PUBLIC HEALTH MINISTRY OF UKRAINE
KHARKIV NATIONAL MEDICAL UNIVERSITY

WORKBOOK FOR PRACTICAL CLASSES IN MEDICAL BIOLOGY

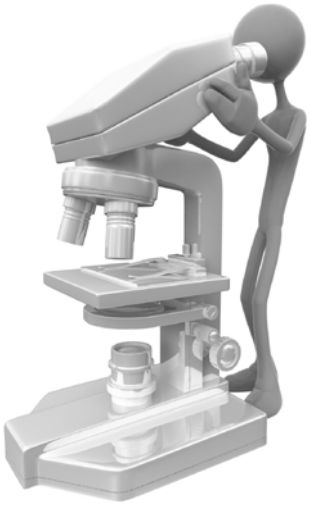
SEMESTER I

OF THE FIRST-YEAR STUDENT OF _____ FACULTY

_____(name, surname)

group № _____

TUTOR_____



KHARKIV 2016

Workbook for practical classes in Medical Biology. Semester I (for the first-year students of general medicine faculty). Authors: Valeriy V. Myasoedov, Ludmila G. Digol, Helena S. Mangeley, Olga E. Fedorchenko, Boris V. Kulachenko, Irene P. Meshcheryakova, Olga B. Khromenkova, Yuriy A. Sadovnychenko. — 2016. — 141 p.

Approved on the Session of Scientific Council of Kharkiv National Medical University
(the record of proceedings *№11* at *22.09.2016*)

Published by Computer Center “MiF”

Medical Biology Syllabus

Medical Biology Course offers medical students understanding of how molecular and cellular events integrate into whole-human systems, knowledge of how they can be used to study human diseases. Also important aspect of Medical Biology is to give an idea of human parasites as causative agents of human diseases. Medical Biology comprehension is necessary for the professional skills progress and learning of relating fundamental courses such as microbiology, biochemistry, pharmacology, physiology etc. Numerous examples, largely relating to human biology, are provided to encourage this process.

Course Content and Format

Course of Medical Biology lasts for one academic year (two semesters) and is composed of three Units. Units 1 & 2 are studied during the Semester I and Unit 3 — during Semester II. The Medical Biology course includes both lectures and classes. Attendance of all lectures and classes is mandatory. A current class and lecture schedules are available on Information board of Medical Biology Department.

Textbooks and learning aids for Semester I:

1. **Cell Biology**: A Short Course by Stephen R. Bolsover, J.S. Hyams, E.A.Shephard, H.A. White, C.G. Wiedemann: 2nd edition published by Wiley, 2003. – 552 pages.
2. **Biology,** 6th edition, by George B. Johnson and Peter H. Raven, published by McGraw-Hill Higher Education, 2002. — 1238 pages.
3. **Langman's Medical Embryology**, 9th Edition: North American Edition by Thomas W Sadler, published by Lippincott Williams & Wilkins, 2003. — 534 pages.
4. **Handouts of Medical Biology Department.**

The printed copies or electronic versions of these materials are available at the Department of Medical Biology (in the Laboratory Room) and on the site of the Department.

Site of Department of Medical Biology:

http://nauka.knmu.edu.ua/medbio

I. Lectures

There are 7 lectures in Semester I and 3 lectures in Semester II. **The lecture material is included in Final Exam!!!**

Remember: it is better to listen to lecture material attentively and actively write down them!! Therefore, attending lecture regularly and keeping good notes is essential for success in this course. The power point slides of lectures (*ppt/pps files) **are not shared** so the students could photocopy the printed texts of lectures (available in Laboratory Room of our Department).

Attendance: If a student misses a lecture (regardless of the reasons) he/she must work it off as oral exam (***verbally***) **before** the credit of each semester. A student is permitted to miss a maximum of 1 lecture per an academic year without working-off.

II. Classes

Classes are practical works to teach students Medical Biology Subject. The students usually have one class per a week. For classes the student needs "*Workbook for practical classes*". After each class, a group tutor signs a studied Theme in student' workbook.

The course content is divided into three Units.

- **Unit 1.** *Molecular-cellular level of organizations in the living world.* It includes 7 Themes in Cell Biology and Molecular Biology (see a list of the Themes on the page 6 of the Workbook).
- **Unit 2.** *Organism level of organization in the living world. Essentials of human genetics*. It includes 10 Themes in Mendelian and Non-Mendelian Genetics and Genetic Disorders (see a list of the Themes on the page 55).
- **Unit 3.** *Population, holocoenotic and biospheric levels of life organization.* It includes 13 Themes in Medical Parasitology.

Attendance: The attendance and punctuality are mandatory for success and are essential component of the course. If a student misses a class, he/she must retake the respective theme ***verbally***!

Class Etiquette: All the students must be present in ***white doctor's coat*** at the both lectures and classes.

Please, attend on time for all of your classes and lectures!!!
Students are expected to be punctual (**every 3 late class arrivals will be counted as 1 class absence**) in class attendance !!!
The tutor has the right to refuse late students!!!

Mobile phones must be turned off during class and lecture!!!

If you must be available via cell phone for potential emergencies, set your phone to vibrate mode. Please be considerate of your neighbors and avoid distractions such as carrying on conversations or entering and exiting during classes and lectures. **Disruptive behavior** (i.e., using of cell phones, coming to class/lecture late, talking to others during the lectures, quizzes or exams, sleeping or laying head down during class, side conversations, and leaving classroom before the end of class/lecture etc) **could result in the student being asked to leave class and an absence being recorded**.

III. Tests and Lab Practical Exams

Students' knowledge is estimated by written multiple-choice tests (MCTs) and/or oral tests following each of the classes. The results of MCTs and/or oral tests are evaluated by *"5" (excellent), "4" (good), "3" (satisfactory), "2" (failed)* marks and are recorded in the *Electronic Register of University*. Every failed test **must be retaken as oral exam (verbally)** and passed **within 2 week** of the original test date. (See Section IV: To work off (retake) the academic debts)!

The students who do not have missed classes and lectures and failed tests are permitted to do a Lab Practical Exam.

A failed Lab Practical Exam must be retaken!

Academic Honesty

Remember: cheating will not be tolerated!!! Students who cheat will receive no points for the exam or assignment. Plagiarism in any form will not be tolerated. No points will be given for plagiarized work.

No copying* of exam material is allowed!!!
***copying includes: written, taking photographs, video or voice recording of material**

- **Exam material may never be removed from the classroom.**
- **NO Photographs, or OTHER ELECTRONIC MEDIA may be – this includes voice recording, video recording or any other forms of copying.**

IV. To work off (retake) the academic debts

All academic debts (missed lectures, missed classes, and failed tests) need to be worked off. The working-offs are realized on weekdays, from 3.00 p.m. to 5.00 p.m. and on Saturdays, from 10.00 a.m. to 1 p.m. by pre-registration list (on the Department website).

The working off of a missed class/lecture within one month since the date of missing does not require a permission of Dean's Office while after one month a student must get a written permission with Vice-dean's or Deans' signature and a stamp.

Permission must be obtained PRIOR to working-off!

At the working-off, a tutor on duty **verifies the student's identity** by examining a student card with photo on it and at least one other form of identification, such as a credit book, passport or driver's license. The student has to have his/her filled *Workbook for practical classes* by him/her.

V. Evaluation

- Current Evaluation of Medical Biology Course

Any student who is regularly attends classes and who satisfies the requirements will receive credit at the end of each semester.
A student may be permitted to Final Exam during Summer examination period if he/she has credits in both Semester I and II.

At the end of each semester, a Student's marks are converted into points according to current grading scale.

Semester's Current Score is possible from minimal 70 pts to maximal 120 pts. *Current Score* is evaluated as arithmetical mean of both *Semester's Current Scores*.

- Final Evaluation of Medical Biology Course

Result of Final Exam is from minimal 50 pts to maximal 80 pts.

Final Grade is a **SUM** of both *Current Score* and *Exam Result* and is a range from 122 to 200 pts.

$$\text{Final Grade} = \text{Current Score} + \text{Exam Result}$$

Each student will receive a triple grade (*Range* / *Letter Grade* / *Mark.,* e.g, 155/C/4) for this course, which will be officially registered in a student's credit book and recorded by the Deans' Office.

Letter Grade	Range, points	Mark
A	180 - 200	5
B	160 - 179	4
C	150 - 159	
D	130 - 149	3
E	122 - 129	
F, F_X	Failing grade	2

VI. Rules and regulations

Students are treated as adults and are expected to behave as such and act responsibly!!!

An international and multicultural environment is a basic concept of the Kharkiv National Medical University. Students of a variety of race, color, gender, social background, national origin and religion attend this university and this enriches university life.

Discriminative behavior of any kind humiliates people and will not be tolerated by the University and Department!!!

A student must take care of the department property, the furniture and equipment, and will be billed for any damage (permissive waste or voluntary waste). Students are also responsible for the cleanliness and tidiness of their own classrooms.

In the case of permissive waste/voluntary waste, a student must compensate for damage that means the student must be ordered:

- to restore the property to its original state, or
- to substitute the waste of new equal worth, or
- to repay the cost of goods/equipment according to the current University rules.

Unit 1

Biological features of human vital functions

№	Date	Themes	Mark
1		*Cellular and non-cellular life. Cell membranes. Transport of materials across cell membranes*	
2		*Cell morphology. Structural components of cytoplasm and nucleus*	
3		*Morphology of chromosomes. Human karyotype*	
4		*Cell cycle. Cell division*	
5		*Characteristics of nucleic acids*	
6		*Gene structure in prokaryotes and eukaryotes. Structural and regulator genes, genes of tRNA, rRNA. Flow of information in cell*	
7		*Molecular mechanisms of variation in humans. Control of gene expression*	
8		***Lab Practical Exam 1***	

Theme 1. Cellular and non-cellular forms of life. Cell membranes. Transport of materials across cell membrane

Objectives: study the forms of life; explore the structure and functions of cell membrane; conceive the relationship between metabolic processes in cell; have a look at types of receptors and mechanisms of membrane transport.

Task 1. Characterize the forms of organization of living systems and give examples of various forms of life.

Features	*Non-cellular organisms*		*Cellular organisms*	
	Viruses	*Prions*	*Prokaryotes*	*Eukaryotes*
Genetic material				
Structure				
Properties of life				
Size				
Example				

Task 2. Study the scheme figures of prokaryotic cell and eukaryotic animal cell, note the main differences in their structures. Make the designations of cell components.

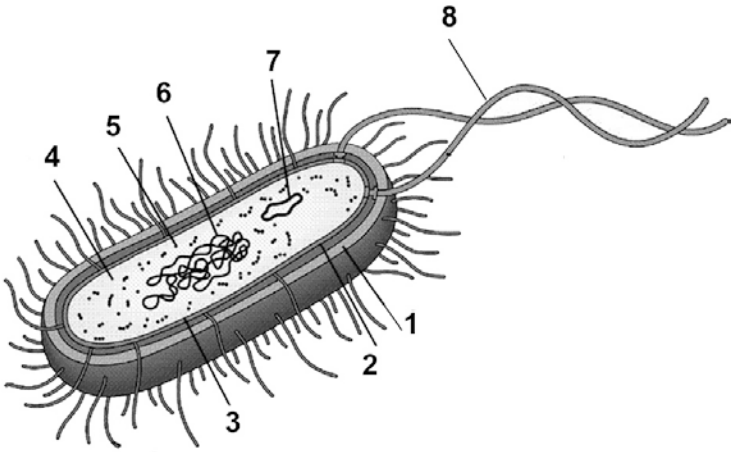


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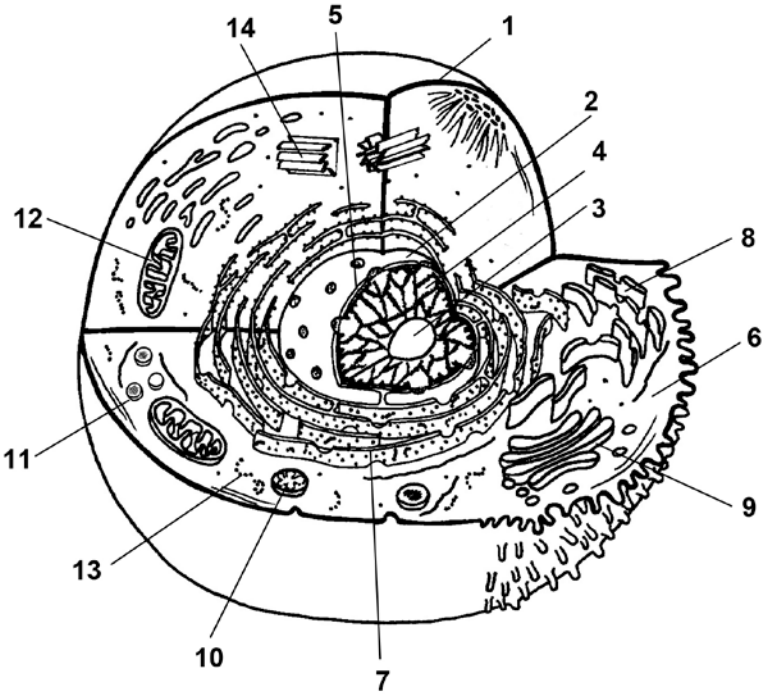
Fig. 1. *Prokaryotic cell*



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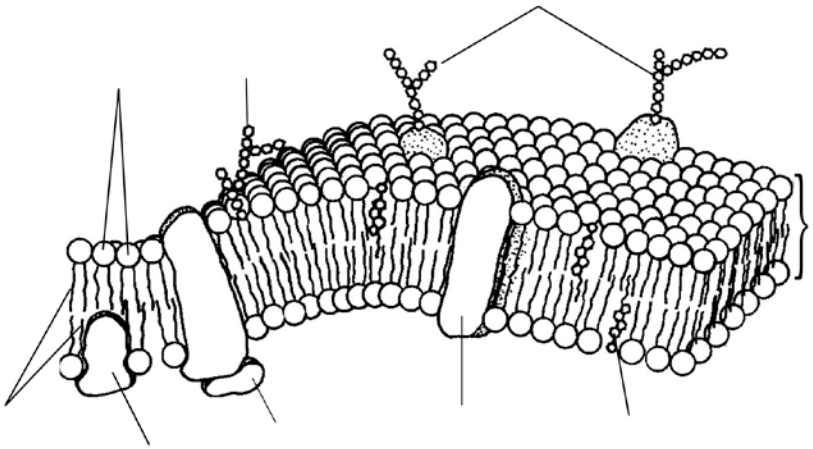
11. _____
12. _____
13. _____
14. _____

Fig. 2. *Eukaryotic cell*

Task 3. Note the postulates of Cell Theory.

Task 4. Study the chemical makeup and physical organization of cell membrane (plasma membrane). Designate the components of cell membrane on the figure (*lipid bilayer, phospholipid polar (hydrophilic) heads, nonpolar (hydrophobic) fatty acid chains, peripheral and integral proteins, glycolipids, cholesterol, oligosaccharide chains of glycoproteins*.



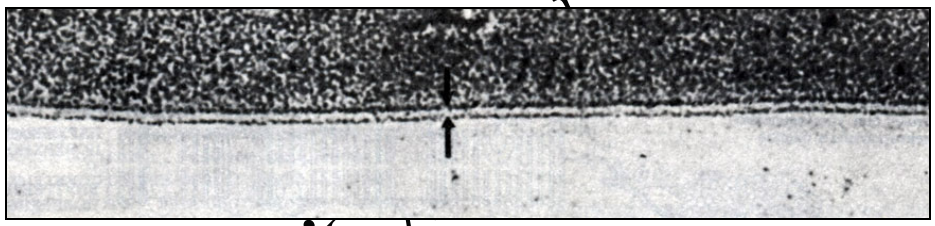


Fig. 1. Electron micrograph of plasma membrane of red blood cell**;** × 250000.

Chemical components

Membrane structure

Functions of plasma membrane

Task 5. Fill the table below.

Types of membrane transport

Type of membrane transport	*Characteristics*	*Substances that are transmitted*	*Medical significance*
Transport of small molecules			
Passive transport			
Simple diffusion			
Facilitated diffusion			
Osmosis			
Active transport			
Ion pumps (ATPases)			
Vesicular transport			
Endocytosis			
a) Phagocytosis			
b) Pinocytosis			
c) Receptor-mediated endocytosis			
Exocytosis			

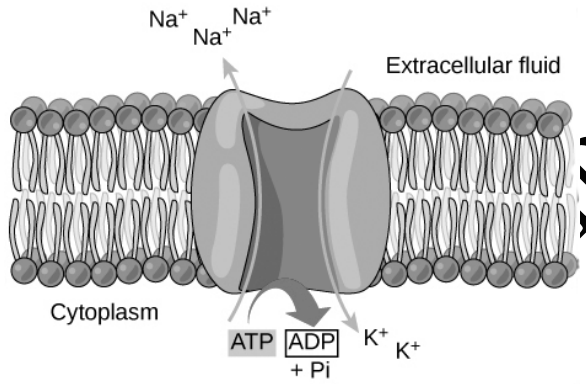
Clinical consideration

!!! More than 20 inherited disorders of membrane transport have been revealed in human. In most of them intestine or/and kidneys are involved in pathogenic process. In inborn errors of metabolism the transport of substances of many classes is disturbed, including amino acids, sugars, ions, vitamins and water.

An example of human disease caused by inherited defect of membrane transport is ***cystinuria***. Cystinuria is an autosomal-recessive defect in reabsorptive transport of cystine and the dibasic amino acids ornithine, arginine, and lysine from the luminal fluid of the renal proximal tubule and small intestine. Cystinuria is characterized by the formation of cystine stones in the kidneys, urethra, and bladder

Task 6. Study the mechanism of sodium-potassium pump.

Sodium-potassium pump: This is an important example of carrier-mediated active transport system of cells. The plasma membrane is ordinarily permeable to both sodium (Na^+) and potassium (K^+) ions. K^+ ions are required in the cells for the activity of many enzymes, and protein synthesis. Hence, cells in general maintain a high internal concentration of K^+ ions, but a low concentration of Na^+ ions. Conversely, the extracellular fluid (ECF) always has a high concentration of Na^+ and a low concentration of K^+ ions. Due to their concentration gradients, K^+- ions keep escaping out of cells and Na^+ ions keep entering into them. Cells, therefore, have to forcibly extrude Na^+ and take in K^+ against their concentration gradients through carrier proteins by spending about 10% to 70% (in nerve cells) of their total energy output. This is called ***sodium-potassium pump***.



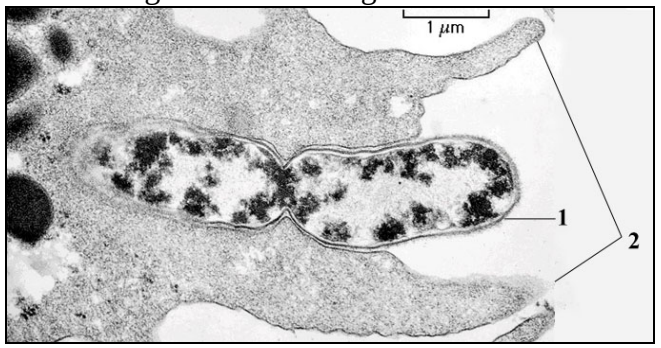
The carrier protein of plasma membrane to operate this pump is an **enzyme** called **Na^+-K^+-ATPase**. This enzyme molecule has a binding site which can alternately face the cytosol or ECF due to conformational changes which the enzyme molecule periodically undergoes.

When this binding site faces the cytosol three Na^+ ions link with the enzyme molecule. This triggers such a change in the structure of the enzyme molecule that its binding site is now exposed towards ECF. Here, it releases the Na^+ ions and binds two K^+ ions in exchange. Again, the molecular configuration changes and the binding site now faces the cytosol. Here, it releases the K^+ ions and binds three Na^+ ions in exchange. This is a continuous process operating in most cells to maintain the normal concentrations of Na^+ and K^+ ions in cytoplasm and ECF.

This process also generates a potential difference across cell membrane. This is called the **membrane potential**, and all animal cells have it. It varies from 20 to 200 mV, but and is always negative inside the cell.

Pay attention: three sodium ions are pumped **out** of the cell and **two potassium** ions are pumped **into** the cell

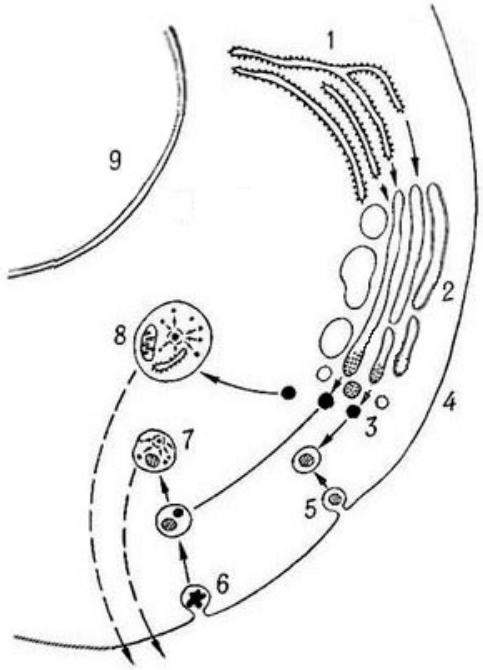
Task 7. Look at the electron micrograph of a leukocyte phagocyting a bacterium. Make designations to the figure.



1 - _____

2 - _____

Task 8. Study the scheme “Intracellular lysosomal digestion and the types of lysosomes involved”. Make designations.



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9 – _____

Clinical consideration

Lysosomal storage diseases (LSDs) are hereditary disorders caused by a deficiency in specific lysosomal enzymes *acid hydrolases*. Therefore, lysosomes *are unable to degrade certain compounds,* which accumulate and interfere with cell function. There are more than 40 known LSDs. They affect different body organs or systems including the skeleton and joints, eyes, heart, lungs, kidneys, skin, and frequently the central nervous system.

Task 9. Give a notion of *receptor*, write the functions of receptors. Study a diagrammatic representation of transduction signal, using the figure.

Receptor – _____

_____

_____

_____

_____

Receptors can be classified depending on the localization in a cell:

- Cell surface receptors
- Intracellular receptors (in the cytoplasm or nucleus).

Functions of receptors

_____

_____

_____

_____

_____

Most hormones circulate via the blood, thus coming into contact with all kinds of cells throughout the body. However, a given hormone usually affects only a limited number of cells, which are called "target cells" for that hormone. A target cell responds to a hormone because it bears "receptors" for that hormone.

In human body the effect of steroid hormones and thyroid hormones is the regulation of rate of gene expression. The *hormones bind to specific receptors in cytoplasm and nucleus of the target cells*. It results in conformational rearrangement of protein molecules of the receptor and in the formation of dimers which have high affinity for DNA.

The binding of the dimers of the hormone – receptor complex to double-stranded DNA (see Fig. 3) activates the synthesis of specific mRNA of key cellular proteins and thus increases the amount of produced proteins. In lack of hormones the corresponding receptors inhibit the gene expression.

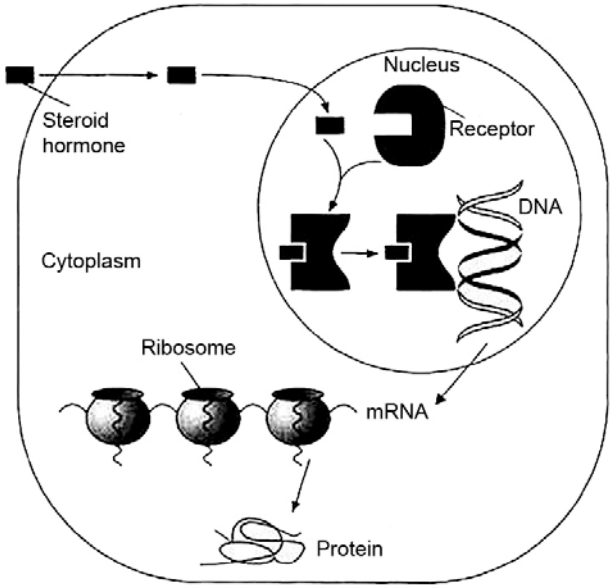


Fig. 3.
Transduction of hormonal signals by intracellular receptors.

By chemical synthesis the substances which are not identical to hormones but able to bind to receptors are produced. Substances causing the same effect as that of the natural hormones are called ***agonists***. For example, the synthetic oral contraceptives are agonists of estrogen and progesterone.

Substances which bind to the receptor but do not induce biological effects are called ***antagonists***. Antagonists of hormones are used in therapy of tumors. To evaluate whether a given tumor is hormone-dependent and whether it is sensitive to the antagonists the so called expression of hormone receptors (rate of synthesis of gene product) is detected in a tissue sample.

Multiple-Choice Tests for Control of Theme 1

1. Cell membrane is made up of
A. glycoproteins
B. phosphoproteins
C. phospholipids and proteins
D. double layer of proteins
E. double layer of glycoproteins

2. From secretory cells of intestine the digestive enzymes are secreted by:
A. facilitated diffusion
B. simple diffusion
C. pinocytosis
D. phagocytosis
E. exocytosis

3. Phagocytosis was discovered by
A. Ilya Mechnikov
B. Robert Brown
C. Robert Hooke
D. Dmitri Iwanowsky
E. Theodor Schwann

Date	Signature

Theme 2: Cell morphology. Structural components of cytoplasm and nucleus

Objectives: study structure of eukaryotic cell in norm and pathology; conceive relationship between structure and function of the cell.

Task 1. Study a specimen of spinal cord. Sketch a neuron. Designate a nucleus, nucleolus, cytoplasm and processes.

(×)

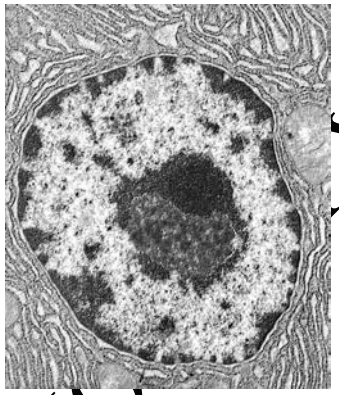
Fig. 1. *Nerve cell.*

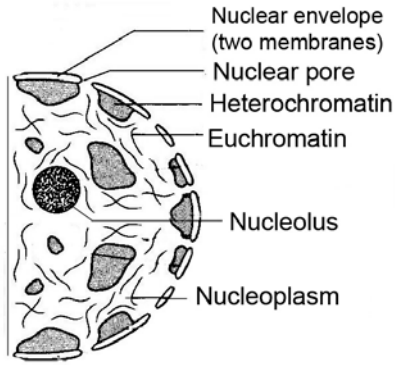
Task 2. Study a specimen of striated muscles, or skeletal muscles. Sketch the cross-striated muscle fibers. Make designations.

×)

Fig. 2. *Cross-striated muscle fiber.*

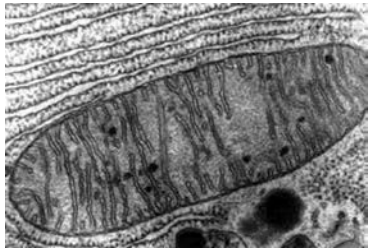
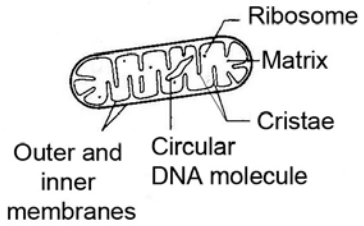
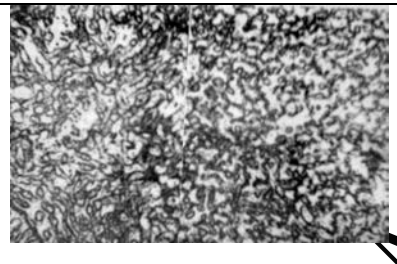
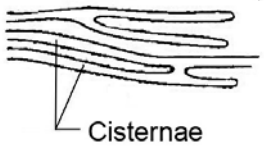
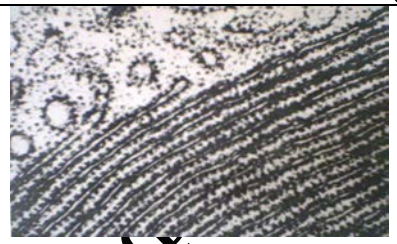
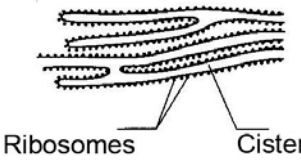
Task 3. Study the structure of nucleus. Fill in the table.

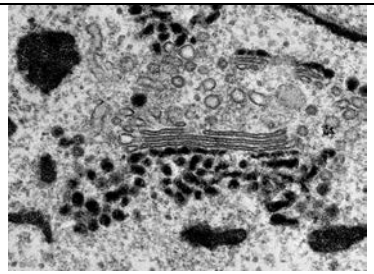
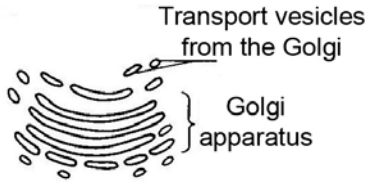
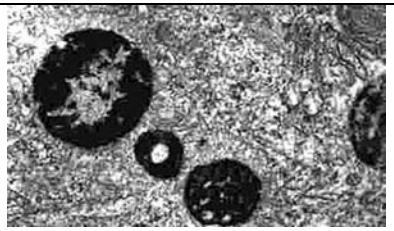
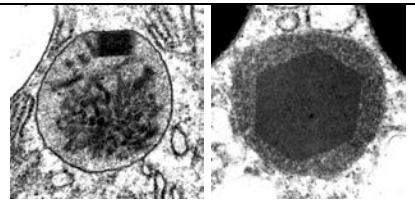
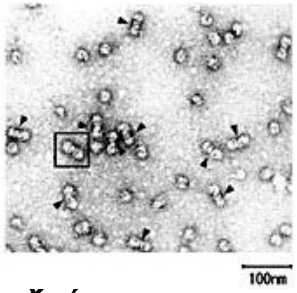
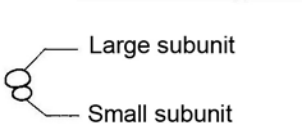


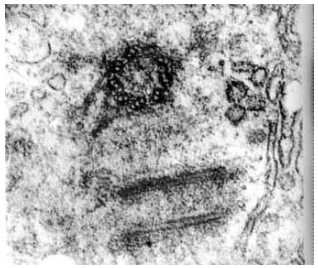
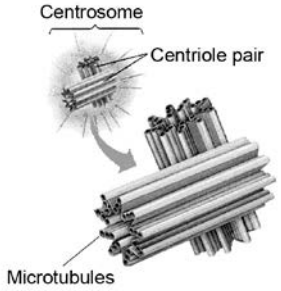
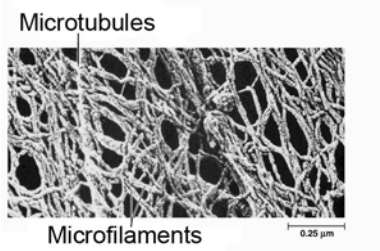
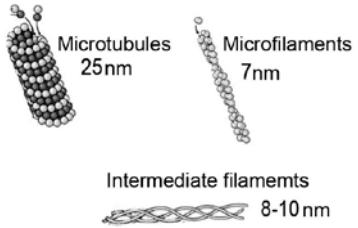
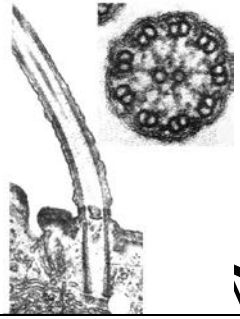
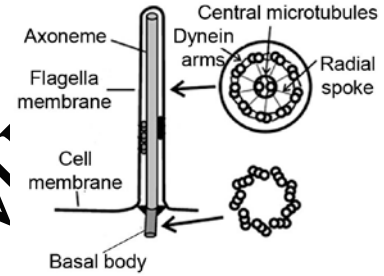
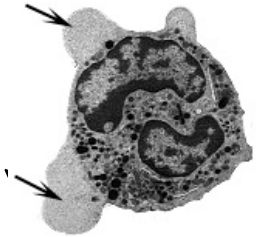
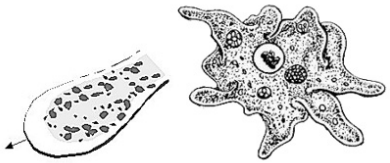


	Name	Organization	Function
1	Nuclear envelope		
2	Nuclear matrix		
3	Chromatin		
4	Nucleolus		

Task 4. Study the electron micrograph of a cell and write down the function of main cell components and organelles.

Structures and organelles	*Ultrastructure*	*Scheme*	*Functions*
1	*2*	*3*	*4*
Double-membrane organelles			
Mitochondrion			
Single- membrane organelles			
Smooth endoplasmic reticulum			
Rough endoplasmic reticulum			

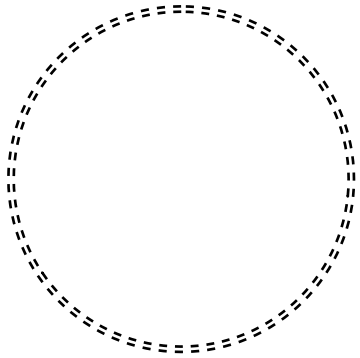
1	*2*	*3*	
Golgi apparatus			
Lysosome			
Peroxisome			
Non-membranous organelles			
Ribosome			

1	*2*	*3*	
Centrosome			
Cytoskeleton (microtubules, microfilaments, and intermediate filaments)			
		Locomotory organelles	
Flagella and cilia			
Pseudopodia (false legs)			

Task 5. Give a definition of *cytoplasmic inclusions.*

Cytoplasmic inclusions – _____
_____
_____
_____

Examine the specimens of inclusions, sketch them in your notebook, and make designations.



(×)

Fig. 3. *Glycogen inclusions in liver cells.*

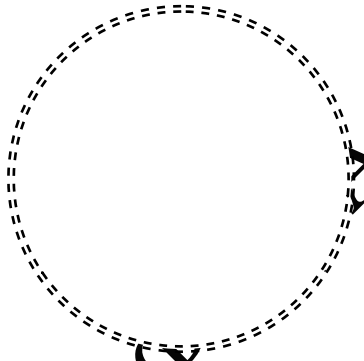


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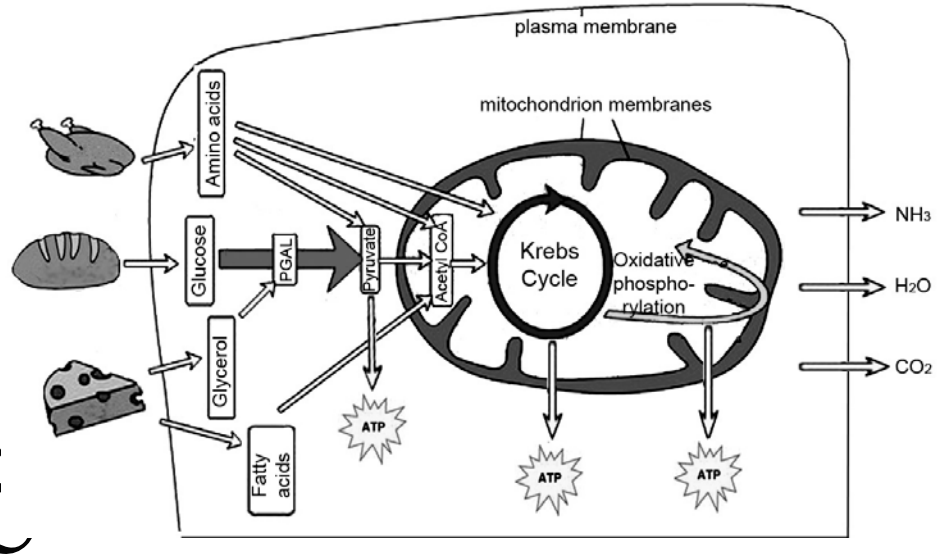
Fig. 4. *Lipid droplets (fat inclusions) in connective tissue.*

Task 6. Study a scheme of metabolism and complete the definitions

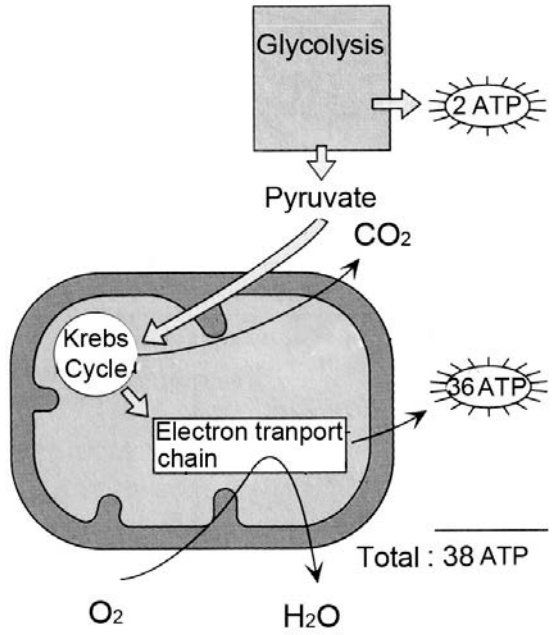


1. Sum of all the chemical and physical changes that take place within the body is _____

2. A constructive metabolic process whereby energy is consumed to synthesize or combine simpler substances, such as amino acids, into more complex organic compounds, such as enzymes and nucleic acids is _____

3. A type of metabolic process by which complex molecules are broken down to produce energy and reducing power is _____

Task 7. One of the most important organelles are mitochondria – main energy transformers of cells. Energy metabolism is composed of three stages. Study a scheme of energy metabolism and fill in the table



Stages of Energy Metabolism

Stages of energy metabolism	*Localization of process and distinctive alteration of substances*	*Biological significance*
Preparatory stage		
Anoxic (oxygenless) stage		
Oxygen stage		

Biological significance of energy metabolism – _____

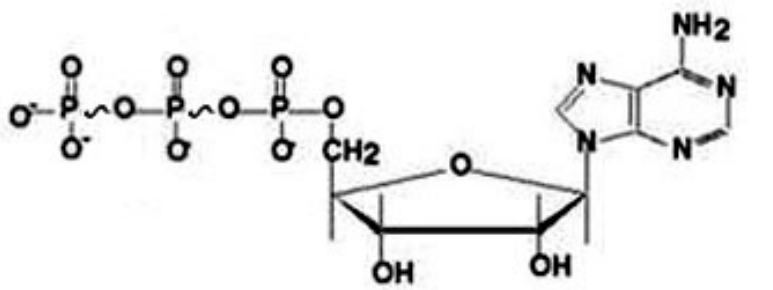
_____

_____

_____

Task 8. Study the structure of adenosine triphosphate (ATP), designate its components.

Chemical structure of adenosine triphosphate (ATP)



Task 9. Cell pathology is structural basis of human pathology.

On the initial stage the influence of one or some internal and/or external factors leads to the damage of elementary cell structures and violation of their functions. In future development of both pathology of a separate cell and pathology of cellular co-operations is possible. Knowledge of cellular pathology helps to understand morphological essence of pathological process in tissues and organs. Some diseases can be and were first diagnosed only at ultrastructural level.

It is important to notice that the earliest, initial stages of pathological process, showing up only at the ultrastructural level of cell, as a rule, convertible or can be compensated.

Study electron micrographs of cell damages and fill in the table below.

Multiple-Choice Tests for Control of Theme 2

1. Prokaryotic cell would not have which of these structures?
A. cell wall
B. cell membrane
C. ribosomes
D. nucleus
E. cytoplasm

2. A structure most closely associated with the destruction of worn out cell organelles is
A. lysosome
B. Golgi apparatus
C. endoplasmic reticulum
D. centrosome
E. vacuole

3. There are many small particles visible in electron micrographs of all cells. Chemical analysis shows that they contain both RNA and protein. What are these?
A. mitochondria
B. ribosomes
C. membrane fragments
D. centrioles
E. microtubules

Date	Signature

ALTERATIONS OF SOME CELLULAR STRUCTURES ASSOCIATED TO SOME STATES OF ORGANISM

Organelles	*Damage factor*	*Alteration of ultrastructure*	*Alteration of function*
1	*2*	*3*	*4*
Plasma membrane	Ionizing radiation, carcinogens, chemical poisons, viral infection, variations of temperature.		Disorder of a barrier function of membrane, receptor function of membrane and cell metabolism.
Hyaloplasm	Ionizing radiation, hypoxia, intoxication, viral infection.		Disorder of streaming or “cyclosis” of the protoplasm.
Mitochondria	Hypoxia, intoxication, hypovitaminosis, starvation. Hypertrophy, inflammation, tumoral processes.		Reduction of ATP synthesis. Increase of ATP synthesis.
Rough endoplasmic reticulum	Intoxication, viral infection. Starvation, tumoral processes, physiological aging of cell.		Increase of protein synthesis. Decrease of protein synthesis.

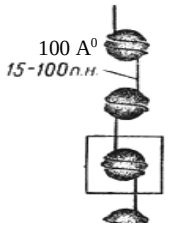
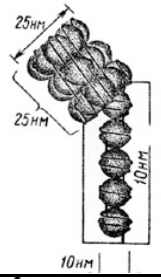
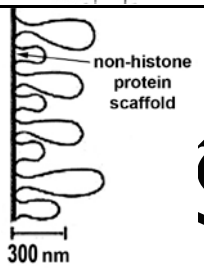
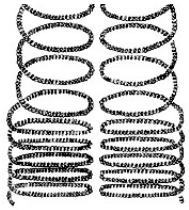
1	2	3	4
Smooth endoplasmic reticulum	Intoxication, viral infection, starvation. Liver diseases, physiological aging of cell.		Increase of synthesis of non-protein substances (steroid hormones, phospholipids, cholesterol, glycogen). Decrease of synthesis of non-protein substances.
Lysosomes	Any factors that are caused gene mutation. Ionizing radiation, shock, intoxication, hypovitaminosis, effect of bacterial endotoxin.		Decrease of activity of lysosomal enzymes. Necrosis. Autolysis.
Peroxisomes	Intoxication, viral infection. Hypoxia, inflammation, ionizing radiation, tumor processes.		Intensification of oxidation. Disorder of oxidation of amino, uric and lactic acids. Disturbance of decomposition H_2O_2.
Ribosomes	Intoxication		Reduction of protein synthesis.
Nucleus	Hypoxia, ionizing radiation, physiological aging of cell. Regeneration, intensive reproduction in the embryonic period.		Decrease of nucleic acids synthesis. Increase of nucleic acids synthesis.

Theme 3: Morphology of chromosomes. Human karyotype

Objectives: study the chromosome structure; be able to recognize the types of chromosomes in human ideograms; know the methods of karyotyping.

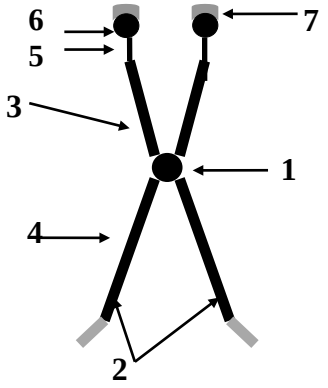
A term "*chromosome*" means a coloured body (Gr. *chrome* – colour; *soma* – body). It points to the fact that the chromosomes easily take up biological stains.

Task 1. Characterize the different levels of DNA organization.

Level	Structure	Characteristics
I Nucleosome		
II 30-nm fiber		
III Looped domain		
IV Metaphase chromosome		

Task 2. Designate the components of a metaphase chromosome. Note that a chromosome is made up of two sister chromatids, which separate during anaphase by splitting of centromere. After that each sister chromatid is known as a chromosome, made up of one short arm, one long arm and a centromere.

Structure of metaphase chromosome (ready for division)



1 _____
2 _____
3 _____
4 _____
5 _____
6 _____
7 _____

Task 3. Draw the morphological types of chromosomes. Describe them.

Morphological types of chromosomes as seen in metaphase

1	2	3	4

1. Metacentric – _____
_____
_____
_____

2. Submetacentric – _____
_____
_____
_____

3. Acrocentric – _____
_____
_____
_____

4. Telocentric – _____
_____
_____
_____

Task 4. Give definition of *autosomes*, *heterochromosomes* and *karyotype*.

Karyotype – _____
_____
_____

Autosomes – _____
_____

Heterochromosomes – _____
_____

Task 5. Examine a specimen of human chromosomes in leukocyte culture under the microscope.

The preparation is a smear of human peripheral blood treated with ***phytohemagglutinin*** (that stimulates cells to the division) and ***colchicine*** (violates the microtubules of mitotic spindle). The cells are then placed onto a slide and spread out. They are viewed under a microscope which is specially adapted with a camera to take a picture of the chromosomes from one of the cells.

Task 6. Give definition of *chromosome analysis,* read and remember the principles of chromosome analysis.

Chromosome analysis **(**also ***cytogenetic analysis*****)** _____
_____
_____
_____

Main principles of chromosome analysis

1. Chromosomes are studied on stages of prophase (prophase analysis), metaphase (metaphase analysis – the most informative) or anaphase (anaphase analysis).
2. Making of the specimens. Chromosomes are studied on tissue sections, but squashes and smears are more suitable.
3. Chromosomes are stained with basic dyes. Two principal staining techniques are:
   a) *conventional staining techniques* used to uniformly stain chromosomes and leave the centromeres constricted, thus enabling the measurement of chromosome length, centromeric position, and arm ratio;
   b) *banding*, or differential staining techniques, used to facilitate the identification of specific structural abnormalities. The most common staining is *G-banding*. They take their name from the Giemsa dye, but can be produced with other dyes. It yields a series of lightly and darkly stained bands (the individual "striation" of each chromosome). The dark regions tend to be *heterochromatic*, the light regions tend to be *euchromatic*. Cytogenetics employs several techniques (C-, Q- R-, T-bandings, etc.) to visualize the different aspects of specific chromosome abnormalities.
4. The metaphase plates with good allocation of chromosomes and without the considerable layers are appropriate for analysis. (If there are few chromosomes in metaphase plate such plate is considered an artifact and is ignored).
5. Depending on research purpose the chromosome analysis is carried out with or without karyotyping.
6. Except shape and general length, two additional parameters are used for characteristics of chromosomes:
   a) centromere index (CI) - ratio of short arm length to total length of chromosome (it is 0,5 for metacentric chromosome);
   b) ratio of arms (it is 1 for metacentric chromosome).

Clinical consideration

Cytogenetic analysis is undertaken to diagnose *chromosomal disorders* when a diagnosis is suspected clinically, to identify carriers of familial chromosomal rearrangements (structural abnormalities) when there is a family history and to provide information related to therapy and prognosis in certain tumor conditions.

Some of the main indications for performing chromosomal analysis are

Prenatal (before the birth)
- Abnormalities on ultrasound scan
- Increased risk of chromosome disease as Down syndrome (maternal age)
- Previous child with a chromosomal abnormality

Postnatal (after the birth)
- Newborn infants with birth defect
- Children with learning disability
- Infertility
- Recurrent miscarriages

Task 7. Denver and Paris classifications of chromosomes

In 1960, at the conference in Denver (Colorado, USA), cytogeneticists classified 23 pairs of human chromosomes into 7 groups. The basis of classification includes chromosomal features such as length of chromosomes, centromere position, and relative length of arms for conventionally stained chromosomes.

Study the table “Denver classification of human chromosomes”.

DENVER CLASSIFICATION OF HUMAN CHROMOSOMES

Group	Number	Size, mcm	Characteristics
A	1-3	11-8,3	1, 3 - large, metacentric, 2 - large, submetacentric
B	4-5	7,7	Large, submetacentric
C	6-12, X	7,2-5,7	Medium, submetacentric
D	13-15	4,2	Medium, acrocentric
E	16-18	3,6-3,2	16, 17 - short, submetacentric, 18 - short, acrocentric
F	19-20	2,2-2,8	Very short, submetacentric.
G	21-22,Y	2,3	Very short, acrocentric

In chromosome analysis the metaphase chromosomes of a patient are depicted (by rearranging a microphotograph) in a standard format: in pairs, ordered by size and position of centromere for chromosomes of the same size. In modern cytogenetic studies drawing karyogram is performed by computer programs.

Study a normal human chromosome complement. The metaphase chromosomes with two chromatids held together by the centromere are clearly seen. Find the morphological types of chromosomes: metacentric, submetacentric, acrocentric.

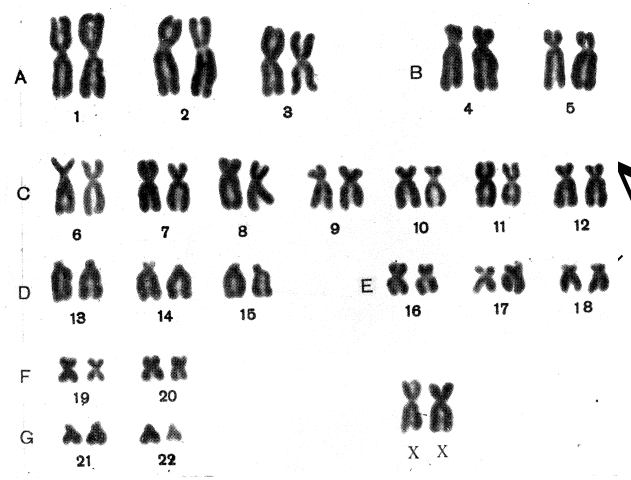


Fig. 1. *Human karyogram:* the conventionally stained chromosomes arranged according to the Denver classification

Paris classification of human chromosomes

The development of various *banding methods* helped to understand the morphology of each chromosome. In 1971, Paris Conference adopted the main principles of unequivocal identifications of individual chromosomes and regions using banding methods and also proposed an *ideogram* (diagrammatic representation of banding patterns) to depict the normal band morphology of each chromosome as well as a unique numbering system to help record specific bands and regions.

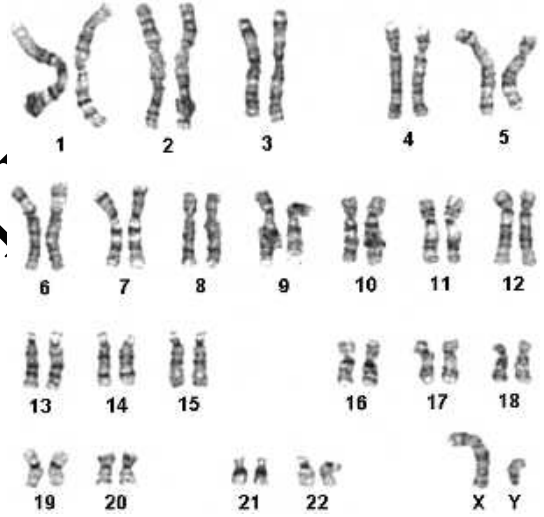


Fig. 2. *Human karyogram*: G-banded chromosomes are arranged according to the Paris classification.

Task 8. Study the characteristic features of *karyogram* and *ideogram*.

Karyogram	***Ideogram***
Set of chromosomes of one cell, belonging to an one concrete organism, and reproduced in all details and arranged according to some order.	Diagrammatic generalized representation of banding patterns of karyotype of a concrete biological species.

Principles of arrangement of chromosome include: (i) the chromosomes are matched up and are arranged in pairs according to size and location of a centromere; (ii) the chromosomes pairs are numbered from the largest to the smallest; (iii) the last pair is a pair of sex chromosomes.	On an ideogram, the haploid set of chromosomes, features of their condensation with euchromatin and heterochromatin regions are usually represented
It is the result of chromosome (cytogenetic) analysis. It can represent both conventionally stained and the differentially stained (G-banded) chromosomes.	It is the genetic "golden standard" of certain biological species. It always represents differentially stained (G-banded) chromosomes

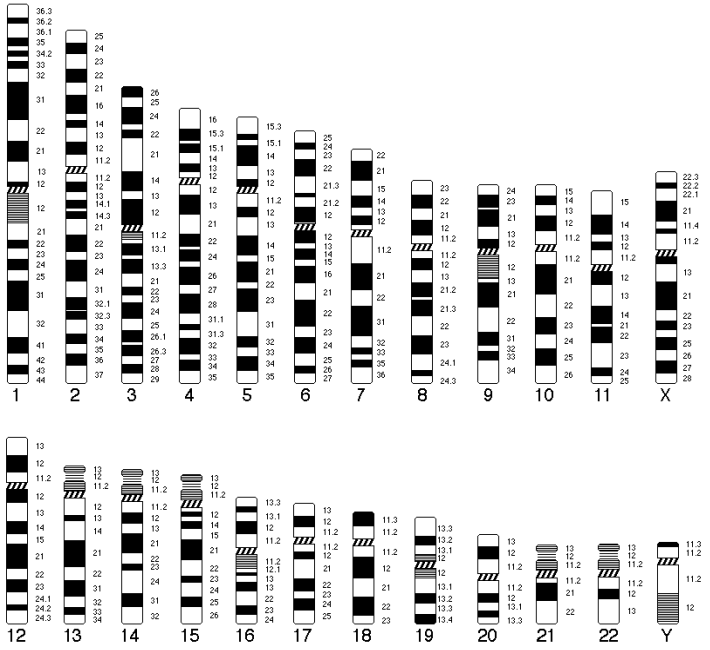


Fig. 3. *Ideogram of human chromosomes*

Task 9. Compare the types of chromatin: euchromatin and heterochromatin.

EUCHROMATIN		*HETEROCHROMATIN*

<u>Task 10</u>. Polytene, or giant, chromosomes

In tissues of most species, chromosomes are not visible during interphase. One exception is the giant chromosomes in the salivary glands of many dipteran (two-winged) flies (the larvae of *Drosophila* fruit fly), discovered in 1933. Called *polytene* (multistranded) chromosomes, they are much larger than the chromosomes of other cells in the larva. The giant size of polytene chromosomes is 3000 mcm lengthways, 15-20 mcm in thickness. They begin as normal chromosomes, but through repeated rounds of DNA replication without any cell division (called *endoreplication*), they become large, banded chromosomes. Thus a single chromosome consists of many chromatids (about 1000) because of process of continuous replication.

Examine the giant chromosomes in cells of the salivary glands of *Drosophila*. One can see the condensed thickenings (chromomeres) along the interphase chromosome. Chromomeres are those areas, where chromosomal material is coiled tightly and stained by hematoxylin dye. Owing to staining the chromosomes appear to have a pattern of transverse bands. The patterns of bands - their thickness, spacing, sharpness or diffuseness - are individual for each chromosome.

Sketch the polytene chromosomes. Designate the euchromatin and heterochromatin regions.

(×)

Fig. 4. *Polytene chromosomes in cells of the salivary glands of Drosophila.*

Multiple-Choice Tests for Control of Theme 3

1. In what stage of cell division chromosomes are most distinctly visible?

A. prophase
B. prometaphase
C. metaphase
D. anaphase
E. telophase

2. Chemical analysis of eukaryotic chromosomes indicated that they consist of:

A. DNA, RNA, proteins, lipids, water
B. DNA, RNA, carbohydrates
C. DNA, RNA, proteins, carbohydrates
D. DNA, RNA, proteins, enzymes, ions
E. DNA, RNA

3. A chemical inhibitor of the formation of the mitotic spindle is

A. nitrous acid
B. phytohemagglutinin
C. formalin
D. colchicine
E. nucleotide

Date	Signature

Theme 4: Cell cycle. Cell division

Objectives: have a look at the cell cycle; be able to analyze the alterations of cell and cell structures at the time of life cycle; study the mitotic abnormalities; study how the division process distributes the genetic material.

Task 1. Give the definition of *cell cycle*. Describe the main processes of interphase.

Cell cycle – _____

_____

_____

_____

Interphase – _____

_____

_____

_____

***G*$_1$** (Gap 1) _____

_____

_____

_____

S (Synthesis) _____

_____

_____

_____

***G*$_2$** (Gap 2) _____

_____

_____

_____

Task 2. Fill the table "***Types of cell division***"

Types of cell division	Characteristics
Mitosis	
Endomitosis	
Amitosis	
Polyteny	
Meiosis	

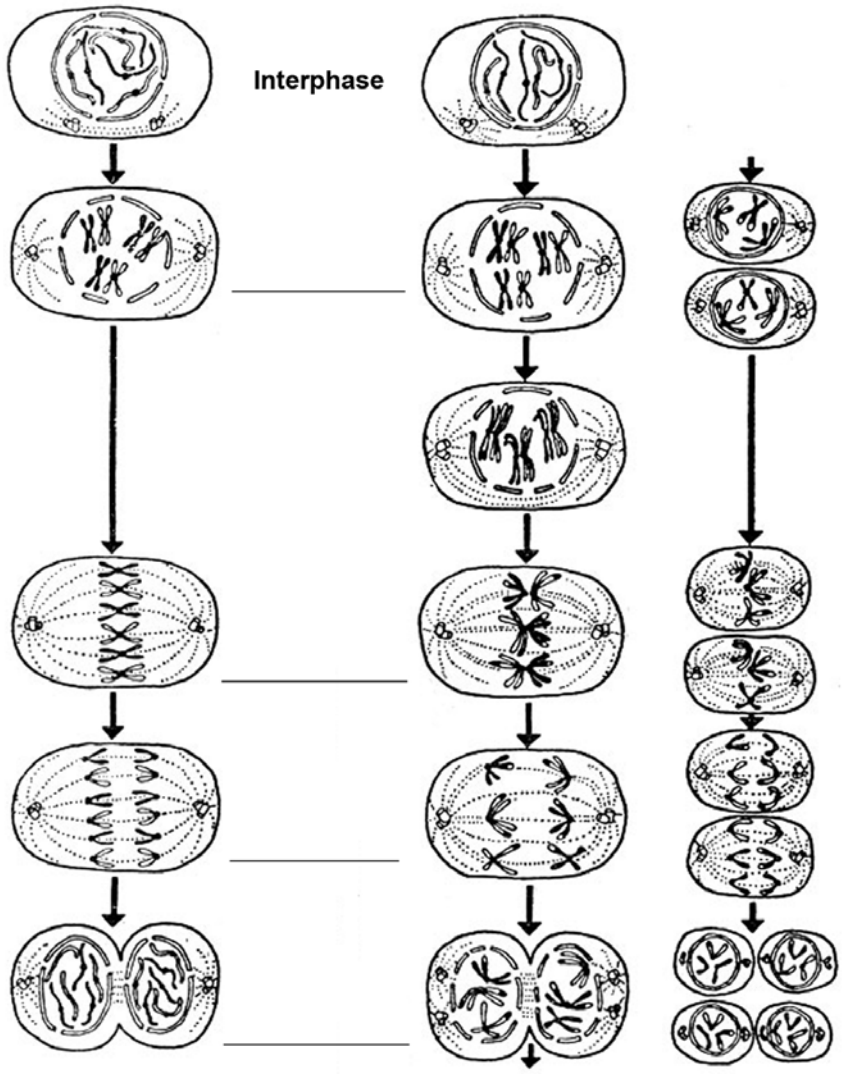
Task 3. Study the schemes of mitosis and meiosis, give the names of stages. Describe the main events which occur in nucleus during mitosis and meiosis.

The first meiotic division (meiosis I). The chromosome number is reduced from diploid to haploid.

Prophase I _____

_____

_____



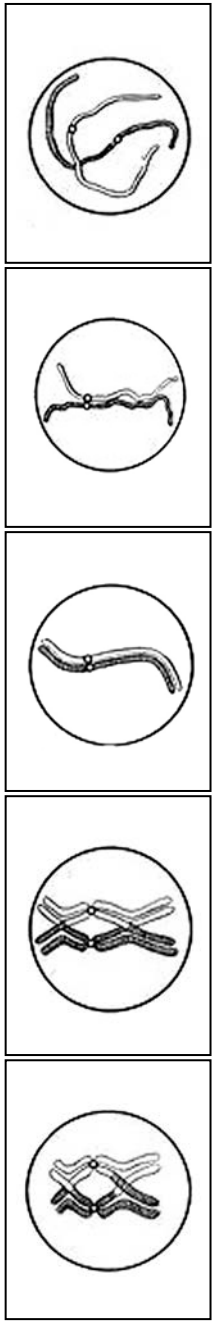
Leptotene _____

Zygotene _____

Pachytene _____

Diplotene _____

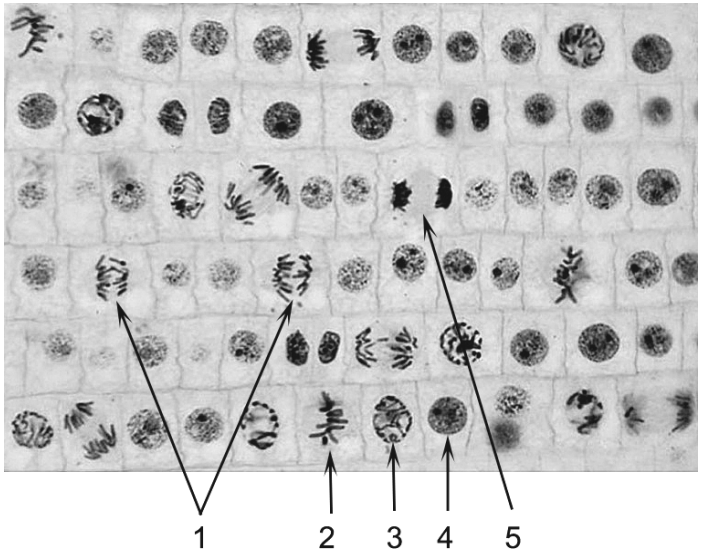
Diakinesis _____



Comparison of mitosis and meiosis

Feature	**Mitosis**	**Meiosis**	
What cells come in division			
A number of divisions			
How many and what cells are produced during divisions			
		Meiosis I	*Meiosis II*
Interphase			
Phases of mitosis			
- prophase			
- metaphase			
- anaphase			
-telophase			
Biologycal significance			

Task 4. Examine the cells of onion root tips with high power objective of microscope. Find the different stages of cell cycle.
Identify the stages of cell cycle on the picture below.



1. _____ , 2. _____ , 3. _____ ,

4. _____ , 5. _____

Task 5. Study a notion "*mitotic index*" and characterize the mitotic activity of tissues.
Mitotic index (MI) – characteristic of mitotic activity of tissues or tissue culture. It displays the specific number of cells, which are in mitosis, per 1000 investigated cells on histological (cytological) specimen.

$$[m] = \frac{N_m}{N},$$

where $[m]$ – mitotic index, N_m – number of cell in mitosis,
N – total number of cells in the investigated aggregate.

Analysis of mitotic mode is widely used in clinic in the investigation of biopsy specimen to exclude the cell malformation.

Mitotic mode involves such parameters:

- mitotic index;
- ratio number of cells, which are on the different mitotic stages;
- relative number of all mitotic abnormalities;
- percentage (portion) of particular types of mitotic abnormalities.

Mitotic activity of tissues

high	**medium**	**low**

Task 6. Study how the regulation of the cell cycle occurs.
Give the definition of *cell cycle checkpoints* and *growth factors.*

1. *Cell cycle checkpoints*

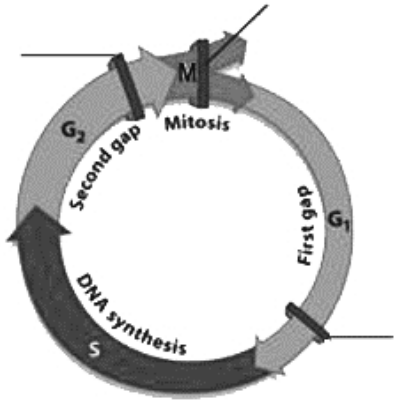
Cell cycle checkpoints – _____
_____
_____
_____

The cell cycle is controlled by interaction of ***three types of regulatory proteins,*** which initiate and/or introduce progression through the cell cycle:

1. cyclin-dependent kinases (CDKs)
2. cyclins that interact with CDKs with formation of complexes;
3. inhibitors of cyclin-dependent kinase complexes

Regulation of cell cycle is carried out by the reversible phosphorylation/dephosphorylation of regulatory proteins.

There are three checkpoints in cell cycle. Designate the checkpoints on the picture below.



Checkpoint	*Time of control*	*What happens*
G_1 check-point, or res-tricttion point	the end of G_1 phase, G_1/S transition	If conditions are not suitable for replication, the cell will not proceed to S phase but will instead enter a resting phase, G_0.
G_2 checkpoint	the end of G_2 phase, G_2/M transition	If conditions are not suitable, transition to the M phase will be delayed. If DNA is damaged, cell division will be delayed to allow time for DNA repair.
M checkpoint	Metaphase/ana-phase transition	If the chromosomes are aligned properly and ready for division, the cell will proceed from metaphase to anaphase, during which it will divide.
		If the chromosomes are not aligned properly, the anaphase stage will be delayed.

Clinical consideration

1. Transformed cells have lost their ability to respond to regulatory signals controlling the cell cycle. They may undergo cell division indefinitely, thus becoming cancerous.
2. A basic method of oncotherapy is suppression of cell division. The normal human cells are divided slower than tumour ones, therefore chemotherapeutic drugs, which block the cell reproduction, influence on a tumour much stronger, than on adjacent tissues.
3. In cancer therapy, *Vinca alkaloids* (drugs derived from the periwinkle plant, *Vinca rosea*) – vincristine, vinblastine, vindesine – are well-established cancer chemotherapeutic agents. They inhibite the assembly of tubulin into microtubules. Disruption of the microtubules arrests mitosis in metaphase because the cell can not run **M** checkpoint.
4. The drugs that block purine and pyrimidine synthesis may arrest cells in S-phase of cell cycle.

2. *<u>Growth factors</u>*

Growth factors – _____
_____
_____
_____

1. _____
2. _____
3. _____
4. _____
5. _____

6. _____
7. _____

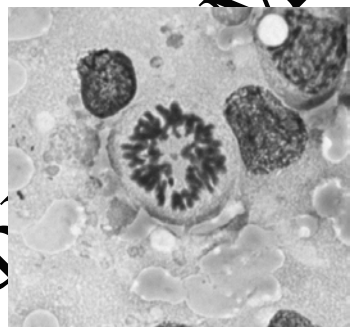
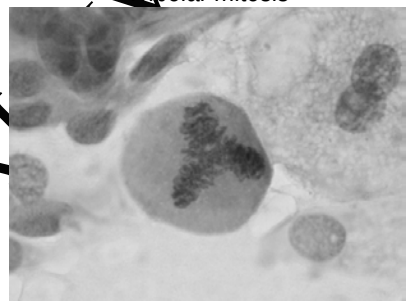
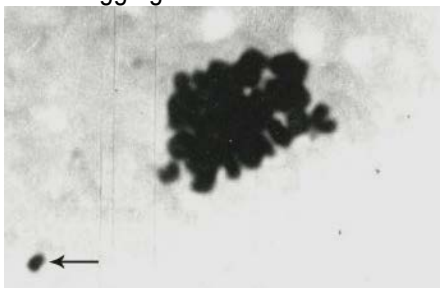
Task 7. Study the mitotic abnormalities.

Violation of normal mitotic course (mitotic abnormalities, mitotic aberrations) and incorrect distribution of chromosomes among daughter cells can result in cells with unbalanced karyotype, causing mutations, and, in particular, somatic aneuploidy.

In normal tissues of adult people, the rate of mitotic abnormalities isn't more than 2-4% of dividing cells. In cell cultures, it amounts to 5-15% at normal cell growth. The rate of mitotic abnormalities in tissues is the important parameter in diagnostics. The beginnings of mitotic abnormalities are typical feature of neoplastic hyperplasia (tumor process). Hence, the study of mitotic abnormalities is very important in differential diagnostics of neoplastic or benign processes.

There are **three types of mitotic abnormalities** classified according to morphophysiological principles:

- abnormalities caused by chromosome damage;
- abnormalities caused by damage of mitotic apparatus;
- violation of cytokinesis.

Disease	*Morphological manifestation*
Cancer of lymphatic tissue (lymphoma)	Hollow metaphase 
Skin cancer (squamous cell carcinoma)	Tripolar mitosis 
Viral infection	Lagging of a chromosome 

Task 8. Complete the definition below.

1. The cell death which can be caused by a variety of chemicals and toxic substances is _____

*Examples:*_____
_____
_____

2. Programmed cell death, process of cellular self-destruction is
_____

Examples: _____
_____
_____

Comparison of apoptosis and necrosis

Sign	Apoptosis	Necrosis
Prevalence	Single cell	Group of cells
Induction	It is activated by physiological or pathological stimuli	Different depending on the damaging factor
Biochemical alterations	Volatile changes in DNA fragmentation by endogenous endonucleases. Lysosomes are not damaged	Disturbance or termination of ion exchange. Enzymes are released from lysosomes
DNA breakup	Intranuclear condensation with splitting into fragments	Diffuse localization in necrotic cell
Integrity of cell membrane	Retained	Violated
Morphology	Cell shrinkage and fragmentation	Swelling and cell lysis
Inflammatory response	No	Usually yes
Removal of dead cells	Absorption (phagocytosis) by of neighboring cells	Absorption (phagocytosis) by neutrophils and macrophages

Multiple-Choice Tests for Control of Theme 4

1. Which of the following is the longest phase of cell cycle?
- A. G_1
- B. G_2
- C. mitosis
- D. S
- E. any phase

2. Which of the following occurs during anaphase II of meiosis?
- A. Chromosomes cluster at the two poles of the cell
- B. Chromosomes align down the center of the cell
- C. Crossing over occurs
- D. Chromatids moves toward a pole
- E. Bivalents are formed

3. What is the effective mechanism of action of the *Vinca* alkaloids?
- A. Inhibition of the function of microtubules
- B. Damage and prevention of repair of DNA
- C. Inhibition of DNA synthesis
- D. Inhibition of protein synthesis
- E. Inhibition of purine synthesis

Date	Signature

Theme 5: Characteristics of nucleic acids

Objectives: study the structure of DNA molecule and different types of RNA; study the mechanisms of replication and DNA repair.

Task 1. Study the experiments that proved the genetic role of DNA, using a table of medical illustrations. Write what experiments of what scientists proved the genetic role of DNA.

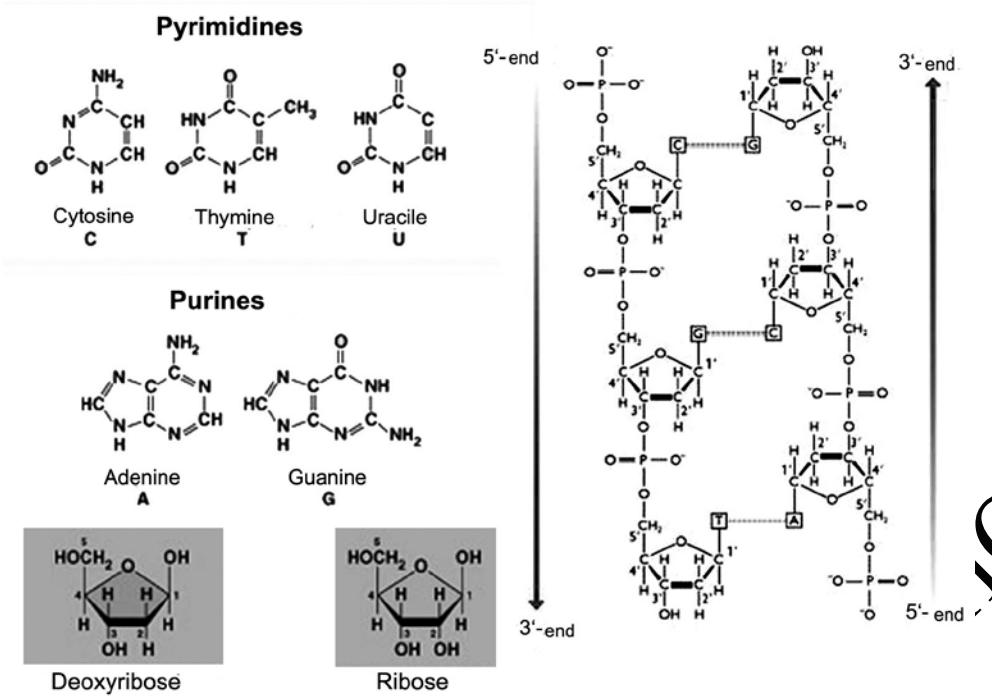
Task 2. Give the definition of *transformation, transduction, conjugation.*

Transformation – _____

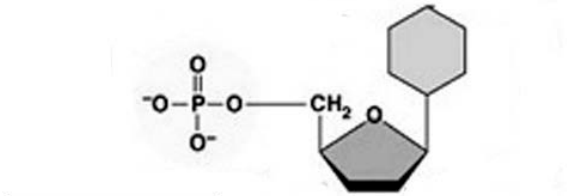
Transduction – _____

Conjugation – _____

Task 3. Designate the components of nucleotide and study DNA structure.



Nucleotide structure



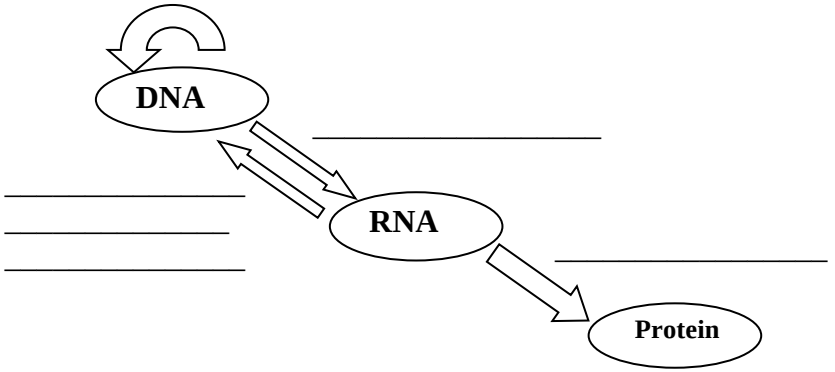
Task 4. Chargaff's Rules.

In 1950, a biochemist Erwin Chargaff formulated important generalizations about DNA structure.

1. _____
2. _____
3. _____

Task 5. Note the processes of the flow of genetic information according to **Central dogma of Molecular Biology**.

The Central dogma of molecular biology was first articulated by Francis Crick in 1958 and re-stated in a *Nature* paper published in 1970.



Mitochondrial inheritance

The mitochondria have own DNA (mtDNA). It was first discovered in 1963. The mitochondrial genome is a circular DNA molecule of 16569 nucleotides, multiple copies of which are located in the mitochondria. Somatic cells and gametes have about 8000 copies of the mitochondrial genome, 10 or so in each mitochondrion.

Mitochondrial genome is much smaller than the nuclear genome, and it contains just 37 genes. Thirteen of these genes code for proteins involved in the respiratory complex, the main biochemical component of the energy-generating mitochondria; the other 24 specify the non-coding RNA molecules that are required for expression of the mitochondrial genome. The genes in this genome are much more closely packed than in the nuclear and they do not contain introns.

Mutations in mitochondrial genes have been identified are the causes for a ***variety of diseases and, potentially, aging.***

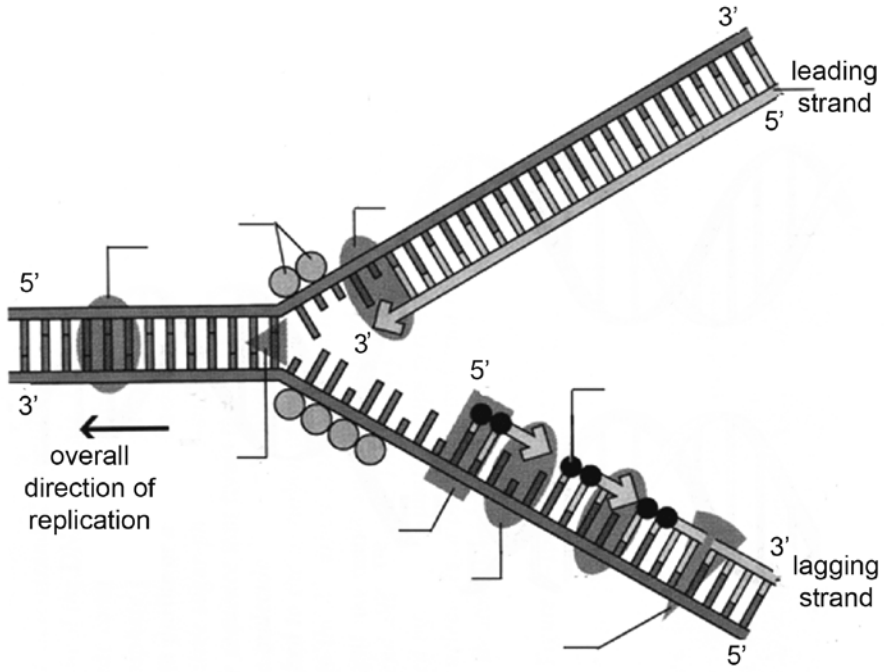
Task 6. Give the definition of a term "*replication*". Note a significance of replication.

Replication – _____
_____
_____
_____

Significance of replication_____
_____
_____
_____

Task 7. Analyze a scheme of DNA replication. Note the arrangement of enzymes that take part in replication. Write down the functions of enzymes and proteins.

Scheme of DNA replication



Enzymes and their functions

1. **Topoisomerase** - _____
_____
_____

2**. Helicase** - _____
_____
_____

3. **DNA-polymerase** - _____
_____
_____

4. **DNA-ligase** - _____
_____
_____

5. **DNA-primase** - _____
_____
_____

6. **RNA-primer** - _____
_____
_____

7. **Stabilizing proteins** - _____
_____
_____

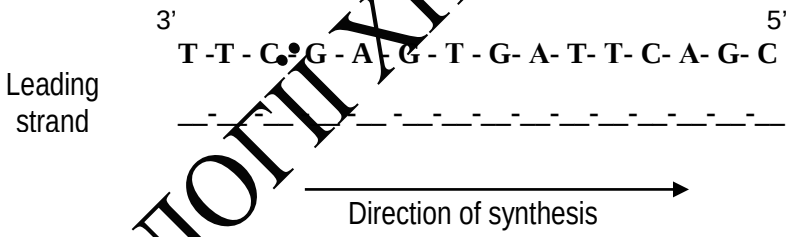
Fill in the table.

Stages of DNA replication

	Stage	Characteristics
1	Initiation	
2	Elongation	
3	Termination	

Task 8. Solve the problem.

a) Write the nucleotide sequence of the second strand of the leading chain of DNA molecule if the sequence of the coding chain is:



b) Calculate the percentage of thymine nucleotides in this fragment of DNA molecule.

Task 9. Give the definition of DNA repair, note a significance of DNA repair. Fill in the table.

DNA repair - _____
_____
_____
_____

DNA repair mechanisms

	Photoreactivation	*Excision repair*
Factor of damage		
DNA repair mechanism		

Name the diseases caused by disorder of DNA repair.

1. _____
2. _____
3. _____

Significance of DNA repair

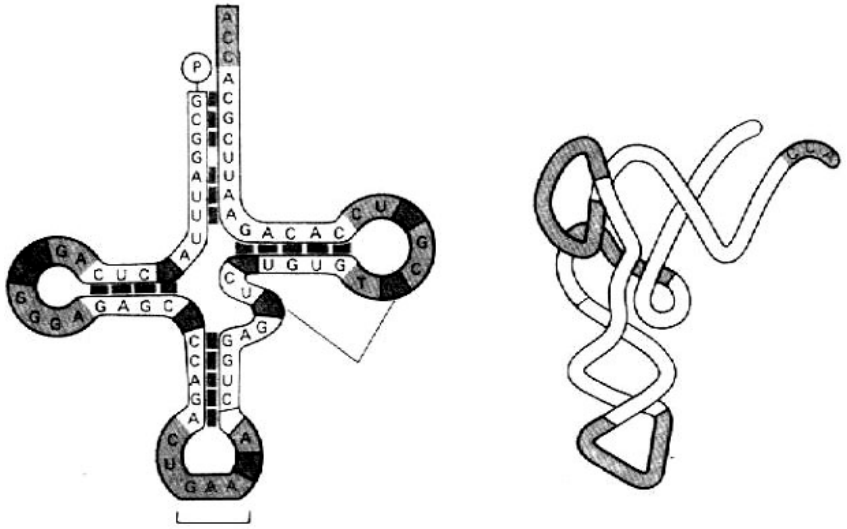
_____
_____
_____

Task 10. Study the structure of transfer RNA (tRNA), designate the functional sites of tRNA.

Transfer RNAs are short molecules (70-90 nucleotids), that have secondary and tertiary structure.

All tRNAs have a similar secondary structure (cloverleaf) and a 3′-terminal **CCA** sequence. The amino acid is attached to the extreme 3′-end of the tRNA, to the adenosine (**A**) of the invariant **CCA** terminal sequence.

Tertiary structure is like as a boomerang. Variety of tertiary structures is 20 (as number of amino acids).



Task 11. Write the differences between DNA and RNA in the table.

Differences between DNA and RNA

Features	DNA	RNA
Localization in cell		
Structure of molecule		
Nucletide structure		
Types of nucleotides		
Properties		
Functions		

Multiple-Choice Tests for Control of Theme 5

1. Which of the following are purines?
A. adenine and cytosine
B. adenine and guanine
C. adenine and thymine
D. cytosine and thymine
E. cytosine and guanine

2. The two polynucleotide strands in DNA are:
A. parallel
B. antiparallel
C. semidiscontinuous
D. semiconservative
E. discontinuous

3. All of the following enzymes are involved in DNA replication ***except***:
A. topoisomerase
B. helicase
C. DNA polymerase
D. RNA polymerase
E. DNA primase

Date	Signature

Theme 6: Gene structure in prokaryotes and eukaryotes. Structural and regulatory genes, genes of tRNA and rRNA. Flow of information in cell

Objectives: study the structure of eukaryotic and prokaryotic genes; analyze main characteristics of gene code; be able to use the table of genetic code; pay attention to the features of translation and its stages.

Task 1. Give the definition of a term "*gene*", write the types of genes.

Gene – _____

_____

_____

_____

_____

Types of genes

- housekeeping genes _____

_____

_____

_____

- luxury genes – _____

_____

_____

_____

- structural genes – _____

_____

_____

_____

- regulatory genes – _____

_____

_____

_____

- genes of tRNA – _____

_____

_____

- genes of rRNA – _____

_____

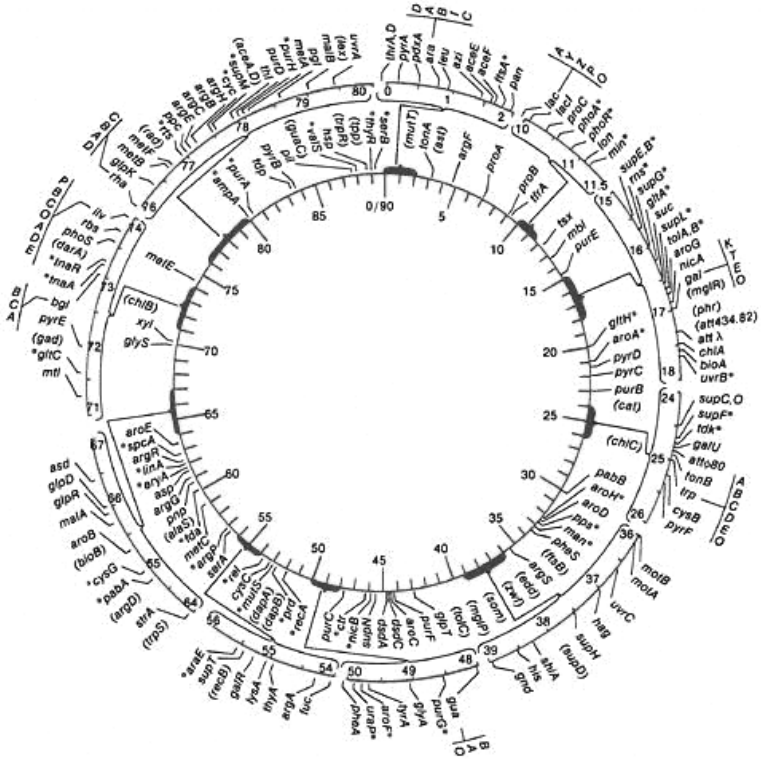
_____

- mobile genetic elements – _____

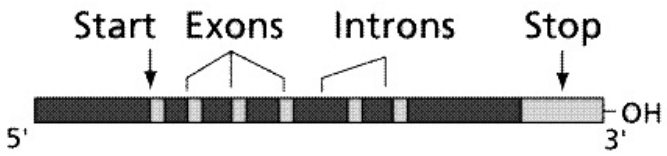
_____

_____

Task 2. Compare structure of eukaryotic gene with prokaryotic genes.



A



B

Fig. Organization of prokaryotic genome – circular chromosome of *E. coli* (A) and the structure of an typical eukaryotic gene – transcripton (B).

Take into consideration:

- all the ***genetic information of prokaryotes*** is usually contained in an ***circular DNA molecule – the bacterial chromosome (nucleoid)*** and ***eukaryotic nuclear DNA*** is organized in non-closed molecules – ***chromosomes***, whereas ***mitochondrial DNA and plastid DNA are circular***;
- ***prokaryotic genomes are short*** (0.25-3 mm DNA in cell) because a part of their genes is organized in operons. There are few repetitive genes and non-coding regions between the genes (spacers) are short;
- ***eukaryotic genomes are redundant*** (about 1.8 m in each cell of human body), because they contain a lot of ***copies*** of some genes, ***"silent" genes,*** and long non-coding inserts within genes (***introns***) and between them ***(spacers)***;
- ***bacterial*** chromosome has ***histone-like*** proteins whereas ***eukaryotic chromosomes*** have ***histone*** proteins. Histones are involved in DNA packaging;
- ***In eukaryotes, regulation of gene expression is more complex and precise*** than in prokaryotes.

Task 3. Give the definition of the terms "*intron*" and "*exon*".

Exon – _____
_____
_____

Intron - _____
_____
_____

Task 4. Write the stages of protein biosynthesis.

1. _____
2. _____

Task 5. Give the definition of the term "*transcription*", fill the tables and note significance of transcription.

Transcription - _____
_____
_____
_____

Stages of RNA transcription

	Stage	Characteristics
1	Initiation	
2	Elongation	
3	Termination	

Features	*Transcription*	*DNA Replication*
principal enzyme		
nucleotides		
pairings		
strand "copied"		
regions "copied"		

Significance of transcription _____
_____
_____
_____
_____

Task 6. Solve the problem.
Write the nucleotide sequence of pro-mRNA, which will be formed in transcription.

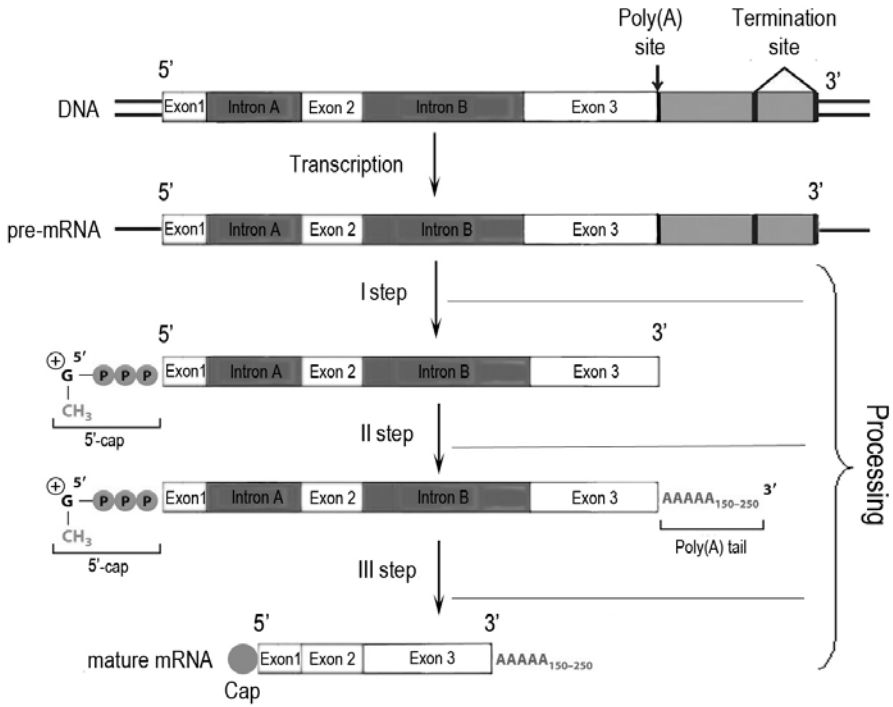
Coding DNA strand **C –G –T –A –G – T –A –A –G –A –A –G –A –G –T**

DNA strand (template) **G –C –A –T –G – A –T –T –C –T –T –C –T –C –A**

pre-mRNA _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Task 7. Study the scheme of RNA processing (splicing) and an order of transformation of heredity information in eukaryotic cell. Make designations.

Scheme of RNA processing



Enzymes that take part in RNA processing:

nucleases _____
_____

ligases _____
_____

Significance of processing – _____
_____
_____
_____
_____

Task 8. Give the definition of *genetic code* and study the table of genetic code. Write down the main characteristics of genetic code.

Genetic code – _____

_____

_____

_____

_____

THE GENETIC CODE

Position of a nitrogen containing base in RNA codon					
1st	2nd				3rd
	U	C	A	G	
U	Phenylalanine	Serine	Tyrosine	Cysteine	U
	Phenylalanine	Serine	Tyrosine	Cysteine	C
	Leucine	Serine	STOP	STOP	A
	Leucine	Serine	STOP	Tryptophan	G
C	Leucine	Proline	Histidine	Arginine	U
	Leucine	Proline	Histidine	Arginine	C
	Leucine	Proline	Glutamine	Arginine	A
	Leucine	Proline	Glutamine	Arginine	G
A	Isoleucine	Threonine	Asparagine	Serine	U
	Isoleucine	Threonine	Asparagine	Serine	C
	Isoleucine	Threonine	Lysine	Arginine	A
	Methionine	Threonine	Lysine	Arginine	G
G	Valine	Alanine	Aspartic Acid	Glycine	U
	Valine	Alanine	Aspartic Acid	Glycine	C
	Valine	Alanine	Glutamic Acid	Glycine	A
	Valine	Alanine	Glutamic Acid	Glycine	G

* Biosynthesis of all proteins in prokaryotic and eukaryotic cells begins translation from start-codon AUG (methionine, methionine).

** Three codons – UAA, UGA and UAG – are stop codons or termination codons. They do not encode any amino acid, but signal the end of a polypeptide chain.

Main characteristics of genetic code

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Task 9. Solve the problem:
Calculate a number of codons (triplets) in the fragment of the DNA strand.

T A C A A G G G C C A T A A A C G C

Task 10. Solve the problem:
Find the nucleotide sequence of anticodons for the strand.

A T G G C C A T T C A G

mRNA — — — — — — — — — — — — — —

_____ — — — — — — — — — — — — — —

Task 11. Solve the problem:
Find what amino acids are encoded by the region of DNA strand:

Coding DNA strand **GAA AGT ACC TGC TTA GGG CCG ACC AGG**

DNA strand (template) _____

mRNA _____

amino acids _____

Task 12. Give the definition of *translation*, note significance of translation.

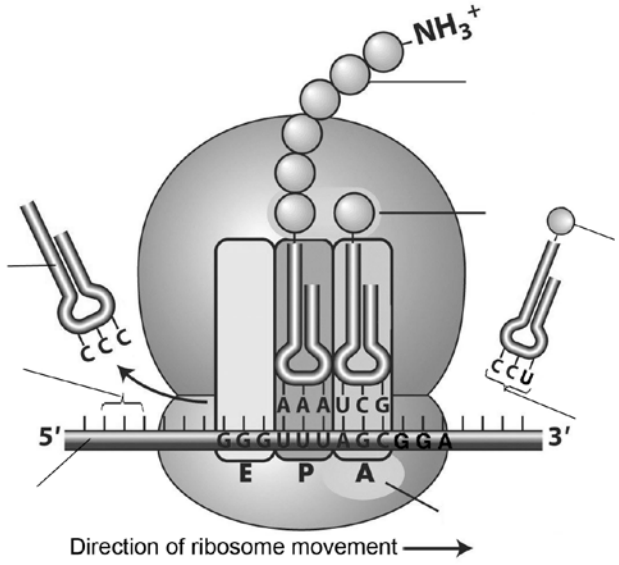
Translation – _____
_____
_____
_____

Stages of translation

	Stage	Characteristics
1	Initiation	
2	Elongation	
3	Termination	

Significance of translation _____
_____
_____
_____

Task 13. Study the scheme of protein synthesis. Make the designations and write down the requirements for protein synthesis.



_____
_____
_____
_____
_____

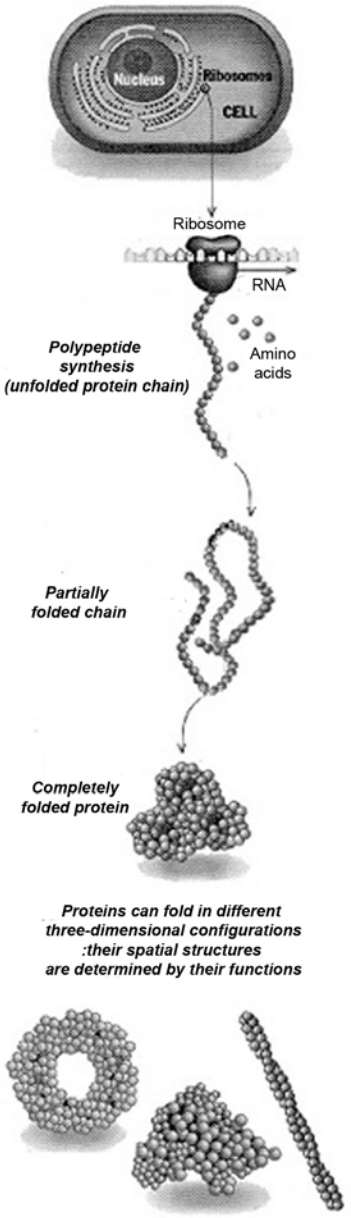
Task 14. **Posttranslational modification of proteins** includes *protein folding* and *chemical modification* of a protein after its translation. It is one of the later steps in biosynthesis for many proteins.

Proteomics is methodology for characterizing the protein content of a cell**.** More than 300 types of modifications of proteins were described by proteomics to 2001.

- **Protein folding**

Protein folding is the folding of polypeptide chain into their correct three-dimensional structures after protein synthesis. The tertiary structure results from folding the secondary structural components of the polypeptide into a specific three-dimensional configuration. Notable that protein takes only one beforehand known configuration of millions of potentially possible spatial combinations.

The tertiary structure is stabilized by various chemical forces, notably hydrogen bonding between individual amino acids, and hydrophobic forces, which dictate that amino acids with non-polar (i.e. 'water-hating') side-groups must be shielded from water by embedding within the internal regions of the protein. There may also be covalent bonds called disulfide bridges between cysteine amino acids at various places in the polypeptide.



Protein folding can occurs in several stages and takes from a few seconds to a few minutes. The folding is provided for such enzymes as ***foldases*** and ***isomerases***. Sometimes specific proteins (***chaperonins***, or chaperone proteins) take place in folding.

In some cases, the protein makes the wrong 'choice'. Such event occurs in organism of the person, which has the Alzheimer disease – senile dementia. About 10% of people upwards 65 years old and about 50% of people upwards 85 years old have this disease. According to statistics, about 100 thousand people die annually in USA alone because of this disease.

- **Chemical modification**

Chemical modification may involve the formation of disulfide bridges and attachment of any of a number of biochemical functional groups, such as acetate, phosphate, various lipids and carbohydrates. Enzymes may also remove one or more amino acids from the amino end of the polypeptide chain, or cut the polypeptide in the middle of the chain. For instance, the peptide hormone insulin is cut twice after disulfide bond formation to remove “a propeptide” from the middle of the chain, leaving a protein consisting of two polypeptide chains connected by disulfide bonds. In other cases, two or more polypeptide chains that are synthesized separately may associate to become subunits of a protein with quaternary structure.

Some chemical modification extends the range of possible functions a protein can have by introducing other chemical groups into the makeup of a protein (e.g., carbohydrate chains). Such chemical changes may alter the hydrophobicity of a protein and thus determine if the modified protein is cytosolic or membrane-bound. Other modifications like phosphorylation are part of common mechanisms for controlling the behavior of a protein, for instance, activating or inactivating an enzyme.

Types of posttranslational modifications include:

- phosphorylation, the addition of a phosphate group, usually to serine, tyrosine, threonine or histidine
- acetylation, the addition of an acetyl group, usually at the N-terminus of the protein

- alkylation, the addition of an alkyl group (e.g. methyl, ethyl)
  - methylation the addition of a methyl group, usually at lysine or arginine residues (this is a subtype of alkylation)
- glycosylation, the addition of a glycosyl group to either asparagine, hydroxylysine, serine, or threonine, resulting in a *glycoprotein.*

Multiple-Choice Tests for Control of Theme 6

1. Copying of DNA information to RNA is called
A. translation
B. transformation
C. transcription
D. replication
E. polymerization

2. A gene segment that contains directions for making a protein is
A. gene
B. chromosome
C. primer
D. intron
E. exon

3. Proteins are:
A. invariably enzymes
B. branched chains of nucleotides
C. linear, folded chains of nucleotides
D. linear, folded chains of amino acids
E. branched, folded chains of amino acids

Date	Signature

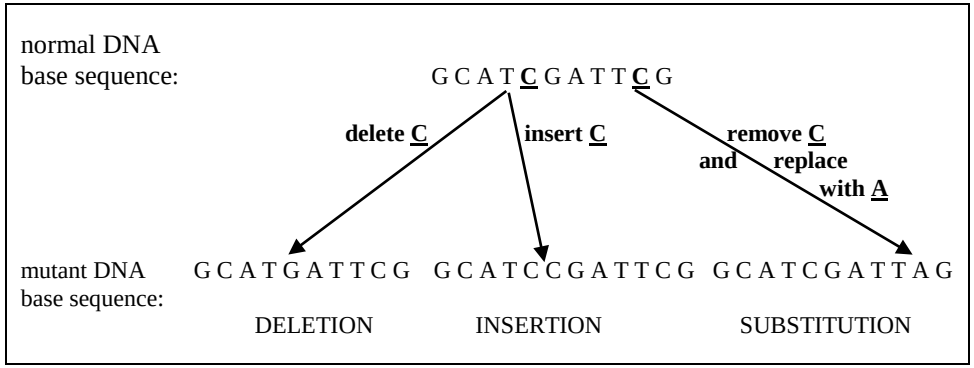
Theme 7: Molecular mechanisms of variation in humans. Control of gene expression

Objectives: take a look at the molecular mechanism of variability and gene regulation.

Task 1. Study the molecular mechanisms of variability.

The model of DNA double helix, discovered by Watson and Crick, corresponds to its biological functions: ability to replication of genetic material and constancy from generation to generation, from cell to cell. These properties of DNA account for molecular mechanisms of variability (mutation, recombination): some errors of a structural gene, errors of replication are exactly reproduced in daughter molecules of DNA in future. It accounts for genotypic heterogeneity of populations and polymorphism of proteins, molecular causes of hereditary diseases and their manifestations, hereditary intolerance to some foodstuffs (for example, lactose) or some medicaments (for example, dithylinum, primaquine).

Study the mechanisms by which the deletion, insertion and substitution mutations can arise.



Sickle-cell anemia as an example of substitution mutation

Haemoglobin of red blood cells (Hb) is a complex of globin protein and non-protein ferruginous part (haem, heme). Normal globin (HbA) of adult person consists of two α - and two β-polypeptide chains.

In healthy people, there is a glutamic acid on the 6th position from N-end in β-chain. Patients with sickle-cell anemia (genetic disease) have a valine in place of a glutamic acid. It arises from the substitution mutation in mRNA. Because of this point mutation hemoglobin HbA transforms to abnormal haemoglobin HbS: it loses solubility and leaves sediment that deforms the erythrocyte.

Task 2. Study the point mutation that results in sickle-cell anaemia.

Effect of substitution mutation on expression of gene for normal haemoglobin (HbA) β-chains leading to synthesis of sickle-cell haemoglobin (HbS)

Normal haemoglobin (haemoglobin A)

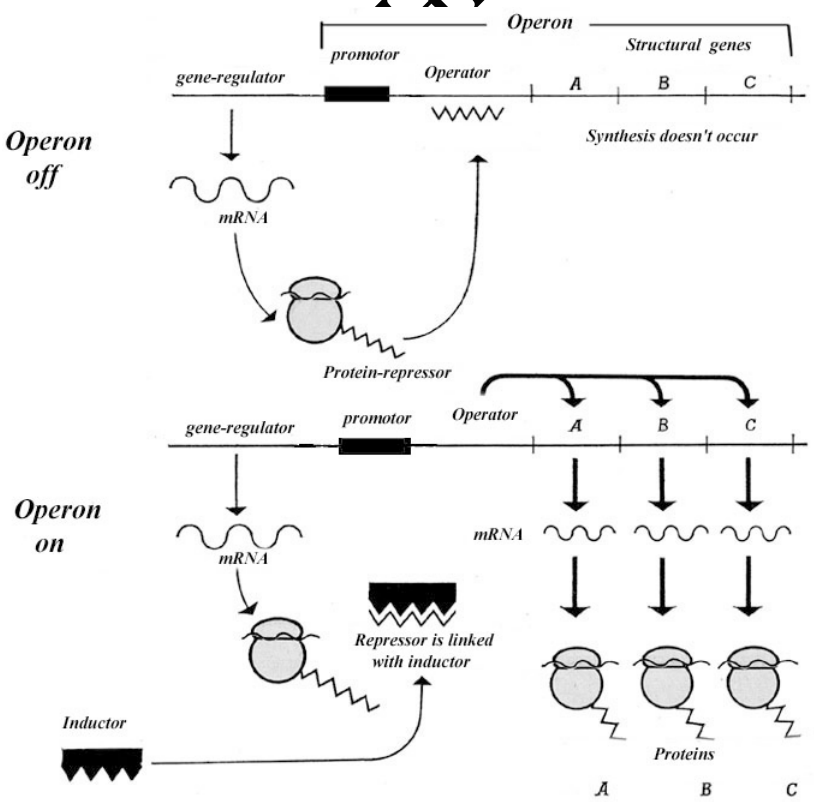
DNA	●●●●●●●●●●●●● CTC ●●●●●●●●●●●●●
mRNA	●●●●●●●●●●●●● GAG ●●●●●●●●●●●●●
β-chain of haemoglobin molecule	Val – His – Leu – Thr – Pro – **Glu** – Glu – Lys

Sickle-cell haemoglobin (haemoglobin S)

DNA	●●●●●●●●●●●●● CAC ●●●●●●●●●●●●●
mRNA	●●●●●●●●●●●●● GUG ●●●●●●●●●●●●●
β-chain of haemoglobin S	Val – His – Leu – Thr – Pro – **Val** – Glu – Lys

Task 3. Study operon model of gene regulation and answer the questions.

Scheme of the functioning of lactose operon of E. coli



What is the function of promotor?_____

_____

_____

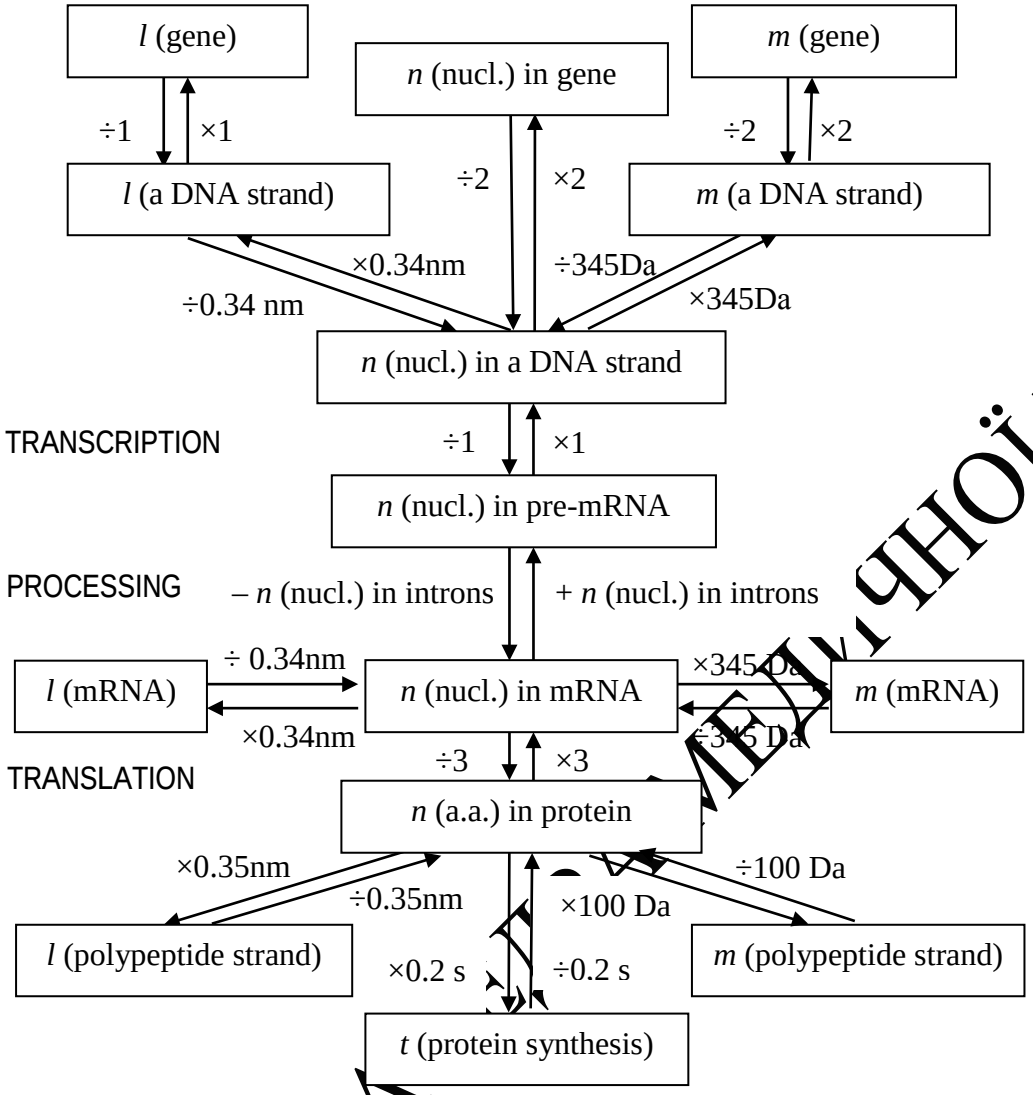
_____

What is the function of a regulator gene?_____

_____

_____

Task 4. Study a scheme that explains an algorithm of solving of the problems in molecular biology.



In solving of Molecular Biology problems, you have to remember the following constants:

1. Average molecular mass of a nucleotide is **345 Da**
2. Distance between two adjacent nucleotides in DNA is **0.34 nm**
3. Average molecular mass of an amino acid is **100 Da**
4. Distance between two adjacent amino acids in protein is **0.35 nm**

Task 5. Solve the problems:

Problem 1. An average molecular mass of a nucleotide is 345 Da. What is the weight of the gene that codes for a protein consisting of 155 amino acids?

Solving:

Problem 2. A gene codes for a protein composed of 185 amino acids. What is a length of the gene? It is known a distance between two adjacent nucleotides in DNA is 0.34 nm.

Solving:

Problem 3. How many amino acids are in a protein if the synthesis of its molecule took 3 minutes? An amino acid is linked up into a polypeptide over 1/6 of second.

Solving:

Problem 4. A DNA strand consists of 1694 nucleotides and introns (noncoding inserts) are composed of 220, 173 and 371 nucleotides. Find a number of amino acids that are encoded by this DNA strand.

Solving:

Problem 5. A protein molecule consists of 798 monomers. Find a number of nucleotides in the gene responsible for the synthesis of this protein if introns are 55 % of nucleotides.

Solving:

Problem 6. The synthesis of a protein molecule took 12 minutes. Calculate a number of nucleotides in the gene that codes for this protein if a number of nucleotides in exons is 80% and one amino acid is linked up into a polypeptide over 1/6 of second.

Solving:

Multiple-Choice Tests for Control of Theme 7

1. In genetic disease sickle cell anemia, a disease-causing substitution mutation occurs. In mutated haemoglobin, an amino acid
A. valine is instead of glutamic acid
B. glutamic acid is instead of valine
C. valine is instead of glutamine
D. glutamine is instead of valine
E. glutamic acid is instead of glutamine

2. What enzymes take part in protein folding?
A. primases
B. isomerases
C. ligases
D. nucleases
E. helicases

3. F. Jacob and J. Monod won the 1965 Nobel Prize for proposing the _____ model of gene regulation and organization in prokaryotes.
A. operon
B. repressible
C. inducible
D. operator
E. regulator

Date	Signature

PROBLEMS TO THEME 7 FOR SELF-WORK

Problem 1. There are 32% guanine nucleotides of total number of nucleotides in DNA molecule. Calculate the percentage of other types of nucleotides in this molecule.
Solving:

Problem 2. A light chain of human immunoglobulin protein has 23kDa in weight. What is the length of the gene that codes for this polypeptide chain? An average molecular mass of an amino acid is 100 Da, a distance between two adjacent nucleotides in DNA is 0.34 nm (*Answer: 234.6 nm)*
Solving:

Problem 3. Length of a gene is 65.28 nm. Exons are 25% of total number of DNA monomers. Find the weight of a polypeptide encoded by this gene *(Answer: 1600 Da)*

Solving:

Problem 4. The length of primary protein structure is 256.9 nm. Distance between two adjacent amino acids in protein is 0.35 nm

a) Determine a number of amino acids in this polypeptide (*Answer: 734)*

b) Find the length of the gene that codes for this protein (*Answer: 748.68 nm*)

c) Calculate the time of synthesis of this protein if one amino acid is linked up into a polypeptide over 0.2 second (*Answer: 146.8 sec*)

Solving:

Themes of individual work for the Unit 1

1. Levels of organization in the living world and their importance in medicine.
2. Techniques used to study cell structure and function
3. Flow of information in a cell.
4. Life of cells outside the organisms. Cloning.

Sample Lab Practical Exam 1 Questions

1. The science of biology. The importance of biology in medical education.
2. The concept of life. Characteristics of living things. Life forms.
3. Levels of organization of the living world. Their importance in medicine.
4. The cell theory, present state. The importance of the cell theory in medicine. General plan of cellular organization common to all cells.
5. The cell: basic structural and functional unit of life. Prokaryotic and eukaryotic cells.
6. Techniques used to study cell structure and function.
7. The chemical composition of cell.
8. Morphology and physiology of eukaryotic cell. Cytoplasm. Double-membranous organelles.
9. Single-membranous organelles.
10. Non-membranous organelles. Locomotor organelles. Cytoplasmic inclusions.
11. Cell membrane: chemical composition, structure and functions. Glycocalix.
12. Transport across cell membrane. Its medical importance.
13. The cell as an open system. Substance and energy flow in cells. Cellular energy supply.
14. Structure and functions of the nucleus. Euchromatin and heterochromatin. Hierarchies in eukaryotic genome organization. Sex chromatin.
15. Chromosome composition and morphology. Chromosomes during the cell cycle. Polytene chromosomes.
16. Human karyotype. Human chromosome classification. Medical applications of chromosome analysis.
17. Ultrastructural pathology of the cell.
18. Molecular level of organization of genetic information. Nucleic acid structure and function.
19. Modes of genetic transfer in bacteria: transformation, transduction, conjugation. Their medical importance.
20. Organization of eukaryotic and prokaryotic genomes. Structural and regulatory genes. The tRNA and rRNA genes. Mobile genetic elements.
21. Organization of the flow of genetic information in the cell. DNA replication. DNA repair.
22. Important properties of genetic code.
23. Protein synthesis steps. Transcription.
24. Translation: initiation, elongation and termination steps. Post-translational protein modification.
25. Gene expression in prokaryotes and eukaryotes. Exon-intron structure of eukaryotic genes. Processing, splicing.
26. Regulation of gene expression in prokaryotes and eukaryotes.
27. Genetic engineering and biotechnology.
28. Cell life, its courses and periods. Cell cycle. Interphase.
29. Cell division. Mitosis.
30. Mitotic abnormalities. Somatic mutations. Amitosis.
31. Cell cycle regulation. Cell growth. Growth factors. Mitotic activity in the tissues.
32. Cell death: apoptosis, necrosis.
33. Cell and tissue cultures. Cell cloning. Applications of cell culture in medicine.

Unit 2
Organism level of organization in the living world. Essentials of human genetics

№	Date	Themes	Mark
9		Features of human genetics. Manifestation of Mendelian laws of inheritance on the example of human traits (mono-, di- and polyhybrid crosses). Multiple alleles. Phenomenon of pleiotropy	
10		Interaction of allelic genes. Genetics of blood groups	
11		Interaction of non-allelic genes	
12		Linked inheritance	
13		The genetics of sex in human beings. Sex-linked inheritance	
14		Gene diseases, the methods of their diagnostics	
15		Chromosome diseases. Cytogenetic method of their diagnostics	
16		Dermatoglyphics. Methods of prenatal diagnosis. Medical genetic consultation	
17		Population genetics. Hardy – Weinberg law	
18		Biological features of human reproduction. Gametogenesis. Features of human development. Biological mechanisms of homeostatic maintenance in living organisms	
19		**Lab Practical Exam 2**	

Theme 9: Features of human genetics. Manifestation of Mendelian laws of inheritance on the example of human traits (mono-, di- and polyhybrid crosses). Multiple alleles. Phenomenon of pleiotropy

Objectives: formulate the significance of human genetics; on the basis of heredity principles discovered by G. Mendel, study pedigree analysis for inheritance and distribution of certain genetic traits in human beings; evaluate the probabilities of birth of healthy or affected child in family with hereditary pathology; determine a mode of inheritance of human traits.

Task 1. Characterize the features of Human Genetics and answer the multiple-choice tests:

Features of Human Genetics

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

1. The specific allelic combination for a set of genes is
- A. environment
- B. phenotype
- C. genotype
- D. genetic code
- E. number of chromosomes

2. The environmentally and genetically determined observable physical appearance of an organism is
- A. homozygous trait
- B. gene
- C. allele
- D. phenotype
- E. genotype

3. Full complement of genes of haploid set in particular biological species is
- A. gene
- B. genome
- C. karyotype
- D. genotype
- E. phenotype

4. The alternative traits are the traits which:
- A. complement each other
- B. strengthen each other
- C. mutually eliminate appearance of each other
- D. weaken each other
- E. determine appearance each other

5. When two chromosomes resemble each other in size, shape and the kinds of hereditary information carried, they are said to be:
- A. gametes
- B. somatic
- C. homozygous
- D. homologous
- E. haploid

6. Alternative forms of the same genes at one locus are known as:
- A. genotypes
- B. heterozygotes
- C. homozygotes
- D. alleles
- E. gametes

7. *Recessive allele* is an allele that

A. is expressed (manifests itself) in most offspring
B. is expressed in both homozygous and heterozygous condition
C. is only expressed in homozygous state
D. suppresses the expression of dominant allele
E. is always responsible for the manifestation of a disease

8. For *dominant allele* everything is true, ***except***:

A. It suppresses the expression of recessive allele
B. It is expressed in the genotype regardless of the presence of other allele this gene
C. It is expressed (manifests itself) in most offspring
D. In genetic nomenclature it is written as capital letter
E. In genetic nomenclature it is written as lower-case letters

9. An organism that has two identical alleles for a particular trait is _____.

10. An organism that has two different alleles for a given gene is called _____.

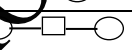
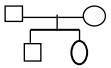
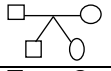
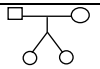
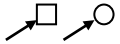
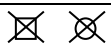
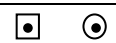
11. What cross results in the genotypic and phenotypic ratio 1:1:1:1? _____

12. In cross of two homozygous organisms that are different in one pair of alternative traits, all F_1 offspring is uniform in both genotype and phenotype. It is _____

13. In gamete formation, the alternative forms, alleles, segregate into different gametes and are never found in the same gamete.
It is _____

14. During gamete formation the segregation of the alleles of one allelic pair is independent of the segregation of other allelic pair. It is _____

Task 2. Write the meanings of international genetic symbols for human pedigree charts.

	
	
	
	
	
	
	
	
	
	
	
	
	
	
A	
a	
AA	
Aa	
aa	

Task 3. Find a number of gamete types produced by the listed genotypes.

Genotypes	AA	Aa	aa
Gametes			
Location of alleles in chromosomes			

Task 4. Calculation of probability in solving of genetics problems.

$$P = \frac{m}{n}$$

where ***P*** is probability, ***m*** **-** individual event, ***n*** – all possible events.

The probability scale ranges from 0 to 1. If an event is absolutely certain to happen, its probability is 1. If it cannot happen, its probability is 0. The simplest way to express probability is by means of vulgar fractions. We also can express probability by decimal fractions and by percentage. The low of segregation is a specific case of the basic principles of probability.

Problem 1. *Autosomal dominant polycystic kidney disease* (ADPCD) is a multisystemic and progressive disorder that causes the formation and enlargement of cysts in the kidney and other organs (e.g., liver, pancreas, spleen).

A mother is healthy but a father is ill with polycystic kidney disease. The father's mother (the grandmother) was healthy but his father was affected.

Draw up the pedigree of the family. Calculate the probability of birth of an affected child.

Solving:

Trait	allele	genotype
Polycystic kidney disease		
Healthy		

- **PRINCIPLE 1**. In two or several independent events, the probability of a following event does not depend on the foregoing (previous) one.

Problem 2. Disease *maxillofacial dysostosis* is autosomal recessive trait. It is rare inherited disorder characterized by underdeveloped cheek bones and upper jaw, overdevelopment of lower jaw, ear and eye abnormalities.

The parents are healthy but they have an affected child. Determine the probability of birth of a following child with disease.

Solution:

Trait	allele	genotype
Maxillofacial dysostosis		
Healthy		

PRINCIPLE 2. To find the combined probability of independent events, multiply the probabilities of the individual events.

Problem 3. *Dentinogenesis imperfecta* (hereditary opalescent dentin) is autosomal dominant disorder of dentin (layer of tooth beneath the enamel). Teeth are also weaker than normal, making them prone to rapid wear, breakage, and loss.

Both parents suffer from this disease. There is a healthy child in the family.

Determine:

a) the probable genotypes of all family members;
b) the probability of a birth of a child with *dentinogenesis imperfecta*;
c) the probability of a birth of daughter with the disease in this family;
d) the probability of a birth of three children with *dentinogenesis imperfecta* in this family.

Solving:

Trait	allele	genotype
Dentinogenesis imperfecta		
Healthy		

Task 5. You can define a quantity of gametes according to a formula

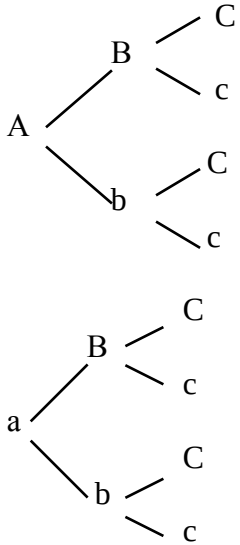
2^n, where **n** - number of heterozygous pairs in genotype.

Find a number of gamete types for genotypes below using the formula. Dispose genes on chromosomes in condition that genes locate in different pairs of homologous chromosomes.

Genotype	**AABB**	**Aabb**	**AaBb**
Number of gametes types			
Gametes			
Location of alleles in chromosomes			

Task 6. A dichotomous method (or a forked-line method**)** is used for determining the gamete types.

a) For example, the genotype is ***AaBbCc***.



b) Using the dichotomous method, write the gamete types for an organism with the genotype ***AaBbCcDd***.

Task 7. Answer the multiple-choice tests.

a*)** How many types of gamete does an organism with genotype ***AABbccKkMMNnSs produce?

A. 2
B. 4
C. 8
D. 16
E. 32

b*)** How many types of gamete does an organism with genotype ***AabbCcDDEeFfNnppRrttVvZZ produce?

A. 16
B. 32
C. 36
D. 64
E. 128

c*)** Two organisms with genotypes ***AaBbCcDd were crossed. What is probability to get the offspring that is recessive homozygous in all four traits?

A. 1/4
B. 1/8
C. 1/16
D. 1/64
E. 1/256

d*)** What is probability to get the dominant homozygous offspring in the cross of ***BbDdkkPPRrTt × ***BbDdkkpprrTT*** ?

A. 0
B. 1/2
C. 3/64
D. 9/32
E. 9/128

Task 8. ***Dihybrid testcross***.
The testcross allows defining a genotype of an organism with dominant phenotype. For testcross it is necessary to cross this organism with a recessive homozygote. If all the offspring of the testcross has dominant phenotype it means an analyzed parent is also homozygous. If the other parent is heterozygous for both pairs of characters (i.e., diheterozygous), then the offspring of testcross will have a phenotypic ratio 1:1:1:1.

Problem. Recessive gene ***d*** determines the inherited deaf-mutism, recessive gene ***b*** determines fair hair in humans.
a) A fair-haired, inherently deaf-mute man is married to dark-haired woman with normal hearing. Their child has normal hearing and dark hair. Is it possible to find the mother's genotype?
b) Inherently deaf-mute woman with fair hair is married to dark-haired man with normal hearing. Their fair-haired son is deaf-mute. Is it possible to find the father's genotype?

Solving:

Trait	allele
Dark hair	
Fair hair	
Normal hearing	
Deaf-mutism	

a)

b)

Task 9. Solve the genetic problems.
Problem 1. *Hereditary spherocytosis* is an autosomal dominant hemolytic disorder caused by the defective red blood cells (RBCs), which have abnormal shape and fragile membranes. Normal blood cells are round-shaped (recessive trait). Brown colour of eyes is dominant over blue colour.
a) A blue-eyed man has spherocytosis, his brown-eyed wife is healthy. Her mother had blue colour of eyes. What characters may their children have?
b) A man and his wife are heterozygous for both pairs of the characters. What characters may their children have?

Solving:

Trait	allele	genotype
Hereditary spherocytosis		
Healthy (normal RBCs)		
Brown color of eyes		
Blue color of eyes		

***a*)**

Problem 2. Dark-haired brown-eyed parents who are afflicted with disease *familial hypercholesterolemia* have got a fair-haired blue-eyed healthy daughter. Familial hypercholesterolemia is dominant over normal level of blood serum cholesterol.

Calculate the probability of birth of a following two children who will look like the first daughter.

Solving:

Trait	allele	genotype
Dark hair		
Fair hair		
Brown color of eyes		
Blue color of eyes		
Familial hypercholesterolemia		
Healthy (normal level of blood serum cholesterol)		

Task 10. Give the definition of the term "*multiple alleles*",

Multiple alleles - _____
_____
_____
_____

Task 11. Give the definition of a term "*relativity of dominance*" and examples of trait.

Relativity of dominance - _____
_____
_____
_____
_____

Examples_____
_____
_____
_____

Task 12. Give the definition of *penetrance* and solve the genetic problems.

Penetrance - _____
_____
_____
_____

Problem 1. Some forms of *schizophrenia*, a mental disorder, are inherited as autosomal dominant trait. Homozygotes have 100% of penetrance. Heterozygotes have 20 % of penetrance.

a) A husband is heterozygous for gene of schizophrenia. His wife is healthy. Calculate the probability of schizophrenia in their children.

Solving:

Trait	allele
Schizophrenia	
Healthy	

b) Parents are heterozygous. Calculate the probability of schizophrenia in their children.

Solving:

Trait	allele
Schizophrenia	
Healthy	

Problem 2. *Dystonia* is a syndrome of involuntary spasms and sustain contractions of the muscles. One form of the disease is childhood dystonia, an autosomal dominant disorder with 40% penetrance. Calculate the probability of the disease in children of heterozygous parents.

Solving:

Trait	allele
Dystonia	
Healthy	

Problem 3. *Inborn diabetes mellitus* is autosomal recessive disease. Its rate of phenotypic manifestation is 70% for men and 90% for women. Calculate the probability of the disease in a family where parents are both carriers of this pathological allele.

Solving:

Trait	allele
Healthy	
Diabetes mellitus	

Task 13. Give the definition of the term "expressivity".

Expressivity - _____
_____
_____

The environment influence on the expressivity of the genotype may lead to problems in correct diagnosis and interpretation of pedigree, especially in an autosomal dominant inheritance. Clinically, variable expressivity of the genotype is exhibited by mild, moderate or severe form of the disease. Examples of dominant genes expressivity are different degrees of cleft lip and cleft palate, bifurcation of pendulous palate, different depth of cotiloid cavity, different degree of polydactyly.

!!! *Incomplete penetrance* **<u>should never be confused</u>** with *variable expressivity*. In diseases with variable expressivity the patient <u>always</u> expresses some symptoms of the disease and varies from very mildly affected to very severely affected. In autosomal dominant diseases with incomplete penetrance, a person *<u>either</u>* <u>expresses</u> the disease phenotype *<u>or</u>* he/she <u>doesn't</u>.

<u>Task 14</u>. Give the definition of the term "*pleiotropy*".

Pleiotropy - _____
_____
_____
_____

There are two kinds of pleiotropy: primary and secondary.

Primary pleiotropy - _____
_____
_____
_____

Secondary pleiotropy - _____
_____
_____
_____

Find the kind of pleiotropy for the listed human diseases:

- arachnodactyly (Marfan's syndrom) _____
- albinism _____
- Ehlers – Danlos syndrome _____
- sickle-cell anaemia _____
- phenylketonuria _____

Task 15. Give the definition of *lethal alleles*, read the description below and solve the genetic problems.

Lethal alleles – _____
_____
_____
_____

Lethal alleles can be dominant and recessive. Dominant lethal alleles are quickly eliminated from a population, because usually cause death before an individual can reproduce. Recessive lethal alleles cause death if in homozygous recessive state only.

In humans, the examples of dominant disorders are *brachidactyly* (abnormally short fingers), *achondroplasia* (bone disorder that causes dwarfism), *Huntington's disease* (also *Huntington's chorea*) and *retinoblastoma* (rare form of eye cancer).

Recessive diseases are *cystic fibrosis* (disorder of exocrine secretions), *sickle-cell anemia*, and *thalassemia*, also *congenital ichthyosis* in males.

Sickle-cell anemia

Sickle-cell anemia is characterized by sickle-shaped erythrocytes. Change of erythrocyte shape is due to the presence of a defective type of hemoglobin (hemoglobin S) (*see* the *pages 42-43*) in RBCs. In sickle-cell anemia the defective cells rupture and block the blood flow to tissues, depriving them of oxygen. This also produces a variety of other symptoms like pain, fever, swelling, jaundice, low resistance to infection, and kidney disorders.

An affected person may have heterozygous genotype, i.e., to have one gene for normal hemoglobin and one gene for sickle-cell hemoglobin (HbA, HbS). Heterozygous carriers produce both normal and sickled RBCs. They are essentially normal, having only mild or occasional symptoms of sickle-cell anaemia.

Marriage of two carriers produces carriers and normal (disease-free) children in the ratio of 2:1.

Birth of children with fatal sickle-cell anaemia can be avoided by discouraging marriages among the heterozygotes (carriers). The heterozygotes can be identified by microscopic examination of their blood.

Problem 1. Calculate the probability of birth of a child who is a carrier of *sickle-cell gene* in the family of heterozygous parents.

Solving:

Trait	allele	genotype
Healthy		
Sickle-cell anaemia		

Problem 2. *Chondrodystrophy* (abnormal cartilage development) is determined by dominant gene in most cases. Homozygous dominant individuals perish before the birth (intrauterine death). Living heterozygotes has abnormalities of extremities and skull base.

Parents are ill with chondrodystrophy. Determine the probability of a birth of healthy child in this family?

Solving:

Trait	allele	genotype
Chondrodystrophy		
Healthy		

Multiple-Choice Tests for Control of Theme 9

1. Mendel's Law of Segregation states that:
- A. two factors for the same trait separate in the production of gametes
- B. two different traits will be inherited independently of each other
- C. gametes are produced by meiosis
- D. all of the above
- E. none of the above

2. A monohybrid cross is…
- A. constructed by mating individuals from a single strain of plant
- B. constructed by mating individuals from a single strain of animal
- C. constructed by mating individuals from two parent strains, each of which shows one of the two contrasting forms of the character under study
- D. constructed by mating individuals from two parent strains, both exhibit two contrasting forms of character.
- E. none of the above

3. A disease is said to show _____ penetrance when an individuals carrying a disease associated genotype always develops the condition
- A. complete
- B. incomplete
- C. reduced
- D. penetrant
- E. expressive

Date	Signature

GENETIC PROBLEMS TO THEME 9 FOR SELF-WORK

Problem 1. A woman is Rh-positive and both of her parents are Rh-positive. She marries an Rh-negative man. Is there any chance that they may have any Rh-negative children? Explain. Draw up the possible variants of family pedigree.

Solving:

Trait	allele

Problem 2. *Thompsen's disease*, an autosomal dominant condition, is characterized by muscle hypertrophy with myotonia.

A man is afflicted with Thompsen's disease and his wife is healthy. The man's father was ill with Thompsen's disease but mother was healthy. Draw up pedigree of the family. Determine the probability of a birth of an affected child.

Solving:

Trait	allele

Problem 3. In human, chin cleft is dominant over no chin cleft; normal hearing is dominant over deaf-mutism.
a) The parents both have chin cleft and normal hearing. Their son is deaf-mute and has no chin cleft. Find the genotypes of the parents and their child.

Solving:

Trait	allele	genotype

b) A deaf-mute man with chin cleft, whose father had no chin cleft, is married to a healthy (normal hearing) woman with no chin cleft. The woman's mother was deaf-mute. In this man's family the first-born child has normal hearing with chin cleft. Draw up family pedigree.
Find: 1) genotypes of the parents and their child; 2) the probability of a birth of a deaf-mute child; 3) the probability of a birth of two deaf-mute children.
Solving:

Problem 4. Left-handedness and cataract (opacity in the lens of eye, resulting in blurred vision) are autosomal recessive traits. The parents both are right-handed and lack of cataract. In this family the first child is healthy and left-handed, the second child is right-handed and suffers from the disease of eyes – cataract. Draw up family pedigree.
Find: a) genotypes of the parents and their children; b) probability of birth of a following child who is left-handed with normal vision

Solving:

Trait	allele

Solving:

Trait	allele	genotype

a)

b)

Problem 5. In humans, long eyelashes are dominant over short eyelashes; and normal pigmentation is dominant over disease *albinism* (lack of pigmentation of eye iris, skin and hair).

a) A healthy man with short eyelashes is married to a healthy woman with long eyelashes. Their son is albino with long eyelashes, daughter is healthy and has short eyelashes.

Draw up family pedigree and find the genotypes.

b) In the second marriage the man has two healthy children with long eyelashes. His new wife is healthy with long eyelashes.

Draw up the family pedigree and find the genotypes (all possible variants).

Theme 10: Interaction of allelic genes. Genetics of blood groups

Objectives: study the main types of interaction of allelic genes and their significance to an understanding of human genetic disorders; explore how some genes modify expression of other genes.

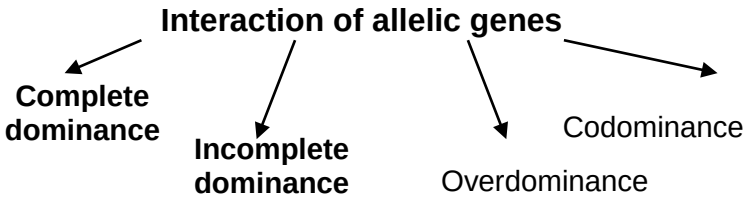
Mechanism of gene interaction – _____

_____

_____

_____

_____



Task 1. Give the definition of the term "*complete dominance*"

Complete dominance _____

_____

_____

Task 2. Give the definition of the term "*incomplete dominance*" and solve the genetic problems.

Incomplete dominance_____

_____

_____

_____

_____

Problem 1. *Anophthalmia* (lack of eyeballs) is an autosomal recessive disorder. A dominant allele of this gene controls normal development of eyes. In heterozygotes eyeballs are reduced.

What traits will children have in the family where both parents have reduced eyeballs?

Solving:

Trait	allele	

Problem 2. *Cystinuria* is an autosomal recessive disorder. Recessive homozygotes for this gene have cystine stones in kidneys (nephrolithiasis). Heterozygotes have just the heightened content of cystine in urine.

A hair type is a trait inherited by incomplete dominance: by incomplete dominance: dominant homozygous individuals (*WW*) have curly hair, heterozygotes (*Ww*) – wavy hair, recessive homozygotes (*ww*) – straight hair.

A wavy-haired man is afflicted with stones in his kidneys. His wife has the same type of hair and heightened content of cystine in urine. Make conclusion about degree of cystine metabolism disorders in their future children. What types of hair are possible? Draw up the family pedigree, find the genotypes of all generations.

Solving:

Trait	Allele(s)	genotype
Healthy		
Cystinuria		
Heightened content of cystine		
Curly hair		
Straight hair		
Wavy hair		

Task 3. Give the definition of "*overdominance*" (*superdominance*).

Overdominance - _____
_____
_____
_____

In overdominance, the heterozygotes, as a rule, do not have the special external traits. An advantage is associated with the biochemical features. One of overdominance examples is high rate of sickle-cell anemia allele in human populations that live in conditions of high risk of malaria infection.

Overdominance also causes a biological phenomenon known as ***heterosis***, which is widely used to get highly productive cattle and high-yielding varieties of wheat, maize and other cultured plants in agriculture.

Task 4. Give the definition of the term "*codominance*".

Codominance - _____
_____
_____
_____
_____

Examples of such gene interaction are inheritance of human blood groups: blood group *MN* and blood group *AB* of system AB0.

Problem. There are three human blood groups: *M*, *N*, and *MN* in MNS blood antigen system. A father has *M* antigen in blood and a mother has *N* antigen. What blood group will their children have? Draw up family pedigree.

Solving:

Trait	allele	genotype
Blood group M		
Blood group N		

Blood groups of ABO system

In 1901, Karl Landsteiner (1868-1943), an Austrian physician, discovered the first three human blood groups. Shortly thereafter, in 1907, Jan Janský (1873-1921), Czech neurologist and psychiatrist, revealed there are four blood groups, rather than the three groups discovered by K. Landsteiner. J. Janský was thus the first who proposed the first classification of blood into the four groups, or types.

These four blood groups: group *A*, group *B*, group *AB* and group *O* are different by glycoproteins located on the surfaces of erythrocytes. Synthesis of these antigens is controlled by a set of three alleles. Alleles $\mathbf{I^A}$ and $\mathbf{I^B}$ are both dominant over an allele $\mathbf{I^0}$, or **i**, but not over each other. The $\mathbf{I^A}$ determines the production of glycoprotein ***A***, and the allele $\mathbf{I^B}$ determines the production of glycoprotein ***B***. The allele **i** determines the absence of specific substances on the red blood cells.

Each person has just two of these alleles, one from each parent. Both I^A and I^B are fully expressed in the presence of other (codominance). A person with genotype I^AI^B produces both the glycoproteins.

Detection of blood group is used in medicine, in practice of criminalists and forensic biologists, and in paternity lawsuits (also known as an affiliation proceeding) to determine a legal biological parent (to confirm or disprove paternity).

Phenotype (Blood group)		Allele	Genotype	Antigen
International system	Russian system*			
O	I	i	ii	none
A	II	I^A	I^AI^A or I^Ai	glycoprotein A
B	III	I^B	I^BI^B or I^Bi	glycoprotein B
AB	IV	I^A and I^B	I^AI^B	Both A and B

* The Russian system makes sense in the evolutionary context, since it's chronological, i.e. the types are numbered in the order of their historic appearance.

Task 5. Solve the genetic problems.

Problem 1. A husband is with blood group *A*, his wife is with blood group *B*. Both parents are heterozygous. What blood groups may their children have?

Solving:

Trait	allele	genotype
Blood group A		
Blood group B		

Problem 2. It was suspected that two babies had been exchanged in a hospital. Mr. and Mrs. Jones received baby #1 and Mr. and Mrs. Smith received baby #2. Blood typing tests on the parents and the babies showed the following:

Mr. Jones: Group A	Mr. Smith: Group AB
Mrs. Jones: Group O	Mrs. Smith: Group O
Baby #1: Group A	Baby #2 Group O

Were the babies switched? Explain your answer.

Solving:

Trait	allele	genotype
Blood group 0		
Blood group A		
Blood group AB		

Problem 3. Ms. Alice Redford filed a paternity lawsuit against Thomas Smith to obtain support for her newborn son and for payment of bills incident to the pregnancy and the birth. The court ordered blood test on the parties.

The lab test revealed: Alice's blood is Rh-negative with blood groups *A (II)* and *M*, her son is Rh-negative with blood groups *0 (I)* and *MN*. The accused man has Rh-positive blood groups *B (III)* and *N*.

It is additionally known that Thomas's father is Rh-negative with blood group *0 (I)*.

What did the lab result indicate? (Rh-positivity is a dominant trait).

Solving:

Trait	allele	genotype
Blood group 0 (I)		
Blood group A (II)		
Blood group B (III)		
Blood group M		
Blood group N		
Blood group MN		
Rh-positivity		
Rh-negativity		

Multiple-Choice Tests for Control of Theme 10

1. The type of gene interaction in which both heterozygotes and dominant homozygotes have the same phenotype is

A. complete dominance
B. incomplete dominance
C. overdominance
D. codominance
E. none of the above

2. Which scheme corresponds to the incomplete dominance?

A. A > a → trait
B. Aa> AA →trait
C. A + a→ trait
D. A + A' → trait
E. A ⨯ B → trait

3. A TV star's former girlfriend filed paternity lawsuit seeking child support payments for her son, who is a little more than a month old. Results of the lab test ordered by court show the child's blood group is *AB*, his mother's blood group is *A*. So the man ***cannot be*** the child's biological father when his blood group is

A. *O*
B. *A*
C. either *O* or *A*
D. *B*
E. *AB*

Date	Signature

GENETIC PROBLEMS TO THEME 10 FOR SELF-WORK

Problem 1. *Elliptocytosis* (from Greek *elleiptikos* – elliptic and *kytos* is a cage, vessel) is autosomal dominant disease resulting in change of most RBCs: they have oval shape. In heterozygotes the disease may be asymptomatic or with mild anaemia while homozygous people often suffer from severe hemolytic anaemia.

Parents are two heterozygotes and they are worried about whether their child will be healthy. What is the probability of producing a healthy offspring?

Solving:

Trait	Allele(s)	genotype

Problem 2. A man with blood group *B* is married to a woman with blood group *A*. Their first child has blood group *O*. The man says this is impossible and accuses his wife of infidelity.

a) Is it possible to produce a child with group *O* in these parents?

b) What are the genotypes of both parents?

c) Draw a Punnet square to show the possible blood groups of their children.

Solving:

Trait	Allele(s)	genotype

Problem 3. A mother is with blood groups *N* and *O*. A father is with blood groups *MN* and *B*. The parents have a daughter with blood groups *B* and *N* and a son with blood groups *N* and *O*. Calculate the probability of a birth of the next child with blood groups *MN* and *O*.

Solving:

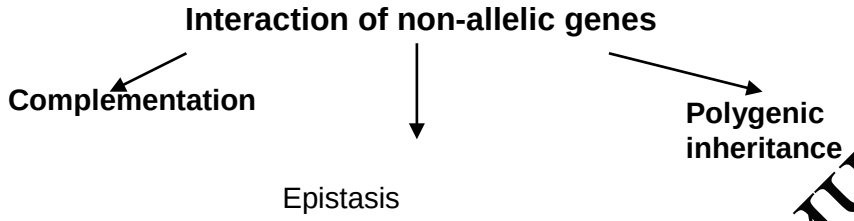
Trait	allele

Theme 11: Interaction of non-allelic genes

Objectives: study the main types of interaction of non-allelic genes and their significance to an understanding of human genetic diseases; explore how some genes modify expression of other genes.

Task 1. Give the definition of "*non-allelic genes*" and study the scheme below.

Non-allelic genes – _____
_____
_____



Task 2. Give the definition of the term "*complementation*" and solve the genetic problems.

Complementation - _____
_____
_____
_____

Problem 1. Two dominant genes determine normal hearing. One gene controls normal development of acoustic nerve. The other controls normal development of cochlea.

Both parents are deaf-mute. Their three children are with normal hearing. Find the genotypes of parents and children.

Solving:

Trait	allele	genotype
Developed acoustic nerve		
Undeveloped acoustic nerve		
Developed cochlea		
Undeveloped cochlea		

Problem 2. A molecule of interferon, a protein produced by the cells of the immune system in response to challenges viruses, parasites and tumor cells, consists of two polypeptide chains – *A* and *B*. Both interferon chains are encoded by dominant alleles. The genes coding for these chains are in the loci of non-homologous chromosomes.

What is a chance that a child will unable to synthesize interferon in a family where parents both are able to synthesize it and are heterozygous for both pairs of genes but a mother is heterozygous just for the gene coding for a chain *A*?

Solving:

Trait	allele	genotype
Chain *A*		
Absence of chain *A*		
Chain *B*		
Absence of chain *B*		

Solving:

Trait	allele
Black fur	
Brown fur	
Epistatic gene (suppresses colour)	
Gene that does not suppress colour	

Task 3. Give the definition of the term "*epistasis*", study two types of epistasis and solve the problem.

Epistasis - _____
_____
_____
_____

Genes that suppress the action of other genes are called *epistatic*, or *inhibitors*, or *suppressors*. The suppressed gene is called *hypostatic*.
There are two types of epistasis: *dominant* and *recessive*.
In dominant epistasis, one dominant gene suppresses the manifestation of other non-allelic dominant gene.
In recessive epistasis, inhibition effect is due to influence of recessive allele in homozygous condition.

Problem. In dogs, a dominant allele of gene ***A*** determines a black colour of fur, recessive allele ***a*** – brown. Dominant gene-inhibitor ***I*** suppresses the manifestation of both allelic genes and determines a white colour. Recessive allele of the gene-inhibitor ***i*** does not affect upon colour of fur. What offspring can be expected from crossing of black heterozygous dog with diheterozygous white?

Bombay Phenotype

Bombay Phenotype is example of *recessive epistasis* in human. It is an extremely rare ABO group, which derives the name *Bombay* because it was first discovered (in 1952) to exist among some people living in the region of Bombay (now Mumbai), India. Although the group is more likely to occur in East Indians, it is a very rare group even among this population: frequency of 1 in 7600. Also, it is not restricted to East Indians and has been found to exist in Caucasians, Blacks, Japanese, etc.

Inheritance: The Bombay group (O_h) results from the inheritance of two rare recessive ***h*** genes, which occur at a locus other than the ABO gene locus. The gene ***h*** in homozygous state suppresses the dominant alleles of ABO system.

Because the ***h*** gene is very rare, Bombays often result from consanguineous matings in which parents are blood relatives (e.g., first cousins). Whenever inbreeding occurs, the proportion of rare homozygotes increases in frequency.

Significance in blood transfusion: Bombay people would be incompatible when crossmatched with red cells of all normal ABO groups (groups O, A, B and AB).

If they require blood transfusion, they must receive blood from another Bombay. Donors must be sought among their blood relatives (especially siblings) or from the rare donor file maintained by the Red Cross.

Task 9. Assuming *Bombay Phenotype* and existence of a recessive allele ***h***, find the phenotypes of people who have given genotypes:

Genotype	***Phenotype (Blood group)***
iiHh	
I^Bihh	
I^AiHH	
I^AI^Bhh	
iihh	

-Task 10. Give the definition of the term "*polygenic inheritance*" and solve the genetic problems.

Polygenic inheritance - _____
_____
_____
_____

Height, mass, intelligence, skin and eye colours in human are polygenic traits. The differences of given traits are in degree only. Continuity of qualitative changes is due to the additive effect of several genes. Such traits are more stable than those are coded by one gene.

Problem. Short height of human beings is determined by dominant genes *A* and *B*. Tall height is determined by recessive genes *a* and *b*. What stature may children have, if both parents are diheterozygous?

Classification of human height

Number of dominant alleles in genotype	**Example of genotype**	**Height**
4	AABB	very short (under 155 cm)
3	AaBB, AABb	short (155-159 cm)
2	AaBb, AAbb, aaBB	medium (160-169 cm)
1	Aabb, aaBb	tall (170-180 cm)
0	aabb	very tall (above 180 cm)

a) What height may children have if their parents both have short height phenotype but different genotypes?

Trait	**allele**	**genotype**
Short (155-159 cm)		
Short (155-159 cm)		

b) What height may children have if parents both are diheterozygous?

Solving:

Multiple-Choice Tests for Control of Theme 11

1. When a single phenotypic trait is generated by two or more separate alleles, the trait is

A. additive
B. complementary
C. epistatic
D. pleiotropic
E. none of the above

2. The Bombay phenotype is a result of ____ interacting genes and is an example of ___.

A. 2, complete dominance
B. 2, incomplete dominance
C. 3, incomplete dominance
D. 2, epistasis
E. 3, epistasis

3. Human skin color is determined by three different genes working together to produce a wide range of possible skin tones. This is an example of

A. blending inheritance
B. codominance
C. polygenic trait
D. polyploidy
E. multiple alleles

Date	Signature

GENETIC PROBLEMS TO THEME 11 FOR SELF-WORK

Problem 1. Coloration of hen feather is determined by two pairs of genes. In one pair a dominant allele determines colored feather while a recessive allele determines white color. In other pair, a dominant allele suppresses coloration while a recessive allele does not suppress. What offspring will appear in the crossing of diheterozygous hen and homozygous recessive cock? Point out the feathering coloration in parental organisms and offspring.

Solving:

Trait	allele
Colored feather	
White feather	
Epistatic gene (suppresses color)	
Gene that does not suppress color	

Problem 2. Chromosomes 3, 6 & 10 carry the genes for hair color. In total human has 6 alleles that control hair color. If a person has a gene of red pigmentation on chromosome #4 she/he may still not have red hair because of the dominance of hair color:

Number of dominant alleles in genotype	Example of genotype	Phenotype
6	AABBCC	black
5	AaBBCC, AABbCC, AABBCc	dark brown
4	AABBcc, AAbbCC, AABbCc, AaBBCc, AaBbCC, aaBBCC	brown
3	AaBbCc, AABbcc, AaBBcc, aaBBCc, aaBbCC, AAbbCc	light brown
2	AAbbcc, aaBBcc, aabbCC, AaBbcc, AabbCc, aaBbCc	dirty blonde
1	Aabbcc, aaBbcc, aabbCc	blonde
0	aabbcc	white

A man with black hair has the genotype *AABBCC*. A woman with dirty blonde hair has the genotype *AAbbcc*. If these two individuals are married, what will the genotype of their offspring be?

Theme 12: Linked inheritance

Objectives: explore the linkage and inheritance of linked genes; analyze the complete and incomplete linkage; note the significance of crossing over for explanation of incomplete linkage and making of genetic maps; study how to solve the genetics problems in linked inheritance.

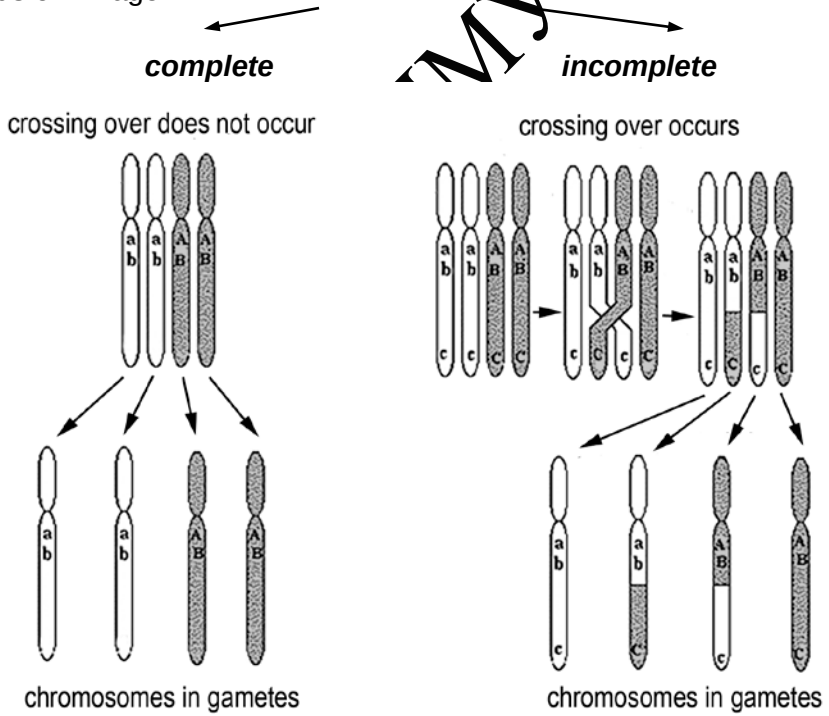
Task 1. Note the main statements of *Chromosome theory of inheritance.*

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Task 2. Give the definition of the terms "*linkage*" and "*linkage group*".

Linkage – _____
_____
_____

Kinds of linkage



Linkage group – _____
_____
_____

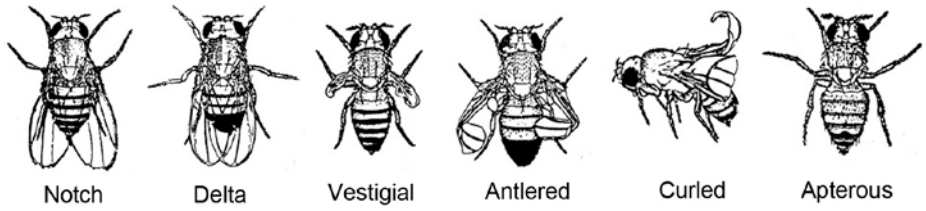
Problem. Find a number of linkage groups for given species if it is known that the pea plant has 14 chromosomes, *Drosophila* fruit fly – 8 chromosomes, and a human – 46 chromosomes:

– pea plant _____;
– *Drosophila* _____;
– human_____.

Task 3. Examine a preparation of *Drosophila melanogaster* with microscope.

American geneticist T.H. Morgan (1866-1945) was the first who used fruit fly *Drosophila melanogaster* for his vast studies. *Drosophila* became the classic tool of genetic researches because of certain advantages:

1. Fruit fly breeds rapidly, attaining maturity in 12 days. One can receive 30 generations of *Drosophila* for a year.
2. This fly has clearly marked characters: different colors of body and eyes, size and shape of wings.
3. It has relatively simple karyotype (4 pairs of chromosomes) and polytene chromosomes in salivary gland cells.

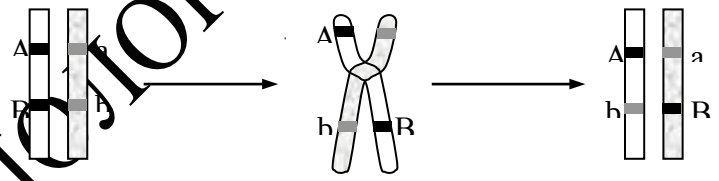


After years of breeding flies and hundreds of experiments, T.H. Morgan discovered that white color of eyes is sex-linked trait in *Drosophila* and contributed to the *Chromosome Theory of Inheritance*. For his work, T.H. Morgan was awarded the Nobel Prize in 1933.

Task 4. Study the mechanism of crossing over and solve the genetic problems.

The dominant genes ***A*** and ***B*** from one parent lie in one homologous chromosome of a pair and their recessive alleles from the other parent lie in the other homologous chromosome of the pair. The individual, being heterozygous, will produce only two types of gametes (*AB* and *ab*) if crossing over does not occur between the genes. If crossing over occurs between the genes, the individual will form four types of gametes (*AB*, *Ab*, *aB*, *ab*). In the absence of crossing over, the genes ***A*** and ***B***, as also ***a*** and ***b***, remain linked and pass together into the gametes and the offspring. In the event of crossing over, the genes separate and pass into different gametes and offspring. Thus, linkage and crossing over are antagonistic to each other, the former keeps the genes of a chromosome together, and the latter separates them.

Crossing over:



Types of gametes:

Non-crossovers **Crossovers**

SINCE THE PROBABILITY OF CROSSING-OVER IS LOW, A NUMBER OF NON-CROSSOVER GAMETES FORMED IS ALWAYS MORE THAN CROSSOVER ONES

IN INCOMPLETE LINKAGE, FRACTION OF INDIVIDUALS WITH NEW COMBINATIONS OF TRAITS (CROSSOVERS) IS LESS THAN 50% OF THE TOTAL NUMBER OF OFFSPRING

Problem. In diheterozygous individual with genotype *AaBBCc* the genes ***A***, ***B*** and ***c*** are linked. Write the types of gametes produced by an individual with and without crossing over between genes. What types of gametes will be more in crossing over? Dispose genes on chromosomes.

Solving:

Task 5. Examine Morgan's *Drosophila* experiment: solve the genetic problem.

Problem. In *Drosophila melanogaster* the genes for grey body color and normal wings are dominant and locate on the same chromosome. The recessive alleles are for black body color and vestigial wings.

a) The flies homozygous for grey body and normal wings were crossed with flies with the two recessive traits. What traits did the F_1 flies have?

Solving:

Trait	**allele**
Grey body	
Black body	
Normal wings	
Vestigial wings	

b) In a testcross, the F_1 males were mated with black bodied, vestigial winged females. What traits did the F_1 flies have? It is known, that in males of *Drosophila* crossing over does not occur! Determine the kind of linkage.

Solving:

c) In reciprocal cross the dihybrid *Drosophila* female with black-bodied, vestigial-winged male the following results were received:

grey body, normal wings - 32 %,
black body, vestigial wings - 32 %
grey body, vestigial wings - 18 %,
black body, normal wings – 18 %.

Explain the results of mating. Determine the kind of linkage.

Solving:

Task 6. Study the genetic mapping method and solve the genetic problem.

Recombination is defined as the occurrence of progeny with combinations of genes other than those that occurred in the parents due to independent assortment or crossing over.

The frequency of crossing over (recombination frequency) is calculated from the proportion of recombinants over total offspring:

$$\text{Frequency of crossing over} = \frac{\text{number of recombinants}}{\text{total number of offspring}} \times 100\%$$

If among the offspring 80 per cent have the parental combination of dominant genes *A* and *B*, and 20 per cent have a new combination of genes *A* and *B* not found in either parent, the genes are said to show 20 per cent recombination, i.e., they are 20 map units apart.

Distances between any two genes are measured in terms of **map units** (m.u.)**,** one map unit is also known as a **centimorgan (**cM**),** being equal to 1 per cent of crossing over. The frequency of recombination gives the frequency of crossing over and thereby the distance, between any two loci on a given chromosome, in map units.

Problem. Genes ***P, Q*** and ***R*** are linked. The genes ***Q*** and ***R*** show the recombination frequency 24%, genes ***P*** and ***Q*** – 15%, ***P*** and ***R*** – 9%. Find the sequence of the genes on a chromosome defining 1 cM of map distance as equivalent to 1% recombination frequency. Make a scheme.

Task 7. Solve the genetic problems.

Problem 1. Two autosomal recessive mutations, "dumpy" (*dp*, a reduction in wing size) and "net" (*net*, extra veins in the wing), are linked on chromosome 2 of *Drosophila* fruit fly. Normal wing size and veins are dominant traits (wild type).

Homozygous wild-type females were first crossed to net, dumpy males. Then in testcross the F_1 females were mated with homozygous recessive males. The F_2 offspring were found:

normal wings, normal veins (wild-type) – 226
dumpy wings, net veins – 174
normal wings, net veins – 27
dumpy wings, normal veins – 25

Estimate the map distance between loci *dp* and *net*

Solving.

Trait	Allele	Phenotype
normal wing size	D	 wild type *dp* *net*
dp	d	
normal veins	N	
net	n	

Problem 2. In humans, Rh-factor gene and gene responsible for erythrocyte shape are located in the same pair of chromosomes. The distance between them is 3 cM. Rh-positivity and elliptocytosis are dominant traits. Rh-negativity and normal (round) shape of erythrocytes are recessive traits.

A man is heterozygous for both characters. He inherited Rh-positivity from his father and elliptocytosis from his mother. His wife is Rh-negative and has normal erythrocytes. Find the ratio of possible genotypes of children in this family.

Solving:

Trait	**allele**
Elliptocytosis	
Normal shape of RBCs	
Rh-positivity	
Rh-negativity	

Problem 3. *Nail-patella syndrome*, hereditary defect of nails and kneepan, is controlled the dominant autosomal gene. The disorder is linked to the ABO blood group locus. The distance between them is 10cM.

A man with blood group A suffers from hereditary defect of nails and kneepan. His healthy father has blood group O. His mother with blood group AB suffers from nail-patella syndrome.

This man is married to a healthy woman having blood group B and homozygous for both traits. Draw up family pedigree. What is the probability of birth of children suffering from hereditary defect of nails and kneepan in this family? What blood groups can be expected in these children?

Solving:

Trait	**allele**
Nail-patella syndrome	
Healthy	
Blood group O	
Blood group A	
Blood group B	
Blood group AB	

Multiple-Choice Tests for Control of Theme 12

1. T.H. Morgan contributed to:
A. the law of segregation
B. the chromosome theory of heredity
C. the principle of uniformity
D. the law of dominance
E. the law of independent assortment

2. Two genes are known to be 32.6 map units apart. The expected percentage of parental (non-recombinant) offspring from a dihybrid testcross is:
A. 16.3%
B. 32.6%
C. 50%
D. 75%
E. 67.4%

3. If the map distance between genes *A* and *B* is 10 map units and the map distance between genes *B* and *C* is 25 map units, what is the map distance between genes *A* and *C*?
A. 5 map units
B. 15 map units
C. 35 map units
D. Either 15 map units or 35 map units, depending on the order of the genes.
E. The map distance between *A* and *C* can not be predicted from these data.

Date	Signature

GENETIC PROBLEMS TO THEME 12 FOR SELF-WORK

Problem 1. Determine the sequence of genes along a chromosome based on the following recombination frequencies: A-B, 8 map units; A-C, 28 map units; A-D, 25 map units; B-C , 20 map units; B-D, 33 map units.

Problem 2. In a plant, leaf color and leaf shape are controlled by two linked genes. Leaves of the wild-type plant are red. A recessive mutation in this gene causes white leaves. Wild-type leaves are pointed, and a recessive mutation in this gene causes them to be smooth.

The following crosses were performed:

Cross 1: (pure breeding white, smooth plant) × (pure breeding wild type plant) gives F_1: all red, pointed

Cross 2: (red, pointed plant of F_1) × (pure breeding white, smooth plant) gives F_2:

white, curly – 40 red, pointed – 36
white, pointed – 10 red, curly – 14

a) Determine the plant genotypes in every generation.
b) What is the recombination frequency between the gene for color and for shape?

Solving:

Trait	**allele**	**allele location**

Solving:

Trait	allele	allele location

Problem 3. *Alkaptonuria*, or black urine disease, is a rare inherited disorder of phenylalanine and tyrosine metabolism. The recessive gene for alkaptonuria has recently been shown to lie on chromosome 9 and to be linked to the gene encoding the ABO blood type, with a distance 11 cM between the loci.

A healthy woman has blood type *AB*. Her father with blood type *B* is also healthy and homozygous for both characters. Her mother with blood type *A* suffers from alkaptonuria. The woman is married to affected man with blood type *O*. Draw up the family pedigree. What is the probability of birth of affected children in this family? What blood types can be expected in the children?

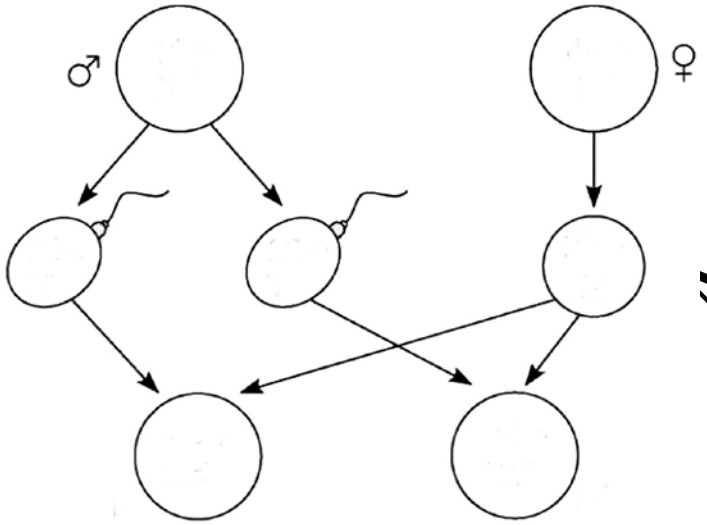
Theme 13: The genetics of sex in human beings. Sex-linked inheritance

Objectives: study the mechanism of sex determination in animals and human; identify the features of sex-linked inheritance.

Task 1. Give the definition of the term "*sex chromosomes*".

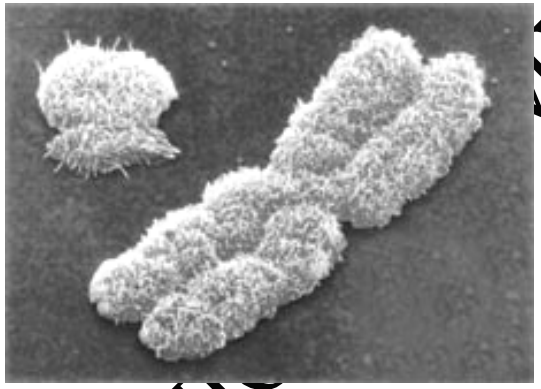
Sex chromosomes – _____
_____
_____
_____

Task 2. Fill the scheme "Sex determination on chromosomal level".
Pay attention: since a male is heterogametic transmitting either X or Y, the sex of a child depends upon whether a father contributes an X or a Y.



Gender ratio in birth corresponds about _____

The sex is determined at the moment of fertilization by the kind of sperm that fuses with an ovum!!!



The **X** chromosome is a submetacentric chromosome belonged to group *C*. There are about 2000 human X-linked genes. It is about 6% of the total DNA. The **Y** chromosome, a member of group *G*, is a small acrocentric chromosome and contains just 78 genes. Traits coded for by genes on the Y chromosome are said to be *holandric*.

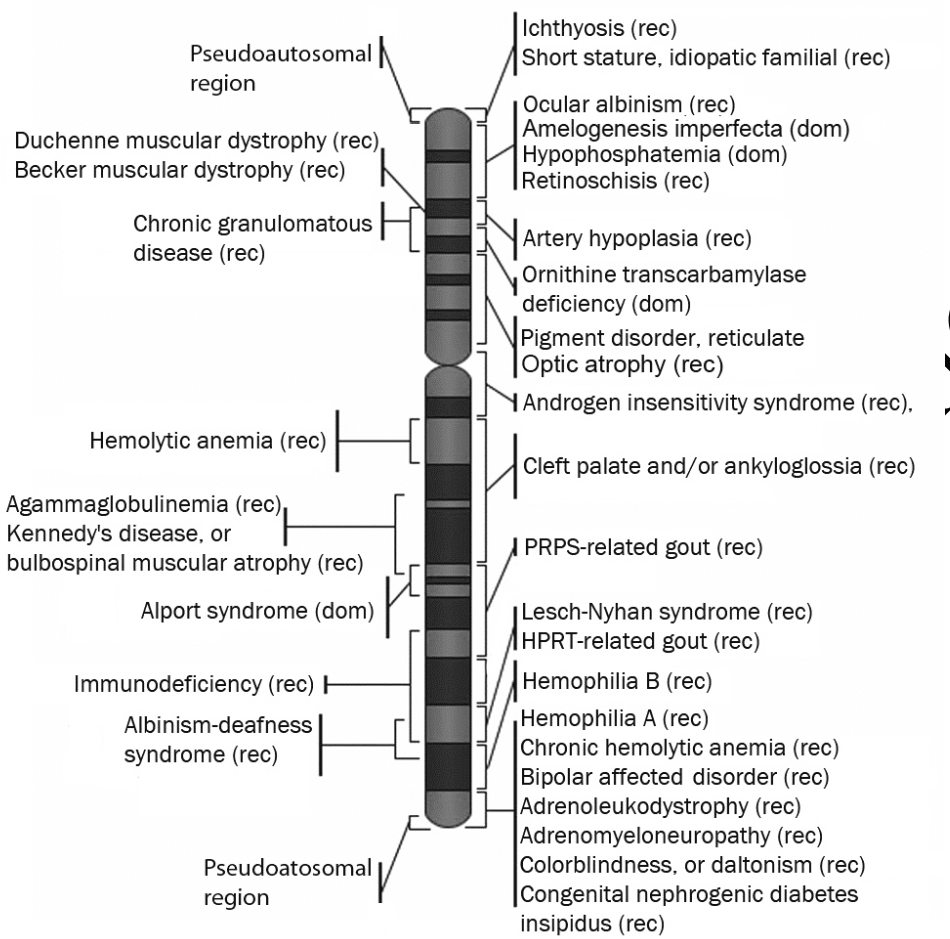
• **Task 3.** The sexual identity of an individual is determined at several levels:

Level	***Events***	***Timing***
Chromosomal / genetic	XY = male XX = female	Fertilization
Gonadal sex	Undifferentiated structure becomes testis or ovary	9-16 weeks after fertilization
Phenotypic sex	Development of external and internal reproductive structures continues as male or female in response to hormones	8 weeks after fertilization
Gender identity	Strong feeling of being male or female develop	From childhood, possibly earlier

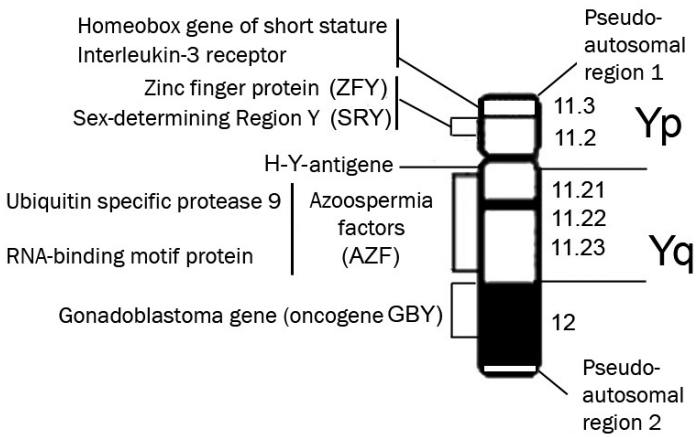
Task 4. Study the scheme of gene location on sex chromosomes.
More than 250 X-linked disorders have now been identified compared to just 20 Y-linked ones.

Scheme of gene location in the sex chromosomes

X-chromosome



Y-chromosome



Clinical consideration

Human males differ from human females in the fact that they have an Y chromosome and females do not. In 1990, the **SRY gene** (which stands for ***S***ex-***D***etermining region ***Y*** gene) was found. In humans, a single functional copy of the *SRY* gene, normally located on the Y chromosome, determines phenotypic maleness by causing gonads to differentiate into testes. This gene codes for **TDF protein** (***T***estis ***D***etermining ***F***actor). In the absence of a functional SRY gene, gonads differentiate into ovaries and the individual is phenotypically female.

Task 5. What will be the phenotypic sex of a human with the following gene or chromosomes or both?

#	***Genotype***	***Phenotypic sex***
1	XY with the SRY gene deleted	
2	XY with the SRY gene translocated on an autosomal chromosome	
3	XX with the SRY gene on an autosomal chromosome	
4	XO with a copy of SRY gene on an autosome	
5	XXY with the SRY gene deleted	
6	XXYY with one copy of the SRY gene deleted	

Task 6. ***Sex- Linked, Limited, and Influenced Traits***

Sex traits can be categorized into three types of inheritance:

1) sex-linked,
2) sex-limited,
3) sex-influenced.

Sex-linked traits - _____
_____
_____
_____
_____

X-linked recessive traits are generally expressed much more often in males than in females.

Sex of human beings influences on some other characters, the development of which is determined by the genes located in autosomes of both sexes.

Study the table «**Sex limited and sex influenced inheritance**».

Difference	***Kind of character***	
	Sex limited traits	*Sex influenced traits*
Expression (Manifestation)	Traits expressed in only one sex. (It may be controlled by sex linked or autosomal loci).	They are expressed in both men and women, but variously (different degree of expressivity).
Examples	All secondary sexual characters. Genes determining beard growth or mammary glands (breast size).	Pattern baldness is a condition which is dominant in men but recessive in women; kind of human singing voice (bass, baritone, tenor, soprano, mezzo-soprano, contralto)

Task 7. Solve the genetic problem.

Problem. A man is ill with *hemophilia*. His wife is healthy. In this family the boy was born with hemophilia. Draw up family pedigree. Find the genotypes:

Trait	allele	allele location
Hemophilia	h	X^h
Normal blood clotting	H	X^H

a) Point out, from which of parents the son inherited this disease.
b) Calculate the probability of birth of two sons with hemophilia.
c) What is *hemizygous* condition of gene?

Solving:

Task 8. Write the gamete types produced by individuals with given genotypes:

Genotypes	X^hY	X^h_dY	X^HX^h	$X^H_dX^h_D$
A number of gametes:				
non-crossover				
crossover				

Homologous (pseudoautosomal) and non-homologous regions of X and Y chromosomes

The pseudoautosomal region is homologous section of X and Y chromosomes (*see Task 4, page 86*), i.e., a region of similarity between sex chromosomes. The region is responsible for pairing the X and Y chromosomes during meiotic prophase I. In this region genes are present in two copies in males and females and thus are inherited like autosomal genes, whereas other Y-linked genes are passed on only from father to son.

These genes are also known as *incompletely sex-linked* because crossing over may occur in the homologous sections of X and Y chromosomes. Certain examples of such "X-linked genes" in humans are *achromatopsia* (total colour blindness), *nephritis, xeroderma pigmentosum*, etc.

Task 9. The genes *K* and *L* are sex-linked, i.e. located on the same X-chromosome. The distance between them is 16 cM.
a) How many gamete types does a dihetorozygous woman produce?
b) How many gamete types does a man produce?
Write down the solving as the table.

	Woman	Man
Genotype		
Gametes		

Task 10. Solve the genetic problems.
Problem 1. Freckles are dominant to plain skin and the freckle gene is on an autosome. *Becker muscular dystrophy* is inherited as X-linked recessive trait.

The parents are healthy and both have freckles. They have an affected son with plain skin. Draw up the family pedigree. Find the genotypes.
a) What is the chance that they will have a daughter who has the disease and who has freckles?
b) What is probability of birth of a healthy son with freckles?
c) What is probability of birth of two affected sons with plain skin?
Solving:

Trait	allele	allele location
Freckles		
Plain skin (no freckles)		
Healthy muscular system		
Becker muscular dystrophy		

Problem 2. In human beings, the genes for *hemophilia* and *color blindness* (*daltonism*) are recessive and locate on the X-chromosome. The distance between them is about 10 cM.

A woman is heterozygous for both characters. She inherited the haemophilia gene from her father, and the daltonism gene from her mother. This woman is married to a healthy man. Draw up family pedigree. Find genotypes and the ratio of gametes.

a) What is probability of birth of a son with both abnormalities?

b) What is probability of birth of a healthy son?

Solving:

Trait	allele	allele location
Normal blood clotting		
Hemophilia		
Normal color vision		
Color blindness (daltonism)		

Problem 3. A father suffers from two X-linked recessive diseases – *color blindness* and *chronic hemolytic anemia*. May his children inherit just one of two pathological genes?

Problem 4. In 1995, in medical journal "Ophthalmic Genetics", Dr. Zhao G.-Y. et al. reported a 4-generation Chinese family in which eye disease *retinitis pigmentosa* affected only males. All sons of affected males were affected, but all 4 daughters of affected males (and all children of these daughters) were healthy.

Determine the mode of inheritance of the disease in this family. How is this trait called?

Solving:

Trait	**allele**	**allele location**
Retinitis pigmentosa		
Healthy		

Multiple-Choice Tests for Control of Theme 13

1. How many genes does a child inherit from his/her father?

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

2. Which of the following describes hemophilia?

A. multiple allele trait
B. codominant trait
C. dominant trait
D. sex-linked trait
E. pleiotropic trait

3. Green color blindness in human is a sex-linked recessive trait. In a family, the daughter has normal vision, whereas the son is colorblind. One can realistically surmise:

A. the mother was heterozygous for colorblindness
B. the father was heterozygous for colorblindness
C. the father was homozygous for color blindness
D. the mother most probably was colorblind
E. the father most probably was colorblind

Date	**Signature**

GENETIC PROBLEMS TO THEME 13 FOR SELF-WORK

Problem 1. *Vitamin-D resistant rickets* is X-linked dominant disorder. The parents suffering from this disease have a healthy son. What phenotypes are possible for the future son born in this family?

Solving:

Trait	allele	allele location

Problem 2. *Ichthyosis* is a heterogeneous family of genetic skin disorder. All types of ichthyosis have dry, thickened, scaly or flaky skin.

One type of ichthyosis is autosomal recessive trait, another one is X-linked recessive one. A mother is heterozygous for both pairs of genes, a father is healthy and has dominant alleles of both genes only. What is probability of birth of a sick child in this family?

Trait	allele	allele location

Problem 3. One form of *syndactily* is presence of cutaneous membranes between toes. A man has cutaneous membranes but his wife does not. There are five children in this family. Three sons have cutaneous membranes but two their sisters do not. Grandsons in the line of sons have the same abnormality. Draw the family pedigree and determine the mode of inheritance.

Solving:

Trait	allele	allele location
Syndactily		
Healthy		

Theme 14: Gene diseases, the methods of their diagnostics

Objectives: to study the genetic essentials, manifestation and patterns of inheritance of gene diseases in human, to acquire the knowledge about the methods of their diagnostics.

The branch of genetics which deals with the inheritance of characters in human is ***Human Genetics***. The division of Human Genetics, which carries out a research into the causes of hereditary diseases, develops the methods of their diagnostics and prophylaxis is called ***Medical Genetics***.

Task 1. Study the differences between *congenital* and *hereditary* diseases.

Congenital diseases are disorders present at birth as a result of the following:

1. genetic factors, e.g., chromosomal disorder as Down`s syndrome; gene disorder as hemophilia etc.
2. acquired *in utero* from environmental factors, e.g., congenital syphilis from maternal infection.
3. combined genetic and environmental factors, e.g., cleft palate, congenital heart disease.

Although the factors responsible for some congenital diseases are present at birth, the signs and symptoms of these conditions may not develop until a varying period of time. In some instances this may be many years (e.g., Huntington`s chorea or adult polycystic kidney).

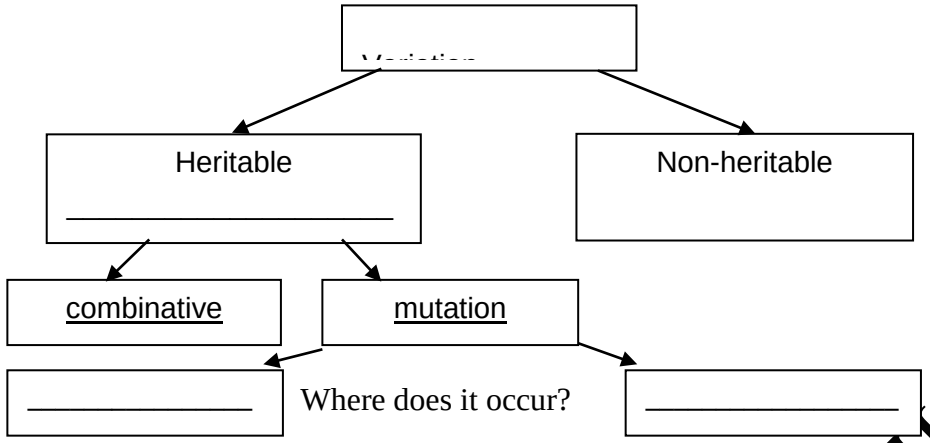
CLASSIFICATION OF HEREDITARY DISEASES

According to a mutation type, mode of gene interaction and environmental factors, all genetic disorders are classified into 5 categories:

1. **Gene diseases** caused by a mutation in a single gene (e.g., point mutation – alteration in DNA at molecular level) or several genes. Examples are albinism, hemophilia, partial color blindness.
   Gene diseases subdivide in monogenic and polygenic ones:
   i) **Monogenic diseases** are caused by a single mutant gene (albinism, hemophilia). Their modes of inheritance follow Mendel's law of inheritance and segregation.
      There are 3 groups of diseases resulting from mutations affecting single genes do not follow the Mendelian rules of inheritance:
      (a) Diseases caused by triplet repeat mutations (e.g., fragile X syndrome, Huntington`s chorea)
      (b) Diseases caused by mutations in mitochondrial genes (e.g., Leber's hereditary optic atrophy)
      (c) Diseases associated with alteration of imprinted regions of the genome (e.g., Prader – Willi syndrome and Angelman syndrome)
   ii) **Polygenic diseases** are determined by a number of genes, each having minor effect in expression of a single trait (gout, diabetes mellitus). They follow the pattern of polygenic inheritance for transmission from generation to generation.
2. **Chromosome diseases** caused by chromosomal (i.e., structural) and genomic (numerical) mutations. Examples are a Cri du chat syndrome, Turner's syndrome, Down`s syndrome.
3. **Multifactorial diseases,** where both genetic and nongenetic, or environmental, factors are involved in determining the trait and these factors are multiple. Examples are atherosclerosis, ulcer diseases, and hypertension.
4. **Gene diseases of somatic cells** (e.g., cancer, autoimmune diseases).
5. **Diseases due to incompatibility of genes**. Example is hemolytic disease of newborns, in which fetal red blood cells die earlier due to the action of antibodies formed by a mother against fetal Rh-antigen.

Task 2. Give the definition of term "*variation*", and fill the scheme.

Variation – _____
_____
_____
_____



Task 3. Study the notion *mutation* as an alteration of genetic material.

Mutations, or heritable alterations in the genetic material, may be *gross* (at the level of the chromosome) or *point* alterations. The latter can involve just a single nucleotide pair in DNA.

Clinical consideration

Tumor suppressor gene is a protective gene that normally limits the growth of tumors. When a tumor suppressor gene **is mutated** (altered), it may fail to keep a cancer from growing. Several familial inheritable cancers are associated with the loss of function of a tumor suppressor gene.

Gene *BRCA1* (located on chromosome 17), an example of tumor suppressor genes, was the first breast cancer gene to be identified; mutated forms of this gene are responsible for some cases of inherited breast cancer, especially those that occur in younger women. Germline mutations in the *BRCA1* or *BRCA2* (located on chromosome 13) tumor-suppressor genes are strong predictors of breast and/or ovarian cancer development.

Non-heritable or ***somatic variation*** occurs in the somatic cells of individuals due to the influence of environment. These are acquired by the individual during its life time and are lost with its death. Therefore, somatic variations are also called acquired variations.

Somatic variations are caused by three types of factors:

1. Environmental factors (habitat, light, temperature, air, humidity, pressure, food etc.)
2. Use and disuse of organs
3. Human conscious efforts (education, learning, training, nutrition etc.

Task 4. Mutagens

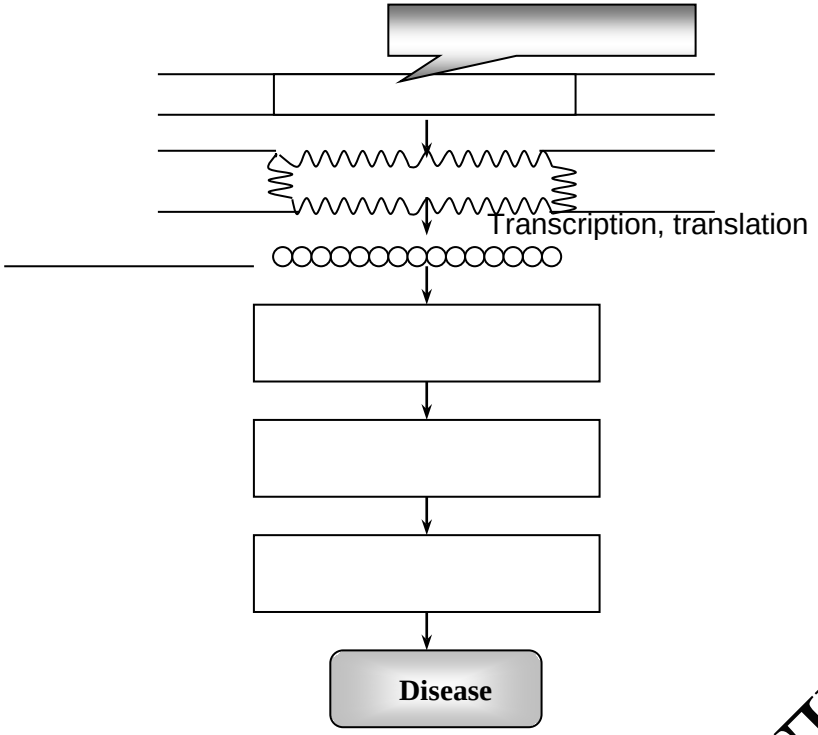
A mutagen is a natural or human-made agent (physical, chemical or biological), which can alter the structure or sequence of DNA.

Write the examples of mutagens.

Mutagens

biological	**physical**	**chemical**
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Task 5. Study the scheme of development of gene diseases.



Task 6. Analyze classification of monogenic diseases according to the mode of inheritance. Give the characteristics of basic patterns of inheritance: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, Y – linked and mitochondrial inheritance.

Autosomal dominant inheritance:_____

Examples of autosomal dominant traits are rare conditions like polydactyly, osteogenesis imperfecta, achondroplasia, brachydactyly (short fingers), Huntington`s chorea, congenital dislocation of the hip, arachnodactyly (Marfan's syndrom) and etc. The overall incidence of autosomal dominants is about 7.0 per 1000.

Autosomal recessive inheritance:_____

Examples of autosomal recessive traits are cystic fibrosis, albinism, galactosemia, Gaucher`s disease, hemoglobinopathies, mucopolysaccharidoses, phenylketonuria, porphyria, Wilson`s disease (hepatolenticular degeneration) etc.

X-linked dominant inheritance:_____

Examples of X-linked dominant inheritance are vitamin D resistant rickets (or X-linked hypophosphatemia), enamal hypoplasia and etc.

X-linked recessive inheritance:_____

_____

_____

_____

_____

_____

_____

Examples of X-linked recessive inheritance are haemophilia, partial colour blindness, Duchenne muscular dystrophy, glucose-6-phosphate dehydrogenase deficiency (favism), optic atrophy etc.

Y – linked inheritance (holandric inheritance): _____

_____

_____

_____

Examples of Y – linked inheritance are hairy ears (hairy pinna).

Mitochondrial diseases (MD) affect people regardless of sex but are inherited only from mother (through the ovum, sperm mitochondria never contribute to the zygote population of mitochondria. In some patients, only one organ is affected, while in other patients all the organs are involved. Depending on how severe the mitochondrial disorder is, the illness can range in severity from mild to fatal.

Examples of MD: Alzheimer's disease, Leber's hereditary optic neuropathy, subacute sclerosing encephalopathy, Maternal Myopathy and Cardiomyopathy (MMC) etc.

Task 7. Have a look at the features of genealogical method. Designate capabilities of this method.

GENEALOGICAL METHOD

The study of a particular trait in a family usually begins with a person first found to exhibit the trait and through whom the family draws the attention of the investigator. Such a person is referred to as the *propositus* when a male and *proposita* when a female (also called ***proband*** or ***index case***)

The procedure starts with gathering information of the disorder, age of onset, duration of complaints and any other major illness.

The second step is to collect information regarding the first degree relatives, parents, sibs and offspring of the proband. The following information is to be recorded - name, surname, date of birth, age, age of death, cause of death, stillbirths and abortions, any obvious deformity in fetus or still-born baby or in deceased infant.

The data collected from a family over a number of generations can be represented in a *genealogical chart* (*pedigree chart*, *family tree*) using international conventional symbols.

Genealogical method allows determining:

a) _____

_____

b) _____

_____

c) _____

_____

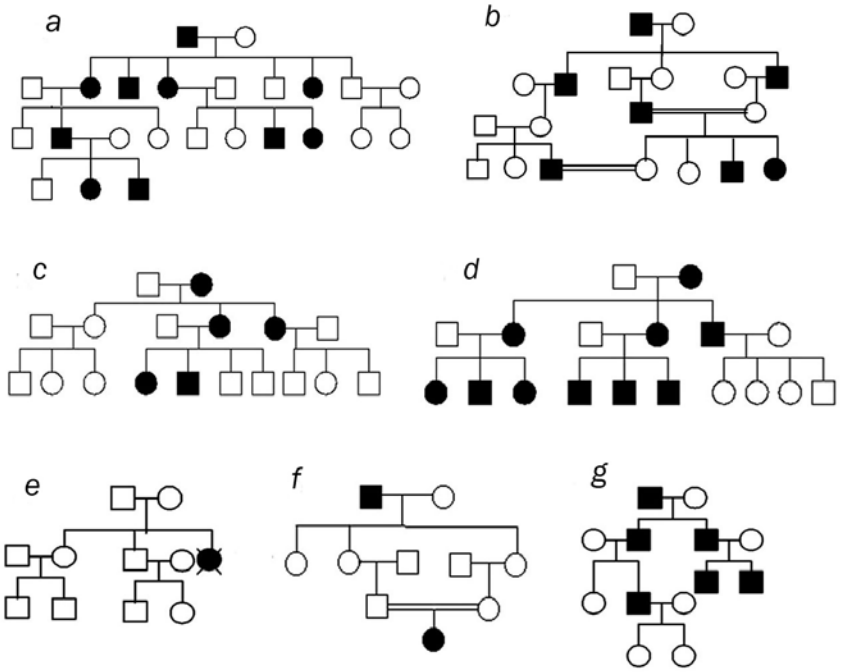
d) _____

_____

e) _____

_____

Task 8. Determine the modes of inheritance and possible genotypes.



Task 9. Study theoretical aspects to twins methods

TWINS METHOD

Twins are the commonest form of multiple pregnancy, resulting from the simultaneous intrauterine development of two embryos. Twins are of two types: monozygotic (MT), or *identical*, and dizygotic (DT), or *fraternal*. The overall incidence of twinning is 1:80-90 births, and that of identical twinning is 1:270 births. Twins provide important study material in genetics.

MONOZYGOTIC TWINS (MT) develop from a single zygote which divides in the early embryonic life. Fetal membranes vary depending upon the time of twinning. If division of inner cell mass occurs after formation of amniotic cavity, i.e. after eight days, then the monozygotic twins shall have one amnion and one chorion. If the separation of embryonic primordium occurs before development of amnion then there are 2 amnions, 2 chorions and 2 placentae. This may pose difficulty in determining the twin zygosity. Since monozygotic twins result from a single zygote they are always of the same sex. They are genetically identical and are alike in their genetic markers. Dissimilarity between monozygotic twins for certain traits like birth weight or size is influenced by environment, e.g. prenatal nutrition.

DIZYGOTIC TWINS (DT), account for about two-third of the twins. They are due to the simultaneous fertilization of two ova from the same or different ovarian follicles by separate sperms. Each has its own chromosomal constitution, chorionic sac, and placenta. The sex and blood type may not be the same. Genetically they are no more than brothers and sisters born at different times. Dizygotic twins have an average half of their genes in common. Tendency of dizygotic twins repeats in family.

Detection of twin zygosity. The detection of zygosity - whether monozygotic or dizygotic - of a twin pair helps to conduct research in genetic and developmental disorders in twins. It also helps in the selection of donors in cases of transplantation of tissues and organs. In transplantation, a monozygotic co-twin is the most useful donor, whereas a dizygotic co-twin is genetically like any other sibling.

Zygosity is detected by the examination of the placenta and fetal membranes, and by using various genetic markers indicating the similarities and differences between the co-twins. Other characters such as eye color, finger prints also help in the determination of twin zygosity.

In 1875 English physician and geneticist ***Francis Galton*** paid attention to the importance of twin studies for comparison of the effects of heredity and environment.

In twins method the these are compared:

1) monozygotic twins (mz) and dizygotic ones (dz);
2) siblings in mono- and dizygotic twin pairs with each other;
3) data of analysis of twin sample and general population.

Presence of the same trait in both members of a pair of **twins** is called ***concordance*** (concordance rate). ***Discordance*** (coefficient of differences) - the rate of absence of an analyzed trait in one of twins when present in other one.

Twins are said to be *concordant* for a given trait if both exhibit the trait. For the diseases presumably caused by genetic factors, monozygotic twins show higher *concordance rate* than dizygotic twins. ***If monozygotic twins do not demonstrate full concordance for a given condition, it can be concluded that non-genetic factors are also playing a part in their etiology.***

Task 10. Karl J. Holzinger`s formula is used for comparison of the effects of heredity (H) and environment (E) in development of a trait.

$$H = \frac{Cmz - Cdz}{100 - Cdz} \times 100\%$$

where C_{mz} и C_{dz} – concordance rate of monozygotic and dizygotic twins respectively.

$$E = 100\% - H$$

If H = 1 or 100%, it means a trait analyzed is determined by inheritance only. признак обусловлен только наследственностью.
If H = 0, it means that all variation is determined by environmental factors.

Example. For a particular trait the concordance rate of monozygotic twins is 80, whereas concordance rate of dizygotic twins is 30, then

$$H = \frac{80 - 30}{100 - 30} \times 100\% = \frac{50}{70} \times 100\% = 0.71 \times 100\% = 71\%$$

E = 100% – 71% = 29%

Hence, the given trait is due to 71% of heredity and 29% of environmental effect.

Task 11. Calculate the contribution of genetic factors and environment in the trait expression using K. Holzinger's formula. Fill in the table.

№	Trait	Concordance rate		Factor of heredity	Factor of environment influence
		C_{mz}	C_{dz}	**H**	**E**
1	Shape of nose	100	30		
2	Papillary pattern	92	40		
3	Multiple sclerosis	25	5		
4	Coeliac disease	71	9		
5	Stutter	63	19		
6	Measles	98	94		
7	Idiopathic chronic fatigue	55	19		
8	Hypertension	25	9		
9	Nephrolithiasis	32	17		
10	Myocardial infarction	20	16		
11	Cocaine addiction	47	8		
12	Appendicitis	29	16		
13	Tuberculosis	67	23		

Task 12. Study the features of biochemical method.

BIOCHEMICAL METHOD

Biochemical methods are used for diagnosis of inborn errors of metabolism. Biochemical method includes 2 stages: the first - *screening* test or instant diagnosis; the second - *quantitative assays* as chromatography, electrophoresis. Instant diagnosis is founded on the exposure of metabolic product in urine or blood. More precise definition of diagnosis is conducted with the help of more complicated methods of determination of enzymes and amino acids in the second stage.

An *inborn error of metabolism* is defined as a genetically determined biochemical disorder in which a specific enzyme defect produces a metabolic block that may have pathological consequences. Some characteristic examples are *phenylketonuria*, *albinism* and *galactosaemia*.

Task 13. Study the classification of the hereditary metabolic disorders.

According to classification of the World Health Organization hereditary disorders of metabolic processes divide into 11 groups:

1. Amino acid metabolism (phenylketynuria, albinism);
2. Lipid metabolism [Tay-Sachs disease (GM\22 gangliosidosis infantile amaurotic familial idiocy), Niemann-Pick disease (a sphingomyelin lipidosis)], Gaucher's disease (hereditary deficiency of the glucocerebrosidase) enzyme. These three diseases belong to group of so called lysosomal storage diseases.
3. Carbohydrate metabolism (galactosaemia);
4. Steroids metabolism (male pseudohermaphroditism);
5. Purine and pyrimidine metabolism (Lesch-Nyhan syndrome);
6. Amino acid transport (cystinuria);
7. Metal metabolism (Wilson`s disease [hepatolenticular degeneration]);
8. Mucopolysaccharide metabolism (Hurler`s syndrome, Hunter`s syndrome);
9. Disorders of heme and porphyrin structure (congenital erythropoietic porphyria);
10. Disorders of metabolism in erythrocytes and their structure (glucose-6-phosphate dehydrogenase variant [favism]);
11. Disorders of structure and function of enzymes and proteins of plasma (agammaglobulinemia).

Task 14. Study the mechanism of genetically determined biochemical defects.

An inborn error of metabolism is defined as a genetically determined biochemical disorder in which a specific enzyme defect produces a metabolic block that may have pathological consequences

Usually the mutation in the gene, which codes for the normal enzyme, involves substitution of a single amino acid. Clinically the picture is diverse, ranging in severity from relatively mild harmless disorders to the lethal.

The clinical picture is the result of disorders brought about by the metabolic block which leads to:

1. Accumulation of a precursor just preceding the step where there is a block. The accumulated precursor itself can have toxic effects, or with alternate minor pathways, may lead to production of toxic metabolites.

2. Stoppage of subsequent steps in the metabolism. Whenever a feedback mechanism is involved in the control of metabolism, such deficiency would lead to overproduction of the stimulating agent.

Task 15. In a metabolic pathway a series of reactions takes place. Each reaction is catalyzed by a different enzyme. Look at the pathway below:

	Enzyme A		***Enzyme B***		***Enzyme C***	
Substance W	→	Substance X	→	Substance Y	→	Substance Z

A mutation of the gene that codes for an enzyme may result in the protein produced having a different tertiary structure so that it cannot function.

Suppose that the gene for enzyme B mutates, and no enzyme B is produced.

1. Explain why production of substance Z stops.

_____

_____

_____

_____
_____

2. Explain why substance X accumulates.

_____
_____
_____
_____

3. Explain what would happen if substance Y was then supplied.

_____
_____
_____
_____

Task 16. Study the typical example of the hereditary metabolic disorder.

A typical example is *phenylketonuria* (PKU) – disorder that is characterized by an inability to utilize *phenylalanine* amino acid. Clinically the child is found to have severe mental retardation, many untreated patient have IQ less than 20. Because of tyrosine deficiency arising from metabolic block, there is reduction in melanin formation. Affected children have diluted pigmentation; regions of the brain which are normally pigmented such as the *substantia nigra* may also lack pigment.

Common symptoms also include epilepsy, a musty odor, small head, short stature, eczema and flat feet.

In most of metabolic disorders, it is difficult to provide any substitute for the deficient enzyme. The principal treatment is to remove from the diet those articles of food which are rich in the substances which the patient cannot metabolize, so that these toxic substances will not accumulate. For PKU, removal of *phenylalanine* (which is found mostly in high-protein foods) from the diet constitutes an effective treatment. Special nutritional drinks - supplementary infant formulas are used in PKU-babies to provide the amino acids and other necessary nutrients that would otherwise be lacking in a low-phenylalanine diet.

Content of phenylalanine in the proteins of some food-stuffs

Protein	Content of phenylalanine, %
Zein of maize	7.6
Lactoglobulin of milk	3.5
Casein of milk	5.5
Cucurbitin of pumpkin seeds	8.5

It has been suggested that the screening of newborn population should be carried out for conditions like PKU, since phenylketonuric children are deceptively normal at birth as the maternal enzyme substitutes the missing enzyme during intrauterine development. Treatment is most effective when the diagnosis is made *soon after birth* and measures instituted immediately. If the child is given phenylalanine even for some time, irreversible mental retardation occurs because of accumulation of toxic metabolites of phenylalanine in the brain. The condition can be diagnosed by tests, which detect phenylpyruvic acid in the urine (ferric chloride test) or excess of phenylalanine in the blood (Guthrie test).

Task 17. Study the table “Summary of genetically determined biochemical disorders”. Designate the causes of given diseases.

q – long arm of a chromosome
p – short arm of a chromosome

AD – autosomal dominant inheritance
AR – autosomal recessive inheritance
XR – X-linked recessive inheritance
XD – X-linked dominant inheritance

SOME GENETICALLY DETERMINED BIOCHEMICAL DISORDERS

Disorder	Frequency	Mode of inheritance	Gene location in chromosome	Main clinical manifestations	Enzyme/protein defect
Phenylketonuria (PKU)	aa 1:10000 Aa 1:100	AR	12q	Diluted pigmentation, microcephaly, mental retardation, convulsion, muscular hypertension.	Phenylalanine hydroxylase
Albinism	aa 1:25000 Aa 1:50000	AR	11q, X	Lack of pigment in skin, hair and eyes, photophobia, visual disorders.	Tyrosinase
Sickle-cell anaemia	1:10000	AR	7, 11	The defective cells rupture and block the blood flow to tissues, depriving them of oxygen. It also produces a variety of other symptoms like pain, fever, swelling, jaundice, low resistance to infection, and kidney problems	Haemoglobin S (valine replaces glutamic acid in the sixth position of β-chain of HbS molecule).
Cystic fibrosis (mucoviscidosis)	1:4000	AR	7q	Persistent coughing, frequent lung infections; wheezing or shortness of breath; poor growth/weight gain frequent greasy, bulky stools or difficulty in bowel movements	Protein CFTR (cystic fibrosis transmembrane regulator) responsible for Cl^- ions transport by the epithelial cells
Galactosaemia	aa 1:35000 Aa 1:100000	AR	9p	Hepatosplenomegaly, cirrhosis of liver, cataracts, mental retardation	Galactose-1-phosphate uridyl transferase
Tay – Sachs disease	aa 4:100000, 1:3600 newborns	AR	15q	Damage of brain and spinal cord results in degenerative neurological changes, severe physical and mental retardation, paralysis; onset 4 to 6 months of age, death 2 to 4 years. There is cherry-red spot on macula	Hexosaminidase A
Niemann – Pick disease	1:300000	AR	18q	Hepatosplenomegaly, convulsions, severe damage of central nervous system, cherry-red spot on macula.	Sphingomyelinase

Gaucher's disease: a) infantile severe form b) chronic form		AR AD	1q	Destruction of bones, mental retardation, Anaemia, hemorrhages	Glucocerebrosidase
Wilson's disease (hepatolenticular degeneration)	aa 2-3:100000 Aa 1:100	AR	13q	Liver cirrhosis, Kayser-Fleisher ring in cornea (yellowish- greenish color), neurological problems.	Not known, affects copper metabolism
Lesch – Nyhan syndrome	1:300000 newborn	XR	Xq	Mental retardation, aggressiveness of behavior, increased level of uric acid, hematuria, and kidney dysfunction.	Absence of hypoxanthine-guanine-phospho-ribosyltransferase
Mucopolysaccharidosis (Hurler's syndrome)	1:100000 newborn	AR	4p	"Gargoyle" faces, dwarfism, mental retardation, hearing defect, hepatosplenomegaly, corneal clouding, cardiovascular problems	Absence or deficiency of α-L-iduronidase; results in muco-polysaccharide accumulation
Marfan's syndrome	1:20000	AD	15q	Abnormalities of skeleton (arachnodactyly, scoliosis), *eyes* (lens subluxation), blood vessels (aneurysms of the ascending aorta), muscular underdevelopment, high incidence of hernias	Absence of glycoprotein fibrillin
Ehlers – Danlos syndrome	1:5000	AD AR XR	2q, 8q, 7q, 17q 1p Xq	Group of connective-tissue disorders: joint hypermobility, cutaneous fragility, and hyper-extensibility, abnormal wound healing. Delay of motor skill development in infants. In Type IV, internal complications may include rupture of large vessels, hernia of stomach, spontaneous rupture of the intestine	Classic type: defect of collagen alpha-1(V) or the collagen alpha-2(V)
Favism		XR	Xq	Haemolysis in response to some drugs (e.g., antimalarial agents (primaquine, pamaquine), sulfonamides (sulfamethoxazole), phenacetin, and even vitamin K) and food-stuffs (after eating fava beams) or inhaling pollen from fava plants (a reaction called *favism*).	Glucose-6-phosphate dehydrogenase deficiency

Multiple-Choice Tests for Control of Theme 14

1. A change in a gene structure due to damage or being copied incorrectly is called
- A. evolution
- B. meiosis
- C. mitosis
- D. segregation
- E. a mutation

2. What disease is lysosomal storage disease?
- A. Gaucher's disease
- B. Tay-Sachs disease
- C. Niemann-Pick disease
- D. all of the above
- E. none of the above

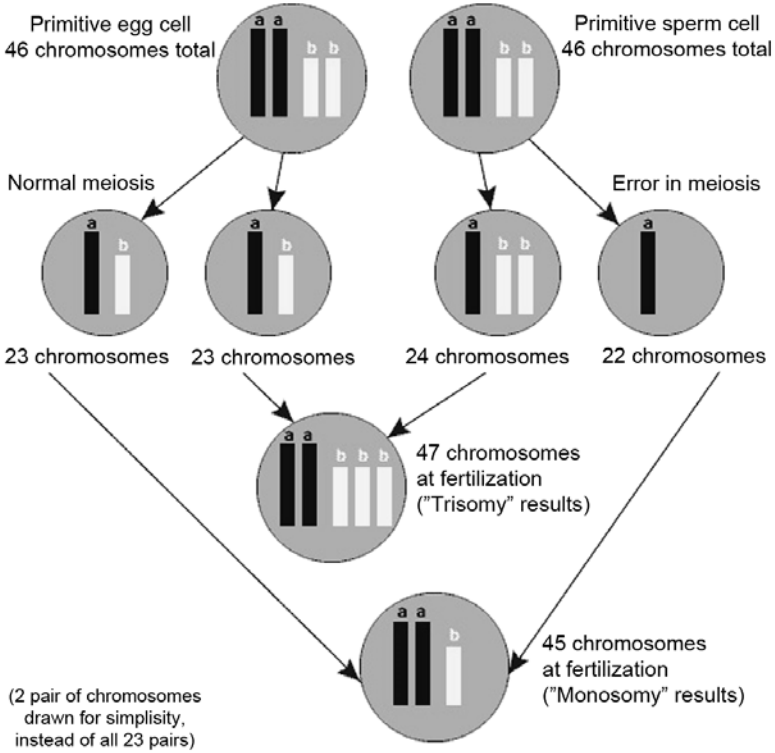
3. Phenylketonuria is a human genetic disorder that can be treated by
- A. injecting insulin
- B. blocking an enzyme that converts phenylalanine to tyrosine
- C. reducing tyrosine in the diet
- D. eliminating phenylalanine from the diet
- E. eating a phenylalanine-rich diet

Date	Signature

Theme 15: Chromosome diseases, the methods of their diagnostics

Objectives: to study the cytological basis of chromosome diseases, phenotypic features of these diseases; to acquire the knowledge about the methods of their diagnostics; to know how to calculate the probability of child birth with chromosome abnormality.

Task 1. Study the scheme of *chromosome non-disjunction* that causes errors in chromosome number such as trisomy and monosomy diseases.

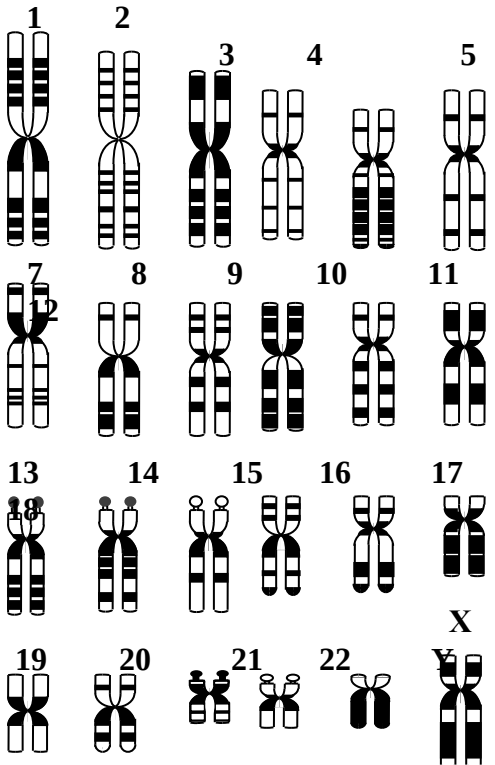


Non-disjunction can occur _____
_____
_____
_____

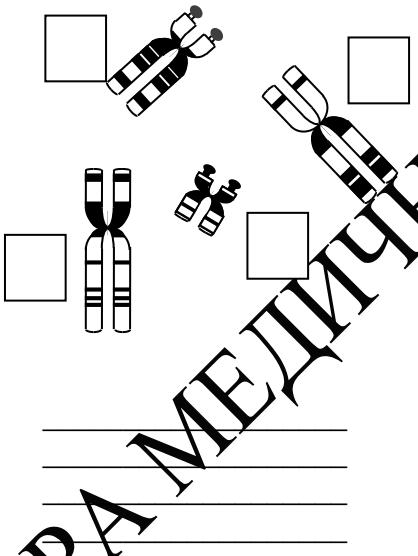
Task 2. Recall the notion of karyotype, morphological classification of chromosomes, principles of chromosome analysis according to Denver and Paris classifications (*pages 30-32*).

Study the scheme of G-banded human chromosomes. Distinct regions along the length of each chromosome show a varied stain intensity, so that the chromosomes can be individually identified.

Find how many pairs of chromosomes have satellites.



Identify the chromosome numbers



Task 3. Chromosome numerical abnormalities

Abnormal chromosomes are the vehicles of inherited abnormalities. The abnormalities may be either *numerical* or *structural* or both, and may occur during *either* mitosis *or* meiosis. Write the formulas of haploid and diploid sets and numerical abnormalities.

Set of chromosomes	*Formula*	*A number of chromosomes*
Haploidy		
Diploidy		
Polyploidy		
Aneuploidy		
- trisomy		
- monosomy		
- nullisomy		

Task 4. A use of Human Chromosome Nomenclature.

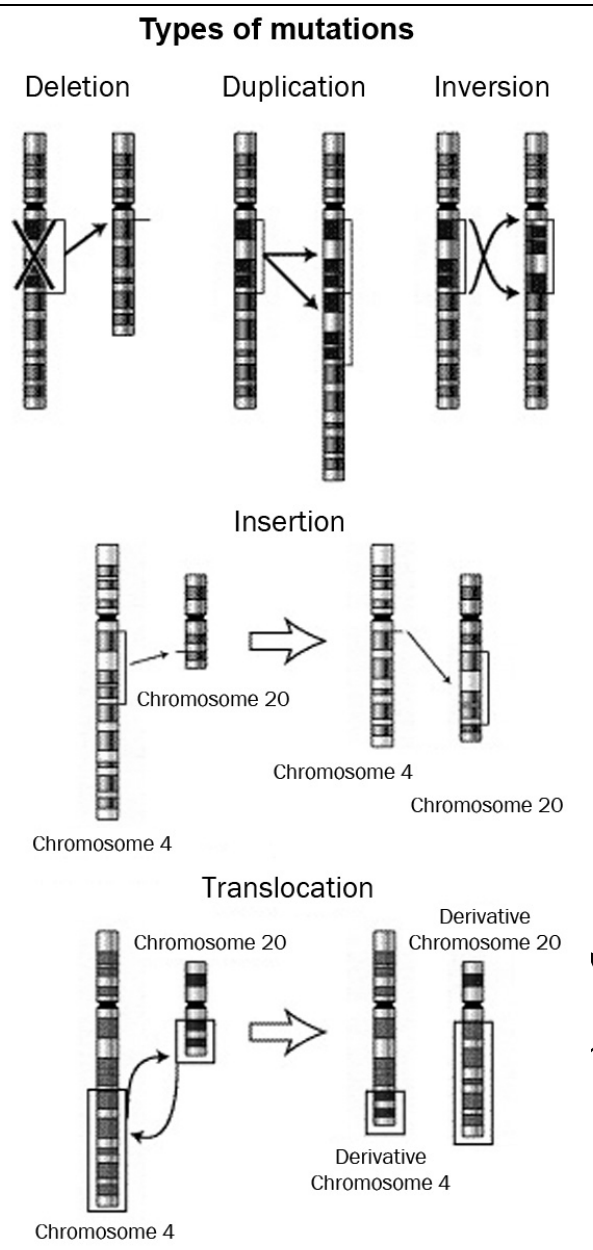
1. The karyotype formula begins with the total number of chromosomes, followed by the notation of the sex chromosomes.
2. An extra or a missing chromosome is designated with a "+" or "–" sign, respectively, before the number of chromosome.
3. For *mosaics* a double slash is used to separate the components of the chromosomal mosaic. (*Mosaicism* is the condition where an organism (derived from a single zygote) develops with two or more major cell lines of different genotypes).

Examples: 46, XY (healthy man); 47, XX, +21 (trisomy in chromosome 21); 45, XY, -15 (monosomy in chromosome 15)

Task 5. Structural chromosome aberrations result from single or multiple breaks along the chromosomal length. The broken fragments are then either destroyed (deleted) or rearranged in various ways, or shifted (translocated) to the other chromosomes. It is only through the abnormal gametes formed at meiosis that chromosomal anomalies can be passed on from one generation to the next.

The usual forms of structural abnormalities are *deletions*, *duplications*, *translocations*, *inversions*, and *ring chromosomes*.

Study the scheme "Types of chromosome mutations" and briefly characterize the given types of chromosomal aberrations.



Deletion (del)

Duplication (dup)

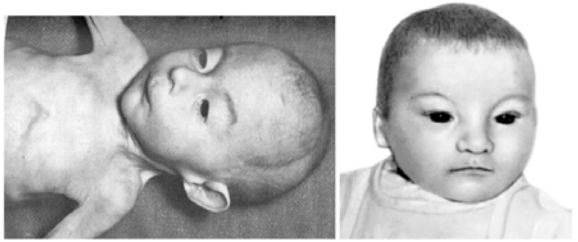
Inversion (inv)

Insertion (ins)

Translocation (t)

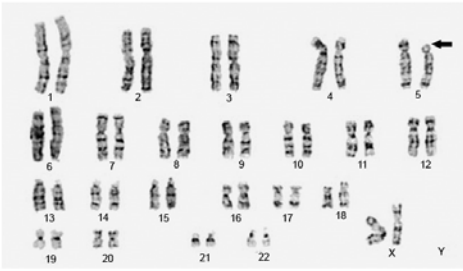
Task 6. ABNORMALITIES OF CHROMOSOME STRUCTURE

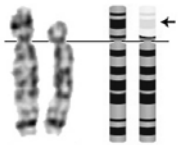
The common example of structural chromosome aberration in humans is the ***Cri du chat*** syndrome, where the terminal part of the short arm of chromosome 5 is deleted. So patients have karyotype 46, XY, del5p or 46, XX, del5p. It was first described by Lejeune and named a *Cri-du-chat* syndrome because the cry of affected baby mimics mewing of a cat due to defects in throat structure.



Low birth weight and slow growth
Moonlike face
Downward slant to the eyes
Epicanthal folds of eyes
Some flattened nose
Short neck

Microcephaly
Dolichocephaly (back head is long and narrow)
Low set ears
Small jaw (micrognathia)
Arched palate
Abnormally developed throat
Congenital disorders of heart and vessels
Kidney abnormalities
Low muscle tone
Mental retardation





Prade -Willi syndrome* (PWS) and *Angelman syndrome (AS)

These syndromes both are due to a ***microdeletion in chromosome 15***, region 15q11-q13, although the abnormality is on the *paternally derived* chromosome 15 for PWS and the *maternally derived* 15 for AS. The syndromes are *clinically distinct complex disorders* and have characteristic neurologic, developmental, and behavioral phenotypes plus other structural and functional abnormalities.

Task 7. ABNORMALITIES OF AUTOSOMES

Karyotype: _____

**DOWN`S syndrome** (Trisomy 21, Mongolism). It was first identified by Langdon Down in 1866. However, the chromosomal defect was unidentified till 1959. In this year Lejeune and his colleagues found that patients with Down`s syndrome have 47 chromosomes instead of the normal 46. The extra chromosome was identified from the G group, a small acrocentric chromosome 21. Down`s syndrome is the most common, viable autosomal trisomy.

Overall about 96% are due to a primary non-disjunction, and about 95% of these involve errors in the formation of the ovum rather than the sperm.

In 5% of cases, the extra chromosome 21 is translocated to chromosome 14 (or sometimes to other D group chromosomes: 13 or 15). In about 1% cases the disease is due to *mosaicism* (karyotype 46/47). They show a 2 cell lines, a normal cell line of 46 and an abnormal cell line of 47 chromosomes (with trisomy 21). These patients (mosaics) are less severely affected. Mental retardation is relatively lesser as compared to a typical trisomy 21. The incidence of Down`s syndrome increases about 1 in 1200 in mothers under 30 years to about 1 in 100 at the age of 39 years, and at present accounts for about a third of all cases of severe mental handicap in children of school age.

To calculate the risk to a mother of having a Down baby is a problem of genetic counseling. It depends upon a number of factors:

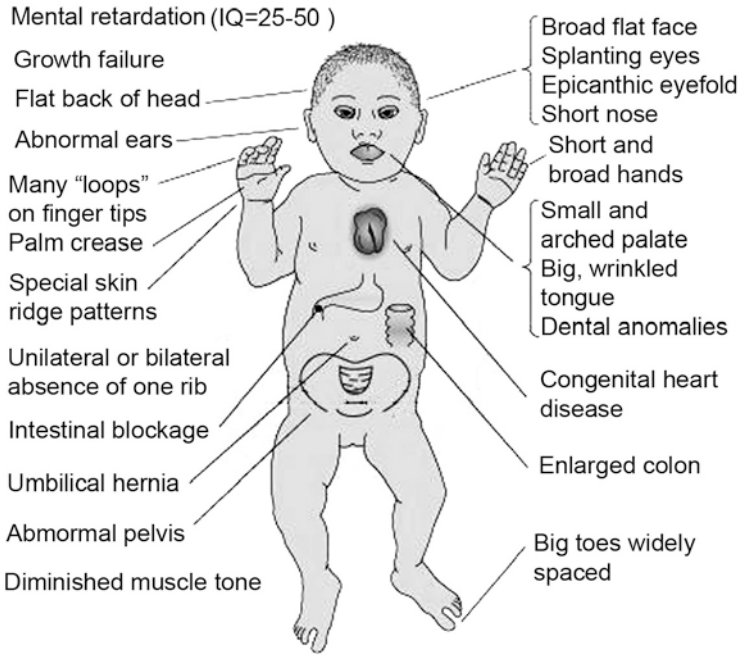
1. Maternal age.

2. Does a couple have a Down baby already?

3. What is the karyotype of the baby (typical trisomy 21 or translocation)?

4. Is one of the parents a translocation carrier?

Prenatal (before a child's birth) diagnosis of the pathology can be made with the chorion villous biopsy or by amniocentesis.



Problem. A woman has 46 chromosomes but has translocation chromosome 21 to chromosome 21. What is the risk of birth of a child with Down`s syndrome in this woman?

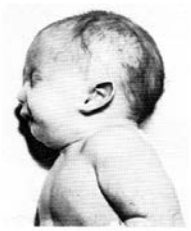
Solving:

EDWARD`S syndrome (Trisomy 18 or E trisomy). It was first described by J.H. Edwards in 1960. Trisomy 18 is the second most common autosomal trisomy among liveborn children after trisomy 21.

It is relatively rare to find a live born trisomy 18 baby. About 95% of the fetuses abort. Those which are born usually do not live beyond a few months. Few may survive to about 15 years. Around 80% of those affected are females.

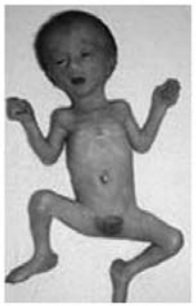
Karyotype: _____

Mental retardation
Growth retardation
Low-set malformed ears
Micrognathia (small low jaw)



Malformed fingers and clenched fists
Abnormal dermatoglyphics
"Simian crease"

Dolichocephaly (prominent occiput)
Congenital heart defects
Congenital defects of visceral organs



High muscle tone
Short sternum
Deformed thigh
Rocker bottom feet

Types of Trisomy 18

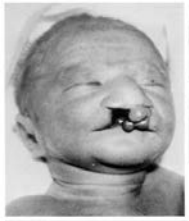
Unlike *full Trisomy 18*, a *mosaic Trisomy 18* is very rare. It occurs when the extra chromosome is present in some of the cells of the body.

Partial Trisomy 18 occurs when only part of an extra chromosome is present. An unaffected person can carry a rearrangement of genetic material between chromosome 18 and another chromosome, i.e., two copies of chromosome 18, plus a "partial" piece of extra material from chromosome 18. This rearrangement is called *a balanced translocation* because there is no extra material from chromosome 18.

PATAU`S syndrome (Trisomy 13 or D trisomy). It was first identified in 1960 by Patau and his colleagues. About half of the live born trisomy 13 babies die within a month.

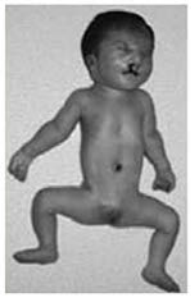
Karyotype: _____

Mental retardation
Growth retardation
Microcephaly
Microphthalmia
Low-set malformed ears
Deafness



Abnormal palm pattern
Malformed fingers and nails
"Simian crease"
Polydactily

Cleft lip and/or cleft palate



Congenital heart defects
Umbilical hernia
Kidney defects
Double ureter

Abnormal genitalia
Prominent heel and rocker-bottom feet

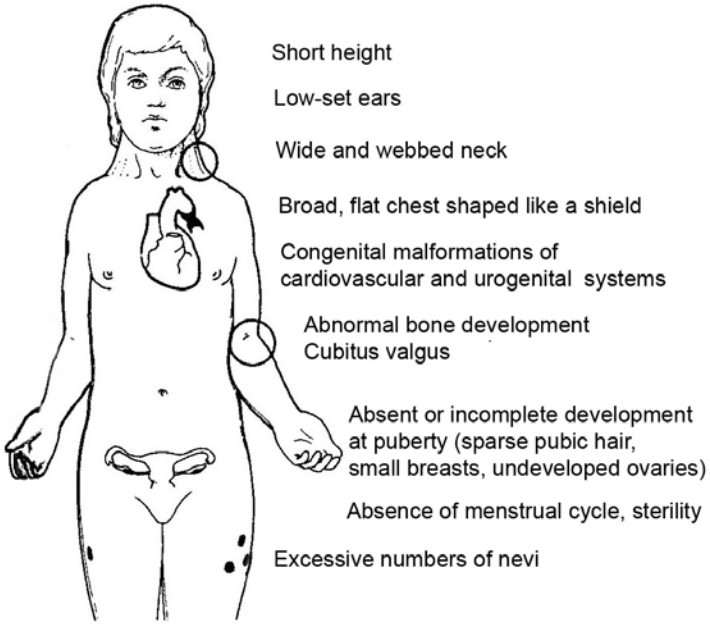
Problem. A woman has 46 chromosomes. There is translocation chromosome 13 to chromosome 2. What is the risk of birth of a child with Patau`s syndrome in such woman?

Solving:

Task 8. SEX CHROMOSOME ABNORMALITIES

TURNER`S syndrome (Ovarian dysgenesis). It is also referred to as X monosomy. It was first described by Turner in 1938. However, the precise nature of cytogenetic abnormality was identified in 1959 by Ford and his colleagues at Harwell.

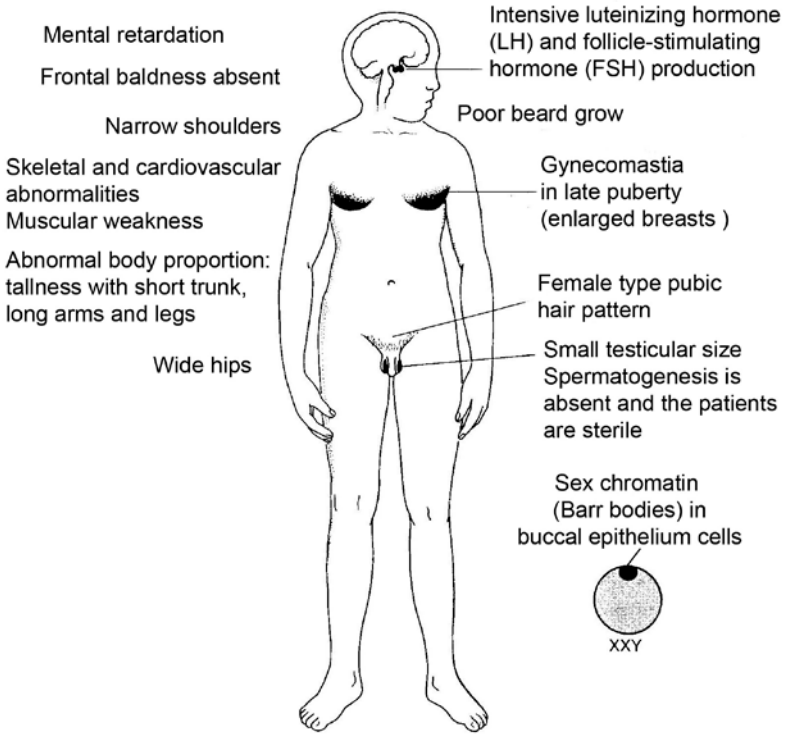
Karyotype: _____



TRIPLE X and other X polysomies. 47, XXX types are usually normal in external appearance, but may be mentally subnormal or psychotic. Whenever they have borne children, all of them have been normal. Patients with four or five X chromosomes are also physically normal but show severe mental retardation.

KLINEFELTER`S syndrome. This condition was first described by Harry Klinefelter in 1942. However, the chromosomal defect was unidentified till 1959. That year Jacobs and Strong found that karyotype of these patients has extra X chromosome.

Karyotype: _____



XYY or JACOB'S syndrome is trisomy due to extra Y chromosome in male karyotype (47, XYY). Frequency is 1 in 1,000. The effect of having an extra Y chromosome in some or all cells varies between individuals. Some correlation has been found between XYY and aggressive, psychopathic or criminal behavior, possibly due to a higher testosterone level. XYY males originate by paternal non-disjunction at the second meiotic division, which produces YY sperm. 48, XXYY and 49, XXXYY males are less common.

Task 9. Study the table and determine human karyotype of the following syndromes.

Type of chromosomal pathology	Frequency of chromosomal disorders in live births	Karyotype
Down`s syndrome	1:700-800	
Edward`s syndrome	1:3000	
Patau`s syndrome	1:15000	
Turner`s syndrome	1:2500 females	
Klinefelter`s syndrome	1:1000 males	
Cri du chat syndrome	1:50000	
Triple-X	1:1200 females	

Task 10. According to the following karyotypes, write the names of diseases and sex of the given organisms.

Karyotype	*Name of disease*	*Sex of organism*
46, XX, del 5p		
47, XY, +21		
46, XY		
47, XXX		
47, XXY		
45, X0		
47, XY, +13		
47, XX, +18		
46, XX/47,XX,+21		

Task 11. Considering the medical situations, solve the genetic problems.
Problem 1. A color-blind man marries to a woman with normal vision whose father was color-blind. They have a color-blind son with Klinefelter syndrome. In which of parents did the non-disjunction occur?

Solving:

Trait	allele	allele location
Healthy		
Color blindness (daltonism)		

Problem 2. Karyotype found in genetic analysis is 47, +21. The phenotype is normal including intellect. How can it be explained?

Problem 3. A couple who has one Down`s child wants to know the probability of birth of a healthy child. What answer one can give? Is it necessary to carry out the additional tests?

_____
_____
_____
_____
_____
_____

Task 12. Study the features of cytogenetic methods.

CYTOGENETIC METHODS

Cytogenetic method includes *karyotyping*, *detection of sex chromatin* and *amniocentesis* (method of prenatal diagnosis).

SEX CHROMATIN. In 1949, a Canadian physician and medical researcher M.Barr with graduate student E.G. Bertram discovered a small chromatin body in the nuclei of female cats' neurones. The chromatin body is also called the ***sex chromatin*** or ***Barr body***.

Sex chromatin is seen as a small chromocentre densely stained with basic dyes in the interphase nuclei. It can be found attached to the nuclear membrane, as in cells of the oral mucosa; and seen as a nuclear expansion, in about 3% of neutrophil leucocytes, forming a small rod called *drumstick*.

The rate, with which the sex chromatin can be detected in females, varies from tissue to tissue. In nervous tissue the rate may be 85%, whereas in whole mounts of amniotic or chorionic epithelium, it may be as high as 96%. In oral smears the rate varies between 20 and 50% in normal females. In normal male the sex chromatin occurs in 0-3 %.

The test for nuclear sex determination includes the detection of drumstick in leucocytes and the Barr body in the cells of the oral mucosa and amniotic fluid. The study of sex chromatin is widely used in medicine. It helps to link certain congenital diseases with sex chromosomal anomalies.

Sex chromatin, or Barr body, is derived from *one of the two X-chromosomes* which become inactivated and condensed. The observations indicated that only one X is active in cellular metabolism; the other X, chosen randomly appearing as the sex chromatin body. In the male, the single X is uncoiled and active for all times, and consequently there is no sex chromatin.

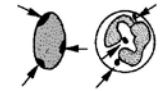
In 1961 Mary Lyon proposed a mechanism for equalizing the gene dosage by inactivation of one of the two X chromosomes in females

A number of Barr bodies is thus one less than the number of X-chromosomes. Thus, at the interphase the number of sex chromatin bodies is equal to ***n(X) – 1***.

Barr bodies are absent in oocytes and female germ cells, and only appear at about the 12th day of gestation in extra-embryonic membranes, and by about the 16th day in embryo cells, with some variation from tissue to tissue.

It has been observed that at the time of cell division one of the X chromosomes completes its replication of DNA later than the other, and is usually located peripherally, in the region of the nucleus where the sex chromatin is found.

Task 13. Study the scheme explaining relationship between the number of X-chromosomes, the number of Barr bodies in cells of the oral mucosa and the number of the drumsticks in the nuclei of neutrophil leucocytes. Fill in the table.

1 X		Normal man (XY) or sick woman with Turner`s syndrom (XO)
2 X		Normal woman (XX) or sick man with Klinefelter`s syndrome(XXY)
3 X chromosomes		Sick woman with Triple X (XXX) or sick man with Klinefelter`s syndrome (XXXY).
4 X		Polysomy (XXXX) or sick man with Klinefelter`s syndrome(XXXXY)

Karyotype	*A number of Barr bodies*
46, XX 46, XY 47, XXY 48, XXXY 47, XXX 45, X0	_____ _____ _____ _____ _____ _____

Task 14. Solve the problem.

Several patients have been prescribed the detection of sex chromatin. Examination of buccal smears revealed the following percentage of Barr bodies. Analyze in what cases can one suspect the pathology.

#	*Patient's sex*	*Percentage of Barr bodies*	*Conclusion*
1	female	35 %	
2	female	0 %	
3	female	13 %	
4	male	50 %	
5	male	0%	
6	male	2 %	

Multiple-Choice Tests for Control of Theme 15

1. The theory that Barr body is an inactivated X-chromosome is
- A. the chromosome theory of inheritance
- B. the cell theory
- C. the evolution theory
- D. the Lyon hypothesis
- E. the cancerogenesis hypothesis

Theme 16: Dermatoglyphics. Methods of prenatal diagnosis. Medical genetic counseling

Objectives: study the method of dermatoglyphics and the principles of medical genetic counseling.

Task 1. Study the features of the method of dermatoglyphics.

DERMATOGLYPHICS

Dermatoglyphics is the study of patterns of the ridged skin of the palms, fingers, soles and toes.

Ridges on the skin of fingers correspond to dermal papillae. Interpapillar deepenings form furrows. On the upper surface of ridges there are sudoriferous glands and in the dermal papillae there are endings of the sensory nerves. The ridge patterns on hands and feet start developing around the 13th week of gestation and are completed by about the 16th week. Formation of dermal relief depends on character of location of nerve fibers. Dermal patterns remain invariable until the end of life. In case of damage of dermal patterns (burning, frostbite, trauma) their graphs are regenerated after a few time like past.

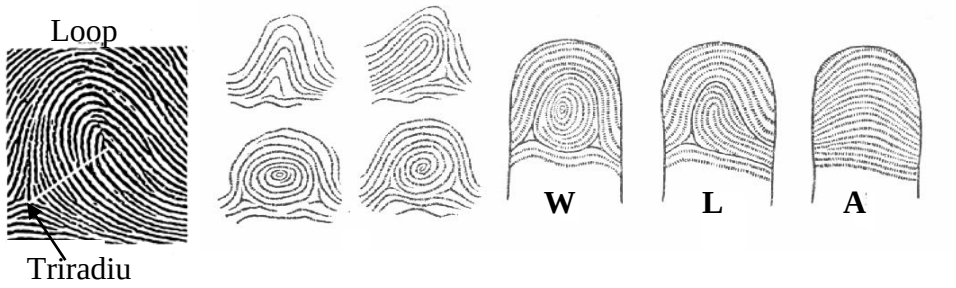
The scientific basis of dermatoglyphics was laid down by F.Galton much earlier. In 1961 Harold Cummins introduced the term "*dermatoglyphics*".

The patterns studied are:
1. The flexion creases of the palm.
2. Dermal patterns:
   a) Fingerprints
   b) Palmar patterns
   c) Plantar patterns.

The flexion creases, referred to as heart, head and life lines in palmistry form during the same period as dermal ridges. About half the Down`s syndrome patients show a unique feature, i.e. single transverse crease on palm, called *simian crease*. However, simian crease in place of the usual two creases is also found in 1% of Caucasians and in a larger percentage of Asiatics.

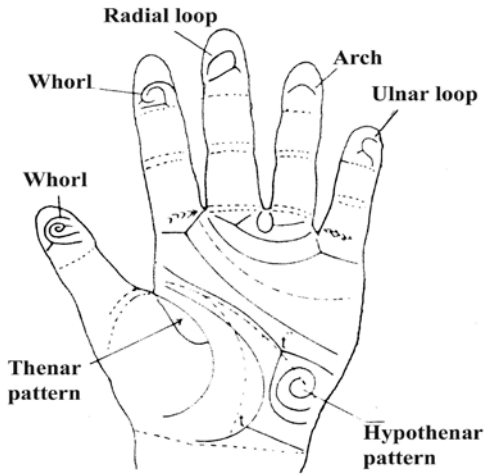
Fingerprints.

According to F.Galton`s system the fingerprints can be classified into three basic patterns - arches, loops and whorls. This classification is based on a number of triradii. A triradius is a point from which three ridge systems course in three different directions at angles of about 120˚.



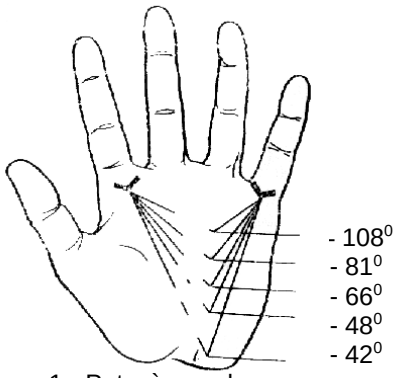
Arch has no triradius, loop has one and whorl has two triradii. Loops are further subclassified as radial or ulnar loops. It depends upon whether the loop opens on the radial or ulnar side of the finger. Archs occur 6%, loops - 60% and whorls - 34%.

The size of a finger pattern is expressed as the **ridge count**, i.e. the number of ridges that come across a line drawn from the triradial point to the pattern core. An arch has a count of zero, as it has no triradius. The **total ridge count** (TRC) of the 10 digits is used as a dermatoglyphic parameter. In men total ridge count is 144.98 ±51.08, in women – 127.23 ± 52.51.



Palmar patterns.

The four digital triradii, near the distal border of the palm and an axial triradius, commonly placed over the fourth metacarpal near the base of the palm, provide the landmarks for palmar patterns. Normally, the axial triradius is situated near the base of the palm, somewhere along the fourth metacarpal. It is displaced distally in Down`s syndrome and other chromosomal disorders. Its location is measured as the "*atd* angle" or in terms of the total length of the palm.

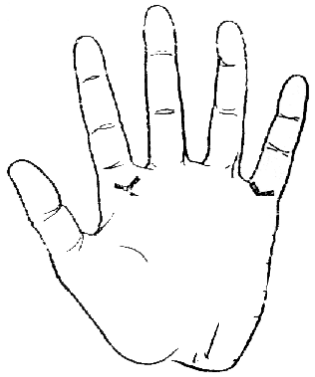


1 - Patau`s syndrome;
2 - Down`s syndrome;
3 - Turner`s syndrome;
4 – normal;
5 -Klinefelter`s syndrome

And *atd* angle greater than 57˚ is more common in patient with Down`s syndrome and several other chromosomal syndromes than in the general population.

In a normal palm the ridges commonly course obliquely towards the proximal portion of the ulnar side. Interdigital patterns of loops or whorls are formed, if the recurving ridges are present between the digital triradii. Hypothenar and thenar patterns may be present.

Task 2. Study the dermal patterns of your own palms. Find triradii **a**, **b**, **c**, **d** and axial triradius **t**. Plot the **atd** angle and determine its quantity. This angle is not more than 57° in norm.



Task 3. Determine the types of your fingerprints and write them in the notebook. Remember that in a fingerprint formula, the patterns are conventionally listed as:

left 5, 4, 3, 2, 1; right 1, 2, 3, 4, 5.

Example of fingerprint formula: Left $L^uL^uW\ L^rA$
Right $L^uL^uW\ L^uL^r$

Left ___ ___ ___ ___ ___

Right ___ ___ ___ ___ ___

Task 4. Study the table below

Characteristic dermatoglyphic patterns seen in some chromosomal abnormalities

Chromosomal abnormality	*Karyotype*	*Changes of dermatoglyphics*
Trisomy 13	47, +13	Many arches. Low TRC. The atd angle is 108˚. Single flexion crease. Thenar pattern.
Trisomy 18	47, +18	6-10 arches (also on toes). Very low TRC. Single flexion crease.
Down`s syndrome	47, +21	Many ulnar loops (usually 10). Radial loop on 4th and/or 5th digits. The atd angle is 81˚. Single flexion crease. Low TRC.
Cri du chat syndrome	46, del 5p	Many arches. Many whorls. Low TRC. Single flexion crease.
Klinefelter`s syndrome	47, XXY	Many arches. Low TRC. Axial triradius slightly more proximal (42˚).
Turner`s syndrome	45, X0	Large loops or whorls. High TRC.Axial triradius slightly more distal (60˚).
Trisomy X	47, XXX	Increase frequency single flexion crease. Many loops and whorls. Low TRC.

Task 5. Pay attention: in some cases the genetic heterogeneity can exist.

Genocopy – a trait that is a phenotypic copy of a genetic trait but is caused by other different genetic mechanism (other gene).

A genotype at one locus that produces a phenotype which at some levels of resolution is indistinguishable from that produced by another genotype; e.g., two types of elliptocytosis that are genocopies of each other, two types of *hemophilia (A and B)* and *talassemia (α-* and *β-forms)*.

Phenocopy – an environmentally induced, nonhereditary variation in an organism, closely resembling a genetically determined trait.

A phenocopy is an individual whose phenotype (generally referring to a single trait), under a particular environmental condition, is identical to the one of another individual whose phenotype is determined by the genotype. In other words, the phenocopy is environmental condition that mimics the phenotype produced by a gene.

An example of a phenocopy is a baby's cleft palate due to mother' syphilis infection unlike the cleft palate due to Patau's syndrome.

Task 6. PRENATAL DIAGNOSTIC TESTS

Prenatal diagnosis employs a variety of techniques to determine the health and condition of an unborn fetus. There are a variety of *non-invasive* (e.g., ultrasonography) and *invasive* (e.g., amniocentesis, chorionic villus sampling, fetal blood cells in maternal blood etc.) techniques available for prenatal diagnosis. Each of them can be applied only during specific time periods during the pregnancy for greatest utility.

1. Transabdominal amniocentesis (also referred to as **amniotic fluid test or AFT**). It is one of the prenatal diagnostic procedures with wide applications.

Specifically, the test is helpful:

1. If one of the parents is a balanced translocation carrier.

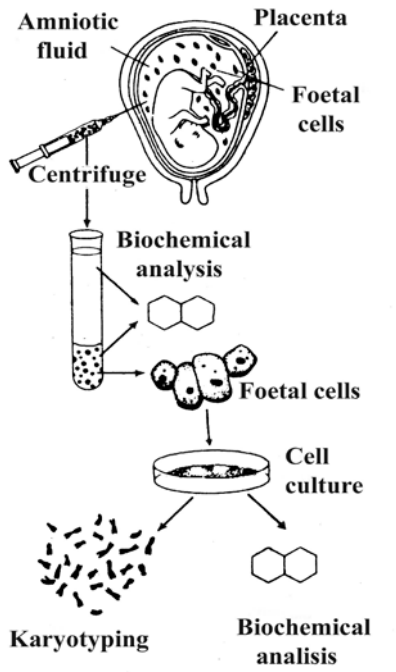
2. In case of an autosomal or X-linked recessive metabolic disorder which is severe but detectable prenatally.

3. Maternal age above 35/40 years.

4. Couple already has one child with a neural tube defect.

The ideal time to undertake this test is between 14-16 weeks when a sufficient amount of amniotic fluid is available for tapping, without harming the conceptus. This also ensures relatively easier acceptance of termination of pregnancy with an unfavourable outcome of amniocentesis results, around 18 weeks or so. Beyond this time, the patient`s attitude towards termination of pregnancy alters because the fetal movement starts.

Under an ultrasound control placental localization is done. Then under local anaesthesia the fluid is tapped per abdomen avoiding injury to the placenta. About 10-20 cc of fluid is taken out and is subjected to analysis in the laboratory. The cells and fluid are separated by centrifugation. The cells can be studied directly or subjected to culture studies for obtaining a fetal karyotype.



The fluid component is subjected to biochemical analysis for estimation of various ingredients.

The results of the culture study take about 2-3 weeks or may be more. The risk involved in amniocentesis are abortion (less than 1% now), amnionitis, foetal puncture, amnionitic fluid leakage and maternal vaginal bleeding.

2. Chorionic villus sampling (CVS) is done between 10 and 12 weeks with a higher risk than for amniocentesis (1/100 risk of miscarriage). The procedure is usually done though the vagina and cervix but can be done transabdominally.

A piece of the chorionic villi is removed and the maternal cells dissected away. (Even so there always is a chance of maternal cell contamination, however, cytogeneticists have methods for detecting it). A direct cell preparation can give preliminary results since there are many dividing cells in this tissue. However, the CVS cells are also cultured and examined as is done for amniotic fluid cells. CVS tissue is extra embryonic and the selection against chromosome abnormalities is not so great, therefore, one often sees confined placental mosaicism (CPM).

Task 7. Write the goal of medical genetic counseling, its tasks and stages.

The goal of medical genetic counseling

Tasks of medical genetic counseling

Stages of medical genetic counseling

1. *Diagnostics*

2. *Prognosis*

3. *Documentation of the counseling session*

4. *Genetic counselor's advice* (specific medical recommendations)

Multiple-Choice Tests for Control of Theme 16

1. The scientific study of fingerprints is called
A. criminalistics
B. printology
C. dermatoglyphics
D. detectology
E. genealogy

2. Everything is the stages of medical genetic counseling, ***except***
A. diagnostics
B. prognosis
C. treatment
D. documentation
E. recommendation

Date	Signature

Theme 17: Population genetics. Hardy – Weinberg law

Objectives: study modern concept of evolution; explore the laws carried out on population level; analyze the significance of Hardy – Weinberg law for research of human populations.

Population Genetics **deals with the study of genes in population.** It also tells us about how distribution of genes and the genotypes are maintained or changed in population. The change in the gene and genotype frequencies is the basis of evolution. The population genetics restricts itself to the study of one species, while evolution encompasses many of them. Population genetics and evolution are together designated as ***evolutionary genetics.***

Task 1. Give definition of *population* and *genetic pool*. Write the characteristics of population.

Population is a group of individuals of a species living in a particular geographic area and interbreeding in nature.

Characteristics of population:

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

Gene pool _____
_____
_____
_____

_____
_____

Task 2. **Genetic structure of a population includes:**

1. _____
2. _____
3. _____
4. _____
5. Factors, which change the gene pool of population:

a. _____
b. _____
c. _____
d. _____
e. _____

Factors influencing equilibrium of allele frequencies

The Hardy-Weinberg equilibrium is altered if there is **non-random mating**. Random mating (panmixis) ensures that the frequencies of the different kinds of mating are determined only by the relative frequency of the genotypes in the population. In practice, the requirement of random mating is not commonly fulfilled. The preferential selection of a mate with a particular genotype is common and such a mating is referred to as **assortative,** or **nonrandom, mating**. Consanguineous mating is a special form of assortative mating. It disturbs the Hardy-Weinberg equilibrium by reducing the heterozygotes and thus increasing the proportion of homozygotes.

Mutation is another factor disturbing the Hardy-Weinberg equilibrium. Mutation usually causes loss or change of function of a gene. The spontaneous mutations occur with a frequency ranging from 1 in 10,000 to 1000000 per locus per generation. An average rate of mutation is about 1 in 100000.

Natural selection is an important factor operative in evolution. The Darwinian theory of biological fitness is considered to be the relative

ability of an organism to survive and transmit its genes to the next generation. It is determined by the number of offspring who reach reproductive age. Fitness is unity (or 100 per cent) if a person has at least two such offspring. In the modern era, survival of the fittest is interpreted as operative through the action of selection upon new genotypes, which have arisen by mutation or recombination. Autosomal dominant genes are always expressed and are exposed to the scrutiny of selection, in contrast to autosomal recessive genes. As a result, the effects of selection are more obvious and can be more readily measured for dominant genes than for recessive ones.

Genetic drift. This involves a variation in the number of children produced by individuals having different genotypes. This does not affect gene frequencies in large populations but in small isolated populations this alters gene frequencies and disturbs the Hardy-Weinberg equilibrium.

Migration and miscegenation. Mass migration of people into new territories would bring them in contact with diverse populations resulting in an exchange of genes between two groups. This is called ***gene flow***. For example the frequency of the gene responsible for *B* blood type is above 25% in Asiatic countries; however as we move westward, it decreases. In Scandinavia it is less than 10 %. This has been explained by the migration of Mongoloids towards the west from 500 AD to 1500 AD.

Task 3. Hardy – Weinberg law

Study Hardy – Weinberg law and its significance for medicine.

Known phenotypes can lead us to knowing the related genotypes, from which the frequencies of different alleles in a given population can be readily ascertained on the basis of the **HARDY-WEINBERG LAW**. It was put forward independently by an *English mathematician, G.H. Hardy*, and a *German physician, W. Weinberg*, in 1908.

The law states that **"*gene frequencies in a population remain constant from generation to generation, if no evolutionary factors such as migration, mutation, selection and drift are operating*".** The law provides a simple algebraic formula to calculate expected gene and genotype frequencies in population.

Population genetics using Hardy – Weinberg law can ascertain the distribution of hereditary diseases, ratio of homozygotes and heterozygotes for pathological gene in the population. That is important for prophylaxis of hereditary diseases.

GENE FREQUENCIES IN POPULATION

A number of organisms having certain allele is determined by frequency of this allele in given population. Gene frequencies are expressed as fractions of unity. For example, in human a frequency of a dominant allele responsible for normal pigmentation of skin, hair and eyes is 0.99 (99%). Frequency of recessive allele responsible for absence of pigmentation (albinism) is 0.01 (1%). Total frequency of alleles in given population is 1 (100%). Assuming frequencies as p and q, $p + q = 1$. It means that knowing of frequency of one allele allows to determine frequency of other ($p = 1 - q$; $q = 1 - p$).

GENOTYPE FREQUENCIES IN POPULATION

If we consider a system of two alleles ***A*** and ***a*** with frequencies ***p*** and ***q***, respectively, there is a possibility of genotypes, **AA**, **Aa** and **aa**. The genes **A** and **a** occur with the same frequency in sperm and ova. The frequencies of offsprings from such mating would be $\mathbf{p^2}$ (AA), **2pq** (Aa) and $\mathbf{q^2}$ (aa) (Fig. 1).

Gametes		Sperms	
		(p)A	(q) a
Ova	A(p)	(p^2) AA	(pq)Aa
	a(q)	(pq)Aa	(q^2)aa

Fig.1. *Gametic combinations in the two allele system of A and a. Gene frequencies are given in parenthesis.*

If these progeny were to mate with each other the resultant would be as follows:

Mating type	Frequency	Offspring		
		AA	Aa	aa
AA × AA	p^4	p^4	-	-
AA × Aa	$4p^3q$	$2\ p^3q$	$2\ p^3q$	-
Aa × Aa	$4p^2q^2$	p^2q^2	$2\ p^2q^2$	p^2q^2
AA × aa	$2p^2q^2$	-	$2\ p^2q^2$	-
Aa × aa	$4pq^3$	-	$2\ pq^3$	$2\ pq^3$
aa × aa	q^4	-	-	q^4

If we sum up the various types of offsprings:
Total of ***AA*** offsprings: $p^4 + 2\ p^3q + p^2q^2 = p^2\ (p^2 + 2pq + q^2)$
Total of ***Aa*** offsprings: $2\ p^3q + 4\ p^2q^2 + 2\ pq^3 = 2pq\ (p^2 + 2pq + q^2)$
Total of ***aa*** offsprings: $p^2q^2 + 2\ pq^3 + q^4 = q^2\ (p^2 + 2pq + q^2)$

Eliminating the common factor $(p^2 + 2pq + q^2)$ the proportions of genotypes, AA, Aa and aa appear to be the same, $p^2 : 2pq : q^2$ as the previous generation. The result would be the same if we continue to calculate for many generations. This clearly indicates that the gene and genotype frequencies are maintained from generation to generation. With the help of this formula one can calculate frequencies of various genotypes if the frequency of one of the homozygote is known. If the frequency of an autosomal recessive trait is 1 in 10,000

$$q^2 = 1/10000,\ q = 1/100 \text{ and } p = 1 - 1/100 = 99/100.$$

The frequency of carrier - $2pq = 2 \times 99/100 \times 1/100 = 1/50$. From this example we learn that the frequency of carriers in population is much more than affected individuals.

Thus Hardy – Weinberg law lets find _____
_____
_____
_____

Task 4. Mathematical formulas of Hardy – Weinberg equilibrium are:

$$p\ (A) + q\ (a) = 1$$

where ***p*** – _____

q – _____

$$p^2\ (AA) + 2pq\ (Aa) + q^2\ (aa) = 1$$

where p^2 – _____

$2pq$ – _____

q^2 – _____

Task 5. Summarize the theoretical material of Task 2 and Task 3 and characterize real and ideal populations

Ideal population	Features	Real populations
	Population size	
	Crossing (mating)	
	Mutations	
	Migration	

Task 6. Solve the genetic problems.

Problem 1. Rhesus factor system is controlled by gene RHD on chromosome 1. The gene has two alleles: dominant Rh(+) and recessive Rh(-). The rate of the dominant alleles is 0.57 in Ukrainians (*Nazarova A.F., Altukhov S.M., 1999*). Calculate the rate of the recessive allele and the recessive genotype in Ukrainians.

Solving:

Trait	Allele	Frequency
Rhesus-positive		
Rhesus-negative		

Problem 2. In Nigerian population the frequency of allele *M* of *MN* blood group is 0.548 (*W.Boyd, 1950*). Calculate the frequency of allele *N* and genotype frequencies of *MN* blood system.

Solving:

Trait	Allele	Frequency
Blood group M		
Blood group N		
Blood group MN		

Problem 3. Sixteen percent of the human population is known to be able to wiggle their ears. This trait is determined to be a recessive gene. Calculate the frequency of the dominant allele and dominant phenotype.

Solving:

Trait	Allele	Frequency
Inability to wiggle ears		
Ability to wiggle ears		

Problem 4. In a population, the frequency of brown-eyed people accounts for 51 %. Determine the genetic structure of the population.

Solving:

Trait	Allele	Frequency
Brown color of eyes		
Blue color of eyes		

Problem 5. Rh-positivity is dominant over Rh-negativity. Among Turkmens Rh-positive people make up 95% (*Nazarova AF, Altukhov SM, 1999*). Determine the percentage of Rh-negative allele.

Solving:

Trait	Allele	Frequency
Rhesus-positive		
Rhesus-negative		

Problem 6. Tay-Sachs disease is an autosomal recessive disease that affects 1 in 3600 from Central European Jewish. Determine the frequencies of the pathological and normal alleles in the population.

Solving:

Trait	Allele	Frequency
Healthy		
Tay-Sachs disease		

Problem 7. *Fanconi anaemia* is a rare autosomal recessive blood disorder that leads to bone marrow failure and variety of congenital malformations. In the Afrikaans population of South Africa the frequency of the disease is 1: 22000 – the highest frequency in the world (*Rosendorff et al., 1987*).

Calculate a number of heterozygous carriers in a city with a population of 2 million people

Solving:

Trait	Allele	Frequency
Healthy		
Fanconi anaemia		

Problem 8. *Congenital dislocation of the hip* is inherited as autosomal dominant trait with 25% of penetrance. The disease occurs with frequency 7/2000 in Aseer region of Saudi Arabia (*T. Mirdad, 2002*).

Calculate a number of recessive homozygotes per 10000 persons in the population

Solving:

Trait	Allele	Frequency
Congenital dislocation of the hip		
Healthy		

Multiple-Choice Tests for Control of Theme 17

1. Members of the same species which are capable of interbreeding is best described as a(n):

A. biosphere
B. ecosystem
C. community
D. population
E. system

2. Frequency of any heterozygous genotype is

A. product of allele frequencies
B. product of squared allele frequencies
C. 2 × product of allele frequencies
D. 2× sum of allele frequencies
E. sum of allele frequencies

3. According to Hardy-Weinberg, if the frequency of gene ***A*** is **26**%, the frequency of gene ***a*** is

A. 26%
B. 50%
C. 52%
D. 64%
E. 74%

Date	Signature

GENETIC PROBLEMS TO THEME 17 FOR SELF-WORK

Problem 1. *Phenylketonuria (PKU)* is an autosomal recessive disease. The incidence rate of it in Belarus is 1 : 6000. Determine the genetic structure of the populations.

Solving:

Trait	Allele	Frequency
Healthy		
Phenylketonuria		

Problem 2. In Iraqi population, 92% of people are Rh-positive (*M.S Jaff, 2010).* Calculate the percentage of heterozygous males in Iraqi population.

Solving:

Trait	Allele	Frequency
Rhesus-positive		
Rhesus-negative		

Problem 3. *Podagra (gout)* occurs in 8% of people. It is autosomal dominant trait, which does not manifest in women. In men podagra manifests with 20% of penetrance. Determine the genetic structure of the population.

Solving:

Trait	Allele	Frequency
Podagra		
Healthy		

Theme 18: Biological features of human reproduction. Gametogenesis. Features of human development. Biological mechanisms of homeostatic maintenance in living organisms

Objectives: to explore the cytogenetic mechanism of reproduction; to investigate the structure and formation of gametes, features of fertilization; to study the features of human prenatal development and biological importance of genetic control of organism development; to study the crucial periods of human embryogenesis and their relationship with teratogenic birth defects; to explore the features of postnatal ontogenesis; to learn to interpret the modern theories and mechanisms of aging, problems of human longevity; and determine the types of regeneration and its significance for homeostasis; to be able to classify the types of tissue transplantation and to correlate the transplantation process with the immunity system.

Task 1. Give the definition of "ontogeny". Characterize the ontogeny periods of human development.

Ontogenesis – _____
_____
_____
_____

Period	***Characteristics***
embryonic	
postembryonic	

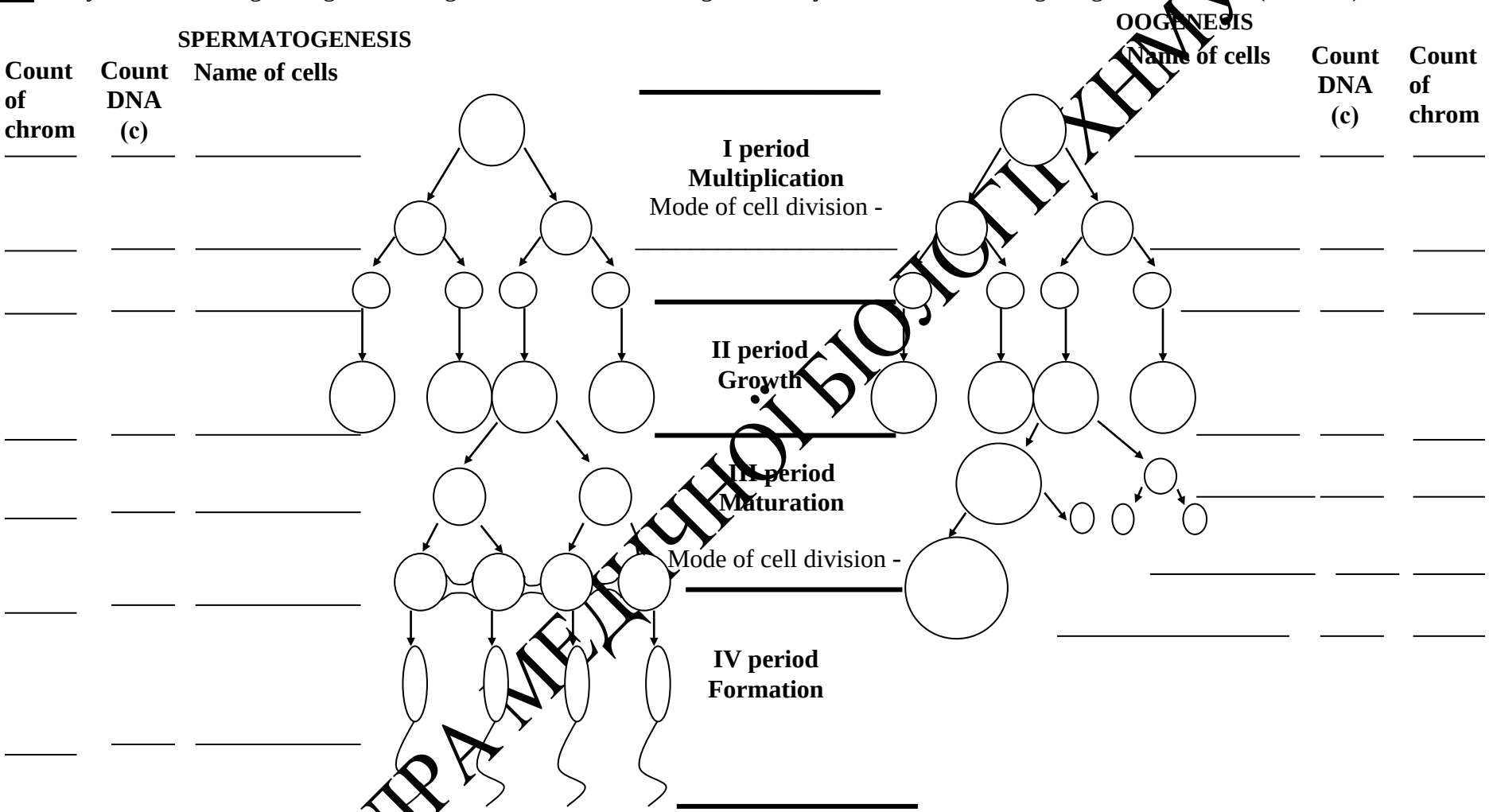
Task 2. Give the definition of *reproduction*, sexual reproduction. Write down the characteristics of sexual reproduction, explaining its significance.

Reproduction – _____
_____
_____
_____

Sexual reproduction: _____
_____
_____
_____
_____

Biological significance of sexual reproduction _____
_____
_____
_____
_____
_____

Task 3. Study the scheme of gametogenesis using the table. Make the designation. Pay attention to the change of genetic material (2n → 1n).



Spermatogenesis	Oogenesis

Task 4. Examine the spermatozoa of guinea-pig under the microscope. Study the structure of spermatozoon and make designations.

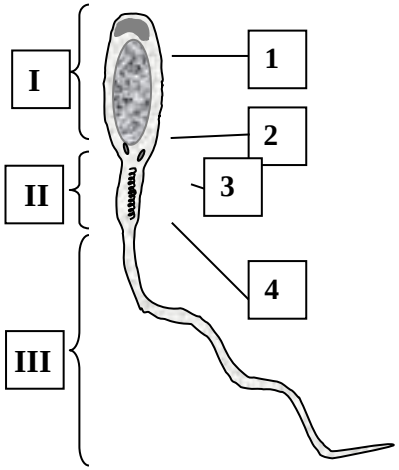


Fig. 1. *Structure of spermatozoon*.

I - _____
1- _____
2- _____
II - _____
3- _____
4- _____
_____
III - _____

Task 5. Examine a section of the mammalian ovary with the microscope. Study structure of ovum and make designations.

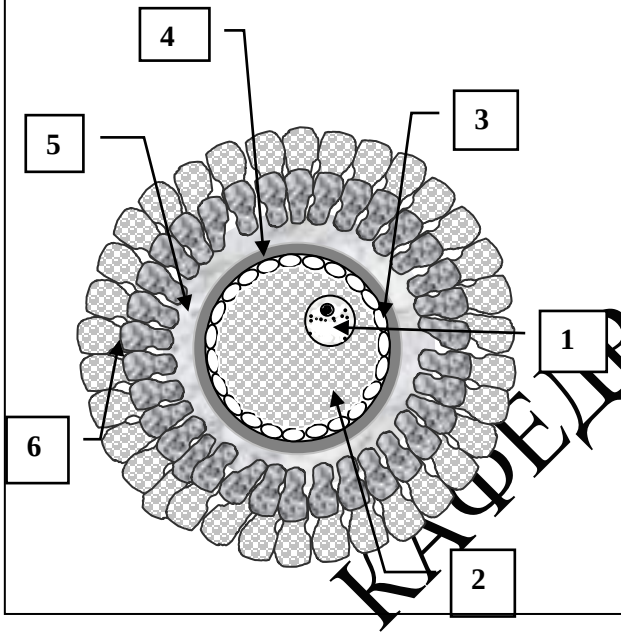


Fig. 2. *Structure of ovum.*

1- _____
_____
2- _____
_____
3 _____
_____
4- _____
_____
5- _____
_____
6- _____
_____

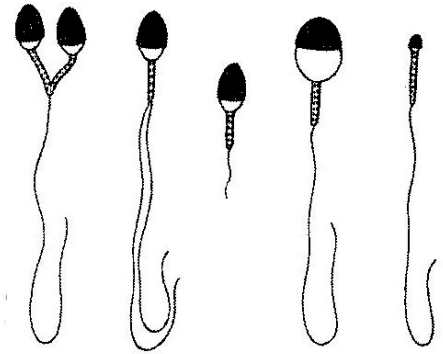
Features of gametogenesis in man

_____
_____
_____
_____
_____

Clinical consideration

In a healthy man both normal and structurally abnormal spermatozoa are present but the quantity of latter is not more than 20-25%. The head or the tail may be abnormal; spermatozoa may be giants or dwarfs; and sometimes they are joined. Sperm with morphologic abnormalities lack normal motility and probably do not fertilize oocytes. Exceeding of this number can result in male sterility or in congenital malformations of a fetus.

Pathology in sperm structure



Features of gametogenesis in woman

_____
_____
_____
_____

Task 6. Give the definition "*fertilization*", study the scheme of fertilization (Fig. 3), and describe the fertilization stages.

Fertilization – _____
_____
_____
_____

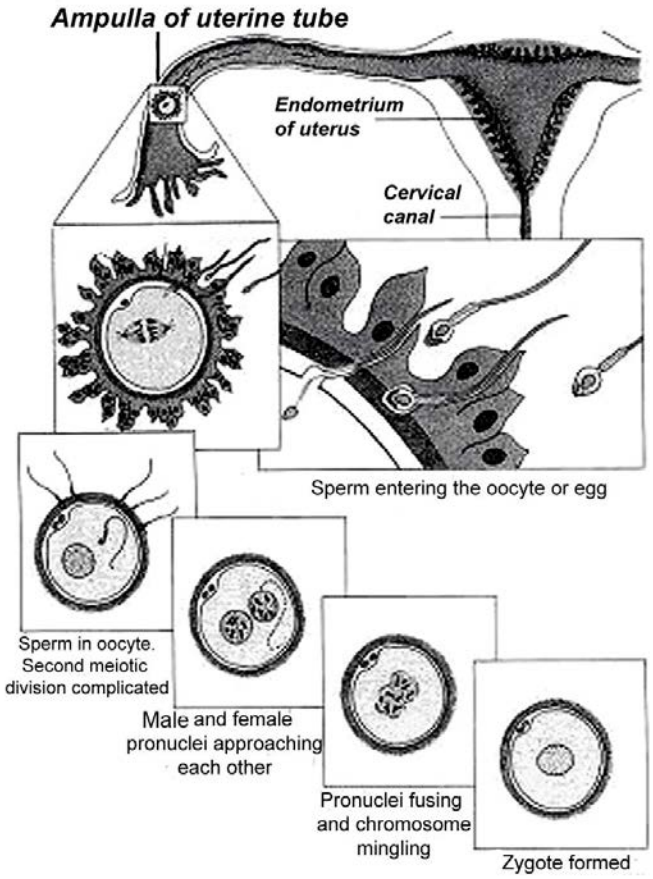


Fig 3. *Scheme of fertilization: events that lead to formation of zygote.*

1. Distant interaction _____
_____
_____
_____
_____
_____
_____

2. Contact interaction _____
_____
_____
_____
_____
_____
_____

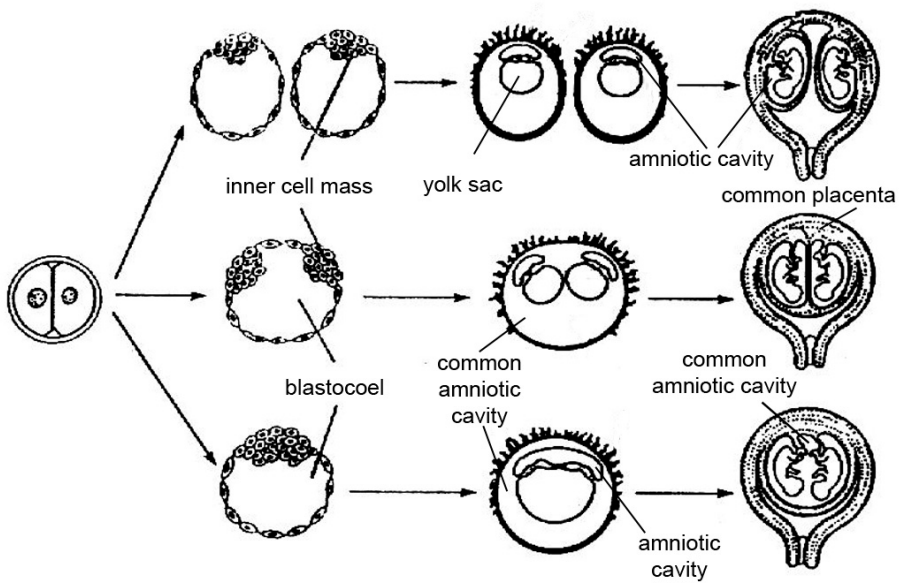
3. Sperm entering the oocyte and cortical reaction _____
_____
_____
_____
_____
_____
_____

Task 7. **Twins in animal biology** is a form of multiple births in which the mother gives birth to two offspring from the same pregnancy - some of the same gender, others of opposite. Giving birth to twins is a relatively rare event in humans, where occurrences vary considerably across populations. The human female usually has a single baby in each pregnancy; but one in 90 pregnancies is a twin pregnancy; one in 8100 pregnancies is a triplet pregnancy; and one in 729000 pregnancies is a quadruplet pregnancy.

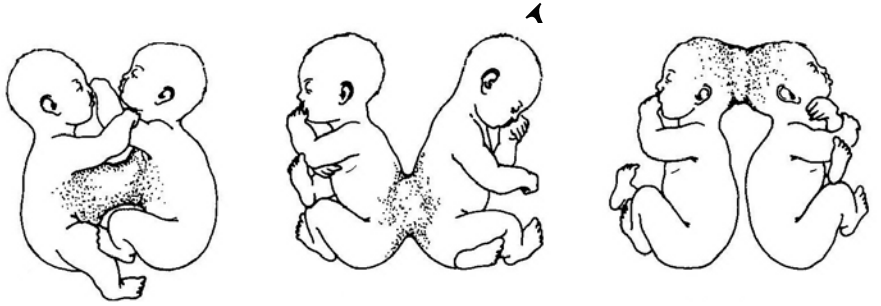
Dizygotic twins occur when two eggs are released at a single ovulation and are fertilized by two different sperm and their incidence of 7 to 11 per 1000 births increases with maternal age. These two fertilized eggs then implant independently in the uterus. Dizygotic twins share the same type of genetic relationship as non-twin siblings, hence the term *fraternal.* Approximately two-thirds of twins are dizygotic.

Monozygotic twins develop when a single egg is fertilized by a single sperm and, at some stage in the first two weeks after conception, the developing embryo *splits into two* (or rarely more). As a result, two, *genetically identical* babies develop.

Study the scheme of development of monozygotic twins



At later stages of development (after 13th day), partial splitting of the primitive node and streak may result in formation of *conjoined* **(***Siamese***)** *twins***.**



Frequency of twinning in human population

There is variation in the frequency of twinning among human populations. In general, the rate is high among people of African origin, intermediate among Europeans and low among most Asiatic populations. East Asian populations have the lowest rate (3-4 per 1000), Sub-Saharan populations have the highest (at least 16, up to 40-50 per 1000), and European and Middle Eastern populations have an intermediate (8-14 per 1000) frequency of twins. In Europe, a progressive increase has occurred in the twinning rate from south (Spain) to north (Norway, Denmark, and Netherlands).

The suggestion of a genetic cause for population differences in twinning rates appeared to be bolstered by reports that admixed New World populations have twinning rates intermediate between those of their parental populations. For example, in the USA, populations of African ancestry have higher frequencies of twinning than do those of European origin, although lower than those reported in Africa. Specifically in the U.S., “Blacks” have a frequency of 12.5 and 13.2, and “Whites” of 10.1 and 10.05.

The birthrate of monozygotic (MZ) twins is constant world wide (~ 4 per 1000 births). Birth rates of dizygotic (DZ) twins vary by race. The highest birth rate of DZ twinning occurs in African nations, and the lowest birth rate of DZ twinning occurs in Asia. The Yorubas of western Nigeria have a birth rate of 45 twins per 1000 live births, and approximately 90% are dizygotic.

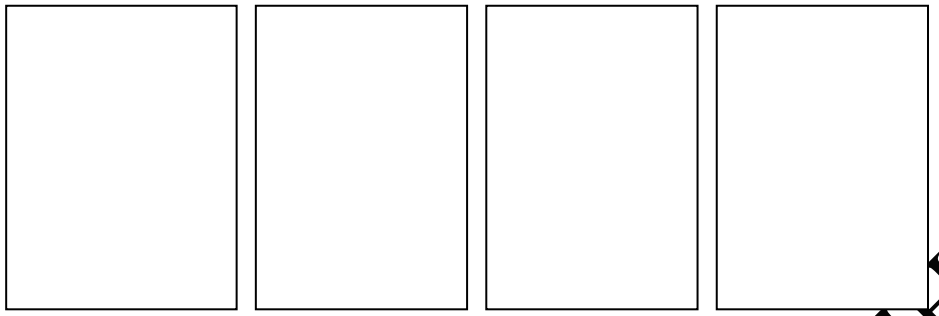
Task 8. Record the order of stages and events of embryonic period.

The zygote → _____ → _____ → _____

→ _____ → _____ → _____.

Task 9. Sketch out the main types of cell movements in gastrulation.

Main types of cell movements in gastrulation



Invagination **Epiboly** **Delamination** **Immigration**

Task 9. Give the definition of the terms *histogenesis*, *organogenesis*, *germ layers*. Fill in the table, indicating examples of tissues and organs that the germ layers form.

Histogenesis – _____
_____
_____

Organogenesis – _____
_____
_____

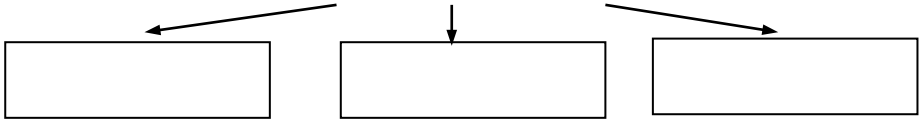
Germ layers – _____
_____
_____

Germ layer	***Derivatives of germ layers***
Ectoderm	
Entoderm	
Mesoderm	

Task 10. Give the definition of *teratogenesis* and examples of teratogenic effects.

Teratogenesis – _____
_____
_____
_____

Teratogenic influences



_____ _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

_____ _____ _____

Task 11. Give the characteristics and examples of *birth defects*.

Birth defect is a widely-used term for a structural malformation of a body part, recognizable at birth, which is significant enough to be perceived as a problem.

About 2-3% of babies are born with significant congenital birth defects. By organ system, birth defects involving brain are the largest group at 10 per 1000 live births), compared to heart at 8 per 1000, kidney at 4 per 1000, and limbs at 2 per 1000. All other defects have a combined incidence of 6 per 1000 live births.

CLASSIFICATION OF BIRTH DEFECTS

Classifi-cation (according to)	The type of birth defect	Characteristics
etiology	inheritable	
	exogenous	
	multifactorial	
stage of manifestation	gametopathy	
	blastopathy	
	embryopathy	
	fetopathy	
order of formation	primary	
	secondary	
spread and localization	isolated	
	systemic	
	multiple	
degree of severity	lethal	
	moderate severity	
	minor anomaly of development	

Task 12. Study the table "Stages of postnatal period in human ontogenesis".

Stage	Age
Neonatal stage	The first four weeks after birth
Infancy	From 10 days to 12 months
Childhood • early childhood • late childhood	From 12 months to 3 years From 4 to 11 or 12 years
Puberty	From 13 to 16 years (for boys) From 12 to 15 years (for girls)
Adolescence	From 17 to 21 years (for male) From 16 to 20 years (for female)
Adulthood	From 22 to 60 years (for male) From 21 to 55 years (for female)
Senescence • early senescence • late senescence	From 61 to 74 years (for male) From 56 to 74 years (for female) From 75 to 90 years (for male and female)
Long-lived people	90 years and older

Task 13. Give the definition of the term "*growth*". Study the mechanisms of growth.

Growth – _____
_____
_____
_____

Mechanisms of growth

1. _____
_____

2. _____
_____

3. _____
_____

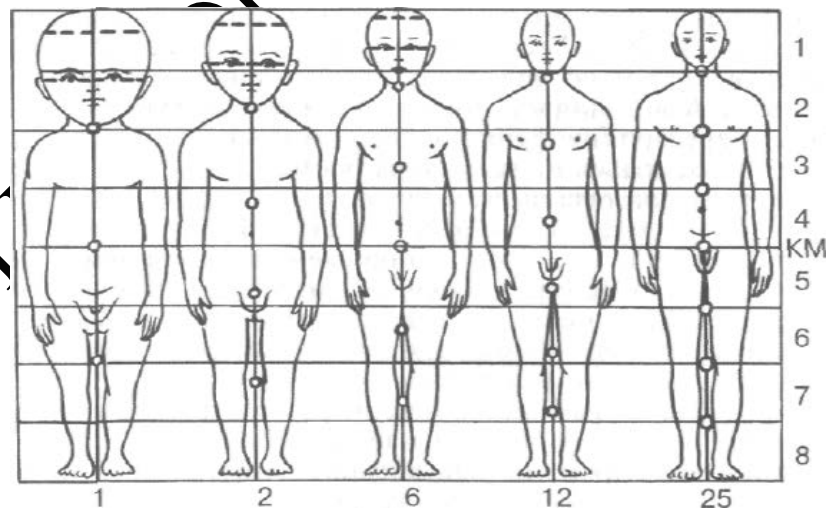


Fig. 1. The characteristic age changes of body proportions in process of human growth. KM is a middle line. The numbers on the right show correlation of human body parts among from baby to adult, the numbers down are age.

<u>Task 14.</u> Critical periods of human development

A *critical period* is time during an organism's life span when it is more sensitive to environmental influences or stimulation than at other times during its life.

Fill in the table.

Critical period	*Term*	*Characteristics*
Fertilization		
Implantation	6th to 8th day	
Gastrulation	beginning of 2nd week	
Differentiation of germ layers	3nd week	
Differentiation of axial organs	3d to 8th weeks	
Placentation	15th to 20th weeks	
Organogenesis	20th to 24th weeks	
Neonatal stage	Birth and 1-10 days of life	
Infancy	3 to 6 months	
Early childhood	1 to 2 years	
Late childhood	6 years	
Puberty period		

Task 15. Write down the features of puberty period.

_____
_____
_____
_____
_____
_____
_____
_____

Task 16. Point out optimum human age for birth of children.

For man	For woman

Task 17. Study the Tables 1 and 2. Analyze age-related risk of birth of child with the inherited pathology. Write the conclusion.

Table 1

Average age of fathers of newborns with gene diseases

Diseases	Father's age (years)	
	proband	control
Marfan syndrome	36.6	29.8
Neurofibromatosis, type 1	34.2	30.7
Achondroplasia	36.4	29.9

Table 2

Average age of mothers of newborns with chromosome diseases

Maternal age (years)	Autosomal aneuploidy			Sex chromosome aneuploidy		
	Down's +21	Edward's +18	Patau's +13	Triple X XXX	Kleinfelter XXY	Turner's X0
35	0.35	0.07	0.05	0.07	0.09	0.05
36	0.57	0.08	0.03	0.08	0.08	0.1
37	0.68	0.09	0.03	0.07	0.04	0.06
38	0.81	0.15	0.04	0.08	0.08	0.08
39	1.09	0.19	0.06	0.12	0.16	0.03
40	1.23	0.25	0.12	0.06	0.15	0.04
41	1.47	0.36	0.17	0.15	0.29	-
42	2.19	0.63	0.19	0.28	0.35	0.03

Conclusion: _____
_____
_____
_____
_____

Task 18. Write the definitions gerontology and heriatry

Gerontology – _____
_____
_____
_____

Geriatrics – _____
_____
_____
_____

Task 19. Give the definition of *regeneration*.

Regeneration – _____

Regeneration

Physiological	Reparative	Pathological

Task 20. Give the definition of *transplantation*.

Transplantation – _____

Transplantation

Autograft	Isograft	Allogfaft	Xenograft

Multiple-Choice Tests for Control of Theme 18

1. Sexual reproduction
- A. creates offspring that are genetically different from the parents
- B. requires haploid gametes
- C. results in a diploid zygote
- D. all of the above
- E. none of the above

2. Which of the following has stages arranged in the sequence in which they occur?
- A. egg – gastrula – morula – embryo – fetus
- B. egg – gastrula – blastula – morula – fetus
- C. zygote – blastula – morula – gastrula – fetus
- D. zygote – morula – blastula– gastrula – fetus
- E. egg – zygote — gastrula – blastula – fetus
- A. third trimester

Date	Signature

Themes to individual work for Unit 2

1. Genetic engineering. Biotechnology. Notion of gene therapy.
2. Methods of human genetics: dermatoglyphics, immunological, hybridization of somatic cells.
3. Genetic maps. Methods of human chromosome mapping. Current status of investigation of the human genome.
4. Genetic risk of environmental pollution. Mutagens and antimutagens.
5. Ageing as stage of human ontogenesis. Theories of ageing.
6. Concept of biological fields, biorhythms and their medical significance.

Sample Lab Practical Exam 2 Questions

1. Subject and tasks of Subject and objectives of Human Genetics and Medical Genetics. Pharmacogenetics and Immunogenetics.
2. Human genotype: system of interacting genes.
3. Human phenotype: complex of specific and individual characters and features of an organism. Quantitative and qualitative traits.
4. Principles of inheritance in monohybrid cross. Mendel's law of segregation. Mendelian traits. Monogenic traits in humans.
5. Principles of inheritance in di- and trihybrid crosses. Mendel's law of independent assortment.
6. Multiple alleles. Blood type genetics. Their medical importance.
7. Interaction of allelic genes: complete dominance, incomplete dominance, overdominance, codominance.
8. Interaction of non-allelic genes: complementation, epistasis.
9. Polygenic inheritance in humans. Pleiotropy.
10. Linked inheritance (T.H. Morgan law). Crossing over. Genetic and cytological maps of chromosomes.
11. Chromosomal theory of inheritance.
12. Human genome research, present state. Genetic maps of human chromosomes.
13. Genes of autosomes and sex-chromosome. Sex-linked traits, sex-influenced traits, sex-limited traits. Hemizygosity.
14. The genetics of sex. Genetic mechanism of sex determination. Gene dosage. Gene position effect.
15. Variation, its forms. The ontogenetic and evolutionary significance of variation.
16. Modifications, their characteristics. Reaction norm.
17. Multifactorial principle of phenotype appearance. Role of environmental factors in gene expression: penetrance and expressivity. Phenocopies.
18. Genotypic variation, its forms. Combinative variation. The mechanisms of its appearance and significance.
19. Mutations and their phenotypic manifestations. Mutation theory. Classification of mutations. Their medical importance.
20. Mutagens. Classification of mutagens. Genetic monitoring. Risk-reducing factors of mutation.
21. Gene mutations, mechanisms of their appearance. The concept of monogenic diseases.
22. Chromosome aberrations. Mechanisms of their appearance. Examples of human diseases due to chromosome aberrations.
23. Mechanisms of genomic mutations (polyploidy, haploidy, polysomy and monosomy).
24. Classification of human hereditary diseases. Principles of their diagnostics.
25. Methods of studying of human heredity: genealogical method, twin method, molecular cytogenetic techniques, molecular genetic methods (DNA analysis), biochemical method, microbiological method, immunological, dermatoglyphics, population statistical method, somatic cell hybridization. Genetic markers.
26. Genealogical method. Modes of inheritance.
27. Single-gene (molecular) diseases: enzymopathies, disorders of metabolism of amino acids, carbohydrates, lipids, nucleic acids, mineral substances, vitamins, hormones; mechanisms of their appearance and principles of laboratory diagnostics.
28. Single-gene disorders due to primary pleiotropy.
29. Nonchromosomal heredity. Mitochondrial genome. Mitochondrial diseases.
30. Hereditary diseases due to unknown primary biochemical defect.
31. Disorders caused by numerical abnormalities of autosomes and sex chromosomes; mechanisms of their appearance and principles of laboratory diagnostics.
32. Germ and somatic mutations, their importance. Mosaicism.
33. Genetic heterogeneity of hereditary diseases. Genocopies.
34. Genetic predisposition to a disease. The concept of multifactorial diseases.
35. Medical and genetic aspects of family. Medical genetic consultation

36. Prenatal diagnosis of hereditary diseases. Newborn metabolic screening programs.
37. Prophylaxis and treatment of hereditary diseases. Genetic consultation. Perspectives of gene therapy.
38. Reproduction as universal characteristics of life. Types and forms of reproduction. Possibilities of organism cloning.
39. Meiosis. Genetic variation due to meiosis.
40. Gametogenesis: spermatogenesis, oogenesis.
41. Human sex cells, their cytogenetic characteristics. Qualitative differences of gametes and somatic cells.
42. Fertilization. Parthenogenesis. Biological features of human reproduction.
43. Ontogenesis, its periods. Embryogenesis, its steps. Extraembryonic organs.
44. Genetic control of development. Differentiation of cells, germ layers and tissues. Embryonic induction. Cell and tissue cloning.
45. Features of prenatal period of human development. Critical periods of human embryonic development. Environmental teratogens.
46. Congenital disorders, their classification: hereditary, exogenic, multifactorial, embryopathies and fetopaties; due to phylogenesis and non-phylogenetic.
47. Postnatal development of human ontogeny, its periods.
48. Interaction of ontogenesis and phylogenesis. Biogenetic law (recapitulation theory), A.N. Severtzov's interpretation.
49. Phylogenesis of integument, skeleton, digestive, respiratory, circulatory, nervous, excretory and reproductive systems of vertebrates. Congenital disorders due to ontophylogenetic conditionality.
50. Neurohumoral regulation of growth of development.
51. Ratio of the growth and differentiation processes in postembryonic period.
52. Ageing as a stage of ontogenesis. Theories of ageing.
53. Life expectancy and longevity problems. The concept of gerontology and geriatrics.
54. Clinical death and biological death.
55. Tissue and organ regeneration. Types of regeneration. Regenerative biology and medicine.
56. Features of regenerative processes in humans, their importance. Typical and atypical regeneration. Neoplastic growth.
57. Regulation of regenerative process.
58. Tissue and organ transplantation. Types of transplantation. Tissue incompatibility and its management.
59. The concept of homeostasis. Homeostatic regulatory mechanisms at the different levels of organization of life.
60. Modern evolutionary theory: Synthesis of darwinism and population genetics.
61. Biological species concept. Species: reality and dynamics. Species criteria. Gene pool of species.
62. Species structure. Population: structural unit of species. Population Characteristics: morphological, ecological, genetic. Gene pool of population.
63. Idealized and real populations. Law of constancy of genetic structure of idealized populations (Hardy-Weinberg law). Its use in calculation of genetic structure of real populations and human population.
64. The concept of microevolution. Population: elementary unit of species.
65. Factors of evolution, their interaction.
66. Natural selection as a driving force of evolution. Types of natural selection.
67. The results of evolution: speciation, genetic polymorphism, adaptation.
68. Types of speciation.
69. Genetic heterogeneity and genetic polymorphism of natural populations as a basis of their evolutionary plasticity.
70. Genetic load of a population.
71. Adaptation of organisms to their habitat. Origin of biological expedience.
72. Human population. Population structure of mankind. Large and small populations (deme, genetic isolates).
73. The effect of marriages structure and demographic rates on gene pool of human populations.
74. The effect of mutagenesis, isolation, migration on genetic structure of population and genetic constitution of humans. Genetic drift in isolates.
75. Features of natural selection in human populations. Selection and counter-selection.
76. Genetic and phenotypic polymorphism of mankind. Genetic polymorphism: adaptive (ecological), balanced (heterozygous).
77. The concept of macroevolution. Interaction of macro- and microevolution.
78. Taxonomic position of *Homo sapiens* species within the living world. Qualitative features of humans. Relation of biological and social factors during anthropogenesis.
79. The origin of the human races as a reflection of adaptive laws of human development. The unity of mankind.

GLOSSARY

Acentric A chromosome fragment without a centromere.

Acrocentric A chromosome having centromere at one end. Such chromosomes have satellited short arms carrying genes for rRNA.

Adenine It is a purine base in DNA and RNA.

Alleles They are alternative forms of gene at the same locus on homologous chromosomes. When there are more than two alleles at a given locus, they are called multiple alleles.

Amino acid An organic compound having both carboxyl and amino groups.

Amniocentesis A procedure by which amniotic fluid is obtained for prenatal diagnosis.

Anaphase The stage of cell division in which chromosomes migrate to opposite poles of the cell.

Aneuploid A chromosome number which is not an exact multiple of the haploid number, i.e. 2N+1 or 2N-1, where N denotes haploid number of chromosomes.

Anophthalmia A developmental defect characterized by absence of the eyes (rare).

Antigen A macromolecule that evokes antibody production by immunocompetent cells and specifically reacts with the same antibody.

Arachnodactyly A condition characterized by abnormally long and slender fingers and toes.

Assortative mating The preferential selection of a mate with particular genotype.

Assortment It is random distribution of maternal and paternal chromosomes during gametogenesis. This also permits independent assortment of nonalklic genes to the gametes.

Autosome Any chromosome other than sex chromosomes. There are 22 pairs of autosomes in man.

Banding Procedure of staining chromosomes to visualize typical pattern of cross bands.

Base Refers to nitrogenous bases in nucleic acids, DNA and RNA (A-adenine, C-cytosine, G-guanine, T-thymine and U-uracil).

Base pair In DNA complementary bases are A pairs with T and C pairs with G.

Birth defect An abnormality of structure, function, or body metabolism which often results in a physical or mental handicap. It may be inherited (genetic) or environmental.

Bivalent A pair of synapsed homologous chromosomes seen at metaphase of the first meiotic division.

Blood group Refers to system of red cell antigens.

Brachycephaly A "short" head due to a short anteroposterior diameter.

Brachydactyly Short fingers, all digits or only one or two.

Carrier A person who is heterozygous for a normal gene and an abnormal gene which does not express phenotypically but can be detected by specific tests.

Centimorgan (cM) Also called a map unit, it is used in linkage and is equivalent to 1 % recombination.

Centriole A pair of cell organelles forming the points of focus of the spindle during cell division. They migrate to opposite poles of the cell during cell division.

Chorion villous biopsy A procedure to obtain chorionic villous sample for prenatal diagnosis around 9-12 weeks under ultrasound control.

Chromatid During cell division each chromosome appears to be constituted by two parallel strands called chromatids held together by the centromere.

Chromatin The nucleoprotein fibres constituting chromosomes.

Chromosomal aberration A structural or numerical abnormality of chromosomes.

Cistron The smallest unit of genetic material that specifies synthesis of a particular polypeptide.

Clone A cell line derived from successive mitosis of a single diploid ancestral cell.

Codominant When both alleles of a pair are expressed in heterozygote state, the alleles are said to be codominant.

Codon A triplet of three nitrogenous bases that codes for one amino acid.

Concordant When both members of a twin pair exhibit the same trait they are called concordant.

Congenital Refers to an abnormality present at birth; it may or may not be genetic in nature.

Consaguinity A relationship by descent through a common ancestor.

Crossing over Exchange of genetic material between two chromosomes of a pair such as in chiasmata formation in diplotene stage.

Cytogenetics It is a branch of genetics that deals with the study of chromosomes.

Cytoplasmic inheritance Refers to transmission of a trait through the genes present in cytoplasmic organelles such as mitochondria.

Deletion A chromosomal aberration in which a part of chromosome is lost.

Dermatoglyphics The study of patterns of skin ridges of fingers, palms and soles.

Dictyotene The stage of the first meiotic division. Human oocyte remains in this stage from prenatal life until ovulation.

Diploid The number of chromosomes in somatic cells of an individual. It is double the number found in gametes. In human diploid number is 46 (2N).

Discordant When only one member of a twin pair shows a particular trait and the other does not, they are said to be discordant.

Dizygotic twins Twins produced by fertilization of two separate ova by two different sperms.

DNA, Deoxyribonucleic acid Nucleic acid in chromosomes that stores and transmits genetic information.

Dominant A trait that expresses even in heterozygote state for a particular gene.

Drift The fluctuations in gene frequencies which tend to occur in small isolated populations.

Duplication A chromosomal aberration in which a part of chromosome is duplicated.

Endonucleases Enzymes which can cleave bonds in DNA or RNA strand.

Epicanthal fold A vertical fold of skin on either side of the nose, covering the inner canthus (comer of the eye).

Euchromatin Represents genetically active regions of the chromosomes.

Exon A segment of gene which is represented in mRNA product and codes for protein.

Expressivity Refers to severity of the expression of a particular gene.

First filial generation The first generation progeny of a mating.

Fetoscopy A procedure of direct visualization of fetus for prenatal diagnosis.

Gamete A germ cell (ovum or sperm) having haploid number of chromosomes.

Gene A part of DNA molecule that directs synthesis of a polypeptide chain or RNA molecule. It consists of many codons.

Gene flow Diffusion of genes from one population to another, through migration and mating.

Gene map Represents human karyotype showing chromosomal localization of the genes.

Gene pool Total genes present at a given locus in the population.

Genetic code Triplet of bases that specifies amino acids.

Genetic counselling Deals with providing information to patients and the relatives at the risk of a genetic disorder, the consequences of the disorder of, the probability of recurrence and the ways by which it may be prevented or mitigated.

Genetic lethal Refers to the gene or genetically determined trait which leads to failure of reproduction in an affected individual.

Genetic screening The screening tests in population designed to identify individuals at risk of having a specific disorder or are likely to produce an offspring with such a disorder.

Genome All genes present on a set of chromosomes.

Genotype The genetic constitution of an individual (genome).

Haploid The number of chromosomes in a normal gamete. In humans it is 23(n).

Hardy-Weinberg' s Law The law states that in large randomly mating population relative proportions of the different genotypes remain constant from one generation to another provided no evolutionary processes like

migration, selection and drift are operating.

Hemizygous A term used to denote genes on X chromosome in males.

Heritability The proportion of the total variation of a character attributable to genetic as against environmental factors.

Heterochromatin Genetically inactive regions of the chromosomes.

Heterogametic sex The sex that produces gametes of two different types. In humans male is heterogametic, as he produces X and Y bearing sperms.

Heteromorphism The heritable structural polymorphism in chromosomes.

Heterozygote Refers to an individual possessing two different alleles at a given locus on a pair of homologous chromosomes.

Histone Type of protein associated with DNA in chromosomes, rich in lysine and arginine.

Holandric inheritance The pattern of inheritance of genes on Y chromosome. They pass from father to all his sons but to none of his daughters.

Homologous chromosomes A pair of chromosomes, one from each parent, carrying genes for the same traits, in the same order. In a karyotype, the members of a homologous pair look alike (e.g., a pair of 1s, 2s, etc.).

Homozygote An individual who has two identical alleles at a given locus on a pair of homologous chromosomes.

Hybrid Refers to progeny of cross between two genetically different organisms.

Hydrocephalus A condition marked by dilation of the ventricles of brain.

Hypertelorism Increased distance between the eyes.

Inborn error A specific enzyme defect leading to a metabolic block and resulting in a genetically determined biochemical disorder.

Inbreeding The mating between closely related individuals.

Index case, proband The affected family member through whom the family is ascertained.

Inducer The molecule that interacts with a regulator protein and triggers transcription of gene.

Insertion Term denotes a structural chromosomal aberration involving addition of DNA sequence from nonhomologous chromosomes.

Interphase Part of the cell cycle between two successive cell divisions.

Intron The part of a gene which is initially transcribed into the primary transcript but is then removed and is not present in mRNA.

Inversion A structural chromosomal abnormality in which a part of chromosome is inverted.

Isochromosome An abnormal chromosome resulting from transverse division of centromere in which one arm is duplicated and the other is deleted. An isochromosome therefore has two arms of equal length bearing same genes.

Isolate A small population group in which matings occur exclusively between members of the same population group.

Karyotype The term denotes chromosome set. It is also used for photomicrographof an individual's chromosomes arranged according to standard classification.

Ligase An enzyme used to join DNA molecules.

Linkage The genes located close together on the same chromosome are said to be linked.

Locus The site of a gene on a chromosome. Alternative forms of genes (alleles) may occupy the locus.

Meiosis It is a special type of cell division occurring in germ cells and results in the formation of gametes with haploid number of chromosomes. There are two meiotic divisions, meiosis I and II. Chromosome number is reduced in meiosis I.

Messenger RNA (mRNA) It is transcribed from DNA and forms template for translation of protein.

Metaphase The stage of mitosis or meiosis in which chromosomes are condensed to their maximum capacity and are lined up at the equatorial plate of the cell.

Microcephaly Small head size, usually associated with mental retardation.

Missense mutation The term denotes mutation, changing codon for one amino acid to specify another amino acid.

Mitochondrial DNA The circular DNA of mitochondria, a cytoplasmic structure. It is maternally inherited.

Mitosis The type of cell division that occurs in somatic cells. The daughter cells have the same chromosome complement as that of the parent cell.

Monosomy Absence of one chromosome from a pair. For example 45, XO (Turner's syndrome). Partial monosomy may also occur.

Monozygotic twins. Identical twins The type of twin derived from a single fertilized ovum.

Mosaic An individual with at least two cell lines with different genotypes but derived from a single zygote.

Multifactorial Refers to the combination of multiple factors controlling inheritance, such as genetic factors and also the nongenetic (environmental) factors. It should be distinguished from polygenic.

Mutagen An agent which increases the mutation rate by changing DNA structure.

Mutation A permanent heritable alteration in genomic DNA sequence. When it involves a single gene it is called point mutation.

Nondisjunction Two members of a chromosome pair fail to separate (disjoin) during cell division. As a result both pass to the same daughter cell.

Nucleosome The primary repeating unit of DNA structure in chromatin fibre.

Nucleotide Many nucleotides constitute nucleic acid. Each nucleotide comprises a nitrogenous base, a pentose sugar and a phosphate group.

Nucleus A structure within the cell that contains nucleolus and the chromosomes.

Operator gene A gene that switches on an adjacent structural gene.

Operon It consists of an operator gene and the structural gene which it controls.

p Denotes 1) the short arm of a chromosome; 2) frequency of more common allele of a pair in population genetics.

Pedigree A diagram of family history indicating normal and affected individuals, their relationship to the proband and their status with respect to a particular genetic disorder.

Penetrance The proportion of heterozygotes who express a trait even though mildly.

Pharmacogenetics science that studies drug responses and their gentically controlled variations.

Phenocopy It is a copy of a pheotype. A condition that is due to environmental factors but mimics one which is genetic.

Pleiotropy The phenomenon of a single gene presenting multiple effects.

Polydactyly The presence of extra digits (fingers and toes) on the hands and feet.

Polygenic A trait determined by many genes at different loci, should be distinguished from multifactorial trait in which the environmental factors operate.

Polymorphism The occurrence in a population of two or more genetically determined forms, each with such frequencies that the rarest of them cannot be maintained by mutation alone.

Polyploid Any multiple of haptoid number, other than diploid, such as 3n, 4n, etc.

Proband See *index case*.

Processing Includes alterations in RNA which occur during transcription; these are splicing, capping and polyadenylation.

Prophase The first visible stage of cell division in which chromosomes are seen as discrete structures. Subsequently they thicken and shorten.

q Denotes 1) the long arm of a chromosome; 2) frequency of rarer allele of a pair in population genetics.

Random mating, Panmixis Selection of a mate without considering the genotype.

Recessive A trait that expresses only in homozygotes.

Recombination Refers to crossing over between two linked loci.

Reduction division The first meiotic division in which the chromosome number is reduced from diploid to haploid.

Regulator gene In accordance with the operon concept a regulator gene synthesizes a repressor substance which inhibits the action of operator gene.

Restriction endonuclease An enzyme that cleaves DNA at a specific base sequence producing fragments of DNA, used in recombinant DNA technology.

Reverse transcriptase An enzyme that catalyses the synthesis of DNA from RNA.

Ring chromosome A structural chromosomal aberration in which the terminal portion of both arms of a chromosome break off and the remaining chromosome forms a ring.

RNA Ribonucleic acid is mainly found in nucleolus and ribosomes. It has pentose sugar ribose. RNAs are of the following classes: messenger RNA

(mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA) and viral RNA.

Robertsonian translocation A translocation involving two acrocentric chromosomes by fusion at the centromere and loss of their short arms.

Satellite A distal part of chromosome separate from the rest of the chromosome by a narrow stalk.

Segregation Refers to separation of alleles at meiosis, as a result two members of allelic pair pass to two different gametes.

Selection It refers to the operation of forces which determine the relative fitness of a genotype in population.

Sex chromatin, Barr body A darkly stained mass located at the periphery of the nucleus of a female mammalian cell during interphase. It represents an inactive X chromosome.

Sex chromosomes The chromosomes responsible for determination of sex, XX in females and XY in males.

Sex influenced A trait which is not X-linked but still expresses differently either in degree or in frequency, in males and females, e.g. congenital adrenal hyperplasia.

Sex limited A trait which is expressed in only one sex though it is not determined by an X-linked gene, e.g. precocius puberty in males.

Sex linkage Denotes genes carried on sex chromosomes. Since there are very few genes on Y chromosome, the term is often used synonymously for X- linkage.

Sibs A person's brothers and sisters.

Simian line Single crease on the palm, common in Down syndrome.

Solenoid Refers to a coil of wire wound round a hollow core. In cytogenetics the term is used to describe the coiled structure into which nucleosomes are wound during chromatin condensation.

Somatic mutation A mutation that occurs in somatic cell rather than in the germ cell line.

Spindle A structure which is responsible for the movement of the chromosomes during cell division. It consists of intracellular microtubules.

Structural gene A gene coding for RNA or protein product other than regulator gene.

Syndrome The complex of symptoms and signs which are found together in any particular disorder.

Syntenic genes Two genes that occur in different loci on the same chromosome.

Telophase The stage of cell division which commences when the daughter chromosomes reach the poles of the dividing cell and completes when the two daughter cells take an appearance of interphase cells.

Termination codon, stop codon There are three of these codons: UAG, UAA and UGA. Any one of them can terminate protein synthesis.

Transcription The synthesis of mRNA or DNA template.

Translation Refers to the process by which genetic information along mRNA is translated into protein synthesis.

Translocation The transfer of genetic material from one chromosome to another nonhomologous chromosome is translocation. If the two nonhomologous chromosomes exchange genetic material, it is called reciprocal translocation. See also Robertsonian translocation.

Triplet, codon In molecular genetics a unit of three bases in DNA or RNA that codes for an amino acid.

Triradius In dermatoglyphics, the term denotes a point from which the dermal ridges course in three directions at angles of approximately 120°.

Trisomy Refers to a state of having three representatives of a given chromosome instead of normal two, e.g. Down's syndrome or trisomy 21.

Ultrasonography A procedure in which high frequency sound waves are used to delineate the outline of various internal structures.

Unifactorial Inheritance controlled by a single gene pair.

Zygote A diploid cell resulting from union of male and female gamete (fertilization).