

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

PART 2
BIOCHEMISTRY OF HORMONES.
METABOLISM OF CARBOHYDRATES AND LIPIDS

**Self-Study Guide for Students of
General Medicine Faculty in Biochemistry**

ЧАСТИНА 2
БІОХІМІЯ ГОРМОНІВ.
ОБМІН ВУГЛЕВОДІВ ТА ЛІПІДІВ

Методичні вказівки
для підготовки до практичних занять
з біологічної хімії
(для студентів медичних факультетів)

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SOURCES

For preparing to practical classes in «Biological Chemistry»

Basic Sources

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CLASS 1 (4 hours)

TOPIC 1 (4 hours): General characteristics of hormones. Hormones of hypothalamic-pituitary axis

IMPORTANCE. One of the conditions for the normal functioning of all organs and systems is homeostasis, i.e. the ability to maintain and provide quantitative and qualitative constancy of the internal environment through a complex mechanism of regulation, coordination and integration of processes taking place in it. The pivotal role in this process is played by the central nervous system and endocrine glands. Hormones are biologically active substances that play a regulatory role in metabolism and functioning of organs and tissues.

AIM. Familiarize yourself with the general idea of hormones, their properties and features of the endocrine system, as well as the following classifications of hormones based on: 1) their place of synthesis; 2) chemical nature; 3) maintenance of homeostasis; 4) the primary contact with cells. Study the concept of receptors, their structure, localization and interaction with hormones. Read the main properties of hydrophilic and lipophilic hormones and features of their action on target tissues; molecular mechanisms of hormonal signal transduction for hormones of protein-peptide nature and derivatives of amino acids, steroid hormones and thyroid hormones. It is necessary to become familiar with the role of cyclic nucleotides, phosphoinositides, Ca^{2+} /calmodulin in hormonal signal transduction. Learn and be able to describe the hormones of the hypothalamic-pituitary axis in accordance with the following scheme: 1) its name; 2) its place of synthesis; 3) features of its structure; 4) mechanisms of action and

THEORETICAL QUESTIONS

- 1 Hormones: general characteristics, role in intercellular integration of functions of the human body.
- 2* Methods for the investigation of hormones
- 3 Properties of hormones and features of the endocrine system.
- 4 Classification of hormones based on their place of synthesis, chemical nature, maintenance of homeostasis. Groups of hormones and their representatives.
- 5 Classification of hormones based on their primary interaction with cells. Membrane (ionotropic, metabotropic), cytosolic and nuclear receptors.
- 6 Mechanisms of action for hormones of protein-peptide nature and derivatives of amino acids. Biochemical systems of intracellular hormonal signal transduction: G-coupled proteins, second messengers (cAMP, cGMP, Ca^{2+} /calmodulin, IP_3 , DAG).
- 7 Adenylyl cyclase messenger system. Structure of ATP and cyclic AMP.
- 8* Guanylyl cyclase messenger system. Structure of GTP and cyclic GMP.
9. Molecular and cellular mechanisms of action for steroid and thyroid hormones.
- 10* Role of hormones in mechanisms of self-regulation and maintenance of homeostasis.

* – questions for self-study biological significance; 5) disorders associated with its abnormal synthesis.

- 11 Hormones of hypothalamus – liberins and statins. Their structure and role in neurohumoral regulation.
- 12 Hormones of adenohipophysis. Pathological processes associated with dysfunctions of these hormones.
- 13 "Growth hormone (somatotropin) – prolactin – chorionic somatomammotropin" family; pathological processes associated with dysfunctions of these hormones.
- 14 Group of glycoproteins – pituitary tropic hormones (TSH, FSH, and LH).
- 15* Proopiomelanocortin family (POMC) – products of POMC processing (ACTH, lipotropins, endorphins).
- 16 Vasopressin and oxytocin: structure, biological functions. Pathological processes associated with vasopressin deficiency.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<i>1. Methods used for investigation of hormones.</i>	<p><i>1.1. Research methods for hormones: biological, colorimetric, polarographic, chromatographic, fluorimetric, radioisotope.</i></p> <p><i>1.2. Modern research methods: radioimmunoassay (RIA method):</i></p> <ul style="list-style-type: none"> <i>- It is used to determine very low amounts of protein-peptide and steroid hormones (hypothalamic hormones, pituitary hormones, hormones of the thyroid gland and parathyroid glands, adrenal glands, ovaries, endocrine apparatus of the pancreas);</i> <i>- This method is the most accurate and informative for determining blood hormone concentrations;</i> <i>- RIA kits with radioactive tracers (hormones) are used;</i> <i>- The method is based on competition: antibodies bind the radiolabelled antigen. This process is inhibited by the unlabeled antigen.</i>
<i>2. Guanylyl cyclase messenger system. Structure of GTP and cyclic 3',5'-GMP.</i>	<p><i>2.1. Components of the guanylyl cyclase messenger system: guanylyl cyclase-coupled receptors, guanylate cyclase, cGMP as a second messenger, cGMP-dependent protein kinases that amplify hormonal signals.</i></p> <p><i>2.2. Types of guanylyl cyclase:</i></p> <ul style="list-style-type: none"> <i>- Cytosolic: 2 subunits (α and β), prosthetic group – heme; activator - NO;</i> <i>– Membrane-bound: transmembrane glycoprotein (regulators - natriuretic factor, intestinal peptide – guanylin, etc.).</i> <p><i>2.3. Second messenger - cGMP (cyclic guanosine monophosphate) is synthesized due to the activation of membrane-bound or soluble guanylyl cyclase with</i></p>

	<p><i>GTP (under the action of phosphodiesterases cGMP is degraded to 5'-GMP);</i></p> <p><i>Structure of GTP: nitrogenous base - guanine, carbohydrate - ribose, phosphate moieties;</i></p> <p><i>- Structure of cGMP: 3',5'-diphosphoric esters of guanyl acid (GMP).</i></p> <p><i>2.4. Stages of transduction and transformation of hormonal signals: The interaction of hormone guanylyl cyclase-coupled receptors → activation of guanylyl cyclase → formation of cGMP → activation of cGMP-dependent protein kinases → cell response;</i></p> <p><i>-For example, natriuretic hormone acts via the guanylate cyclase messenger system in kidney cells causing sodium and water excretion, which leads to vasodilation.</i></p>
<p><i>3. Role of hormones on self-regulation that maintains the dynamic constancy of internal environment.</i></p>	<p><i>3.1. The role of hormones in the intercellular integration of functions:</i></p> <ul style="list-style-type: none"> <i>- Coordination of cellular and tissue reactions on changes in internal and external environments;</i> <i>- Coordination between cells and tissues.</i> <p><i>3.2. Classification of hormones based on their role in homeostasis :</i></p> <ul style="list-style-type: none"> <i>- hormones that determine sex and regulate the reproductive function of the body;</i> <i>- regulators of growth and development;</i> <i>- immunomodulators;</i> <i>- hormones that are responsible for adaptation to environmental changes;</i> <i>- hormones that regulate homeostasis of calcium and phosphorus;</i> <i>- hormones that regulate water-salt metabolism;</i> <i>- hormones that affect lactation;</i> <i>- hormones that take part in regulation of blood glucose level.</i>
<p><i>4. Proopiomelanocortin (POMC) family.</i></p>	<p><i>4.1. Proopiomelanocortin (POMC) family includes products of posttranslational POMC processing: adrenocorticotrophic hormone (which serves as a precursor of alpha-melanocyte-stimulating hormone, corticotropin-like peptide of the intermediate lobe of the pituitary gland), beta-lipotrophic hormone (serves as a precursor of γ-lipotrophic hormone, beta-melanocyte-stimulating hormone, endorphins).</i></p> <p><i>4.2. Location of POMC synthesis - basophil cells of the pituitary gland.</i></p>

	<p>4.3. Structure of POMC – glycoprotein made up of 239 amino acid residues. Mechanisms of formation of physiologically active peptide hormones and neurotransmitters from POMC: limited proteolysis; covalent modification (glycosylation, acetylation).</p> <p>4.5. Location of POMC processing - anterior and intermediate lobes of the pituitary gland, peripheral tissues: placenta, intestine, male sex glands.</p>
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TESTS FOR SELF-CONTROL

1. Which hormone stimulates the activity of adenylyl cyclase?
 - A. Adrenaline
 - B. Aldosterone
 - C. Testosterone
 - D. Progesterone
 - E. Calcitriol
2. Which glands are steroid hormones synthesized in?
 - A. Thyroid glands
 - B. Pancreas glands
 - C. Adrenal cortex
 - D. Adrenal medulla
3. Which hormone regulates the function of thyroid glands?
 - A. Thyrotropin-releasing hormone
 - B. Transcortin
 - C. Thyroid-stimulating hormone
 - D. Growth hormone-releasing hormone
4. Which hormone regulates water balance and osmotic pressure of blood plasma, stimulates the contraction of smooth muscle?
 - A. Prolactin
 - B. Growth hormone-release inhibiting hormone
 - C. Corticotropin-releasing hormone
 - D. Vasopressin
 - E. Glucagon
5. Which substance that imitates the effects of morphine but is synthesized in CNS is applied for analgesia?
 - A. Growth hormone-releasing hormone
 - B. Oxytocin
 - C. Calcitonin
 - D. Endorphin
 - E. Vasopressin
6. A patient complains of headache, alterations of his appearance (large feet, hands, face). Objectively: enlarged brow-arches; nose, lips. What is the cause of such changes?
 - A. Aldosterone deficiency
 - B. Glucagon deficiency
 - C. Thyroxine deficiency
 - D. Somatotropin overproduction
 - E. Corticosteroids overproduction
7. Some hormones are the products of protein hydrolysis and modification. Which protein is the precursor of lipotropin, ACTH and MSH?
 - A. Proopiomelanocortin
 - B. Neuroalbumin
 - C. Neurostromin
 - D. Neuroglobulin
 - E. Thyroglobulin
8. Ca ions may function as second messengers. They are activators of many processes if they react with:
 - A. Calcitonin
 - B. Calmodulin
 - C. Calciferol
 - D. Myosin
 - E. Phosphorylase
9. A patient suffers from diabetes insipidus after a haemorrhage of brain with damage of hypothalamic nuclei. Diabetes is accompanied by polyuria in result of:
 - A. Hypoglycemia
 - B. Decreased potassium reabsorption
 - C. Enhancing of renal filtration
 - D. Hyperglycemia
 - E. Decreased water reabsorption

10. Which of the below-mentioned hormones is hydrophilic and doesn't require the specific transport protein?
A. Dihydrotestosterone B. Progesterone C. Parathyroid hormone
D. Aldosterone E. Estradiol
11. Which of the below mentioned hormones diffuses to its target cell and interacts with cytosolic receptors?
A. Estradiol B. Oxytocin C. Parathyroid hormone
D. Adrenaline E. Growth hormone
12. Growth hormone action is characterized by:
A. Anabolic effect B. Diabetogenic effect C. Lactogenic effect
D. Erythropoietic effect E. All the above mentioned
13. Which of the below mentioned hormones is lipophilic and requires its specific transport protein?
A. Testosterone B. Insulin C. Adrenaline
D. Growth hormone E. Vasopressin
14. The formation of cAMP from ATP is provided by activation of the enzyme:
A. ATPase B. Adenylyl cyclase
C. Phosphatase D. Phosphodiesterase
15. The basis of self-regulation in the endocrine system is a feedback regulation, when a regulated parameter has the reverse influence on the production of hormone. Choose the corresponding example:
A. Adrenaline level in blood and secretion of melatonin
B. Thyroid hormones level in blood and secretion of thyrotropin-releasing hormone
C. Corticosteroids level in blood and secretion of somatoliberin
16. Functions of oxytocin:
A. Stimulates the relaxation of smooth muscles, stimulates the lactation
B. Stimulates the contraction of smooth muscles, inhibits the lactation
C. Stimulates the contraction of smooth muscles, stimulates the lactation
D. Stimulates the relaxation of smooth muscles, inhibits the lactation
E. Stimulates the contraction of smooth muscles, facilitates the reabsorption of water in renal channels
17. Which hormones act on the cellular genetic apparatus?
A. Protein hormones B. Peptide hormones
C. Steroid hormones D. Amino acid derivatives
E. Polypeptide hormones
18. A man was diagnosed with angina pectoris. The complex of drugs prescribed to the patient included phosphodiesterase inhibitors. Which substance concentration will increase in the cardiac muscle?
A. AMP B. GMP C. cAMP D. ADP E. ATP
19. A patient complains of thirst, frequent and abnormal urination. The urine analysis revealed: daily diuresis – 19 L; urine density – 1.001. Which disease causes such changes?
A. Diabetes mellitus B. Steroid diabetes C. Diabetes insipidus
D. Thyrotoxicosis E. Addison's disease

20. A boy was delivered to the hospital for an examination concerning his growth retardation. He has become only 3 cm taller for two years. Which hormone deficiency was observed?
- A. *Somatotropin* B. *Corticotropin*
 C. *Gonadotropin* D. *TSH* E. *Parathyroid hormone*
21. A pregnant woman with primary uterine inertia was hospitalized to a maternity ward. Which hormone should be prescribed?
- A. *Hydrocortisone* B. *Oxytocin* C. *ACTH*
 D. *Methandrostenolone* E. *Progesterone*
22. A woman complains of no lactation after delivery. Which hormone deficiency can cause this?
- A. *Vasopressin* B. *Calcitonin* C. *Glucagon*
 D. *Growth hormone* E. *Prolactin*
23. A patient complains of polyuria (8 liters per day) and polydipsia. Disorders of carbohydrate metabolism were not found. Which endocrine gland can be affected?
- A. *Adenohypophysis* B. *Adrenal medulla*
 C. *Neurohypophysis* D. *Pancreatic islets* E. *Adrenal cortex*
24. Inositoltriphosphates in tissues of the body are formed by hydrolysis of phosphatidylinositoldiphosphates. They act as second messengers of hormones. They influence cells via:
- A. *Calcium release from its intracellular depots*
 B. *Adenylyl cyclase activation* C. *Protein kinase C inhibition*
 D. *Protein kinase A activation* E. *Phosphodiesterase inhibition*
25. Early diagnosis of pregnancy includes investigation of urine. Which hormone appears in the urine during pregnancy?
- A. *17-Beta-estradiol* B. *Testosterone* C. *Progesterone*
 D. *Chorionic gonadotropin* E. *Estriol*
26. Numerous effects of growth hormone are mediated by protein factors that are produced in the liver under the influence of growth hormone. Such factors are called:
- A. *Lipotropins* B. *G-proteins* C. *Somatomedins*
 D. *Endorphins* E. *Atrial peptides*
27. Somatotropin has a wide range of activities. The action of this hormone leads to:
- A. *Fatty acid synthesis activation* B. *Activation of lipogenesis*
 C. *Activation of phospholipid hydrolysis* D. *Inhibition of lypolysis*
 E. *Activation of lipolysis*
28. Vasopressin has two types of receptors (V1 and V2), which have different messenger systems. Which messenger system is involved in promotion of vasopressin vasoconstrictor effects?
- A. *Phosphatidylinositol system* B. *Adenylyl cyclase system*
 C. *Gyanylyl cyclase system* D. *All options are wrong*
 E. *All options are correct*
29. An individual has an increased blood volume and reduced plasma osmotic pressure. These changes are accompanied by high urine output primarily due to reduced secretion of:
- A. *Aldosterone* B. *Natruretic factor* C. *Renin*
 D. *Vasopressin* E. *Adrenaline*

30. A patient with pituitary tumor complains of high daily diuresis (polyuria). Glucose concentration in blood plasma is 4.8 mmol/L. Which hormone can cause this if its secretion is altered?

- A. Vasopressin B. Insulin C. Natriuretic hormone
D. Angiotensin I E. Aldosterone

31. A man visited a doctor. The examination showed enlarged hands, feet, and lower jaw. Spinal deformity (kiphosis) and hormonal disorders (erectile dysfunction, testicular atrophy) were observed. Which endocrine gland is affected?

- A. Adenohypophysis B. Pineal gland C. Parathyroid glands
D. Adrenal glands E. Thyroid glands

32. An adult male's diuresis reached 22 liters. The urine's specific gravity was low. The most probable cause is a deficiency of:

- A. Aldosterone B. Natriuretic factor C. Renin
D. Parathyroid hormone E. Vasopressin

33. In the experiment, adenohypophysis was surgically removed from an animal. This resulted in an atrophy of the thyroid gland and the adrenal due to a deficiency of:

- A. Thyroid hormones B. Tropic hormones
C. Somatotropin D. Cortisol E. Thyroxine

34. A woman complains of poor lactation a month after delivery. Which hormone is deficient?

- A. Somatostatin B. ACTH C. Insulin
D. Prolactin E. Glucagon

35. An adult male with a proportional body structure and normal mental development is 100 cm tall. Which hormone was produced insufficiently in his childhood?

- A. Gonadotropin B. ACTH C. TSH
D. Prolactin E. Somatotropin

36. A man after blood loss of 1.5 liters has reduced diuresis. The increased secretion of which hormone caused such diuresis alteration?

- A. Parathormone B. Corticotropin
C. Vasopressin D. Cortisol E. Natriuretic

37. What is the second messenger for adrenaline?

- A. cTMP B. cGMP C. cUMP D. cAMP E. cCMP

1**. Prepare a presentation in accordance with the following topic: "History of endocrinology".

2**. Prepare a brief review in accordance with the following topic: "Hypothalamus is a site of interconnection between neuroreflectory and humoral mechanisms of metabolism regulation."

CLASS 2 (4 hours)

TOPIC (2 hours): Protein-peptide and amino acid derivative hormones. Qualitative reactions for hormones.

AIM. Learn and be able to characterize hormones of protein-peptide nature and amino acid derivatives in accordance with the following scheme: 1) its name; 2) its place of synthesis; 3) features of the structure; 4) mechanisms of action, biological role; 5) disorders. Familiarize yourself with qualitative reactions for hormones.

THEORETICAL QUESTIONS

- 1 Hormones of the thyroid gland: iodothyronines and calcitonin. Major types of thyroid dysfunction.
- 2 Hormones of parathyroid glands. Role of parathyroid hormone and calcitonin in the regulation of phosphate and calcium metabolism. Signs of parathyroid gland dysfunction.
- 3 Hormones of the pancreas. Mechanisms of insulin and glucagon influence on metabolism.
- 4 Hormones of the adrenal medulla: structure, role, metabolism (synthesis and breakdown), functional significance and role of their metabolites.
- 5* Hormones of the gastrointestinal tract: gastrin, secretin, cholecystokinin.
- 6* General characteristics of thymus hormones, their structures and role.
- 7 Structure and role of melatonin, place of synthesis.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<i>1. Hormones of the gastrointestinal tract.</i>	<p><i>1.1. Gastrin:</i></p> <ul style="list-style-type: none"> - <i>Place of synthesis: G-cells of the antrum and duodenal mucosa;</i> - <i>Target organs: stomach, pancreas;</i> - <i>Role: it stimulates the secretion of HCl and pepsin in the stomach, pancreatic secretion and motor functions of the antrum.</i> <p><i>1.2. Cholecystokinin:</i></p> <ul style="list-style-type: none"> - <i>Place of synthesis: mucosal I-cells of the duodenum and proximal small intestine;</i> - <i>Target organs: pancreas, gall bladder;</i> - <i>Role: it stimulates contraction of the gallbladder filled with bile; it increases secretion of pancreatic digestive enzymes; it slows down gastric emptying; it stimulates growth and development of pancreatic exocrine elements.</i> <p><i>1.3. Secretin:</i></p> <ul style="list-style-type: none"> - <i>Place of synthesis: S-cells of the duodenum and proximal small intestine;</i> - <i>Target organs: pancreas;</i> - <i>Role: it stimulates the excretion of bicarbonate and water by pancreatic acinar cells; it stimulates the secretion of pancreatic enzymes.</i> <p><i>1.4. Pancreozymin (identical to cholecystokinin):</i></p> <ul style="list-style-type: none"> - <i>Place of synthesis: small intestinal endocrine cells;</i> - <i>Target organs: pancreas, gall bladder;</i> - <i>Role: It stimulates contraction of the gallbladder filled with bile; it increases the secretion of pancreatic digestive enzymes.</i>

	<p>1.5. Enteroglucagon: - Place of synthesis: small intestinal endocrine cells; - Target organs: pancreas; - Role: It stimulates the secretion of pancreatic exo- and endocrine functions.</p>
<p>2. General characteristics of thymic hormones.</p>	<p>2.1. General characteristics of thymic hormones: - autocrine and paracrine effects; Target cells: T lymphocytes; Chemical nature: peptides; Synthesis and secretion can change depending on the age; Role: synthesis of non-thymic hormones, cytokines, particularly interleukin-2, by activated T cells, expression of interleukin receptors; it participates in the correction of induced immunodeficiency.</p> <p>A) Thymulin: - Place of synthesis: thymic epithelial cells; it is active in a complex with Zn^{2+}; it reacts with T lymphocytes; the maximum concentration is observed between 10 and 12 years of age, followed by a decrease in 36 years.</p> <p>B) Thymosins: - α_1-Thymosin: a N-terminal fragment of the intracellular protein α-prothymosine; it is synthesized in the thymus and nervous system; it interacts with T-helper cells and NK-cells and regulates hypothalamic functions; Diagnostic significance: It is a prognostic factor of the intestinal carcinoma and a marker of immunity-related disorders; - β_4-Thymosin belongs to a family of peptides with a molecular weight of 5 kDa; It is expressed in the spleen, thymus, lung, macrophages, and platelets; It acts as an inductor of chemotaxis, angiogenesis inhibitor of inflammation, proliferation of bone marrow stem cells, and activator of metalloproteinases.</p> <p>B) Thymopoietin is a protein hormone synthesized in the thymus that controls the differentiation of T-lymphocytes, increases proopiomelanocortin expression, secretion of ACTH beta-endorphin, beta-lipotropin, growth hormone, cortisol; It inhibits the induction of B-cell early differentiation and B-lymphocyte late differentiation.</p>

TESTS FOR SELF-CONTROL

1. Which hormones regulate the levels of calcium and phosphorus in blood?
- A. Parathyroid hormone B. Calcitonin
C. Adrenocorticotrophic hormone
D. Progesterone E. Testosterone

2. Which hormone stimulates biosynthesis of glycogen and increases anabolic processes?
A. Adrenaline *B. Noradrenaline* *C. Cholecystokinin*
D. Insulin *E. Thyroxin*
3. Tachycardia, loss of weight, increased body temperature and overexcitation are observed in the patient. These changes are caused by increased level of hormone:
A. Thyroxin *B. Vasopressin* *C. Growth hormone*
D. Insulin *E. Adrenocorticotropic hormone*
4. Heart beat rate of a sportsman after training increases to 120 per minute. Which hormones provide this effect?
A. Glucocorticoids *B. Catecholamines* *C. Releasing-factors*
D. Sex hormones *E. Mineralocorticoids*
5. Disturbance of the hormone synthesis results in development of different pathologic states. Which hormone synthesis deficiency leads to inhibition of growth without disturbance of mental activity?
A. Thyroxin *B. Prolactin* *C. Growth hormone*
D. Adrenaline *E. Gonadotropin*
6. Extremities fractures due to bone fragility were observed in the organism of a boy. Functions of which endocrine organ was affected?
A. Parathyroid gland *B. Thyroid gland* *C. Epiphysis*
D. Adrenal gland *E. Pancreas*
7. Some substances facilitate uncoupling of mitochondrial inner membrane oxidation and ADP phosphorylation processes. Choose one of these substances.
A. Vasopressin *B. Insulin* *C. Oxytocin*
D. Adrenaline *E. Thyroxin*
8. A man was under severe stress. Adrenaline and noradrenaline levels in blood were increased. Which enzymes catalyze inactivation of these hormones?
A. Glucosidases *B. Monoaminoxidases* *C. Peptidases*
D. Carboxylases *E. Tyrosinases*
9. Weight loss, overexcitation, light increase in body temperature, exophthalmus, hyperglycemia and azotemia are observed in patient. Which hormone overproduction results in the appearance of these symptoms?
A. Adrenaline *B. Thyroxin* *C. Calcitonin*
D. Aldosterone *E. Vasopressin*
10. A patient with low blood pressure is observed to have increased blood pressure, glucose and lipids levels after the injection of a hormone. Which hormone was injected?
A. Insulin *B. Glucagon* *C. Adrenaline*
D. Progesterone *E. Follicle-stimulating hormone*
11. Goiter is a disease widely spread in some biogeochemical areas of the Earth. Which element deficiency causes this disease?
A. Iron *B. Iodine* *C. Zinc*
D. Copper *E. Cobalt*

22. A patient complains of heart palpitations, sweating, nausea, blurred vision, tremor, and high blood pressure. According to his anamnesis, he was diagnosed with pheochromocytoma 2 years ago. The cause of this pathology is hyperproduction of:
- A. *Thyroid hormones* B. *ACTH* C. *Catecholamines*
 D. *Glucocorticoids* E. *Aldosterone*
23. A two-year-old child had seizures due to reduced blood plasma calcium levels. Which endocrine organ is less active?
- A. *Pineal gland* B. *Pituitary gland* C. *Thymus*
 D. *Adrenal cortex* E. *Parathyroid hormone*
24. A man with diffuse toxic goiter underwent thyroid resection surgery. Marked anorexia, dyspepsia, increased neuromuscular excitability were observed after the operation. Body weight was normal. Body temperature was not affected. What is the possible cause of such changes?
- A. *Overproduction of thyroliberin*
 B. *Overproduction of thyroxine*
 C. *Low production of parathyroid hormone*
 D. *Overproduction of calcitonin*
 E. *Low production of parathyroid thyroxine*
25. Parents of a 5-year-old child brought him to a hospital. The examination revealed mental and growth retardation. The child was inactive. Metabolic rate was reduced. What is the possible diagnosis?
- A. *Cretinism* B. *Lesch-Nyhan syndrome* C. *Phenylketonuria*
 D. *Hyperthyroidism* E. *Endemic goiter*
26. A five-month boy hospitalized due to tonic convulsions. He has been ill since his birth. Brittle nails and hair, pale and dry skin were found during his examination. The biochemical analysis of blood revealed: calcium - 0.5 mmol/L (reference ranges – 2.25-2.75 mmol/L), phosphorus – 1.9 mmol/L (reference ranges – 0.646-1.292 mmol/L). Such changes can be associated with:
- A. *Hypoaldosteronism* B. *Hypothyroidism*
 C. *Hypoparathyroidism* D. *Hyperparathyroidism*
 E. *Hyperaldosteronism*
27. The short-term physical activity is associated with an increase in heart rate and systemic blood pressure. What hormone primarily participates in the development of pressor response under such conditions?
- A. *ACTH* B. *Cortisol* C. *Thyroxine*
 D. *Adrenaline* E. *Vasopressin*
28. A weak hydrochloric acid solution was injected into the duodenum of an animal in acute experiment. It may lead to an oversecretion of one of the following hormones:
- A. *Histamine* B. *Neurotensin* C. *Gastrin*
 D. *Motilin* E. *Secretin*
29. A dog had the following symptoms 1-2 days after the parathyroid gland surgical removal: fatigue, thirst, a sharp increase in neuromuscular excitability with the development of tetany. Which electrolyte disorder is observed?
- A. *Hypermagnesemia* B. *Hypomagnesemia* C. *Hypercalcemia*
 D. *Hyponatremia* E. *Hypocalcemia*

30. Periodontitis is treated with calcium supplements and a hormone that is able to stimulate teeth mineralization and inhibit bone resorption, namely:
- A. Thyroxine B. Adrenalin C. Calcitonin
D. Aldosterone E. Parathyroid hormone
31. A patient has elevated plasma calcium concentrations, whereas its level in bones is reduced. Which hormone excessive secretion can cause such changes?
- A. Parathyroid hormone B. Aldosterone C. Thyroxine
D. Calcitonin E. Triiodothyronine
32. Active form of vitamin D₃ (calcitriol) is synthesized in the kidney under the influence of:
- A. Thyroxine B. Parathyroid hormone
C. Insulin D. Growth hormone E. Adrenaline
33. Inactive proinsulin is converted by the active form by:
- A. Addition of a regulatory subunit
B. Changes in the tertiary structure
C. Phosphorylation\dephosphorylation
D. Addition of C-peptide E. Limited proteolysis
34. A man has heart palpitations, intense sweating, and headache. The examination revealed hypertension, hyperglycemia, increased basal metabolic rate, and tachycardia. Which pathology of adrenal glands can be associated with such changes?
- A. Hypofunction of adrenal cortex B. Primary aldosteronism
C. Hyperfunction of adrenal medulla D. Hyperfunction of adrenal cortex
E. Hypofunction of adrenal medulla
35. As a result of accidental household trauma a patient had significant blood loss accompanied by low blood pressure. Which hormones can restore blood pressure and compensate for blood loss?
- A. Cortisol B. Aldosterone C. Sex hormones
D. Adrenaline, vasopressin E. Oxytocin
36. The leading symptoms of primary hyperparathyroidism include osteoporosis and kidney disorders associated with the development of kidney stones. Which substances participate in the kidney stone formation in this disease?
- A. Calcium phosphate B. Bilirubin C. Cholesterol
D. Cystine E. Uric acid
37. A woman complained of weight loss, enhanced sweating, low-grade fever, and nervousness. Hyperfunction of the sympathoadrenal system and increased basal metabolic rate were observed. Which hormone hypersecretion can cause this phenomenon?
- A. Corticotropin B. Somatotropin C. Insulin
D. Aldosterone E. Thyroxine
38. A child has short disproportionate stature and mental retardation. Which hormone insufficiency may cause such symptoms?
- A. Thyroxine B. Glucagon C. Insulin
D. Cortisol E. Somatotropin
39. Insulin, like other protein hormones, peptide has receptors located on the surface of cell membranes. What is the mechanism of insulin action on target cells?

- A. *Adenylyl cyclase messenger system*
 B. *Guanylyl cyclase messenger system*
 C. *Protein kinase cascade*
 D. *Phosphoinositide messenger system*
 E. *All options mentioned above are correct*
40. A patient mistook excessive dose of thyroxine. What changes in the secretion of thyrotropin-releasing hormone and thyrotropin can be observed?
 A. *High secretion of both hormones*
 B. *No changes in their secretion*
 C. *High secretion of thyroliberin and low secretion of TSH*
 D. *Low secretion of thyroliberin and high secretion of TSH*
 E. *Low secretion of both hormones*
41. A special diet resulted in reduced blood Ca^{2+} levels. Which hormone will be compensatory overproduced?
 A. *Calcitonin* B. *Thyroxine* C. *Vasopressin*
 D. *Parathyroid hormone* E. *Somatostatin*
42. A patient with high blood pressure, tremor, and tachycardia was diagnosed with a benign tumor of the adrenal medulla. Which hormone hypersecretion can cause such symptoms?
 A. *Glucagon* B. *Adrenaline* C. *Insulin*
 D. *Thyroxine* E. *Growth hormone*
43. A patient with thyrotoxicosis has high body temperature, bulimia, and weight loss. Such changes can be associated with abnormal:
 A. *ATP breakdown* B. *Coupling of oxidation and phosphorylation*
 C. *Synthesis of fats* D. *Citric acid cycle* E. *β -Oxidation of fatty acids*
44. As a result of a significant decrease in calcium plasma concentration, a 2-year-old child experienced tetanic contractions of the respiratory and pharyngeal muscles. Which hormone reduced secretion can cause such changes?
 A. *Calcitonin* B. *Aldosterone*
 C. *Growth hormone* D. *Cortisol* E. *Parathyroid hormone*
45. A male individual has had methionine-poor diet for a long period of time, leading to nervous and endocrine disorders. This may develop due to abnormal synthesis of:
 A. *Adrenaline* B. *Pyruvate* C. *Tyrosine*
 D. *Fatty acids* E. *Glucagon*
46. A woman went to the endocrinology department with marked tremor. Which hormones can be oversecreted in this case?
 A. *Thyroxine* B. *Somatostatin* C. *Adrenaline*
 D. *Insulin* E. *ACTH*
47. The patient's clinical examination revealed the enlarged thyroid gland (goiter), increased basal metabolic rate, weight loss, disorders of thermoregulation, increased appetite, increased excitability and irritability, exophthalmia, and tachycardia. Which endocrine disorder may lead to the appearance of such symptoms?
 A. *Parathyroid hypofunction* B. *Pituitary hyperfunction*
 C. *Pineal hypofunction* D. *Thyroid hypofunction* E. *Thyroid hyperfunction*

48. A woman has deficient amounts of pancreatic enzymes. Which gastrointestinal hormone secretion can be its cause?

- A. *Somatostatin* B. *Secretin* C. *Cholecystokinin-pancreozymin*
D. *Gastric inhibitory peptide (GIP)* E. *Vasoactive intestinal peptide (VIP)*

49. It was found by indirect calorimetry that a man had a 30% decrease in basal metabolic rate. Which hormones may be reduced in his blood plasma?

- A. *Calcitonin, parathyroid hormone* B. *Glucocorticoids*
C. *Catecholamines* D. *Triiodothyronine, thyroxine*
E. *Somatoliberin, somatostatin*

50. It has been known that diabetic patients have a tendency to inflammatory processes, reduced regeneration, slow wound healing. The possible reason is:

- A. *Increased rate of lipolysis* B. *Increased rate of gluconeogenesis*
C. *Low rate of lipolysis* D. *Activation of catabolism*
E. *Low rate of protein synthesis*

51. A patient constantly feels thirsty, drinks a lot of water, reports frequent urination, increased appetite, itching, weakness, furunculosis after epidemic parotitis. There are the following results of blood tests: glucose - 16 mmol/L, ketone bodies - 1.2 mmol/L. What disease can be diagnosed?

- A. *Insulin-dependent diabetes mellitus*
B. *Noninsulin-dependent diabetes mellitus*
C. *Steroid diabetes* D. *Diabetes insipidus* E. *Atherosclerosis*

52. Glucose levels decrease within a few seconds after insulin injections. This happens due to the activation of:

- A. *Glucose transport into the cells* B. *Glycolysis*
C. *Glycogen synthesis* D. *Synthesis of lipids*
E. *Pentose phosphate pathway*

PRACTICAL WORK
Qualitative determination of hormones

Task 1. Confirm the protein nature of insulin.

Geller's reaction. Pour gently 10 drops of concentrated nitric acid on the wall of the test tube and the same volume of insulin solution. The tube is tilted at an angle of 45° so that both liquids can be mixed. A white amorphous precipitate in the form of small rings appears at the boundary between two liquids.

Biuret reaction. Add 5 drops of 10% NaOH solution and 1 drop of 1% solution of CuSO₄ to 10 drops of insulin. The liquid formed in the test tube turns purple.

Task 2. Reaction for epinephrine with iron (III) chloride (ferric chloride).

Principle. The method is based on the ability of pyrochatechin group of adrenaline to form an emerald green complex compound with ferric chloride.

Procedure. Pour 10 drops of 0.1% adrenaline solution into the test tube and add 1 drop of 0.15 mol/L iron (III) chloride. You can observe the appearance of the peculiar coloration.

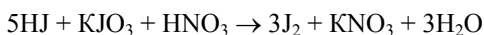
Task 3. Carry out a reaction for adrenaline with diazobenzene sulfonic acid.

Principle. The method is based on the ability of epinephrine to form a red-colored compound with diazobenzene sulfonic acid.

Procedure. Add 3 drops of 1% sulfonic acid solution and 5% nitrite solution to the test tube. Mix the solution formed. Then add 5 drops of 0.1% adrenaline solution and 3 drops of 10% sodium carbonate to the test tube. Mix and observe the change in color.

Task 4. Identify iodothyronines.

Principle. The method is based on removing of iodic acid from thyroid hormones (iodothyronines) via acid hydrolysis. The interaction of iodic acid with potassium iodate releases free iodine:



Free iodine, dissolved in chloroform, gives purple color.

Procedure. Put a few crystals of thyreoiodine into the test tube, add 10 drops of concentrated nitric acid and heat for 3-5 minutes upon a water bath. Then pour 20 drops of 10% potassium iodate solution. Mix and cool. Add 15 drops of chloroform to the test tube, mix by shaking. The color is changed.

Fill in the table:

Hormones	Place of synthesis	Chemical structure	Qualitative reaction	Mechanism of reaction	Color
Insulin					
Iodothyronines					
Epinephrine					

Practical significance. Methods of qualitative and quantitative analysis are widely used in clinical and biological laboratories for the determination of hormones in biological material for diagnosis and prognosis of various endocrine diseases.

1**. Prepare a presentation in accordance with the following topic: "Features of the receptor system and intracellular insulin signaling."

2**. Prepare a brief review in accordance with the following topic: "Iodinated thyroid hormones. Role of iodine in the interaction of TSH and iodine-containing thyroid hormones."

3**. Prepare a brief review in accordance with the following topic: "Catecholamines: receptors and mechanism of action, role in carbohydrate and lipid metabolism."

TOPIC 3 (2 hours): Steroid hormones. Eicosanoids. Qualitative determination of 17-ketosteroids in the urine.

AIM. Learn and be able to characterize steroid hormones in accordance with the following scheme: 1) its name; 2) its place of synthesis; 3) its structure; 4) its mechanism of action; 5) its biological role; 6) disorders. Familiarize yourself with eicosanoids, their synthesis, properties and role in the body. Study a method of qualitative determination of 17-ketosteroids in urine and its clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1 Steroid hormones: nomenclature, classification, scheme of synthesis.
- 2 Steroid hormones of the adrenal cortex (C₂₁-steroids): cortisol, corticosterone, aldosterone. Physiological and biochemical effects of corticosteroids.
- 3 Glucocorticoids; role of cortisol in the regulation of gluconeogenesis; anti-inflammatory properties of glucocorticoids. Cushing's disease and Cushing's syndrome.
- 4 Mineralocorticoids; role of aldosterone in the regulation of water-salt metabolism; aldosteronism.
- 5 Female sex hormones: estrogens – estradiol, estron (C₁₈-steroids); progesterone (C₂₁-steroids). Physiological and biochemical effects, connection with the phases of the menstrual cycle, regulation of synthesis and secretion.
- 6 Male sex hormones (androgens) – testosterone, dihydrotestosterone (C₁₉-steroids): physiological and biochemical effects, regulation of synthesis and secretion.
- 7* Clinical use of analogues and antagonists of sex hormones.
- 8 Eicosanoids: general characteristics, nomenclature, synthesis.
- 9 Biosynthesis of prostanoids and thromboxanes: prostaglandin synthase complex (cyclooxygenase, peroxidase). Biosynthesis of leukotrienes (5-lipoxygenase).
- 10* Biological and pharmacological properties of eicosanoids and their clinical administration.
- 11* Aspirin and other non-steroidal anti-inflammatory drugs as inhibitors of prostaglandin synthesis..

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<p>1. Clinical application of sex hormone analogues and antagonists.</p> <p>Prostaglandins – PG; thromboxanes – TX; leukotriens – LT.</p>	<p>1.1. Drugs containing female sex hormones: - Hormone-containing drugs of follicles (estradiol, sinestrol) are used as stimulating (they normalize the menstrual cycle in women of reproductive age), correcting (in hormonal disorders - fibromyoma, polyposis, uterine bleeding), replacement (menopause, surgical removal of the ovaries) therapy; antiestrogens (clostelbegyt, tamoxifen, toremifene, clomiphene citrate) - drugs that inhibit synthesis, secretion, transport and reduce the effect of estrogens). They are used to treat female infertility breast cancer;</p> <p>- Hormone-containing drugs of the corpus luteum (progesteron and its analogues) are used to treat uterine bleeding, infertility, miscarriages, menstrual irregularities; Antigestagens (mifepristone) is used to normalize the menstrual cycle.</p> <p>1.2. Drugs of male sex hormones:</p> <p>- Androgens (testosterone) are used as anabolic agents (methandrostenolone); They are used by males in abnormal functions of sex glands, infantilism, erectile dysfunction, male menopause; They are used by females in dysfunctional uterine bleeding, breast cancer, and ovarian cancer;</p> <p>- Antiandrogens (flutamide, cyproterone, finasteride) are drugs that suppress biosynthesis, secretion and transport of androgens or weaken their effect.</p>
<p>2. Biological and pharmacological properties of eicosanoids, their clinical application.</p>	<p>2.1. Biological properties of eicosanoids:</p> <p>- Participation in smooth muscle contraction and relaxation, in particular, dilation and narrowing of bronchi; uterine contraction, contraction of the gastrointestinal tract; vasoconstriction and vasodilation;</p> <p>- Participation in water-electrolyte metabolism: stimulation of renal diuresis and sodium excretion; inhibition of sodium excretion;</p> <p>- Proinflammatory action (the main sources of PGs in the site of inflammation are platelets, activated leukocytes, endothelial cells, and mast cells);</p> <p>- Effects on the cardiovascular system (e.g., PGE1, PGE2 increase blood flow by vascular dilatation with a decrease in peripheral resistance, which leads to an increase in cardiac output and reduction of blood pressure);</p>

- Effects on the nervous system (PG is present in the nervous tissue and is released upon stimulation of peripheral nerves; It modulates the action of adrenergic factors and serves as antagonists of some catecholamine-induced effects);
- Effects on the gastrointestinal tract (PGs inhibit gastric secretion but stimulate pancreatic secretion and mucus secretion in the intestine; They increase intestinal motility, inhibit the flow of sodium ions into the cells of the intestinal mucosa via stimulation of intestinal adenylyl cyclase);
- Effects on the reproductive system;
- They participate in blood clotting;
- They act on immunity;
- Effects on the skin and other organs.

Examples:

- PGE2 → it is synthesized in most tissues, especially kidney → biological effects: It relaxes smooth muscles, dilates blood vessels, initiates childbirth, inhibits the leucocyte migration, T-cell proliferation;
- PGF2α → it is synthesized in most tissues → biological effects: It provides smooth muscle contraction, constricts blood vessels, bronchi, stimulates the contraction of uterine smooth muscles;
- PGD3 → it is synthesized in the smooth muscle → biological effects: It causes vasodilation, reduces platelet and leukocyte aggregation;
- PGI2 → it is synthesized in the heart, vascular endothelial cells → biological effects: It reduces platelet aggregation, dilates blood vessels, increases cAMP formation in target cells;
- TXA2, THA3 → they are synthesized in platelets → biological effects: They stimulate platelet aggregation, constrict blood vessels and bronchi, reduce cAMP formation in cells;
- LTB4 → it is synthesized in leukocytes, epithelial cells → biological effects: It stimulates chemotaxis and leukocyte aggregation, release of lysosomal enzymes by leukocytes, increases vascular permeability.

2.2. Pharmacological properties of eicosanoids:

- PGE2, PGE2α - pharmacological preparations that stimulate uterine smooth muscle contraction; They are used to induce childbirth;

	- PGE1 and PGE2 analogues - pharmacological agents that accelerate gastric ulcer and duodenal ulcer healing (due to the ability to inhibit hydrochloric acid secretion in the stomach by blocking histamine type II receptors in gastric mucosal cells) and others.
3. Acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs as inhibitors of prostaglandin synthesis.	3.1. They are used as anti-inflammatory agents. 3.2. They Inhibit the production of prostaglandins by irreversible inhibition of cyclooxygenase (COX-1). 3.3. Inhibition of eicosanoid cyclooxygenase pathway - biochemical basis of antiplatelet and antithrombotic action of acetylsalicylic acid.

TESTS FOR SELF-CONTROL

1. Arachidonic acid (an essential component of food) is the precursor of biologically active substances. Which substances are synthesized from arachidonic acid?
A. Ethanolamine B. Choline C. Noradrenaline
D. Prostaglandin E₁ E. Triiodothyronine
2. A patient complains of continuous thirst. The analysis revealed hyperglycemia, polyuria and increased level of 17-ketosteroids in urine. Which disease causes the symptoms?
A. Steroid diabetes B. Diabetes mellitus C. Myxedema
D. Addison's disease E. I type of glycogenosis
3. Hyperglycemia is observed due to Cushing's disease. Which process is stimulated in this state?
A. Glycolysis B. Phosphorolysis of glycogen C. Krebs cycle
D. Pentose phosphate pathway of glucose oxidation
E. Gluconeogenesis
4. Which hormone stimulates the synthesis of corticosteroids?
A. Parathormone B. Thyrotropin C. Corticotropin
D. Calcitonin E. Corticosterone
5. Which of the below mentioned hormones directly activates the transcription process in nuclear chromatin?
A. Insulin B. Adrenaline C. Progesterone
D. Glucagon E. Noradrenaline
6. Medical examination of a patient revealed hypokaliemia, hypernatremia, and hypervolemia. What is the possible cause of such changes?
A. Hyperaldosteronism B. Hypoaldosteronism C. Addison's disease
D. Basedow's disease E. Diabetes mellitus
7. The intake of oral contraceptives containing sex hormones inhibits the secretion of pituitary hormones. Which of the below mentioned hormones secretion is inhibited in that state?
A. Vasopressin B. Somatotropin C. Oxytocin
D. Follitropin E. Corticotropin

8. Testosterone and its analogues increase the mass of skeletal muscles that allows applying them for treatment of dystrophy. Which cellular substrate should the hormone interact with to cause this action?

- A. Membrane receptors* *B. Chromatin* *C. Ribosomes*
D. Nuclear receptors *E. Proteins-activators of transcription*

9. A patient had been taking glucocorticoids over a long period of time. The abolition of this medicine led to an acute pathologic state displayed with the decrease of the arterial pressure and weakness. This phenomenon is explained by:

- A. The appearance of adrenal gland insufficiency*
B. Cumulative effect *C. Drug addiction*
D. Overproduction of ACTH *E. Sensibilisation*

10. A patient had been taking glucocorticoids over a long period of time. After the sharp abolition of the medicinal preparation they complain of myalgia, fatigue, emotional instability and headache. The medicine abstinent syndrome was developed. Which medicine must be prescribed to correct this state?

- A. ACTH* *B. Glucocorticoids* *C. Mineralocorticoids*
D. Adrenaline *E. Corticosteroids*

11. A prevalence of proliferation processes is found in a patient with chronic dermatitis. Which hormone deficiency can result in this?

- A. Cortisol* *B. Aldosterone* *C. Insulin*
D. Somatotropin *E. Thyroxin*

12. A patient with Cushing's syndrome has the increased blood level of cortisol. Which endocrine gland pathology causes this state?

- A. Adrenal cortex* *B. Adrenal medulla* *C. Pancreas*
D. Hypophysis *E. Thyroid gland*

13. A man had prolonged stress. The considerably increased level of 17-ketosteroids in the urine of the man indicates in the first place the overproduction of:

- A. Estradiol* *B. Aldosterone* *C. Estriol*
D. Cortisol *E. Progesterone*

14. A patient was hospitalized with complaints of general weakness, cramps of arms, arterial pressure 160/100 Hg. Results of investigation: glucose of blood – 6.5 mmol/L, cholesterol – 6 mmol/L, calcium – 2 mmol/L, phosphorus – 1 mmol/L, sodium – 160 mmol/L, diuresis - 700 ml/day. Which pathology can be the most possible cause of his state?

- A. Hypoaldosteronism* *B. Thyrotoxicosis* *C. Rickets*
D. Hyperaldosteronism *E. Hyperparathyroidism*

15. Aspirin shows anti-inflammatory action inhibiting the activity of cyclooxygenase. Which biologically active substances levels will decrease?

- A. Catecholamines* *B. Prostaglandins* *C. Melatonin*
D. Iodothyronines *E. Mineralocorticoids*

16. A patient has obesity, hirsutism, moon face, purple scars on the skin of the thighs. Arterial pressure is 180/110 mm Hg. His blood level reaches 17.2 mmol/L. Which changes in adrenal hormonal secretion can cause such symptoms?

- A. Low production of glucocorticoids*
B. High production of mineralocorticoids
C. Low production of mineralocorticoids

D. Low production of adrenaline

E. High production of glucocorticoids

17. Sweating in those who are adapted to high temperature is not accompanied by sodium chloride loss via sweat. Which hormone promotes such effects via acting on sweat glands?

A. Aldosterone

B. Vasopressin

C. Cortisol

D. Thyroxine

E. Natriuretic factor

18. Hyperkalemia developed in a patient who had been prescribed to take potassium for a long period of time. Which hormonal changes will be observed in this case?

A. Low aldosterone secretion

B. High vasopressin secretion

C. High aldosterone secretion

D. Low vasopressin secretion

E. Low renin secretion

19. A 30-year-old woman has virilism (hair growth, hair loss on temples, disorders of the menstrual cycle). Which hormone is produced in higher amounts?

A. Estriol

B. Testosterone

C. Relaxin

D. Oxytocin

E. Prolactin

20. A patient has moon face, central obesity, striae on the anterior abdominal wall, and hirsutism. High 17-hydroxyketosteroid levels are found in the urine. The symptoms mentioned above are typical for:

A. Pheochromocytoma

B. Conn's disease

C. Cushing's disease

D. Primary hypoaldosteronism

E. Secondary hyperaldosteronism

21. A patient who was suffering from Cushing's disease consulted concerning excessive body weight. It was found out that the energy value of his diet is 1,700-1,900 kcal per day. What is the leading cause of obesity in this case?

A. Hypodynamia

B. Insulin insufficiency

C. Insulin overexpression

D. Glucocorticoid insufficiency

E. Overproduction of glucocorticoids

22. A patient with rheumatoid arthritis started to complain of arrhythmia after three weeks of prednisolone treatment. What is the reason for the development of this undesirable effect?

A. Hypokalemia

B. Hyperuricemia

C. Hyperglycemia

D. Hypoglycemia

E. Hyperkalemia

23. Secretion of adrenal hormones is regulated by pituitary ACTH. Which hormones are secreted by adrenal glands under the influence of ACTH?

A. Catecholamines

B. Androgens

C. Mineralocorticoids

D. Glucocorticoids

E. Prostaglandins

24. Glucocorticoids and non-steroidal anti-inflammatory drugs are widely used in medical practice. One of the negative effects of long-term glucocorticoid therapy is:

A. Polyuria

B. Hyponatremia

C. Hyperkalemia

D. Osteoporosis

E. Hypotension

25. Corticosteroids regulate the processes of adaptation to changes in environmental conditions and maintain internal homeostasis. Which hormone activates the hypothalamic-pituitary-adrenal axis?

A. Somatoliberin

B. Somatostatin

C. Corticostatin

D. Thyroliberin

E. Corticoliberin

26. A female patient had adenoma derived from cells of the glomerular zone of the adrenal cortex. As a result, primary hyperaldosteronism or Conn's disease developed. Which ion metabolism is regulated by aldosterone?

- A. Magnesium* *B. Iron* *C. Phosphorus*
D. Calcium *E. Sodium*

27. A young bodybuilder took a synthetic analogue of testosterone to increase his muscle weight. Which biochemical process is stimulated by this drug in the anabolic way?

- A. Fatty acid synthesis* *B. Lipolysis* *C. Protein synthesis*
D. Glycogenolysis *E. Tissue respiration rate*

28. A patient complaining of fatigue, decreased appetite was hospitalized to the endocrinology department of the regional hospital. Data from anamnesis: He has been treated with corticosteroids due to asthma for a long time. Examination data: blood pressure – 90/60 mm Hg., skin hyperpigmentation. Which disease can be suspected?

- A. Tay-Sachs disease* *B. Graves' disease* *C. Gaucher disease*
D. Addison's disease *E. Cushing's disease*

29. A woman has a threat of premature termination of pregnancy. This can be caused by the insufficient secretion of:

- A. Progesterone* *B. Aldosterone*
C. Testosterone *D. Oxytocin* *E. Estradiol*

30. Bronze color of the skin that is characteristic of Addison's disease appeared in a patient after sepsis. The hyperpigmentation mechanism includes overproduction of:

- A. TSH* *B. Growth hormone*
C. MSH *D. Gonadotropin* *E. β -Lipotropin*

31. The examination of a patient with high blood pressure showed secondary hypertension. It was found that the cause of the patient's condition was a hormonally active tumor of the adrenal cortex. Which hormone is produced in higher amounts causing arterial hypertension?

- A. Insulin* *B. Adrenaline* *C. Thyroxine*
D. Cortisol *E. Glucagon*

32. A patient suffers from the impaired endocrine function of the ovarian follicular cells as a result of inflammation. Synthesis of one of the following hormone is reduced:

- A. LH* *B. Follistatin* *C. Estrogens*
D. Progesterone *E. FSH*

33. To prevent a graft-versus-host disease, it is necessary to prescribe a hormone therapy in order to provide immunosuppression. Which hormones can be used for this purpose?

- A. Mineralocorticoids* *B. Glucocorticoids*
C. Sex hormones *D. Thyroid hormones* *E. Catecholamines*

34. A patient with neurodermatitis has taken prednisolone for a long time. The examination revealed elevated blood sugar concentrations. Which link of carbohydrate metabolism is affected by prednisolone?

- A. Activation of gluconeogenesis* *B. Activation of glycogenesis*
C. Activation of is insulin breakdown
D. Glycogen synthesis inactivation
E. Increased glucose absorption in the intestine

35. A girl was diagnosed with congenital adrenal hyperplasia (pseudohermaphroditism). Which adrenal hormone excessive secretion can cause this pathology?
- A. *Adrenaline* B. *Estrogen* C. *Cortisol*
 D. *Aldosterone* E. *Androgen*
36. Concentrated sodium chloride solution was injected intravenously to an animal leading to a decrease in tubular sodium reabsorption. Which changes in hormonal secretion are responsible for such conditions?
- A. *Low vasopressin* B. *High aldosterone*
 C. *Low natriuretic factor*
 D. *High vasopressin* E. *Low aldosterone*
37. A patient with an upper type of obesity had hypertension, hyperglycemia, and glycosuria. He died from a brain hemorrhage. The post-mortem examination revealed a basophilic pituitary adenoma and adrenal hyperplasia. What is the most plausible diagnosis?
- A. *Diabetes mellitus* B. *Cushing's disease*
 C. *Adiposogenital dystrophy* D. *Acromegaly*
 E. *Pituitary dwarfism*
38. Parents of a 10-year-old boy went to the hospital. They noted excessive hair growth, moustache formation, and deep voice in their child. Oversecretion of which hormone can be assumed?
- A. *Testosterone* B. *Estrogen* C. *Cortisol*
 D. *Growth hormone* E. *Progesterone*
39. A patient had hyperkalemia and hyponatremia. Which hormone may be secreted in small amounts?
- A. *Cortisol* B. *Parathyroid hormone* C. *Vasopressin*
 D. *Aldosterone* E. *Natriuretic factor*
40. Experimental studies have shown that steroid hormones affect synthesis of proteins. Which stage of protein synthesis is affected by these hormones?
- A. *ATP synthesis* B. *Specific tRNA synthesis* C. *GTP synthesis*
 D. *Specific mRNA synthesis* E. *Specific rRNA synthesis*
41. Cushing's disease (hyperfunction of the adrenal cortex with overproduction of corticosteroids) leads to hyperglycemia. Which process is stimulated by glucocorticoids?
- A. *Gluconeogenesis* B. *Glycogen phosphorylysis*
 C. *Krebs cycle* D. *Glycolysis*
 E. *Pentose phosphate pathway*
42. A patient has high blood plasma potassium levels (7 mmol/L). What are the possible reasons for hyperkalemia?
- A. *Elevated aldosterone level* B. *Reduced thyroid hormones*
 C. *Reduced aldosterone level* D. *Elevated thyroid hormones*
 E. *Elevated sex hormones*
43. A patient's blood plasma sodium level reaches 180 mmol/L. What is the possible cause of this?
- A. *Reduced aldosterone* B. *Elevated aldosterone*

C. Elevated glucocorticoids D. Elevated thyroid hormones
E. Elevated natriuretic factor

44. Which substance serves as a precursor of prostaglandins in the human body?

A. Palmitic acid B. Stearic acid
C. Arachidonic acid D. Oleic acid
E. Palmitoleic acid

PRACTICAL WORK

Qualitative determination of 17-ketosteroids in urine

Task. Identify 17-ketosteroids (17-KS) in urine.

Principle. A qualitative reaction for 17-KS is performed with *meta*-dinitrobenzene. A condensation product colored in cherry-red color is formed. This reaction is also used for the quantitative determination of 17-KS in urine.

Procedure. Pour 5 drops of urine, 5 drops of 30% sodium hydroxide solution, 5 drops of *meta*-dinitrobenzene into the test tube and mix. The solution turns cherry-red within 2-3 minutes.

Clinical and diagnostic significance. All steroids with a ketone group at the 17th carbon atom are called 17-ketosteroids. They are formed from steroids which have OH-group in the 17th position (e.g., cortisol, testosterone). Determination of products of 17-KS metabolism in clinical practice is used for assessing the functional state of the adrenal and sex glands. For example, their content increases in patients with steroid diabetes and their reduced excretion in women correlates with high frequency of breast cancer. Normally, the concentration of 17-KS in urine per day is 0.10-0.16 g in males and 0.06-0.13 g in females.

1**. Prepare a brief review in accordance with the following topic: "Osteoporosis is a manifestation of sex hormone deficiency".

2**. Prepare a presentation in accordance with the following topic: "Molecular mechanisms of glucocorticoid signaling. Effects of glucocorticoids on the genetic apparatus."

CLASS 3 (4 hours)

Topic 4 (2 hours): Digestion and absorption of carbohydrates in the gastrointestinal tract. Metabolism of glycogen. Blood glucose level and its regulation. Determination of glucose in urine.

IMPORTANCE. Carbohydrates are responsible for several important functions: energy, structural, protective, etc. Any human organism can synthesize some carbohydrates from substrates such as glycerol and amino acids. However, most carbohydrates derive from food. Dietary carbohydrates are broken down in the gastrointestinal tract to simple sugars that are subsequently absorbed. Glucose serves as a main "fuel" for cellular metabolism and a precursor of other carbohydrates such as ribose, which is necessary for the synthesis of nucleic acids, carbohydrate components of glycoproteins, and glycosaminoglycans. Diabetes mellitus, galactosemia, disorders of glycogen synthesis and breakdown are associated with abnormal carbohydrate metabolism.

AIM. Study enzymes involved in digestion of carbohydrates, biochemical mechanisms of monosaccharide absorption in the gastrointestinal tract. Familiarize yourself with enzymatic reactions of glycogenesis and glycogenolysis, cascade mechanisms of cAMP-dependent regulation of glycogen phosphorylase and glycogen synthase activities, hormonal regulation of glycogen metabolism in the liver and muscles. Learn and be able to describe the genetic disorders of glycogen metabolism: glycogen storage diseases. Be able to characterize blood glucose level, its regulation and possible causes of hyperglycemia and glycosuria. Study the methods of glucose determination in urine and their clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1* Role of carbohydrates in living organisms.
- 2*. Major representatives of carbohydrates in the body: chemical structure, properties, and biological significance.
- 3* Energy value of carbohydrates. Daily requirements for carbohydrates.
- 4 Major dietary carbohydrates. Their structures.
- 5 Digestion and absorption of carbohydrates in the gastrointestinal tract. Enzymes engaged in their digestion
- 6 Mechanisms of monosaccharide absorption.
- 7 Glycogen biosynthesis (glycogenesis) in the liver and muscles: chemistry and key enzymes of the process, physiological significance.
- 8 Glycogen breakdown in the liver and muscles (glycogenolysis). Tissue differences. Reactions of glycogen hydrolysis and phosphorolysis.
- 9 Role of adrenaline, glucagon and insulin in the regulation of glycogen metabolism in muscles and liver. Mechanisms of cAMP-dependent regulation of glycogen phosphorylase and glycogen synthase activities.
- 10 Mechanisms of glycogenolysis and glycogenesis reciprocal regulation.
- 11 Genetic disorders of glycogen metabolism enzymes (glycogen storage diseases).
- 12* Blood glucose concentration. Its regulation.
- 13* Methods for determination of glucose in blood and urine, their significance.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<i>1. Role of carbohydrates in the organism.</i>	<ul style="list-style-type: none"> - Energy supply of the body's vital functions; - Structural (e.g., glycosaminoglycans that serve as components of the extracellular matrix; structural components of nucleotides, hormones, glycoproteins); - Participation in the maintenance of cell-cell interactions, formation and maintenance of shape of cells and organs, formation of the framework in the formation of tissues; - Metabolic (substrates for the synthesis of lipids, amino acids, nucleotides);

	<ul style="list-style-type: none"> - <i>Hydroosmotic (e.g., hyaluronic acid attracts extracellular water, cations, regulates osmotic pressure);</i> - <i>Protective (immunoglobulins, anticoagulant heparin);</i> - <i>Receptor function, etc.</i>
<p>2. Major representatives of carbohydrates in the body: chemical structure, biological significance.</p>	<p>2.1. Monosaccharides and their derivatives. <u>The most common monosaccharides are pentoses and hexoses that participate in cellular metabolism cages and serve as structural components of other biomolecules.</u></p> <ul style="list-style-type: none"> - <i>Pentoses:</i> - <i>D-Ribose → It forms a part of nucleotides, ribonucleic acids and free ribonucleotides, several coenzymes (NAD, NADP, FAD, FMN);</i> - <i>2-Deoxy-D-ribose → It forms a part of nucleotides of the deoxyribonucleic acid;</i> - <i>Hexoses (glucose, fructose, galactose) → energy, plastic, metabolic role.</i> <p><u>The most common derivatives of monosaccharides in the body are the following ones:</u></p> <ul style="list-style-type: none"> - <i>amino derivatives (amino sugars):</i> - <i>N-acetylated hexosamines (N-acetyl-glucosamine, N-acetylgalactosamine) → they form heteropolysaccharides called glycosaminoglycans (components of proteoglycans), as well as oligosaccharide chains of glycoproteins and glycolipids;</i> - <i>Neuraminic acid in the form of N- and O-acyl derivatives (sialic acid) → structural components of glycolipids in biological membranes (gangliosides), glycoproteins, proteoglycans of biological fluids, connective tissue, and mucus → immunochemical and mechanical functions;</i> - <i>uronic acid (D-glucuronic, D-galacturonic) → they are formed due to glucose and galactose oxidation → structural elements of heteropolysaccharides; D-glucuronic acid performs detoxification function by forming conjugates (glucuronides) with xenobiotics, metabolites of protein breakdown, porphyrins;</i> - <i>N-glycosides - nucleosides → structural components of nucleotides, nucleic acids, and certain coenzymes.</i> <p>2.2. Oligosaccharides:</p> <ul style="list-style-type: none"> - <i>Lactose, sucrose, maltose → components of diet.</i>

	<p>2.3. Homopolysaccharides: - Starch → the major dietary carbohydrate; - Glycogen → energy storage (excessive glucose obtained with food is stored as glycogen).</p> <p>2.4. Heteropolysaccharides: Glycosaminoglycans (hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate, heparan sulfate, heparin) → they perform their functions upon binding to proteins, forming proteoglycans → they serve as components of the skin, tendons, cartilages, joints → they provide mechanical strength and elasticity of extracellular matrix; Heparin is a natural anticoagulant.</p>
<p>3. Energy value of carbohydrates. Daily requirements for carbohydrates.</p>	<p>3.1. Energy value: 1 g of carbohydrates - 17.1 kJ (4.1 kcal).</p> <p>3.2. Daily requirements - 450-500 g</p>
<p>4. Blood glucose. Regulation of blood glucose level.</p>	<p>4.1. Blood glucose concentration: 3.3-6.1 mmol/L</p> <p>4.2. Blood glucose regulation :</p> <ul style="list-style-type: none"> - In the absorptive and post-absorptive periods (glycogen synthesis and breakdown); - During prolonged starvation (activation of gluconeogenesis); - At rest and during exercise (glycogen breakdown, gluconeogenesis); - Hormonal regulation: Insulin, somatostatin decrease blood glucose levels; prolactin, epinephrine, norepinephrine, T3, T4, somatotropin, glucocorticoids increase blood glucose concentrations.
<p>5. Methods of glucose determination in the blood and urine, their significance.</p>	<p>5.1. Determination of blood glucose levels.</p> <p>5.1.1. Reductometric (Hagedorn-Jensen method).</p> <p>5.1.2. Colorimetric:</p> <ul style="list-style-type: none"> - Enzymatic: glucose oxidase; UV methods (based on the hexokinase reaction); - Non-enzymatic: Folin-Wu method, Somogyi, etc. (based on the ability of glucose to reduce Cu^{2+} to Cu^+). <p>5.1.3. Other methods:</p> <ul style="list-style-type: none"> - Determination of the glucose content using luminol; - Glucose analyzers manufactured by "Backman Diagnostics", "Eksma", etc.; - Polarographic determination of glucose; - Express determination by the "dry chemistry" method;

	<p>- <i>Mass-fragmentography</i>; - <i>Glucometers</i> and "<i>Glucourotest</i>" test strips "<i>GlucoFAN</i>" and others.</p> <p>5.2. <i>Qualitative determination of glucose in the urine</i>: - <i>Fehling test</i>: Glucose reduced Cu^{2+} in alkaline solution while heating with the formation of yellow or red precipitate; - <i>Nylander test</i>: Bismuth hydroxide is reduced to the metal in the presence of glucose with the appearance of dark coloration; - "<i>Glucotest</i>" test strips.</p> <p>5.3. <i>Quantitative determination of glucose in the urine</i> - <i>Althausen test</i> (a color of urine is compared to a standard scale).</p>
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TESTS FOR SELF-CONTROL

1. Digestion of carbohydrates occurs in the intestine under the action of pancreatic enzymes. Which enzyme hydrolyzes α -1,4-glycosidic bonds?
A. Elastase *B. Lipase* *C. Carboxypeptidase*
D. Trypsin *E. α -Amylase*
2. Which is the first reaction of glucose conversion when it enters the cells of different organs and tissues?
A. Oxidation *B. Reduction* *C. Amination*
D. Phosphorylation with participation of inorganic phosphorus
E. Phosphorylation with participation of ATP
3. Vomiting, diarrhea, general dystrophy, hepato- and splenomegaly had been observed in a newborn. These symptoms decreased after exclusion of milk from the diet. Which main hereditary defect results in the pathology?
A. Disturbance of galactose metabolism
B. Disturbance of phenylalanine metabolism
C. Hypersecretion of endocrine glands
D. Disturbance of glucose metabolism
E. Glucose-6-phosphate dehydrogenase deficiency
4. Fructose is mainly supplied to the organism as:
A. Maltose *B. Sucrose* *C. Starch*
D. Lactose *E. Glycogen*
5. A newborn feels well after breast-feeding. Vomiting, abdominal ache, diarrhea, hypoglycemia appear after addition of fruits and juices to the diet. What is the cause?
A. Hyperglycemia *B. Ketosis* *C. Gierke's disease*
D. Glucosuria *E. Hereditary fructose intolerance*
6. Postsynthetic covalent modification plays an important role in enzymes activity regulation. How are glycogen phosphorylase and glycogen synthase activities regulated?
A. Methylation *B. Adenylation* *C. Limited proteolysis*
D. ADP-ribosylation *E. Phosphorylation-dephosphorylation*

7. Blood glucose concentration of healthy individuals varies:
 A. 2-4 mmol/L B. 3.3-5.5 mmol/L C. 10-25 mmol/L
 D. 6-9.5 mmol/L E. 1-2 mmol/L
8. Tolerance of a patient to physical load is decreased, but glycogen content in skeletal muscles of the patient is higher. Which enzyme activity decrease can explain this phenomenon?
 A. *Phosphofructokinase* B. *Glucose-6-phosphate dehydrogenase*
 C. *Glycogen phosphorylase* D. *Glycogensynthase*
 E. *Glucose-6-phosphatase*
9. Fatty liver, galactosuria and aminoaciduria are observed in a newborn. Which substance must be excluded from diet?
 A. *Milk sugar* B. *Fatty acids* C. *Phenylalanine*
 D. *Cholesterol* E. *Sucrose*
10. Glucose-6-phosphatase deficiency, hypoglycemia and hepatomegaly were found in a child with a point mutation of genes. Which pathology is characterized by these signs?
 A. *Gierke's disease* B. *Cori's disease* C. *Addison's disease*
 D. *Parkinson's disease* E. *Mc-Ardle's disease*
11. A baby is weak and apathic. Its liver is enlarged and liver biopsy test reveals excessive content of glycogen. Glucose blood level is reduced. What is the cause of this?
 A. *Decreased (minimal) activity of liver glycogen phosphorylase*
 B. *Decreased (minimal) activity of glycogen synthetase*
 C. *Increased activity of glycogen synthetase*
 D. *Decreased (minimal) activity of glucose-6-phosphatase*
 E. *The deficiency of gene responsible for the synthesis of glucose-1-phosphate uridylyltransferase*
12. Gierke's disease is an illness which develops due to the excessive accumulation glycogen in the liver and kidney. Which enzyme deficiency is the cause of this disease?
 A. *Glycogen phosphorylase* C. *Phosphorylase kinase*
 B. *Glucose-6-phosphatase* E. *Glucokinase*
 D. *Phosphoglucomutase*
13. A patient suffers from milk intolerance. Which digestion enzyme deficiency explains this phenomenon?
 A. *Amylase* B. *Lactate dehydrogenase* C. *Maltase*
 D. *Lipase* E. *Lactase*
14. One of characteristic features of a glycogenesis is muscle pain, pain during the performance of physical work. Which enzyme inherited deficiency causes this pathology?
 A. *Glycogen phosphorylase* B. *Glucose-6-phosphatase*
 C. *Glycogen synthase*
 D. *Amylo-1-6-glucosidase* E. *Lysosomal glucosidase*
15. Which of the below mentioned carbohydrates is heteropolysaccharide?
 A. *Starch* B. *Glycogen* C. *Maltose*
 D. *Heparin* E. *Cellulose*

16. A newborn had dyspepsia (diarrhea, vomiting) after breastfeeding. When glucose solution was offered, symptoms disappeared. Which enzyme that participates in the digestion of carbohydrates is deficient?

- A. *Amylase* B. *Sucrase* C. *Lactase*
D. *Isomaltase* E. *Maltase*

17. Severe fasting hypoglycemia was observed in a patient. The amount of glycogen in liver biotates is decreased. Which enzyme deficiency can be a reason for this disease?

- A. *Glycogen synthase* B. *Phosphorylase a*
C. *Fructose bisphosphatase* D. *Pyruvate carboxylase* E. *Aldolases*

18. Synthesis of glycogen polysaccharide requires a precursor, namely an active form of glucose. The direct donor of glucose residues for the glycogen synthesis is:

- A. *ADP-glucose* B. *Glucose-6-phosphate*
C. *Glucose-3-phosphate* D. *UDP-glucose* E. *Glucose-1-phosphate*

19. Alimentary hyperglycemia appears after meals. It stimulates the secretion of:

- A. *Adrenaline* B. *Noradrenaline* C. *Cortisol*
D. *Insulin* E. *Glucagon*

20. Pancreas is a both exocrine and endocrine organ. Endocrine beta cells produce insulin, which affects the carbohydrate metabolism. How can it affect the activity of glycogen phosphorylase (GP) and glycogen synthetase (GS)?

- A. *It inhibits both GS and GP* B. *It activates both GS and GP*
C. *It inhibits GP and activates GS* D. *It activates GP and inhibits GS*
E. *It does not affect GS and GP*

21. A one-year-old child has mental retardation. Vomiting, convulsions, loss of consciousness are observed in the mornings. Fasting hypoglycemia is found. Which enzyme is insufficient?

- A. *Glycogen synthase* B. *Phosphorylase* C. *Arginase*
D. *Sucrase* E. *Lactase*

22. The diet should include fiber-containing products. It has been known that fibers are not digested by digestive enzymes and are not absorbed by the body. Which role is played by them?

- A. *It inhibits the secretory function of the gastrointestinal tract*
B. *It stimulates peristalsis*
C. *It inhibits intestinal secretion*
D. *It inhibits absorption in the gastrointestinal tract*
E. *It inhibits peristalsis*

23. When a newborn started to receive food products in addition to breast milk, dyspepsia, diarrhea, flatulence, and physical retardation developed. The biochemical basis for this disease is the deficiency of:

- A. *Cellulose* B. *Lactate and cellobiases*
C. *Trypsin and chymotrypsin* D. *Lipases and creatine kinases*
E. *Sucrases and isomaltases*

24. Intense physical activity leads to the lactic acid accumulation in muscles. It diffuses into the bloodstream and is taken up by the liver and heart cells. Which process provides glycogen storage regeneration in the muscles?

- A. *Cori cycle* B. *Pentose phosphate pathway*

C. *Ornithine cycle*

D. *Citric acid cycle*

E. *Oxidative phosphorylation*

25. Major triggers that switch on cellular effector systems in response to the action of hormones are protein kinases that can change catalytic activity of certain regulatory enzymes by ATP-dependent phosphorylation. Which of the enzyme mentioned below is active in the phosphorylated form?

A. *Glycogen synthase*

B. *Acetyl-CoA carboxylase*

C. *Pyruvate kinase*

D. *Glycogen phosphorylase*

E. *HMG-CoA reductase*

26. A child was diagnosed with Gierke's disease, which manifests by severe hypoglycemia. The reason for this condition is glucose-6-phosphatase deficiency. Which process is affected in this pathology?

A. *Glycogen synthesis*

B. *Ketogenesis*

C. *Glycogen mobilization*

D. *Glycolysis*

E. *Gluconeogenesis*

27. Glycogen breakdown in the liver is stimulated by adrenaline. Which second messenger is formed in hepatocytes under the influence of adrenaline?

A. *cGMP*

B. *cAMP*

C. *CO*

D. *NO*

E. *TAG*

28. A patient has the reduced activity of the salivary digestive enzyme. Which substance is hydrolyzed less in this case?

A. *Lipids*

B. *Proteins*

C. *Cellulose*

D. *Milk sugar*

E. *Carbohydrates*

29. It has been known that many hormones act through the adenylyl cyclase system, which leads to the activation of enzymes by phosphorylation. Which enzyme is activated under the action of hormonal signal and provides glycogen breakdown?

A. *Phosphorylase*

B. *Phosphotransferase*

C. *Glucomutase*

D. *Phosphatase*

E. *Tyrosinase*

30. A patient has the reduced tolerance to physical stress, while there is an increased glycogen content in skeletal muscles. Which enzyme activity is reduced?

A. *Glucose-6-phosphate dehydrogenase*

B. *Phosphofructokinase*

C. *Glycogen phosphorylase*

D. *Glycogen synthase*

E. *Glucose-6-phosphatase*

PRACTICAL WORK

Determination of glucose in the urine

Task 1. Determination of glucose in the urine by Fehling's method.

Principle. Fehling's test is based on the ability of glucose to reduce Cu^{2+} in an alkaline medium during heating. Yellow copper hydroxide precipitate or red copper oxide precipitate will be formed.

Procedure. Add 5 drops of Fehling's reagent to 5 drops of urine. Both liquids are mixed with a stirring rod and boiled. It should be noted that urine contains a lot of organic substances (uric acid, creatinine, etc.) which can also reduce heavy metals after prolonged boiling. On the contrary, reduction of metals in the presence of glucose occurs before reaching the boiling point.

Fehling's reagent contains potassium-sodium tartrate, NaOH, copper (II) sulfate.

Task 2. Determine glucose in urine by Nilander's method.

Principle. Nilander's test is based on bismuth hydroxide reduction to the metal in the presence of glucose. Bismuth salts are particularly suitable for the determination of sugar in urine, because bismuth is not reduced by uric acid unlike copper.

Procedure. Add Nilander's reagent to the test tube with 1 ml of urine and gently boil during approximately two minutes. Initially the solution will be brown. Then it will turn black.

Nilander's reagent contains bismuth nitrate, potassium-sodium tartrate, ammonia.

Task 3. Determine glucose in urine by an express method (semi-quantitative determination of glucose in urine).

Procedure. Grind 1 g of copper sulfate and 10 g of anhydrous sodium carbonate to powder in a mortar. Put a small amount of powder on a glass slide, add a few drops of urine and boil. Blue color indicates lack of glucose, yellowish-green color confirms the presence of glucose whose percentage does not exceed 0.5%, green - 1%, brownish-red - 2%, intensely red - above 2%.

Task 4. Determine glucose in urine using a "Glucotest" kit.

Principle. The method is based on the visual assessment of changes (*orthotolidyn*) in the color of dye impregnated in a paper strip "Glucotest." Using a color scale available in the kit, the approximate glucose level in the urine is determined. Color of strips can vary from yellow through various shades of green to dark blue depending on the amount of glucose in urine. This method has high substrate specificity and allows determining glucose urine concentrations ranging from 0.09 to 0.5% or even higher. It has the great clinical importance due to its high specificity, speed, and simplicity of analysis implementation. A patient can independently monitor his or her own glucose urine levels and therefore their changes.

Procedure. The first "Glucotest" strip is moistened by normal urine and the second one by pathological urine that contains glucose. Compare color of strips after a few minutes with a color scale. Urine glucose levels are determined in accordance with a color strip that matches the scale in the best way (0.1%, 0.5%, 2% and other glucose solutions).

Clinical and diagnostic significance. *Urine glucose levels in healthy humans are extremely low (without exceeding 0.4 g/L). Therefore, they cannot be revealed by routine chemical methods. Glycosuria is observed when hormonal regulation of carbohydrate metabolism is impaired, for example, in patients with pancreatic diseases and disorders that affect renal reabsorption. Renal glycosuria can be revealed after consumption of large amounts of alcohol, opium, adrenaline, chloroform and other substances.*

TOPIC 5 (2 hours): Anaerobic and aerobic glucose oxidation. Gluconeogenesis. Quantitative determination of lactate in blood and pyruvate in the urine.

IMPORTANCE. Knowledge of carbohydrate metabolism in the human body helps understand its features both under normal conditions (physiological state) and

pathological conditions accompanied by changes in carbohydrate metabolism (diabetes mellitus, liver diseases, etc.). Since the vast majority of animal and plant cells exist normally under aerobic conditions, carbohydrates are completely oxidized to CO₂ and H₂O via the Krebs cycle. Thus, biologically the energy available in glucose molecules is released. Knowledge of glucose oxidation pathways is very important to future doctors. This is explained by the fact that that knowing their role in the energy and plastic processes it is possible to normalize them.

AIM. Become familiar with aerobic and anaerobic glucose oxidation and gluconeogenesis, their role in the body. Study the methods of quantitative determination of lactate and pyruvate in biological fluids and their clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1 Anaerobic oxidation of glucose: enzymatic reactions, biological role, and localization in the body and inside the cells.
- 2 Glycolytic oxydoreduction, substrate-level phosphorylation in glycolysis. Energy balance of anaerobic glucose oxidation.
- 3 Regulation of glycolysis. Key enzymes of the process.
- 4* Alcoholic fermentation and other types of fermentation.
- 5 Stages of aerobic glucose oxidation.
- 6* Interactions between anaerobic and aerobic glucose oxidation pathways in the cell. Pasteur effect.
- 7 Oxidation of cytosolic NADH in mitochondria (glycerol phosphate and malate-aspartate shuttles).
8. Comparison of energy balance of aerobic and anaerobic glucose oxidation.
- 9 Gluconeogenesis: substrates, key enzymes, reactions, intracellular localization, and physiological significance of the process. Energy supply of gluconeogenesis.
- 10 Metabolic and hormonal regulation of gluconeogenesis.
- 11* Reciprocal regulation of glycolysis and gluconeogenesis in the body. Glucose-lactate and glucose-alanine cycles.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<i>1. Alcoholic and other types of fermentation.</i>	<p><i>1.1. Fermentation is a biochemical process which is used by anaerobic or aerobic organisms to meet their energy needs synthesizing ATP under insufficient provision of oxygen.</i></p> <p><i>1.2. Alcoholic fermentation:</i></p> <ul style="list-style-type: none"> <i>- It is performed by yeasts;</i> <i>- Its mechanism is similar to glycolysis. The pathways start differing after the formation of pyruvate:</i> <p><i>-pyruvate → acetaldehyde + CO₂ (piruvate decarboxylase);</i></p>

	<p>-acetaldehyde + $NADN_2 \rightarrow NAD^+ + \text{ethanol}$ (alcohol dehydrogenase);</p> <p>- Final products - ethanol and CO_2;</p> <p>- Localization - intestinal lumen under the influence of enzymes of yeasts. Approximately 1.5 g of ethanol is produced daily.</p> <p>1.3. Lactic fermentation:</p> <p>- It is performed by lactic acid bacteria (two groups of bacteria: the first group forms only lactate when fermenting carbohydrates; the second group produces lactate, ethanol, CO_2);</p> <p>- Resemblance to the alcoholic fermentation; Differences - pyruvate is reduced to lactate by NADH-dependent LDH.</p>
<p>2. Interconnection between anaerobic and aerobic glycolysis. Pasteur effect.</p>	<p>2.1. General information: enzymatic reactions of anaerobic and aerobic glycolysis are identical until pyruvate is formed.</p> <p>2.2. Aerobic conditions: pyruvate conversion to acetyl-CoA and its oxidation in the Krebs cycle.</p> <p>2.3. Anaerobic conditions: pyruvate is reduced to lactate by NADH-dependent LDH.</p> <p>2.4. Pasteur effect: in the presence of oxygen anaerobic glycolysis or fermentation is switched to respiration (low glucose consumption rate and termination of lactate accumulation in the presence of oxygen):</p> <p>- Significance – it allows cells to switch to the most efficient and economical way to produce energy;</p> <p>- Biochemical mechanism of the effect - the competition between cytosolic lactate dehydrogenase and mitochondrial respiratory chain for NADH (H^+).</p>
<p>3. Reciprocal regulation of glycolysis and gluconeogenesis. Glucose-lactate and glucose-alanine cycles.</p>	<p>3.1. Regulation of glycolysis - influence of inhibitors or activators on the activity of enzymes that catalyze irreversible reactions:</p> <p>- Glucose-6-phosphate is an allosteric inhibitor of hexokinase in muscles;</p> <p>- ATP and citrate act as inhibitors, and fructose-6-phosphate and AMP serve as activators of phosphofructokinase;</p> <p>- ATP, acetyl-CoA, fatty acids are pyruvate kinase inhibitors.</p> <p>3.2. Regulation of gluconeogenesis.</p> <p>3.2.1. Allosteric regulation:</p> <p>- Acetyl-CoA is an activator of pyruvate carboxylase;</p> <p>-ATP is an activator, and AMP is an inhibitor of fructose-1,6-bisphosphatase => gluconeogenesis is</p>

activated by reducing glucose (as evidenced acetyl-CoA accumulation) and sufficient supply of cell with ATP. It is inhibited by a decrease in acetyl-CoA levels (which reflects low glucose oxidation rate) and insufficient supply with ATP. 3.2.2. Hormonal regulation:

Glucagon, adrenaline, glucocorticoids activate synthesis of phosphoenolpyruvate kinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase;

- Insulin inhibits synthesis phosphoenolpyruvate kinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase.

3.3. Glucose-lactate cycle (Cori cycle):

- It links lactate formation in myocytes during anaerobic glycolysis and lactate use in gluconeogenesis in hepatocytes;

- Role: utilization of lactate, prevention of lactate accumulation and acidification.

3.4. Glucose-alanine cycle (Cahill cycle):

- Alanine which is formed in skeletal muscles is a substrate for hepatic gluconeogenesis;

- Glucose (muscle) → pyruvate (muscle) → alanine (muscle) → alanine (liver) → pyruvate (liver) → glucose (liver) → glucose (muscle);

- Role: transport of amino nitrogen from muscles to the liver in order to prevent lactic acidosis.

TESTS FOR SELF-CONTROL

- Which substance is involved in substrate-level phosphorylation in glycolysis?
 A. Glucose-6-phosphate B. Phosphoenolpyruvate
 C. Fructose-1,6-bisphosphate
 D. Glyceraldehyde-3-phosphate E. 2-Phosphoglycerate
- Choose a substance which serves as a substrate for gluconeogenesis:
 A. Glycogen B. Glucose C. Pyruvate
 D. Fructose E. Galactose
- Gluconeogenesis in the liver is activated in an athlete after an intense workout session. Indicate the main substrate for this process:
 A. Serine B. Lactate C. α -Ketoglutarate
 D. Aspartate E. Glutamate
- Choose an enzyme that catalyzes the reaction of glucose-6-phosphate formation from glucose in the liver:
 A. Hexose-phosphate isomerase B. Glucokinase C. Pyruvate kinase
 D. Glucose-6-phosphatase E. Phosphoglucomutase
- Indicate the final products of anaerobic glycolysis:
 A. CO_2 and H_2O B. Oxaloacetate C. Malate
 D. Pyruvate E. Lactate

6. Pyruvate kinase deficiency in erythrocytes is found in the organism of a child with symptoms of anemia. Which process is disturbed in RBCs?
- A. Oxidative phosphorylation
 B. Tissue respiration
 C. Anaerobic glycolysis
 D. Elimination of peroxides
 E. Deamination of amino acids
7. Choose the main regulatory enzyme of glycolysis:
- A. Phosphofructokinase
 B. Phosphorylase
 C. Lactate dehydrogenase
 D. Succinate dehydrogenase
 E. Pyruvate kinase
8. Choose an enzyme that catalyzes an irreversible reaction of glycolysis:
- A. Pyruvate kinase
 B. Aldolase
 C. Phosphoglycerate kinase
 D. Glyceraldehyde phosphate dehydrogenase
 E. Triosphosphate isomerase
9. Point out an enzyme that catalyzes the conversion of pyruvate under aerobic conditions:
- A. Pyruvate dehydrogenase
 B. Lactate dehydrogenase
 C. Aldolase
 D. Hexokinase
 E. Triosphosphate isomerase
10. Choose a substance which is not formed as a result of pyruvate oxidative decarboxylation:
- A. Acetyl-CoA
 B. CO₂
 C. NADH
 D. Glycerol-3-phosphate
 E. FADH₂
11. Select a metabolite which is used in the malate-aspartate shuttle system for hydrogen and electron transport of cytosolic NADH to the mitochondrial matrix.
- A. Aspartate
 B. α-Ketoglutarate
 C. Glutamate
 D. Glycerol-3-phosphate
 E. Malate
12. Point out final products of aerobic conversion of glucose in human tissues:
- A. Lactate
 B. Pyruvate
 C. CO₂ and H₂O
 D. Malate
 E. Acetone
13. The second stage of glucose aerobic oxidation in the cells is pyruvate oxidative decarboxylation. Point out the main product of this process:
- A. Succinyl-CoA
 B. Pyruvate
 C. Citrate
 D. Oxaloacetate
 E. Acetyl-CoA
14. Energy in the form of ATP is necessary for vital functions of erythrocytes. Which process provides these cells with the sufficient amount of ATP?
- A. Anaerobic glycolysis
 B. Aerobic oxidation of glucose
 C. Pentose phosphate pathway
 D. Tricarboxylic acid cycle
 E. β-Oxidation of fatty acids
15. Enzymes of glycolysis are localized in:
- A. Mitochondria
 B. Nucleus
 C. Cytosol
 D. Microsomes
 E. Polysomes
16. Carbohydrates are nonessential components of the human diet. They are synthesized in the body by means of gluconeogenesis from:
- A. Glycerol, fatty acids, leucine
 B. Lactate, cholesterol, carnitine
 C. Alanine, glycerol, lactate
 D. Choline, pyruvate, acetyl-CoA
 E. Glutamate, leucine, butyrate
17. Which of the enzymes mentioned below catalyzes the reaction that leads to the formation of a macroergic substance:
- A. Hexokinase
 B. Phosphofructokinase
 C. Pyruvate kinase
 D. Glyceraldehydophosphate dehydrogenase
 E. Phosphoglycerate mutase

18. Untrained people have delayed onset muscle soreness due to lactate accumulation in muscles after a sprint. Which biochemical process is intensified?

- A. *Gluconeogenesis* B. *Pentose phosphate pathway*
C. *Glycolysis* D. *Lipogenesis* E. *Glycogenesis*

19. A girl has marked signs of anemia. Laboratory tests revealed pyruvate kinase deficiency in red blood cells. Which process that plays a major role in the development of anemia is affected?

- A. *Anaerobic glycolysis* B. *Oxidative phosphorylation*
C. *Tissue respiration* D. *Peroxide breakdown*
E. *Amino acid deamination*

20. The following process is activated in the liver and kidney of a patient exhausted by starvation:

- A. *Urea synthesis* B. *Bilirubin synthesis* C. *Gluconeogenesis*
D. *Hippuric acid formation* E. *Uric acid synthesis*

21. Anaerobic glucose breakdown to lactic acid is regulated by the appropriate enzymes. Which enzyme is the main regulator of this process?

- A. *Glucose-6-phosphate isomerase* B. *Aldolase* C. *Enolase*
D. *Lactate dehydrogenase* E. *Phosphofructokinase*

22. Carbohydrate storage in the human body is quickly depleted due to prolonged starvation. Which metabolic process increases blood glucose levels in this case?

- A. *Anaerobic glycolysis* B. *Aerobic glycolysis* C. *Gluconeogenesis*
D. *Glycogenolysis* E. *Pentose phosphate pathway*

23. A large number of glucose oxidation metabolites are dissolved in the cytoplasm of myocytes. Give a name of the one of them that is directly converted to lactate:

- A. *Pyruvate* B. *Glucose-6-phosphate* C. *Glycerol phosphate*
D. *Fructose-6-phosphate* E. *Oxaloacetate*

24. A woman has inflammation of the gums (gingivitis), which is accompanied by tissue hypoxia. Which glucose metabolism metabolite is significantly increased in periodontal tissues?

- A. *Glycogen* B. *Lactate* C. *Ribose-5-phosphate*
D. *Glucose-6-phosphate* E. *NADPH*

25. Lactic acid is accumulated during intense muscular activity as a result of anaerobic glycolysis due to restricted blood flow. What is its metabolic fate?

- A. *It is used by tissues to synthesize ketone bodies*
B. *It is used by tissues to synthesize fatty acids*
C. *It is excreted by kidneys in the urine*
D. *It is used in muscles to produce amino acids*
E. *It serves as a substrate for gluconeogenesis in the liver*

26. Prolonged starvation increases the secretion of glucocorticoids by the adrenal cortex that enhance hepatic synthesis of gluconeogenesis enzymes. The terminal enzyme of this process is:

- A. *Glucose-1-phosphatase* B. *Fructose-2,6-bisphosphatase*
C. *Glucose-6-phosphatase* D. *Fructose-1-phosphatase*
E. *Fructose-1,6-bisphosphatase*

27. Insulin secretion by the pancreas in response to elevated glucose concentrations is impaired in diabetes mellitus. Which glycolysis enzymes are regulated by insulin?

- A. Aldolases, lactate dehydrogenases
- B. Phosphoglycerate mutases, lactate dehydrogenases
- C. Enolases, aldolases
- D. Glucokinases, phosphofructokinases
- E. Phosphoglycerate kinases, enolases

28. Hormonal regulation of gluconeogenesis is performed by glucocorticoids that increase the rate of its key enzymes in hepatocytes. Give their names.

- A. Aldolase
- B. Fructose-1,6-bisphosphatase
- C. Pyruvate kinase
- D. Hexokinase
- E. Glucokinase

29. Dietary glycogen is hydrolyzed in the gastrointestinal tract. What is the final product of this process?

- A. Glucose
- B. Lactate
- C. Lactose
- D. Galactose
- E. Fructose

30. Andersen disease belongs to a group of hereditary diseases that develop due to congenital deficiency of certain enzymes of glycogenolysis. Which enzyme deficiency is the molecular basis of this glycogen storage disease?

- A. Amylo(1,4-1,6)transglucosidases
- B. Glycogen synthase
- C. Glucose-6-phosphatase
- D. Lysosomal glucosidases
- E. Phosphofructokinase

31. In some anaerobic bacteria pyruvate that is produced as a result of glycolysis is converted into ethanol (alcoholic fermentation). What is the biological significance of this process?

- A. Lactate formation
- B. ADP formation
- C. NAD^+ generation
- D. NADPH generation
- E. ATP formation

32. Chronic glucocorticoid overdose leads to hyperglycemia. Give a name of the carbohydrate metabolism pathway whose activation increases blood glucose levels.

- A. Gluconeogenesis
- B. Glycogenolysis
- C. Aerobic glycolysis
- D. Pentose phosphate pathway
- E. Glycogenesis

33. After a week of starvation glucose level is maintained at a proper level. This happens due to the activation of:

- A. Glycogenolysis
- B. Glycolysis
- C. Gluconeogenesis
- D. Krebs cycle
- E. Glycogen phosphorylysis

34. A patient who had been prescribed with therapeutic fasting had normal blood glucose levels maintained by gluconeogenesis. Which amino acids were used as the substrates for glucose synthesis?

- A. Glutamate
- B. Lysine
- C. Valine
- D. Alanine
- E. Leucine

35. Normal fasting glucose level is maintained by the activation of gluconeogenesis. Which substance can be used as a substrate for this process?

- A. Ammonia
- B. Adenine
- C. Alanine
- D. Urea
- E. Guanine

36. The prolonged starvation leads to hypoglycemia, which is enhanced by alcohol consumption, since one of the following processes is inhibited:

- A. Gluconeogenesis
- B. Glycolysis
- C. Glycogenolysis
- D. Lipolysis
- E. Proteolysis

test tube on ice, continuously mixing it with a glass rod. Then the solution is heated upon a water bath and cooled to 20 °C. Add 1 drop of freshly prepared alkaline *para*-hydroxydiphenyl solution (50 mg *para*-hydroxydiphenyl dissolved in 3 ml of 3% sodium hydroxide) to the cooled mixture and put the test tube upon a water bath at 30 °C for 30 minutes, occasionally shaking it. Blue color appears in the test tube. Place the test tube for 90 seconds into intensely boiling water bath. The blue color turns purple. Then the mixture is cooled and photometrically using a PEC (green filter) in a cuvette with a layer thickness of 10 mm against water.

The lactate concentration in mmol/L is calculated in accordance with the following formula:

$$\text{Concentration of lactate} = \frac{C \cdot 1000}{0.1 \cdot 1000}$$

where C is the amount of lactic acid in the sample calculated using a calibration graph (mmol); 0.1 is a volume of blood taken for analysis (ml); 1,000 (the scaling factor for calculating per L of blood); 1,000 (the scaling factor for micromole-to-millimole conversion).

Clinical and diagnostic significance. Under normal conditions the blood lactic acid level is 0.50-2.50 mmol/L. Its elevated concentration can be observed in case of intense muscular work, as well as in diseases associated with hypoxia (cardiac insufficiency, chronic bronchitis, anemia, etc.).

Task 2. Determine the pyruvic acid concentration in the urine.

Principle. The method is based on the ability of pyruvate to form hydrazones with 2,4-dinitrophenylhydrazine in alkaline medium. Hydrazones are of yellow-orange color. The intensity of color is proportional to the pyruvate concentration.

Procedure. The control and experimental samples are placed simultaneously (use dry test tubes, pipettes, and thick cells only). Take two test tubes, add 1 ml of distilled water to the control one and pour 1 ml of urine into the experimental one. Then pour 1 ml of 2.5% KOH alcoholic solution into both test tubes, mix for 1 min and add 0.5 ml of 0.1% 2,4-dinitrophenylhydrazine solution, mix with a stirring rod and leave to stand for 15 min at room temperature. After that, determine the absorbance of the test sample versus control cuvettes with a layer thickness of 5 mm with light green color filters by photocolometric method. The resulting optical density values are used to find the pyruvate content (mg) in 1 ml of urine in accordance with the analytical curve. The calculation is carried out in the following way:

$$\text{Pyruvate (mg/day)} = a \times 1.5 \text{ (or 1.2)}$$

where a is an amount of pyruvate present in the sample solution estimated by the analytical curve; 1.5 (or 1.2) are coefficients that take into account the daily diuresis and conversion from μg into mg.

Clinical and diagnostic significance. Under normal conditions the pyruvate content in the urine is 10-25 mg/day (113.7-283.9 mmol/day). High pyruvate levels are observed in patients with thiamine deficiency, diabetes mellitus, cardiac insufficiency, overactive pituitary-adrenal axis, due to vigorous exercises, consumption of certain medications, e.g., camphor, strychnine, and adrenaline. Reduced pyruvate levels are observed as a result of anesthesia.

1**. Prepare a review in accordance with the following topic: "Mechanisms of transmembrane monosaccharide transport into the cells. Glucose transporters."

2**. Prepare a presentation in accordance with the following topic: "Sugar loading tests: procedure, types of glycemic curves, diagnostic significance."

3**. Prepare a brief review in accordance with the following topic: "Glucuronic pathway of glucose metabolism."

CLASS 4 (4 hours)

Topic 6 (4 hours): Pentose phosphate pathway of glucose oxidation. Metabolism of fructose and galactose. Regulation and pathology of carbohydrate metabolism. Determination of blood glucose levels by glucose oxidase method.

IMPORTANCE. Apart from the major pathways of intracellular glucose metabolism (aerobic oxidation and glycolytic cleavage) the alternative pathways of its transformation are available in the body (the pentose phosphate pathway, conversion to glucuronic acid, etc.). Knowledge of these pathways and fructose and galactose metabolic pathways, their roles in the energy and plastic processes of cells are important for the future doctors, since it will be necessary to normalize them. Glycosaminoglycans (GAGs) (mucopolysaccharides) are heteropolysaccharides which structural fragments are disaccharides. The composition of GAGs includes hexuronic acid, glucosamine or galactosamine N-acetyl derivatives. GAGs catabolism occurs in lysosomes by specific glycosidases. Hereditary defects of these enzymes lead to the development of mucopolysaccharidoses – severe diseases which cause serious disorders of children’s development affecting duration of their lives. Changes in the concentration of carbohydrates, their metabolites and enzyme activity indicate fairly objectively carbohydrate metabolism abnormalities during various diseases.

AIM. Study the biochemical features of alternative pathways of monosaccharide metabolism: pentose phosphate pathway of glucose oxidation, fructose and galactose metabolism. Familiarize yourself with glycosaminoglycans and their metabolism in the body. Learn the basic questions about specific peculiarities of carbohydrate metabolism under normal and pathological conditions. Be able to analyze changes in blood glucose levels, mechanisms of their hormonal regulation, pathological manifestations of disorders of glucose metabolism: diabetes mellitus, starvation. Explain the molecular basis of hereditary enzymopathies of fructose, galactose, glycogen, and glycosaminoglycans metabolism. Interpret the concept of normo-, hyper- and hypoglycemia, glycosuria as normal and pathological states of glucose metabolism. Be able to link theoretical knowledge with specific results of laboratory tests and use them as criteria for the assessment of normal and pathological conditions. Read about the glucose oxidase method used for determination of blood glucose and its clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1 Pentose phosphate pathway of glucose oxidation: key stages, biological role.
- 2 Role of the pentose phosphate pathway of glucose oxidation in RBCs. Hereditary disorders of activity and synthesis of glucose-6-phosphate dehydrogenase in erythrocytes.
- 3 Metabolism of fructose and galactose.

- 4* Glycosaminoglycans. Structure and role. Features of metabolism.
- 5* Effects of glucagon, adrenaline, glucocorticoids, growth hormone, and insulin on blood glucose levels. Their mechanisms.
- 6 Normal blood glucose level and its disorders (hyper- and hypoglycemia). Glycosuria.
- 7 Clinical and biochemical characteristics of diabetes mellitus (insulin-dependent and noninsulin-dependent types).
- 8. Inherited disorders of monosaccharide metabolism (fructosemia, galactosemia).
- 9. Mucopolysaccharidoses. Genetic disorders of glycosaminoglycans metabolism.
- 10* Changes in carbohydrate metabolism in hypoxia.
- 11* Neonatal hypoglycemia.
- 12* Disorders of carbohydrate metabolism associated with deficiency of disaccharidases (lactase, maltase, sucrase).
- 13* Inherited disorders of glycogen metabolism (glycogen storage diseases).

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<p><i>1. Glycosaminoglycans. Structure, role. Their metabolism.</i></p>	<p><i>1.1. Glycosaminoglycans (GAGs) are heterosaccharides whose monosaccharide components are hexuronic acid (D-glucuronic acid, L-iduronic acid) and N-acetyl derivatives of hexosamines (glucosamine, galactosamine). They are always attached to proteins (proteoglycans):</i></p> <ul style="list-style-type: none"> <i>- Representatives: hyaluronic acid, chondroitin sulfates, dermatan sulfates, keratan sulfates, heparan sulfates, and heparin;</i> <i>- They perform their functions after binding to proteins, forming proteoglycans → components of the skin, tendons, cartilages, joints → they provide mechanical strength and elasticity of organs and joints; they perform protective (mucus components, physiological lubricants) and hydroosmotic (hyaluronic acid) roles;</i> <i>- Heparin acts as a natural anticoagulant;</i> <i>- GAG synthesis:</i> <i>- Polysaccharide chains are synthesized by the sequential attachment of monosaccharides;</i> <i>- Their synthesis is catalyzed by the following enzymes: Transferases are localized on the membranes of the Golgi apparatus; protein components that are produced on polyribosomes are transferred via channels of endoplasmic reticulum to last through the channels. Monosaccharides are</i>

	<p>attached forming polysaccharide chains;</p> <ul style="list-style-type: none"> - Amino sugars are synthesized from glucose; a direct precursor of N-acetylglucosamine, N-acetylgalactosamine and sialic acid is fructose-6-phosphate, and glutamine serves as a source of NH₂ groups; amino sugars are acetylated using acetyl-CoA; - Sources of glucuronic acid source: food, intracellular lysosomal degradation of GAGs and its synthesis; active form - UDP-glucuronate is produced by UDP-glucose oxidation; - L-Iduronic acid is synthesized after incorporation of D-glucuronic acid in the carbohydrate chain in the epimerization reaction. - GAG breakdown is carried out by exo- or endoglycosidases, sulfatases (hyaluronidase, glucuronidase, galactosidase, iduronidase, etc.); - Disorders: - Mucopolysaccharidoses are caused by genetic defects of enzymes involved in GAG catabolism → excessive accumulation of GAGs in tissues; increased urinary excretion → skeletal abnormalities, enlargement of organs that contain significant amounts of extracellular matrix elements; damage to tissues that normally synthesize the highest amount of GAGs → mental retardation, damage to vessels, corneal clouding, skeletal deformity, reduced life expectancy. <p>For example, Sly disease: β-glucuronidase genetic defect → accumulation of chondroitin sulfates; Hurler disease - α-L-iduronidase deficiency → accumulation of dermatan- and heparan sulphates.</p>
<p>2. Effects and mechanisms of action of glucagon, adrenaline, glucocorticoids, growth hormone, and insulin on blood glucose level.</p>	<p>2.1. Glucagon (hyperglycemic effect): It increases the rate of key gluconeogenesis enzymes in hepatocytes – phosphoenolpyruvate kinase, fructose-1,6-bisphosphatase, glucose-6-phosphatase; it stimulates glycogen phosphorolysis activating the adenylyl cyclase system in the membranes of hepatocytes.</p> <p>2.2. Adrenaline (hyperglycemic effect): It stimulates glycogen phosphorolysis in muscles and liver; It activates synthesis of gluconeogenesis enzymes in the liver - phosphoenolpyruvate kinase, fructose-1,6-bisphosphatase, glucose-6-phosphatase.</p> <p>2.3. Glucocorticoids (hyperglycemic effect): They stimulate gluconeogenesis by activating</p>

	<p><i>phosphoenolpyruvate kinase and enzymes that produces substrates for gluconeogenesis - glucogenic amino acids.</i></p> <p><i>2.4. Growth hormone (hyperglycemic effect): It decreases the permeability of cell membranes of muscle cells and adipose tissue to glucose; It activates hepatic gluconeogenesis.</i></p> <p><i>2.5. Insulin (hypoglycemic action): It inhibits synthesis of gluconeogenesis enzymes - phosphoenolpyruvate kinase, fructose-1,6-bisphosphatase, glucose-6-phosphatase; It increases the permeability of cell membranes to glucose; It stimulates the synthesis of key enzymes of glycolysis - hexokinase, phosphofructokinase, pyruvate kinase; It stimulates glycogen synthesis in the liver and muscles.</i></p> <p><i>2.6. Other hormones that participate in blood glucose level regulation: somatostatin, prolactin, thyroid hormones (T3, T4), etc.</i></p>
<p><i>3. Changes in carbohydrate metabolism in hypoxic conditions.</i></p>	<p><i>3.1. Activation of anaerobic glycolysis - stimulation of phosphofructokinase.</i></p> <p><i>3.2. Low rate of pyruvate oxidation and Krebs cycle compared to the rate of glycolysis.</i></p> <p><i>3.3. Accumulation of lactate and pyruvate in the blood.</i></p> <p><i>3.4. Inhibition of gluconeogenesis.</i></p> <p><i>3.5. Lactate acidosis.</i></p>
<p><i>4. Neonatal hypoglycemia.</i></p>	<p><i>4.1. Types: transient, persistent, congenital abnormalities of carbohydrate metabolism.</i></p> <p><i>4.2. Transient state:</i></p> <ul style="list-style-type: none"> <i>- In the first 72 hours of life blood glucose level varies from 1.67 to 2.2 mmol/L; according to the WHO recommendations, glucose level that exceeds 2.6 mmol/L is safe; the minimum level is observed during 30-90 minutes of life; glucose levels for the first day of life should exceed 2.5 mmol/L;</i> <i>- Causes: maternal insulin-dependent diabetes, intracranial fetal malnutrition, perinatal asphyxia, cooling, infections;</i> <i>- Symptoms: tremor, irritability, convulsions, muscle hypotonia, hypodynamia, cyanosis, etc.</i>
<p><i>5. Disorders of carbohydrate metabolism caused by deficiency of disaccharidases (lactase,</i></p>	<p><i>5.1. Lactase deficiency: Lactose intolerance. Lactose undergoes fermentation performed by intestinal microorganisms; Clinical symptoms: diarrhea, flatulence;</i></p>

<i>maltase, sucrase).</i>	<i>5.2. Sucrase and isomaltase deficiency: It manifests when newborns start eating fruit juices, purees; Symptoms - diarrhea, flatulence, growth retardation.</i>
<i>6. Inherited disorders of glycogen metabolism (glycogen storage diseases).</i>	<p><i>6.1. Glycogen storage diseases are hereditary disorders associated with deficiency of glycogenolysis enzymes → glycogen accumulation in the internal organs and tissues; Symptoms - hypoglycemia, hepatomegaly, fatty liver, cirrhosis, cramps during exercise: Gierke's disease (glucose-6-phosphatase deficiency); Pompe's disease (insufficiency of lysosomal glycosidases); Forbes' disease (amylo-1,6-glucosidase - deficiency); Andersen disease (amylo-transglucosidase); McArdle disease (muscle glycogen phosphorylase); Hers' disease (liver glycogen phosphorylase deficiency); Tarui's disease (muscle phosphofructokinase deficiency).</i></p> <p><i>6.2. Glycogen storage disease type 0 is an inherited disease associated with glycogen accumulation due to genetic defects in the formation of glycogen synthase; Symptoms - hypoglycemia, especially on an empty stomach, coma.</i></p>

TESTS FOR SELF-CONTROL

1. Hypovitaminosis B₁ was found in a patient. Which pentose phosphate pathway enzyme activity was decreased?
 - A. *Transketolase*
 - B. *Ketoisomerase*
 - C. *Transaldolase*
 - D. *Glucose-6-phosphate dehydrogenase*
 - E. *Gluconolactonase*
2. Point out a localization of reactions and enzymes of pentose phosphate pathway of glucose metabolism in cells of tissues:
 - A. *Nucleus*
 - B. *Mitochondria*
 - C. *Cell membrane*
 - D. *Cytosol*
 - E. *Ribosome*
3. Glucose oxidation pathways of glycolysis and pentose phosphate pathway are bifurcated at:
 - A. *Cleavage of fructose-1,6-bisphosphate*
 - B. *Pyruvate formation*
 - C. *Glucose-6-phosphate conversion*
 - D. *Lactate formation*
 - E. *Phosphoenolpyruvate formation*
4. Pentose phosphate pathway of glucose oxidation is the source of:
 - A. *Fatty acids and ATP*
 - B. *Nucleic acids and FADH₂*
 - C. *Essential amino acids and ATP*
 - D. *Nonessential amino acids and FADH₂*
 - E. *Ribose-5-phosphate and NADPH*
5. Activated hemolysis was observed in a child who had had the increased body temperature and had been given aspirin. Which enzyme congenital deficiency could cause hemolytic anemia?
 - A. *Glycerol phosphate dehydrogenase*
 - B. *Glucose-6-phosphatase*

C. *Glycogen phosphorylase* D. *Glucose-6-phosphate dehydrogenase*
E. *γ-Glutaminyltransferase*

6. A boy has the cataract, enlarged liver and spleen. His blood sugar level is also elevated, albeit glucose tolerance test results are normal. The cause of such changes is hereditary impaired metabolism of a substance. What is the name of this substance?

A. *Glucose* B. *Fructose* C. *Galactose*
D. *Maltose* E. *Sucrose*

7. Select an enzyme whose inherited deficiency is the cause of fructosemia:

A. *Fructokinase* B. *Phosphofructokinase* C. *Hexokinase*
D. *Glucokinase* E. *Pyruvate kinase*

8. Which substance concentration has to be determined in the blood of patients with glycogen storage disease VI type?

A. *Glucose* B. *Fructose* C. *Galactose*
D. *Alanine* E. *Uric acid*

9. Give a name to a metabolic process whose activity is reduced in insulin-dependent diabetes mellitus:

A. *Glucose uptake by tissues* B. *Glycogenolysis* C. *Proteolysis*
D. *Gluconeogenesis* E. *Lipolysis*

10. Point out a hormone that reduces blood glucose concentration if it exceeds 6.8 mmol/L.

A. *Thyroxine* B. *Glucagon* C. *Testosterone*
D. *Epinephrine* E. *Insulin*

11. Patient's fasting blood glucose level had been 5.55 mmol/L, 1 hour after the sugar load it changed to 8.55 mmol/L and after 2 hours it changed to 4.95 mmol/L. Such levels are typical for:

A. *Healthy individual* B. *Patient with thyrotoxicosis*
C. *Patient was a latent form of diabetes mellitus*
D. *Patients with insulin-dependent diabetes mellitus*
E. *Patients with insulin-independent diabetes mellitus*

12. The cataract develops in aged women as a complication of diabetes mellitus. Give a name to the process whose stimulation causes clouding of the lens.

A. *Lipogenesis* B. *Lipolysis* C. *Gluconeogenesis*
D. *Glycosylation of proteins* E. *Proteolysis*

13. A patient complains of fatigue, constant thirst. Preliminary diagnosis is diabetes mellitus. Select a plasma glucose concentration that confirms the diagnosis.

A. *8.5 mmol/L* B. *2.0 mmol/L* C. *4.5 mmol/L*
D. *5.0 mmol/L* E. *3.3 mmol/L*

14. Liver and kidney enlargement, growth retardation, convulsions (due to hypoglycemia) were found in a newborn. The following examination revealed the lack of glucose-6-phosphatase. Point out the type of glycogen storage disease caused by a hereditary defect of this enzyme synthesis:

A. *Gierke's disease* B. *Pompe's disease* C. *Anderson's disease*
D. *Mc-Ardle's disease* E. *Tompson's disease*

15. Renal threshold for glucose is:

A. *5-7 mmol/L* B. *8-10 mmol/L* C. *10-15 mmol/L*
D. *2-3 mmol/L* E. *15-20 mmol/L*

16. A patient has hemolysis caused by glucose-6-phosphate dehydrogenase deficiency after intake of aspirin and sulfonamides. Which coenzyme formation is impaired in this pathology?
 A. *NADH₂* B. *FADH₂* C. *Pyridoxal phosphate*
 D. *FMNH₂* E. *Ubiquinone*
17. An infant was hospitalized to the intensive unit due to vomiting, diarrhea, growth and development retardation, cataract, and mental retardation. He was diagnosed with galactosemia. Which enzyme deficiency was observed?
 A. *Glucokinase* B. *Hexose-1-phosphate uridyltransferase*
 C. *UDP-glucose-4-epimerase* D. *Glucose-6-phosphate dehydrogenase*
 E. *UDP-glucose pyrophosphorylase*
18. High galactose levels were found against the background of lower glucose concentrations. Cataract, mental retardation, and fatty liver were observed. Which disease can be diagnosed?
 A. *Diabetes mellitus* B. *Lactosemia* C. *Steroid diabetes*
 D. *Fructosemia* E. *Galactosemia*
19. Purine ring is synthesized using ribose-5-phosphate. What is its source in the body?
 A. *Glycolysis* B. *Glycogenesis* C. *Pentose phosphate pathway*
 D. *Gluconeogenesis* E. *Glycogenolysis*
20. A patient's blood glucose fasting level is 5.6 mmol/L. One hour after sugar loading it is 13.8 mmol/L. After 3 hours it reaches 9.2 mmol/L. Such changes are typical for:
 A. *Wilson's disease* B. *Acromegaly*
 C. *Latent diabetes mellitus* D. *Graves' disease* E. *Health*
21. A 40-year-old woman complaining of thirst, increased appetite was hospitalized to the endocrinology department with diabetes. Which pathological components can be found in the patient's urine?
 A. *Protein, amino acid* B. *Glucose, ketone bodies*
 C. *Protein, creatine* D. *Bilirubin, urobilin* E. *Blood*
22. An individual's blood glucose level is 15 mmol/L (the reabsorption threshold is 10 mmol/L). What will this cause?
 A. *Low vasopressin secretion* B. *Low diuresis*
 C. *Low aldosterone secretion* D. *Glucosuria*
 E. *Low glucose reabsorption*
23. A woman has a cataract (clouding of the lens) and diabetes mellitus. What type of protein modification occurs in diabetic cataract?
 A. *Glycosylation* B. *Methylation* C. *ADP-ribosylation*
 D. *Limited proteolysis* E. *Phosphorylation*
24. Glucose catabolism in the pentose phosphate pathway allows forming various monosaccharide phosphates. Which of these substances can be used for nucleic acid synthesis?
 A. *Erythrose-4-phosphate* B. *Ribose-5-phosphate*
 C. *Ribulose-5-phosphate* D. *Sedoheptulose-7-phosphate*
 E. *Xylulose-5-phosphate*
25. Which glycosaminoglycan is the most common for bone tissue and plays a key role in the formation of cartilages and bones?

- A. Dermatan sulfate* *B. Chondroitin sulfate*
C. Keratan sulfate *D. Heparin* *E. Hyaluronic acid*

26. A 58-year-old patient was hospitalized in severe condition: altered consciousness, dry skin, sunken eyes, cyanosis, and odor of rotten apples out of his mouth. Blood glucose level is 15.1 mmol/L. The content of glucose in the urine is 3.5%. What is the possible cause?

- A. Hyperglycemic coma* *B. Uremic coma*
C. Hypovolemic coma *D. Hypoglycemic coma* *E. Obstructive jaundice*

27. A 6-month-old baby had symptoms of dyspepsia (diarrhea, flatulence) after addition of fruit juices to his diet. Which enzyme deficiency is observed?

- A. Rennin* *B. Pepsin* *C. Sucrase*
D. Alpha-amylase *E. Lactase*

28. Fructose-containing diet provoked fructosemia, fructosuria, and severe hypoglycemia. Which enzyme is deficient?

- A. Fructokinase* *B. UDP-galactose-4-epimerase*
C. Fructose-1-phosphate aldolase *D. Phosphoglucomutase*
E. Galactokinase

29. The oxidative phase of pentose phosphate pathway is accompanied by the formation of NADPH and ribose-5-phosphate. Ribose-5-phosphate is directly used for the synthesis of:

- A. Nucleotides* *B. Aminoacids* *C. Vitamins*
D. Fatty acids *E. Lipoproteins*

30. A 16-year-old teenager was hospitalized due to insulin-dependent diabetes mellitus. The glucose level in his blood was 18 mmol/L. Insulin was injected. Two hours later blood glucose level dropped to 8.2 mmol/L, since insulin promotes:

- A. Inhibition of ketone bodies synthesis from glucose*
B. Stimulation of glycogen breakdown in muscles
C. Stimulation of glucose conversion into glycogen and TAGs in the liver
D. Stimulation of glucose uptake by brain and liver cells
E. Stimulation of glycogen synthesis in muscles

31. Patients with diabetes mellitus have the high activity of the metabolic pathway that converts glucose into fructose. Which substance is accumulated in the lens in addition to fructose and is the biochemical basis of diabetic cataract?

- A. Skatole* *B. Indole* *C. Alkapton*
D. Glycosaminoglycans *E. Sorbitol*

32. A 38-year-old unconscious female patient was delivered to the intensive care unit. The reflexes are absent. Blood sugar level is 2.1 mmol/L. He has been suffering from diabetes mellitus since he turned 18 years. Which type of coma is observed?

- A. Ketonemic* *B. Hypoglycemic* *C. Lactate acidosis*
D. Hyperosmolar *E. Hyperglycemic*

33. A 12-year-old patient has dramatically lost weight during 3 months. His blood glucose level reaches 50 mmol/L. He had a coma. What is the main mechanism of its development?

- A. Hypoglycemic* *B. Ketonemic* *C. Lactate acidosis*
D. Hyperosmolar *E. Hypoxic*

34. An ill child has mental retardation, liver enlargement, problems with vision. The physician suspects galactose-1-phosphate uridylyltransferase deficiency. Which pathological process is observed?

- A. Galactosemia B. Fructosemia C. Hyperglycemia
D. Hypoglycemia E. Lactate acidosis

35. A five-year-old-boy has growth and mental retardation, coarse facial features. These features have been observed since he turned 18 months. L-Iduronidase deficiency is found. Metabolism of which substances is impaired?

- A. Nucleotides B. Proteins C. Vitamins
D. Phospholipids E. Glycosaminoglycans

36. A child who was breastfed had dyspepsia, weight loss, jaundice, and liver enlargement. The doctor had prescribed a special diet instead of breast milk, which made the child feel better. Which disease could cause such symptoms?

- A. Homocystinuria B. Cystic fibrosis C. Galactosemia
D. Phenylketonuria E. Fructosemia

37. Vomiting and diarrhea after taking fruit juices were revealed in a 8-month-old child. A fructose load test caused hypoglycemia. Which enzyme inherited deficiency is responsible for such symptoms?

- A. Fructokinase B. Hexokinase C. Phosphofructokinase
D. Fructose-1-phosphate aldolase E. Fructose-1,6-bisphosphatase

38. Erythrocytes of individuals with inherited glucose-6-phosphate dehydrogenase deficiency have a tendency to hemolysis. Which metabolic process is affected?

- A. Pentose phosphate pathway of glucose oxidation
B. Gluconeogenesis C. Aerobic glucose oxidation
D. Glycogen synthesis E. None of them

39. A diabetic patient fainted after injection of insulin. He had convulsions. Which result (mmol/L) of the blood glucose analysis is plausible?

- A. 8.0 mmol/L B. 3.3 mmol/L
C. 2.5 mmol/L D. 10.0 mmol/L E. 5.5 mmol/L

40. An unconscious patient was hospitalized. According to those who accompanied him, he had fainted at the end of the marathon. What kind of coma can be diagnosed?

- A. Hyperglycemic B. Hypoglycemic C. Ketonemic
D. Hypothyroid E. Hepatic

PRACTICAL WORK

Quantitative determination of blood glucose levels by glucose oxidase method

Task. Determine the blood glucose concentration by glucose oxidase method.

Principle. Glucose oxidase method is specific and widely used in clinical and diagnostic laboratories to determine the true blood glucose level in the presence of various carbohydrates and other reducing substances of non-carbohydrate nature. It is especially appropriate to use the glucose oxidase method for diagnosing diabetes mellitus and other diseases associated with impaired carbohydrate metabolism. The method is based on the specificity of the enzyme glucose oxidase, which oxidizes glucose to gluconic acid. Glucose oxidase is a flavoprotein whose prosthetic group is

FAD. A transfer of two hydrogen atoms to FAD leads to its reduction and then FADH₂ transfers them to molecular oxygen with the formation of hydrogen peroxide. The resulting hydrogen peroxide oxidizes *ortho*-toluidine in the presence of enzyme peroxidase. Reduced toluidine is colorless, and the oxidized one turns blue. The intensity of the color formed in the reaction is determined with the help of PEC.

Procedure. Add 0.1 ml of blood to the centrifuge tube. Mix it with 1.1 ml of isotonic sodium chloride solution. Add 0.4 ml of 5% zinc sulfate solution and 0.4 ml of 0.3 mmol/L sodium hydroxide solution and mix. After 10 minutes, centrifugate it at a speed of 2,500 rpm for 10 min. Add 3 ml of the enzyme-chromogenic reagent to 1 ml of supernatant, mix and measure the absorbance of the solution after precisely 20 minutes in a cuvette with a layer thickness of 10 mm at a wavelength of 625 nm against a control sample in which water is added instead of supernatant. Time between addition of enzyme-chromogenic reagent and measurement of optical density must be the same for all samples. Determine the optical density of the standard sample solution with glucose concentration of 27.8 mmol/L diluted 5 times.

The content of glucose in the sample is calculated in accordance with the following formula:

$$\text{Glucose concentration} = D_{\text{exp}} \cdot C / D_{\text{st}}$$

where D_{exp} is an optical density of the test sample; D_{st} is an optical density of the standard sample of glucose; C is a concentration of glucose in the standard sample solution.

Clinical and diagnostic significance. *It is important to have an objective picture of the carbohydrate metabolism, whose major index is the blood glucose level, in diagnosis of certain diseases (diabetes mellitus, pathological conditions associated with abnormal functions of the liver and kidney, endocrinopathies, tumors of the brain, pancreas, adrenal glands, thiamine deficiency, and inherited enzymopathies). Normal glucose concentration in capillary blood is 3.38-5.55 mmol/L; it is 3.3-5.5 mmol/L for serum and plasma. Elevated blood glucose level is called hyperglycemia and is observed in the following cases: 1) after intake of excessive amounts of carbohydrates - alimentary hyperglycemia; 2) during stress (in cases of severe emotional and mental stimulation); 3) diabetes mellitus, acute pancreatitis, pancreatic cirrhosis which are associated with lower levels of insulin in the body; 4) in patients with an overactive thyroid gland, adrenal cortex and adrenal medulla, pituitary gland; 5) in patients with toxic, traumatic, or mechanical damages to the central nervous system (trauma, brain tumors, epilepsy, meningitis), carbon monoxide, cyanide, ether poisoning, etc.*

There are the following causes of a glucose decrease in blood (hypoglycemia): 1) fasting, unbalanced diet (alimentary hypoglycemia); 2) abnormal digestion and absorption of carbohydrates due to diseases of the small intestine; 3) an overdose of insulin in the treatment of diabetes mellitus; 4) kidney diseases when impaired tubular reabsorption of glucose is observed; 5) heart failure (sometimes); 6) hypofunction of the pituitary and thyroid glands, adrenal cortex and medulla; 7) phosphorus, benzene, chloroform poisoning; 8) large loss of blood; 9) hyperfunction of pancreatic Langerhans' islets.

1.** Draw a scheme of the hormonal regulation for carbohydrate metabolism.

2**. Prepare a brief review in accordance with the following topic:
"Carbohydrate metabolism in Cushing's disease."

3**. Prepare a review in accordance with the following topic:
"Mucopolysaccharisoses and possible ways of their treatment."

CLASS 5 (4 hours)

**Topic 7 (4 hours): Digestion and absorption of lipids. Role of bile acids.
Resynthesis of fats in the intestine. Reactions for bile acids.**

IMPORTANCE. Lipids serve as structural components of cell membranes in the body. They are storage forms of metabolic "fuel." Lipids protect organs, blood vessels, and nerves, enveloping them and preventing mechanical damage. Lipids or their derivatives may serve as biologically active substances such as hormones, vitamins, and prostaglandins. Digestion of dietary lipids occurs mainly in the intestine. One of the key steps of the process is emulsification. It is also necessary to provide active pancreatic lipase. The main emulsifier of lipids is bile. It contains bile acids whose functions include not only emulsification of lipids but also activation of pancreatic lipase and active participation in the process of absorption of fatty acids, formation of micelles, and stabilization of cholesterol. Causes of abnormal digestion of dietary lipids are changes in functioning of the pancreas, gallbladder, liver and intestine leading to the development of other diseases. Since lipids are hydrophobic substances, they are transported in plasma attached to proteins only. Fatty acids are transported by albumins, and other lipids are transported in the form of lipoproteins. The imbalance of lipoprotein fractions is a factor that affects the blood vessels, that is why their content is often determined in clinical practice. In addition, the measurement of blood lipoprotein content allows evaluating the functional state of the liver.

AIM. Study the biochemical mechanisms of digestion of dietary lipids in the gastrointestinal tract, the role of bile acids in this process, mechanisms of fat resynthesis in the intestinal wall, steatorrhea types: pancreatic, hepatogenic, enterogenic. Read about the qualitative reactions for bile acids and their clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1*. Lipids. Biological role. Classification. Structure and functions of simple lipids.
- 2*. Lipids. Structure and functions of complex lipids (phospholipids and glycolipids).
3. Daily requirements for lipids. Digestion and absorption of dietary lipids.
4. Structures of bile acids. Role of bile acids in the digestion and absorption of lipids.
5. Lipases of the gastrointestinal tract. Role of pancreatic lipase.
- 6*. Resynthesis of fats in enterocytes. Its importance and role of MAG in this process.
7. Disorders of digestion and absorption of lipids.
8. Blood plasma lipoproteins – transport forms of lipids. Classification, chemical composition, functions, metabolism.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<p>1. Lipids. Biological role. Classification. Structure and functions of simple lipids.</p>	<p>1.1. Definition of lipids as compounds insoluble in water and other polar solvents and soluble in non-polar liquids.</p> <p>1.2. Biological role: energy, structural (cell components, especially abundant in biological membranes), regulatory (steroid hormones, eicosanoids, vitamin D), protective, insulative, precursors of biologically active compounds, storage (TAG), etc.</p> <p>1.3. Classification:</p> <ul style="list-style-type: none"> - Simple (their hydrolysis forms alcohol and fatty acids): acylglycerols, sterols, waxes; - Complex (hydrolysis forms alcohol - glycerol, sphingosine or inositol, as well as phosphate, nitrogen-containing compounds, carbohydrates): <ul style="list-style-type: none"> - phospholipids (glycerophospholipids, sphingophospholipids); - glycolipids (glycosylglycerols, glycosphingolipids - cerebrosides, gangliosides, sulfatides, globosides); - Derivatives of lipids: steroid hormones, bile acids, eicosanoids. <p>1.4. Structure and functions of simple lipids:</p> <ul style="list-style-type: none"> - Acylglycerols are esters of glycerol and fatty acids; role – energy storage, protection; localization - adipocytes of the adipose tissue; - Steroids are esters of sterols (e.g., cholesterol) and fatty acids; role of cholesterol - structural (cell membrane component), precursor of biologically active substances (vitamin D₃, sex hormones, corticosteroids); - Waxes are esters of fatty acids and alcohols (beeswax, lanolin).
<p>2. Lipids. Structure and functions of complex lipids (phospholipids and glycolipids).</p>	<p>2.1. Definition: lipids which are cleaved by hydrolysis to alcohol, phosphate, carbohydrates, and nitrogen-containing compounds.</p> <p>2.2. Phospholipids:</p> <ul style="list-style-type: none"> - Glycerophospholipids are esters of glycerol and fatty acids (derivatives of phosphatidic acid): phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol; - Sphingolipids are esters of sphingosine and fatty acids (sphingomyelins);

	<ul style="list-style-type: none"> - Role - structural (found in biological tissues); secondary messengers (phosphatidylinositols). 2.3. Glycolipids are compounds whose lipid part is covalently attached to the carbohydrate fragment (glucose, galactose, and their derivatives or oligosaccharide groups): esters of fatty acids and glycerol or sphingosine: <ul style="list-style-type: none"> - Glycosylglycerols (glycerol esters); - Glycosphingolipids - glycolipids are esters of N-acylsphingosines: cerebrosides are monohexoses of ceramides (galactocerebrosides and glucocerebrosides); sulfatides (galactocerebroside sulfates); globosides are oligosaccharide derivatives of ceramides; gangliosides; - Role - structural (in particular, structural components of cell membranes).
<p>3. Resynthesis of fats in enterocytes, its significance; role of β-MAG in this process.</p>	<p>3.1. Monoglyceride pathway (smooth endoplasmic reticulum of enterocytes) – from β-monoglycerides and fatty acids which entered the intestinal epithelial cells via absorption:</p> <ul style="list-style-type: none"> - Fatty acid activation - formation of acyl-CoA by acyl-CoA synthetase; - Formation of diacylglycerols by intestinal monoacylglycerol acyltransferase; - Formation of triacylglycerols by diacylglycerol acyltransferase. <p>3.2. α-Glycerolphosphate pathway (rough endoplasmic reticulum of enterocytes) occurs when intestinal epithelial cells receive primarily fatty acids:</p> <ul style="list-style-type: none"> - Fatty acid activation - formation of acyl-CoA by acyl-CoA synthetase; - Formation of α-glycerolphosphate by glycerol kinase; - Conversion of alpha-glycerolphosphate in phosphatidic acid by glycerolphosphate acyltransferase; - Conversion of phosphatidic acid into by phosphatidate phosphohydrolase; - Acetylation of diacylglycerol to form triacylglycerol by diglyceride acyltransferase. <p>3.3. Role: "adaptation" of dietary fats to body fats during re-synthesis.</p>

TESTS FOR SELF-CONTROL

- The main emulsifiers of fats are:
A. Polyunsaturated fatty acids *B. Saturated fatty acids*
C. Bile acids *D. Bicarbonates* *E. Phosphates*
- A patient complains of bad feeling after a fatty meal. He has frequent diarrhea, loss of weight. Causes of these events may be all the below-mentioned except for:
A. Pancreatitis *B. Enterocolitis* *C. Gastritis*
D. Cholelithiasis *E. Hepatitis*
- Bile acids in bile are present in conjugated forms with:
A. Cholesterol *B. Bilirubin* *C. Glycine and alanine*
D. Glycine and taurine *E. Taurine and valine*
- Which of the acids mentioned below belongs to bile acids?
A. Linoleic acid *B. Arachidonic acid* *C. Oleic acid*
D. Cholic acid *E. Myristic acid*
- Lysophospholipids in the intestine are formed under the action of:
A. Phospholipase A₁ *B. Phospholipase A₂* *C. Phospholipase C*
D. Phospholipase D *E. Phospholipase B*
- Bile acids are derived from:
A. Cholesterol *B. Phospholipids* *C. Triacylglycerols*
D. Glycogen *E. Glycolipids*
- Cholesterol performs all the functions mentioned below except for:
A. It is a component of cell membranes
B. It is a substrate for bile acid synthesis
C. It is a substrate for vitamin D₃ synthesis
D. It is a source of energy
E. It is a substrate for of steroid hormones synthesis
- Linoleic and linolenic acids are necessary for the organism as precursors of eicosanoids. The basic source of these acids for humans is:
A. Alimentary factor *B. Biosynthesis of fatty acids*
C. Cholesterol degradation
D. Microsomal oxidation *E. Oxidation of fatty acids*
- Which pancreatic enzyme is activated by bile acids?
A. Trypsin *B. Chymotrypsin* *C. Amylase*
D. Proelastase *E. Lipase*
- Prostaglandin E₂ is used for stimulation of childbirth. Which acid is this substance synthesized from?
A. Phosphatidic acid *B. Palmitic acid* *C. Stearic acid*
D. Glutamic acid *E. Arachidonic acid*
- What is the function of bile acids in digestion and absorption of lipids in the gastrointestinal tract?
A. They catalyze hydrolysis of lipids
B. They prevent the cleavage of proteins
C. They emulsify fats *D. They transport monosaccharides*
E. They provide excretion of fats from the organism

12. Which of the below-mentioned fatty acids is not synthesized in the human organism?
A. Oleic acid *B. Linoleic acid* *C. Palmitic acid*
D. Stearic acid *E. Palmitooleic acid*
13. A patient has vomiting and steatorrhea after a fatty meal. What is its cause?
A. Deficiency of amylase *B. Increased secretion of lipase*
C. Disturbance of phospholipase synthesis
D. Disturbance of trypsin synthesis *E. Deficiency of bile acids*
14. A patient feels discomfort after eating fatty food. His feces contain undigested fat droplets. The reaction for bile acids in the urine is positive. The reason for this pathology is the deficiency of:
A. Fatty acids *B. Chylomicrons* *C. Bile acids*
D. TAGs *E. Phospholipids*
15. In humans, triacylglycerols (TAGs) are mainly stored in the adipose tissue. However, their synthesis occurs in hepatocytes. Which substance transports TAGs from the liver to the adipose tissue?
A. Chylomicrons *B. LDL* *C. HDL*
D. TAG-albumin complex *E. VLDL*
16. The patient's examination revealed elevated blood serum LDL levels. Which disease can be predicted?
A. Renal disorders *B. Acute pancreatitis* *C. Atherosclerosis*
D. Gastritis *E. Pneumonia*
17. A patient feels nausea, fatigue after eating fatty food. Steatorrhea appeared. His cholesterol level is 9.2 mmol/L. His condition is due to the deficiency of:
A. TAGs *B. Bile acids* *C. Fatty acids*
D. Phospholipids *E. Chylomicrons*
18. The patient's blood plasma is found to be turbid study 4 hours after eating fatty food. The most possible reason for this condition is high plasma concentrations of:
A. Chylomicrons *B. HDL* *C. LDL*
D. Cholesterol *E. Phospholipids*
19. Which enzyme insufficiency leads to incomplete digestion of fats in the gastrointestinal tract and appearance of neutral fats in feces?
A. Phospholipases *B. Enterokinases* *C. Pancreatic lipases*
D. Amylases *E. Pepsin*
20. A patient suffers from atherosclerosis of the lower extremities and coronary heart disease. The examination revealed disorders of the lipid blood lipid spectrum. The excess of certain lipoproteins can serve as the main link in the pathogenesis of atherosclerosis? Give a name of these lipoproteins:
A. Cholesterol *B. Chylomicrons* *C. IDLs*
D. LDLs *E. HDLs*
21. A patient has frequent diarrhea, especially after eating fatty food, body weight loss. Laboratory studies showed steatorrhea and hypocholic feces. What can serve as the reason for such pathology?
A. Inadequate diet *B. Pancreatic lipase insufficiency*
C. Small intestinal inflammation *D. Bile duct obstruction*
E. Pancreatic phospholipase insufficiency

22. Lipoprotein lipase deficiency that hydrolyzes triglycerides of chylomicrons on the surface of endothelial cells in the adipose tissue is found in a female patient. Which biochemical abnormalities should be expected?

- A. *Hyperlipoproteinemia IIa* B. *Hyperlipoproteinemia IV*
C. *Hyperlipoproteinemia I* D. *Hyperlipoproteinemia III*
E. *Hyperlipoproteinemia IIb*

23. High HDL levels reduce the risk of atherosclerosis. What is the mechanism of their anti-atherogenic activity?

- A. *Extraction of cholesterol from tissues*
B. *Delivery of cholesterol to tissues*
C. *Participation in cholesterol breakdown*
D. *Activation of cholesterol conversion into bile acids*
E. *Contribution to cholesterol absorption in the intestine*

24. A patient who had undergone the anti-atherosclerotic therapy had high levels of the anti-atherogenic lipoprotein fraction. Select a lipoprotein whose high blood levels confirm the effectiveness of the anti-atherosclerotic therapy:

- A. *VLDL* B. *LDL* C. *IDL* D. *HDL* E. *Chylomicrons*

25. A patient has normally colored feces that have inclusions of free fatty acids. The plausible reason for this is abnormal:

- A. *Bile secretion* B. *Hydrolysis of fats* C. *Lipase secretion*
D. *Bile formation* E. *Absorption of fats*

26. The coprological test revealed that feces were colorless. There were drops of neutral fat. The most plausible cause is abnormal:

- A. *Gastric acidity* B. *Pancreatic secretion*
C. *Bile secretion into the duodenum*
D. *Intestinal secretion* E. *Intestinal absorption*

27. The patient's feces are grayish-white and contain a lot of undigested fats. Select the possible reason for this phenomenon:

- A. *Bile duct obstruction*
B. *Insufficient activation of pepsin by hydrochloric acid*
C. *Vitamin deficiency* D. *Enteritis*
E. *Alteration of intestinal epithelial cells*

28. A patient prefers eggs, lard, butter, milk, and meat. His blood tests showed: cholesterol - 12.3 mmol/L, total lipids - 8.2 g/L, high low density lipoproteins. Which type of hyperlipoproteinemia is observed?

- A. *Hyperlipoproteinemia I* B. *Hyperlipoproteinemia IIb*
C. *Hyperlipoproteinemia IV* D. *Hyperlipoproteinemia IIa*
E. *Hyperlipoproteinemia III*

29. The bile flow into the duodenum is stopped due to the common bile duct obstruction (revealed by X-ray analysis). What will be affected?

- A. *Absorption of amino acids* B. *Hydrolysis of carbohydrates*
C. *Emulsification of fats* D. *Hydrochloric acid secretion*
E. *Inhibition of salivation*

30. Choose a class of lipoproteins that contain the highest amount of protein.

- A. *IDL* B. *VLDL* C. *Chylomicrons* D. *LDL* E. *HDL*

PRACTICAL WORK
Qualitative reactions for bile acids

Aim. Carry out a qualitative reaction for bile acids.

A) *Guy's reaction.*

Principle. Bile acids have the ability to reduce the surface tension of urine.

Procedure. Add 20-30 ml of urine to a glass and then sift finely pounded sulfur powder on the urine through gauze. If the urine contains bile acids, the sulfur precipitates in 5 minutes. Sulfur remains on the surface in the absence of bile acids in the urine, even after shaking mildly the glass. This test becomes positive when the concentration of bile acids and their salts in the urine exceeds 0.01%.

B) *Petenkoffer's reaction.*

Principle. The interaction of bile acids with hydroxymethylfurfural forms purple products. Hydroxymethylfurfural is formed from fructose (sucrose) after its interaction with concentrated sulfuric acid.

Procedure. Put 2-3 drops of urine, 2 drops of sucrose solution into either a Petri dish or a slide and mix thoroughly with a glass rod. Then add 7 drops of concentrated sulfuric acid and mix again with a glass rod. Red color appears in the presence of bile acids in a few minutes, which gradually transforms. Then it gradually turns purple-red.

C) *Reaction with peptone and salicylic acid.*

Procedure. Filter 5-10 ml of urine until it becomes absolutely transparent; if necessary, acidify it with acetic acid and dilute to the relative density below 1.008. Measure 2 ml of the filtered and diluted urine and add 5 ml of a reagent containing peptone and salicylic acid. Milk-like turbidity appears in the presence of bile acids in the urine.

Clinical and diagnostic significance. Bile acids play an important role in the digestion and absorption of lipids. They provide emulsification of fats, activation of pancreatic lipase and formation of mixed micelles. Under normal conditions bile acids undergo enterohepatic circulation and are excreted from the body through the intestine. Normal urine does not usually include bile acids. They appear in the urine in case of obstructive jaundice. Their amount increases if the obstruction of the bile ducts lasts for a long time. Bile acids in the urine can be also detected in parenchymal jaundice.

1**. Prepare a presentation in accordance with the following topic: "Modified lipoproteins."

2**. Prepare a review in accordance with the following topic: "Essential dietary lipids."

CLASS 6(4 hours)

Topic 8 (2 hours): Metabolism of triacylglycerols and phospholipids. Quantitative determination of blood serum lipoproteins.

IMPORTANCE. Fat depots contain large amounts of triacylglycerols, which are substrates for lipolysis. Lipolysis is performed by the action of cellular lipases, which are activated by norepinephrine and epinephrine. The breakdown of lipids in the cells is accompanied by the release of energy, and their synthesis (lipogenesis) is stimulated by insulin. Phospholipids are a group of lipids containing phosphate and

often nitrogen-containing moieties (choline, ethanolamine, etc.). A number of pathological conditions are accompanied by impaired metabolism of triacylglycerols and phospholipids.

AIM. Study general features of TAG and phospholipid metabolism, as well as its regulation. Study the method for quantitative determination of blood serum lipoproteins and its clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1 Catabolism of triacylglycerols in adipocytes (lipolysis), reactions.
- 2 Neurohumoral regulation of lipolysis by epinephrine, norepinephrine, glucagon, and insulin.
- 3 Biological role of triacylglycerol synthesis in intestinal enterocytes, liver, and adipose tissue.
- 4* Metabolism of phosphoglycerols and sphingolipids.
- 5* Genetic disorders of sphingolipid metabolism – sphingolipidoses. Lysosomal storage diseases: Niemann-Pick disease, Tay-Sachs diseases, Gaucher disease.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<p>1. <i>Metabolism of phosphoglycerols and sphingolipids.</i></p>	<p>1.1. <i>Metabolism of phosphoglycerols.</i></p> <p>1.1.1. <i>Stages of glycerophospholipid synthesis:</i></p> <ul style="list-style-type: none"> - <i>Formation of phosphatidic acid via GAP and DAP;</i> - <i>Removal of phosphate from phosphatidic acid by phosphatidase and diacylglycerol formation;</i> - <i>Formation of the active form of the phospholipid "polar" head;</i> - <i>Interaction of diacylglycerol with cytidine diphosphate (CDP) derivatives and formation of phospholipids.</i> <p>1.1.2. <i>The main component of lung surfactant is dipalmitoylphosphatidylcholine (80% of total phospholipids).</i></p> <p>1.2.3. <i>Synthesis of phosphatidylinositol and cardiolipin:</i></p> <ul style="list-style-type: none"> - <i>Formation of CDP-DAG, and then phosphatidylinositol and cardiolipin;</i> - <i>Cardiolipin is a component of the mitochondrial inner membrane, lung surfactant.</i> <p>1.2.4. <i>Catabolism of glycerophospholipids:</i></p> <ul style="list-style-type: none"> - <i>Role of phospholipases (cell membranes, lysosomes);</i> - <i>Formation of second messengers and precursors in the synthesis of eicosanoids;</i> - <i>Role of phospholipase A1 and A2 in fatty acid synthesis.</i>

	<p><i>1.2. Metabolism of sphingolipids.</i></p> <p><i>1.2.1. Sphingolipids are derivatives of ceramide (sphingosine and fatty acid): sphingomyelins and glycosphingolipids; distribution in cell membranes different of tissue, especially in the nervous tissue.</i></p> <p><i>1.2.2. Synthesis of sphingolipids:</i></p> <ul style="list-style-type: none"> - <i>Formation of sphingosine from palmitoyl-CoA and serine by NADPH-dependent dehydrogenase;</i> - <i>Formation of ceramide by N-acetylation of sphingosine amino groups by a particular fatty acid;</i> - <i>Formation of glycosphingolipids via addition of monosaccharide residues and their derivatives to -CH₂OH groups of ceramides.</i> <p><i>1.2.3. Catabolism:</i></p> <ul style="list-style-type: none"> - <i>Sphingolipids are catabolyzed gradually by lysosomal hydrolases: sphingomyelin → ceramide + phosphocholine;</i> - <i>Glycosphingolipids are gradually catabolyzed by removing monosaccharide residues from the oligosaccharide end of the molecules.</i>
<p><i>2. Genetic disorders of sphingolipid metabolism – sphingolipidoses.</i></p> <p><i>Lysosomal storage disease.</i></p>	<p><i>2.1. Sphingolipidoses ("lysosomal storage diseases") are genetic diseases caused by deficiency of one of the glycosphingolipid metabolism enzymes, which may lead to death at an early age, abnormal accumulation of sphingolipids and their metabolites in the brain and other tissues.</i></p> <p><i>2.2. Niemann-Pick disease is an inherited sphingomyelinase deficiency;</i> <i>Symptoms: hepato- and splenomegaly (accumulation of sphingomyelins in lysosomes), mental retardation.</i></p> <p><i>2.3. Farber disease is a genetic ceramidase defect;</i> <i>Symptoms: hepato- and-splenomegaly; affected joints (pain, swelling).</i></p> <p><i>2.4. Gaucher disease is a genetic glucocerebrosidase deficiency;</i> <i>Symptoms: hepato- and splenomegaly, damage to bones, neuropathy.</i></p> <p><i>2.5. Tay-Sachs disease is a beta-hexosaminidase deficiency;</i> <i>Symptoms: mental retardation, blindness, neurological disorders.</i></p>

TESTS FOR SELF-CONTROL

- Choose a second messenger that participates in activation of hormone-sensitive triacylglycerol lipase:
A. cGMP *B. cAMP* *C. Diacylglycerol*
D. Ca²⁺ *E. Inositol triphosphate*
- Choose a substance that is the precursor of phosphatidylcholine:
A. Phosphatidylethanolamine *B. Phosphatidylserine*
C. Phosphatidylinositol *D. Plasmalogen* *E. Cardiolipin*
- Choose a macroergic substance whose energy is used for the synthesis of triacylglycerols:
A. CTP *B. GTP* *C. ATP* *D. UTP* *E. ADP*
- Select enzymes splitting phospholipids:
A. Pancreatic lipase *B. Monoacylglycerol lipase*
C. Lysophospholipase
D. Intestinal lipase *E. Phospholipases A₁, A₂, D*
- Point out a hormone-sensitive enzyme of lipolysis in the adipose tissue:
A. Triacylglycerol lipase *B. Diacylglycerol lipase*
C. Monoacylglycerol lipase *D. Phospholipase*
E. Cholesterol esterase
- Point out lipids transported by chylomicrons:
A. Endogenous fats *B. Exogenous fats* *C. Cholesterol*
D. Phospholipids *E. Cholesterol and its esters*
- Select a substrate used for the formation of glycerol-3-phosphate in triacylglycerol biosynthesis in the adipose tissue:
A. Glyceraldehyde phosphate *B. Glycerol* *C. Glycerate*
D. Dihydroxyacetone phosphate *E. Pyruvate*
- Alimentary hyperlipemia manifests by an increase in the blood level of:
A. Phospholipids *B. Triacylglycerols* *C. Cholesterol*
D. Glycolipids *E. Chylomicrons*
- Fatty liver is prevented by lipotropic substances. Which of the below-mentioned substances belongs to this group?
A. Methionine *B. Cholesterol* *C. Bilirubin*
D. Glycine *E. Glucose*
- A hormone that inhibits lipolysis in the adipose tissue is called:
A. Insulin *B. Adrenaline* *C. Glucagon*
D. Thyroxin *E. Corticotropin*
- Atherogenic factors containing the highest amount of cholesterol are called:
A. Chylomicrons *B. α -Lipoproteins* *C. β -Lipoproteins*
D. Pre- β -lipoproteins *E. Albumins*
- Synthesis of phospholipids is affected in patients with fatty liver. Which of the substances mentioned below can stimulate the process of methylation in synthesis of phospholipids?
A. Methionine *B. Vitamin C* *C. Glucose*
D. Glycerol *E. Citrate*

- 13.** A patient has an elevated LDL blood level. Which disease may be diagnosed?
A. Gastritis *B. Renal diseases* *C. Acute pancreatitis*
D. Atherosclerosis *E. Pneumonia*
- 14.** Adipose tissue is the main organ for triacylglycerol storage in the human organism. Synthesis of TAGs also occurs in the liver. Which substances transport TAGs from liver to adipose tissue?
A. Chylomicrons *B. VLDL* *C. LDL*
D. HDL *E. Complex with albumins*
- 15.** Pheochromocytoma is observed in a man. Elevated levels of adrenaline and noradrenaline are found in his blood. The concentration of fatty acids is 11 times higher. Which enzyme activation enhances lipolysis under the action of adrenaline?
A. TAG lipase *B. Lipoprotein lipase* *C. Phospholipase A*
D. Phospholipase C *E. Cholesterol esterase*
- 16.** Lipolysis is an enzymatic process of fat hydrolysis to fatty acids and glycerol. The fatty acids formed as a result enter the bloodstream and are transported by:
A. LDL *B. Globulins* *C. HDL*
D. Albumins *E. Chylomicrons*
- 17.** Accumulation of significant amounts of lipids was found in the lysosomes in a cell culture derived from a patient with the lysosomal pathology. Which disease can be diagnosed?
A. Phenylketonuria *B. Gout* *C. Wilson's disease*
D. Tay-Sachs disease *E. Galactosemia*
- 18.** A 2-year-old child showed signs of the dramatic neurodevelopmental disability, affected sense of hearing and vision, a substantial liver and spleen enlargement. Niemann-Pick disease was diagnosed. Which genetic defect could cause this disease?
A. Amylo-1,6-glucosidase deficiency *B. Acid lipase deficiency*
C. Xanthine oxidase deficiency *D. Glucose-6-phosphatase deficiency*
E. Sphingomyelinase deficiency
- 19.** Prolonged negative emotional stress is accompanied by the release of catecholamines. It can cause significant weight loss. What is the cause of this?
A. Activation of lipolysis *B. Enhancement of oxidative phosphorylation*
C. Abnormal synthesis of lipids *D. Activation of protein degradation*
E. Disorders of digestion
- 20.** A dry cleaning worker has the fatty liver. Which substance synthesis is affected in case of this pathology?
A. Tristearyl glycerol *B. Urea* *C. Phosphatidylcholine*
D. phosphatidic acid *E. Cholic acid*
- 21.** Lack or insufficient formation of lipotropic factors in the human body may lead to the fatty liver. Which substances belong to lipotropic ones?
A. TAGs *B. Choline* *C. Cholesterol*
D. Fatty acids *E. Riboflavin*
- 22.** Higher levels of free fatty acids are observed in a diabetic patient. What is the cause of this?
A. Activation of TAG-lipase in adipocytes
B. Accumulation of palmitoyl-CoA in cytosol
C. Activation of ketone bodies catabolism

D. Activation of apo A-1, A-2, A-4 synthesis

E. Inactivation of blood plasma phosphatidylcholine cholesterol acyltransferase

23. Steatosis is caused by accumulation of triacylglycerols in hepatocytes. One of its mechanisms is a decrease in the utilization of VLDL neutral fats. Which lipotropic substances prevent the development of steatosis?

- A. Alanine, B₁, PP* *B. Arginine, B₃, B₁₂* *C. Valine, B₃, B₂*
D. Isoleucine, B₁, B₂ *E. Methionine, B₆, B₁₂*

24. A female woman complains of her child's poor health: loss of appetite, sleeplessness, irritability. The biochemical investigation revealed the absence of glucocerebrosidase. What is the possible diagnosis?

- A. Niemann-Pick disease* *B. Gierke's disease* *C. Gaucher disease*
D. Tay-Sachs disease *E. Pompe disease*

25. A young male consumes excessive amounts of carbohydrates (600 grams per day). This amount exceeds his energy requirements. Which process is activated in this case?

- A. Gluconeogenesis* *B. Lypolysis* *C. Oxidation of fatty acids*
D. Glycolysis *E. Lipogenesis*

26. Abnormal myelination of nerve fibers leads to neurological disorders and mental retardation. These symptoms are typical for hereditary and acquired metabolic disorders of:

- A. Neutral fats* *B. Cholesterol* *C. Sphingolipids*
D. Fatty acids *E. Phosphatidic acids*

27. A vitamin-like substance choline forms a part of phospholipids that serve as the major components of biological membranes. The donor of methyl groups for their synthesis is a sulfur-containing amino acid called:

- A. Methionine* *B. Serine* *C. Alanine*
D. Glycine *E. Threonine*

28. A protein hormone that is synthesized in adipocytes controls the hypothalamic regulation of food intake and energy catabolism. Which of the following hormones prevents the development of obesity?

- A. Anserine* *B. Glutathione* *C. Insulin*
D. Leptin *E. Glucagon*

29. A two-year mentally retarded child with severe neurologic disorders was diagnosed with Gaucher disease. Which substances are accumulated in the brain in this disease?

- A. Sulfatides* *B. Globulins* *C. Gangliosides*
D. Sphingolipids *E. Glucocerebrosides*

30. Lipids are stored in adipocytes as lipid droplets. Such droplets are primarily composed of:

- A. TAGs* *B. Phospholipids* *C. Cholesterol*
D. Cholesterol esters *E. Lipoproteins*

31. Triacylglycerols in humans are synthesized triacylglycerols from glycerol and activated fatty acids. Select an organ with the highest rate of TAG synthesis:

- A. Brain* *B. Intestine* *C. Liver, adipose tissue*
D. Lungs, adrenal glands *E. Skeletal muscles*

PRACTICAL WORK

Quantitative determination of blood serum LDL, VLDL, and total lipids

Task 1. Determine the serum content of LDL and VLDL by turbidimetric Burstein's and Samail's method.

Principle. The method is based on the ability of heparin to form a complex with serum LDL and VLDL which precipitates under the influence of calcium chloride. The degree of the solution turbidity is proportional to the blood serum content of these lipoproteins.

Procedure. Pour 2 ml of 0.025 mol/L calcium chloride solution into the left-side and the right-side 0.5 cm thick photocolormetric cells. Set a 720 nm wavelength (red light filter) for the left-side one. Add 0.2 ml serum using a micropipette to the right-side cell, wash the pipette several times. Note the initial value of the extinction E_1 and then add 0.04 ml of heparin solution containing 1000 units per 1 ml to the right-side cell using a micropipette, wash the micropipette several times. Mix the content of the cell. After 4 minutes (monitor this with a stopwatch) measure again the extinction E_2 . The content of LDL and VLDL (X) in g/L in serum is calculated in accordance with the following formula:

$$X = (E_2 - E_1) \times 11.65,$$

where 11.65 is an empirical coefficient for gram per liter conversion of LDL and VLDL concentrations.

Clinical and diagnostic significance. Ultracentrifugation can separate blood lipoproteins according to their different densities: high (HDL), low (LDL), very low (VLDL), etc. Lipoprotein fractions differ in their protein content and a percentage of certain lipid components. HDLs have large amounts of proteins (50-60%) and a higher density (1.063-1.210), while LDLs and VLDLs contain less protein, a significant amount of lipids (up to 95% by weight). In addition, they have low relative density (1.010-1.063). The concentration of serum lipoproteins varies between 3.6 g/L and 6.5 g/L. An enhanced blood serum concentration is most commonly observed for β -lipoproteins. Elevated lipoprotein levels are closely related to cholesterol excess in blood, since β -lipoproteins are especially rich in cholesterol. Elevation of β - and pre- β -lipoproteins is observed in atherosclerosis, diabetes mellitus, and other diseases.

Task 2. Determine the content of blood serum total lipids.

Principle. The method is based on the ability of the breakdown products of unsaturated lipids to form colored compounds with phosphovanillyl reagents. The intensity of color is proportional to the content of total lipids in blood serum.

Procedure. Add 0.1 ml of serum to a dry experimental test tube and gently add 2.9 ml of concentrated sulfuric acid. Then add 0.2 ml of water and 5.8 ml of concentrated sulfuric acid to the control test tube. Solutions in both test tubes should be thoroughly mixed with a glass rod and placed upon a boiling water bath for 10 min (caution!). Then both test tubes should be rapidly cooled to room temperature under running cold water. Add 0.2 ml from the experimental tubes and 0.4 ml of chilled mixture from the control tubes to other test tubes where the phosphovanillyl reagent is present: 3 ml should be in the experimental test tubes and 6 ml of the reagent should be in the control ones. After mixing with a glass rod, samples are placed in a dark place at room temperature for 45 minutes to provide conditions for changing their color.

Photometry the experimental sample against the control one at PEC at 500-560 nm (green filter) in 0.5 cm thick cells. The content of serum total lipids X in g/L is calculated in accordance with the following formula:

$$X = (m \times 10,000 \times 3) / (0.2 \times 1,000)$$

where m is the amount of total lipid in a sample calculated according to the analytic curve (mg); 10,000 is the scaling factor for volume conversion per 1 liter of blood serum; 1,000 is the scaling factor for milligram-to-gram conversion; 3 is the total volume of the original mixture (0.1 ml serum plus 2.9 ml of concentrated sulfuric acid); 0.2 ml is a volume of mixture taken for the colored reaction (ml).

Clinical and diagnostic significance. *The content of blood lipids (including triglycerides, phospholipids, cholesterol, fatty acids) attached to proteins (albumins) and as lipoproteins is an important diagnostic parameter. The normal content of serum total lipids is 4-8 g/L. High levels of lipids in the blood (hyperlipemia) as a physiological phenomenon are observed within 1-4 hours after consumption of lipid-rich food. Fasting levels of total lipids are usually lowered (hypolipemia). Elevated concentrations of lipids in the blood can be revealed in diabetes mellitus (up to 10-20 g/L), liver cirrhosis, atherosclerosis, obesity, coronary heart disease, lipid nephrosis (kidney disease), acute hepatitis, pancreatitis; due to alcohol abuse.*

Topic 9 (2 hours): Metabolism of fatty acids and ketone bodies. Glycerol metabolism. Qualitative reactions for ketone bodies.

IMPORTANCE. Fatty acids primarily play an energy role. When fatty acids are intensely oxidized, a significant amount of ketone bodies (acetoacetate and β -hydroxybutyrate) is produced in the liver. Ketone bodies are transported to blood and tissues, where they are completely oxidized in the Krebs cycle. Under pathological circumstances (severe forms of diabetes mellitus, starvation) an intensive formation and accumulation of ketone bodies is observed. Glycerol metabolism in the cells of the body plays an important role in the release of energy. In addition, glycerol can be converted into carbohydrates.

AIM. Study basic information about fatty acid metabolism (synthesis and β -oxidation) and the ways of its regulation. Familiarize yourself with ketogenesis and ketolysis, impaired metabolism of ketone bodies. Learn basic metabolic pathways of glycerol metabolism. Study qualitative reactions for ketone bodies in the urine and their clinical and diagnostic significance.

THEORETICAL QUESTIONS

1. β -Oxidation of saturated and unsaturated fatty acids. Localization and mechanism of the process. Its relationship to the Krebs cycle and tissue respiration. Role of carnitine in the transport of fatty acids from cytosol to mitochondria.
2. Activation of fatty acids. Show it using stearic acid as an example. Determine the energy value of its complete oxidation.
3. Energy value of fatty acid β -oxidation
4. β -Oxidation of butyric acid. Vitamins involved in the formation of coenzymes required for this process.

5. β -Oxidation of caproic acid. Energy value of its complete oxidation.
6. Biosynthesis of fatty acids. Features and functions of acetyl-CoA carboxylase and palmitate synthase complex. Regulation of the process.
- 7*. Biosynthesis of monounsaturated fatty acids in humans.
8. Ketone bodies. Reactions of biosynthesis and utilization of ketone bodies: localization in the organism, biological significance. Ketonemia and ketonuria in diabetes mellitus, starvation, and other diseases.
- 9*. Glycerol metabolism: oxidation to CO_2 and H_2O , conversion to carbohydrates. Reactions.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
1. Biosynthesis of monounsaturated fatty acids in the body.	1.1. Key representatives – palmitoleic and oleic acids. 1.2. Synthesis: - By dehydrogenation of the corresponding saturated acids (palmitic and stearic acids); - by the fatty acid desaturation system (acyl-CoA oxygenase); - Role of NAD(P)H and cytochrome b5.
2. Glycerol metabolism: oxidation to CO_2 and H_2O ; conversion to carbohydrates.	2.1. ATP-dependent glycerol activation by glycerol kinase with conversion to glycerol-3-phosphate. 2.2. Glycerol-3-phosphate oxidation by mitochondrial NAD-dependent dehydrogenase forming glyceraldehyde- 3-phosphate. 2.3. Phospholipid biosynthesis. 2.4. Pyruvate metabolism. 2.5. Oxidation to CO_2 and H_2O ; the energy balance of the complete glycerol oxidation is 22 ATP molecules. 2.6. Participation in gluconeogenesis.

TESTS FOR SELF-CONTROL

1. Select the final product of β -oxidation of fatty acids with even number of carbon atoms:

<i>A. Succinyl-CoA</i>	<i>B. Acetyl-CoA</i>	<i>C. Acetoacetyl-CoA</i>
<i>D. Propionyl-CoA</i>	<i>E. Hydroxymethylglutaryl-CoA</i>	
2. Which of the substances mentioned below belongs to ketone bodies?

<i>A. Acetic acid</i>	<i>B. Butyric acid</i>	<i>C. Palmitic acid</i>
<i>D. Oleic acid</i>	<i>E. Acetoacetate</i>	
3. Which of the blood proteins mentioned below transports fatty acids?

<i>A. Globulins</i>	<i>B. Hemoglobin</i>	<i>C. Albumins</i>
<i>D. α-Lipoproteins</i>	<i>E. β-Lipoproteins</i>	
4. Which pathology is associated with the development of ketonemia?

<i>A. Myocardial infarction</i>	<i>B. Atherosclerosis</i>	<i>C. Diabetes mellitus</i>
<i>D. Rheumatism</i>	<i>E. Acute viral infections</i>	

5. Which product is formed by condensation of 2 acetyl-CoA molecules in ketone bodies synthesis?
 A. *Hydroxybutyrate* B. *Acetoacetate* C. *Acetone*
 D. *Succinyl-CoA* E. *Acetoacetyl-CoA*
6. Point out a place of ketone bodies synthesis in organism:
 A. *Liver* B. *Kidney* C. *Muscles*
 D. *Pancreas* E. *Lungs*
7. Select a vitamin-like substance that participates in the transport of fatty acids from cytosol to mitochondria:
 A. *HS-CoA* B. *Carnitine* C. *Biotin*
 D. *Pantothenic acid* E. *Folic acid*
8. How many carbon atoms are removed from fatty acid carbon skeleton by means of 1 cycle of β -oxidation?
 A. *3 carbon atoms* B. *4 carbon atoms* C. *2 carbon atoms*
 D. *1 carbon atom* E. *0 carbon atoms*
9. A woman complains of thirst and enhanced appetite. She is delivered to the endocrine hospital with diagnosis of diabetes mellitus. Which pathologic components can be identified in the urine during the laboratory analysis?
 A. *Protein, ketone bodies* B. *Protein, creatine*
 C. *Glucose, ketone bodies* D. *Bilirubin, urobilin* E. *Blood*
10. Aerobic oxidation of substrates is typical for cardiac muscle. Point out the major one:
 A. *Fatty acids* B. *Triacylglycerols* C. *Glycerol*
 D. *Glucose* E. *Amino acids*
11. What is the initial substrate for the synthesis of ketone bodies in the liver?
 A. *Butyryl-CoA* B. *Acyl-CoA* C. *Acetyl-CoA*
 D. *Propionyl-CoA* E. *Succinyl-CoA*
12. Hyperketonemia is observed in all cases mentioned below except for:
 A. *Starvation* B. *Diabetes mellitus*
 C. *Excess of carbohydrates in diet*
 D. *Chronic stress* E. *Thyrotoxicosis*
13. Select the final product of β -oxidation of fatty acids with odd number of carbon atoms:
 A. *Succinyl-CoA* B. *Acetyl-CoA* C. *Acetoacetyl-CoA*
 D. *Propionyl-CoA* E. *Hydroxymethylglutaryl-CoA*
14. Oxidation of ketone bodies (acetoacetate) occurs in one of the pathways mentioned below:
 A. *Glycolysis* B. *Oxidative decarboxylation of ketoacids*
 C. *Tricarboxylic acid cycle* D. *Pentose phosphate pathway*
 E. *Respiratory chain*
15. Which of the following states is the consequence of hyperketonemia:
 A. *Fatty liver* B. *Acidosis* C. *Obesity*
 D. *Exhaustion* E. *Atherosclerosis*
16. A medicine containing carnitine is recommended to an athlete to increase his results. Which process is activated by carnitine?
 A. *Ketone bodies synthesis* B. *Tissue respiration* C. *Lipid synthesis*
 D. *Transport of fatty acid to mitochondria*
 E. *Steroid hormone synthesis*

17. Ketoacidosis developed in a patient who was suffering from diabetes. The biochemical cause of this condition is the reduced acetyl-CoA utilization as a result of an enzyme deficiency:

- A. *Hydroxyglutarate* B. *Glutamate* C. *Oxaloacetate*
D. *Aspartate* E. *Succinate*

18. A child was hospitalized with signs of muscle injury. Carnitine deficiency in muscles was found. What forms the biochemical basis for this pathology?

- A. *Transport of fatty acids to mitochondria*
B. *Regulation of mitochondrial Ca^{2+} levels*
C. *Phosphorylation* D. *Lactate utilization*
E. *Synthesis of actin and myosin*

19. A patient in coma was hospitalized. He has been suffering from diabetes mellitus for 5 years. The examination revealed: rapid and deep breathing, odor of acetone was detected. Blood glucose level is 15.2 mmol/L, ketone bodies - 1.3 mmol/L. Which complication is characterized by such changes?

- A. *Hepatic coma* B. *Hypoglycemic coma*
C. *Uremic coma* D. *Ketonemic coma*
E. *All the options mentioned above are correct*

20. Biotin deficiency causes an impairment of fatty acid synthesis. Which metabolite is not formed under such conditions?

- A. *Alanine* B. *Serotonine* C. *Malonyl-CoA*
D. *Pyruvate* E. *Succinyl-CoA*

21. Fatty acids which are high-energy compounds are metabolized in mitochondria with the release of a large amount of energy. How is this process called?

- A. *Beta-oxidation* B. *Transamination* C. *Deamination*
D. *Reduction* E. *Decarboxylation*

22. The rate of fatty acid synthesis is reduced in biotin deficiency. Which enzyme inactivation is observed in this case?

- A. *Pyruvate dehydrogenase* B. *Citrate synthase*
C. *Enoyl reductase* D. *Alanine aminotransferase*
E. *Acetyl-CoA carboxylase*

23. A male patient with diabetes mellitus in anamnesis was hospitalized due to ketonemic precoma. Which metabolite is elevated in his blood?

- A. *Alpha-ketoglutarate* B. *Acetoacetate* C. *Aspartate*
D. *Malonate* E. *Citrate*

24. Each cycle of fatty acid oxidation includes four successive reactions. What substances are formed per one cycle?

- A. *Acetyl-CoA only* B. *NADH only* C. *FADH₂ only*
D. *Acetyl-CoA, NADH, FADH₂* E. *NADH and FADH₂ only*

25. It has been known that fatty acid synthesis occurs in the cytosol. Which substance acts as a reducing agent in this process?

- A. *NADH* B. *NADPH* C. *FADH₂*
D. *FAD* E. *NAD*

26. An obese patient was recommended to use carnitine as a dietary supplement to "burn" fats. How carnitine is involved in oxidation of fats?

- A. Transport of fatty acids from cytosol to mitochondria
- B. Transport of fatty acids from adipocytes to tissues
- C. Participation in one of the reactions of beta-oxidation
- D. Activation of fatty acids
- E. Activation of intracellular lipolysis

PRACTICAL WORK

Qualitative reactions for ketone bodies in the urine

Task. Carry out qualitative reactions for ketone bodies in the urine.

A) *Legal's reaction for acetone and acetoacetic acid (AAA).*

Principle. Acetone and AAA give an orange-red color with sodium nitroprusside in an alkaline medium. Acidification with glacial acetic acid intensifies the coloration of the solution.

Procedure. Place 1 drop of urine, 1 drop of 10% sodium hydroxide, and 1 drop of freshly prepared 10% sodium nitroprusside solution on a slide glass. Orange-red coloration appears. Addition of 3 drops of glacial acetic acid causes the development of cherry-red coloration. The coloration is not stable and disappears while standing.

B) *Gerhard's reaction for AAA*

Principle. The method is based on the interaction of Fe^{3+} with enol form of AAA with the formation of the red-purple-colored complex.

Progress. 5 drops of urine should be added dropwise to 5% ferric chloride solution leading to ferric phosphate precipitate formation. In the presence of AAA the further addition of ferric chloride leads to the appearance of cherry-red coloration. While standing, color fades due to spontaneous decarboxylation of AAA. The reaction is nonspecific. Creatinine of urine gives a similar color with sodium nitroprusside, but in that case the addition of concentrated acetic acid does not lead to cherry color formation.

C) *Express test for acetone and AAA.*

Principle. Semiquantitative determination of ketone bodies in the urine and blood serum can be carried out using diagnostic strips "Ketofan." They contain alkaline buffer mixed with sodium nitroprusside. So, purple color appears while interacting with acetone and AAA. Its intensity is directly proportional to the concentration of ketone bodies in the experimental fluid.

Procedure. A strip is dipped for 1-2 seconds in an experimental fluid and after 1 min it is necessary to compare a color of the indication zone with the color scale of comparison that is printed on the label. Some shades of the comparison scale from slightly purple to dark purple correspond to approximately 1.2 to 1.5 g/L of AAA or higher.

Clinical and diagnostic significance. *The content of ketone bodies in the blood of a healthy person varies from 0.1 to 0.6 mmol/L. In normal urine, their amount is negligible (less than 0.01 g/day) and is not detected with qualitative reactions, since these reactions are positive only when the excretion of large quantities of ketone bodies is observed (e.g., in diabetes mellitus, starvation, exclusion of carbohydrates from diet). Ketonuria may occur in diseases associated with increased utilization of carbohydrates (hyperthyroidism), hemorrhage, traumatic brain injuries, infectious*

diseases (scarlet fever, influenza, tuberculosis, meningitis). Acute diseases of the digestive tract (dysentery, salmonella infection) may be accompanied by ketonemia and ketonuria in early childhood as a result of starvation and malnutrition.

1**. Prepare a review in accordance with the following topic: "Biochemical aspects of obesity."

2**. Prepare a presentation in accordance with the following topic: "Hormones of the adipose tissue. Their structures and functions."

3**. Prepare a brief review in accordance with the following topic: "Disorders of fatty acid oxidation in the body."

CLASS 7 (4 hours)

Topic 10 (2 hours): Cholesterol metabolism. Regulation and disorders of lipid metabolism. Determination of blood serum cholesterol.

IMPORTANCE. Cholesterol is the most abundant representative of all steroids. It serves as a precursor of other steroids: bile acids, hormones, vitamin D₃, as well as the structural component of cell membranes. Cholesterol in the body derives from dietary cholesterol and cholesterol synthesized in the organism. Pathological conditions such as atherosclerosis, cholelithiasis, and hyperlipoproteinemia are accompanied by abnormal cholesterol metabolism.

Regulation of lipid metabolism is neurohumoral. The cerebral cortex regulates lipid metabolism via the sympathetic and parasympathetic nervous system, as well as endocrine glands. Knowledge of the lipid metabolism under normal and pathological conditions is of great practical importance for future doctors, in particular, for proper diagnosis and rational selection of drugs for treating various disorders of lipid metabolism. Diseases related to lipid metabolism impairment (atherosclerosis, obesity, myocardial infarction) are most common among the population of developed countries that increases the importance of their laboratory diagnosis. This problem is extremely important, because it is impossible to have an objective view on the functional ability of a number of vital organs (e.g., liver and kidney) in a variety of diseases without analysis of lipid metabolism parameters. Elevated blood levels of lipids serve as a symptom of some diseases in which impairment of lipid metabolism is secondary (diabetes mellitus, hypothyroidism, pancreatitis, alcoholism, etc.). The basic biological material for biochemical investigation of lipidoses (disorders of metabolism of lipids and lipoids – lipid-like substances) is the patients' blood whose major lipid components are free cholesterol and its esters, total lipids, phospholipids, and lipoproteins.

AIM. Study the features of cholesterol metabolism under normal and pathological conditions; familiarize yourself with the regulation and disorders of lipid metabolism. Be able to apply knowledge of theoretical material analyzing the results of laboratory work and the ability to use lipid metabolism tests as prodiagnostic parameters. Study the method of quantitative determination of blood serum cholesterol and its clinical and diagnostic significance.

THEORETICAL QUESTIONS

- 1 Biosynthesis of cholesterol: localization, scheme of reactions, regulation.
- 2 Pathways of cholesterol biotransformation, localization in the body: esterification, formation of bile acids, steroid hormones, and active form of vitamin D₃.
- 3 Biochemical mechanisms of atherosclerosis. Coefficient of atherogeneity. Atherogenic and antiatherogenic lipoproteins.
- 4* Regulation of lipid metabolism.
- 5* Pathologies of lipid metabolism: steatorrhea, obesity, atherosclerosis, hyperlipoproteinemia.
- 6* Abnormalities of lipid metabolism in obesity, diabetes mellitus.

Recommendations for self-study of theoretical questions

<i>Question</i>	<i>Information</i>
<i>1. Regulation of lipid metabolism.</i>	<p><i>1.1. Regulation of fatty acid synthesis and oxidation:</i></p> <ul style="list-style-type: none"> - <i>Short-term regulation: regulatory enzyme - acetyl-CoA carboxylase, formation of malonyl-CoA;</i> - <i>Long-term regulation: changing the amount of enzymes;</i> - <i>energy supply of cells (high concentrations of ATP inhibit oxidation of fatty acids and stimulate their synthesis; when ADP levels are high, the rate of fatty acid oxidation increases);</i> - <i>Neurohumoral regulation.</i> <p><i>1.2. Hormonal regulation of lipogenesis and lipolysis (insulin, adrenaline, glucagon).</i></p> <p><i>1.3. Regulation of cholesterol metabolism:</i></p> <ul style="list-style-type: none"> - <i>Hormonal;</i> - <i>Regulation of the key enzyme of cholesterol synthesis - hydroxymethylglutaryl-CoA reductase.</i>
<i>2. Disorders of lipid metabolism.</i>	<p><i>2.1. Steatorrhea is an increase in the amount of undigested fat in feces due to abnormal hydrolysis and malabsorption of dietary lipids in the intestine: a) pancreatic - lipase deficiency observed in pancreatic diseases;</i></p> <p><i>b) hepatogenic - lack of bile observed in diseases of the liver and gall bladder;</i></p> <p><i>c) enterogenic - inhibition of lipolysis and TAG synthesis in the intestine (gastrointestinal diseases).</i></p> <p><i>2.2. Obesity is a condition characterized by the accumulation of triacylglycerol (the rate of fat breakdown is constantly lower than the rate of its synthesis) in adipocytes. Causes:</i></p> <ul style="list-style-type: none"> - <i>Hypercaloric diet;</i> - <i>Insufficient use of energy due to physical inactivity;</i> - <i>Genetic predisposition;</i>

- Changes in the hormonal profile (thyroid system, thyroid receptors, sex hormones, glucocorticoids);
- Brain damage;
- mental disorders;
- Leptin-associated disorders (a hormone synthesized by adipocytes).

2.3. Atherosclerosis is a disease whose major manifestation is formation of "plaques" in the vascular walls.

2.3.1. Risk factors for atherosclerosis:

- Hypercholesterolemia; increase in LDL, TAG; low atherogenic coefficient due to reduced HDL levels;
- Genetic predisposition;
- Insufficient dietary intake of polyunsaturated fatty acids;
- Damage to the vascular endothelium (high blood pressure, inflammatory processes, stress, blood clotting disorders, action of nicotine, etc.);
- Endocrine disorders.

2.3.2. Consequences: vasoconstriction, increased blood clotting, coronary heart disease, myocardial infarction, stroke.

2.3.3. Treatment: diet (it aims at lowering blood cholesterol), inhibitors of cholesterol synthesis (in particular, inhibitors of hydroxymethylglutaryl-CoA reductase).

2.4. Hyperlipoproteinemia - clinical and biochemical syndrome characterized by high blood plasma concentrations of LP, as well as triacylglycerols and cholesterol.

2.4.1. Classification of causes for its development: a) Primary (genetic) – they are caused by genetic defects in the synthesis of lipid metabolism enzymes (lipoprotein lipase, etc.); b) Secondary (alimentary or due to certain diseases - hepatitis, cirrhosis, etc.).

2.4.2. Classification based on changes in the lipoprotein spectrum:

- I - hyperchylomicronemia;
- IIa - hyper- β -lipoproteinemia;
- IIb - hyper- β -lipoproteinemia with hyperpre- β -lipoproteinemia;
- III - hyperlipoproteinemia with abnormal β -lipoproteins;
- IV - hyperpre- β -lipoproteinemia (excessive VLDL levels);

	<i>V</i> - hyperpre- β -lipoproteinemia and hyperchylomicronemia.
3. Abnormal lipid metabolism in obesity and diabetes mellitus.	<p>3.1. Obesity-associated disorders:</p> <ul style="list-style-type: none"> - Excessive consumption and biosynthesis of neutral fats and carbohydrates in tissues that exceed energy requirements; - Genetically determined high activity of enzymes involved in lipogenesis; - Abnormal endocrine control. <p>3.2. Metabolic disorders in diabetes mellitus type II:</p> <ul style="list-style-type: none"> - Hypertriglyceridemia (VLDL synthesis is activated in hepatocytes); - Stimulation of lipolysis in the adipose tissue, a decrease in the inhibitory effect of insulin; - TAG lipase activation; - High blood levels of non-esterified fatty acids; - Activated synthesis of ketone bodies (keto-genesis); - Reduction of cholesterol, HDL.

TESTS FOR SELF-CONTROL

1. Choose a process affected by excessive supply of cholesterol with food.
 - A. Synthesis of endogenous cholesterol is accelerated
 - B. Catabolism of cholesterol to CO₂ and H₂O is activated
 - C. Synthesis of cholesterol in the liver decreases
 - D. β -Hydroxymethylglutaryl-CoA reductase activity increases
 - E. β -Hydroxymethylglutaryl-CoA synthase activity diminishes
2. The major final product of cholesterol metabolism in the liver is:
 - A. Vitamin D
 - B. Hippuric acid
 - C. Animal indican
 - D. Bile acids
 - E. Skatole
3. Choose the regulatory enzyme of cholesterol synthesis:
 - A. Acetyl-CoA-acetyl transferase
 - B. β -Hydroxymethylglutaryl-CoA reductase
 - C. β -Hydroxymethylglutaryl-CoA synthase
 - D. Acetyl-CoA carboxylase
 - E. Thiolase
4. Select products that are not formed in cholesterol catabolism:
 - A. CO₂ and H₂O
 - B. Bile acids
 - C. Vitamin D₃
 - D. Corticosteroids
 - E. Sex hormones
5. Choose the major transport form of cholesterol from the liver:
 - A. VLDL
 - B. Chylomicrons
 - C. LDL
 - D. HDL
 - E. IDL
6. Select the final product to which mevalonic acid is converted to during the second step of cholesterol synthesis:
 - A. Lanosterol
 - B. Isoprene
 - C. Farnesylpyrophosphate
 - D. Squalene
 - E. Geranylpyrophosphate
7. Point out an organ where cholesterol synthesis is the most intensive:
 - A. Kidney
 - B. Liver
 - C. Intestine
 - D. Adrenal cortex
 - E. Reproductive organs

8. Choose an initial substance for cholesterol synthesis:
 A. *Crotonyl-CoA* B. *Palmityl-CoA* C. *Hydroxybutyryl-CoA*
 D. *Acetyl-CoA* E. *Butyryl-CoA*
9. Select functions of cholesterol in the organism:
 A. *It is an obligatory component of biological membranes*
 B. *Bile acids are synthesized from cholesterol*
 C. *It is a precursor of corticosteroids and sex hormones*
 D. *It is a precursor of vitamin D₃*
 E. *All the functions mentioned above*
10. Point out a substance formed after the condensation of 3 molecules of acetyl-CoA and further reduction during cholesterol synthesis:
 A. *Butyric acid* B. *Mevalonic acid*
 C. *β-Hydroxymethylglutaryl-CoA* D. *Fumarate* E. *Citrate*
11. Colloidal properties of bile are affected in inflammatory processes of gallbladder. This can lead to the formation of bile stones. Which substance crystallization is the basic cause of their formation?
 A. *Urates* B. *Chlorides* C. *Cholesterol*
 D. *Oxalates* E. *Phosphates*
12. The major reducing agent for cholesterol synthesis is:
 A. *NADPH₂* B. *FADH₂* C. *FMNH₂*
 D. *CoQH₂* E. *NADH₂*
13. A patient complains of dryness in the oral cavity, thirst, and general weakness. Biochemical analysis revealed hyperglycemia and hyperketonemia. Ketone bodies and glucose were found in the urine. Her electrocardiogram showed diffuse changes in the myocardium. What is the most plausible diagnosis?
 A. *Alimentary hyperglycemia* B. *Acute pancreatitis*
 C. *Diabetes insipidus* D. *Coronary artery disease*
 E. *Diabetes mellitus*
14. Atherogenic factors that contain cholesterol are:
 A. *Chylomicrons* B. *HDL* C. *LDL*
 D. *VLDL* E. *Albumins*
15. A patient suffers from arterial hypertension and atherosclerotic vascular disease. Which lipid should be limited in diet?
 A. *Cholesterol* B. *Oleic acid* C. *Lecithin*
 D. *Glycerol monooleate* E. *Phosphatidylserine*
16. Data of subjective and objective examinations allow suggesting that a patient has inflammation in the gallbladder, abnormal colloidal properties of bile, high risks for gallstone formation of gallstones. What can cause their formation?
 A. *Urates* B. *Oxalates* C. *Chlorides*
 D. *Cholesterol* E. *Phosphates*
17. Data of subjective and objective examinations allow suggesting that a patient has inflammation in the gallbladder, abnormal colloidal properties of bile, high risks for gallstone formation of gallstones. What can cause their formation?
 A. *All the answers mentioned below are correct*
 B. *Inhibition of intestinal cholesterol absorption*
 C. *Inhibition of cholesterol biosynthesis*

D. Activation of cholesterol metabolism

E. Stimulation of cholesterol excretion

18. A female patient suffers from cholelithiasis. Signs of the acholic syndrome due to obstruction of bile ducts have recently appeared. Which nutrients may be poorly absorbed in this case?

- A. Proteins* *B. Lipids* *C. Nucleic acids*
D. Electrolytes *E. Carbohydrates*

19. Sleeplessness, headache, aggressiveness, and unbearable itching appeared in a patient at the beginning of the second week of viral hepatitis. The examination revealed: substantial reduction of blood pressure, blood clotting, reflexes, and bradycardia. What can cause such changes?

- A. Hyperlipemia* *B. Urobilinemia* *C. Stercobilinemia*
D. Cholemia *E. Hypercholesterolemia*

20. Serum cholesterol level of a 12-year-old male patient reaches 25 mmol/L. In anamnesis, he has hereditary familial hypercholesterolemia whose cause is abnormal synthesis of receptors to:

- A. IDL* *B. LDL* *C. HDL*
D. VLDL *E. Chylomicrons*

21. Cholesterol is excreted from the body in several ways. Which product is formed from cholesterol in the large intestine under the influence of intestinal bacteria?

- A. Hydroxycholesterol* *B. Pregnenolone* *C. Coprostanol*
D. Cholic acid *E. Cholecalciferol*

22. Modern anti-atherosclerotic drugs are used for prevention and treatment of atherosclerosis. Drugs such as fenofibrate inhibit cholesterol biosynthesis by inhibiting one of the following enzymes:

- A. β -HMG Coa reductase* *B. Hexokinase*
C. Acyl-CoA-cholesterol acyltransferase
D. Glucose-6-phosphatase *E. Acyltransferase*

23. A patient with atherosclerosis takes an anti-atherosclerotic drug called fenofibrate. What is the mechanism of action for this drug?

- A. It improves blood microcirculation*
B. It inhibits cholesterol absorption in the intestine
C. It renovates endothelial negative charge
D. It decreases cholesterol levels
E. It increases LDL uptake and inhibits endogenous cholesterol synthesis

24. It is recommended to prefer fats with a high content of polyunsaturated fatty acids in order to prevent atherosclerosis, coronary heart disease, and cerebrovascular disorders. One of such fatty acids is:

- A. Linoleic acid* *B. Oleic* *C. Lauric*
D. Palmitoleic *E. Stearic*

25. A patient lost his weight, drank a lot of water, noted frequent urination, increased appetite, itching, weakness, and furunculosis after epidemic parotitis. The following blood parameters were studied: glucose – 16 mmol/L, ketone bodies - 1.6 mmol/L. Which disease is observed?

- A. Insulin-dependent diabetes mellitus* *B. Steroid diabetes*
C. Noninsulin-dependent diabetes mellitus *D. Diabetes insipidus*
E. Diabetes mellitus of insufficient nutrition

26. The long-term toxic influence of alcohol on the patient's body caused hepatic steatosis. Which lipoprotein synthesis was affected and caused TAG accumulation in the body?

A. Chylomicrons

B. VLDL

C. LDL

D. HDL

E. IDL

27. Fatty liver was developed in an experimental animal with protein-free diet due to the deficiency of methylating agents. Select a metabolite whose formation was affected in the experimental animal:

A. Choline

B. DOPA

C. Cholesterol

D. Acetoacetate

E. Linolenic acid

28. A patient who has cholelithiasis periodically suffers from steatorrhea. Which vitamin deficiency may develop as a complication of this disease?

A. Vitamin B₆

B. Vitamin C

C. Vitamin P

D. Vitamin K

E. Vitamin B₁₂

29. It has been known that the pentose phosphate pathway in adipocytes forms a cycle. What is the main function of this cycle in the adipose tissue?

A. Production of ribose phosphates

B. Detoxification of xenobiotics

C. NADPH₂ generation

D. Generation of energy

E. Glucose oxidation to final products

PRACTICAL WORK

Enzymatic determination of the serum cholesterol concentration with the help of a kit

Task. Determine the blood serum cholesterol concentration.

Principle. Free cholesterol is formed as a result of hydrolysis of cholesterol esters by cholesterol esterase. Cholesterol formed by hydrolysis from cholesterol esters and blood non-esterified cholesterol are oxidized by atmospheric oxygen by cholesterol oxidase to form equimolar amounts of hydrogen peroxide. Peroxidase oxidizes the chromogenic substrates with the help of hydrogen peroxide to form a colored compound whose coloration intensity is directly proportional to the blood cholesterol concentration. It is determined photometrically at the wavelength of 540 nm.

Procedure. Prepare three chemical test tubes (experimental, calibration, blank). Add 0.01 ml of serum to the experimental test tube, 0.01 ml of the calibration solution to the standard test tube, 0.01 ml of distilled water to the blank test tube. Take 1 ml of reagent and add it to the experimental, calibration and blank test tubes, respectively. Mix the content of test tubes and incubate them for 10 min at 37 °C or for 20 min at room temperature. Measure the extinction of the experimental and calibration test tubes against the blank one at a wavelength of 540 nm. Calculate the blood serum cholesterol concentration in accordance with the following formula:

$$C = E_{\text{ex}}/E_{\text{c}} \times 5.2$$

where C is a concentration of cholesterol in the sample (mmol/L); E_{ex} is an extinction of the experimental solution; E_c is an extinction of the calibration solution; 5.2 is the cholesterol content in the calibration solution (mmol/L).

If the concentration of cholesterol exceeds 19.4 mmol/L, try to dilute the sample with isotonic sodium chloride solution and multiply the result by the dilution factor.

Clinical and diagnostic significance. Exogenous cholesterol (0.3-0.5 g per day) comes from food and endogenous (0.8-2 g per day) is synthesized in the body. A lot of cholesterol is synthesized in the liver, intestine, and skin. Large amounts of cholesterol are present in the nervous tissue (20-30 g/kg). The concentration of cholesterol is determined in conjunction with other tests for the determination of hyperlipoproteinemia. Its serum concentration varies from 3.0 to 5.7 mmol/L in healthy individuals. Prolonged increased blood cholesterol concentrations contribute to atherosclerosis. Lipoproteins play a key role in pathogenesis of atherosclerosis. It has been established that atherosclerosis and related diseases develop when a significant increase in a plasma LDL fraction and, in many cases, VLDL is observed. It has been shown that chylomicrons cannot penetrate the vascular wall because of their large size, whereas HDL, LDL, and VLDL are partially able to do this. However, HDLs are the smallest lipoproteins, so that they can be easier removed from the vascular walls via the lymphatic system. In addition, HDLs have the highest protein and phospholipid content, so that they can be easier metabolized in the vascular wall and quickly removed from it compared to cholesterol- and triglycerides-rich LDL and VLDL. The latter is referred to as atherogenic lipoproteins and can penetrate into the vascular wall from blood plasma and serve as the primary substrate causing atherosclerotic arterial damage. Hypercholesterolemia is observed in patients with hypertension, coronary heart disease, diabetes mellitus, obesity, jaundice, nephritis, nephrosis, syphilis, and hypothyroidism. Reduced cholesterol concentrations (hypocholesterolemia) occur in tuberculosis, typhus, parenchymatous jaundice, hyperthyroidism, anemia, cancer cachexia, fever, some CNS disorders, and starvation.

1**. Prepare a presentation in accordance with the following topic: "Molecular mechanisms of atherosclerosis pathogenesis."

2**. Prepare a scheme for assessing disorders of lipid metabolism using biochemical parameters for various pathological conditions.

3**. Prepare a brief review in accordance with the following topic: "Steatohepatitis: causes, biochemical manifestations."

FINAL MODULE CONTROL № 2 – BIOCHEMISTRY OF HORMONES. METABOLISM OF CARBOHYDRATES AND LIPIDS

(2 hours)

- 1 Hormones: general characteristics, role in intercellular integration of functions of the human body.
- 2 Classification of hormones.
- 3 Response of target cells to hormones. Membrane (ionotropic, metabotropic) and cytosolic receptors.
- 4 Biochemical systems of intracellular transmission of hormonal signals.
- 5 Molecular and cellular mechanisms of action for steroid and thyroid hormones.
- 6 Hormones of hypothalamus.
- 7 Pituitary hormones: growth hormone, lactotropin. Pathological processes associated with dysfunction of these hormones.

- 8 Vasopressin and oxytocin: structure, biological functions.
- 9 Insulin: structure, biosynthesis and secretion, influence on metabolism of carbohydrates, lipids, amino acids, and proteins.
- 10 Glucagon: regulation of carbohydrate and lipid metabolism.
- 11 Thyroid hormones: structure, biological effects of T₃ and T₄. Changes in metabolic processes in patients with hypo- and hyperthyroidism.
- 12 Catecholamines (epinephrine, norepinephrine, dopamine): structure, biosynthesis, physiological effects, and biochemical mechanisms of action.
- 13 Steroid hormones of the adrenal cortex - glucocorticoids and mineralocorticoids: structure, properties, biological effects, disorders.
- 14 Female sex hormones. Physiological and biochemical effects, connection with phases of the ovulation cycle.
- 15 Male sex hormones. Physiological and biochemical effects of androgens, regulation of synthesis and secretion.
- 16 Hormonal regulation of calcium homeostasis in the body.
- 17 Eicosanoids: structure, biological and pharmacological properties. Aspirin and other non-steroidal anti-inflammatory drugs as inhibitors of prostaglandin synthesis.
- 18 Carbohydrates. Biological role. Classification. Structure and functions of mono-, oligo- and polysaccharides.
- 19 Classification of carbohydrates. Structure and functions of polysaccharides.
- 20 Glycosaminoglycans: structure and role.
- 21 Major dietary carbohydrates: daily requirements, structure, digestion, and absorption in the gastrointestinal tract.
- 22 Aerobic and anaerobic glucose oxidation.
- 23 Anaerobic glucose oxidation: reactions and enzymes.
- 24 Aerobic glucose oxidation; steps and final products.
- 25 Glycolytic oxidation: substrate-level phosphorylation and shuttles that transfer NADH.
- 26 Comparison of bioenergy balance of aerobic and anaerobic glucose oxidation, Pasteur effect.
- 27 Glycogen in the liver.
- 28 Glycogen. Its structure and functions.
- 29 Phosphorylolytic pathway of glycogen breakdown in the liver and muscles. Regulation of glycogen phosphorylase.
- 30 Glycogen biosynthesis: enzymatic reactions, physiological significance. Regulation of glycogen synthase.
- 31 Mechanisms of reciprocal regulation of glycogenolysis and glycogenesis.
- 32 Role of adrenaline, glucagon and insulin in hormonal regulation of glycogen metabolism in the liver and muscles.
- 33 Genetic disorders of glycogen metabolism.
- 34 Gluconeogenesis: substrates, enzymes, physiological significance.
- 35 Glucose-lactate (Cori cycle) and glucose-alanine (Cahill cycle) cycles.
- 36 Blood glucose (glucosemia): normo-, hypo- and hyperglycemia, glycosuria. Diabetes mellitus as a pathology of glucose metabolism.

- 37 Hormonal regulation of carbohydrate metabolism and blood glucose concentration.
- 38 Pentose phosphate pathway of glucose oxidation: scheme and biological significance.
- 39 Pathways of fructose and galactose metabolism; hereditary enzymopathies.
- 40 General understanding of glycosaminoglycan metabolism. Mucopolysaccharidoses. Genetic disorders of glycosaminoglycan metabolism.
- 41 Regulation of carbohydrate metabolism.
- 42 Disorders of carbohydrate metabolism.
- 43 Lipids. Biological role. Classification. Structure and functions of simple lipids.
- 44 Lipids. Structure and functions of complex lipids.
- 45 Basic dietary lipids and their structure. Daily requirements for lipids. Digestion and absorption in the gastrointestinal tract.
- 46 Bile acids and their role in digestion and absorption of lipids.
- 47 Lipases of the gastrointestinal tract. Role of pancreatic lipase.
- 48 Resynthesis of fats in intestinal epithelial cells: its importance, role of β -MAG.
- 49 Catabolism of triacylglycerols in adipose tissue: reactions, regulation.
- 50 Neurohumoral regulation of lipolysis.
- 51 Oxidation of fatty acids, role of carnitine.
- 52 Energy balance of β -oxidation of fatty acids.
- 53 Glycerol oxidation: enzymatic reactions, energy balance.
- 54 Ketone bodies: reactions of biosynthesis and utilization, physiological significance. Disorders.
- 55 Metabolism of ketone bodies under pathological conditions (diabetes mellitus, starvation).
- 56 Biosynthesis of fatty acids. Reactions of saturated fatty acid (palmitate) synthesis and regulation.
- 57 Biosynthesis of mono- and polyunsaturated fatty acids in humans.
- 58 Biosynthesis of triacylglycerols and phosphoglycerols.
- 59 Metabolism of sphingolipids. Sphingolipidoses.
- 60 Cholesterol biosynthesis. Reactions. Regulation.
- 61 Pathways of cholesterol biotransformation.
- 62 Blood plasma lipoproteins: lipid and protein composition. Hyperlipoproteinemiae.
- 63 Disorders of lipid metabolism: atherosclerosis, obesity, diabetes mellitus, steatorrhea.
- 64 Relations between carbohydrate metabolism and lipid metabolism. Regulation and disorders.

Навчальне видання

ЧАСТИНА 2
БІОХІМІЯ ГОРМОНІВ.
ОБМІН ВУГЛЕВОДІВ ТА ЛІПІДІВ

Методичні вказівки
для підготовки до практичних занять з біологічної хімії
(для студентів медичних факультетів)

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