cells are present;
b) organism where many alleles of gene in the somatic cells are present;
c) organism where identical alleles of gene in the somatic cells are present.

9. What is the hybridologic method of heredity studying*:*
a) method of inherited properties of an organism studying;
b) analyzing of few generations in one family by a certain trait;
c) such method uses the directed crossing of the organisms which are different by alternative traits with the subsequent analysis of posterities research.

10. What organism is named heterozygous*:*
a) organism where different alleles of gene are present in somatic cells;
b) organism where many different alleles are present in somatic cells;
c) organism where only one allele of gene is present in somatic cell.

11. How many allelic genes are coding the character:
a) in diploid organism;
b) in triploid organism;
c) in tetraploid organism;
d) in haploid organism?

12. Enumerate a few human traits*:*
skin with freckles (B), dark hair (D), blue eyes (A), five fingers (F), light hair (C), wavy hair (X), rhesus factor
(antigen D), brown eyes (E), polydactyly (P), straight hair (S); absence antigen D (d).
Define which from the enumerated traits are alternative. Write alternative traits by pairs.

13. Six individuals have the following genotypes*: AA, aa, Bв, CC, Cc, Ee.*
Name: a) homozygous; b) heterozygous.

14. What from the following examples belong to the monohybrid crossing and what to the polyhybrid one*:*
a) crossing of red and green tomatoes;
b) crossing of two plants with red fruits and red caulis;
c) crossing of black bull with red cows;
d) crossing of black mouse with long wool and mouse with white short wool;
e) blue-eyed fairy-headed woman with a I(0) blood group gets marriage with the brown-eyed, dark-headed man with III(B) blood group.

15.One of the human forms of deafness is recessive. What phenotype will have the following individuals:
a) homozygote by recessive gene;
b) heterozygotes;
c) homozygote by dominant gene.

16. What statements belong to the description of genotype:
a) set of genes in gametes;
b) haploid set of chromosomes;
в) totality of external and internal traits of an organism;
d) system of genes that localized in the chromosomes of somatic cells.

17. What genotype of parental organisms do not give the segregation in first generation by phenotype:
a) crossing of heterozygote with a homozygote by recessive gene;
b) crossing of two heterozygotes;
c) crossing of homozygote by dominant gene with a homozygote by recessive gene;

d) crossing of heterozygote with a homozygote by dominant gene.

18. What correlation of genotype in posterity by analyzing crossing if a heterozygote is analyzed by one pair of allelic gene:

a) 3 : 1;
b) 9 : 3 : 3 : 1;
c) 1 :1;
d) do not segregate.

19. What correlation of genotypes and phenotypes in F2 is possible to expect by crossing of two initial homozygous individuals which differ by pair of alternative traits in case of incomplete dominance*:*

a) 2 : 1;
b) 1 : 1: 1 : 1;
c) 1 : 2: 1;
d) 3: 1.

20. What correlations in segregation by phenotype (2: 1, 1: 2: 1 or 3: 1) it is possible to expect in the second generation by monohybrid crossing, if:

a) incomplete dominance is observed;
b) complete dominance is observed;
c) homozygotes by dominant gene do not viable.

21. What correlation of phenotypes and genotypes it is necessary to expect in posterity of the married couples - heterozygous carriers of recessive lethal gene which causes death and resorption of embryo on the early stages of development?

22. Write the types of gametes which appear in individuals with such genotype:

a) for individuals with the genotype AA;
b) with the genotype Bв;
c) with the genotype Cc;
d) for individuals with the genotype AAвв;
e) for individuals with the genotype AAccDD.

23. Human polydactyly (six or more fingers on the hands) dominates above the normal structure of hand. How many types of gametes appear:

a) in homozygous six-fingered woman;
b) in six-fingered heterozygous man;
c) in five-fingered man.

24. In the woman organism with the genotype Bв gene B has got to the egg during gametogenesis, where will gene b get in?

a) to the other egg;
b) to the spermatozoon;
c) to the polar body;
d) to the somatic cell.

25. Human gene of normal synthesis of pigment melanin in a skin is dominant character but gene of absence of melanin (albinism) is a recessive one.

Write the genotype of heterozygous organism by skin pigmentation. What will be the phenotype of this skin? How many types of gametes appear in this case?

26. How many genotypes can be present for a man with a dark hair colour? Dark color is a dominant character, light is a recessive.

27. What correlation of phenotypes in posterity at the analyzing crossing, if analyzable individual is homozygote:

a) 1:1;
b) 3:1;
c) 1:1:1:1;
d) 9:3:3:1
e) 1 : 2 : 1.

28. What correlation of phenotypes in posterity at the analyzing crossing, if analyzable individual is heterozygote*:*

a) 1:1;
b) 3:1;
c) 1:1:1:1;
d) 9:3:3:1
e) 1 : 2 : 1.

29. What correlation of phenotypes in posterity at the analyzing crossing, if analyzable individual is heterozygote by one pair of alleles*:*

a) 1:1;
b) 3:1;
c) 1:1:1:1;
d) 9:3:3:1
e) 1 : 2 : 1.

30. What statement is the cytologic base of 3th law of Mendel:

a) location of genes in a heterochromosome;
b) location of genes in the same autosome;
c) location of genes in non-homological chromosomes;
d) being of genes on the corresponding areas of homological chromosomes.

31. Genotype is:

a) set of genes in gametes;
b) haploid set of chromosomes of somatic cages;
c) totality of external and internal traits of an organism;
d) set of genes in the chromosomes of somatic cells.
e) system of interactive genes of an organism, that determines its development and phenotype.

32. How many types of gametes do the organism forms with the genotype AaBв if it is known that between genes A and B exists the complete linking of genes (independent inheritance):

a) one type;
b) two types of gametes;
c) four types of gametes;
d) 2n, where «n» is a degree of heterozygosity.

33. Absence of molars is predefined by a dominant autosome gene. What progeny will have this anomaly if mother has not molars and she is homozygotic by this gene:

a) all children;
b) only daughters;
c) only sons;
e) half of daughters.

34. What features of inheritance of the characters which show up at the polyhybrid crossing:

a) linked inheritance;
b) sex-linked type of inheritance;
c) independent inheritance;
d) autosomal type of inheritance.

35. How many types of gametes and what correlation form the organisms with such genotype – AaBв:

a) one type;
b) two types with identical probability;
c) four with identical probability;
d) many;

e) four with different probability.

36. What crossing of the organisms is named as polyhybrid:

a) crossing of the organisms that differ from each other by the alternative variants of characters;

b) crossing where inheritance of characters by certain alleles appears by influence of different (non-allelic) genes;

c) crossing by many pairs of genes;

d) crossing by many pairs of allelic genes.

37. **What is cytologic explanation of 3rd law of Mendel:**

a) location of non-allelic genes in heterochromosomes;

b) location of non-allelic genes in the same autosome;

c) location of non-allelic genes in non-homological chromosomes;

d) location of genes on the corresponding areas of homological chromosomes;

e) independent divergence of homological chromosomes in the anaphase II meiosis;

f) independent divergence of non-homological chromosomes in the anaphase i meiosis.

38. What crossing is named as analyzing:

a) crossing which define possibility to set genotype of the organism;

b) crossing of an organism with a dominant phenotype and unknown genotype with an organism having a recessive phenotype;

c) crossing of phenotypically similar organisms.

39. What is cytological mechanisms of segregation during monohybrid crossing:

a) segregation in a posterity is provided by independent divergence of chromosomes in meiosis;

b) segregation in posterity is provided by divergence of homological chromosomes in different gametes and casual joining of gametes during fertilization;

c) segregation in a posterity is provided by a crossing-over between homological chromosomes and casual combining of gametes during fertilization.

40. Name the genotypes:

a) AaBвCc;

b) Aaввcc;

c) aaBвCC.

41. What genotypes of parents gives the uniformity of hybrids of first generation:

a) AABB x AaBв;

b) AABB x AABB;

c) AABв x aaBB;

d) AABB x aabb;

e) AABB x aabb.

42. Whether the law of independent inheritance and casual combining of the characters will express if genes that encode different characters are:

a) in one chromosome and in a distance 30 morganids;

b) in one chromosome and closely linked;

c) in the different pairs of homological chromosomes;

d) in X-chromosome.

43. What genotypes of parents F1 will be observe in a segregation 9 : 3 : 3 : 1?

a) AaBb x AaBb;

b) AABB x AABB;

c) AABB x aaBB;

d) AaBb x aabb;

e) aabb x aabb.

44. Which crossing of genotypes in posterity makes 3:1?

a) AABB x AaBb;
b) AaBв x aaBB;
c) AaBв x AaBв;
d) AaBвcc x aaBвcc.

45. What phenotypes ratio in posterity is observed after analyzing crossing, if analyzed individual is homozygous by the first pair of dominant allele and heterozygote by second one:

a) 1:1;
b) 3 : 1;
c) 1 : 1 : 1 : 1;
d) 9 : 3 : 3 : 1.

46. How many types of gametes makes:

a) diheterozygote;
b) triheterozygote;
c) tetraheterozygote;
d) heterozygous organism by 23 pairs of genes, if genes which encode different characters are located in the different non-homological chromosomes?

47. How many types of gametes appear for a woman (a) and for a man (b), if they are heterozygotes by 23 pairs of genes which are located in non-homological chromosomes?

48. How many types of gametes will form the organisms with such genotypes:

a) AABB;
b) AABB;
c) aaBB;
d) AABЬ;
e) AABB;
f) AABЬ;
g) AaBB;
h) aaBB?

49. **Among the following organisms choose**: 1) monohybrids; 2) dihybrids; 3) trihybrids. Genotypes of organisms:

a) Aa;
b) AaBb;
c) Bb;
d) AACc;
e) AABbCc;
f) AaBbCcOO;
g) AABBCc;
h) BbCcOo.

50. In what case the law of independent inheritance and casual combining of traits will express if genes that encode different traits are:

a) in one chromosome and in the distance 20 morganids;
b) in one chromosome and closely linked;
c) in the different pairs of homological chromosomes;
d) in X-chromosome?

51. Human polydactyly (gene A) dominates above the normal amount of fingers - (a), and shortsightedness (B) - above the normal sight (в). Define the amount of fingers and sight for the people with such genotypes:

a) aabb;
b) AABЬ;
c) AABB;

d) aaBB;
e) AABЬ;
f) AAbb.

52. Organisms have a genotype AaBвCc. How many phenotypes and genotypes is possible to observe in their posterity after self-pollination (in case of the complete and incomplete dominating of genes)?

53. Human brown-eyedness and presence of freckles are dominant traits, their genes are located in different chromosomes. Brown-eyed man without freckles got marriage with a blue-eyed woman with freckles. Define the possible genotypes and phenotypes of their posterity, if:

a) man and woman are homozygotes by the two pairs of genes;

b) man is heterozygous by the brown-eyedness and woman is heterozygous by the presence of freckles.

54. What phenotypes ratio is necessary to expect in the second generation during dihybrid crossing AABB x aaBB if the male gametes AB do not exist (combinative lethal gene)?

a) 9 : 3 : 3 : 1;
b) 6 : 3 : 3 : 1;
c) 3: 3 : 3 : 1;
d) other segregation.

55. Human browneyedness and presence of freckles are dominant traits, their genes are localized in different chromosomes. Man is brown-eyed without freckles got marriage with a blue-eyed woman with freckles. Define possible genotypes and phenotype in their posterities, if:

a) man and woman are homozygotes by two pairs of genes;

b) man is heterozygous by browneyedness and woman is heterozygous by presence of freckles.

Monohybrid crossing tasks

1. Right-handed person has a dominant gene by this character but left-handed is recessive one. Parents are right-handed and their child is left-handed. Define the genotypes of all family members.
2. Man has a polydactyly which is determined by a dominant gene. From the marriage of six-fingered man and woman with the normal structure of hand two children were born: five and six-fingered. What genotype of their father?
3. Deafness is inherited as a recessive character. Whether is possible to birth deaf child if his parents are healthy?
4. Absence of molars is inherited as a dominant autosomal character. What probability of child birth with this anomaly in the family where parents are heterozygous by analysing character?

Dihybrid crossing tasks

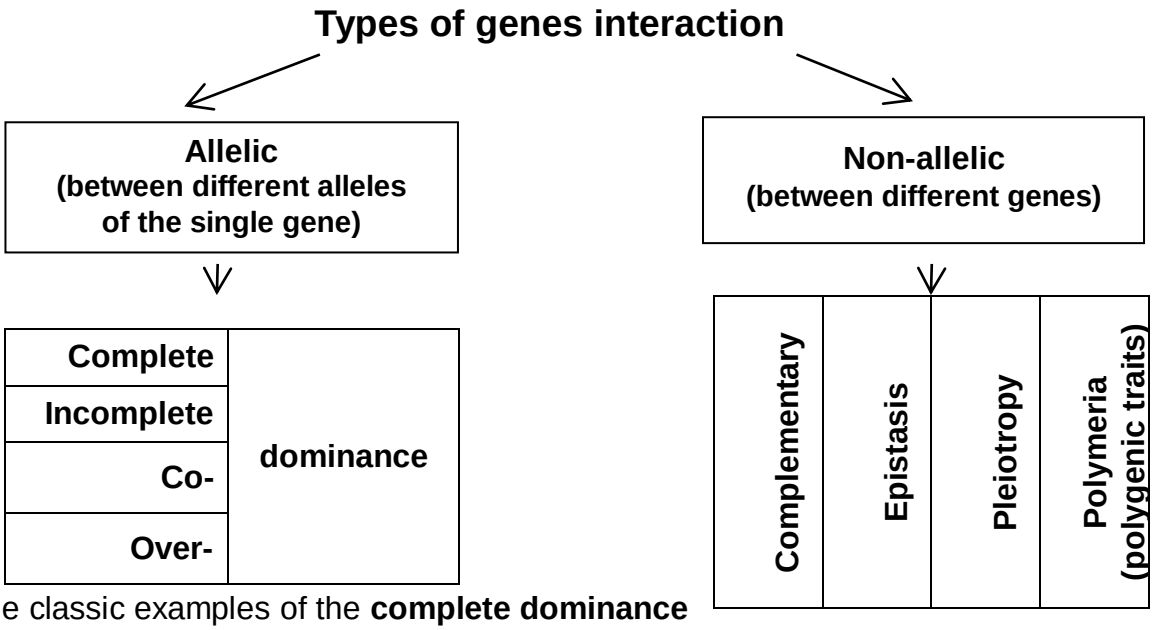
5. Short-sighted (dominant character) without freckles man got married with a normal-sighted woman with freckles (dominant character). There are three children in the family, all children are short-sighted and with freckles. Define the genotypes of parents and children.
6. Father with curly hair (dominant character) without freckles and mother with a straight hair and freckles (dominant character) have three children: curly hair and freckles, curly hair and without freckles, straight hair and freckles. Define the genotypes of parents and all possible genotypes of their children.
7. Father is deaf-and-dumb (recessive character) with white ringlet over the forehead (dominant character) and mother is healthy without white ringlet. Their child was born deaf-and-dumb with white ringlet over the forehead. Is it possible approving that the child inherits these characters from his father.

TOPIC: Allelic and non-allelic genes interactions. Pleiotropy. Polygenic traits. Genetics of the human blood groups.

Interactions of allelic genes (complete dominance, incomplete dominance, codominance) and non-allelic genes (complementary, epistasis, polygenic traits).

Inheritance of the human blood group by antigen systems AB0 and MN. Rhesus factor. Rhesus-conflict. Immunogenetics: object, tasks. Tissue and specific specificity of the proteins, their antigen properties.

Gene interactions is a result of realization of genetic information of certain group of genes that determine formation depending on their combinations, different variants of characters or phenotypes.



The classic examples of the **complete dominance** in human beings are characters which are inherited as monogenic traits:

- ability to roll up a tongue in a pipe;
- free pinna of an ear
- ability to bend the tongue back.

Well-studied human diseases are inherited as dominant characters. For example, polydactyly (six or more fingers on the hand). If one of the parents has the gene of polydactyly (Aa) the probability of affected child birth is 50%:

P ♀Aa x ♂aa

F_1 Aa : aa

50% : 50%

If both parents have polydactyly, the probability of affected children birth increases:

P ♀Aa x ♂Aa

F_1 Aa : 2Aa :aa

75%

The severe disorder – Huntington disease, described by the English doctor in 1872 inherited in the dominant manner. The course of this disease is that it manifests in adults only (over 35-40 years) and results in damage of central nervous system.

Achondroplasia (poor long bones development) is also an example of dominant pattern of inheritance as well as elliptocytosis (ellipsoid shape of erythrocytes).

Recessive character appears in case of both parents are heterozygous:

P ♀Aa x ♂aa

F_1 Aa : 2Aa : aa

25%

The possibility of affected children birth in such families is 25%. The following diseases are inherited in such a way:

1. cystic fibrosis (disorder of all excretory glands functions – bronchial, tear, pancreatic especially);
2. phenylketonuria (disorder of phenylalanine metabolism);
3. albinism (disorder of melanin metabolism) etc.

At the beginning of the XX century the regular study of heredity mechanisms of plants and animals showed that sometimes it has been impossible to explain the results of organism crossing according to Mendel's laws. It was found that many characters are not mendelian but the interaction of allele and non-allele genes are present.

It is known that dominant gene does not always completely suppress the recessive ones action. The classic example is the inheritance of the flower color in the plant "fore-o'clock":

P	♀AA	x	♂ aa	
	red		white	
F_1		Aa		
		pink		
F_2	AA	2Aa	aa	
	red	pink	white	

This phenomenon was named **incomplete dominance.**

Multiple alleles is the phenomenon of more than two (3, 4, 5…) alleles existence. It is the consequence of several mutations of one gene, forming intermediate alleles. They are recessive regarding the initial dominant one, but dominant regarding the recessive one.

A>A1>A2>a

No matter how many genes of that type exist, in one person there may be only two of them. Combination of pairs in different ways defines various characters.

Aa AA1 A1A2 AA2 A1a A2a

The inheritance of ABO group

It is a bright example of multiple allelism. There are three genes in this allele: I^a, I^b, I^o. Besides, there is another interesting phenomenon of codominance between I^A and I^B genes. Codominance – the state when both genes are dominant and do not suppress one another, and the typical features of both are manifested.

The ABO system determines four blood groups in people:

Protein molecules – A antigen – were found on the surface of erythrocytes of people with second group, so they are marked as II (A). On the erythrocyte surface of people with the third blood group B antigen protein molecules are found, so they are marked as III (B).

No antigens were found on the surface of I (0) group erythrocytes. But in people with IV-th group both antigens A and B were found. Consequently antibodies against each mentioned antigen were found, though antigens and complement antibodies were not found in the blood of the same person.

It was found out that antigen A presence depends on the dominant gene I^A, while the B antigen presence is controlled by I^B gene. Their absence was explained by recessive allele I^0. Genes A and B expression within people of IV group is the result of I^AI^B codominance.

So, 4 phenotype variants are determined by 3 genes and 6 genotype variants.

Knowledge of ABO system blood groups genetic basis has a great value in practical medicine, especially in such fields as Paediatry and Neonatology, Obstetrics and Gynaecology, Surgery, Transfusiology, Medicine of Extreme States, Forensic Medicine (person identification, paternal identification) and so on.

Inheritance of blood groups ABO

(Karl Landsteiner, 1900; Bernstein, 1925)

Blood group	Genes	Genotype	Genetics markers	
			Antigenes	Antibodies
I (0)	I^O	$I^O I^O$	-, -	**α, β**
II (A)	I^A	$I^A I^A$, $I^A I^O$	**A,** -	-, **β**
III (B)	I^B	$I^B I^B$, $I^B I^O$	-, **B**	**α,** -
IV (AB)	I^A, I^B	$I^A I^B$	**A, B**	-, -

Inheritance of Rh-factor

Rh – factor	Gene	Genotype	Phenotype
Rh^+ – positive (85%)	**D**	**DD, Dd**	**D antigene is present**
Rh^- – negative (15%)	**d**	**dd**	**D antigene is absent**

Rh-factor inheritance

Rh-factor is inherited in a multiple allele type. It is a protein that is found in Macaque-rhesus monkey and in human blood too. That is where the name originates from. It is defined by three closely linked genes C, D, E. Each of them is presented by multiple alleles.

Two alleles are distinguished in practice, the one that defines positive blood (Rh+) and the one defining negative blood (Rh-).

Rh determination is of great practical importance for medicine – for Paediatry and Neonatology, Obstetrics and Gynaecology, Surgery, Transfusiology best of all.

Rh-factor may be a reason of mother-fetus incompetibility, which may lead to disease or even death of hild. The conflict occurs when a mother has negative blood and a fetus has a dominant gene (D) from positive-blood father.

P ♀ dd x ♂ DD or Dd

Gametes d D or D, d

F_1 Dd

Placenta is a perfect barrier between fetus and mother¹s immune systems. But when the first child is born and placenta detaches, child's blood infuses into mother's organism. Antibodies against Rh-antigens are produced and antibodies for Rh-antigen appear in mother organism.

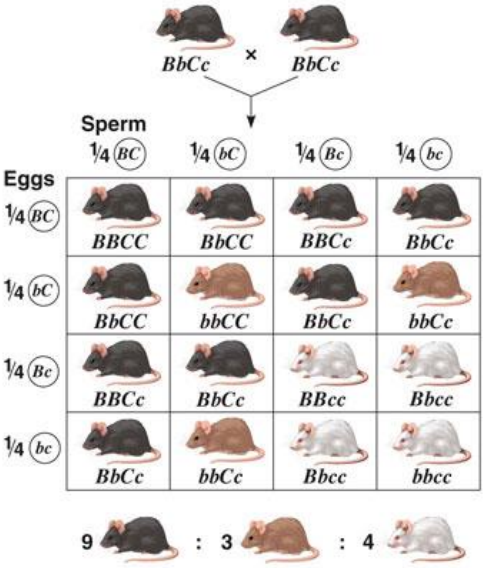
During the next pregnancy with Rh-positive fetus a huge amount of antibodies are produced against its Rh-antigens. Antibodies are small in size and penetrate through placenta and react with rh-antigens on the surface of fetus erythrocytes. Erythrocytes are ruined and the fetus debts severe hemolytic anaemia.

Some genes cause serious disorders in human being organism or in the process of metabolism that leads to death in early childhood and sometimes – before birth. Such genes are called ***lethal genes*****.** If the lethal gene is dominant, the individuals with AA and Aa genotype don't survive. This causes quick elimination of these genes from the population. In case of recessive lethal gene only recessive homozygotes do not survive, but AA homozygotes are healthy, Aa heterozygotes are either ill or healthy but they all are able viable. The recessive gene which causes the disease of Tay-Sachs may be an example of a lethal gene. In heterozygotes one of enzymes of glycolipid substance metabolism is absent in the cells of brain's grey matter, that causes severe damage of the CNS and children die before they are four or five. The disease can be found among Jews in Eastern Europe often. That is explained with the high rate (1/30) of heterozygotes bb out of the population.

Non-allelic genes interactions

Complementary is an form of two or more dominant genes of different allele pairs that results into a new feature. In other words, complementary is a supplement of both genes.

The best example of complementary is mice' hair colour inheritance. When white and black mice were crossed all mice were grey in F1. When hybrids were crossed with each other the ratio of the F_2 was not correlating with Mendel's laws.



It was found that mice had a dominant gene A that provided the synthesis of pigment. Besides, they had gene (c) that providing the spreading of pigment along the hair length.

Dominant allele C causes the pigment to spread along the hair. So, such hair has grey color.

The mice with Aacc genotypes are black.

The pigment is synthesized but spread along the hair in the way determined by the recessive gene c. White mice have dominant gene C, but they have no pigment synthesis, because gene A is in recessive state (aa).

P ♀Aacc black x ♂aaCC white

F_1 AaCc grey

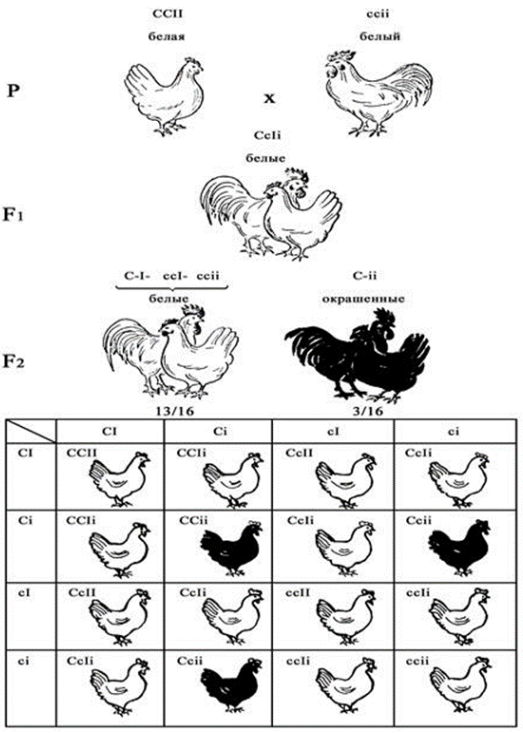
F_2 AC grey (9); Acc black (3); aaC white (3) ; aacc white (1).

Total ratio: 9 grey, 3 black, 4 white.

In human being hemoglobin consists of 4 protein molecules, synthesis of each is defined by non-allele gene.

Normal person hearing depends on formation and development of cochlea (D) in internal ear and acoustic nerve (F) which approaches it. Homozygoted (DD FF) and heterozygotes (Dd Ff) have normal hearing. Homozygotes with one recessive allele pair are deaf (D ff; dd F).

Phenomenon opposite complementary, the case when one gene action is suppressed by another non-allele gene action is called **epistasis.** Gene that is suppressed is referred to as *hypostatic*, the one that supresses is *epistatic* or *supressor*. Epistasis was studied in different plants and animals but less in humans.



An example of epistasis in humans is the so-called *«Bombay phenotype»*. In 1952 in India the baby with AB blood group was born in a family where mother had 0 groups and father had A group. It was found that formation of blood group depends not only on genes I^A, I^B and I^0, but on gene H that determine the formation of special antigen H – precursor of a and B antigen. In its absence (genotype hh) blood group 0 is formed even is genes I^a and I^b are present.

Inheritance of plume colouration in chickens at dominant epistasis

C – coloured

c – absence of colour (white)

I – epistatic gene (suppressor, inhibitor)

i – absence of inhibition

I > C

F_1: all are CcIi – white

F_2: 9 C_I_ – white

3 ccI_ – white

3 C_ii – coloured

3 ccii – white

The dominant epistasis in chickens: gene ratio in F_2 is 13 white : 3 coloured

Next interaction type of non-allele genes are **polygenic traits.** It is a phenomenon when few non-allele genes influence one character. Polygenic traits were discovered in 1908 by Swedish scientist Nilson-Elle, who studied wheat seeds color inheritance. This example proves to be the best for phenomenon understanding.

When having crossed wheat sorts with dark red and white seeds Nilson-Elle found monotonous hybrids with red seeds in the first generation, though the color intensity was twice less. It was possible to assume that it was incomplete dominance. But in the second generation seeds expression of color vary from dark to white and were not exactly alike their parents or grand-parents.

The scientist supposed that there were at least two non-allele genes taking part in this character inheritance. Such genes were termed as polygenes (multiple or cumulative genes). They are marked with the same letters but have different indexes. The scheme of such crossing is as follows:

$P \ ♀ A_1A_2A_1A_2 \ x \ ♂a_1a_2a_1a_2$

$F_1 \ A_1a_1a_2a_2 \ x \ A_1a_1A_2a_2$

Number of dominant genes in F_2 defines the intensity of color:

4 dominant genes – dark red;

3 dominant genes – red;

2 dominant genes – light red;

1 dominant gene – pink;

absence of dominant gene – white.

Total ratio is 15 with different color : 1 white.

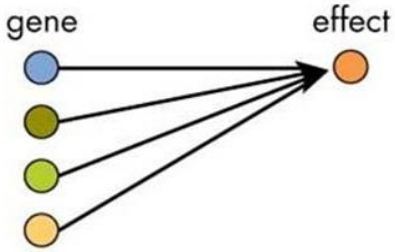
In human this cumulative action that reinforces the sign is found in such examples as inheritance of:

- height;
- weight;
- blood pressure;
- skin color;
- intelligence etc.

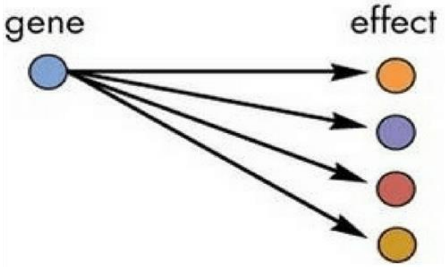
It was found that skin color inheritance is defined by 4 to 6 gene pairs. American geneticists Jansen examined numerous Jamaican mixed marriages in 1912. They found out that in marriage between persons of black and white races all children are mulattors. Their skin color is twice lighter than the one of black race. In mulatto's marriages kids may look like parents or grand parents.

Pleiothropy (or pleiotropy, or pleyothropy) the phenomenon when one pair of genes is responsible for the manifestation of several characters. For example, it is the Marphan's syndrome that includes (all these characters are determined by one dominant gene):

- arachnodactyly (spider fingers or long slender fingers);
- long stature;
- heart abnormalities.



Polygenic trait: Many genes contribute to a single effect.



Pleiotropy: the multiple effect of a single gene.

One more example of this phenomenon is albinism. It is observed in persons who are homozygous in recessive autosomic gene a and thus skin, hair, iris are depigmented, photophobia and eyesight abnormalities are observed.

So, in many cases in plants, animals and humans manifestation of characters is the result of non-allele genes interaction. Environment has a great influence on all characters manifestation. All this gave individual variety with different signs combination.

Understanding of such complex gene interaction explains etiology, pathogenesis of hereditary diseases and is important for diagnosis and possible medical treatment.

1st level tests

(one correct answer)

1. Scientists had discovered that some forms of adults immunity were determined by two genes A_1 and A_2. Homozygotes organisms – immunity is absent and heterozygotes (A_1A_2) – is present. What form of interaction between genes takes place at determination of such form of immunity?

A. Polygenic traits
B. Incomplete dominance
C. Complementary
D. Overdominance
E. Complete dominance.

2. The married couples are sick by the easy form of sickle-cell anemia. They gave birth a died child because of such disease. Specify the form of genes interactions that explains a phenotypical difference between parents and child in this family.

A. Polygenic traits
B. Incomplete dominance
C. Complementary
D. Overdominance
E. Complete dominance.

3. Some clinically healthy people in the conditions of highland living have signs of anemia. Blood test revealed sickle-shaped erythrocytes. What genotype is more probable for such people:

A. ss
B. Ss
C. SS
D. X^SX^s
E. X^SY.

4. In some students family which arrived from Africa, a child was born with the signs of anemia; this child has died soon. It is discovered that child had sickle-shaped erythrocytes. What is the most credible genotypes of wife and husband (parents of the child), if it is known that they have an easy form of this illness:

A. Aa AA
B. Aa aa

C. AA AA
D. aa aa
E. Aa Aa.

5. What kind of blood types of parents gives the conflict by rhesus factor during the pregnancy?
A. Female Rh-, male Rh+ (homozygote)
B. Female Rh+, male Rh+ (homozygote)
C. Female Rh+, male Rh+ (heterozygote).
D. Female Rh-, male Rh-
E. Female Rh+ (heterozygote), male Rh+ (homozygote).

6. Woman with I (0) Rh- has married with a man IV(AB) Rh+, What variant of blood group and rhesus factor can be expected for their children?
A. III (B) Rh+
B. I (0) Rh-
C. IV (AB) Rh+
D. IV (AB) Rh-
E. I (0) Rh+.

7. Woman with III blood group by system of AB0 and Rh- gave birth a child with IV blood group sick by hemolytic disease as a result of Rh-conflict. What genotype can be possible for a father?
A. $I^A I^A$ Rh Rh
B. $I^A I^A$ rh rh
C. $I^A I^0$ rh rh
D. $I^B I^B$ Rh rh
E. $I^0 I^0$ Rh rh.

8. Woman with III(B), Rh- blood group gave birth a child with II(A) blood group. Newborn child has hemolytic disease as a result of rhesus-conflict. What blood type and rhesus factor are possible for a father?
A. II (A) Rh+
B. I (0) Rh+
C. III (B) Rh+
D. I (0), Rh-
E. II (A), Rh-.

9. Human cystinuria shows up as a presence of cystine stones in the kidney (homozygote) or increased level of cystine in urine(heterozygote). Disease cystinuria is monogenic. Define the type of genes interaction of cystinuria and normal level of cystine in urine.
A. Incomplete dominance
B. Epistasis
C. Complete dominance
D. Complementary
E. Codominance.

10. Boy has a I blood group but his sisters is IV. What blood types for the parents of these children?
A. II ($I^A I^0$) and III ($I^B I^0$)
B. II ($I^A I^A$) and III ($I^B I^0$)
C. I ($I^0 I^0$) and IV ($I^A I^B$)
D. III ($I^B I^0$) and IV ($I^A I^B$)
E. I ($I^0 I^0$) and III ($I^B I^0$).

11. In the situation when one of parents has a blood I (0) type, and other AB, a child can have a blood type:
A. II (A) or III (B)

B. I (O) or IV (AB)
C. IV (AB)
D. I (0) or IV (AB) or II (A) or III (B)
E. I (0) or II (A) or III (B).

12. Man IV (AB) blood type, a woman – III (B). The father of woman has I (0) blood type. They have 5 children. Specify the genotype of the child that can be considered as out of marriage:
A. $I^0 I^0$
B. $I^A I^B$
C. $I^B I^B$
D. $I^A I^0$
E. $I^B I^0$.

13. Parents with I (0) and (III, heterozygous) blood group by system of AB0 have a child. What is a probability of presence I (0) blood group for this child?
A. 0 %
B. 75 %
C. 25 %
D. 100 %
E. 50 %.

14. According to the second law of G. Mendel the correlation of phenotypes at the crossing of two heterozygous individuals (incomplete dominance) will be such:
A. 1 : 1
B. 1 : 2 : 1
C. 3 : 1
D. 1 : 1 : 1 : 1
E. 2 : 2.

15. According to the second law of G. Mendel the correlation of genotypes at the crossing of two heterozygous individuals (incomplete dominance) will be such:
A. 1 : 1
B. 1 : 2 : 1
C. 3 : 1
D. 1 : 1 : 1 : 1
E. 2 : 2.

16. Define the blood group of the child if his parents have the first blood group by the system of AB0:
A. IV
B. III
C. I
D. II
E. I and IV.

17. New-born child has a dislocation of lens in the eye, long fingers, thin and long legs, aneurysm of aorta too. What disease these signs are characteristic for?
A. Down syndrome
B. Marphan syndrome
C. Patau syndrome
D. Edwards syndrome
E. Kleinfelter syndrome.

18. Skin pigmentation is controlled by a few non-allelic dominant genes. It is set that increasing of amount of these genes gives the pigmentation more intensive. What type of interaction between these genes?
A. Pleiotropy
B. Polygenic traits

C. Overdominance
D. Complementary
E. Epistasis.

19. Deaf-mute parents with the genotypes DDee and ddEE gave birth children with a normal hearing. What form of genes interaction between D and E:
A. Pleiotropy
B. Polygenic traits
C. Overdominance
D. Complementary
E. Polygenic traits.

20. Child with sickle-cell anemia has such pathological signs: anaemia, increased spleen, defeat of skin, heart, kidneys and brain. How do the plural action of one gene is named?
A. Pleiotropy
B. Polygenic traits
C. Overdominance
D. Complementary
E. Polygenic traits.

21. The color of human skin is controlled by a few pairs of non-linked genes. Pigmentation of human skin with the genotype A_1A_1 A_2A_2 A_3A_3 is:
A. Black
B. White
C. Yellow (Mongolian)
D. Brown (Mulattoes)
E. Albino.

22. Biochemists had established that haemoglobin of the adults contained 2 alpha- and 2 beta-polypeptide chains. Genes that encode these chains are located in the different pairs of homological chromosomes. What form of genes interaction is observed?
A. Polygenic traits
B. Epistasis
C. Complementary
D. Overdominance
E. Pleiotropy.

23. Define how do the genes that repress work of other genes are named:
A. Operators
B. Repressors
C. Inhibitors
D. Transpozoons
E. Regulators.

24. Phenomenon of dependence of a few signs from one gene is named as:
A. Pleiotropy
B. Polygenic traits
C. Overdominance
D. Complementary
E. Polygenic traits.

25. Define the polygenic sign:
A. Presence, or absence of hearing
B. Left- of right-handed person
C. Body weight
D. Positive or negative rhesus factor
E. Presence or absence of freckles.

26. Phenomenon when a few genes determine development of one sign is named as:

A. Polygenic traits
B. Epistasis
C. Complementary
D. Overdominance
E. Pleiotropy.

27. Define the concept of polygenic traits from the stated below examples:
A. Interaction of dominant non-allelic genes that forming only one sign
B. Interaction of dominant non-allelic genes that forming a few signs
C. Interaction of dominant allelic genes that forming a few signs
D. Degree of phenotypical display of sign that is controlled by this gene.
E. Frequency of phenotypical display of gene in the population of individuals (carriers).

28. Which ratio has explained segregation in the second generation at the inheritance of chicken feathers color as a result of dominant epistasis:
A. 9 : 3 : 3 : 1
B. 10 : 2 : 4
C. 15 : 1
D. 13 : 3
E. 12 : 3 : 1.

29. What correlation is observed at the typical segregation of the hybrids in the second generation in a case of polygenic traits:
A. 9 : 3 : 3 : 1
B. 10 : 2 : 4
C. 15 : 1
D. 13 : 3
E. 12 : 3 : 1.

30.Cystinuria in humans shows itself in form of cystine stones in kidneys (homozygotes) or else an increased rate of cystine in urine (heterozygotes). Cystinuria is a monogenic disease.Specify the type of interaction between cystinuria genes and normal rate of cystine in urine:
A. Semidominance
B. Epistasis
C. Complete dominance
D. Complementarity
E. Codomination.

31. Hurtnup's disease is caused by point mutation of only one gene. This results in abnormal absorption of
tryptophane in the intestine as well as its abnormal reabsorption in renal tubules. This causes synchronous disorders in digestive and urinary excretion systems. What genetic phenomenon is observed in this case?
A. Pleiotropy
B. Complementary interaction
C. Polymery
D. Codominance
E. Semidominance.

32. As a result of prophylactic medical examination a 7 year old boy was diagnosed with Lesch-Nyhan syndrome (only boys fall ill with it). The boy's parents are healthy but his grandfather by his mother's side suffers from the same disease. What type of disease inheritance is it?
A. Recessive, sex-linked
B. Dominant, sex-linked
C. Autosomal recessive
D. Autosomal dominant

E. Semidominance.

33. An 18-year-old male has been diagnosed with Marfan syndrome. Examination revealed a developmental disorder of connective tissue and eye lens structure, abnormalities of the cardiovascular system, arachnodactylia. What genetic phenomenon has caused the development of this disease?

A. Pleiotropy
B. Complementarity
C. Codominance
D. Multiple allelism
E. Incomplete dominance.

2nd level tests

1. Examples of pleiotropic genes interactions for the humans are:
a) Marphan disease;
b) the Bombay phenomenon at the inheritance of blood group by system ABO;
c) height, pigmentation of skin;
d) phenylketonuria;
e) galactosemia.

2. Phenomenon of the dependence of a few traits from one gene is named as:
a) polygenic traits;
b) pleiotropy;
c) codominance;
d) epistasis.

3. Examples of epistasis genes interactions for the humans are:
a) Marphan disease;
b) the Bombay phenomenon at the inheritance of blood group by system ABO;
c) height, pigmentation of skin;
d) phenylketonuria;
e) galactosemia.

4. Thalassemia is predefined by a recessive gene. Frequency of gene is too high in some populations in tropical Africa. Explain why the gene of thalassemia does not disappear as a result of natural selection:
a) heterozygosity of an organism;
b) homozygosity by a recessive gene;
c) dominance of a gene;
d) natural selection against homozygote;
e) advantages of heterozygous carriers of thalassemia gene in a concrete environment.

5. How many allelic genes are coding blood group by system ABO:
a) in a population;
b) in each individual;
c) in a gamete?

6. How many allelic genes (1, 2, 3, 4 or 100) are coding human β-haemoglobin:
a) in a population;
b) in a somatic cell;
c) in a gamete?

7. What forms of genes interaction (complete dominance, incomplete dominance, codominance) do exist between alleles of gene of blood AB0 types:
a) $I^B I^O$;
b) $I^A I^O$;
c) $I^A I^B$;
d) $I^O I^O$?

8. Define what blood group is possible for the children, if parents have:
a) I (0);

b) II (A0;
c) III (B);
d) IV (AB).

9. Define all possible blood groups by AB0 system for the children in such cases:

a) if mother I (0), father – II(A);
b) if mother I (0), father – IV;
c) if mother I (0), father – III.

10. Is it possible for the children to inherit the genotype and phenotype of parents in the following case:

a) if mother I (0) and father – II (A);
b) if mother II (0) and father – IV (AB);
c) if mother II (A) and father III (B).

11. Blood group of three pairs of parents are known:

1) mother II, MM, Rh-, father – 0 (I), MM Rh+;
2) mother III, MN, Rh-, father – B (III), MM Rh+
3) mother II, MM, R +, father – B (III), MN, Rh-

Every couple has one child. Blood group of their children are:

1) AB (IV), MM, Rh -
2) 0 (I), NN, Rh -
3) I, MM, Rh -

Define, what pair of parents every child belongs to.

12. Mother has a blood group 0(I), MM, but possible father – B (III), MM. Three children of this woman can have such blood groups:

1) 0 (I), MM;
2) II, MM;
3) 0 (I), MM

For what children it is possible to exclude the paternity?

13. What kind of segregation will take place in a posterity of hybrids P1 (diheterozygotes) at different variants of complementary genes interaction:

a) 9:3:3:1;
b) 9:7;
c) 12:3:1;
d) 13:3;
e) 9:3:4;
f) 15:1.

14. How is it possible to explain the different degree of phenotype that is determined by genes A1 and A2, in the genotypes $A_1A_1A_2A_2$ and $A_1a_1A_2a_2$:

a) by an epistatic interaction;
b) by a polymeric interaction;
c) by a modifying action.

15. Choose the examples of the human polygenic traits:

a) Marphan syndrome;
b) phenylketonuria;
c) height;
d) pigmentation of skin.

16. What inheritance is named as polygenic:

a) inheritance of the traits which are depending on interaction of allelic genes;
b) inheritance of the traits which are depending on interaction of non-allelic genes.

Tasks on lethal gene action and incomplete dominance

1. What correlation of phenotypes and genotypes must be expected in offspring of husband and wife – heterozygous carriers of recessive lethal gene that cause a death

and resorption of embryo in early developmental stages?

2. What a possibility of birth a healthy child in a family in which a child died from the disease Tay-Sachs (accumulation a fat substance in brain that leads to the brain tissue degeneration and blindness in an age of 4–5 years). Tay-Sachs disease is caused by the recessive lethal gene.
3. The person has a circle-cell anemia (recessive character). Homozygous by this gene die in an early childhood from hemolytic anemia. In heterozygous people this disease has a light course. Determine the possibility of birth healthy children and children with light disease form in parents suffering from light sickle-cell anemia form.
4. Seldom anomaly – anophtalmy (eyeball absence) is determined by autosome gene (a). In homozygous by this character eyeballs are absent, in heterozygous they are much smaller than under physiological conditions. What a possibility of birth of a healthy children birth in a family where one of parents has smaller eyeballs and other one – normal?

Multiple alleles. Inheritance of blood groups

1. Heterozygous woman of II blood group has married of heterozygous man of III blood group. What blood group and genotype may have their children?
2. Rh-positive woman with the blood of II group the father of which had I (O) Rh- blood has married with I (O) Rh- man. What possibility of the fact that the child will inherit both fathers' characters?
3. IV (AB) RH- man has married of III (B) woman. Wife's father had blood I (O) Rh-. Two children were born: III (B) Rh- and I (O) Rh+. Forensic medical examination established that one of these children is natural (out of marriage). By what sign one can determine the paternity?
4. The father with blood groups M and O has a child with B and B blood groups. What genotype may be in his mother?
5. The parents are Rh+, but the father is blue-eyed and the mother is brown-eyed. They have 5 children from which 4 are Rh+ but 2 are blue-eyed and 2 are brown-eyed. One child is blue-eyed and Rh-. Determine parents' and children's' genotypes (Rh+ and brown-eyedness are dominant characters).
6. The parents with blood II (A) have a son with blood I (O) suffering from haemophilia. The parents were healthy. Determine the possibility of birth of second child healthy and possible blood groups.
7. The parents have blood groups:

Mother	Father	Children
1. A, MN, Rh+	1. O, M, Rh+	1. AB, M, Rh-
2. B, N, Rh-	2. B, MN, Rh+	2. O, N, Rh-
3. A, M, Rh-	3. B, MN, Rh-	3. A, MN, Rh+

Determine by which blood group systems one can exclude the paternity?

Non-allelic genes interactions

1. There are several forms of inherited near-sightedness in the person. Moderate form (from –2.0 till –4.0) and severe (more than –5.0) are transmitted as characters autosome-dominant not-linked between each others. In the family where the mother was near-sighted and the father had normal sight two children had been born, the daughter and the son. The daughter had a moderate near-sightedness form and the son – high one. What possibility of birth of next child in the family without any anomalies if it's known that only one of mother's parents was suffering from near-sightedness. It should be taken into account that in people that have both n near-sightedness forms only one form (high) is expressed.
2. The human's height is controlled by several pairs of non-linked genes interacting by polymery type. If one doesn't take into account environmental factors than one can

content (limit) with three gene pairs: in human population people with low height have recessive genes (150 cm), tall – dominant genes and 180 cm. Determine human height which are heterozygous on all three height gene pairs.

3. The woman of small height has married with the man of intermediate height. They had 4 children with the height os 165 cm, 160 cm, 155 cm and 150 cm. Determine parents' genotypes and their height.
4. The inherited deafness in person can be determined by genes a and b. For normal hearing it's necessary the existence of two dominant genes A and B in genotype. Determine genotype of both parents in the family where both parents are deaf and 5 children have normal hearing.
5. Give genetic explaining of mentioned inheritance cases in human:
   deaf parents but all their children have normal hearing;
   deaf parents and all their children are also deaf;
   normal parents and many children. About ¾ of them have normal hearing and ¼ were deaf.
6. Negroid skin color is controlled by two gene pairs from different allele pairs. Intensive black of their skin is determine by dominant genes of both pairs, skin color in the whites – by their recessive alleles. Establish possible color of children's skin from the marriage of:
   white men and Negro woman;
   mulatto (woman) with the white;
   possibility of birth of white child from the marriage of two mulattoes.

TOPIC: Theory of linkage. Inheritance of sex

Chromosomal theory of heredity. Mechanism of the crossing-over, cytologic explaination, biological value.

Genetic maps of chromosomes. Methods of mapping of the human chromosomes. Modern state of researches of the human genome. Non-chromosomal heredity.

Inheritance of human sex. Mechanisms of genetic determination of human sex and their disorders. Features of sex-linked inheritance, laws of their inheritance. Sex-linked inheritance and human diseases. Characters limited by sex and dependent upon the sex.

The concept of linked gene inheritance

At the beginning of the XX century, it was observed that the number of hereditary features of the organism significantly exceeds the number of chromosomes of the haploid set. For example, there are only four chromosomes in the haploid set of a classic genetic research object – *Drosophila* flies – but the number of inherited traits, and therefore the genes that determine them, are definitely much larger. This means that many genes are located in each chromosome. Therefore, along with the traits that are inherited independently, there must also be traits that are inherited together or linked to one another.

Linked inheritance is the inheritance of traits whose genes are localized in one chromosome.

The linked inheritance was discovered in 1905 by William Betson and co-workers, calling it *"gametic coupling"*. In experiments with the fragrant peas of *Lathyrus odoratus*, they, when studying the inheritance of petal color and pollen form, found that no independent inheritance was observed for this pair of traits, that is, the pair of traits that characterize the parent plant tends to be inherited together.

Therefore, ***the genes of one chromosome form a cluster group and are inherited***

together. Thus the number of groups of linkage is equal to the number of chromosome pairs, or the number of chromosomes in the haploid set (for example, in *Drosophila* 1n = 4, in human 1n = 23).

Between homologous chromosomes, in the course of meiosis, a ***crossing over*** can occur – the exchange of identical sites with allelic genes.

In the absence or presence of crossing over homologous chromosomes it can be distinguished complete or incomplete gene linkage.

With ***complete linkage*** the crossing over does not occur and the traits are always inherited together, and the parent individuals form only ***two types of gametes:***

$\frac{AB}{ab} \rightarrow \underline{AB}$ і $\underline{ab}$

With ***incomplete linkage*** at the expense of the crossing over features can be recombined, and in the parent individuals are formed not two, but four types of gametes: non-crossover (there are always more) and crossover:

$\frac{AB}{ab} \rightarrow \underline{AB}$ і $\underline{ab}$ (non-crossover gametes) та $\underline{Ab}$ *і* $\underline{aB}$ (crossover gametes)

Organisms that arise from the crossover gametes are called ***crossovers*** or ***recombinants***, and those that arise from non-crossover gametes are called ***non-crossovers***.

Crossing over occurs in the prophase of meiosis I after conjugation and leads to the redistribution of genes in chromosomes. This phenomenon is random and can occur in any site of homologous chromosomes.

Patterns of crossing over:

- the cohesive force between two genes located in the same chromosome is inversely proportional to the distance between them; therefore, the greater the distance, the more often the crossing over occurs;
- the frequency of crossing over depends on the distance between the genes and is expressed as a percentage;
- the frequency of crossing over between two genes located in the same chromosome is a constant for each specific pair of genes;
- the crossing over is measured by the ratio of the number of crossover individuals to the total number of individuals in the offspring generation.

Although the frequency of the crossing over is constant, it can be influenced by some factors of the external and internal environment: changes in the structure of individual chromosomes, temperature,
X-rays, some chemical compounds, etc.

Detailed experimental studies of the phenomenon of linked gene inheritance were conducted by the eminent American geneticist Thomas Hunt Morgan (1866–1945) with his collaborators – Calvin Bridges, Alfred Sturtevant, Herman Joseph Meller.

A classic object for Morgan and his school's genetic experiments was the *Drosofila melanogaster* (fruit fly):

- easy to keep in laboratories;
- high fertility;
- rapid change of generations (every one and a half or two weeks);
- a small number of chromosomes that simplifies observation.

In experiments of T. Morgan and his colaborators they crossed Drosophila, which had dominant features: gray body and normal wings, with flies that had recessive features: black body and vestigial wings.

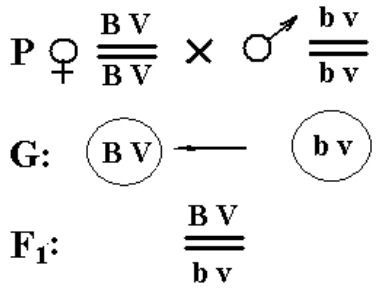
B is a gray body gene, **b** is a black body gene.

V – gene of normal wings length; **v** – gene of vestigial (rudimentary) wings.

$\frac{BV}{BV}$ - genotype of dihomozygotes by dominant alleles in groupe of gene linkage.

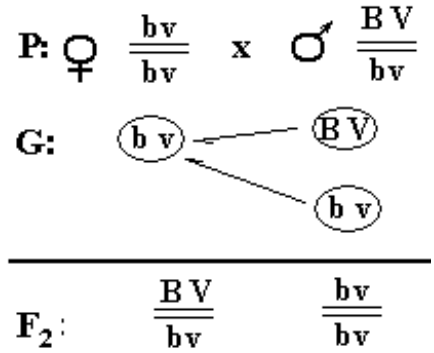
$\frac{bv}{bv}$ - genotype of dihomozygotes by recessive alleles in groupe of gene linkage.

$\frac{BV}{bv}$ - genotype of diheterozygotes in groupe of gene linkage.



100% diheterozygous fruit flies – gray with normal wings

In the first generation, all descendants were monotonous – gray body and normal wing length. After that the analysis (reciprocal) crossing was carried out.

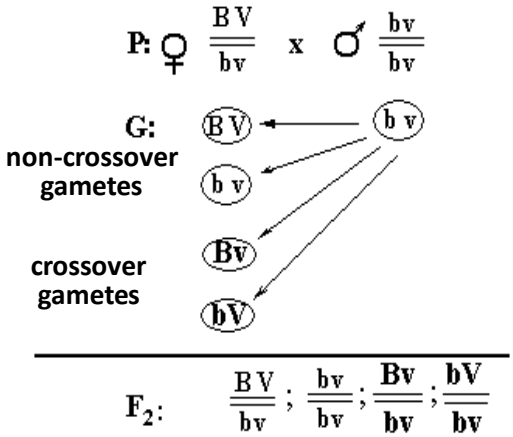


I variant of analysing crossing

Hybrid males were crossed with recessive females. Offspring received 50% of gray flies with normal wings and 50% of black with vestigial wings.

Conclusion (Morgan law): genes that localized in one chromosome form the one group of linkage and are inherited together.

In F_2: Splitting by phenotype and genotype 1 : 1 (50% gray with normal wings; 50% black with vestigial wings).



II variant of analysing crossing

Hybrid females were crossed with recessive males. The offspring received 41.5% of gray with normal wings and 41.5% of black with rudimentary wings and 17% of recombinant forms (8.5% of gray with short and 8.5% of black with normal wings).

Conclusion: The violation of linkage groups occurs as a result of crossing over.

Morgan's Law: The linkage force between genes is inversely related to the distance between them.

In F_2: 41.5% gray with normal wings;
41.5% black with vestigial wings;
8.5% gray with vestigial wings;
8.5% are black with normal wings.

Chromosomal theory of inheritance

Although during the second half of the XIX century chromosomes were already discovered and described (C.W. von Nägeli, 1842; W. Hofmeister, 1848; I. Chistyakov, 1873; E. Strasburger, 1875; O. Bütschli, 1876; W. Flemming, 1879, 1882; in 1888 German

anatomist and histologist Heinrich Wilhelm Gottfried Waldeyer introduced the term «chromosomes»), and Gregor Mendel formulated the laws of heredity (1865), at the beginning of the XX century the question of the primary nature of hereditary factors remained open.

In 1902 American zoologist Walter Sutton and German zoologist Theodore Boveri independently correlated Mendel's conclusion about genes (or inherited traits) to the behavior of chromosomes during mitosis and meiosis, giving the basis of the Chromosomal theory of inheritance:

- Genes as physical factors of heredity are located on chromosomes on specific loci.
- Chromosomes are presented by pairs in diploid cells.
- Homologous chromosomes separate during meiosis so that alleles are segregated.
- Gamete has one of each homologous chromosome but not both.
- Fertilization restores the pairs of chromosomes.
- During the formation of gametes non-homologous chromosomes segregate independently.

Later, the results of experimental studies of the linked gene inheritance conducted by Thomas Morgan and colleagues supplemented the Sutton-Boveri chromosomal theory of heredity, finally defining the chromosomes as physical carriers of hereditary information.

The chromosomal theory of heredity
(T. Morgan, A. Sturtevant, H. Muller, 1911–1916)

1. Genes are located in chromosomes. Each homologous chromosome is unique.
2. Allelic genes are in the same loci of homologous chromosomes.
3. The genes in the chromosome are arranged in a certain sequence in a linear order. Genes that are in one chromosome forms a linkage group and is inherited together.
4. The number of linkage groups corresponds to the haploid number of chromosomes.
5. Disruption of the groups of linkage and the formation of new groups of linkage occurs as a result of crossing over.
6. The linkage force between genes is inversely related to the distance between them.
7. Each species is characterized by a specific set of chromosomes (karyotype) and its own groups of linked genes.

The significance of chromosomal theory of heredity for the development of biology:

- it helps to clarify the material basis of the laws of inheritance established by Gregory Mendel;
- assigned to the genes the role of elemental units of heredity, which are localized in chromosomes;
- explains the deviation of trait inheritance in presence of linkage of gene.

In 1933 Thomas Morgan was awarded the Nobel Prize in Physiology and Medicine for discovering the role of chromosomes in heredity.

Genetic maps of chromosomes. Human genome

The study of crossing over allowed T. Morgan's school to develop the principle of constructing genetic maps of chromosomes. T. Morgan proposed to determine the distance between genes in the percentage of crossing over between them. Later, the unit of distance between the genes, which equaled one percent (1%) of the crossing over frequency, was called ***morganide*** (A.S. Serebrovsky).

To measure the distance between genes by analyzing crossing, use the formula:

$$X = \frac{a+b}{N} \cdot 100$$

where X is the distance between genes in morganides;

a + b – the number of individuals that evolved from the gametes where the crossing over occurred;

N is the total number of descendants in this experiment.

The gene occupies a certain place in the group of linkage. The percentage of crossing over frequency is an indicator of the distance between genes. Knowing the percentage of crossing over and the distance between genes, you can get an imagination about the location of genes in the chromosome, which makes it possible to draw a genetic map of the chromosome.

Genetic maps are a graphical representation of chromosomes with the order of the gene's location and distance between them.

The size of the maps is determined by the sum of the distances between the genes. Genetic maps of most organisms look like a straight line, but bacteria and viruses have a closed ring.

Genetic maps of chromosomes are compiled for many organisms. All 24 groups of linkage are known in humans (22 pairs of autosomes, X and Y chromosomes). Linkage groups number correspondes to number of pairs of homologous chromosomes. Maps are made on the basis of the following methods: hybridological analysis, hybridization of somatic cells of different species, labeled DNA fragments, etc. Data on linkage groups and gene localization are required for the diagnosis of hereditary diseases.

The Human Genome program was completed in 2003, and studies have shown that number of genes in the human genome is approximately ≥35000 and the exact location of genes in chromosomes are being investigated, but research is still ongoing.

The concept of sex. Types of sex determination

Biological sex is a set of genetically and hormonally determined characteristics of an organism, which integrates its various specific reproductive (sexual) features, that determine the role of this organism in the process of fertilization during sexual reproduction.

Sexual characteristics is a set of different structural and functional features of organs of the body that determine the sex of this individual.

Sexual characteristics are divided into biological (primary and secondary) and gender (tertiary).

Primary and secondary traits are genetically determined, their structures are formed in the fertilized egg long before the baby is born. Further development of sexual characteristics occurs with the participation of hormones.

Primary sexual characteristics are related to the peculiarities of the structure of the reproductive system (genital organs – internal (including glands) and external (copulatory); ensure the formation of gametes and their combinations in the process of fertilization, are defined during the fertilization of the egg with a sperm, are formed at the third month of prenatal life and are noticeable after birth.

Secondary sex characteristics distinguish one sex from another, serve to attract individuals of another sex (among human: in men – mustache, beard, Adam's apple; in women – the development of the breast, broad pelvis; among animals – a bright plumage male birds, odorous glands, well-developed horns, tusks in male mammals); they begin to show up during puberty (in girls – slightly earlier than in boys, but it depends on heredity, climate and nutrition).

Types of sex determination:

Programic: before the formation of a zygote, in the process of ovogenesis (in rotifers, aphids, round worms).

Syngamic: at the time of zygote formation (in most organisms).

Epigamic: after the formation of zygote (in the Bonellia viridis sea worm).

Haplo-diploid: depending on the fact of fertilization (in bees, wasps, ants, riders, sex chromosomes are absent, and sex determines the multiplicity of the chromosomal set: from a fertilized egg, diploid females are formed, and from unfertilized – haploid males).

The sex of animals and plants is genetically determined by one pair of chromosomes, which have been called ***sex chromosomes,*** or ***honosomes.***

Types of chromosomal sex determination

Type of sex determination	Species	Somatic cells		Gametes		Heterogametic sex
		♀	♂	ovum	spermatozoa	
XY	Human, fruit fly and most part of other species	XX	XY	X and X	X and Y	Male
XY **ZW**	Butterflies, fishes, birds, reptiles	XY ZW	XX ZZ	X and Y Z and W	X and X Z and ZZ	Female
X0	Grasshoppers, bedbugs, spiders, some nematodes	XX	X0	X and X	X and 0	Male
X0	Moth, phylloxera, aphids	X0	XX	X and 0	XX	Female

Inheritance of sex in human. Traits, linked with sex, patterns of their inheritance. Hemizygosity

Sex chromosomes, in addition to sex determination, also perform other functions because they contain genes that affect different systems of body. Inheritance of traits and properties caused by genes localized in the sex chromosomes (in humans these are X and Y chromosomes) are called ***sex-linked inheritance.*** This phenomenon was discovered by T. Morgan in 1910.

In his experiments with *Drosophila*, Morgan crossed the female of the wild type with red eyes (dominant allele) and the male with white eyes (recessive allele). All descendants, as expected, had red eyes. Crossing these offspring with each other, Morgan received the expected Mendelian splitting: 75% of red-eyed individuals and 25% of white-eyed individuals. However, there was one significant feature in this ratio: 25% of individuals with white eyes were exclusively male.

Variant 1

X^W is a red eye gene localized in the X chromosome,

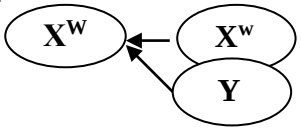
X^w is a white eye gene localized in the X chromosome,

$X^W X^W$ – genotype of homozygous red-eyed females,

X^wY – genotype of hemizygous white-eyed males.

P: ♀ $X^W X^W$ × ♂ $X^w Y$

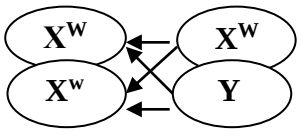
G:



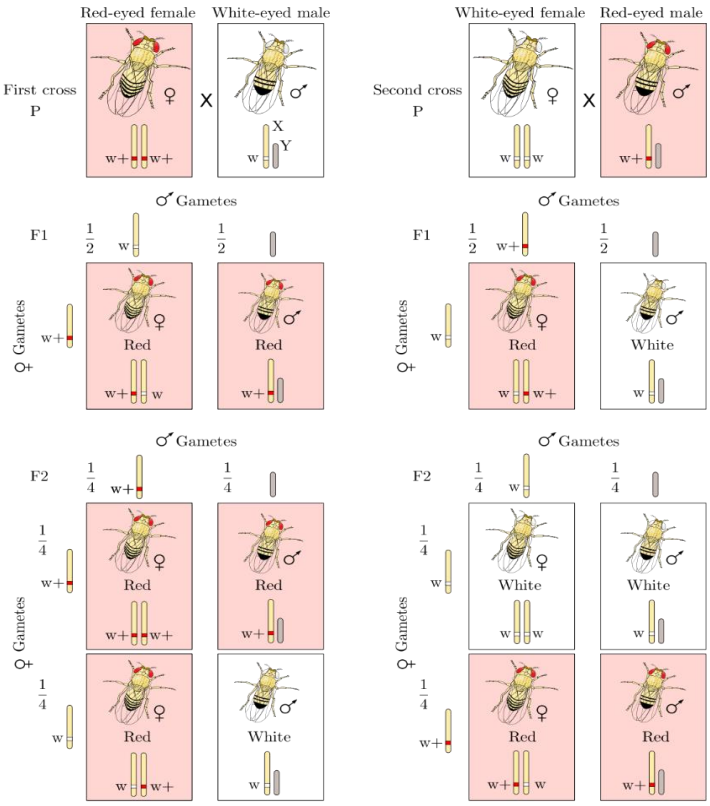
F_1: $X^W X^w$ $X^W Y$

P: ♀ $X^W X^w$ × ♂ $X^W Y$

G:



F_2: $X^W X^W$ $X^W X^w$ X^W y $X^w Y$

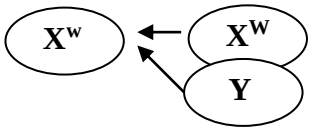


Splitting by phenotype 3 : 1
(75% with red eyes
and 25% with white eyes)
by genotype: 1 : 1 : 1 : 1
(25% homozygous red-eyed females,
25% heterozygous red-eyed females,
25% hemizygous red-eyed males,
25% hemizygous white-eyed males).

Variant 2

$X^w X^w$ – genotype of homozygous white-eyed females,
$X^W Y$ – genotype of hemizygous red-eyed males.

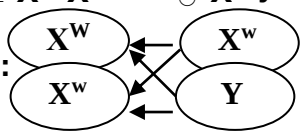
P: ♀ $X^w X^w$ × ♂ $X^W Y$

G: 

F_1: $X^W X^w$ $X^w Y$

In F_1 a splitting is 1 : 1
(50% of red-eyed heterozygous females and 50% of hemizygous white-eyed males).

P: ♀ $X^W X^w$ × ♂ $X^w y$

G: 

F_2: $X^W X^w$ $X^W Y$ $X^w X^w$ $X^w y$

In F_2 a splitting is 1 : 1
(50% of red-eyed and 50% of white-eyed individuals).
by genotype: 1 : 1 : 1 : 1
(25% heterozygous red-eyed females,
25% hemizygous red-eyed males,
25% homozygous white-eyed females,
25% hemizygous white-eyed males).

Therefore, the gene that determines the color of eyes is localized in chromosomes associated with the sex determination in *Drosophila* (in the X chromosomes).

The sex chromosomes X and Y are partially homologous because they have small common homologous sites in which allelic genes are localized. Homologous X- and Y-chromosome regions contain allelic genes that are equally likely to exist in individuals of both sexes. The traits determined by such allelic genes are inherited by the classic Mendelian rules.

However, the X- and Y-chromosomes differ significantly in shape, size and genetic content, since they contain a large number of non-allelic genes. The X-chromosome contains genes that are not in the Y-chromosome, and vice versa. In this case, the trait is determined not by a pair of allelic genes as a normal mendelian trait, but by only one allele. Such a condition of the gene is called ***hemizygous,*** and the traits, the development of which is due to a single allele located in one of the alternative sex chromosomes, have been called ***sex-linked.*** Such features develop mainly in individuals of the same sex and are inherited in different ways in men and women.

Hemizygote is a diploid organism that has only one allele of a particular gene.

Hemizygosity is a trait inherent in heterozygous organisms that have a single allele of

the gene in the sex chromosomes of the diploid set and accordingly exhibit a coded trait in the phenotype.

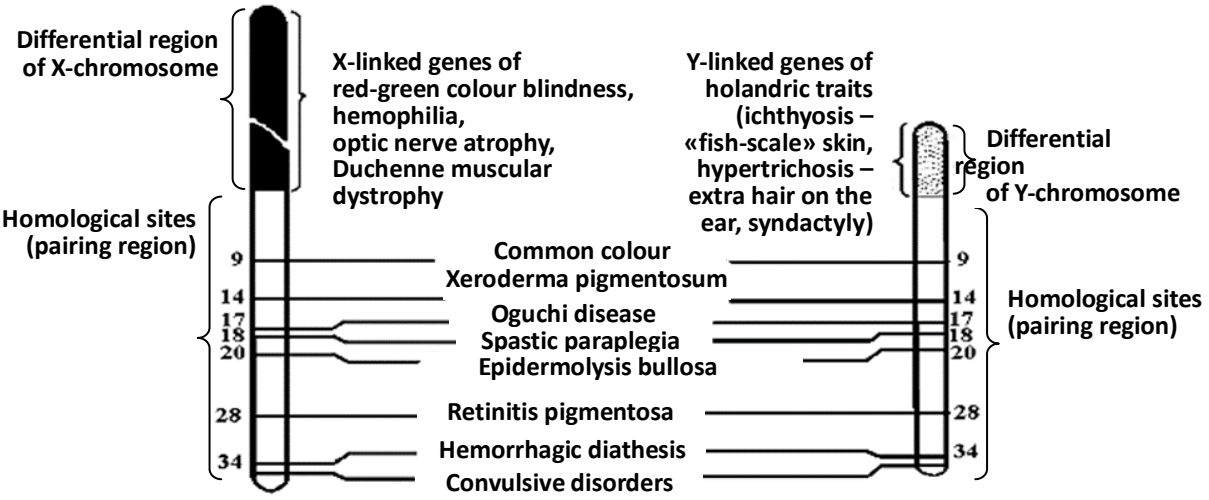
The genetic significance of the X-chromosome in humans is much greater than that of the Y-chromosome. However, both the X-chromosome and the Y-chromosome have genes that are unrelated to reproductive function.

The location of some genes in human genome

Chromosome	**Genes**
1	Rh factor, salivary and pancreatic amylase, 5S rRNA
6	Transplantation antigens (HLA), prolactin, pepsinogen
7	Erythropoietin, histones
9	ABO blood groups, interferon
11	B-chain of haemoglobin, insulin
12	Peptidase B
14	Heavy chains of antibodies
15	Some mitochondrial enzymes (dehydrogenase)
16	A-chain of haemoglobin
17	Collagen, growth hormone
18	Peptidase A
X	Clotting factor VIII (absence produces haemophilia)

Localization of some genes in human sex chromosomes, causing hereditary diseases: X-linked, Y-linked, incomplete linked with sex

(numbers indicate crossing over frequency – distance between genes)



Despite the fact that most types of cells in the female sex have two X-chromosomes and the male –one, the expression level of genes linked to the X chromosome in males and females is almost the same. There is a genetic mechanism to compensate for the X-dependent dose of genes. In placental mammals (human, cat, mouse), dose compensation is due to the inactivation (heterochromatization, lionization) of one of the X chromosomes. In the interphase nuclei of somatic cells of females, one of the X chromosomes concentrates near the membrane of the nucleus and forms a **Barr's body**. Both (maternal and paternal) X-chromosomes of females are inactivated in different embryonic cells by chance.

Examples of X-linked dominant disorders:

- hypophosphatemic (vitamin D resistant) rickets;

- incontinentia pigmenti (including dark enamel of teeth);
- excessive keratinization of the skin epidermis, etc.

Examples of X-linked recessive disorders:

- red-green colour blindness,
- hemophilia,
- optic nerve atrophy,
- Duchenne muscular dystrophy, etc.

Holandric genes – ones located in Y-chromosomes that have no alleles in X-chromosome. They are inherited only from father to son.

Examples:

- hypertrichosis – ear hairiness (pilosity);
- syndactyly – membraneous fingers;
- muscle force genes;
- some height genes;
- some histoin compatibility antigens genes.

Genes defined sex characters ale located not only in sex chromosomes. There are characters the genes of which may stay in autosomes or sex chromosomes of both sexes but they are expressed only in one of them. Such characters are named **limited by sex.** For instance, voice timbre in man is a good example of such characters. Baritone, bass, tenors are expressed in men but these characters are determined by autrosomic genes both in men and in women.

At last, **characters dependent from sex –** the characters determined by autosomic genes in men and women but their dominance is dependent from the sex hormones. Examples:

baldness (its gene is dominant its recessive allele determine normal hair);
gout (podagra) (male sex hormone increases its expression more than female ones).

1st level tests

(one correct answer)

1. Extra hair on the ear (hypertrichosis) is determined by a gene which located in Y chromosome. This characters in inherited by the male line. What probability of birth the son with such character:

A. 75 %
B. 0 %
C. 25 %
D. 35 %
E. 100 %.

2. The hypoplasia of the teeth enamel is determined by a dominant gene in X-chromosome. A mother has a normal enamel of teeth but father has a hypoplasia of enamel. This anomaly can be present at:

A. All sons
B. All children
C. Only daughters
D. Half of daughters
E. Half of sons.

3. Large size of teeth is a character dependent on a gene localized in Y-chromosome. A mother has teeth with normal size, her son is large. What is the probability of a son with this anomaly being born in this family?

A. 100 %
B. 75 %
C. 50 %
D. 25%

E. 12.5 %.

4. New-born boy has a dry skin which covered by the thick layer of scale. Medical research of the genealogy of this family is revealed that this sign is observed in all generations only for men. What from the following biological statements shows up in this case?

A. Law of independent inheritance of the characters
B. Law of uniformity
C. Law of segregation
D. Sex-linked inheritance
E. Linked inheritance of the genes.

5. Proband, his three sons, brother and father has a syndactyly. His sisters and two daughters do not have this character. This character belongs to the:

A. Autosomal-recessive
B. Autosomal-dominant
C. Holandric
D. X-linked dominant
E. X-linked recessive.

6. To the medical consultation the married couples have appealed with a question about probability of a child birth with hemophilia. The married couples are healthy, but the father of wife is sick with hemophilia. It is possible to be sick in this family:

A. Half of sons
B. Sons and daughters
C. Only daughters
D. Half of daughters
E. All children.

7. Hypertrichosis is a Y-linked character. A father has this character but mother is healthy. Define the probability of birth in this family the child with hypertrichosis:

A. 50 %
B. 25 %
C. 12.5 %
D. 75 %
E. 100 %.

8. Study of genealogy of some family is revealed that hypertrichosis is observed in each generation only for men and inherited from a father to the son. Define the type of inheritance:

A. Y-linked
B. Autosomal-recessive
C. Autosomal-dominant
D. X-linked recessive
E. X-linked dominant.

9. A son was born in family, sick by hemophilia. Parents are healthy but his grandfather by the maternal line is sick. Define the type of inheritance

A. Y-linked
B. Autosomal-recessive
C. Autosomal-dominant
D. X-linked recessive
E. X-linked dominant.

10. Genealogical analysis of the family showed the traits of anomaly of teeth (dark enamel), this trait was passed from a mother equally to the daughters and sons, but from a father only to daughters. Define type of inheritance:

A. Y-linked
B. Autosomal-recessive

C. Autosomal-dominant
D. X-linked recessive
E. X-linked dominant.

11. Genealogical analysis of the family with the inherited pathology – disorder of the teeth enamel forming is revealed that a disease shows up in every generation. For women this anomaly is observed more often than for men. Sick men passes this trait only to the daughters. What type of inheritance takes place in this case:
A. Y-linked
B. Autosomal-recessive
C. Autosomal-dominant
D. X-linked recessive
E. X-linked dominant.

12. Frequency of the crossing-over is measured in such units:
A. Percent
B. Nanometers
C. Morganids
D. Units of crossing
E. Centigram.

13. Numbers of linked groups of genes in the organisms of every biological kind is equal to the:
A. Haploid set of chromosomes
B. Diploid set of chromosomes
C. Number of pairs of allelic genes
D. Numbers of gonosomes
E. Number of sexual chromosomes.

14. Holandric characters are passed through the generation from the:
A. Father to all daughters
B. Mother to the sons
C. Father to all sons
D. Mother to all sons and daughters
E. Mother only to daughters.

15. Determine the holandric character:
A. Presence of freckles
B. Rh+ factor
C. Daltonism
D. Hemophilia
E. Hypertrichosis.

16. Determine the character limited by sex:
A. Presence of freckles
B. Rh+ factor
C. Daltonism
D. Hemophilia
E. Low voice timbre.

17. Determine the character depended on sex:
A. Presence of freckles
B. Baldness
C. Daltonism
D. Hemophilia
E. Hypertrichosis.

18. Name the period of ontogenesis where human genetic sex is determined:
A. During embryogenesis
B. During the sexual maturation

C. During gametogenesis
D. During fertilization
E. During blastogenesis.

19. Name a scientist who has determined that genes localized in one chromosomes is linked:
A. T. Schwann
B. G. Mendel
C. T. Levitsky
D. T. Morgan
E. W. Johanssen.

2nd level tests

1. How is it possible to explain segregation by human sex in a ratio 1: 1?
2. How many types of gametes do the homogametic sex forms:
a) one type
b) two types
c) many types
d) four types.
3. How many types of gametes do the heterogametic sex forms:
a) one type
b) two types
c) many types
d) four types.
4. What of mentioned characters are holandric ones?
a) hypertrichosis (cochlear hairiness)
b) haemophilia
c) syndactyly of the big toe and fore toe
d) dark hair
e) blood groups according to the ABO system.
5. What characters mentioned are inherited depending on the sex?
a) haemophilia
b) baldness
c) color darkness
d) podagra.
6. What characters mentioned are inherited as linked with the sex?
a) primary sex characters
b) secondary sex characters
c) somatic characters
d) determined by autosomic genes
e) determined by genes located in sex chromosomes.
7. Genes encoding two characters are located in:
a) In non-homological chromosomes
b) In one X-chromosome
c) In one autosome.
8. What from the following variants do belong sex-linked inheritance:
a) genes located in homological areas of X- and У-chromosomes
b) genes located in non-homological area of X-chromosome
c) genes located in non-homological area of У-chromosome.
9. What features of transmission of holandric genes in generations:
a) passed to the sons from a mother
b) passed from a father to the daughters
c) passed to all posterity

d)passed from a father to the sons.

10. What features of transmission of x-linked genes in generations:

a) passed to all posterity

b) passed from a mother all posterity

c) passed through the line of heterogametes sex.

Tasks

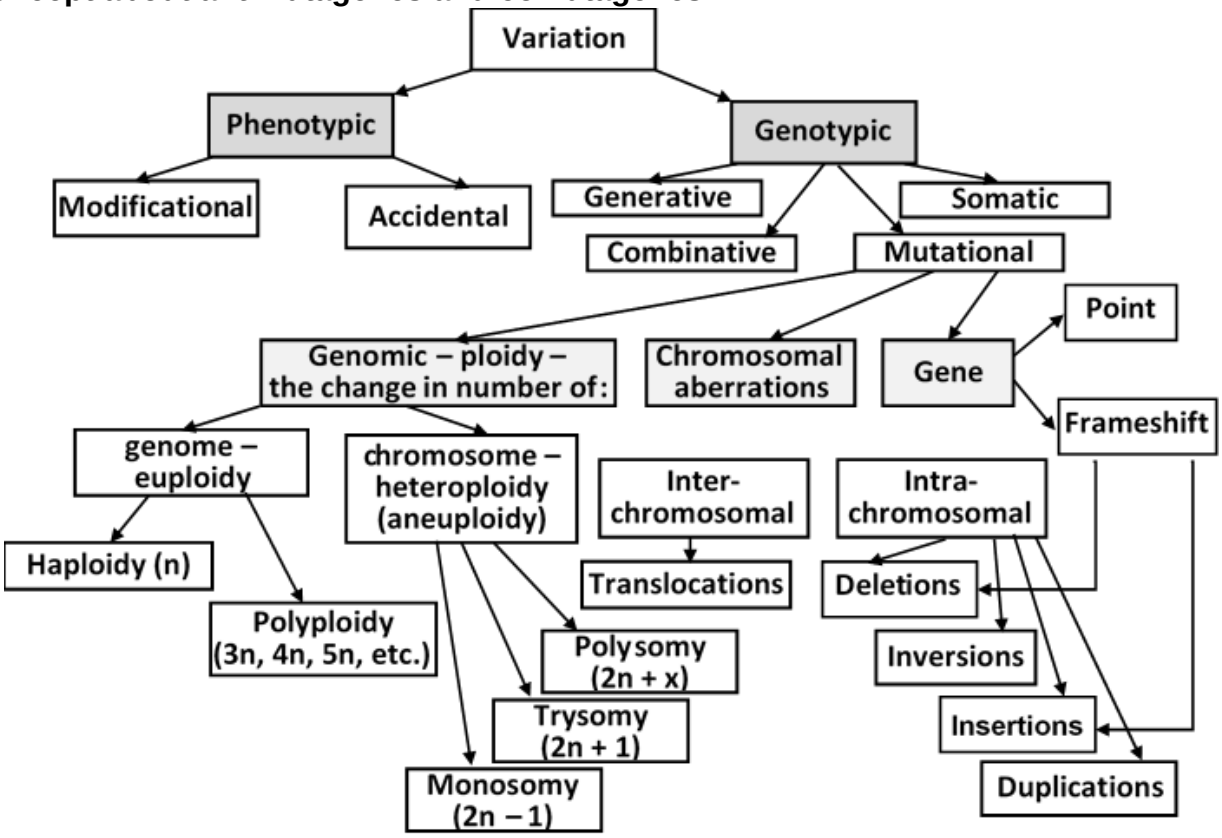
1. Woman suffering from color blindness got married to man with normal sight. What will be the color perception in sons and daughters of these parents?
2. What will be the genotypes and phenotypes of children that were born from the marriage of the man suffering from haemophilia and the woman suffering from color blindness? What will be the phenotypes of granddaughters and grandsons if the children will be married with healthy people (wife's relatives didn't suffer from haemophilia)?
3. The sweat-secreting glands absence in an in individual is a recessive character linked with X-chromosome, albinism is an autosomal-recessive character. In a healthy married couple the sons was born with both of diseases. Indicate possible parents' genotypes. What a possibility of existence such anomalies in second son? What a possibility of a healthy child birth?
4. Enamel hypoplasy in human is inherited as X-linked character (dominant one). The parents in the family are suffering from this anomaly and the son was born with normal tooth. What may be the other son's phenotype?
5. Hypertrichosis (excessive hairiness) is transmitted through Y-chromosome. What a possibility of birth a child with hairiness of cochlea if this character is expressed in father?
6. Tooth enamel darkening is determined by two dominant genes one of which is located in autosome and the other – in X-chromosome. In a parent's family with dark tooth a girl and a boy with normal tooth color were born. Indicate the possibility of birth of next child in this family also without disorder if dark mother's tooth are determined by the gene X-linked and father's dark tooth – by autosomic gene. Write down the genotypes of healthy people.
7. One of rickets form resistant as for calcipherols (vit. D) is determined by dominant X-linked gene. Determine the possibility of birth of ill children in a family where mother was suffering from such rickets form.
8. Right-handed woman the father of which was left-handed person and was suffered from haemophilia, got married to healthy right-handed man. What a possibility that in the family healthy left-handed child will be born?
9. Recessive haemophilia gene (h) and recessive gene of color blindness (a) in human are located in X-chromosome at the distance of 9.8 morganides. What gametes types and in what quantity forme the individuals having such genotypes?

$$\frac{X^{AH}}{X^{ah}}$$

$$\frac{X^{ah}}{Y}$$

TOPIC: Human variability as a property of life and a genetic phenomenon

Variation: forms and expression of an organism level: phenotypical and genotypic variation. Law of homological rows of variation, its practical value. Modifications and norm of reaction. Statistical laws of modificational variation. Combinative variation, its sources. Mutational human variation, phenotypical expression. Classification of mutations: genome, chromosomal aberrations, gene. Natural mutagenesis, induced mutagenesis. Mutagenes: physical, chemical, biological. Genetic monitoring. Genetic contamination of environment hazard. Concept about antimutagenes and comutagenes.



Variation is the tendency or potential of an organism to vary (Wagner and Altenberg, 1996);

is the ability of living organisms to acquire new features in the process of individual development.

Variation is realized at the cellular and organismal levels in the process of organism development.

By the ability to inheritance it is distinguished phenotypic (not inherited) and genotypic (can be inherited) variation.

Phenotypic variation – change of phenotype under the influence of external factors, which do not lead to genotype disturbance.

Genotypic variation is the difference in DNA among individuals due to recombination or mutation of genetical material on the different levels of its organization (karyotype, chromosomes, genotype).

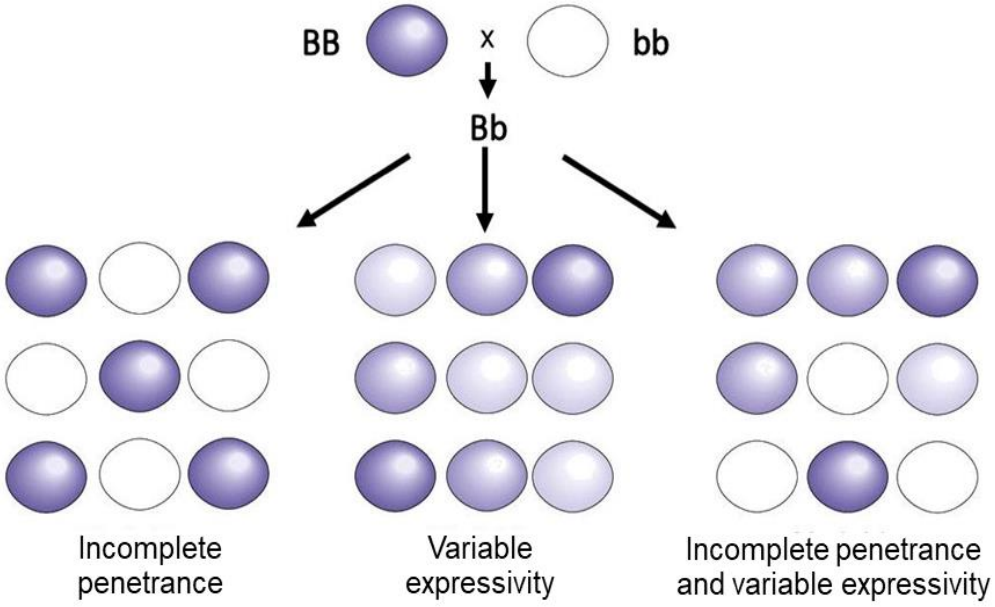
Norm of reaction (W. Johannsen, 1909) – hereditarily fixed limits of modification variability of a particular trait (or whole genotype) under fluctuations of environmental conditions (range of variability within the limits of its depending on environmental conditions the same genotype is capable to give different phenotypes). The norm of reaction is inherited (for some features – broad, for others – narrow).

Penetrance (N. Timofeev-Ressovsky, 1927) is the frequency of phenotypic manifestation of a gene allele in different individuals of a population. Penetrance is characterized by a ratio of individuals at which the given gene is shown in a phenotype, to the general number of individuals at which the gene could be shown.

There is a *complete P.* (allele manifested in all individuals who have it in genotype) and *incomplete P.* (allele is phenotypically not manifested in the part of individuals that have it in genotype). If, for example, the mutant gene is shown at all individuals, speak about complete (100%) penetrance, in other cases – about incomplete and specify percent of individuals at which the gene is shown. So, inheritance of groups of blood in humans on system ABO has absolute (100%) penetrance, diseases: epilepsy – 67%, a diabetes – 65%, a congenital dislocation of a hip – 20%, etc.

Expressivity (N. Timofeev-Ressovsky, 1927) – the degree of phenotypic manifestation of the same gene allele in different individuals. In the absence of variability of the trait controlled by this allele of the gene E. is constant, in cases of different variant of the trait E. is called variable. Reasons: 1) influence of different environmental conditions; 2) modifying effect of other genes in the same environmental conditions; 3) dependence on the combination of certain genes in the genotype.

There are two forms of variation – hereditary and not hereditary. First of them is connected to change of a genotype, the second – of a phenotype.



Phenotypic (nonhereditary) variation

Modifications are phenotypic changes which arise under influence of conditions of environment. Scope of modificational variation is limited by norm of reaction. Modification changes of an attribute are not inherited, but their range, norm of reaction, are genetically caused and inherited. Modification changes do not cause changes of a genotype. Modificational variation, as a rule, has expedient character. It answers conditions of dwelling, is adaptive.

Under influence of external conditions phenotypical growth of animals and plants, their weight, color, etc. change. Occurrence of modification is connected by conditions of environment which influence on enzymatic reactions which proceed in an organism and definitely change their course.

As examples of modification variability at the person can serve amplification of pigmentation under influence of ultra-violet irradiation, development of muscular and bone systems as a result of physical exercises, etc.

Phenocopy (R. Goldschmidt, 1935) is a non-hereditary change of phenotype

(modifications), which resembles some changes of genotype in mutations and influenced by environmental conditions (physical, chemical or biological factors) in genetically normal organism during its individual development. Some diseases (e.g. toxoplasmosis) which were transferred by mother during pregnancy, also can become the reason of phenocopies of some hereditary diseases and developmental anomalies of newborns. Presence of phenocopies complicates statement of the diagnosis, therefore the doctor should know, that phenocopies are not inherited.

Accidental phenotypic variation – presented by *morphosis* – non-hereditary changes of the phenotype, which occur under the influence of extreme environmental factors, are not adaptive and not reversible. Examples: scars, tattoos, ethno-cultural body modifications.

Genotypic (hereditary) variation

Combinative variation – is a type of hereditary (genotypic) variation, which is based on recombination of genetical material during sexual reproduction (gene reshuffling) by ways of genetic recombination:

1) independent assortment of homologous chromosomes during meiosis I and nonidentical sister chromatids during meiosis II (inter-chromosomal recombination);

2) crossing over – exchange of fragments between homologous chromosomes during prophase I of meiosis (intra-chromosomal recombination);

3) random fusion of gametes during fertilization (genomic recombination).

Mutational variation – is a type of hereditary (genotypic) variation, which is caused by violation of hereditary material on all levels of its organization (genomic, chromosomal, gene).

Genes thus do not change, but arising new combinations of genes result in occurrence of organisms with other genotype and a phenotype. Combinative variation is widely distributed in nature. One of its example is heterosis.

Heterosis (modification, transformation), or «hybrid force», can be observed in the first generation at hybridization between representatives of different kinds or sorts. It is shown in the form of the increased viability, increase in growth and other features.

Mutational variation

Mutation (Hugo de Fries, 1901) (from Latin *mutatio* – change) – are sudden, natural or artificially induced heritable changes of genetic material, leading to a change in certain signs of the body.

Mutations among all classes of animals, plants and viruses are now known. There are many human mutations. Mutations cause polymorphism of human populations: presence of different groups of blood, different pigmentation of a skin, hair, color of eyes, the form of a nose, ears, chin, etc. As a result of mutations appear and hereditary anomalies in a structure of a body and hereditary diseases of the person. Evolution is connected to mutational variation – process of formation of new kinds, sorts and breeds.

On character of changes of the genetic apparatus they distinguish mutations which are caused by:

a) Change of quantity of chromosomes (genome);

b) Change of structure of chromosomes (chromosomal aberrations);

c) Change of molecular structure of a gene (gene, or point mutations).

Genome variation. Mutations which are caused by change of quantity of chromosomes, name ***genomic.***

Polyploidy – increase diploid number of chromosomes by addition of the whole chromosomal sets as a result of disturbance of meiosis.

Sexual cells have haploid set of chromosomes (n), but zygote and all somatic cells

have diploid set (2n). In polyploid forms the increasing of chromosomes' number, multiple haploid set is observed: 3n – triploid, 4n – tetraploid, 5n – pentaploid ect. Probably, evolution of some floral plants went by polyploidy. Cultural plants in the majority are polyplods. In selection practice with the purpose of getting polyploids on plants operate with critical temperatures, radiation, chemical substances (the most widespread alkaloid colchicin).

Forms which result from increase in quantity of chromosomes of one genome, refer to *autopolyploidy*. Other form of polyploidy – *allopolyploidy* (increase in quantity of chromosomes of genomes from two different kinds of organisms) is known also.

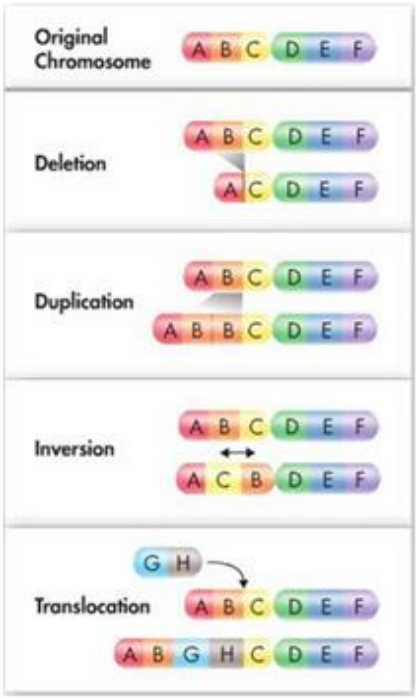
Aneuploidy is change of the chromosome number unequal to the haploid set.

Increasing on one homological chromosome (on the given pair), refers to trisomy. If it is observed trisomy on one chromosome such organism named trisomic and its chromosomal set will be 2n+1. Trisomy can be on any of chromosomes and even on several. Double trisomic has a set of chromosomes 2n + 2, threefold 2n + 3 etc.

It is known trisomy of plants and animals, and also at the person (syndrome of Down, Patau, Edwards for example). Trisomics are not viable more often, as they have a number of pathological changes (lacks of development) which are incompatible with life.

Loss of one chromosome from pair in diploid set, refers to monosomy, and an organism – monosomic; its karyotype – 2n-1. Absence of two different chromosomes the organism will be double monosomic (2n-2). If from diploid set drop out both homological chromosomes, the organism refers to zerosomic. Such organisms are not viable.

So heteroploidy results in changes in a structure and decreases viability of an organism. Such disturbance of the balanced set of chromosomes cause in the human chromosomal diseases.



Chromosomal aberrations result from reorganization of chromosomes as consequence of break of chromosomes with formation of their fragments which then incorporate, but thus the normal structure of a chromosome is not restored. There are such kinds of chromosomal aberrations: intrachromosomal: deficiency (deletion), doubling (duplication), inversions; interchromosomal: translocation.

Deletions arise owing to loss by a chromosome of this or that site. Deletions in an average part of a chromosome – lethal, loss of insignificant sites causes change of hereditary properties – chromosomal diseases.

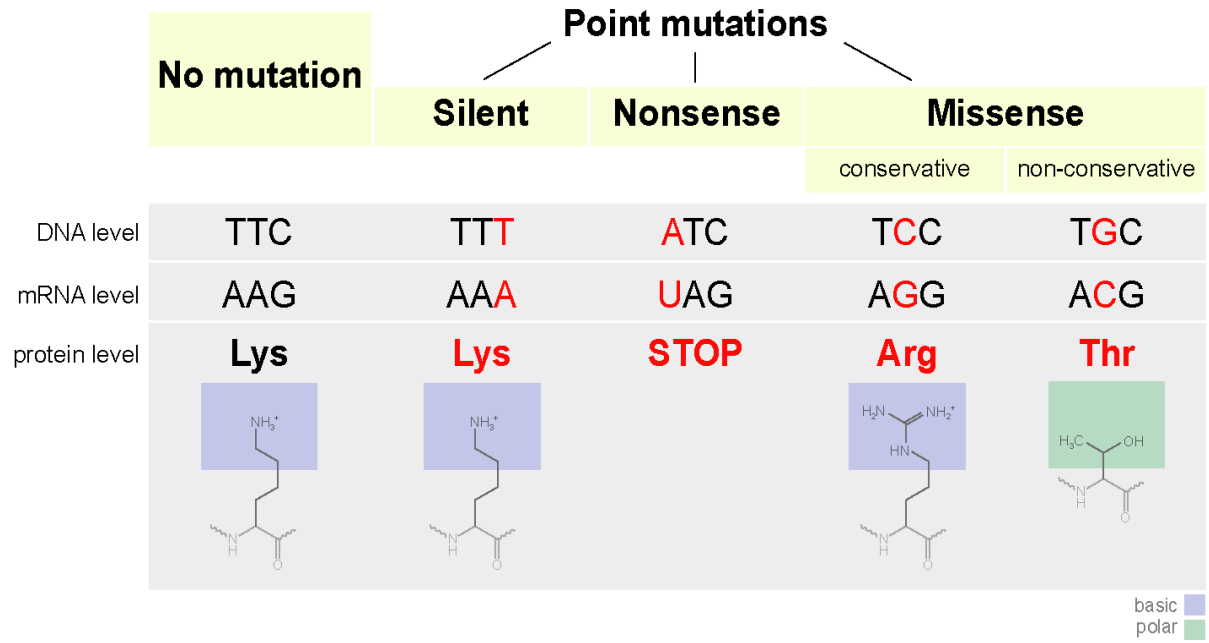
Duplications is connected with inclusion of extra duplicating piece of a chromosome. It also conducts to occurrence of new attributes.

Inversions are observed during break of chromosomes and turn of the torn off site on 180°. If break has taken place in one place, the fragment is attached to a chromosome by the opposite end if in two places the average fragment is turning and attached to places of break by the opposite ends, it results in occurrence of new groups of linking.

Translocations arise when the site of a chromosome from one pair is attached to non-homological chromosome, i.e. to a chromosome from other pair. Translocation for one of chromosomes (21st) it is known at the person; it can cause illness of Down. The majority of large chromosomal aberrations in gametes and zygotes of the person results in heavy anomalies and developmental anomalies, to destruction of gametes, zygotes, embryos.

Gene mutations – change structure of the gene. Mutations can change sites of

molecule DNA of different length. The least site, which change results in occurrence of a mutation, refers to muton (one pair of nucleotides). Change of nucleotides sequence in DNA predetermines change in sequence of triplets and eventually changes a genetic code. Infringement in structure DNK result in mutations only when there is no reparation.



Somatic and generative mutations

Mutations arise in any cells therefore them divide on somatic and generative. Biological importance is unequal and also connected to way of reproduction of organisms.

During the division of a somatic mutant cell new properties are transferred to the their offsprings. If in a plant the mutation has arisen in a cell in which the bud is formed, and then sprout will get new properties. So, on a bush of a black currant the twig with white berries can appear. During the vegetative reproduction the new attribute which has arisen as a result of a mutation of a somatic cell is kept in their offsprings.

During the sexual reproduction attributes which appear as a result of somatic cells mutations are not transferred to the offsprings. However in individual development they can influence on formation of an attribute. If in earlier ontogenesis the mutations take place the result of this can be larger, part of tissue with this mutation. Such individuals refer to mosaics. For example, mosaics are people which have different colour of the right and left eyes or animals which have special colour the stains of other colour on their body can appear ect. It is considered that somatic mutations which influence on metabolism are one of the reasons of ageing and malignant tumor.

If the mutation occurs in cells from which gametes develops the mutation will be shown in the nearest or the following generations. Researches show that the majority of mutations harmful to an organism. It speaks that functioning of each body is balanced under the attitude both to other bodies and to an environment. Infringement of existing balance usually conducts to decrease in ability to live and destruction of an organism. Mutations which reduce viability is named as **semilethal.** Mutations incompatible with life are named as ***lethal*** (Latin *letalis* – fatal). Nevertheless the certain part of mutations can be useful. Such mutations are a material for progressive evolution.

Mutagenesis – process of occurrence of inherited changes.

Depending on the reasons causing mutations, distinguish spontaneous and induced mutagenesis.

Spontaneous mutagenesis – process of occurrence of hereditary material changes in alive organisms in natural environment of their existence. The principal causes resulting in spontaneous mutations the following:

- mistakes of DNA reduplications (result in replacement of the bases);
- mistakes of DNA recombination (change number of nucleotides);
- mistakes of DNA reparation (fix the arisen changes);
- presence of special genes in genome – **mutators** which induce mutagenesis;
- accumulation in the cells some chemical substances which influence is harmful on genetic apparatus during the life activity.

Induced mutagenesis is an artificial increase of mutations frequency under influence of mutagenes. **Mutagenes** – the factors which influence on organism results on mutations occurrence.

Classification of mutagenes: physical (all kinds of radiations, X-rays, ultra-violet radiations, high and low temperatures, etc.), chemical (nitrogenous acid, analogues of the nitrogenous bases, etc.), biological (viruses, special toxins, etc).

The factors lowering frequency of a mutation. Mutations only in unusual cases reach a final stage of the realization. During evolution the nature has created a number of mechanisms which reduce number of phenotypical manifestations of mutations:

- degeneracy of genetic code (the mutation frequently replaces one triplet with another which codes the same amino acid);
- diploidy of organism (mutant genes frequently recessive, one attribute codes two genes and if an organism is heterozygous recessive gene can not be shown);
- reparation (restoration of damaged mutagenes and DNA sites).

The law of homologous lines of hereditary forms of variability (N.I. Vavilov, 1920)

Genetically close kinds and species are characterized by similar lines of hereditary variability so, that, knowing a line of forms within the limits of one kind it is possible to provide existence of parallel forms in other kinds and sorts. The genetically closer the organism in the general common system of sorts and kinds, the is more full similarity in the ranks of their variability.

N.I. Vavilov's law has determined the formula:

G1 (a + b + c … … …),

G2 (a + b + c … … …),

G3 (a + b + c … … …),

Where G – different kinds (species) of organisms,

a, b, c – different variable attributes.

The law of homologous lines in hereditary variability has the direct attitude to studying human hereditary diseases. The question of treatment and prevention of hereditary diseases cannot be solved without research on animals with hereditary anomalies which are similar to the person one.

According to N.I. Vavilov's law, phenotypes which are similar to the human hereditary diseases can be observed on animals. Really, many pathological conditions which are revealed in animals, can be models of human hereditary diseases. So some dogs have the hemophilia which is X-linked. Hereditary deafness exists in guinea-pigs, mice and dogs. Hereditary diseases of metabolism such as an obesity and diabetes can have the mice. In spite of already known mutations, by influence of mutagen factors, it is possible to receive many new anomalies from the laboratory animals and study them in experiment.

1st level tests

(one correct answer)

1.Different disorders in the processes of mitosis result the formation of cells with different karyotypes that is one of the mechanisms of somatic aneuploidy. What the name has got such mitosis:

A. Genome
B. Anomaly
C. Chromosomal
D. Pathological
E. Gene.

2. Healthy parents have a child with Down's syndrome (karyotype 46 chromosomes) but one of chromosomes from group D had elongated short shoulder. It was found out the unbalanced translocation of 21st chromosome. What form of variation do such case belongs to?
A. Recombination
B. Genome mutation
C. Modification
D. Gene mutation
E. Chromosomal mutation.

3. Patient with a sickle-cell anemia which developed as a result of replacement of glutamine asids by valine in the molecule of haemoglobin. What mutation did the pathology have:
A. Genome
B. Chromosome
C. Gene
D. Deletion
E. Duplication.

4. What type of mutation is possible to name for some organism with the following trisomy: 13th chromosome (syndrome of Patau), 18th chromosome (syndrome of Edwards) and 21th chromosome (Down's syndrome):
A. Phenocopy
B. Aneuploidy autosomes
C. Chromosomal aberrations
D. Aneuploidy gonosomes
E. Somatic mutations.

5. Dietotherapy can prevent the clinical expression of inherited illnesses. What form of variation is caused by a dietotherapy:
A. Modification
B. Gene mutation
C. Chromosomal mutation
D. Teratogenic
E. Genome mutation.

6. In a cell under the influence of mutagene the spindle of division has broke partly. Karyotyping of metaphase plate has revealed presence 49 chromosomes. This mutation is named:
A. Mosaicism
B. Polyploidy
C. Heteroploidy
D. Triploidy
E. Duplication.

7. A patient has a trisomy by 21st chromosome pair among the somatic cell with normal karyotype. What is the mechanism of this mutation:
A. Nondisjunction of 21 pair in spermatogenesis
B. Nondisjunction of 21 pair in ovogenesis
C. Nondisjunction of 21 pair in mitosis
D. Chromosomal aberration
E. Gene mutation.

8. It is known that gene which responsible for development of anomalous form of teeth is dominant and not sex-linked. Man has large teeth that growing forward. His brother and sister have normal teeth by form and position. What variation is observed in this family:

A. Somatic mutation
B. Generative mutation
C. Gene mutation
D. Chromosomal mutation
E. Cytoplasmic mutation.

9. As a result of damage of genetic apparatus of sexual cells can be:

A. Inherited diseases
B. Malignant tumors
C. Autoimmune processes
D. Aging
E. Inhibition of apoptosis.

10. Cytogenetic research of the patient with leucosis the loss of small area of 21th chromosome was found. Such mutation is named as:

A. Deletion
B. Translocation
C. Duplication
D. Inversion
E. Polyploidy.

11.The young married couples gave birth a child with the eyes of different colors. How do such variation name:

A. Somatic mutation
B. Generative mutation
C. Mutational variation
D. Combinative variation
E. Cytoplasmic mutation.

12. Otosclerosis (pathological trait that shows up as the loss of hearing) is determined by a autosomal-dominant gene. Penetrance of gene is 50%. Which probability of sick children birth at the healthy heterozygous carriers of this gene:

A. 37,5 %
B. 75 %
C. 100 %
D. 50 %
E. 0 % .

13. There is a severe limit of time staying on a height over 800 meters above a sea level without oxygen bulbs exists for the humans. What is the limiting factor for life in this case:

A. Temperature
B. Level of ultraviolet radiation
C. Level of humidity
D. Pressure of oxygen
E. Gravitation.

14. Anaphase of mitosis has stopped by a colchicine that blocks divergence of chromosomes to the opposite poles. What type of mutation can be applied in this case:

A. Polyploidy
B. Heteroploidy
C. Deletion
D. Duplication
E. Translocation.

15.Predilection of diabetes is caused by autosomal recessive gene. This gene shows up

only for 30% homozygous individuals. This partial expression is the example of the following property of gene:

A. Mutation
B. Penetrance
C. Heredity
D. Expressivity
E. Polymery.

16. For the humans the same genotype expresses the development of disease with the different degrees of phenotypes. Degree of a trait during realization of genotype in the different limits of environment is named as:

A. Mutation
B. Penetrance
C. Heredity
D. Expressivity
E. Polymery.

17. One of forms of rachitis is inherited by a dominant type. Men and women are sick. This disease is a result of:

A. Recombination
B. Genome mutation
C. Modification
D. Gene mutation
E. Chromosomal mutation.

18. Albinism is observed in all classes of vertebrates. This inherited pathology is observes also for a human and determine by autosomal-recessive gene. Define the law which determines the presence of albinism for the humans and for the representatives of all classes of vertebrates:

A. The law of homologous lines of hereditary forms of variability
B. Biogenetic law of Gekkel
C. 1st law of Mendel
D. 2nd law of Mendel
E. Linked inheritance by T. Morgan.

19. Parents of 5-years sick girl have addressed to a medical consulting. Karyotype researches revealed 46 chromosomes in her karyotype but one chromosomes from 15th pair was longer than usual because it was joined form 21st chromosome pairs. What type of mutation takes place in such case:

A. Deletion
B. Duplication
C. Translocation
D. Polyploidy
E. Heteroploidy.

20. Genetically healthy woman during her pregnancy was sick by a viral german measles. The deaf child was born with a cleft palate as a result of:

A. Phenocopy
B. Combinative variation
C. Genome mutation
D. Gene mutation
E. Chromosomal mutation.

21. Penetrance is:

A. Property of genotype to provide variation of a character depending on changes of environment limits
B. Frequency of phenotypical expression of gene in the population of individuals that have this gene in genotype

C. Degree of phenotypical expression of character which controlled by this gene
D. Interaction of non-allelic genes
E. Plural alleles.

22. Expressivity is:

A. Property of genotype to provide variation of a character depending on changes of environment limits
B. Frequency of phenotypical expression of gene in population of individuals that have this gene in genotype
C. Degree of phenotypical expression of character which controlled by this gene
D. Interaction of non-allelic genes
E. Plural alleles.

23. Sickle-cell anemia is caused by the following type of variability:

A. Modification
B. Mutational
C. Combinative
D. Ontogenetic
E. Correlative.

24. Tetracycline taking in the first half of pregnancy causes abnormalities of fetus organs and systems, including tooth hypoplasia and alteration of their colour. What type of variability is the child's disease related to?

A. Modification
B. Combinative
C. Mutational
D. Hereditary
E. Recombinant.

25. In a cell the mutation of the first exon of structural gene took place. The number of nucleotide pairs has decreased – 250 pairs instead of 290. Determine the type of mutation:

A. Inversion
B. Deletion
C. Duplication
D. Translocation
E. Nonsense-mutation.

26. A woman got infected with rubella during pregnancy. The child was born with malformations, namely cleft lip and palate. The child's genotype is normal. These malformations are a manifestation of:

A. Modification variability
B. Polyploidies
C. Combinatory variability
D. Chromosomal mutations
E. Aneuploidies.

27. In some regions of South Africa there is a spread sickle-shaped cell anemia, in which erythrocytes have shape of a sickle as a result of substitution of glutamin by valine in the hemoglobin molecule. What is the cause of this disease?

A. Transduction
B. Disturbance of mechanisms of genetic information realization
C. Crossingover
D. Genomic mutations
E. Gene mutation.

28. 46 chromosomes were revealed on karyotype examination of the 5-year-old girl. One of the 15th pair of chromosomes is longer than usual due to connected chromosome from the 21 pair. What type of mutation does this girl have?

A. Translocation

B. Deletion
C. Inversion
D. Insufficiency
E. Duplication.

29. A cell at the stage of mitosis anaphase was stimulated by colchicine that inhibits chromosome separation to the poles. What type of mutation will be caused?

A. Polyploidy
B. Inversion
C. Deletion
D. Duplication
E. Translocation.

30. An alcoholic woman gave birth to a girl with mental and physical developmental lag. Doctors diagnosed the girl with fetal alcohol syndrome. What effect is the cause of the girl's state?

A. Malignization
B. Mutagenic
C. Teratogenic
D. Carcinogenic
E. Mechanic.

31. A mother had taken synthetic hormones during pregnancy. Her daughter was born with hirsutism formally resembling of adrenal syndrome. Such manifestation of variability is called:

A. Phenocopy
B. Mutation
C. Recombination
D. Heterosis
E. Replication.

Situational tasks

1. To the genetic consultation the woman came for advice because of 3 children birth from two marriages with plural congenital developmental anomalies. The result of cytogenetical researches there are 45 chromosomes have been found. Her karyotype is 45 XX, t (13). Karyotypes of parents and sibs of women were normal. The woman was the carrier of translocation between homologous chromosomes in 13 pair which has arisen de novo. It was offered to this woman to refuse the further birth. She has not accepted advice and one year later has given birth a child with the plural anomalies incompatible with a life.

Determine types of gametes which form proband and her husband (genotypically healthy). Is it possible for her to have a healthy child? Give the explanation.

2. Diphyllobothriasis patient has an avitaminosis B-12. What type of variability has observed in such case?

3. DNA molecule has the following structure: ATGCCAA. After mutation the nucleotides sequence has changed on ATCCCAA. What kind of a mutation this change belongs?

4. In DNA molecule the nucleotides sequence is: AATGCATTGCGAAGC. Sixth nucleotide from left side has dropped out. What kind of mutation?

5. The participants of liquidation of the Chernobyl accident have radiation disease. Name the kind of variation. Is it possible to be inherited the radiation disease?

TOPIC: Bases of medical genetics. Methods of study of human heredity

Man as specific object of genetic analysis. Methods of study of human heredity. Genealogical method. Rules of pedigree analysis. Genetic analysis of genealogies. Twins method. Determination of influence of genotype and environment on the expression of pathological human characters. Dermatoglyphics and immunological methods of hybridization of somatic cells.

The basic laws of a heredity and variability were open due to application hybrydological method of the genetic analysis (G. Mendel, 1865). To the person as to object of the genetic researches, the given method cannot be applied. First, for the person cannot be applied the directed crossing is artificial. Second, small number of descendants makes impossible use of the statistical analysis. Thirdly, slow alternation of generations (on the average in 25 years) enables to observe for a life change only 3–4 generations.

All listed features have led scientists to development of specific methods of studying of genetics of the person, and modern experimental methods have allowed to establish groups of coupling almost on each chromosome, to decipher a genetic code. Considerable help in studying genetics of multifactorial attributes the biometric approach (gives F. Galton, 1865) which opportunities have increased due to application of modern computer technical equipment.

The following methods are applied to study human genetics:

- Genealogical method
- Twins method
- Dermathoglyphic method
- Cytogenic method
- Biochemical method
- Immunological method
- Population-statistical method
- Methods of molecular biology and genetic engineering

The genealogical method (F. Galton, 1865) is based on researching of any attribute in a number of generations with the indication of related connections between members of a family tree. Genealogy, in wide understanding of a word – a family tree of the person.

Data gathering begins with **a proband** – persons for whom the family tree (is made by him (her) can be the sick or healthy person – the carrier of any attribute). Brothers and sisters a proband refer to **siblings**.

The method includes two stages: gathering of data on families, drawing up of a family tree and the genealogic analysis.

For drawing up of a family tree make short records about each member of a family tree with the exact indication of his(her) related connections in relation to a proband (anamnesis).

Then do graphic representations of a family tree; for drawing up of the circuit standard symbols are accepted.

Drawing up of a family tree of generation it is possible to designate in the Roman figures from top to down (to the left of a family tree). The posterity of one generation (sibs) settles down in one horizontal number (line) by way of a birth (from left to right). Within the limits of one generation each member of a family tree is designated by the Arabian figures. Each member of a family tree can be designated by the corresponding code, for example II – 5, III – 7.

The genealogic method will be more informative if there is more than authentic data on presence of concrete attributes at relatives of proband. At gathering genealogic data and their analysis it is necessary to mean, that the attribute can be shown with different expressivity and incomplete penetrance.

After drawing up of a family tree the second stage – the genealogic analysis which

purpose is the establishment of genetic laws begins.

The genealogic method allows to establish:

1. Character of inheritance of an attribute;
2. Type of inheritance (A-D, A-R, X-D, X-R);
3. Zygous of proband and other members of a family tree;
4. Probability of occurrence of an attribute of proband, his (her) future children;
5. Expressivity and penetrance of an attribute (at the analysis of many family trees to identical attributes);
6. On what line (father or mother) the attribute is transferred.

Patterns of Mendelian inheritance:

1. Autosomal-Dominant
2. Autosomal-Recessive
3. X-Linked Dominant
4. X-Linked Recessive
5. Y-Linked

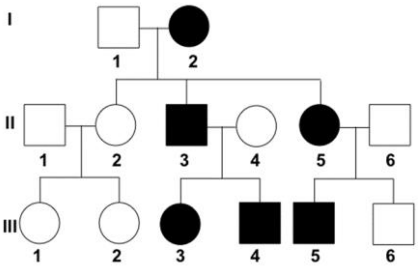
Among of human monogenic disorders ≈ 65% are autosomal dominant, ≈ 25% are autosomal recessive, ≈ 5% are X-linked.

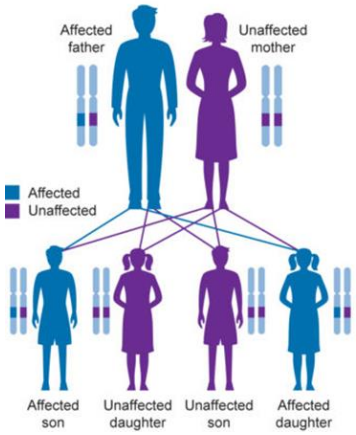
In case of revealing hereditary character of an attribute it is necessary to establish type of inheritance: dominant, recessive, X-linked.

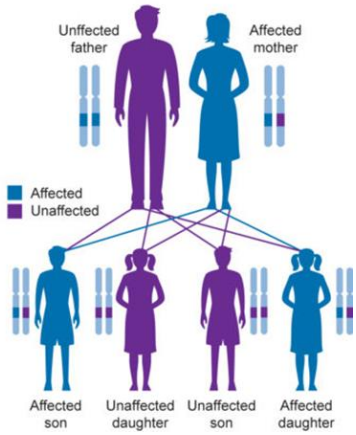
Attributes of the autosomal-dominant type of inheritance:

1. The attribute is observed in a family tree on a vertical (it is transferred from generation to generation).
2. Male and a female individuals can be sick equally.
3. One of parents of the sick child, as a rule, is sick.
4. The probability of display of an attribute at descendants makes 50%–100% (at heterozygosity of one of parents – 50 %, at heterozygosity of two parents – 75 %, at homozygosity of one of parents – 100 %).

Examples: polydactily, Marfan syndrome (spider man disease), Ehlers-Danlos syndrome, neurofibromatosis, achondroplasia.



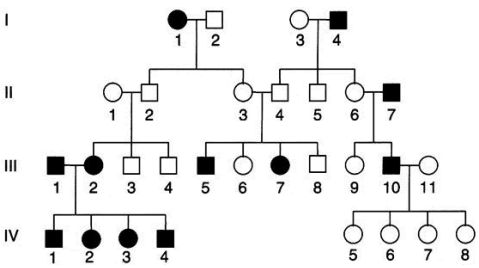


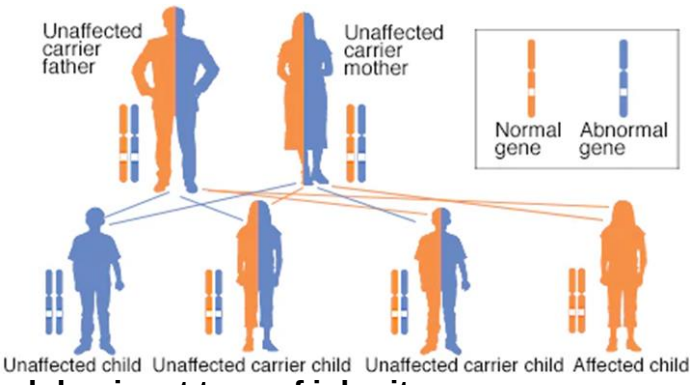


Attributes of the autosomal-recessive type of inheritance:

1. The pathological heredity is shown in a family tree across (for example, cousins).
2. Individuals of both sexes are sick.
3. Parents of the sick child are often phenotypically healthy, but they are heterozygous carriers of recessive gene.
4. The probability of a birth of the sick child makes 25 % (at heterozygosity of two parents).
5. The probability of display of a pathological attribute grows at consanguinity.

Examples: phenylketonuria, pigment xeroderma, cystic fibrosis, alcaptonuria, galactosemia.

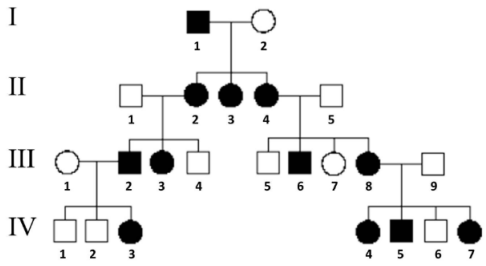


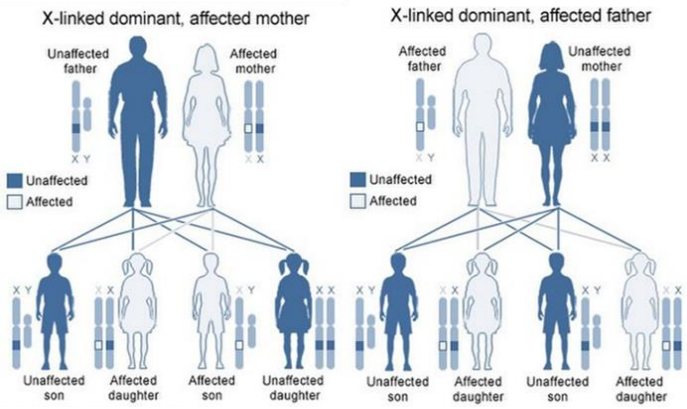


Attributes of the X-linked dominant type of inheritance:

1. The attribute is equally shown both at men and at women.
2. The attribute is shown in a heterozygous state at women, at men in hemizygous state.
3. One of parents of the sick child is sick.
4. Man transfers a mutant gene to all daughters.
5. The pathological heredity is traced and on a vertical, and across.

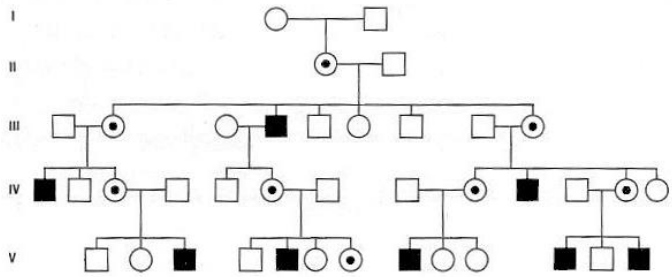
Examples: fragiles X syndrome, Rett syndrome, hypophosphatemic (vitamin D resistant) rickets, incontinentia pigmenti.

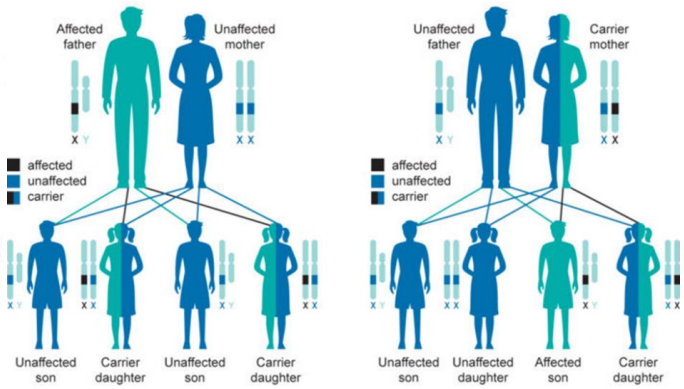




Attributes of the X-linked recessive type of inheritance:

1. The attribute is observed in a family tree across and verticals, frequently through generation, native sibs are sick, relatives on the mothers side (the uncle a proband).
2. Mainly males are sick. The pathological gene is shown in hemizygous state.
3. In family half of sons are sick, and half of daughters – heterozygous carriers of a mutant gene.
4. On the side of mother of the sick child there are sick relatives of a male.





Study of twins (F. Galton, 1876, G. Simens, 1924) – one of classical methods of studying of human genetics. Among twins allocate two groups: monozygotic twins (MZ) and dizygotic (DZ). For today on the average on everyone 100 sorts are necessary one birth of twins. Demographers have calculated, that on the Earth lives about 50 million pairs of twins. Approximately one third of all twins is

made MZ, and with two thirds – DZ. Study of twins enables to establish a role of a genotype and environment in display of an attribute.

If analyzed attributes are shown in both pairs twins with identical expressivity named **concordant** (Latin *concordre* – to agree, similar). Concordance is a percent in of similarity to researched attributes. Absence of an attribute at one of twins – **disconcordance**.

The analysis of inheritance of attributes of DZ twins allows to analyze other variant – influence of identical conditions of environment on phenotypical display of attributes at different genotypes.

For an establishment of influence of a genotype on display of an attribute use K. Holtsinger's formula, where H – factor of a heredity, AB – MZ twins, DB – DZ twins.

H = (% Similarities AB – % of similarity DB) / 100 % – % of similarity DB

When **H=1**, the attribute is completely defined by a genotype; when **H**=0, the determining role in display of an attribute makes with influence of environment. Factor **H** close to 0,5 gives approximately identical influence of a heredity and environment in formation of an attribute.

Influence of environment (C) is defined by the formula:

C = 100 % – H,

Dermatoglyphics (F. Galton, 1892) (ancient Greek: *derma* – skin, *glyph* – carving) is a study of configurations of epidermal ridges on certain body parts, namely:

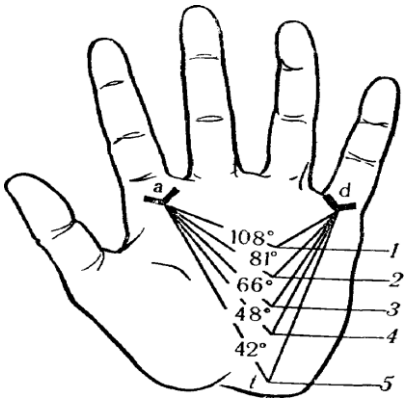
- fingers (dactyloscopy)
- palms (palmoscopy)
- soles and toes (plantoscopy).

As against other parts of a body here are available epidermal ledges – crests which form complex patterns. Patterns on fingers and palms, as well as a genotype of the person, are strictly individual. On the Earth there are no two people with identical figures on fingers (except of MZ twins).

Dermatoglyphic patterns begin to develop in the 10th week of gestation and are completed by the 24th week. At the same period the formation of nervous system takes place. Both papillary ridges and nervous system structures have common origin in ectoderm (the outer layer of the early embryo). That's why dermatoglyphic is a very useful link in diagnosing the genetic abnormalities (it is an express method, which doesn't require high-cost equipment).

Dactyloscopy. Crests on skin of fingers of hands correspond to papilla of derma therefore named also as papilla lines, the relief of these ledges repeats a layer of epidermis. Interpapilla deepenings form grooves. Full formation of details of a structure of tactile patterns comes to the end about six months then they remain constant up to the end of a life. Dermatoglyphics researches have great value in definition of twins' zygousity, in diagnostics of some hereditary diseases, in forensic medicine, in criminalistics for person's identification.

The main elements of finger skin relief are loops, whorles and arches. Their ratio may vary in patients with different chromosomal diseases: in Edwards and Kleinfelter syndromes the arches are prevail; in Down syndrome the loops are mostly observed; in Turner syndrome there are more loops and whorls.



The main elements of finger skin relief: 1 – whorles, 2 – loops, 3 – arches.

Palmoscopy. The relief of a palm is very difficult because of number of lines, small hills and palmlines. Central palm fossa surround six eminences – small pillows.

At the basis of the big finger – tenar, at opposite edge of a palm – hypotenar, against interfinger intervals is four interfingers small pillows. At the basis II, III, IV and V fingers are fingers threeradius – points in which converge three current papilla lines on different directions; them designate Latin letters and, b, with, d. Close to bracelet fold which separates a hand from a forearm, settles down main (axial) palm threeradius. If to line the lines from threeradius and d to t it is formed palm corner atd, in norm it does not exceed 57°, and at chromosomal diseases changes.

Corner *atd* in norm and in chromosomal diseases: 1 – syndrome of Patau; 2 – Down's syndrome; 3 – Turner's syndrome; 4 – norm; 5 – Kleinefelter's syndrome.

Population-statistical method (G. Hardy, W. Weinberg, 1908) allows to study: genetic structure of populations of people, frequency of genes in different populations. Usually carry out direct selective research of a part of a population or study archives of hospitals and other medical institutions, and also carry out interrogation of the population by questioning. The choice of a way depends on the purpose of research. Last stage will consist in the mathematical analysis of the received data.

In 1908, the English mathematician G. Hardi and the German physician W. Wainberg formulated the law of population genetics: ***Gene frequencies in ideal populations remain unchanged from generation to generation.***

The ratio of Hardy-Weinberg Law:

$p + q = 1$

$(p + q)^2 = p^2 + 2pq + q^2$, where

p – the frequency of the dominant allele of gene (A);

q – frequency of recessive allele (a).

To study the frequencies of polymorphic genes use the ratio:

$p + q + r = 1$

$(p + q + r)^2 = 1$, where

p, q, r – polymorphic genes.

It is one of the simplest and universal mathematical methods of the analysis of frequencies of genotypes and genes in a population. Researched populations can differ by biological attributes, geographical state of a life, an economic condition. Studying of prevalence of genes in the certain territories shows, that they can be divided into such categories:

1) Having universal distribution, such genes meet in all regions and populations, but different frequency (the majority of known genes are genes PKU, hemophilia, some forms of intellectual retardation). For example, the gene PKU has frequency about 1% in the population of Europe; a gene of daltonism occurs with frequency 7% for men and 13% – women (in a heterozygous state).

2) Meeting locally, mainly in the certain regions, for example, a gene of sickle-cell anemia which is distributed in the countries of Africa and the Mediterranean region.

The knowledge of genetic structure of populations is of great importance for medicine, in particular, for social hygiene and preventive medicine.

Molecular-genetic methods: the method of sequencing, reverse transcription of DNA, reproduction (cloning) of individual DNA fragments by including them in bacterial plasmids, the formation of DNA probes.

The main stages of molecular genetic methods:

1) Obtaining DNA or RNA samples from cells of blood leukocytes, chorion, amniotic fluid, skin fibroblasts.
2) Accumulation of the required amount of DNA (gene amplification in vitro – polymerase chain reaction).
3) Restriction of DNA into fragments using restriction enzymes.
4) Electrophoresis of DNA fragments.
5) Identification of DNA fragments.

The following methods allow:

1. to study genetic material (sequence of genes in DNA), to determine the localization of disorders at the molecular level (gene mutations);

2. determine the nucleotide sequence of DNA and genes;

3. multiply structural genes (cloning) by inclusion in the bacterial cell;

4. recombine DNA molecules to obtain the necessary substances (genetic engineering) based on human genes;

5. determine the exact location of the gene mutation (DNA probes).

The development of these methods has made it possible to decipher the nucleotide sequences of both structural and regulatory regions of the human genome (the program «Human Genome»), as well as in the future treatment of genetic diseases at the molecular level (gene therapy).

Immunological (immunogenetic) methods – these are methods of studying genetic patterns with the use of immunological reactions (interaction of antigen-antibody with the formation of complexes).

Immunogenetic methods allow to study:

- genetic determinism and polymorphism of immune systems;
- genetics of immunoglobulins and the complement system;
- genetics of histocompatibility complex, transplant antigens of immunoregulatory factors;
- genetics of the human HLA system and genetic determination of resistance to diseases that depend on this system;
- polymorphism of erythrocyte antigens and genetics of blood groups.

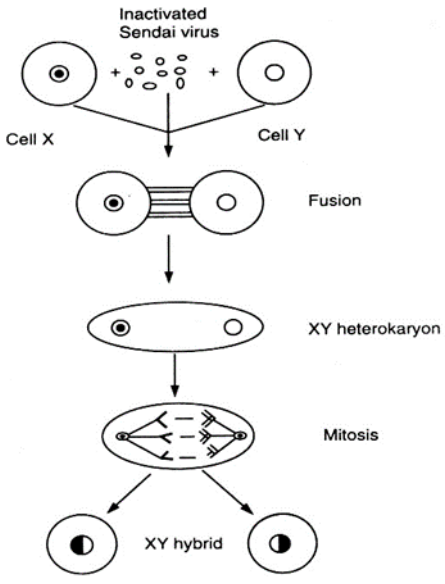
The following is used for research:

- biological fluids (blood, saliva, cerebrospinal fluid) and tissues;
- cell cultures (HLA, endocrine glands, bone marrow, leukocytes).

To identify the corresponding genes, their genetic markers (antigens) are determined.

Immunogenetic methods are important for solving problems of organ and tissue transplantation, for the diagnosis of hereditary pathology of monogenic and multifactorial diseases; to identify genetic predisposition and resistance to disease; to establish genetic maps of human chromosomes; correlations between immunological markers and diseases.

Methods of somatic cell hybridization. In the 1960s techniques were developed that made it possible to grow cells under artificial conditions and to study cellular processes under experimental conditions. This contributed to the development of somatic cell genetics (GSC) methods. Such methods are used to study heredity and variability in somatic cell cultures, which compensates for the impossibility of applying hybridological analysis to humans. GSC methods are based on the cultivation of human cells under artificial conditions, followed by analysis of cellular genetically determined processes (primarily metabolic processes).



For genetic research use:

1) growing cell culture;
2) cloning;
3) cell selection;
4) cell hybridization.

Methods of somatic cell genetics allow:

1. to study the coupling of genes and their localization in chromosomes;
2. establish the primary action of genes and their interaction;
3. to study the genetic heterogeneity of hereditary pathology;

4. diagnose hereditary pathology in the prenatal period.

1st level tests

(one correct answer)

1. According to the data of scientists in 60–70 years of XX century considered that scoliosis disease was inherited by autosomal-dominant type. But analysis of genealogy of the families with scoliosis proved that this trait was characterized by a variable expressivity and incomplete penetrance. Frequency of a trait is increased in the sick families. Such features of expression is specify by:

A. Autosomal-recessive type of inheritance
B. Autosomal-dominant type of inheritance
C. Multifactorial type of inheritance
D. X-linked
E. Dependent only from the environment.

2. Marriages between the relatives take place in some groups of people. What type of inheritance in such families where mostly sick children were born:

A. X-linked recessive
B. X-linked dominant
C. Autosomal-dominant
D. Autosomal-recessive
E. Mithochondrial.

3. Miotonic dystrophy is characterized by a muscular weakness, myotonia, cardiac arrhythmia. The analysis of genealogy has observed: this disease expresses in every generation, identically for the individuals of both sexes, parents equally transmitted the disease to the children. Define the type of inheritance of disease:

A. X-linked recessive
B. X-linked dominant
C. Autosomal-dominant
D. Autosomal-recessive
E. Mithochondrial.

4. Woman has appealed to the genetic consultation because in her family the Rieger syndrome is observed. It was known from the anamnesis that father of proband is healthy but mother and brother of mother are sick. A grandfather from the side of mother was sick too but grandmother is healthy. Define the type of inheritance of syndrome of Rieger:

A. X-linked recessive
B. X-linked dominant
C. Autosomal-dominant
D. Autosomal-recessive
E. Y-linked.

5. Clinical investigation of a boy has revealed the syndrome of Lesh-Hyhan. Parents are healthy but grandfather from a maternal line had the same disease. What type of inheritance of this disease:

A. Autosomal-dominant
B. Autosomal-recessive
C. Y-linked
D. X-linked recessive
E. Incomplete dominance.

6. 16-years old girl has appealed to the dentist concerning of the dark enamel of teeth. The study of her genealogy has revealed that this pathology is transmitted from father to all girls and from a mother to 50 % boys. What type of inheritance of disease:

A. X-linked dominant
B. Autosomal-dominant

C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

7. Changes in human karyotype can be cause of chromosomal disease. Specify, what from these disorders are lethal:
A. Monosomy by autosomes
B. X-chromosome monosomy
C. X-chromosome polysomy
D. Y-chromosome polysomy
E. Trisomy by autosomes.

8. A man which suffered from the inherited disease has married with a healthy woman. They gave birth 5 children: three girls and two boys. All girls inherited disease from the father. What type of inheritance of this disease:
A. X-linked recessive
B. X-linked dominant
C. Autosomal-dominant
D. Autosomal-recessive
E. Y-linked.

9. To the geneticist the young 18-years old boy has addressed. He has narrow shoulders, wide pelvis, high height, insignificant hair on the face. The preliminary diagnosis Kleinfelter syndrome was made. What method of medical genetics will help to confirm this diagnosis:
A. Cytogenetics
B. Genealogical
C. Twins
D. Dermatoglyphics
E. Population-statistical.

10. Mother and father were phenotypically healthy and heterozygous by a genotype. They gave birth to a sick child, in his urine phenylpyruvic acid was found. A preliminary diagnosis - phenylketonuria was made. Specify the type of inheritance of this disease:
A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

11. On the basis of genealogy analysis a doctor-geneticist determined that a character is apparent in every generation, women and men inherit this character with identical frequency and transmitted it to the children. Define, what type of inheritance is it typical of:
A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

12.There are trisomy, translocation and mosaic forms of Down's syndrome can be observed. What method of human genetics it is possible to use for the differention of the Down's syndrome form:
A. Cytogenetics
B. Genealogical
C. Twins
D. Dermatoglyphics
E. Population-statistical.

13.Genealogical analysis has observed: presence of the same pathology for the

relatives in all generations, large amount of patients by horizontal line. What type of inheritance is it typical of:

A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

14. During analysis of genealogy the doctor-geneticist has revealed that disease is present in men and woman but not in all generations. Sick children can be born to a healthy parents. What type of inheritance of this disease:

A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

15. A man, his son and daughter have absence of small molars. Such anomaly was observed also in grandmother from the line of father. What type of inheritance of this anomaly:

A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

16. One form of ectoblast dysplasia shows up as defeat of teeth, hair and bones. After analysis of genealogy the presence of pathology is observed in every generation for men and women. What type of inheritance is this character:

A. X-linked dominant
B. Autosomal-dominant
C. Autosomal-recessive
D. Y-linked
E. X-linked recessive.

17. A man suffering from a hereditary disease married a healthy woman. They got 5 children, three girls and two boys. All the girls inherited their father’s disease. What is the type of the disease inheritance?

A.Dominant, X-linked
B. Autosomal-recessive
C. Autosomal-dominant
D. Y-linked
E. Recessive, X-linked.

18. Very big teeth is an Y-linked sign. Mother's teeth are of normal size, and her son's teeth are very big. Probability of father's having very large teeth is:

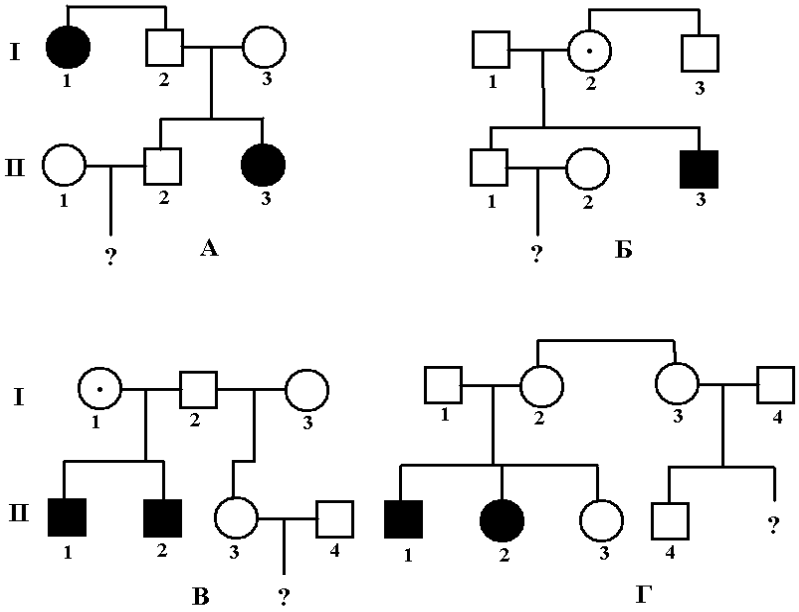
A. 100%
B. 75%
C. 50%
D. 25%
E. 12.5%

Situational tasks

1. In one family one of forms deafness is observed. Probands – the deaf-and-dumb girl, her brother, mother and father are healthy. On the side of the father of proband the aunt and the grandfather are healthy, and the grandmother is deaf. Mother of proband has the deaf-and-dumb brother and healthy brother and the sister. The grandfather and the grandmother from the mother side with normal hearing. Make a family tree. Define type

of inheritance of an attribute and genotypes of members of a family tree.

2. Probands – the boy with freckles. His brother hasn't freckles, sister – with freckles. Mother and father of proband with freckles. Father has been married twice. From the second wife – three children (the daughter and two sons) all without freckles. Make a family tree, define character of inheritance of an attribute and genotypes of all members of a family tree.
3. In family of healthy parents the boy of five years was ill on one of myopathy forms (atrophy of muscles is observed). The uncle of proband from mother line and the aunt's son from mother side are sick. Aunt of proband from mother side, mother of the sick child, her husband, and also the grandmother and the grandfather from mother side are healthy. Make a family tree of family, define type of inheritance of disease and specify heterozygotic carriers of a pathological
4. Establish type of inheritance of attributes in each family tree, probability to birth of a sick child.



TOPIC: Chromosomal disease. Cytogenetics methods and diagnostics

Classification of inherited human diseases. Chromosomal diseases caused by abnornal chromosome structures and numbers. Cytogenetics mechnisms. Karyotyping. Methods of definition of X- and Y-chromatines and method of diagnostics of human hereditary diseases. Diseases classification.

Hereditary diseases are called the diseases, caused by mutations. Hereditary diseases occur due to changes in the hereditary apparatus of the cell (mutations), which are caused by radiation or heat energy, chemicals and biological factors (viruses, migrating elements – transposons, live vaccines, helminth toxins, etc.).

Among the diseases of hereditary origin there are those for the manifestation of which requires the influence of harmful environmental factors. These include gout, some forms of diabetes and others. Such diseases are called **diseases with a hereditary predisposition.** Hereditary diseases should not be confused with **congenital diseases.** The latter already exist at the birth of a child. They can be caused by hereditary and non-hereditary factors. In the case of non-hereditary genesis, such diseases are defined as phenocopies of hereditary malformations.

At the same time, not all hereditary diseases are congenital. Many of them occur at a later age. Hereditary diseases are characterized by a great variety and the majority is

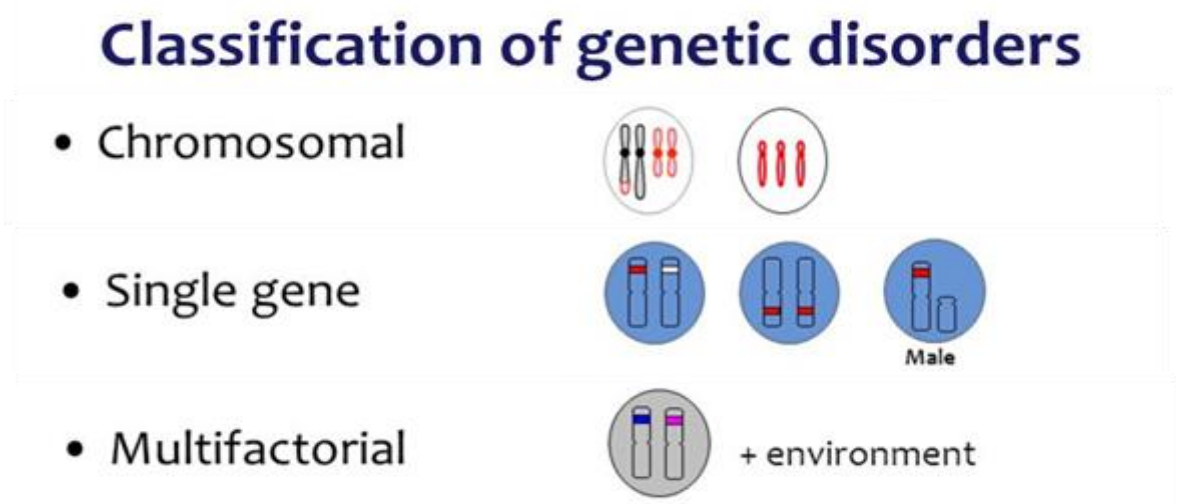
involved in the process of more than one system, and generalized damage to tissues and even organs. Therefore, hereditary diseases manifest themselves in the form of **syndromes** or a complex of pathological signs.

Classification of hereditary diseases. Hereditary diseases, depending on the level of damage to hereditary structures are divided into two major groups: genetic and chromosomal. Monogenic and polygenic diseases are distinguished by the number of loci involved in the mutation process. Gene mutations are passed down from generation to generation without change, while most chromosomal diseases, especially due to chromosome abnormalities (aneuploidy), are not inherited at all. Inversions, translocations are inherited with additional recombinations.

Chromosomal diseases are divided depending on the type of mutations into syndromes caused by numerical (polyploidy, aneuploidy) or structural changes (deletions, inversions, translocations, duplications) of chromosomes. Chromosomal diseases are characterized by multiple lesions without a specific pathogenetic link. If the mutation originated in germ cells, then the full form of the disease is distinguished. If chromosome nondisjunction or structural aberration appeared at different stages of zygote fragmentation, mosaic forms develop.

Monogenic diseases are caused by the action of a gene that has undergone a mutation. Their development is associated with the primary product of one gene (lack of protein, enzyme or abnormal structure). There are autosomal dominant, autosomal recessive, X-linked diseases. These include hereditary metabolic disorders (hereditary enzymopathy).

Polygenic diseases are diseases with a complex nature of inheritance and are determined by multiple genes. They carry out their pathological manifestation in interaction with a complex of environmental factors.



Cytogenetics method

Cytogenetics is a branch of human genetics that studies human karyotype and chromosomal disorder.

Cytogenetic method is a study of chromosome (their number, structure, function and behavior in relation to gene inheritance, organization and expression).

Cytogenetic method includes:

Karyotyping.

Detection of sex chromatin.

Differential staining of chromosomes.

Using of cytogenetic method allows to study:

1) Normal morphology of chromosomes and karyotype;

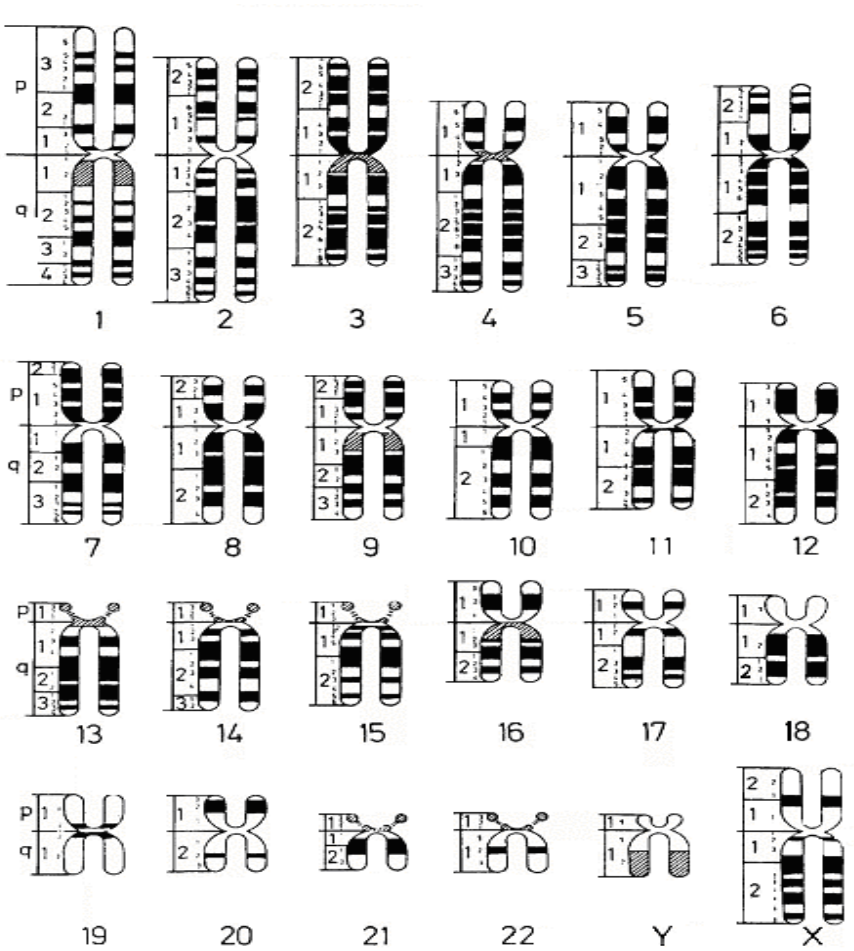
2) Definition of genetic sex of an organism;
3) Diagnosis of the chromosomal diseases caused by number of chromosomes or abnormality of their structure;
4) Mutagenesis processes.

Karyotyping – is getting and drawing up the ideogram according to the Denver system of classification of human chromosomes. It is necessary for the doctor to know the forms of normal and abnormal karyotypes. Thus use the following rules:

1. In the beginning the common number of chromosomes is underlined.
2. Further there is a structure of sexual chromosomes; for example: 46, XX - normal female karyotype; 46, XY – man's karyotype; 47, XXY – Kleinfelter syndrome.
3. Additional autosomes are designated by corresponding number and it is familiar «+», for example: 47, XY, 21 + is the boy with trysomy 21 (syndrome of Down).

Karyotyping is analysis of metaphase chromosomes which have been banded using trypsin mainly followed by Giemsa. This creates special banding patterns on the chromosomes.

Several chromosome-banding techniques are used in cytogenetics laboratories. Quinacrine banding (Q-banding) was the first staining method used to produce specific banding patterns. This method needs a fluorescence microscope and is no longer as widely used as Giemsa banding (G-banding). Reverse banding, or R-banding, requires heat treatment and reverses the usual black-and-white pattern that is seen in G-bands and Q-bands. This method is necessary for staining the distal ends of chromosomes. Other staining techniques include C-banding and nucleolar organizing region stain. These latter methods specifically stain certain portions of the chromosome. C-banding stains the constitutive heterochromatin, which usually lies near the centromere, and NOR staining highlights the satellites and stalks of acrocentric chromosomes. High-resolution banding involves the staining of chromosomes during prophase or early metaphase (prometaphase), before they reach maximal condensation.



Segmentation of human chromosomes according to the Parisian nomenclature. Positive G-, Q-segments; negative (black) R-segments, painted – variable segments.

Definition of sexual chromatin

As an express-method revealing changes of number of sexual chromosomes the method of definition of sexual chromatin from the mucous membrane of a cheek is used. Sexual chromatin or Barr body formed from the cells of female organism from one of two X-chromosomes.

It looks like intensively painted body, located at a nuclear membrane. Increasing of quantity of X-chromosomes in cells the Barr bodies are formed, during the reduction of X-chromosomes number (monosomy X) Barr body is absent.

Sexual chromatin it is possible to define in blood smear, in nucleus of segment-nucleus leukocytes. These Barr bodies or X-chromatin have a characteristic as a kind of drum-type sticks. In norm these structures are found out in women in 3–7% of leukocytes, but for man they are generally absent.

In a basis of classification of chromosomal diseases there are two type of mutation: genome or chromosomal. All chromosomal diseases can be divided into two groups:

a) Changes of the chromosomes number;

b) Changes of the chromosomes structures.

Numerical disorders consist of the following changes: 2n–1 (monosomy) or 2n+1, 2n+X (trisomy, polysomy). Genome mutations on separate chromosomes are numerous and make a great amount of chromosomal diseases (syndromes of Down, Edwards, Patau, Klinefelter, Turner, etc.).

The mechanism causing changes of number of individual chromosomes, disorders of their distribution on daughter cells are taking place during 1st or 2nd meiotic divisions in gametogenesis or in the first division of zygotes.

In a basis of change of chromosomes structure and reorganizations of chromosomes there are chromosomal mutations or aberrations. Breaks of chromosomes occur during time of crossing over and under influence of mutagen factors.

Kinds of chromosomal reorganizations:

- deletion – loss of separate sites of chromosomes;
- duplication – doubling of separate sites of chromosomes;
- inversion – turn of a site of chromosomes on 180^0;
- translocation – arises, when the site of one chromosome is attached to a chromosome from other pair.

Chromosomal reorganizations result in loss of a chromosomal material and changes the genetic program of an organism, therefore has an adverse effect on its viability. Result of chromosomal reorganizations there are plural developmental anomalies which are not compatible with a life or coming to spontaneous miscarriage more often.

Chromosomal anomalies arise as well at early stages of embrional developments. Due to such changes appears mosaisim when one cells will have normal karyotype, and others – mutant. Organisms can have mosaics 2–3 or a lot of cellular clones. The pathology is defined by quantity of the changed cells and character of a mutation (on autosomes or to sexual chromosomes, or it is partial monosomy or trisomy).

The basic method of diagnostics of chromosomal illnesses – cytogenetical which includes:

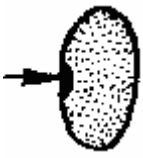
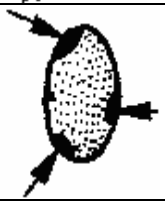
- karyotyping (studying of chromosomal sets);
- definition of «drum-sticks»;
- definition of sexual X-chromatin;

- definition of sexual Y-chromatin (a fluorescent method).

Besides biochemical methods as a consequence of chromosomal illnesses is the effect of «a doze of genes» owing to what concentration of some enzymes changes can be used. For example, trisomy 21 (syndrome of Down) increases in 1.5 times activity of enzyme superoxydismutase.

The certain value for diagnostics has phenotypical analysis (for example, portrait diagnostics) and dermatoglyphic.

Connection between quantity of X-chromosomes, quantity of Barr bodies in somatic cells of a mucous membrane of an oral cavity (A) and quantity of «drum-sticks» in nucleus of leukocytes (B)

Quantity of X-chromosomes	A	B	Karyotype
One X-chromosome			The man – 46, XY (normal), woman – 45, X0 (Turner-syndrome)
Two X-chromosomes			The woman – 46, XX (normal), man – 47, XXY (syndrome of Kleinfelter)
Three X-chromosomes			The woman – 47, XXX (trysomy X), man – 48, XXXY (syndrome of Kleinfelter)
Four X-chromosomes			The woman – 48, XXXX (polysomy X), man – 49, XXXXY (syndrome of Kleinfelter)

Chromosomal diseases caused by quantity of autosomes

Syndrome of Down trisomy 21. Karyotype 47 (21+) chromosomes. Frequency of 1800 newborns. Frequency of a birth with this syndrome is connected with an age of mother (after 36–40 years makes 1 : 50). The syndrome can be caused by trisomy on 21 pair chromosomes, translocation on 21 chromosomes from group D or by mosaics. The most widespread chromosomal diseases in all continents. The patient has a number of characters: the short limbs, a small skull, anomalies of face structure, anomaly of upper eyelid – epicanthus. The mental retardation expressed in a different degree too. In 1966 the patients have been described the karyotype with 46 chromosomes. In this case there are translocational chromosome from other group (13 or 15) have described. This translocational form is syndrome of Down. It can happen not so often, than trisomy on 21. In this case the age of mother has a great importance because children with translocational form can be born in very young mothers.

Syndrome of Patau. Trisomy D, syndrome trisomy 13–15 chromosomes, are more often than 13 chromosomes. Frequency of 17 000 birthes. The additional chromosome is in a group D – karyotype 47 (13 +). Penotypically expressed as: heavy anomalies of a brain structure, the wolf mouth, a harelip, anophtalmy, polydactyly, syndactyly, disorders of

heart, kidneys, digestive system. Life expectancy of such children about one year.

Syndrome Edwards. Trisomy E, syndrome trisomy on 17–18 chromosomes. Frequency of 1 : 7000 birthes. Karyotype 47 (18 +).

Phenotypically it is shown by a complex of various anomalies of development. Retardation in physical and mental development. Muscular atrophies, microphtalm, epicanthus, anomalies of an iris of the eyes. Anomalies of a skeleton, internal bodies (heart, lungs, kidneys). Children perish during 1st year of a life.

Syndrome of "the cat's shout" (a syndrome «cri-du-chat», 1963), deletion of short shoulder of 5 chromosomes (5p-). Frequency among newborns 150000. It is characterized by polymorphism which depends on the size of deletion.

Phenotypically: physical and intellectual retardation, anomaly of internal oragns, microcephally have observed. Such children have disorders of a throat structure due to they in the early childhood make the sounds reminding "purr" of a cat.

Anomalies of sexual chromosomes

Kleinfelter Syndrome (karyotype 47, XXY; 48, XXXY; 49, XXXXY. Kleinfelter and co-authors, 1942). Frequency of 1.5 : 1000 born boys.

Phenotypical expressions: young men of high growth with disproportionate long limbs, gynecomastia, they are sterile. Mental retardation and oligophrenia in different degree are increasing as a result of quantity of X-chromosomes.

Syndrome Shereshevsky-Turner (Shereshevsky, 1925; Turner, 1938), karyotype 45, X0 (monosomy X). Frequency is 0.7 : 1000 girls.

Phenotypically displays: wing-like fold on the neck, disorders of physical development. Low height (130-150 cm). Underdeveloped gonads, hypoplasia of uterus, there are sterile. Anomalies of a skeleton, vascular system, kidneys. Intelligence in most cases within the limits of norm.

X-polysomy are present in women. Karyotype 47, XXX in cases of mosaisism – 46, XX/47, XXX. Frequency of 1 : 1000 births.

Phenotypically expressions are various. Majority of such women have normal physical, intellectual and sexual development. The risk of a child birth with a chromosomal pathology is increased. Somatic anomalies feebly marked, such women suffer schizophrenia mostly.

1st level tests

(one correct answer)

1. Each doctor knows the characteristic of the inherited illnesses markers. A patient have dislocation of lens in his eyes. What syndrome is diagnosed by a doctor, taking into account the forms of hands and foot:

A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. X-trisomy.

2. In the cultivated fibroblasts of child skin with Patau syndrome there are 47 have found. Define the type of this anomaly:

A. Trisomy X
B. Monosomy X
C. Trisomy 21
D. Trisomy 18
E. Trisomy 13.

3.Karyotype of the patient with Turner syndrome has analyzed. Cell division has stopped on the metaphase stage. How many chromosomes do we have on this stage:

A. 44 autosomes + XX
B. 43 autosomes + XX

C. 44 autosomes + X0
D. 45 autosomes + X0
E. 42 autosomes + XXX.

4. For the child a preliminary diagnosis was made: syndrome of "cri-du-chat" characterized by the underdeveloped muscles of larynx and "meowing" timbre of voice. This diagnosis it is possible to confirm by means of such method:
A. Twins
B. Biochemical
C. Cytogenetics
D. Pedigree analysis
E. Statistical.

5. How many Barr's bodies appear in the human buccal mucosa epithelium cells in a person with the Klinefelter (47, XXY) syndrome:
A. 4
B. 2
C. 3
D. 1
E. No Barr bodies.

6.By means of cytogenetics method the karyotype of woman is made with the syndrome of polysomy-X: 47, XXX. How many bodies of sexual chromatin are counted in the nucleus of one cell:
A. No Barr bodies
B. 1
C. 3
D. 4
E. 2.

7. The young man was examined in a medical and genetic consultation. Karyotype 47, XYY was detected. Indicate the most probable diagnosis.
A. «Supermale» syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

8. A 28-years old boy has appealed to the doctor concerning sterility. Medical examination is revealed: underdeveloped ovaries, uterus and according to the karyotype analysis – two Barr's bodies in the most cells. What is the possible diagnosis:
A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

9. A girl appealed to the medical consultation with a preliminary diagnosis «Turner syndrome». What method it is possible to specify a diagnosis:
A. Karyotyping
B. Pedigreee analysis
C. Dermatoglyphics
D. Biochemical
E. Twins.

10. Young man appealed to the doctor concerning disorders in physical and sexual development. A cytogenetic method has made a karyotype: 47 XXY. What inherited pathology it is characteristic for:
A. Down syndrome

B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. X-trisomy.

11. During ovogenesis (meiosis 2) as a result of nondisjunction of sexual X-chromosomes the secondary oocyte with 22 chromosomes has formed. What probability of appearance of a child with the Turner syndrome if this cell will fertilize by a spermatozoa with normal set of chromosomes:
A. 50 %
B. 75 %
C. 25 %
D. 0 %
E. 100 %

12. A man appealed to the doctor concerning sterility. In the nucleus of most cells of epithelium of cheek mucous membrane the Barr body was found. It specifies that a patient has:
A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

13.The preliminary diagnosis Turner syndrome was made for the girl. During karyotyping on the stage of anaphase the amount of chromosomes are:
A. 90
B. 45
C. 46
D. 92
E. 94.

14. On the basis of phenotypical analysis the preliminary diagnosis "X-polysomy" was made for the women. What is the probable karyotype:
A. 48 (XXXY)
B. 48 (XXXX)
C. 48 (XXYY)
D. 47 (XXY)
E. 46 (XX).

15. There are 47 chromosomes were found in the cultivated skin fibroblasts of the child with Down syndrome. Define the type of pathology:
A. Trisomy 21
B. Monosomy X
C. Trisomy 13
D. Trisomy 18
E. Trisomy X.

16. A new-born child has Patau syndrome. What prognosis for his life:
A. Life expectancy about 3 months
B. Life expectancy about 3 weeks
C. Life expectancy about 3 years
D. Life expectancy about 10 years
E. Life expectancy more then 10 years.

17. A man with many female characteristics, mental retardations and sparse body hair. It is typical phenotype for the:
A. Down syndrome
B. Turner syndrome

C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

18. 14-years girl has X-monosomy. This is possible in case of:
A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

19. Clinical inspection of the 12-years old boy the leucosis of unknown etiology has revealed. This disease has inherited nature. It is happen because of:
A. Deletion by 5 pair of chromosome
B. 18 pair trysomy
C. 13 pair trisomy
D. Deletion by 21 pair of chromosome
E. 21 pair trysomy.

20. Specify, what set of sexual chromosomes has a woman if in the nucleus of epithelium of mucous membrane in oral cavity the Barr bodies did not find:
A. ХУ
B. ХХУ
C. Х0
D. ХХХХ
E. ХХ.

21. Pediatrician paid attention that crying of a child reminds a cat scream. By means of cytogenetic method the karyotype 46, XX, 5 p-was made. This disease is caused by:
A. Pleiotropy
B. Duplication
C. Inversion
D. Translocation
E. Deletion.

22. A new-born boy has a dolichocephalic skull, narrow eyes and deformed ears. Karyotype of a child is 47, XY + 18. Name the diagnosis:
A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

23. A patient with a diagnosis – Turner syndrome has a karyotype 45, X0. How many sexual chromosomes should be present in her karyotype:
A. 45
B. 0
C. 2
D. 44
E. 1.

24. 16-years old boy has a anomaly of tooth forms, gingivitis and tooth resorption. Cytologic research of mucous membrane of the oral cavity has revealed 2 Barr bodies. What is the most credible syndrome:
A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Marphan syndrome
E. Edwards syndrome.

25. During ovogenesis the cells with unbalanced amount (22) of chromosomes are formed. X-chromosome was absent. What is probability of appearance of a child with Kleinfelter syndrome if fertilization will take place by spermatozoa with a normal chromosomes number:

A. 0 %
B. 100 %
C. 50 %
D. 25 %
E. 75 %.

26. A woman appealed to the medical consultation. She has a neck with wing-shaped folds (neck "of sphinx"); wide thorax, poorly developed mammary glands. Karyotyping analysis detected absence of X-chromatin. This is possible in case of:

A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Patau syndrome
E. Edwards syndrome.

27. During the cytogenetic examination of the patient with pathology of reproductive function in some cells is normal karyotype 46 ХУ, but in most cells – karyotype with Klenifelter syndrome – 47 ХХУ. What is the name of such pathology:

A. Duplication
B. Inversion
C. Deletion
D. Mosaisism
E. Heterogenesity.

28. The parents appealed to the medical consultations because they have a child with congenital anomalies: microcephaly, narrow eyes, underdeveloped eyeballs, wide nose, cleft of overhead lip. A preliminary diagnosis was made: Patau syndrome. What method should be used to make the right diagnosis:

A. DNA-analysis
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

29. Young man has a high height (187 cm), wrong growth of large teeth with anomalies of dental enamel. Karyotyping analysis has shown two Y-chromosomes. This anomaly is a result of:

A. Trisomy
B. Monosomy
C. Nullesomy
D. Alloploidy
E. Autoploidy.

30. During gametogenesis in meiosis the male sexual chromosomes did not move to the cell opposite poles. The result of this anomaly is:

A. Down syndrome
B. Turner syndrome
C. Kleinfelter syndrome
D. Patau syndrome
E. Edwards syndrome.

31. Cytogenetic method has determined the presence of two little bodies of sexual chromatin in female cells. What chromosomal disease it is characteristic for:

A. Down syndrome

B. Turner syndrome
C. X-polysomy
D. Patau syndrome
E. Edwards syndrome

32. People with Down's syndrome have a typical phenotype. It means that in the karyotype there are:
A. 47, ХХУ
B. 47, ХУ+18
C. 47, ХУ+21
D. 48, ХХХУ
E. 47, ХХХ.

33. Healthy parents gave birth a child with Down's syndrome and karyotype 46 chromosomes. However, one chromosomes from group D had the extended short shoulder. What the reason of disease is this case:
A. Trisomy by 15 pair
B. Translocation
C. Trisomy by 18 pair
D. Deletion
E. X-chromosome monosomy.

34. It is known that in the interphase male somatic cells normally there are no more than 0–5 % bodies of sexual chromatin but female 60–70%. This characteristics is used in practical medicine for the:
A. Express-diagnostics of human sex
B. Studying of X-chromosome
C. Studying of Y-chromosome
D. Determining of chromatin
E. Studying of autosome.

35. Haemophilia is apparent through the generation and can be present within male relatives. What method of medical genetics must be used in this case:
A. DNA-analysis
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

36. Galactosemia is an autosomal-recessive disease results on damage of brain, liver and eyes of a child which has a breast-feeding. What method of genetic examination it is necessary to apply for the exact specification of diagnosis:
DNA-analysis
A. Pedigree analysis
B. Cytogenetics
C. Biochemical
D. Populational-statistics
E. Twins method.

37. What genetics method makes it possible to determine the karyotype of Patau syndrome:
A. Sex chromatin determination
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

38. To conduct the phenylketonuria analysis one can use such method:
A. DNA-analysis

B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

39. For the specification of biological mechanisms of the cleft palate development in the experimental laboratory the similar anomaly has been studied on the mouse organisms. What kind of method has taken place:

A. Modeling
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

40. What methods do geneticists use to establish Down syndrome:

A. DNA-analysis
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

41. A doctor-geneticist investigated the contribution of human genotype and factors of environments in the formation of some inherited pathological characters. What genetic method do we have to apply to make correct reseasches:

A. DNA-analysis
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

42. Hypertrichosis is determined by the gene localized in the Y-chromosome. What is the probability of a man with hypertrichosis having a son with this character:

A. 0%
B. 100%
C. 50%
D. 25%
E. 75 %.

43. Sometimes for the hereditary diseases investigation and diagnostics more special genetic methods are applied such as chromatography. What method do we have to apply to make correct conclusion in this case:

A. Twins
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

44. Galactosemia is a disease provoked by a metabolic disorder. What genetic method can confirm the diagnosis:

A. Cytogenetics
B. Biochemical
C. Populational-statistics
D. Pedigree analysis
E. Immunological.

45. The medical examination of a young girl has revealed that there were no Barr's bodies in her buccal mucosa epithelium cells and she has some features typical of the Turner's syndrome. Which of the below mentioned genetics methods is used:

A. Twins

B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics

46. In the medical-genetic consultation a small boy was preliminary diagnosed with Down's syndrome. What genetic method can confirm this diagnosis:
A. Dermatoglyphics
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

47. The amniotic fluid contains proteins, mineral salt, hormones, urea, and discarded fetus cells. These cells may be used to determine the fetus sex. What genetic method can be applied in this case:
A. Twins
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

48. During the clinical examination of a child some features typical for the phenylketonuria were found by a physician. What method can confirm the diagnosis:
A. Twins
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

49. A tall mentally retarded man has the special characteristics of karyotype: 2 Barr's bodies in nuclei of buccal mucosa epithelium cells. The diagnosis can be confirmed by the following method:
A. Twins
B. Pedigree analysis
C. Cytogenetics
D. Biochemical
E. Populational-statistics.

50. Medical examination at the military registration and enlistment office revealed that a 15-year-old boy was high, with eunuchoid body proportions, gynecomastia, female pattern of pubic hair distribution. The boy had also fat deposits on the thighs, no facial hair, high voice, subnormal intelligence quotient. Which karyotype corresponds with this disease?
A. 47, XXY
B. 45, XO
C. 46, XX
D. 46, XY
E. 47, XXX.

51. According to the phenotypic diagnosis a female patient has been provisionally diagnosed with X-chromosome polysomia. This diagnosis can be confirmed by a cytogenetic method. What karyotype will allow to confirm the diagnosis?
A. 47(XXX)
B. 48(XXXY)
C. 48(XXYY)
D. 47(XXY)
E. 46(XX).

52. Cytogenetic examination of a patient with reproductive dysfunction revealed normal

karyotype 46, XY in some cells, but other cells with karyotype 47, XXY. Such cell heterogenity is called:

A. Mosaicism
B. Inversion
C. Transposition
D. Duplication
E. Monomorphism.

53. Sexual chromosomes of a woman didn't separate and move to the opposite poles of a cell during gametogenesis (meiosis). The ovum is fertilized by normal spermatozoon. Which chromosomal disease can be found in her child?

A. Turner's syndrome
B. Down's syndrome
C. Patau's syndrome
D. Edwards' syndrome
E. Cat cry syndrome.

Situational tasks

1. The woman with karyotype 45 chromosomes is revealed as a result of translocation on 21 chromosome. What risk of a sick child birth with a Down syndrome?
2. Cytological analysis is revealed karyotype 47 (21 +). Phenotype is normal, including intelligence. How it is possible to explain it?
4. In medical-genetic consultation the young couple have addressed because they have a child with Down syndrome. They want to know, whether is possible to birth the healthy child in their family? What answer should be given? Whether it is necessary to carry out additional researches?
5. Researching of blood in leukocytes has detected 2 bodies of sexual chromatin also named «drum sticks. Write the possible karyotype.
6. Researching of epithelium cells from the mucous of cheek has revealed that the bodies of sexual chromatin were not present. What disease can be assumed?
7. In phenotypically female organism the percent of sexual chromatin from the mucous of cheek epithelium is determined. In what cases it is possible to assume the pathology: a) 35 %; b) 0 %; c) 13 %; d) 48 %.
8. In phenotypically male organism the percent of sexual chromatin from the mucous of cheek epithelium is determined. In what cases it is possible to assume the pathology: a) 0 %; b) 2 %; c) 30 %; d) 48 %.
9. In MGC the young family has addressed because they already had the child with a syndrome of Patau. They want to know, is it possible for them to birth the healthy child? Give the answer. Whether additional researches are necessary to do?
7. During the research of blood in leukocytes there are two «drum sticks» have found. Write the possible karyotype of this person and his sex (female or male). Which kind of phenotypical changes can be observed?
9. During the researching of woman the sexual chromatin in the cells of cheeks epithelium was not found. What is her karyotype? What changes of a phenotype can be present?
10. What the meaning of the fact that human with chromosomal diseases are sterile?
11. There are 22% of cells of amniotic fluid include bodies of sexual chromatin. Is it necessary to do the additional researches?

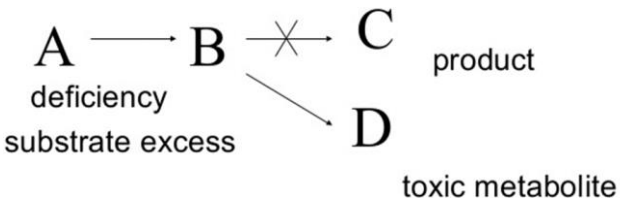
TOPIC: Molecular diseases. Biochemical method and DNA-diagnostics

Molecular pathology caused by gene mutations in chromosomes. Mechanisms and principles of laboratory prenatal diagnistics. Gene engeenering. Biotechnology Basis of gene therapy.

Molecular (gene, monogenic) diseases – are human diseases caused by changes in the molecular structure of the gene. Mutations of genes that control metabolic pathways cause a group of single gene disorders termed as **inborn errors of metabolism.**

For diagnostics of the diseases connected to disorderst of a metabolism are used biochemical methods, genealogical (establishment of type of inheritance) and others. **Biochemical methods (A. Garrod, 1908)** are used to determine the activities of genes within cells and to analyze substrates and products of gene-controlled reactions.

The mechanism of occurrence of gene diseases. Gene diseases is a result of the gene mutations. Gene mutation (changes in structure of a gene) gives a change of enzymes activity, which are catalyzed many parts of reaction in connection with the occurrence of traits changes. Gene mutation is the result of a change in the nucleotide sequence of the DNA molecule in a particular region of the chromosome. Such a change in the base sequence of the gene is transmitted to mRNA during transcription and may result in a change in the amino acid sequence of the polypeptide chain produced from it during translation at the ribosome.



General scheme of metabolic failure in inborn errors of metabolism (Garrod's hypothesis)

Monogenic diseases are divided into groups depending on the character of disorders:

- Enzyme pathology;
- Defects of structural and transport protein;
- Disorders of circulating protein of blood;
- Gene diseases with unknown primary biochemical defect.

According to the WHO classification, monogenic or molecular diseases divided into groups caused by the following disorders:

- ✓ Aminoacids metabolism;
- ✓ Carbohydrate metabolism;
- ✓ Lipids metabolism;
- ✓ Steroid metabolism (defects of biosynthesis of hormones)
- ✓ Purine and pyrimidine metabolism
- ✓ Metabolism of connecting tissue protein, bone and muscles
- ✓ Structure of heme and porphyrine;
- ✓ Metabolism in erythrocyte and disorders of their structure;
- ✓ Anomalies of metabolism of metals;
- ✓ Diseases which are characterized by defect of transport of various substances;
- ✓ Diseases which are characterized by anomalies of structure: functions of enzymes and protein of plasma.

Hereditary defects of metabolism of amino acids

Phenylketonuria – metabolic disorder of phenylalanine. In the first weeks of a child life the clinical displays of neurologic character have developed: convulsive epileptic attacks, the intellectual retardation, the reduced pigmentation of a skin, hair, an iris of the eyes too. Type of inheritance A-R.

Tyrosinosis – metabolic disorder of amino acid tyrosine. The sharp form of disease is characterized by abnormal development of the baby, increase of the liver and spleen, changes in kidneys. Without treatment the children perish in a young age from hepatic or respiratory abnormalities. Chronic disease is characterized by cirrhosis of a liver, rickets changes of bones, defeat of canal systems of kidneys. Type of inheritance A-R.

Albinism – metabolic disorder of tyrosine. Albinism is characterized by lack of dark pigment melanin. Absence of melanin in cells of skin, hair and an iris of the eyes, the increased sensitivity the ultraviolet rays have developed. Type of inheritance A-R.

Alkaptonuria – metabolic disorder of homogentisic acids. Clinical displays begin after 40 years, and expressed in a pathology of joints, limbs, backbone and others where connecting tissue is present. The pigment slowly deposits in the cartilages of ears and nose (pigmentation of color ochra). Plenty of an acid is expose with urine to air and darkening. Type of inheritance A-R.

Hereditary defects of carbohydrates metabolism

Galactosemia – infringement of an exchange of galaktosa which gets with food and splits on mono- and di- sugars. Type of inheritance A-R. Clinical displays – a jaundice of newborns, vomitting, diarrhea, mental retardation, increasing growth of a liver and a spleen, a cataract (dimness of a crystalline lens).

At early diagnostics to the child appoint special (as well as at PKU) a diet – exception of milk of mother and other products which contain lactose or galactose. Development of the child is normalized.

Mucopolysaccharidosis – hereditary illnesses of accumulation which develop as a result of insufficiency of some enzymes participating in splitting complex containing amins of carbohydrates. Mutant enzymes concern to lysosome hydrolase. They defined by mutations of different genes which code different enzymes. Type of inheritance: A-R, X-R.

Hereditary defects of lipids exchange are the group of genetic diseases, the essence of which is the accumulation of lipids (glycerides, cholesterol, non-esterified fatty acids, phospholipids, glycolipids) in organs or blood. Type of inheritance AR, XR. Frequency of different forms is from 1: 4000 newborns to 1: 300 000, the frequency in different populations can vary significantly.

Lipid metabolism diseases include:

- ✓ **Hyperlipoproteinemia** (an inability to break down lipids or fats, specifically cholesterol and triglycerides).
- ✓ **Sphingolypidoses:**

•Niemann-Pick disease. The disease is caused by a hereditary disorder of lipid metabolism (sphingophospholipids). There is an accumulation of sphingomyelin in the liver, brain, spleen, adrenal glands, kidneys, lymph nodes, skin and mononuclear blood cells. Diseases with AR type of inheritance. The frequency of boys and girls is the same. The pathogenesis is associated with a deficiency in the tissues of sphingomyelinase – an acidic lysosomal hydrolase that performs hydrolytic cleavage of sphingomyelin. The clinical picture is manifested in infancy. The initial symptoms are the child's refusal to eat and periodic vomiting, then – a sharp decrease in weight with the development of malnutrition, delayed psychophysical development, increasing the size of the liver and spleen. The skin has a waxy tinge with areas of enhanced pigmentation. There is a lesion

of the nervous system. Muscle hypotension develops, the child's sharp lag in mental development, idiocy, deafness, at patients atrophy of an optic nerve develops. The disease affects the nervous system, liver, spleen. No specific treatment has been developed. The forecast is unfavorable. The disease quickly leads to exhaustion and death. Survival after the age of five is extremely rare.

•**Thay-Sachs disease (amaurotic idiocy)** belongs to the group of intracellular lipidosis. This disease has an AR type of inheritance. There is an increase glycolipid – ganglioside in a brain, liver, spleen, which indicates a generalized disorder of ganglioside metabolism. Histologically, the picture of generalized decay of ganglion cells of the nervous system. The disease begins at the age of 4–6 months. Often this disease is familial. At patients decrease in sight is found early. The child can not fixate, does not watch the toys. Quite early on the fundus is a symptom of «cherry stone» – a cherry-red spot in the macular area, surrounded by a grayish-white ring. Subsequently, optic nerve atrophy and complete blindness develop. Orientational and protective reactions disappear. Violations lead to complete immobility. There is a symptom of an increased reaction to sound stimuli. Death occurs on average 1–2 years after the onset of the disease. No specific treatment for amaurotic idiocy has been developed.

Other examples: Gausher's disease, Farber's diseases, Fabry's disease, Krabbe's disease.

Proteins metabolism disorders

✓ **Oxygen carrying proteins disorders (Haemoglobinopathy) –** a group of hereditary diseases in which the protein chains of hemoglobin (Hb) are disrupted, which leads to changes in their functions and properties:

•**Sickle-cell anemia –** occurs with high frequency in the regions of malaria. Type of inheritance is autosomal, incompletely dominant. The mutant gene (S) causes the synthesis of hemoglobin S, which changes the shape of erythrocytes and weakly attaches oxygen, resulting in anemia and hypoxia. Heterozygotes have both normal and mutant HbS and do not have malaria.

•**Thalassemia** disease in which the content of protein globin in the molecule of hemoglobin (Hb) decreases. Patients has anemia. Type of inheritance A-R or chromosomal aberration (microdeletion). Molecular genetic methods and electrophoresis are used to diagnose the type of thalassemia.

✓ **Connective Tissue Proteins disorders:**

•**Marfan syndrome (spider man disease) –** systemic connective tissue disorder. Includes: arachnodactyly (spider fingers or long slender fingers); long stature; heart abnormalities, etc. Represents A-D type of inheritance.

•**Ehlers-Danlos syndrome (hyperelastisity of skin and joints) –** a group of disorders that affect connective tissues supporting the skin, bones, blood vessels, etc. A-D or A-R type of inheritance.

✓ **Clotting Factors Defficiences (Haemophilia) –** the abnormality in blood clotting due to deficiency of coagulation factors, which leads to prolonged and excessive bleeding. X-R type of inheritance.

Nucleic asids (purine and pyrimidine) metabolism disorders involve abnormalities of nucleotide exchange. The most commonly cited disorder in the neurologic realm is Lesch-Nyhan syndrome which presumably reflects its distinctive feature of self-mutilation. The diseases is rare (1 : 300,000 newborns) and inherited by XR-type. The disease develops at a rough age, examining muscle hypertonia, reaching reflex stimulation, oligophrenia, impulses that have a tendency to self-harm. Primary defect: this is a lack of hypoxanthine-phosphoribosyltransferase (HGPRT) enzyme required for DNA synthesis. It catalyzes the

conversion of free purine bases – guanine and hypoxanthine – to nucleotides. In the absence of this product, the final product breaks down the basic uric acid. The high content of its salt adheres to urate and the development of kidney stones. The accurate diagnosis is possible, which based on the activity of HGPRT in cells.

Diseases with unknown biochemical defects

Achondroplasia (a form of dwarfism) – genetic disorder of bone growth. A-D type of inheritance, frequency 1: 100 000; occurs due to de novo mutations. Phenotypically manifested by skeletal disorders (violation of the formation of cartilage in the epiphyses of the tubular bones, skull bones).

Cystic fibrosis (A-D or A-R type of inheritance, frequency 1: 25 000 newborns). At the heart of the pathogenesis of all forms it is a damage to the endocrine glands (secretory cells of the bronchi, pancreas, intestines, sweat glands, liver), accompanied by the secretion of thick mucus, inflammatory and sclerotic changes in the organs. The main forms are pulmonary and intestinal. Diagnosis – special comprehensive tests (determination of Na content in secretions, determination of the activity of digestive enzymes). It is believed that a significant number of cases in children are not diagnosed.

Myopathies (muscular dystrophies) are a group of inherited diseases that affect striated and smooth muscles. The type of inheritance can be X-R, A-D, A-R. Myopathies are characterized by muscle damage that progresses with age, clinical polymorphism.

Genetic heterogenecity of hereditary diseases and their clinical polymorphism.

Frequently similar phenotypical manifestations of illness is caused by several different mutations. This phenomenon refers to **genetic heterogenecity** of hereditary diseases and can be caused by mutations of the different genes which coding enzymes of one metabolic way, and also to the different loci of the same gene resulting in occurrence of different alleles.

Genocopy is a clinical syndrome that masquerades as a known inherited disease with an established genetic defect but caused by damage to another gene. Genocopy is a consequence of genetic heterogeneity, because the clinical form of hereditary disease can be caused by mutations in different loci or different mutations in one locus (multiple alleles).

Genetic heterogeneity extends to all proteins in the body – there is a hereditary disorder of the synthesis of different proteins or different variants of the same protein. For example: Ehlers-Danlos syndrome (11 forms), glycogenosis (more than 10 forms), neurofibromatosis (6 forms) and many others. The source of genetic heterogeneity are mutations in one locus. In this case, different mutant alleles are manifested phenotypically differently. For example, various thalassemia, mucopolysaccharidosis. Several forms of neuromuscular dystrophies, hereditary forms of dwarfism, and glycogenosis have been studied.

Multifactorial diseases (MD). The MD make 90% of chronic infectious diseases which genetic analysis is very much combined.

Attributes which are inherited by polygenes are characterized by a continuous number of phenotypical changes from subclinical up to well defined clinical symptoms.

Clinical-genealogic analysis of MD taken into account:

- frequency of disease in relatives, sibs which can be more often than populational;
- frequency of disease which are depends on sex and also from the line of inheritance.

Diseases with hereditary predisposition can be both monogenic and polygenic.

Characteristics of MD:

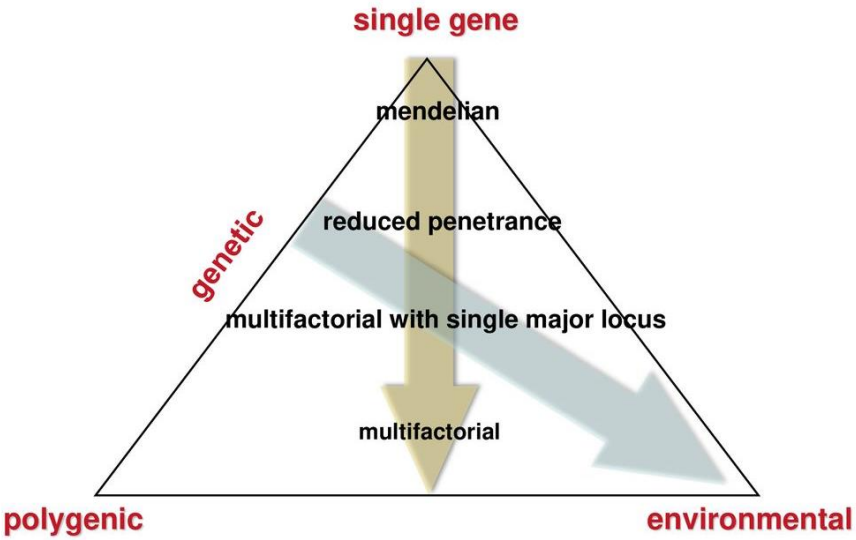
1. High frequency in the population.
2. The existence of clinical forms that form a continuous series, from subclinical to severe

manifestations.

3. Earlier onset and intensification of clinical manifestations in subsequent generations.
4. Significant gender and age differences in population frequency.
5. Relatively low disease rate in monozygotic twins (60% and below) and significantly higher than the corresponding level in dizygotic twins.
6. Inconsistency of inheritance patterns with Mendelian models.
7. The dependence of the degree of risk for relatives of the patient on the frequency of the disease in the population (it is higher, the less common the disease).
8. The similarity of clinical and other manifestations of the disease in the immediate relatives of the proband, which reflects the coefficient of heredity (for polygenic diseases it is 50–60%).

Frequently predisposition to some of diseases is observed to the people with the certain genotypes on polygenic systems of groups of blood, ABO and others.

Examples of MD: asthma, autism, caries, diabetes mellitus, epilepsy, glaucoma, hypertension, ischemic heart disease, multiple sclerosis, obesity, parkinson disease, psoriasis, rheumatoid arthritis, schizophrenia, scoliosis.



Biochemical methods are applied to the main chemical compounds of genetics — DNA and RNA.

Biochemical techniques are used to determine the activities of genes within cells and to analyze substrates and products of gene-controlled reactions. Cells are ground up and the substituent chemicals are fractionated for further analysis. Special techniques like chromatography are used to separate the components of proteins so that inherited differences in their structures can be revealed.

For instance, more than 100 different kinds of human haemoglobin molecules have been identified. Radioactively tagged compounds are valuable in studying the biochemistry of whole cells. For example, thymine is a nitrogenous base found only in DNA; if radioactive thymine is placed in a tissue-culture medium in which cells are growing, genes use it to duplicate themselves.

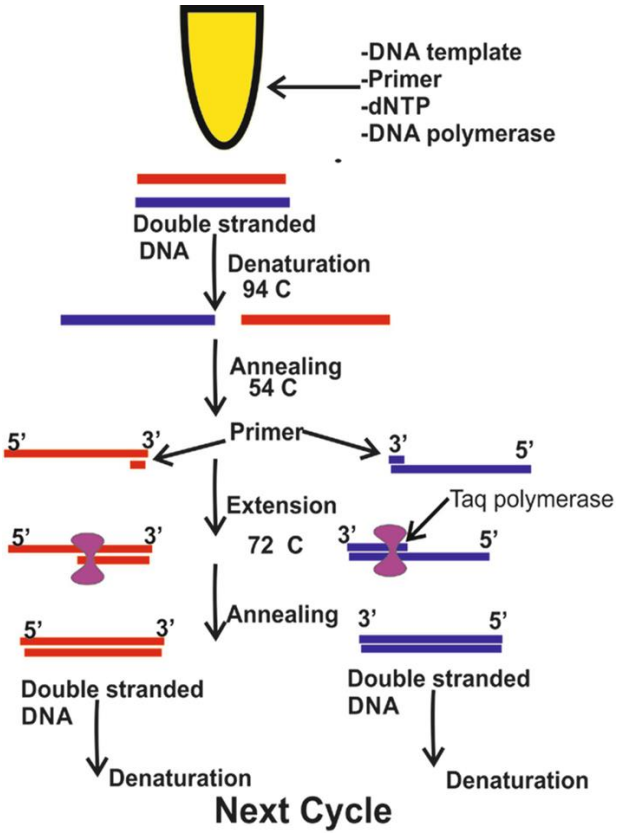
When cells containing radioactive thymine are analyzed, the results show that, during duplication, the DNA molecule splits in half, and each half synthesizes its missing components.

Chemical tests are used to distinguish certain inherited conditions of humans and blood analysis reveal the presence of certain inherited abnormalities – PKU, alkaptonuria, galactosemia and others.

Polymerase chain reaction (PCR) is a technique used to make numerous copies of a specific segment of nucleic acid DNA. The polymerase chain reaction enables investigators to obtain the large quantities of DNA that are required for various experiments and procedures in molecular biology, forensic analysis, evolutionary biology, and medical diagnostics.

PCR was developed in 1983 by Kary Mullis (American biochemist) who won the Nobel Prize for chemistry in 1993 year for his invention.

Before the development of PCR, the methods used to amplify or generate copies of, recombinant DNA fragments were time-consuming and labour-intensive. In contrast, a machine designed to carry out PCR reactions can complete many rounds of replication, producing copies of a DNA fragment, takes only a few hours.



The PCR technique is based on the natural processes a cell uses to replicate a new DNA chain. Only a few biological ingredients are needed for PCR. The integral component is the maternal DNA that contains the region to be copied, such as a gene. As little as one DNA molecule can serve as a template. The only information needed for this fragment to be replicated is the sequence of two short regions of nucleotides at either end of the region of interest. These two short template sequences must be known so that two primer (short stretches of nucleotides) that correspond to the template sequences can be synthesized. The primers bind, or anneal, to the template at their complementary sites and serve as the starting point for copying. DNA synthesis at one primer is directed toward the other, resulting in replication of the desired intervening sequence. Also needed are free nucleotides used to build the new DNA strands and a DNA polymerase, an enzyme that does the building by sequentially adding on free nucleotides according to the instructions of the template. Because DNA from a wide range of sources can be amplified, the technique has been applied to many fields. PCR is used to diagnose genetic disease and to detect low levels of viral infection. In forensic medicine it is used to analyze minute traces of blood and other tissues in order to identify the donor by his genetic fingerprint.

1st level tests

(one correct answer)

1. New-born child which suffers from the attacks of the periodic vomiting has a diagnose: Niemann-Pick syndrome. What metabolic disturbance this disease is related to:

A. Enzymopathy
B. Aminoacids metabolism
C. Carbohydrates metabolism
D. Lipids metabolism
E. Connective tissue.

2. Urine of a sick child have a specific sweet smell. It is related to disorders of exchange of such amino acids as a leucine, isoleucine and valine. What diagnosis is more probable is this case:

A. Alcaptonuria
B. Phenylketonuria
C. Fructosemia
D. Galactosemia
E. Leucinosis.

3. During disorder of exchange of one amino acid the diagnosis confirms by direct determination of activity of histidase in the external layer of skin or liver. What inherited disease has such characteristics:
A. Phenylketonuria
B. Fructosemia
C. Galactosemia
D. Leucinosis
E. Histidinemia.

4. Inherited disease which characterized by combination of hepatocirrhosis, and abnormal processes in a brain and also reduction of cerulloplasmin contents is:
A. Wilson-Konovalov disease
B. They-Sacks disease
C. Niemann-Pick disease
D. Marphan disease
E. Jilber disease.

5. Phenylketonuria is autosomal-recessive disease caused by disorder of exchange of phenylalanine and characterized by a variable expressivity. What is the basic method of prophylaxis and treatment of this disease:
A. Diet with a low concentration of phenylalanine
B. Diet without amino acids
C. Taking special medicines
D. Taking special herbs
E. Diet without lipids

6. Genetic determination of lipid exchange disorders can be related to the deficit of lysosomal enzymes, accompanied with the increase of concentration of lipids in the serum of blood and takes an important role of atherosclerosis development. So there is the total influence of many genes on development of this pathology. The origin of what group of disease causes the higher action of genes:
A. Monogene
B. Multifactorial
C. Chromosomal
D. Mithochondrial
E. Genome.

7. Blood test of a patient is observed: anomalous haemoglobin S and anomalous erythrocytes. The most credible diagnosis is:
A. Sickle-cell anemia
B. Fructosemia
C. Galactosemia
D. Leucinosis
E. Histidinemia.

8. New-born child has a vomiting. A laboratory test specified on increasd contents of amino acids with the ramified chain: valine, leucine, isoleucine. Urine has a smell of maple syrup too. What inherited disease is related to these changes:
A. Phenylketonuria
B. Fructosemia
C. Galactosemia
D. Leucinosis

E. Histidinemia.

9. The parents of a child has addressed to the genetists. After examination the pathology of liver (cirrhosis, high contents of copper) and hemorragic diathesis has revealed. What inherited disease can be suspected in a child:

A. Wilson-Konovalov disease
B. They-Sacks disease
C. Niemann-Pick disease
D. Marphan disease
E. Jilber disease.

10. After medical examination (sweat test) of the 2-years old girl with suspicion on monogenic disease the increased concentration of chlorine and natrium in 5 times has revealed. What inherited disease is it characteristic for:

A. Phenylketonuria
B. Fructosemia
C. Galactosemia
D. Leucinosis
E. Histidinemia.

11. After child birth the positive reaction of urine with a 10% iron chloride is observed. What inherited pathology it is characteristic for:

A. Phenylketonuria
B. Fructosemia
C. Galactosemia
D. Leucinosis
E. Histidinemia.

12. The woman has addressed to the genetists concerning of the genetic risk of haemophilia for her children. Her husband suffers from haemophilia but there were not cases of haemophilia in a family of woman. Specify the risk of a sick child birth:

A. 100%
B. 25%
C. 50%
D. 75%
E. 0%.

13. For the some inherited disease which earlier considered as incurable now it is possible to treat by means of dietotherapy. It is concerns mostly:

A. Sickle-cell anemia
B. PKU
C. Hemophilia
D. Cystic fibrosis
E. Achondroplasia.

14.Woman has a They-Sacks disease which is related to the metabolic disorder. What metabolic anomalities do this disease have:

A. Carbohydrate
B. Mineral
C. Lipids
D. Aminoacids
E. Protein.

15. Some patient with an increased concentration of lipids in the serum of blood and deposits of these substances in nervous cells has a psychological changes. What inherited disease can be supposed at this patient:

A. They-Sacks disease
B. PKU
C. Galactosemia

D. Leucinosis
E. Histidinemia.

16. Child has hospitalized by the age 1 year 6 months. During an inspection the higher nervous activity, imbecility, disorders of motive functions, weak pigmentation of skin, increased concentration of phenylalanine in blood has revealed. What disease these signs are characteristic for:

A. Sickle-cell anemia
B. PKU
C. Galactosemia
D. Leucinosis
E. Histidinemia.

TOPIC: Population-statistical method. Medical-genetic counseling

Population-statistical method. The law of constancy of genetic structure of ideal population. Use of the Hardy-Weinberg formula in medicine for definition of the genetic structure of human population. Medical-genetic aspects of a family. Prenatal diagnostics of hereditary disease.

Population-statistical method

Recently a very large variety of statistical methods, at different levels of complexity, have been put forward to observe a genotype analysis and detect genetic variations that can be responsible for increasing the susceptibility to many diseases. This provides a concise account of a number of selected statistical methods for population-based association mapping, from single-marker tests of association to multi-marker data mining techniques for gene interaction detection.

In 1908 G.H. Hardy (the English mathematician) and W. Weinberg (the German physician) independently worked out the mathematical basis of population genetics. Their formula predicts the expected genotype frequencies using the allele frequencies in a population. Hardy and Weinberg showed in the following mode that if the population is very large and random mating is taking place, allele frequencies remain unchanged (or in equilibrium) over time unless some other factors intervene. If the frequencies of allele A and a (of a biallelic locus) are p and q, then (p + q) = 1.

This means $(p + q)^2 = 1$ too. It is also mathematically correct that $(p + q)^2 = p^2 + 2pq + q^2 = 1$.

In this formula, p^2 corresponds to the frequency of homozygous genotype AA, q^2 to aa, and 2pq to Aa. Since 'AA, Aa, aa' are the three possible genotypes for a biallelic loci , the sum of their frequencies should be 1. In summary, Hardy-Weinberg formula shows that:

$$\underset{AA}{p^2} + \underset{Aa}{2pq} + \underset{aa}{q^2} = 1$$

If the observed frequencies do not show a significant difference from these expected frequencies, the population is said to be in Hardy-Weinberg equilibrium (HWE). If not, there is a disorder of the following assumptions of the formula, and the population is not in HWE. So the three observed genotype frequencies will always sum up to 1. But to check HWE, one starts with p calculated from the observed homozygote genotype frequency and calculate q as (1–p) and estimate expected heterozygote frequency (2pq) and homozygote frequency for the other allele (q^2). If these frequencies are not similar to observed values, the sample may not be in HWE. For examples, frequency of PKU in a population makes 1:40000. Proceeding from the law:

$$q^2(aa) = \frac{1}{40\,000},$$

$$q(a) = \sqrt{\frac{1}{40\,000}} = \frac{1}{200} = 0.005$$

$$p + q = 1 \qquad p = 0.995$$

Frequency of heterozygotic carriers will make 2pq.

2pq = 2 x 0. 995 x 0. 005 = 0. 0995.

Then among the population frequency of carriers will be on:

1000 – 99.5 heterozygotes

10000 – 995 heterozygotes

100000 – 9950 heterozygotic carriers.

Genetic heterogeneity and polymorphism of natural populations

Natural populations and human populations are characterized by heterogeneity and polymorphism.

Genetic heterogeneity (variety) is connected to mutational process which results in occurrence new alleles not directed, casual influence. Sometimes some mutant genes in different populations have high frequency of occurrence. For example, high frequency of a gene of hemoglobin S (Hb) meets in tropical Africa; in the Western Africa a gene of hemoglobin – C (Hb). It is connected to an action of natural selection and drift of genes. For example, people with a gene sickle-cell anemias or thalassemia, homo- and heterozygotes are not sensitive to a malaria, and in the centers of a malaria high frequency of such mutant genes is supported.

Mutational process constantly creates new variants of mutations of different genes. All variety of mutant genes which define a variety of corresponding protein can be divided into two groups: genes which in populations meet frequency less, than 1%, named ***rare***, but genes which meet frequency bigger than 1% named ***polymorphic***. For example, to polymorphic (plural) genes belong to the variants of genes system ABO.

Genetic heterogeneity and polymorphism provide in populations phenotypically; polymorphism in real conditions results in various pressure of selection upon individuals in a population with other conditions of a life.

It is known, that in different human populations the frequency of distribution of blood ABO groups is different. Non-equal distribution of ABO groups is not casual. Regions, with rather low frequency of a gene Io and high with a gene Iв, coincide in a regions of plague. The activator of a plague has H-similar antigene makes group of risk with the given blood group. Really, high frequencies of a gene Io are characteristic for the natives of Australia, Polynesia, Indians of America where plagues did not meet. The relative risk to be ill by smallpox more often at individuals with a gene I (with II (A) and IV (AB) blood groups), in comparison with persons with I (O) and III (B) blood group. In carriers of a gene IA the antibodies which neutralize smallpox antigene do not developed.

Examples of alleles which have adaptive value

Alleles and genotypes	**Geographical distribution**	**Adaptive value**
Groups of blood of system ABO, allele B	Everywhere, more often in Asia	Relative stability to a plague
Allele A	Everywhere	Relative stability to intestinal diseases; to the stomach ulcer and a duodenal gut

Genotypical polymorphism on many loci has been inherited from the previous forms.

For example, at humanoid monkeys the polymorphism on a blood group systems and Rhesus factor also had established.

Medical-genetic counseling

The term ***medical-genetic counseling*** (MGK) was coined in 1947 by Sheldon Clark Reed, who published the book «Counseling in Medical Genetics» in 1955.

Prenatal diagnosis is a variety of techniques to determine the health and condition of an unborn child (fetus). Without knowledge gained by prenatal diagnosis, there could be an untoward outcome for the fetus or the mother or both.

MGK is carried out in four stages: 1) diagnosis; 2) drawing up a forecast; 3) conclusions; 4) family advice on the prevention of the birth of a sick child.

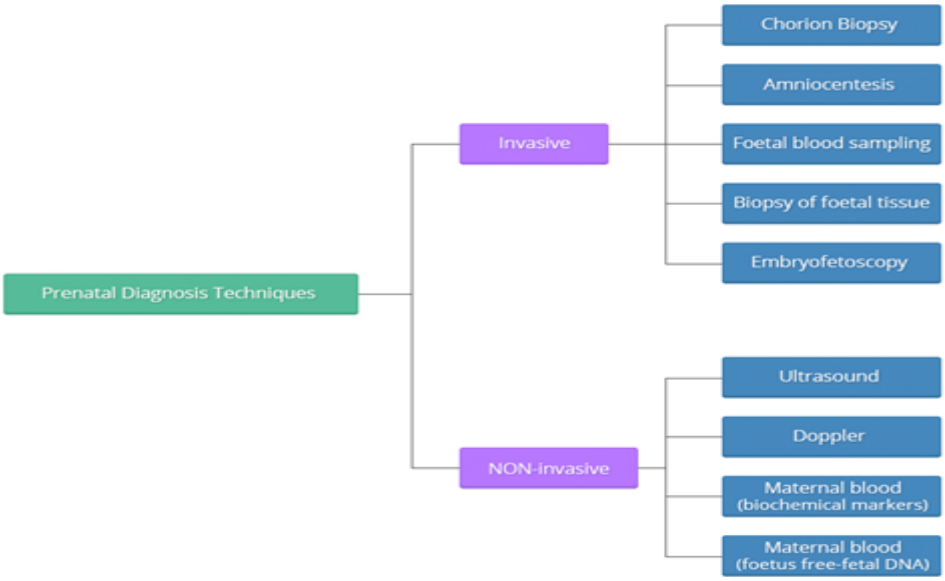
Congenital anomalies account for approximatly 20 to 25% of perinatal deaths. Specifically, prenatal diagnosis is helpful for:

1. Managing the remaining weeks of the pregnancy
2. Determining the outcome of the pregnancy
3. Planning for possible complications with the birth process
4. Planning for problems that may occur in the newborn child
5. Deciding whether to continue the pregnancy
6. Finding conditions that may affect future pregnancies.

Prenatal diagnosis is prescribed in the following cases:

1. The age of the mother is set at 35 years, the father – over 40 years.
2. Presence in the family of a previous child with chromosomal pathology, including Down syndrome (previous aneusomic).
3. The appearance in the family of a well-established hereditary disease.
4. Rearrangements of parental chromosomes.
5. The presence in the family of diseases inherited in connection with sex.
6. The appearance in the mother of an X-linked recessive pathological gene;
7. Fragile X chromosome syndrome.
8. Hemoglobinopathy.
9. Congenital errors of metabolism.
10. Various hereditary diseases diagnosed by adhesion to DNA markers.
11. Neural tube defects of unknown etiology, children with multiple congenital malformations and chromosomal pathology.
12. The appearance of structural rearrangements of chromosomes (especially translocations and inversions) in one of the parents.
13. Heterozygosity of both parents on one pair of alleles in autosomal recessive diseases.
14. Pregnant women from the zone of high radiation pollution, with teratogenic effects, etc.
15. There is polyhydramnios or dehydration during this pregnancy.
16. Increase in level of alpha-fetoprotein in blood more than 2.5 MoM (multiple of median) or decrease to 0.5 MoM.
17. Suspicion of congenital malformations of the fetus at ultrasound.
18. There were viral diseases in the first trimester of pregnancy.
19. Extragenital diseases of a pregnant woman (hypertension, diabetes, thyroid disease, congenital and acquired heart defects).

There are a variety of non-invasive and invasive techniques available for prenatal diagnosis. Each of them can be applied only during specific time periods during the pregnancy for greatest utility.



Non-invasive methods

Ultrasound is a non-invasive procedure that is harmless to both the fetus and the mother. High frequency sound waves are utilized to produce visible images from the pattern of the echos made by different tissues and organs, including the baby in the amniotic cavity. The developing embryo can first be visualized at about 6 weeks of gestation. Recognition of the major internal organs and extremities to determine if any are abnormal can best be accomplished between 16 to 20 weeks of gestation.

Although an ultrasound examination can be quite useful to determine the size and position of the fetus, the size and position of the placenta, the amount of amniotic fluid, and the appearance of fetal anatomy, there are limitations to this procedure. Subtle abnormalities may not be detected until later in pregnancy, or may not be detected at all. A good example of this is Down syndrome (trisomy 21) where the morphologic abnormalities are often not marked, but only subtle, such as nuchal thickening.

Amniocentesis

This is an invasive procedure in which a needle is passed through the mother's lower abdomen into the amniotic cavity inside the uterus. Enough amniotic fluid is present for this to be accomplished starting about 14 weeks of gestation. For prenatal diagnosis, most amniocenteses are performed between 14 and 20 weeks of gestation. However, an ultrasound examination always proceeds amniocentesis in order to determine gestational age, the position of the fetus and placenta, and determine if enough amniotic fluid is present. Within the amniotic fluid are fetal cells (mostly derived from fetal skin) which can be grown in culture for chromosome analysis, biochemical analysis, and molecular biologic analysis.

In the third trimester of pregnancy, the amniotic fluid can be analyzed for determination of fetal lung maturity. This is important when the fetus is below 35 to 36 weeks of gestation, because the lungs may not be mature enough to sustain life. This is because the lungs are not producing enough surfactant. After birth, the child will develop respiratory distress syndrome from hyaline membrane disease. The amniotic fluid can be analyzed by fluorescence polarization (fpol), for lecithin: sphingomyelin (LS) ration, and/or for phosphatidyl glycerol (PG).

Risks with amniocentesis are uncommon, but include fetal loss and maternal Rh sensitization. The increased risk for fetal mortality following amniocentesis is about 0.5% above what would normally be expected. Rh negative mothers can be treated with RhoGam. Contamination of fluid from amniocentesis by maternal cells is highly unlikely. If

oligohydramnios is present, then amniotic fluid cannot be obtained. It is sometimes possible to instill saline into the amniotic cavity and then remove fluid for analysis.

Chorionic villi sampling (CVS) and trophoblast examination is performed in the first trimester of pregnancy (9–11th week) under ultrasound control. The procedure is performed transabdominally or transcervically. The resulting chorionic cells are examined to determine the chromosome set, DNA, enzymes, sex of the fetus, the presence of hemoglobinopathies (sickle cell anemia, P-thalassemia).

Invasive methods

Chorionic villi sampling (CVS) and trophoblast examination is performed in the first trimester of pregnancy (9–11th week) under ultrasound control. The procedure is performed transabdominally or transcervically. The resulting chorionic cells are examined to determine the chromosome set, DNA, enzymes, sex of the fetus, the presence of hemoglobinopathies (sickle cell anemia, P-thalassemia).

Amniocentesis – the extraction of amniotic fluid with a fine needle to obtain and study fetal cells that are in them. The most common is the transabdominal method (through the abdominal wall). It is performed under ultrasound control during the period of 12–18 weeks of pregnancy. Fetal cells are examined either immediately or cultured for 2–4 weeks for subsequent cytogenetic, molecular genetic, biochemical studies. The method makes it possible to detect chromosomal abnormalities, metabolic disorders.

In the third trimester of pregnancy, the amniotic fluid can be analyzed for determination of fetal lung maturity. This is important when the fetus is below 35 to 36 weeks of gestation, because the lungs may not be mature enough to sustain life. This is because the lungs are not producing enough surfactant. After birth, the child will develop respiratory distress syndrome from hyaline membrane disease. The amniotic fluid can be analyzed by fluorescence polarization (fpol), for lecithin: sphingomyelin (LS) ration, and/or for phosphatidyl glycerol (PG).

Risks with amniocentesis are uncommon, but include fetal loss and maternal Rh sensitization. The increased risk for fetal mortality following amniocentesis is about 0.5% above what would normally be expected. Rh negative mothers can be treated with RhoGam. Contamination of fluid from amniocentesis by maternal cells is highly unlikely. If oligohydramnios is present, then amniotic fluid cannot be obtained. It is sometimes possible to instill saline into the amniotic cavity and then remove fluid for analysis.

Cordocentesis – puncture of the vessels of the umbilical cord of the fetus to draw blood. It is carried out under ultrasonic control. Blood samples are used for the same purposes as in amniocentesis. However, cordocentesis has the advantage that blood is a more convenient object for research than amniotic fluid cells. Blood cells are cultured faster (within 2–3 days) and more reliably than amniocytes.

Fetal tissue biopsy is performed in the 2nd trimester of pregnancy under ultrasound control without fetoscopy. To diagnose hereditary skin diseases (ichthyosis, bullous epidermolysis), a skin biopsy is performed. The material is examined under a light or electron microscope. To diagnose Duchenne muscular dystrophy, a muscle biopsy is performed, followed by an immunofluorescent test that detects the dystrophin protein. Patients do not have such a protein because the normal gene that produces it does not function.

Fetoscopy – a visual examination of the fetus with an endoscope (fetoscope). An endoscope inserted into the amniotic cavity (through the anterior abdominal wall or posterior vault) makes it possible to examine parts of the fetus, perform a blood sample, skin biopsy for analysis. The method allows to diagnose visible congenital malformations (polydactyly, achondroplasia, etc.), to detect ichthyosis, bullous epidermolysis in the study of skin biopsies. This method can also be used to diagnose hereditary hemoglobinopathies, erythrocyte enzymopathy, immunodeficiency. It is performed only in

cases of special indications at 18–23 weeks of pregnancy under ultrasound control. In 7–8% of cases after fetoscopy miscarriages are registered.

In recent years, the hypothesis of preconceptive prevention has been developing. It begins a few months before conception and continues during the early stages of embryonic development. Preparation of the mother's body (vitaminization, antioxidant therapy, increased immunity, lack of stress) for conception and compliance with these conditions in the early stages of embryonic development (up to 10 weeks) helps to reduce the frequency of congenital malformations. According to M.P. Bochkov (1997), in women who underwent additional vitaminization, the frequency of rebirth of a child with neural tube defects decreased from 4.6 to 0.7%.

1st level tests

(one correct answer)

1. The parents with a child have appealed to the medical consultation concerning Down's syndrome. What method of genetics is more expedient to be used when diagnosing such syndrome:

A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

2. Phenotypically healthy pregnant woman has the cells with Y-chromosome in her amniotic fluid. It is the reason of:

A. Suspected PKU
B. X-linked dominant pathology
C. X-linked recessive pathology
D. Probability of a child birth with Kleinfelter syndrome
E. Male sex of a child.

3. Women ages about 35–40 years more often give birth to a child with inherited diseases. What is the basic factor that influences on appearance of heavy anomalies of a child:

A. Not sufficient hormone activity
B. Not sufficient number of ovocytes
C. Metabolism decreasing
D. Genetics defects in egg during women’s life
E. Reproduction disorders.

4. For the woman the determination of sexual chromatine percentage in the cells of epithelium has determined. In what case must be suspected the pathology:

A. In 0 % cells
B. In 65 % cells
C. In 50 % cells
D. In 38 % cells
E. In 30 % cells.

5. Healthy parents has a child with Down's syndrome, but with karyotype 46 chromosomes. One of chromosomes from group D had the extended short shoulder. What method should be used for the revealing unbalanced translocation of 21th chromosome?

A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

6. A healthy young woman has a father which suffers from the Taybi syndrome (genetic disease that involves broad thumbs and toes, short stature, distinctive facial features and

others) has appealed to the geneticist. Illness is inherited as X-linked recessive. Give the prognosis of a sick child birth if her husband is healthy:

A. 25 %
B. 37.5 %
C. 50 %
D. 56.25 %
E. 75 %.

7. What type of inheritance do the hemophilia have:

A. Autosomal-recessive
B. X-linked dominant
C. Autosomal-dominant
D. X-linked recessive
E. У-linked.

8. Young man has appealed to the genetists concerning disorders of physical and sexual development. Microscopy of the mucous membrane has revealed one Barr body. Specify the most reliable karyotype:

A. 47, ХУУ
B. 47, ХХУ
C. 47, 18+
D. 47, 21+
E. 45, ХО.

9. The married couples have appealed to the doctor with a question about probability of child birth with X-linked form of rachitis. A father is healthy, but mother and grandmother from the maternal line suffer from this disease. Define the probability of the sick children birth in this family:

A. All children
B. All daughters
C. Only sons
D. Half of sons and daughters
E. No correct answer.

10. Pregnant women has addressed to the doctor concerning the possible inherited pathology of the future child. What method should be used in this case:

A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

11.The Morr's syndrome is inherited as a dominant and accompanied with the numerous anomalies of skeleton (brachydactylia), disorders of tooth formation and others. What methods of anthropogenetics must be used to distinguish this pathology from the possible genocopy and make the prognosis of possible pathology for descendants:

A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

12. Genetic determination of lipid exchange disorder can be related to the deficit of lysosomal enzymes and has increased concentration of lipids in the blood serum and also plays an important role of atherosclerosis development. Thus there is the total influence of many genes on development of pathology. What group of illnesses gives the higher marked genes interactions:

A. Genome

B. Monogenic
C. Chromosomal
D. Mithochondrial
E. Multifactorial.

13. Which of the below mentioned group of disease do the scoloisis belong:
A. X-linked
B. Autosomal-dominant
C. Autosomal-recessive
D. Multifactorial
E. Dependence only from the environment

14. Genetically healthy parents have a child sick by phenylketonuria (autosomal-recessive inherited disease). What genotypes of the parents:
A. Aa x aa
B. AA x AA
C. AA x Aa
D. Aa x Aa
E. aa x aa

15. A man has some inherited monogenic disease. It is:
A. Hemophilia
B. Hypertension
C. Stomach ulcers
D. Hymenolepiasis
E. Diabetes.

16. Child with a light hair, pale skin has a cramps and signs of mental retardation. What methods it is necessary to apply for the establishment of diagnosis of this inherited disease:
A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

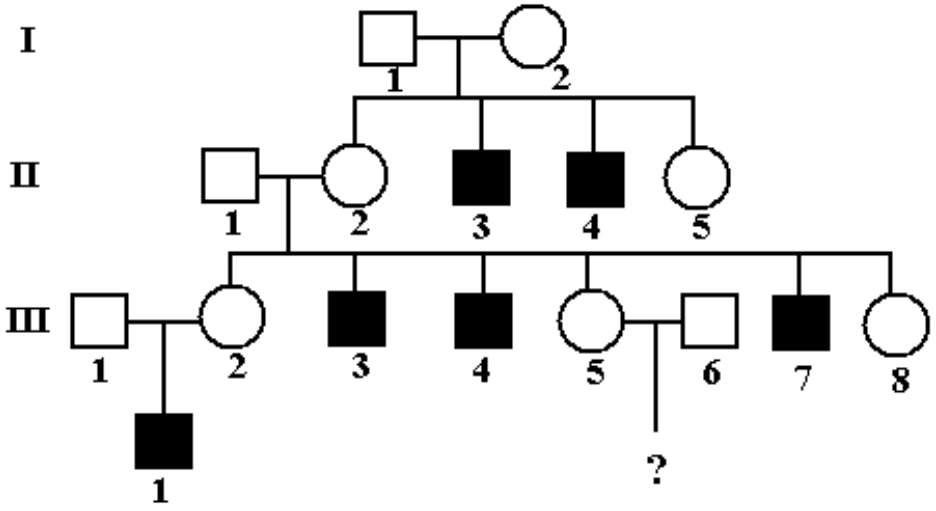
17. Phenylpyruvic acid is found in urine and blood of the patient. The preliminary diagnosis PKU was made. What method should be used for the clarification of diagnosis:
A. Cytogenetics
B. Biochemical
C. Twins
D. Dermatoglyphics
E. Immunological.

18. Amniotic liquid contains proteins, carbohydrates, mineral salts, hormones, urine and also cells of a fetus. What method is used for the determining of the child sex:
A. Cytogenetics
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

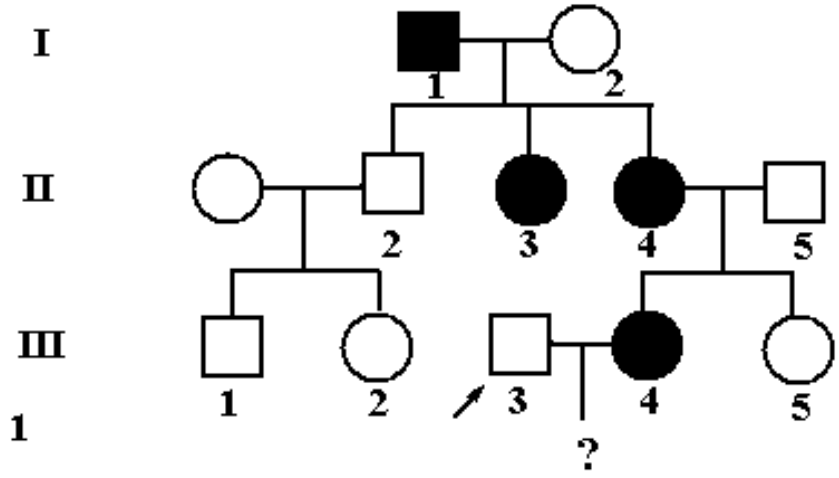
19. For the diagnostics of metabolic disease caused by changes of enzymes activity is used the following method:
A. Twins
B. Biochemical
C. Genealogical
D. Dermatoglyphics
E. Immunological.

Situational tasks

1. One type of deafness is inherited as a X-linked character but other type – as autosomal-recessive type. Two young people with normal hearing (groom and bride) have addressed to the medical-genetic consultation because of presence of hearing anomaly in both families. The groom had a deaf brother and uncle from the mother line, the cousin (the aunt's son from the line of mother); but mother and father are healthy. The bride had deaf brother and sister, but her parents were healthy. Make a family tree. Define type of inheritance of deafness in each family. Define the genetic risk of the deaf children birth.
2. The woman has addressed to the medical-genetic consultation, her six relatives suffering from the progressing muscular dystrophy (syndrome of Dushen). Taking into account this circumstance, she is afraid about future child health. The family tree (probands III, 5) has been made. Define probability of a birth in her family the child with Dushen syndrome.
3. Analyze the family trees with Dushen dystrophy and vitamin D-resistant rickets (see figures below). Define type of inheritance. What probability of a sick children birth in the families: III – 5 and III – 3?



A family tree of the family with cases of progressing Dushen muscular dystrophy.



A family tree with vitamin D-resistant rickets.

4. In medical-genetic consultation the woman sick of cerebellar ataxia has addressed. Her

husband is healthy. There are five sons and three daughters in this family. One son and one daughter are sick, all others are healthy. Proband has one healthy and three sick brothers. Father of proband is sick, mother is healthy. Make a family tree.

5. Man which suffers from a congenital cataract has addressed to the medical-genetic consultation, his mother, and also uncle and grandmother from the mother line have this disease too. The grandfather and aunt from the side of mother, the husband of aunt and her 3 sons are healthy. Father of proband, aunt from the side of the father, and also the grandfather and the grandmother from the side of father, the wife a proband, her sister, two brothers and parents are healthy. There are two sons of proband are healthy, but daughter is sick by congenital cataract. Make a family tree and define type of inheritance of the given disease, probability of occurrence of disease.
6. The group consists of 40 individuals (Aa) and 60 (aa). Calculate frequencies of dominant and recessive alleles. What will be structure of a population (in %) through the generation under conditions of gene balance.
7. The population consist of 49 % (AA), 9 % (aa) and 42 % (Aa). Define the frequencies of alleles A (p) and a (q) in a population. Whether the structure of a population through the generation (under condition of gene balance) will change?
8. Calculate the frequency of genotypes AA, Aa and aa (in %) in a population if aa makes in a population about 3 %.
9. In city with the population of 300 thousand the PKU (A-R disease) has revealed in 22 individuals. Define frequencies of genes (p, q) and quantity of heterozygotes – carriers of a gene PKU?

TOPIC: Practical skills of modules 2 and 3 «Peculiarities of heredity and variation», «Methods of human heredity studying. Hereditary diseases».

The place of genetics among the biological sciences and a special interest in it are determined by the fact that it studies the basic properties of organisms, namely heredity and variability.

Heredity and variability in humans is the subject of studying human genetics at all levels of its organization: molecular, cellular, organismic, and populational. Genetics of man by his successes is largely due to medical genetics - a science that studies the role of heredity in human pathology. The applied part of Medical Genetics is a clinical genetic, which utilizes the achievements of medical genetics, human genetics and general genetics in solving the clinical problems that arise in humans.

According to experts from the World Health Organization (WHO), one child in 100 newborns suffers from severe hereditary illness due to chromosomal abnormalities, and 4% of children have various genetic defects. Genetic defects cause 40% of spontaneous abortions. Each person is the carrier of 15-20 potentially defective genes.

The development of modern biochemical, cytological and genetic methods of research contributed to the disclosure of the molecular nature of many diseases. It is established that in the development of both hereditary and non-hereditary (exogenous) diseases, the state of the genetic apparatus of the cells of the organism is of great importance. Today, genetics is the basis for all biological sciences, including medical sciences. The task of modern medicine is a gradual transition from the sphere of treatment of patients to the sphere of preventing diseases and preserving the health of the population.

The study of human genetics is associated with certain difficulties: a small number of descendants, late puberty and associated with this a slow change of generations, a large number of chromosomes, the impossibility of experimenting and creating the same conditions of life. However, the use of modern research methods has made it possible to

study human genetics at the level of classical genetic objects (bacteria, viruses, Drosophila flies).

1st level tests

1. Phenylketonuria is inherited by autosomal-recession type. In family, where a mother and father are healthy, a sick boy was born (phenylketonuria). What genotypes of mother and father by these genes?
   A. AA Aa
   B. AA AA
   C. Aa Aa
   D. Aa aa
   E. Aa AA.
2. Gene that determines the dark enamel of teeth for the humans is dominant and localized in autosomes. Husband is homozygous by dominant gene but his wife has a normal color of enamel of teeth. What biological law is the basis of inheritance of such sign for the children of this couples?
   A. The law of unit characters
   B. The law of segregation
   C. The law of independent assortment
   D. Phenomenon of linked inheritance
   E. Phenomenon of sex-linked inheritance.
3. Children have analysed from one family. One of parent is homozygote by dominant gene of polydactyly and second – healthy (homozygote by recessive gene). In this case the following law has observed:
   A. The law of unit characters
   B. The law of segregation
   C. The law of independent assortment
   D. Phenomenon of linked inheritance
   E. Law of «cleaness gametes».
4. Recessive gene of phenylketonuria is suspected in one parent. What risk of sick child birth in this family:
   A. 0%
   B. 25%
   C. 50%
   D. 75%
   E. 100%.
5. Name a scientist which suggested to name a gene as discrete units of heredity :
   A. T. Schwann
   B. G. Mendel
   C. T. Levitsky
   D. T. Morgan
   E. B. Johansen
6. An area of chromosome where gene is located has named:
   A. Triplet
   B. Codon
   C. Telomere
   D. Locus
   E. Anticodon
7. Allele genes are:
   A. Genes which are located in one chromosome
   B. Genes which are located in non-homologous chromosomes
   C. Genes which are located in the same loci of homologous chromosomes
   D. Genes which determines polymeric traits

E. Genes inherited by Mendel laws.

8. Determine the correct definition of genotype:
   A. Diploid chromosomes number
   B. Haploid chromosomes number
   C. Number of all genes
   D. External features of an organism
   E. Internal features of an organism

9. Determine the correct definition of phenotype:
   A. Diploid number of chromosomes in somatic cells
   B. Haploid number of chromosomes in sexual cells
   C. All genes of an organism
   D. All features of an organisms which form during individual development by influence of environment
   E. All genes in sexual chromosomes.

10. Define the amount of variants of sorts of gametes that produces diheterozygous individual in condition of location of genes in the different pairs of homological chromosomes:
   A. 16
   B. 8
   C. 4
   D. 6
   E. 2.

11. The young married couples gave birth a child with the eyes of different colors. How do such variation name:
   A. Recombination
   B. Genome mutation
   C. Modification
   D. Gene mutation
   E. Chromosomal mutation.

12. Otosclerosis (pathological trait that shows up as the loss of hearing) is determined by a autosomal-dominant gene. Penetrance of gene is 50%. Which probability of sick children birth at the healthy heterozygous carriers of this gene:
   A. 37,5 %
   B. 75 %
   C. 100 %
   D. 50 %
   E. 0 %.

13. There is a severe limit of time staying on a height over 800 meters above a sea level without oxygen bulbs exists for the humans. What is the limiting factor for life in this case:
   A. Temperature
   B. Level of ultraviolet radiation
   C. Level of humidity
   D. Pressure of oxygen
   E. Gravitation.

14. Anaphase of mitosis has stopped by a colchicine that blocks divergence of chromosomes to the opposite poles. What type of mutation can be applied in this case:
   A. Polyploidy
   B. Heteroploidy
   C. Deletion
   D. Duplication
   E. Translocation.

15. Predilection of diabetes is caused by autosomal recessive gene. This gene shows up only for 30% homozygous individuals. This partial expression is the example of the following property of gene:

A. Mutation
B. Penetration
C. Heredity
D. Expressivity
E. Polymery.

16. For the humans the same genotype expresses the development of disease with the different degrees of phenotypes. Degree of a trait during realization of genotype in the different limits of environment is named as:

A. Mutation
B. Penetration
C. Heredity
D. Expressivity
E. Polymery.

17.One of forms of rachitis is inherited by a dominant type. Men and women are sick. This disease is a result of:

A. Recombination
B. Genome mutation
C. Modification
D. Gene mutation
E. Chromosomal mutation.

18. Albinism is observed in all classes of vertebrates. This inherited pathology is observes also for a human and determine by autosomal-recessive gene. Define the law which determines the presence of albinism for the humans and for the representatives of all classes of vertebrates:

A. The law of homologous lines of hereditary forms of variability
B. Biogenetic law of Gekkel
C. 1st law of Mendel
D. 2nd law of Mendel
E. Linked inheritance by T. Morgan.

19. Parents of 5-years sick girl have addressed to a medical consulting. Karyotype researches revealed 46 chromosomes in her karyotype but one chromosomes from15th pair was longer than usual because it was joined form 21st chromosome pairs. What type of mutation takes place in such case:

A. Deletion
B. Duplication
C. Translocation
D. Polyploidy
E. Heteroploidy.

20. Genetically healthy woman during her pregnancy was sick by a viral german measles. The deaf child was born with a cleft palate as a result of:

A. Phenocopy
B. Genome mutation
C. Modification
D. Gene mutation
E. Chromosomal mutation.

2nd level tests

1. What essence of the «law of cleanness of gametes»:

a) gamete is clean, contains genes in the homozygous state;
b) clean are gametes which have formed only by homozygous organisms;

c) gametes which form any organism are clean and contain information about possibility of development only one variant of every character.

2. At crossing of what organisms the segregation in posterity by genotype and phenotype will not take place in next generations:

a) at crossing of phenotypically similar organisms;
b) at crossing of organisms which are different by alternative traits;
c) at crossing of organisms which are homozygous by the same alleles;
d) at crossing of genotypically similar organisms.

3. Whether is possible to consider as alternative the following traits:

a) normal coagulation of blood and sickle-cell anemia;
b) normal metabolism of phenylalanine and phenylketonuria;
c) presence of dark pigment in a skin and its absence(albinism);
d) brown eyes and light hear;
e) short fingers on hands(brachydactylia) and high height;
f) dark and light enamel of teeth.

4. Thalassemia is predefined by a recessive gene. Frequency of gene is too high in some populations in tropical Africa. Explain why the gene of thalassemia does not disappear as a result of natural selection:

a) heterozygosity of an organism;
b) homozygosity by a recessive gene;
c) dominance of a gene;
d) natural selection against homozygote;
e) advantages of heterozygous carriers of thalassemia gene in a concrete environment.

5. How many allelic genes are coding blood group by system AB0:

a) in a population;
b) in each individual;
c) in a gamete?

Situational tasks

1. Albinism (lack of melanin) – autosomal recessive disorder that is phenotypically manifested after the birth of a child. Why can children with normal skin pigmentation be born in albino parent?
2. Healthy parents have a child with phenylketonuria. What type of inheritance is this? What is the probability of having a second child healthy?
3. 6-months old child has neurological symptoms: irritability, increased muscle tone, tremors, convulsions, develops microcephaly, mental retardation, decreased pigmentation of the skin, hair and iris of the eye. What disease can be assumed? How to confirm the diagnosis? What methods do geneticists use to establish if the disease is hereditary or not?
4. A special diet and exclusion of mother's milk for a child with phenylketonuria do not help, symptoms of disease have not disappeared. What nature did the pathology have?
5. Microscopy of the child’s blood has revealed both of normal erythrocytes and sickle-cell erythrocytes. Does the result of blood test confirm hereditary disease? Does the child need the special treatment?
6. Child has an increased elasticity of the skin, the high mobility of joints, internal hemorrhage without rupture of blood vessels. Are there any hereditary diseases have such phenotypic changes? Which metabolic disorder leads to such symptoms?
7. A pregnant women came for advice to a medical-genetic counsultation (her brother was diagnosed with phenylketonuria) with a question about probability having a healthy child. What laboratory method is more expedient to be used?
8. Newborn baby’s urine takes the color of ocher in the air. Could this situation indicate a hereditary disease? Does the child need appropriate treatment?
9. Achondroplasia – a genetic disease with an autosomal-recessive type of inheritance.

Healthy parents have a child with this disorder. Determine the probability of birth to a healthy child.

10. In healthy parents had a child with Duchenne's syndrome (X-linked recessive inheritance) which characterized by progressive degeneration of the muscles and death. Determine the probability of having a healthy child (boy, girl).
11. To the genetic consultation the woman came for advice because of 3 children birth from two marriages with plural congenital developmental anomalies. The result of cytogenetical researches there are 45 chromosomes have been found. Her karyotype is 45, XX, t (13). Karyotypes of parents and sibs of women were normal. The woman was the carrier of translocation between homologous chromosomes in 13 pair which has arisen de novo. It was offered to this woman to refuse the further birth. She has not accepted advice and one year later has given birth a child with the plural anomalies incompatible with a life. Determine types of gametes which form proband and her husband (genotypically healthy). Is it possible for her to have a healthy child? Give the explanation.
12. In one family one of forms deafness is observed. Probands – the deaf-and-dumb girl, her brother, mother and father are healthy. On the side of the father of proband the aunt and the grandfather are healthy, and the grandmother is deaf. Mother of proband has the deaf-and-dumb brother and healthy brother and the sister. The grandfather and the grandmother from the mother side with normal hearing. Make a family tree. Define type of inheritance of an attribute and genotypes of members of a family tree.
13. Probands - the boy with freckles. His brother hasn't freckles, sister – with freckles. Mother and father of proband with freckles. Father has been married twice. From the second wife – three children (the daughter and two sons) all without freckles. Make a family tree, define character of inheritance of an attribute and genotypes of all members of a family tree.
14. In family of healthy parents the boy of five years was ill on one of myopathy forms (atrophy of muscles is observed). The uncle of proband from mother line and the aunt's son from mother side are sick. Aunt of proband from mother side mother of the sick child, her husband, and also the grandmother and the grandfather from mother side are healthy. Make a family tree of family, define type of inheritance of disease and specify heterozygotic carriers of a pathological.
15. The sweat-secreting glands absence in an in individual linked with X-th chromosome is a recessive character, albinism is an autosome-recessive character. In a healthy married couple the sons was born with both of diseases. Indicate possible parents' genotypes. What a possibility of existence such anomalies in second son? What a possibility of a healthy child birth?
16. Enamel hypoplasy in human is inherited as X-linked character (dominant one). The parents in the family are suffering from this anomaly and the son was born with normal tooth. What may be the other son's phenotype?
17. Hypertrichosis (excessive hairiness) is transmitted through Y-chromosome. What a possibility of birth a child with hairiness of cochlea if this character is expressed in father?
18. Tooth enamel darkening is determined by two dominant genes one of which is located in autosome and the other – in X-chromosome. In a parent's family with dark tooth a girl and a boy with normal tooth color were born. Indicate the possibility of birth of next child in this family also without disorder if dark mother's tooth are determined by the gene X-linked and father's dark tooth – by autosomic gene. Write down the genotypes of healthy people.
19. Short-sighted (dominant character) without freckles man got married with a normal-sighted woman with freckles (dominant character). There are three children in the family, all children are short-sighted and with freckles. Define the genotypes of parents

and children.

20. Father with curly hair (dominant character) without freckles and mother with a straight hair and freckles (dominant character) have three children: curly hair and freckles, curly hair and without freckles, straight hair and freckles. Define the genotypes of parents and all possible genotypes of their children.
21. Father is deaf-and-dumb (recessive character) with white ringlet over the forehead (dominant character) and mother is healthy without white ringlet. Their child was born deaf-and-dumb with white ringlet over the forehead. Is it possible approving that the child inherits these characters from his father.
22. There are several forms of inherited near-sightedness in the person. Moderate form (from –2.0 till –4.0) and severe (more than –5.0) are transmitted as autosome-dominant characters not-linked between each others. In the family where the mother was near-sighted and the father had normal sight two children had been born, the daughter and the son. The daughter had a moderate near-sightedness form and the son – high one. What possibility of birth of next child in the family without any anomalies if it's known that only one of mother's parents was suffering from n near-sightedness. It should be taken into account that in people that have both n near-sightedness forms only one form (high) is expressed.
23. The human's height is controlled by several pairs of non-linked genes interacting by polymery type. If one doesn't take into account environmental factors than one can content (limit) with three gene pairs: in human population people with low height have recessive genes (150 cm), tall – dominant genes and 180 cm. Determine human height which are heterozygous on all three height gene pairs.

TOPIC: Molecular genetic mechanisms of ontogenesis. Features of prenatal human development. Disorders of ontogenesis and their place in human pathology

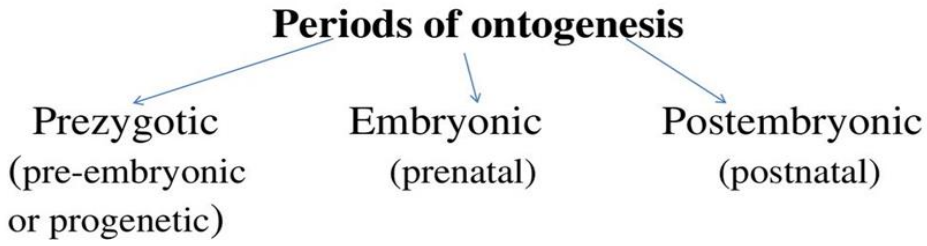
Ontogenesis: the types, periods, phases. Embryonic stages of human development. Differentiation on the molecular genetic, cellular and tissue levels. Congenital malformations. Classification: hereditary, exogenous, multifactorial, gametopathy, blastopathy, embryopathy, fetopathy.

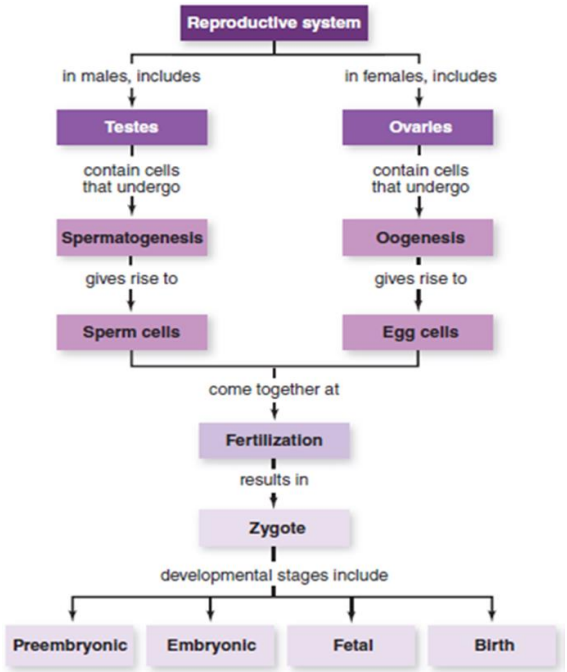
Regulation of gene function in ontogenesis. Experimental study of embryonic development. The problem of determination and interaction of blastomeres. Embryonal induction. Regulation of the cleavage process and its disorders (twins and developmental abnormalities). Critical periods of development. Teratogenesis. Teratogenic environmental factors.

Ontogenesis (individual development) – is a complete continuous process in which the individual events are related to each other in space and time.

Ontogenesis (also, **ontogeny** from the Greek – «ontos» – «being, existence» + «genesis» – «origin») is the set of morphological, phisiological and biochemical transformations from the moment of germing up to death; the entirety of an organism's lifespan.

Human ontogenesis can be divided into 3 periods: prezygotic (before fertilization), prenatal (before birth) and postnatal (after birth).





Progenesis – is a period of maturation of specialized generative cells – gametes. This maturation process is called spermatogenesis in males and oogenesis in female.

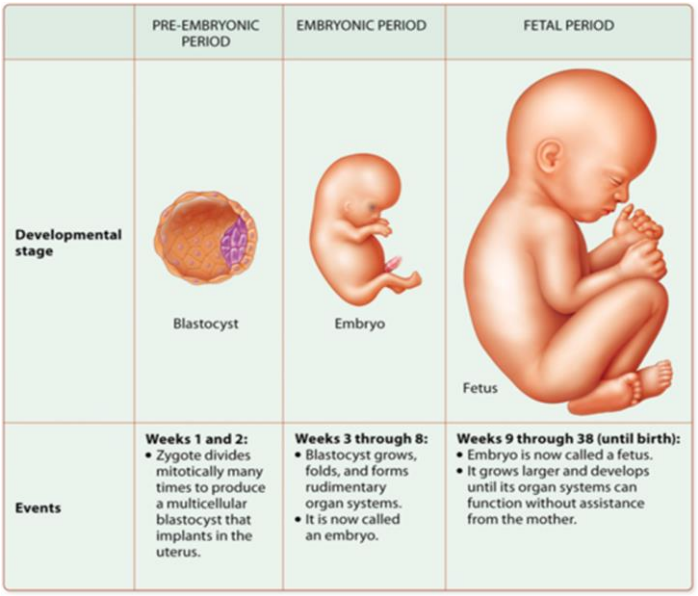
Prenatal period – is a perod from fertilization till birth. It includes: preembrionic (weeks 1–2), embrionic (weeks 3–8) and fetal (weeks 9–40) stages.

Postnatal period – is a perod from birth till death. It includes: juvenile, maturity, old age.

Main processes of prenatal period:

✓ **Fertilization** is fusion of a female and male gamete with forming of zygote:

♀ gamete (n) + ♂ gamete (n) = zygote (2n)



✓ **Cleavage** is the series of rapid cell divisions of the zygote with the formation of blastula (2–8 cells), morula (solid ball of 12-16 cells) and blastocyst (hollow ball of many calls with inner cavity – *blastocoel*):

zygote→morula→blastocyst

✓ **Gastrulation** is the process of formation in embryo the three germ embryonic layers (ectoderm, mesoderm and endoderm):

blastocyst→gastrula+extraembryonic membranes

✓ **Histogenesis**

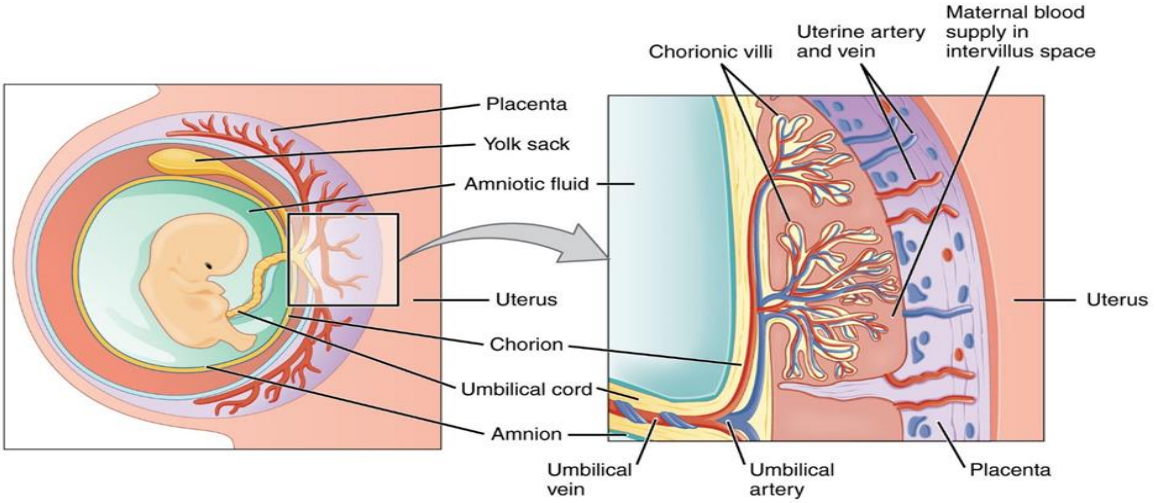
✓ **Organogenesis.**

Provisional organs (extraembryonic membranes) – are temporary organs formed by the embryo during embryogenesis and which ensure its growth and development.

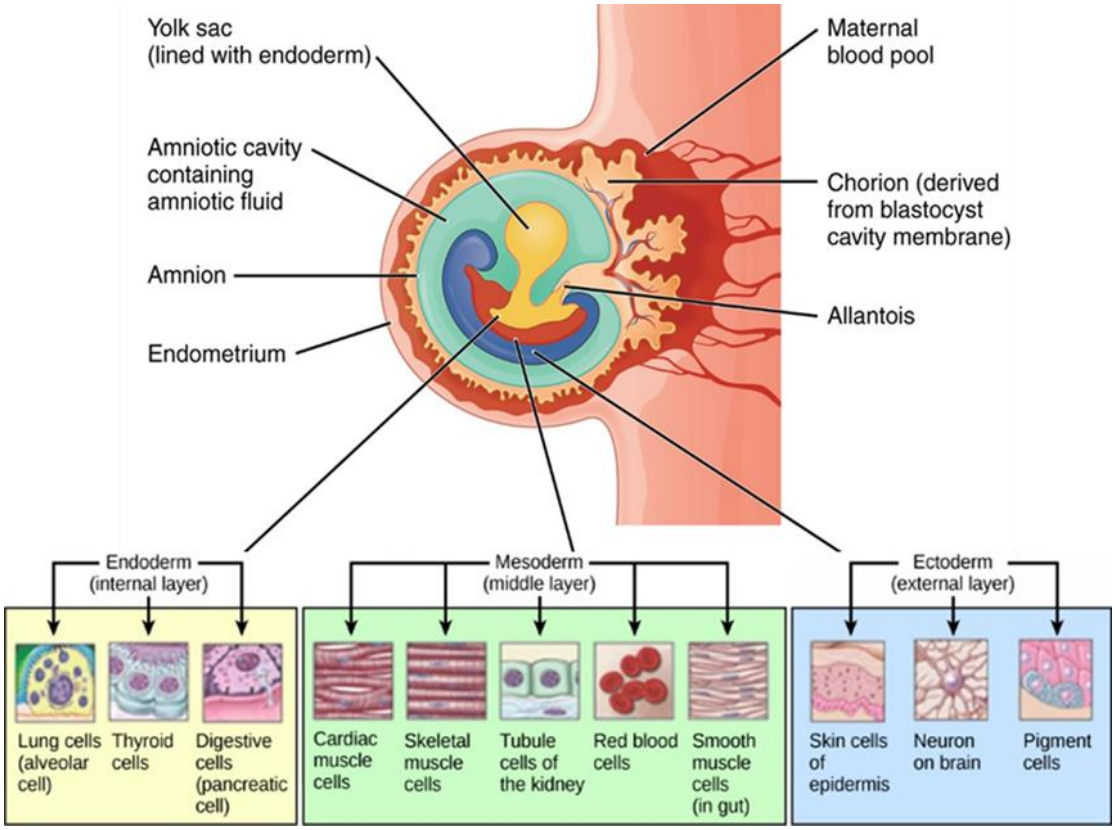
- ***amnion*** – originates from epiblast, forms an amniotic membrane that produces amniotic fluid, which creates the aqueous environment for embryo development;
- ***chorion*** *(chorionic villi)* – originates from trophoblast, surrounds embryo and all other membranes, penetrates the lining of the uterus and forms the placenta with it;
- ***yolk sac*** – originates from hypoblast, site of early blood cell formation, actively involved in the nutrition and respiration of embryo, but 8 weeks later undergoes a reversal;
- ***allantois*** *(urinary sac)* – outpocketing of embryo's gut, incorporated into umbilical cord, is an organ of nutrition, gas exchange and excretion in the early stages of embryonic development, and in the 2nd month of embryogenesis is reduced;
- ***placenta*** is a special organ that:
  - provides the fetus with nutrients and oxygen, absorbs the end products of

metabolism, secretes hormones, and serves as a barrier to harmful substances;
- functions as a fetomaternal organ which develops on 23-rd day of embryonic development from fetal chorion and allantois, and the maternal uterine tissue;
- within the placenta there is no mixing of maternal and fetal blood;

• ***umbilical cord*** provides the embryo with nutrients and oxygen, prevents the penetration of harmful substances from the placenta into the embryo.



e germinal layers give rice to various tissues and organs of animals (histo- and organogenesis):



According to the medical point of view, the periodization of human ontogenesis where all possible malfunctions takes place is very important.

Periodization of the human ontogenesis taking into account developmental malformations

1. ***Progenesis (gametopathy).*** During progenesis the formation and maturation of

gametes — gametogenesis take place where many possible disorders arising as a result of mutations or recombinations at the molecular and cellular levels. Mutant (unbalanced) gametes in most cases destroyed (eliminated) but during fertilization and formation of a zygote monogenic and chromosomal disorders can occur too. Most genetic disorders are associated with the occurrence of gametopathy.

2. Kimatogenesis (kimatopathy):

a) blastogenesis (blastopathy) – from fertilization to 15 days of gestation (cleavage, forming of embryoblast + trophoblast). Disorders lead to the death of the embryo;

b) embryogenesis (embryopathy) – disorders occur from 15 days to 8 weeks of embryonic development - (organogenesis, formation of the amnion + chorion). Form the basis of congenital malformations;

c) fetogenesis (fetopathy) – after 10 weeks of embryonic development (the development of the fetus, placenta formation, childbirth). During this period, characterized by abnormalities in the form of lower body weight, delayed intellectual development, etc.

Critical periods of development – are periods of the development of the embryo, during which the embryo is particularly sensitive (less resistant) to the effect of various environmental factors. These periods are characterized by enhanced cell differentiation, morphogenesis changes in the transition from one period to another (transition zygote to cleavage, beginning of gastrulation, etc.) as well as embryo transfer from one conditions to another (modified food conditions, gas exchange ect).

In humans, there are following **critical periods of development:**

1st period — implantation. Introduction of a zygote in wall of the uterus (6^{th}–7^{th} day after fertilization). The influence of unfavorable factors can cause pathological processes, for example embryo can stay in the oviduct or implanted in wall (ectopic pregnancy), which represents as a threat to the life of the fetus and mother.

2nd period – first three weeks of fetal life – the formation of embryonic layers. Unfavorable effects may disrupt the normal development of the fetus and cause his death.

3rd period – from third to sixth weeks of pregnancy – the formation of the placenta. The negative effect leads to the birth of sick children.

4th period – perinatal (birth). The developed fetus exposure to the new conditions of existence. The restructuring of all organ systems (respiratory, circulatory, digestive) takes place. This is a crucial moment in the life of an organism.

The study of critical periods of embryogenesis shows the necessity of protection of the mother's body from the harmful factors, especially in the very early weeks of pregnancy.

After the birth the **postnatal stage of ontogenesis** begins, which includes such periods:

1. juvenile (before puberty);
2. maturity (an adult puberal stage);
3. old age (ageing), which ends to death.

The mechanisms of the organism development. The development of any multicellular organism – is a complex of multi-step processes.

Tissue cells of the same multicellular organism characterized by morphological, biochemical and physiological characteristics because they have different specialization. The achievement of the final state of specialized cells is called cell differentiation.

Despite of the great variety of cells in the body, all of them have the same number of chromosomes because during mitosis the gene are uniform distribute between the new cells. One cell – zygote – contain all genetic information of a given individual. What are the mechanisms of realization? There is a theory that in every cell of the body do not function all genes but only a certain part of them, providing differentiation of cells of this type, the rest of genes inactive. Functioning of different genes take place in different stages of individual development. Some genes are «turned on» to the work but others — «turned

off».

Periodic activity of individual chromosome can be observed by means of microscope on the «giant chromosomes» of larval salivary gland of Drosophila fly and other dipterous as blisters (puffs) arise as despiralization of chromosomal threads on the special chromosomal regions. The positions of these swellings are changing at different stages of development. They also vary in the cells of various tissues. The differentiation of the cells is determined by the activity of tissue-specific genes.

It is likely that cause of the activation of various genes in the nuclei of the embryo cells in the early stages of its development is a different quality of the sites of egg's cytoplasm. The genes are repressed in a zygote. First of all the activation of genes that control the processes of cell division and general metabolism begins. At the gastrula stage are depressing the first tissue-specific genes that determine the formation of the stem (progenitor) cells, each of them are forming a clone (row) cells as a result of reproduction. From the number of cells clones then appear the rudiments of organs.

During histo- and organogenesis intracellular effects are particularly important because of inducing of the development of various tissues and organs. Substances which are formed in some cellular systems penetrate into the cells of other systems and then tissue-specific genes are activated which leads to the synthesis of tissue specific proteins and tissue differentiation.

Gene derepression occurs mainly under the influence of hormones in the later stages of the development.

Congenital malformations are persistent morphological changes of an organ which occurs before birth, revealed immediately or after birth and cause organ disfunction.

Congenital malformations include the following developmental disorders:

Aplasia – congenital absence of an organ.

Atresia – lack of natural channels or holes.

Hypoplasia – congenital disorder of organ's maturation (lack of mass or size).

Hypertrophy – congenital increasing of weight and size by means of increasing of cells' number or size.

Ectopia – location of an organ in unusual place.

Duplication – doubling as well as increasing of the number of organs or their parts (doubling of uterus, a double aortic arch).

Stenosis – narrowing of the channel or hole.

Fusion of organ (syndactyly, simpodia) or two symmetrically or asymmetrically conjoined twins.

Persistence – the rest of embryonic structures (e.g. Botall duct in a child older than 3 months).

Dysraphia — incomplete closure of embryonal gaps (e.g. cleft lip).

Congenital defects are divided into:

by affected structure:

1) cellular (cell heterocopies, heteroplasia, immaturation of cells and their structures, persistence, aplasia);
2) tissue (tissue heterotopia, syndactyly);
3) organ.

by the sequence of arising:

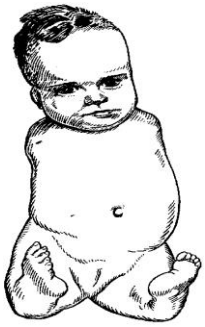
1) primary (caused by the action of the harmful factors, according to WHO, 1971 classification are divided into:
   - hereditary (genetic, chromosomal);
   - exogenous (damage of the embryo or fetus caused by teratogenic factors);
   - multifactorial (genetic + exogenous factors);
2) secondary – a complication of the primary defects.

Teratogenic environmental factors

Factors that may cause developmental disorders (anomalies and defects) are called *teratogenic* (from the Greek. *teratos* – injury). The science of congenital anomalies of development called *teratology.*

Teratogens influence on the certain critical periods. For every body the critical period is the time of its growth and formation of characteristic structures. Different organs have different critical periods. The heart is formed between the 3rd and 4th weeks. The brain and skeleton are constantly sensitive to the harmful effects, starting on the third week after fertilization until the end of pregnancy.

There is a lot of teratogens that act more strongly at certain periods of development causing gametopathy, embryopathy, fetopathy and ontophylogenetical malformations. Some factors cause gene mutations such as ionizing radiation, drugs lead to chromosome destruction and changes of the DNA structure of DNA.



All environmental factors which have a pathogenic influence can be divided into following groups:

1. The time factor (the frequency of children birth with disorders depends on the year and season).
2. Geographical factors (there is information about the different frequencies of the birth of children with pathology in different geographical areas and populations).
3. Maternal factors (hormonal status of the mother, family history, which is determined by polygenic systems of antigens, immunoglobulins ect.).
4. Intrauterine factors (mechanical and hormonal processes which are associated with childbirth, twins pregnancy, fetal position etc.).
5. Fetal factors (external factors that act directly on the fetus and inhibit its development).
6. Teratogenic factors (X-rays, illness during pregnancy, food, medicines).
7. Factors affect on the body in pre- and postnatal period (various factors provoke the development of disease).

The majority of factors can belong to the indicator and provocative factors and only the factors of the groups 4, 6, 7 have the potential teratogenic effects.

Congenital pathology caused by disorders of fetal growth occurs in approximately 2% of infants and it is the most common cause of neonatal mortality and morbidity. In the most cases of abnormalities of chromosomal damage do not observe and they are not inherited. Because the fetus is less susceptible to morphologic alterations when the developmental process of the majority of organs has been completed, the most common anomalies associated with teratogenic exposures during the fetal period are fetal growth restriction (intrauterine growth retardation) and mild errors of morphogenesis (abnormalities of phenogenesis), such as epicanthic folds, clinodactyly, and others. Thus, teratogenic exposures result in a wide variety of effects that range from infertility, prenatal onset growth restriction, structural defects, and functional abnormalities to miscarriage or fetal death. In despite of identification of many teratogenic agents, the cause of much of the damages are unknown.

The most studied causes of gametopathy, embryos and fetopathy are as follows:

Ionizing radiation has a direct damage effect on DNA and cells of the fetus and it is the cause of many birth defects as a result of its influence during pregnancy.

Teratogenic infections (viral, protozoan): rubella virus is the strongest teratogen virus, i.e. it causes a large number of birth defects. Transplacental infection of the fetus with the virus during the first trimester of pregnancy results in a majority of congenital anomalies. Rubella syndrome combines the triad of congenital anomalies: heart defects, deafness and cataracts. Described as cases of microcephaly, mental retardation and

microphthalmia. The risk of fetal infection with rubella virus has fallen as a result of immunization against the infection. Teratogenic effect of other viral infections is discussed. There are reports of teratogenicity of influenza viruses, chickenpox.

Teratogenic effects have some Protozoa from class Sporozoa – *Toxoplasma gondii*. If the mother is ill with toxoplasmosis the infection is disseminated through the placenta to the offspring in 40%, with maternal infection through the placenta. Malformations do not occur; however, hydrocephalus and microcephaly result from chronic destructive meningoencephalitis. Chorioretinitis may progress to scarring and loss of vision. Hydrocephalus and cerebral calcifications, hepatitis, and lymphadenopathy are the most common complications in infants infected prenatally. Organisms have been recovered from the brain of a congenitally infected infant after 5 year.

Medicines: during pregnancy the medicines should be excluded except the situations when it is necessary to save the life of the mother or fetus. There are no medicines that can be completely safe, especially during the early period of pregnancy. Many medicines can cause birth defects. For example, quinine can cause deafness.

Another medicine – t**halidomide –** a mild sedative which is widely used in Europe in the 60s until there where evidences that it was the cause of significant disorders of fetal development when used during pregnancy. The women who took thalidomide gave birth more than 7,000 children with developmental disabilities. The children had normal intelligence. The sensitive period for production of human thalidomide birth defects was 23 to 28 days post-conception, with the critical period no longer than 14 days. About 20% of pregnancies exposed during this period resulted in infants with anomalies, the most notable of which were limb defects ranging from triphalangeal thumb to tetraamelia or phocomelia of the upper and lower limbs, at times with preaxial polydactyly of six or seven toes per foot. Thalidomide is an inhibitor of angiogenesis; its antiangiogenic activity correlates with its teratogenicity.

Alcohol. Alcohol consumption by mother during organogenesis in early pregnancy leads to congenital disorders, the phenotypic effect of which depends on the amount of alcohol consumed, the woman could not know that she is pregnant. Structural and functional impairments occur in up to one half of infants born to alcoholic women who drink heavily. Functional and growth disturbances without other morphologic changes can occur in infants whose mothers drink moderately. But the risk of spontaneous abortion is twice the normal rate in women who drink ethanol twice a week. Binge drinking in the first trimester may be a cause of fetotoxicity. According to the limited understanding of the effects of prenatal exposure to alcohol, abstinence from alcohol during pregnancy is a wise precaution.

Fetal Alcohol Syndrome (FAS). Patients with fetal alcogol syndrome must have same characteristics such as: prenatal and postnatal growth retardation, facial anomalies, ect. The full picture of syndrome usually occurs in babies born to alcoholic mothers or those who drink regularly or binge-drink. So, no amount of alcohol is safe. Even light or moderate drinking can affect the developing fetus. Acetaldehyde is implicated as the cause of syndrome through its inhibiting effects on DNA synthesis, placental amino acid transport, and development of the fetal brain. The biologic basis for syndrome is related to genetic polymorphisms identified for alcohol dehydrogenase, which converts alcohol to acetaldehyde, and acetaldehyde dehydrogenase, which converts acetaldehyde to acetate. Genetic differences in ADH alleles make some infants exposed to the same level of alcohol in utero more likely to have longer or higher levels of exposure to acetaldehyde. This may explain the greater frequency in American blacks and Native Americans.

Many of the chemicals used by man may also teratogenic. For example, **pesticides and organic chemicals** which contain mercury can cause abnormalities and neurological anomalies in the behavior of children when their mothers during pregnancy consumed products containing these substances.

One of the causes of birth defects can be considered as **hypoxia** which inhibits placentation and, in some cases, can lead to birth defects and fetal death.

Malnutrition of mother, micronutrient deficiencies such as zinc lead to the development of disorders of the nervous system of the fetus (hydrocephalus, spine curve, heart defects, etc.).

Endocrine diseases of pregnant women can lead to spontaneous abortion or pathology of morphological and functional differentiation of the fetus, neonatal mortality.

The dependence of the health of children from the **age of parents** is known. For example, congenital disorders of the musculoskeletal and respiratory systems are more common in children of young mothers than among mothers 22–35 years. Mothers older than 35 years increases the risk of having a baby with multiple malformations of all organ systems. The most clear dependence on the age of the mother is observed in the cases of children born with trisomy 13, 18, 21 pairs of chromosomes. It is established that the occurrence of fetal cleft lip and palate, achondroplasia depends on the age of the father. However, in developed countries, the frequency of multiple births with congenital disorders is significantly reduced due to the development of genetic counseling and prenatal diagnosis of congenital abnormalities.

1st level tests

(one correct answer)

1. During embryonic development the process of realization of genetic information was broken. As a result of this an organism development was disturbed giving rise to a pathology. Give an explanation for this phenomenon:

A. Light
B. Antimutagen
C. Antigen
D. Comutagen
E. Teratogen.

2. Two-layer embryo forms by means of separation of ectoderm cells at human embryo during first phase of gastrulation. What type of gastrulation is it:

A. Delamination
B. Immigration
C. Epiboly
D. Invagination
E. Mixed.

3. At the late gastrula stage of human embryo the third embryonic layer (mesoderm) is formed by moving of group of endoderm cells which are not collected into one layer. What type of gastrulation is it:

A. Immigration
B. Invagination
C. Delamination
D. Mixed
E. Epiboly.

4. The primary sexual cells arise when gonads have not yet begun to develop. Later the undifferentiated sexual cells migrate to the gonads and stay there. Which provisory (temporary) organ is the source of these cells?

A. Chorion
B. Alantois
C. Placenta
D. Yolk
E. Amnion.

5. The birth of two, three, four or even seven monozygotic twins in humans happens

due to the fact that the isolated blastomere develops into a complete organism. What is the name of this phenomenon?

A. Totipotency
B. Embryonal induction
C. Labile differentiation
D. Stable differentiation
E. Decoding organization.

6. In human embryogenesis as well as the absolute majority of vertebrates six pairs of gill arteries are formed but vessels of the fourth pair are more developed. Which human blood vessel is homologue to this pair of gill arteries?

A. The left aortic arch
B. The right aortic arch
C. Carotid artery
D. The pulmonary artery
E. The upper hollow vein.

7. Child was born with respiratory disorder due to compression of the trachea and partially esophagus. X-ray examinations revealed: the left aortic arch is absent, another vessel originates from the left ventricle and turns right. Which pair of arterial arches have malformations in this case:

A. Fourth
B. Third
C. Second
D. Fifth
E. Sixth.

8. 4-year old girls has a thumb consists of three bones instead of two. This structure has a finger of amphibians and reptiles. What is the name of this anomaly?

A. Polyphalangy
B. Polydactyly
C. Oligodactyly
D. Brachydactyly
E. Syndactyly.

9. Six women who have had viral infection (German measles) in the first trimester of pregnancy gave birth to children with congenital heart defects, deafness and cataracts. Which effect of this virus has observed in this case?

A. Teratogenic
B. Cancerogenic
C. Combinatorics of genes
D. Malignancy
E. Genocopy.

10. Experiments of D. Gurdon in 1964–1966 has shown that during transplanting of the nuclei of somatic cells in various stages of development in non-nucleated (without nucleus) ovum of the frog the tadpole's development is normal and very rarely – adult frog. What can be shown by these experiments?

A. All cells have the same genes
B. Totipotency of cells
C. The phenomenon of embryonic induction
D. In the zygote the genes are inactive
E. The differentiation of germ cells.

11. In pregnant women with toxoplasmosis during embryogenesis the process of fetus's mesoderm laying was disturbed because the woman was sick of toxoplasmosis. Which of the below mentioned system the pathology is typical of?

A. Nervous

B. Excretory
C. Intestinal epithelium
D. Liver
E. Pancreas.

12. Women who become pregnant during the massive use of pesticides in the countryside the embryonic ectoderm forming was disrupted. Which congenital malformations may occur in the newborns in this situation

A. Nervous system
B. Skeleton
C. Derma
D. Liver
E. Pancreas.

13. Congenital malformations of the heart and blood vessels in humans are associated with the disorders of vessels forming during embryogenesis. Name the pathology that occurs as a result of the lack of reduction of the right aortic arch:

A. Open ductus arteriosus
B. Reduction of the inferior vena cava
C. Aortic ring
D. The presence of the two upper caval
E. Truncus arteriosus.

14. A woman who regularly used alcohol, gave birth to a girl with a significant retardation of the physical and mental development. Doctors diagnosed fetal alcohol syndrome (FAS). Which factor is the reason of this pathology?

A. Malignancy
B. Cancerogenic
C. Mutagenic
D. Teratogenic
E. Genocopy.

15. In the course of human embryogenesis on 6-7th day after fertilization begins to form a blastocyst which is significantly different from the specific structural features of a typical blastula of lancelet. These features are typical for the:

A. Animal and vegetal poles
B. Large number of blastomeres
C. Primary mouth
D. Trophoblast and embryoblast
E. Secondary cavity.

16.The placenta is an organ that connect the developing fetus to the uterine wall. What kind of provisional (temporary) layer forms this organ?

A. Alantois
B. Amnion
C. Yolk
D. Umbilical cord
E. Chorion.

17. Fifteen years old boy has a splenic rupture with hemorrhage into the abdominal cavity as a result of fall. In course of time after the removal of the spleen in this place the renewed spleen was formed due to reproduction of the rest cells of spleen. What type of regeneration took place in this case?

A. Morphallaxis
B. Regenerative hypertrophy
C. Epimorphosis
D. Compensatory hypertrophy
E. Heteromorphosis.

18. The young couple had a child with nondisjunction of bifida and cleft palate. What is the name of malformations that remind the relevant organs of human ancestors?

A. Atavistic
B. Non-phylogenetic
C. Genocopy
D. Phenocopies
E. Allogeneic.

19. At a certain stage of human ontogenesis between the blood system of the mother and fetus is established physiological connection. This function is performed provisionally organ:

A. Alantois
B. Yolk
C. Amnion
D. Serosa
E. Placenta.

20. Woman was taking actinomycin D during her pregnancy. As a result of this situation her child was born with microcephaly. Which germinal layers had this teratogen acted?

A. Endoderm and mesoderm
B. Endoderm
C. Mesoderm
D. Ectoderm
E. All layers.

21. During experiment on the head of frog embryo at the stage of neurula the process of transcription in the nucleus of nerve cells has blocked. Which congenital abnormalities can be observed?

A. Anencephaly
B. Not fusing of palate
C. Spinal hernia
D. Chord does not form
E. Cleft lip.

22. During the experiment on a frog on blastula stage of 16 blastomeres one blastomere were removed. Isolated cell continued to develop normally and gave rise to a new embryo. What is the feature of blastomeres has been demonstrated?

A. The ability to differentiate
B. The ability to induce embryonic induction
C. Totipotency
D. Formation of the pole of embryo
E. Formation of germ layers.

23. During physiological development of the child's spine there are two lordosis and kyphosis have formed. It’s happens because of the development of ability to:

A. Sitting
B. Swim
C. Crawl
D. Upright posture
E. Lying.

24. During ontogenesis of a healthy person at the organismic level have showed such changes: reduce of the body size, the skin has lost its elasticity, eyesight and hearing deteriorated. Most likely it is a period:

A. Juvenile
B. Aging
C. Adolescence
D. Beginning of adulthood

E. Youth.

25. During human ontogenesis at the organismic level have showed such changes: decreased vital capacity, increased blood pressure, atherosclerosis developed. Most likely it is a period:

A. Youth
B. Juvenile
C. Adolescence
D. Beginning of adulthood
E. Aging.

26. In human cells reduced the intensity of DNA and RNA synthesis, synthesis of essential proteins and metabolism have disrupted, mitotic activity is low. Most likely these changes take place in the period:

A. Aging
B. Juvenile
C. Adolescence
D. Beginning of adulthood
E. Youth.

27. A person has the clinical death registered. In this case the following vital functions have stopped:

A. DNA replication
B. Cell renewal
C. Metabolism
D. The absence of heartbeat
E. Absence of movement.

28. A seriously injured man has a biological death registered. Evidence of this is:

A. Loss of consciousness
B. Disorganization of chemical processes
C. Autolysis of cells takes place
D. Absence of heartbeat and respiration
E. Absence of movement.

29. In 1950s in Western Europe the mothers who took thalidomide as a sedative drug, several thousand children were born with hypoplasia or absence of limbs, disturbance of skeletal structure, other pathologies. What is the nature of this pathology?

A. Phenocopy
B. Trisomy
C. Monosomy
D. Triploidy
E. Gene mutation.

TOPIC: Postnatal period of ontogenesis. Biological mechanisms of homeostasis

Periods of postembryonic human development. The processes of growth and differentiation in the postnatal period of the human development. Features of postnatal development in relation of its bio-social essence. The concept of biological fields, biological rhythms and their medical importance. Types and ways of regeneration. Forms of human tissue transplantation. Old age as the final stage of human ontogenesis. Theories of aging.

Periodization of ontogenesis

After the organism has gone out of ovum shells (birth), there begins its postembryonic (postnatal) period of its development.

In humans, 5 periods are singled out:

1) juvenile period (before puberty);
2) puberty (sexual maturing);
3) maturity;
4) aging;
5) death.

After the pubertal period, there develop definitive body proportions and organ systems come to the mode of functioning inherent to a mature organism.

According to a scheme adopted by the VII All-Union Conference on age morphology, physiology and biochemistry (Moscow, 1965) there are:

Period	Age		Some specific age events
	Male	Female	
Newborns	Birth to 10 days		Starting of accelerate growth in length. Often decreasing of the body weight.
Breast-feeding	From 10 days to 1 year		Feeding by the «mature» milk. Appearance of first teeth (from 6 months); period of maximum intensity of the growth process, the start of straightening of the body (the formation curves of the spine), sitting, standing and first steps. Start of cognitive development (seeing the recognition). «Childish» language.
Early childhood	1–3 years		Completion of eruption of first generation teeth. Decreasing of the rate growth. Recognition of pictures, fantasy, animation objects, selection and choosing of goodwill object, «I am».
First childhood	4–7 years		Often the first growth «jump» has noticed. From 6 years is the beginning of permanent teeth eruption. At the end of the first period – manifestations of sexual dimorphism and beginning of sexual identity (gender awareness). Visual symbolic thinking, concepts of time sequence. The bases of ethics and group behavior. Leading activity – subject role-playing game.
Second childhood	8–12 years	8–11 years	Eruption of permanent teeth (except third molars – «wisdom teeth»). Beginning of development of secondary sex characteristics (sexual maturation) and activation of the growth process. Transition from visual thinking to the logical one, social adaptation. The development of memory and attention. Selective and perspective drawing.
Teens age	13–16 years	12–15 years	Second (real) growth rate. Sexual maturation and enhanced growth of the body in length. All this determines the greatest morphological and functional shifts in all body systems. At the early beginning – the language abstract thinking. The intense intellectual development (self-analysis), high gender identity, personal

			and emotional instability.
Adolescence	17–21 years	16–20 years	Finishing of intensive growth and formation of the body. Beginning of the stabilization of personality, self-determination and formation of an outlook. Oftenly a social activity is expressed as destructive manifestations.
First maturity	22–35 years	21–35 years	Actually maturity – relative stability of the body parameters, formation of a «typical female» and «typical male» traits. Leading importance of circadian, bicircadian, weekly, seasonal and other rhythmic physiological functions. At the end of this period – the end of the female reproductive cycle – menopause and complex psycho-physiological changes (climax).
Second maturity	36–60 years	36–55 years	
Aging	61–74 years	56–74 years	Continuation of the period of social activity. The beginning of involution changes of an organism including actual negative growth. The fall of adaptive opportunities. Disintegration of the body functions at all levels of the organization. Finishing of the male reproductive period. Structural and functional changes in the central nervous system, signs of "mental aging".
Senium	75–90 years		
Centenarians	90 years more		This period is characterized by relative stability of all parameters on the achieved qualitative and quantitative level, particularly at the expense of compensating (compensatory senile) processes.
Neutral childhood – time from 1 year to 7 years when boys and girls do not differ from one another by the growth rate.			

The main mechanisms of ontogenesis:

- proliferation (cell division);
- migration (cell movement);
- cell sorting;
- cell death;
- cell differentiation;
- induction and competence (contact interactions);
- distant interaction of cells, tissues and organs (humoral, nervous mechanisms of integration).

Characteristics of postnatal period of ontogenesis:

- **Growth** – is an increase in the mass and linear dimensions of an organism (and its parts).
  In the basic of the growth, there lie the processes of protein biosynthesis, increase in dimensions and number of cells and non-cellular structures.
  It is a universal feature of the living matter characteristic of any level of its organization – from the molecular to the biospheric.
- **Development** – is an increase in the mass and linear dimensions of an organism (and its parts).
  In the basic of the growth, there lie the processes of protein biosynthesis, increase in dimensions and number of cells and non-cellular structures. It is a universal feature of the living matter characteristic of any level of its organization – from the molecular to the biospheric.

- **Regeneration** – is the restoration of the lost parts of the organism (cells, tissues or organs):
  - *Physiological regeneration* – restoration of the structures, which loss is a natural event of ontogenesis. Example: renewal of erythrocytes, the epidermis of the skin, intestinal epithelium, and etc.
  - *Reparative regeneration* – restoration of structures which were damaged or lost as a result of the injury or disease. Example: healing of the cuts, the restoring of the lost tail at a lizard, etc.

Types of reparative regeneration:

  - ***Homomorphosis (typical regeneration)*** – the lost structure is replaced by exactly the same (tails in lizards);
  - ***Heteromorphosis (atypical, or pathological regeneration)*** – *the lost structure is replaced by distinctly another (tail except of leg in lizard).*

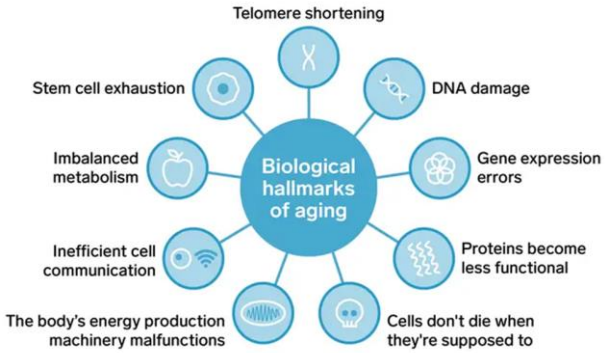
Mechanisms of reparative regeneration:

  - **Endomorphosis** – regenerating the size, but not the shape of the lost organ. Example: human liver after its partial removal.
  - **Epimorphosis** – regenerating both the size and shape of the lost organ. Example: the tail of a lizard or body of Hydra.
  - **Morphollaksis** – regenerating the shape, but not the size of the lost organ. Example: insect limb.
  - **Epithelization –** the healing of the wounds with a damaged epithelium. Example: cuts of the skin.
  - **Compensatory hypertrophy –** the hypertrophy of the organ after the damage other organ this system. Example: increase in size and increased function of the second kidney after removal of the first one.

- **Maturation** (the process of becoming completely developed physically, mentally or emotionally) and **aging** (a regular process of age-decaying changes of the organism resulting in a decrease in the organism adaptation ability and in an increase in the probability of the death.

External signs of the old age:

- changes in bearing (carriage) and gait;
- decrease in mobility;
- changes in the voice timbre;
- skin wrinkles;
- decrease of memory characteristic;
- changes in behavior, way of life, place and position in society.



- **Death –** is the termination of the organism life activity, the extinction of the organism as an isolated living system.

Types of death:

✓ *Physiological:* is the termination of the organism life activity, the extinction of the organism as an isolated living system.
✓ *Premature:* caused by illnesses and diseases, damages of organs important for life.
✓ *Clinical:* reversible state. Reanimation is possible in the absence of damages of life-important organs.
✓ *Biological:* irreversible state; reanimation is not possible even in the absence of damages in life-important organs.

Signs and characteristics of clinical death:

- absense of heart-beating;

- absence of respiration;
- absense couscionsness;
- absense of the pupil reflex;
- duration: 6–7 minutes. the cortex of large hemispheres, sub-cortex structure and marrow stem do not function, but retain (preserve) a life ability. cells of all organs and tissues remain alive in a human being.

Signs and characteristics of biological death:

- preservation (retention) of a changed form of the pupil at constraining the pupil of an eye;
- appearance of putrid (cadaverous) spots;
- sings of tissue decomposition;
- it comes after the clinical death. The Harward criterion – death of cerebral marrow (including marrow stem) with the disappearance of all the stem reflexes. it is characterized by a certain sequence (not simultaneons of the death of all tissue cells and organs of a human being).

1st level tests

(one correct answer)

1. During development of the child's backbone gradually acquired two lordosis and two kyphosis. This can explain the development of the ability to:
   A. Sitting
   B. Swimming
   C. Crawling
   D. Erect posture
   E. Lying.
2. During ontogenesis of a healthy person at the organismic level such changes have showed: reduce of body size, the skin has lost its elasticity, vision and hearing faint. Most likely it is a period:
   A. Adolescences
   B. Teens age
   C. Maturity
   D. Puberty period
   E. Aging
3. During ontogenesis of a healthy person at the organismic level such changes have showed: decreased vital capacity, increased blood pressure, atherosclerosis. Most likely it is a period:
   A. Adolescences
   B. Teens age
   C. Maturity
   D. Puberty period
   E. Aging.
4. Intensity of the DNA and RNA synthesis has reduced in human body, necessary protein synthesis and metabolism has reduced, mitotic activity is insignificant. Most likely these changes take place in the period of:
   A. Aging
   B. Teens age
   C. Maturity
   D. Puberty period
   E. Adolescence.
5. Clinical death has registered. In this case following vital functions have stopped:
   A. DNA replication
   B. Self-renewal of cells

C. Metabolism process
D. Absence of heart beating and breathing
E. Absence of movement.

6. Seriously injured person has a natural death. Evidence of this is:
A. Lost concessnes
B. Disorders of chemical processes
C. Cell autolysis
D. Absence of heart beating and breathing
E. Absence of movement.

7. Which period is called the «neutral childhood»?
A. From one to seven years
B. Early childhood
C. Newborn period
D. Period of puberty
E. Before one year.

8. In what period of postnatal development the puberty takes place?
A. Neutral period
B. Teens age
D. Adolescence
E. First childhood period
F. Second childhood period.

9. What gland is activated in puberty period, boys 13–15 years old, girls 11–13 years old:
A. Pancreas
B. Liver, lungs
C. Parathyroid glands
D. Salivary glands
E. Adrenal glands.

10. Which hormones stimulates adrenals?
A. Somatotropic
B. Androgen
C. Testosterone
D. Tyrocsin
E. Insuline.

11. In what critical period of postnatal development an involution of the thymus, changes of receptor sensitivity to androgens and estrogens take place:
A. Adolescences
B. Teens age
C. Maturity
D. Puberty period
E. Aging.

12. In what period of postnatal development the inclusion of the own systems of thermoregulation combination of anaerobic glycolysis and oxidative phosphorylation, the formation of homeostasis take place:
A. Adolescences
B. Teens age
C. Maturity
D. Puberty period
E. Aging.

13. In what period of ontogenesis the gradual progress of increasing of the adaptive capacities and vital functions of an individual happen:
A. Adolescences
B. Teens age

C. Maturity
D. Puberty period
E. Aging.

14. In what period of ontogenesis the growth rate gradually reduced, then becomes constant and in particular age gives a «jump»:
A. Adolescences
B. Teens age
C. Maturity
D. Puberty period
E. Aging.

15. What processes are characterized by the periods of depression and growth in the early postnatal development?
A. Increase cell proliferation
B. Increase differentiation
C. Disorder of homeostasis
D. Activation of immune system
E. Increase of nerve regulation.

16. Which system of the homeostasis regulating mechanisms has a crucial importance?
A. Nervous system
B. Immune system
C. Hypothalamic-pituitary system
D. Gene expression
E. System cellular immunity.

17. Aging process is characterized by the following changes:
A. Increase of the neuron's size
B. Increase of connectios between neurons
C. Increase of the neuron's density
D. Increase of the neuron's sensitivity
E. Reduced operability of neurons.

18. There are many features are formed during performing of specific functions. Typical shape of spine which has two forward and two backward bending and develops in first 1.5–2 years. Neck lordosis is formed:
A. 1–1.5 months
B. 2.5–3 months
C. 6–6.5 months
D. 11.5–12 months
E. 18–18.5 month.

19.Human growth is accompanied by an increase in height and weight but it occurs irregular. In some periods a man grows rapidly while others slow. The most intensive growth is observed within the following year:
A. First
B. Second
C. Forth
D. Tenth
E. Fifteenth.

20. Age changes can be diversified. During aging period some functional parameters progressively reduced while others do not change significantly but some increases such as:
A. Heart construction
B. Hormonal activity of the gonads
C. Hearing acuity
D. Number of red blood cells
E. Cholesterol level.

21. Age changes in different organs and systems of the body occur asynchronously in various periods. Such changes is called heterochronic. Thymus atrophy begins in:

A. 3–5 years
B. 13–15 years
C. 23–25 years
D. 43–45 years
E. 73–75 years.

22. The physiological processes of regeneration occurring constantly that is why cells of intestinal epithelium updating during several days. Relatively quickly updated erythrocytes. What is the average duration of their functioning in the peripheral blood:

A. 5 days
B. 20 days
C. 55 days
D. 80 days
E. 125 days.

23. Human regenerative hypertrophy begins after wound healing when increases the rest part of an organ. It is happens due to cell proliferation. In which case the regenerative hypertrophy occurs:

A. In case of loss of the upper limb
B. In case of loss of the lower limb
C. In case of kidney removal
D. In the case of liver removal
E. In case of deep burns.

24. Success final result of transplantation significantly depend on complications related to the immune system response to transplant. They do not appear if peformed:

A. Xenotransplantation
B. Autotransplantation
C. Allotransplantation from mother to son
D. Allotransplantation from father to son
E. Allotransplantation from brother to sister.

25. Disturbance of physiological regeneration can lead to the formation of malignant or benign tumors. Benign tumors are able to:

A. Germinate to the adjacent tissue
B. Differentiation
C. Cell atypia
D. Transfer to the places which are distant from the primary tumor
E. Metastasis.

Recommended literature:

1. **Medical Biology : text-book** / Bazhora Yu. I., Bylyk R. Ye., Chesnokova M. M. et al. – 2nd ed., revised and updated. – Vinnytsia : Nova Knyha, 2019. – 448 p.
2. **Lazarev K.L. Medical Biology:** Text-book. – Second edition. – Simferopol: IAD CSMU, 2003. – 592 p.
3. **Medical biology:** The study guide of the practical classes course / O.V. Romanenko, O.V. Golovchenko, M.G. Kravchuk, V.M. Grinkevych. – Edited by O.V. Romanenko. – K.: Medicine, 2008. – 304 p.
4. **Bekish O.-Y.L. Medical biology:** Textbook for students of higher educational establishments. – Vitebsk: VSMU Press, 2003. – 346 p.
5. **Green N.P., Stout G.W., Taylor D.I. Biological Science**. – Cambridge, 1994.

Contents