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Department of Biological Chemistry

FEATURES OF BIOCHEMICAL AND PATHOLOGICAL PROCESSES IN THE LIVER.

Educational and methodological recommendations

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FEATURES OF BIOCHEMICAL AND IIATOLOGICAL PRO-

TSESSOV IIIECHENI: Textbook / A.E. Gurin, L.Kh. Dzotsieva. Vladikavkaz, 2017 .-- 95 p.

Authors:

A.E. Gurina - Candidate of Medical Sciences, Associate Professor, Head. Department of Biological Chemistry, Federal State Budgetary Educational Institution of Higher Education, SOGMA, Ministry of Health of Russia;

L.Kh.Dzotsieva - Candidate of Medical Sciences, Assistant of the Department of Biological Chemistry of the Federal State Budgetary Educational Institution of Higher Education SOGMA of the Ministry of Health of Russia.

Reviewers:

A.B.Mvanov - Doctor of Biological Sciences, Professor, Head. Department of Normal and Pathological Physiology of the Faculty of Medicine of the Federal State Budgetary Educational Institution of Higher Education "Kabardino-Balkarian State University named after H.M. Berbekova "

AA Baigipdina - Doctor of Medical Sciences, Professor of the Department of Biological Chemistry of the Federal State Budgetary Educational Institution of Higher Education "Bashkir State Medical University" of the Ministry of Health of Russia.

The textbook covers the main sections of biochemistry and pathobiochemistry of the liver from a modern standpoint: anatomical and functional features, methods of biochemical diagnostics, pathobiochemical mechanisms of liver dysfunction. Liver syndromes and differential diagnostics of jaundice are described in detail. For independent work of students and control of knowledge, the manual contains test tasks and situational tasks, which facilitates the assimilation of the discipline program, ensures the systematization of knowledge and makes it possible to assess the level of self-preparation. The manual is illustrated with original tables and diagrams.

It is intended for students studying in educational organizations of higher education in the specialties "General Medicine", "Pediatrics", in the discipline "Clinical Biochemistry".

FOREWORD.

CONTENTpage 6

FOREWORD

This textbook presents modern data on the anatomical and biochemical characteristics of the liver, functions and methods of their assessment, pathogenetic mechanisms of the development of pathological processes in the liver, algorithms for biochemical diagnostics of the main syndromes are presented. The manual allows you to gain additional knowledge on the exchange of bilirubin and the differential diagnosis of jaundice, to use them in clinical practice. The manual sets out the basic algorithms for biochemical diagnosis of various disorders, indicating the normative indicators that can be taken into account by students when solving situational problems. For self-control, a set of test tasks and situational tasks is presented.

Situational tasks are a necessary tool for consolidating and systematizing knowledge, developing analytical and associative thinking. Some of them are based on specific clinical examples, which brings the educational process closer to practical medicine.

The manual contains visual materials - tables, figures. The information contained in the tables and figures forms a holistic understanding of the etiology and mechanisms of the formation and development of pathological reactions, processes, compensatory phenomena, decompensation factors and cause-and-effect relationships in pathology.

This manual will help students acquire knowledge in understanding the biochemical mechanisms of the development of pathological processes in the liver and use them in clinical practice.

It is intended for medical students enrolled in the specialty "General Medicine" and "Pediatrics" in the discipline "Clinical Biochemistry".

The topic: "FEATURES OF BIOCHEMISTRY AND PATHOLOGICAL PROCESSES OF THE LIVER"

PURPOSE of studying the topic: to familiarize students with modern methods of biochemical research and their interpretation, to teach how to evaluate and use the data of biochemical analysis for diagnostic and prognostic purposes in pathological processes in the liver.

As a result of studying the topic, the student must know:

• anatomical and biochemical features of the liver;

• liver function and methods of their assessment;

• the relationship between the violation of the structure, functions of the liver and biochemical parameters in the blood plasma;

• basic patterns of metabolic disorders (proteins, lipids, carbohydrates, etc.) in pathological processes in the liver;

• hepatic syndromes;

• exchange of bilirubin in normal and pathological conditions;

• differential diagnosis of jaundice;

• biochemical markers of liver diseases; be able to:

• determine the concentration of total, free and bound bilirubin;

• determine the activity of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase and

• interpret the received data.

ANATOMO-BIOCHEMICAL PECULIARITIES OF THE III.

The structure of the liver.

The liver is one of the largest and most unique organs of the human body, performing various functions, playing an important role in the processes of digestion, metabolism, and detoxification. The macca of the liver of an adult is 1300-1800 g. The liver is located in the right upper quadrant of the abdomen and is covered with ribs. Anatomically, two lobes are distinguished in the liver - right and left. The right lobe is almost 6 times larger than the left; two small segments are distinguished in it: caudate pain on the back surface and square pain on the lower surface. The right and left lobes are separated: in front - by a fold of the peritoneum, the so-called falciform ligament; behind - the groove, in which the venous ligament passes, and below - the groove, in which the round ligament is located.

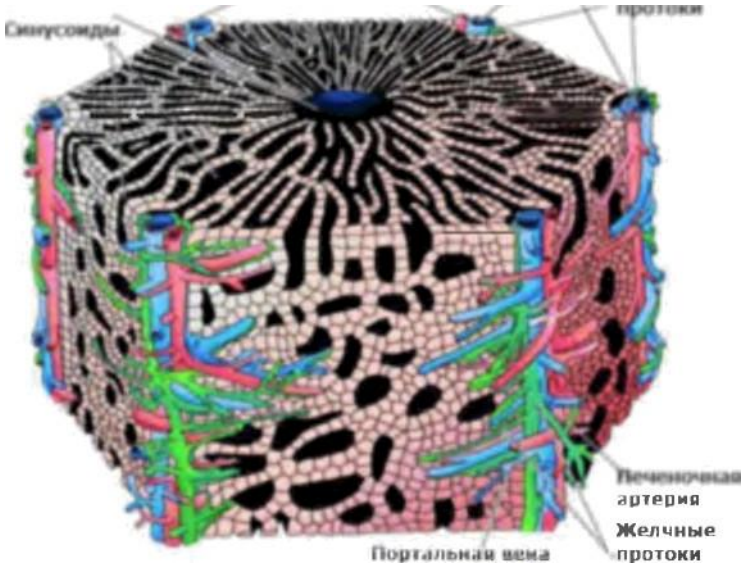
The liver is supplied with blood from two sources: the portal vein carries venous blood from the intestines and spleen, and the hepatic artery extending from the celiac trunk provides arterial blood supply. The vessels enter the liver through a depression called the hepatic hilum, which is located on the lower surface of the right lobe closer to its posterior edge. The portal vein and hepatic artery at the hepatic hilum give branches to the right and left lobes, and the right and left bile ducts join and form a common bile duct. The innervation of the liver is carried out by the fibers of the seventh to tenth thoracic sympathetic ganglia, which are interrupted at the synapses of the celiac plexus, as well as by the fibers of the right and left vagus and right phrenic nerves.

The structure of the liver.

The structural unit of the liver is the acinus or hepatic lobule. It has a pyramidal shape, consisting of a centrally located hepatic vein and peripherally located portal tracts containing the bile duct, branches of the portal vein and the hepatic artery. Between these two systems there are beams of hepatocytes and sinusoids containing blood.

The liver tissue is represented by two systems of channels - portal tracts and hepatic central channels, which are located in such a way that they do not touch each other; the distance between them is 0.5 mm. These channel systems are perpendicular to each other. Blood from the terminal branches of the portal vein enters the sinusoids; in this case, the direction of blood flow is determined by the higher pressure in the portal vein as compared to the central one.

Fig. 1 The structure of the hepatic lobule (source 1ife4we11.ru)



The central hepatic canals are surrounded by a border plate of hepatic cells.

The portal tracts contain the terminal branches of the portal vein, the hepatic arteriole, and the bile duct with a small amount of round cells and connective tissue. They are surrounded by a borderline plate of hepatic cells.

There are a number of functional zones of acini, in the center of each of which lies a portal triad with terminal branches of the portal vein I, hepatic artery and bile duct - zone 1. Acini are located mainly perpendicular to the terminal hepatic veins of neighboring acini. The peripheral, poorer blood-supplied parts of the acini, adjacent to the terminal hepatic veins (zone 3), suffer the most from damage (viral, toxic or anoxic). Areas located closer to the axis, formed by the carrying vessels and bile ducts, are more viable, and later hepatic cell regeneration can begin in them.

Hepatocytes - liver cells make up about 60% of the liver mass. They are polygonal and approximately 30 μm in diameter. The hepatocyte borders on the sinusoid and the Disse space, on the bile duct and adjacent hepatocytes. There is no basement membrane in hepatocytes.

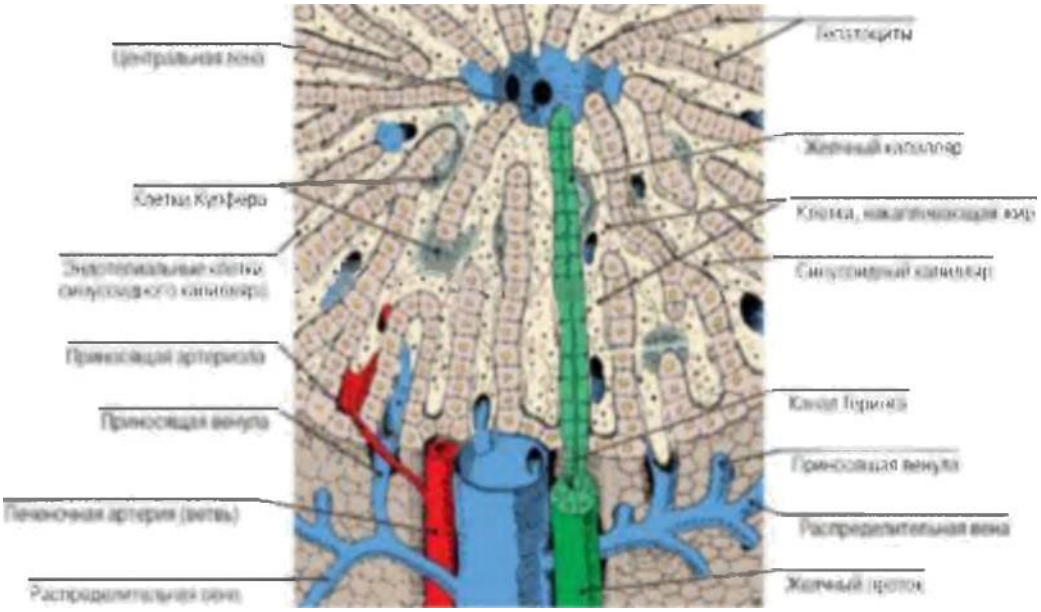
Sinusoids are lined with endothelial cells. Sinusoids include phagocytic cells of the reticuloendothelial system (Kupffer cells), stellate cells, also called fat-storing cells, Ito cells or lipocytes.

The tissue space between hepatocytes and sinusoidal endothelial cells is called the Disse space. Lymphatic vessels pass through the perisinusoidal connective tissue, which are lined with endothelium throughout. Tissue fluid seeps through the endothelium into the lymphatic tissues I.

The branches of the hepatic arteriole form a plexus around the bile ducts and flow into the sinusoidal network at its various levels. They supply blood to structures located in the portal tracts. There are no direct anastomoses between the hepatic artery and the portal vein.

The excretory system of the liver begins with the bile ducts. The plasma membrane is permeated with microfilaments that form a supporting cytoskeleton. The surface of the tubules is separated from the rest of the intercellular surface by connecting complexes consisting of tight junctions, gap junctions, and desmosomes. The intralobular network of tubules is drained into thin-walled terminal bile ducts or ductula (cholangioli, Hering's tubules), they end in larger (interlobular) bile ducts located in the portal tracts. The latter are divided into small (less than 100 μm in diameter), medium (3100 μm), and large (more than 100 μm).

Pic. 2 The structure of the bile ducts (source mvslide.m)



The surface of hepatocytes is flat, with the exception of a few attachment sites (desmosomes). From them, evenly spaced microvilli of the same size protrude into the lumen of the bile ducts. On the surface facing the sinusoid, there are microvilli of different lengths and diameters, which penetrate into the perisinusoidal tissue space. The presence of microvilli indicates active secretion or absorption (mainly of fluid).

The nuclear annapam of the cell contains deoxyribonucleoprotein. One or two nucleoli are found in the chromatin network. The nucleus has a double circuit and contains pores that provide

exchange with the surrounding cytoplasm. It is believed that increased polyploidy indicates a precancerous condition.

Mitochondria are cell organelles surrounded by a double membrane, the inner layer of which forms folds, or cristae, containing their own DNA. Mitochondria have a wide variety of functions, of which the main one is the synthesis of ATP by oxidative phosphorylation.

Mitochondria contain many enzymes, including those involved in the citric acid cycle and beta-oxidation of fatty acids. The energy released in these cycles is then stored as ATP. Heme synthesis also takes place here.

Rough endoplasmic reticulum in it specific proteins are synthesized, especially albumin, proteins of the blood coagulation system and enzymes, glucose-b-phosphatase. Triglycerides are synthesized from free fatty acids, which are secreted in the form of lipoprotein complexes by exocytosis. SHER may be involved in glucogenesis.

The smooth endoplasmic reticulum (GER) contains microsomes and is the site of bilirubin conjugation, detoxification of many drugs and other toxic substances (P450 system). Here steroids are synthesized, including cholesterol and primary bile acids, which are conjugated with the amino acids glycine and taurine.

Peroxisomes are located close to smooth EPS and glycogen granules. They exhibit activity - urate oxidase, D-amino acid oxidase, catalase, lactate oxidase.

Lysosomes are dense bodies adjacent to the bile ducts. They contain hydrolytic enzymes, upon release of which the cell is destroyed. Ferritin, lipofuscin, bile pigment and copper are deposited in them.

Annapam Golgi consists of a system of cisterns and vesicles, which also lie near the tubules. It can be called a “storehouse of substances” intended for excretion into bile. The Golgi apparatus, lysosomes and tubules undergo especially pronounced changes in cholestasis.

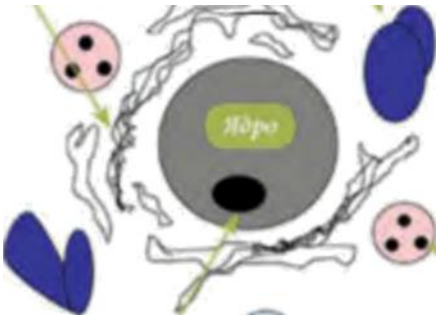
The cytoplasm contains glycogen granules, lipids and fine fibers. Here, glycolysis reactions, many reactions of gluconeogenesis, pentose-phosphate cycle, synthesis of higher fatty acids, activation of amino acids, glycogen synthesis, glycogenolysis and most reactions of urea synthesis take place.

Sinusoidal cells (endothelial cells, Kupffer cells, stellate and pit cells), together with the portion of hepatocytes facing the sinusoidal lumen, form a functional and histological unit. They line the sinusoids and contain fenestres, which form a stepped barrier between the sinusoid and the Disse space. Kupffer cells are attached to the endothelium.

The stellate cells of the liver are located in the Disse space between hepatocytes and endothelial cells. The Disse space contains tissue fluid, which flows further into the lymphatic vessels of the portal zones. With an increase in sinusoidal pressure, the production of lymph in the Disse space

increases, which plays a role in the formation of ascites in case of impaired venous outflow from the liver.

Fig. 3 Hepatocyte structure (source umedp.ru)



They carry out retinal-mediated apoptosis, transport into the J} space of macromolecules saturated with retginol and XC, bind and absorb NP.

* Synthesis of specific proteins in the proteins of the coagulation system y k (call, synthesis of triglyceJntAO in ns FFA, l ›ipoprotein AN N.x complexes, gl m cogenesis.

Activation of cytochrome P 450 systems, synthesis of steroids: cholesterol, primary fatty acids.

^ G-oxidation of virn bix to v_slot.

'i Za.tyaat and metabolism IIPNP, ENA T KC ›‹ H-specific function of TNF-o cytokines, hepses specific specific receptors for insulin, PP.

* Xpa nyat retinoia *. “Produce collagen.

7 REMOVING flau ›‹ *> A «pny receptors.

Kupffer's cells of the liver are highly motile macrophages associated with the endothelium, which are stained with peroxidase and have a nuclear envelope. They phagocytose large particles and contain vacuoles and lysosomes. These cells are formed from blood monocytes and have only a limited ability to divide.

They phagocytose by the mechanism of endocytosis (pinocytosis or phagocytosis), which can be mediated by receptors (absorption) or occur without the participation of receptors (liquid phase).

Functional features of Kynfera cells:

1. absorb aged cells, foreign particles, tumor cells, bacteria, yeast, viruses and parasites;

2. capture and process oxidized low density lipoproteins (which are considered atherogenic) and remove denatured proteins and fibrin in disseminated intravascular coagulation;

3. contain specific membrane receptors for ligands, including an immunoglobulin Fc fragment and a complement C3 component, which play an important role in antigen presentation;

4. are activated in case of generalized infections or injuries. They specifically absorb endotoxin and in response produce a number of factors, such as tumor necrosis factor, interleukins, collagenase and lysosomal hydrolases. The toxic effect of endotoxin, therefore, is due to the secretion products of Kupffer cells, since it is in itself non-toxic;

5. also secrete metabolites of arachidonic acid, including prostaglandins;

6. have specific membrane receptors for insulin, glucagon and lipoproteins. The carbohydrate receptor for N-acetylglycosamine, mannose, and galactose can mediate pinocytosis of some glycoproteins, especially lysosomal hydrolases. In addition, it mediates the uptake of IgM-containing immune complexes;

7. perform an erythroblastoid function in the liver of the fetus. Recognition and rate of endocytosis by Kupffer cells depend on opsonins, plasma fibronectin, and immunoglobulins.

Endothelial cells - cells form the wall of sinusoids. Fenestrated areas of endothelial cells (fenestra) have a diameter of 0.1 μm and form sieve plates, which serve as biological a filter between sinusoidal blood and plasma filling the Disse space. Endothelial cells have a mobile cytoskeleton that maintains and regulates their size. These "liver sieves" filter macromolecules of various sizes. Large chylomicrons saturated with triglycerides do not pass through them, but smaller residues, poor in triglycerides, but saturated with cholesterol and retinol, can penetrate into the Disse space. Sinusoidal endothelial cells actively remove macromolecules and small particles from the circulation using receptor-mediated endocytosis. They carry surface receptors for hyaluronic acid (the main polysaccharide component of connective tissue), chondroitin sulfate and glycoprotein containing mannose at the end, as well as type II and III receptors for IgG Fc fragments and a receptor for a protein that binds lipopolysaccharides. Endothelial cells perform a cleansing function by removing enzymes that damage tissues and pathogenic factors (including microorganisms). In addition, they cleanse the collagen from the blood and bind and absorb lipoproteins.

Ito's children are located in the subendothelial space of Disse. They contain long outgrowths of the cytoplasm, some of which are in close contact with parenchymal cells, while others reach several sinusoids, where they can participate in the regulation of blood flow and affect portal hypertension. In the normal liver, these cells are the storage site for retinoids. They contain actin and myosin and are contracted when exposed to endothelin-1. When hepatocytes are damaged, stellate cells lose fat droplets, proliferate, migrate to zone 3, acquire a phenotype similar to that of myofibroblasts, and produce collagen types I, III, and IV, as well as laminin. In addition, they secrete cell matrix proteinases and their inhibitors, for example a tissue inhibitor of a

metalloprotein. Collagenization of the Disse space leads to a decrease in the intake of protein-bound substrates into the hepatocyte.

Natural killer cells or pit cells are lymphocytes attached to the endothelial surface facing the sinusoidal lumen. Their pseudopodia penetrate through the endothelial lining, connecting with the microvilli of parenchymal cells in the Disse space. These cells do not live long and are renewed at the expense of circulating blood lymphocytes differentiating in sinusoids. The pit cells are spontaneously cytotoxic towards tumor and virus-infected hepatocytes.

Liver enzymes

Most often, blood serum is used as an object for research, the enzyme composition of which is relatively constant. The normal activity of enzymes in the blood serum reflects the relationship between biosynthesis and release of enzymes (during normal cell renewal), as well as their clearance from the bloodstream. An increase in the rate of enzyme renewal, cell damage usually leads to an increase in the activity of enzymes in the blood serum.

By the activity of serum liver enzymes, it is possible to establish the variant of liver damage (parenchymal or cholestatic).

The localization of enzyme systems in the liver is as follows: The cytoplasm of the cell contains the following series of enzymes:

1.alanine aminotransferase (ALT),

2.part of aspartate aminotransferase (AcAT),

3.lactate dehydrogenase (LDH),

4.part of gamma-glutamyl transpeptidase (11 111)

5. other enzymes.

The mitochondrial fraction, it contains:

1.Most of AcAT (about 70%),

2.glutamate dehydrogenase (GlDH),

3. alcohol dehydrogenase and many others.

Rough endoplasmic reticulum contains cholinester-R U (ChE) and P

The smooth endoplasmic reticulum contains:

1.glucose b-phosphatase,

2. UDP-glucuronyl transferase,

3.heme-containing membrane-bound cytochrome P-450, etc.

Lysosomes contain acid hydrolases (acid phosphatase, ribonuclease, etc.), which are activated when the cell pH decreases.

The biliary pole contains membrane-dependent enzymes such as alkaline phosphatase (ALP), 5-nucleotidase, part 11 111, leucine aminopeptidase (LAP). The distribution of enzymes within the cell explains the unequal increase in the activity of enzymes in various pathological processes. For example, with damage to the central sections of the lobules (acute alcoholic hepatitis, acute venous congestion, etc.), the activity of mitochondrial glutamate dehydrogenase increases, as a result of a lack of oxygen and damage to mitochondria, and with damage to the portal tracts (acute viral hepatitis, chronic active hepatitis - CAH), the activity of cytoplasmic transaminases increases.

The functions of cells located in the peripheral zone of blood circulation of the acinus, adjacent to the terminal hepatic veins (zone 3), differ from the function of cells adjacent to the terminal hepatic arteries and portal veins (zone 1).

Obviously, these zones differ in oxygen supply: the cells of zone 3 receive oxygen last and are especially prone to anoxic damage.

Cytochrome P4s0 enzymes involved in drug metabolism in

mainly concentrated in zone 3. The highest concentrations of toxic products of drug metabolism are found in hepatocytes of zone 3. In addition, the concentration of glutathione is reduced in them, therefore hepatocytes of zone 3 are especially susceptible to drug damage to the liver.

Table 1. Metabolism of geiatocytes depending on their location in zone 3 (central) or in zone 1 (periportal) (according to Sh. Sherlock, J. Dooley).

	The first zone	The third zone
Carbohydrates	Gluconeogenesis	Glycolysis
proteins	The synthesis of albumin and fib-	Albumin synthesis and fibrinogen

	rhinogen	
Cytochrome P450	+	++
Glutathione	++	
Oxygen supply	+ + +	+
Bile formation dependent on bile acids	++	
Bile production independent of bile acids	-	++
Sinusoids	Small Many anastomoses	Direct Radial

Zone 1 hepatocytes receive blood with a higher concentration of bile acids and therefore play a particularly important role in the production of bile, which is dependent on bile acids. Zone 3 hepatocytes are involved in bile production independent of bile acids.

The reasons for metabolic differences between zones are different. Some functions (gluconeogenesis, glycolysis, ketogenesis) depend on the direction of movement blood transcription along sinusoids, others (carried out by cytochrome! '450) - from the rate of gene transcription, which is not the same in perivenular and periportal hepatocytes. For example, with alcohol damage, the microcirculation of the liver may be disrupted due to collagenization of the space.

Disse, formation of the basement membrane under the endothelium and changes in its fenestration. All these processes are most pronounced in zone 3. They lead to the loss of nutrients intended for hepatocytes, and to the development of portal hypertension.

In pathological processes, lymphocytic infiltration is found in the liver. Receptors on the surface of lymphocytes, an antigen associated with leukocyte function (LFA-1), and intercellular adhesion molecules (ICAM-1 and ICAM-2) interact with each other. Normally, ICAM-1 is expressed mainly on the cells lining the sinusoids and to an insignificant extent on the portal and hepatic endothelium.

The sinusoidal membrane of the hepatocyte is a domain that contains a large number of receptors and has a high metabolic activity. It is separated from the bile duct by a lateral domain, which is involved in intercellular interactions. Receptor-mediated endocytosis mediates the transfer of large molecules such as glycoproteins, growth factors, and carrier proteins (transferrin). These ligands bind to sinusoidal membrane receptors, which form clathrin-bordered pits that initiate endocytosis. The fate of the ligand within the cell is different. Many ligands are transferred to the lysosomes, where they are destroyed, and the receptors are returned to the sinusoidal membrane for reuse. Some ligands are transported in vesicles through the cell and released into the lumen of the bile ducts.

The main functions of the liver

The liver is the most important organ that takes part in the metabolism, both formed in the body and entering it. In terms of the variety of metabolic reactions, it surpasses all other organs. Some metabolic processes (for example, urea synthesis) take place only in the liver, since only the liver has the necessary enzyme systems for them. The metabolism in the liver is necessary not only to maintain the structure and function of this organ, but also for the production of certain substances, which then enter the bloodstream and participate in the implementation of important functions of other organs. Homeostasis of a number of substances that are substrates of metabolism (for example, glucose) is also provided by the liver.

1. Synthetic. The liver carries out the synthesis of proteins, enzymes, blood coagulation factors, cholesterol, phospholipids, etc. The main formation of ketone bodies occurs in the liver.

2. Detoxifying for endogenous and exogenous substances. Detoxification of drugs includes 2 phases: 1 - modification of drugs in redox reactions using cytochrome P450, 2 phase - conjugation of drugs with water-soluble substances by adding glucuronic, sulfuric acids, glutathione, etc. In liver diseases, the reactions of the first phase are reduced or absent ...

3. Secretory. The bile secreting apparatus includes bile ducts, microvilli, adjacent lysosomes and the Golgi complex. The mechanism of bile secretion includes the release of cholesterol, bile acids, pigments, phospholipids in the form of a specific macromolecular complex - bile micelle. The primary bile acids formed in the liver enter the intestines, where, under the influence of the intestinal flora, they are converted into secondary bile acids. The latter are absorbed in the intestine and re-enter the liver (intestinal-hepatic circulation). The liver conjugates them with glycine and taurine, converting them into amphiphilic compounds with a high ability to emulsify hydrophobic substances. Any processes that cause a violation of the ratio of components in bile (hormonal, inflammatory, etc.) lead to an impairment of bile secretion - cholestasis.

4. Excretory - excretion of various substances, including solids, with bile.

Participation of the liver in various types of metabolism.

1. Protein-synthetic function.

1.albumin 100%,

2.o i-globulins 90%,

3.o 2-globulins 75 ° o,

4.b-globulins 50%,

5.y-globulins - a small amount,

6.fibrinogen,

7.coagulation factors (including vitamin K-dependent)

8.pseudocholinesterase (ChE)

Albumin is one of the lightest proteins in the blood, OMM 65-70 kDa, and is synthesized exclusively by the liver. Albumin maintains oncotic pressure, and a decrease in content leads to edema. If the decrease in albumin concentration is not associated with malnutrition, malabsorption in the intestine, or a large loss of protein, it is due to a pronounced decrease in liver function. Albumin plays an important role in the transport of substances that are poorly soluble in water (hydrophobic). These substances include bilirubin, cholesterol, fatty acids, a number of hormones and drugs. Violation of the transport function of albumin leads to many pathological changes.

The liver maintains amino acid levels, incl. cyclic (tyrosine, tryptophan, phenylalanine), neutralizes ammonia, converting it into urea.

2. Lipid metabolism. Cholesterol synthesis is 90% carried out by the liver and intestines. A significant part of cholesterol in the liver is converted into bile acids, steroid hormones, vitamin D. The liver converts short-chain fatty acids toxic to the brain (4-8 carbon atoms - nylon, isovaleric, etc.) into long-chain fatty acids (16-18 carbon atoms).

3. Carbohydrate metabolism. The liver is the central organ of glucose homeostasis through glycogenesis, glycogenolysis, gluconeogenesis. The liver produces insulinases - enzymes that break down insulin, maintaining the level of lactic and pyruvic acids.

4. Pigment metabolism involves the transformation in the hepatocyte by conjugation with glucuronic acid of toxic fat-soluble indirect bilirubin, into non-toxic water-soluble direct bilirubin. The release of bilirubing glucuronide can occur either by direct secretion into the bile capillary, or by incorporation into the bile micelle.

5. The exchange of porphyrins includes the synthesis of heme, which consists of a complex of protoporphyrin with iron. Heme is necessary for the synthesis of heme-containing liver enzymes (cytochromes, etc.). Congenital impairment of heme synthesis in the liver leads to diseases - hepatic porphyria.

6. Exchange of hormones. In liver diseases, there is an increase in the level of hormones associated with a violation of their secretion with bile or a distortion of the normal hormone metabolism (insufficient destruction). The level of adrenaline and norepinephrine (mediators of the sympathetic nervous system), the mineralocorticoid aldosterone, sex hormones, especially estrogens, tissue hormones serotonin and histamine increases.

7. Exchange of trace elements. The liver synthesizes proteins for the transport and storage of iron; it is also the main iron depot. The liver plays an important role in the metabolism of copper: it synthesizes ceruloplasmin, a glycoprotein that binds up to 90% of blood copper, and also

absorbs copper loosely bound to albumin from blood plasma, and excretes excess copper through lysosomes with bile into the intestine.

Biochemical research.

Biochemical studies play an important role in the diagnosis and determination of the severity, prognosis and course of liver disease. In most cases, this assessment becomes possible not on the basis of the results of a separate test, but on the basis of the interpretation of the data obtained using several tests. For a more convenient assessment, it is advisable to group the tests used depending on the studied liver function. Biochemical tests can be used to characterize:

• the integrity of hepatocytes;

• excretion of bile;

• synthetic liver function;

• other special functions.

Assessment of the integrity of hepatocytes, violations of which in mild cases are manifested by increased permeability of the cell membrane, and in severe cases - by cell necrosis, is carried out on the basis of the detection of liver cell enzymes in the blood plasma. Most often, for this purpose, they use the determination of the activity of transaminases - aspartate aminotransferase (AcAT) and alanine aminotransferase (ALT). The transaminase sensitivity is high. Glutamate dehydrogenase (GLDH) is contained exclusively in mitochondria and is characterized by the highest activity in perivenous hepatocytes of acinus. This explains why the greatest rise in the activity of this enzyme is observed in venous stasis in the liver and in shock. To assess the excretion of bile, the determination of the activity of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase is used (11 111). The increase in the activity of these enzymes in the blood plasma during cholestasis is explained by their increased release from the canalicular membranes.

hepatocytes and their increased synthesis. An increase in GGTP activity is not considered specific for cholestasis, since it can also occur in violation of the integrity of hepatocytes. This enzyme is currently the most sensitive clinical and biochemical marker of diseases of the hepatobiliary system; its increase occurs relatively early and is very pronounced with alcoholic liver damage.

Hyperbilirubinemia as a symptom of cholestasis is characterized by rather low sensitivity and specificity. However, the determination of bilirubin fractions has an important differential - diagnostic value, since it allows to distinguish between conjugated and unconjugated hyperbilirubinemia. The study of the level of bilirubin also helps in assessing the prognosis for certain chronic liver diseases.

To assess the synthetic function of the liver, the study of the level of blood coagulation factors, which are produced only in the liver and have a short half-life in plasma (for example, factor VII), is used primarily. Quik's prothrombin time is most often determined, which depends on coagulation factors I, II, V, VII and X synthesized in the liver. Since some of these factors (II, VII and X) also require the presence of vitamin K, an increase in prothrombin time may be caused not only by a decrease in the synthetic function of the liver, but also by a decrease in the absorption of vitamin K due to cholestasis. Serum cholinesterase activity also reflects the state of synthetic liver function. This enzyme is produced in the liver and has a blood half-life of about 10 days. On the contrary, the determination of the level of albumin in plasma as an indicator reflecting the reduced synthetic function of the liver is characterized by rather low sensitivity and specificity. Although albumin is produced exclusively in the liver, its reserve capacity in this regard is so high that the level of albumin in plasma begins to decrease only with severe damage to the liver parenchyma. In addition, a decrease in albumin synthesis can be compensated for by a decrease in its degradation. Other causes leading to hypoalbuminemia can be diseases accompanied by malabsorption syndrome.

Clinical and biochemical methods for assessing special liver functions are used to diagnose certain diseases. Thus, polyclonal hypergammaglobulinemia is induced in chronic liver diseases by antigens of the gastrointestinal tract, which, as a result of reduced liver function or due to the formation of portocaval anastomoses, are not sufficiently removed from the blood. These antigens stimulate the production of antibodies by plasma cells derived from lymphocytes.

The presence of fibrosis can be determined by measuring the serum level of the type III procollagen peptide.

Table 2.

Biochemical indicators for liver diseases

indicator	Reference values	**Diagnostic value**
Total bilirubin	5-21 μmol / l *	Identification of jaundice, assessment of severity
Associated bilirubin	0,0-5,1 μmol / l *	Gilbert's disease, hemolysis
Alkaline phosphatase	98-280 ME/l	Diagnostics of the cholestasis, liver infiltration
AcAT	0-37 ME/l	Early diagnosis of hepatocellular damage, control over the dynamics of the disease
ALAT	0-40 ME/l	In alcoholism, the activity of ALT is lower than AcAT activity
I I III	10-61 ME/l	Diagnostics of the alcoholic injury and biliary cholestasis
Albumen	35-50 g/l	Assessment of the severity of liver damage
u-Globulin	5-15 g/l	Diagnostics of chronic hepatitis and cirrhosis, control over the dynamics of the disease
Prothrombin time	12-16 sec	Assessment of the severity of liver damage

Indicators of pigment metabolism.

Total serum bilirubin.

The content of total bilirubin in serum is normally 3.4 - 20.5 μmol / l.

Serum bilirubin levels increase in both cholestatic and hepatocellular lesions and is accompanied by an increase in the activity of hepatic enzymes. In this case, bilirubin is predominantly in a bound state. An isolated increase in serum bilirubin levels (without an increase in enzyme activity) may be familial or due to hemolysis.

It is important to evaluate patients with jaundice. Discolored stool is indicative of cholestatic jaundice, but may also occur in parenchymal lesions. With hemolytic jaundice, the color of the stool is normal. Rarely, discolored feces are observed with severe deficiency of UDP-glucuronyl transferase.

In patients with cholestatic liver damage, a small amount of bound plasma bilirubin is filtered by the renal glomeruli. In the renal tubules, part of it is reabsorbed, and the remainder is excreted in the urine, giving it a dark color.

Clinical and diagnostic value of bilirubinuria. In acute viral hepatitis, bilirubin is found in the urine before urobilinogen appears or jaundice develops. In fever of unclear etiology, the presence of bilirubinuria is evidence in favor of hepatitis.

Urobilinogen

Under the influence of bacteria, bilirubin in the intestine is converted into colorless tetrapyrrole compounds, which are called a general term

"Urobilinogen. Approximately 20% of its total is absorbed in the intestines and then re-excreted by the liver in bile. A small proportion of urobilinogen is excreted in the urine. The content of urobilinogen in urine is used in the differential diagnosis of liver and biliary tract diseases. With complete obstruction of the bile duct, when bilirubin does not enter the intestine, urobilinogen may be absent in the urine.

Direct serum bilirubin

The content of direct bilirubin in serum is normally 0.00-5.1 μmol / l. The study is usually carried out for the differential diagnosis of jaundice.

With parenchymal jaundice, the destruction of liver cells occurs, the excretion of direct bilirubin into the bile capillaries is impaired, and it enters the blood directly, where its content increases significantly. In addition, the ability of hepatic cells to synthesize bilirubing glucuronides decreases; as a result, the amount of indirect bilirubin in the blood also increases.

With obstructive jaundice, bile secretion is impaired, which leads to a sharp increase in the content of direct bilirubin in the blood. The concentration of indirect bilirubin also increases slightly in the blood. With hemolytic jaundice, the content of direct bilirubin in the blood does not change.

Indirect serum bilirubin

The content of indirect bilirubin in serum is normally 3.4-13.7 μmol / l. The study of indirect bilirubin plays an important role in the diagnosis of hemolytic anemias. Normally, 75% of total bilirubin in the blood is accounted for by indirect (free) bilirubin and 25% by direct (bound) bilirubin.

Indirect bilirubin increases with hemolytic anemia, pernicious anemia, with neonatal jaundice, Gilbert's syndrome, Crigler-Nayyar syndrome. The increase in indirect bilirubin in hemolytic anemia is due to its intensive formation due to the remolysis of erythrocytes, and the liver is unable to form a large amount of bilirubin glucuronides. With the listed syndromes, the conjugation of indirect bilirubin with glucuronic acid is impaired Determination of the activity of serum enzymes.

Alkaline phosphatase

ALP activity increases with cholestasis and, to a lesser extent, with damage to hepatocytes. An increase in ALP synthesis by hepatocytes is associated with an increased production of protein and RNA. The release of the enzyme into the serum may be due to its penetration from the tubules into the sinusoids through the loosened tight contacts. An increase in ALP activity is also associated with an increased release of ALP in sinusoids from the plasma membranes of hepatocytes.

An isolated increase in alkaline phosphatase activity may be due to the intestinal fraction of the enzyme. In the course of the hepatobiliary origin of alkaline phosphatase, a simultaneous increase in the activity of GGTP indicates. An increase in ALP activity is sometimes observed in primary or metastatic liver tumors, even in the absence of jaundice or bone damage. An increase in alkaline phosphatase activity with a normal level of bilirubin in serum is also noted with other focal and infiltrative lesions of the liver, for example, with amyloidosis, abscesses, leukemia, or granulomas.

Gamma Glutamyl Transpeptidase

The level of gamma-glutamyl transpeptidase activity is normally 8-61 IU / L in men; in women - 5-36 IU / L.

The activity of GGTP increases with cholestatic and parenchymal lesions. In cholestasis, this increase occurs in parallel with an increase in ALP activity and serves as confirmation of the

hepatobiliary origin of ALP. The concentration of GGTP increases with metastatic liver tumors. This increase, although not constant, is observed more often than an increase in ALP activity.

An isolated increase in serum GGTP activity is observed in people who abuse alcohol, even in the absence of gross liver changes. This is possibly a consequence of the induction of the activity of microsomal enzymes.

Transaminases

Aspartate aminotransferase (AcAT) is a mitochondrial enzyme present in large quantities in the heart, liver, skeletal muscle and kidney. The level of AcAT activity is normally 10-38 IU / L. The activity of this enzyme in serum is increased in any acute tissue injury, apparently due to its release from damaged cells.

Alanine aminotransferase (ALT) is a cytoplasmic enzyme also found in the liver. The level of ALT activity is normally 7 - 41 IU / L. The absolute amount of this enzyme is less than AcAT; moreover, the liver contains more of it than in the myocardium and skeletal muscles. Thus, compared with AcAT, an increase in serum ALT activity is more specific for liver damage.

Determination of transaminase activity plays a role in the early diagnosis of viral hepatitis. It should be determined as early as possible, since within a week after the onset of the disease, it decreases to normal. It is important to determine the activity of transaminases over time.

Especially high activity of enzymes of this group can be observed in the early stages of acute cholestasis, in particular with choledocholithiasis and circulatory failure.

A more rare reason for an increase in transaminase activity is a deficiency of e1-antitrypsin.

In cirrhosis, the activity of transaminases can be different. Especially high activity of enzymes is detected in chronic hepatitis with an active inflammatory process. For alcoholic liver damage, a significant increase in the activity of transaminases is uncharacteristic. The de Ritis coefficient is the ratio AcAT / ALT, normally 1.33, in case of liver disease it is lower than this value, and in case of heart disease it is higher.

Lactate dehydrogenase (LDH) is a relatively insensitive indicator of parenchymal lesions. The LDH activity level is normally 240-480 IU / L. In acute viral hepatitis, LDH activity is increased in the first days of the icteric period, and in mild and moderate forms of the disease, it quickly returns to normal. In obstructive jaundice in the first stages of blockage of the bile ducts, LDH activity is normal, at later stages there is an increase in activity due to secondary liver damage. A significant increase in LDH activity is observed in patients with various tumors, especially with liver involvement.

Lipid metabolism

The liver is an organ in which the processes of lipid metabolism (cholesterol, phospholipids, triglycerides) and lipoproteins (LP) are actively proceeding.

Cholesterol (XC) is a component of cell membranes and is a precursor to bile acids and steroid hormones. It is synthesized in the liver, small intestine and other organs. Some of the cholesterol is absorbed in the intestines and reaches the liver in a bound state with chylomicrons. It is formed mainly from acetyl-CoA in the microsomal fraction and in cytosol. In the biosynthesis of cholesterol, the key reaction is the conversion of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) into mevalonate with the participation of the enzyme HMG-CoA reductase. XC contained in membranes and in bile is predominantly represented by the free fraction. The main route of excretion of cholesterol is its excretion with bile. Cholesterol esters (cholesterol esterified by long-chain fatty acids) are also found in plasma and some organs, such as the liver, adrenal glands and skin. Esters XC are less polar than free cholesterol, and therefore even less soluble in water. Esterification takes place in

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plasma under the action of the enzyme lecithin cholesterol acyltransferase (LCAT) synthesized in the liver.

Phospholipids are a heterogeneous group of substances. They consist of one or more phosphoric acid residues and another polar group. The polar group is represented by various bases such as choline or ethanolamine. In addition, phospholipids contain long-chain fatty acid residues.

Phospholipids are more chemically active than cholesterol and its esters and are an important constituent of cell membranes involved in many chemical reactions. Of the phospholipids of plasma and cell membranes, the largest part is phosphatidylcholine.

Neutral fats (TAG) - the main constituent of the TAG molecule is glycerin, the hydroxyl groups of which are esterified with fatty acids. TAGs serve as an energy depot and a means of transferring energy from the intestines and liver to the tissues.

Lipoproteins

Lipoproteins are the transport form of lipids. They are particles of different density, which are separated by ultracentrifugation into separate fractions. The surface layers are composed of several types of apolipoproteins, free XC, and phospholipids. The inner part is represented by XC esters, TAG and fat-soluble vitamins.

Table.3 Properties of lipoproteins (Shevchenko O.P., Dolgov V.V., 2006)

lipoproteins	**apolipoproteins**	The place of	**functions**

		education	
HM	B-48, A-I, C-II, E	intestines	Exogenous TAG
LPVLD	B-100, C-Я, E	liver	Endogenous TAG and XC
LPLD	B-100	Formed from LPVLD	HS
LPHD	A-I, A-II	tissue	Ether HS

Exogenous fats are absorbed in the small intestine and incorporated into chylomicrons. The latter enter the bloodstream (through the thoracic lymphatic duct), where TAGs are removed with the participation of the enzyme lipoprotein lipase. TAGs are utilized or accumulate in tissues. The remains of chylomicrons are captured by the liver, and XC is metabolized, included in the plasma membranes, or excreted in the bile.

Triglycerides are incorporated into the very low density lipoproteins (VLDL) synthesized in the liver, and triglycerides are cleaved from VLDL in the blood under the action of lipoprotein lipase. In this case, VLDL particles decrease in size and form LP of intermediate density, and then-LP of low density, which are the main carriers of endogenous XC. LDL is predominantly removed by specific receptors on the surface of hepatocytes.

High-density LP (HDL) "scrub" XC from tissues, while the XC contained in HDL is captured by the liver or included in the composition

IDL, leading to the formation of mature LDL. The high level of HDL-C in the blood prevents the development of coronary heart disease.

Apolipoproteins in most cases are formed in the liver, and some of them are synthesized in the intestine. Some apolipoproteins, being a structural component of LP, also perform other functions: apo A-I activates LCAT in plasma, C-II activates lipoprotein lipase.

Changes in lipid parameters in pathological processes in the liver. With cholestasis, the level of total and free XC in serum increases. The mechanism of this increase is unknown. Apparently, 4 factors are involved in the increase in serum cholesterol level: the transfer of C from bile into the bloodstream, an increase in the formation of C in the liver, a decrease in the activity of LCAT, regurgitation of lecithin contained in bile, which promotes the transition of tissue cholesterol into the plasma. While in acute cholestasis there is sometimes a slight (1.5-2 times) increase in the level of XC, in chronic diseases, especially with postoperative strictures and primary biliary cirrhosis, this indicator reaches very high values. Inadequate nutrition leads to a decrease in the level of XC in the serum, which explains the normal content of XC in some patients with mechanical obstruction of the biliary tract with a malignant tumor.

The content of XC esters in cholestasis decreases due to LCAT deficiency. The TAG level rises. The serum contains abnormal lipoprotein, which contains large amounts of free XC and lecithin. Changes in erythrocytes in cholestasis are associated with a violation of the content of XC and LP.

Hepatocellular lesion. When hepatocytes are damaged, the serum TAG level rises due to the accumulation of LDL, which are rich in TAG. The concentration of XC esters is reduced due to the low activity of the LCAT enzyme. In cirrhosis of the liver, serum total XC levels are usually normal. Its decrease indicates a malnutrition or decompensation of cirrhosis. In fatty liver of alcoholic etiology, along with an increase in the content of TAG, the level of VLDL increases. When the liver is damaged by hepatotoxic drugs, a violation of the synthesis of apoproteins leads to a violation of the excretion of TAG with VLDL and the subsequent development of fatty degeneration.

Bile acids

Bile acids (BA) are produced in the liver. Daily 250-500 mg of FA is synthesized and lost with feces. Primary FAs are synthesized from XC: cholic and chenodeoxycholic. Synthesis is regulated by the amount of fatty acids that are returned to the liver during enterohepatic circulation. Under the action of intestinal bacteria, primary FAs undergo dehydroxylation with the formation of secondary FAs: deoxycholic and a very small amount of lithocholic. Tertiary FAs, mainly ursodeoxy-cholic, are formed in the liver by isomerization of secondary FAs. In human bile, the amount of trihydroxy acid (cholic acid) is approximately equal to the sum of the concentrations of two dihydroxy acids - chenodeoxycholic and deoxycholic.

FAs are combined in the liver with the amino acids glycine or taurine. This prevents their absorption in the biliary tract and small intestine, but does not prevent absorption in the terminal ileum. FA salts are excreted into the bile ducts against a large concentration gradient between hepatocytes and bile. Excretion is partly dependent on the value of the intracellular negative potential, which is approximately 35 mV and provides voltage-dependent accelerated diffusion, as well as the diffusion process mediated by the carrier (glycoprotein with a molecular weight of 100 kDa). FA salts penetrate into micelles and vesicles, combining with XC and phospholipids. In the upper parts of the small intestine, micelles of FA salts, rather large in size, have hydrophilic properties, which prevents their absorption. They are involved in the digestion and absorption of lipids. In the terminal section of the ileum and the proximal part of the colon, fatty acids are absorbed, and in the ileum, absorption occurs by active transport. Passive diffusion of non-ionized FAs occurs throughout the intestine and is most effective in relation to unconjugated dihydroxy FAs. Oral administration of ursodeoxycholic acid interferes with the absorption of chenodeoxycholic and cholic acids in the small intestine.

The absorbed salts enter the portal vein system and the liver, where they are intensively captured by hepatocytes. The process takes place by the functioning of the system of transport of molecules through a sinusoidal membrane, based on a sodium gradient. Chlorine ions are also

involved in this process. The most hydrophobic FAs (unbound mono- and dihydroxy bile acids) penetrate into the hepatocyte by simple diffusion (by the “flip-flop” mechanism) through the lipid membrane. The mechanism of FA transport through the hepatocyte from the sinusoids to the bile ducts remains unclear.

This process involves cytoplasmic proteins that bind FA. FAs are re-conjugated and re-excreted in bile.

Disturbance of intrahepatic fatty acid metabolism may play an important role in the pathogenesis of cholestasis.

The entry of fatty acids into the blood in patients with jaundice leads to the formation of target cells in the peripheral blood and the excretion of conjugated bilirubin in the urine. If FAs are deconjugated by bacteria in the small intestine, the resulting free FAs are absorbed. The formation of micelles and the absorption of fats are impaired. This partially explains the malabsorption syndrome, which complicates the course of diseases that are accompanied by stasis of intestinal contents and increased growth of bacteria in the small intestine.

Removal of the terminal ileum interrupts enterohepatic hepatic circulation and encourages a large number of primary FAs to reach the colon and are dehydroxylated by bacteria, thereby reducing the pool in the body. An increase in the amount of FAs in the colon causes diarrhea with a significant loss of water and electrolytes.

Amino acid metabolism

Amino acids that enter the body with food are metabolized in the liver. Some of them undergo transamination or deamination. Another part of the amino acids is converted into ammonia and urea (ornithine cycle). In chronic liver diseases, the maximum rate of urea formation is significantly reduced. An increase in the concentration of ammonia in the blood also indicates a violation of the synthesis of urea and is accompanied by the development of hepatic encephalopathy.

Diagnostic value of changes in the level of amino acids Aminoaciduria - damage to the liver parenchyma. In patients with severe liver disease, the characteristic feature is an increase in plasma methionine and aromatic amino acids tyrosine and phenylalanine and a decrease in branched-chain amino acids valine, leucine and isoleucine. These changes can be explained by impaired liver function, portosystemic shunting of the blood and an increase in the concentration of insulin and glucagon in the blood. In patients with minimal liver damage, changes in the level of amino acids are also noted, in particular, a decrease in the level of proline in plasma, which may indicate an increase in collagen synthesis. The presence or absence of hepatic encephalopathy does not affect the ratio of BCAAs to aromatic amino acids.

Plasma Protein Determination

On the polyribosomes of the rough endoplasmic reticulum of hepatocytes, plasma proteins are synthesized from where they then enter the plasma. A decrease in their level usually reflects a violation of protein synthesis in the liver, although it can be caused by a decrease in the volume of circulating plasma and loss of protein through the intestine or in the urine.

Hepatocytes synthesize albumin, fibrinogen, e1-antitrypsin, haptoglobin, ceruloplasmin, transferrin and prothrombin, etc. Some proteins formed in the liver are referred to as acute phase proteins. Plasma levels rise in response to tissue damage such as inflammation. These proteins include fibrinogen, haptoglobin, 31-antitrypsin, complement C3, and ceruloplasmin. The acute phase response can cause an increase in serum levels of these proteins even with concomitant liver tissue damage.

The acute phase response mechanism is complex; the role of cytokines (interleukin-1, interleukin-6, tumor necrosis factor. by promoter loci at the 5'-end of genes of some acute phase proteins. There are also post-transcriptional and transcriptional mechanisms of regulation. Cytokines not only stimulate the synthesis of acute phase proteins, but also suppress the formation of albumin, transferrin and a number of other proteins.

Table 4.

Proteins synthesized in the liver

proteins	Reference values
Albumen	40-50 g/l
α 1-antitrypsin	2-4 g/l
α fetoprotein	< 10 mkg/l
β2-macroglobulin	2,2-3,8 g/l
Ceruloplasmin	0,2-0,4 g/l
Transferrin	2-3 g/l
Fibrinogen	2-4 g/l
Hemopexin	0,8-1,0 g/l

Deficiency of a1-antitrypsin refers to genetic hereditary diseases.

Haptoglobin is a glycoprotein composed of polypeptide chains α and β that are covalently linked by disulfide bonds. Haptoglobin is produced primarily in hepatocytes. Low haptoglobin levels are observed in severe chronic liver disease and hemolytic crisis.

Ceruloplasmin (ferro-O2-oxidoreductase) is a multifunctional copper-containing protein that carries out nonspecific antioxidant defense of the body. In Wilson's disease, the level of ceruloplasmin is reduced. A low concentration of ceruloplasmin is observed in severe decompensated liver cirrhosis of a different etiology (not associated with Wilson's disease). High levels of ceruloplasmin can be detected in pregnant women, with estrogen treatment and with obstruction of the bile ducts.

The level of complement C3 component in liver cirrhosis is reduced, in chronic hepatitis within normal limits, and in compensated biliary cirrhosis is increased. The decrease in the content of the complement component C3 is also explained by the increased consumption of proteins of the complement system due to its activation. A transient decrease in the level of the complement C3 component is detected at the early immunocomplex stage of acute hepatitis B.

Alpha-fetoprotein (AFP) is a serum protein of the developing human embryo. In adults, it almost completely disappears from the blood soon after birth, but appears with the development of hepatocellular carcinoma (HCC), as well as testicular and ovarian cancer. Expression of the AFP gene in the liver occurs during the processes of necrosis and inflammation in the liver, accompanied by a violation of the intercellular interaction of hepatocytes.

To the greatest extent, cell-matrix interactions in the liver are disturbed in HCC, which is confirmed by the fact that the highest serum AFP levels are recorded in this pathology, and its concentration depends on the volume and rate of tumor growth. In addition, elevated AFP levels are a risk factor for the development of HCC in patients with liver cirrhosis. An increase in the AFP level is also characteristic of CP, since this disease also disrupts the cell-matrix interactions of hepatocytes due to increased fibrosis in the liver.

Carbohydrate metabolism.

The liver plays a major role in carbohydrate metabolism. The mechanisms of its violation in cirrhosis are complex and not fully disclosed.

In patients with liver cirrhosis, when examined on an empty stomach, the role of carbohydrates as a source of energy decreases and the proportion of fats increases. This may be due to a decrease in the production of glucose by the liver or a decrease in the storage of glycogen in the liver tissue. After a meal in patients with liver cirrhosis, as in healthy people, there is a rapid utilization of food carbohydrates, which is even more pronounced due to a violation of the liver's ability to store them. This is accompanied by the mobilization of triglycerides as an energy source.

Pigment exchange.

Bilirubin exchange

Bilirubin is a tetrapyrrole pigment with a molecular formula of C33H56N406 and a molecular weight of 584.65 D. It is formed in the process of catabolism of the heminic part of hemoglobin (protoporphyrin IX) of erythrocytes that have completed their life cycle. In addition, bilirubin can be formed during the catabolism of other heme-containing proteins (myoglobin, catalase, peroxidase), albeit in much smaller quantities. With an average life expectancy of erythrocytes of 120 days per day, bilirubin is formed in the body in an amount of 3.8 + 0.6 mg / kg of body weight.

The erythrocyte is destroyed mainly in the cells of the RES of the liver and spleen, lymph nodes and bone marrow. With aging of erythrocytes, the content of sialic acids in the composition of glycoproteins of the cytoplasmic membrane decreases. The altered carbohydrate components of erythrocyte membrane glycoproteins bind to the receptors of the RES cells, and the erythrocytes are absorbed by the cells by endocytosis. The hemoglobin contained in erythrocytes undergoes the decay process. Initially, the methane bridge breaks between I and II pyrrole cores of the porphyrin ring with simultaneous oxidation of Fe + 2 in Fe + 3 with the participation of the enzymatic complex of heme oxygenase. The resulting pigment is called verdoglobin. Further transformations lead to the loss of iron and globin by verdoglobin. At the same time, iron replenishes the reserves of the depot, globin is hydrolyzed by lysosomal enzymes with the formation of free amino acids, which are used by the body for protein synthesis. The porphyrin ring of heme unfolds into a chain with the formation of a green bile pigment - biliverdin. Biliverdin is reduced with the participation of the enzyme biliverdin reductase in the main and most important red-yellow pigment of bile - bilirubin. When 1 g of hemoglobin breaks down, 35 mg of bilirubin is formed.

This bilirubin formed in RES cells:

Insoluble in water, therefore does not pass through the renal filter;

1. Well soluble in lipids, therefore:

- easily penetrates the lipid layer of cell membranes;

is able to accumulate in lipid-rich tissues (especially in nervous tissue);

2. Possesses pronounced toxicity, as it disrupts the processes of oxidative phosphorylation in cells, disrupts protein synthesis, the flow of potassium ions through cell membranes.

3. Indirect, since it gives a reaction with a diazo-reactive only after the transition to a soluble compound with the addition of an accelerator (caffeine).

Bilirubin, formed outside the liver, circulates in the blood in non-covalent bonds with albumin. This prevents the reverse diffusion of bilirubin in the tissue and, possibly, contributes to its targeted entry into the liver. Some endogenous and exogenous substances are able to displace bilirubin from its association with albumin.

Bilirubin bound to albumin enters the liver through the pores of endothelial cells into the Disse space and directly contacts the sinusoidal membrane of hepatocytes. Transport proteins for bilirubin are built into the membrane, which facilitate its entry into the cell by diffusion. The transport function of the most quantitatively important transport protein depends on both sodium and chlorine ions. This protein is characterized by saturation kinetics, and it provides transport of both indirect and direct bilirubin. Drugs and other exogenous substances compete for this transport protein.

Bilirubin entering the cell binds to proteins. Thus, its accumulation in a non-toxic form can be ensured and its reverse diffusion into the blood is prevented. The most important intracellular binding protein is ligandin, an isoenzyme or subunit of glutathione S-transferase. The conjugation of bilirubin in hepatic cells is the main stage in the exchange of bilirubin and serves as a prerequisite for its subsequent excretion with bile. Upon conjugation, both propionic acid residues of bilirubin undergo esterification with glucuronic acid. In this case, first a monoglucuronide arises, and then bilirubin-diglucuronide.

Unconjugated bilirubin is a non-polar (fat-soluble) substance. In the conjugation reaction, it turns into a polar (water-soluble substance) and can therefore be released into bile. This reaction proceeds with the help of the microsomal enzyme uridine diphosphate glucuronyl transferase (UDPGT), which converts unconjugated bilirubin into conjugated bilirubin mono- and diglucuronide. UDPGT is one of several isoforms of the enzyme that provides the conjugation of endogenous metabolites, hormones, and neurotransmitters.

The UDFGT gene for bilirubin is located on the 2nd pair of chromosomes. The structure of the gene is complex. In all isoforms of UDPGT, exons 2 - 5 at the 3'-end of the gene's DNA are constant components. For gene expression, one of the first few exons must be involved.

The details of the gene structure are important for understanding the pathogenesis of unconjugated hyperbilirubinemia (Gilbert and Crigler-Nayyard syndromes), when the content of enzymes responsible for conjugation is reduced in the liver.

The activity of UDPGT in hepatocellular jaundice is maintained at a sufficient level, and even increases in cholestasis. In newborns, the activity of UDFGT is low.

In humans, bilirubin in bile is represented mainly by diglucuronide. The conversion of bilirubin to monoglucuronide, as well as to diglucuronide, occurs in the same microsomal glucuronyl transferase system. With an overload of bilirubin, for example, with hemolysis, mainly monoglucuronide is formed, and with a decrease in the intake of bilirubin or with induction of the enzyme, the content of diglucuronide increases.

The most important is conjugation with glucuronic acid, but a small amount of bilirubin is conjugated with sulfates, xylose and glucose; with cholestasis, these processes are enhanced.

In the later stages of cholestatic or hepatocellular jaundice, despite the high content in plasma, bilirubin in the urine is not detected. Obviously, the reason for this is the formation of monoconjugated type III bilirubin, which is covalently bound to albumin. It is not filtered in the glomeruli and therefore does not appear in the urine. This reduces the practical significance of samples used to determine the content of bilirubin in urine.

The excretion of bilirubin into the tubules occurs via a family of ATP-dependent multispecific transport proteins for organic anions. The rate of transport of bilirubin from plasma to bile is determined by the stage of excretion of bilirubin glucuronide.

Bile acids are transported to bile by another transport protein. The presence of different mechanisms of transport of bilirubin and bile acids can be illustrated by the example of Dubin-Johnson syndrome, in which the excretion of conjugated bilirubin is impaired, but normal excretion of bile acids remains. Most of the conjugated bilirubin in bile is found in mixed micelles containing cholesterol, phospholipids, and bile acids. The importance of the Golgi apparatus and microfilaments of the cytoskeleton of hepatocytes for the intracellular transport of conjugated bilirubin has not yet been established.

Further, conjugated bilirubin, together with other components of bile, enters the small intestine, the ingested bilirubing glucuronides are hydrolyzed by specific bacterial enzymes (g-glucuronidases, which hydrolyze the bond between bilirubin and the remainder of glucuronic acid). The bilirubin released during this reaction is reduced by the action of the intestinal microflora with the formation of colorless tetrapyrrole compounds - urobilinogens. In the small intestine, part of the urobilinogen (mesobilinogen -15-20%) is reabsorbed and enters the liver with the blood of the portal vein, where it is oxidized to form pyrroles, which are further excreted with bile into the intestine. Therefore, under physiological conditions, urobilinogen is not present either in the general bloodstream system or in urine.

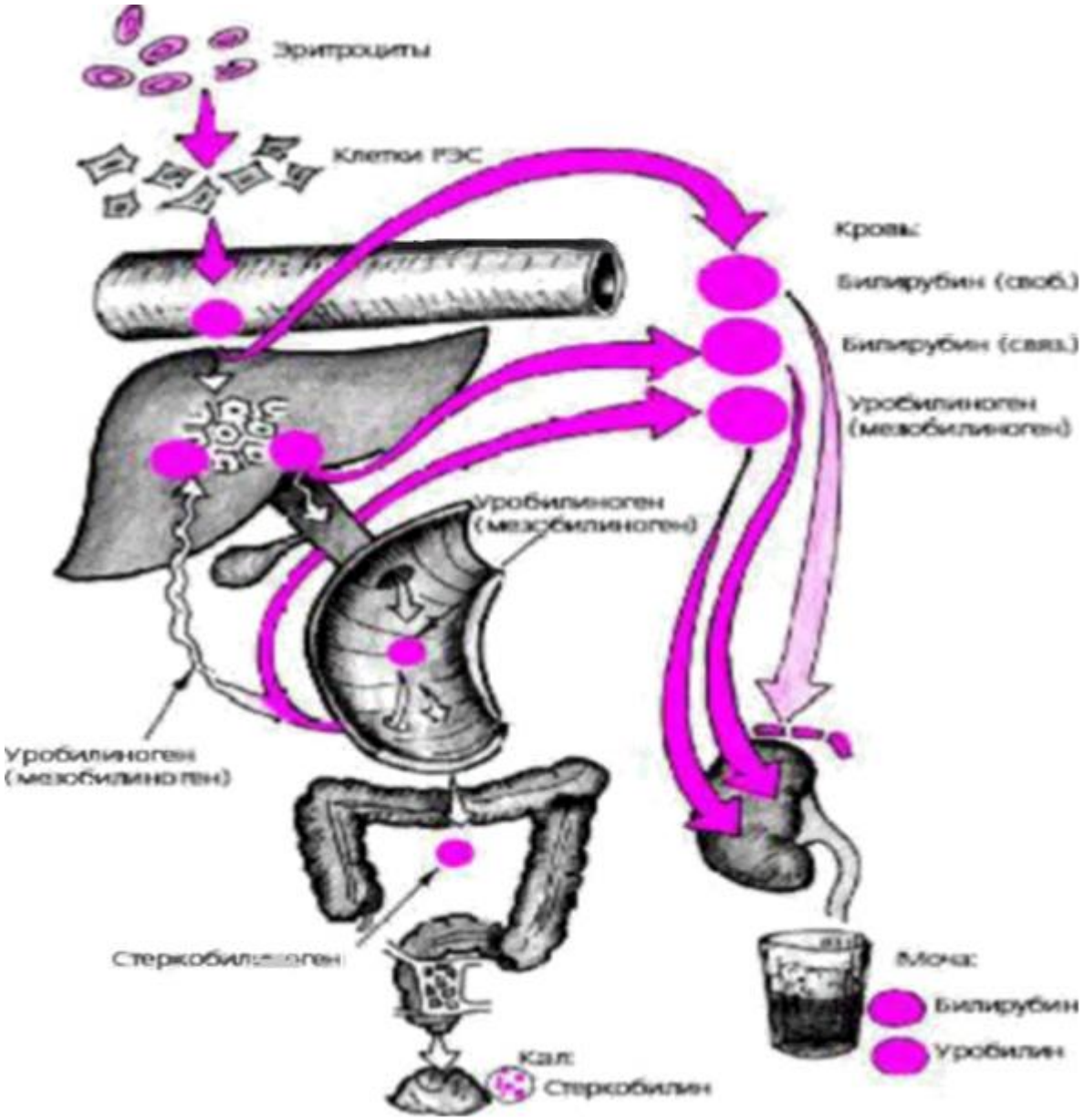
In the large intestine, urobilinogen is converted into stercobilinogen under the action of intestinal microflora enzymes.

In the lower parts of the large intestine, part of the stercobilinogen is absorbed by the intestinal wall and through the hemorrhoidal vein system enters the general bloodstream system and from there into the urine.

The so-called urine urobilin, in essence, is predominantly an oxidized stercobilinogen, and in liver diseases, urobilinogen is added to the latter due to the inability of the liver to utilize it. In air, both compounds are rapidly oxidized, transforming into red-brown colored products, denoted by the general term urobilin bodies (urobilinoid).

In the large intestine, most of the stercobilinogen is oxidized to stercobilin, which causes the normal color of feces.

Figure b. The exchange of bilirubin is normal (source eepatit5neo.ru)



Differential diagnosis of jaundice.

An increase in the level of total bilirubin in the blood serum to a level above 20.5 μmol / L is called hyperbilirubinemia. This condition may be due to the production of more bilirubin than the normal liver can excrete; liver damage that interferes with the excretion of bilirubin in normal amounts, as well as due to blockage of the bile ducts of the liver, which prevents the excretion of bilirubin. In all these cases, bilirubin accumulates in the blood and

upon reaching certain concentrations, the tissue diffuses, staining them yellow. This condition is called jaundice. Depending on what type of bilirubin is present in cravi's serum, unjugated (indirect) or conjugated (direct), hyperbilirubinemia is classified as unconjugated I and regurgitant (conjugated), respectively. In clinical practice, the most widespread division of jaundice into hemolytic, parenchymal and obstructive. Hemolytic and parenchymal jaundice is

unconjugated and obstructive conjugated hyperbilirubinemia. In some cases, jaundice can be mixed in pathogenesis.

An increase in the content of bilirubin in the blood may be due to the following reasons:

1.increase in the intensity of erythrocyte hemolysis;

2. damage to the liver parenchyma with impairment of its bilirubin-excretory function;

3. violation of the outflow of bile from the biliary tract into the intestines;

4. identification of the enzyme link providing biosynthesis of bilirubin glucuronides.

5. impairment of hepatic secretion of conjugated (direct) bilirubin into bile.

Hemolytic jaundice. An increase in the intensity of hemolysis is observed in hemolytic anemias. Hemolysis can also be enhanced with B12-deficient anemias, malaria, massive hemorrhages in the tissue, pulmonary infarctions, and crush syndrome (unconjugated hyperbilirubinemia). As a result of increased hemolysis, an intensive formation of free bilirubin from hemoglobin occurs in the reticuloendothelial cells. At the same time, the liver is unable to form such a large amount of bilirubing glucuronides, which leads to the accumulation of free bilirubin (indirect) in the tissue. However, even with significant hemolysis, unconjugated hyperbilirubinemia is usually insignificant (less than 68.4 μmol / L) due to the high ability of the liver to conjugate bilirubin. In addition to an increase in the level of total bilirubin, with hemolytic jaundice, the excretion of urobilinogen in urine and feces increases, since it is formed in the intestine in large quantities.

The most common form of unconjugated hyperbilirubinemia is "physiologic jaundice" in newborns. It is caused by hemolysis of erythrocytes and the immature state of the hepatic system of absorption, conjugation (decreased activity of UDP-glucuronyl transferase) and secretion of bilirubin.

Due to the fact that bilirubin accumulating in the blood is in an unconjugated (free) state, when its concentration in the blood exceeds the saturation level of albumin (34.2-42.75 μmol / l), it is able to overcome the blood-brain barrier. This can lead to hyperbilirubinemic toxic encephalopathy.

In hepatocellular (parenchymal) jaundice, destruction of hepatocytes occurs, the excretion of direct (conjugated) bilirubin into the bile capillaries is impaired, and it enters the blood directly, where its content increases significantly. In addition, the ability of liver cells to synthesize bilirubin-glucuronide decreases, as a result of which the amount of indirect bilirubin also increases. An increase in the concentration of direct bilirubin in the blood leads to its appearance in the urine due to filtration through the membrane of the renal glomeruli. Indirect bilirubin, despite the increase in blood concentration, does not enter the urine. The defeat of hepatocytes is accompanied by a violation of their ability to destroy the mesobilinogen (urobilinogen) absorbed from the small intestine to di and tripyrroles. An increase in the content of urobilinogen in urine

can be observed even in the pre-icterus period. In the midst of viral hepatitis, a decrease or even disappearance of urobilinogen in urine is possible. This is because the increasing stagnation of bile in the liver cells leads to a decrease in the release of bilirubin and, consequently, to a decrease in the formation of urobilinogen in the biliary tract. Later, when the function of the liver cells begins to recover, bile is secreted in large quantities, while urobilinogen appears again in large quantities, which in this situation is regarded as a favorable prognostic sign. Stercobilinogen enters the systemic circulation and is excreted by the kidneys in the urine in the form of urobilin.

The main causes of parenchymal jaundice are acute and chronic hepatitis, cirrhosis of the liver, toxic substances (chloroform, carbon tetrachloride, acetaminophen), massive spread of cancer in the liver, alveolar echinococcus and multiple liver abscesses.

In viral hepatitis, the degree of bilirubinemia correlates to some extent with the severity of the disease. So, with hepatitis B with a mild course of the disease, the bilirubin content is not higher than 90 μmol / l (5 mg%), with moderate hepatitis - within 90-170 μmol / l (5-10 mg%), with severe - over 170 μmol / l (above 10 mg%). With the development of hepatic coma, bilirubin can increase to 300 μmol / L or more. However, it should be borne in mind that the degree of increase in bilirubin in the blood does not always depend on the severity of the pathological process, but may be due to the rate of development of viral hepatitis and liver failure.

Obstructive (obstructive, subhepatic) jaundice is caused by obstruction of the extra- or intrahepatic biliary tract, which causes partial or complete cessation of the outflow of bile. When the common bile duct is obstructed (stone, inflammation, swelling, etc.) due to congestion

Table 5.

The main indicators for diseases manifested by jaundice

	Cholelithiasis	Duodenal papilla cancer	Viral hepatitis acute phase	Medicinal jaundice Cholestatic
itching	+	+	Transient	+
The rate of development of jaundice	Honey is developing lazily	Honey is developing lazily	Is developing quickly	Is developing quickly
Peculiarities jaundice	"Fluctuating"	Developing in	Is developing	Expressed in

	or constant	most cases, but not always	decreases rapidly, slowly as you recover	varying degrees, usually soft
Expressiveness jaundice	Moderate	Significant	Various	Various, sometimes accompanied by rashes
Кал (цвет)	Периодически светлый	Светлый	Различный, от белого до темно-	light
Скрытая кровь		+		
Urine: urobilinogen or urobilin	+	-	Missing in the onset of the disease, appears in further	Missing in the beginning of the disease
Serum bilirubin level, μmol / l	Usually 50 - 170	Unswerving raising up to 250 - 500	Depends on the severity of the disease	Different
ALP activity	More than 3 times higher than normal	More than 3 times higher than normal	Less than 3 times higher than normal	More than 3 times above normal
Activity	Less than 5 times higher than	Less than 5 times higher	More than 10 times higher	More than 5 times

AcAT	normal	than normal	than normal	above normal

bile in the hepatic capillaries bile (direct, conjugated bilirubin) passes into the blood capillaries between the membranes of the liver cells (hepatocytes). The level of conjugated bilirubin in the blood plasma rises and then exceeds the renal threshold. The renal filter allows direct bilirubin to pass freely. Bilirubinuria with obstructive jaundice is a constant phenomenon. A decrease in the content of bilirubin in the urine or its complete disappearance indicates a partial or complete restoration of the patency of the biliary tract. Jaundice progresses, serum levels of conjugated bilirubin, the activity of the liver fraction of alkaline phosphatase, GGTP, as well as the level of total cholesterol and conjugated bile acids increase. As a result of steatorrhea, body weight decreases and the absorption of vitamins A, D, E, K, as well as calcium, is impaired.

Hereditary hyperbilirubinemia.

Although 20 μmol / L (0.8 mg%) is usually taken as the upper limit of the normal serum bilirubin level, almost 5% of healthy blood donors have higher concentrations (22-50 μmol / L). If we exclude patients with hemolysis or liver disease, people with hereditary disorders of bilirubin metabolism remain. The most common of these is Gilbert's syndrome. There are also other syndromes. The prognosis for these disorders of bilirubin metabolism is favorable. Diagnosis is based on family history, duration of illness, absence of stigma of hepatocellular damage and splenomegaly, hemolysis, normal serum transaminase activity, and, if necessary, liver biopsy data.

Gilbert's syndrome

The syndrome is defined as benign familial unconjugated hyperbilirubinemia of moderate severity (serum bilirubin concentration in the range of 17-85 μmol), not associated with hemolysis and having a benign course. Hyperbilirubinemia is familial and is not accompanied by a violation of the biochemical parameters of liver function. The prognosis is favorable. Jaundice is confident and intermittent.

In Zhilber's syndrome, the binding of bilirubin with glucuronic acid in the liver decreases to 30% of normal. In bile, the content of predominantly bilirubin monoglucuronide and, to a lesser extent, diglucuronide increases.

Table 6.

Isolated elevation of serum bilirubin

Bilirubin type	Diagnostic criteria
Unconjugated	

Hemolysis	Splenomegaly. Reticulocytosis. Coombs test
Gilbert's syndrome	Serum bilirubin rises with fasting and decreases when taking phenobarbital. Transaminase activity is normal
Crigler-Nayyar Syndrome: type 1	Lack of enzymes in the liver that carry out conjugation. Death usually occurs early in life with kernicterus
Crigler-Nayyar Syndrome: type 2	Absence in the liver of enzymes that carry out conjugation, or a decrease in their content.
Conjugated	
Dubin-Johnson Syndrome	An increase in the level of predominantly conjugated bilirubin, alkaline phosphatase activity and serum bile acid levels remain within the normal range.
Rotor Syndrome	Liver biopsy does not reveal any pathological changes. The cholecystographic picture is normal. In the bromsulfalein test, the dye is not captured

At the heart of Gilbert's syndrome is a genetic defect in the presence of an additional dinucleotide on the promoter region of the gene encoding UDPGT 1 * 1. This defect is inherited in an autosomal recessive manner; therefore, for the development of the disease, the patient must be homozygous for this allele. The lengthening of the promoter sequence disrupts the binding of the transcription factor, and this, in turn, leads to a decrease in the formation of the enzyme UDPGT 1, but a decrease in the synthesis of enzymes alone is not enough for the development of Gilbert's syndrome; the presence of other factors is necessary, for example, latent hemolysis and impaired transport of bilirubin in the liver.

Gilbert's syndrome can be combined with an increase in alkaline phosphatase activity of intestinal origin.

If paracetamol does not bind to glucuronic acid, it is catabolized in the cytochrome P450 system with the formation of a toxic metabolite. In Gilbert's syndrome, hereditary insufficiency of UDFGT predisposes to the manifestation of the toxic effect of paracetamol, especially when taking large doses of it.

Erigler-Nayyar syndrome

In this form of familial non-hemolytic jaundice, serum levels of unconjugated bilirubin are very high. In the liver, a deficiency of the conjugating enzyme can be detected.

Type 1

Crigler-Najjar syndrome type 1 is inherited in an autosomal recessive manner. In the liver there is no activity of the conjugating enzyme, in bile there is conjugated bilirubin. Bilirubin glucuronides are not detected in serum. Since serum bilirubin levels stabilize over time, an alternative pathway for bilirubin metabolism should be assumed.

Usually, although not always, people die within the first year of life with nuclear jaundice. Taking phenobarbital is ineffective.

Type 2

Crigler-Najjar syndrome type 2 is also inherited in an autosomal recessive manner. The activity of the enzyme that conjugates bilirubin in the liver is significantly reduced and cannot be determined by conventional methods. Prescribing phenobarbital leads to a pronounced effect, and patients survive to adulthood.

In some relatives of patients with Crigler-Nayyard syndrome, an increase in serum bilirubin level is detected, which, although not as high as in patients, is higher than its level in Gilbert syndrome. Crigler-Najjar syndrome type 2 is not always benign, and to ensure bilirubin levels below 450 μmol / L (26 mg%)

Dubin-Johnson syndrome

Chronic benign disease, manifested by persistent jaundice with an increase in the level of predominantly conjugated bilirubin and biliribinuria. It is inherited in an autosomal recessive manner. The syndrome is based on impairment of transport to bile.

many organic anions, not related to bile acids, which is caused by a defect in the ATP-dependent transport system of the tubules. Dubin-Johnson syndrome is not accompanied by itching; ALP activity and serum bile acid levels remain within the normal range.

The excretion of organic anions into bile is impaired. Their absorption by the liver is not affected. The disease may first manifest itself as jaundice during pregnancy or while taking oral contraceptives (both of these conditions cause a deterioration in the excretory function of the liver). The prognosis is pleasant.

Rotor Syndrome

Rotor syndrome (chronic familial non-hemolytic jaundice with conjugated hyperbilirubinemia and normal liver histology without unidentified pigment in hepatocytes) is hereditary and

transmitted in an autosomal recessive manner. The pathogenesis of Rotor syndrome is similar to the pathogenesis of Dubin-Johnson syndrome, but the defect in bilirubin excretion is less pronounced.

The main syndromes in liver diseases.

The following main syndromes are distinguished:

1. Cytolytic syndrome (cytolysis) occurs due to a violation of the structure of liver cells, an increase in membrane permeability, as a rule, due to an increase in the processes of lipid peroxidation (LPO) and the release of enzymes into the blood. In cytolytic syndrome, both cytoplasmic and mitochondrial components of enzymes enter the bloodstream, but the main level of activity is determined by cytoplasmic isozymes. Cytolysis accompanies mainly acute liver diseases and increases with exacerbation of chronic ones. The following main mechanisms of cytolysis are distinguished:

1.toxic cytolysis (viral, alcoholic, medicinal);

2. immune cytolysis, incl. autoimmune;

3. hydrostatic;

4. hypoxic ("shock liver", etc.);

5. tumor cytolysis;

6. cytolysis associated with nutritional deficiencies and nutritional deficiencies. The main available markers of cytolysis in acute hepatitis are alanine (ALT) and aspartic (AcAT) transaminases, gamma-glutamyl transpeptidase (11 111), lactate dehydrogenase (LD1).

An increase in the activity of AlAT and AcAT is observed in 88-97% of patients, depending on the type of hepatitis. The maximum activity is characteristic for the 2nd-3rd week of the disease, and a return to normal at 5-6 weeks. Exceeding the time for normalization of activity is an unfavorable factor. AlAT activity AcAT, which is associated with the distribution of AcAT between the cytoplasm and mitochondria. The predominant increase in AcAT is associated with damage to mitochondria and is observed in more severe liver damage, especially alcoholic. The activity of transaminases increases moderately (2-5 times) in chronic liver diseases, more often in the acute phase, and liver tumors. For cirrhosis of the liver, an increase in the activity of transaminases, as a rule, is not typical.

LsLH increases in acute hepatitis and other severe lesions of hepatocytes. A moderate increase is observed in obstructive jaundice, in patients with liver metastases and cirrhosis. The de Pitca coefficient, that is, the AcAT / ALAT ratio (normally equal to 1.33) in liver disease is lower than this value, and in heart disease it is higher.

The level of activity of alanine amine transferase (ALT) is normally 7-41 IU / L.

In liver diseases, ALT activity changes primarily and most significantly in comparison with AcAT. In acute hepatitis, regardless of its etiology, the activity of aminotransferases increases in all patients. The activity of ALT contained in the cytoplasm especially changes, which contributes to its rapid exit from the cell and its entry into the bloodstream, therefore ALT is a more sensitive test for early diagnosis of acute hepatitis than AcAT. Half-life of about 20 hours, responds to more severe damage to the hepatocyte. In acute viral hepatitis, ALT and AcAT increase 10-15 days before the onset of jaundice in hepatitis A, and for many weeks in hepatitis B, and they increase simultaneously, but ALT is much more. In a typical course of viral hepatitis, ALT activity reaches a maximum at 2-3 weeks of illness. If its course is favorable, the activity of ALT is normalized after 30-40 days, the activity of AcAT - after 25-35 days. A repeated or progressive increase in aminotransferase activity indicates new necrosis or relapse of the disease. Prolongation of the period of increased aminotransferase activity is often an unfavorable sign, because may indicate the transition of an acute process to a chronic one.

Chronic hepatitis is characterized by moderate to moderate hyperenzymemia.

In latent forms of liver cirrhosis, the activity of the enzyme, as a rule, is not increased. In active forms, a persistent, albeit insignificant, rise in aminotransferase activity occurs in 74-77% of cases.

An increase in the activity of AlAT and AcAT can also be detected in practically healthy carriers of the surface antigen of hepatitis B, which indicates the presence of outwardly asymptomatic active processes in the liver.

Gamma-glutamyl transpeptidase GT, GGTP, y-GT) is contained in the cytoplasm (low molecular weight isoform) and is associated with the membranes of the biliary pole (high molecular weight isoform). An increase in its activity may be associated with cytolysis, cholestasis, alcohol or drug intoxication, tumor growth; therefore, an increase in GGTP activity is not specific for a particular disease, but to a certain extent universal or screening for liver diseases, although it suggests additional searches for the cause diseases. The enzyme is more sensitive to abnormalities in liver cells, ALT, AcAT, alkaline phosphatase, succinate dehydrogenase, glutamate dehydrogenase, etc.

Lactate dehydrogenase (LDH) is increased in many diseases. The diagnostic value of the total activity is small and is limited to determination to exclude tumor and hemolytic processes, as well as for the differential diagnosis of Gilbert's syndrome (normal) and chronic hemolysis (increased). For the diagnosis of liver diseases, the assessment of the hepatic isoenzyme LDH - LDH5 is more significant.

In acute viral hepatitis, serum LDH activity is increased in the first days of the icteric period, and in mild and moderate forms of the disease, it quickly returns to normal levels. Severe forms of viral hepatitis, and especially the development of liver failure, are accompanied by a pronounced and more prolonged increase in LDH.

With obstructive jaundice in the first stages of blockage of the bile ducts, LDH activity is normal, at later stages there is an increase in activity due to secondary damage to the liver.

In liver carcinomas or cancer metastases to the liver, an increase in LDH activity may occur.

2. Cholestatic syndrome (cholestasis) is characterized by impaired bile secretion. Some authors distinguish a rare anicteric form of cholestasis associated with a change in the normal ratios of bile components (hormonal changes, disturbances in the intestinal-hepatic circulation of cholesterol). Allocate intrahepatic cholestasis associated with impaired secretion of bile by hepatocytes or impaired formation of bile in the bile ducts, and extrahepatic cholestasis due to obstruction of the bile ducts with a stone, tumor, or the administration of drugs that cause cholestasis. During cholestasis, substances that are excreted in the bile in healthy people enter and accumulate in the blood plasma, and the activity of the so-called indicator enzymes of cholestasis increases. The typical icteric form of cholestasis is characterized by pruritus and jaundice.

With cholestasis, the content of bile acids increases; bilirubin with a predominant increase in conjugated, which is part of bile (cholebilirubin); cholesterol and - lipoproteins; activity of enzymes ALP, GGTP, 5-nucleotidase.

Alkaline phosphatase (ALP) is active at pH 9-10 and is found in the liver, intestines, and bone tissue, but the liver is the main excretory organ. In the hepatocyte, alkaline phosphatase is associated with the membranes of the biliary pole and microvilli of the epithelium of the bile ducts. The causes of hyperenzymemia are a delay in the excretion of the enzyme into bile and the induction of enzyme synthesis, which depends on the block of intestinal-hepatic circulation. An increase in activity in liver diseases most often indicates cholestasis, in which the activity of the enzyme increases on days 4-10 to 3 or more times, as well as liver tumors. With an increase in alkaline phosphatase activity, differential diagnosis with bone diseases should be carried out.

5-nucleotidase belongs to the group of alkaline phosphatases, changes in parallel with them, but the increase in its activity is associated exclusively with cholestasis.

GN is also a membrane-bound enzyme and increases in cholestasis due to the activation of synthesis. The study of GGTP in cholestasis is considered mandatory.

Impaired bile excretion leads to impaired emulsification of fats and a decrease in the absorption of fat-soluble substances in the intestine, including vitamin K. A decrease in the content of vitamin K in the body leads to a decrease in the synthesis of vitamin-K-dependent blood coagulation factors and a decrease in the prothrombin index (III I) ...

3. Hepatodepressive syndrome includes any abnormalities in liver function not accompanied by encephalopathy. The syndrome is observed in many liver diseases, but is most pronounced in chronic processes. The least stable in liver diseases is the synthetic function, and first of all, the synthesis of those substances that are formed mainly in the liver decreases. Available and informative indicators of hepatodepression can be the following:

1. Albumin is almost completely synthesized by the liver. A decrease in its concentration is observed in half of patients with acute and in 80-90% of patients with CAH and liver cirrhosis. Hypoalbuminemia develops gradually, the result may be a decrease in oncotic blood pressure and edema, as well as a decrease in the binding of hydrophobic and amphiphilic compounds of endogenous and exogenous nature (bilirubin, free fatty acids, drugs, etc.), which can cause intoxication. Informative parallel determination of albumin and total protein. A decrease in albumin to 30 g / l and less indicates the chronicity of the process.

2. α-Antipincin glycoprotein, which makes up 80-90% of the α-globulin fraction, an acute phase protein, synthesized in the liver, is a sensitive indicator of inflammation of parenchymal cells. Exceptional diagnostic value is associated with congenital protein deficiency, leading to severe forms of damage to the liver and other organs in children.

3. Cholinesterase (pseudocholinesterase, butyrylcholinesterase - ChE, BChE)

serum, synthesized by the liver, belongs to fi2-globulins. In chronic processes, especially liver cirrhosis, the activity of the enzyme decreases, and the degree of reduction has a prognostic value. Another reason for the decrease in activity is poisoning with organophosphorus compounds.

4. Fibrinogen, factor I of blood coagulation, an acute phase protein, belongs to fi2 globulins. The fibrinogen level naturally decreases in severe chronic and acute liver diseases.

5. NFN decreases due to impaired synthesis of vitamin K-dependent blood coagulation factors (II, VII, IX, X). Unlike cholestasis, the level of PTI is not normalized with intramuscular administration of vitamin K. PTI is a marker of the severity of acute liver dysfunction.

6. Cholesterol in the blood decreases in patients with chronic hepatitis and liver cirrhosis, more often with a subacute course. With fatty liver disease, cholesterol levels may increase.

For chronic liver diseases in the stage of compensation, an increase in enzyme activity is uncharacteristic. However, a moderate increase (by 1.5 - 3 times) in the activity of transaminases with a higher level of AcAT indicates damage to subcellular structures, in particular, mitochondria.

4. Mesenchymal-inflammatory syndrome is caused by damage to the mesenchyme and stroma of the liver, is an immune response to antigenic stimulation of intestinal origin. This syndrome

accompanies both acute and chronic liver diseases. The markers of the syndrome are γ-globulins, immunoglobulins, thymol test, antibodies to cellular elements, etc.

Determination of γ-globulins refers to the mandatory tests for the liver. The rise in γ-globulins, which are essentially immunoglobulins, is characteristic of most liver diseases, but is most pronounced in CAH and liver cirrhosis. Recently, it has been shown that γ-globulins can be produced by Kupffer's cells and plasma cells of inflammatory liver infiltrates. With cirrhosis of the liver, against the background of a low concentration of albumin due to a violation of the synthetic function of the liver, a significant increase in γ-globulins is observed, while the concentration of total protein may remain normal or increased.

Immunoglobulins (Ig) are proteins that are part of the γ-globulin fraction and have the properties of antibodies. There are 5 main Ig classes: IgA, IgM, IgG, IgD, IgE, but the first three are used for diagnosis. In chronic liver diseases, the content of all Ig classes increases, but the most pronounced increase in IgM. With alcoholic liver damage, an increase in IgA is observed.

Thymol npo6a is a nonspecific but affordable test method, the result of which depends on the content of IgM, IgG and lipoproteins in the blood serum. The test is positive in 70-80% of patients with acute viral hepatitis in the first 5 days of the icteric period, in 70-80% of patients with CAH, in 60% - with liver cirrhosis. The sample is normal with obstructive jaundice in 95% of patients.

Antibodies to tissue and cellular antigens (nuclear, smooth muscle, mitochondrial) make it possible to identify autoimmune components in liver diseases.

Table 7

syndrome	**Biochemical indicators**
1.Citolysis necrosis	**AlAT1, AcAT1, LDG1, I I HIS**
2.cholestasis	bile acids, alkaline phosphatase 1, 11 HIS,

	bilirubin 1, cholesterol 1, PTI
3.Hepatodepression	albumin, cholesterol +, fibrinogen 1, poultry, HEL, (decrease in synthetic function), AST + ALAT
4.Mesenchymal **inflammatory**	γ-globulins (Ig) 1, thymol test: negative, - cholestasis (95%) + o. hepatitis (80%), CAH (80%), cirrhosis (60%)
5.Liver **failure**	 phenols, cyclic amino acids, fat short-chain acids1 (butyric, valeric, nylon), synthetic function is reduced)

5. Liver failure is caused by a violation of the basic functions of the liver, as well as the entry into the bloodstream, bypassing the liver, of toxic substances from the intestine, followed by the development of encephalopathy. Indicators of liver bypass surgery include ammonia and its derivatives, phenols, cyclic amino acids, short-chain fatty acids.

Ammonia is formed during the deamination of amino acids and is an extremely toxic compound for the brain. The neutralization of ammonia is carried out by the liver by converting it into urea.

Phenols, which are cyclic hydrophobic compounds that are toxic to the brain, increase dramatically in hepatic coma.

Cyclic amino acids (tyrosine, phenylalanine, tryptophan) increase in severe liver damage. In healthy people, the overall level of amino acids, as well as the ratio of their different types, support the liver. In the absence of a regulating function of the liver, the amount of amino acids changes disproportionately, and some of them, being in excess, can have a toxic effect.

Short-chain fatty acids include butyric (C4), valeric (Cd), nylon (C6), which are formed in the intestines and neutralized by the liver. Normally, fatty acids, like all toxic and active hydrophobic compounds, are associated with albumin. With liver failure, the acid content increases, and the albumin content naturally decreases, therefore, they can freely render toxic

effect on the synapses of nerve cells, slowing down the conduction of nerve impulses.

Distinguish between minor liver failure and major liver failure, which can be caused both by the intake of toxic substances from the intestine (liver bypass surgery), and damage or destruction of liver cells.

Table 8.

Differential diagnosis of liver failure by signs

sign	little	big
Hepathogenic encephalopathy	-	+
Presence of hepatodepression	Generally moderate	Generally expressed
Increase in shunting indicators	Missing or moderate	Expressed

The main characteristics of liver failure.

Hepatic cell failure (true coma) is associated with the destruction of cells or their replacement with other cells (connective tissue, tumor, etc.). The disease is characterized by encephalopathy, jaundice and hemorrhagic syndrome. Patients have a pronounced hepatodepressive syndrome (a decrease in blood coagulation factors, lllI, cholesterol, ChE, albumin), an increase in both fractions of bilirubin by 10-20 times, edema associated mainly with a decrease in the level of albumin, an increased level of indicators of liver shunting - ammonia, cyclic amino acids - lot, short-chain fatty acids, cytolysis enzymes can be enhanced. A decrease in the content of enzymes against the background of coma is an unfavorable sign, which is due to a decrease in the ability of the liver to synthesize enzymes.

Portal hepatic failure (shunt coma) is primarily caused by the ingress of substances into the general bloodstream that are normally rendered harmless by the liver and are regarded as indicators of shunting - ammonia, cyclic amino acids, short-chain fatty acids, mercaptans. The leading role in the development of coma is played by ammonia, the increase of which disrupts the energy metabolism of nerve cells.

TASKS FOR SELF-MONITORING TEST TASKS

1. The structural and functional unit of the liver is:

1) hepatocyte

2) Kupffer cage

3) hepatic lobule

4) vascular endothelium

2. The liver does not form:

1) albumin

2) coagulation factors

3) myoglobin

4) bile acids

3. The precursor of bilirubin is

1) myoglobin

2) hemoglobin

3) porphyrin

4) cytochrome

5) all of the above

4. Where does the metabolic breakdown of hemoglobin mainly occur?

1) reticuloendothelial system

2) erythrocytes

3) liver cells

4) renal tubules

5) all of the above

5. What value should not exceed the concentration of total serum bilirubin in the norm:

1) 8.5 μmol / l

2) 20.5 μmol / l

3) 30.5 μmol / l

4) 35.5 μmol / l

5) 58.5 μmol / l

6. Conjugated bilirubin in normal blood is up to: 1) 5%

2) 25%

3) 50%

4) 75%

5) 100%

7. What is used for the synthesis of conjugated bilirubin:

1) UDP-glucose

2) UDP-glucuronate

3) glucose

4) glucuronic acid

5) mannosamine

8. In the differential diagnosis of parenchymal and hemolytic jaundice, the following tests are informative:

1) bilirubin fractions

2) LDH isozymes

3) aminotransferase

4) reticulocytes

5) all of the above is true

9. The urine of a healthy person contains:

1) biliverdin

2) stercobilinogen

3) mesobilirubin

4) bilirubin

5) all of the above

10. The appearance of urobilin in urine with obstructive jaundice may indicate:

1) restoration of patency of the biliary tract

2) blockage of the biliary tract

3) damage to the gallbladder

4) restoration of liver function

5) increased unconjugated bilirubin

11. The absence of urobilin in urine indicates:

1) hemolytic jaundice

2) obstructive jaundice

3) parenchymal jaundice in the prodromal period

4) Gilbert's disease

5) all diseases

12. Select a characteristic that has nothing to do with indirect bilirubin:

1) is formed in the liver from direct bilirubin

2) in the blood is in a complex with the protein albumin

3) poorly soluble in water and not filtered into urine

4) toxic, passing through the blood-brain barrier, causes encephalopathy

5) reacts slowly with Ehrlich's diazo reagent

13. Note the characteristic unrelated to hemolytic jaundice:

1) occurs due to massive destruction of red blood cells

2) total blood bilirubin increases due to indirect bilirubin

3) bilirubin in urine is not detected, the content of urobilinogen is increased

4) feces are colored normally

5) decreased activity of the enzyme UDP-glucuronyl transferase

14. Note a characteristic that is not related to obstructive jaundice:

1) occurs due to a violation of the normal outflow of bile into the intestine

2) the content of both direct and indirect bilirubin is increased in the blood

3) the content of total bilirubin does not exceed 20 μmol / l

4) feces are weakly colored, up to discoloration

5) in the urine, the content of bilirubin is sharply increased, there is no urobilinogen

15. Name one of the distinguishing features of hemolytic (suprahepatic) jaundice from mechanical (subhepatic) and hepatocellular (hepatic) jaundice:

1) icteric staining of the sclera and skin

2) darkening of urine

3) increased blood levels of both unconjugated (indirect) and conjugated (direct) bilirubin

4) an increase in the content of conjugated (direct) bilirubin in the blood

5) increased blood levels of unconjugated (indirect) bilirubin

16. Hepatocellular jaundice is caused by damage to hepatocytes and bile capillaries, for example, in acute viral infections, chronic and toxic hepatitis. Name one of the main distinguishing features of hepatocellular jaundice from hemolytic and obstructive jaundice:

1) icteric staining of the sclera and skin

2) darkening of feces

3) increased blood levels of unconjugated and conjugated bilirubin

4) increased blood levels of unconjugated (indirect) bilirubin

17. A sign of obstructive jaundice is the presence in the urine:

1) conjugated bilirubin

2) indicana

3) proteins

4) cylinders

5) lactose

18. The color of feces is influenced by:

1) admixture of blood

2) bilirubin

3) green parts of vegetables

4) stercobilin

5) all of the above

19. Normal color of feces is determined by:

1) carbohydrate food

2) fats

3) protein food

4) stercobilin

20. The appearance of bilirubin in feces is a sign of:

1) gastritis

2) acute enteritis

3) duodenitis

4) pancreatitis

5) dysbiosis

Situational tasks

Situational task number 1

A patient with liver disease was admitted to the hospital. A biochemical analysis of blood ureas was carried out.

1. Is this test useful to assess the severity of liver disease?

2. What additional research needs to be done to exclude changes in renal excretory function?

Situational task number 2

When examining employees of the Khimchistka association, one female employee was found to have an increase in the activity of alanine aminotransferase (ALT) in the blood by 5.7 times, and aspartate aminotransferase (AcAT) - by 1.5 times. Practitioner A suggested that this was due to the increased consumption of meat products the day before, and there was no cause for concern. Practitioner B suggested that this worker be hospitalized, suggesting that she had liver damage from organic solvents.

1. Which one is right and why?

2. What is the diagnostic value of determining the activity of aminotransferases in blood serum?

Situational task number 3

In severe viral hepatitis, patients may develop hepatic coma, caused, in particular, by the toxic effect of ammonia on brain cells. What is the reason for such a significant accumulation of ammonia in the blood?

Situational task number 4

In two patients, the concentration of bilirubin is 100 μmol / l, but in the first, free bilirubin prevails, and in the second, bound. Which patient's condition is more severe and why?

Situational task number 5

In a newborn, the content of bilirubin in the blood is increased (due to free), the feces are intensely colored, bilirubin was not found in the urine.

1. What kind of jaundice are we talking about?

2. What drug can be used to prevent this disease and why?

Situational task number 6

The patient has bright yellowness of the skin, sclera, mucous membranes. Dark beer-colored urine, faeces discolored. In the blood, the content of bilirubin is increased, bilirubin is determined in the urine. What type of jaundice are we talking about?

Situational task number 7

Why the use of salicylates, sulfonamides, antibiotics in large doses as medicinal products can cause hemolytic jaundice of newborns with possible subsequent encephalopathy?

Situational task number 8

Patient F., 32 years old, was admitted to the infectious diseases hospital unconscious, with severe jaundice. There is a "liver" odor from the mouth. Regional lymph nodes are not enlarged. With percussion of the chest, pulmonary sound, with auscultation, vesicular breathing. Heart sounds are muffled. Rhythmic pulse, weak filling, 120 / min., BP - 110/70

mmHg. The liver and spleen are not palpable. With percussion, the lower edge of the liver is determined 2.0 cm above the costal arch along the mid-clavicular line on the right. Corneal reflexes are preserved.

From the anamnesis: 3 months ago the patient underwent appetzdectomy. Jaundice appeared yesterday; a week before admission, a “cold illness” began.

1. Bam the alleged diagnosis and its rationale.

2. What biochemical studies are necessary to determine the etiology of the disease?

3. What biochemical index indicates hepatocellular failure?

Situational task number 9

A 29-year-old man is an active donor, for the last 6 months he has been a plasma donor. He was sent to the hepatocenter by a blood transfusion station due to an increase in transaminases that appeared in him: ALT - 250 μmol / L. Previously, such an increase in enzyme tests was not registered. No complaints. On examination, a slight enlargement of the liver was noted.

From the epidemiological history: an increase in aminotransferases was detected

another 2x donors of this station. ELISA diagnostics for markers to viral hepatitis B, C, D showed a negative result.

1. Your estimated diagnosis.

2. How to confirm the diagnosis?

Situational task number 10

Patient K., 47 years old, consulted a doctor with complaints of frequent attacks of acute pain in the right hypochondrium, radiating to the right half of the neck, shoulder, lasting up to 3 hours, accompanied by an increase in body temperature to subfebrile numbers, nausea, vomiting with an admixture

bile. They occur, as a rule, after ingestion of spicy and fatty foods. Stool daily, decorated, brown, without pathological impurities. Considers himself a patient for about 2 years, when pain first appeared in the right hypochondrium. Since that time, after errors in the diet, such exacerbations were not examined, she took antispasmodics on her own, and

used a heating pad. Yesterday, after errors in the diet, pains resumed, nausea and vomiting with an admixture of bile joined in, today the body temperature rose to 37.70C, called an ambulance, and was taken to a dignity. checkpoint.

Professional history: housewife, often irregular food intake, consumption of fatty and fried foods.

On superficial palpation, it was soft, painful in the right hypochondrium, peritoneal symptoms were negative. The blistering symptoms of Kepa, Murphy, Ortner are positive.

Additional research methods data:

1. Complete blood count: erythrocytes —3.8-10 * 12 / l, Hb — 135 g / l., CP — 1.0, ESR —18 mm / h,

platelets - 320-10 * 9 / l,

leukocytes —11.3-10 * 9 / l: e-1%, n-20%, c-58%, lf-12%, m-9%.

2. General urine analysis:

light yellow, transparent, acidic pH, specific gravity 1016; protein, caxap - no, leukocytes - 1-2, epithelium - 3-4 in the field of view,

erythrocytes, cylinders - no, oxalates - a small amount. 3.Biochemical blood test:

glucose 3.3 mmol / l,

fibrinogen - 3.4 g / l, prothrombin index - 90%, AcAT - 0.38 mmol / l,

ALT - 0.36 mmol / l, cholesterol - 5.5 mmol / l, total bilirubin - 59.0 mmol / l,

direct - 44.0 μmol / l, indirect - 15.0 μmol / l,

amylase - 5.7 g / l h, creatinine - 0.07 mmol / l, total protein - 75 g / l,

albumin —54%, globulins —46%: e1-5%, e2-10%, g —15%, y —16%.

1. Select syndromes, select the leading syndrome.

2. Justify the preliminary diagnosis.

3. Explain the mechanism of development of jaundice.

4. Evaluate the data of the biochemical blood test.

Situational task number 11

Patient K., 33 years old, consulted a doctor with complaints of severe weakness, fatigue, decreased ability to work. Stool daily, decorated, brown, without pathological impurities. Urination 3-4 times a day, painless. Considers herself sick for about a year, when for no apparent reason the above complaints appeared, gradually increased, which forced her to see a doctor. Previously not examined, not treated.

Professional history: dentist. Denies bad habits.

Denies tuberculosis, viral hepatitis.

Objectively: the general condition is closer to satisfactory, the consciousness is clear, the position is active. Skin and visible mucous membranes with an icteric shade, dry, palmar erythema, single telangiectasias on the skin of the chest with a diameter of up to 5 mm. The abdomen is of the correct shape, both halves are equally involved in the act of breathing. On palpation, it is soft, slightly painful in the right hypochondrium, symptoms of Kepa, Murphy, Ortner are positive.

Data of additional research methods: 1. General blood test:

erythrocytes —3.8-10 * 12 / l, leukocytes —11.3-10 * 9 / l: e-1%, n-20%, c-58%, lf-12%, m-9%, platelets —320 * 109 / l, Hb — 135 g / l., CP — 1.0, ESR —18 mm / h

2.General analysis of urine:

light yellow, transparent, acidic pH, specific gravity 1016; protein, caxap - no, leukocytes - 1-2, epithelium - 3-4 in the field of view,

erythrocytes, cylinders - no, oxalates - a small amount. 3.Biochemical blood test:

glucose 3.3 mmol / l,

fibrinogen - 3.4 g / l,

prothrombin index - 90%,

AcAT - 0.38 mmol / l,

ALAT - 0.36 mmol / l,

cholesterol - 5.5 mmol / l, total bilirubin - 59.0 mmol / l, direct 34.0 mmol / l,

indirect —15.0 μmol / l,

amylase - 5.7 g / l h, creatinine - 0.07 mmol / l,

total protein - 75 g / l, albumin - 54%,

globulins 36%: e1-5%, e2-10%, g —15%, y —16%.

5. Ultrasound:

The gallbladder is of normal size, the wall is 4 mm thick, and there are multiple calculi in the lumen.

1. Select syndromes, mark the leading syndrome.

2. What is the preliminary diagnosis, its rationale

3. Evaluate the data of the biochemical blood test.

Situational task number 12

Patient 3., 4 years old, complains of intense itching of the skin, mainly in the evening, a slight increase in abdomen in size, a feeling of heaviness in the right hypochondrium, severe weakness, fatigue, decreased ability to work. Physiological functions are normal. Considers himself a patient near Zlet, when weakness and itching of the hands and feet first appeared at night, for which she was treated for a long time by a dermatologist without effect. Gradually, the severity in the right hypochondrium was added, the abdomen increased, the weakness intensified, the itching became more intense and widespread. In connection with the progressive deterioration of her condition, she applied to the polyclinic at her place of residence. The district doctor is directed to hospitalization for examination and selection of therapy.

Past diseases: childhood infections, ARVI. Professional history: accountant, denies professional harm. Follows a diet. Denies bad habits. Tuberculosis, viral hepatitis denies.

Objectively: general condition of moderate severity, clear consciousness, active position. The skin and visible mucous membranes are yellow, dry, on the back, abdomen, forearms and legs there are traces of scratching. The belly is of regular shape, evenly enlarged, both halves equally participate in the act of breathing. On palpation, it is soft, slightly painful in the right hypochondrium. The liver is moderately painful on palpation, dense, the edge is sharp

Data of additional research methods: 1. General blood test:

erythrocytes —3.7-10 * 12 / l, Hb —130 g / l., ESR —32 mm / h, platelets — 250-10 * 9 / l, leukocytes —7.8-10 * 9 / l: e -3%, n-2%, s-58%, lf-28%, m-9%.

2. General urine analysis:

light yellow, transparent, acidic pH, specific gravity 1017; protein, caxap - no, leukocytes - 1-2, epithelium - 3 in the field of view, erythrocytes, cylinders - no, oxalates - a small amount.

3. Biochemical blood test: glucose 3.1 mmol / l, fibrinogen - 2.0 g / l, prothrombin index - 75%,

AcAT - 2.48 mmol / L, AlAT - 3.67 mmol / L,

cholesterol - 8.5 mmol / l, total bilirubin - 149.0 mmol / l,

direct —112.0 μmol / l., indirect —37.0 μmol / l,

amylase - 6.7 g / l h, creatinine - 0.06 mmol / l,

total protein -56 g / l, albumin 34%, globulins -56%: e1-5%, e2-15%, §

—15%, y —21%, 11 111 —460 U / l.

4. Markers of viral hepatitis were not found.

1. Select syndromes, select the leading syndrome.

2. Justify the preliminary diagnosis.

3. Evaluate the data of the biochemical blood test.

Situational task number l5

Patient G., 45 years old, complains of aching pains in the right hypochondrium, constant, decreases after taking no-shpa after 30-40 minutes, weakness, malaise, loss of appetite, daytime sleepiness and sleeplessness at night, weight loss (how much and for what period of time - cannot specify), periodically bleeding of the gums and hemorrhoids. He considers himself ill for about 5 years, when pains in the right hypochondrium began to appear, and passed on their own. She did not seek medical help. About a year ago, weakness, malaise, worsened appetite, began to notice a decrease in body weight. A month ago, bleeding of the gums and hemorrhoids was added.

History: alcohol abuse.

Past diseases: ARVI, chronic bronchitis of a smoker.

Professional history: works as a mechanic. Does not eat regularly, does not follow a diet.

Bad habits: smokes 1 pack of cigarettes a day for 15 years, often drinks strong alcoholic beverages.

Heredity is not burdened. Allergic history is not burdened.

Objectively: a state of moderate severity, clear consciousness, active position. The skin and visible mucous membranes are yellow, normal humidity, turgor and elasticity are reduced, there are multiple telangiectasias on the chest up to 0.5-1.0 cm in diameter, hyperemia of the tenor and hypotenor, both palmar surfaces. Subcutaneous adipose tissue is poorly developed, evenly distributed, gynecomastia. The abdomen is enlarged, both halves are equally involved in the act of breathing, an enlarged venous pattern is determined along the lateral surfaces of the abdomen. On superficial palpation, the abdomen is soft, painless in all parts, the peritoneal symptoms are negative, the fluctuation symptom is positive. Palpation of all parts of the large and small intestine is difficult, the palpation area is painless.

Deep palpation reveals pain on palpation of the liver + 2 cm from under the edge of the costal arch along the midclavicular line.

Additional research methods data:

1. Complete blood count:

erythrocytes - 3.3-10 * 12 / l, Hb - 105 g / l., CP - 1.0, ESR - 18 mm / h,

platelets - 220-10 * 9 / l,

leukocytes - 4.3-10 * 9 / l: e-3%, n-4%, c-51%, lf-32%, m-10%. 2.General analysis of urine:

light yellow, transparent, acidic pH, specific gravity 1008; protein, caxap - no, leukocytes - 1-2, epithelium - 2-4 in the field of view, erythrocytes, cylinders

—No, oxalates — a small amount. 3.Biochemical blood test:

glucose 3.3 mmol / l,

fibrinogen - 1.4 g / l, prothrombin index - 60%,

AcAT - 1.38 mmol / L, AlAT - 1.36 mmol / L, cholesterol - 2.5 mmol / L, total bilirubin 39.0 μmol / L,

direct -14.0 μmol / l., indirect -35.0 μmol / l,

amylase - 5.3 g / l h, creatinine - 0.07 mmol / l, total protein - 55 g / l,

albumin —34%, globulins —66%: e1-6%, e2-20%, g —16%, y —24%.

1. Select syndromes, mark the leading syndrome. 2. Justify the preliminary diagnosis.

3. Evaluate the data of the biochemical blood test.

Situational task number 14

Patient R., 29 years old, complains of weakness, malaise, decreased appetite, yellowness of the skin and mucous membranes, nausea after eating, fever up to 39 ° C, without chills, in the evening, itchy skin all over the body, mainly in the evening and night time. He considers himself ill for about a month, when relatives noted yellow coloration of the skin and mucous membranes. He did not seek medical help, did not receive medical treatment on his own. About a week ago, weakness, malaise, skin itching joined in, appetite worsened, and the intensity of jaundice increased. Three days ago, he noted an increase in body temperature.

History: alcohol abuse for about 3 years, during the last month, daily consumption of beer up to 1 liter per day, occasionally strong alcoholic beverages. A year ago, my wife received inpatient treatment in an infectious diseases hospital for viral hepatitis C. Past illnesses: childhood infections, ARVI, appendectomy in childhood.

Professional history: works as a finisher at a construction site. Does not eat regularly, does not follow a diet.

Bad habits: for 9 years he smokes 1 pack of cigarettes a day, often drinks strong alcoholic beverages.

Objectively: a state of moderate severity, clear consciousness, active position. Skin and visible mucous membranes of yellow color, normal humidity, turgor and elasticity are reduced, on the skin of the face, chest and back telangiectasias 0.5-1.0 cm in diameter, on the face multiple xanthomas up to 3 mm in diameter, tenor hyperemia and hypotenor. Trace I scratches all over the body.

The abdomen is slightly increased in size, both halves equally participate in the act of breathing.

On superficial palpation, it is soft, painless in all parts, the peritoneal symptoms are negative, the fluctuation symptom is negative. With deep palpation, pain is determined on palpation of the lower edge of the liver + 2 from under the edge of the costal arch along the midclavicular line -

Research Institute.

Additional research methods data:

1.General blood count:

erythrocytes - 4.3-10 * 12 / l, Hb - 135 g

/ l., CP - 1.0, ESR - 38 mm / h, platelets - 320-10 * 9 / l,

leukocytes —24.3-10 * 9 / l: e-3%, n-22%, s-53%, lf-22%, m-1%. 2.General analysis of urine:

light yellow, transparent, pH alkaline, specific gravity 1016; protein —0.033, caxap — no, leukocytes — 1-2, epithelium — 3-4 in the field of view, erythrocytes, cylinders — no, oxalates — a small amount.

3. Biochemical blood test:

glucose 3.3 mmol / l,

fibrinogen - 2.4 g / l, prothrombin index - 70%,

AcAT 3.38 mmol / L, AlAT - 5.36 mmol / L, cholesterol - 3.5 mmol / L, total bilirubin - 349.0 μmol / L,

direct —214.0 mmol / l., indirect —135.0 mmol / l,

ALP -356 μmol / l., 11 111 -234 μmol / l.,

amylase - 5.3 g / l h, creatinine - 0.07 mmol / l,

total protein - 55 g / l, albumin 34%,

globulins -56%: e1-6%, e2-20%, g -16%, y -24%.

1. Select syndromes, identify the leading syndrome. 2. Justify the preliminary diagnosis.

3. Evaluate the data of the biochemical blood test. 4. Evaluate the data of the general blood test.

Situational task number 15

Patient O., 55 years old, complains of aching pains in the right hypochondrium, constant, decreases after taking no-shpa in 30-40 minutes, weakness, malaise, decreased appetite, yellowness of the skin and mucous membranes. Stool daily, once, brown, without pathological impurities. Considers himself a patient for about 5 months, when, during treatment in the neurological department for lumbar osteochondrosis while taking diclofenac, nise pains began to appear in the right hypochondrium, which passed on their own, short-term jaundice of the skin and mucous membranes. After discharge, I felt satisfactory. About a week ago, pains in the lumbar region resumed, and therefore took tempalgin, no-shpu, indomethacin up to 10 tablets a day .. Three days ago, pains arose in

the right hypochondrium, without irradiation, not associated with taking food, noted yellowness skin and mucous membranes, weakness, malaise, loss of appetite.

Past diseases: appendectomy in childhood, lumbar osteo-

HOND] EOZ.

Professional history: works as an accountant.

Does not eat regularly, does not follow a diet. Denies bad habits. Objectively: the general condition is closer to satisfactory, the consciousness is clear, the position is active. The skin and visible mucous membranes are jaundice, normal moisture, turgor and elasticity are normal. Deep palpation reveals pain on palpation of the lower edge of the liver + 1 cm. from under the edge of the costal arch along the midclavicular line.

Additional research methods data:

1. Complete blood count:

erythrocytes 3.3-10 * 12 / l, Hb —135 g / l, CP — 1.0, ESR —10 mm / h, platelets — 320-10 * 9 / l,

leukocytes - 4.3-10 * 9 / l: e-3%, n-4%, c-51%, lf-32%, m-10%. 2.General analysis of urine:

light yellow, transparent, acidic pH, specific gravity 1014; protein, caxap - no, leukocytes - 1-2, epithelium - 2-3 in the field of view, erythrocytes, cylinders

—No, oxalates — a small amount. Z. Biochemical blood test:

glucose 3.3 mmol / l,

fibrinogen - 3.4 g / l, prothrombin index - 80%,

AcAT 3.48 mmol / L, AlAT - 5.56 mmol / L, cholesterol - 2.5 mmol / L, total bilirubin - 29.0 μmol / L,

direct -14.0 μmol / l., indirect -15.0 μmol / l,

ALP —45 μmol / l., 11 111 —67 μmol / l., Amylase —5.3 g / l h,

creatinine - 0.07 mmol / l,

total protein - 72 g / l, albumin 34%

1. Select syndromes, mark the leading syndrome. 2. Justify the preliminary diagnosis.

H. Causes of jaundice

4. Evaluate the data of the biochemical blood test. 5. Evaluate the data of the general blood test.

Situational task number 16

A patient - a student, 18 years old, complains of pain in the right hypochondrium, weakness, poor appetite, joint pain. One and a half years ago he suffered from viral hepatitis B. He did not follow a diet, he was a beer lover.

On examination: “bruises” on the skin of the limbs and trunk, which, according to the patient, are formed at the slightest bruises. The skin and sclera are icteric. The liver is enlarged, hardened, the spleen is palpable.

Additional research methods data:

Bilirubin - 30 mmol / L, indirect - 17 mmol / L. ALAT - 0.5 mmol / L, AcAT - 0.6 mmol / L, prothrombin index - 50%,

thymol test - 40 units

Found: HBsA, HBeA, anti-HBsJgM.

1. What is your presumptive diagnosis?

2. What syndromes have been identified?

3. Evaluate the blood test data

Situational task number 17

Patient, 17 years old. According to his mother, he has been suffering from jaundice since early childhood. In recent years, periodically worried about a feeling of heaviness in the right hypochondrium, accompanied by increased jaundice, after exercise,

NYATY SPO] THIS.

On examination: the condition is satisfactory. The sclera of the eyes and the skin are moderately icteric. The language is clean. The abdomen is soft, painless on palpation. The liver and spleen are not palpable.

Analysis of blood and urine without changes.

Bilirubin - 32.1 mmol / L, indirect - 28.1 mmol / L. AcAT - 0.3 units, ALAT - 0.4 units.

1. What is your presumptive diagnosis?

2. What explains the jaundice?

3. What kind of jaundice should be excluded?

Situational task number 18

Patient B., 28 years old, was under observation in the hospital for 2 months. Complaints of icteric staining of the skin and mucous membranes, weakness, nausea, itching. The malaise appeared soon after childbirth. The liver is enlarged, painful.

Blood - direct bilirubin 82 μmol / l, bilirubin was found in urine, no urobilin, the reaction to stercobilin is weakly positive, erythrocytes - 3.8 1012 / l, Hb - 110 g / l.

The patient underwent an operation, as a result of which a stone was removed from the common bile duct, which completely covered the lumen.

1. Name the syndrome that was observed in the patient.

2. State the reason for its development.

3. Explain its mechanism.

4. Explain why direct bilirubin is found in the blood.

5. Explain why there is no urobilin in urine with this syndrome?

Situational task number 19

Patient Sh. 48 years old, a nurse of a tuberculosis hospital, during a week noted general weakness, pain in muscles, joints of arms and legs, itching of the skin, constant nausea (vomiting once), loss of appetite. Within 4 days, fever was noted up to 37.5 37.80C. On the recommendation of a doctor, she took antigrippin.

She was admitted to the hepatological center after the onset of jaundice in a state of moderate severity. To the previous complaints were added persistent itching of the skin, poor sleep and headaches.

On physical examination: pronounced jaundice of the skin, sclera and

mucous membranes. Isolated hemorrhages are visible on the skin. Tongue coated with white bloom. The liver is 3 cm below the costal arch, soft, sensitive to palpation and tapping. The spleen is not enlarged.

Additional research methods data:

1. Complete blood count:

HB - 120 g / l, erythrocytes - 4.5 x 1012 / l, leukocytes - 4.7 x 109 / l, ESR - 27mm / h.

2. Biochemical blood test

The activity of ALT is four times higher than the norm, the activity of alkaline phosphatase is increased.

Total bilirubin - 156.9 μmol / l, bilirubin index - 81%. An "Australian" antigen and an increased IgG content were detected. The prothrombin index is 73%, the content of proaccelerin and proconvertin is reduced, the albumin-globulin coefficient is reduced.

Fasting blood glucose ranges from 2 to 4.5 mmol / l. The jaundice and itching persisted for about 45 days.

She was discharged two months later with ALAT readings twice the norm.

1. What type of jaundice does the patient have?

2. Possible reasons for its development?

3. Give reasons for your conclusion.

4. Explain the mechanism of symptoms and changes in biochemical indicators.

5. What syndromes are detected in the patient?

6. What changes can be found in the patient's urine

Situational task number 20

Patient R., 50 years old, went to the doctor with complaints of itching, yellowness of the skin and sclera, darkening of urine, clarified feces, weight loss, itching and bleeding of the gums, flatulence,

constipation, "fatty feces". The listed symptoms first appeared 2 months ago.

Fibrogastroduodenoscopy revealed a tumor in the area of the large duodenal papilla, and ultrasound examination of the abdominal organs revealed an enlarged lymph nodes.

Objectively: a patient with low nutrition, the skin and sclera are icteric, traces of scratching on the skin, petechial rashes, blood pressure 110/60 mm Hg. Art., heart rate 52 min 1

Additional research methods data:

1. Biochemical blood test:

total protein 67 g / l, albumin 57%, globulins 43% fibrinogen 4 g / l

thymol test 4 units

creatinine 52 μmol / l, urea 6.5 mmol / l, glucose (plasma) 5.3 mmol / l,

total cholesterol 14.2 mmol / l, total bilirubin 270.7 μmol / l direct bilirubin 252.1 μmol / l, indirect bilirubin 18.6 μmol / l hemoglobin 80 g / l

urobilin - no, bile acids +++

AcAT 59 u / l, ALAT 47 u / l, ALP 283 u / l.

2. General urine analysis:

dark beer color, protein - absent, urobilin absent, glucose absent, bilirubin +++, bile acids +++.

1. Indicate the cause and type of jaundice observed in the patient, justify your conclusion.

REFERENCES OTBETOB WITH TEST REFERENCE

1-3 6-5 11-2 16-3

2-3 7-2 12-1 17-1

3-5 8-5 13-5 18-5

4-1 9-2 14-2 19-4

5-2 10-1 15-5 20-5

STANDARDS OTBETOB TO TWO TWO PROBLEMS

Answer to problem number 1

Urea synthesis occurs in the liver. Its content can serve to assess the synthesizing ability of the liver, but for this it is necessary to exclude the change in the excretory function of

the kidneys and to determine the residual nitrogen, as well as the activity of ALT in the blood serum.

Answer to problem number 2

Practitioner B. Physician is right. The ALT enzyme has a specific organ localization in the liver and, when cells are destroyed, it enters the bloodstream, where its activity sharply increases, which is observed in the patient.

Answer to problem number 3

With viral hepatitis, the functions of hepatocytes are impaired. The synthesis of urea is reduced, which leads to the accumulation of ammonia.

Answer to problem number 4

Both patients have hyperbilirubinemia, but the first patient is in a more serious condition (he may have hemolytic jaundice) than the second (he may have mechanical or parenchymal jaundice), since free bilirubin is more toxic (penetrates the BBB into the brain and affects the subcortical nuclei). For the differential diagnosis of the type of jaundice, it is necessary to additionally examine urine for bilirubin, excretions for stercobilin (its absence in feces indicates obstructive jaundice) and carry out enzyme diagnostics (an increase in LDH5 activity, ALT> AcAT is characteristic of parenchymal jaundice, and ALP and 11 111 for obstructive jaundice).

Answer to problem number 5

a) Hemolytic jaundice of newborns.

b) Phenobarbital, inducer of UDP-glucuronyl transferase gene transcription.

Answer to problem number 6

The patient is likely to have obstructive jaundice. To clarify the diagnosis, it is necessary to carry out enzymodiagnostics; determine the activity of LDH5, ALT, ALP, 11 111. With obstructive jaundice, the activity of ALP and GGT is increased.

Answer to problem number 7

1. These drugs can compete with BR for binding sites on albumin; as a result, the toxic effect of free BR, mainly on the brain, increases.

2. Biochemical blood test in dynamics, protein and its fractions, PTI, HBV markers (ELISA) - IgM to HBcor Ag, HBsAg, HBeAg; PCR - HBV DNA. Answer to problem number 8

1. Acute viral hepatitis B, fulminant form, complicated by OPE, coma I stage.

The diagnosis was made on the basis of an acute onset, a short prodromal period according to the influenza-like variant, severe jaundice, a sharp reduction in the size of the liver, "hepatic" bad breath, tachycardia, lack of consciousness, preservation of corneal reflexes, information from an epidemiological anamnesis (surgical intervention 3 months ago).

2. Markers for viral hepatitis B, D (ELISA), PCR diagnostics - PCR - HBV DNA, flCP - RNA HD V.

Z. Prothrombin index (PTI), serum albumin.

Answer to problem number 9

1. Acute viral hepatitis C, anicteric form, mild severity. The diagnosis was made on the basis of information from the epidemiological history (active plasma donor), subclinical course of the disease, high ALT activity

2. PCR - diagnostics for the detection of HCV RNA, determination of the re-type of the virus.

Answer to problem X • 10

1. Cholestatic syndrome

2. Cholelithiasis. Chronic calculous cholecystitis, in the acute stage. Taking into account the characteristic abdominal pain syndrome (pain in the right hypochondrium with irradiation to the right and upward, occur after errors in the diet, positive bladder symptoms), the presence of risk factors (female gender, age), signs of jaundice and fever.

3. The syndrome of jaundice develops as a result of blockage of the ducts by calculus, which leads to a violation of the outflow of bile.

4. In the biochemical analysis of blood, signs of obstructive jaundice.

Answer to problem number 11

1. Syndrome of cytolysis (asthenic syndrome, hepatocellular failure, jaundice syndrome.

2. Chronic viral hepatitis C? Based on clinical

pictures (leading cytolysis syndrome), professional history.

3. Biochemical analysis of blood shows signs of parenchymal jaundice (hyperbilirubinemia due to both fractions) and cytolysis syndrome (increased transaminases).

Answer to problem number 12

1. Cholestasis syndrome, cytolysis syndrome (asthenic syndrome, hepatic cell failure, hepatomegaly), jaundice syndrome, portal hypertension syndrome.

2. Primary biliary cirrhosis of the liver. Portal hypertension. Ascites. Cholestasis.

3. In the biochemical analysis of blood, signs of subhepatic jaundice (hyperbilirubinemia due to the direct fraction of bilirubin), cytolysis syndrome (increased transaminases), hepatocellular (decreased protein,

albumin, fibrinogen, prothrombin index), cholestasis syndrome (increased cholesterol and 11 111).

Answer to problem number 13

1. Syndrome of cytolysis (hepatocellular failure), syndrome of parenchymal jaundice, liver failure.

2. Based on the above syndromes, history of alcohol abuse, more data for liver damage, chronic hepatitis, liver cirrhosis.

3. In the biochemical analysis of blood there are signs of cytolysis syndrome, hepatic-cellular insufficiency, parenchymal jaundice.

Answer to problem number 14

1. Syndrome of cytolysis (hepatosplenomegaly, hepatocellular failure), parenchymal jaundice syndrome, cholestasis syndrome, mesenchymal inflammation syndrome.

2. Based on the above syndromes, anamnesis - alcohol abuse, contact with an infected hepatitis C virus, liver damage can be assumed - chronic hepatitis, qi liver disease.

3. In the biochemical analysis of blood there are signs of cytolysis syndrome, hepatic cell failure, parenchymal jaundice, cholestasis.

4.In the general analysis of blood, signs of mesenchymal syndrome were revealed

minimal inflammation: accelerated ESR, leukocytosis with a shift of the leukocyte formula to the left.

Answer to problem number 15

1. Syndrome of cytolysis (asthenic, hepatocellular insufficiency, hepatomegaly, pain), jaundice syndrome.

2. Based on the identified syndromes, anamnesis, taking hepatotoxic drugs, more data for toxic liver damage.

Z. Jaundice develops due to the development of cytolysis syndrome - the direct destruction of hepatocytes with the release of bilirubin, as well as due to liver dysfunction.

4. In the biochemical analysis of blood there are signs of cytolysis syndrome, parenchymal jaundice, hepatocellular failure.

5. Indicators of a general blood test are within normal limits.

Answer to problem X • 16

1. Chronic active hepatitis, hepatocellular insufficiency

Night.

2. Severe cytolysis syndrome.

3. In the biochemical analysis of blood, there are signs of cytolysis syndrome, hepatic-cellular insufficiency.

Answer problem Wa 38

1. Benign hyperbilirubinemia - Gilbert's disease.

2. Impaired uptake of bilirubin from hepatocyte plasma, defect in conjugation of bilirubin with glucuronic acid.

3. Hemolytic (reticulocytosis, osmotic resistance, serum iron).

Answer to problem X • 19

1. Jaundice.

2. Stone of the bile duct

3. Obstruction in the biliary tract leads to stagnation and increased pressure of bile, expansion and rupture of bile capillaries and the flow of bile into the blood.

4. Direct (conjugated) bilirubin enters the blood as part of bile.

5. There is no urobilin in the urine when the duct is completely closed. bile does not enter the intestines and urobilin is not formed.

Answer to problem X • 20

Hepatic (parenchymal) jaundice in a patient with type B viral hepatitis. against the background of high hyperbilirubinemia, there are signs of a significant decrease in liver function: the synthesis of albumin (decreased A / G ratio) and procoagulants (prothrombin, proaccelerin, proconvertin), impaired carbohydrate metabolism (hypoglycemia). An increase in ALT (cytolytic enzyme) indicates damage to hepatocytes.

The patient is squeezed in a state of incomplete recovery (increased

Alat)

The patient is diagnosed with the following syndromes: jaundice, cholestasis (an increase in alkaline phosphatase in the blood is a marker), cholemia (itching of the skin is associated with an increase in fatty acids in the blood), hepatocellular insufficiency syndrome.

The patient's urine should be dark due to the content of PB in it (since its amount in the blood exceeds 34 μmol / L and it easily passes the renal filter) and should foam when shaken due to the presence of FAs in it, which lower the surface tension of the liquid.

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